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# ABBREVATIONS

| | |
|---|---|
| $NH_3$ | Ammonia |
| $NH_4VO_3$ | Ammonium metavanadate |
| $Bi(OTf)_3$ | Bismuth triflate |
| br.m | Broad multiplets |
| br.s | Broad singlet |
| $CuCl_2$ | Copper chloride |
| $CDCl_3$ | Deuterated chloroform |
| DNA | Deoxyribonucleic acid |
| $CH_2Cl_2$ | Dichloromethane |
| DIC | Diisopropylcarbodiimide |
| DMAP | N, N-dimethylaminopyridine |
| DMF | Dimethylformamide |
| d | Doublet |
| dd | Doublet of doublets |
| ddd | Doublet of doublets of doublets |
| dt | Doublet of triplets |
| EtOAc | Ethyl acetate |
| Hz | Hertz |
| HIV | Human immunodeficiency virus |
| HCl | Hydrochloric acid |
| HOMO | Highest occupied molecular orbital |
| $I_2$ | Iodine |
| LCMS | Liquid-Chromatography Coupled Mass Spectrometry |
| LiCl | Lithium chloride |
| LUMO | Lowest unoccupied molecular orbital |
| IR | Infra-red Spectroscopy |
| $MgSO_4$ | Magnesium sulphate |
| MeOD | Methanol-$d_4$ |
| MWI | Microwave irradiation |
| m | Multiplets |
| NMR | Nuclear Magnetic resonance |

| | |
|---|---|
| NaCl | Sodium chloride |
| *o*-PD | *o*-phenylenediamine |
| PE | Petroleum Ether |
| PPA | Polyphosphoric acid |
| PPMA | Phosphorus pentoxide/ methanesulfonic acid |
| *p*-TsOH | p-Toluenesulfonic acid |
| TLC | Thin- Layer Chromatography |
| RNA | Ribonucleic acid |
| s | Singlet |
| td | Triplet of doublets |
| UV/vis | Ultra-violet/visible |
| WHO | World Health Organisation |

# 1. Introduction to cancer treatment

## *1.1 Background information*

The existence and endeavour of finding the cure for cancer dates back to 3000 BC. The initial signs of cancer were detected in the bones of ancient Egyptian and Peru mummies, who lived in the 3000 BC.[1] The high mortality rate associated with cancer worldwide is the reason for the ongoing search for the cure for this disease. Four methods of treatment have been discovered; these are: surgery, radiotherapy, hormonal therapy and chemotherapy. Surgery has been the most popular form of treatment, but over the last five years there has been an increase in the use of chemotherapy. Surgery involves careful removal of the malignant cells from the patient's body and have been reported very effective for removal of small tumours. Surgery treatment has also shown effectiveness when used in combination with radiotherapy or chemotherapy.[1]

Radiotherapy, which involves destroying cellular components of tumour cells by high energy waves, has also been reported highly effective for cancer treatment though it is limited to treating small tumours. Another form of cancer treatment is hormonal therapy which involves starving tumour cells of hormones, subsequently inhibiting cell growth of small tumour cells compared to large ones.[1] Although cancer can be treated by one or combination of the above methods, chemotherapy is still the most effective line of treatment.

## *1.2 Chemotherapy*

### 1.2.1 Introduction

The use of chemicals to kill malignant cells dates back to 1946. Nitrogen mustard was the first chemathepeutic agents discovered by Louis Goodman.[2] Research conducted on the mode of action of these drugs, led to their division into eight main categories. These are alkylating agent, antimetabolites, antitumor antibiotics, topoisomerase inhibitors, spindle

inhibitors, miscellaneous agents, biological response modifiers and hormones.[3] Figure (**1**) shows the site of activity of some of these groups.

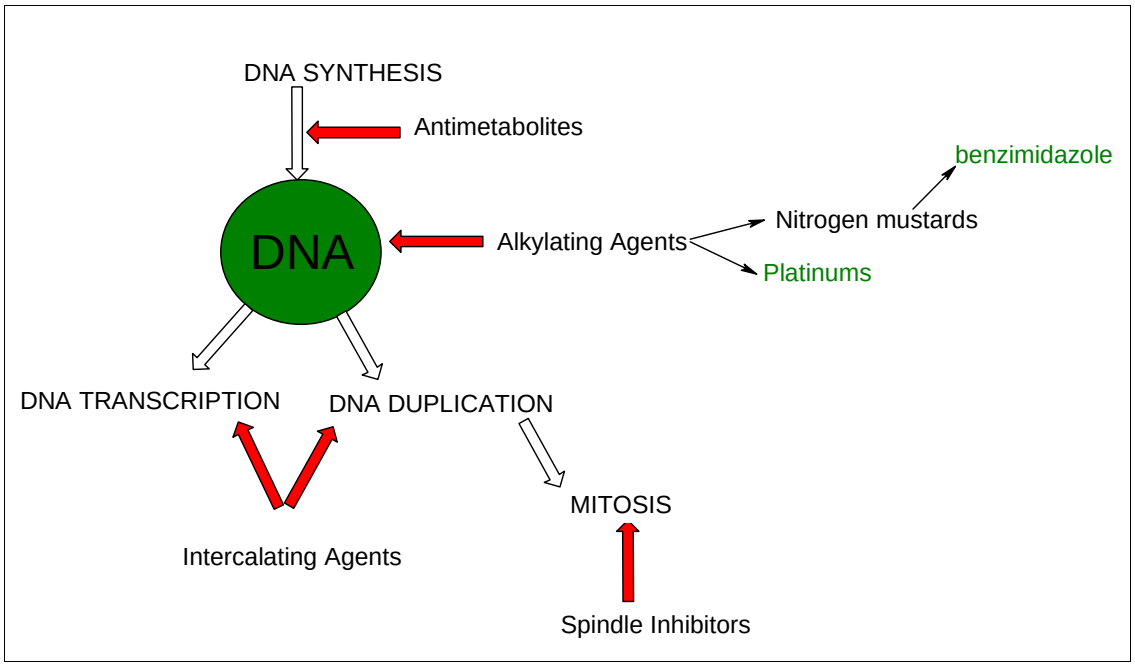
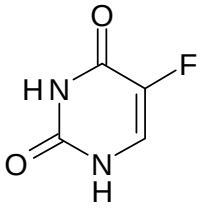



***Figure 1**:[1] Sites of action of cytotoxic agents.*

Notably, the group names of these chemotherapeutic agents are derived from their mode of action. For example, the antimetabolite 5-fluorouracil (**1**) inhibits DNA synthesis by mimicking the structure of uracil, a pyrimidine base required for DNA replication.[3] In this thesis, alkylating agents will be discussed in details.



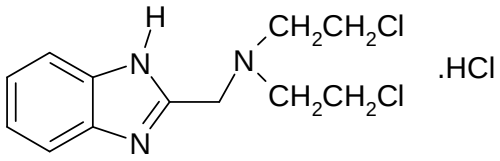

**1**

### 1.2.2 Alkylating Agents

Alkylating agents are the oldest group of chemotherapeutic drugs.[2] Nitrogen mustards, ethylenemines, alkylsulfonates, nitrosourea, and triazes are all members of alkylating agents.[2-3] For the purposes of this study, we will focus on nitrogen mustards. Nitrogen

mustards and other alkylating agents damage the DNA by attacking oxygen or nitrogen atom of the nucleobases and phosphodiester bonds between bases.[2] However, limitations such as, toxicity and low drug efficacy lowers the use of nitrogen mustard. Many studies have been conducted to develop nitrogen mustard derivatives showing high efficacy and low toxicity. Derivatives were synthesized by changing the alkylating portion or the carrier of the alkylating portion of the mustard.

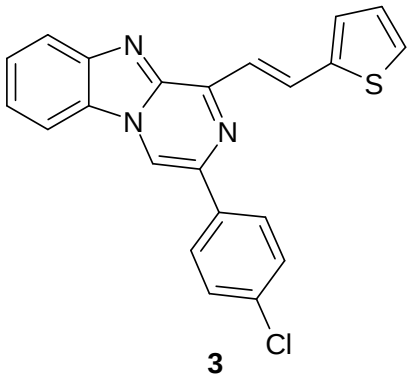
Inspired by the structural similarity between benzimidazole nucleus and the purine bases of the DNA, Hirschberg, *et al*. studied the use of benzimidazole as carriers for the alkylating portion in the synthesis of nitrogen mustard derivatives. The hypothesis behind this study was that the cellular uptake of these new compounds will increase as a result of the benzimidazole nucleus. Benzimidazole mustard, [2-(di-(2-chloroethyl) aminomethyl] benzimidazole hydrochloride (**2**) was synthesized. This compound was found to inhibit mammary Adenocarcinomas 755, E 0771, and Sarcoma 180 when tested against various mouse tumours.[4]




**2**

Recently, the wide spectrum of biological activities associated with benzimidazole has been of huge interest. This include activity against viruses such as HIV, human cytomegalovirus (HCMV), herpes (HSV-1), RNA, and influenza.[5-6] These compounds have also been reported to act as anti-inflammatory, anthelemintic, antiparasite, topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonist, 5-lipoxygenase inhibitors, and factor Xa inhibitors.[5-6] These properties, coupled with the findings that benzimidazole mustard compounds show antitumor activity, inspired more research to design benzimidazole derivatives and test them for antitumor activity.

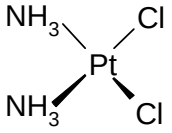
Pyrazino[1,2-a]benzimidazole derivative (**3**) has shown anti-cancer activity when *in vitro* tests were done against 60 human tumour cell lines.[7]




**3**

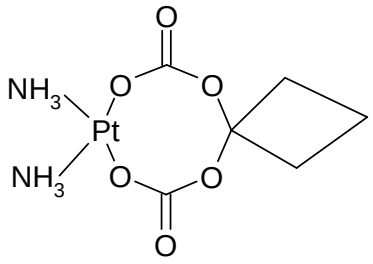
### 1.2.3 Benzimidazoles and Platinums

Although benzimidazole compounds have proven active against various cancers, there are recent reports on their combinatorial use with platinums to treat cancer. Platinums are chemotherapeutic drugs consisting of platinum (II) complexed with various donor ligands. Cisplatin (*cis*-diamminedichloroplatinum(II))(**4**) is one of the platinums that has gained worldwide popularity since 1970s.[8] Cisplatin is reported active against testicular, ovarian, bladder, head and neck cancers.[9] Despite these antitumor activities, neurological disorders, such as, nephrotoxicity, mylosuppression, ototoxicity greatly limit the use of cisplatin.[10] Moreover, it has been reported that various cancer cells become resistant to this drug, for instance, murine ADJ/PC6 plasmacytoma.[8]

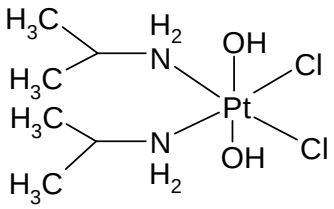



**4**

For more than three decades, many research groups have focused on developing cisplatin analogues with less toxicity, improved activity and active on cisplatin resistant tumours. In a collaborative study between the Institute of Cancer Research, Sutton, and Johnson Matthey, two cisplatin analogues were discovered, that is, JM8 (diamine (1,1-cyclobutane dicarboxylate) platinum (II), carboplatin (**5**), and JM9 (cis- dichloro-*trans*-dihydroxo-cis-bis (isopropylamine) platinum (IV), iproplatin (**6**).[8] These were both reported less toxic than cisplatin; but carboplatin was the most active analogue.



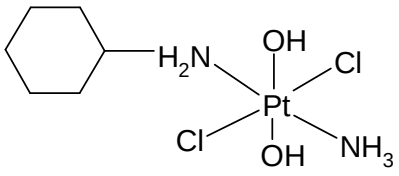
**5**



**6**

Regardless of the antitumor activity of compounds (**5**) and (**6**), resistance to these compounds is a problem. Studies conducted on determining the factors that results into cisplatin resistance showed five factors. These are, the decreased drug transport, increased cellular detoxification, changes in DNA repair mechanisms, increased tolerance of DNA adducts and changes in apoptotic cell death pathway. The idea of using sterically hindered N-containing ligands instead of the previously used $NH_3$ came along this time. It was hypothesized that the sterically hindered ligands will be less susceptible to attack by the thiol molecules in the cytoplasm.[9] In this way, decreasing cellular detoxification of the drug.

Cisplatin analogues, such as, JM 335 (*trans*-ammine (cyclohexylamine-dichlorodihydroxo) platinum (IV) (**7**) and ZD0473 (*cis*-amminedichloro(2-methylpyridine) platinum (II) (**8**) were synthesised.[8] JM 335 tested positive for antitumor activity against human ovarian carcinoma xenografts, cisplatin- resistant murine ADJ/ PC6 plasmacytoma and L 1210 leukaemia models.[8, 10]



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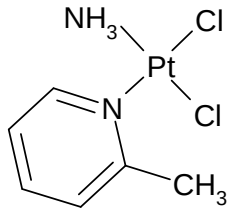
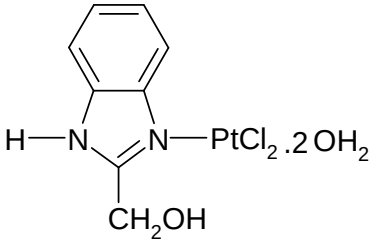


**8**

Recently, the development of cisplatin analogues with N-heterocyclic non-leaving ligands, such as, benzimidazole, benzoxazole, benzithiazole and imidazole have gained enormous interest.[9] While these ligands provide a more sterically hindered environment around the platinum centre, their biological properties are of great interest.[9] 2-[Di-(2-

chloroethyl)aminomethyl]benzimidazole (**9**) have shown activity against mammary Adenocarcinomas 755, E 0771 and Sarcoma 180 when tested in vitro in a mouse. *In vitro* test on compound (**10**) has shown relatively high activity against human MCF-7 and HeLa cell lines.

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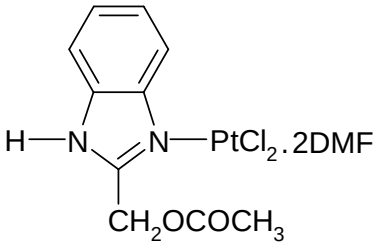



**10**

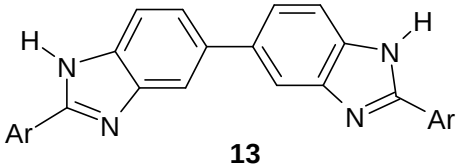
### 1.2.4 Research Aims and Thesis Arrangement

To the best of our knowledge, no literature is available on the use of 2-aryl-substituted-1*H*-benzimidazole, 2-aryl-1-arylmethyl-1*H*-benzimidazole and bisbenzimidazole as ligands for complexation to platinum (II) and testing these complexes for antitumor activity. Four objectives guided this research. The first objective was to synthesize a small library of 2-substituted-1*H*-benzimidazole with the common nucleus shown in (**11**)**.** The second objective was to synthesize a group of 2-aryl-2-methyl-1*H*-benzimidazole with the general structure as shown in (**12**). The third objective was to prepare a small library of novel bisbenzimidazole derivatives as shown in (**13**). The final aim of the study was to complex the synthesized benzimidazole and bisbenzimidazole ligands with platinum (II).


**11**




**12**




**13**

The thesis is arranged in chapters, with the introduction in chapter one and the literature review in chapter two. Results and discussion of the synthesis of 2-substituted-1*H*-benzimidazole and 2-aryl-1-arylmethyl-1*H*-benzimidazole are contained in chapter three. Chapter four contains the results and discussion of the synthesis of bisbenzimidazole derivatives. The synthesis of platinum (II) complexes of benzimidazole derivatives is discussed in chapter five. The final chapter (chapter 6) constitute the experimental section

## *1.3 References*

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# 2. Benzimidazole and its derivatives

## *2.1 Introduction*

The literature is reviewed in five different sections. The first section covers the historical background to benzimidazole in general and the biological importance of various types of benzimidazoles. The second section focuses on 2-substituted-1*H*-benzimidazole, their biological importance and the synthetic methodologies used to obtain these compounds. Section three will constitute an in depth discussion on 2-aryl-1-arylmethyl-1*H*-benzimidazoles, that is, their biological activities as well as useful synthetic procedures to obtain these compounds. The fourth section will be reviewing synthetic procedures and biological activities of symmetrical bisbenzimidazole. The last section will be a review of benzimidazole as platinum complexes, in particular, the activities of these complexes and reported synthetic methods.

## *2.2 Background information*

The history of benzimidazole dates back to more than 50 years ago when these compounds were used as fungicides.[1] Benzimidazole gained a increased popularity in Israel and other countries worldwide in 1970s, when they were used for the control of scrab disease caused by *Venturia Pirina Aderh* in pear orchards.[1-2] Benzimidazole compounds, such as, methyl [1-[(butylamino) carbonyl-1H-benzimidazol-2-yl] carbamate, thiophate-methyl (dimethyl 4, 4'-*o*-phenyl-enebis (3-thiollophanate)] and methyl-2-benzimidazole-carbamate hydrochloride were used extensively for scrab control.[2-5] Fungal resistance to these compounds posed threats to the agrochemical industry for the development of new type of fungicides.[3] This lead to the synthesis of libraries of benzimidazole derivatives which were explored for fungal activity.

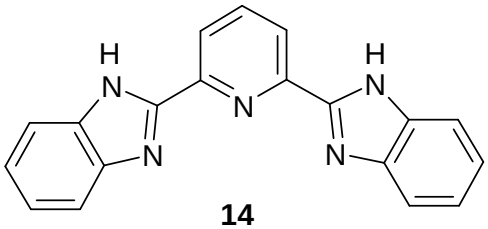
The structural similarities of benzimidazole nucleus to biological compounds, such as, the purine base of the DNA and the occurrence of this nucleus in vitamin $B_{12}$ have been of great interest to pharmaceutical industry. This similarity is believed to enable easy recognition of benzimidazole by biological systems. As a result, benzimidazoles have been

termed 'privileged structures' for drug design. Moreover it is reported that benzimidazole exhibit high affinity for enzyme and protein receptors. Thus, as a continuation of their reported fungicidal activity, more research has been done aimed at synthesising various derivatives of benzimidazole and testing them for biological activities.

## *2.3 Applications of Benzimidazole*

### 2.3.1. Metal Chelation

The ability of benzimidazole and its derivatives to form complexes with transition metals has been widely reported in literature. Studies performed on the complexes of this nature have confirmed a wide variety of biological properties associated with them. These include, cytotoxicity, antiviral, antiamoebic, antimicrobial and DNA cleaving properties. For example, the Ruthenium (I) and Zinc (II) complexes of 2,6-bis (benzimidazole-2-yl) pyridine (**14**) have shown DNA cleaving ability.[6] On the other hand, copper complexes of 2-(4'-thiazolyl) benzimidazole (**15**) have been reported to display antimicrobial activity.[6] Also, the chelation of benzimidazole to iron has been studied and the complexes formed showed variety of biological activities. For example, the tetranitrosyl iron complex with benzimidazole-2-thiolyl, $[Fe_2(SC_7H_5N_2)_2(NO)_4].2C_3H_6O$, showed antiproliferative activity on human ovarian carcinoma cell lines.[7]

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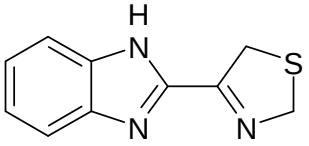
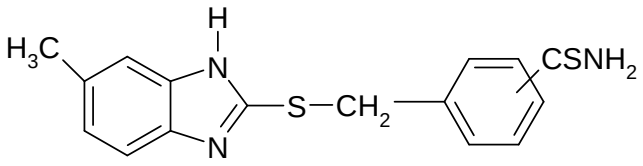



**15**

Of interest in the present study is the platinum chelation ability of benzimidazole and its derivatives. Examples and biological properties of some benzimidazole-platinum complexes are discussed in the general introduction.

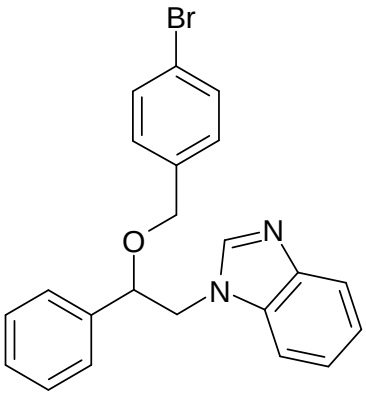
### 2.3.2 Other biological activities

Antimicrobial activity against various types of bacteria has been reported, however the activity of 2-Benzylsulfanyl derivative of 5-methylbenzimidazole (**16**) against mycobacteria strains is very interesting. Tuberculosis is one of the leading causes of death worldwide, resulting into 3 million people deaths per year according to the World Health Organisation (WHO) reports.[8] Nowadays, there has been tremendous increase in the numbers of people affected by this disease, mainly because of its relation to poverty and HIV infection. The reported activity of benzimidazole derivatives to this bacterium is of great significance due to the drug-resistant and multi-drug-resistant of this bacterium.[8] This is because, a library of compounds can be synthesised based on the benzimidazole nucleus.




**16**

Another example of antimicrobial activity is that shown by some phenyl and benzimidazole substituted benzyl ethers, such as (**17**) and (**18**). These compounds have been tested active against Gram-positive drug-resistant bacteria.[9] Gram-positive bacteria, such as, *Staphylococcus aureus* is the bacterium responsible for skin and mucous infections in humans.[10] The drug vancomycin is the only drug reported active against this bacterium, however, cases of resistance of *S.aureus* are reported. For example, derivative of 1,2-disubstituted-1*H*-benzimidazole-N-alkylated-5-carboxyamidines, such as, (**19**). [10]

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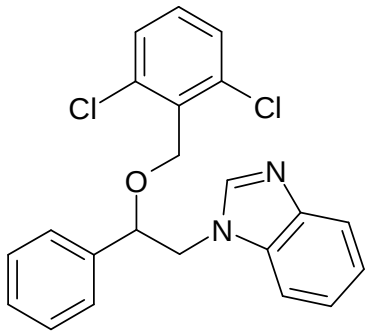


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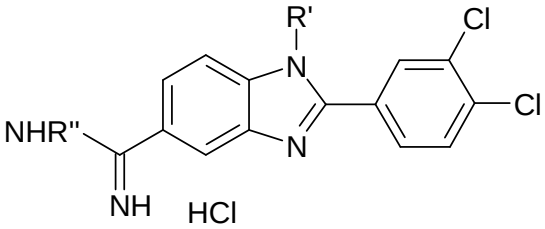
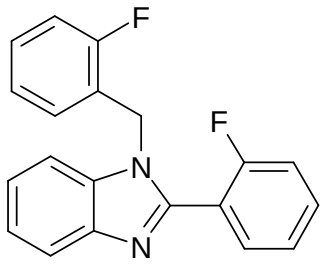



**19**

R'= $CH_2$-1-naphtyl
R''= isopropyl

The benzimidazole nucleus is also reported to be contained in molecules active against viruses such as, HIV, human cytomegalovirus (HCMV), herpes (HSV-1), RNA, influenza.[11-14] For instance, various types of 2-aryl-1-benzylbenzimidazole, such as that shown in (**20**) have been reported to exhibit anti-HIV activity. This compound is reported to be a non-nucleoside reverse transcriptase inhibitor (NNRTI). Therefore, it inhibits HIV-1 reverse transcriptase enzyme by changing the conformation of the polymerase active site as the benzimidazole derivative bind to the pocket near the active site. [11]




**20**

Benzimidazole compounds are also reported as topoisomerase inhibitor, antitumor, selective neuropeptide YY1 receptor antagonism, 5-lipoxygenase inhibitor, and factor Xa

inhibitors.[12-14] Benzimidazole uses also extend to their inclusion in the preparation of anti-inflammatory, anithelemintic and antiparasitic drugs. These compounds are also reported to inhibit photosynthesis and exhibit herbicidal properties.[15]

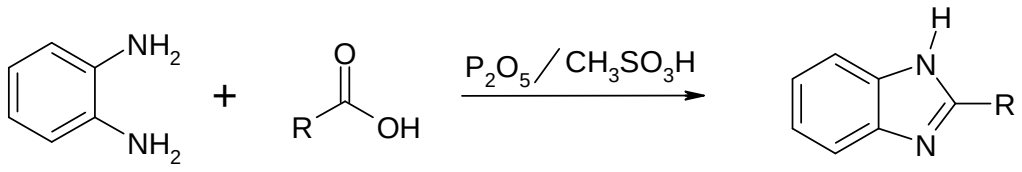
## *2.4 2-Substituted-phenyl-1H- benzimidazole*

A variety of synthetic methodologies have been reported for the synthesis of 2-substituted-1*H*- benzimidazoles. Recently, methods such as, conventional methods using strong acids as oxidising agents, methods using transition metal salts as catalysts and microwave assisted methods have been reported. The condensation reaction between *o*-phenylenediamine and aldehydes in a 1:1 ratio has been reported to yield benzimidazole. However, long reaction times and occurrence of side reactions, such as, schiff base formation posed a need for a continued research to eliminate these limitations.

### 2.4.1 Conventional method

The condensation of *o*-phenylenediamine with carboxylic acid and its derivatives in the presence of strong acids as oxidising agents have been known since 1980s.[16] Acids such as, polyphosphoric acid (PPA), polyphosphoric acid esters, hydrochloric acid, hydrobromic and boric acids were the reported condensation agents, however, polyphosphoric acid and its esters were the most common reagents used for the condensation reactions. This was because of the high yields of 2-substitued benzimidazole obtained when polyphosphoric acid was used. These high yields were attributed to the neutralising effect of polyphosphoric acid.[16]

Although the use of polyphosphoric acid and its esters had gained popularity during 1980, five years later, a better oxidising agent compared to PPA was reported. Phosphorus pentoxide/ methanesulfonic acid, commonly known as PPMA, was reported to give higher yields and requires mild reaction conditions for the synthesis of 2-substituted benzimidazole compared to PPA.[17] Scheme **1** below shows the synthesis of 2-substituted benzimidazole from the condensation of *o*-phenylenediamine and aromatic carboxylic acid in the presence of PPMA.

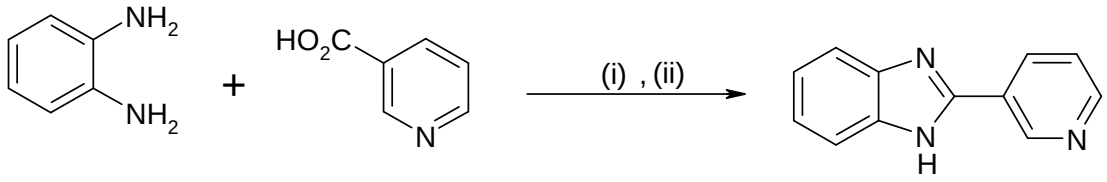



***Scheme 1**: [17] The condensation of o-phenylenediamine with carboxylic acid in the presence of PPMA*

Other strong acids, such as, hydrochloric acid (HCl) have also been used in conjunction with PPA. However, the use of strong acids is limited by generation of aqueous waste when a base, such as ammonia, is used to neutralize the acid. Nevertheless, cleaner techniques have been reported for the synthesis of 2-substitued-1*H*-benzimidazoles. These are solid phase and microwave assisted synthesis and these will be discussed below.

