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Review Article

Syntheses, Complexation and Biological Activity of Aminopyridines: A Mini-Review

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Abstract: Aminopyridines are among the classes of heterocyclic compounds that have been extensively studied in the last few decades owing to their interesting biological activities. They exist in three isomeric forms: 2-aminopyridine, 3-aminopyridine and 4-aminopyridine. The diversity in their pharmacological activities has attracted the attention of many researchers to explore the reasons for their wide potential. This study examines recent advances related to the efficient procedure for synthesizing different types of aminopyridine derivatives, its coordination site with metals and biological activities using systematic literature review and content analysis. Other important concepts of aminopyridines discussed are basicity, electric hindrance as related to percentage yield of isomeric forms and spectra updates on the characterization of aminopyridines. The findings from this study also reveal the array of solvents used for purification processes; ideas on isomers that have not been used in the synthesis of aminopyridine derivatives and their respective biological activities. The significance of this study is on the various synthetic methods revealed, which may be helpful to the development of newer compounds with aminopyridines moieties that could offer high bioactivity and lesser toxicity.

Keywords: Syntheses, Bioactivity, Aminopyridines, Basicity, Electric Hindrance

1. Introduction

The emergence of pathogenic bacteria resistant to many or current antibiotics is a major public health concern in the clinical setting. The world economic forum recently identified antibiotic resistance as one of the greatest threats to human health [1, 2]. Metal complexes have become an emerging tool in drug discovery being widely used as therapeutic compounds to treat several human diseases such as infection, diabetes, anti-inflammatory and neurological disorder [3, 4]. A significant interest in the synthesis of metal complex-based drugs with unique research, therapeutic and diagnostic opportunities is currently observed in medicinal organic chemistry.

Among the various 6-membered heterocyclic compounds, aminopyridines have drawn special attention because of the various pharmacological activities associated with the presence of it in targeted molecules. Researchers have shown that the presence of a small molecule of aminopyridine is an advantage for the medicinal properties of the target molecule, whether it is a simple molecule, with just a few groups on it, or is a complicated one, with more heterocycles present in the structure [4, 5].

Aminopyridine is an organic compound that contains an amino group and an aromatic heterocyclic pyridine. It has the molecular formula, $C_5H_6N_2$ and three isomers: 2-aminopyridine, 3-aminopyridine and 4-aminopyridine [6]. Several derivatives of aminopyridine are used as precursors in the pharmaceutical industries for the preparation of antibacterial and antiviral drugs, herbicides and dyes [7, 8].

In the light of this interest, the study examines the recent advances related to the efficient procedure for synthesizing different types of aminopyridine derivatives, its coordination site with metals and biological activities using systematic

literature review and content analysis. The research also considered the basicity of various isomers of aminopyridine, which in turn we help the researchers to consider the appropriate pH medium for synthesis involving aminopyridine. Oftentimes, reactions involving the different isomer of aminopyridines present different percentage yields at the same reaction condition.

This issue associated with synthesis has been attributed to electric hindrance as related to the percentage yield of isomeric forms. The study further discussed spectra updates in line with spectroscopic characterization of aminopyridines using UV-VIS, FTIR and NMR.

2. Isomers of Aminopyridines

2.1. 2-aminopyridine

2-Aminopyridine is a colourless solid used in the production of drugs such as sulphapyridine, piroxicam, tenoxicam and tripelennamine. Figure 1 shows molecular structures with aminopyridine constituents.

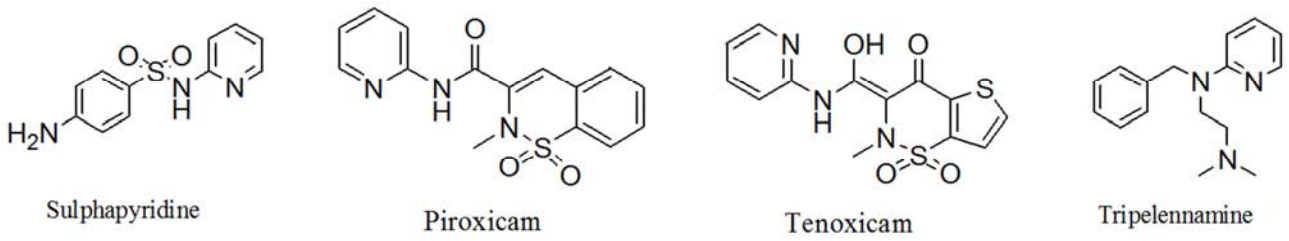


Figure 1. *Drug molecular structures with aminopyridine constituents*

Both substituted and unsubstituted aminopyridines are also used as precursors for the production of other heterocyclic compounds for medicinal use [9]. For example, 2-(methylamino)nicotinonitrile or 2-amino-3-nitropyridine was used as synthetic precursor of 1*H*,3*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione[10] or pyrido[2,3-*b*]pyrazines and imidazo[4,5-b]pyridines, respectively [11].

2-Aminopyridine is synthesized by the reaction of pyridine with sodium amide (Chichibabin amination) [12]. It is obtained in high yield after the hydrolysis of the intermediate salt [13, 14]. The reaction is shown below (figure 2).

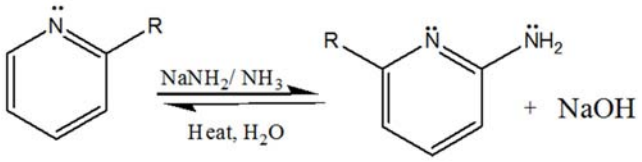


Figure 2. *Chichibabin amination.*

Substituted 2-aminopyridines can also be synthesized from pyridine *N*-oxides with 84% isolated product in a one-pot, two-step process which involves an in situ deprotection of an isolable *N*-formylaminopyridine intermediate [14]. This method (as shown below) worked for the synthesis of 2-aminopyridines, unlike most other methods according to Liu et al.

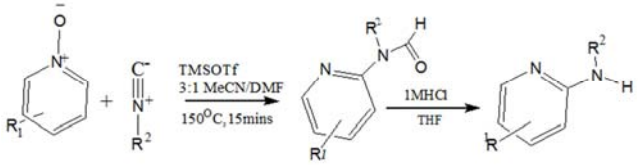


Figure 3. *2-Aminopyridine fom pyridine N-oxide.*

2.2. 3-aminopyridine

3-aminopyridine is used as an intermediate for agrochemicals, pharmaceuticals and colourants [13, 15], and is also listed as a plant growth regulator [16]. Derivatives of 3-aminopyridine are used as luminescent and liquid crystal materials as well as in photosensitizer and metal complex chemistry. Shneine and coworkers [15] reported that 3-aminopyridine can also be used in the production of dyes, amoxicillin sodium raw materials, Piroxicam, Tenoxicam, and Ampiroxicam. Rehman and co-workers [17] opined that 3-aminopyridine can be used as chelating ligands to form a complex with a transition metal ion and also as a monomer for polymerization. The amino group in 3-aminopyridine is very similar to that of aniline, and the diazonium salt derived from it is reasonably stable and undergoes a range of normal diazonium salt reactions [18]. It can also be used in the synthesis of the organic ligand, 3-pyridylnicotinamide and as a plant growth regulator [16].

Preparation of 3-Aminopyridine was done by heating nicotinamide with sodium hypobromite which was generated in situ by the reaction of sodium hydroxide and bromine at 70°C [19].

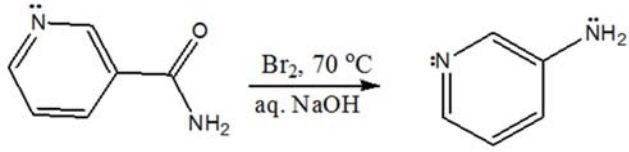


Figure 4. *Synthesis of 3-Aminopyridine.*

2.3. 4-aminopyridine

4-aminopyridine, an odourless white crystalline material has been reported to be used as an intermediate and as a fixer in the production certain textile dyes [20]. The preparation

starts with ammoxidation of 4-methylpyridine and the pyridine carboxamide generated from the corresponding nitrile is Decarbonylated with sodium hypochlorite via Hofmann rearrangement [9] as shown below.

