

T.R.
GEBZE TECHNICAL UNIVERSITY
GRADUATE SCHOOL

**NIR-ABSORBING PHTHALOCYANINES FOR
PHOTOSENSITIZING NANOPARTICLES**

AYMEN NABEEL YASEEN YASEEN

A THESIS OF DOCTORATE
DEPARTMENT OF CHEMISTRY

ADVISOR: PROF.DR. AYŞE GÜL GÜREK

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ABSTRACT

The research is focused on nanoparticles derived from phthalocyanines due to their Enhanced Permeation and Retention effect, which facilitates high exciton and electron coupling between chromophore units in the Near-Infrared (NIR) region. Moreover, zinc is recognized as an optimal metal for phthalocyanines in the photosensitized production of singlet oxygen. Phthalocyanine with an octa non-peripheral SR substitution pattern displays a red-shifted maximum electronic absorption, contributing to the NIR shift of the absorption up to 800 nm.

The aim of this study is to synthesize octa substituted non-peripheral tetra or octa zinc phthalocyanines. We then strive to functionalize these compounds with propargyl group or ϵ -caprolactone units at non-peripheral positions. The structures of these compounds were characterized using techniques such as FT-IR, ^1H NMR, ^{13}C NMR, and MALDI-TOF Ms.

An octahydroxylated photosensitizing Zn phthalocyanine was successfully synthesized and employed as an initiator in the ring-opening polymerization of ϵ -caprolactone. This process resulted in three distinct phthalocyanine-core star polymers, each arm of which was functionalized with either 20, 30, or 40 units. These polymers were designed to absorb in the first NIR phototherapeutic window. The structures of all the star polymers were confirmed by FT-IR, ^1H NMR, GPC, and their thermal properties were analyzed. Their UV-vis absorption was also studied in DCM and THF solvents at various concentrations.

The phthalocyanine cores were self-encapsulated into their polycaprolactone arms, resulting in biocompatible star polymeric nanoparticles. These nanoparticles exhibited significant absorption centered at 782 nm and an outstanding logarithmic extinction coefficient value in water. The size of the star polymeric nanoparticles was measured by DLS and TEM, and their absorption was studied in water as a solvent.

Keywords: Phthalocyanine, Poly(ϵ -caprolactone), Near-Infrared (NIR), Nanoparticles, Photodynamic Therapy (PDT).

ÖZET

Araştırma, yakın kızılötesi (NIR) bölgesindeki kromofor birimleri arasında yüksek eksiton ve elektron eşleşmesini kolaylaştıran geliştirilmiş geçirgenlik ve tutma etkisinden dolayı ftalosiyanınlerden türetilen nanopartiküllere odaklanıyor. Ayrıca çinkonun ışığa duyarlı singlet oksijen üretiminde ftalosiyanınler için optimal bir metal olduğu kabul edilmektedir. Okta non periferik SR konum modeline sahip ftalosiyanın, kırmızıya kayan bir maksimum elektronik absorpsiyon sergileyerek, absorpsiyonun NIR kaymasına 800 nm'ye kadar katkıda bulunur.

Bu çalışmanın amacı okta konumlarda non periferik tetra veya okta çinko ftalosiyanınlerin sentezlenmesidir. Daha sonra bu bileşikler non periferik konumlarda propargil grubu veya ϵ -kaprolakton birimleriyle işlevselleştirmeye çalışıyoruz. Bu bileşiklerin yapıları FT-IR, ^1H NMR, ^{13}C NMR ve MALDI-TOF Ms gibi teknikler kullanılarak karakterize edildi.

Oktahidroksillenmiş ışığa duyarlı Zn ftalosiyanın başarıyla sentezlendi ve ϵ -kaprolaktonun halka açılması polimerizasyonunda başlatıcı olarak kullanıldı. Bu işlem, her bir kolu 20, 30 veya 40 birim ile işlevselleştirilmiş üç farklı ftalosiyanın çekirdekli yıldız polimeriyle sonuçlandı. Bu polimerler ilk NIR fototerapötik pencerede absorbe edilecek şekilde tasarlandı. Tüm yıldız polimerlerin yapıları FT-IR, ^1H NMR, GPC ile doğrulandı ve termal özellikleri analiz edildi. UV-vis absorpsiyonları ayrıca çeşitli konsantrasyonlarda DCM ve THF solventlerinde de incelenmiştir.

