UNIVERSITY OF KWAZULU-NATAL

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Synthesis of Novel Imidazo[1.5-a]pyridyl Compounds

Submitted in fulfillment of the requirements

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By

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THESIS DECLARATION

I hereby certify that this research is as a result of my own investigation, which has not already been accepted in substance for any degree and is not submitted in candidature for any other degree.

Signed…….

Vuyisa Mzozoyana

I hereby certify that this statement is correct.

Signed……..

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ABBREVIATIONS

NH_3	Ammonia
$Bi(OTf)_3$	Bismuth triflate
$CuCl_2$	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
td	Triplet of doublets
tt	triplet of triplet
m	multiplets
s	singlet
EtOAc	Ethyl acetate
Hz	Hertz
HIV	Human immunodeficiency virus
HCl	hydrochloric acid

I_2	Iodine
LCMS	Liquid-Chromatography Coupled Mass Spectroscopy
LiCl	Lithium chloride
IR	Infra-red Spectroscopy
o-PD	*o*-phenylenediamine
$MgSO_4$	Magnesium sulphate
br.m	Broad multiplets
NMR	Nuclear Magnetic resonance
RNA	Ribonucleic acid
br.s	Broad singlet
NaCl	Sodium chloride
TLC	Thin- Layer Chromatography
PE	Petroleum Ether
PPA	Polyphosphoric acid
PPMA	Phosphorus pentoxide/ methanesulfonic acid
p-TsOH	p-Toluenesulfonic acid
UV/vis	Ultra-violet/visible
WHO	World Health Organisation
NHC	N-heterocyclic carbene

ABSTRACT

Imidazo[1,5-a]pyridines are an important and versatile class of *N*-heterocyclic compounds due to their stability, unique biological, and photochemical properties. Due to the conjugation and charged structure, their properties are extended to conducting electricity and also have electronic properties. They can be used for chelating transition metals especially heavy metals that can be harmful to living things (including human).

The aim of this research was to develop more useful imidazo[1,5-a]pyridines which are stable in both free and complexed state. A variety of imidazo[1,5-a]pyridyl compounds was synthesized following three useful methods namely (i) The first route includes the isolation of imine intermediates which were then treated with phosphorus oxychloride in one case and hydrochloric acid in another case as catalysts. Both cases resulted in the yield of the same imidazo[1,5-a]pyridyl compounds. (ii) The second route was the development on the first route for those imine intermediates that could not be isolated and only hydrochloric acid catalyst was used. In both the first and second routes, paraformaldehyde was used for the ring-closure step of the reaction. The last route for the formation of imidazo[1,5-a]pyridyl compounds did not involve the use of the paraformaldehyde reagent. The suitable routes were followed depending on the nature of the targeted products and the reaction yields were moderate to excellent.

CHAPTER 1 INTRODUCTION

1.1. Definition of microbes as problematic organisms

Microbial organisms may be problematic or lead to a huge damage to human beings, either directly or indirectly. The term direct, is referred to the situation whereby a human being is affected by micro-organisms causing sickness or disorder. The indirect infection refers to a scenario whereby humans are not affected directly. For instance, the situation where micro-organisms affect living or non-living things that are essential for sustainance of life. For example, micro-organisms can affect our live stock like cattle and crops that we grow. Micro-organisms are very small in a way that some can not be seen with naked eyes, that makes them more problematic. Therefore, it is very important for scientists to do more research about controlling these problematic micro-organisms.

Antibiotics can be classified in four ways:

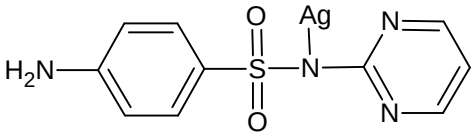
- Based on their chemical structure and their biosynthetic pathway.
- According to the class of antibiotic producing organism.
- Based on the manner in which they target pathogens.
- Lastly, according to their mode of action towards to their target.

In this research, however, antibiotics are classified on the bases of their chemical structure as well as their mode of action.

1.2. Silver nitrate as solution to microbial damages

Silver nitrate has been a solution to this problem; it has been used as an antimicrobial agent back in 17th century. In 1880, Crede, reported the usage of prophylactic 2% silver nitrate eye solution which was used as a prevention of an ophthalmia neonatorum in newborn mammals, and the method is still used today. Due to its popularity, silver nitrate ended up being used as a treatment of open wounds, chronic skin ulcers and suppurating wounds in early 1900s.[1] In the

20th century, it was realized that silver nitrate can be irritative which led to the discovery of the usage of colloidal silver solutions. Silver-based antimicrobials lost favor after the second world war following the emergence of penicillin and other new antibiotics.[2] However, some micro-organisms such as *Proteus morgani*, *Proteus mirabilis* and *P. aeruginosa* became resistant to these new emerging antibiotics which resulted in the revival of silver nitrate by Moyer in 1965. As a result, the true revival of silver antimicrobial came following the introduction of silver sulfadiazine (**1.1**) (figure 1.1) by Fox in 1968.



1.1

Figure 1.1: *Structure of silver sulfadiazine*

1.3. Silver complexes as solution to problematic microbes

The closer view of silver sulfadiazine that makes it the most important and effective antibiotic and remains as a widely used topical antibiotic for burn treatment is explained below.[1,2] Kascatan-Nebiglu *et al*[2] explain the usage of silver sulfadiazine as a burn wounds' treatment and that was designed to combine silver with the antibiotic sulfonamide, sulfadizine, in order to attain a wide spectrum antibiotic. In the solid state, sulfadiazine is a polymeric water soluble complex. Silver sulfadiazine is commercially available as a water soluble cream, Silvadene cream 1%, and has also been proven to be active against a number of gram-positive and gram-negative bacteria. It remains one of the most effective, widely used antimicrobial for topical burn infections.

1.3.1. Mode of action of silver complexes

Silver is considered as an effective antibiotic against a broad range of gram-positive and gram-negative bacteria, yeast and fungi. Silver metal is inactive on its own but in the presence of

moisture, silver cations (Ag^+) are formed which are active against microbes. There are different ways of the mechanism of actions of the silver ions that were suggested by different researchers depending on the study that was done, but is not well understood. The mode of action by silver is still debated as discussed below.

One way that was suggested by Feng and co-workers is that silver cations attack the bacterial cell wall and cause a significant change on their morphology, the studies were observed on transmission electron microscope (TEM) and X-ray microanalysis. They further described that silver cations attack cytoplasmic membrane with condensed DNA, thus stops condensed DNA from replicating and this results in the cytoplasmic membrane detachment from the cell wall due to its shrinkage.

Another proposed mechanism is that silver cations bind to the surface of bacteria cell and interfere with proteins and enzymes that are responsible for cell wall synthesis. On the same hand, silver cations also affect respiratory electron transport chain and thus depriving the cell of the energy currency, ATP. It also affects the metabolism, RNA, DNA as well as subcellular organelle structure leading to cell death.

The mechanism of silver complexes is that, silver cations are released slowly. It was discovered that, even though silver sulfadiazine and silver nitrate have been observed to kill bacteria quickly but their effectiveness does not last for long time, leading to the reinfection of the wounds. Furthermore, the problem continues since other microbes are known to be resistant to silver. In order to overcome this problem, NHC ligands with strong binding to silver need to be synthesized and thus release the silver even more slowly, thus increasing its bioavailability. Hopefully, this research meets all these requirements, that is, our ligands bind strongly to silver, thus form more stable complex.

1.4. Uses of quaternary ammonium compounds

Silver complexes were not the only chemical compounds that were or are still used for treating microbial infections. There were other chemical treatments which will be covered in the next

chapter, however, in this research we will restrict our discussion to quaternary ammonium compounds (QAC). They are commercially available, mainly as environmental disinfectants and in hospitals as medicinal equipment disinfectants.[3]

1.4.1. Historical background of quaternary ammonium compounds

The discovery of the first QAC known as Zephird (disinfectant) was by Domagk in 1938. In 1926 Browning *et al* explained the activity of heterocyclic QACs derivatives towards bacteria and fungi. Preston in 1983, pointed the efficiency of dialkyl QACs with the effect of the structural features, and hence QACs with 22-24 carbon atoms were expected to be highly active. In 1996, Pernak reported the quantitative analysis for quaternary alkylthiomethylimidazolium chlorides, that is the relationship between critical micellar concentration (CMC) and minimum inhibitory concentration (MIC) against bacteria and the hydrophobicity index (HI).

1.4.2. Mode of action for quaternary ammonium compounds

Quaternary ammonium compounds are rated as one of the most important and powerful antimicrobials because of their ability to interact with cytoplasmic membrane of bacteria which results in the lost of permeability properties of the membrane. In adequate concentrations, QACs impede with ATP synthetic process and respiration process, and can result in membrane leakage and liberation of the cellular constituents resulting in cell death.[4] Quaternary ammonium compounds antimicrobial are reported to have close related properties to surfactants. The number of carbon atoms in an alkyl chains is crucial. Quaternary ammonium compounds with shorter alkyl chain than certain length will not have strong surfactant properties, and thus, appear as an inactive antimicrobial agent. furthermore, the amphiphilicity of quaternary ammonium compounds may have a great influence on its microbial efficiency.[5] Quaternary ammonium compounds are widely used as antimicrobial

because of wide spectrum of their bioactivity properties and relative safety even on direct applications.[6] Despite all the above mentioned advantages of using quaternary ammonium compounds as antimicrobial, microbes developed resistance against them. Due to the increase in the resistance phenomenon, Demberelnyamba and coworkers proposed new potential antimicrobials: 1-alkyl-3-methylimidazolium halide (**1.2**) and 1-alkyl-3-hydroxyethyl-2-methylimidazolium chloride (**1.3**)[3] which firmly attach to the cell wall, thus improving bioactivity.

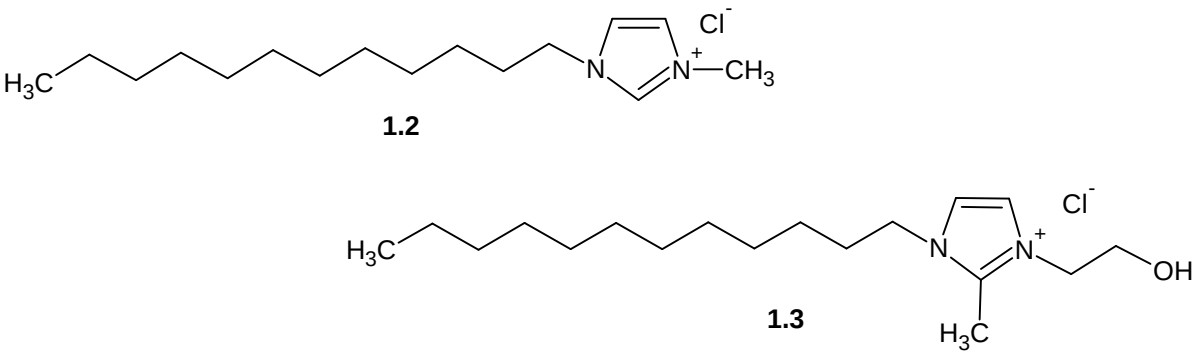
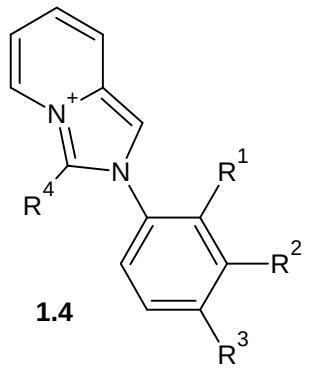


Figure 1.2: *Structures of 1-alkyl-3-methylimidazolium chloride (**1.2**) and 1-alkyl-3-hydroxyethyl-2-methylimidazolium chloride (**1.3**)*

1.5. Research objectives

Commercial antimicrobials are not sufficiently effective against all kinds of micro-organisms since there are bacteria which are reported to be resistant to most antimicrobials. Therefore there is a need to develop a significant variety of new compounds with unique chemical structure in order to defeat this drastic increasing resistance phenomenon. More research has been done, aiming to formulate studies of new active antimicrobial by introducing new molecular parameter such as heteroatoms, aromatics and chemical functions in order to improve the performance of antimicrobial agents. In this research, we propose new and potential antimicrobial agents that are imidazolium structured with aromatic groups substituted on both nitrogen atoms, and one of the nitrogen atoms is quaternary, that is speculated to enhance the antimicrobial activity. By looking at the general structure (**1.4**) in figure 1.3, suggests that the conjugation, quaternary nitrogen and the aromatic group that is substituted to

the quaternary nitrogen would improve the antimicrobial activity. A series of this kind of compounds were synthesized in this research.



1.4

Figure 1.3:*General structure of the series of synthesized imidazolium salts (counter ion is Cl^-)*

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CHAPTER 2 MICROORGANISMS AND ANTIMICROBIALS

2.1. Definition of micro-organisms

Microbes are the main causes of sickness to most of living organisms. This is a global problem and has cost many lives. The term microbe is referred to fungi, bacteria, parasites and viruses which cause infectious diseases. Fisher *et al*[1] defines bacteria and viruses as microorganisms that are diverse and are able to adapt and reproduce in a flush. They can succeed under conditions that we regard as harsh, such as high temperatures and in the absence of oxygen. Ages ago, microbes were not known, until they were known they were untreated. That is when the ongoing antimicrobial research started. Back in 17th century, silver was introduced as an active antimicrobial.[2] Many other antimicrobials were introduced mainly because some microbes tend to be resistant against silver treatments. Lately, new classes of natural antimicrobials such as penicillin were introduced to overcome this resistance phenomenon. The mechanism of antibiotic resistance in bacteria (discussed in the next section) had to be known in order to be overcome.

2.1.1. Mechanism of antibiotic resistance in bacteria

Generally bacteria are frequently referred to as being resistant to antibiotics, but the biochemical meaning of resistance is rarely considered. Even the bacteria that are referred to to be the most resistant ones can be killed by sufficiently high concentration of antibiotics.[3] However, highly concentrated antibiotics can not be used because it may have exceeded the level that human body can take. For example, most strains of *Streptococcus pneumonia* are inhibited by the minimum concentration of 0.01 mg/l of benzylpenicillin of which the body can manage, whereas, for *Escherichia coli*, a minimum of 60 mg/l is required, which has exceeded the level the human body can take, and this resistance is called a clinical resistance.

The other aspect of the antibiotic resistance is whereby a microorganism's cellular physiology and the structure of the microorganism change due to alterations in its usually genetic makeup leading to the protection of the bacteria from the action of an antibiotic drug, and the

mechanism is called a microbial resistance.[4] There are four main principles in which microorganisms may acquire the ability to resist the effect of a microbial agent:

- Extrusion of the antibiotic agent (active efflux) before it can damage the microorganism.
- Alteration in the drug target for antibiotic action: mutations in the target, production of alternative targets or protection of the target. Thus leading to the ineffectiveness of the drug.
- Inactivation of the antibiotic drug. This is whereby the microorganism produces a drug-inactivating enzyme that destroys the drug's ability to kill the microorganism.
- Changed access: alteration in the bacterial outer membrane, making it hard for a drug to bind to the exterior of the microorganism.

Microorganisms can also acquire resistance to an antibiotic drug to which it was sensitive before. This can be due to the results of these mechanisms resulting from genetic mutations, the acquisition of resistance genes from the other microorganisms via gene transfer and combination of both events.[4] The strive has been ongoing towards the synthesis of new antibiotics and the development on the modification of existing drugs to solve this problem.

2.2. ANTIBIOTICS (ANTIMICROBIALS)

2.2.1. Discovery of Antibiotics

Since the discovery of antimicrobial agents, there has been a substantial reduction of threat posed by infectious diseases. The history of antibiotic agents started with Ehrlichs research and development of the magic bullet, an arsenic derived drug (Salvarsan) in 1907.[5] In 1928, Alexander Fleming discovered the effect of penicillin from fungus *Penillium notatum*, but it was not known that it can be used as therapeutic agent until 1940.[6] The discovery of penicillin drew the attention to nature as a source of biologically active agents. As a result, more investigation about microorganisms as source of bioactive pharmaceutical compounds was

done. Many new antibiotics were then quickly discovered including: sulfonamides (1935), *β*-lactams, aminoglycosides, chloramphenicol, cephalosporins, tetracyclines, macrolides, lincosamides, streptogramins, glycopeptides, rifamycin, nitroimidazole, quinolone and trimethoprim (1968).[7] Twenty two years later, oxazolidinones, lipopeptides and glycylcylinones were introduced in 2000. The research for new and more effective antibiotics is still on today.

2.2.2. Definition of antibiotics

Antibiotics (antimicrobial) are any kind of chemical compounds that kill or inhibit microorganisms by any kind of action. Back then, antibiotics used to be defined as chemical compounds produced by microorganisms whereby it has an ability to kill or inhibit the growth of the other microorganisms even in small concentrations.

In 1978, Hammond[8] and coworkers defined antibiotics as substances produced by microorganisms antagonistic to the life or growth of other microorganisms at low concentrations. While Hutter[9] and coworkers defined antibiotics as the products of secondary metabolites with an incidental action on growth processes even in high dilution. The mode of action of most antibiotics is almost the same as that of silver. They affect the metabolism, RNA, DNA; also affect respiratory electron transport chain and thus depriving the cell of the energy currency, ATP; inhibit the cell wall synthesis and cell membrane synthesis, thus affect its permeability. In this chapter we will look at some of the above mentioned antibiotics; their chemical structures and mode of action.

2.2.3. Classification of antimicrobials

In the previous chapter, it was stated that antibiotics classification can be achieved by four methods namely:

- Chemical structure and biosynthetic pathway.
- The class of antibiotic producing organism.

- The manner in which they target pathogens.
- The mode of action towards to their target.

In this research, however, we will restrict ourselves on classifying antibiotics mostly on the bases of chemical structure as well as their mode of action.

2.2.3.1. *β*-Lactam Antibiotics

The *β*-Lactam antibiotics are characterized by their mode of action which is inhibition of cell wall synthesis and their chemical structure which has a Lactam ring.[1] *β*-Lactam antibiotics are widely used because of their high effectiveness, minimal side effects, low cost and easy to deliver. *β*-Lactam antibiotic class is one of the three large groups of antibiotics that play an important role in saving people's lives. The other two large classes of antibiotics are fluoroquinolones and macrolides. *β*-Lactam antibiotic class, initially, was limited to the penicillin (sulfur-containing penams) and then the cephalosporin (sulfur-containing cephems). But now *β*-Lactam family includes natural and synthetic monocyclic *β*-Lactams, oxapenams, carbacephems, carbapenems and oxaphenems (see Figure 2.1).[1] There has been a significant improvement on the properties of these antibiotics simply by the chemical addition of side chains to their ring structures.

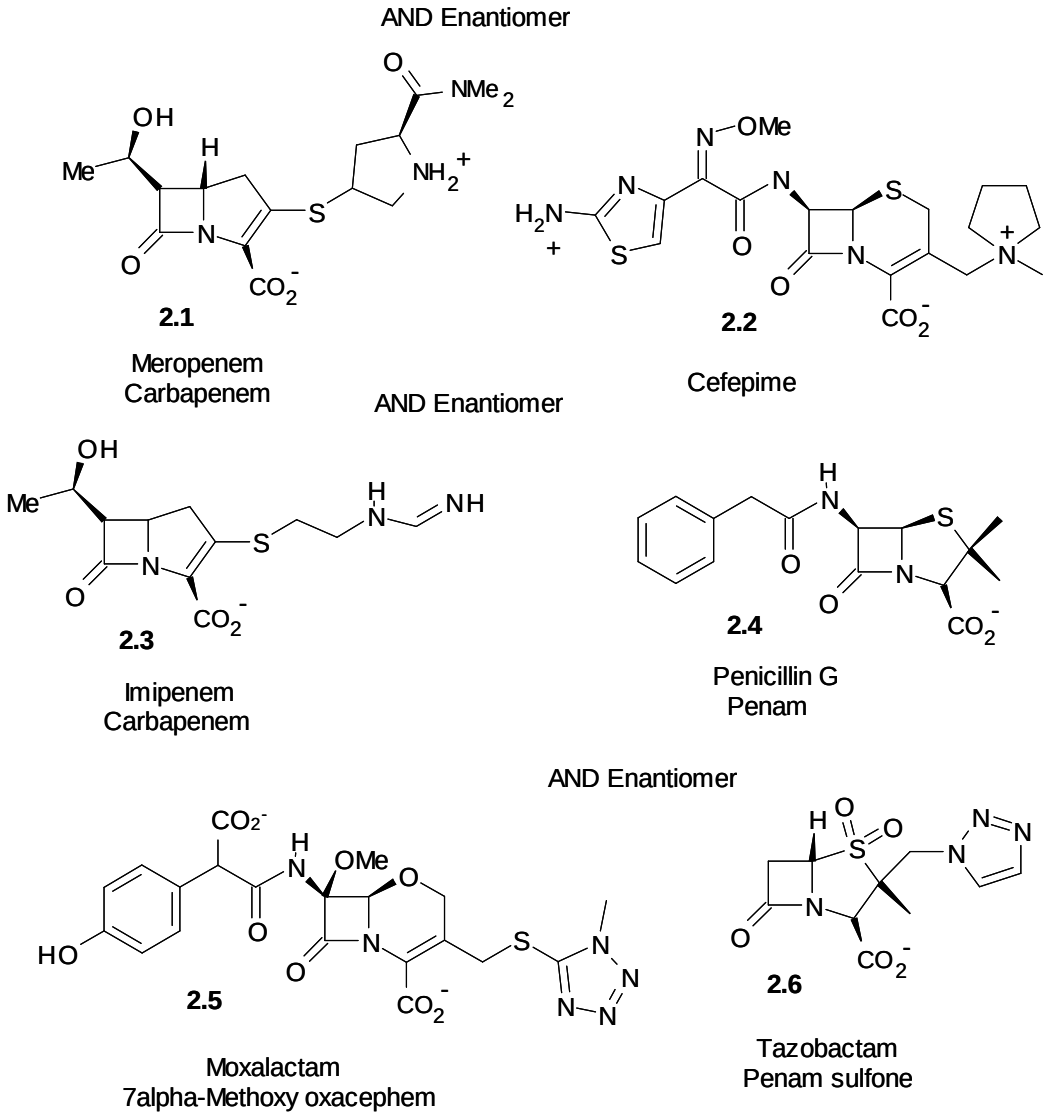
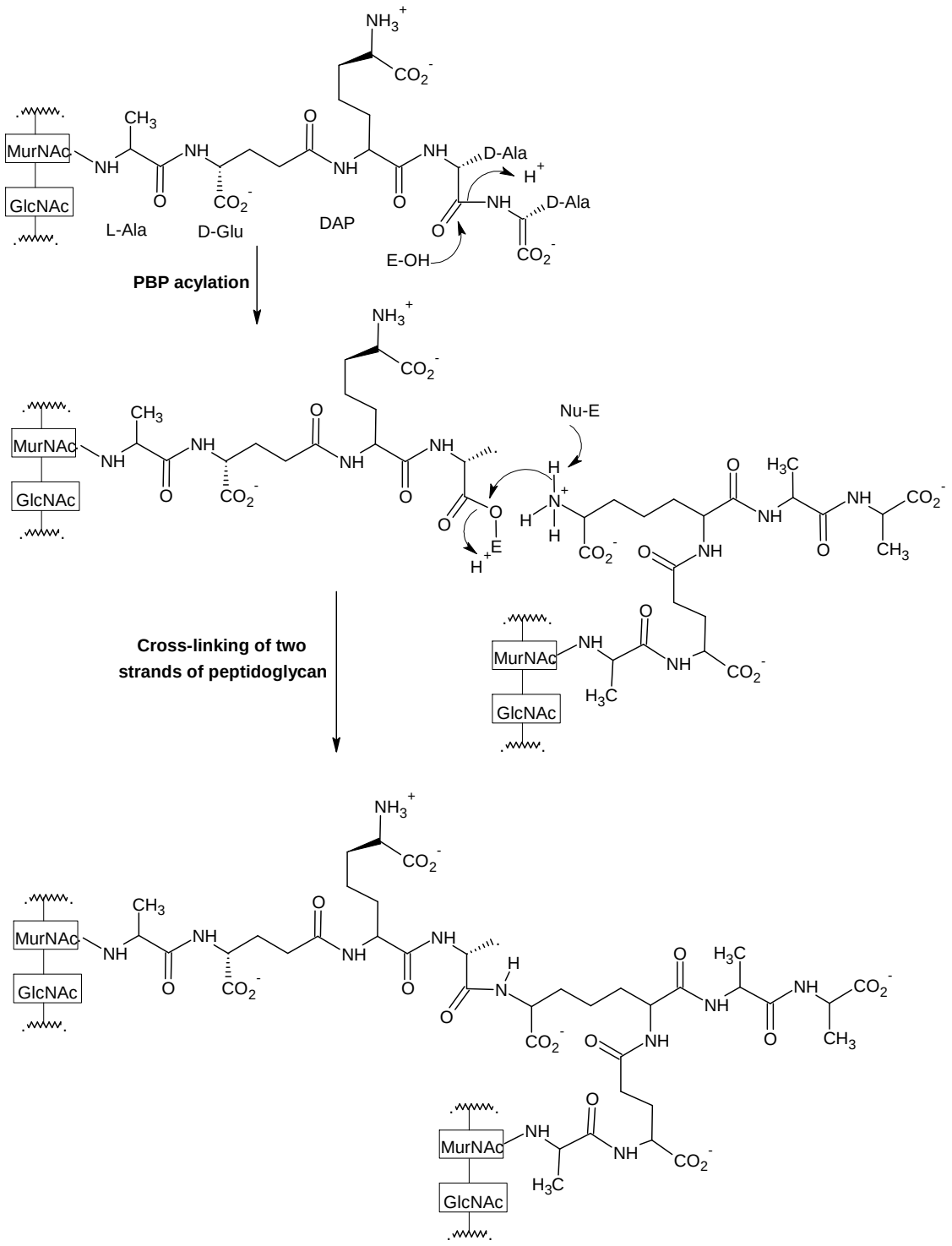
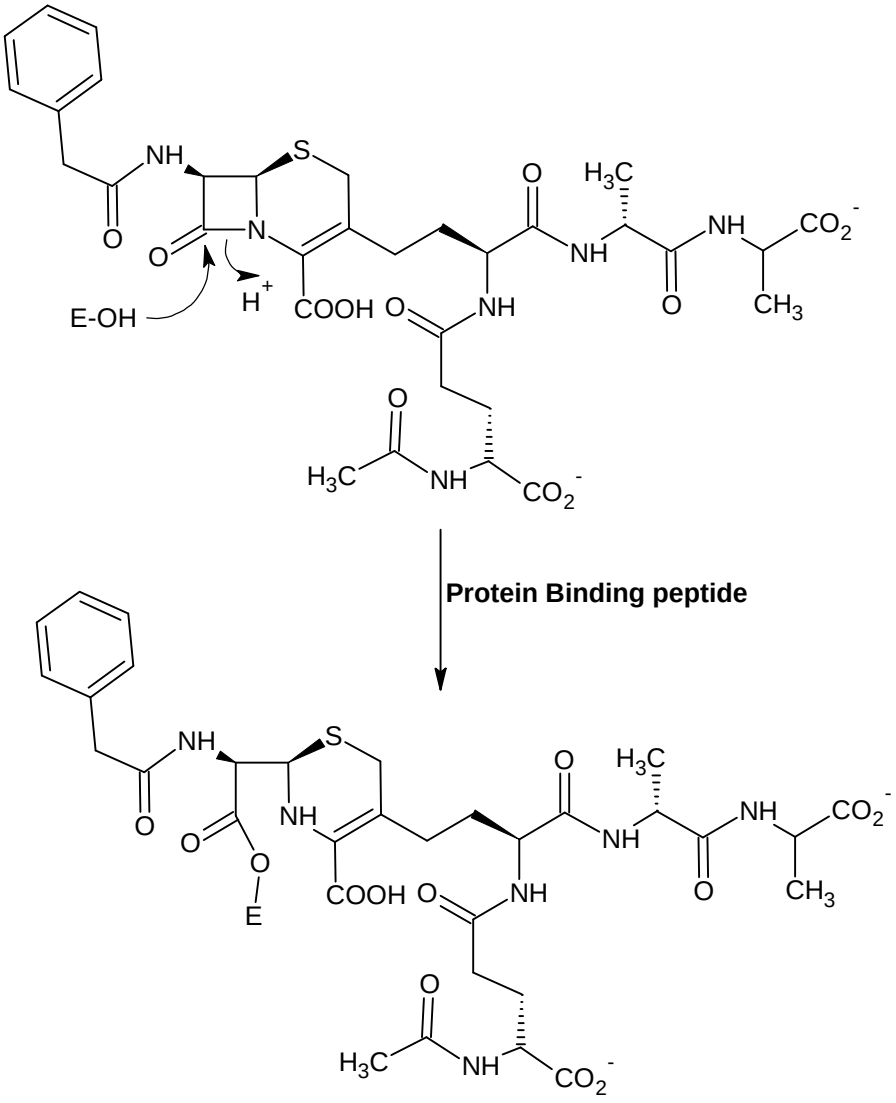


Figure 2.1: *Examples of β-Lactam antibiotics*

The bacterial cell wall is composed of a tightly cross-linked peptidoglycan net (see scheme 2.1) that prevents the cell wall from osmotic pressure. The *β*-Lactam antibiotics turn this cross-linked peptidoglycan net into their binding sites (see scheme 2.2) and inhibit enzymes involved in the synthesis of this composed structure of the cell wall. This causes the lyses of the cell and eventually the cell dies.



Scheme 2.1: *Biosynthesis of bacterial cell wall.*



Scheme 2.2: *Incorporation of cephalosporin onto the bacterial cell wall.*

2.2.3.1.1. Carbapenems

Carbapenems such as imipenem (**2.7**), meropenem (**2.8**) and panipenem (**2.9**) are groups of *β*-lactam antibiotics. They have a broad-spectrum activity, including antimicrobial activity against gram-positive, gram-negative, and anaerobic bacteria.[10] Imipenem and meropenem are the very bioactive primary carbapenems and are approved for clinical usage as parenteral antimicrobials. Panipenem is the most important antibiotic but it has been approved for the

usage only in Japan. Carbapenems target microbes by binding to the penicillin-binding proteins and inhibit bacterial cell wall biosynthesis, thus the cross linking step in cell wall biosynthesis fails.