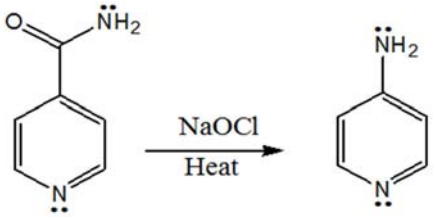


Figure 5. *Syntheis of 3-Aminopyridine.*

4-Aminopyridine is also produced by heating pyridine with sodium amide in *N,N*-dimethylaniline at 180ºC. Another method of preparing 4-aminopyridine is via peroxidation/nitration/nitro reduction of pyridine in 2-aminopyridine [21, 22]. 4-Aminopyridine is considered toxic by all routes of contact, although skin, inhalation and eye contact are the known primary routes of exposure [21, 23]. More severe human poisoning incidents of 4-aminopyridines involving convulsions, respiratory failure, and death have been reported [24]. It is worthy of note that exposure to aminopyridines can cause skin irritation, headache, dizziness, nausea, increased blood pressure, with high exposures leading to convulsions and respiratory failure in man. In this light, researchers are expected to take all precautionary measures, to exploit all the condiments of 2-aminopyridine in researches.

3. Some Properties of Aminopyridine

3.1. Basicity

The basicity of aminopyridines is considered on two main factors: the nitrogen on the pyridine moiety and the nitrogen on the exo-amine. Aromatic pyridine has a pKa of 5.5 (which is 10 times more basic than aniline with a pKa of 4.6). This is because the lone pair of electrons on exo-amine nitrogen is delocalized into the π-system of the benzene ring, thus, making the lone pair of electrons on the exo-nitrogen less available for donation (which is the basis for basicity) [25]. The lone pair of electrons on pyridine is localized on the ring nitrogen since it is perpendicular to the π-system. The nitrogen in the pyridine ring is also sp^2 hybridized and this accounts for the difference in alkalinity when compared with cyclohexylamine with sp^3 nitrogen [26].

The basicity difference in the isomer of aminopyridines is therefore attributed to the electronic properties of the extra exo-amine function on the pyridine rings. The lone pair of electrons on exo-amine nitrogen interacts with the lone pair of electrons on the nitrogen in the ring via positive mesomeric effect (+*M*), that is, the donation of electrons by a substituent to the ring. The exo-amine can also interact by a negative inductive effect, which implies exo-nitrogen withdrawing electrons from the ring nitrogen [22]. In aminopyridines, the effect of mesomerism is stronger than the inductive effect. More so, the stability of the conjugated system in either cyclic or acyclic chains increases according to the number of carbon atoms at the conjugated centre while the inductive effect decreases as the distance between the substituent and the functional group increases [18]. Other important factors that affect the basicity of aminopyridines are steric hindrance and intramolecular hydrogen bonding (hydrogen atoms on the neighbouring amine moiety interact with the lone pair of ring-nitrogen). This leads to extra stabilization of the lone pair of electrons on the nitrogen in the pyridine ring and thus lowers the basicity [27].

Based on the explanations above, 4-aminopyridine (pKa = 9.17) is more basic than 2-aminopyridine (pKa = 6.86). 3-Aminopyridine (pKa = 6.0) is less basic than the other two isomers (*o-, p-*). This is fundamentally based on the fact that the mesomeric effect of the exo-amine leads to extra electron density on the ring nitrogen. The structures (figure 6) represent the resonance effect of exo-nitrogen on the basicity of the aminopyridine [26, 28].

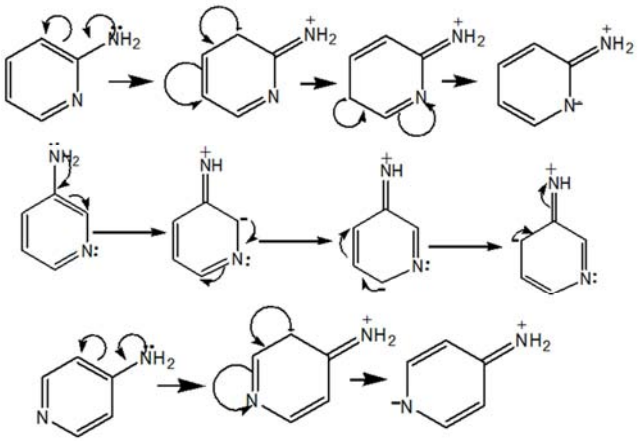


Figure 6. *Resonance structures of Aminopyridines.*

3.2. Reactivity

Reactivity of an aminopyridine can be seen in the conditions that favour the pyridine ring and the amino moiety. The pyridine ring is susceptible to nucleophilic substitution reaction on position 2-, 4- and 6- of the ring, relative to the position of the amino group. The hetero nitrogen, carbon position 3 and carbon position 5 are not susceptible to nucleophilic substitution reaction [28].

Generally, the electrophilic substitution of benzene analogues presents a lot of difficulties. This is because its rate-determining step has a high activation energy and occurs at high temperatures (250-400°C) [28]. Consequently, Lewis acids ($AlCl_3$, $AlBr_3$, $FeBr_3$ etc, are used in the reactions. Electrophilic substitution reaction of the pyridine rings at C-3 and C-5 are difficult, except on the heterocyclic nitrogen.

In the reactions of aminopyridines, the preferential reaction of α- and γ-amino-substituted azines with electrophiles at the ring nitrogen atom presents a problem when the desired reaction is at the exocyclic amino group [29]. The electron density ought to be concentrated at the exocyclic nitrogen

atom. The treatment of 2- and 4-aminopyridines with a non-nucleophilic base such as sodamide, alkyl-lithiums, sodium trioxocarbonate (IV) results in the deprotonation and formation of a powerful nucleophilic anion, which reacts with electrophiles preferentially at the exocyclic nitrogen atom [29].

In the absence of a non-nucleophilic base, aminopyridines alkylation normally occurs at the ring. This is because the hetero nitrogen atom is a more active nucleophilic site than the exocyclic nitrogen (The lone pair on the side-chain amino nitrogen participates in conjugation with the ring). But in the presence of a non-nucleophilic base, e.g., sodamide, alkylation occurs on the exocyclic nitrogen, this is attributed to the deprotonation of the substituted amino group [30]. The structural equation in figure 7 below depicts the alkylation of exocyclic nitrogen in the presence of a base and the alkylation of ring hetero nitrogen in the absence of a base.

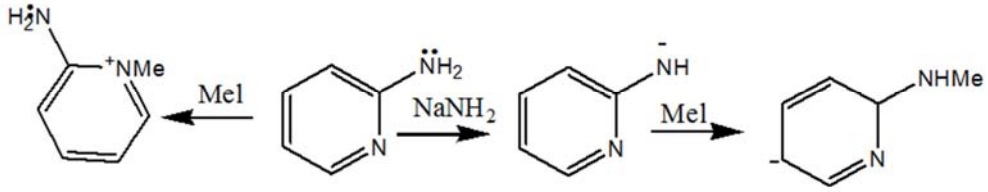


Figure 7. *Alkylation of 2-Aminopyridine.*

3.3. Electric Hindrance and Percentage Yield in Isomers

Electric hindrance is the build-up and rejections of electric positive charges in a step/stage of a reaction involving isomers [31]. Electric hindrances are mostly responsible for the significant differences observed in an isomeric product during organic synthesis. The differences in regioisomeric yields in the reaction of isomeric aminopyridines have been associated with theoretical concepts like; steric hindrance, dipole moment and reaction. In some aromatic electrophilic substitution reactions, the isomeric yield is in most cases attributed to steric hindrance and dipole moment [32]. However, the large differences in isomeric yield could be associated with the presence of an electric rejection between positive charges in the reaction stage. Sanchez-viesca & Gome [32] reported on the percentage yield of 2-aminopyridine nitration. This observation provides an extended theory on this subject, which is in line with the observation of the regiochemistry and the reaction yields of the isomeric products.