Ftalosiyanın çekirdekleri polikaprolakton kollarına kendi kendine kapsüllendi, bu da biyoyumlu yıldız polimerik nanopartiküllerin oluşmasını sağladı. Bu nanopartiküller, 782 nm merkezli önemli bir soğurma ve suda olağanüstü bir logaritmik sönme katsayısı değeri sergiledi. Yıldız polimerik nanoparçacıkların boyutu DLS ve TEM ile ölçülmüş ve bunların bir çözücü olarak suda emilimi incelenmiştir.

Anahtar Kelimeler: Ftalosiyanın, Poli(ϵ -kaprolakton), Yakın Kızılötesi (NIR), Nanopartiküller, Fotodinamik Terapi (PDT).

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LIST OF SYMBOL AND ABBREVIATION

BS NPs	: Bridge silsesquioxanes nanoparticles
CO ₂ RR	: Carbon dioxide reduction reaction
CTAB	: Hexadecyltrimethylammonium bromide
DBN	: 1,5-diazabicyclo[4.3.0]non-5-ene
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene
DEHA	: Diethylhydroxylamine
DIC	: Differential (Normanski) interference contrast
DMAE	: 2-(N,N-dimethylamino)ethanol
DMF	: N, N-dimethylformamide
DSCs	: Dye-sensitized solar cells
EPR	: Enhanced Permeability and Retention
HER	: Hydrogen evolution reaction
HMDS	: Hexamethyldisilazane
LAG	: Liquid-assisted grinding
LED	: Light emitting diode
MONs	: Mesoporous organosilica nanoparticles
MSNs	: Mesoporous silica nanoparticles
NIR	: Near Infrared
OER	: Oxygen evolution reaction
ORR	: Oxygen reduction reaction
Pc	: Phthalocyanine
PDT	: Photodynamic therapy
PMO NPs	: Periodic mesoporous organosilica nanoparticles
PS	: Photosensitizer
ROS	: Reactive oxygen species
STY	: Space–time–yield
TEOA	: Triethanolamine
TEOS	: Tetraethoxysilane
THF	: Tetrahydrofuran
UV-vis	: Ultraviolet-visible

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1. INTRODUCTION

A unique class of nanoparticles that has drawn considerable attention is bridged silsesquioxane nanoparticles due to their wide usages and applications in versatile fields, such as photovoltaics, electrochromism, heterogeneous catalysis, environment, and environment nanomedicine.

Nanoparticles made from phthalocyanines are of interest in our research due to the Enhanced Permeation and Retention effect and allow for high exciton and electron coupling between chromophore units in the NIR region.

In addition to that, zinc is considered one of the best metals for phthalocyanines for the photosensitized generation of singlet oxygen. On the other hand, phthalocyanine with octa non-peripheral SR substitution pattern exhibits a red-shifted maximum electronic absorption. This combination of factors is responsible for the NIR shift of the absorption up to 800 nm. As hydroxyl groups are necessary to prepare the nanoparticles, octa SR non-peripheral Zn phthalocyanines with four hydroxyl group functions have been designed and will be prepared.

As a result, nanoparticles made of NIR-absorbing phthalocyanines have excitation with NIR wavelengths are preferred and are going to be synthesized for two main reasons: deeper tissue penetration of the light and no excitation of endogenous chromophores.

2. THEORETICAL BASIS AND STATE OF ART

2.1. Phthalocyanines

The large, aromatic, macrocyclic phthalocyanine (Pc) is of theoretical or specialized interest in chemical dyes, photoelectricity, phototherapies, catalysis, organic solar cells and many other fields. It consists of four isoindole units connected by a nitrogen atom. The cyclotetramerization of phthalonitrile, diiminoisoindole, phthalic anhydride, and phthalimides results in phthalocyanine, two other tetrapyrrole macrocycles, share structural similarities with phthalocyanines is porphyrin Figure 2.1 [1].