### 2.4.2 Microwave- assisted synthesis

The aim behind microwave synthesis is to enhance the speed and reproducibility of the reaction. Microwave synthesis has also been reported crucial for scaling up procedures. Microwave has been used in the synthesis of 2-substitued-1*H*-benzimidazoles and this gave high yields. After optimization of reaction conditions, 2-pyridine-1*H*-benzimidazole was formed in a 100 % conversion, 58 % isolated yield from a microwave assisted condensation of *o*-phenylenediamine and 3-pyridine carboxylic acid (scheme **2**). Pyridine was found to be a better solvent and acids were added, such as glacial acetic acid, hydrochloric, sulfuric and polyphosphoric acids.[18]



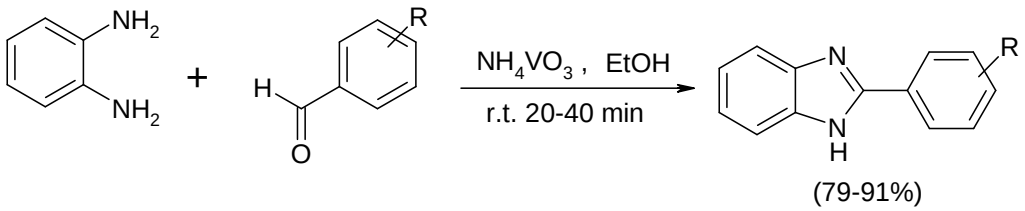

(i) $P(OPh)_3$, μM; (ii) 220°C, 10 min

***Scheme 2**: [18] Microwave-assisted synthesis of 2-substituted-1H-benzimidazole.*

### 2.4.3 Metal salt catalysts

Limitations, like low yields, long reaction times, difficult work-up, occurrence of side reactions, non reusability of the catalyst and drastic conditions all resulted into a pursued search of a better catalyst for the synthesis of 2-substituted-1*H*-benzimidazoles.[19] The reported use of transition metal triflate salts as catalysts for the synthesis of 2-substituted benzimidazole stems from their ability to address the above mentioned problems. Transition metal triflates, such as, $Sc(OTf)_3$, $Yb(OTf)_3$ and indium triflate [$In(OTf)_3$] are the preferred catalysts. This is also reported to be due to their commercial availability and stability in various solvents, especially the stability of [$In(OTf)_3$] in water.[19]

Recently, the reaction between *o*-phenylenediamine and aromatic and heteroaromatic aldehydes, scheme (**3**), has been reported to give higher yields of the product, much faster and require milder reaction conditions when ammonium metavanadate ($NH_4VO_3$) is used as a catalyst. The high yields from this reaction, that is 79-91 % as shown in scheme 2, are as a result of the activation of the aldehyde by the catalyst. The vanadium atom (V) of $NH_4VO_3$ is reported to pull electrons from the oxygen atom of the aldehyde into its vacant d-orbitals thus the aldehyde carbon become more electrophilic enhancing the attack by $NH_2$ group of *o*-phenyldiamine.[20]




***Scheme 3**: [20] Synthesis of 2-substitued benzimidazole using $NH_4VO_3$ catalyst.*

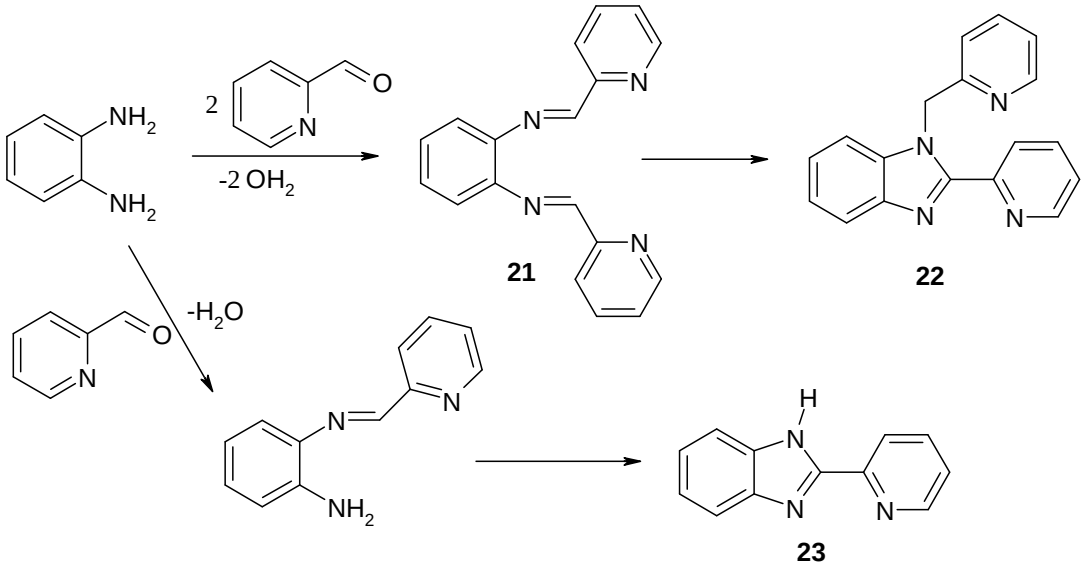
## *2.5 Synthesis of 2-aryl-1-arylmethyl-1H-benzimidazole*

The importance of benzimidazole nucleus in drug discovery is the reason for the intense research conducted to find a synthesis method that would be simpler, faster, reproducible, cheap and produce high yields of the product. The reported synthetic methods for 2-aryl-1-arylmethyl-1*H*-benzimidazole will be discussed in this section. Traditional synthesis

towards 2-ary-1-arylmethyl-1*H*-benzimidazole is the reaction between *o*-phenylenediamine and carboxylic acid and its derivatives, like, nitriles, amidates and orthoester at increased temperatures. Procedures, such as, solid-phase synthesis and acid-catalysed reactions are also reported.[21-25]

### 2.5.1 Direct condensation

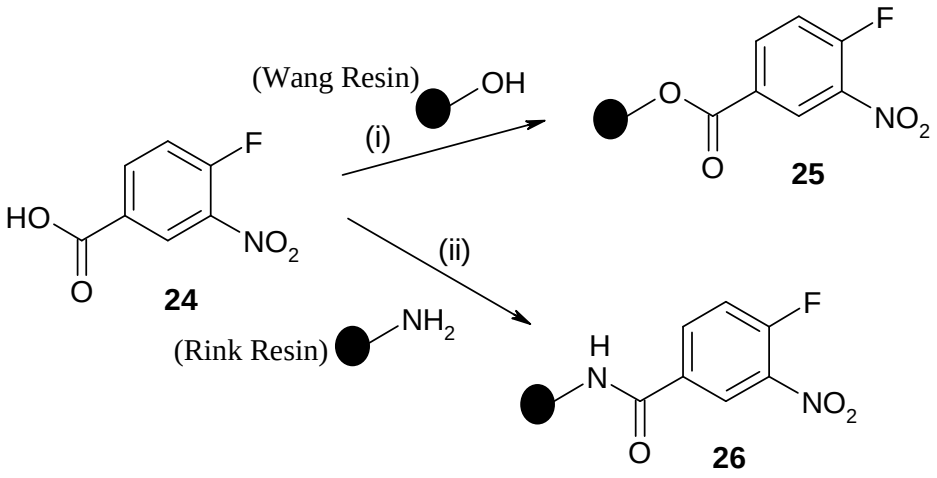
The condensation reaction between o-phenylenediamine and aliphatic or aromatic aldehydes requires the use of 2 equivalents of the aldehyde molecule. As shown in scheme (**4**), this reaction proceeds through the formation of a Schiff base intermediate (**21**); this subsequently undergoes intramolecular cyclisation giving the required product (**22**). Although this is a one-pot synthesis procedure, the formation of the side product (**23**) has been a drawback to the use of this method.[21] After the addition of aldehyde unit to the phenylenediamine, the formed Schiff base is very reactive toward nucleophilic attack, thus the competitive ring closure reaction occurs resulting in the formation of compound (**23**).




***Scheme 4**:[21] Synthesis of 2-aryl-1-arylmethyl-1H-benzimidazole*

### 2.5.2 Solid phase support

For many years, drug discovery has evolved around solution phase synthesis. Recently, a better method for library synthesis is reported. Solid phase synthesis is reported to require less demanding synthetic conditions compared to solution phase.[22-23] This is because of the flexibility, maximal use of commercially available inputs, mild reaction conditions and readily adaptability to polymer support and automated operations of this method.[22] The conditions provided by the use of solid phase support are crucial for acceleration of lead generation and optimisation phases of drug discovery.[22-23] Although the solid phase synthesis is not well developed for a majority of systems, there are a lot of reports on solid phase synthesis of benzimidazoles due to their popularity in drug discovery.[24-25] However, the method reported by Mayer and coworkers will be used as an example (schemes **5** and **6**). Scheme **5** shows the coupling of 4-fluoro-3-nitrobenzoic acid (**24**) to Wang or Rink resin using diisopropylcarbodiimide (DIC) and N, N-dimethylaminopyridine (DMAP).[22]

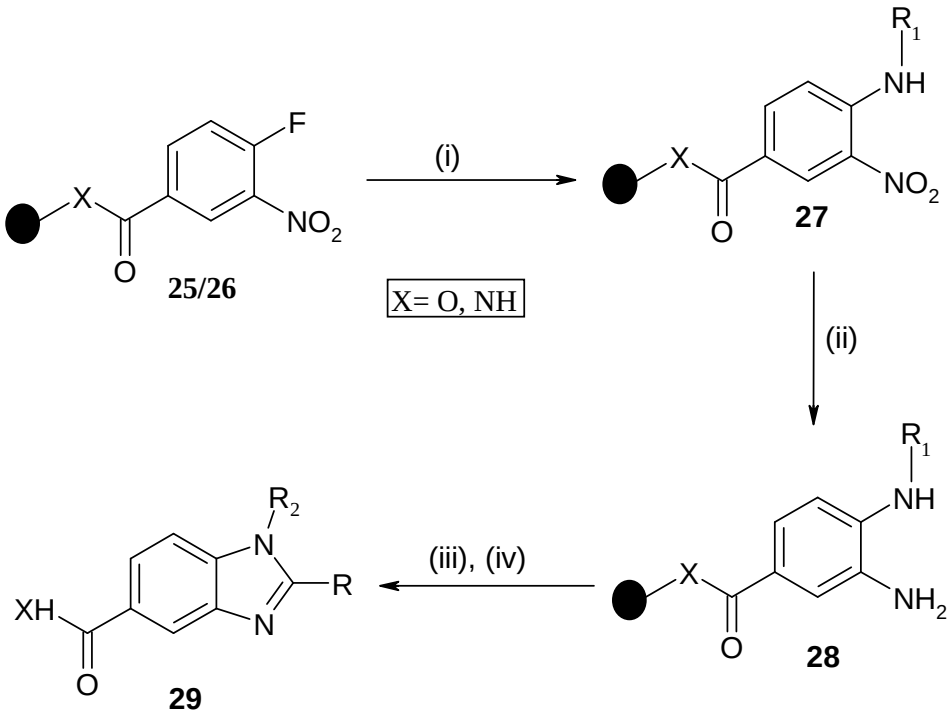



Legend: (i) 4.0 eq. 4-fluoro-3-nitrobenzoic acid, 2.0 eq. DIC, 0.1 eq. DMAP in DMF, 12 hours, (ii) 3.0 eq. 4-fluoro-3-nitrobenzoic acid, 1.5 eq. DIC in DMF, 3 hours.

***Scheme 5 :***[22] *DIC/DMAP promoted coupling of 4-fluoro-3-nitrobenzoic acid to the Wang or Rink resin.*

The treatment of the polymer supported product (**25**) and (**26**) with primary amine followed by reduction of nitroaniline (**27**) by tin (II) chloride afford for solid supported *o*-

phenylenediamine (**28**). This is then reacted with aldehydes and the resin cleaved resulting to the required products (**29**) in excellent yields, 69-99 % (Scheme **6**).[22]

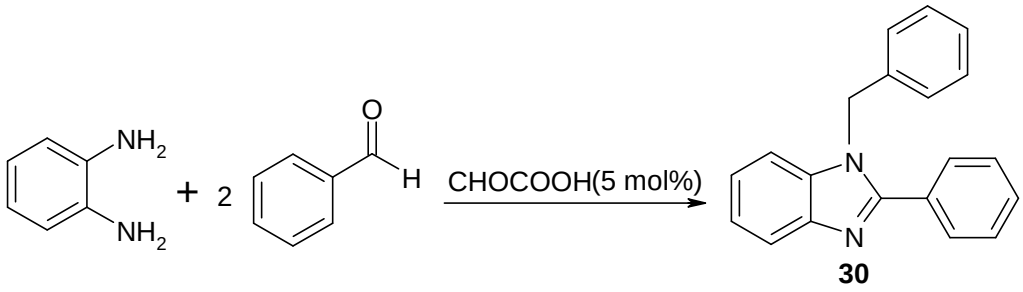



Legend: (i) 5.0 eq. amine, 5% DIEA in NMP or DMF, (ii) 3.0 M $SnCl_2$ in DMF, 5 hours, (iii) 4.0 eq. aldehyde, 2.0 eq. DDQ in DMF, 5 hours, (iv) 50% trifluoroacetic acid in DCM, 2 hours**.**

***Scheme 6**: [26] Synthesis of 2-substituted benzimidazole on a solid support.*

### 2.5.3 Acid-Catalysed synthesis

There are various reports on the acid-catalysed synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidaozole. All of these papers depict no formation of 2-substituted-1*H*-benzimidazole as a side product. There has also been an increasing interest in acid-catalysed reactions towards benzimidazole in aqueous medium.[27] This is because, water is an environmental friendly solvent and high yields are obtained when used as a solvent. An article by Pawar, *et al.*[27] describes the use of glyoxylic acid as a catalyst in aqueous medium. According to this paper, only the N-methylated product (**30**) is formed at 95 % yield when the reaction is in water at 25°C (scheme **7**).[27]




**30**

***Scheme 7**: [27] Glyoxalic acid catalysed synthesis of 2-aryl-1-arylmethyl-1H-benzimidazole*

It is also reported in this article that when other acids, such as *p*-TsOH were used, very low yields were obtained (table **2.1**).

**Table 2.1: Effect of acid catalyst on the reaction of *o*-phenylenediamine and benzaldehyde in water at 25° C.[27]**

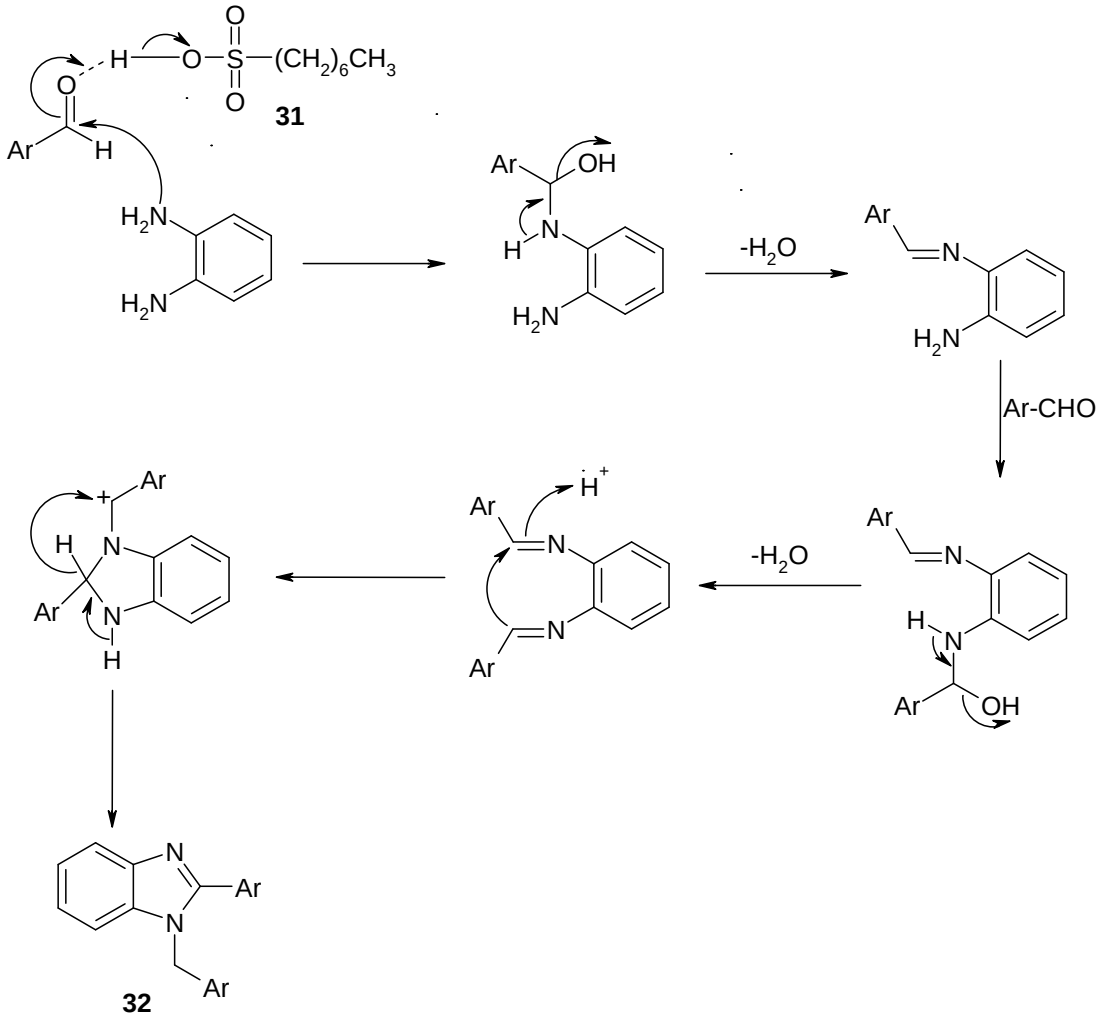
| Catalyst | Time (min) | Yield (%)* |
|---|---|---|
| *p*-TsOH | 180 | 55 |
| Silica sulphuric acid | 150 | 65 |
| $I_2$ | 90 | 55 |
| Glyoxylic acid | 20 | 95 |

The results shown in table 1 are in good agreement with those reported by Salehi, *et al.*[12] This article reports the use of silica sulphuric acid as a catalyst at room temperature and using water as a solvent. After 2 hours, 50 % of 2-aryl-1-arylmethyl-1*H*-benzimidazole is formed, however if LiCl is added, 85 % of the product is isolated. This is reported to be due to the increase of dielectric constant of water by LiCl salt.[12]

Recently, the use of heptasulfonic acid sodium salt (**31**) as a catalyst has been reported.[28] Scheme **8** shows the activation of the carbonyl carbon of the aldehyde by heptasulfonic acid and the formation of subsequent benzimidazole. Jadhav, *et.al* [28] reported this reaction results into 82-92 % of desired product when performed at room temperature using 8:2 ratio of acetonitrile: water as a solvent for 40-60 min. It is also reported in this article that the side product, 2-substituted-1*H*-benzimidazole was formed as a major product when 1 equivalent of aldehyde was used.[28] This paper also confirms the formation of 2-aryl-

* Isolated yields based upon starting *o*-phenylenediamine.

1arylmethyl-1*H*-benzimidazole as a major product when 2 equivalents of the aldehyde were used (**32**).

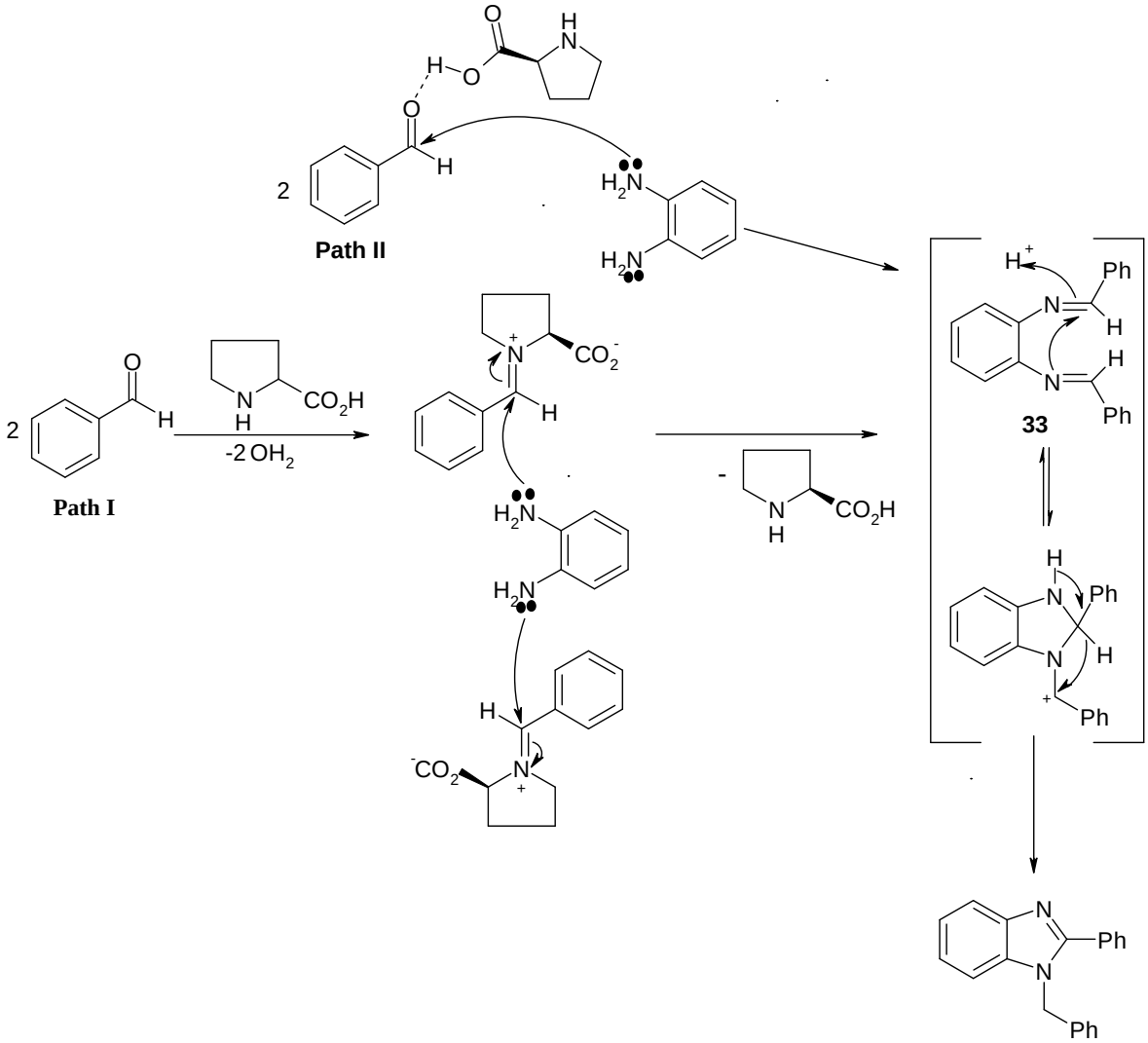



***Scheme 8**:[28] Acid-catalysed synthesis of 2-aryl-1-arylmethyl-1H-benzo[d] imadazoles*

Microwave promoted organic reactions have attracted a lot of attentions nowadays. This is because of the advantages associated with microwave, that is, shorter reaction time, high yields, mild reaction conditions and environmental benign of these methods. Another acid-catalysed method is reported, though it is performed under microwave irradiation (MWI). According to literature, this reaction is performed neat in the presence of montmorillorite K-10.[29] Montmorillorite K-10 serves as an acid catalyst whilst the MWI shorten the reaction time. The condensation between *o*-phenylenediamine (*o*-PD) and benzaldehyde resulted in 90 % of the required product in 10 minutes.[29]

### 2.5.4 Other catalysts

Other methods involving the use of catalyst, like, L-proline, $BF_3.Et_2O$, $SiO_2$/ $ZnCl_2$ and bismuth (III) have been reported. L-proline is a cheap and commercially available amino acid. Excellent yields, 72-95 % of 2-aryl-1-arylmethyl-1*H*-benzimidazole is reported to be obtained when 10 % mol of L-proline in chloroform at room temperature is used.[13] Literature reports L-proline to act via two pathways, shown in scheme **9**. Path I involves the formation of dibenzylidene-*o*-PD (**33**) followed by ring closure and hydride transfer to afford the required product. In similar manner as acid catalysis, L-proline can form hydrogen bonding with the oxygen atom of the aldehyde thus enhancing nucleophilic attack by *o*-phenylenediamine.[13] Path II in scheme **9** shows this acid catalysis reaction.



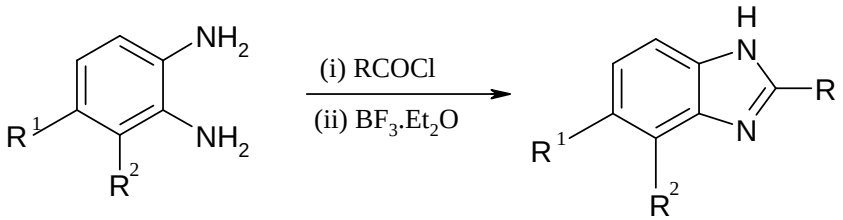

***Scheme 9**:[13] L-proline catalysed synthesis of 1,2-disubstituted benzimidazole*

Regardless of the excellent yields obtained from the L-proline catalysed synthesis, the use of chloroform as a solvent has triggered more research to find an alternative environmental benign solvent for this reaction. In another paper, Ravi, *et al.*[14] have reported the use of Zn $(proline)_2$ complex as a catalyst in water at ambient temperature. For the condensation of benzaldehyde, 95 % of benzimidazole was obtained after 5 hours when L-proline was employed as catalyst. In contrast, after 2 hours, 92 % of the product was obtained when Zn $(Pro)_2$ was used as a catalyst. This shows that the Zn $(Pro)_2$ enhances the yields whilst environmental friendly reagents are used.[14]

The use of bismuth (III) triflate ($Bi(OTf)_3$) as a Lewis acid has gained considerable interest in many organic reactions. This is because of the compatibility of $Bi(OTf)_3$ in water, cheap and easily prepared compared to lanthanide triflates. Yadav, *et al.*[30] reported the use of $Bi(OTf)_3$ as a catalyst in the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole. Excellent yields (75-97 %) are reported when 10 mol% of the catalyst at room temperature was employed.[30]

Recently, $SiO_2$/ $ZnCl_2$ has been reported as an efficient catalyst for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole. $SiO_2$/ $ZnCl_2$ is used under solvent free conditions at room temperature, however, microwave irradiation was also employed. The applicability of this method to aliphatic aldehydes is the reason for the high interest.[31]

Other methods have employed cyclodehydration reagents, for example, $BF_3.Et_2O$, as shown in scheme (**10**).[32]




**92-98%**

***Scheme 10**:[32] $BF_3.Et_2O$ promoted one pot synthesis of 2-substituted benzimidazole*

The above reaction is reported to proceed via the formation of N-acyl-1,2-phenylenediamine intermediate from the reaction of 1,2-phenylenediamine with the acid chloride (1 equivalent). Subsequent addition of $BF_3.Et_2O$ to this intermediate result into

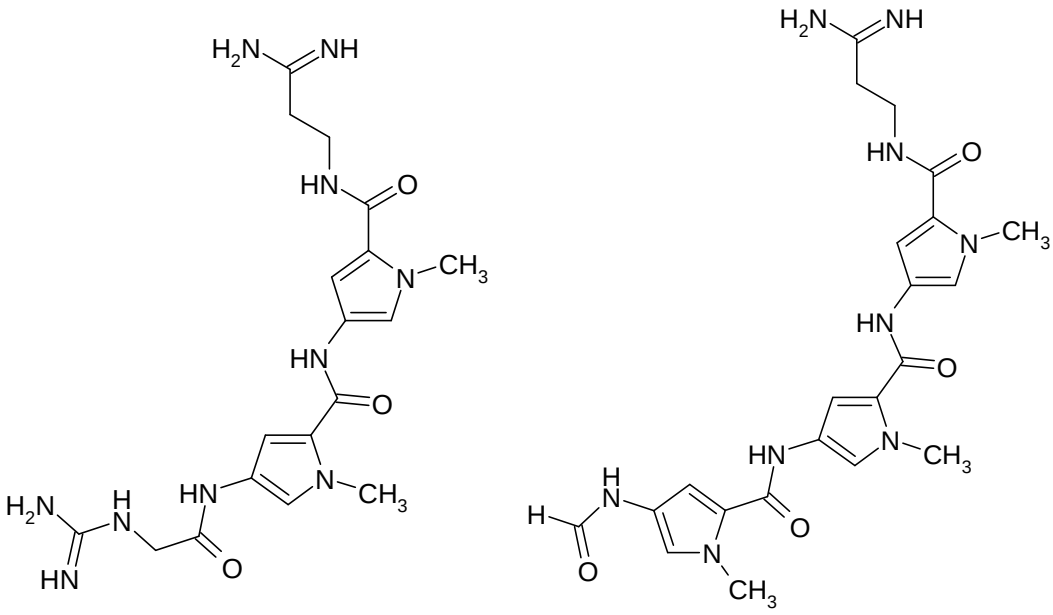
92-98 % yield of several benzimidazoles. Tandon and Kumar have reported this to be an efficient method based on these high yields, one-pot synthesis and tolerance of the $BF_3.Et_2O$ reagent to various types of aldehydes.[32]

## *2.6 Bisbenzimidazole*

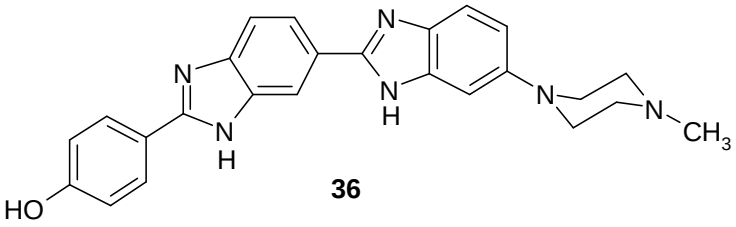
### 2.6.1 Introduction

Chemotherapeutic drugs are divided into various groups, as discussed in the introduction. Regardless of the different modes of actions of these drugs, they are all aimed at destroying the double stranded DNA molecule of the tumour cells. For example, antimetabolites damage the DNA as they get incorporated into the growing DNA strand. This is because the insertion of the antimetabolite, such as, fluorouracil instead of uracil disrupts the sequence and the DNA replication process.[33] On the other hand, the alkylating agents damage the DNA by binding into the N7 and O6 positions of guanine and 3-position of adenine. This blocks the pairing of bases for the formation of a double-stranded DNA molecule.[33-35]

Recently, an additional group of chemotherapeutic agent is reported. These drugs are reported to bind to the minor groove of the DNA molecule and recognise a specific base sequence. The first drugs discovered with this mode of action were the natural occurring Netropsin (**34**) and Distamycin (**35**). Later, a synthetic bisbenzimidazole, Hoechst 33258 (**36**) [36-39], was found to exhibit the same properties as Netropsin.[40-42] This thesis will focus on Hoechst, in particular, the synthetic procedures towards its analogues.