4. Aminopyridine Derivatives

4.1. Characterization

The characterization of aminopyridines is based on the pyridine ring moiety and the amino group. The information obtained from the pyridine ring without any substituent is constant, with regards to the relationship between carbon and nitrogen in the pyridine base. The position/nature of the substituent on the pyridine ring creates a variation on the bands/peaks during structural elucidation. Amino group and other substituents on pyridine ring increase/decrease the value of bands/peaks. The substituent could have a positive or negative resonance or inductive effect on the pyridine ring.

UV-Visible spectroscopy. The chromophores due to pyridine derivatives have characteristic bands in the region of 362-460nm. The frequency absorption band of 391-460nm is assigned to the presence of electron-donating chromophores on the ring. Whereas, the absorption band in the region of 362-415 nm is due to the presence of electron receptor chromophores on the pyridine ring. Amethoxy electron-donating chromophores at positions C-4 and C-3 give a bathochromic shift (red) but nitro group acceptors are responsible for a hypsochromic (blue) shift [33].

FT-IR Spectroscopy. Analytically, FTIR technique used to characterize chemical compounds in solid and liquid states. The information on the geometry, functional group and other aspects of chemical compounds are extensively studied using this technique. The pyridine molecule contains various IR active moieties, its IR spectrum gives characteristic peaks corresponding to groups present therein i.e., νC=N 1570-1654 cm^{-1}, νC=C 1593-1597 cm^{-1}, NH_2 3588-3911 cm^{-1} [34].

NMR-spectroscopy. The Six-member heterocyclic aromatic ring of pyridine with a substituted group shows different chemical shift values of all the proton and carbon atoms when compared with the unsubstituted pyridine ring. Signals corresponding to a particular proton present in a pyridine molecule appear in the range of 6.5-9.2 ppm [35, 36]. Aromatic substituent with electron-donating properties attached to position 3 of the pyridine ring will make the proton chemical shift value appear in the range of (8.05-9.00). The presence of carbonyl-containing groups or other aromatic groups at position 3, will make the proton of the pyridine appears at (7.56-9.00), and the proton at position 2 is most deshielded compared with the other protons of the pyridine ring [36]. The peak at 8.29-8.37 will indicate the hydrogen in an amide functional group located at position 2 of the pyridine ring. An R (alkyl) group at position 2 to nitrogen will give rise to the proton with the peak in the range of 7.66-8.74, the proton at position 6 is deshielded to 8.74 but with the presence of R' at position 3, the proton of the pyridine ring appear at (7.60-9.2) and the proton at position 2 is deshielded to 9.2. When this group is at para to nitrogen (position 4), the proton appears in a range of 7.94-8.82 [35].

4.2. Synthesis of 2-Aminopyridine Derivatives

4.2.1. Pyridine-2-yl-Benzylidene-Imines

Alsughayer et al. [36] worked on the synthesis of some new pyridine-2-yl-benzylidene-imines. From their findings, a

mixture of substituted aryl aldehydes and 2-aminopyridine derivatives in 80 ml methanol was boiled under reflux with stirring for 9 hours at 80˚C in an oil bath and then concentrated by rotary evaporation to give a yellow liquid. Thereafter, it was treated with n-hexane to precipitate the crude product, which was recrystallized from dichloromethane and with n-hexane to give a yellow precipitate that was subsequently dried (70% - 90% yield). The sample was analysed using microanalysis, m.p., ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm), FTIR and GC-MS (see figure 8).

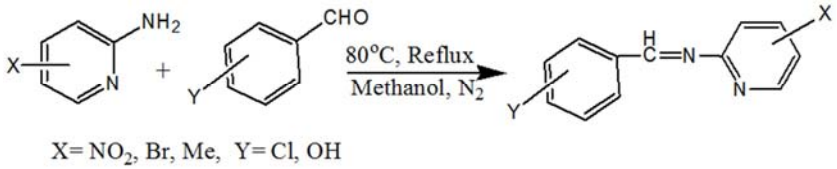


Figure 8. *Synthesis of pyridine-2-yl-Benzylidene-Imines.*

4.2.2. N-(2-hydroxylbenzylidene)pyridin-2-amine

Vinita et al. [37] reported the synthesis of *N*-(2-hydroxylbenzylidene)pyridin-2-amine. A solution of 2-aminopyridine with two drops of formic acid was added to a mixture of ethanol and 2-hydroxybenzaldehyde. Thereafter, the reaction mixture was boiled under reflux for 6 hours. A yellow-orange precipitate was collected by filtration and recrystallized from ethanol-hexane. The yield was 33% and the melting point was 60-62°C. The spectral characterisation of the product was done via IR (cm^{-1}) and ^{1}HNMR ($CDCl_3$, 400 MHz) (see reaction in figure 9).

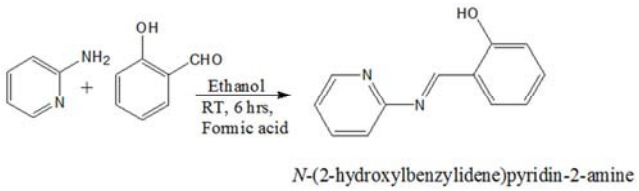


Figure 9. *Synthesis of N-(2-hydroxylbenzylidene)pyridin-2-amine*

4.2.3. 2-mercaptobenzothiazole, 2-mercaptobenzoxazole and 2-mercapto pyrimidine derivative

In the work by Falih et al. [28], the synthesis of new 2-amino pyridine derivatives was based on the reaction of 2-aminopyridine with 2-mercaptobenzothiazole, 2-mercapto pyrimidine and 2-mercaptobenzothiazole, respectively, in 30 ml ethanol, and boiled under reflux for 7-12 hours. The precipitated solids were recrystallised from ethanol and characterised using GC-MS, FTIR and ^{1}HNMR. The reactions in figure 10 below represent the derivatives of 2-aminopyridine

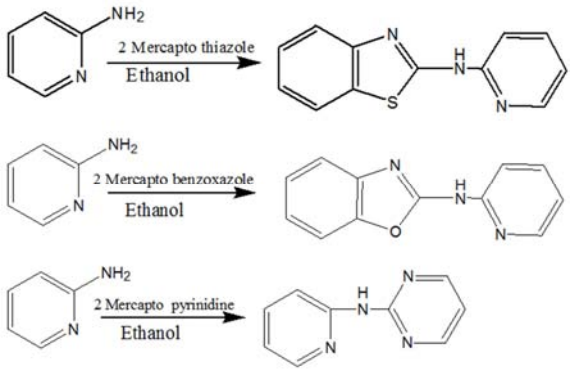


Figure 10. *Synthesis of 2-mercaptobenzothiazole, 2-mercaptobenzoxazole and 2-mercapto pyrimidine derivative*

4.2.4. N[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-pyridin-2-amine

The synthesis of *N*[(1E)-(1,3-diphenyl-*1H*-pyrazol-4-yl)methylene]-pyridin-2-amine via the mixture of 1,3-diphenyl-*1H*-pyrazole-4-carbaldehyde and 2-aminopyridine in absolute ethanol and few drops of glacial acetic acid was reported by Parmar et al. [38]. The mixture was refluxed for 6 hours on a water bath and thereafter, the solid was recrystallised from ethanol. The reaction is depicted figure 11.