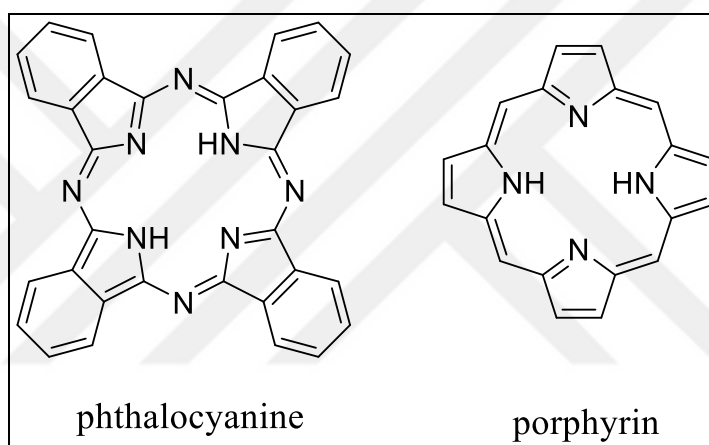


Figure 2.1: Structures of phthalocyanine and porphyrin.

Pcs are commonly utilized as dyes because of their outstanding absorption spectra in the ultraviolet-visible (UV-vis) range. This is attributed to their significantly conjugated systems of 18 π -electrons and the intersecting orbitals of the core metal [2]. Unsubstituted phthalocyanines have a strong light absorption in the 600 to 700 nm range, which gives them a blue or green appearance. By substituting, the absorption can be moved towards longer wavelengths, altering the color from pure blue to green and even to colorless when the absorption occurs in the near-infrared spectrum [3]. There are many ways to classify phthalocyanines, as they have a lot of structural variation possibilities Figure 2.2:

- Whether they are metalated or not

- The pattern of substitution, which can be either symmetric (A4) or asymmetric
- The presence of axial substituents, which depends on the metalation
- The type of grafting atoms used to introduce the substituents
- Their solubility, for example, they can be water-soluble or organo-soluble.

Peripheral substituents are located at the outermost boundaries of the molecule, while non-peripheral ones are situated nearer to the centre. Axial substituents, on the other hand, are positioned either above or below the phthalocyanine molecule's plane.