**34** **35**



**36**

## 2.6.2 Mode of Action of Hoechst 33258

The mechanism of action (figure **2**) of the DNA minor groove binding agents involves two steps. Initially, the binding agent is hydrophobically transferred from solution into the DNA minor groove. The second step involves the formation of H-bonding or van der Waals interactions between the binding agent and the specific sequence in the DNA.[41]

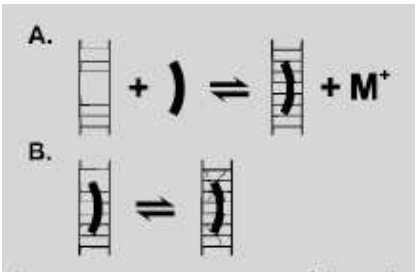
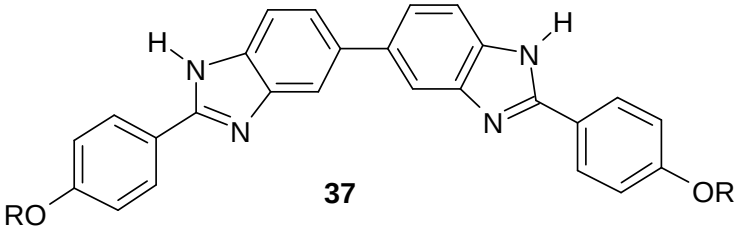



***Figure 2**:[41] Hypothetic representation of mechanism of action in the DNA minor groove.*

As mentioned above, Hoechst 33258 has high affinity for DNA sequences rich in A/T bases.[38-40, 42-43] However, in some studies, this molecule has been reported to also bind to sequences rich in G/C bases. Hoechst has interesting properties which facilitate its DNA binding. These include, (i) crescent shape matching the shape of the minor groove walls, (ii) H-bonding between the drug and DNA nucleobases and (iii) the positive charge which ensures attraction towards negatively charged phosphodiester backbone of the DNA.[36, 44]

### 2.6.3 Biological properties

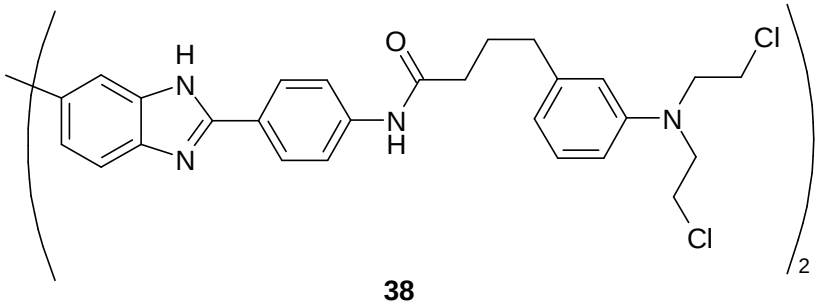
In many reports, Hoechst 33258 have mainly been reported as a DNA minor groove binding agent.[36-38, 40-41, 43, 45] Inspired by this DNA binding property, various studies have been conducted to determine anticancer activity of this compound. Hoechst was found to be active against L1210 murine leukaemia. Unfortunately, this compound never succeeded clinical trials because of its toxicity levels.[39] The toxicity and difficult multistep synthesis towards Hoechst motivated research groups to synthesis simpler analogues of this compound and test them for biological activity. Symmetrical bisbenzimidazole, such as, **37** have been synthesised and tested active against a variety of cultured human cancer cell lines.[46]




**37**

37a R=H, 37b R=Me, 37c R= $(CH_2)_3NMe_2$

Symmetrical bisbenzimidazoles have also been used as drug delivery agents. For example, the anticancer agent chlorambucil was attached onto the bisbenzimidazole core. The resulting compound (**38**) was found to show anticancer activity against MCF-breast cancer with an $IC_{50}$ of 0.47μM.[45]

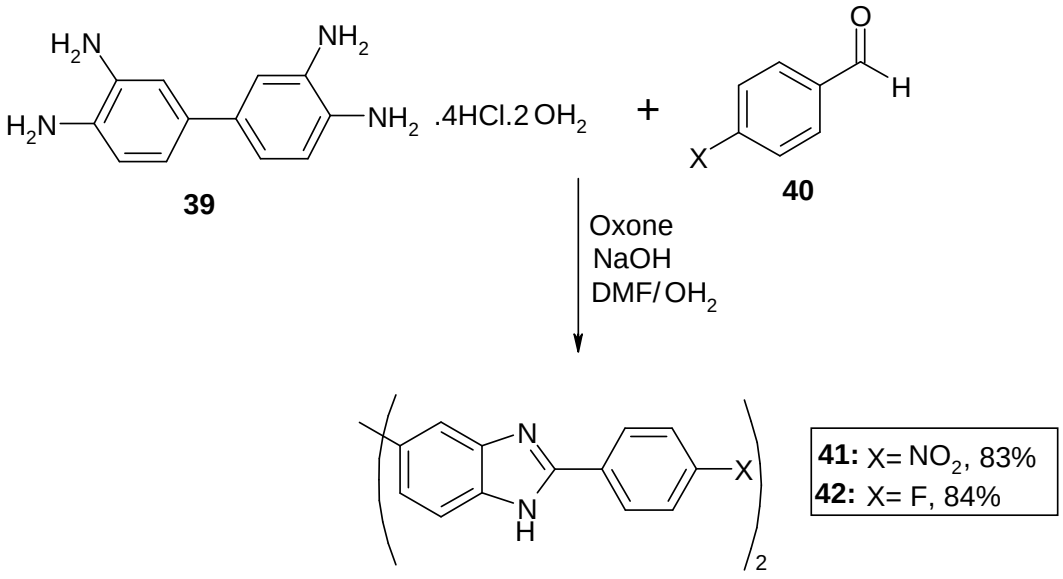


**38**

Hoechst 33258 has also been reported as a chromosome-staining agent and has showed antihelmintic activity.[40]

### 2.6.4 Synthetic Approaches

The synthetic approach reported for the synthesis of symmetrical bisbenzimidazole involves the condensation of 3, 3', 4, 4'-tetraaminobiphenyl (**39**) with aromatic or heteroaromatic aldehydes (**40**) in the presence of an oxidising agent.[26] In a study conducted by Neidle and coworkers, nitrobenzene was used both as a solvent and an oxidising agent. In addition, this reaction took 8-10 hours at 150°C while 25-40 % of the required product was obtained.[36] On the other hand, Sann and coworkers reported that they obtained excellent yields of bisbenzimidazole when oxone was used as an oxidising agent (scheme **11**).




***Scheme 11**:[45] Synthesis of bis-benzimidazole using Oxone as an oxidising agent.*

In particular, Sann and coworkers reported that 83% of 2-(4'-nitrophenyl)-bis-benzimidazole (**41**) was obtained when 4'-nitrobenzaldehyde was used as an aldehyde. Alternatively, the use of 4-fluorobenzaldehyde resulted into 84% yield of 2-(4'-fluorophenyl-bis-benzimidazole (**42**) was obtained.[45]

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# 3. Synthesis of Benzimidazole derivatives

## *3.1 Introduction*

A vast majority of procedures have been reported for the synthesis of benzimidazoles and its derivatives. The details of the methods have been discussed in chapter 2. Nevertheless, there is still an ongoing search for better synthetic methods towards these compounds. This is because of the diverse structural differences of these derivatives. As a result, one method may be highly efficient for a particular type, while less so for another structurally different derivative. Likewise, one of the major objectives of this work was to determine the suitable method for the synthesis of novel bisbenzimidazole derivatives. But, first, the synthesis and the reaction mechanism of closely similar derivatives reported in literature had to be understood. Therefore, the synthesis of a small library of 2-aryl-1*H*-benzimidazole and 2-aryl-1-arylmethyl-1*H*-benzimidazoles will be discussed in the following section.

## *3.2 Synthesis of 2-substituted-1H-benzimidazole*

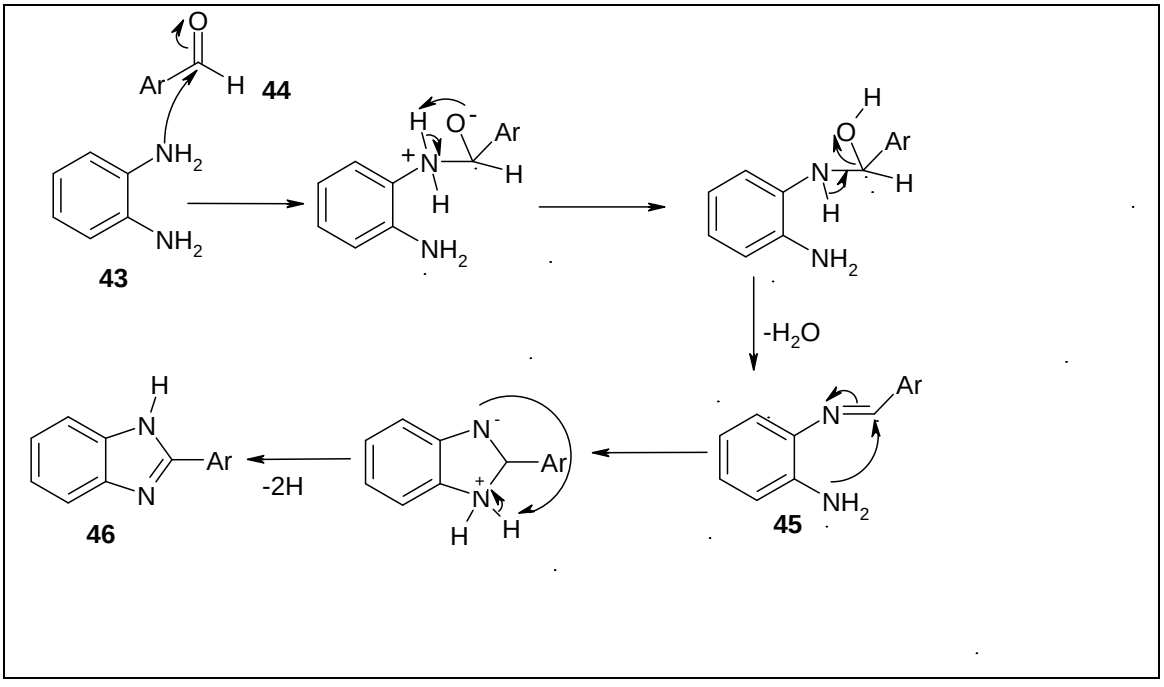
### 3.2.1 Introduction

The study conducted by Ueda and coworkers on the synthesis of 2-substituted-1*H*-benzimidazole in 1985 was amongst the first study focusing on the synthesis of these compounds.[1] All recently reported methods[2-4] are modification of this procedure. These are discussed in details in chapter 2. Noteworthly, most of these methods rely on the use of strong acids or metal based Lewis acids as catalysts. On the other hand, some researchers have reported the use of metal based catalyst to be cumbersome because of their high costs, non-stability in some organic solvents and non-reusability.[4] Also, the difficulties in the work-up procedure when strong acids have been used as catalyst present a need for a continued search for a better synthetic procedure towards 2-substituted-1*H*-benzimidazoles.[1] Direct

condensation of 1, 2-phenylenediamine and heteroaromatic aldehydes, which is previously reported [3], still seems to be the only one pot synthetic method that does not require catalysts.[3, 5] In this work, we therefore, decided to explore this route in the preparation of 2-substituted-1*H*-benzimidazole.

### 3.2.2 Synthesis and General Characterization

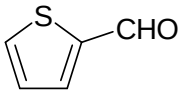
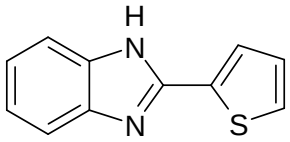
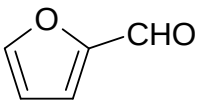
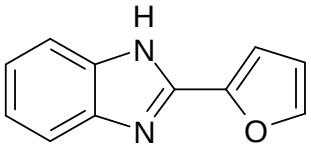
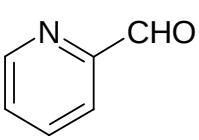
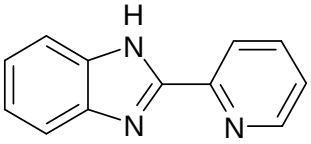
As expected, the treatment of *o*-phenylenediamine (*o*-PD) (**43**) with equimolar amount of heteroaromatic aldehyde (**44**) resulted into 2-substituted-1*H*-benzimidazole (**46**). As observed from table **3.1**, the yields obtained depend on the heteroaromatic aldehyde used. In order to understand the reasons behind the isolated yields, the mechanism for this reaction is discussed. The mechanism (scheme **12**) is comprised of two major steps. The first step involves nucleophilic attack of the primary amine ($NH_2$) of *o*-phenylenediamine (*o*-PD) on the partially positive carbonyl carbon of the heteroaromatic aldehyde. This ultimately results in the formation of a schiff base (**45**). The second step then involves intramolecular ring closure, as a result of the nucleophilic attack of the second $NH_2$ on the slightly positive imine carbon. The subsequent loss of a hydrogen atom results into the formation of the required product (**46**).




***Scheme 12**: Direct condensation of o-phenylenediamine and heteroaromatic aldehydes.*

With respect to the yields, the use of 2-pyridinecarboxyaldehyde resulted into the highest yield (79 %). Conversely, the use of 2-furancarboxyaldehyde resulted into the lowest yield of 44 % while thiophene containing benzimidazole was obtained in moderate yield. In other words, nucleophilic attack is enhanced in the pyridine containing system. These findings were not surprising since pyridine is known to be an electron deficient heteroaromatic ring compared to thiophene and furan.[6] Therefore, the carbonyl carbon in the *alpha* position of pyridine is more positive compared to the one of thiophene and furan. As a result, nucleophilic attack is more favoured when 2-pyridinecarboxyaldehyde is used. The use of 2-thiophenecarboxyaldehyde also results into better yield than 2-furancarboxyaldehyde (table **3.1**). This can be explained in terms of electron donating ability of oxygen compared to sulfur into the *alpha* carbonyl carbon. Both oxygen and sulfur posses two lone pairs of electrons. While these are in the 2p orbital for oxygen, in sulfur they are in the 3p orbital. Since the vacant orbital for carbon is 2p, the overlap between carbon and oxygen is more favoured compared to sulfur. Consequently, the carbonyl carbon in position 2 of furan is more positive than that of thiophene. The result of this is the enhancement of nucleophilic attack in thiophene containing system compared to furan system.

**Table 3.1 : Synthesis of 2-substituted-1*H*-benzimidazole**

| Aldehyde | Product | Yields (%) |
|---|---|---|
|  |  **46a** | 65 |
|  |  **46b** | 44 |
|  |  **46c** | 79 |

$^{1}H$ and $^{13}C$ nuclear magnetic resolution spectroscopy (NMR); liquid-chromatography coupled mass spectroscopy (LCMS) and infra-red (IR) spectroscopy and melting points were used to characterize compounds (**46a-c**). IR spectra were firstly used to confirm the coupling of *o*-phenylenediamine to the aldehyde. The aromatic primary amine ($NH_2$) and aldehyde stretching signals were not observed at approximately 3378 and 1667 $cm^{-1}$, respectively. Similarly, using the $^{1}H$ NMR spectrum, the primary amine and the aldehyde signals were both absent at 3.5-4 and 9-10 ppm, respectively. The proposed structures of products were also confirmed by LCMS spectra. For all the compounds, the found masses were in very good agreement with the calculated masses. Also, the melting points of all the synthesized products were in good agreement with the reported values.[7]

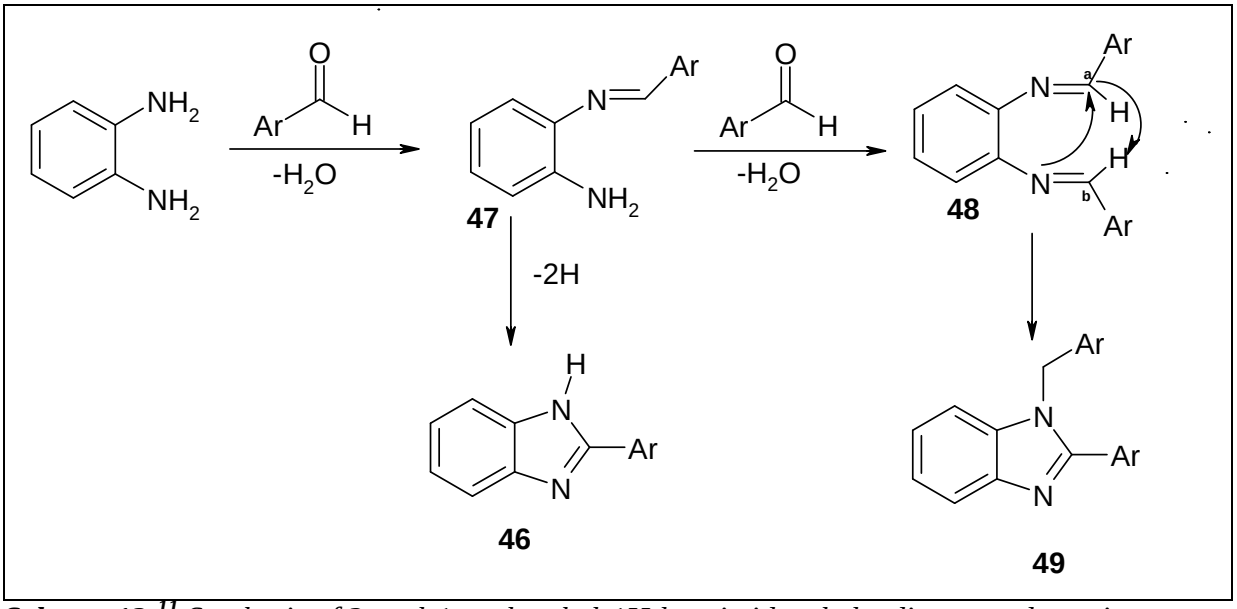
## *3.3 Synthesis of 2-aryl-1-arylmethyl-1H-benzimidazole*

### 3.3.1 Introduction

Similarly to the synthesis of 2-substituted-1*H*-benzimidazole, the use of acid catalyst is the most common procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole.[8] The use of acids, such as, glyoxylic, $Bi(OTf)_3$, *p*-toluenesulfonic acid (*p*-TsOH) and heptasulfonic acid have been reported .[9] The mechanism for each type of acid is discussed in chapter two. It is important to point out here that acid catalysts have gained increased popularity because (i) one step is required to obtain high yields of the product, (ii) mild reaction conditions are employed, (iii) the acid tremendously reduces reaction time.[8, 10] Inspired by these advantages, we wanted to explore the use of acid catalyst in the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole. However, our success in the synthesis of 2-substituted-1*H*-benzimidazole using direct condensation motivated us to initially pursue this route before the addition of an acid catalyst.

### 3.3.2 Direct Condensation

As discussed in chapter 1, Knodler and coworkers have reported the synthesis of 2-pyridyl-1-pyridylmethyl-1*H*-benzimidazole by direct condensation. In this section, the applicability and efficiency of this procedure when different heteroaromatic aldehydes are used is investigated. Accordingly, the treatment of *o*-phenylenediamine (1mmol) with aldehydes (2 mmol) afforded the required products (**49a-c**) in moderate yields. As reported by Knodler, 2-substituted-1*H*-benzimidazoles (**46a-c**) were also isolated. The formation of these products can be accounted for by the mechanism described in scheme **(13)**. Similarly to the mechanism of direct condensation using 1:1 equivalent of the starting materials (described in scheme **12**), the first step of this mechanism involves nucleophilic attack of one $NH_2$ to the carbonyl carbon of the aldehyde. Following the loss of water, the Schiff base intermediate (**47**) is formed. Because excess aldehyde was used, two routes are possible for the consumption of intermediate (**47**). The first route is the nucleophilic attack of the second $NH_2$ on the second aldehyde molecule resulting into intermediate (**48**). This intermediate then undergoes intramolecular ring closure followed by 1, 3- hydride transfer, subsequently resulting into the formation of the required 2-aryl-1-arylmethyl-1*H*-benzimidazole (**49**). Alternatively, intermediate (**47**) can undergo intramolecular cyclisation by the attack of the second $NH_2$ into the imine carbon. 2-substituted-1*H*-benzimidazole (**46**) is formed from this process.




***Scheme 13:***[11] *Synthesis of 2-aryl-1-arylmethyl-1H-benzimidazole by direct condensation.*

As shown in table **3.2**, the ratio of the yields of 2-aryl-1-arylmethyl-1*H*-benzimidazole (**49**) versus 2-substituted-1*H*-benzimisazole (**46**) depends on the heteroaromatic aldehyde used. In the case of furan and thiophene adducts, the yield of benzimidazole (**49**) is double that of (**46**). However, these yields are closely similar for pyridine and quinoline adducts. This is because pyridine is an electron deficient system, therefore will retard the attack of (**b**) on (**a**) in intermediate (**48**). In contrast, thiophene and furan are electron excessive; therefore donate electrons into the *alpha* imine carbon. This enhances attack of (**b**) on (**a**) in intermediate (**48**).

Although furan and thiophene are electron excessive, they are less so than pyrrole. Due to electron-electron repulsions (shown in figure **3**), the attack of (**b**) on (**a**) is not possible in the pyrrole containing system and intermediate (**48**) was isolated as the final product. Likewise to the reported data, N,N'-Bis(2-pyrrolylmethylidene)-1,2-phenylenediamine (**48a**) was obtained in excellent yield (76 %).[12-16]

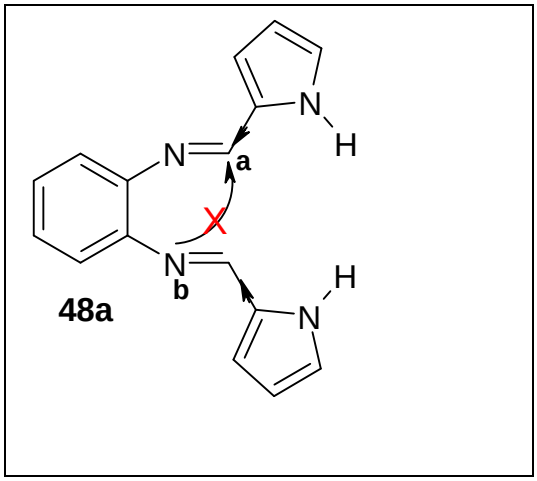
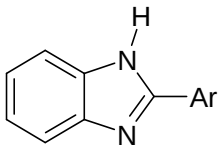
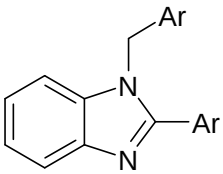
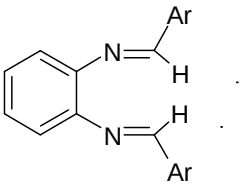
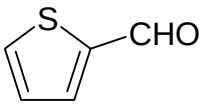
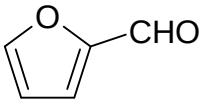
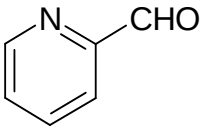
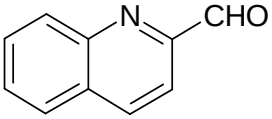
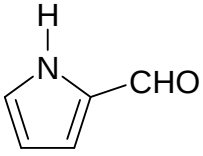



***Figure 3**: Schematic representation of electron-electron repulsion in N, N'-Bis (2-pyrrolylmethylidene)-1, 2-phenylenediamine (**48a**).*

**Table 1.2: Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles by direct condensation.**

| Entry | Aldehyde | Yields of 46 (%) | Yields of 49 (%) | Yields of 48 (%) |
|---|---|---|---|---|
| | |  |  |  |
| **46/49a** |  | 29 | 54 | - |
| **46/49b** |  | 23 | 62 | - |
| **46/49c** |  | 44 | 51.3 | - |
| **49d** |  | 33 | 60 | - |
| **48a** |  | - | - | 76 |

Compounds (**49a-d**) were characterized by $^{1}H$, $^{13}C$ NMR, IR, and LCMS. The disappearance of the primary amine ($NH_2$) signal of phenylenediamine at 3.5-4 ppm and at 3378 $cm^{-1}$ in the $^{1}H$ NMR and IR spectrum, respectively, indicated successful coupling of *o*-phenylenediamine to the aldehyde. Furthermore, the aldehyde proton at 9-10 ppm in the NMR and the aldehydes carbonyl stretch signal at 1667 $cm^{-1}$ in the IR spectrum also confirmed the success of the reaction. [6] Products (**49a-d**) exhibited a singlet signal at 5.50-7.00 ppm. This was assigned to the two methylene protons. The chemical shift of this singlet is affected by the electron withdrawing ability of the heteroatom involved. This singlet appeared at 5.73 and 5.63 ppm for thiophene and furan adducts (**49a** and **49b**) respectively. On the other hand, for pyridine and quinoline adducts (**49c** and **49d**), these protons resonate more downfield at 6.31 and 6.68 ppm, respectively. This is because thiophene and furan are electron excessive and therefore, provide better shielding compared to pyridine and quinoline systems.

Also when comparing thiophene (**49a**) and furan (**49b**) adducts, the methylene protons resonate more upfield for furan compared to thiophene. The reason for this is that the oxygen's lone pair of electrons is in the 2p orbital and the vacant orbital of the *alpha* carbon is the 2p. Therefore, electron donation from oxygen to carbon is facilitated by this match of orbital. This is not the case with sulfur as its lone pair is in 3p orbital; therefore, donation to 2p orbital of carbon is retarded. Also, the methylene protons of the quinoline adduct (**49d**) are more deshielded than those of pyridine adduct. This is attributed to the additional magnetic field induced by the π electrons of the benzene ring in the quinoline. As a result, protons in quinoline adduct sense more effective magnetic field which shifts them to higher frequency.

Except in the case of quinoline adduct (**49d**), the imidazole protons for different heteroaromatic adduct appear in closely similar environments (table **3.3**). The numbering system used for 2-aryl-1arylmethyl-1*H*-benzimidazole is shown in figure (**4**). These findings suggest that the electronic effect of sulfur, oxygen or nitrogen atoms is insignificant on the imidazole protons. The observed deshielding in the case of quinoline can then be attributed to ring effect (as described above). Imidazole protons closer to quinoline substituent experience more deshielding than those far away. For instance, while H-7 of quinoline adduct resonates at

7.95; H-7 of pyridine adduct appears at 7.39 ppm. In contrast, H-6 of quinoline and pyridine adducts appear at 7.36 and 7.32 ppm, respectively.