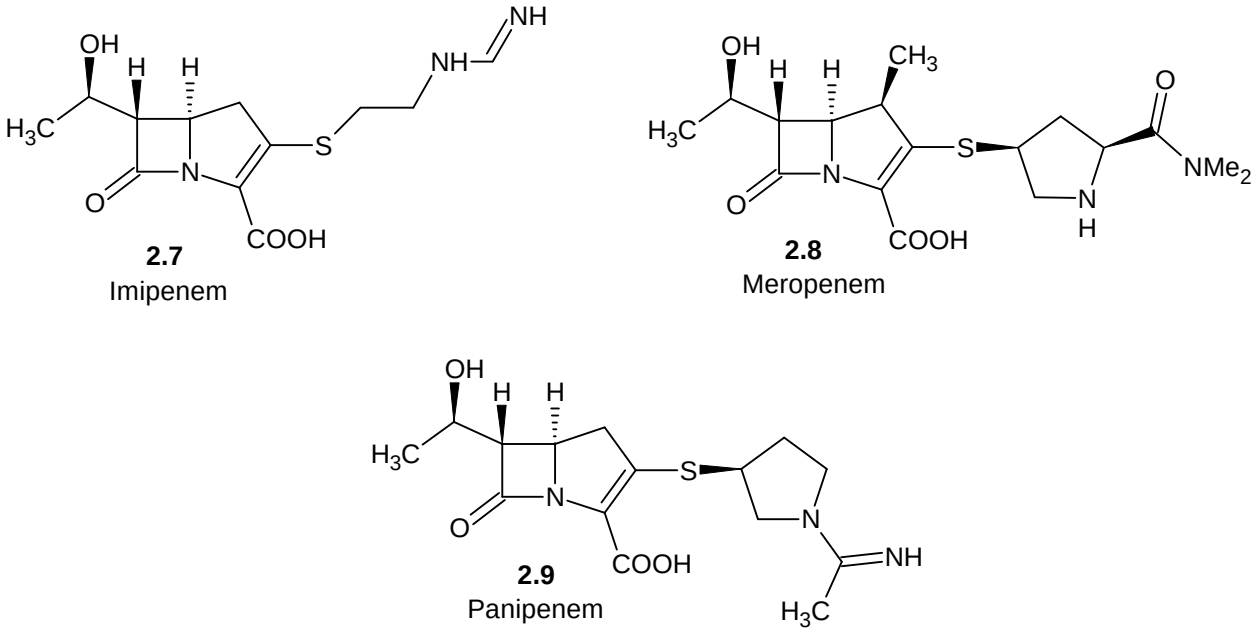


Figure 2.2: *Examples of Carbapenems*

2.2.3.2. Quinolones

This class of antimicrobial agents is among the drugs that drew most attention in the anti-infective chemotherapy field. Different kinds of quinolones' derivatives have been introduced into clinical use, and each derivative comes with its own biological activity.[11] That resulted in the achievement of significant improvements in antimicrobial spectrum and activity. The introduction of norfloxacin, fluoroquinolones resulted in a drastic change in the landscape of antibacterial chemotherapy.[12] Although fluoroquinolones are reported to have a clinical important activity against gram-positive pathogens, their activity is relatively moderate. In addition, due to the extensive use of fluoroquinolones, some pathogens became resistant. Due to this resistance phenomenon, new quinolones with the developed structures to enhance the

antimicrobial activity of this class, including gatifloxacin (**2.10**), gemifloxacin (**2.11**), sitafloxacin (**2.12**), moxifloxacin (**2.13**) and BMS-284756 (T-3811) (**2.14**) were introduced.[10]

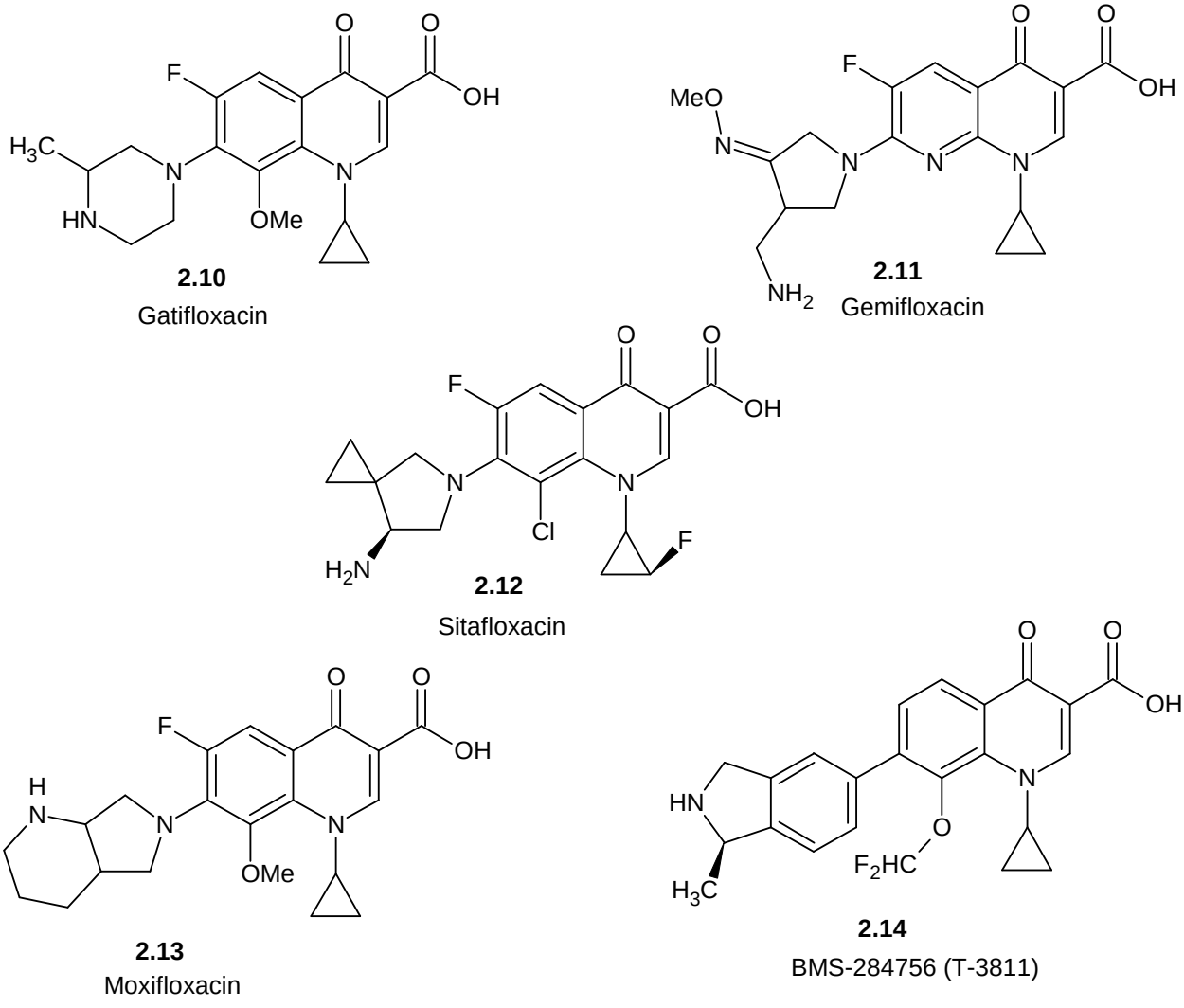


Figure 2.3: *Examples of quinolone antimicrobials*

The quinolones' targets in microbial cells are the bacterial topoisomerase IV and DNA gyrase, enzymes responsible for regulation of super coiling and decatenation of bacteria DNA.[13] Before the introduction of quinolones, there were other compounds with similar activity that were used such as nalidixic acid. They had a limited activity and poor systemic distribution, and were used mainly for gram-negative urinary tract infections. Fluoroquinolones (norfloxacin, ciprofloxacin and ofloxacin) were introduced as next generation which actively

act on DNA topoisomerase, were more readily absorbed, increased activity against gram-negative bacteria. Moxifloxacin and levofloxacin are new fluoroquinolones with highly improved activity against many gram-positive and gram-negative bacteria.

Since moxifloxacin and levofloxacin are effective against chlamydia, mycoplasma and legionella, are therefore, used for treatment of atypical pneumonia. Ciprofloxacin is widely used mainly for upper tract urinary infections and exacerbations of chronic bronchitis both in hospital and ambulatory settings.

2.2.3.3. Glycopeptides and Lipoglycopeptides antibiotics

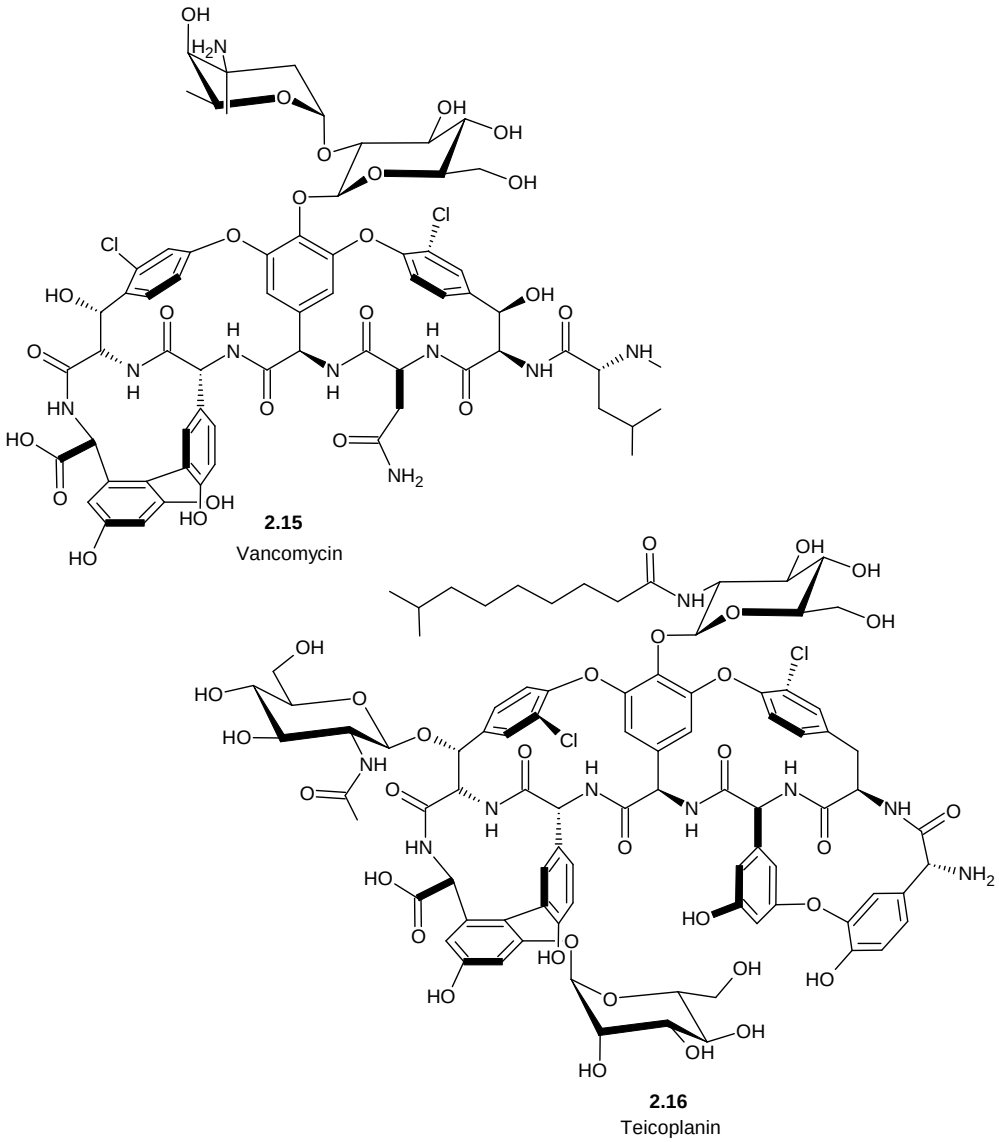
Vancomycin (**2.15**) and teicoplanin (**2.16**) are the most important glycopeptides antibiotics that are approved for human therapy (see structures in Figure 2.4). Micro-organisms are hardly becoming resistant to these two glycopeptides, should it happen, it would pose a serious threat to human health. These antibiotics are widely used, especially to gram-positive bacterial infections that are resistant against other antibiotics like β-Lactam antibiotics.[14]

Vancomycin and teicoplanin are both natural products extracted from soil bacteria. Vancomycin isolated from *Amycolatopsis orientalis* in 1950s and teicoplanin was isolated from *Actinoplanes teichmyceticus* in 1980.[15] The structure of vancomycin is very complex which made it difficult for its structure to be elucidated. The elucidation process of vancomycin's structure started in 1965 and was not achieved until 1996 when Sheldrick completed it.[16]

2.2.3.3.1. Mode of action of Vancomycin and Teicoplanin

Glycopeptide antibiotics target bacterial peptidoglycan biosynthesis pathway which is essential for the survival of micro-organisms. Most of the antibiotics that target bacterial peptidoglycan biosynthesis are derived from natural products which are produced by micro-organisms.[17] Glycopeptides antibiotics (including Vancomycin and Teicoplanin) are cell wall active and inhibit the last steps of peptidoglycan biosynthesis pathway. It has not been clear

why these antibiotics inhibit the final steps, however, Kahne *et al*, stated that the possible reason could be that, because the extracellular enzymes involved which makes them easy targets for compounds that would not penetrate the cell membrane.[14] These antibiotics inhibits bacterial peptidoglycan biosynthesis pathway by binding to the substrate (D-Ala-D-Ala terminus) of transglycosylases and transpeptidases (as shown in figure 2.5). This results in the inhibition of the transglycosylation and transpeptidation stages of peptidoglycan synthesis, weakening of the peptidoglycan layers causing the cell to be susceptible to lyses because of the change in its osmotic pressure.



2.15
Vancomycin

2.16
Teicoplanin

Figure 2.4: *Examples of a glycopeptide and a lipoglycopeptide antibiotics.*[14]

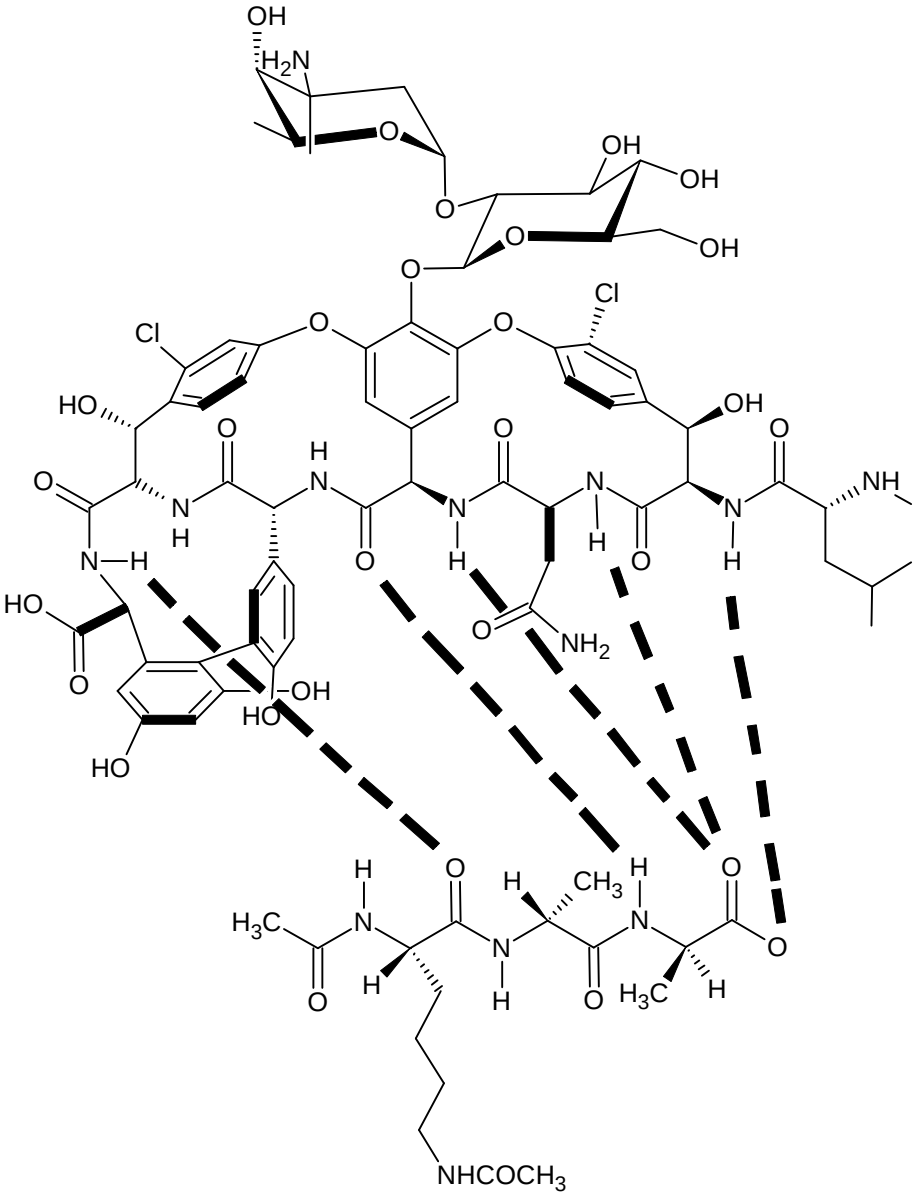


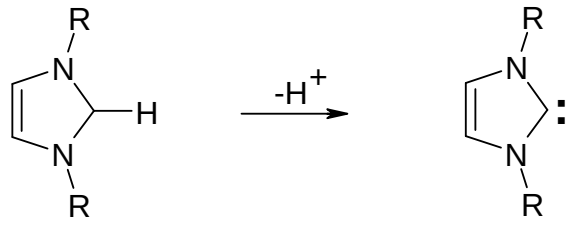
Figure 2.5: *Binding of vancomycin with N-acyl-D-Ala$_4$-D-Ala$_5$ termini: five hydrogen bonds between the underside of the glycopeptide and the acyl-D,D-dipeptide moiety.*[18,19]

2.2.3.4. Imidazolium antimicrobials

2.2.3.4.1. Imidazolium compounds: Background

The other group of antimicrobial agents that will be discussed in this thesis is imidazolium compounds (that are biological active). Imidazo[1,5-a]pyridines are an important and versatile class of *N*-heterocyclic compounds due to their stability, they also have their unique biological (antimicrobial), and photochemical properties.[20-22] The beauty about this type of compounds is that they can be converted into many different structural compounds with different properties. For example, the imidazolium compounds can be converted into imidazolium carbenes (as shown in scheme 2.2), which have a wide range of chemistry and properties. They can also be used for chelating transition metals especially heavy metals that can be harmful to living things (including humans) or metals that have antimicrobial properties like silver. Some imidazolium compounds are antimicrobial themselves. Due to the conjugation and the charge on their structure, their properties are extended to conducting electricity and electronic properties.

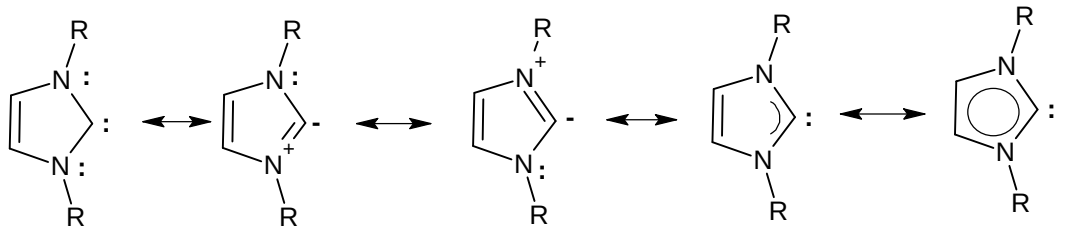
N-Heterocyclic carbenes (NHC) are a group of heterocyclic compounds which are proven to have a very important and unique chemistry. They are cyclic carbenes that contain two electron donors. They are derived from the deprotonation of imidazolium salt (as shown in scheme 2.2).[23,24]



2.17 **2.18**

Scheme 2.2: *General representation of deprotonation of imidazolium salts to form NHC carbene.*

The resonation of the nitrogen electrons (shown in scheme 2.3) around or towards the carbene carbon is the main key for the stabilization of N-heterocyclic carbene.[23] These kind of N-heterocyclic carbenes are imidazolium compounds which have their unique reactivity, stability, function and properties.



2.18

Scheme 2.3: *The representation of the resonation carbene structures and the aromaticity.*

In spite of the fact that the free N-heterocyclic carbenes are stable due to the resonation of their structure, they are also stable in their complexed form. N-heterocyclic carbenes (imidazolium carbenes in particular) are strong nucleophiles and often complex to transition metals to form stable complex than phosphines.[23] Kascatan-Nebiglu *et al*[2] reported that the stabilization energy of the carbene carbon atom of N-heterocyclic compounds due to the p_π-p_π electron donation of the two adjacent nitrogen atoms is approximately 70 kcal/mol. Kascatan-Nebiglu *et al*[2] also stated that the stabilization energy that can be contributed as an additional energy by an unsaturated aromatic systems is 25 kcal/mol (figure 2.6). The lone pair electrons of the carbene carbon is being stabilized by the inductive effect of the adjacent nitrogen atoms. Kascatan-Nebiglu and Hindi reported that N-heterocyclic carbenes are not just sigma donors but are also π-back acceptors for certain metal centres. Hindi *et al* also stated the quantitative analysis of the metal-ligand donor-acceptor interactions using charge decomposition analysis (CDA) which is measured as *d/b,* where *d* is an estimate of the degree of NHC to metal σ-donation and *b* is metal to NHC π-back-donation.[24] For the effective σ-donation ligand the *d/b* ratio is big whereas a small *d/b* ratio suggests the greater metal to NHC π-back-donation. Hindi *et al* reported the following observation of *d/b* ratio for some metals: i) Pd-NHC

complexes ranging from 2.59 to 3.99 which are very small, ii) for Au-NHC complexes, *d/b* ratios range between 5.23 and 5.88 and iii) for Ag-NHC complexes have *d/b* ratios range from 7.8 to 12.68.

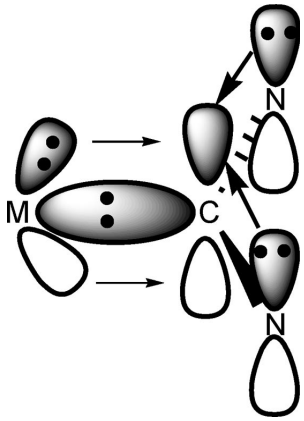
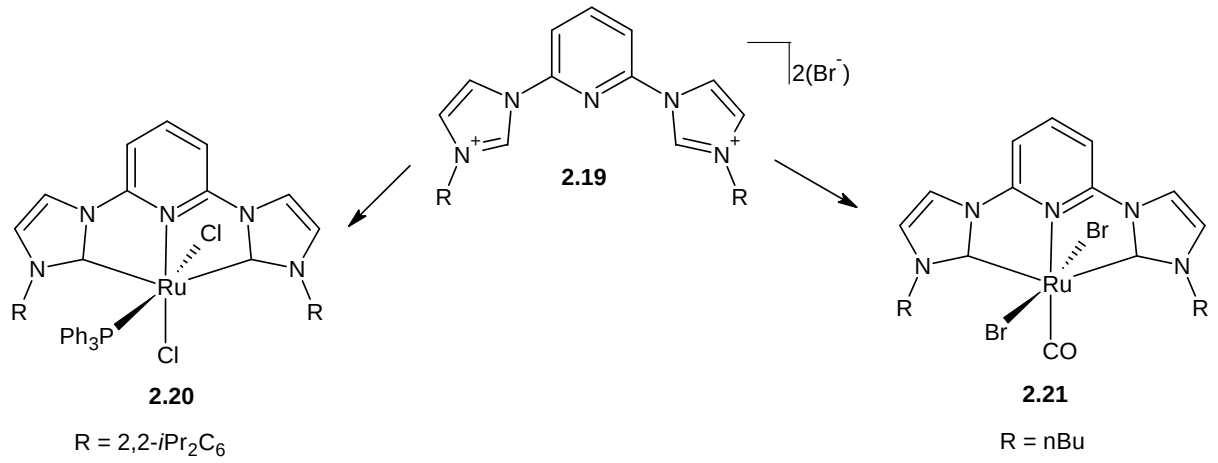


Figure 2.6: *Orbital diagram of bonding of NHCs to metal centre.*[23,24]

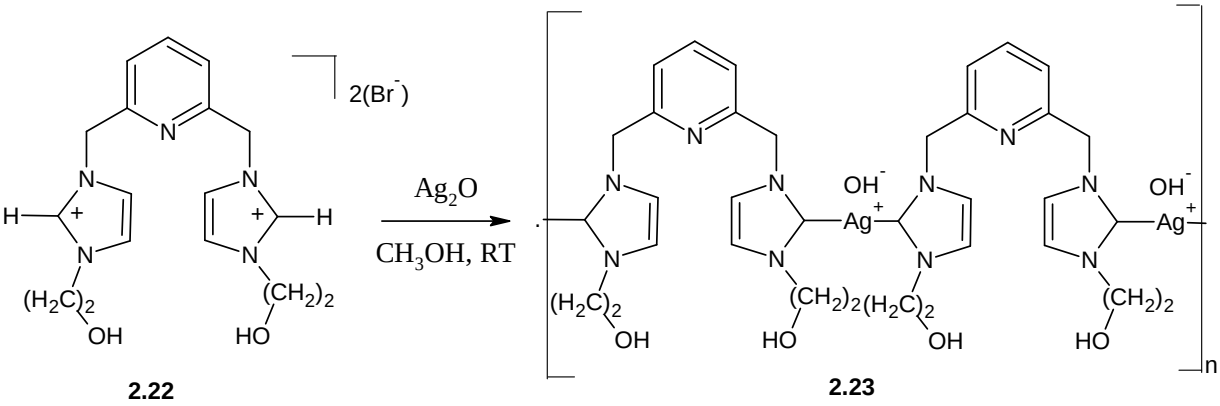
2.2.3.4.2. Applications of imidazolium compounds

As stated above, imidazolium compounds can have many applications such as chelating to metals and/or as antimicrobial agents. One example of their applications is as shown in scheme 2.4., 2,6-pyridyl-bisimidazolium salt **(2.19)** is a stable ligand and is complexed to ruthenium metal to form very stable catalysts.[25] Complexes **2.20** and **2.21** were reported to be good catalysts for the hydrogenation of carbonyl groups; alkyl and aryl ketones were hydrogenated into their corresponding alcohols.[26]



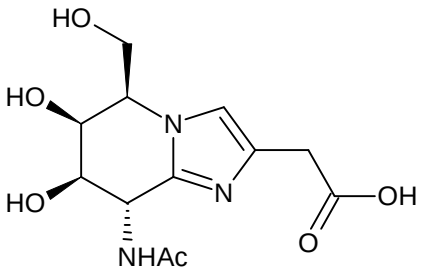
Scheme 2.4: *Complexation of 2,6-pyridyl-bisimidazolium salt (**2.19**) to Ruthenium to form **2.20** and **2.21**.*[27]

Another example of complexed imidazolium compound is imidazolium-silver complexes such as complex **(2.23)**. It is proven to be a good antimicrobial agent because of its stability. The reason for its good antimicrobial activity is that, the imidazolium ligand **(2.22)** strongly binds the silver metal to form a stable complex that can slowly release silver ions. It thus remains an effective antimicrobial for a long time.[2] It is thus active against a broad spectrum of gram-positive and gram-negative bacteria.



Scheme 2.5: *Synthesis of an antimicrobial imidazolium-silver complex (**2.23**).*

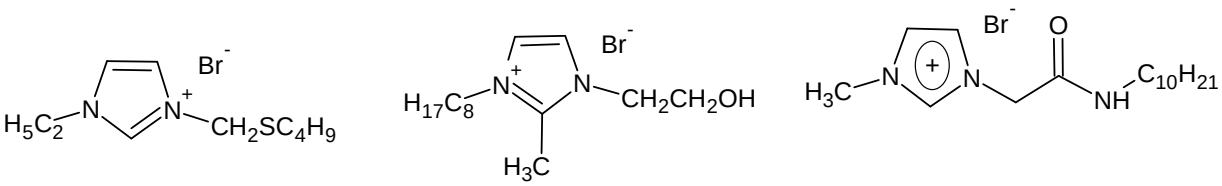
Despite the fact that the imidazolium compounds are good ligands, they are also active against micro-organisms in a non-complexed form. Some imidazole antimicrobials like nagstatin (**2.24**) are naturally occurring. The structure of nagstatin was elucidated by Aoyagi, Aoyama and coworkers in 1992, they also showed the potency of this imidazole sugar in the inhibition of some *glucosaminidases*.[28] The discovery of nagstatin triggered the interest to many researchers on exploring the chemistry of imidazole antimicrobials.[29]



2.24

Figure 2.7: *Structure of Nagstatin.*

As a result, different kinds of imidazolium antimicrobials were discovered, however, we will discuss about the imidazolium compounds with at least one nitrogen atom of the imidazole ring is quaternary. 3-Butylthiomethyl-1-ethylimidazolium (**2.25**) is one of the earliest reported quaternary imidazolium antimicrobials by Pernak and Skrzypczak in 1996.[30] This antimicrobial (**2.25**) was found to be active against various micro-organisms such as fungi, rods, cocci and bacilli. 1-Alkyl-3-hydroxyethyl-2-methylimidazolium (**2.26**) was reported by Demberelnyamba and coworkers and was found to be an effective antimicrobial.[31] Kanjilal *et al*[32] reported the structure and the activity of 1-(decylcarbamoyl)-3-methyl-1H-imidazol-3-ium bromide (**2.27**). This antimicrobial was reported to be active against various micro-organisms such as *C. rugosa, Candida albicans, A. niger, Aspergillus flavus, Saccharomyces cerevisiae* and many other mico-organisms.



2.25 **2.26** **2.27**

Figure 2.8: *Examples of quaternary imidazolium antimicrobial salts.*

The number of multi-drug resistance microbes is increasing day by day and this is a global problem.[33] This clearly shows that commercially available antimicrobials are not keeping up to the demand. There is a need of developing a significant variety of new compounds with unique chemical structure in order to defeat this drastic increasing resistance phenomenon possible working through mechanisms of actions that are known.[34] More research has been done, aiming to formulate studies of new active antimicrobial by introducing new molecular parameter such as heteroatoms, aromatics and chemical functions in order to improve the performance of antimicrobial agents. Imidazolium class of compounds is among those antibiotics that have gained synthetic interest in recent years due to their wide spectrum of biological activities. In this research, we propose new and potential antimicrobial agents that are imidazolium structured with aromatic groups substituted on both nitrogen atoms, and one of the nitrogen atoms is quaternary. It is hoped that this will enhance the antimicrobial activity. By looking at the general structure (**1.4**) in figure 1.3, the conjugation, quaternary nitrogen and the aromatic group that is substituted to the quaternary nitrogen can improve the antimicrobial activity. A series of this kind of compounds were synthesized in this research, to some compounds the sulfonamide group was incorporated which will hopefully enhance the biological activity since sulfonamide group is biological active on its own.

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CHAPTER 3 REVIEW FOR THE SYNTHESIS OF IMIDAZOLES

3.1. Introduction

Some imidazolium derivatives have interesting biological and photochemical properties,[1-4] but our interest lies mainly in their antibiotic activity. Their synthesis is thus of ever growing importance with the intension of improving the biological activity on the already existing antibiotics or discovering new imidazolium compound with high biological activity. For example, some imidazole compounds are antimicrobials, this means that they kill or inhibit microorganisms by some kind of action. Historically, antibiotics were defined as chemical compounds produced by microorganisms whereby they kill or inhibit the growth of the other microorganisms even in small concentrations. An antibiotic is preferred when it is effective at very low concentrations, lasts longer and has the least or no side effects. Therefore, the aim of this research was to meet these requirements.

However, in this chapter, we will explore the different methods reported in the literature on the synthesis of the imidazolium compounds. Imidazolium compounds are grouped into two categories which are non-pyridyl fused imidazolium (**3.1**) and pyridyl fused imidazolium compounds (**3.2** and **3.3**) as shown in figure 3.1. The pyridyl fused imidazolium compound is referred to the structure whereby the imidazole and the benzene rings are fused together in a manner so that one nitrogen atom and one carbon atom are being shared by both rings as represented by structure **3.2** and **3.3**. Section 3.2 will focus on different synthetic approaches for the formation of the non-pyridyl imidazolium (**3.1**). Secondly, we will briefly discuss the synthetic pathway for the imidazo[1,2-a]pyridine system (**3.2**) which is one kind of the pyridyl fused imidazolium compounds in section 3.3. Our main interest, however, is in the imidazo[1,5-a]pyridine system (**3.3**) which is discussed in more details in section 3.4. Lastly, we will interrogate the synthesis of quaternary imidazo[1,5-a]pyridyl compounds in section 3.4.

