



# A Review on Synthesis, Metal Complexes, Applications of Porphyrin Schiff Bases and its Possibility to be used as a Ligand for Quantitation of Metals

Shan Nicolai A. Villaluna<sup>1</sup>, Shiela Marie O. Bueno<sup>2</sup>, ShynneIzza F. Clemente<sup>3</sup>, Abigail P. Cid-Andres<sup>4</sup>

Department of Physical Sciences

College of Science Polytechnic University of the Philippines, Anonas St., Sta. Mesa, Manila, 1016 Philippines

## Abstract:

There have been increasing interests in developing synthetic routes for the synthesis of compounds as these have become one of the dominant ways in developing the studies in the field of chemistry. This review paper mainly aims to highlight the different procedures conducted from previous and recent studies regarding the synthesis and metal complexation of porphyrin Schiff bases. Some Modifications were discussed in order to identify their effect on the Characteristic of the Porphyrin. These compounds exhibit various applications on different fields but this paper focused more on its application for metal quantitation. Porphyrin are known to have strong complexing ability and was successfully complexed with different kinds of metals. Relatively, Schiff Bases was used in many studies about method development for metal quantitation. Developing studies about porphyrin Schiff base complexes could solve some environmental or health issues regarding heavy metal management.

**Keywords:** Porphyrins, Schiff bases, Porphyrin Synthesis, Metalloporphyrin, Metal Quantitation

## 1. Introduction

Many chemical substances do not occur naturally and a wide variety of products we use and consume are made up of synthesized chemicals. The fact that chemical synthesis gives us the ability to make these chemical compounds shows how important and valuable chemical synthesis is. Synthesis comes from the Greek word “syntithenai” which means to “put together, combine” and is defined as a process by which one or more chemical reactions are performed with the aim of converting a reactant or starting material into a product or multiple products [1].

Chemical synthesis, throughout the years, have become one of the dominant ways in developing the studies in the field of chemistry. As evidently seen in different studies, there have been numerous applications of chemical synthesis in different fields of science [2].

The production of graphene using precursor other than graphite is one product of chemical synthesis. Graphene is known to have these outstanding attributes such as having a high carrier mobility, current carrying capacity, thermal conductivity, and mechanical strength. Keeping these facts, graphene makes it as a highly functional material for the electronics sector[2]. Synthesized hydrogels, another product of chemical synthesis, have been studied for its capacity to adsorb heavy metals specifically lead, as it is considered to be the most toxic metal among the heavy metals [3].

### 1.1 Porphyrins

Porphyrins are unique class of compounds, and like Schiff bases it exhibits potential applications in all disciplines of science. Porphyrins are nitrogenous biological pigments made

out of four pyrrole rings associated by methine spans. The carbon on the methine (-CH=) bridge are called meso-position, while the peripheral pyrrolic positions are called as B-positions. Also, porphyrins contain 22 conjugated  $\pi$  electrons but only 18  $\pi$  electrons are necessary to maintain a closed conjugated aromatic system. The 4 remaining  $\pi$  electrons located in the two B,B'-double bonds are cross conjugated with the aromatic system. Allowing it to be described as an  $18+4 \pi$  Hückel Structure [4].

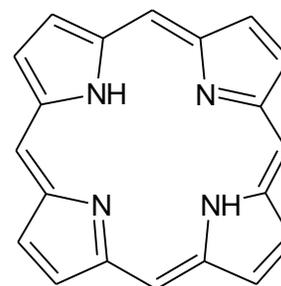


Figure 1. General Structure of a Porphine Macrocycle. The parent structure of porphyrins

Porphyrin itself is a family of intensely colored, fully unsaturated aromatic macrocycles [4]. Porphyrins are omnipresent in nature, as a heme cofactor of hemoglobin, cytochromes, and other redox dynamic compounds, and, as more soaked analogs, in the photosynthetic contraption in plants and microscopic organisms [5].

Porphyrins and its metal complexes, metalloporphyrins are essential to the life of bacteria, fungi, plants and animals and have received considerable attention from many investigators in various fields. Synthetic porphyrins, especially meso-tetraphenylporphyrin derivatives substituted in the para-

positions with soluble acidic, basic and neural groups are of potential interest in medicinal chemistry because they can form chelates either with some toxic heavy metals or with a gamma-ray emitting radioisotopes [6].

## 1.2 Schiff Base

Schiff bases are compounds that are usually used as intermediates in organic synthesis. These are compounds containing an azomethine group (-CH=N) and are products of condensation of an aldehyde or ketone with a primary amine and were first reported by Hugo Schiff in 1864 [1].

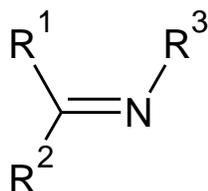


Figure 2. General Structure for Schiff Bases

Having nitrogen donor atom in its structure, Schiff bases have been studied throughout many years for its capability to complexate with various transition metal ions. A hydroxyl or methoxy group, present ortho to C=N bond forms a very convenient site for transition metal ions. These properties of Schiff base make it especially essential in the field of coordination chemistry [1]-[7]

Besides being useful as synthetic intermediate, Schiff bases exhibit a wide range of applications in different fields. There are studies that demonstrate their use as electrochemical sensors, their biological applications that include antibacterial, antifungal, and anti-tumor activities. Schiff bases are also have been studied for their interesting and important properties, as for example, its ability to reversibly bind oxygen, in catalysis of many reactions like carboxylation, hydro formulation, oxidation, reduction, photochromic properties, and adsorbing ability towards some toxic metals [8].

## 1.3 Applications of Porphyrins

### 1.3.1 As Metal Adsorbent

Traditional methods including chemical precipitations, electroplating, ion exchange, and membrane separation have been adopted for the treatment of heavy metal ions. Compared with these methods, absorption is identified as one of the most promising methods due to its simplicity, high efficiency, and cost-effectiveness. Throughout the years, there has been increasing interest in the studies about the capability of Schiff bases to adsorb some toxic metals [3].

### 1.3.2 In Photodynamic Therapy for Treatment of Cancer

Porphyrin and their metal complexes founded to have technical and medical applications. They have been utilized as sensitized dyes in the photodynamic therapy treatment of cancer. Photosensitizers based on tetrapyrrole structures has gained great interest regarding treatment of cancer due to the feasibility to modulate their photophysical properties by peripheral substituents and internal metal complexation as well as their therapeutic benefits [9].

### 1.3.3 Biomimetic Catalyst

The potential of metal-porphyrins as an alternative biomimetic catalyst have been investigated. The complex of the metal-porphyrin has been found to have a remarkable activity

for photodegradation of organic dyes under visible-light illumination. This proves that the compound can be used as a biomimetic catalyst [10].