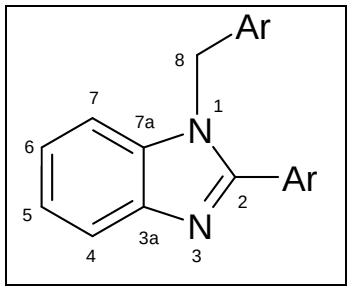



***Figure 4****: Numbering system used in 2-aryl-1-arylmethyl-1H-benzimidazole (**49a-d**)*

**Table 3.3: The chemical shifts (in ppm) and J values (in Hz) of the aromatic region protons of benzimidazole (49a-d).**

| Entry | $^1$H NMR ($CDCl_3$) $\sigma_H$ (in ppm) and *J* (in Hz) | | | |
|---|---|---|---|---|
| | **H-4** | **H-5** | **H-6** | **H-7** |
| **49a** | 7.85 *dd* ($J_{4,5}$ = 6.21, $J_{4,6}$ = 2.18) | 7.32 *m* | 7.32 *m* | 7.39 *dd* ($J_{7,6}$ = 5.94, $J_{7,5}$ = 1.98) |
| **49b** | 7.67 *dd* ($J_{4,5}$ = 1.83, $J_{4,6}$ = 0.81) | 7.32 *m* | 7.32 *m* | 7.35 m |
| **49c** | 7.89 *dd* ($J_{4,5}$ = 7.10, $J_{4,6}$ = 1.55) | 7.32 *m* | 7.32 *m* | 7.39 *d* ($J_{7,6}$ = 7.73) |
| **49d** | 8.18 *d* ($J_{4,5}$ = 8.55) | 7.78 *td* ($J_{5,4}$ = 8.56, $J_{5,6}$ = 8.56, $J_{5,7}$ = 1.56) | 7.36 *td* ($J_{6,7}$ = 7.41, $J_{6,5}$ = 7.41, $J_{6,4}$ = 1.02) | 7.95 *d* ($J_{7,6}$ = 7.51) |

It is important to note that H-5 and H-6 appear as multiplets for benzimidazoles (**49a-49c**). This is because of signal overlap as these protons are in similar chemical environment. As

discussed above, the ring current from quinoline significantly affect the imidazole proton and therefore, they appear in different chemical shifts. As shown in table **3.3**, H-5 and H-6 of quinoline adduct appear as triplets of doublets as they experience no overlap. In addition, $^{13}C$ NMR spectrum was used to confirm the proposed structures. This was done by comparing $^{13}C$ NMR of each 2-aryl-1-arylmethyl-1*H*-benzimidazole to the 2-substituted-1*H*-benzimidazole. For instance, $^{13}C$ NMR spectrum (figure **5**) of benzimidazole (**49c**) consists of 17 signals corresponding to the number of carbons in this compound.

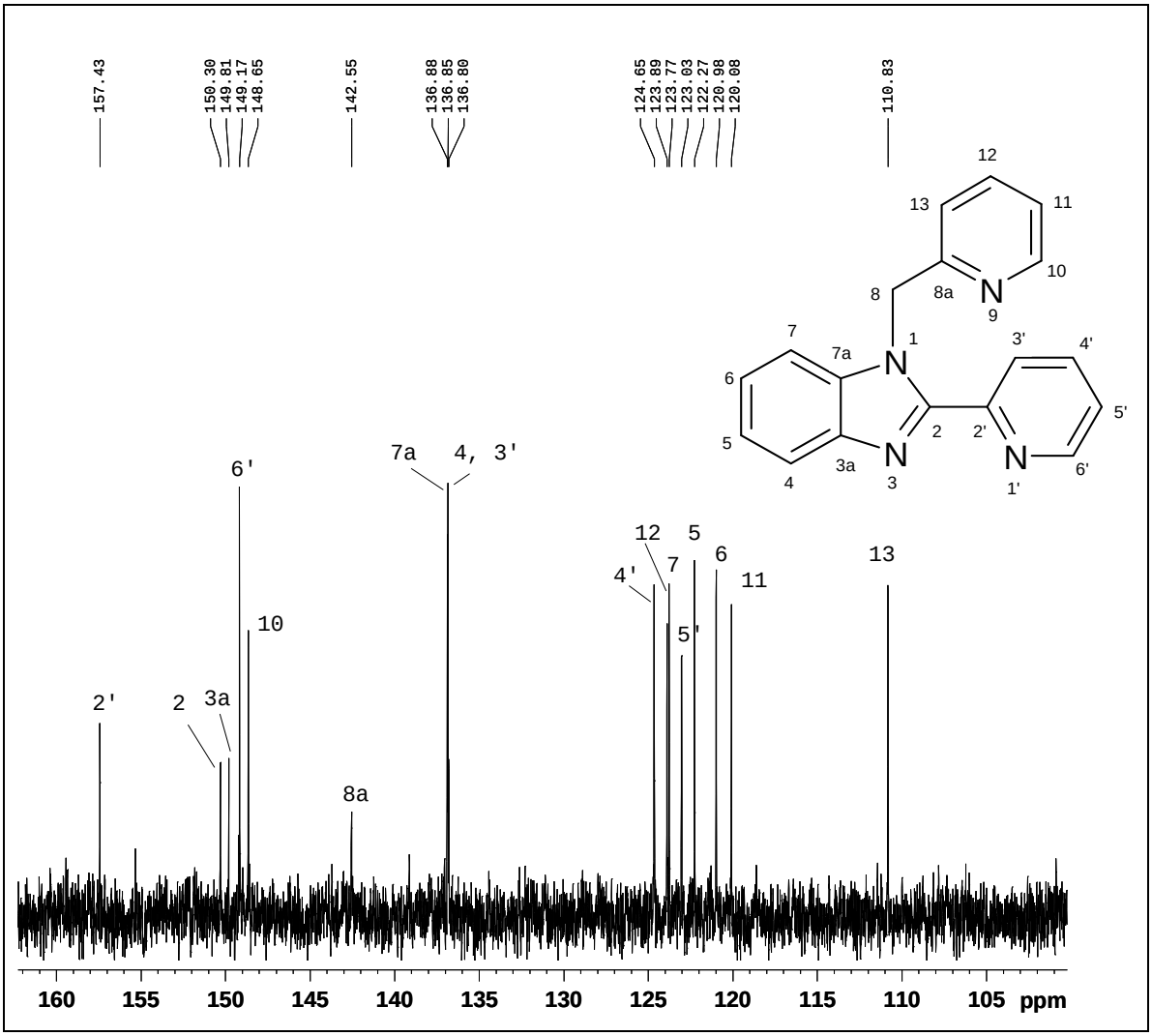



***Figure 5**: $^{13}C$ NMR Spectrum of 2-pyridyl-1-pyridylmethyl-1H-benzimidazole (**49c**)*

In contrast, the spectrum of benzimidazole (**46c**) (figure **6**) only consists of 7 peaks instead of 12 peaks. This was however expected as the chemical environments for (**C-5** and **C-6)**, (**C-4** and **C-7**), (**C-3a** and **C-7a**), and (**C-2** and **C-2'**) are similar. Using LCMS spectra for these compounds (**49a-d**), the proposed structures were confirmed to be correct as the calculated masses were in good agreement with the experimental masses.

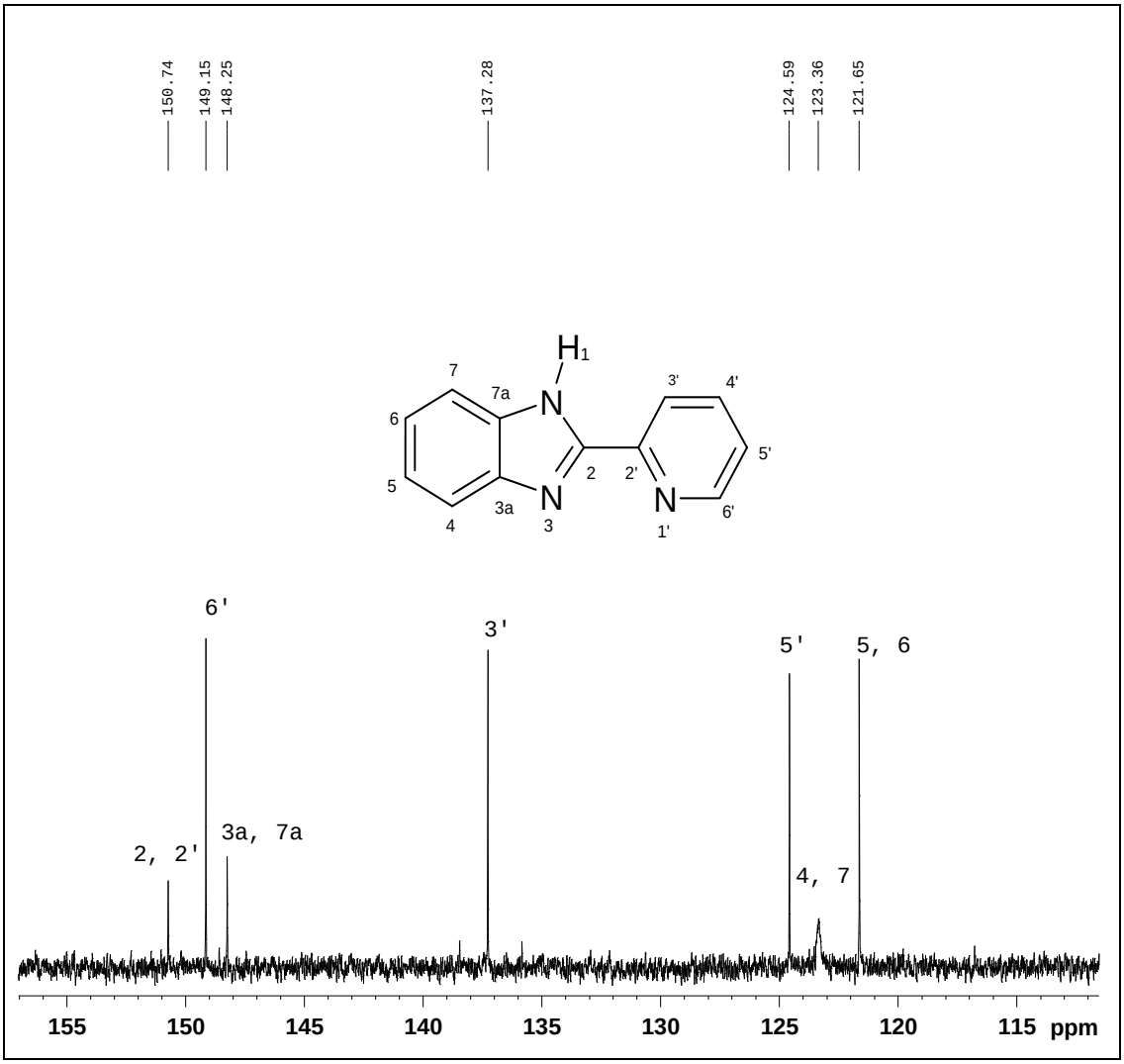



***Figure 6**: [13]C NMR Spectrum of 2-pyridyl-1H-benzimidazole (**46c**)*

Alternatively, using [1]H and [13]C NMR spectra (figures **7** and **8**) of pyrrole adduct (**48a**), a singlet corresponding to the schiff base proton and carbon is observed at 7.76 and 150.5 ppm, respectively. Moreover, since **(48a)** is symmetrical, half the number of signals should be

observed in $^{1}H$ and $^{13}C$ NMR. As expected, 6 and 8 signals, which are half the signal number, are observed in $^{1}H$ and $^{13}C$ NMR spectra, respectively. The appearance of (H-2 and H-3) and (H-1 and H-4) in the same chemical shift also confirms that this compound is symmetrical. The final evidence that the proposed structure of (**48a**) is correct was attained from LCMS spectrum, which showed good agreement between the expected and the calculated mass.

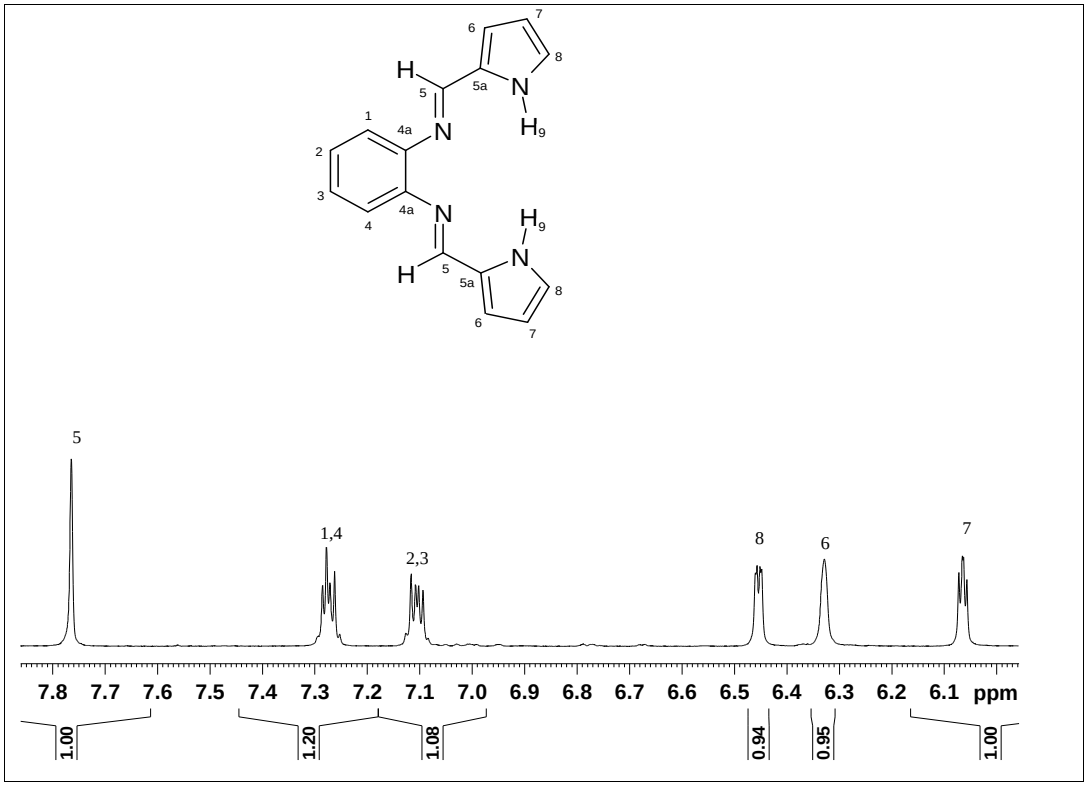



***Figure 7**: $^{1}H$ NMR Spectrum of N, N'-Bis (2-pyrrolylmethylidene)-1, 2-phenylenediamine in $CDCl_3$*

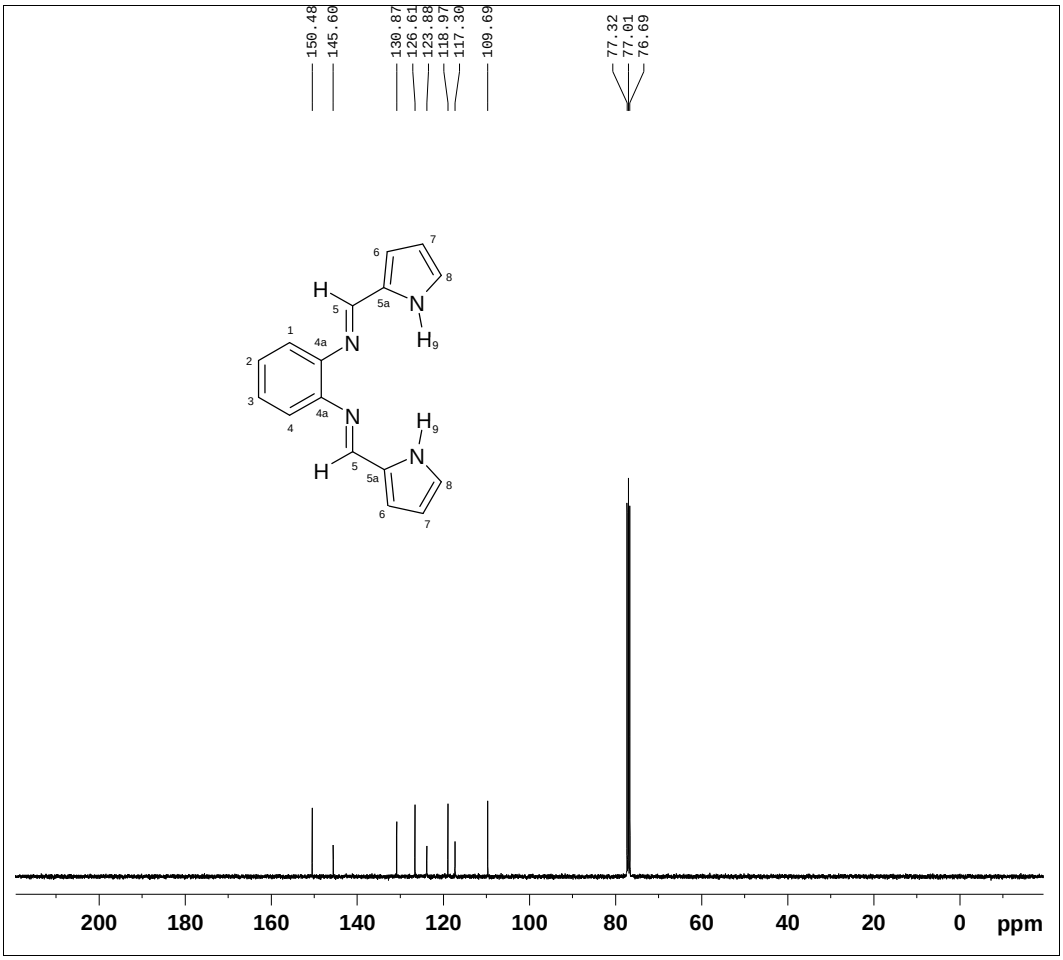



***Figure 8**: $^{13}C$ NMR Spectrum of N, N'-Bis (2-pyrrolylmethylidene)-1, 2-phenylenediamine in $CDCl_3$*

Benzimidazoles (**49a-d**) were also analyzed by the UV/vis absorption spectra. These were measured at room temperature in methanol. Figure **9** represents the combined UV/vis absorption spectra of benzimidazoles (**49a-d**). The spectrum shows four moderately intense absorption bands in the visible region at 332, 316, 303 and 283 nm corresponding to the absorption bands of the quinoline adduct (**49d**). This shifting of (**49d**) towards longer wavelength can be explained in terms of the amount of conjugated systems in this molecule.[6] This compound is highly conjugated as it contains the aromatic benzimidazole nucleus and two quinoline systems. Also, shown in figure **9** is the absorption spectrum of benzimidazole (**49b**). This is made up of an intense band at 307 and two weak bands at 245 and 204 nm. These absorption bands are of lower energy (as they appear at a longer wavelength) compared to the thiophene (**49a**) and pyridine (**49c**) containing benzimidazole. It is notable that both

benzimidazole **(49a)** and (**49c**) show an intense absorption band at 307 nm. However, (**49a)** shows another moderately intense band at 238 nm, which is of lower energy than the weak unresolved band at 203 nm showed by benzimidazole **(49c**). The reason behind these observations is that furan and thiophene have two lone pairs of electrons; one is the part of the conjugated system while the second is localized in the heteroatom. In this way, furan and thiophene containing systems are more electron rich than pyridine containing systems (**49c**). Hence, the absorption bands of benzimidazole (**49c**) appear at a shorter wavelength compared to the other benzimidazoles, figure **9**.

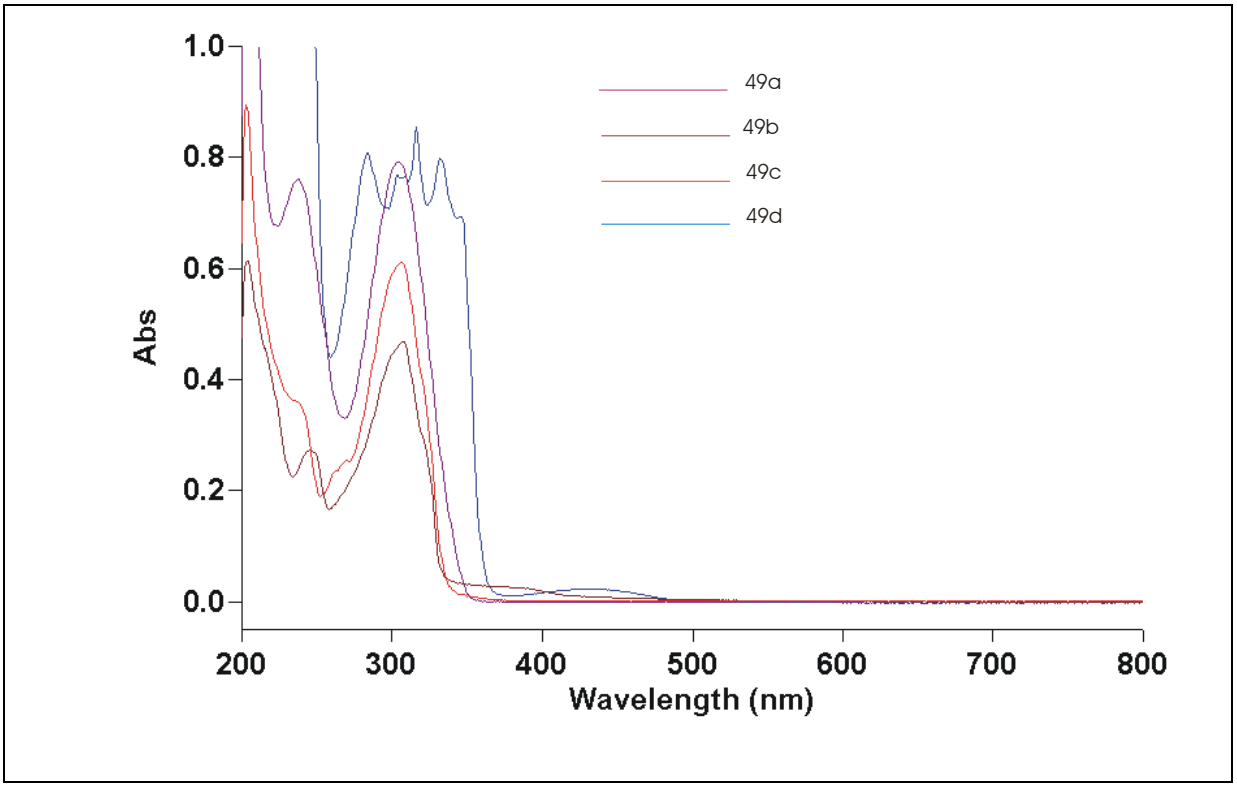



***Figure 9**: UV/vis Absorption Spectrum of benzimidazole (**49a-d**) in methanol at room temperature.*

Although, the required benzimidazoles (**49a-c**) were successfully isolated using direct condensation method, the formation of significant amounts of the side product (**46a-c**) was of great concern. This was especially intriguing in the case of 2-pyridinecarboxyaldehyde where the amounts of benzimidazoles (**46c**) and (**49c**) were similar. Since at this stage the behaviour

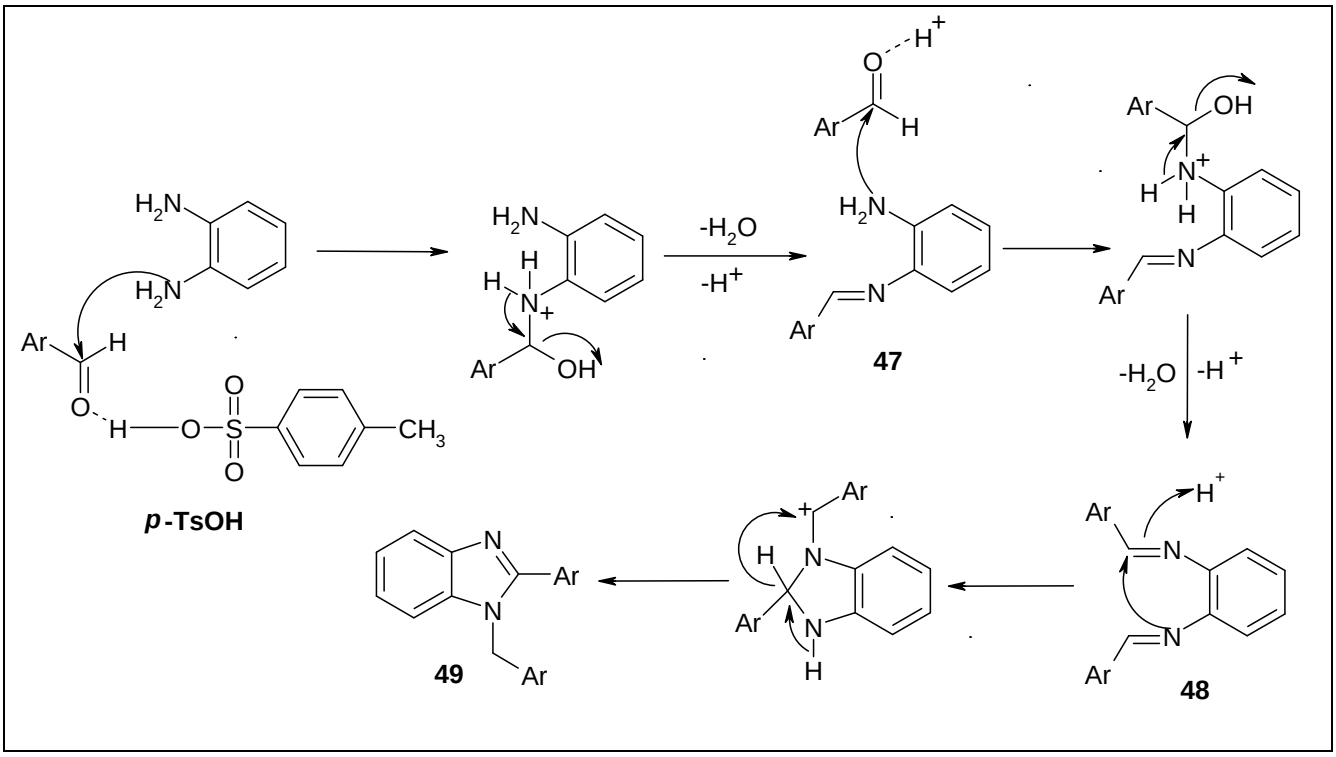
of the studied heteroaromatic aldehydes was understood, the use of acid catalysis was explored merely to improve the yields of 2-aryl-1-arylmethyl-1*H*-benzimidazole (**49**).

### 3.3.3 Acid-Catalyzed Synthesis

In this section we describe the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole using acid catalysts. The modification of a method reported by Pawar and coworkers (described in chapter 2) was employed. The objectives of Pawar, *et. al*., was to explore the efficiency of glyoxylic acid, nonetheless, they also tested other acids, such as *p*-toluenesulfonic acid (*p*-TsOH). According to their findings, 55 % of 2-aryl-1-arylmethyl-1*H*-benzimidazole was obtained when *p*-TsOH was used as an acid catalyst in water.[8] In the present study, we decided to investigate the efficiency of *p*-TsOH in ethanol as opposed to water. We envisage that if ethanol, which unlike water, readily dissolve the starting materials, was used the yields would improve.

Consequently, the treatment of *o*-phenylenediamine (1 mmol) with aromatic aldehydes (2 mmol) in the presence of 5 mol% of *p*-TsOH in absolute ethanol resulted in the formation of the required benzimidazoles (**49a-d**). The mechanism of the acid catalyzed synthesis of 2-aryl-1-arlymethyl-1*H*-benzimidazole (scheme **14**) was proposed by Jadhav and coworkers and it follows the same steps as that in direct condensation.[18] As discussed for direct condensation, intermediate (**47**) has a possibility of following two routes: (i) nucleophilic attack of second $NH_2$ attack on a second aldehydes molecule, (ii) intramolecular ring closure resulting into 2-substituted-1*H*-benzimidazole. In the presence of the acid, the second route is suppressed as the carbonyl carbon of the aldehydes is more electrophilic. [6, 8, 17] Through the formation of hydrogen bonding between the acid and the oxygen atom of the carbonyl, the carbonyl carbon becomes more positive thus more susceptible to nucleophilic attack. Therefore, formation of intermediate (**48**) is enhanced.