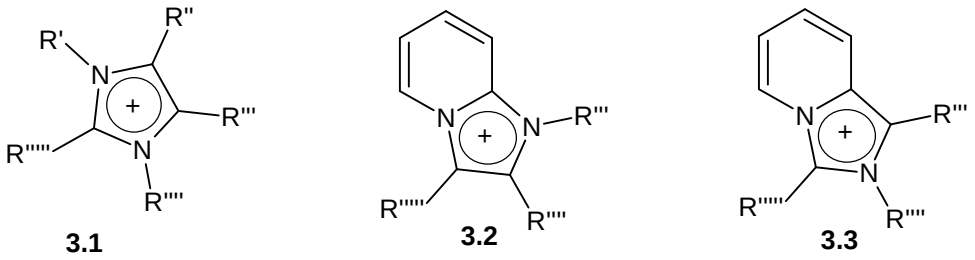


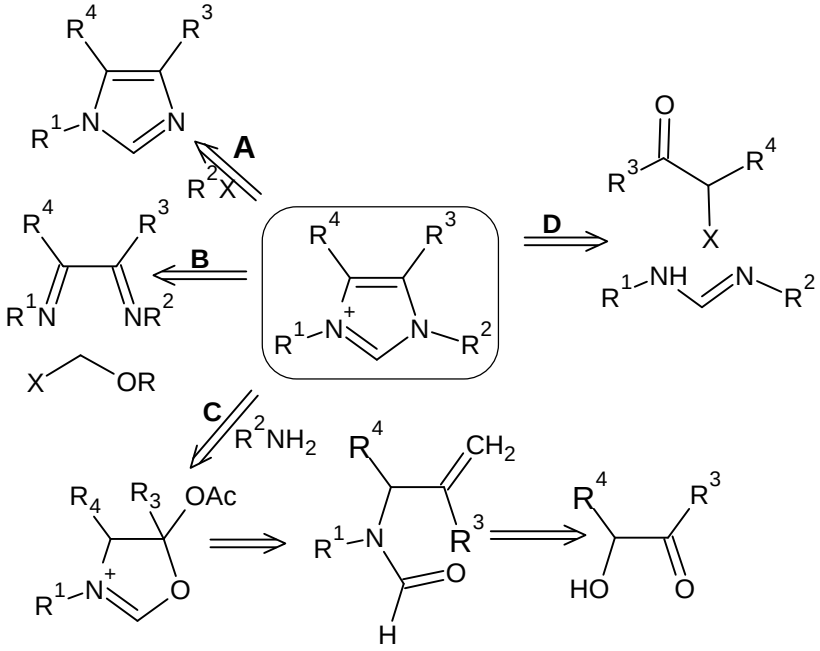
Figure 3.1: *Structure of non-pyridyl imidazole (**3.1**) and pyridyl imidazole compounds (**3.2** and **3.3**)*

3.2. Non- pyridyl fused imidazoles

Non-pyridyl fused imidazoles (**3.1**) are any compounds with an imidazole ring as a functional unit without be pyridyl imidazole ring system. These compounds have a wide range of applications that have been reported such as antimycobacterial,[5] antitumour,[6] corticotropin relaxing hormone receptor antagonist,[7] cyclin-dependent kinase inhibitors,[8] xanthine oxidase inhibitors,[9] anticonvulsant[10] and anti-rhinovirus agents.[11] They also appear in cofactors and nucleic acids that play a vital role in the modulation of protein function and signal transduction.[12] There are many other non-pyridyl imidazole derivatives (**3.1**) with various substituents R and their chemical synthetic pathways are entirely different.

Imidazole compounds are also considered as one class of heterocyclic compounds which have a wide range of applications such as being precursors for the formation of heterocyclic carbenes. Most of these carbenes and imidazole compounds are used as ligands for chelating metals. For example, when chelated to heavy metals such as silver (which is known to be active against micro-organisms), the activity is enhanced because some of the imidazolium compounds are biological active themselves. They are also used as ligands in organometallic chemistry and transition metal catalysts[13,14] and as organocatalysts by themselves[15]. However, in this chapter, we will focus on different synthetic routes for the formation of the imidazolium compounds.

We will start by showing the disconnection of the imidazolium ring as shown in scheme 3.1 (Retrosynthesis). Out of all routes shown in scheme 3.1, the routes that are widely used are routes **A** and **D**. Route **A** is one of the standard routes for the formation of imidazolium salts which is the alkylation of imidazoles. Various alkyl groups have been used to make various analogues of imidazolium salts. The other route that is popular is route **B** which involves the alkylation-cyclization of 1,2-bisimines.[16] However, there are some limitations with these approaches and they generally do not allow the superficial formation of differently 4,5-disubstituted or 1,3-diaryl-substituted imidazolium salts.[17] These limitations were recently overcome by Fürstner *et al* by developing a new procedure, route **C**. This procedure allows the formation of variety of imidazolium compounds with substitution pattern such as differently 1,3-diaryl-substituted imidazoles.[18] However, there is a huge drop in the overall reaction yield for the formation of imidazolium salts via this route because its step count is quite high.

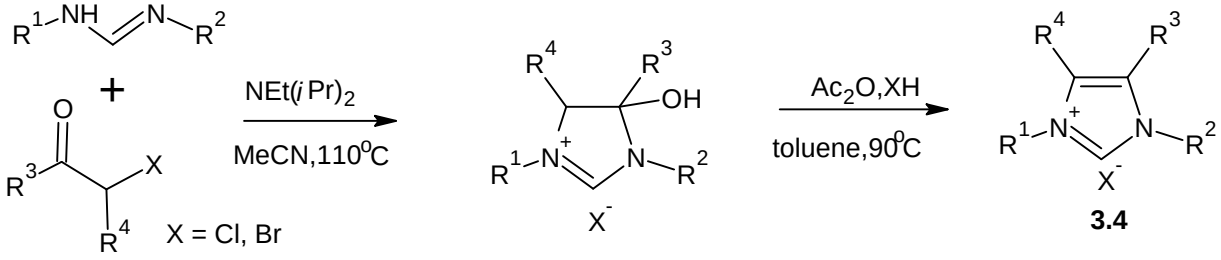


Scheme 3.1: *Retrosynthesis for the imidazolium compounds*

More research was done in order to come up with the highly developed methods. That includes some reports such as Bertrand and coworkers' report which describes their

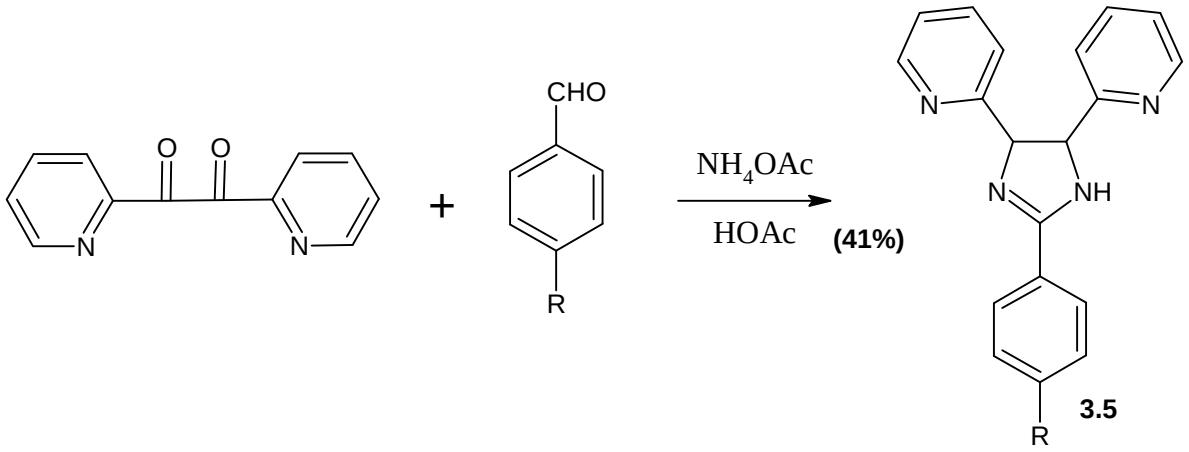
retrosynthetic disconnection of imidazolium compounds and their preparation involving alkylation of lithiated formamidines.[19] Subsequently, Grubbs and others reported powerful method for the formation of imidazolium compounds by coupling 1,2-dichloroethane with formamidines.[20]

Lastly, retrosynthetic disconnection **D** has also been done, for example by Glorius *et al* who reported the synthesis of various imidazolium salts via route **D** as shown in scheme 3.2.[21] They started by reacting *N*,*N*'-dimesithylformamidine with commercially available 3-chlorobutan-2-one in polar aprotic solvents such as acetonitrile (MeCN) at 110 °C to afford a hydroxyimidazolidinium intermediate, and diisopropylethylamine ($NEt(iPr)_2$) was used to optimize the yield of the product. The last step was the dehydration of the intermediate using acetic anhydride and elimination of acetic acid in the presence of hydrochloric acid in toluene at 90 °C to give the product (**3.4**).



Scheme 3.2: *Synthesis of highly substituted imidazolium salts.*

The other example of non-pyridyl fused imidazolium compounds is 4,5-bis-(2-pyridyl)-2-phenylimidazolidine (**3.5**) and derivatives as shown in scheme 3.3 which initially was formed as a side product. However, Wang and coworkers,[22] decided to optimize its yield. Treatment of 2,2'-pyridyl and benzaldehyde with ammonium acetate in the presence of acetic acid was carried at 118 °C and was optimized to 41% when the ratio of pyridyl, aldehyde and ammonium acetate is 1:1:8.

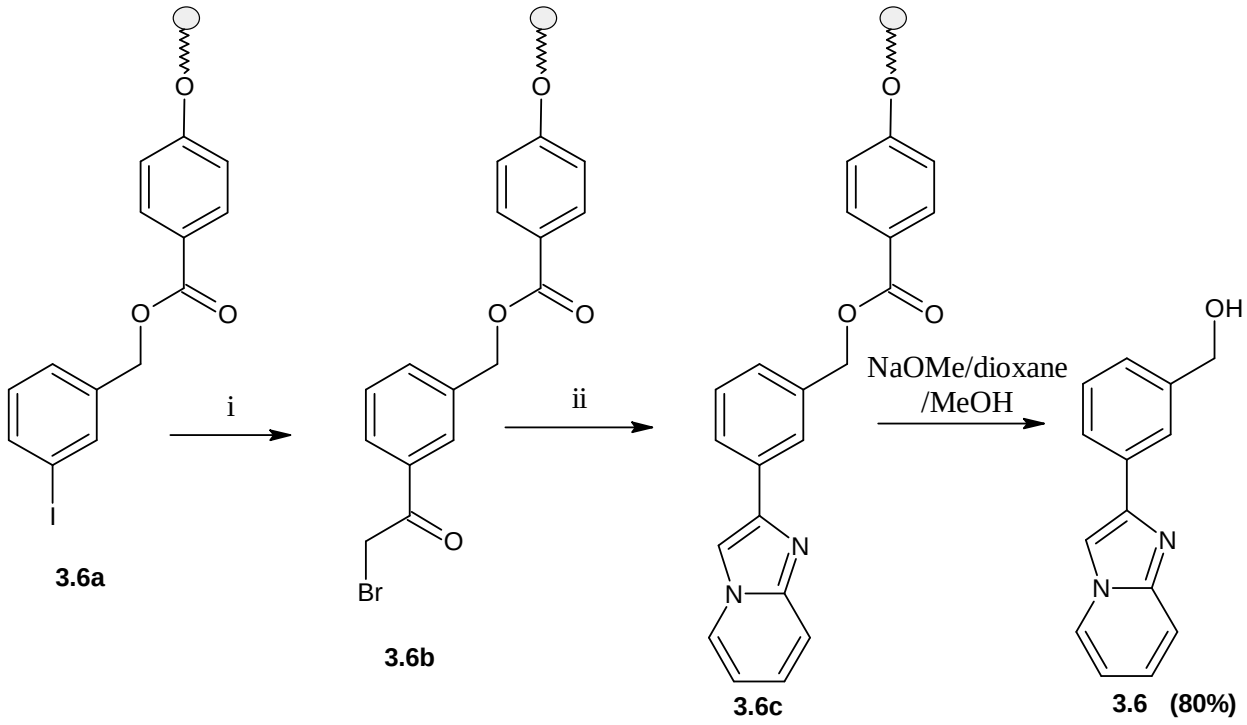


Scheme 3.3: *Synthesis of 4,5-bis-(2-pyridyl)-2-phenylimidazolidine (**3.5**).*

3.3. Synthesis of imidazo[1,2-a]pyridine system (3.2)

In this section, we considered two kinds of synthesis that have been reported in the literature allowing the formation of imidazo[1,2-a]pyridine (**3.2**). The first one involved the reaction of 2-aminopyridine and aldehyde/isonitrile.[23,24] The second one is with the use of benzenesulfinate as a traceless linker.[25] After these methods were established, a variety of this kind of imidazoles with various biological activities such as antiulcer,[26] antifungal, antiviral,[27] antibacterial,[28] herbicidal, have been reported. More recently, Zhuang and coworkers[29] described 2-arylimidazo[1,2-a]pyridines as ligands for detecting β Amyloid (Aβ) plagues in the brain, whose production is essential in the pathology of Alzheimer's disease.

Kazzouli and coworkers[30] described the new method of synthesizing imidazo[1,2-a]pyridine (**3.6**) from an α-bromoketone (**3.6b**) bound to solid support used for thiazole analogs. As shown in scheme 3.2, the α-bromoketone was generated from an aromatic iodide (**3.6a**) bound to polystyrene. The α-bromoketone (**3.6b**) intermediate further reacted with 2-aminopyridine at 50 °C to yield **3.6c**. Imidazo[1,2-a]pyridine (**3.6**) was obtained from the cleavage of resin **3.6c** by transesterification with NaOMe in a mixture of 1,4-dioxane and methanol. There are many other imidazo[1,2-a]pyridine compounds that have been reported with different synthetic approaches but we limited ourselves to the ones discussed above.



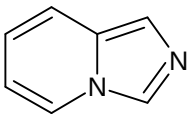
Scheme 3.4: *Synthesis of Imidazo[1,2-a]pyridine (**3.6**)*[31]. *Reagents and conditions*: (i) tributyl(1-ethoxyvinyl)tin (2 equiv.), Ph_3As (0.4equiv.), $Pd_2(dba)_3$ (2 equiv.), 1,4-dioxane, 50°C, 24 h (×2); NBS (2.5 equiv.) in THF/H_2O (4/1), 1 h (ii) 2-aminopyridine(6 equiv.) or 2-aminopyrimidine derivatives, DMF, rt, 72 h or EtOH, 50°C, 48 h.

3.4. Synthesis of imidazo[1,5-a]pyridine (3.3)

Imidazo[1,5-a]pyridines are heterocyclic compounds which are fused imidazopyridine ring systems that represent a good potency from a pharmacological point of view. These compounds are known to be selective inhibitors of aromatase estrogen production suppressors,[32] HIV-protease inhibitors, platelet aggregation and thromboxane A_2 synthetase inhibitors[33] and are potential positive inotropic agents.[34] The structure of these compounds is known to form part of the skeleton of natural alkaloids,[35] playing a role in short-acting neuromuscular blocking agents,[36] of reversible inhibitors of the K^+, H^+-ATPase enzyme with a antisecretory activity[37] and of potent of sedative-hypnotics of the nervous system. In addition, they have been investigated from a photophysical point of view and found to have potential

applications in organic light-emitting diodes (OLED),[38] in organic thin-layer field effect transmitters (FET)[39] and as precursors for *N*-heterocyclic carbenes.

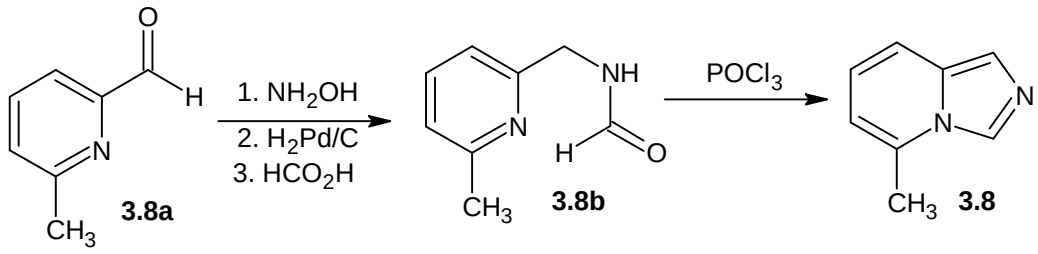
The first synthesis of an imidazo[1,5-a]pyridine (**3.7**) was carried out by Bower and Ramage in 1955. They first formylated 2-aminomethylpyridine using Friedel-Crafts conditions and then cyclised the resulting product with phosphorous oxychloride.[40]



3.7

Figure 3.2: *The first synthesized structure of imidazo[1,5-a]pyridine (**3.7**)*

20 years after the first imidazo[1,5-a]pyridine (**3.7**) was synthesized, Fuentes and Paudler[41] reported an improved synthetic method for the formation of imidazo[1,5-a]pyridine (**3.8**), as shown in scheme 3.5. They treated aldehyde (**3.8a**) with NH_2OH to form an oxime, followed by the reformation of an aldehyde with an extra carbon **3.8b**. The last step was the ring closure of **3.8b** to form imidazo[1,5-a]pyridine (**3.8**) in the presence of phosphorus oxychloride ($POCl_3$).

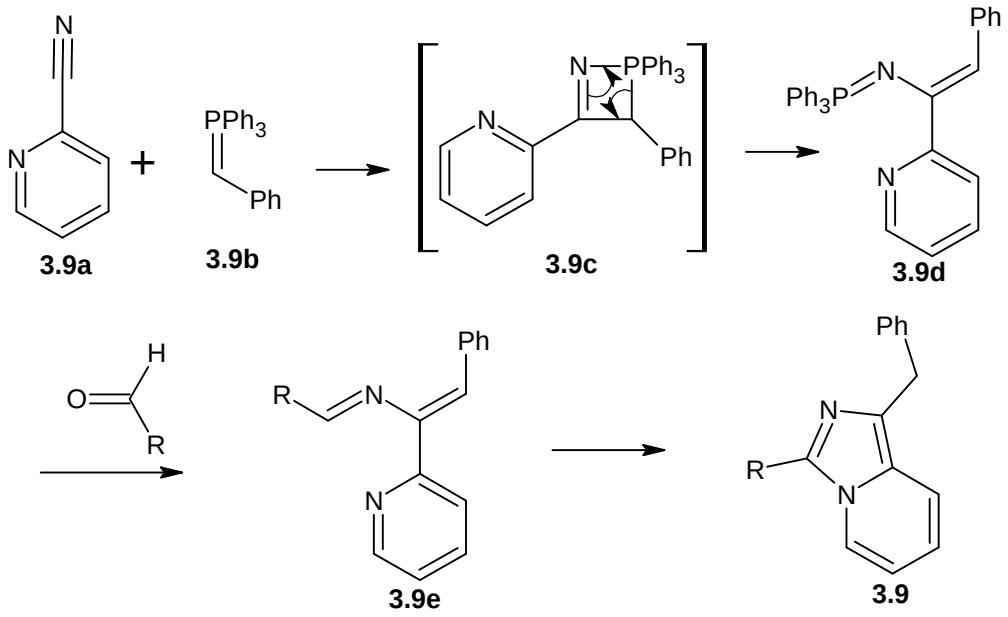


Scheme 3.5: *Synthesis of imidazo[1,5-a]pyridine (**3.8**)*

3.4.1. Direct synthesis of imidazo[1,5-a]pyridine

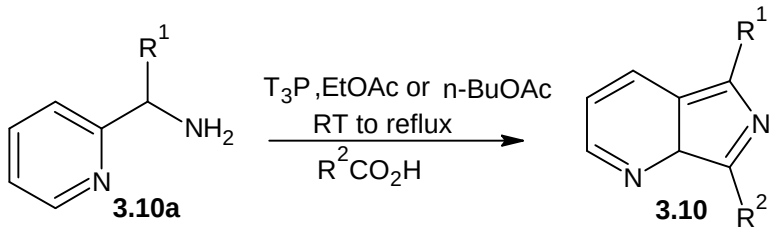
3.4.1.1. System 1

Palacios and others[42] prepared imidazo[1,5-a]pyridine (**3.9**) by reacting benzyldenetriphenylphosphorane (Wittig reagent) (**3.9b**) and 2-cyanopyridine (**3.9a**) and yield phosphazene intermediate (**3.9d**) which further reacted with aldehyde as shown scheme 3.6. The imidazo[1,5-a]pyridine (**3.9**) was formed via the imidazo annelation of imino-functionalised pyridine (**3.10e**) generated in situ from Aza-Wittig reaction of phosphazene (**3.9d**) and aldehyde. The reaction between **3.9e** and an aldehyde to form **3.9** is called 1,5-electrcyclic ring closure process and is very important in heterocyclic chemistry for the synthesis of five membered heterocycles.



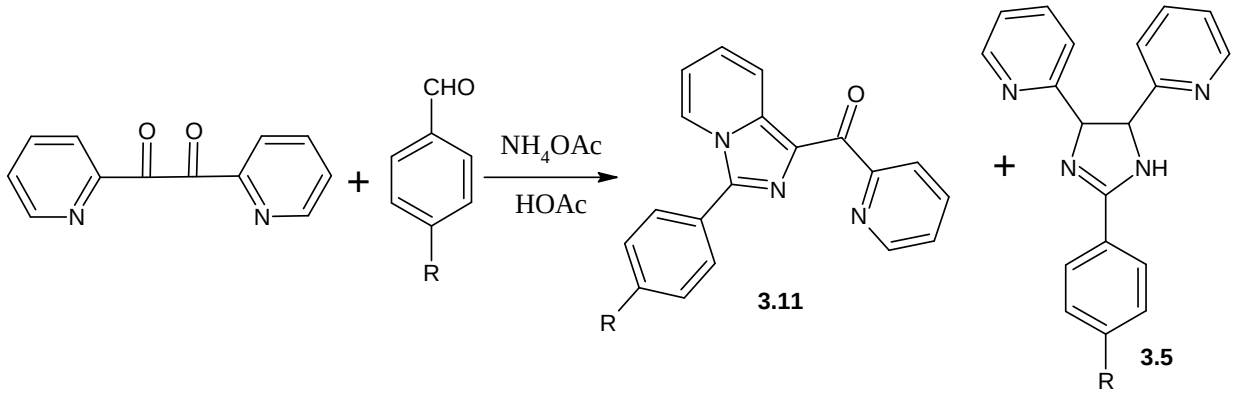
Scheme 3.6: *Aza-Wittig reaction to form imidazo[1,5-a]pyridines (**3.9**)*

Crawforth and Paoletti[43] reported the synthesis of imidazo[1,5-a]pyridines (**3.9**) starting from carboxylic acids and 2-methylaminopyridines using propane phosphoric acid anhydride (T3P®) (which acts as a water scarvenger) in ethyl acetate as shown in scheme **3.7**. In general terms, this reaction can be regarded as an amide formation followed by dehydration.



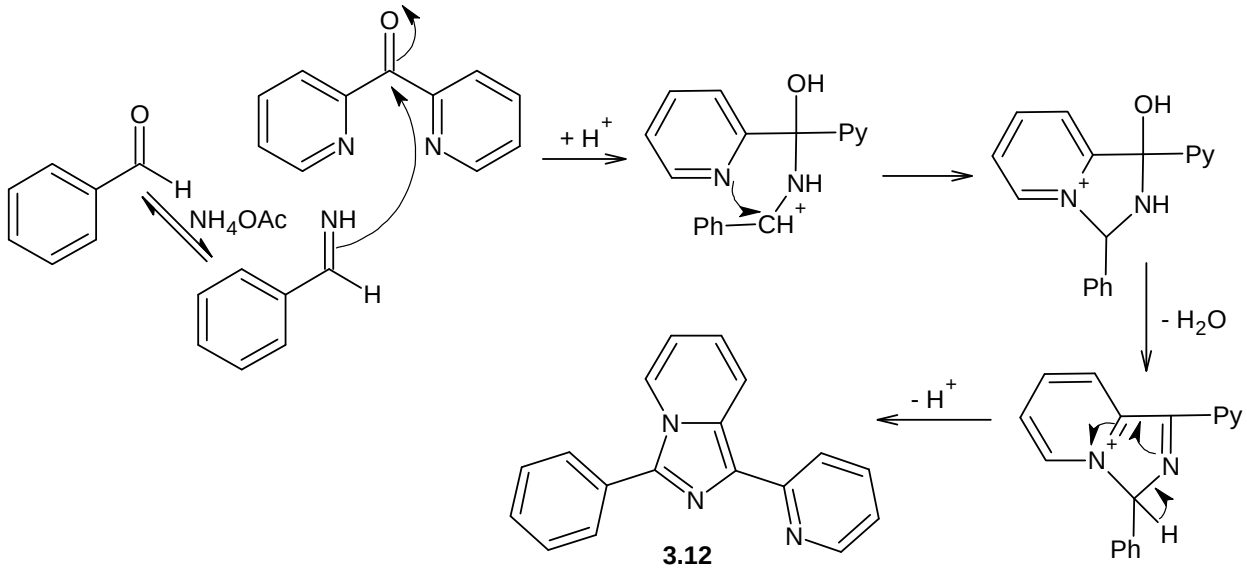
Scheme 3.7*: A one-pot synthesis of imidazo[1,5-a]pyridines (**3.10**)*

Wang and coworkers[22] reported the synthesis of 1-(2-pyridoyl)-3-phenylimidazo[1,5-a]pyridines (**3.11**) and 4,5-bis-(2-pyridyl)-2-phenylimidazole (R = H) (**3.5**). **3.5** was formed as a side product as described above. **3.11** was obtained by the treatment of 2,2'-pyridyl and benzaldehyde (R = H) with ammonium acetate in the presents of acetic acid. The reaction was carried at 118 °C and was optimized to 68% when the ratio of pyridyl, aldehyde and ammonium acetate is 2:1:2. It is worth noting that both products can be optimized depending on the reaction conditions and the ratio of pyridyl, aldehyde and ammonium acetate. When the ratio of pyridyl to aldehyde to ammonium acetate is 1:1:8, **3.5** was produced in greater amount and when the ratio was changed to 2:1:2, **3.11** was optimally produced.



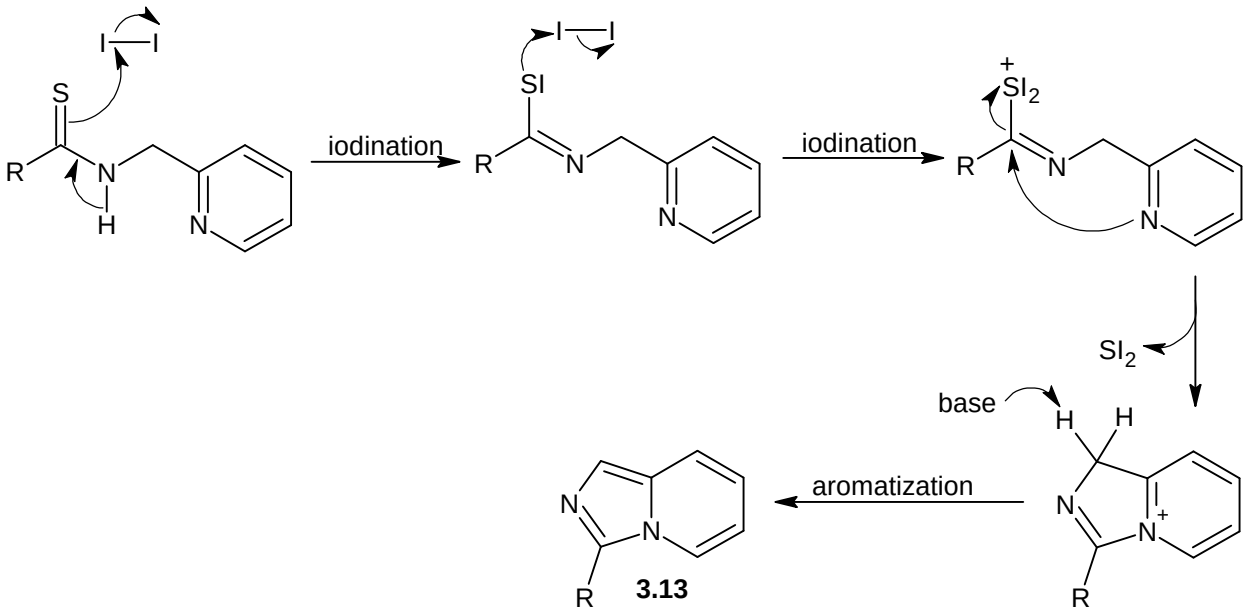
Scheme 3.8: *Synthesis of 1-(2-pyridoyl)-3-phenylimidazo[1,5-a]pyridines (**3.11**).*

Bu and coworkers[44] reported the synthesis of 1-(2-pyridyl)-3-phenylimidazo[1,5-a]pyridine (**3.12**) which involved the reaction of benzaldehyde with 2,2'-dipyridyl ketone and ammonium acetate in acetic acid with the yield of 69 %. A series of benzaldehyde derivatives with different substituents were also used to yield corresponding imidazole compounds. To optimize reaction yields, reaction conditions such as ketone, aldehyde and ammonium acetate molar ratios were varied to give yields varying from 55 % to 90 %.



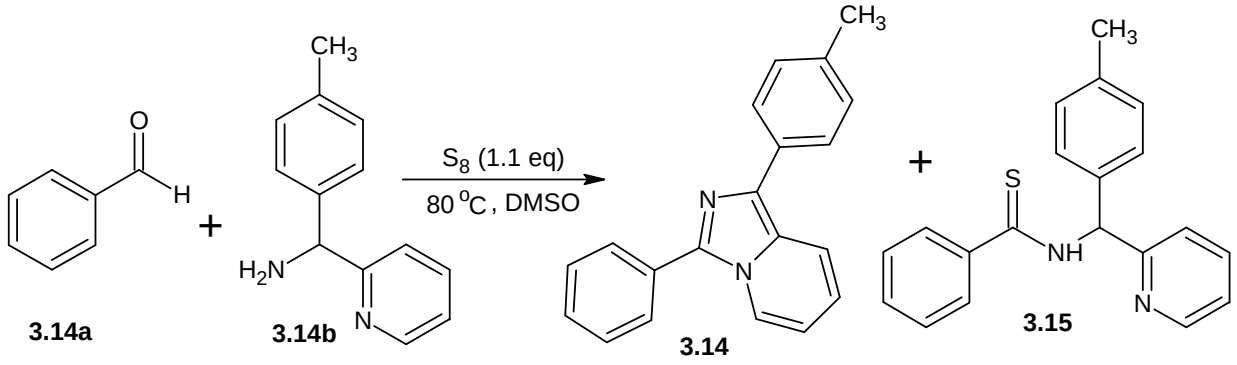
Scheme 3.9: *Synthesis of 1-(2-pyridyl)-3-phenylimidazo[1,5-a]pyridine (**3.12**).*

Shibahara *et al*[45] reported the synthesis of 2-azaindolizine (**3.13**) following the method called iodine-mediated, oxidative desulfurization promoted cyclizations of *N*-2-pyridylmethyl thioamides. This was achieved by reacting *N*-2-pyridylmethyl thioamides with iodine (3 equivalents) in the presence of pyridine (3 equivalents) in 0.5 M THF and stirred for 15 min at room temperature to give a yield of 89 %. Various derivatives of this kind of products were also synthesized in this manner where R group was varied to afford yields ranging from 59 to 95 %.



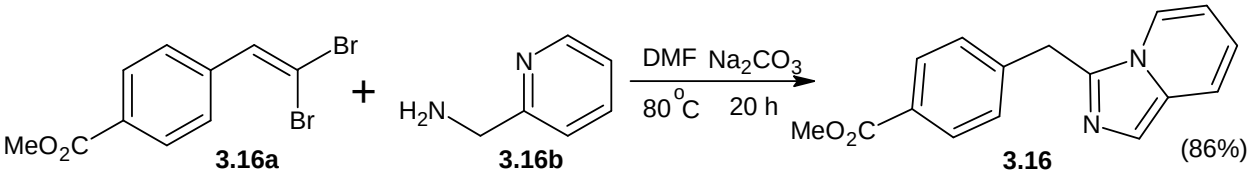
Scheme 3.10: *Synthesis of 2-azaindolizine (**3.13**)*

Shibahara and coworkers[46] described the oxidative condensation-cyclization of an aldehyde (**3.14a**) and aryl-2-pyridylmethylamine (**3.14b**) in the presence of elemental sulfur. Sulfur was used as an oxidant in the absence of catalyst. They firstly did this reaction in dimethyl formamide (DMF) solvent and two products were formed, 1-(4-tolyl)-3-phenylimidazo[1,5-a]pyridine (**3.14**) and N-(2-pyridyl-4-tolymethyl)benzenecarbothioamide (**3.15**) in yields of 46 % and 33 %, respectively. When the solvent was changed to DMSO, only the desired product (3.14) was formed in 64 % yield.



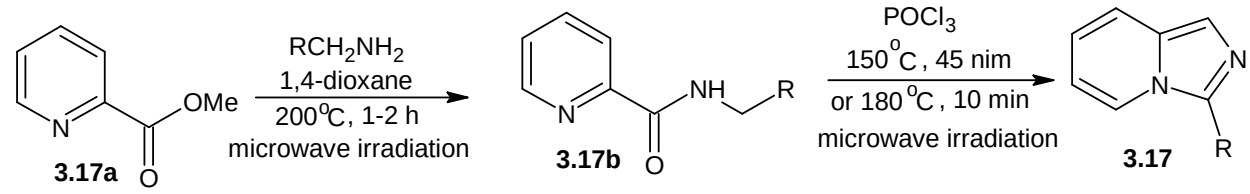
Scheme 3.11: *Synthesis of a 1,3-diarylated imidazo[1,5-a]pyridine (**3.14**)*

Recently, Shen and coworkers[47] synthesized imidazo [1,5-a]pyridine (**3.16**) by reacting methyl 4-(2,2-dibromovinyl)benzoate (**3.16a**) with 2-aminomethylpyridine (**3.16b**). The reaction yield was optimized to 86 % by heating the reaction up to 80 °C in DMF in the presence of sodium carbonate (Na_2CO_3).