### 1.3.4 Chemical Sensors

Free base porphyrin is considered to have excellent metal coordinating property. Various studies are conducted in line with its application and one of these are chemosensors. An electrochemical sensor has been developed using a hybrid of polypyrrole with meso-(tetracarboxyphenyl) porphyrin (TCPP@ppy). The sensor was made for the detection of metal ions specifically cadmium (II) ions by differential pulse voltammetry technique. Lead (II) detection was carried out using a probe made of a DNA functionalized iron-porphyrinic metal-organic framework[11].

## 2. Methodology

This Part of the Review will give a preview about the different routes and modifications of synthesis of porphyrins and their metal complexes as well as the procedure in applying porphyrins in different fields.

### 2.1 Synthesis of Porphyrin

The synthetic path or route of porphyrins depends on the symmetry features of the desired product. Vicente and Smith discussed three of the most typical synthetic approaches to porphyrins. First, Porphyrins synthesis from simple polymerization of monopyrroles will be discussed followed by MacDonald Route and finally synthesis through cyclization. The best examples of Porphyrins from simple monopyrrole polymerization are Octaethylporphyrin (OEP) which is a  $\beta$ -substituted Porphyrin and Tetraphenylporphyrin (TPP) a meso-substituted porphyrin [12].

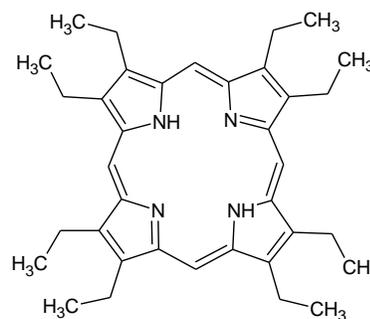


Figure 3a. Structure of the Classical Octaethylporphyrin

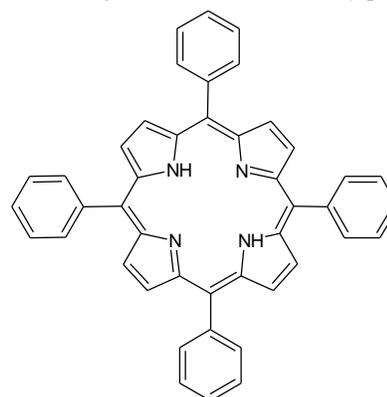


Figure 3b. Structure of 5,10,15,20-Tetraphenylporphyrin

Attempting to synthesize Octaethylporphyrin, the best approach is to use a monopyrrole which bears a 2-substituent that will provide the four interpyrrolic carbon in the product or

using 2,5-diunsubstituted with a separate reagent that will furnish the one-carbon bridging atoms.

Synthesizing Tetraphenylporphyrin, simply requires to react the pyrrole with an alkylaldehyde under acidic conditions hence, it is reasonable to say that it is the easiest porphyrin to synthesize [12].

### 2.1.1 Synthesis of meso-Tetraarylporphyrins

In 1936, Ruthemund Developed an approach to synthesize Tetraphenylporphyrin. The process includes direct condensation of Benzaldehyde and Pyrrole in Pyridine in a sealed glass tube at High Temperature [13]. The experiment resulted in poor yields because of the harsh conditions [4].

Adler and Longo modified the process by involving the use of refluxing propionic acid instead of sealed tubes increased produced yields of TPP.

This procedure of Adler and Longo includes addition of equimolar amounts of pyrrole and Aldehydes to refluxing propionic acid. After heating it up for half an hour, it was allowed to cool. The compound will readily crystallize out of the solution and is ready to be separate via filtration processes. Another Study by Lindsey's group in 1980 shows higher yields by 4x4 condensation method. However, this is just limited to small scale synthesis because thus procedure requires highly diluted conditions in the presence of Lewis acid catalyst. The initial product formed was the oxidized to porphyrin using 2,2-dichloro-5,6-dicyanobenzoquinone (DDQ). Comparing the three method developments, both Rothemund and Adler-Longo uses straight forward synthesis which produces highly crystalline products but is contaminated by at least 2%-10% of 5,10,15,20-tetraphenylchorin. While Lindsey used highly diluted

reaction plus treatment of the product with DDQ which converts the contaminants into Porphyrin accomplished a higher yielding method [4]-[5]-[13]-[14].

Acid catalyst is an important requirement for synthesis of meso-substituted Porphyrins. The Acid Catalyst protonates the carbonyl group of the aldehydes which to be attacked by the pyrrole in an aromatic electrophilic substitution. This result to the formation of the tetrapyrrolic chain. In Adler's Methodology, the condensation took place in an acidic medium under aerobic conditions. The process uses acid such as acetic acid, Chloroacetic acid, Trifluoroacetic acid and Propionic acid. Lindsey's process uses sequential process of condensation and oxidation. By condensing Pyrrole and Aldehyde in dichloromethane, at room temperature using trifluoroacetic acid, BCl<sub>3</sub>, BF<sub>3</sub>-etherate as Lewis acid catalyst. After that, stoichiometric quantity of DDQ or p-Chloranil is added to oxidize the porphingens to form Chlorin-free porphyrins. Also, overall yields can vary depending on the aldehydes used [14].

Later studies stated that it is possible to synthesize Chlorin-free products with good yields by adding acetic or propionic acid as catalyst with 30% of nitrobenzene at 120°C in aerobic conditions. This approach however led to form high ratio of unsymmetrical Porphyrins due to the Nitrobenzene. Recently, Microwave assisted synthesis has been used to synthesize meso-tetraarylporphyrins. The use of Microwave assisted synthesis led to new and important results and fictionalizations. By using this kind of this route not only the porphyrin can be synthesized but also their metal complexes. For example, Tetraphenylporphyrins has been synthesized with good yields by condensing Pyrrole and Benzaldehyde in Propionic acid under Microwave assisted irradiation at 200°C for 5 minutes [14].