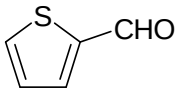
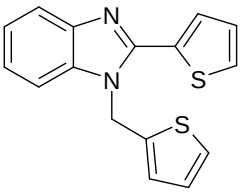
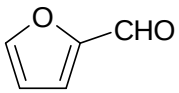
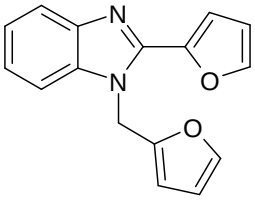
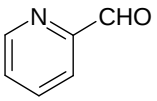
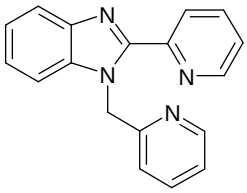
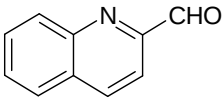
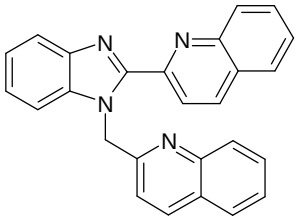
Intermediate (**48**) then undergoes ring closure by the attack of (**a**) on (**b**). The required product (**49**) is then isolated after 1,3-hydride transfer as shown in scheme (**14**).[6]




***Scheme 14**:[18] Acid-catalyzed condensation of o-phenylenediamine with heteroaromatic aldehydes.*

The mechanism described above is supported by the yields isolated for benzimidazole (**46**) and (**49**). It can be observed from table **3.4** that the addition of an acid catalyst significantly increases the yields of benzimidazoles (**49a**, **49c** and **49d**). This confirms the suppression of the formation of 2-substituted-1*H*-benzimidazoles (**46**). However, when 2-furancarboxyaldehyde was used (**49b**), yield stayed the same as in the direct condensation. This is attributed to the fact that furan is a good electron donor to the *alpha* carbon even without the acid. For all the heterocycles, the activation of carbonyl carbon by the acid, satisfy two roles: (i) suppression of the formation of 2-substituted-1*H*-benzimidazoles, (ii) lowering the activation energy thus increasing the reaction rate. In the case of furan adduct, the formation of 2-furanyl-1*H*-benzimidazole (**46b**) is suppressed by oxygen's electron donating ability. As a result, addition of the acid increases reaction speed. This was proven by the fact that acid catalysed reactions were stirred at room temperature for approximately two hours. Contradictory, direct condensation reactions were refluxed overnight.

**Table 3.4: *p*-TsOH catalyzed synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles.**

| Aldehyde | Product | Yield[2] (%) | Mp (°C) found | Mp (°C) lit. |
|---|---|---|---|---|
|  |  **49a** | 64 | 151-152 | 150-152 |
|  |  **49b** | 62 | 88.4-89.3 | 88-89 |
|  |  **49c** | 60 | 127-129.8 | 123-128 |
|  |  **49d** | 72 | 172-175 | No lit.[3] |

[2] Isolated yields
[3] No literature value

## *3.3 Conclusions*

The direct condensation of *o*-phenylenediamine (1 mmol) and appropriate heteroaromatic aldehydes (1 mmol) gave the required 2-aryl-1*H*-benzimidazoles (**46a-c**) in 44-79 % yields. When direct condensation procedure was employed for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles, both the required products (**49a-d**) and 2-aryl-1*H*-benzimidazoles (**46a-c**) were isolated in 51-62 % and 23-44 %, respectively. Yields of 2-aryl-1-arylmethyl-1*H*-benzimidazoles were successfully improved to 60-72 %, by the use of *p*-toluenesulfonic acid as a catalyst.

## *3.4 References*

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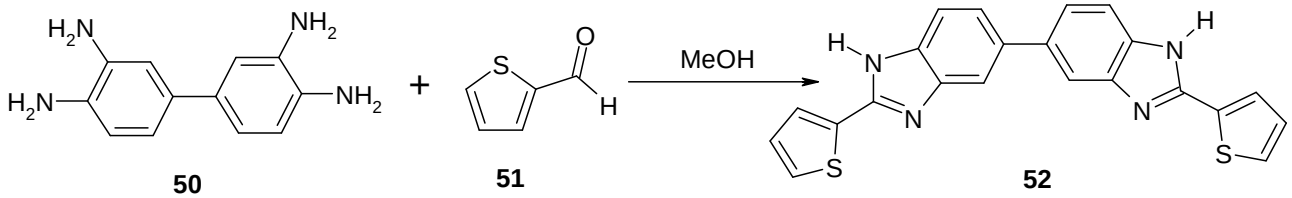
# 4. Synthesis of Bisbenzimidazole

## *4.1 Introduction*

In the previous section, it was discovered that direct condensation is efficient for the synthesis of 2-substituted-1*H*-benzimidazole. Therefore, in this work the use of direct condensation of 3, 3'-diaminobenzidine is used instead of *o*-phenylenediamine is investigated. In addition, the effect of acid catalysis is also investigated. Literature available on the synthesis of bisbenzimidazole is discussed in chapter 2. Noteworthly, all these procedures require harsh reaction conditions and the use of oxidizing agents. For instance, in the method reported by Sann and coworkers, oxone is used as an oxidizing agent. Other groups have reported the use of nitrobenzene. Safety concerns and high boiling points make the use of these reagents cumbersome.[1-2] The methods proposed here, which are: direct and acid catalyzed condensations require mild reaction conditions, environmentally friendly and low boiling point solvents.

## *4.2 Synthesis and Characterization*

As expected, direct condensation of 3,3'-diaminobenzidine (**50**) (1mmol) and 2-thiophenecarboxyaldehyde (**51**) (2mmol) in methanol afforded the required bisbenzimidazole (**52**) in 65 % yield.




**50** **51** **52**

***Scheme 15**: Synthesis of 2, 2'-di-2-thienyl-5, 5-Bi-1H-benzimidazole (**52**) by direct condensation.*

Characterization of the product was achieved by $^{1}H$, $^{13}C$ NMR, IR and LCMS spectroscopy. $^{1}H$ NMR spectrum of (**52**) (figure **10**) shows the disappearance of the primary amine ($NH_2$) of *o*-phenylenediamine and the aldehyde signals at 3.5-4 and 9-10 ppm, respectively. This was supported by IR spectrum, where no signal at 1667 and 3378 $cm^{-1}$ corresponding to the carbonyl group and the primary amine stretching frequencies were observed. Also, the number of signals observed on $^{1}H$ and $^{13}C$ NMR (figure **11**) spectra corresponds to the signals in the proposed structure.

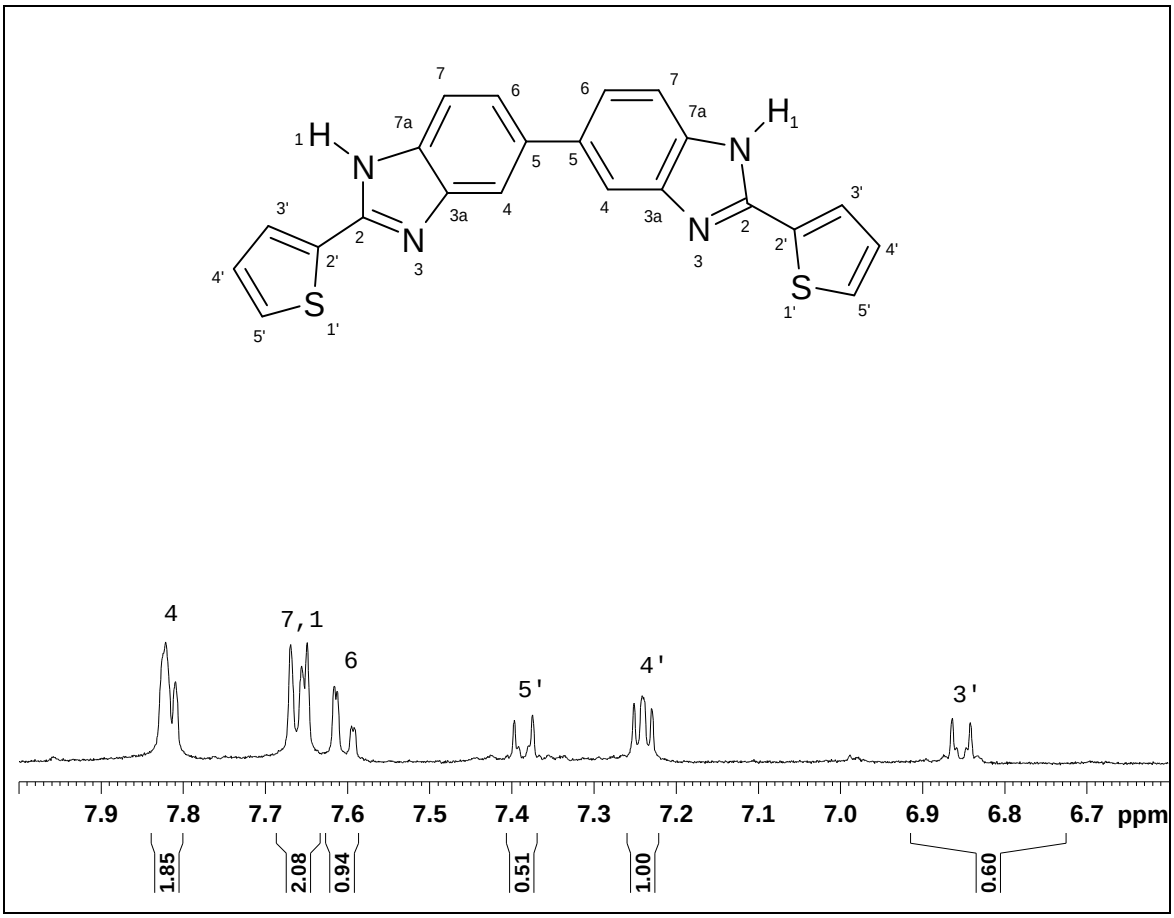



***Figure 10**: $^{1}H$ NMR Spectrum of 2, 2'-di-2-thienyl-5, 5-Bi-1H-benzimidazole (**52**) in MeOD.*

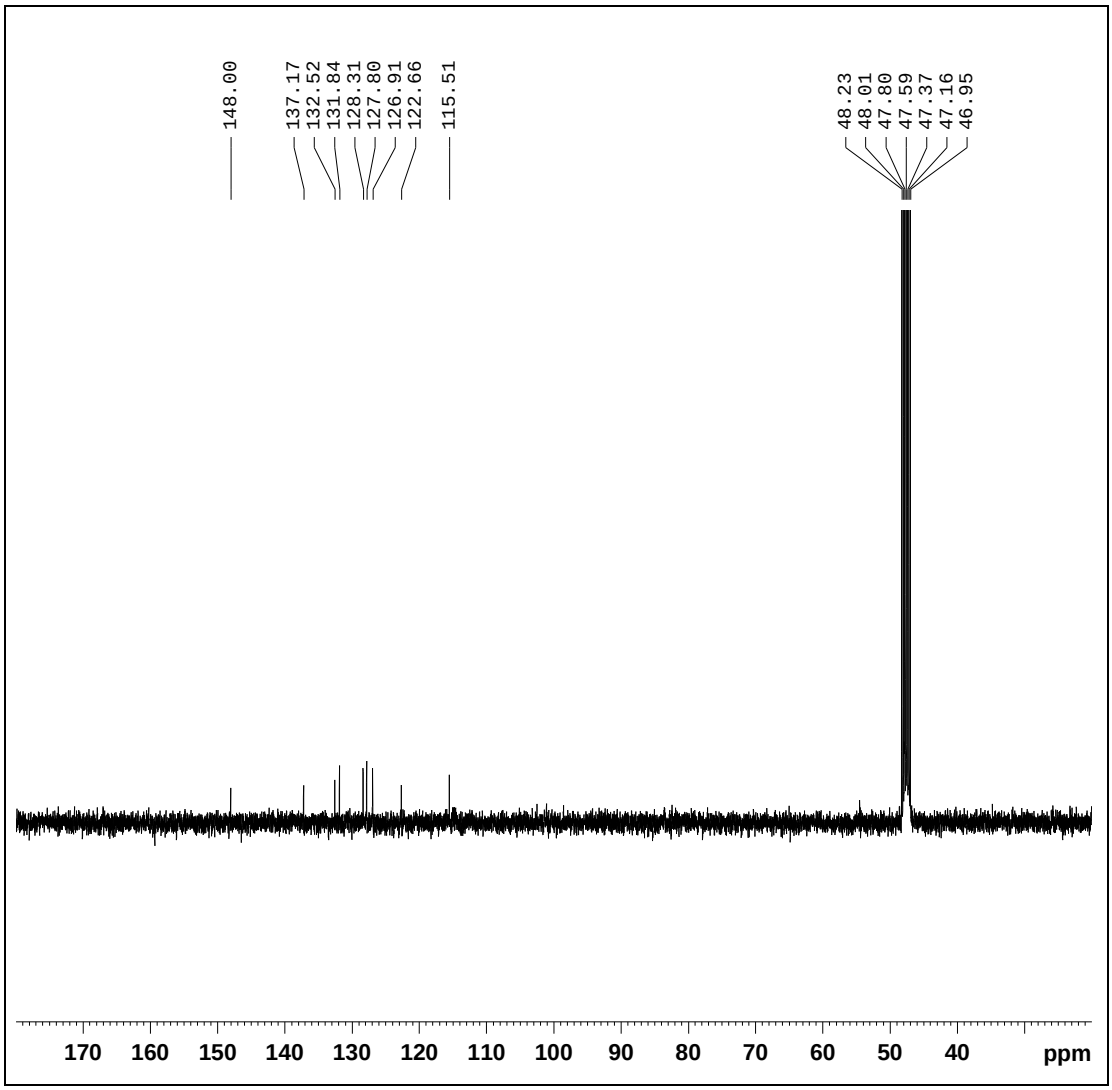
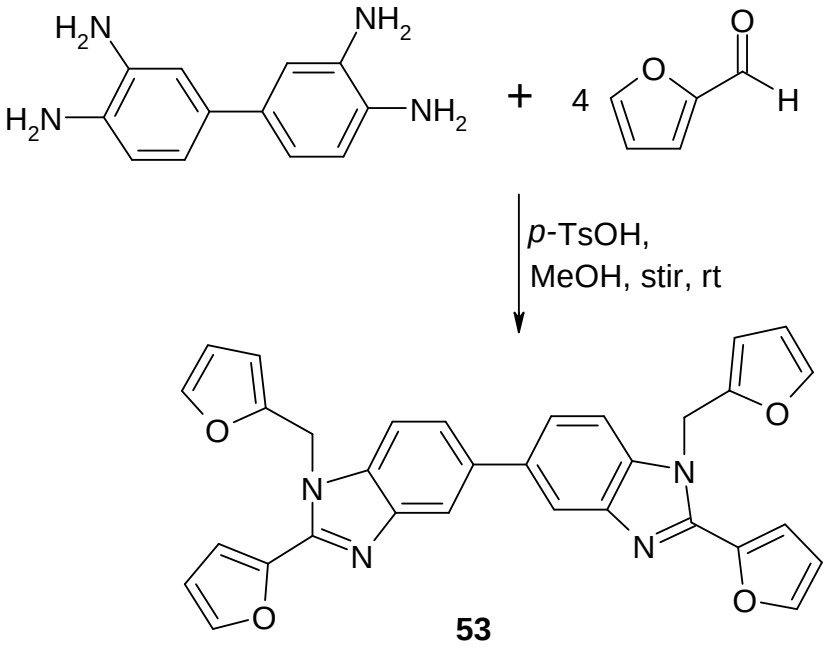



***Figure 11**: $^{13}C$ NMR Spectrum of 2, 2-di-2-thienyl-5, 5'-Bi-1H-benzimidazole (**52**) in MeOD.*

Inspired by the good yield of 2, 2'-di-2-thienyl-5, 5-Bi-1*H*-benzimidazole (**52**), various aldehydes, such as, 2-furan, 2-pyrrole and 2-pyridinecarboxyaldehydes were individually used under the same reaction conditions. After several attempts and modifications of the reaction procedures, we were unsuccessful in isolating the required products. Reasons for this behavior were not clear to us.

Since we were able to achieve 2:1 addition of the aldehyde to 3, 3'-diaminobenzidine, we envisaged that if 4 equivalents of the aldehyde were added, 1, 2-di-2-arylmethyl-2-aryl

benzimidazole would form. Our findings from previous study, confirmed acid catalyzed condensation to be more efficient for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole. Structural similarities between the proposed bisbenzimidazoles and 2-aryl-1-arylmethyl-1*H*-benzimidazole encouraged us to explore acid catalysis in the present work. Accordingly, the stirring of 3, 3'-diaminobenzidine (1 eq.), 2-furancarboxyaldehyde (4 eq.) and catalytic amount of *p*-TsOH in methanol at room temperature resulted into 53 % of light-brown microcrystalline solid of the desired product (**53**) (scheme **16**).




**53**

***Scheme 16**: Acid-catalyzed synthesis of 1, 2- di- 2-furanylmethyl-2, 2- di- 2-furanyl benzimidazole (**53**) in methanol at room temperature.*

Initial identification of the product was achieved by $^{1}H$ and $^{13}C$ NMR spectra (figures **12** and **13**). The singlet assigned to the two methylene protons and carbon is observed at 5.87 ppm and 41.3 ppm, respectively. Since the proposed structure of (**53**) is symmetrical, 11 signals in $^{1}H$ NMR and 16 signals in the $^{13}C$ NMR spectra were expected. Hence, the expected number of signals was observed in the NMR spectra. Furthermore, the number of signals in bisbenzimidazole (**53**) shows that the two furanyl groups on each half of the molecule are in a different chemical environment. This is true

for N-alkylated compounds since the bridging methylene group between furanyl and the imidazole ring donate electrons into the imidazole ring. As a result, H-10 and H-11 appear more upfield compared to H-3' and H-4'. Since this is closer to H-10 and H-11, these protons will be more shielded than H-3' and H-4'. It should also be noticed that H-9 and H-5' appear more downfield compared to the other protons in the same ring. This is because of the electronegativity of oxygen atom.

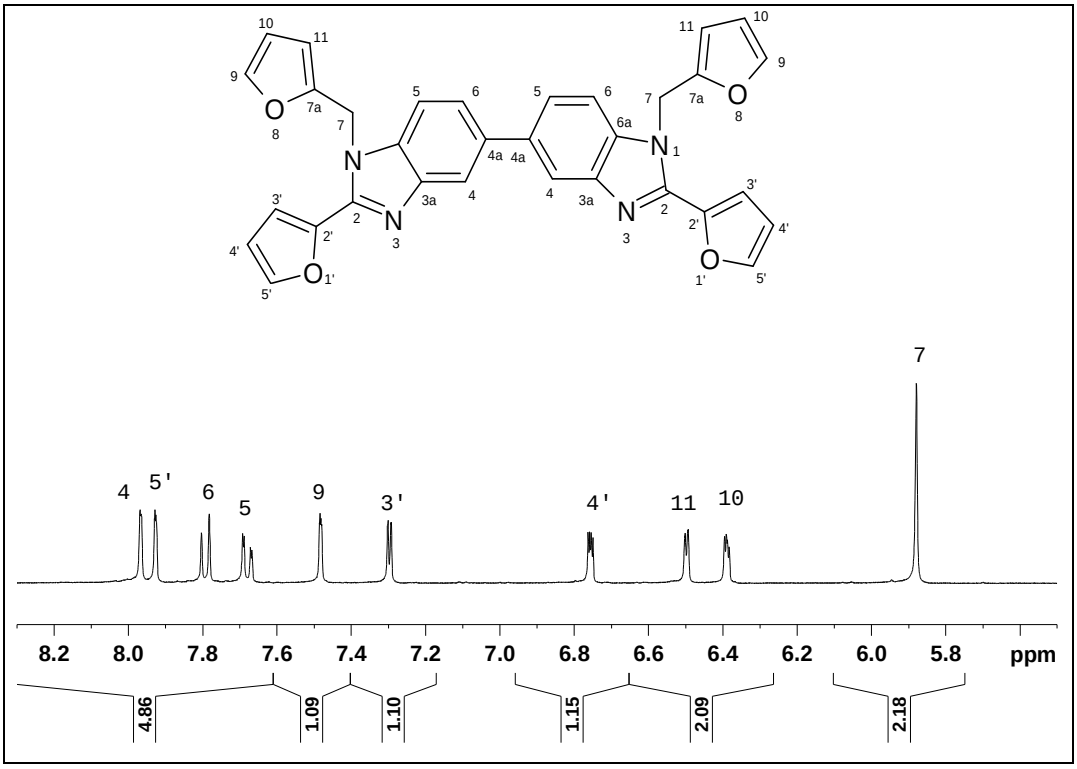



***Figure 12**: [1]H NMR spectrum of 1, 2-di-2-furanylmethyl-2, 2-di-2-furanylbenzimidazole (**53**) in acetone-d6.*

Using LCMS, the difference between the calculated and found mass of the product is 0.0003. This confirms that the proposed structure is indeed the structure of the isolated bisbenzimidazole (**53**).

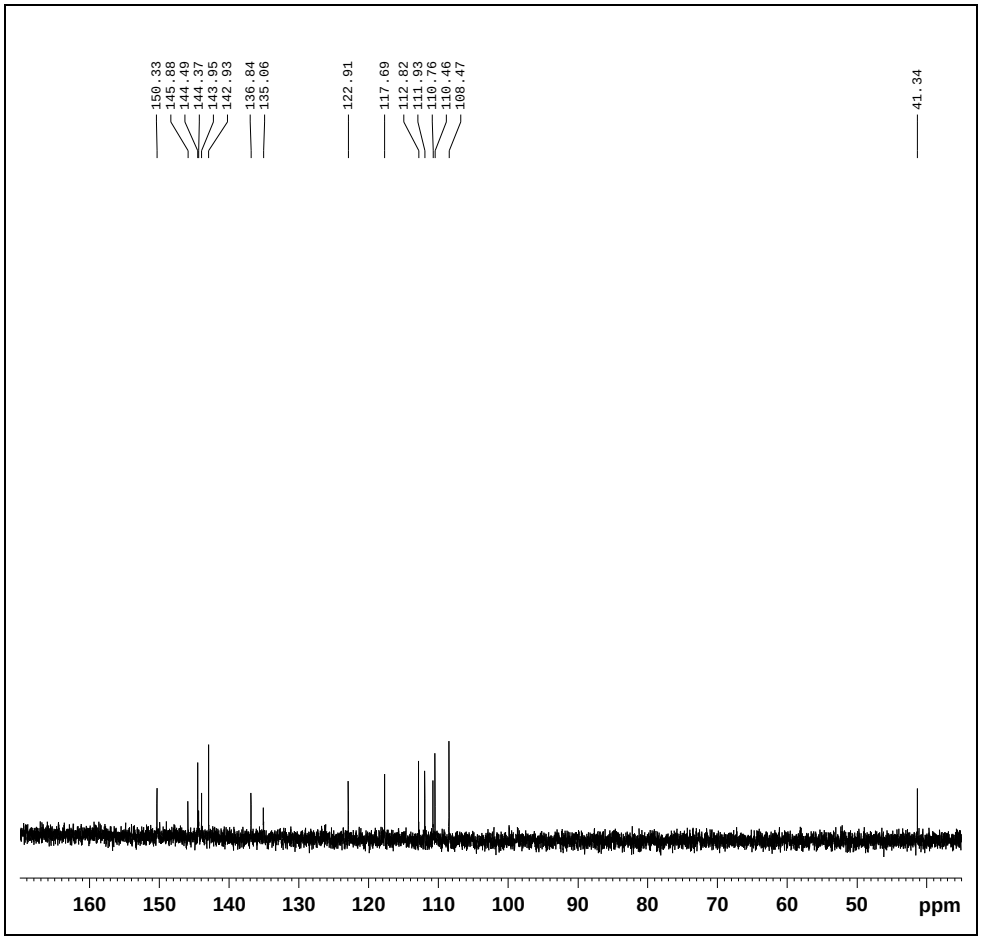
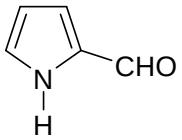
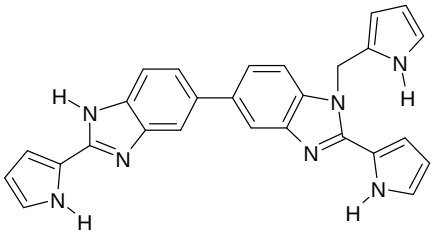
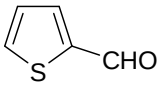
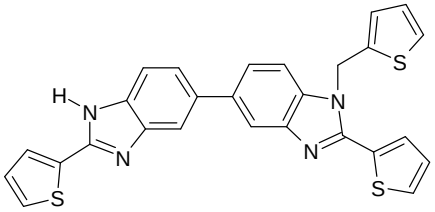
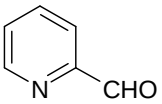
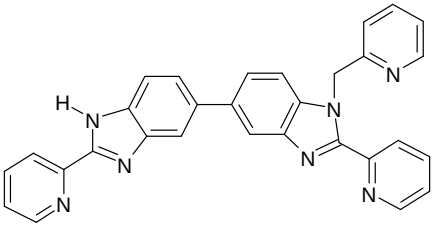



***Figure 13**: $^{13}C$ NMR Spectrum of 1, 2-di-2-furanylmethyl-2, 2-di-2-furanyl benzimidazole (**53**)*

2-Thiophene, 2-pyrrole and 2-pyridinecarboxyaldehyde were also used under the same reaction conditions. Surprisingly, for all of these, the heteroaromatic aldehyde added three times on 3, 3' diaminobenzine. Yields obtained in these reactions are shown in table **4.1**. Note; 2-pyrrolecarboxyaldehyde resulted into excellent yield, 85 %. These results are contradicting our findings from previous work (discussed in chapter 3). According to our previous discussion, the highest yields should have been obtained when 2-pyridinecarboxyaldehyde was used. This is because pyridine is the most electron deficient heterocyclic ring. Therefore, the imine carbon close to pyridine will be more positive and more susceptible to nucleophilic attack. However, the more electron-rich heterocyclic system; pyrrole, resulted into highest yields of the N-alkylated product. Low

yield was also obtained when 2-thiophenecarboxyaldehyde was used. At this stage we are uncertain of the reasons behind these yields.

**Table 4.1: *p*-TsOH catalyzed synthesis of bisbenzimidazole derivatives (55-57)**

| Aldehyde | Product | Yields % |
|---|---|---|
|  |  **54** | 85 |
|  |  **55** | 12 |
|  |  **56** | 10 |

Because of low yields of bisbenzimidazole **(55** and **56**), we attempted to optimize the reaction conditions. The reaction of 2-thiophenecarboxyaldehyde (4 eq.) with 3, 3'-diaminobenzidine was repeated over 24 hours in refluxing methanol. However, the yields were not improved.

The three times addition of the heteroaromatic aldehyde was confirmed by $^{1}H$, $^{13}C$ NMR and LCMS spectra. The aromatic region of $^{1}H$ NMR spectrum of bisbenzimidazole **54** is shown in figure **14**. According to the integration analysis from $^{1}H$ NMR spectrum, compound (**54**) has 17 signals. This is in agreement with the number of signals in the proposed structure. For 1:2 and 1:4 additions of 3, 3'-diaminobenzidine to the

heteroaromatic aldehyde (discussed above), the products are symmetrical and the number of signals is 7 and 11, respectively. Therefore, the structure of (**54**) is clearly not similar to bisbenzimidazoles (**52**) and (**53**). In terms of $^{1}$H NMR spectrum, it should be noted that H-11 and H-12 appear more upfield compared to H-3', 4', 3''' and H-4'''. This is because of the electron donating ability of the methylene group which is closer to H-11 and H-12. It is also important to realize that H-3' and H-4' appear more downfield compared to H-3''' and H-4'''. This is because of the additional electron withdrawal experienced by H-3' and H-4' from the N-1 bound pyrrole ring. On the other hand, protons closer to the pyrrole nitrogen; H-10, H-5' and H-5''' appear in closely similar chemical environment.