Scheme 3.12: *Synthesis of methyl 4-(imidazo[1,5-a]pyridine-3-ylmethyl)benzoate (**3.16**)*

Yet and others[48] have reported a microwave-assisted synthesis of 3-substituted imidazo[1,5-a]pyridines (**3.17**) from methyl picolinate (**3.17a**) and a series of substituted benzylamines. Methyl picolinate was firstly converted to the corresponding picolinamides (**3.17b**) and subsequently cyclized to the required products in the presents of phosphorus oxychloride ($POCl_3$). This reaction similar is to that followed by Fuentes and Paudler[41] 35 years ago but the reaction time is considerably reduced.

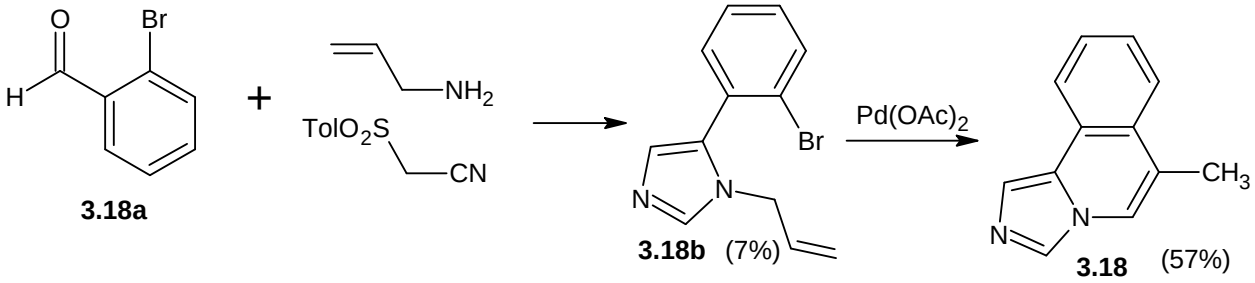


Scheme 3.13: *Synthesis of 3-substituted imidazo[1,5-a]pyridines (**3.17**)*

3.4.1.2. System 2

Beebe and coworkers,[49] however, decided to use a multi-component reaction strategy which uses a sequential Leusen/intermolecular Heck cyclization to give the fused imidazo[1,5-

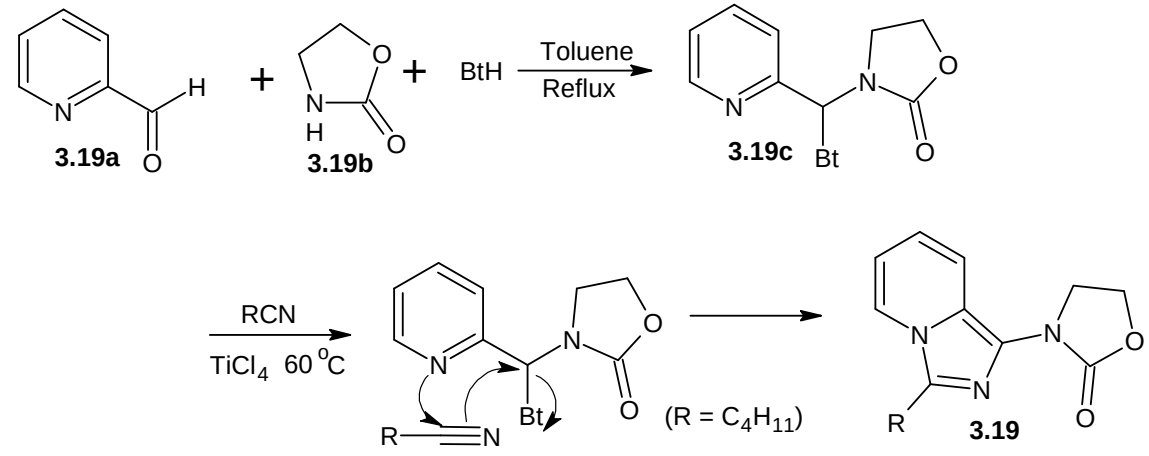
a]pyridines (**3.18**). The van Leusen imidazole synthesis involved using an appropriate aldehyde (**3.18a**) containing a vinylogous bromide and condensing it with an amine containing a double bond to give an imine which was treated with tosylmethyl isocyanides ($TolO_2SCH_2NC$) in the presence of base. All these cyclization occurred at room temperature. The resulting imidazole (**3.18b**) was further subjected to Heck cyclization which was palladium catalyzed to give the desired imidazo[1,5-a]pyridine (**3.18**).



3.18a **3.18b** (7%) **3.18** (57%)

Scheme 3.14: *Synthesis of fused imidazo[1,5-a]pyridine (**3.18**)*

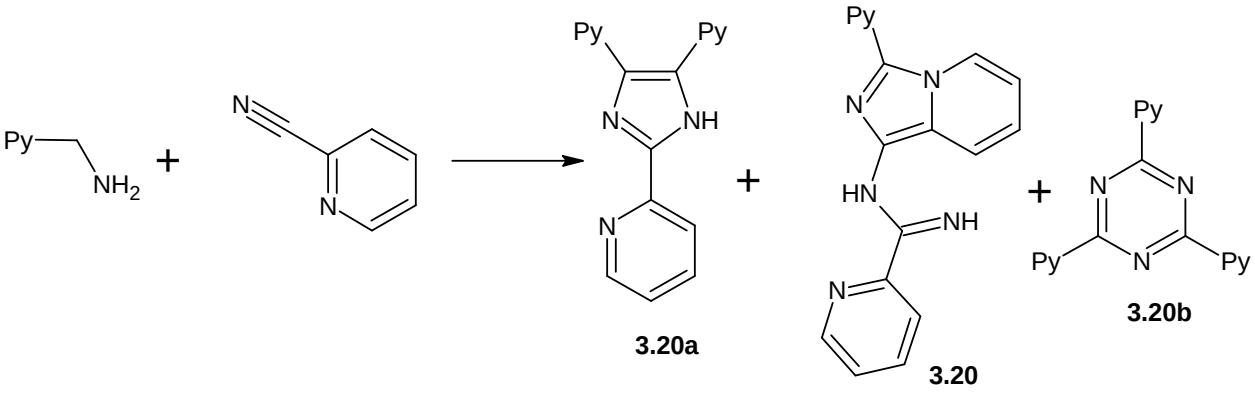
Katrizky and Qiu synthesized imidazo[1,5-a]pyridine from the addition of 2-pyridinecarboxaldehyde (**3.19a**) and benzotriazole with 2-oxazolidinone (**3.19b**) to yield Mannich adduct (**3.19c**) which further reacted with aliphatic cyanides at 60 °C in the presence of $TiCl_4$ to give **3.19**.



Scheme 3.15: *Synthesis of 1-amino-3-alkylimidazo[1,5-a]pyridines (**3.19**)*

3.4.2. Indirect synthesis of imidazo[1,5-a]pyridines

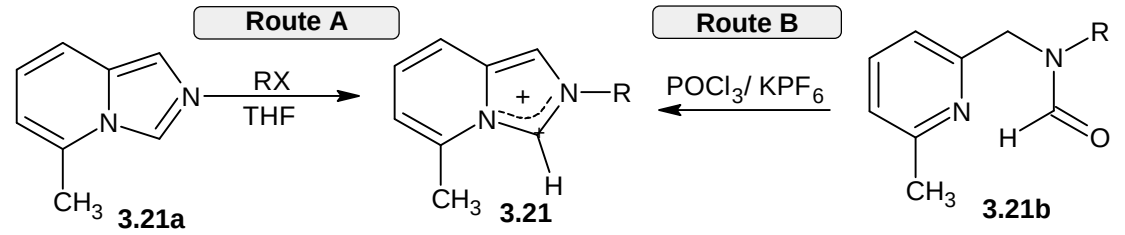
Imidazo[1,5-a]pyridines have also been synthesized indirectly, for instance, Manivannan and coworkers,[50] heated a neat 1: 2 mixture of 2-picolylamine and 2-cyanopyridine and then treated the resulting red gummy substance with aqueous potassium hydroxide to get 2,4,5-tris-(2-pyridyl)imidazole (**3.20a**) (70 %), **3.20b** (20 %) and *N*-(3-(2-pyridyl)imidazo[1,5-a]pyridine)picolinamidine (**3.20**) in a minor yield of 5 %, as a side product.



Scheme 3.16: *Synthesis of N-(3-(2-pyridyl)imidazo[1,5-a]pyridine)picolinamidine (**3.20**) as a side product*

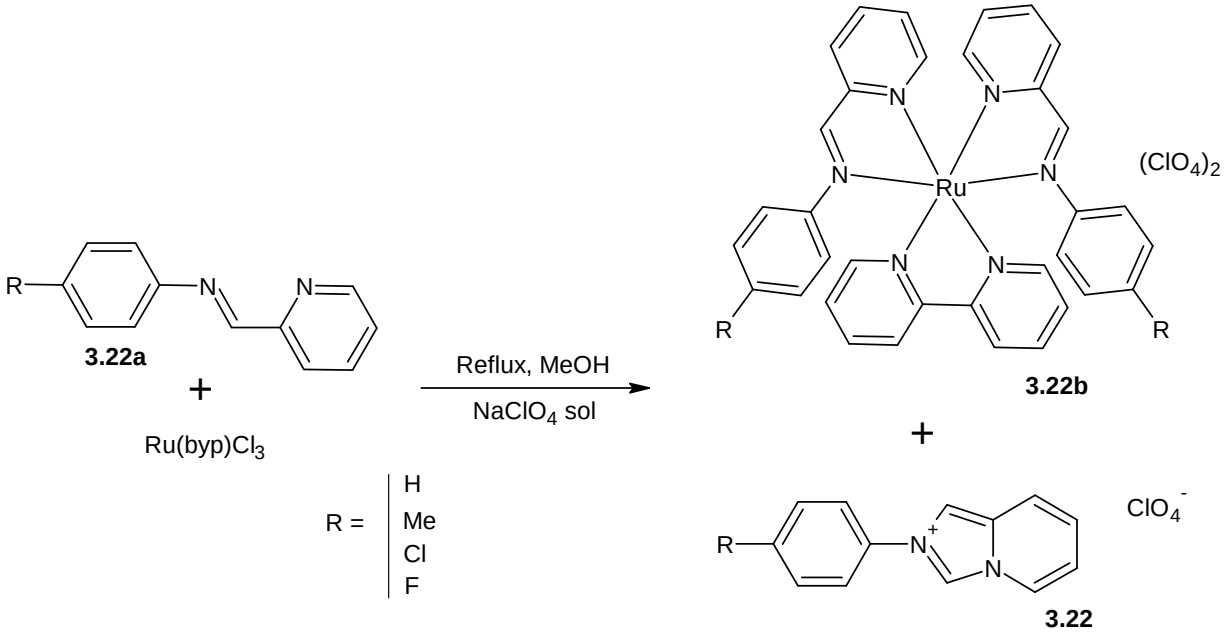
3.5. Synthesis of quaternary imidazo[1,5-a]pyridine

Lassaletta and coworkers,[51] developed the synthesis of quaternary imidazo[1,5-a]pyridines (**3.21**) via two routes, **A** and **B,** as shown in scheme 3.17. Route **A** involves the alkylation of pyridyl imidazole through tertiary nitrogen atom to give the desired product. The second (route **B**) was accomplished by cyclization of formamide (3.21b) in the presence of phosphorus oxychloride ($POCl_3$) to give *N*-alky/aryl imidazo[1.5-a]pyridinium salts (**3.21**). They found the route **B** to be the most versatile method with fewer restrictions. But their aim was to synthesize NHC carbenes which they used for chelating metals.



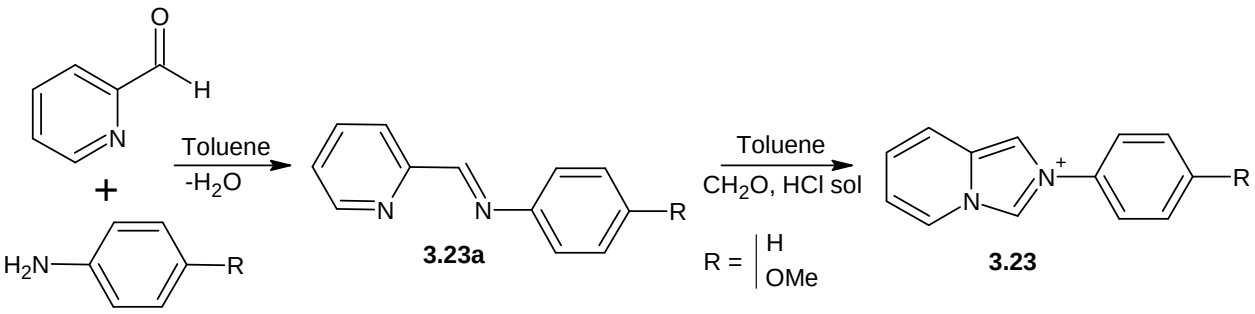
Scheme 3.17: *Synthesis of N-alky/aryl imidazo[1.5-a]pyridinium salts (**3.21**)*

Chattopadhyay and others,[52] synthesized aryl imidazo[1.5-a]pyridinium salts (**3.22**) as side products from refluxing ruthenium ($Ru(byp)Cl_3$) with *N*-(aryl) pyridine-2-aldimine (**3.22a**) in methanol. They further explained the mechanism of formation of aryl imidazo[1.5-a]pyridine as that, the ruthenium complex oxidizes the solvent methanol to formaldehyde which then react with *N*-(aryl) pyridine-2-aldimine (**3.22a**) to give **3.22**.



Scheme 3.18: *Synthesis of N-aryl imidazo[1.5-a]pyridinium salts (**3.22**)*

Mashima and coworker,[53] reported a two-step synthesis aryl imidazo[1.5-a]pyridinium salts (**3.23**) as shown in scheme 3.19. The first step involves the condensation of 2-formylpyridine with aniline in toluene to give 2-pyridyl-*N*-(phenyl)methylimine (**3.23a**). The second step involving the cyclization of the imine was achieved by treating imine (**3.23a**) with paraformaldehyde in the presence of hydrochloric acid in toluene.



Scheme 3.19: *Synthesis of N-aryl imidazo[1.5-a]pyridinium salt (**3.23**)*

As shown above, there are different kinds of imidazolium compounds with different synthetic methods, however, our interest is in imidazo[1.5-a]pyridine compounds. Though, there are quite number of imidazopyridinium compounds that have been reported so far but *N*-aryl imidazo[1.5-a]pyridinium derivatives are rare. More imidazolium compounds of this kind were synthesized following the procedure where phosphorus oxychloride ($POCl_3$) and hydrochloric acid (HCl) were used separately. In this project, we did a comparative study of both Chattopadhyay method and the Mashima method. The results and discussion of our findings will be disclosed in the next chapter.

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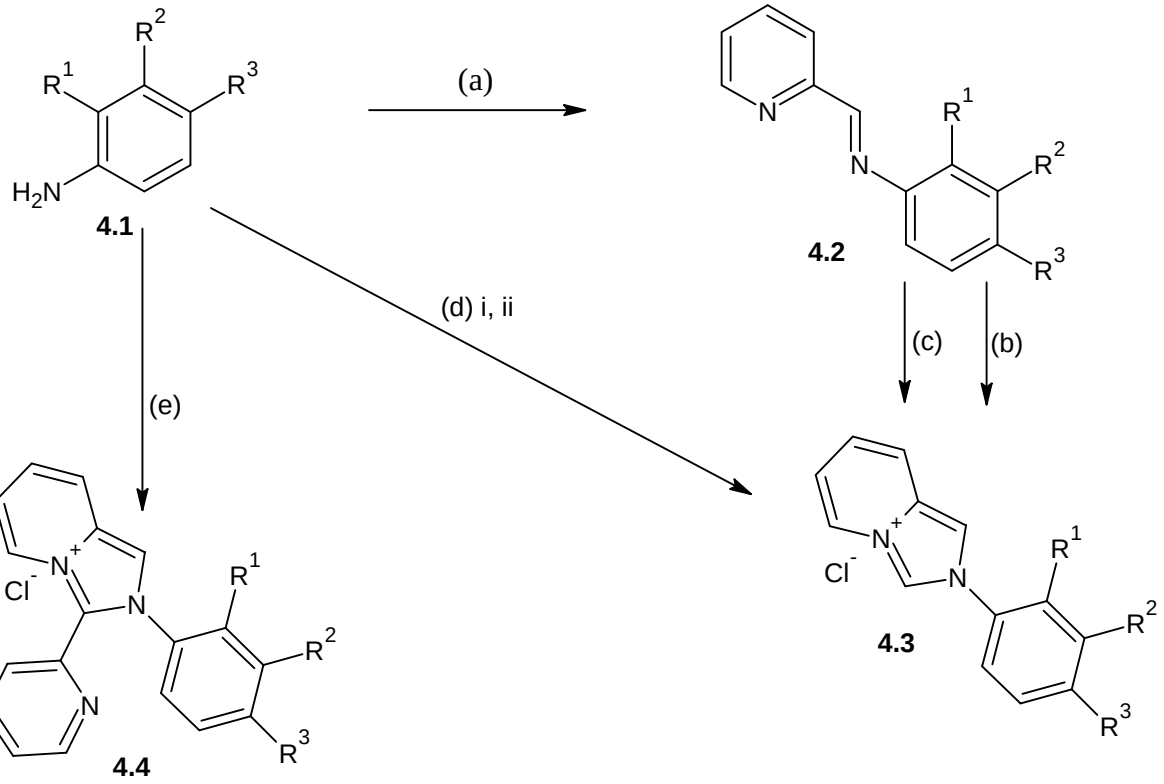
CHAPTER 4 RESULTS AND DISCUSSION

4.1. Synthesis of the imidazo[1,5-a]pyridinium compounds

As mentioned in the previous chapters, the imidazo[1,5-a]pyridine skeletons (2-azaindolizines) have potential applications in material chemistry as organic light-emitting diodes (OLEDs),[1] as organic thin layer effect transistors (FETs)[2] and as precursors of *N*-heterocyclic carbenes which not only have potential use as therapeutic agents but also as ligands to metals in catalysis. The pharmaceutical applications include their use as aromatase inhibitors in estrogen-dependent diseases, thromboxane A_2 synthase inhibitor, and angiotensin II receptor antagonists.

A variety of methods have been reported in the literature for the synthesis of these azaindolizines. Most of the methods used were variations of the traditional Vilsmeier-type cyclization of *N*-2-pyridyl methyl amides or its carboxylic acid derivatives with various catalysts such as dicyclohexylcarbodiimide, mercuric salts, and iodine/pyridine. These methods generally give low to moderate yields, require harsh conditions whilst giving tarry products and require the use of environmentally toxic reagents.

In this chapter we will outline the synthesis of 2-azaindolizines by first reacting pyridine-2-aldehyde with various amines to give the corresponding Schiff's reagents. We will describe the scope and limitations of this method. We will also describe the cyclization of 2-pyridyl-*N*-(phenyl)methylimine and their derivatives with paraformaldehyde using first $POCl_3$ and then HCl as catalysts. Finally, we will attempt to synthesize 2-azaindolizines directly from pyridine-2-aldehyde, aniline derivatives and paraformaldehyde without the isolation of the proposed Schiff bases. All these procedures are outlined in scheme 4.1 below.



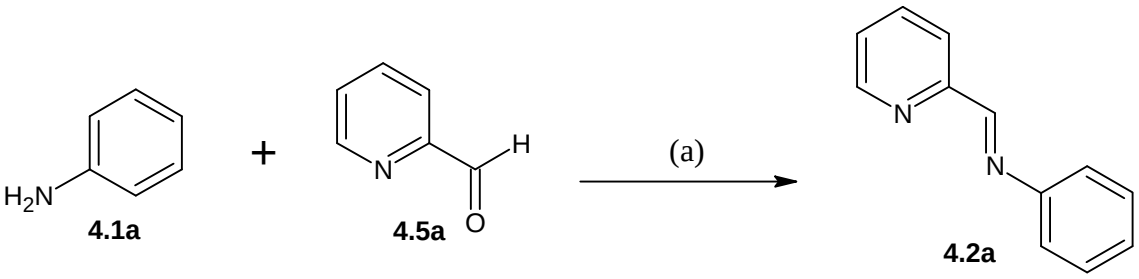
Reagents and conditions: (a) Pyridine-2-aldehyde, EtOH, 41-92 %; (b) HCOH, $POCl_3$, toluene, 60-86 %; (c) HCOH, HCl, toluene, 66-97 %; (d) i) Pyridine-2-aldehyde, EtOH, ii) HCOH, HCl, toluene, 67-73 %; (e) Pyridine-2-aldehyde (2eq), EtOH, HCl, 58-62 %.

Scheme 4.1: *Synthesis of the imidazolium compounds.*

4.1.1. Synthesis of imines, the intermediates (4.2)

In the last decade, Schiff bases derived from 2-pyridine carbaldehyde have received much attention, particularly in coordination chemistry and supramolecular systems. In this thesis we report the synthesis, and spectroscopic characterizations of Schiff base derived from 2-pyridine carboxaldehyde and aniline derivatives. When 1 equivalent (1eq) of pyridine-2-carbaldehyde (**4.5a**) was reacted with 1eq of aniline (**4.2a**) under reflux in the presence of methanol, 2-pyridyl-*N*-(phenyl)methylimine was obtained as a light brown liquid as shown in scheme 4.2. Characterization techniques such as nuclear magnetic resonance (NMR), infrared

(IR), mass spectra (LCMS) and ultra-violet absorption (UV) were used to verify the formation of 2-pyridyl-*N*-(phenyl)methylimine (**4.2a**).



Scheme 4.2: *Formation of 2-pyridyl-N-(phenyl)methylimine (**4.2a**)*

The completion of the reaction was confirmed by the disappearance of the strong carbonyl peak stretching at 1708 cm^{-1} in the IR spectrum shown in figure 4.3. The aldehydic C-H moderate peak which resonates at 2900 cm^{-1} in IR spectrum also disappeared. The appearance of strong peaks for C=N and C-N at 1627 cm^{-1} and 1346 cm^{-1} respectively confirmed the structure of **4.2a**.

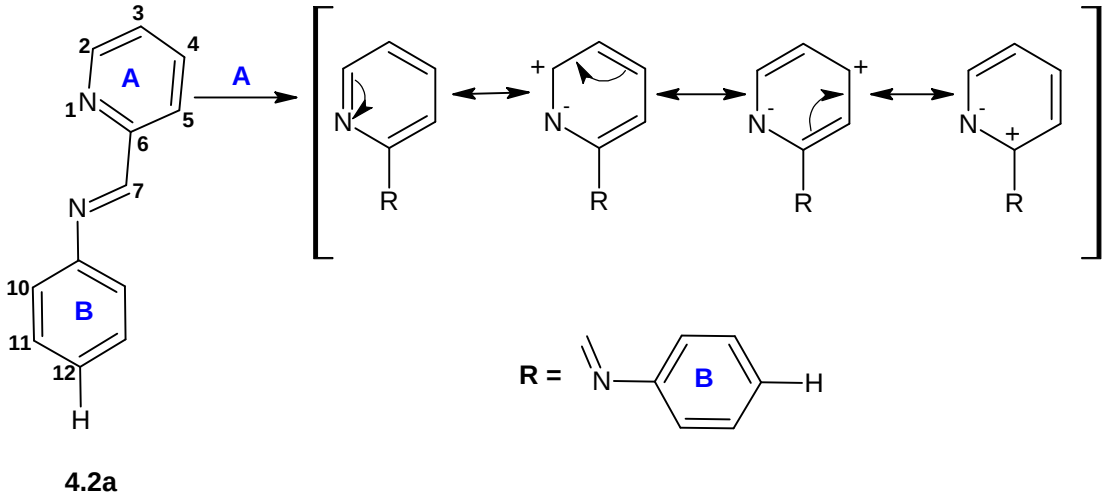
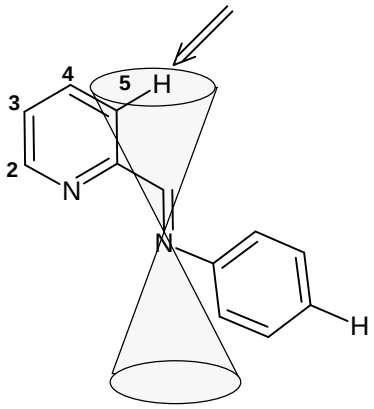


Figure 4.1: *Resonation of electrons on the conjugated structure of imine (**4.2a**).*

The protons in the pyridyl ring are more deshielded than those of benzene ring, thus more downfield on the NMR spectrum as in figure 4.4. This is because of the inductive effect of the nitrogen atom of pyridyl ring which tends to withdraw the cloud of electrons towards itself. The closer view of the pyridyl ring protons reveals the following: due to the mesomeric effect on the ring, **H-2** (8.70 ppm) and **H-4** (7.77 ppm) were shifted more downfield than **H-3** (7.33 ppm). This was made possible by the ability of nitrogen atom to gain more electrons, thus becomes negatively charged as shown in figure 4.1 (**A**). This effect results in the formation of partially positive centers on **H-2** and **H-4**. Furthermore, **H-2** was shifted further downfield than **H-4** because of the additional inductive effect caused by the more electronegative nitrogen atom which is adjacent to **C-2**. Surprisingly, **H-5** was shifted more downfield than **H-4** because of the anisotropic effect caused by the N=C bond on **H-5** as shown in figure 4.2. All the protons in the shaded cone such as **H-5** were deshielded, as a result **H-5** was shifted downfield.



4.2a

Figure 4.2: *Anisotropic effect on the proton-5 on the structure of imine (**4.2a**).*

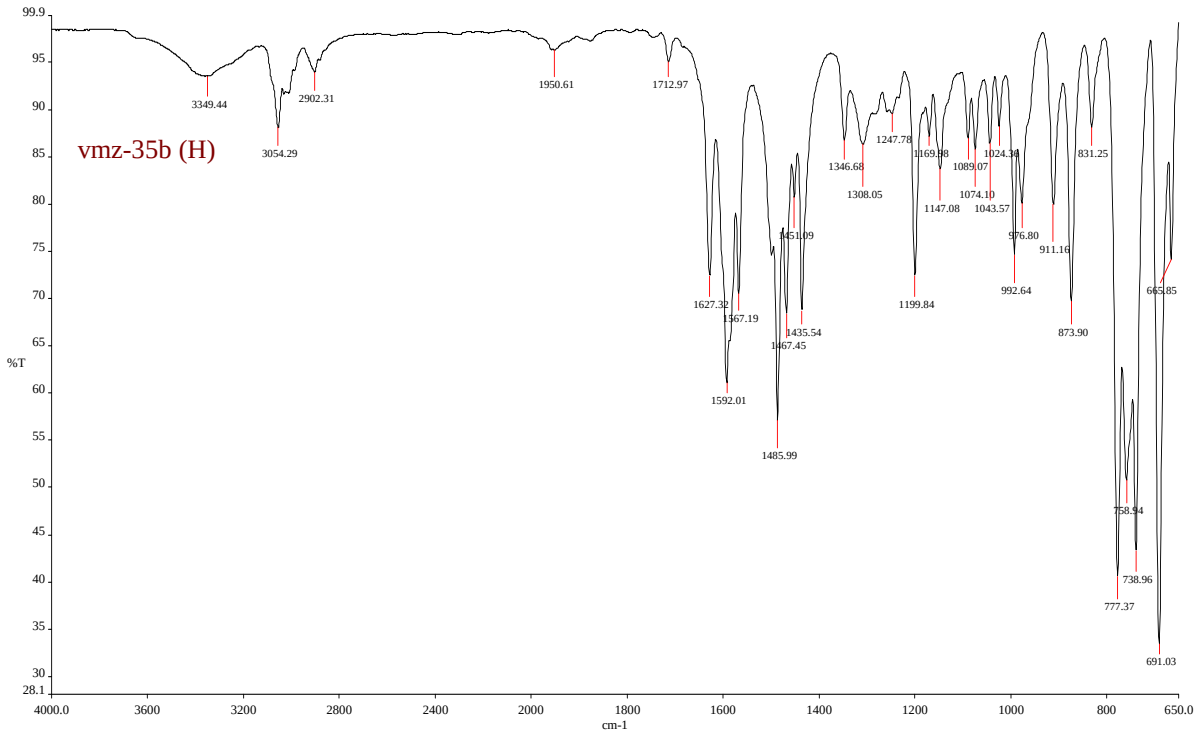


Figure 4.3: *The IR spectrum of 2-pyridyl-N-(phenyl)methylimine (**4.2a**)*

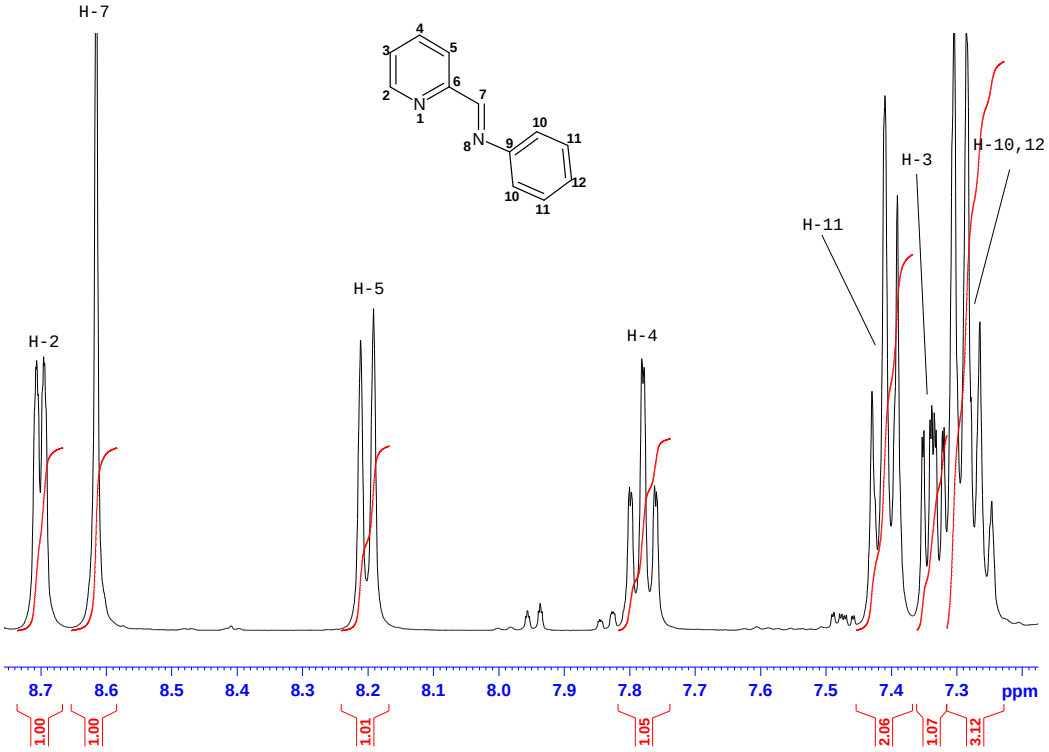
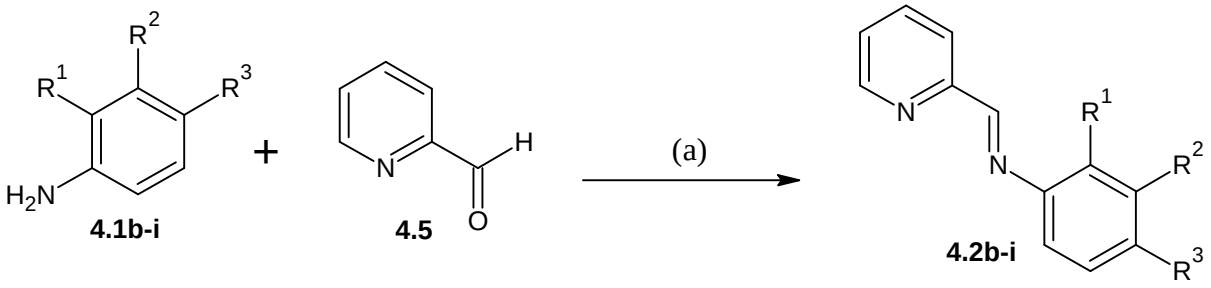


Figure 4.4: *^{1}H NMR spectrum of 2-pyridyl-N-(phenyl)methylimine (**4.2a**)*

4.1.2. Reaction of pyridine-2-aldehyde (4.5) with *ortho, meta* and *para* substituted anilines (4.1b-i)

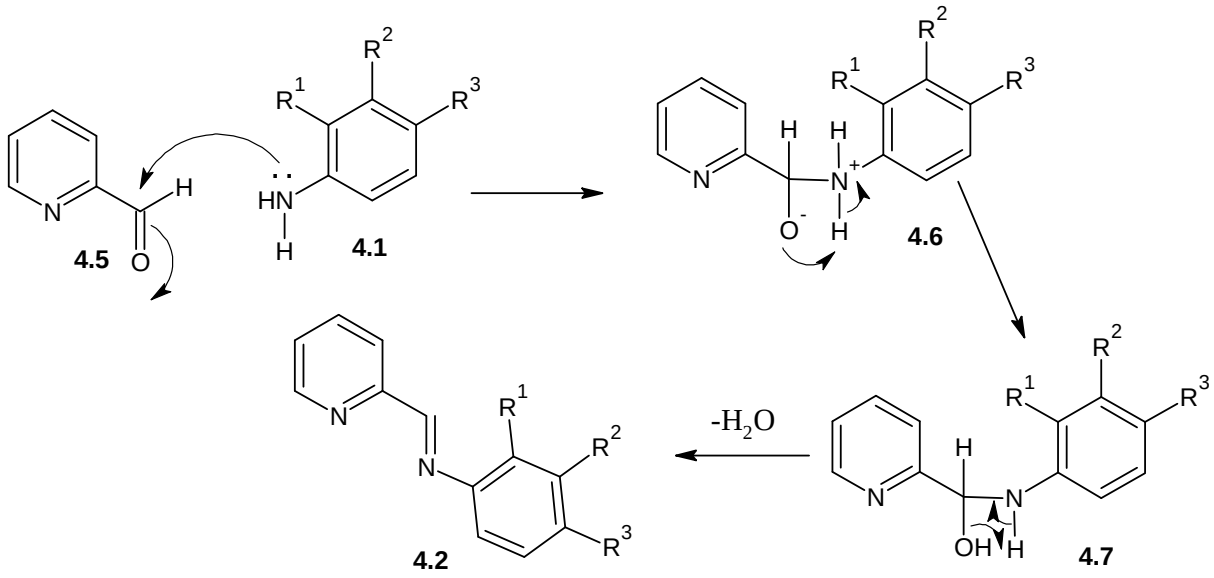
The reaction of one equivalent (1eq) of pyridine-2-carbaldehyde (**4.5**) with one equivalent (1eq) of *ortho, meta* and *para* substituted aniline (**4.1b-i**) where R^1, R^2 or R^3 are electron-donating or mildly electron withdrawing yielded corresponding imine intermediates (**4.2b-i**) as shown in scheme 4.3.