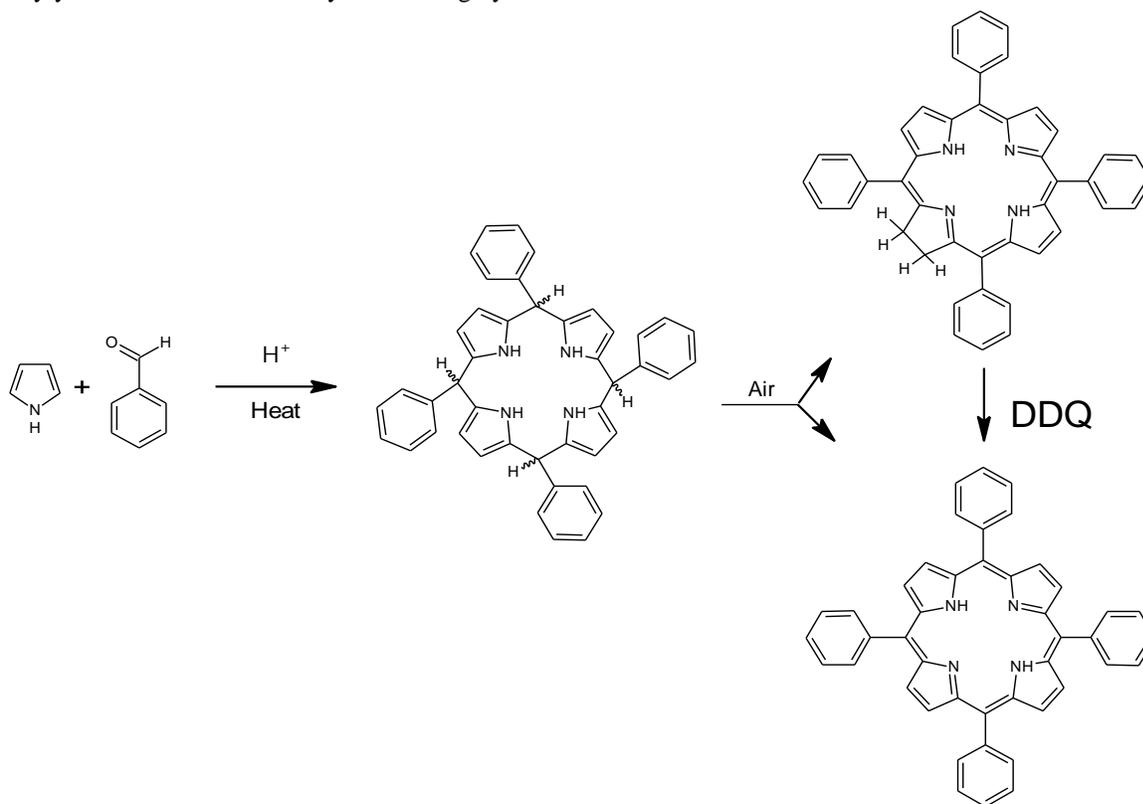


Figure 4. Mechanistic approach in synthesizing meso-porphyrins

### 2.1.2 Synthesis of $\beta$ -substituted Porphyrins

Synthesis of Octaethylporphyrin, an example of  $\beta$ -substituted porphyrin was described by Dolphin to be tedious and erratic, particularly whenever more than a few grams were required. Earlier synthesis studied uses 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole. The 2-ethoxycarbonyl-3,4-diethyl-5-methylpyrrole was brominated to produce  $\alpha$ -bromomethylpyrrole. After, it was quenched with excess diethylamine to form pyrrolylmethylamine then later purified by extraction into ice-cold acid then prompt regeneration by basification with ammonia to form aminomethylpyrrole carboxylate salt it was then treated with in situ using excess acetic acid. It was warmed to be able to reflux in the stream of air. The porphyrins have then crystallized out of the solution. There are instances that contaminants such as octaethylporphyrinogen is present. Refluxing the contaminant

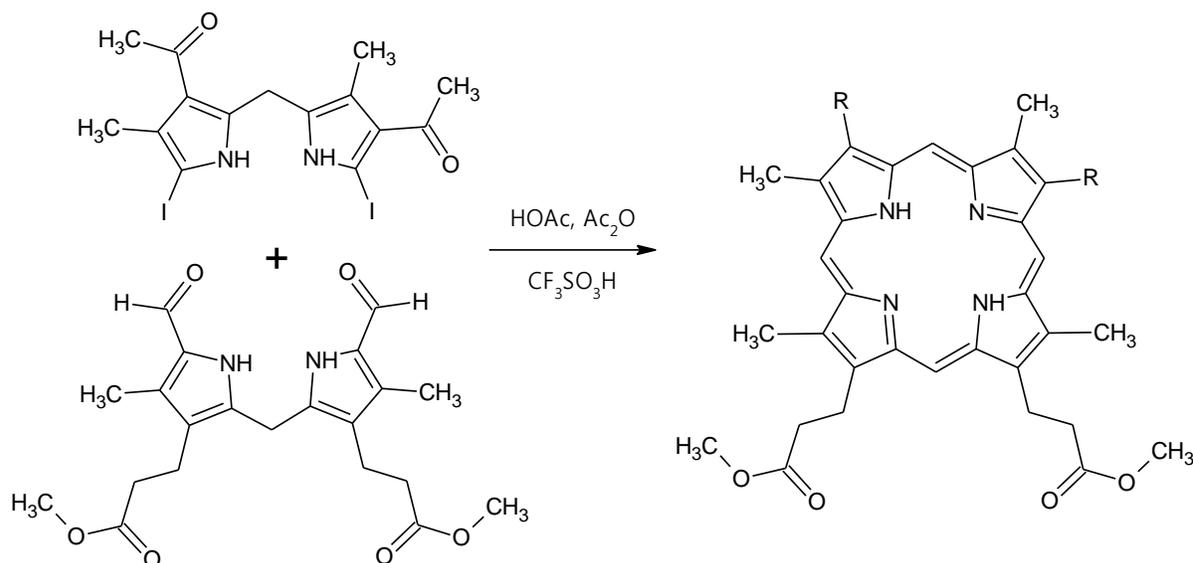


Figure 5. Synthesis of  $\beta$ -Porphyrins using [2+2] Route

### 2.1.3 MacDonald Synthesis The [2+2] Route

The [2+2] route of Porphyrin synthesis is intermediated by synthesis of Dipyrrromethanes. Discussion by Vicente and Smith shows different approaches in synthesis of symmetrical dipyrrromethanes such as self-condensation of bromoethylpyrroles in hot methanol, Heating 2-acetoxymethylpyrroles in methanol or hydrochloric acid, or oxidation of methylpyrrole with lead tetra-acetate. This route would lead to formation of 1,9-dicarboxylic acid which can be formylated by using the Vilsmeier reagent. On the other hand, Unsymmetrical dipyrrromethanes was synthesized by using 2-acetoxymethylpyrroles with 2-unsubstituted pyrroles in acetic acid and a catalytic amount of p-toluenesulfonic acid. Condensation of two unsymmetrical dipyrrromethanes will result into two unsymmetrical porphyrins. This is because the dipyrrromethanes could react in either two orientations related by a 180 degrees rotation of one of the dipyrrromethanes. MacDonald showed that reaction between a symmetrical 1,9-diformyldipyrrromethane and the unsymmetrical 1,9-di-unsubstituted dipyrrromethane in the presence of hydriodic acid catalyst will give pure porphyrins that have high yields.