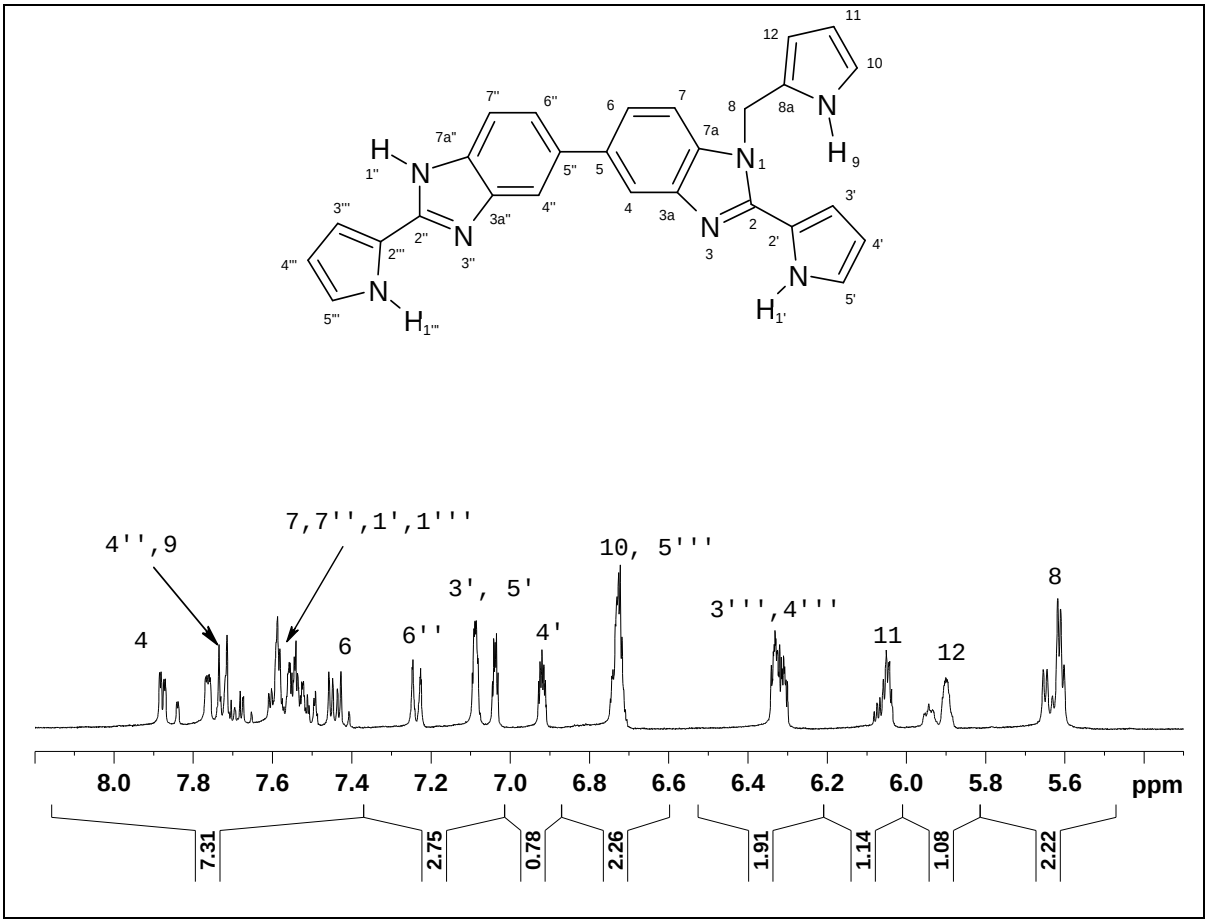



***Figure 14**: $^{1}$H NMR Spectrum of 1, 2- di- 2-pyrrolylmethyl-2, 2- di- 2-pyrrolyl benzimidazole (**54**) in MeOD.*

Furthermore, 27 signals observed on $^{13}C$ NMR spectrum (figure **15**) of bisbenzimidazole (**54**), confirms that the required product, 1, 2- di- 2-pyrrolylmethyl-2, 2- di- 2-pyrrolyl benzimidazole was isolated. For final characterization, product (**54**) was submitted for LCMS analysis, where the calculated and experimental masses of the product were found to be 0.0001 apart. This is a very good indication that the proposed structure is correct structure for the isolated product.

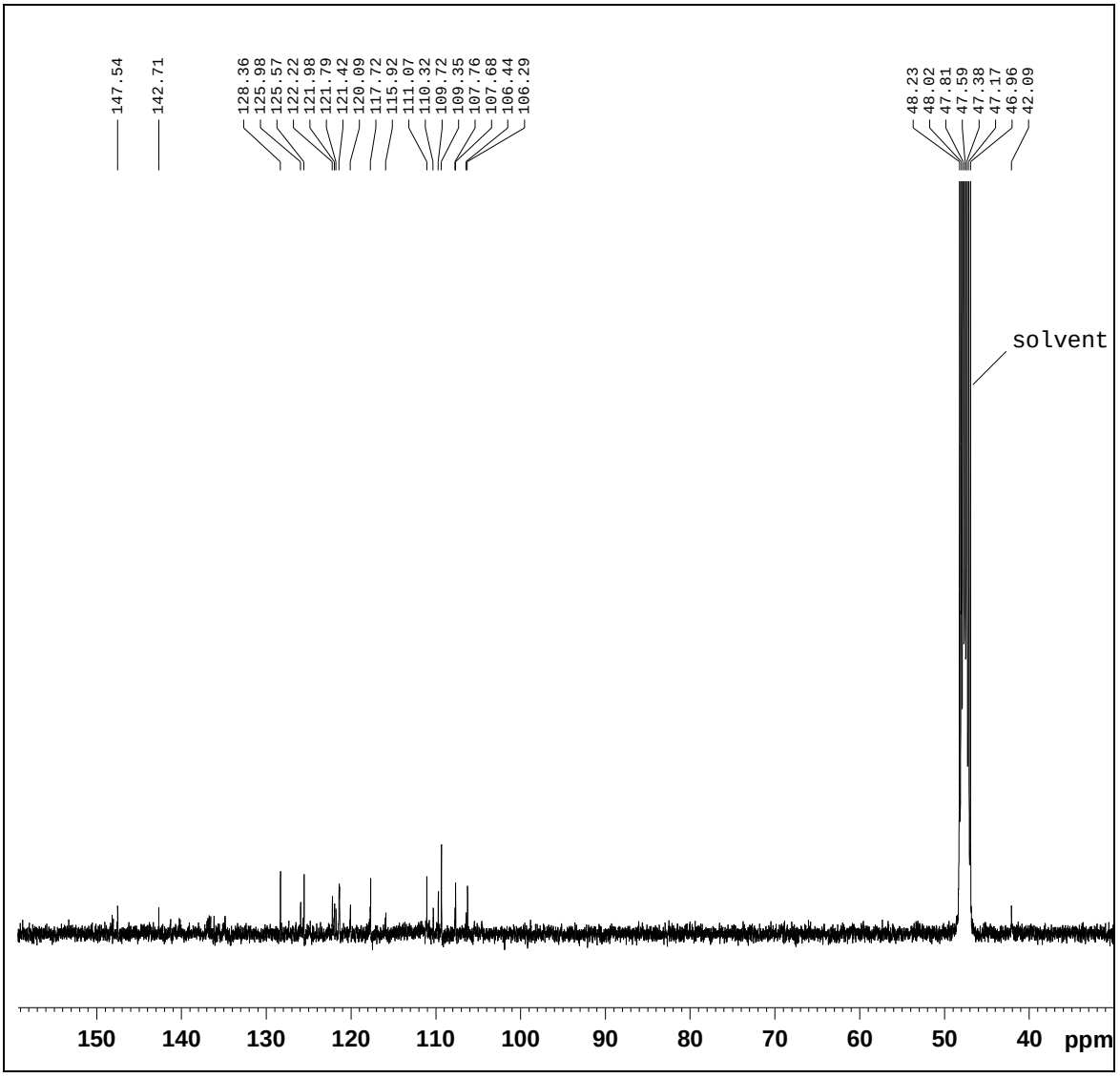



***Figure 15:*** *$^{13}C$ NMR Spectrum of 1, 2- di- 2-pyrrolylmethyl-2, 2- di- 2-pyrrolyl benzimidazole (**54**) in MeOD.*

## *4.3 Conclusions*

2, 2'-di-2-thienyl-5, 5-Bi-1*H*-benzimidazole (**52**) was successfully prepared from the direct condensation reaction of 3,3'-diaminobenzidine (1mmol) and 2-thiophenecarboxyaldehyde (2 mmol). However, the synthesis of the bisbenzimidazole derivatives derived from 2-furan, 2-pyridine and 2-pyrrolecarboxyaldehyde proved to be difficult. *p*-Toluenesulfonic acid catalyzed condensation of 3, 3'-diaminobenzidine (1 mmol) and 2-furancarboxyaldehyde (4 mmol) afforded 1, 2- di- 2-furanylmethyl-2, 2- di-2-furanyl benzimidazole (**53**) in 53 % yield. On the other hand, 1:4 ratio of 3, 3'-diaminobenzidine to 2-pyrrole, 2-thiophene and 2-pyridinecarboxyaldehyde gave unexpected novel 1, 2-di-2-pyrrolylmethyl-2, 2-di-2-pyrrolyl; 1, 2-di-2-thienylmethyl-2, 2- di- 2-thienyl; and 1, 2-di-2-pyridylmethyl-2, 2-di-2-pyridyl benzimidazoles (**54-56**).

## *4.4 References*

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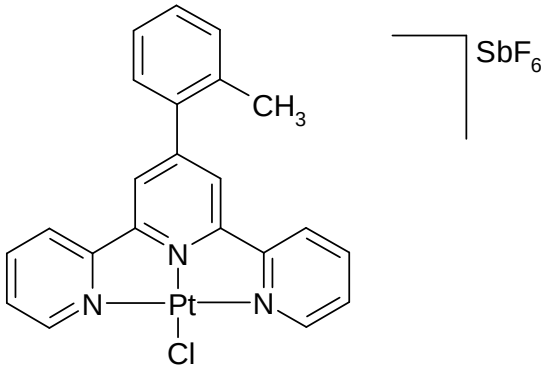
# 5. Synthesis of benzimidazole platinum (II) complexes

## *5.1 Introduction*

Platinum (II) complexes of benzimidazoles have gained considerable attention recently. This is due to their wide variety of properties, including, antitumor activity.[1] Examples of these complexes and their properties are discussed in chapter 1. At this point, it should be noted that in all reported complexes, platinum is coordinated to the benzimidazole through one nitrogen atom (N-1). It is also mentioned in the general introduction that the recent interest towards Pt (II) complexes of benzimidazoles as chemotherapeutic agents, is due to their structural characteristics. Of utmost importance is the steric hindered environment provided by these ligands, which reduces the ease of replacement by sulfur containing molecules in the cell.[1] In this section, the synthesis of tridentate chelated platinum (II) complexes of benzimidazoles is reported.

Although no literature was available to us on the synthesis of tridentate Pt (II) complexes of benzimidazoles, some research has been conducted on structurally related ligand, such as, terpyridine. The synthesis of terpyridine-platinum (II) complexes, including (**57**) has been widely studied.[2-7]




**57**

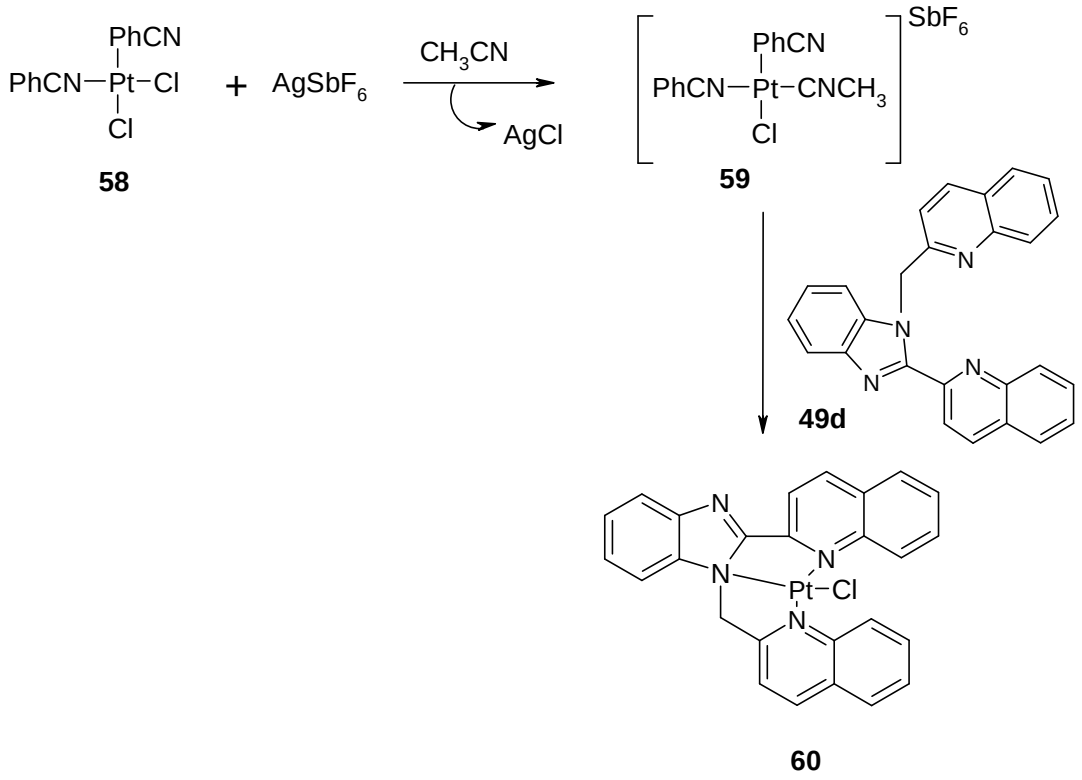
The first study was conducted by Morgan and Burstall in 1930s. In this study, the target complex, [Pt(terpy)Cl]Cl. $2H_2O$, was obtained from refluxing 2, 2′:6′, 2″-terpyridine with potassium tetrachloroplatinate.[5-7] Over the last decade, research conducted in this field led

to the discovery of a synthetic approach involving counter-ion metathesis on [Pt(terpy)Cl]Cl to obtain complexes of the formula, [Pt(terpy)Cl]X, where X=$SbF_6^-$, $CF_3SO_3^-$, $PF_6^-$. [3] In this study, the modification of both methods is employed.

## *5.2 Results and Discussion*

The mechanism towards the synthesis of platinum (II) complexes of benzimidazole involves two steps (scheme **17**). [7] The first step is the displacement of one chlorine atom in $[Pt(PhCN)_2Cl_2]$ (**58**) with equimolar amount of $AgSbF_6$ to form $[Pt(PhCN)_2CNCH_3Cl]SbF_6$ (**59**). The driving force for this reaction is the precipitation of silver chloride salt (AgCl). Since $SbF_6^-$ is a non-coordinating ligand, the acetonitrile used as a solvent also serves as a coordinating ligand. Anhydrous conditions were also crucial for this step as silver salts are moisture sensitive. The significance of equimolar quantities of $[Pt(PhCN)_2Cl_2]$ and $AgSbF_6$ is that the second chlorine is easily replaced in an excess of silver salt. Note, in this study we used $SbF_6^-$ as a counter-ion because of its big size which stabilizes the metal complex more than smaller ions. The second step of this synthesis entails the reaction of equimolar amount of the ligand and $[Pt(PhCN)_2CNCH_3Cl]$ $SbF_6$ (**59**). In this case, both PhCN and $CNCH_3$ are displaced by the ligand.[7] 2-quinolyl-2-quinylmethyl-1*H*-benzimidazoles (**49d**) was used as ligand. The required product (**60**) was obtained as brownish sticky solid.

Product (**60**) was characterized by $^{195}Pt$, $^{1}H$, $^{13}C$ NMR and UV spectroscopy. $^{195}Pt$ NMR spectrum (figure **16**) of this complex shows three singlets at -2260, -2310, -2416 ppm. At this point, it became clear to us that three individual Pt (II) complexes were present in the mixture. According to the reported $^{195}Pt$ NMR spectrums of tridentate N, N, N-bound Pt (II) , the typical region where Pt (II) resonate is -2300 to -2400.[7] Therefore, the signal at -2416 ppm (**a**) was assigned to the Pt (II) signal for the expected product (**60**). However, this is not the major product in the mixture. A signal at -2310 ppm (**b**) corresponds to the major product, and there is an additional minor product (**c**) at -2260 ppm.




***Scheme 17**:[7] Synthesis of Pt(II) complex of 2-quinolyl-2-quinolylmethyl-1H-benzimidazole (**60**).*

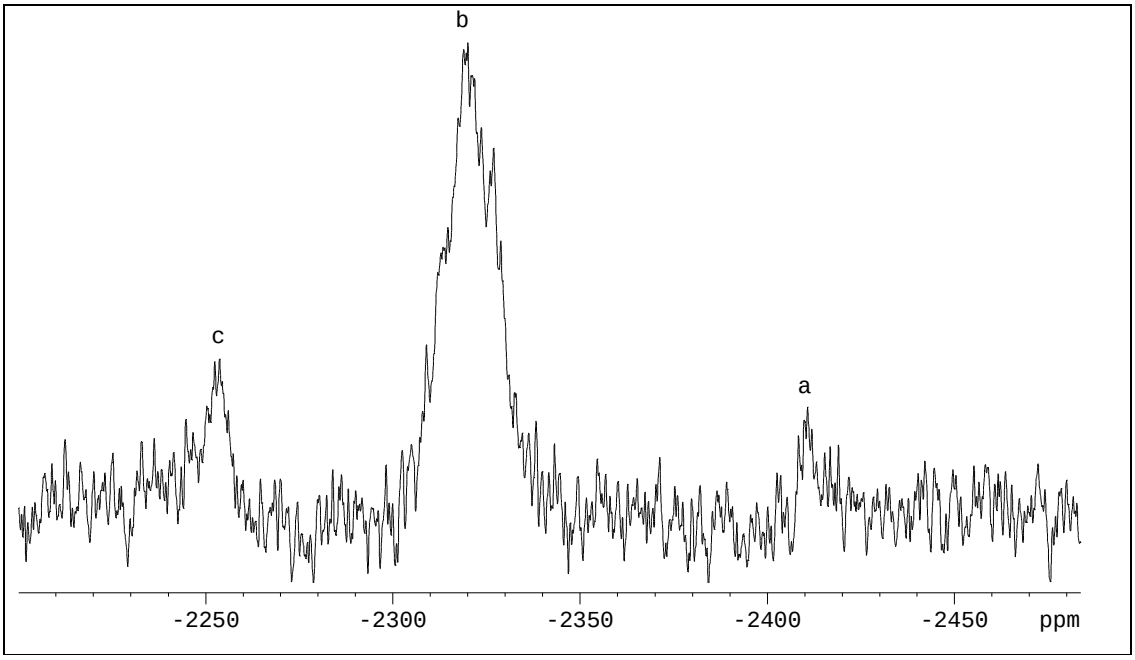
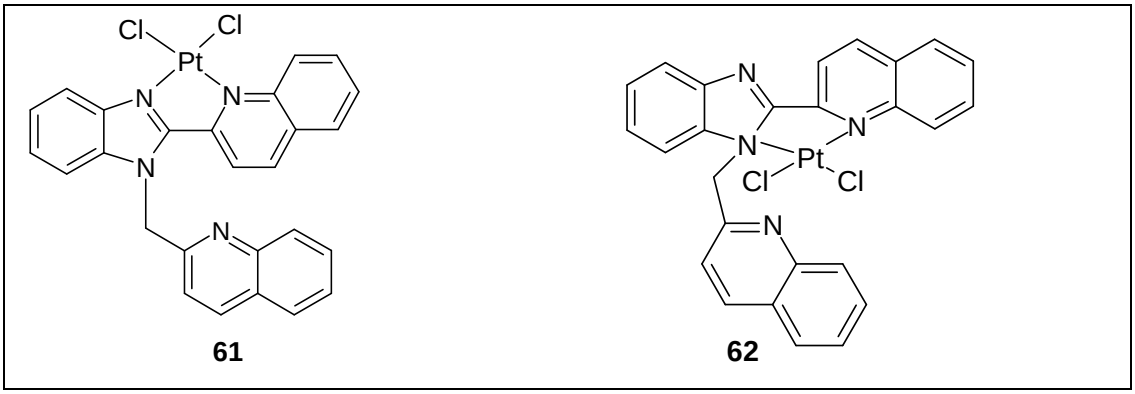



***Figure 16**: [195]Pt NMR spectrum of Pt (II) complex of 2-quinolyl-2-quinolylmethyl-1H-benzimidazole in methanol.*

The first step of this synthesis involved the use of one equivalent of $AgSbF_6$ to displace one chlorine atom. Excess $AgSbF_6$ results into the removal of both chlorine atoms, while if less amount is used, a mixture of products result, that is, one with one chlorine displaced and others where no displacement took place. An addition of benzimidazole ligand to this will result into a mixture of products, as observed in this study. The major signal at -2310 ppm is assigned to complex (**61**). This is proposed to be the most stable product since the Pt (II) coordination site is less sterically hindered. On the other hand, a third minor product at -2260 ppm was assigned to the sterically hindered complex (**62**). The chemical shift values for complexes (**61** and **62**) were expected based on the data for similar compounds reported in literature. For example, Vollano and coworkers reported that $^{195}Pt$ spectrum of $[Pt(DACH)Cl_2]$, where DACH=1, 2-diaminocyclohexane, shows a signal at -2287 ppm.[8-10]




**61** **62**

In order to eliminate the formation of a mixture of product, the reaction (described in scheme **17**) was repeated using exactly equimolar amounts of $[Pt(PhCN)_2Cl_2]$ and $AgSbF_6$. Only one signal at -2407 ppm in $^{195}Pt$ NMR spectrum was observed. The similarity in the shape of this peak to the peak at -2410 ppm in figure **17** confirmed these two signals to result from the same complex. The slight differences in chemical shift can be associated to the use of different solvents for recording $^{195}Pt$ NMR spectrum. $^{195}Pt$ spectrum in figure **16** was run in methanol, while, the spectrum in figure **17** was recorded in dimethylformamide.

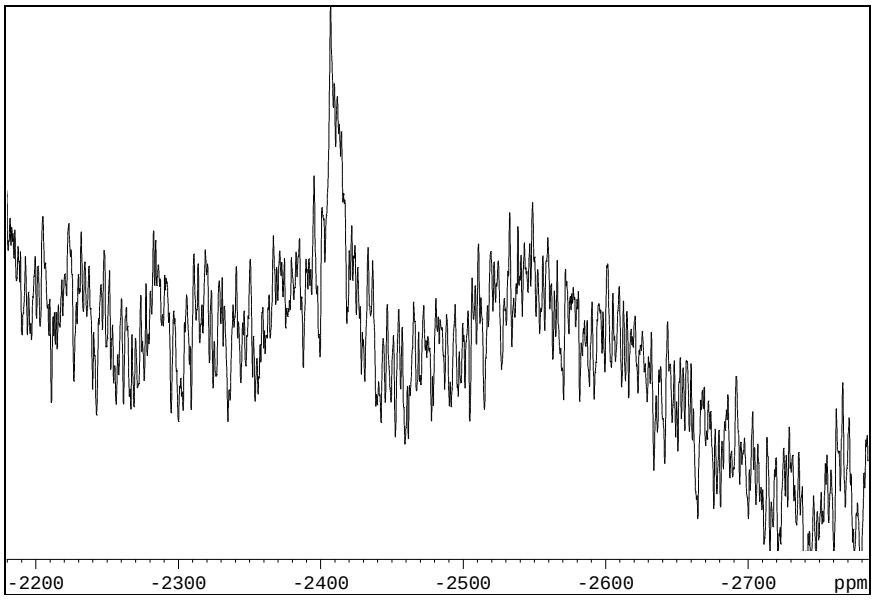
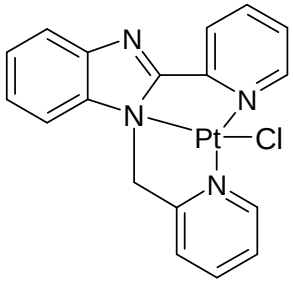



***Figure 17**: [195]Pt NMR spectrum of Pt (II) complex of 2-quinolyl-2-quinolylmethyl-1H-benzimidazole (**60**) in DMF.*

Motivated by these results, 2-pyridyl-2-pyridylmethyl- and 2-thienyl-2-thienylmethyl-1*H*-benzimidazoles were also used as a ligand. However, the method reported by Morgan and Burstall was employed.[5-6] As expected, a singlet peak at -2458.3 ppm corresponding to complex (**63**) was observed. As discussed above, this is the expected region for a tridentate-N, N, N-bound Pt (II) centre. Moreover, this chemical shift is closely similar to the one for complex (**60**). This was expected since there is no significant difference in electron withdrawing or donating ability of pyridine and quinoline systems.




**63**

The comparison between $^{1}H$ and $^{13}C$ NMR spectra of the free ligands and products (**60** and **63**) also confirmed platination. Figures **18** and **19** shows the aromatic region of 2-pyridyl-1-pyridylmethyl-1*H*-benzimidazole (**49c**) and its platinum (II) complex (**63**). It is observed from these figures (**18** and **19)** that all signals corresponding to complex (**63**) are shifted

upfield. For instance, while the methylene protons (H-8) resonate at 6.41 ppm in the complex, in the free ligand these appear at 6.56 ppm. This means that platinum (II) chelation provides an electron rich environment. This can be accounted for by two factors: (i) Pyridine is a π-accepting ring system and, therefore, accepts electrons from the metal into its empty π* orbitals; (ii) Dimethylformamide (used as a solvent) can coordinate to platinum (II) and donate electrons towards this centre. Notably, pyridine accepts π-electrons through π-backbonding. This implies that, although pyridine donates σ electrons to the Pt (II) for the bond formation, it also accepts electrons via backdonation after bond formation. Since DMF was used for recording the NMR spectra, backdonation is enhanced. This is because of the electron donating ability of DMF.