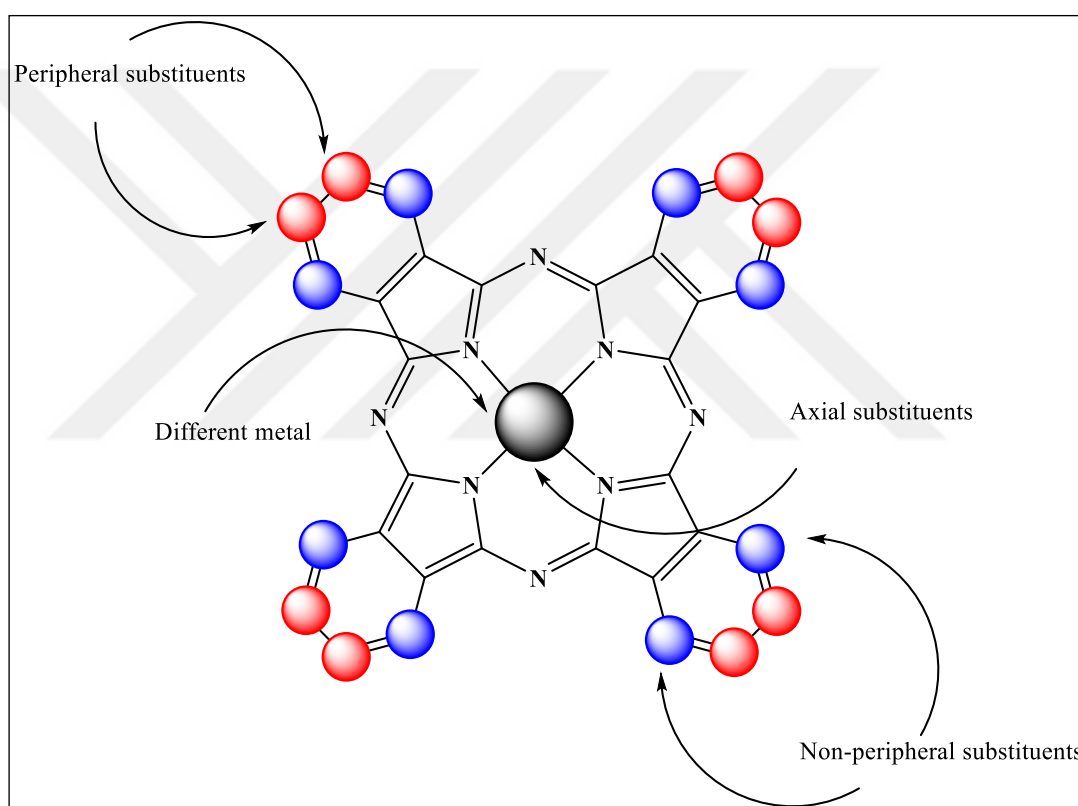


Figure 2.2: Substituent positions for phthalocyanines.

The position of the substituents can significantly influence the solubility and other characteristics of the phthalocyanine molecule. For example, introducing alkoxy or alkyl substituents onto the phthalocyanine core at the non-peripheral or peripheral positions can result in derivatives that dissolve in numerous organic solvents [4].

The position of substituents on the phthalocyanine molecule can greatly affect its absorbance properties too. This is especially the case when considering how

electron-withdrawing or electron-donating groups affect the location of the Q-band in the UV-vis spectra of substituted phthalocyanines [5].

The Q-band is typically shifted to higher wavelengths (a bathochromic shift) by electron-withdrawing groups, while it is shifted to lower wavelengths (a hypsochromic shift) by electron-donating groups. This occurs as electron-withdrawing groups reduce the electron extent in the phthalocyanine, which widens the energy gap between the ground and excited states, thereby lengthening the absorbed light's wavelength. On the other hand, electron-donating groups enhance the electron density in the ring, which narrows this energy gap and consequently shortens the absorbed light's wavelength [5]. The properties of the phthalocyanines and their applications can be adapted by modifying all the structural variations Figure 2.3.

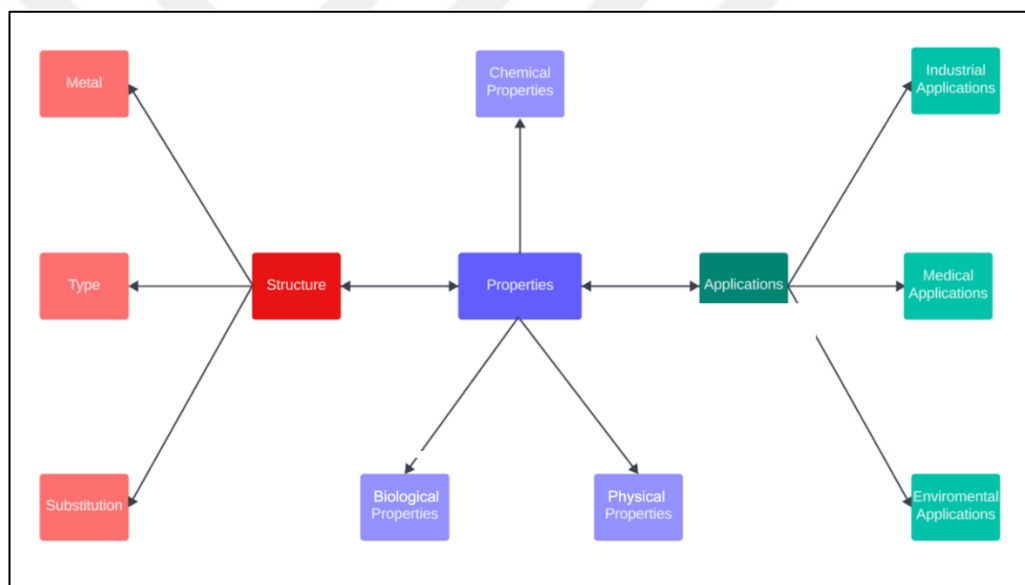


Figure 2.3 The interrelation between various structures and their applications.