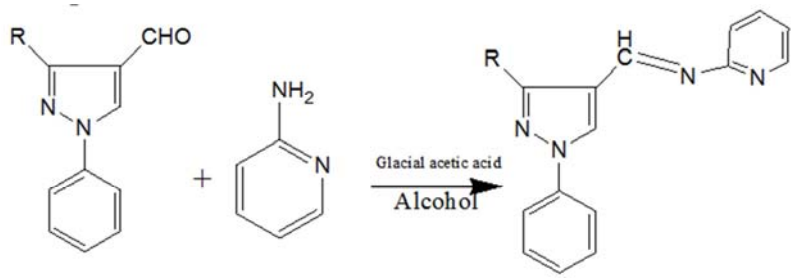


Figure 11. *Synthesis of N[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-pyridin-2-amine.*

4.2.5. 2-amino-5-bromopyridine

Salgado-Zamora et al. [39] investigated the reaction of 2-aminopyridine with barbituric acid derivatives. It was found that the reaction of 2-aminopyridine with 1,3-dimetylbarbituric and barbituric acids yielded an unexpected condensation product whose formation resembles a Mannich-type reaction. While the reaction with

5,5-dibromobarbituric acid yielded the corresponding 2-amino-5-bromopyridine. The synthesis of 2-amino-5-bromopyridine by Salgado-Zamora and co-worker was done by dissolving 2-aminopyridine in EtOH. Thereafter, 5,5-dibromobarbituric acid in ethanol was added. The suspension formed was dissolved upon warming (70ºC) and was left at this temperature and a stirrer overnight. The product (300 mg) was a yield of 83.8%, with a melting point range 134-136ºC (Lit. mp 132 - 135ºC).

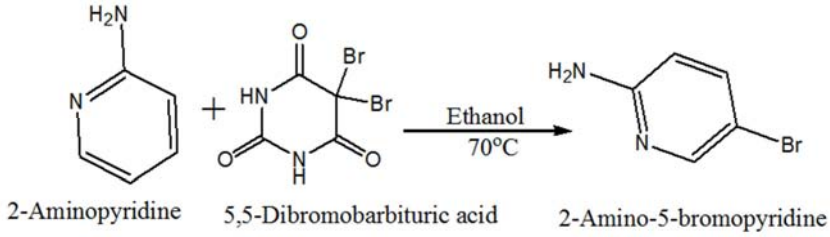


Figure 12. *Synthesis of2-amino-5-bromopyridine.*

The synthesis of 1,3-dimethyl-5-methylidene(2-aminopyridyl)barbituric acid also by Salgado-Zamora and co-workers was done by dissolving 2-Aminopyridine and 1,3-dimethylbarbituric acid in DMF (25 mL) and heated for 4 hours at 70°C. The reaction mixture was cooled, poured into iced water and extracted with EtOAc (3 × 15 mL). The white floppy plates solid was collected by filtration to give the product (350mg) at 17.24% yield. The melting point range was 200 – 201 ºC. The structural elucidation was achieved via ^{1}H NMR ($CDCl_3$), GC-MS and microanalysis [39].

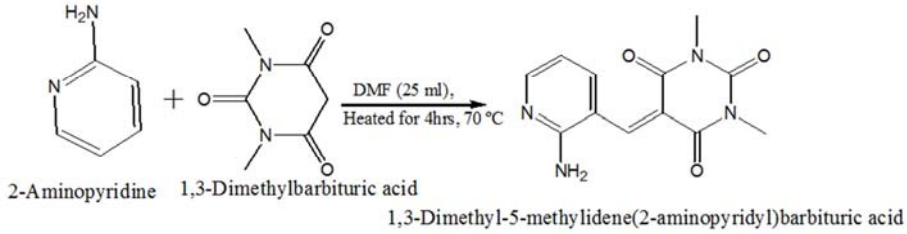


Figure 13. *Synthesis of1,3-dimethyl-5-methylidene(2-aminopyridyl)barbituric acid.*

Further, synthesis of 5-Methylidene(2-aminopyridyl)barbituric acid by Salgado-Zamora and coworkers involved the reaction of 2-aminopyridine and barbituric acid. The percentage yield was 17.1% (310 mg) and the melting point range 253.5 – 254.5ºC. The structural elucidation was done via ^{1}H NMR ($CDCl_3$), GC-MS and microanalysis

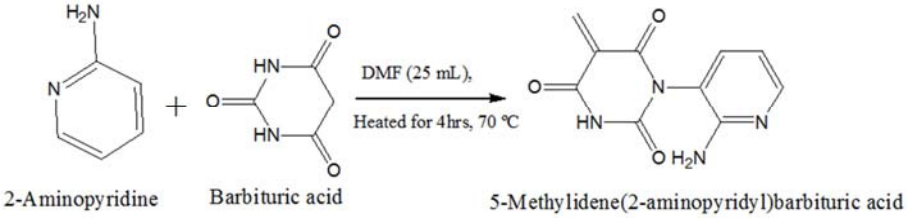


Figure 14. *Synthesis of 5-Methylidene(2-aminopyridyl)barbituric acid.*

4.2.6. N-(2-hydroxylbenzylidene)pyridin-2-amine

A method of synthesizing *N*-(2-hydroxylbenzylidene)pyridin-2-amine which involved the addition of 2-hydroxybenzaldehyde in ethanol to the stirred solution of 2-aminopyridine in ethanol with two drops of methanoic acid was reported by Dueke–Eze et al. [40]. The reaction mixture was refluxed for 6 hours, thereafter, the precipitates were collected by filtration and recrystallized from ethanol-hexane (1:1). The yellow-orange crystal gave a percentage yield of 35%; with a melting point range of 62-64°C. The product (in figure 13) was characterized by IR (cm^{-1}) and ^{1}HNMR ($CDCl_3$, 400 MHz).

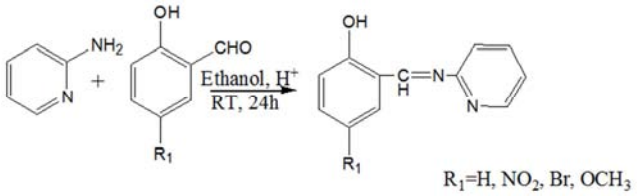


Figure 15. *Synthesis of N-(2-hydroxylbenzylidene)pyridin-2-amine.*

4.2.7. N-(Pyridin-2-yl)benzene Sulphonamide

The synthesis of sulphonamide under simple dynamic pH control via the use of amine completely dissolved in water and

benzene sulphonyl chloride was conducted by Abdul Qadir et al. [41]. According to their method, the pH of the reaction was effectively monitored to ascertain when the reaction was complete. The precipitates formed were filtered, washed several times with distilled water, and recrystallized using methanol and dried using a rotary evaporator. The reaction depicted in figure 16 below represents the synthesis of *N*-(pyridin-2-yl)benzene sulphonamide.