Scheme 4.3: *Reaction of pyridine-2-aldehyde (**4.5**) with ortho, meta and para substituted anilines (**4.1b-i**)*

Scheme 4.4 shows the mechanism of the formation of imines intermediates (**4.2a-i**) following the condensation of pyridine-2-carbaldehyde (**4.5**) with *ortho, meta* and *para* substituted anilines (**4.1a-i**). Not all groups of the substituted anilines produced intermediate (**4.2**) but only the groups where R^3 is electron donating and mild electron withdrawing. When R^3 is electron withdrawing the formation of intermediates (**4.2**) was not possible.

When R^3 is an electron donating group, the lone pair of electrons on the nitrogen of anilines (**4.1**) is highly available for nucleophilic attack to the carbonyl carbon of pyridine-2-carbaldehyde (**4.5**) to form **4.6**. The intermediate (**4.6**) formed has a quaternary nitrogen atom which leads to the proton transfer to form **4.7**. The imine intermediate is formed subsequently from the dehydration of intermediate (**4.7**).



Scheme 4.4: *Proposed mechanism for the synthesis of imine intermediates (**4.2**)*

On the other hand, when R^3 is an electron withdrawing group, the lone pair of electron on the nitrogen of aniline (**4.1**) is less available for nucleophilic attack. That could be the reason as why the intermediates for this kind of substituents could not be formed.

The first imine intermediate (**4.2a**) was readily made following the condensation of pyridine-2-carbaldehyde (**4.5**) with aniline (**4.1**). Various *ortho*, *meta* and *para* substituted imine analogues (**4.2b-i**) were also synthesized in the same manner. The yield of these imine intermediates ranged from 41-92 % as shown in brackets in figure 4.5. It is important to note that the structures of these imine intermediates are conjugated.

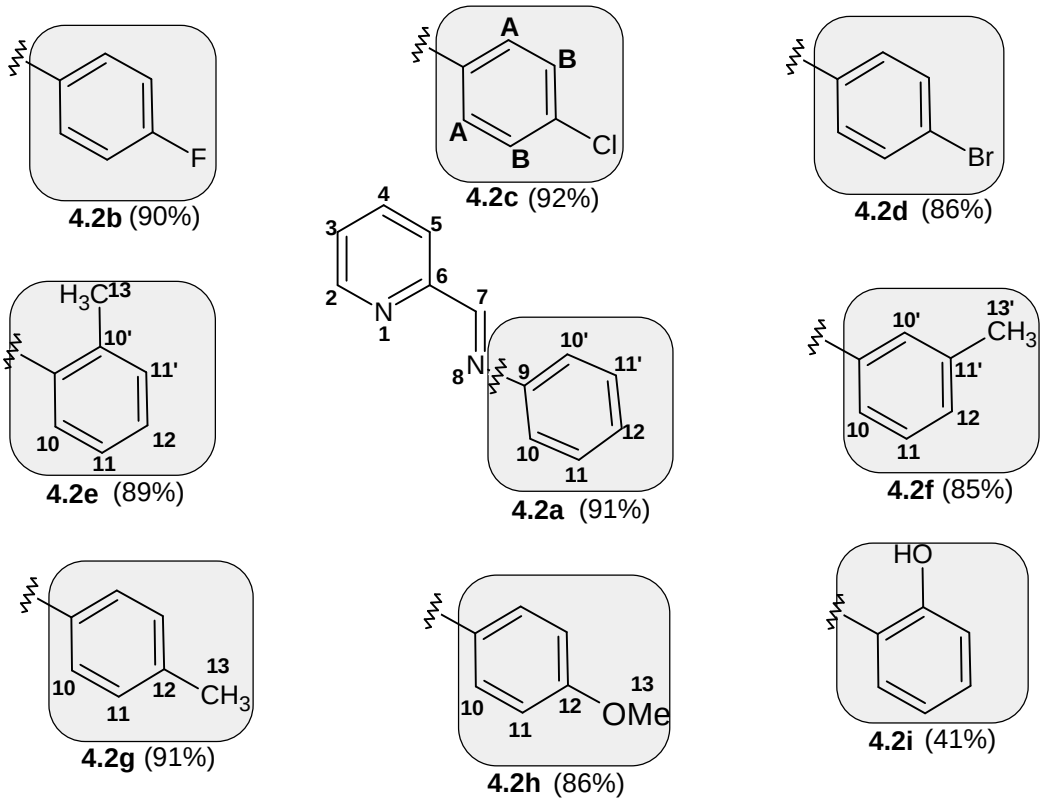


Figure 4.5: *Various imine intermediates (**4.2**) synthesized and their yields in brackets*

This is confirmed for example by the proton NMR spectrum of 2-pyridyl-N-(*m*-methylphenyl)methylimine (**4.2f**) in figure 4.6, wherein, a singlet peak (**H-13**) for the methyl group appears upfield (2.41 ppm) verifying the incorporation of the *meta* methyl-substituted aniline. For the *para* substituted aniline the AA'BB' system is observed as shown in table 4.1 (AA'BB' system indicates the symmetrical *para* substitution where the two substituents are not the same). The protons in the pyridine ring are arranged as in figure 4.4 and those of the benzene ring their chemical shifts, splitting and coupling constants values are summarized in table 4.1. A comparative study of the aromatic region of various imine intermediates as shown in table 4.1 indicates that there is no significant change in the chemical shift of the aromatic protons. Any changes are due to the effect of the substituents.

	^{1}H NMR ($CDCl_3$) δ_H (in ppm) and J coupling (in Hz)					
	H-10	H-11	H-12	H-10'	H-11'	H-13
(4.2a)	**7.28 d** $J_{10,11}$ 8.6 $J_{10,12}$ 2.1	**7.41 dd** $J_{11,10}$ 8.6 $J_{11,12}$ 7.9	7.29 tt $J_{12,11}$ 7.9 $J_{12,10}$ 2.1	Same as H-10 –		
(4.2b)	**7.10 d** $J_{10,11}$ 8.6	**7.29 d** $J_{11,10}$ 8.6		–		
(4.2c)	**7.24 d** $J_{10,11}$ 8.5	**7.37 d** $J_{11,10}$ 8.5		–		
(4.2d)	**7.15 d** $J_{10,11}$ 8.2	**7.51 d** $J_{11,10}$ 8.2		–		
(4.2e)	**7.03 d** $J_{10,11}$ 7.5	**7.24 d** $J_{11,10}$ 7.5	**7.17 t** $J_{12,(11,13)}$ 7.5		**7.24 d** $J_{13,12}$ 7.5	**2.43 s**
(4.2f)	**7.11 t** $J_{10,11}$ 7.4	**7.31 t** $J_{11,(10,12)}$ 7.4	**7.12 d** $J_{12,11}$ 7.4	**7.13 s**		**2.41 s**
(4.2g)	**7.14 d** $J_{10,11}$ 7.5	**7.15 d** $J_{11,10}$ 7.5		**–**		**2.34 s**
(4.2h)	**7.29 d** $J_{10,11}$ 7.8	**6.91 d** $J_{11,10}$ 7.8				**3.78 s**
(4.2i)	**7.41 d** $J_{10,11}$ 7.8	**6.95 t** $J_{11,(10,12)}$ 7.8	**7.26 t** $J_{12,(11,13)}$7.8		**7.05 d** $J_{13,12}$ 7.8	**1.78 br**

Table 4.1: *^{1}H NMR spectral data of the benzene region of various imine intermediates.*

The success of the reaction was also marked by the disappearance of the aldehydic proton at a chemical shift (δ) 9.7 ppm and the appearance of the imminium proton at δ 8.62 ppm. However, a comparative study of the chemical shifts of the various imminium protons, CH^1=N, are shown in the table 4.2. When the substituent on the para position is a halogen, we

can clearly observe a pattern emerging in the change in chemical shifts. Bromine has the greatest change in chemical shift (Δδ) of 0.04 ppm followed by chlorine with Δδ of 0.02 ppm, the imminium proton clearly shifts upfield as we move from the more electronegative (fluorine) to the less electronegative (chlorine). When the substituent on the aromatic ring is a methyl group (4.2e, 4.2f and 4.2g) another trend is observed. The imminium proton is not affected by methyl group at the *para* and *meta* positions. However, when the methyl group is at the *ortho* position, a slight upfield shift (Δδ is 0.06 ppm) was observed. The most pronounced change in chemical shift, however, is observed with the *ortho* hydroxyl group. The imminium proton shifted from δ 8.61 ppm to δ 8.86 ppm (Δδ is 0.25 ppm). This chemical shift may be due to the imminium proton forming intramolecular hydrogen bonding with the hydroxyl oxygen as shown in scheme 4.5.

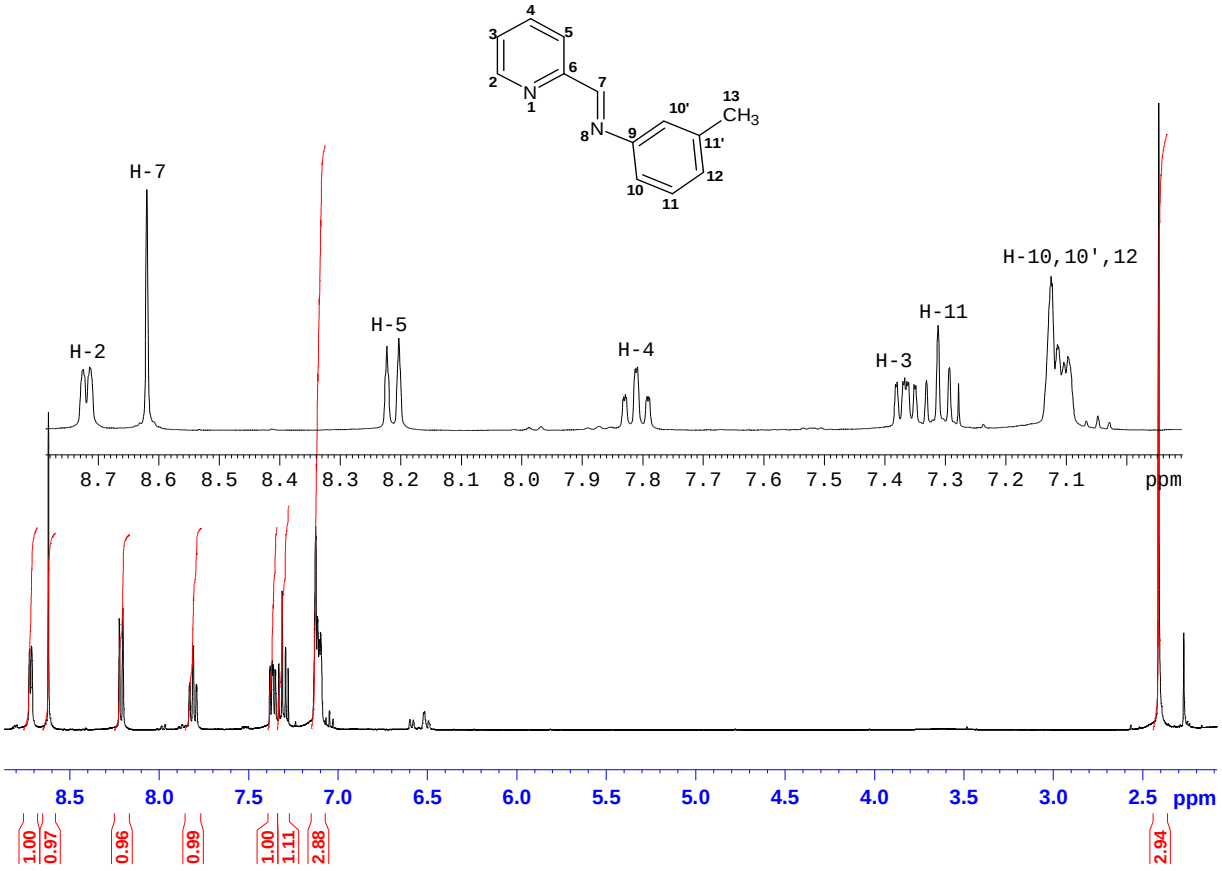
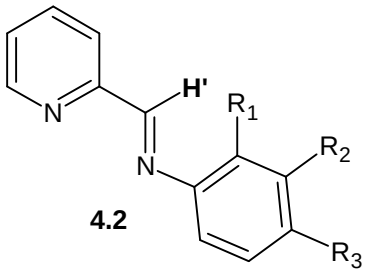


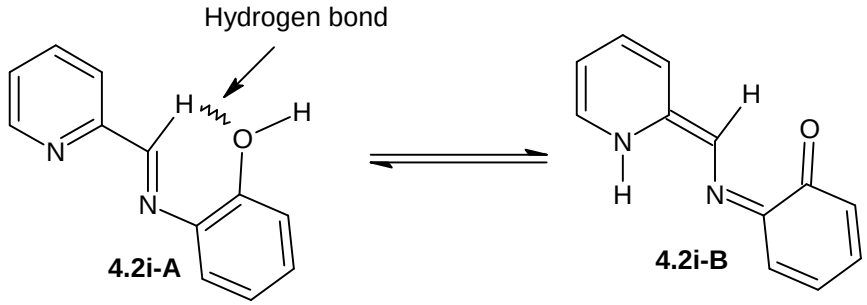
Figure 4.6: *^{1}H NMR spectrum of 2-pyridyl-N-(m-methylphenyl)methylimine (**4.2f**)*



4.2

Phenyl substituents				Chemical shift (δ, ppm)	Change in chemical shift for H' (Δδ, ppm) (No.-4.2a)
No.	R_1	R_2	R_3	for H'	
4.2a	H	H	H	8.61	0
4.2b	H	H	F	8.60	-0.01 (upfield)
4.2c	H	H	Cl	8.59	-0.02 (upfield)
4.2d	H	H	Br	8.57	-0.04 (upfield)
4.2e	Me	H	H	8.55	-0.06 (upfield)
4.2f	H	Me	H	8.62	0.01 (downfield)
4.2g	H	H	Me	8.61	0
4.2h	H	H	OMe	8.60	-0.01 (upfield)
4.2i	OH	H	H	8.86	0.25 (downfield)

Table 4.2: *Chemical shifts for H' on different R substituents*



Scheme 4.5: *Tautomerism and intramolecular hydrogen bonding in 2-pyridyl-N-(o-hydroxyphenyl)methylimine (**4.2i**)*

The disappearance of an aldehydic C-H stretching band at 2730 cm^{-1} in the infrared spectrum confirmed the successfulness of the reaction. The infrared spectrum also showed the stretching frequencies of various functional groups such as C=N (shown in table 4.3), C-N and that of the aromatic region. The stretching frequencies varied with the substituents. For imines, the C=N stretching band occurs in the region 1690 – 1620 cm^{-1} (5.92 – 6.17 µm), but the closeness of this bond to C=C conjugated system presents difficulties. Conjugated cyclic systems containing C=N have variable intensity due to the stretching-vibration in the region 1660 – 1480 cm^{-1} (6.02 – 6.76 µm). A comparative study of the $\nu_{C=N}$ stretching frequency of these Schiff bases shows very small derivations from that of **4.2a**, ν is1627 cm^{-1}. However, that of **4.2i** shows movement to smaller wavenumber (1585 cm^{-1}, $\Delta\nu_{C=N}$ is 24). This indicates that there must be a group that is pumping electrons in to C=N. This observation supports the idea that there is intramolecular hydrogen bonding. It is the oxygen of the hydroxyl group that is pumping in electrons as shown in scheme 4.5. The intramolecular hydrogen bonding is also confirmed by the observation of a broad O-H peak at 3373 cm^{-1}in the IR spectrum in figure 4.7. This phenomenon of Schiff base constituting intramolecular hydrogen bonding and tautomerism of the structure forming enol (**4.2i-A**) and ketone (**4.2i-B**) as shown in scheme 4.5 has been reported before by Helnert *et al*[3] and Ledbetter, Jr[4]. They had a structure similar to ours which was *N*-aryl imine of *o*-hydroxybenzenaldehyde and they observed a peak at 1513 cm^{-1} that they assigned to the C=N stretching vibration of the conjugated imine. This peak agrees with our observation of C=N peak at 1585 cm^{-1}. They also observed a carbonyl

(C=O) peak at 1635 cm^{-1} which is close to our observed weak peak at 1650 cm^{-1} which confirms the tautomerism of the structure to form ketone (**4.2i-B**).

The high resolution mass spectra (HRMS) were also key to determining the mass of each compound as proof of the incorporation of aniline analogues to pyridine-2-barbaldehyde.

Phenyl substituents				Wavenumber (cm^{-1}) and change in C=N stretch	
No.	R_1	R_2	R_3	C=N stretch	$\Delta\nu$ (C=N) stretch
4.2a	H	H	H	1627	_
4.2b	H	H	F	1627	0
4.2c	H	H	Cl	1623	- 4
4.2d	H	H	Br	1622	-5
4.2e	Me	H	H	1631	4
4.2f	H	Me	H	1629	2
4.2g	H	H	Me	1625	-2
4.2h	H	H	OMe	1624	-3
4.2i	OH	H	H	1585	-24

Table 4.3: *The effect of the substituents on the energy (in Wavenumber) of the C=N functional group*

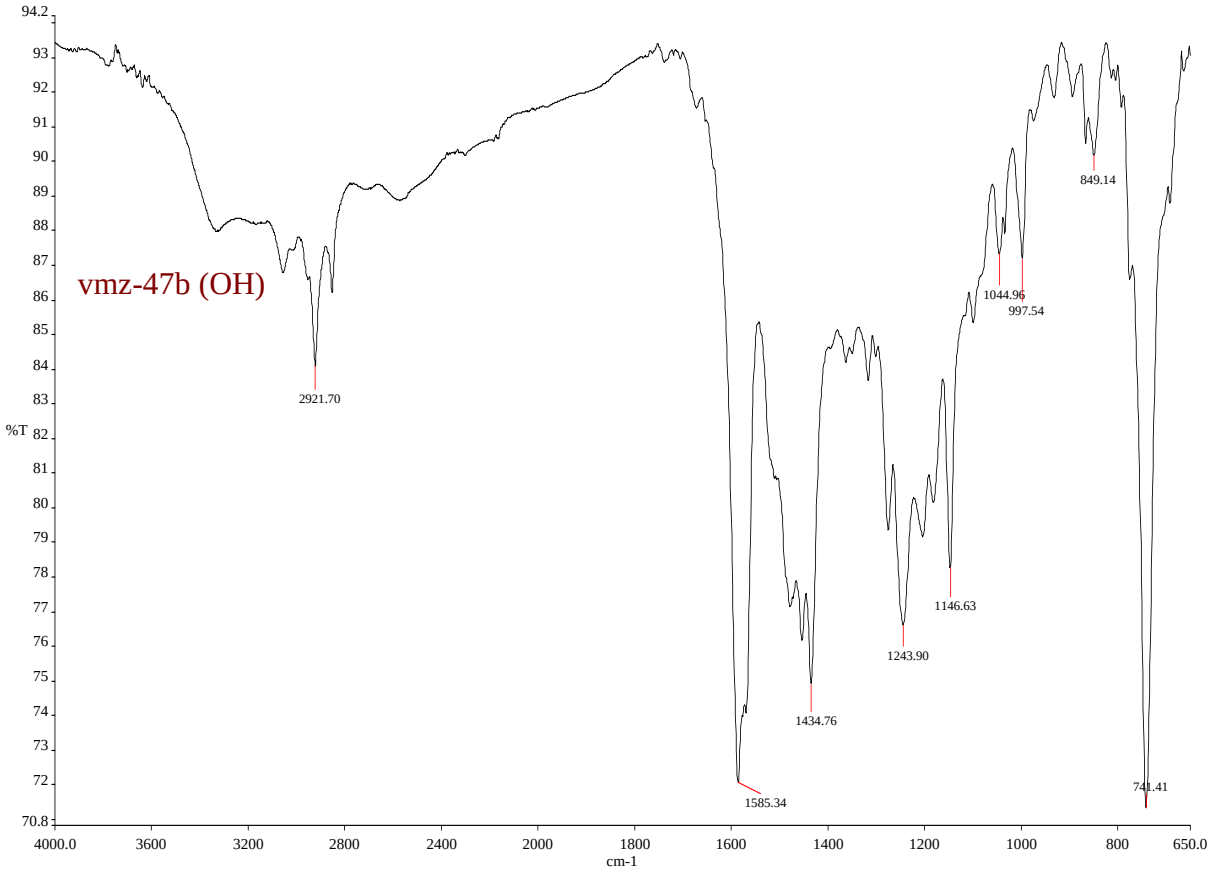


Figure 4.7: *IR spectrum of 2-pyridyl-N-(o-hydroxyphenyl)methylimine (**4.2i**)*

However, not all reactions for the formation of imine intermediates (**4.2**) that were carried out were successful. Some of the failed reactions were the reaction of pyridine-2-carbaldehyde (**4.5**) with aniline derivatives (**4.1i-m**) shown in figure 4.8. As it is stated earlier in this section that, when R^3 is an electron withdrawing group, the imine intermediates (**4.2**) were not isolated, and the reason could be either because of the less availability of the lone pair electron of the nitrogen group for the nucleophilic attack to the carbonyl carbon of **4.5** as shown in scheme 4.4. Different techniques such as Dean Stack and catalyst were tried and did not work still. Because these imine intermediates (**4.2i-k**) could not be isolated so the imidazole compounds **(4.3i-k)** could not be formed following the method shown in section 4.1.2.1 and 4.1.2.2 where $POCl_3$ and HCl, in the presence of the parafomaldehyde were used respectively to catalyze the reaction of formation of the imidazolium compounds (**4.3**). Then we had to

develop new methods to overcome this problem and we came up with one method that is described in section 4.1.3.

Aniline derivatives that could not be isolated as imine intermediates (**4.2**)

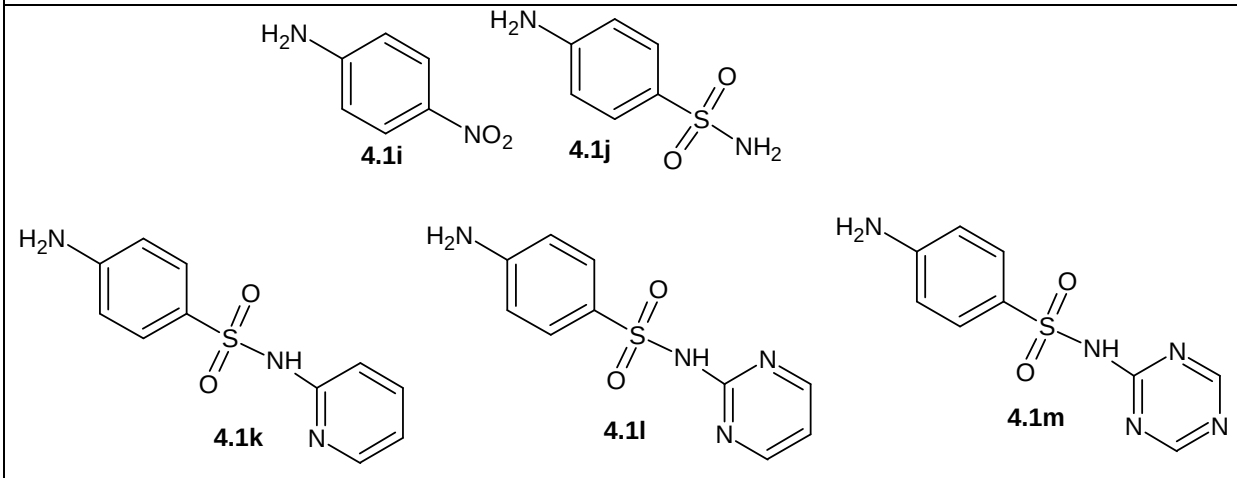


Figure 4.8: *Aniline derivatives that failed to react to form imine intermediates (**4.2**)*

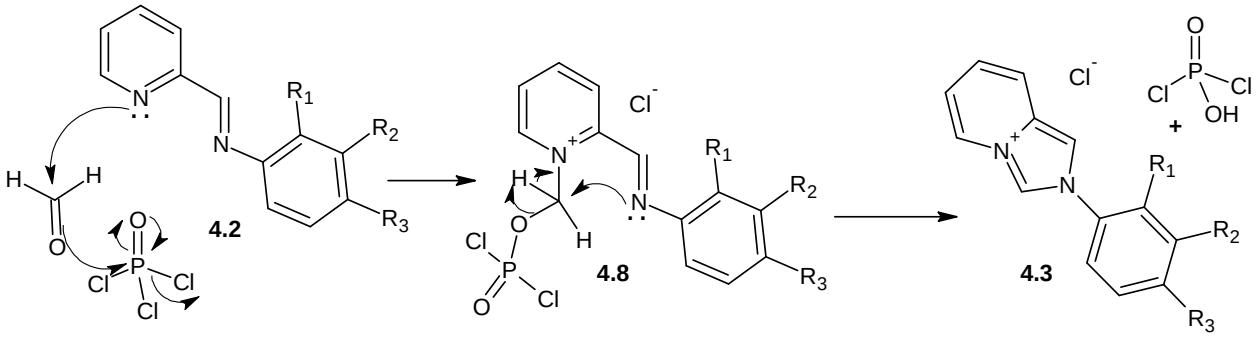
4.1.3. Synthesis of the imidazole pyridinium compounds (4.3) (for R^3 is electron donating group)

4.1.3.1. The use of $POCl_3$ as a catalyst (refer to route b in scheme 4.1)

The synthesis of imidazo[1,5-a]pyridines are well documented as discussed in chapter 3. Most methods involve reaction of 2-picolylamine with a one-carbon unit. Acylation of 2-piconylamine followed by cyclization with phosphorus oxychloride ($POCl_3$) or phosphoric acid gives the required product. Ramage and Bower[5] in 1955 reported the first synthesis of imidazopyridine, formed by reaction of 2-picolylamine with formic acid in the presence of $POCl_3$. More recently, Chattopadhyay and coworkers[6] reported the synthesis of imidazopyridine from 2-pyridyl-*N*-(phenyl)methylimine and formaldehyde in the presence of

ruthenium catalyst and sodium perchlorate. In this report we investigated this later reaction in the absence of ruthenium and sodium perchlorate.

The reaction of imine intermediates (**4.2**) with formaldehyde in the presence of $POCl_3$ yielded the corresponding imidazolium compounds (where R^3 is electron donating group). $POCl_3$ was added to catalyze the reaction by activating the carbonyl carbon of formaldehyde for the nucleophilic attack as shown in scheme 4.6. Using this catalyst, the yields of the imidazopyridinium derivatives ranged from 60 to 86 %.



Scheme 4.6: *Mechanism for the synthesis of imidazolium compounds (**4.3**) using $POCl_3$ catalyst.*

The reaction was successful as marked by not only the increase in the number of proton signals but also the number of carbon signals in the NMR spectra. For example, in figure 4.9, we can observe an additional deshielded singlet peak of **H-7'** at 10.1 ppm and the reappearance of a singlet peak of the imminium proton (C**H**^{7}=N, **H-7**) at relatively upfield 8.53 ppm.

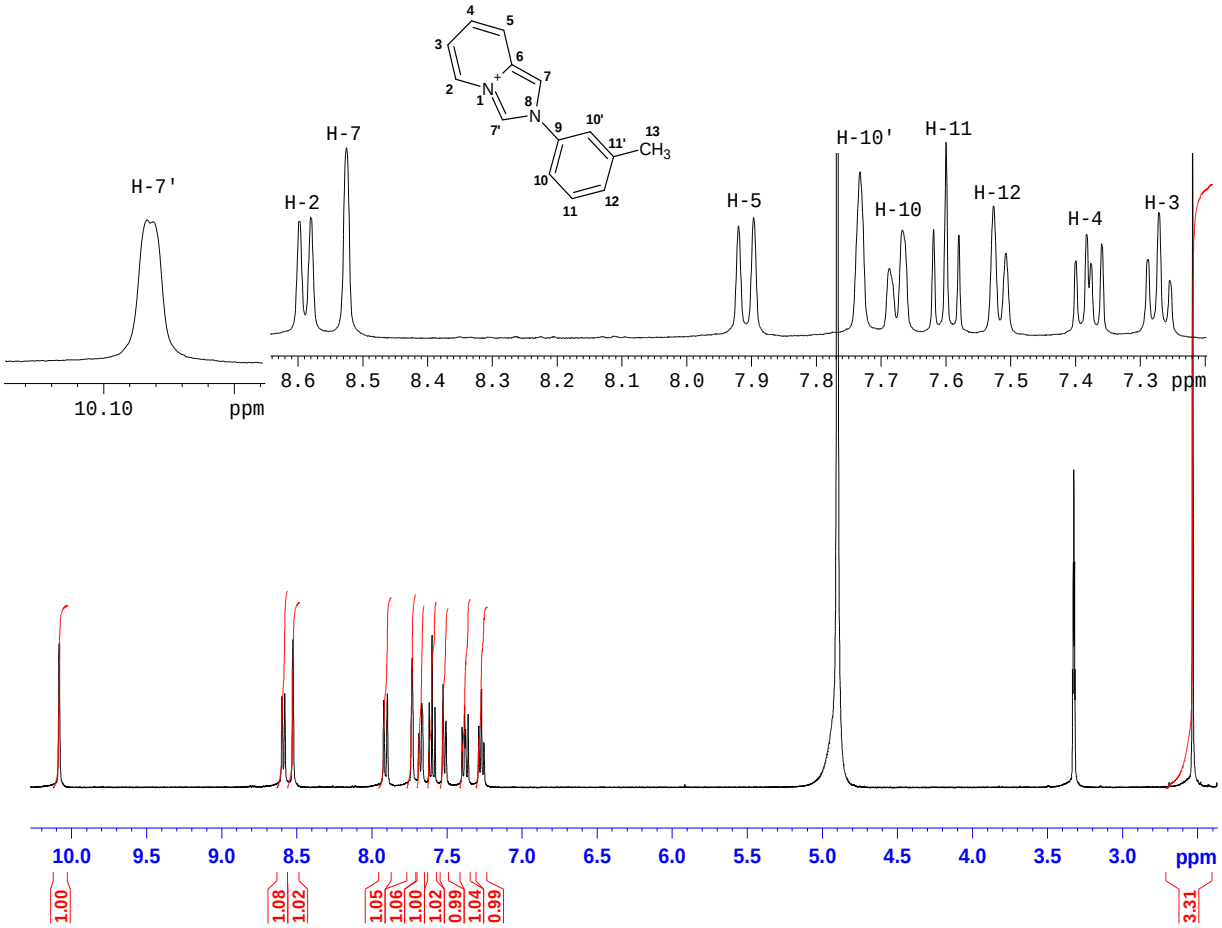


Figure 4.9: *^{1}H NMR spectrum of Pyridyl[1,5-a]-4-(m-methyl)phenylimidazolium chloride (**4.3f**).*

The change in the stretching frequencies from infrared spectra of the C=N functional group is recorded in table 4.4. If the change on the stretching frequency is negative (as shown in column 3 of table 4.4), implies a drop on in energy from that of its corresponding imine intermediate. However, all imidazoles showed an increase in C=N stretching frequencies ranging from 25 to 33 cm^{-1}, except for **4.3a** which decreased by 13 cm^{-1} and **4.3b** remain the same. This increase in energy implies the electron deficiency in the structure that is caused by the positive charge in the imidazolium ring because of the quaternary nitrogen atom. The C=N stretching for imidazolium pyridine (for **4.3a**) is at 1614 wavenumbers (cm^{-1}). When R_3 is fluorine (**4.3b**), the wavenumbers for the C=N stretching changed marginally to 1627 cm^{-1}.