2.1.1. Properties and Applications of Phthalocyanines

Phthalocyanines have different properties depending on their structures, making them suitable for various applications such as electrocatalysts for CO₂ reduction, gas sensors, photodynamic therapy and photothermal therapy.

2.1.1.1. Electrocatalysts for Energy Applications

The unique properties and characteristics of phthalocyanines make them excellent for electrocatalytic applications too such as the oxygen reduction reaction (ORR), the carbon dioxide reduction reaction (CO₂RR), the oxygen evolution reaction (OER), and the hydrogen evolution reaction (HER), which have recently attracted a lot of interest. One specific example, Cobalt Phthalocyanine, has been extensively studied for its electrocatalytic performance. Its application in the electrocatalytic conversion of CO₂ to CO is seen as a hopeful approach to substitute fossil fuels and tackle the climate change issues brought about by rising CO₂ emissions. This method has been gaining traction recently [6].

2.1.1.2. Sensing Applications

Phthalocyanines, including nickel phthalocyanines and lead phthalocyanines, have been found to be useful in the development of gas sensors. These particular phthalocyanines have been selected due to their semiconductor behaviour, which enables them to change their resistance upon contact with various gases. This is due to their large conjugated π -system, which is a system where the π -electrons are spread out or delocalized over several atoms in the molecule. This allows for the movement of these electrons, which is a crucial characteristic of semiconductors. Additionally, these phthalocyanines possess excellent photoelectric properties, making them ideal for use as gas sensors as they can absorb light and convert it into electrical energy [7].

2.1.1.3. Photodynamic Therapy (PDT)

Phthalocyanines, when designed appropriately, possess remarkable properties that make them an ideal choice for PDT. Owing to their extended absorption wavelengths and elevated extinction coefficients, and customizable photophysical and photochemical properties through chemical modifications, they represent a beacon of hope in the field of PDT [8]. Despite their lipophilic nature, which makes them prone to combining with or dissolving in lipids, these compounds have been incorporated into innovative delivery systems that enable their use in aqueous media. Their potential to revolutionize PDT is truly awe-inspiring [9].

Various methods have been developed to address the insolubility of phthalocyanines in aqueous media. One such approach is modifying phthalocyanines to make them water-soluble. An excellent example of this is the axially disubstituted silicon phthalocyanines, which, after quaternization [10], display remarkable solubility in water. Another strategy is the use of water-soluble aluminium phthalocyanine-polymer conjugates [11]. Additionally, zinc (II) phthalocyanines are photosensitizers with significant potential for photodynamic therapy and are well-known for their water-solubility [12].

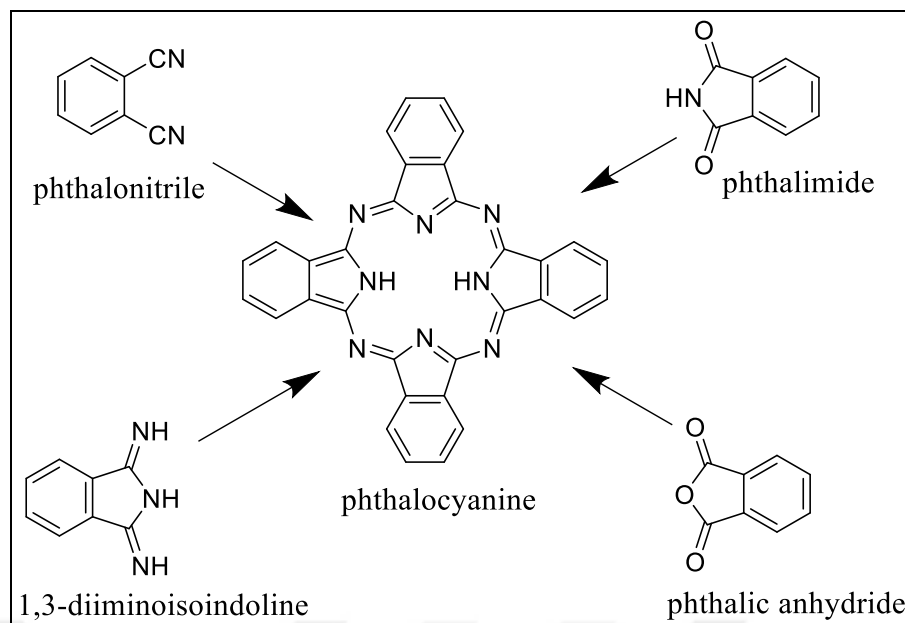
It's important to note that the solubility of a specific phthalocyanine can vary depending on its chemical structure and the presence of any substituents.