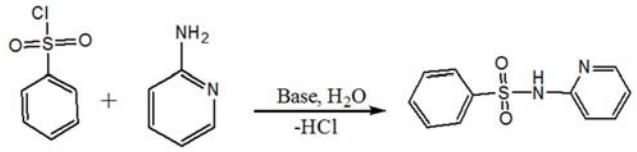


Figure 16. *Synthesis of N-(Pyridin-2-yl)benzene Sulphonamide.*

4.3. Synthesis of 2-Aminopyridine Complexes

4.3.1. Complexes of 2-Aminopyridine

i. Pyridine-2-yl-benzylidene-imines(aminomethyl)pyridi nesalicylaldimine copper(II) complexes: Sobola and Watkins [42] worked on the synthesis Cu(II) complexes of aminopyridine and (aminomethyl)pyridine Schiff bases. In their procedure, a hot ethanolic solution of $CuCl_2 \cdot 2H_2O$ was gradually added to 10 ml ethanolic solution of Schiff base ligands. The resulting solution was warmed while stirred for 30 minutes. Where the precipitate did not form spontaneously on stirring, diethyl ether is used to induce precipitation of the complexes. The bioactivity study confirmed that the methoxyl group enhanced the antimicrobial activity of the salicylaldimine Schiff base ligands and their Cu(II) complexes when screened for their antimicrobial activity against *Staphylococcus aureus* subsp. *aureus*, *Bacillus subtillis* subsp. *spizizenii*, *Escherichia coli* and *Candida albicans* with conventional methods. The complexes obtained were characterized with GC-MS, FTIR, ^{1}HNMR.

ii. Cobalt coordinated polymer with dicyanamide and 2-aminopyridine: Sharma and Narula [43] researched the synthesis of cobalt coordination polymer with dicyanamide and 2-aminopyridine. From their report, 10 ml ethanol/water (1:1) solution of sodium dicyanamide and NaC_2N_3 were added drop-wise to a stirred ethanolic solution (10 ml) of cobalt nitrate hexahydrate ($Co(NO_3)_2.6H_2O$) at room temperature. The resulting mixture was stirred for 1 hour after which a pink precipitate was obtained. The percentage yield was 53% and the melting point was 246°C.

iii. *bis*(2-Aminopyridine)zinc complex: A method of synthesizing *bis*(2-aminopyridine)zinc complex via the mixture of 2-aminopyridine and $Zn(OAc)_2.2H_2O$ in dry ethanol, and an anhydrous condition devoid of oxygen was reported by Mei & Ming [44]. The mixture was refluxed for 14 hours and a white crystal was obtained after filtration and with a percentage yield of 46%

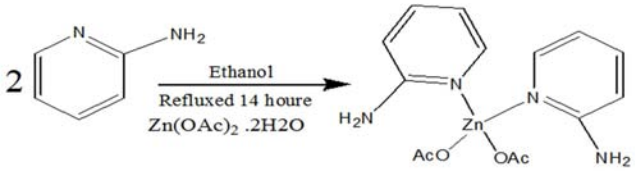


Figure 17. *Synthesis of bis(2-Aminopyridine)zinc complex.*

4.3.2. Complexation of N-(anthracene-9-ylmethylene)pyridine-2-amine

The synthesis, characterization and biological studies of new Cu(II) complexes derived from 9-anthraldehyde and 2-aminopyridine were investigated by Vidya [45]. From his report, the compound *N*-(anthracene-9-ylmethylene)-pyridine-2-amine was prepared by the condensation of 9-anthraldehyde and 2-aminopyridine. A mixture of 2-aminopyridine and 9-anthraldehyde in ethanol solution was boiled for 3-4 hrs under reflux. The solution was cooled at completion of the reaction and the yellow precipitate obtained was collected by filtration and recrystallized from ethanol to get the purified crystal [45].

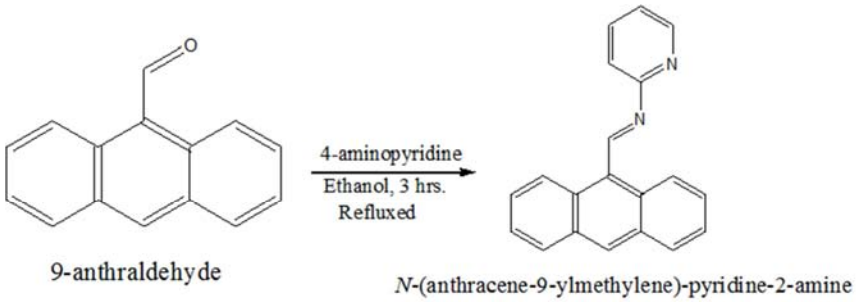
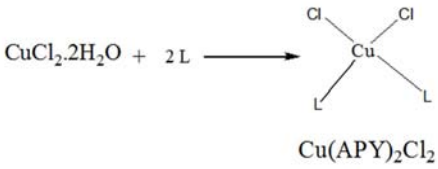


Figure 18. *Synthesis of N-(anthracene-9-ylmethylene)pyridine-2-amine.*

On the synthesis of copper complexes, Vidya reported that a hot methanol solution of *N*-(anthracene-9-ylmethylene)-pyridine-2-amine (APY) and a hot methanol solution of $CuCl_2.2H_2O$ was added drop wise, and the resulting mixture was stirred under reflux for 2 hours. The solvent was filtered off and the formed solid complex washed several times with methanol, dried and kept in a desiccator over dried silica gel. The complexation is shown in figure 19 below.



L=*N*-(anthracene-9-ylmethylene)-pyridine-2-amine

Figure 19. *Complexation of N-(anthracene-9-ylmethylene)pyridine-2-amine.*

iv. Schiff Base complexes *via* 2-aminopyridine and salicylaldehyde. The synthesis of Schiff base complex with 2-aminopyridine and salicylaldehyde using the following respective salts; $Ni(NO_3)_2.6H_2O$; $Cu(NO_3)_2.3H_2O$; $CoCl_2.6H_2O$; $Cd(NO3)_2.4H_2O$ dissolved in10 ml of absolute ethanol respectively was investigated by Hossain et al. [46]. The Schiff base (SB) solution was separately added to the solutions of these salts and stirred for 4 hours at ambient temperature and allowed to stand for half an hour. The precipitates were Schiff base complexes, which were filtered and dried in vacuum over anhydrous $CaCl_2$. The general reaction scheme of all the complexes is shown below:

$$M^{2+} + SB \rightarrow [M(SB)_4].$$

Where, M^{2+} = Ni(II), Cu(II), Co(II) and Cd(II) ions, SB =Schiff base.

Figure 20. *Complexation of Schiff base of 2-aminopyridine derivatives containing salicylaldehyde.*

From their research, the Cu(II) complex showed the highest (more potent) antimicrobial activity against gram-positive and gram-negative pathogenic bacteria according to standard kanamycin and ampicillin. Ni(II), Co(II), and Cd(II) complexes with Schiff base exhibit moderate to less antimicrobial activity against examined pathogenic bacteria.

4.4. Synthesis of 3-Aminopyridines

4.4.1. Acetylation of 3-aminopyridine Using Acetic Anhydride

In a modified Schotten-Baumann reaction process, Zheng et al. [17] acetylated 3-aminopyridine using acetic anhydride in an aqueous system and sodium acetate as a base. Based on the method they reported, an off-white slurry of 3-aminopyridine in distilled water (10 ml) was added to concentrated HCl via a pipette. After removing the colours formed during the reaction with activated charcoal, acetic anhydride was added via syringe, followed by sodium acetate dissolved in 10 ml water. The mixture was allowed to stir overnight at room temperature (see the reaction in figure 21).

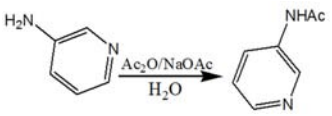


Figure 21. *Synthesis of acetylation of 3-aminopyridine using acetic anhydride.*

4.4.2. o-Vanillin-3-aminopyridine Schiff Base

The synthesis of o-vanillin-3-aminopyridine via the mixing of an equimolecular quantity of o-vanillin and 3-aminopyridine in methanol (25 ml) in a round-bottomed flask equipped with a condenser was reported by Malik et al. [47]. In their investigation, the mixture was boiled under reflux on a water bath for 4 hours and was cooled, filtered and dried in a desiccator over anhydrous $CaCl_2$, then recrystallized from a solution of methanol, to obtain a yellowish crystalline product (see figure 22).