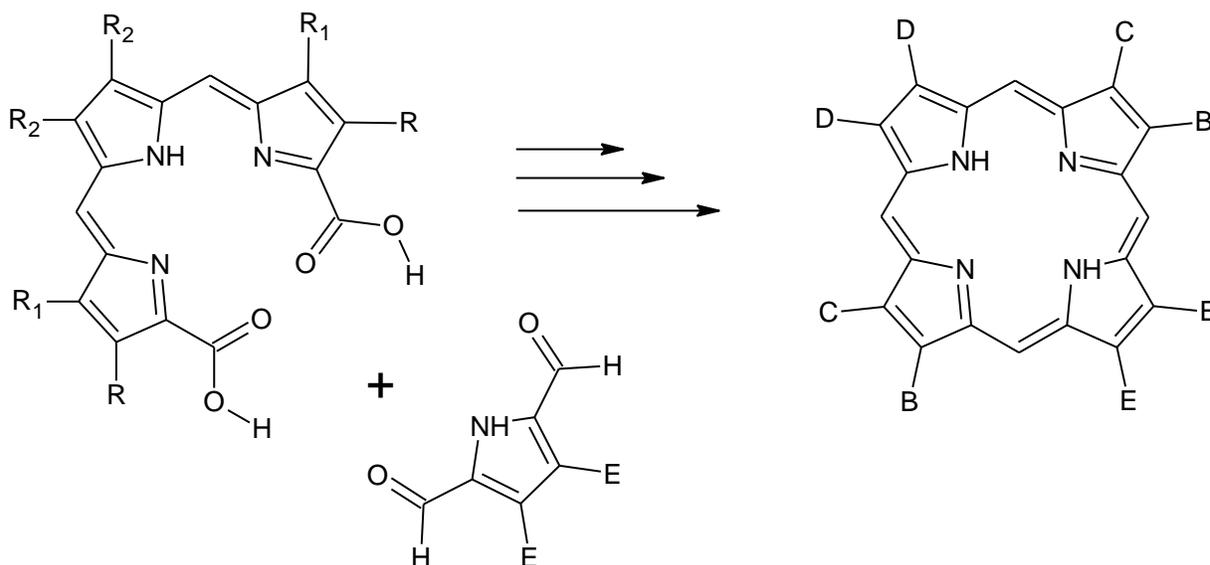
with toluene under air effected completion of the oxidation will convert it to Octaethylporphyrin[15].

Several studies cited by Vicente and Smith stated that modernly, there are two major routes in synthesizing Octaethylporphyrins. First is the tetramerization of 2,5-di-unsubstituted pyrroles with reagent that can provide four meso carbons. An example of this is cyclization of 3,4-diethylpyrrole with formaldehyde yielded 55%-75% of Octaethylporphyrin. Another approach was the tetramerization of pyrroles with CH<sub>2</sub>R substituents in the position adjacent to the amine group. The methylene also needs to be a good leaving group because methylene carbon will eventually the source of the interpyrrolic carbon when nucleophile attacks. After every condensation procedure, oxidation step is necessary to avoid contamination and to give good yields of symmetrical products [12].

Centrosymmetric porphyrins were also synthesized by self-condensation of monofomyldipyrrromethane with the presence of oxidants such as o-chloranil and 2,3-dichloro-5,6-dicyanobenzoquinone [12].

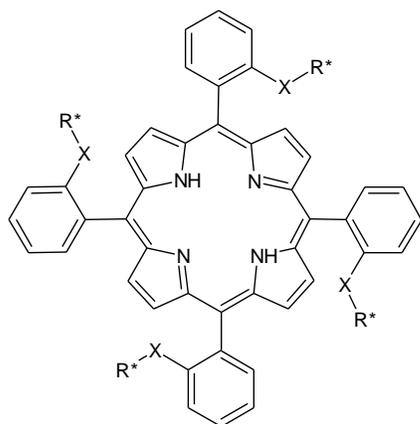
### 2.1.4 Cyclization Synthesis of Porphyrins

This route of synthesis of porphyrins applies the fundamentals of MacDonald approach this time with [3+1] route. While MacDonald [2+2] route includes reaction of two dipyrrromethanes to synthesizes porphyrins, the [3+1] route uses Tripyrrane and monopyrroles as intermediates. This type of synthesis is applied to a vast number of applications. The monopyrrole can be attached with a functional handle group that can be added to the tripyrrane in the final step of synthesis. The study of Sessler as discussed by Vicente and Smith shows the reaction of two identical pyrroles with another pyrrole yielded into a tripyrrane compound. However, the [3+1] approach has limitations when it comes to symmetry this is because of the terminal rings of tripyrranes are usually identical. Advancement in Tripyrrane synthesis is required to remove and conquer the limitation [12].



**Figure 6.** Synthesis of Unsymmetrical Porphyrins using [3+1] Route

## 2.2 Asymmetric Porphyrins



**Figure 7.** Modified Chirality of Porphyrin

Insertion of asymmetric moieties could boost the stability of the porphyrin ligand. There are three commonly ways in preparing chiral porphyrins, first is insertion of chiral units to the porphyrins such as tetra(hydroxy-) or tetra(amino-) 2-substituted or 2,2'-disubstituted tetraphenylporphyrin species. It is achieved by condensing a chiral aldehyde and a pyrrole using Lindsey's route. It is said that tetra(2,2'-disubstituted)phenyl porphyrins can only exist in one confirmation while tetra(2-monosubstituted)phenylporphyrin can exist in four different isomers called atropisomers. These atropisomers differs in the confirmation of the substituent with respect to the tetrapyrrolic macrocycle structure. An example of this kind of synthesis is by condensation of pyrroles and 2-substituted benzaldehyde results in four possible products. Concept of biphenyl-type atropisomerism in ortho-substituted meso-tetraphenylporphyrins was demonstrated by separating the four atropisomers of meso-tetra(2-hydroxyphenyl)porphyrin. The phenyl groups in these molecules are nearly perpendicularly oriented to the porphyrin plane. The four atropisomers could be interconverted that could give statistical abundance ratios. Interconversion possibilities and the temperature at which the equilibration

becomes rapid depends on the bulkiness of the ortho-substituents. Interconversion of two of the most widely used porphyrins as backbone for chiral structures such as tetra(o-aminophenylporphyrin) and tetra(o-hydroxyphenylporphyrin) is possible even on room temperature and becomes very rapid over 70-80 °C.

Picnic Basket Porphyrins or Single Face porphyrins has an open face protected from a protein chain. Some of the examples of single faced porphyrins are porphyrins that has isophthalate moieties. While Double Faced porphyrins can be synthesized using 2,2'-disubstituted or  $\alpha,\beta,\alpha,\beta$ atropisomers of 2-substituted meso-tetra(amino) phenylporphyrin or meso-tetra(hydroxy)phenylporphyrin. Different studies suggest that this is a failure because of the difficult access of substrates to the catalytic center in such encumbered systems. The study of Rose and Co-workers as dicussed used mixed porphyrin backbone that was constructed by condensation of pyrrole with pentafluorobenzaldehyde and 2,6-dinitro-4-tert-butylbenzaldehyde. The pentafluorobenzaldehyde was used to improve the stability of the porphyrin while the substituent 2,6-dinitro-4-tert-butylbenzaldehyde was selected to improve the solubility of the catalyst. A study of kodadek obtained good yields and selectivity for the epoxidation of styrenes catalyzed by manganese complexes by using double face protected  $\alpha,\beta,\alpha,\beta$ -tetra[(R)-1,1'-binaphth-2-yl]porphyrins. Recent study of Salvadori and co-workers modified the chiral walls system of Kodadek. Stating that simple introduction of a methoxy group into the 2' position of each binaphthyl moiety improves the activity of the system. D4-symmetric porphyrins, a different family of double face porphyrins showed very good yields, TON, and ee as complex of iron and manganese [16].