Phthalocyanines possess the remarkable ability to harness optical energy and convert it into thermal energy, thereby generating local hyperthermia that can effectively combat malignant tumours. This groundbreaking technique not only eliminates the need for patients to stay in the dark, but also operates independently of oxygen, making it a truly remarkable and inspiring advancement in cancer treatment [6].

2.1.2. Synthetic Methods of Phthalocyanines

Phthalocyanine macrocycles can be synthesized using one of two methods [14] as shown in Scheme 2.1:

- Employs either phthalic anhydride (which serves as a precursor to phthalimide) or phthalimide as the initial material.
- Start out with phthalonitrile.



Scheme 2.1: Synthesis of phthalocyanines by different precursors.

The simultaneous synthesis of the ligand and the formation of the metal complex are involved in both methods. The synthetic method of phthalocyanine mainly contains the benzene bitter wine-urea method, phthalic nitrile method, o-cyanobenzamide method, and 1,3-diiminoisoindole method [14].

When synthesizing a phthalocyanine, there are some crucial aspects to consider:

- The metal ion introduction: This can be done either during or after the synthesis.
- The substituents' introduction: This can affect the properties of the final product.
- The substitution patterns: This can be either symmetric or asymmetric substitution.
- The choice of the precursors: Different precursors can lead to various products.

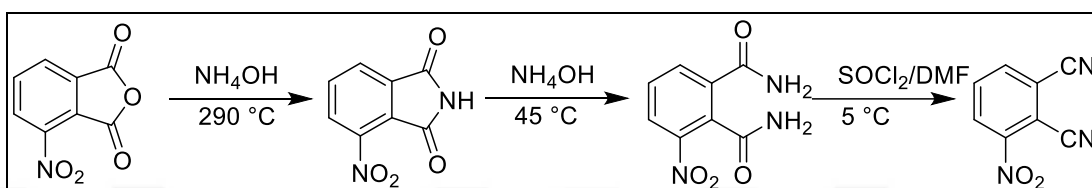
These factors can all influence the final product and should be carefully considered when synthesizing a phthalocyanine.

2.1.2.1. Synthesis of Precursors

The most frequently used starting materials for a substituted phthalocyanine are 3-nitro phthalonitrile, 4-nitrophthalonitrile, 4,5-dichlorophthalonitrile and 3,6-dichloro

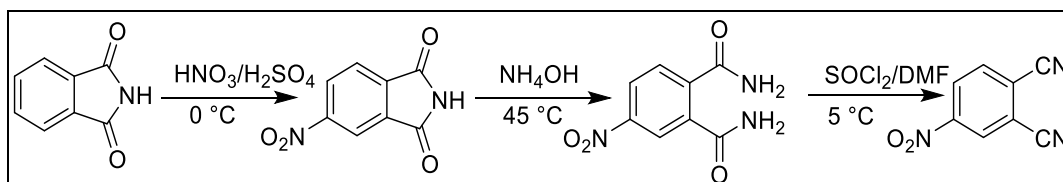
phthalonitrile. These precursors can be used to synthesize various substituted phthalocyanines with different properties and applications [15].

3-nitrophthalonitrile: The synthesis of 3-nitrophthalonitrile can be initiated by the nitration at position 3 of phthalimide, resulting in the formation of 3-nitrophthalimide. Subsequently, dehydration by thionyl chloride in N, N-dimethylformamide (DMF) leads to the production of 3-nitrophthalonitrile Scheme 2.2 [16].