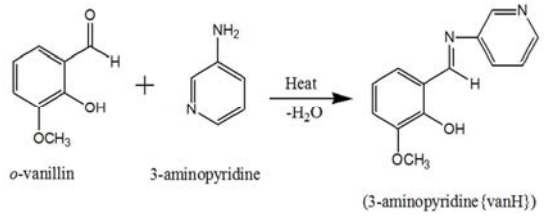


Figure 22. *Synthesis of o-vanillin-3-aminopyridine Schiff Base.*

was refluxed on a steam bath for 4 hours, thereafter; excess solvent was distilled off to obtain the desired products which were recrystallized from dry methanol. The coloured complexes crystallized were filtered, washed with dry methanol and dried in a vacuum desiccator over P_4O_{10}

4.4.3. Zinc Acetate of 3-aminopyridine Complexes

A method of synthesising Zinc(II) Acetates of 3-aminopyridine from an aqueous solution of 3-aminopyridine and a methanol solution of zinc(II) acetate dehydrate was investigated by Dojer et al.[48]. The solution was refluxed for about 2 hours, filtered, cooled slowly and left in the air until most of the solvent was evaporated. A dark red oily mass with some colourless crystals was obtained when the sample was left for 2 days 4°C in the fridge. The product was dried in a desiccator and the percentage yield was 0.873 g (56.3%) (figure 23).

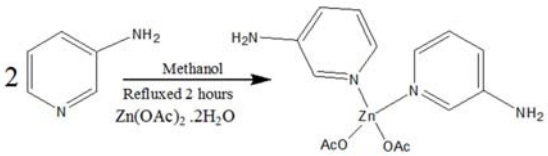


Figure 23. *Synthesis of zinc acetate of 3-aminopyridine complex.*

Dojer and his colleagues [48] also worked on the synthesis of two new zinc(II) coordination compounds with 3- and 4-aminopyridine using an aqueous solution of 3-aminopyridine and a solution of methanol with zinc(II) acetate dihydrate. The mixture was refluxed for about 2 hours. After filtration and slow cooling, the solution was left in the air till most of the solvent was evaporated and a dark red oily mass with some colourless crystals were obtained.

$$[Zn_3(O_2CCH_3)_6.2H_2O \xrightarrow[60\ ^oC,\ 2\ hours,\ Methanol]{3\text{-Aminopyridine}} [Zn_3(O_2CCH_3)_6(3\text{-apy})_2(H_2O)_2]$$

Figure 24. *Synthesis of bis[(μ2-acetato-O,O') (μ2-acetato-O,O)(acetato-O)] diaquabis(3-aminopyridine-N)trizinc(II).*

4.4.4. Methyl-N-methylene-3-aminopyridine-5-carboxylate

From the work of Nagashree et al. [49], the synthesis of methyl-*N*-methylene-3-aminopyridine-5-carboxylate was achieved using an equimolar concentration of different aldehydes and methyl-3-aminopyridine-5-carboxylate in a minimum volume of ethanol. They posited that all the products synthesized were characterized using FT-IR, ^{1}HNMR and GC-MS and were bioactive.

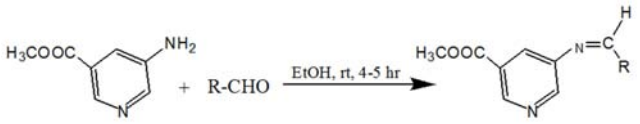


Figure 25. *Synthesis of methyl-N-methylene-3-aminopyridine-5-carboxylate.*

The synthesis of Schiff base ligand *via* an equimolar concentration of furan-3-carboxaldehyde and 3-aminopyridine dissolved in ethanol was conducted by Jisha and Isac Sobana raj [50]. The mixture was boiled under reflux for one hour and the product of the reaction was poured into ice to obtain a yellow precipitate which was then filtered and washed with water. The product was characterized using FT-IR, GC-MS, and ^{1}HNMR. The reaction shown in figure 26 represents the synthesis of Schiff base ligand.

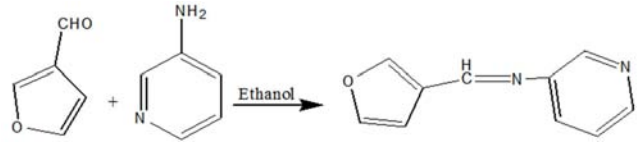


Figure 26. *Synthesis of1N-(furfurylidene)pyridin-3-amine.*

Jisha and Isac Sobana raj also reported the preparation of Schiff base metal complexes via reaction of an aqueous solution of Cu(II) nitrate, Ni(II) nitrate and Co(II) nitrate to the ligand in ethanol in a molar ratio of 1:2 [50]. The reactions were refluxed 12 hours at 80°C, the precipitates were washed with ethanol, diethyl ether and hot water and finally dried under vacuum at 90°C.

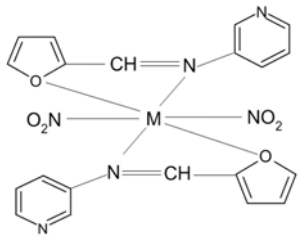


Figure 27. *Complexation of of1N-(furfurylidene)pyridin-3-amine.*

4.5. Synthesis of 4-Aminopyridine Derivatives and Its Complexes

4.5.1. Schiff Bases Derived from 4-aminopyridine

The synthesis and the docking studies of Schiff bases derived using an equimolar concentration of 4-aminopyridine and aldehyde dissolved in toluene and a catalytic amount of glacial acetic acid were investigated by Nandi and Sankar [51]. The mixture was boiled under reflux with a Dean-Stark apparatus till the reactants were fully utilized. From their report, the progress of the reaction was monitored by TLC using acetyl acetate and chloroform (4:6) as eluent. On completion of the reaction, the solvent was distilled off. Thereafter, the crude sample was purified by column chromatography using petroleum ether and ethyl acetate as the eluent. The purified compounds were characterized by FT-IR, ^{1}HNMR and mass spectroscopic techniques (see figure 28).

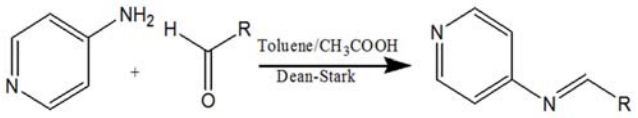


Figure 28. *Synthesis of Schiff bases derived from 4-aminopyridine.*

The docking studies conducted by Nandi and Sankar using Schiff base derivatives obtained from 4-aminopyridine confirmed that both the standard drug isoniazid and the Schiff base derivatives were significant in their results

4.5.2. Bis(acetato-O)bis(4-aminopyridine-N)zinc(II)

Dojer et al. researched on the synthesis of *bis*(acetato-O)*bis*(4-aminopyridine-*N*)zinc(II) using solid zinc acetate dihydrate and a methanol solution of 4-aminopyridine [48]. The mixture was heated and stirred at about 60 °C for 2 hours, after filtration, the solution was allowed for a day for crystals to grow. The crystals were dried in a desiccator above KOH, and the percentage yield was 0.388 g (64.5%) (see figure 29).

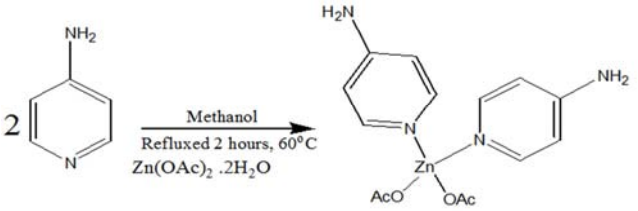


Figure 29. *Synthesis of Bis(acetato-O)bis(4-aminopyridine-N)zinc(II).*

4.5.3. Semicarbazones of 4-aminopyridine

The synthesis of semicarbazones of 4-aminopyridine was obtained by the reaction of 5ml of glacial acetic acid solution of 4-aminopyridine and NaCNO in 25ml of warm water was conducted by Singh et al. [52]. The mixture was stirred and allowed to stand for 4 hours, thereafter; the product was obtained by filtration, washed with water, dried in an oven below the melting point and recrystallized from ethanol to afford key intermediate. The percentage yield was 86.0%, the melting point was 212–214°C and the Rf was 0.65. The reaction showed below in figure 30 represents the semicarbazones of 4-aminopyridine synthesis.