## 2.3 Metal Complexation of Porphyrins

Porphyrins being one of the most important chelating agents in nature, the coordination chemistry of porphyrins involves its tetrapyrrolic core to accommodate metal ions varying in charge and sizes. The metal ions are bound into the nitrogen atoms of the pyrrole rings. Heme pigments and chlorophyll are the heart of the chain of energy supply of life on Earth. Heme of the hemoglobin is synthesized from Iron and Porphyrins and

chlorophyll; the photosynthetic pigments of plant is a magnesium containing porphyrin [17]-[18].

Porphyrins became remarkable because of its extreme stability to coordinate with almost all of the metal ions that are found in the periodic table [19].

A study of Purtaş about porphyrin and its complexes discussed the complexation of 4-ethyl-2,6-bis[5-(4-aminophenyl)-10,15,20-triphenylporphyrin]phenol to metal solutions. The complexation was done by dissolving (0.500 mmol, 0.700g) of the porphyrin Schiff base in 20 ml of dichloromethane followed by addition of 2 millimoles of metal salts such as  $ZnCl_2$ ,  $CuCl_2 \cdot 2H_2O$ ,  $FeCl_3 \cdot 6H_2O$ ,  $K_2[Pt(Cl)_4]$  and  $Mn(AcO)_3$  in 20 ml of ethanol. These solutions were then refluxed for about one hour. The UV-Vis spectrum of the mixtures was monitored every 10 mins interval. After the mixture was cooled up to room temperature, the reaction mixture was added 200 ml of distilled water and was extracted three times. The purity of the complexes was then tested using Thin-Layer Chromatography Methods [20].

Metal complexation of tetraphenylporphyrin with ruthenium was reported by Intrieri. 0.899 millimoles of  $Ru_3(CO)_{12}$  and 2.03 millimoles of meso-tetraphenyl-porphyrin (TPPH<sub>2</sub>) was suspended in a 50 ml dry decalin under nitrogen atmosphere. It was refluxed for about 4 hour and the resulting crystals were collected and washed with n-hexane to remove residual decalin. Then it was purified in flashed chromatography on silica. Toluene was used to elute the remaining unreacted  $Ru_3(CO)_{12}$ . A dichloromethane-n-hexane solution with 7:3 ratio was prepared to elute the TPPH<sub>2</sub> and finally chloroform to yield Ru(TTP) Complex [16].

In the study entitled Synthesis, Characterization and Spectral Properties of Substituted Tetraphenylporphyrin Iron Chloride Complexes, nine substituted tetraphenylporphyrin iron chloride compounds were prepared using the one-pot mixed solvent method and the Adler two-step method. In the Adler two-step method of synthesizing metalloporphyrins, free base porphyrins were reacted with metal salts in refluxing dimethylformamide (DMF) for a long time. Compared with the two-step method, the one-pot mixed solvent method has offered the advantages of higher yields, shorter reaction time and convenient workup of reaction mixtures for the synthesis of iron porphyrin compounds [21].

SevimÇay have synthesized a porphyrin Schiff base ligand 4-methoxy-2,6bis[5-(4-aminophenyl)-10,15,20triphenylporphyrin]phenol from the reaction of 5-(4-aminophenyl)-10,15,20triphenylporphyrin (TTP-NH<sub>2</sub>) and 4-methoxy-2,6-diformylphenol in toluene solution. The complexes of the ligand to metals such as Cu(II), Fe(III), Mn(III), Pt(II) and Zn(II)) were synthesized and characterized by spectroscopic and analytical methods. The binding and complexes of DNA (fish sperm FSdsDNA) and the ligand were also studied under UV-vis spectroscopy. It was found out that the coordination of porphyrin ligand to Mn(II/III) ion enhance significantly the ability to bind to FSdsDNA. Additionally, the superoxide dismutase (SOD) activities of the porphyrin Schiff base metal complexes, electrochemical, photoluminescence and thermal properties of the compounds were investigated [22].

## 2.4 Porphyrin and Schiff Bases

Schiff bases like porphyrin has been widely used as chelating agent for different metal ions.

A study of El-Seidy's group synthesized a porphyrin Schiff base and studied its metal complexes with Cu(II), Co(II), Mn(II), Ni(II), Cd(II) and Fe(III). For Metal Complexes of Copper, A hot methanol solution of Copper(II) acetate was added to a hot methanol solution of the ligand and reflux for three hours. The solvent was evaporated and the precipitate is filtered off and washed with methanol. Finally, it was dried in a vacuum desiccator. The same procedure was done for the other metals using Co(II) acetate, Copper(II) nitrate, Mn(II) acetate, Cd(II) acetate, Iron(III) chloride, and Nickel(II) chloride with 5 Hours, 5 Hours, 4 Hours, 5 Hours, 3 Hours, 6 Hours of refluxing time respectively [23].

The study of Cabillar and colleagues, complexed their Schiff base 4-(4-hydroxy-3-methoxybenzylideneamino)phenol with sixteen different metal salts including  $Ag_2SO_4$ ,  $K_2Cr_2O_7$ ,  $Pb(NO_3)_2$ ,  $SnCl_2$ ,  $FeCl_3$ ,  $BaCl_2 \cdot 2H_2O$ ,  $As_2O_3$ ,  $HgCl_4$ ,  $Cd(C_2H_3O_2)_2 \cdot 2H_2O$ ,  $CoCl_2 \cdot 6H_2O$ ,  $NiCl_2 \cdot 6H_2O$ ,  $Cu(NO_3)_2 \cdot 3H_2O$ ,  $Zn(C_2H_3O_2)_2 \cdot 2H_2O$ ,  $FeNH_4(SO_4)_2 \cdot 6H_2O$ ,  $Al(NO_3)_3 \cdot 9H_2O$ ,  $MgCl_2 \cdot 6H_2O$ ,  $CaCl_2 \cdot 2H_2O$ ,  $Bi(NO_3)_3 \cdot 5H_2O$ , and  $MnSO_4 \cdot H_2O$ . The metal-ligand complexation was carried out in various pH such as pH=3, pH=7, pH=10, pH>12 to see if there is an effect in the rate of complexation in the given pH [1]. The complexation was done by adding 0.01M of the ligand solution into 0.01M of metal ion. The formation of precipitate and/or color change of the mixture will indicate the occurrence of the solution. A series of buffer solution was added to the mixture. Acetic acid buffer was used to adjust the pH of the mixture to pH into 3, phosphate buffer was used to adjust the pH into 7, ammonium buffer was used to adjust the pH of the solution into 10, and finally NaOH buffer was used to adjust the pH above 12 [1]-[24].