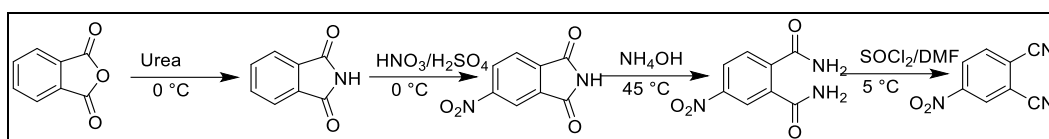
Scheme 2.2: Synthesis of 3-nitrophthalonitrile precursor.

4-nitrophthalonitrile can be synthesized by carried out by various methods, including the reaction of 4-nitrophthalic acid with thionyl chloride and cyanogen chloride. The reaction involves the conversion of the carboxylic group into a chloride group and then into a nitrile group Scheme 2.3 [17].



Scheme 2.3: Synthesis of 4-nitrophthalonitrile precursor.

Another method for producing 4-nitrophthalonitrile is described in a Chinese patent [18]. This method uses phthalic imidine as the raw material and involves the reaction processes of acylation, nitration, aminolysis, and condensation to obtain the final product. The process is characterized by the use of phthalic anhydride and urea to carry out an acylation reaction to generate phthalic imidine. Phthalic imidine is then reacted with nitric acid under the effect of sulfuric acid to generate 4-phthalic imidine. This is followed by an oxidative ammonolysis reaction with ammonia to generate 4-phthalic diamide. Finally, 4-phthalic diamide is reacted with thionyl chloride to carry out a condensation reaction and obtain 4-nitrophthalonitrile Scheme 2.4.



Scheme 2.4: Synthesis of 4-nitrophthalonitrile precursor.

4,5-Dichlorophthalonitrile is a derivative of phthalonitrile that can be derived from 4,5-dichloro-1,2-phthalamide. It serves as an effective reactant in the formation of 4,5-bis(3,4-dimethoxyphenyl)phthalonitrile and 4,5-bis(2,6-dimethoxyphenoxy) phthalonitrile. Additionally, it can be utilized in the production of 4,5-diphenoxyphthalonitrile [19].

2,3-Dicyanohydroquinone is a commonly used starting material in the synthesis of di-substituted functionalized phthalonitrile which is available commercially [19] and used extensively in this work.

2.1.2.2. Generalities of Synthesis of Phthalocyanines

The process consists in the precursors undergoing a cyclotetramerization, where four molecules combine to form a single phthalocyanine and the cyclotetramerization typically occurs under basic conditions and in high-boiling solvents.

If the precursor, such as phthalonitrile, is mono substituted, a tetra-substituted phthalocyanine will be produced. This results in a mixture of regioisomers, as depicted in the Figure 2.4.