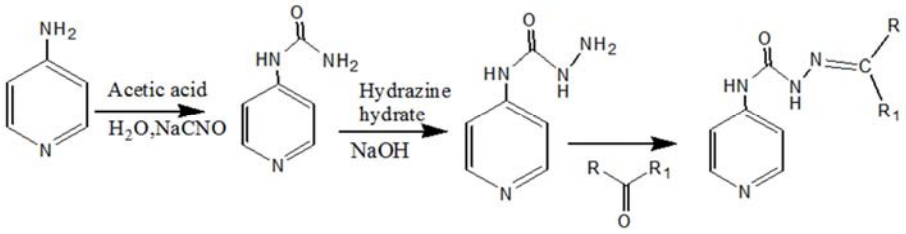


Figure 30. *Synthesis of Semicarbazones of 4-aminopyridine.*

Singh and co-workers opined that the *in-vitro* study of synthesized analogues showed maximum activity of compounds compared to standard drug rivastigmine [52]. They reported that the enzyme kinetic study revealed a non-competitive inhibition of acetylcholinesterase (AChE) and is responsible for the possible interaction of the analogue with the peripheral anionic site (PAS) of AChE, which was however confirmed by molecular docking studies.

In the work of Dueke-Eze et al. [34], the synthesis of *1N*-(2-Hydroxylbenzylidene)pyridin-4-amine was centred on the reaction mixture of 4-aminopyridine, 2-hydroxybenzaldehyde and *p*-toluene sulphonic acid monohydrate in dry toluene under an atmosphere of nitrogen, then the mixture boiled under reflux under Dean-Stark conditions for 24 hours. From their investigation, the solvent was removed under reduced pressure and the residue recrystallized to afford the product as a deep yellow solid at the percentage yield of 81% (12.80 mg,); with a melting point of 76.5°C (see figure 31).

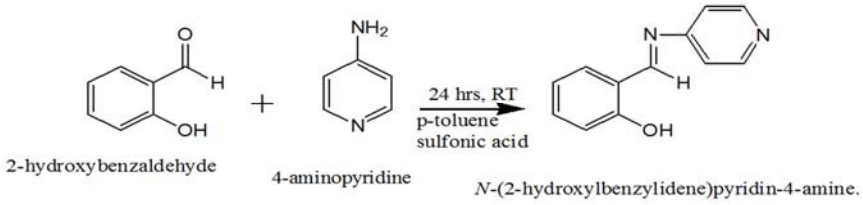


Figure 31. *Synthesis of1N-(2-Hydroxylbenzylidene)pyridin-4-amine.*

Dueke-Eze and co-workers reported that the 4 aminopyridine was dissolved in 5 ml of methanol in a 250 ml conical flask and was stirred at room temperature for 15 min to get a clear solution. Thereafter, an equimolar quantity of each substituted aryl aldehydes (in methanol) was added with few drops of concentrated hydrochloric acid (catalyst) and the reaction mixture was refluxed and stirred for 12–18 hours at 70°C with a magnetic stirrer [34]. The reaction progress was monitored by a TLC using chloroform: methanol (6:4) as mobile phase. On completion of the reaction, the solvent was evaporated to dryness and compounds were obtained by precipitation on the addition of 10 ml ethyl acetate (see the reaction below (figure 32).

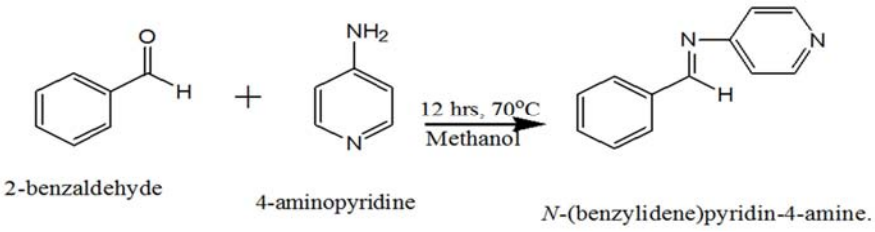


Figure 32. *Synthesis of1N-(benzylidene)pyridin-4-amine.*

4.5.4. Pyridine-4-diazonium Chloride

Tawfiq synthesized diazonium salt of 4-aminopyridine from pyridine-4-amine by adding an equal volume (10 ml) of hydrochloric acid and water in an ice-salt bath at (0-5) °C with stirring [53]. Thereafter, the cold sodium nitrite solution and water were added to the mixture slowly with stirring at 5°C for 1 hour to form a diazonium salt. Tawfig reported that the mixture was diluted with water, and neutralized by the addition of ammonia. Structural elucidation was done with FTIR and ^{1}HNMR. The reaction is depicted figure 33 below

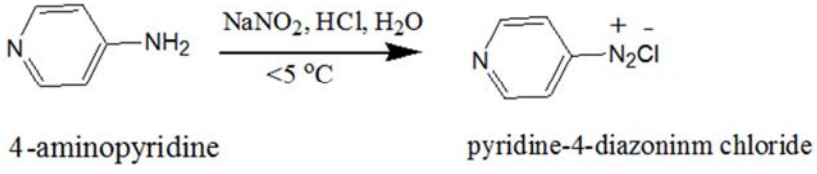


Figure 33. *Synthesis of Pyridine-4-diazonium Chloride.*

He further reported the synthesis of 2-(pyridine-4-yldiazonium)isoindoline-1, 3-dione via the reaction of diazonium chloride salt of 4-aminopyridine and sodium phthalimide in DMF (20 ml) with continuous stirring for 30 minutes at 5°C [53]. The reaction temperature was then gradually raised from the temperature of 25-50°C to obtain a clear yellow solution after 15 minutes. The product obtained from boiling under reflux and continuously stirring was washed with 2% sodium bicarbonate solution, excess distilled water added, and thereafter, recrystallized from ethanol to give bright yellow crystals (figure 34).

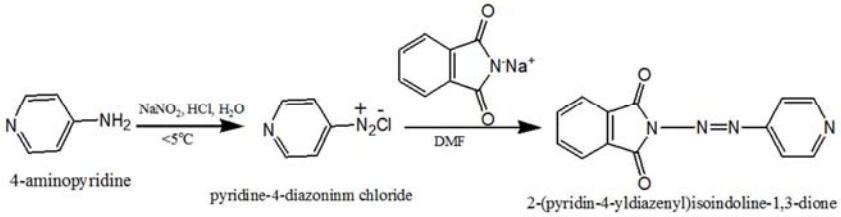


Figure 34. *Synthesis of2-(pyridine-4-yldiazonium)isoindoline-1, 3-dione.*

The synthesis of 2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide through the gradual addition of diazonium chloride salt of 4-aminopyridine to sodium saccharin in DMF (20 ml) with continuous stirring for 30 minutes at 5°C was also investigated by Tawfiq. In the quest to obtain a clear yellow solution, the reaction temperature was kept at the range 25-50°C for 15 minutes. The solution was refluxed with continuous stirring to obtained crystals. The crystals were washed with sodium bicarbonate (2%) solution and the excess distilled water was distilled off and recrystallized from ethanol to give pale yellow crystals. The reaction is shown in figure 35.