Various processes have been developed for the study of synthesis and metal complex of Schiff base ligands. Clavio have studied the preparation of Schiff base namely, 1-8-bis[(4-hydroxy-3-methoxybenzylidene)amino]naphthalene (1-8BHyMBAN) from the condensation reaction of 1,80-naphthalenediamine with 2-hydroxy-3-methoxybenzaldehyde(o-vanillin). Researchers have also studied the synthesized Schiff base ability to form complex with various transition metals at different conditions such as acidic, basic, and neutral conditions [25].

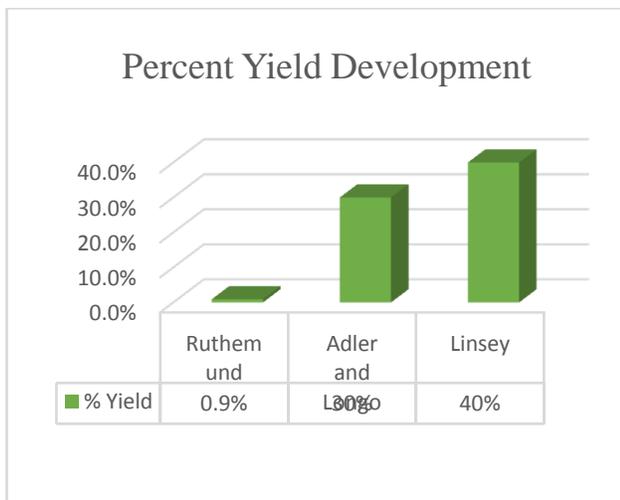
Cruz, Ma. Renalyn studied about synthesizing Schiff base from vanillin and 4,4-diaminophenyl sulfone in three different method: microwave irradiation with 1400W for 30sec, grinding using mortar and pestle, action of juice extract of Citrus aurantium. Researchers have also studied the Schiff base capability to complexate with Arsenic (III) ions [26]. Balasta also synthesized a Schiff base ligand via microwave irradiation. The Schiff base was derived from (S)-2-Amino-3-(4-imidazolyl) propionic acid with indoline-2, 3-dione dissolved in an analytical reagent methanol. The synthesized ligand was then chelated with  $Co^{2+}$ ,  $Sr^{2+}$ ,  $Sn^{2+}$ ,  $Ba^{2+}$ ,  $Ca^{2+}$ , and  $Fe^{2+}$  metals [27].

### 3. Results and Discussion

This part of the review will discuss about the result of the different kinds of synthetic approach to porphyrins, their metal complexes, and applications. This will also give special attention to synthetic yields of some Schiff bases in general. Moreover, discussion about metal quantitation using porphyrins and Schiff bases will be highlighted.

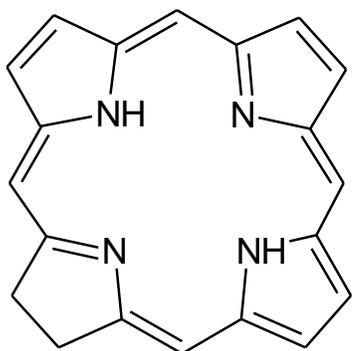
#### 3.1 Yields of Synthesis of Porphyrins

Throughout the years several synthetic approach in synthesizing porphyrins was carried out and was later modified and developed by modern scientist. One of the earliest synthesis was conducted by Ruthemund.



**Figure 8.** Show the illustration on the development of percent yield.

In Ruthemund's synthesis, he yielded about 0.9% of Porphine because of the harsh conditions. Careful examination of this reaction product showed that there is a porphyrinic substance that is present yielding 10%-20% compared to the actual porphyrin. This porphyrinic contamination is later revealed as chlorins with the use of isolation chromatography.



**Figure 9.** Porphyrinic substance called Chlorin.

Re-examining the synthesis of meso-substituted porphyrins, Adler and Longo successfully yielded 30%-40% of porphyrin using acetic acid, mild conditions and DDQ as oxidant which oxidizes the chlorin contaminants into porphyrins. A two-step room temperature synthesis of porphyrins developed by

Linsey resulted in 40% yields using milder conditions and lesser temperature [13].

Method	Conditions	Percentage of Yields
<b>Ruthemund</b>	High concentrations, high temperature in sealed vessels, no addition of oxidant	0.9%
<b>Adler and Longo</b>	Presence of acetic acid, it was able to reflux in glass wares with an open atmosphere, addition of DDQ as oxidant	30%
<b>Linsey</b>	Did not require high temperature, low concentrations	40%

**Table.1** Comparison of Conditions used of different methods of synthesis with their percentage yield results.

With this developments, Different studies arise which includes the synthesis of porphyrins using different intermediates and its metal complexation ability.

#### 3.2 Synthesis and Metal Complexation of porphyrins.

In the study of Intriери regarding the Catalytic Activity of Iron, Ruthenium, and Cobalt porphyrin complexes, different porphyrin ligand has been synthesized such as 1.) meso-tetraphenyl-porphyrin, 2.) meso-tetrakis(2-nitrophenyl) porphyrin, and 3.) meso-tetrakis(2-aminophenyl)porphyrin. The study used simple polymerization of monopyrrole as a synthesis approach. The route resulted in 8.2%, 8.2%, and 13.5% yields respectively. Complexation of meso-tetraphenyl-porphyrin to ruthenium resulted to a 69% yield. Complexes of Iron to a much-complicated porphyrin resulted into 99% percent yield [16].

Purtaş and co-workers aimed to synthesize a novel porphyrin and study its metal complex to determine the Electrochemical, Photoluminescence, DNA-binding and SOD activity. The synthesized 4-ethyl-2,6-bis[5-(4-iminophenyl)-10,15,20-triphenylporphyrin]phenol was then complexes with metal salts such as Cu(II), Fe(III), Mn(III), Pt(II), Zn(II). The copper complex yielded an 87.6% as a green solid, the platinum complex resulted into 83.2% Purple red solid, the Zinc complex yielded 65.4% purple red solid, the iron complex yielded 81.3% purple red solid, and finally the Manganese complex with an 80.1% as purple black solid [20]. A related study which used meso-tetra(1-naphthyl)porphyrin, yielded poorly 5% porphyrin as a purple solid [28]. Çay and co-workers also worked with synthesis of porphyrins to determine the SOD and DNA binding abilities of porphyrins and its metal complexes. The group successfully synthesized 4-methoxy-2,6-bis[5-(4-iminophenyl)-10,15,20-triphenyl porphyrin]phenol with 70% yield. The copper, platinum, Zinc, Iron, and manganese complexes yielded 72%, 75.6%, 67%, 70%, and 75% Respectively [22].