However, the rest of the substituents had more than three-fold change in wavenumber as shown in column 4 of table 4.4.

Mass spectrum (HRMS) for Pyridyl[1,5-a]-4-(*m*-methyl)phenylimidazolium (**4.3f**) in figure 4.11 for example, the calculated mass (209.1079) and experimental mass (209.1080) showing good agreement. For all imidazolium compounds the calculated mass and experimental mass have a good agreement, thus confirming the successfulness of the reaction and the structure of the compounds.

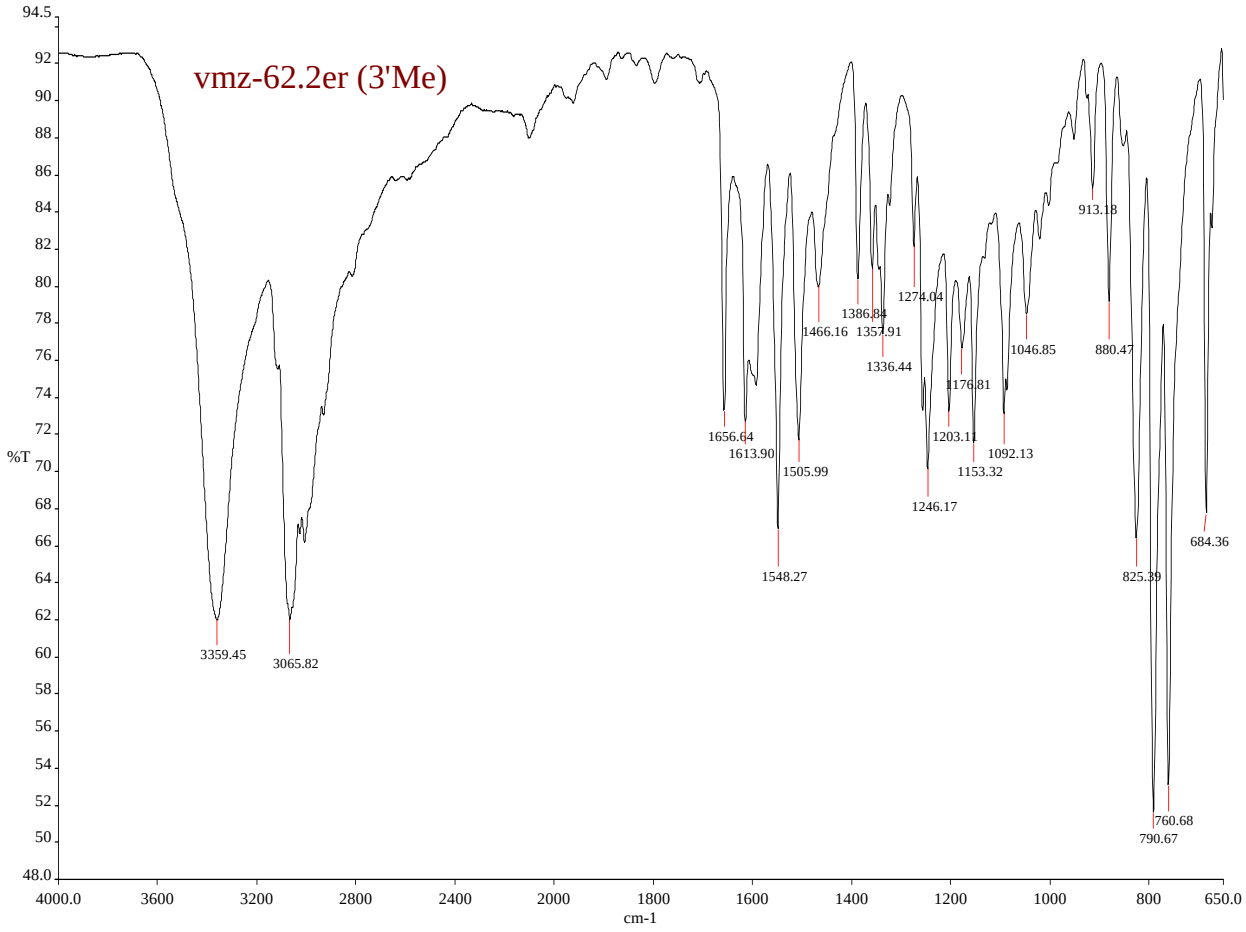


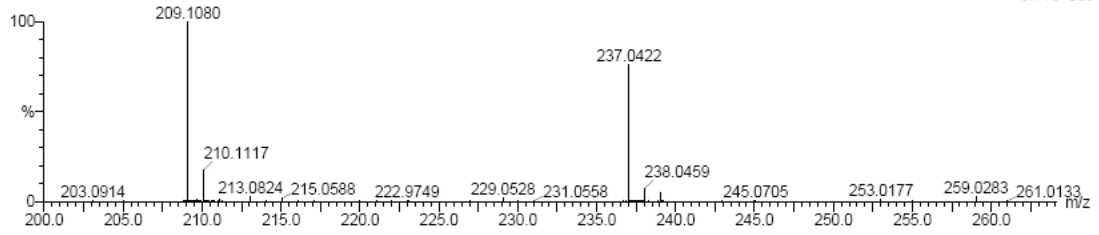
Figure 4.10: *IR spectrum of Pyridyl[1,5-a]-4-(m-methyl)phenylimidazolium (**4.3f**).*

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 10-15 H: 10-15 N: 0-5
Vuyisa Mzozoyana
VMZ_62_2er 13 (0.203)

TOF MS ES+
3.11e+003



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
209.1080	209.1079	0.1	0.5	9.5	199.5	0.0	C14 H13 N2

Figure 4.11: *Mass spectrum HRMS of Pyridyl[1,5-a]-4-(m-methyl)phenylimidazolium (**4.3f**).*

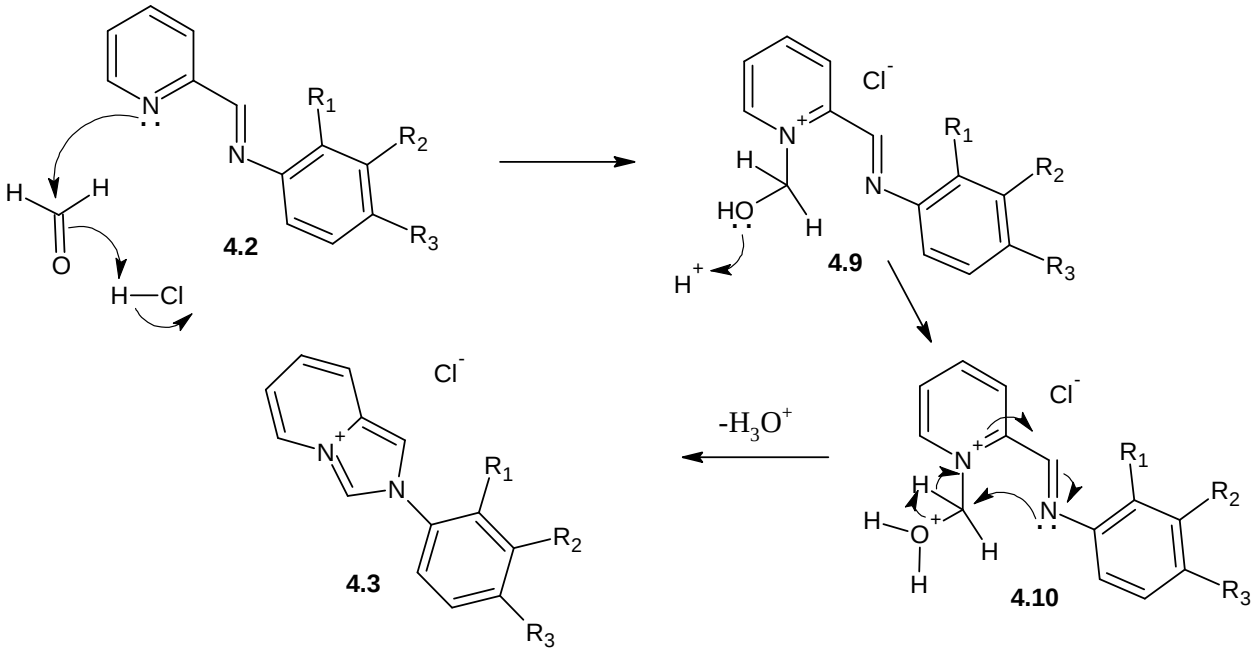
Phenyl substituents				Wavenumber and change relative to imine and **4.2a** (cm^{-1})		
No.	R_1	R_2	R_3	C=N stretch	$\Delta\nu$ (Ref. imine int.)	$\Delta\nu$ (relative to **4.2a**)
4.2a	H	H	H	1614	-13	_
4.2b	H	H	F	1627	0	13
4.2c	H	H	Cl	1656	33	42
4.2d	H	H	Br	1655	33	41
4.2e	Me	H	H	1656	25	42
4.2f	H	Me	H	1656	27	42
4.2g	H	H	Me	1655	30	41
4.2h	H	H	OMe	1656	32	43

Table 4.4: *The effect of the imidazole cycle on the energy (in Wavenumber) of C=N functional group and change relative to the imine intermediate and **4.2a**.*

4.1.3.2. The use of HCl as a catalyst (refer to route c in scheme 4.1)

The yields obtained using $POCl_3$ as catalyst as already mentioned ranged from 60 to 86%. We, however, wanted to investigate whether we could improve the yield further by using hydrochloric acid (HCl). Mashima and coworkers[7] conducted the cyclization of these imines with paraformaldehyde in the presence of HCl in ether solvents. The absence of both heavy metal catalyst and the oxidant would surely result in a more environmentally friendly reaction.

The use of the HCl catalyst[6,8] for the same reactions instead of $POCl_3$ came with a good improvement in the reaction yield, by at least 6% as shown in table 4.5. The aim of the addition of the catalyst was to activate the carbonyl carbon for the nucleophilic attack by nitrogen lone pair of electrons (as shown in scheme 4.7). In scheme 4.7, the last step of the mechanism is the removal of hydronium ion from the intermediate **4.10**. In both scheme 4.6 and 4.7, the counter ion (anion) for the intermediates (**4.9** and **4.10**) and the product **4.3** was chlorine ion (Cl^-). Imidazolium compounds that were synthesized using $POCl_3$ and HCl catalysts are shown in figure 4.12 as **4.3a-h**.



Scheme 4.7: *Proposed mechanism for the synthesis of imidazolium compounds (**4.3**) using HCl catalyst*

Phenyl substituents				Catalyst used, percentage yield and change in yield (%)		
				$POCl_3$ yield	HCl yield	Change in yield
No.	R_1	R_2	R_3			
4.3a	H	H	H	86	97	11
4.3b	H	H	F	83	93	10
4.3c	H	H	Cl	84	95	11
4.3d	H	H	Br	86	96	10
4.3e	Me	H	H	84	96	12
4.3f	H	Me	H	60	66	6
4.3g	H	H	Me	83	96	13
4.3h	H	H	OMe	82	91	9

Table 4.5: *The effect of the catalyst on the yield of reactions*

4.1.4. Synthesis of the imidazolium compounds (4.3) via route d as in scheme 4.1, where R^3 is an electron withdrawing group

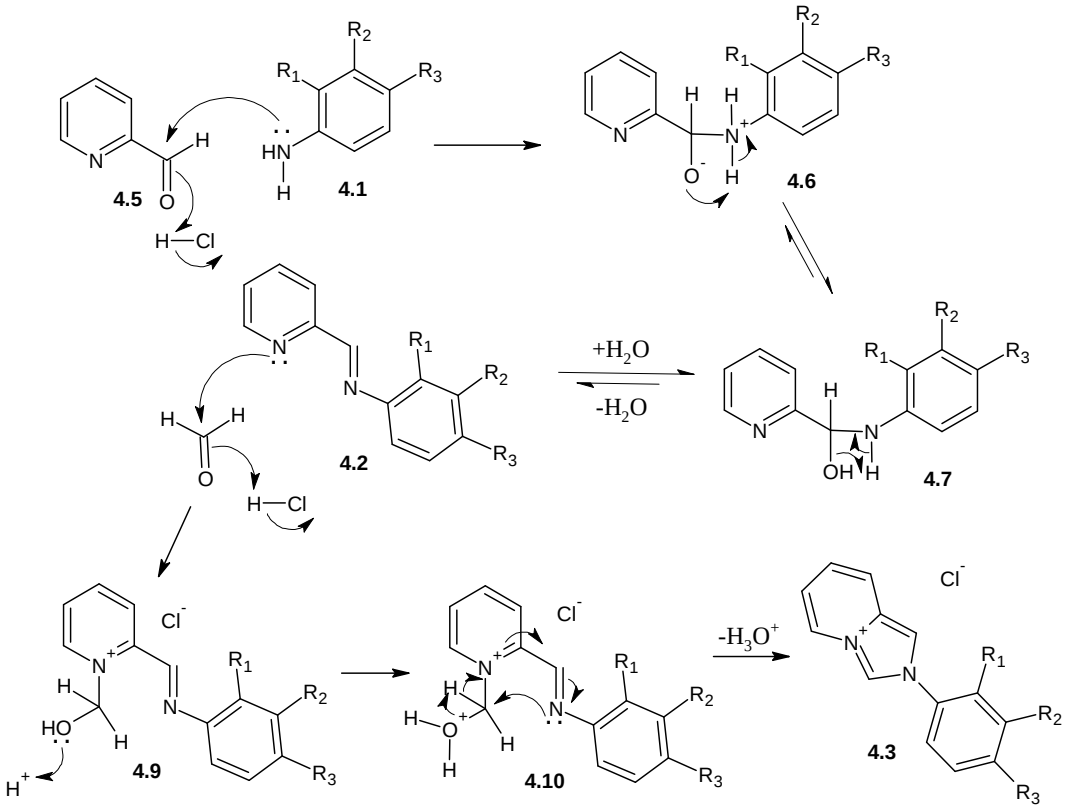
As shown in scheme 4.1, route **d** involves the direct synthesis of imidazolium compounds (**4.3**) without isolating imine intermediates (**4.2**). The imine intermediates **4.2** where R^3 is an electron withdrawing group could not be isolated, therefore a new method had to be developed. One reason speculated to be the cause of this problem was that the lone pair of electrons on the nitrogen atom of anilines (**4.1**) (for R^3 being an electron withdrawing group) is less effective for the nucleophilic attack. To overcome this problem, HCl was used to catalyze the reaction by activating the carbonyl carbon for the nucleophilic attack as in scheme 4.8. However, the imine intermediate was still not isolated.

The other speculation we made was that, intermediates **4.6, 4.7** and **4.2** are at an equilibrium state and the formation of imines (**4.2i-k)** are not favored because of their instability, and thus tend to hydrolyze to form the starting material. This problem was overcome by pushing the equilibrium forward simply by moping all the imine (**4.2i-k**) molecules that were produced by

quickly reacting them with the activated formaldehyde before it hydrolyses back to form **4.7**. In so doing, we synthesized the imidazolium compounds where R^3 is an electron withdrawing group. The use of $POCl_3$ catalyst also did not work.

The synthesis of the imidazolium compounds (**4.3**) via route **d** was successful as described above with good yield ranging from 67-73 %. Various analogues of the imidazolium compounds (**4.3i-k**) with different electron withdrawing substituents on their benzene ring (as shown on figure 4.12) were synthesized following this method. All these imidazolium compounds were positively charged because nitrogen on the pyridine ring is quaternary (**N-1**) and the counter ion was chlorine.

Relevant characterization such as NMR, IR, HRMS and UV absorption spectra for these imidazolium compounds were curried out to verify or/and confirm the successfulness of this method.



Scheme 4.8: *Mechanism for the synthesis of the imidazolium compound (**4.3**) where R^3 is an electron withdrawing group.*

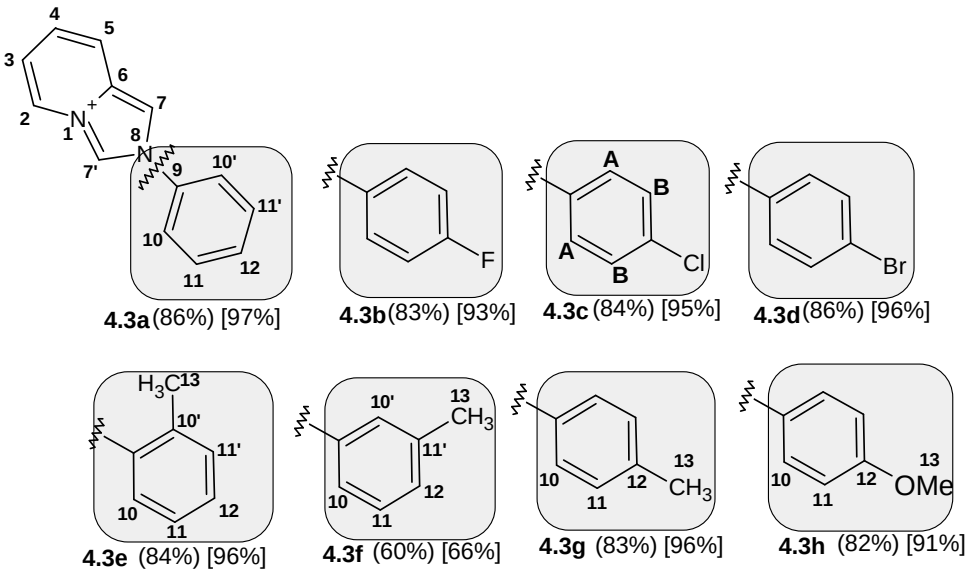
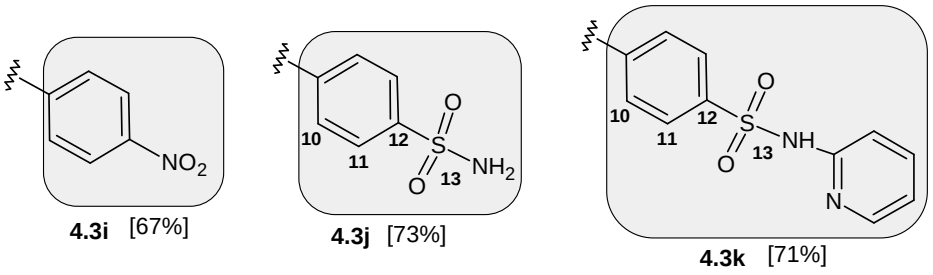
Method used according to the figure 4.1 and catalyst	Aniline substituents in the formation of imidazolium compounds **4.3** (% yield, rounded brackets – $POCl_3$, square brackets – HCl)
b and c ($POCl_3$ and HCl)	
d (i and ii) (HCl only)	

Figure 4.12: *Various analogues of imidazolium compounds (**4.3**) synthesized with their yield.*

In figure 4.9, the ^{1}H NMR spectrum of Pyridyl[1,5-a]-4-(*m*-methyl)phenylimidazolium chloride (**4.3f**) is shown to represent the imidazolium compounds. Proton (**H-7'**) is most deshielded, resonates at 10.1 ppm and is a doublet due to its long rang coupling to **H-2**, J 1.2 Hz. The next proton that is downfield is **H-2** in the pyridyl ring, and the rest of the protons on the pyridyl ring are in the same order as in their corresponding imine intermediates (**4.2**) but the chemical shift changed, **H-5**, **H-4** and **H-3** at 7.9, 7.4 and 7.3 ppm respectively. The strong inductive effect of the quaternary nitrogen (**N-1**) is more pronounced at **H-2**. **H-2** is getting more deshielding which can be explained in terms the mesomeric effect which results in the creation of partially positive centre at **C-2** and **C-4** and negative centers at **C-3** and **C-5**. As a result **H-3** is more upfied followed by **H-4**.

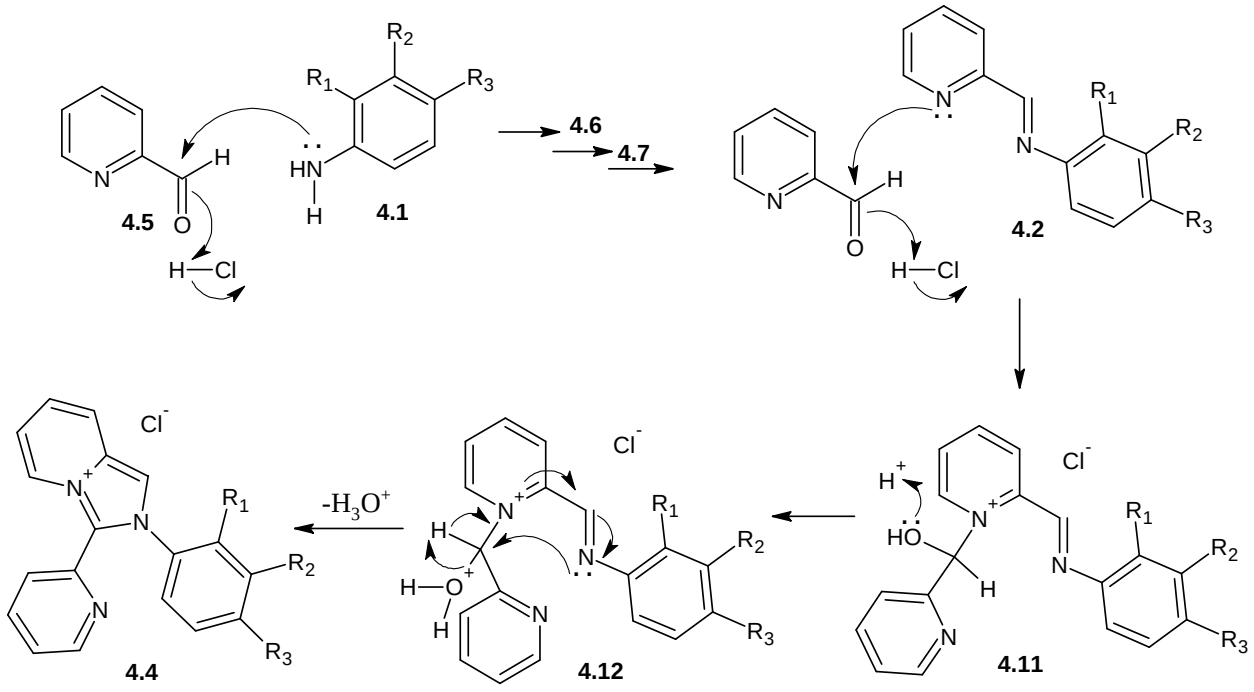
The inductive effect of the imidazole ring had a strong influence on the benzene ring as a result its protons were shifted downfield. As shown in the ^{1}H NMR in figure 4.9, the inductive effect is more pronounced on **H-10, 10'** (7.67 and 7.73 ppm respectively) as they are close to the imidazole ring. Since the inductive effect gets weaker with the distance, **H-11** followed at 7.60 ppm then **H-12** at 7.52 ppm. The chemical shifts and coupling constants for the protons in the benzene ring are summarized in table 4.6.

	^{1}H NMR (MeOD) δ_H (in ppm) and J coupling (in Hz)					
	H-10	H-11	H-12	H-10’	H-11’	H-13
(4.3a)	**7.91 dd** $J_{10,11}$ 8.6 $J_{10,12}$ 1.8	**7.78 dd** $J_{11,12}$ 9.2 $J_{11,10}$ 8.6	**7.36 tt** $J_{12,11}$ 9.2 $J_{12,10}$ 1.8			
(4.3b)	**7.90 d** $J_{10,11}$ 8.5	7.49 t $J_{11,(10,F)}$ 8.5				
(4.3c)	**7.92 d** $J_{10,11}$ 8.8	**7.75 d** $J_{11,10}$ 8.8				
(4.3d)	**7.90 d** $J_{10,11}$ 8.8	**7.83 d** $J_{11,10}$ 8.8				
(4.3e)	**7.61 m**	**7.61 m**	**7.52 t** $J_{12,(11,13)}$ 7.1		**7.61 m**	**2.33 s**
(4.3f)	**7.67 t** $J_{10,11}$ 7.6	**7.60 t** $J_{11,(10,12)}$ 7.6	**7.52 d** $J_{12,11}$ 7.6	**7.73 s**		**2.53 s**
(4.3g)	**7.75 d** $J_{10,11}$ 8.3	**7.54 d** $J_{11,10}$ 8.3				**2.50 s**
(4.3h)	**7.79 d** $J_{10,11}$ 8.	**7.22 d** $J_{11,10}$ 8.6				**3.93 s**
(4.3i)	**8.55 d** $J_{10,11}$ 8.0	**8.19 d** $J_{11,10}$ 8.0				
(4.3j)	**8.20 d** $J_{10,11}$ 8.9	**8.15 d** $J_{11,10}$ 8.9				
(4.2k)	**8.25 d** $J_{10,11}$ 8.7	**8.04 d** $J_{11,10}$ 8.7				

Table 4.6: *^{1}H NMR spectral data of the aromatic region of various imidazolium compounds.*

4.1.5. Synthesis of 5-substituted imidazolium compounds (4.4) (via route e)

This route (e) for the synthesis of 5-substituted imidazolium compounds (**4.4)** involved the condensation of pyridine-2-aldehyde in the absence of paraformaldehyde. In this route, pyridine-2-carbaldehyde (**4.5**) was added twice as shown in scheme 4.9. The first addition of pyridine-2-carbaldehyde resulted in the formation of imines (**4.2**) as described in section 4.1.2. Pyridine-2-carbaldehyde was activated by HCl catalyst and react with imine nucleophiles (**4.3**) to form **4.11**. The imidazolium compounds (**4.4**) were formed from the ring closure of intermediates **4.12**.



Scheme 4.9: *Mechanism for the synthesis of the 5-sustituted imidazolium compounds (**4.4**)*

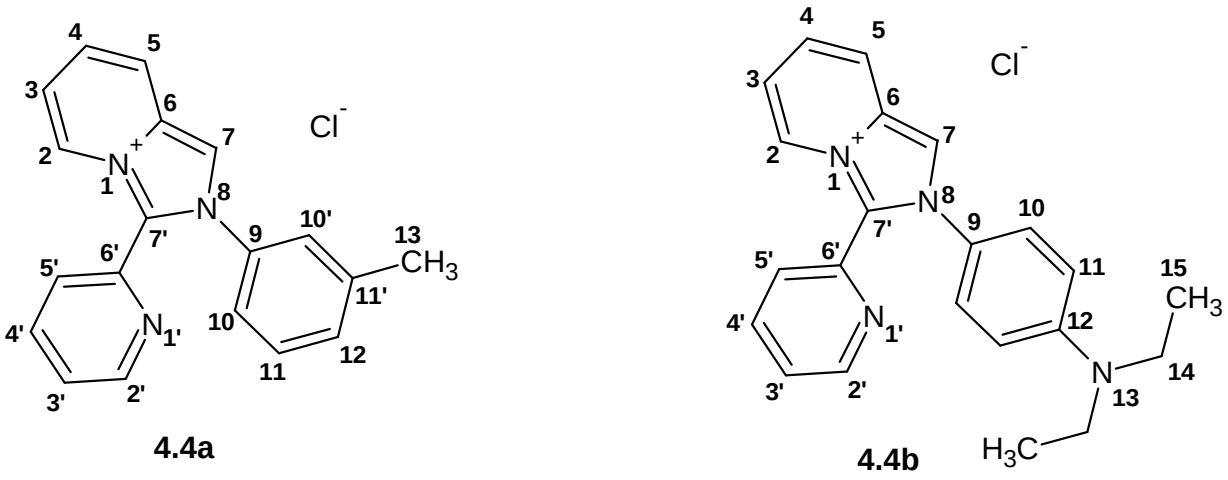


Figure 4.13: *Two analogues of imidazolium compounds (**4.4a** and **4.4b**) synthesized.*

Compounds **4.4a** and **4.4b** were successfully synthesized following the above mentioned method with the yield of 62 and 58 % respectively. Relevant characterization such techniques as NMR, IR, HRMS and UV absorption spectra for these 5-substituted imidazolium compounds were carried out to verify or/and confirm the successfulness of this method. The calculated mass and the experimental mass of **4.4a** are 343.1923 and 343.1920 respectively (see HRMS in figure 4.16) which are in good agreement and thus confirming the success of the reaction method.

In both structures (**4.4a** and **4.4b**), **H-2** was found to be the most deshielded proton (see ^{1}H spectrum in figure 4.14). This is because of the partially positive charge on **C-2** as a result of the mesomeric effect. The next proton is **H-2'** and the reason is the same as for **H-2** but in a different approach. The imidazole ring for this structure (**4.4**) is not as cationic as that of (**4.3**) because the pyridyl ring donates electrons to the imidazole ring. Thus the ring is partially neutralized.