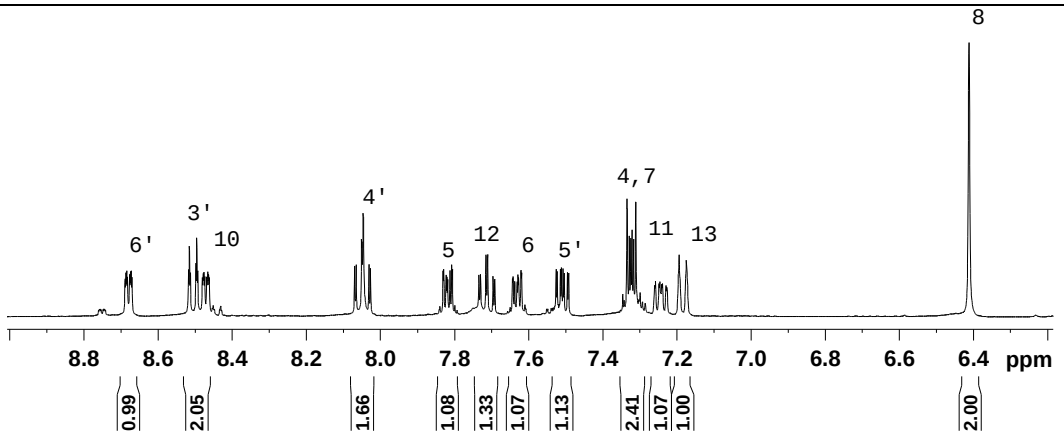



***Figure 18**: [1]H NMR Spectrum of Pt (II) complex of 2-pyridyl-1-pyridylmethyl-1H-benzimidazole (**63**) in DMF.*

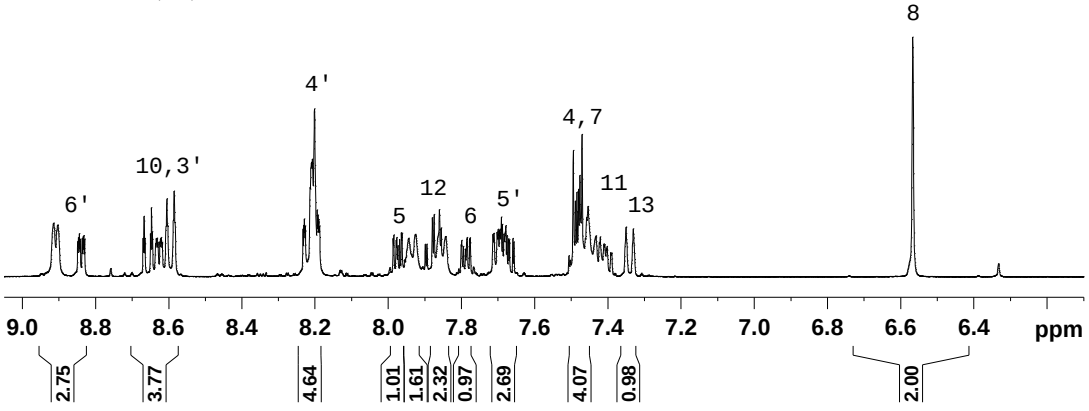
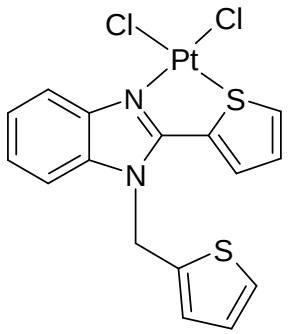



**Figure *19:** [1]H NMR Spectrum of 2-pyridyl-1-pyridylmethyl-1H-benzimidazole (**49c**) in DMF.*

In contrast to the observed similarities between complex (**60** and **63**), the Pt (II) complex of 2-thienyl-2-thienylmethyl-1*H*-benzimidazole (**64**), showed a singlet peak at -2322 ppm. According to literature, a signal expected for S-N-S and one halide coordinated Pt (II) should appear at -3000 to -4000 ppm.[11] This is because the thienyl group is an electron rich system; therefore, the Pt (II) nucleus is more shielded. However, based on the observed chemical shift, the isolated complex (**64**) is also attached to an electron withdrawing group. We propose that only two Cl of potassium tetrachloroplatinate were displaced by the ligand and the observed downward shift is as a result of deshielding by the remaining two Cl atoms.




**64**

In contradiction to the observed (in $^{1}$H NMR) shielding effect as a result of platinum (II) complexation, when 2-thienyl-1-thienylmethyl-1*H*-benzimidazole was used as a ligand; the complex signals are shifted more downfield compared to the free ligand (table **5.1**)

**Table 5.1: Chemical shifts (in ppm) of the protons in 2-thienyl-1-thienylmethyl-1*H*-benzimidazole and its Pt (II) complex (64)**

| Protons | Ligand (49a) | Complex (64) |
|---|---|---|
| **H-8** | 6.21 | 6.25 |
| **H-10** | 7.63 | 8.34 |
| **H-11** | 7.28 | 8.22 |
| **H-12** | 7.18 | 8.20 |
| **H-3'** | 7.89 | 8.31 |
| **H-4'** | 7.52 | 8.43 |
| **H-5'** | 7.96 | 8.43 |
| **H-4** | 8.04 | 8.54 |
| **H-5 & 6** | 7.44 | 8.39 |
| **H-7** | 7.89 | 8.49 |

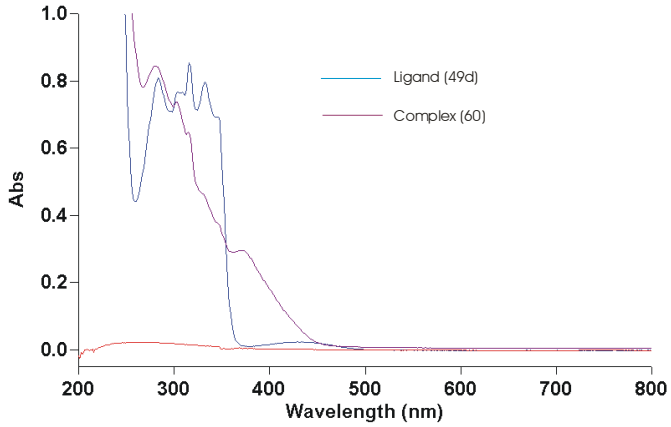
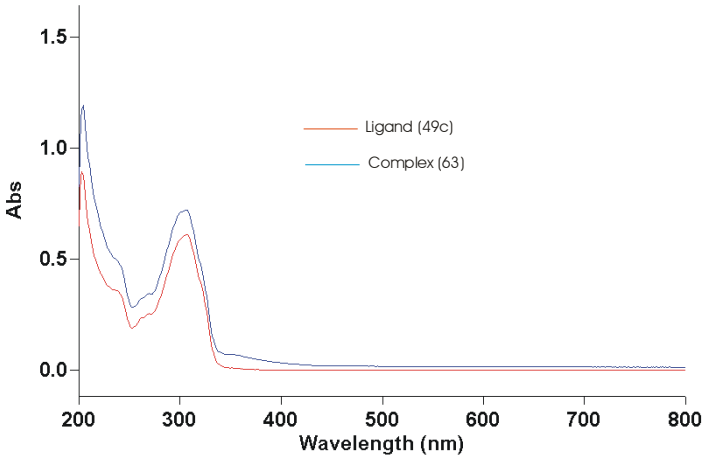
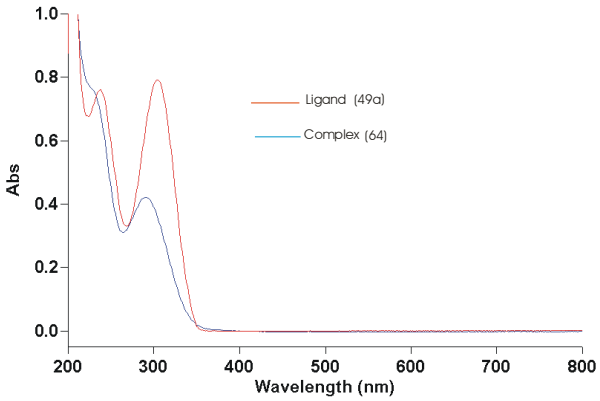
The significant change in chemical shift observed for aromatic protons can be attributed to the fact that thiophene is an electron rich system. Unlike pyridine, thiophene donates electrons to Pt (II). As a result, protons in the complex are more deshielded than in the free ligand. Since in this case, the Pt (II) centre is electron rich, electron donation from DMF is not accepted.

The effect of Pt (II) chelation was also observed from the UV/visible spectra. All UV/vis absorption spectrum of the free ligands were compared with their Pt (II) complexes (table **5.2**). The high energy peaks were assigned to π-π * transitions of the benzimidazole ligand. On the other hand, the broad low energy peaks in the region of 300-400 nm were assigned to MLCT transitions (metal-to-ligand charge transfer). Notable, the MLCT bands are only observed for pyridine and quinoline Pt (II) complexes at 352 nm and 372 nm respectively. This is attributed to the fact that thiophene is an electron rich system and therefore, does not participates in π-backbonding. These assignments of peaks were made based on the available literature of the UV/vis absorption spectrum analysis of terpyridine Pt (II) complexes.[12]

Except in the case of pyridine Pt (II) complex, the bands corresponding to the complexes are shifted towards lower wavelength compared to the free ligand. Also, this shift is more pronounced for thiophene Pt (II) complex. As discussed earlier, pyridine has vacant π* orbitals and thus accepts electrons from the metal through backdonation. As a result, there is no significant difference in conjugation between the free ligand and the Pt (II) complex. In contrast, thiophene is an electron rich system and on complexation, its conjugation is disrupted as it donates electrons to the metal centre. This causes an increase in the energy gap between HOMO and LUMO. Since higher energy will be required for electronic transitions, the absorption bands appear at a lower wavelength.

Besides the shift in the absorption region of the complex peaks as a result of disrupted conjugation, the complex peaks are also weak and unresolved compared to the ligand. Quinoline Pt (II) complex (**60**) shows greater disruption compared to complexes (**63** and **64**).

**Table 5.2: UV/vis Absorption Spectra of the ligands and their Pt (II) complexes (60, 63 and 64) in methanol at room temperature.**

| Entry | UV/vis Absorption Spectra |
|---|---|
| **60** |   |
| **63** |   |
| **64** |   |

## *5.3 Conclusions*

This work describes the successful synthesis of three novel Pt (II) complexes of benzimidazoles. These are the complexes of 2-quinolyl-2-quinolylmethyl (**60**), 2-pyridyl-2-pyridylmethyl (**63**) and 2-thienyl-2-thienylmethyl-1*H*-benzimidazoles (**64**). Based on the reported data for Pt (II) complexes containing planar aromatic ligands, these complexes have a potential of acting as DNA intercalating and antitumor agents against various cancers.[13-16]

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## 6.1 Instrumentation and General Experimental Conditions

Anhydrous reaction conditions were achieved by first drying glassware overnight in an oven at 120 °C, assembling it while hot; remove any excess moisture with a hot air gun and allowing it to cool under nitrogen. Anhydrous solvents were collected from the drying and distilling apparatus, rapidly closed with rubber *septa* and stored over molecular sieves until use.

Preparative thin layer chromatography was carried out on glass plates (20 x 20 cm) coated with silica gel Merk Kieselgel 60 $F_{254}$ using the following procedure. Silica gel (200 g) was homogeneously suspended in water (480 ml) in a round bottom flask. After swirling the contents of the flask, this was allowed to stand for 1 hour before it was spread on clean grease free plates with a spreader. These plates were stored in a draft free place for 48 hours at room temperature and subsequently activated for 2 hours in oven before use. Thin layer chromatography was carried out using Merk Kieselgel 60 $F_{254}$ aluminium backed TLC plates. Visualization was achieved using short ultra violet light (254 nm).

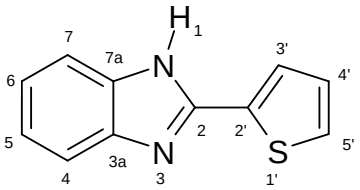
NMR spectra were recorded on Bruker Avance III 400 (9.4 T) and Bruker Avance III 500 (11.7 T) spectrophotometers. All NMR spectra were recorded as parts per million (ppm) relative to the residual protonated solvent in the deuterated solvent for $^{1}H$ and $^{13}C$ and relative to hexachloroplatinic acid in $D_2O$ (external) for $^{195}Pt$. $^{1}H$, $^{13}C$ and $^{195}Pt$ NMR spectra were recorded at 400, 100 and 107 MHz, respectively, and at 30°C . The coupling constants were measured from the spectra and are expressed in Hertz (Hz). The multiplicities are abbreviated as: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (dd) doublet of doublet, (ddd) doublet of doublet of doublet, (dt) doublet of triplet, (tt) triplet of triplet, (br.s) broad singlet and (m) multiplet.

Infra red spectra were recorded neat from the Smiths IdentifyIR spectrophotometer. Melting points were determined from Stuart SMP3 melting point apparatus using open ended capillary tubes and from the Koefler hot stage melting point apparatus. Low and High resolution mass spectra were obtained from Waters LCT Premier. Spectra were obtained using electron impact

mode (EI) or chemical ionization mode (CI). UV and Visible Absorption Spectra were recorded from Cary 100 Bio. Samples for UV/Vis analysis were prepared by dissolving 1 mg of each compound in methanol (10 ml) and this was diluted further to get absorbance reading between 0-1.

## 6.2 Experimental for Chapter 3

### *Synthesis of 2-thienyl-1H-benzimidazole (46a)*




Procedure A: A mixture of *o*-phenylenediamine (0.496 g, 5 mmol) and 2-thiophenecarboxaldehyde (0.733 g, 5 mmol) was refluxed in absolute ethanol at 75°C for 2 hours. The mixture was concentrated *in vacuo* and the crude product was obtained as dark brown crystals. This was purified with column chromatography using petroleum ether/ ethyl acetate (7: 3), $R_f$ 0.23. The titled compound was obtained as brown fine crystals (0.653 g, 65 %); mp 327- 330 °C (lit. 329- 331 °C)[1].

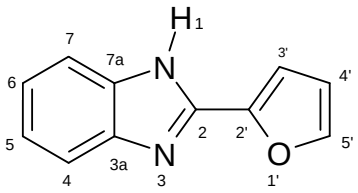
$\delta_H$ (MeOD, 400 MHz): 7.22 (1H, m, *J*= 3.77, 3.79, **H-4**), 7.26 (2H, 4 lines, *J* = 3.24, **H-5 & 6**), 7.57 (2H, 4 lines, *J* = 3.21, **H-4 & 7**), 7.64 (1H, dd, $J_{3',4'}$ = 4.73, $J_{3',5'}$ = 0.97, **H-3'**), 7.78 (1H, dd, $J_{5',4'}$ = 3.76, $J_{5',3'}$ = 0.98, **H-5'**)

$\delta_C$ (MeOD, 100 MHz): 122.6 (C-4), 126.8 (C-5 & 6), 127.7 (C-4 & 7), 128.2 (C-3' & 5')

IR (neat): $\nu_{max}$ 3064, 1422, 745 $cm^{-1}$

HRMS (ESI+); Found $[M+H]^+$, 201.0488; $C_{11}H_9N_2S$ Calc. Mass, 201.0486.

## *2-furanyl-1H-benzimidazole (46b)*




Procedure A was followed using 2-furancarboxaldehyde (0.49 g, 5 mmol). The pure product was obtained as yellow- brown crystals (0.407 g, 44 %); mp 284.5- 287.2 °C (from methanol), (lit. 287-288 °C)[1] after purification on the column chromatography eluting with petroleum ether/ ethyl acetate (50 %), $R_f$ 0.13.

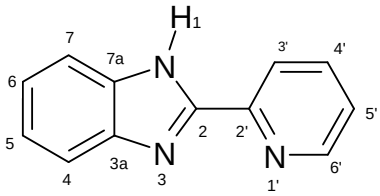
$\delta_H$ ($CDCl_3$, 400 MHz): 6.57 (1H, m, **H-4'**), 7.24 (1H, d, $J_{5',4'}$ = 3.47, **H-5'**), 7.30 (2H, m, $J$ = 3.18, **H-4 & 7**), 7.52 (1H, m, **H-3'**), 7.65 (2H, m, $J$ = 3.15, **H-5 & 6** )

$\delta_C$ ($CDCl_3$, 100 MHz): 110.8 (**C-4'**), 112.5 (**C-3'**), 115.2 (**C-5 & 6**), 123.2 (**C-4 & 7**), 138.4 (**C-2 & 2'**), 143.8 (**C-4 & 7**), 145.3 (**C-3a & 7a)**

IR (neat): $\nu_{max}$ 1597, 731 $cm^{-1}$

HRMS (ESI+); Found $[M+H]^+$, 185.0713; $C_{11}H_9N_2O$ Calc. Mass, 185.0715

## *2-pyridyl-1H-benzimidazole (46c)*




Procedure A was followed using 2-pyridinecarboxyaldehyde (0.536 g, 5 mmol). The solid residue was washed several times with water then diethyl ether then redissolved in methanol and purified by column chromatography eluting with ethyl acetate/ petroleum ether (9:1); $R_f$ 0.60. The required product was obtained as brown very fine light-brown crystals (0.858 g, 78.7 %), mp 218-219°C (from methanol), (lit. 218 °C)[1] .

$\delta_H$ ($CDCl_3$, 400 MHz): 7.31 (2H, m, **H-5 & 6**), 7.39 (2H, dd, $J_{7,6}$ = 4.73, $J_{7,5}$ = 1.02, **H-7**), 7.39 (1H, dd, $J_{4,5}$ = 6.03, $J_{4,6}$ = 1.15, **H-4**), 7.69 (1H, br.s, **H-1**), 7.88 (2H, td, $J_{4',3'}$ = 7.81, $J_{4',5'}$ =

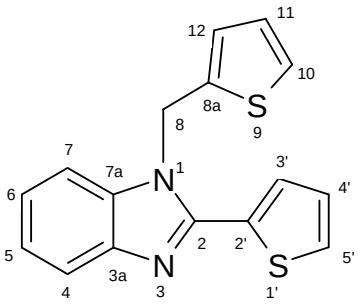
7.81, $J_{4',6'}$ = 1.72, **H-4'& 5'**), 8.47 (1H, dt, $J_{3',4'}$ = 7.81, $J_{3',5'}$ = 1.07, $J_{3',6'}$ = 1.02, **H-3'**), 8.65 (1H, dt, $J_{6',5'}$ = 4.87, $J_{6',4'}$ = 1.72, $J_{6',3'}$ = 1.28, **H-6'**)

$\delta_C$ ($CDCl_3$, 100 MHz): 121.7 (**C-5 & 6**), 123.4 (**C-4 & 7**), 124.6 (**C-5'**), 137.3 (**C-3'**), 148.3 (**C-3a & 7a**) 149.2 (**C-6'**), 150.7 (**C-2 & 2'**)

HRMS (ESI+); Found $[M+H]^+$, 218.0695; $C_{12}H_9N_3$ Na Calc. Mass, 218.0694.

IR (neat): $\nu_{max}$ 3057, 1598, 1318, 1278 $cm^{-1}$

## *Synthesis of 2-thienyl-1-thienylmethyl-1H-benzimidazole (49a)*




Procedure B: A mixture of *o*-phenylenediamine (1.08 g, 10 mmol), 2-thiophenecarboxaldehyde (2.93 g, 20 mmol) and *p*-toluenesulfonic acid (5 mol %) was refluxed in absolute ethanol at 75°C for about 2 hours. The crude product was purified with column chromatography using hexane/ ethyl acetate (7:3), $R_f$ 0.73. The desired product was obtained as light yellowish orange shiny crystals (0.943 g, 64 %); mp 150.5-151.6 °C (from methanol) (lit. 150-152 °C)[2].

$\delta_H$ ($CDCl_3$, 400 MHz): 5.73 (1H, br.s, **H-8**), 6.89 (1H, m, **H-12** ), 6.96 (1H, m, *J* = 4.26, *J* = 4.29, **H-11**), 7.17 (1H, m, *J* = 4.39, 4.46, **H-4'**), 7.26 (1H, dd, $J_{10,11}$ = 4.26, $J_{10,12}$ = 1.08, **H-10**), 7.32 (2H, m, **H-5 & H-6**), 7.39 (1H, dd, $J_{7,6}$ = 5.94, $J_{7,5}$ = 1.98, **H-7**), 7.51 (1H, dd, $J_{3',4'}$ = 3.77, $J_{3',5'}$= 0.94, **H-3'** ), 7.54 (1H, dd, $J_{5',4'}$ = 5.18, $J_{5',3'}$ = 0.94, **H-5'**), 7.85 (1H, dd, $J_{4,5}$ = 6.21, $J_{4,6}$ = 2.18, **H-4**)

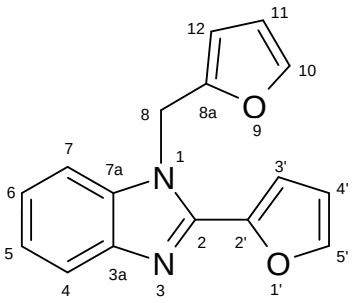
$\delta_C$ ($CDCl_3$, 100 MHz): 44.1 (**C-8**), 109.9 (**C-12**), 119.9 (**C-11**), 123.0 (**C-4'**), 123.4 (**C-10**), 125.5 (**C-5 & 6**), 127.2 (**C-7**), 127.9 (**C-3'**), 128.2 (**C-5'**), 128.9 (**C-4**),131.8 (**C-8a**), 135.9 (**C-2**), 138.8 (**C-2'**), 142.9 (**C-7a**), 147.6 (**C-3a**)

HRMS (ESI+); Found $[M+H]^+$, 319.0340; $C_{16}H_{12}N_2S_2$ Calc. Mass, 319.0340.

IR (neat): $\nu_{max}$ 3077, 1461, 1416,71 $cm^{-1}$

UV: $\lambda_{max}$ 304, 238 nm

### *2-furanyl-1-furanylmethyl-1H-benzimidazole (49b)*




Procedure B was followed using 2-furancarboxaldehyde (1.96 g, 20 mmol). The pure product was obtained as yellowish brown crystals (1.026 g, 62 %); mp 88.4-89.3 °C (from methanol) (lit. 88-89 °C)[1-2] after purification by column chromatography eluting with petroleum ether/ ethyl acetate (50 %), $R_f$ 0.26.

$\delta_H$ ($CDCl_3$, 400 MHz): 5.68 (2H, s, **H-8**), 6.26 (1H, dd, $J_{12,11}$=3.48, $J_{12,10}$ = 0.71, **H-12**), 6.31 (1H, m, $J$ = 2.46, 2.68, 1.42, **H-11**), 6.64 (1H, 4lines, **H-3' & 4'**), 7.32 (2H, m, **H-5 & 6**), 7.35 (1H, m, **H-7**), 7.52 (1H, m, **H-10**), 7.67 (1H, dd, $J_{4,5}$ = 1.83, $J_{4,6}$ = 0.81, **H-4**), 7.81 (1H, m, **H-5'**)

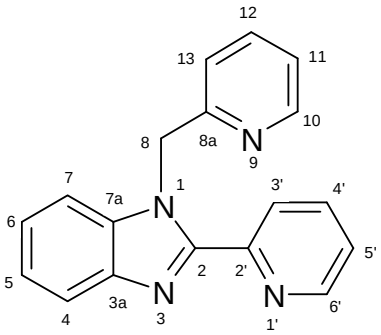
$\delta_C$ ($CDCl_3$, 100 MHz): 41.7 (**C-8**), 108.4 (**C-12**), 110.0 (**C-11**), 110.5 (**C-3' & 4'**), 112.1 (**C-5 & 6**), 113.1 (**C-8a**), 119.8 (**C-7**), 123.2 (**C-10**), 135.4 (**C-2 & 2'**), 142.7 (**C-4**), 144.0 (**C-5'**), 149.6 (**C-3a &7a**)

HRMS (ESI+); Found $[M+H]^+$, 287.0797; $C_{16}H_{12}N_2O_2Na$ Calc. Mass, 287.0796.

IR (neat): $\nu_{max}$ 3139, 1389, 750 $cm^{-1}$

UV: $\lambda_{max}$ 307, 245, 204 nm

### *2-pyridyl-1-pyridylmethyl-1H- benzimidazole (49c)*




Procedure B was followed using 2-pyridinecarboxyaldehyde (2.14 g, 20 mmol). The mixture was extracted with dichloromethane and the organic extract combined. This was dried over anhydrous magnesium sulphate and the solvent evaporated *in vacuo*. The crude product was obtained as dark- brown sticky crystals. This was purified with 20 x 20 cm thin layer chromatography plates using ethyl acetate/ethyl amine (9:1) as an eluting solvent. The desired product was obtained as yellow sticky crystals (0.012 g, 60 %), $R_f$ 0.54; mp 127-129.8 °C (from ethyl acetate), (lit. 123-128 °C)[2].

$\delta_H$ ($CDCl_3$, 400 MHz): 6.31 (2H, s, **H-8**), 6.93 (1H, d, $J_{13,12}$ = 7.74, **H-13**), 7.16 (1H, m, **H-11**), 7.32 (3H, m, **H-5'**, **5** & **6**), 7.39 (1H, d, $J_{7,6}$ = 7.73, **H-7**), 7.51 (1H, td, $J_{12,13}$ = 7.74, $J_{12,11}$ = 7.74, $J_{11,13}$ = 1.89, **H-12**) , 7.86 (1H, td, $J_{4',5'}$ = 7.80, $J_{4',3'}$= 7.80, $J_{4',6'}$ = 1.73, **H-4'**), 7.89 (1H, dd, $J_{4,5}$ = 7.10, $J_{4,6}$ = 1.55, **H-4**), 8.51 (1H, dt, $J_{3',4,}$ = 7.81, $J_{3',5'}$,1.00, $J_{3',6'}$ = 1.00, **H-3'**), 8.59 (2H, m, **H-10** & **H-6'**)

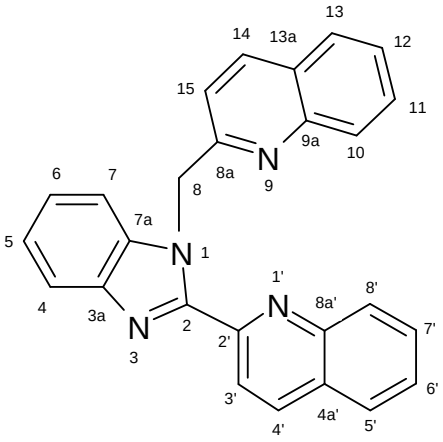
$\delta_C$ ($CDCl_3$, 100 MHz): 51.1 (**C-8**), 110.8 (**C-13**), 120.1 (**C-11**), 120.9 (**C-6**), 122.3 (**C-5**), 123.0 (**C-5'**), 123.8 (**C-7**), 123.9 (**C-12**), 124.7 (**C-4'**), 136.79 (**C-7a**), 136.84 (**C-4** & **3'**), 142.6 (**C-8a**), 148.7 (**C-10**), 149.2 (**C-6'**), 149.8 (**C-3a**), 150.3 (**C-2**), 157.4 (**C-2'**)

HRMS (ESI+); Found $[M+H]^+$, 287.1297; $C_{18}H_{15}N_4$ Calc. Mass, 287.1297.

IR (neat): $\nu_{max}$ 3058.3, 1586.0, 1442.4, 737.0 $cm^{-1}$

UV: $\lambda_{max}$ 306, 204 nm

### *2-quinolyl-1-quinolylmethyl-1H-benzimidazole (49d)*



Procedure B was followed using 2-quinolinecarboxaldehyde (3.14 g, 20 mmol) instead of 2-pyridinecarboxaldehyde. The product was obtained as brown fine crystals (2.78 g, 72 %); mp 171.3-174.7°C (from methanol) after purification with column chromatography eluting with ethyl acetate/ ethylamine (9:1); $R_f$ 0.77.

$\delta_H$ ($CDCl_3$, 400 MHz): 6.68 (2H, s, **H-8**), 7.24 (1H, d, $J$ = 8.52, **H-14**), 7.33 (1H, td, $J_{12,13}$ = 7.41, $J_{12,11}$ = 7.41, $J_{12,10}$ = 1.02, **H-12**), 7.36 (1H, td, $J_{6,7}$ = 7.41, $J_{6,5}$ = 7.41, $J_{6,4}$ = 1.02, **H-6**), 7.50 (1H, m, $J_{13,12}$ = 7.41, **H-13**), 7.54 (2H, m, $J$ = 7.46, 1.36, **H-6' & 7'**), 7.63 (1H, td, $J_{11,12}$ = 7.62, $J_{11,10}$ = 7.62, $J_{11,13}$ = 1.53, **H-11** ), 7.77 (1H, d, $J_{5',6'}$ = 7.78, **H-5'**), 7.78 (1H, td, $J_{5,4}$ = 8.56, $J_{5,6}$ = 8.56, $J_{5,7}$ = 1.56, **H-5**), 7.85 (2H, dd, $J_{8',7'}$ = 8.56, $J_{8',6'}$ = 1.04, **H-8' & 10**), 7.95 (1H, d, $J_{7,6}$ = 7.51, **H-7**), 7.99 (1H, d, $J_{15,14}$ = 8.51, **H-15**), 8.18 (1H, d, $J_{4,5}$ = 8.55, **H-4**), 8.33 (1H, d, $J_{4',3'}$ = 8.34, **H-4'**), 8.68 (1H, d, $J_{3',4'}$ = 8.34, **H-3'**)

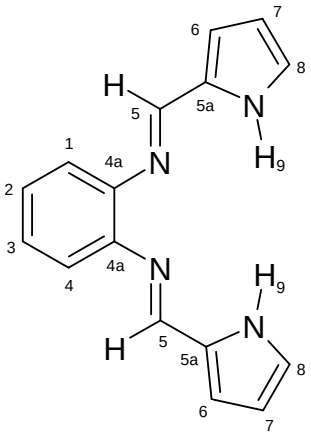
$\delta_C$ ($CDCl_3$, 100 MHz): 52.3 (**C-8**), 110.9 (**C-13**), 119.0 (**C-14**), 120.3 (**C-7**), 121.7 (**C-3'**), 123.2 (**C-6**), 124.2 (**C-12**), 126.4 (**C-6'**), 127.3 (**C-7'**), 127.5 (**C-5' & 5**), 127.6 ( **C-8'**), 128.9 (**C-4**), 129.6 (**C-10**), 129.7 (**11**), 136.8 (**C-4'**), 137.1 (**C-15**), 137.3 (**C-13a**), 147.1 (**C-4a'**), 147.6 (**C-7a**), 149.7 (**C-3a**), 150.0 (**C-2 & 2'**), 158.1 (**C-8a' & 9a**)

HRMS (ESI+); Found $[M+H]^+$, 387.1608; $C_{26}H_{19}N_4$ Calc. Mass, 387.1610.