Lian and co-workers synthesized 5,10,15,20-tetrakis[4-(3,5-dioctyloxybenzamido)phenyl]porphyrin and its metal complexes. The experiment resulted in a 62.4% yield of 5, 10,

15, 20-tetrakis[4-(3,5-dioctyloxybenzamido)phenyl]porphyrin as purple solids. The zinc complex yielded 90.5 % purple red solid, the manganese yielded 82.4% as Dark Green solid, and finally cobalt complex which yielded 85.7% purple red solid [29].

A study about the use of porphyrin as chemosensors for determination of Ruthenium involves the use of 5, 10, 15, 20-tetra(4-nitrophenyl)porphyrin as ligand. The synthesis only yielded 20% [30].

### 3.3 Schiff Bases as General

In general, Schiff bases like porphyrins are used as ligands to complex with metal ions for quantitation of metals. A study of Ferrer et. Al synthesized 4-[(4-hydroxy-3-methoxyphenyl)methylidene] amino}benzene Schiff base to use as ligand for quantitation of manganese. The Schiff base resulted negative for tests such as 2,4-DNP Test, Tollens's Test, and Benedict's Test for determination of Aldehyde and Resulted positive in Nitrous Acid Test for determination of Amine group present in the Schiff base. When the Schiff base was complexed with Manganese, an orange powder was found. The ratio of the ligand to the metal was determined to be 2:3 ration of Ligand to metal [31].

The results of the study Cabrera and co-workers includes 70% yield of their Schiff base N,N'(Propane-1,3-diyl)bis[1-(5-Bromopyridin-2-yl)methanimine. The group complexed the Schiff base with ten metal salts. Upon the results of the metal complexes, Cabrera and group decided to continue the study by using Fe(II) mainly because the Fe(II) complex with N, N'(Propane-1,3-diyl)bis[1-(5-Bromopyridin-2-yl) methanimine displayed a wide variety of color changes in different pH conditions. The Fe(II) complex displayed pale yellow, Orange, Bluish Orange, Dark Blue, Greyish Blue in pH levels such as 1, 5, 7, 10, 12 respectively. Upon running the sample in the UV-Spectrophotometer, there were two peaks observed at 646 nm and 535 nm. However, Cabrera and co-workers only considered the peak at 646nm because it was the closest peak to the desired wavelength relative to the blue color of the solution. In determination of the M-L ratio, the method of continuous variation was used and was able to identify it as 1:1 M-L ratio [32].

The study of Cruz and co-workers synthesized a Schiff base derived from Vanillin and 4,4-diaminodiphenyl sulfone and its ability to complex with arsenic (III) ions displayed negative for all the aldehyde test conducted to the Schiff base. Different process of synthesis was also done such as Solvent-free, Microwave assisted, Grindstone friction activated and natural acid catalyzed synthesis paths. Overall, the synthetic process that showed the highest yield was the solvent free microwave assisted synthesis which yielded 79.2% followed by the natural acid catalyzed synthesis with 70.8% and finally, the friction activated process with 62.4% yield. The molecular weight of the Schiff base was calculated by using the boiling point elevation method using the formula;

$$TbC - TbB = kb \cdot \frac{Wtsolute}{MWsolute \times Wtsolvent (kg)}$$

*Eq.1 Boiling Point Elevation Formula*

The weight calculated 521.11 g/mole was relatively closed to the theoretical value of 516.6 g/mole. The complex of the Schiff base with arsenic (III) ion give an observable intense yellow precipitate [26].

### 3.4 Different Studies for Metal Quantitation

Del Rosario and Co-workers devised a new spectrophotometric method using phenyl-2-pyridyl-ketoxime using metal complexation. The ligand was complexed with metal salts such as Copper, Nickel, Zinc, Aluminum, Cobalt, Cadmium and more. The resulting precipitate of the Metal-Ligand complex was collected and was dried for qualitative test. Using Method of continuous variation and mole ratio method, the ratio of metal to ligand complex was determined to be ML<sub>3</sub>. Results of X-Ray Diffraction Spectroscopy, and FTIR Spectra was also interpreted. Finally, uncertainties of the method development were computed to be at 0.236 [24].

### 4. Conclusion

Porphyrins are present in nature as metalloporphyrin like the heme that are found in our hemoglobin in our blood and chlorophyll in plants that has an important application in our everyday life. Several studies arise in synthesizing porphyrins and metalloporphyrin with different kinds of applications such as chemosensors, photodynamic studies for treatment of cancer, as adsorbent and many more. Porphyrins also showed some of its characteristics like DNA binding activity, SOD activity and antimicrobial and antifungal activity. Porphyrins was successfully complexed with different kinds of metals such as Copper, Iron, Cobalt, Manganese, Platinum and Ruthenium. Literatures concluded that porphyrins can complex with almost all the elements in the periodic table. Because of the strong complexing ability of porphyrins, the application of porphyrins can be possibly improved from forming complex with metal ions to quantitate the metals. This review tackles the possibility of porphyrins to be used as ligand for metal quantitation and it was later concluded Schiff bases like porphyrins has been widely used as ligand for metal complexation and can also be used to quantitate metals.

### 5. Acknowledgement

The Authors would like to thank all the authors of the literatures that was cited in the Review. Proper credits will be given in the Reference Section.

### 6. Reference

- [1] H.Cabillar, C. Canilao, and J. Reyes. (2016). "Synthesis and Metal Complexation of 4-(Hydroxy-3-methoxybenzilydenamino)phenol for Method Development in Gold(III) Quantitation". Bachelor Thesis, Polytechnic University of the Philippines.
- [2] G. Alonto, J. Bernil, M. Romaguera. (2016). "Synthesis and Characterization of Graphene from Superactivated Carbon via Sonication Assisted Liquid-Phase Exfoliation". Bachelor Thesis, Polytechnic University of the Philippines.
- [3] J. Cruz.(2018). "Synthesis and Evaluation of Glucose-Poly(Acrylamide) Hybrid Hydrogel as an Adsorbent for Lead". Bachelor Thesis, Polytechnic University of the Philippines.