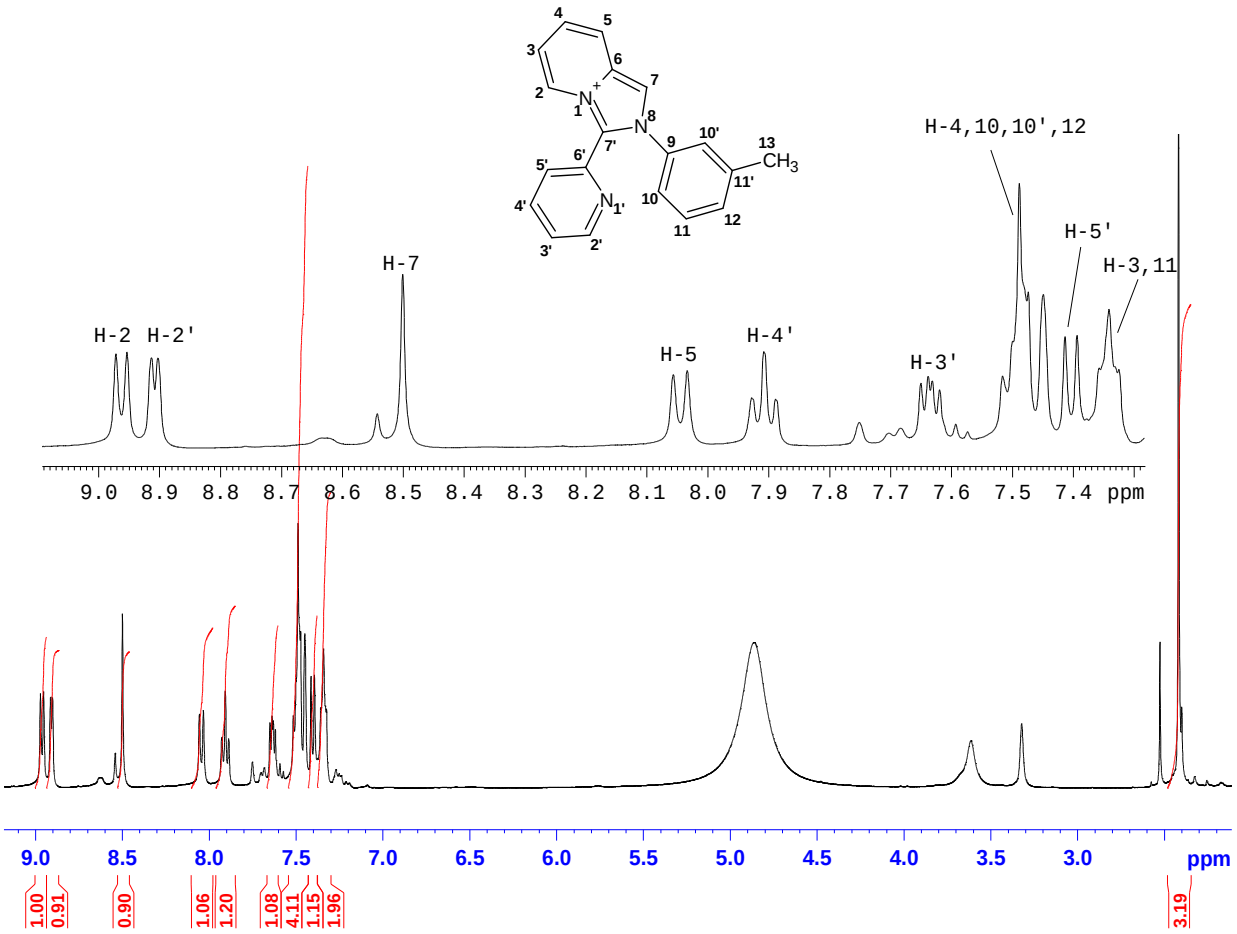


Figure 4.14: *^{1}H NMR spectrum of pyridyl[1,5-a]-4-(m-methyl)pheny-5-pyridylimidazolium chloride.*

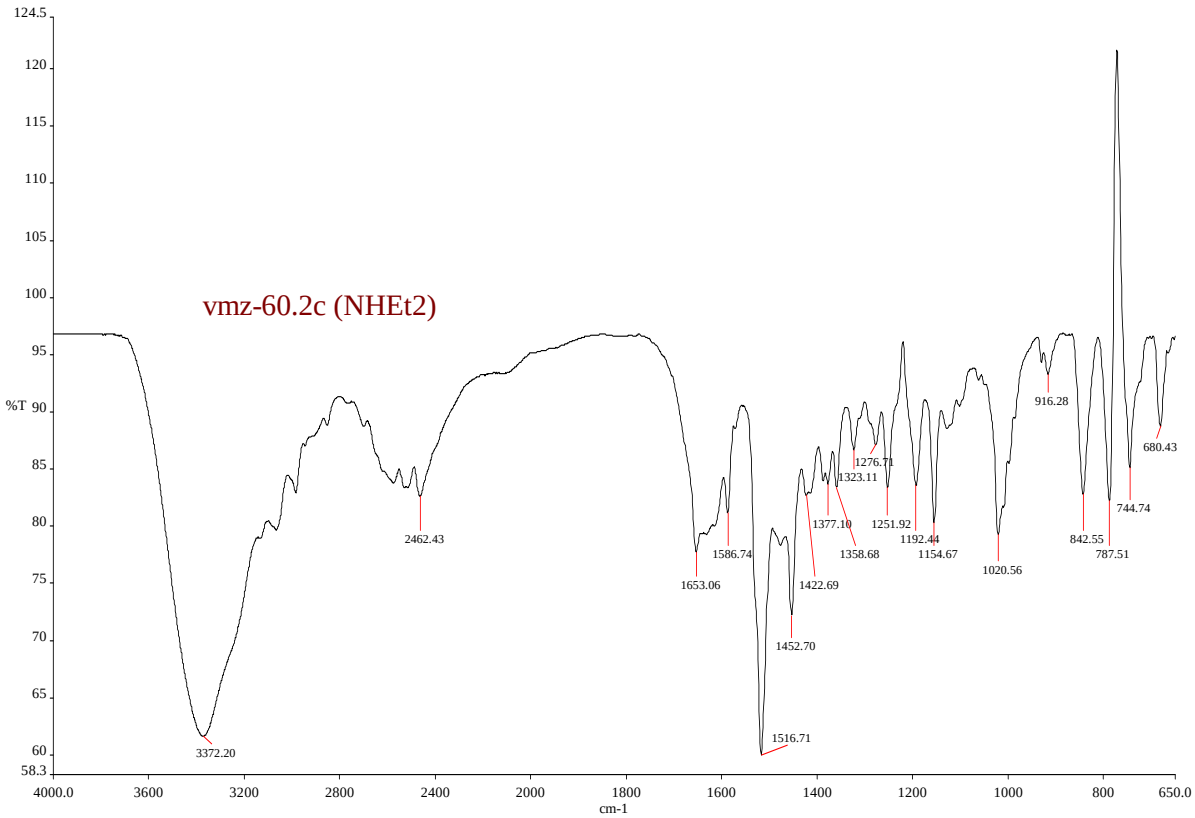


Figure 4.15: *Infrared spectrum (IR) of pyridyl[1,5-a]-4-(m-methyl)pheny-5-pyridylimidazolium chloride.*

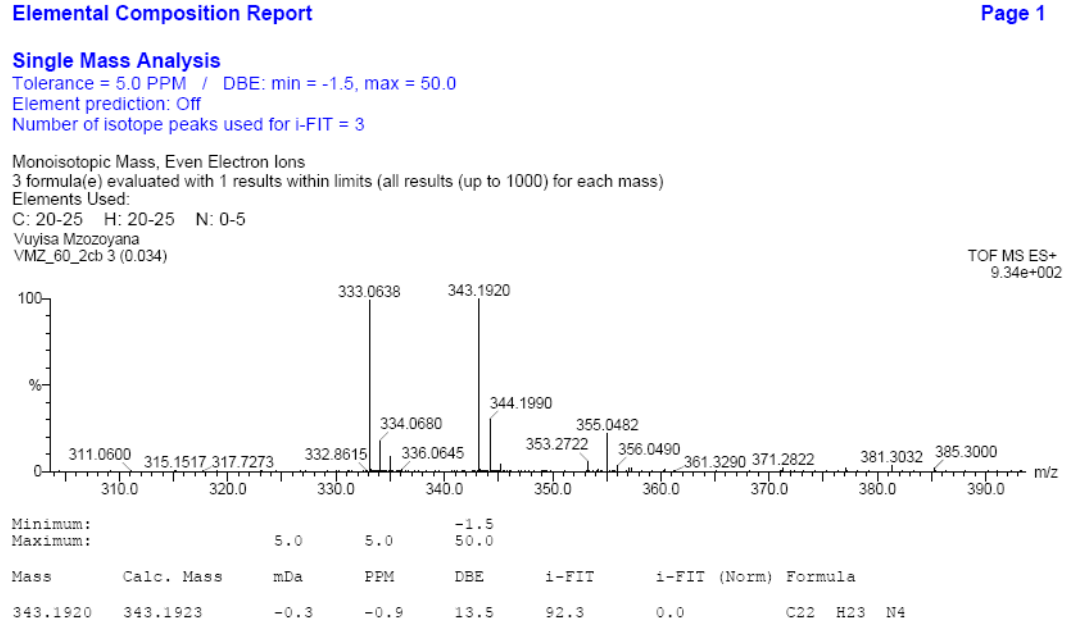


Figure 4.16: *Mass spectrum (HRMS) of pyridyl[1,5-a]-4-(m-methyl)pheny-5-pyridylimidazolium chloride.*

CONCLUSIONS

A variety of imidazo[1,5-a]pyridyl compounds were synthesized following three basic methods which included the condensation of pyridine-2-carbaldehyde with anilines (**4.1**) with different substituents on ortho (R^1), para (R^2) and meta (R^3) positions. Each substituent has its own specific effect on the aromaticity of the ring of anilines and thus the reactivity of the nitrogen group of aniline. Depending on the nature of the substituents on aniline (R^1, R^2, or/and R^3), different methods were followed to give the corresponding imidazolium products.

The first route included the isolation of imine intermediates (**4.2a-i**, yield ranging from 41 to 92 %) which were then treated with phosphorus oxychloride ($POCl_3$) in one case and hydrochloric acid (HCl) in another case as catalysts. Both cases resulted in the yield of same imidazo[1,5-a]pyridyl compounds (**4.3a-h**) with the reaction yields ranging from 60-86 % and 66-97 % for $POCl_3$ and HCl respectively. The imine intermediates (**4.2**) with R^3 an electron withdrawing group could not be isolated.

The second route was the development of the first route for those imine intermediates that could not be isolated (where R^3 was an electron withdrawing group) and only hydrochloric acid catalyst was used to yield **4.3i-k** with the reaction yield range of 67-73 %. In both first and second routes, paraformaldehyde was used for the ring-closure step of the reaction. The last route for the formation of imidazo[1,5-a]pyridyl compounds (**4.4**) was carried out in the absence of paraformaldehyde reagent and the reaction yields were 58 % and 62 %.

FUTURE WORK

Some reactions such as the reaction of anilines (**4.1l-m**), were unfortunately unsuccessful, therefore future studies should be directed towards the development of new methods. Expansion of the existing methods is also necessary in order to produce a wide variety of this kind of imidazolium compounds. The other study should focus on the chelation of these imidazoles, their imine intermediates and their carbene forms to metals and test for their relative biological activities. Some imidazolium compounds are used as catalysts in both neat and complexed form, therefore, study of their catalytic activity should also be investigated.

(1) Nakatsuka, M., Shimamura, T. *Chem. Abstr.* **2001**, *134*, 170632.

(2) Nakatsuka, M., Yamamoto, H. *Chem. Abstr.* **2005**, *142*, 440277.

(3) Helnert, D., Martell, A. E. *J. Am.Chem. Soc.* **1962**, *84*, 3257.

(4) Ledbetter, J. W. *The Journal of Physical Chemistry* **1977**, *81, No. 1*, 55-59.

(5) Bower, J. D., Ramage, G. R. *Heterocyclic Systems Related to Pyrrocoline* **1955**, *Part I,* 2834-2837.

(6) Mishra, D., Naskar, S., Adhikary, B., Butcher, R. J., Chattopadhyay, S. K. *Polyhedron* **2005**, *24*, 201-208.

(7) Chien, C., Fujita, S., Yamoto, S., Hara, T., Yamagata, T., Watanabe, M., Mashima, K. *Dalton Trans.* **2008**, 916-923.

(8) Chien, C., Fujita, S., Yamoto, S., Hara, T., Yamagata, T., Watanabe, M., Mashima, K. *The Royal Society of Chemistry* **2008**, 916-923.

CHAPTER 5 EXPERIMENTAL

5.1. Instrumentation and General Experimental conditions

Unless otherwise stated, all reagents (including solvents) were purchased from the chemical suppliers such as Aldrich and Fluka and used without further purification.

Flash column chromatography was carried out using Merck Kieselgel 60 which was put in a glass column (5 cm diameter). The amount of the silica (Merck Kieselgel 60) could be varied depending on the amount of the sample as well as the impurities. The crude was put on top of the column and allowed to adsorb to the silica on top of the column. Various ratios of elution solvents (ethyl acetate or methanol to distilled hexane) were applied to the column; purified compound was collected from the bottom.

Preparative scaled thin layer chromatography (TLC) was conducted using Merck Kieselgel 60_{254} which was coated onto 20 x 20 cm glass plates. Silica gel (200 g) was homogeneously suspended in 500 ml of water to make up TLC with thickness of 2 mm (silica gel). These plates were kept in a draft free place overnight at room temperature and subsequently activated overnight at 120 °C.

Qualitative thin layer chromatographies were used to monitor the reaction and to determine the purity. These TLC plates (Merck Kieselgel 60_{254} aluminum backed TLC) were bought ready for use. Visualization of the TLC plates was achieved using iodine tank and/or fluorescence on exposure to short wave length ultra violet light (254 nm).

Melting points (Mp) were determined using Stuart melting point apparatus with open ended capillary tubes and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer machine at the frequencies 399.995 MHz and 100.4296 MHz for protons (^{1}H) and carbon (^{13}C) respectively. Chemical shifts (δ) are reported in parts per millions (ppm) and coupling constants (J-values) were measured in hertz (Hz). The solvents used were deuteriochloroform

($CDCl_3$) and deuteriomethanol (MeOD). In all spectra, the internal reference was done using the residual protio solvent resonance. Multiplicities were abbreviated as follows:

Abbreviation	Signal multiplicity	Abbreviation	Signal multiplicity
s	singlet	dd	doublet of doublets
d	doublet	ddd	doublet of doublets of doublets
t	triplet	dt	doublet of triplets
q	quartet	tt	triplet of triplets
br	broadened	td	triplets of doublet

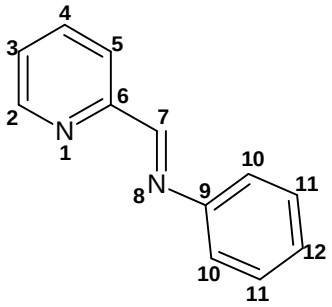
Table 5.1: *Abbreviations and their description of ^1H NMR signal multiplicities.*

Infrared (IR) spectra were recorded on a Weldex spectrometer as neat solid or liquid (the samples were put on the IR machine lens).

Electronic spectra were recorded on a Varian UV/Vis/NIR spectrometer between the wavelengths of 250 nm and 850 nm at room temperature. Methanol was used as a solvent to prepare samples with the concentration varying between 10^{-3} and 10^{-5} mol/L. Quartz cells with the optical length of 1 cm were used to hold solutions.

5.2. Synthesis of imine and imidazole compounds

Synthesis of 2-pyridyl-N-(phenyl)methylimine (4.2a).



Procedure "A"

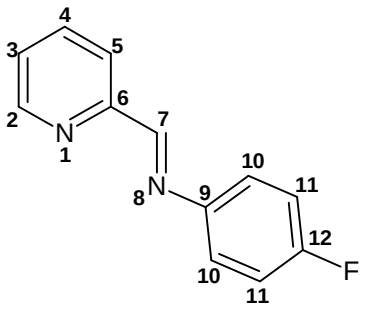
Pyridine-2-aldehyde (1.071 g, 10.0 mmol) and aniline (0.931 g, 10.0 mmol) were refluxed in absolute ethanol (20 ml) for 3 hours. The mixture was filtered under vacuum and washed with minimal amount of cold absolute ethanol. The brown crude product was purified using 20 by 20 cm TLC plate (1:1 ethyl acetate in petroleum ether as an eluting solvent) to give light brown liquid of 2-pyridyl-N-(phenyl)methylimine **(4.2a)** (1.6 g, 91 %). TLC R_f 0.61 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$) 7.29 (3H, m, 10, 12-**H**), 7.33 (1H, ddd, $J_{3,4}$ 7.7, $J_{3,2}$ 4.8, $J_{3,5}$ 1.2, 3-**H**), 7.41 (2H, m, 11-**H**), 7.77 (1H, td, $J_{4,(3,5)}$7.7, $J_{4,2}$ 1.8, 4-**H**), 8.20 (1H, dt, $J_{5,4}$ 7.7, $J_{5,3}$1.2, $J_{5,2}$0.9, 5-**H**), 8.61 (1H, s, 7-**H**), 8.70 (1H, ddd, $J_{2,3}$ 4.8, $J_{2,4}$ 1.8, $J_{2.5}$ 0.9, 2-**H**).

δ_C 121.1 (10-**C**), 121.9 (5-**C**), 125.1 (3-**C**), 126.7 (12-**C**), 129.2 (11-**C**), 136.6 (4-**C**), 149.7 (2-**C**), 151.0 (9-**C**), 154.6 (6-**C**), 160.6 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3054 (s, Ar C-H stretch), 2902 (s, alkyl C-H stretch), 1627 (s, C=N stretch), 1529 (s, Ar C=C stretch), 1485 (s, alkyl C-C stretch), 1346 (s, C-N stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*p*-fluorophenyl)methylimine (4.2b)



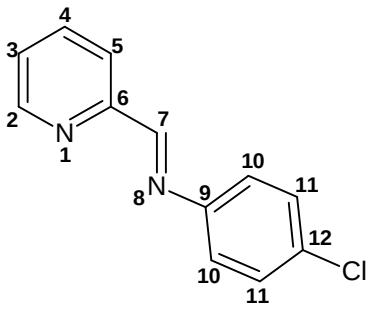
2-pyridyl-N-(*p*-fluorophenyl)methylimine (**4.2b**) was produced following procedure "**A**", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and 4-fluoroaniline (0.931 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 4 hours. The product (4.**2b**) was obtained as a light-brown semi-solid compound (1.8 g, 90%); TLC R_f 0.65 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$) 7.10 (2H, m, 10-**H**), 7.29 (2H, m, 11-**H**), 7.38 (1H, ddd, $J_{3,4}$ 7.7, $J_{3,2}$ 4.9, $J_{3,5}$ 1.2, 3-**H**), 7.82 (1H, td, $J_{4,(3,5)}$ 7.7, $J_{4,2}$ 1.9, 4-**H**), 8.20 (1H, ddd, $J_{5,4}$ 7.7, $J_{5,3}$1.2, $J_{5,2}$1.1, 5-**H**), 8.60 (1H, s, 7-**H**), 8.73 (1H, ddd, $J_{2,3}$ 4.9, $J_{2,4}$ 1.9, $J_{2.5}$ 1.1, 2-**H**).

δ_C 115.7 (10-**C**), 121.9 (5-**C**), 122.8 (11-**C**), 125.1(3-**C**), 136.6(4-**C**), 147.0(12-**C**), 149.8(2-**C**), 154.6 (6-**C**), 160.4 (7-**C**), 160.6 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3053 (s, Ar C-H stretch), 2915 (s, alkyl C-H stretch), 1627 (s, C=N stretch), 1499 (s, Ar C=C stretch), 1465 (s, alkyl C-C stretch), 1347 (s, C-N stretch), 1091 (s, C-F stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*p*-chlorophenyl)methylimine (4.2c)



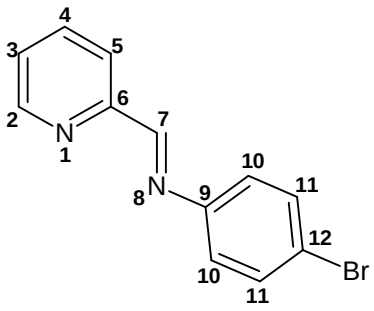
2-pyridyl-N-(*p*-chlorophenyl)methylimine **(4.2c)** was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and 4-bromoaniline (1.720 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 4 hours. The product **(4.2c)** was obtained as a light-orange/yellow amorphous solid (2.0 g 92%), Mp – 68-70 °C; TLC R_f 0.61 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, $J_{10,11}$8.5, 10-**H**), 7.34-7.42 (3H, m, 3,11-**H**), 7.82 (1H, td, $J_{4,(3,5)}$ 7.7, $J_{4,2}$ 1.6, 4-**H**), 8.19 (1H, dd, $J_{5,4}$ 7.7, $J_{5,3}$1.9, 5-**H**), 8.57 (1H, s, 7-**H**), 8.70 (1H, dd, $J_{2,3}$ 4.9, $J_{2,4}$ 1.6, 2-**H**).

δ_C 122.0 (5-**C**), 122.4 (10-**C**), 125.3 (3-**C**), 129.4 (11-**C**), 132.3 (12-**C**), 136.7 (4-**C**), 149.4 (9-**C**), 149.8 (2-**C**), 154.4 (6-**C**), 161.0 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3049 (s, Ar C-H stretch), 2916 (s, alkyl C-H stretch), 1623 (s, C=N stretch), 1566 (s, Ar C=C stretch), 1478 (s, alkyl C-C stretch), 1349 (s, C-N stretch), 832 (s, C-Cl stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*p*-bromophenyl)methylimine (4.2d)



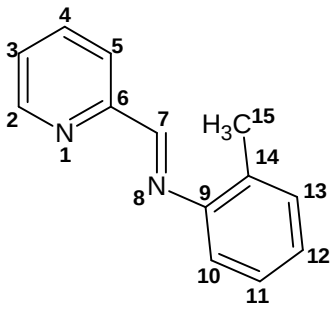
2-pyridyl-N-(*p*-bromophenyl)methylimine (**4.2d**) was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and 4-bromoaniline (1.720 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 4 hours. The product (**4.2d**) was obtained as a light-orange/yellow amorphous crystals (2.2 g, 86%), Mp – 70-72 °C; TLC R_f 0.62 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$) 7.15 (2H, m, 10-**H**), 7.35 (1H, ddd, $J_{3,4}$ 7.7, $J_{3,2}$ 4.9, $J_{3,5}$ 1.6, 3-**H**), 7.51 (2H, m, 11-**H**), 7.78 (1H, td, $J_{4,(3,5)}$ 7.7, $J_{4,2}$ 1.9, 4-**H**), 8.17 (1H, ddd, $J_{5,4}$ 7.7, $J_{5,3}$1.6, $J_{5,2}$1.0, 5-**H**), 8.57 (1H, s, 7-**H**), 8.70 (1H, ddd, $J_{2,3}$ 4.9, $J_{2,4}$ 1.9, $J_{2.5}$ 1.0, 2-**H**).

δ_C 121.9 (5-**C**), 122.8 (10-**C**), 125.4 (3-**C**), 132.7 (11-**C**), 136.6 (4-**C**), 147.0 (12-**C**), 149.8 (2-**C**), 150.0 (9-**C**), 154.4 (6-**C**), 161.2 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3050 (s, Ar C-H stretch), 2925 (s, alkyl C-H stretch), 1622 (s, C=N stretch), 1563 (s, Ar C=C stretch), 1476 (s, alkyl C-C stretch), 1346 (s, C-N stretch), 828 (s, C-Br stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*o*-methylphenyl)methylimine (4.2e)



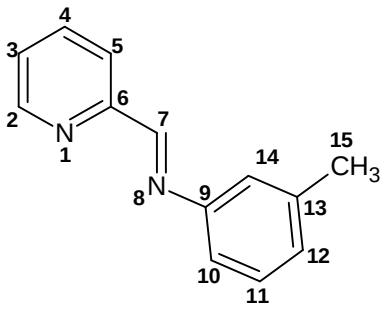
2-pyridyl-N-(*o*-methylphenyl)methylimine (**4.2e**) was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and *o*-toluidine (1.071 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 5 hours. The product (**4.2e**) was obtained as a light-brown/orange liquid (1.74 g, 89%); TLC R_f 0.60 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$); 2.43 (3H, s, 15-**H**) 7.03 (1H, d, $J_{10,11}$ 7.5 10-**H**), 7.17 (1H, t, $J_{12,(11,13)}$7.6,12-**H**), 7.24 (2H, m, 11,13-**H**), 7.31 (1H, dd, $J_{3,4}$ 7.9, $J_{3,2}$ 4.9, 3-**H**), 7.75 (1H, td, $J_{4,(3,5)}$7,9, $J_{4,2}$ 1.3, 4-**H**), 8.26 (1H, d, $J_{5,4}$ 7.9, 5-**H),** 8.55 (1H, s, 7-**H**), 8.70 (1H, d, $J_{2,3}$ 4.9, 2-**H**).

δ_C 18.0 (15-**C**), 117.5 (10-**C**), 121.6 (5-**C**), 124.9 (3-**C**), 126.4 (12-**C**), 126.8 (13-**C**), 130.4 (11-**C**), 132.3 (14-**C**), 136.6 (4-**C**), 149.6 (2-**C**), 150.2 (9-**C**), 154.9 (6-**C**), 160.0 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3053 (s, Ar C-H stretch), 2911 (s, alkyl C-H stretch), 1631 (s, C=N stretch), 1567 (s, Ar C=C stretch), 1486 (s, alkyl C-C stretch), 1345 (s, C-N stretch).

UV: λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*m*-methylphenyl)methylimine (4.2f)



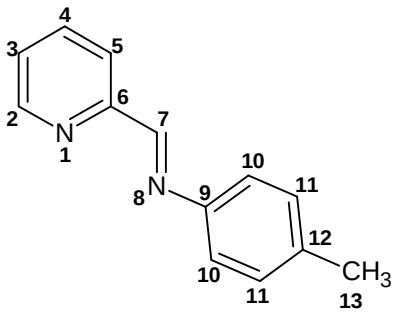
2-pyridyl-N-(*m*-methylphenyl)methylimine **(4.2f)** was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and *m*-toluidine (1.071 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 7 hours. The product **(4.2f)** was obtained as a light-brown semisolid (1.66 g, 85%); TLC R_f 0.60 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$); 2.41 (3H, s, 15-**H**), 7.07-7.15 (3H, m, 10,12,14-**H**), 7.31 (1H, t, $J_{11,(10,12)}$ 7.4, 11-**H**), 7.36 (1H, ddd, $J_{3,4}$ 7.9, $J_{3,2}$ 5.0 $J_{3,5}$ 1.1, 3-**H**), 7.75 (1H, td, $J_{4,(3,5)}$7.9, $J_{4,2}$ 1.7, 4-**H**), 8.21 (1H, dd, $J_{5,4}$ 7.9, $J_{5,3}$1.1, 5-**H)**, 8.62 (1H, s, 7-**H**), 8.72 (1H, dd, $J_{2,3}$ 5.0, $J_{2,4}$ 1.7, 2-**H**).

δ_C 21.0 (15-**C**), 118.0 (10-**C**), 121.8 (5-**C**), 121.9 (14-**C**), 125.0 (3-**C**), 127.5 (12-**C**), 129.0 (11-**C**), 136.7 (4-**C**), 139.1 (13-**C**), 149.6 (2-**C**), 151.0 (9-**C**), 154.7 (6-**C**), 160.5 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3051 (s, Ar C-H stretch), 2922 (s, alkyl C-H stretch), 1678 (s, C=N stretch), 1585 (s, Ar C=C stretch), 1488 (s, alkyl C-C stretch), 1377 (s, C-N stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-N-(*p*-methylphenyl)methylimine (4.2g)



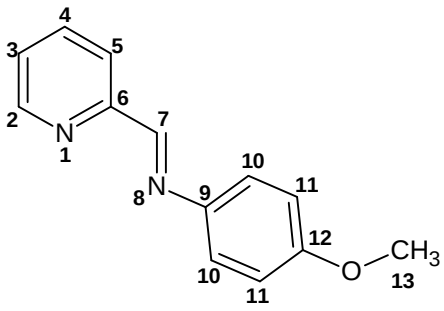
2-pyridyl-N-(*p*-methylphenyl)methylimine **(4.2g)** was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and *p*-toluidine (1.071 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 8 hours. The product **(4.2g)** was obtained as a light-brown/ semisolid (1.8 g, 91%); TLC R_f 0.62 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$); 2.34 (3H, s, 13-**H**) 7.14-7.32 (5H, m, 3,10,11-**H**), 7.73 (1H, td, $J_{4,(3,5)}$7.9, $J_{4,2}$ 1.8, 4-**H**), 8.17 (1H, dd, $J_{5,4}$ 7.9, $J_{5,3}$2.0, 5-**H)**, 8.61 (1H, s, 7-**H**), 8.67 (1H, dd, $J_{2,3}$ 5.2, $J_{2,4}$ 1.8, 2-**H**).

δ_C 21.0 (13-**C**), 121.1 (10-**C**), 121.7 (5-**C**), 124.9 (3-**C**), 128.8 (11-**C**), 136.6 (4-**C**) 136.7 (12-**C**), 148.4 (9-**C**), 149.6 (2-**C**), 154.7 (6-**C**), 159.7 (7-**C**).

IR (neat) ν_{max} (cm^{-1}): 3005 (s, Ar C-H stretch), 2916 (s, alkyl C-H stretch), 1625 (s, C=N stretch), 1504 (s, Ar C=C stretch), 1465 (s, alkyl C-C stretch), 1349 (s, C-N stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-*N*-(*p*-anisiphenyl)methylimine (4.2h)



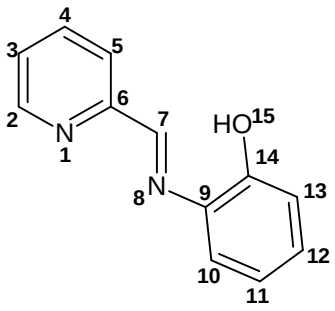
2-pyridyl-N-(*p*-anisiphenyl)methylimine **(4.2h)** was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and 4-anisidine (1.231 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 9 hours. The product **(4.2h)** was obtained as a dark-brown liquid (1.8 g, 86%); TLC R_f 0.68 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, 13-**H**), 6.91 (2H, m, 11-**H**), 7.29 (3H, m, 3,10-**H**), 7.73 (1H, td, $J_{4,(3,5)}$ 7.8, 4-**H**), 8.15 (1H, d, $J_{5,4}$ 7.8, 5-**H**), 8.60 (1H, s, 7-**H**), 8.65 (1H, d, $J_{2,3}$ 5.0, 2-**H**).

δ_C 55.7 (13-**C**), 114.4 (11-**C**), 121.6 (5-**C**), 122.6 (10-**C**), 124.8 (3-**C**), 136.5 (4-**C**), 143.7 (12-**C**), 149.6 (2-**C**), 154.9 (6-**C**), 158.2 (7-**C**), 158.9 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3051 (s, Ar C-H stretch), 2903 (s, alkyl C-H stretch), 1624 (s, C=N stretch), 1579 (s, Ar C=C stretch), 1503 (s, alkyl C-C stretch), 1346 (s, C-N stretch), 1297 (s, C-O stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of 2-pyridyl-*N*-(*o*-hydroxyphenyl)methylimine (4.2i)



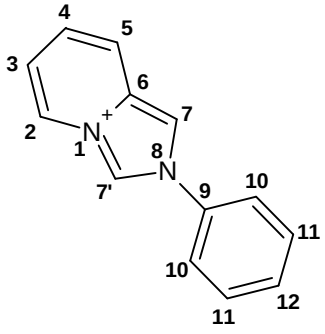
2-pyridyl-*N*-(*o*-hydroxyphenyl)methylimine **(4.2i)** was produced following procedure "A", by refluxing pyridine-2-aldehyde (1.071 g, 10.0 mmol) and *o*-aminophenol (1.091 g, 10.0 mmol) in absolute ethanol (20 ml) and reflux for 14 hours. The product **(4.2i)** was obtained as a dark red powdered solid (0.8 g, 41%), Mp – 97-102 °C; TLC R_f 0.66 (UV-active, EtOAc / PE, 1:1); NMR, δ_H (400 MHz, $CDCl_3$); 1.78 (1H, br, O**H**) 6.95 (1H, t, $J_{11,(10,12)}$ 7.8 11-**H**), 7.05 (1H, d, $J_{13,12}$ 7.8, 13-**H**), 7.26 (1H, t, $J_{12,(11,13)}$7.8 12-**H**), 7.41 (2H, m, 3,10-**H**), 7.85 (1H, t, $J_{4,(3,5)}$7.7, 4-**H**), 8.22 (1H, d, $J_{5,4}$ 7.7, 5-**H),** 8.74 (1H, d, $J_{2,3}$ 4.8, 2-**H**) 8.86 (1H, s, 7-**H**).

δ_C 115.4 (13-**C**), 116.2 (10-**C**), 120.3 (11-**C**), 121.6 (5-**C**), 125.2 (3-**C**), 129.9 (12-**C**), 134.6 (14-**C**), 136.7 (4-**C**), 149.8 (2-**C**), 152.8 (7-**C**), 154.4 (6-**C**), 157.3 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3373 (br, OH), 3053 (s, Ar C-H stretch), 2921 (s, alkyl C-H stretch), 1585 (s, C=N stretch), 1521 (s, Ar C=C stretch), 1434 (s, alkyl C-C stretch), 1321 (s, C-N stretch), 1243 (s, C-O stretch).

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-phenylimidazolium chloride (4.3a)



Procedure "B"

A mixture of 2-pyridyl-N-(phenyl)methylimine (0.91 g, 5.0 mmol) and paraformaldehyde powder (0.15 g, 5.0 mmol) in toluene were stirred at room temperature for 12 h. A white suspension formed. 1 M HCl in diethyl ether (8.0 ml, 8.0 mmol) was added dropwise to the mixture and stirred for 7 h. The solvent was decanted and the precipitate was washed with diethyl ether. The residue was dissolved in methanol and then filtered to remove the unreacted paraformaldehyde and other unwanted solids. The volatile solvents were removed in vacuo to give a dark yellow semisolid which was then purified on a silica gel column and then on the TLC plate to give the desired product (**4.3a**). Pyridyl[1,5-a]-4-phenylimidazolium chloride (**4.3a**) was obtained as a light brown amorphous solid (0.95 g, 97%), Mp – 229-233 °C (Lit. ref. 82-86 °C); TLC R_f 0.4 (UV-active, EtOAc / MeOH, 1:1).