IR (neat): $\nu_{max}$ 3053, 2994, 2956, 1329, 739 $cm^{-1}$

UV: $\lambda_{max}$ 332, 316, 303, 283 nm

## *N, N'- Bis (2-pyrrolylmethylidene)-1, 2-phenylenediamine (48a)*




Procedure B was followed using 2-pyrollecarboxyaldehyde (0.095 g, 1 mmol) and *o*-phenyldiamine (0.0541 g, 0.5 mmol). The product was obtained as light yellowish orange very fine crystals (0.100 g, 76 %), mp 191.4- 197.3 ℃ (from methanol), (lit. 172 ℃) [3]; $R_f$ 0.69 in hexane/ ethyl acetate (7: 3).

$\delta_H$ ($CDCl_3$, 400 MHz): 6.06 (2H, td, $J_{7,6}$ = 3.00, $J_{7,8}$= 3.00, $J$ = 0.90, **H-7**), 6.32 (2H, br.s, **H-6**), 6.45 (2H, dd, $J_{8,7}$ = 3.74, $J_{8,6}$= 1.17, **H-8**), 7.11 (2H, 4 lines, $J$ = 4.55, 4.55, **H-2 & 3**), 7.27 (2H, 4 lines, $J$ = 4.56, 4.63, **H-1 & 4**), 7.76 (2H, s, **H-5**)

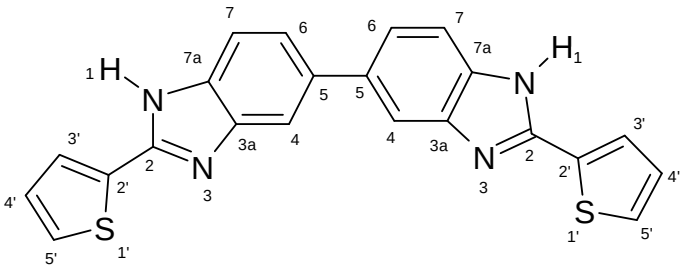
$\delta_C$ ($CDCl_3$, 100 MHz): 109.7 (**C-7**), 117.3 (**C-6**), 118.9 (**C-8**), 123.9 (**C-2 & C-3**), 126.6 (**C-1 & C-4**), 130.9 (**C-4a**), 145.6 (**C-5a**), 150.5 (**C-5**)

LRMS (ESI+); Found $[M+H]^+$, 263.1409; $C_{16}H_{14}N_4$ Calc. Mass, 262.312.

IR (neat): $\nu_{max}$ 3077, 1334, 1302, 737 $cm^{-1}$

# 6.3 Experimental for Chapter 4

## *Synthesis of 2, 2'-di-2-thienyl-5, 5-Bi-1H-benzimidazole (52)*



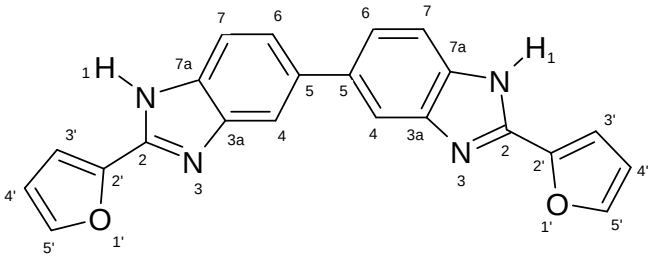
Procedure A: A mixture of 3, 3'diaminobenzidine (0.5 mmol, 0.107 g) and 2-thiophenecarboxaldehyde (0.0981 g, 1 mmol) was stirred in methanol (5 ml) at room temperature overnight. The completion of the reaction was monitored by thin layer chromatography and the mixture was extracted with dichloromethane. The crude product was purified by column chromatography using ethyl acetate/ dichloromethane (50%). The product was obtained as light brown sticky solid (0.259 g, 65 %); mp 188.7-193.5 °C.

$\delta_H$ (MeOD, 400 MHz): 6.85 (1H, d, $J_{3',4'}$ = 8.82, **H-3'**), 7.24 (1H, t, $J_{4',3'}$ = 4.27, $J_{4',5'}$ = 4.27, **H-4'**), 7.38 (1H, d, J5',4'= 8.82, **H-5'**), 7.61 (1H, dd, $J_{6,7}$ = 8.29, $J_{6,4}$ = 1.76, **H-6**), 7.65 (2H, m, **H-7 & 1**), 7.82 (2H, m, **H-4**)

$\delta_C$ (MeOD, 100 MHz): 115.5 (**C-3'**), 122.9 (**C-4'**), 127.8 (**C-5'**), 128.3 (**C-6**), 131.8 (**C-7**), 132.5 (**C-5**), 137.2 (**C-3a & 7a**), 148.0 (**C-2 & 2'**).

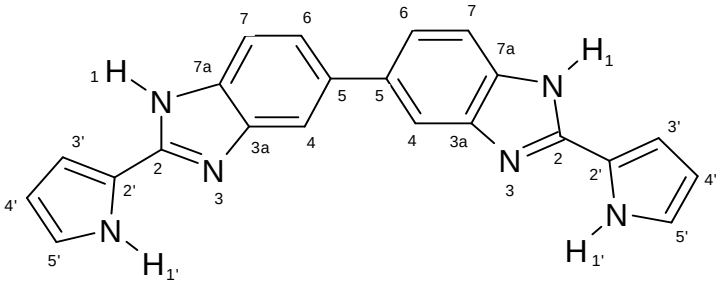
HRMS (ESI+); Found $[M+H]^+$, 399.0735; $C_{22}H_{15}N_4S_2$ Calc. Mass, 399.0738.

### *Attempted synthesis of 2, 2'-di-2-furanyl-5, 5-Bi-1H-benzimidazole (52a)*



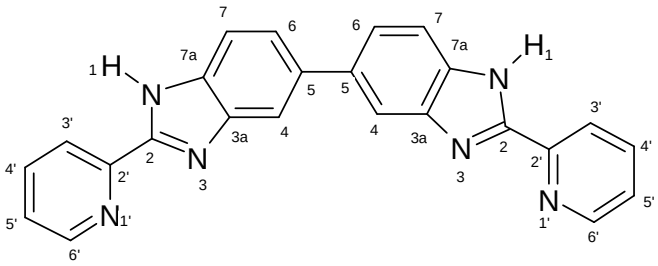
Procedure A was followed using 2-furancarboxaldehyde (1 mmol, 0.0981 g). A light brown sticky solid was obtained, purified by column chromatography using ethyl acetate/ petroleum ether (8:2) and submitted for analysis

### *Attempted synthesis of 2, 2-di-2-pyrollyl-5, 5'-Bi-1H-benzimidazole (52b)*



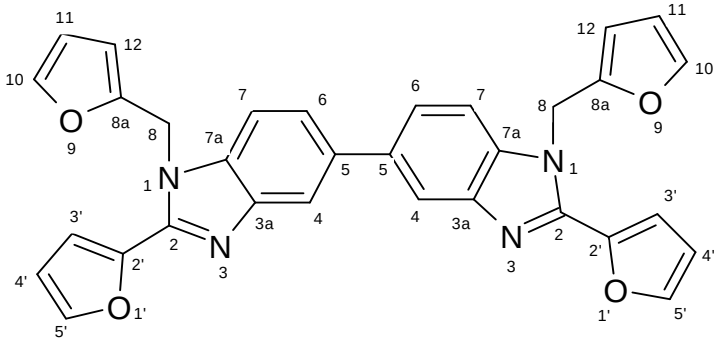
Procedure A was followed using 2-pyrollecarboxaldehyde (1 mmol, 0.0981 g). A reddish brown solid was obtained, purified by column chromatography using ethyl acetate/ dichloromethane (50 %) and submitted for analysis.

### *Attempted synthesis of 2, 2'-di-2-pyridyl-5, 5-Bi-1H-benzimidazole (52c)*



Procedure A was followed using 2-pyridinecarboxaldehyde (1 mmol, 0.107 g). A light brown sticky solid was obtained, purified by column chromatography using ethyl acetate/ dichloromethane (1:1) and submitted for analysis.

### *Synthesis of 1, 2- di- 2-furanylmethyl-2, 2- di- 2-furanyl benzimidazole (53)*



Procedure B: A mixture of 3, 3'diaminobenzidine (0.5 mmol, 0.107 g) and 2-furancarboxaldehyde (2 mmol, 0.196 g) and *p*-toluenesulfonic acid (5 mmol %) was stirred in methanol (5 ml) at room temperature overnight. The completion of the reaction was monitored by thin layer chromatography and the mixture extracted with dichloromethane. The desired product precipitated out of the stirring mixture as dark brown powdery crystals. Further purification of this on column chromatography using ethyl acetate/ dichloromethane (50 %) afforded the pure product as light-brown microcrystalline solid (0.14 g, 53 %), mp 194.3-198.6 °C, $R_f$ 0.31 .

$\delta_H$ (acetone, 400 MHz): 5.87 (2H, s, **H-8**), 6.39 (1H, 4 lines, $J_{10,\,9}$ = 2.27, $J_{10,\,11}$ = 2.73, **H-11**), 6.49 (1H, dd, $J_{11,\,10}$ = 2.93, $J_{11,\,9}$ = 0.48, **H-12**), 6.76 (1H, 4 lines, $J_{4',\,5'}$ = 2.51, $J_{4',\,3'}$ = 2.74, **H-**

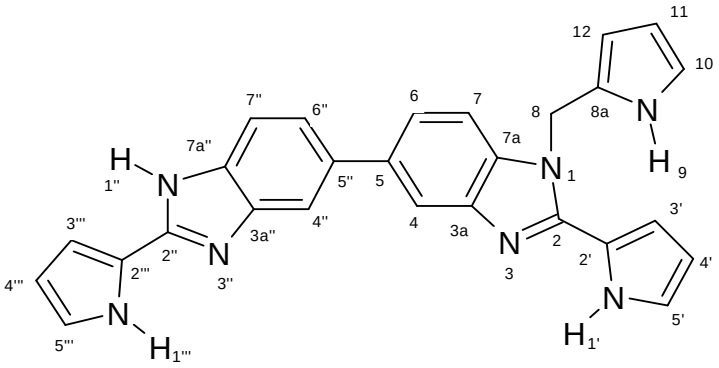
**4'**), 7.28 (1H, dd, $J_{3',4'}$ = 3.24, $J_{3',5'}$ = 0.70, **H-3'**), 7.48 (1H, m, **H-10**), 7.68 (1H, dd, $J_{5,6}$ = 8.49, $J_{5,4}$ = 1.75, **H-6**), 7.79 (1H, d, $J_{6,5}$ = 8.49, **H-7**), 7.92 (1H, m, **H-5'**), 7.96 (1H, d, $J_{4,5}$ = 1.74, **H-4**)

$\delta_C$ (acetone, 100 MHz): 41.3 (**C-8**), 108.5 (**C-11**), 110.5 (**C-12**), 110.8 (**C-4'**), 111.9 (**C-3'**), 112.8 (**C-10**), 117.7 (**C-6**), 122.9 (**C-7**), 135.1 (**C-8a**), 136.8 (**C-3a**), 142.9 ( **C-5'**), 143.95 (**C-7a**), 144.4 (**C-5**), 144.5 (**C-4**), 145.9 (**C-2**), 150.3 (**C-2'**)

IR (neat): $\nu_{max}$ 3101, 2931, 1655, 1422, 750 $cm^{-1}$

HRMS (ESI+); Found $[M+H]^+$, 527.1716; $C_{32}H_{23}N_4O_4$ Calc. Mass, 527.1719.

## *Synthesis of 1-pyrrolylmethyl-2, 2- di- 2-pyrrolyl benzimidazole (54)*




Procedure B was followed using 2-pyrollecarboxyaldehyde (2 mmol, 0.192 g). The crude product was purified by column chromatography using ethyl acetate/ dichloromethane (50 %) as an eluting solvent. The titled compound was obtained as reddish brown very fine crystals (0.214 g, 85 %), mp 200.5- 206.3°C, $R_f$ 0.65.

$\delta_H$ (MeOD, 400 MHz): 5.64 (2H, m, **H-8**), 5.92 (1H, m, **H-12**), 6.05 (1H, m, **H-11**), 6.33 (2H, m, **H-3''' & 4'''**), 6.73 (2H, m, **H-10, & 5'''**), 6.92 (1H, m, **H-4'**), 7.09 (2H, m, **H-3' & 5'**), 7.24 (1H, dd, $J_{6'',7''}$ = 8.16, $J_{6'',4''}$ = 0.75 **H-6''**), 7.44 (1H, dd, $J_{6,7}$ = 8.20, $J_{6,4}$ = 3.69, **H-6**), 7.49- 7.61 (3H, m, **H-7, 7'', 1' & 1'''**), 7.67- 7.78 (2H, m, **H-4'' & 9**), 7.88 (1H, m, $J_{4,6}$= 3.68 , **H-4**)

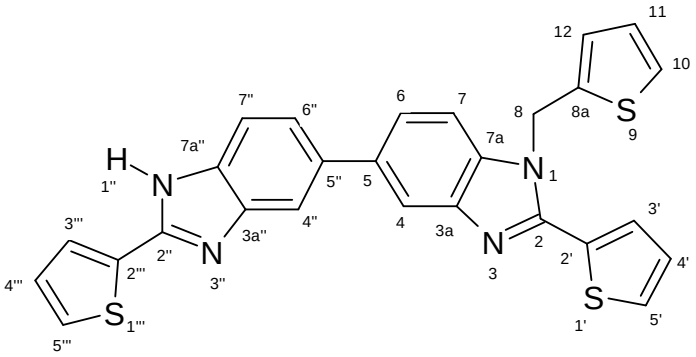
$\delta_C$ (MeOD, 100 MHz): 42.1 (**C-8**), 106.4 (**C-12**), 107.7 (**C-11**), 109.3 (**3''' & 4'''**), 109.7 (**C-10**), 110.3 (**C-5'''**), 111.1 (**C-4'**), 115.9 (**C-3'**), 117.7 (**C-5'**), 120.1 **(C-8a)**, 121.4 (**C-6'' & 6**),

**121.8 (C-3a'', 3a, 7a'' & 7a)**, 121.9 (**C-7**), 122.2 (**C-7''**), 125.6 (**C-4''**), 125.9 (**C-5 & 5''**), 128.4 (**C-4**), 142.7 (**C-2'' & 2'''**), 147.5 (**C-2 & 2'**)

IR (neat): $\nu_{max}$ 3064, 1599, 1398, 724 $cm^{-1}$

HRMS (ESI+); Found $[M+H]^+$, 444.1936; $C_{27}H_{22}N_7$ Calc. Mass, 444.1937.

## *Synthesis of 1-thienylmethyl-2, 2'- di- 2-thienyl benzimidazole (55)*




Procedure B was followed using 2-thiophencarboxaldehyde (2 mmol, 0.293 g). The completion of the reaction was monitored by thin layer chromatography and the mixture extracted with dichloromethane. The crude product was purified by column chromatography using 50% ethyl acetate/ dichloromethane (50%). The product was obtained as light brown sticky solid (0.030 g, 11.6 %), mp 145.5-147.0 °C, $R_f$ 0.79.

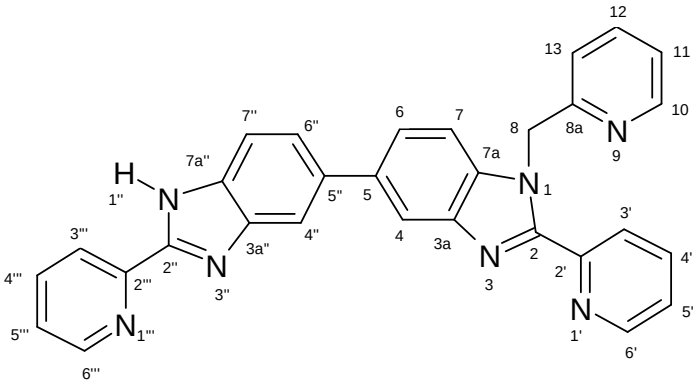
$\delta_H$ ($CDCl_3$, 400 MHz): 5.78 (2H, s, **H-8**), 5.79 (1H, s, **H-12**), 6.93-7.02 (4H, m, **H-11, 4''', 4', 3'''**), 7.19 (2H, m, **H-6''**), 7.29 (1H, m, **H-10**), 7.47 (1H, m, *J* = 7.28, 2.45, **H-5'''**), 7.56- 7.66 (6H, m, **H-6, 7, 4'', 7'', 1'', 3'**), 7.91 (1H, m, *J* = 7.55, 2.60, **H-5'**), 8.11 (1H, m, **H-4**)

$\delta_C$ ($CDCl_3$, 100 MHz): 44.3 (**C-8**), 108.6 (**C-12**), 110.2 (**C-11**), 118.1 (**C-4'''**), 118.4 (**C-4'**), 119.8 (**C-3'''**), 119.9 (**C-6''**), 123.0 (**C-10**), 123.3 (**C-5'''**), 123.6 (**C-7''**), 125.6 (**C-6**), 126.9 (**C-7**), 127.3 (**C-4''**), 128.2 (C-**3' & 5'**), 129.4 (C-**4**), 133.1 (**C-8a**), 135.2 (**C-3a''**), 136.5 (**C-7a''**), 137.0 (**C-3a**), 137.2 (**C-7a**), 137.5 (**C-5**), 138.7 (**C-5''**), 142.3 (**C-2''**), 143.3 (**C-2'''**), 143.6 (**C-2**), 148.0 (**C-2'**)

IR (neat): $\nu_{max}$ 3095, 2925, 1605, 1360, 724 $cm^{-1}$

HRMS (ESI+); Found $[M+H]^+$, 517.0596; $C_{27}H_{18}N_4S_3Na$ Calc. Mass, 517.0591.

### *Synthesis of 1-pyridylmethyl-2, 2- di- 2-pyridylbenzimidazole (56)*



Procedure B was followed using 2-pyridinecarboxyaldehyde (2 mmol, 0.214 g). The crude product was purified by column chromatography using ethyl acetate/ dichloromethane (50 %) as an eluting solvent. The titled compound was obtained as brown wet solid (0.024 g, 10 %), $R_f$ 0.46.

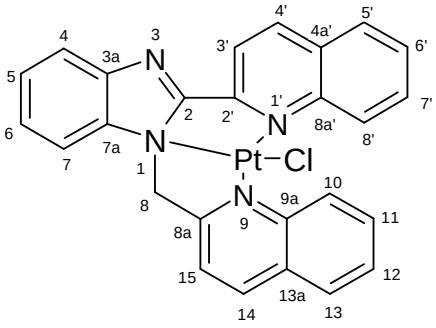
$\delta_H$ (MeOD, 400 MHz): 6.27 (2H, m, **H-8 & 13**), 7.05 (1H, m, **H-12**), 7.24 (2H, m, **H-4''' & 7''**), 7.40-7.74 (6H, m, **H-11, 5''', 3''', 3', 4', 5'**), 7.83 (1H, m, **H-10**), 7.96-8.05 (2H, m, **H-6'' & 4''**), 8.29 (2H, m, **H-6 & 7**), 8.36-8.50 (2H, m, **H-6''' & 6'**), 8.55 (1H, m, **H-4**), 9.44 (1H, br.s, **H-1''**)

$\delta_C$ (MeOD, 100 MHz): 50.0 (**C-8**), 109.1 (**C-13, 12, 4''' & 7''**), 110.9 (**C-11**), 117.3 (**C-3''' & 5'''**), **119.2 (C-4')**, 121.1 (**C-5'**), 121.2 (**C-3'**), 121.3 (**C-10**), 122.5 (**C-6''**), 123.7 (**C-4''**), 123.8 (**C-6**), 124.3 (**C-7**), 137.1 (**C-6'''**), 137.4 (**C-6'**), 137.7 (**C-8a**), 137.9 (**C-3a''**), 141.2 (**C-7a''**), 141.3 (**C-3a**), 142.4 (**C-7a**), 142.5 (**C-5''**), 148.8 (**C-4**), 149.5 (**C-5**), 156.9 (**C-2'' & 2'''**), 169.5 (**C-2**), 180.5 (**C-2'**)

HRMS (ESI+); Found $[M+H]^+$, 480.1940; $C_{30}H_{22}N_7$ Calc. Mass, 480.1937.

# 6.4 Experimental for Chapter 5

## *Synthesis of 2-quinolyl-1-quinolylethyl-1H-benzimidazole Pt (II) complex (60)*




A solution of $[Pt(PhCN)_2Cl_2]$ (0.050g, 0.1063 mmol) in acetonitrile was treated with $AgSbF_6$ (0.0365g, 0.1063 mmol). The mixture was heated to reflux for about 24 hours at 65 °C under nitrogen. The formed white precipitate was filtered under vacuum resulting into a clear yellow solution. 1-(2-quinolylmethyl)-2-(2-quinolyl) benzimidazole (0.0396 g, 0.1063 mmol) was then added to the solution. The mixture was further stirred at 65 °C for 24 hours under nitrogen. The resulting yellow solution was extracted with dichloromethane, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The crude product was obtained as a grayish- brown solid. This was purified by column chromatography using ethyl acetate/ dichloromethane (50 %) as an eluting solvent. The titled compound was obtained as yellowish brown sticky solid (0.054 g, 82 %), $R_f$ 0.872.

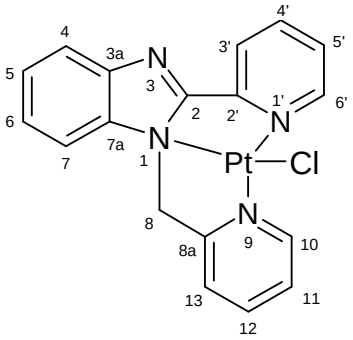
$\delta_H$ (DMF, 400 MHz): 6.89 (2H, s, **H-8**), 7.54 (2H, m, **H-14, 13**), 7.70 (2H, m, **H-12, 6**), 7.81 (1H, td, *J* = 7.27, 1.29, **H-6'**), 7.86-7.99 (3H, m, **H-7', 11, 5'** ), 8.02-8.10 (3H, m, **H-8', 10, 5**), 8.14 (1H, d, J = 8.41, **H-15**), 8.52 (1H, m, **H-4**), 8.77 (1H, d, *J* = 8.69, **H-3'**)

$\delta_C$ (DMF, 100 MHz): 51.6 (**C-8**), 111.3 (**C-14**), 119.5 (**C-13**), 120.1 (**C-12**), 121.5 (**C-6**), 121.7 (**C-6'**), 122.8 (**C-7'**), 123.9 (**C-11**), 126.3 (**C-5'**), 127.6 (**C-8'**), 127.9 (**C-10**), 128.0 (**C-5**), 128.8 (**C-15**), 129.2 (**C-4**), 129.4 (**C-3'**), 137.9 (**C-13a**), 140.9 (**C-4a'**), 143.0 (**C-7a**), 147.0 (**C-3a**), 147.6 (**C-2**), 149.8 (**C-2'**), 150.6 (**C-8a**), 158.4 (**C-9a**)

$\delta_{Pt}$ (DMF, 107 MHz): -2406.9 (s)

UV: $\lambda_{max}$ 372, 302, 281 nm

### *Synthesis of 2-Pyridyl-1-pyridylmethyl-1H-benzimidazole Pt (II) complex (63)*




An aqueous solution of Potassium tetrachloroplatinate (II) (0.0830 g, 0.20 mmol) was treated with a solution of 1-(2-Pyridylmethyl)-2-(2-pyridyl) benzimidazole (0.0573 g, 0.20 mmol) in methanol. The mixture was stirred at 65 °C for 48 hours. The resulting yellow solution was extracted with dichloromethane, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The titled compound was obtained as a yellow sticky solid (0.077 g, 74 %), $R_f$ 0.44 in ethyl acetate/ dichloromethane (50 %).

$\delta_H$ (DMF, 400 MHz): 6.41 (2H, s, **H-8**), 7.18 (1H, d, $J_{13,12}$ = 7.74, **H-13**), 7.24 (1H, m, **H-11**), 7.32 (2H, m, **H- 4 & 7**), 7.51 (1H, ddd, $J_{5',4'}$ = 7.47, $J_{5',6'}$= 7.57, $J_{5',3'}$ = 1.23, **H-5'**), 7.64 (1H, m, **H-6**), 7.71 (1H, td, $J_{12,10}$ = 7.74, $J_{12,13}$ = 7.74, $J_{12,10}$ = 1.76, **H-12**), 7.82 (1H, m, **H-5**), 8.05 (1H, td, *J* = 7.49, 1.78, **H-4'**), 8.47 (1H, m, **H-10**), 8.51 (1H, dt, $J_{3',4'}$ = 7.78, $J_{3',5'}$ = 1.00, $J_{3',6'}$ = 1.00, **H-3'**), 8.68 (1H, m, **H-6'**)

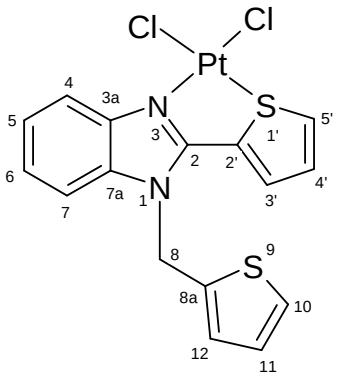
$\delta_C$ (DMF, 100 MHz): 50.4 (**C-8**), 111.3 (**C-6**), 119.8 (**C-5**), 121.3 (**C-13**), 122.5 (**C-11**), 122.6 (**C-4**), 123.5 (**C-7**), 124.3 (**C-5'**), 124.4 (**C-3'**), 136.9 (**C-12**), 137,4 (**C-4'**) 142.9 (**C-8a**), 148.8 (**C-6'**), 149.3 (**C-10**), 149.9 (**C-3a** ), 150.8 (**C-7a**), 157.5 (**C-2 & 2'** )

$\delta_{Pt}$ (DMF, 107 MHz): -2458.3 (s)

IR (neat): $\nu_{max}$ 3056, 1594, 756 $cm^{-1}$

UV: $\lambda_{max}$ 352, 306, 203 nm

### *Synthesis of 2-thienyl-1-thienylmethyl-1H-benzimidazole Pt (II) complex (64)*




An aqueous solution of Potassium tetrachloroplatinate (II) (0.0830 g, 0.20 mmol) was treated with a solution of 1-(2-thienylmethyl)-2-(2-thienyl) benzimidazole (0.0413 g, 0.20 mmol) in methanol. The mixture was stirred at 65 °C for 48 hours. The resulting yellow solution was extracted with dichloromethane, dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The titled compound was obtained as a brown sticky solid (0.0737 g, 63 %), $R_f$ 0.44 in ethyl acetate/ dichloromethane (50 %).

$\delta_H$ (DMF, 400 MHz): 6.25 (2H, s, **H-8**), 8.20 (1H, m, **H-12**), 8.22 (1H, m, **H-11**), 8.31 (1H, dd, $J_{3',4'}$ = 3.78, $J_{3',5'}$ = 1.25, **H-3'**), 8.34 (1H, dd, $J_{10,11}$ = 3.53, $J_{10,12}$ = 1.18, **H-10**), 8.39 (2H, m, **H-5 & 6** ), 8.43 (2H, m, **H-4' & 5'**), 8.49 (1H, dd, $J_{7,6}$ = 5.06, $J_{7,5}$-1.27, **H-7**), 8.54 (1H, dd, $J_{4,5}$=5.18, $J_{4,6}$=1.01, **H-4**)

$\delta_{Pt}$ (DMF, 107 MHz): -2322 (s)

UV: $\lambda_{max}$ 219.0 nm

## 6.5 References

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