- [4] E. Meehan. (2014). "Synthesis of Pyrrole-modified Porphyrins: Oxachlorins, and the Beckmann Rearrangement of Octaethyl-2-oxaa-chlorin Oxime". *UCONN Library*. [Online]. Available: [http://digitalcommons.uconn.edu/gs\\_theses/577](http://digitalcommons.uconn.edu/gs_theses/577)
- [5] A. Adler, R. Longo, J. Finarelli, J. Goldmacher, J. Assour, L. Korsakoff. (1967). "A simplified synthesis for meso-tetraphenylporphine". *Org. Chem.* 32, 476-477.
- [6] P. Bandgar, P. Gujarathi. (2008). "Synthesis and characterization of new meso-substituted unsymmetrical metalloporphyrins". *J. Chem. Sci.*, Vol. 120, No. 2, pp. 259-266.
- [7] D. Dominguez, M. Rodriguez, G. Ortiz, J. Maldonado, M. Nava, O. Garcia, R. Santillan, N. Farfán. (2015). "A Schiff base derivative from cinnamaldehyde for colorimetric detection of Ni<sup>2+</sup> in water. Sensors and Actuators B: Chemical". Volume 207, 2015, Part A, Pages 511-517
- [8] K. Brodowska, E. Chruścińska, (2014). "Schiff bases – interesting range of applications in various fields of science, Institute of General Food Chemistry". Institute of General Food Chemistry, Lodz University of Technology, Lodz, Poland, 68, 2, 129-134
- [9] D. Pan, X. Zhong, W. Zhao, Z. Yu, Z. Yang, D. Wang, H. Cao, W. He. (2018). "meso-substituted porphyrin photosensitizers with enhanced near -infrared absorption: synthesis, Characterization and Biological Evaluation for photodynamic therapy". *Tetrahedron*, 74, 2677-2683
- [10] L. Li, L. Yang, Z.Chen, Y. Huang, B. Fu, J. Du. (2014). "Synthesis and characterization of multifunctional Schiff base and Cu(II) complex: Degradation of organic dyes and an optical property investigation". *Inorganic Chemistry Communications*, Volume 50. Pages 62-64.
- [11] L. Cui, J. Wu, J. Li, and H. Ju. (2015). "Electrochemical Sensor for Lead Cation Sensitized with a DNA Functionalized Porphyrinic Metal–Organic Framework". *Analytical Chemistry* 87 (20), 10635-10641
- [12] G. Vicente, K. Smith. (2015). "Syntheses and Functionalizations of Porphyrin Macrocycles". *Current Organic Synthesis*, 11, 3-28
- [13] K. Kadish, K. Smith, and R. Guilard. (2000). "The Porphyrin Handbook: Synthesis and Organic Chemistry". *Academic Press*. Volume 1
- [14] A. Gomes. (2013). "Acid Catalysis in the Way to Porphyrins: Reaction of Pyrrole/Aldehydes in the Synthesis of meso-Substituted Porphyrins". *Rev.Virtual Quim.*, 5(2), 312-317
- [15] J. Paine III, W. Kirshner, D. Moskowitz, and D. Dolphin. (1975). "An Improved Synthesis of Octaethylporphyrin". Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138
- [16] D. Intrieri. (2013). "Synthesis, Characterization and Catalytic Activity of Iron, Ruthenium and Cobalt Porphyrin Complexes". Department of Chemistry, Milan University.
- [17] R. Gebbink, B. Suijkerbuijk. (2008). "Merging Porphyrins with Organometallics: Synthesis and Applications". *Angewandte Chemie* 47, 7396-7421
- [18] R. Murray, D. Bender, K. Botham, P. Kennelly, V. Rodwell, and P. Weil. (2009). "Harper's Illustrated Biochemistry". *McGraw-Hill LANGE*, Ed 28<sup>th</sup>, pp 271
- [19] J. Buchler, D. Dolphin. (1979). "The Porphyrins". *Academic Press*, New York, Vol 1, p.389.
- [20] S. Purtaş, M. Köse, F. Tümer, M. Tümer, A. Gölcü, and G. Ceyhan. (2015). "A novel porphyrin derivative and its metal complexes: Electrochemical, photoluminescence, thermal, DNA-binding and superoxide dismutase activity studies". *Journal of Molecular Structure*. S00222860(15)30313-6
- [21] Z. Sun, Y. She, Y. Zhou, X. Song, and K. Li. (2011). "Synthesis, Characterization and Spectral Properties of Substituted Tetraphenylporphyrin Iron Chloride Complexes". *Molecule*, Vol 16, 2960-2970.
- [22] S. Çay, M. Köse, F. Tümer, M. Tümer, A. Gölcü. (2015). "SOD activity and DNA binding properties of a new symmetric porphyrin Schiff base ligand and its metal complexes". *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, Volume 151, Pages 821838.
- [23] A. El-Seidy, M. Shakhofa, H. Alshater. (2013). "Synthesis and Characterization of Porphyrin like Schiff Base Ligand, its Metal Complexes and their Investigation as Antimicrobial and Antifungal Agents". *Journal of Applied Science Research*, 9(3):2279-2286
- [24] D. Del-Rosario, J. Rivera, E. Valencia. (2015). "Devising a New Spectrophotometric Method Metal Analysis Using Phenyl-2-pyridylketoxime via Complexation". Bachelor Thesis, Polytechnic University of the Philippines.
- [25] C. Clavio, R. Manaig, J. Peronilla. (2016). "Synthesis of 1,8-bis(4-Hydroxy-3MethoxyBenzylidene)Aminonaphthalene via Condensation Reaction of OrthVanillin and 1,8Naphthalenediamine". Bachelor Thesis, Polytechnic University of the Philippines.
- [26] M.R. Cruz, A. Mejia, D. Rivera, P. Tasi. (2013). "Synthesis and Characterization of a Schiff base from Vanillin and 4,4Diaminodphenyl Sulfone and Its Ability to form Metal Complex with Arsenic (III) Ions". Bachelor Thesis, Polytechnic University of the Philippines.
- [27] R. Binalla, J. Dayap, N. Decio. (2014). "Synthesis, Characterization and Complexation of Schiff Base Ligand from Vanillin and Guanine". Bachelor Thesis, Polytechnic University of the Philippines.

[28] C. da Silveira, E. Garoforo, O. Chaves, P. Gonçalves, L. Streit, and B. Iglesias. (2018). "Synthesis, spectroscopy, electrochemistry and DNA interactive studies of meso-tetra(1-naphthyl)porphyrin and its metal complexes". *Inorganica Chimica Acta* 482 (2018) 542–553.

[29] W. Lian, Y. Sun, B. Wang, N. Shan, and T. Shi. (2012). "Synthesis and properties of 5,10,15,20-tetrakis[4-(3,5-dioctyloxybenzamido)phenyl]porphyrin and its metal complexes". *J. Serb. Chem. Soc.* 77 (3) 335–348.

[30] T. Kangwanwong, W. Pluempanupata, W. Parasuka, H. Keenanb, and A. Songsasena. (2012). "Using 5,10,15,20-tetra(4-nitrophenyl)porphyrin as a fluorescent chemosensor to determine Ru<sup>3+</sup>". *ScienceAsia* 38. pg 278–282.

[31] R. Ferrer, C. Francia, M. Sucaldito. (2012). "Characterization and Antimicrobial Activity of Schiff Base Ligand and its Mn(II) Complex Synthesized from Sulfanilamide and Vanillin through Microwave Irradiation". Bachelor Thesis, Polytechnic University of the Philippines.

[32] D. Cabrera, I. Monte, F. Salazar. (2018). "Microwave Assisted Synthesis of N,N'(Propane-1,3-diyl)bis[1-(5-Bromopyridin-2-yl)methanimine]: Characterization and Metal Complexation". Bachelor Thesis, Polytechnic University of the Philippines.