Procedure "C"

A mixture of 2-pyridyl-N-(phenyl)methylimine (0.91 g, 5.0 mmol) and paraformaldehyde powder (0.15 g, 5.0 mmol) in toluene were stirred at room temperature for 12 h. A white suspension formed. $POCl_3$ (1.1 ml, 8.0 mmol) was added dropwise to the mixture and stirred for 7 h. The solvent was decanted and the precipitate was washed with diethyl ether. The residue was dissolved in methanol and then filtered to remove the unreacted paraformaldehyde and other unwanted solids. The volatile solvents were removed in vacuo to give a dark yellow

semisolid which was then purified on a silica gel column and then on the TLC plate to give the desired product (**4.3a**). Pyridyl[1,5-a]-4-phenylimidazolium chloride (**4.3a**) was obtained as a brown amorphous solid (0.82 g, 86% {$POCl_3$}), Mp – 229-233 °C (Lit. ref. 82-86 °C); TLC R_f 0.4 (UV-active, EtOAc / MeOH, 1:1).

The products obtained were the same when both methods (procedure **"B"** and **"C"**) were followed, NMR; δ_H (400 MHz, MeOD) 7.28 (1H, td, $J_{3,(4,2)}$ 7.3, $J_{3,5}$ 1.1, 3-**H**), 7.36 (1H, tt, $J_{12,11}$ 9.2, $J_{12,10}$ 1.8, 12-**H**), 7.65-7.78 (3H, m, 4-**H**, 11-**H**), 7.86-7.98 (3H, m, 5-**H**, 10-**H**), 8.60 (1H, dd, $J_{2,3}$ 7.3, $J_{2,4}$ 1.0, 2-**H**) 8.77 (1H, s, 7-**H**), 10.39 (1H, s, 7'-**H**).

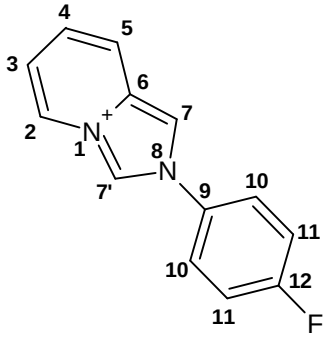
δ_C (400 MHz, MeOD), 112.7 (7-**C**), 118.6 (3-**C**), 118.8 (5-**C**), 123.4 (10-**C**), 124.7 (2-**C**), 125.8 (12-**C**), 126.4 (7'-**C**), 130.2 (6-**C**), 130.8 (11-**C**), 131.0 (4-**C**) 145.6 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3063 (s, Ar C-H stretch), 2912 (s, alkyl C-H stretch), 1614 (s, C=N stretch), 1573 (s, Ar C=C stretch), 1510 (s, alkyl C-C stretch), 1301 (s, C-N stretch).

HRMS (ESI+); Found $[M+H]^+$, 195.0922; $C_{13}H_{11}N_2$ Calc. Mass, 195.0922.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-fluoro)phenylimidazolium chloride (4.3b)



Pyridyl[1,5-a]-4-(*p*-fluoro)phenylimidazolium chloride (**4.3b**) was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*p*-fluorophenyl)methylimine (1.0 g, 5.0

mmol) and stirred for 12 h. The product **(4.3b)** was obtained as a dark brown amorphous solids (0.96 g, 93%; 83% {$POCl_3$}), Mp – 70-72 °C; TLC R_f 0.41 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 7.28 (1H, td, $J_{3,4,2}$ 7.0, $J_{3,5}$ 0.9, 3-**H**), 7.39 (1H, dd, $J_{4,5}$ 9.6, $J_{4,3}$ 7.0, 4-**H**), 7.49 (2H, t, $J_{11,10}$ 8.5, 11-**H**), 7.88-7.95 (3H, m, 5-H, 10-**H**), 8.50 (1H, s, 7-**H**), 8.57 (1H, d, $J_{2,3}$ 7.0, 2-**H**), 10.04 (1H, s, 7'-**H**).

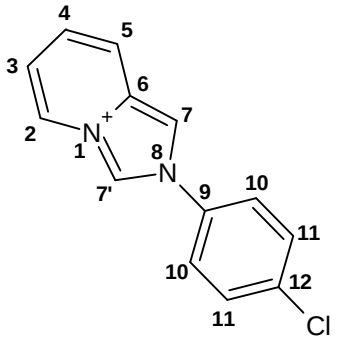
δ_C (400 MHz, MeOD) 112.7 (7-**C**), 117.0 (4-**C**), 117.2 (12-**C**), 118.1 (5-**C**), 118.4 (3-**C**), 123.8 (2-**C**), 125.4 (11,7'-**C**), 125.5 (10-**C**), 130.8 (6-**C**), 162.5 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3066 (s, Ar C-H stretch), 2912 (s, alkyl C-H stretch), 1627 (s, C=N stretch), 1545 (s, Ar C=C stretch), 1509 (s, alkyl C-C stretch), 1344 (s, C-N stretch), 1081 (s, C-F stretch).

HRMS (ESI+); Found $[M+H]^+$, 213.0827; $C_{13}H_{10}N_2F$ Calc. Mass, 213.0828.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-chloro)phenylimidazolium chloride (4.3c)



Pyridyl[1,5-a]-4-(*p*-chloro)phenylimidazolium chloride **(4.3c)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*p*-chlorophenyl)methylimine (1.1 g, 5.0 mmol) and stirred for 12 h. The product **(4.3c)** was obtained as a light brown amorphous solid (1.1 g, 95%; 84% {$POCl_3$}), Mp – 254-256 °C; TLC R_f 0.41 (UV-active, EtOAc / MeOH,

1:1); NMR, δ_H (400 MHz, MeOD) 7.29 (1H, t, $J_{3,(4,2)}$ 7.0, 3-**H**), 7.39 (1H, dd, $J_{4,5}$ 9.6, $J_{4,3}$ 7.0, 4-**H**), 7.75 (2H, d, $J_{11,10}$ 8.8, 11-**H**), 7.88-7.94 (3H, m, 5-**H**, 10-**H**), 8.54 (1H, s, 7-**H**), 8.59 (1H, d, $J_{2,3}$ 7.0, 2-**H**), 10.11 (1H, d, $J_{7,5}$1.2, 7'-**H**).

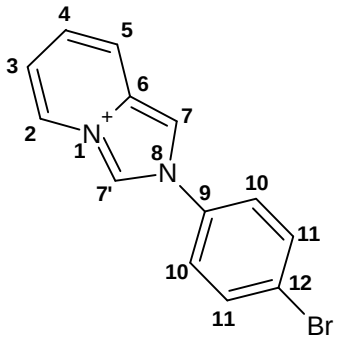
δ_C (400 MHz, MeOD) 112.4 (7-**C**), 118.1 (5-**C**), 118.5 (3-**C**), 123.8 (2-**C**), 124.5 (10-**C**), 125.3 (7'-**C**), 125.4 (4-**C**), 130.4 (11-**C**), 130.9 (6-**C**), 134.0 (9-**C**), 136.5 (12-**C**).

IR (neat) ν_{max} (cm^{-1}): 3056 (s, Ar C-H stretch), 2912 (s, alkyl C-H stretch), 1656 (s, C=N stretch), 1546 (s, Ar C=C stretch), 1504 (s, alkyl C-C stretch), 1343 (s, C-N stretch), 1091 (s, C-Cl stretch).

HRMS (ESI+); Found $[M+H]^+$, 229.0533; $C_{13}H_{10}N_2Cl$ Calc. Mass, 229.0533.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-bromo)phenylimidazolium chloride (4.3d)



Pyridyl[1,5-a]-4-(*p*-bromo)phenylimidazolium chloride **(4.3d)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*p*-bromophenyl)methylimine (1.3 g, 5.0 mmol) and stirred for 12 h. The product **(4.3d)** was obtained as a brown amorphous solid (1.3 g, 96%; 86% {$POCl_3$}), Mp – 320-322 °C; TLC R_f 0.47 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 7.28 (1H, t, $J_{3,(4,2)}$ 6.9, 3-**H**), 7.38 (1H, dd, $J_{4,5}$ 8.9, $J_{4,3}$ 6.9, 4-**H**), 7.83 (2H, d, $J_{11,10}$ 8.8, 11-**H**), 7.87-7.93 (3H, m, 5-**H**, 10-**H**), 8.54 (1H, s, 7-**H**), 8.58 (1H, d, $J_{2,3}$ 6.9, 2-**H**), 10.11 (1H, s, 7'-**H**).

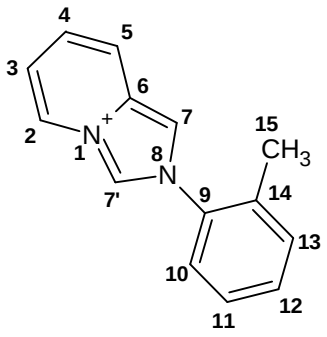
δ_C (400 MHz, MeOD) 112.4 (7-**C**), 118.1 (5-**C**), 118.5 (3-**C**), 123.8 (2-**C**), 144.4 (12-**C**), 124.7 (11-**C**), 125.4 (4,7'-**C**), 130.9 (6-**C**), 133.4 (10-**C**),134.4 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3063 (s, Ar C-H stretch), 2914 (s, alkyl C-H stretch), 1655 (s, C=N stretch), 1545 (s, Ar C=C stretch), 1416 (s, alkyl C-C stretch), 1341 (s, C-N stretch), 744 (s, C-Br stretch).

HRMS (ESI+); Found $[M+H]^+$, 273.0031; $C_{13}H_{10}N_2$ Br Calc. Mass, 273.0027.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*o*-methyl)phenylimidazolium chloride (4.3e)



Pyridyl[1,5-a]-4-(*o*-methyl)phenylimidazolium chloride **(4.3e)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*o*-methylphenyl)methylimine (1.0 g, 5.0 mmol) and stirred for 12 h. The product **(4.3e)** was obtained as colorless brittle solid (1.0 g, 96%; 84% {$POCl_3$}), Mp – 154-155 °C; TLC R_f 0.41 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 2.33 (1H, s, 15-**H**), 7.30 (1H, t, $J_{3,(2,4)}$ 6.7, 3-**H**), 7.42 (1H, t, $J_{4,(3,5)}$ 6.7, 4-**H**), 7.52-7.67 (4H, m, 10-**H**, 11-**H**, 12-**H**, 13-**H**), 7.95 (1H, d, $J_{5,4}$ 6.7, 5-**H**), 8.34 (1H, s, 7-**H**) 8.67 (1H, d, $J_{2,3}$ 6.7, 2-**H**), 9.93 (1H, s, 7'-**H**).

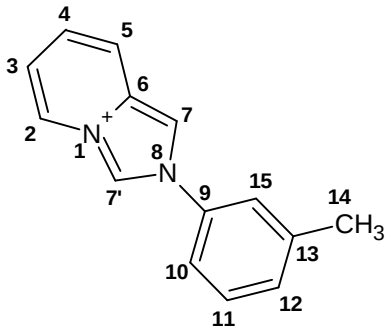
δ_C (400 MHz, MeOD) 16.6 (15-**C**), 115.2 (7-**C**), 118.4 (5-**C**), 118.4 (3-**C**), 124.2 (2-**C**), 125.5 (4-**C**), 126.6 (13-**C**), 127.2 (7'-**C**), 127.4 (12-**C**), 130.5 (6-**C**), 131.2 (10-**C**), 131.8 (11-**C**), 133.7 (14-**C**), 134.9 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3056 (s, Ar C-H stretch), 2912 (s, alkyl C-H stretch), 1656 (s, C=N stretch), 1545 (s, Ar C=C stretch), 1458 (s, alkyl C-C stretch), 1349 (s, C-N stretch).

HRMS (ESI+); Found $[M+H]^+$, 209.1077; $C_{14}H_{13}N_2$ Calc. Mass, 209.1079.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*m*-methyl)phenylimidazolium chloride (4.3f)



Pyridyl[1,5-a]-4-(*m*-methyl)phenylimidazolium chloride **(4.3f)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*m*-methylphenyl)methylimine (1.0 g, 5.0 mmol) and stirred for 12 h. The product **(4.3f)** was obtained as brown brittle solid (0.69 g, 66%; 60% {$POCl_3$}), Mp – 121-126 °C; TLC R_f 0.4 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 2.53 (1H, s, 14-**H**), 7.27 (1H, t, $J_{3,(2,4)}$7.0, 3-**H**), 7.38 (1H, dd, $J_{4,5}$9.4, $J_{4.3}$7.0, 4-**H**), 7.52 (1H, d, $J_{12,11}$7.9, 12-**H**), 7.60 (1H, t, $J_{11,(10,13)}$, 7.9 11-**H**,), 7.67 (1H, d, $J_{10,11}$ 7.9, 10-**H**), 7.73 (1H, s, 15-**H**), 7.91 (1H, d, $J_{5,4}$ 9.4, 5-**H**), 8.52 (1H, s, 7-**H**), 8.59 (1H, d, $J_{2,3}$ 7.0, 2-**H**), 10.08 (1H, s, 7'-**H**).

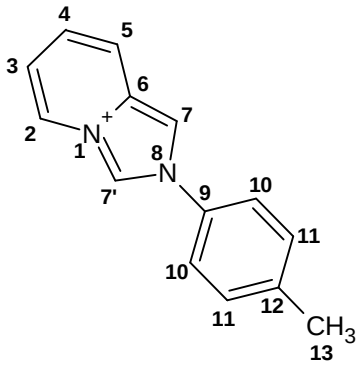
δ_C (400 MHz, MeOD) 20.0 (14-**C**), 112.4 (7-**C**), 118.1 (5-**C**), 118.3 (3-**C**), 119.7 (10-**C**), 123.1 (15-**C**), 123.8 (2-**C**), 125.0 (7'-**C**), 125.2 (4-**C**), 130.0 (11-**C**), 130.8 (6-**C**), 131.2 (12-**C**), 135.3 (13-**C**), 141.1 (9-**C**).

IR (neat) ν_{max} (cm^{-1}): 3065 (s, Ar C-H stretch), 2916 (s, alkyl C-H stretch), 1656 (s, C=N stretch), 1548 (s, Ar C=C stretch), 1466 (s, alkyl C-C stretch), 1336 (s, C-N stretch).

HRMS (ESI+); Found $[M+H]^+$, 209.1080; $C_{14}H_{13}N_2$ Calc. Mass, 209.1079.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-methyl)phenylimidazolium chloride (4.3g)



Pyridyl[1,5-a]-4-(*p*-methyl)phenylimidazolium chloride **(4.3g)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*p*-methylphenyl)methylimine (1.0 g, 5.0 mmol) and stirred for 12 h. The product **(4.3g)** was obtained as light brown brittle solid (1.0 g, 96%; 83% {$POCl_3$}), Mp – 92-94 °C; TLC R_f 0.4 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 2.50 (1H, s, 13-**H**), 7.27 (1H, t, $J_{3,(2,4)}$ 7.0, 3-**H**), 7.38 (1H, dd, $J_{4,5}$ 9.6, $J_{4,3}$ 7.0, 4-**H**), 7.54 (2H, d, $J_{11,10}$ 8.3, 11-**H**), 7.75 (2H, d, $J_{10,11}$ 8.3, 10-**H**), 7.89 (1H, d, $J_{5,4}$9.6, 5-**H**), 8.49 (1H, s, 7-**H**), 8.56 (1H, d, $J_{2,3}$ 7.0, 2-**H**), 10.04 (1H, s, 7'-**H**).

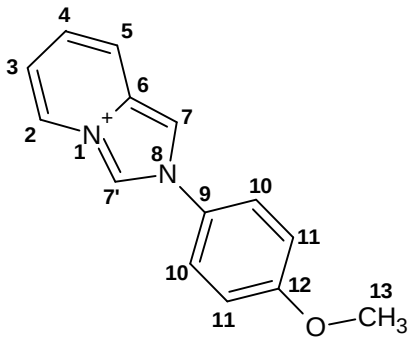
δ_C (400 MHz, MeOD) 19.7 (13-**C**), 112.3 (7-**C**), 118.0 (5-**C**), 118.2 (3-**C**), 122.5 (10-**C**), 123.8 (2-**C**), 125.0 (7'-**C**), 125.2 (4-**C**), 130.7 (11-**C**), 130.8 (6-**C**), 132.9 (9-**C**), 141.5 (3-**C**).

IR (neat) ν_{max} (cm^{-1}): 3067 (s, Ar C-H stretch), 2903 (s, alkyl C-H stretch), 1655 (s, C=N stretch), 1567 (s, Ar C=C stretch), 1454 (s, alkyl C-C stretch), 1379 (s, C-N stretch).

HRMS (ESI+); Found $[M+H]^+$, 209.1078; $C_{14}H_{13}N_2$ Calc. Mass, 209.1079.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-anisy)phenylimidazolium chloride (4.3h)



Pyridyl[1,5-a]-4-(*p*-anisy)phenylimidazolium chloride **(4.3h)** was obtained following the procedure **"B"** and **"C"** starting from 2-pyridyl-N-(*p*-anisiphenyl)methylimine (1.1 g, 5.0 mmol) and stirred for 12 h. The product **(4.3h)** was obtained as dark brown brittle solid (1.0 g, 91%; 82% {$POCl_3$}), Mp – 98-100 °C (Lit. ref. 218-220°C); TLC R_f 0.5 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 3.93 (1H, s, 13-**H**), 7.21-7.29 (3H, m, 3-**H**, 11-**H**), 7.37 (1H, dd, $J_{4,5}$ 9.4, $J_{4,3}$ 6.8, 4-**H**), 7.79 (3H, d, $J_{10,11}$ 8.6 10-**H**), 7.88 (1H, d, $J_{5,4}$ 9.4, 5-**H**), 8.44 (1H, s, 7-**H**), 8.55 (1H, d, $J_{2,3}$ 7.1, 2-**H**), 9.98 (1H, s, 7'-**H**).

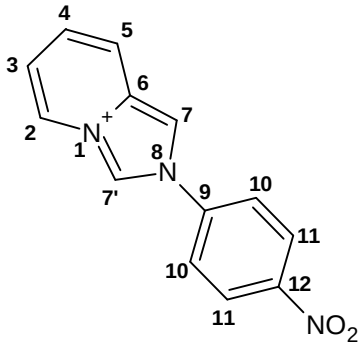
δ_C (400 MHz, MeOD) 55.3 (13-**C**), 112.6 (7-**C**), 115.2 (11-**C**), 118.0 (5-**C**), 118.2 (3-**C**), 123.8 (2-**C**), 124.3 (10-**C**), 125.2 (4,7'-**C**), 128.4 (9-**C**), 130.9 (6-**C**), 161.9 (12-**C**).

IR (neat) ν_{max} (cm^{-1}): 3069 (s, Ar C-H stretch), 2910 (s, alkyl C-H stretch), 1656 (s, C=N stretch), 1547 (s, Ar C=C stretch), 1443 (s, alkyl C-C stretch), 1352 (s, C-N stretch), 1298 (s, C-0 stretch).

HRMS (ESI+); Found $[M+H]^+$, 225.1027; $C_{14}H_{13}N_2O$ Calc. Mass, 225.1028.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-nitro)phenylimidazolium chloride (4.3i)



Pyridyl[1,5-a]-4-(*p*-nitro)phenylimidazolium chloride **(4.3i)** was obtained following the procedure **"A"** (refluxed for 12 h, 4-nitroanaline as a starting material). Crude 2-pyridyl-N-(*p*-nitrophenyl)methylimine was treated as in procedure **"B"** and stirred for 16 h. The product **(4.3i)** was obtained as a light brown brittle solid (67%), Mp – 102-209 °C; TLC R_f 0.55 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 7.32 (1H, t, $J_{3,(4,2)}$ 7.2, 3-**H**), 7.41 (1H, dd, $J_{4,5}$ 9.8, $J_{4,3}$ 7.2, 4-**H**), 7.94 (1H, d, $J_{5,4}$ 9.8, 5-**H**), 8.19 (2H, d, $J_{11,10}$ 8.0, 11-**H**), 8.55-8.65 (3H, m, 2-**H**, 10-**H**), 8.68 (1H, s, 7-**H**), 10.27 (1H, s, 7'-**H**).

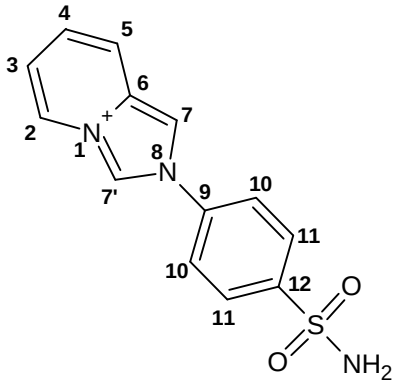
δ_C (400 MHz, MeOD) 112.6 (7-**C**), 118.3 (5-**C**), 118.9 (3-**C**), 124.0 (2-**C**), 124.3 (11-**C**), 125.5 (3-**C**), 125.7 (10-**C**), 126.0 (7'-**C**), 131.1 (6-**C**), 139.6 (9-**C**) 148.9 (12-**C**).

IR (neat) ν_{max} (cm^{-1}): 3064 (s, Ar C-H stretch), 2923 (s, alkyl C-H stretch), 1653 (s, C=N stretch), 1593 (s, Ar C=C stretch), 1527 (s, alkyl C-C stretch), 1342 (s, C-N stretch), 1306 (s, C-O stretch).

HRMS (ESI+); Found $[M+H]^+$, 240.0772; $C_{13}H_{10}N_3O_2$ Calc. Mass, 240.0773.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-sulfanilamidylimidazolium chloride (4.3j)



Pyridyl[1,5-a]-4-sulfanilamidylimidazolium chloride **(4.3j)** was obtained following the procedure **"A"** (refluxed for 12 h, sulfanilamide as a starting material). Crude 2-pyridyl-N-(*p*-sulfanilamidyl)methylimine was treated as in procedure **"B"** and stirred for 18 h. The product **(4.3j)** was obtained as a light brown amorphous solid (71%), Mp – 271-272 °C; TLC R_f 0.53 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 4.81 (2H, br, NH_2), 7.30 (1H, t, $J_{3,(4,2)}$ 7.0, 3-**H**), 7.40 (1H, dd, $J_{4,5}$ 9.4, $J_{4,3}$ 7.0, 4-**H**), 7.95 (1H, d, $J_{5,4}$ 9.4, 5-**H**), 8.16 (2H, d, $J_{11,10}$ 8.9, 11-**H**), 8.20 (2H, d, $J_{10,11}$8,9, 10-**H**), 8.63-8.70 (2H, m, 2-**H**, 7-**H**), 10.30 (1H, s, 7'-**H**).

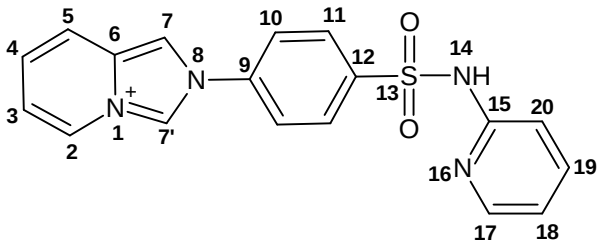
δ_C (400 MHz, MeOD) 112.3 (7-**C**), 118.3 (5-**C**), 118.7 (3-**C**), 123.6 (10-**C**), 124.0 (2-**C**), 124.3 (7'-**C**), 125.6 (4-**C**), 128.2 (11-**C**), 131.0 (6-**C**), 137.6 (9-**C**) 145.5 (12-**C**).

IR (neat) ν_{max} (cm^{-1}): 3091 (s, Ar C-H stretch), 2912 (s, alkyl C-H stretch), 1656 (s, C=N stretch), 1593 (s, Ar C=C stretch), 1424 (s, alkyl C-C stretch), 1336 (s, C-N stretch), 922 (s, N-H (NH_2) stretch).

HRMS (ESI+); Found $[M+H]^+$, 274. 0651; $C_{13}H_{12}N_3O_2S$ Calc. Mass, 274.0650.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-sulphapyridylimidazolium chloride (4.3k)



Pyridyl[1,5-a]-4-sulphapyridylimidazolium chloride **(4.3k)** was obtained following procedure **"A"** (refluxed for 12 h, sulphapyridine as a starting material). Crude 2-pyridyl-N-(*p*-sulphapyridyl)methylimine was treated as in procedure **"B"** and stirred for 18 h. The product **(4.3k)** was obtained as a light brown amorphous solid (71%), Mp – 121-124 °C; TLC R_f 0.51 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 4.81 (1H, br, NH), 6.9 (1H, t, $J_{18,(17,19)}$ 6.0, 18-**H**), 7.28 (1H, t, $J_{3,(4,2)}$ 7.0, 3-**H**), 7.33-7.41 (2H, m, 4-**H**, 20-**H**), 7.81(1H, dd, $J_{19,20}$ 9.2, $J_{19,18}$ 7.0, 19-**H**), 7.90 (1H, d, $J_{5,4}$ 9.4, 5-**H**), 7.96 (1H, d, $J_{17,18}$ 6.0, 17-**H**), 8.04 (2H, d, $J_{11,10}$ 8,7, 11-**H**), 8.25 (2H, d, $J_{10,11}$ 8.7, 10-**H**), 8.56-8.60 (2H, m, 2-**H**, 7-**H**), 10.16 (1H, s, 7'-**H**).

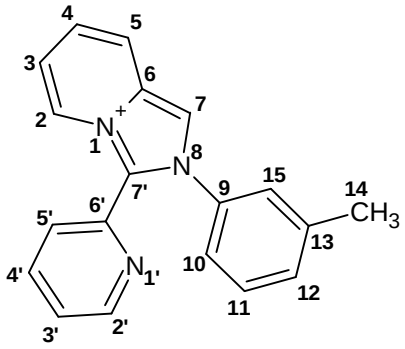
δ_C (400 MHz, MeOD) 112.3 (7-**C**), 114.7 (18-**C**), 115.6 (20-**C**), 118.1 (5-**C**), 118.6 (3-**C**), 123.4 (11-**C**), 123.8 (2-**C**), 125.5 (4,7'-**C**), 128.7 (10-**C**), 130.9 (6-**C**), 137.6 (9-**C**), 140.1 (17-**C**), 141.9 (19-**C**), 144.8 (12-**C**), 154.0 (15-**C**).

IR (neat) ν_{max} (cm^{-1}): 3058 (s, Ar C-H stretch), 2917 (s, alkyl C-H stretch), 1614 (s, C=N stretch), 1537 (s, Ar C=C stretch), 1463 (s, alkyl C-C stretch), 1347 (s, C-N stretch), 770 (s, N-H stretch).

HRMS (ESI+); Found $[M+H]^+$, 351.0919; $C_{18}H_{15}N_4O_2S$ Calc. Mass, 351.0916.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*m*-methyl)pheny-5-pyridylimidazolium chloride (4.4a)



Pyridyl[1,5-a]-4-(*m*-methyl)pheny-5-pyridylimidazolium was produced following procedure "A" by refluxing pyridine-2-aldehyde (2.071 g, 20.0 mmol) and *m*-toluidine (1.071 g, 10.0 mmol) in an absolute ethanol (20 ml) with HCl (5.0 ml, 4 M) and reflux for 24 hours. The product **(4.4a)** was a brown semi-solid (62%, yield); TLC R_f 0.35 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 2.43 (1H, s, 15-**H**), 7.31-7.37 (3H, m, 3-**H**, 11-**H**), 7.40 (1H, d, $J_{5',4'}$ 8.0, 5'-**H**), 7.43- 7.52 (4H, m, 4-**H**, 10-**H**, 12-**H**, 14-**H**), 7.63 (1H, dd, $J_{3',4'}$ 7.9, $J_{3',2'}$ 4.8, 3'-**H**), 7.91 (1H, td, *J* 7.9, $J_{4',2'}$ 0.9, 4'-**H**), 8.04 (1H, d, $J_{5,4}$ 9.1, 5-**H**), 8.50 (1H, s, 7-**H**), 8.91 (1H, d, $J_{2',3'}$ 4.7, 2'-**H**), 8.96 (1H, d, $J_{2,3}$ 7.3, 2-**H**).

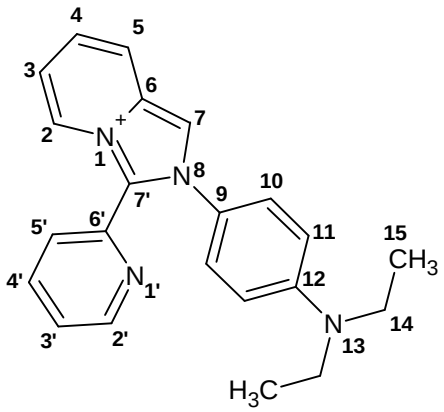
δ_C (400 MHz, MeOD) 20.2 (14-**C**), 116.3 (7-**C**), 118.5 (5-**C**), 119.0 (3-**C**), 123.2 (11-**C**), 123.3 (2-**C**), 126.0 (12-**C**), 126.1 (3'-**C**), 126.5 (4-**C**), 127.2 (5'-**C**), 129.7 (15-**C**), 130.4 (6-**C**), 130.6 (10-**C**), 135.4 (6'-**C**), 137.6 (4'-**C**), 140.9 (7'-**C**), 141.9 (9-**C**), 150.6 (2'-**C**).

IR (neat) ν_{max} (cm^{-1}): 3058 (s, Ar C-H stretch), 2913 (s, alkyl C-H stretch), 1624 (s, C=N stretch), 1548 (s, Ar C=C stretch), 1432 (s, alkyl C-C stretch), 1362 (s, C-N stretch).

HRMS (ESI+); Found $[M+H]^+$, 272.3381; $C_{19}H_{16}N_3$ Calc. Mass, 272.3380.

UV (MeOH): λ_{max} 307, 245, 204 nm

Synthesis of pyridyl[1,5-a]-4-(*p*-N,N-Diethyl)pheny-5-pyridylimidazolium chloride (4.4b)



Pyridyl[1,5-a]-4-(*p*-N,N-Diethyl)pheny-5-pyridylimidazolium chloride was produced following procedure "A", by refluxing pyridine-2-aldehyde (2.142 g, 20.0 mmol) and N,N-Diethyl-*p*- phenylenediamine chlorohydrate (2.007 g, 10.0 mmol) in an absolute ethanol (20 ml) with HCl (5.0 ml, 4 M) and reflux for 24 hours. The product **(4.4b)** was a dark-brown semi-solid (58%, yield); TLC R_f 0.34 (UV-active, EtOAc / MeOH, 1:1); NMR, δ_H (400 MHz, MeOD) 1.23 (3H, t, *J* 7.1 15-**H**, 15'-**H**), 3.78 (2H, q, *J* 7.1, 14-**H**, 14'-**H**), 7.40 (1H, t, *J* 5.7, 3-**H**), 7.54 (1H, dd, $J_{4,5}$ 9.8, $J_{4,3}$ 6.7, 4-**H**), 7.60 (1H, d, $J_{5',4'}$ 7.6, 5'-**H**), 7.68 (1H, dd, $J_{3',4'}$ 7.9, $J_{3',2'}$ 5.0, 3'-**H**), 7.91 (2H, d, $J_{11,10}$ 8.6, 11-**H**), 7.95-8.03 (3H, m, 4'-**H**, 10-**H**), 8.10 (1H, d, $J_{5,4}$ 9.3, 5-**H**), 8.67 (1H, s, 7-**H**), 8.88 (1H, d, $J_{2',3'}$ 4.5, 2'-**H**) 8.92 (1H, d, $J_{2,3}$ 6.3, 2-**H**).

δ_C (400 MHz, MeOD) 9.6 (15,15'-**C**), 53.3 (14,14'-**C**), 116.3 (7-**C**), 118.7 (5-**C**), 119.5 (3-**C**), 123.1 (2-**C**), 124.2 (4'-**C**), 126.3 (4-**C**), 126.5 (3'-**C**), 127.5 (5'-**C**), 128.9 (11-**C**), 130.6 (6-**C**), 132.0 (6'-**C**), 136.2 (7'-**C**), 138.0 (10-**C**) 140.0 (9-**C**), 141.4 (12-**C**), 151.0 (2'-**C**).

IR (neat) ν_{max} (cm^{-1}): 3107 (s, Ar C-H stretch), 2917 (s, alkyl C-H stretch), 1653 (s, C=N stretch), 1516 (s, Ar C=C stretch), 1452 (s, alkyl C-C stretch), 1358 (s, C-N stretch), 1154 (s, N-H stretch).

HRMS (ESI+); Found $[M+H]^+$, 343.1920; $C_{22}H_{23}N_4$ Calc. Mass, 343.1923.

UV (MeOH): λ_{max} 307, 245, 204 nm