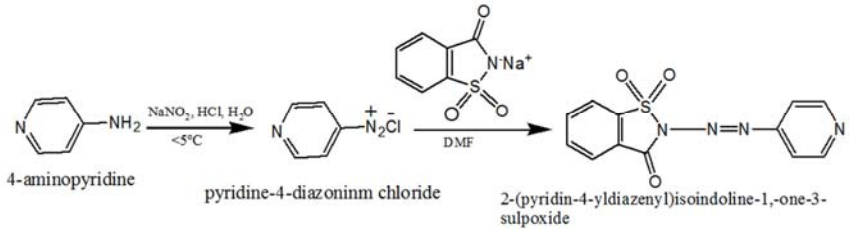


Figure 35. *Synthesis of2-(pyridine-4-yldiazonium) isoindoline-1-one-3-sulphoxide.*

The bioactivity of the compounds synthesized of 2-(pyridine-4-yldiazonium)isoindoline-1, 3-dione and 2-(pyridine-4-yldiazonium)isoindoline-1-one-3-sulphoxide were further explored by Tawfiq [53]. The prepared compounds were assayed for antimicrobial activity in vitro against Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aurous)*. The biological effectiveness test showed that the compounds have a high antibacterial effect on both bacteria (*E. coli and S. aureus*).

4.5.5. Complexation of 4 Aminopyridine

Dhaveethu et al. [54] researched on the synthesis of mixed ligand complexes of Zn (II), Cd (II) and Hg(II) derived from 4 aminopyridine and nitrite ion, using thermal and microwave investigation. A warm ethanolic solution (20ml) of zinc nitrate hexahydrate $Zn(NO_3)_2.6H_2O$/cadmium nitrate tetrahydrate, $Cd(NO_3)_2.4H_2O$ /mercuric nitrate monohydrate, $Hg(NO_3)_2.H_2O$ were respectively mixed with warm ethanol solution (20 ml) of 4 aminopyridine with constant stirring. The resultant solution was then treated with an ethanolic suspension of sodium nitrite with continuous stirring and the mother liquor kept for few hours. From the report of Dhaveethu & co-workers [54], the corresponding complexes of Zn(II), Cd(II) and Hg(II) were filtered, washed with cold ethanol and dried in a vacuum desiccator over anhydrous calcium chloride. The resulting crystals were characterised via GC-MS, FTIR and HNMR. The reaction depicted in figure 33 below shows the complexation of (II), Cd(II) and Hg(II) with 4 aminopyridines.

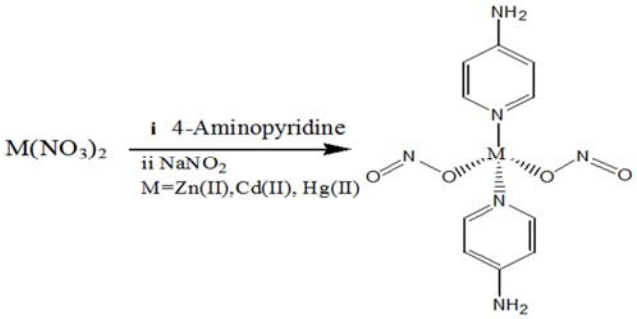


Figure 36. *Complexation of 4-aminopyridine.*

The antibacterial and antifungal activity study conducted by Dhaveethu & co-workers implied that the complexes were more toxic than the free ligands when tested against bacteria and fungi, and the antimicrobial activities of the complexes were concentration-dependent. The Cd (II) complex showed

better antibacterial and antifungal activity than the other two complexes.

5. Bioactivity of Aminopyridines

Aminopyridines are important in pharmaceutical industries mainly because they can elicit a wide range of biological responses in several different organisms. The compounds of aminopyridine were among the first effective antibiotics and their therapeutic applications are still relevant today [6]. Different aminopyridines have shown potent pharmacological properties like antifungal [48], anti-microbial [54] and insecticidal activities [55]. Heterocyclic moieties of aminopyridine can be found in a large number of compounds that display biological activity. This biological activity of the compounds is mainly dependent on their molecular structures [56]. Compounds containing the pyridine core are important in medicine and pharmaceutical chemistry, due to their ability to inhibit enzymes and are currently used in drugs, vitamins, food flavours and dyes [37]. Some of the drugs containing aminopyridine moieties that are already in the market and have anti-inflammatory properties are piroxicam, tenoxicam and sulphasalazine. Other products such as delavirdine have been used as an anti-HIV drug, sulphapyridine as an antibacterial and tripelennamine as an antihistaminic drug.[2] A series of aminopyridines have been synthesized and evaluated for androgen antagonist activities. Hu *et al.* [58] reported that the compound (R)-(+)-6[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile has displayed potent androgen receptor antagonist activity as well as favourable pharmacokinetic agent, and also demonstrated remarkable potency for stimulating hair growth in a male mouse.

Also, simple or complex structures with a grafted moiety of aminopyridine have been reported to be effective as antitumor, antidiabetic, antimicrobial, antiviral, analgesic, anti-inflammatory, antiparasitic, antimalarial, antihistaminic anticonvulsant, etc. [52]. 2-Aminopyridine derivatives have attracted considerable interest recently, though well known for a long time, because of their applications in various fields, especially in pharmaceutical research. For example, the use of 2-aminopyridines has been reported as glucokinase activators or selective inhibitors of neuronal nitric oxide synthase [59]. 4-aminopyridine has been approved by the FDA to manage some of the symptoms of multiple sclerosis and is indicated for the symptomatic improvement of walking in adults with several variations of the disease. It has a role as an avicide, a potassium channel blocker, and an orphan drug in the US [59, 60].

6. Conclusions

Aminopyridine derivatives are very important chemicals with a wide range of biological applications. It contains some functional moieties with essential characters. These moieties have been attributed to a wide spectrum of biological activities in medicine and the environment. It has been used as an anticancer, anti-inflammatory, antiviral, antifungal and antitumor agent in medicine. These characters have inspired the authors to review the various methods of synthesizing compounds containing aminopyridine and its derivatives. Further findings from the literature indicate that aminopyridine derivatives can be synthesised using a sonicator, microwave irradiation, refluxing at different temperature and also stirring at ambient temperature. The synthesis of aminopyridine derivatives was found to be solvent independent since the different solvent media (both as single/ binary mixture) afford a maximum percentage yield of about 50- 95% of the products. The high yields affirm the success of the synthetic methods and techniques reviewed. The study reveals that the melting point of the different isomers of aminopyridine derivatives varies from 150 to 300°C. This variation is associated with the products of different isomer of aminopyridine when coupled with different reagent could be attributed to electric hindrance, which is seen to be the build-up and rejections of electric positive charges in a step/stage of a reaction involving isomers. The study also reveals the different site of complexation in the structure of aminopyridines and its derivatives. The hetero-nitrogen and the exo-nitrogen of aminopyridines are potential sites for metal complexation. This is based on the availability of the lone pair of electrons, which are not involved in resonance. The exo-nitrogen (amine) of aminopyridines form a Schiff base with carbonyl compounds which are essential in the coordination reaction of metals. There are conditions where both the hetero-nitrogen and exo-nitrogen are involved in coordination reaction, thus, making aminopyridine an ambidenatate ligand. This occurs mostly when the exo-nitrogen has been converted to Schiff base. Further findings also revealed that the purification of aminopyridine derivatives could be achieved through recrystallization either with single/ mixed solvent and TLC analysis with the different solvent mixture. Most of the solvents successfully used by researchers were ethyl acetate, methanol, ether, light petrol, tetrahydrofuran (THF) and acetic acid. The study also revealed some microorganisms that were inhibited by aminopyridine derivatives. The isolates of *Escherichia coli*, *Staphylococcus aureus, B. subtilis, B. licheniformis, B. linens, K. pneumonia, Streptococcus pyogenes, Aspergillusniger* and *Candida albicans* were found to be sensitive to tosylamide derivatives at different concentration. The study recommends the use of a sonicator for the synthesis of aminopyridine derivatives that are stable to heat. The study also recommends the synthesis, complexation and biological activity of tosylated aminopyridine. The significance of this study is on the various synthetic methods revealed, which may be helpful to the development of newer compounds with aminopyridines moieties that could offer high bioactivity and lesser toxicity. This will also help researchers to identify the gaps within the concepts under review.

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