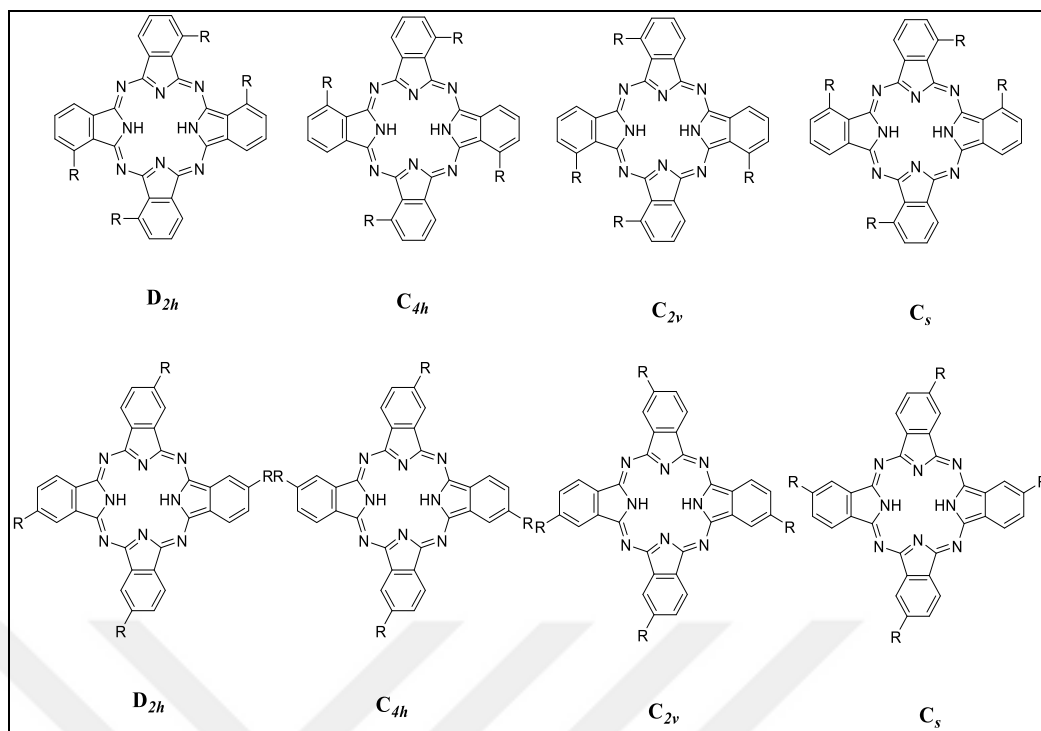


Figure 2.4: Four possible positional isomers of tetrasubstituted phthalocyanines.

However, if the goal is to produce an octa-substituted phthalocyanine, a disubstituted phthalonitrile will undergo cyclomerization.

2.1.2.3. Synthesis of Free-base Phthalocyanines

To synthesize free-base phthalocyanine, phthalonitrile or diiminoisoindoline can be used as a common starting material. It is important to exercise caution during the preparation process to prevent the accidental induction of metal ions.

To directly produce phthalocyanine from phthalonitrile, cyclotetramerization is required, which entails a reduction of two electrons and the participation of two protons that can come from either a co-reactant or a solvent. Hydroquinone and 1,2,3,6-tetrahydropyridine are reliable reducing agents that can be incorporated into cyclotetramerizations conducted in the melt at 275°C to achieve a high yield of phthalocyanine [20],[21].

Another frequently used method to accomplish cyclotetramerisation includes heating phthalonitrile in a solution that contains either lithium or sodium pentanoate dissolved in a primary alcohol such as pentanol. Subsequently, the resulting Pc is cleansed with an aqueous acid to eliminate the unstable alkali-metal ion [22]. This approach is often

known as the “Linstead method.” A recent adaptation of this method has been made, where a solution of phthalonitrile and alkoxide in alcohol (particularly octan-1-ol) is allowed to remain for prolonged periods at moderate temperatures (60°C) or at room temperature [23]. An alternative method involves the use of a catalytic quantity of a non-nucleophilic base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), to start cyclotetramerisation in a protic solvent like n-pentan-1-ol. Alternatively, only 2-(N,N-dimethylamino)ethanol (DMAE) can be used, which acts both as a base and a solvent [24].

By heating a protic solvent, four molecules of diiminoisoindoline, which is a compound formed by the addition of ammonia and phthalonitrile, can be conveniently transformed into Pc through cyclotetramerization.

Several modified methods have also reported:

- Using a domestic microwave oven to irradiate a mixture of phthalonitrile, hexamethyldisilazane (HMDS), ammonium sulfate, and DMF in a sealed glass tube. This method has been reported to produce a 75% yield of the desired product [25].
- Stirring a mixture of phthalonitrile and the functional ionic liquid, ammonium butyl(2-hydroxyethyl)dimethylacetate. Under a nitrogen atmosphere, this mixture is subjected to heating at 100°C for a duration of 2 hours. It is reported that this process yields the desired product with a 62% efficiency [5].
- A mixture of phthalonitrile and diethylhydroxylamine (DEHA) is placed in methanol, and the mixture is then refluxed for 4 hours. This process reportedly results in a 60% yield of the desired product [26].
- Heating a mixture of phthalic acid, ammonium molybdate, and urea in quinoline at 180°C in an autoclave for 8 hours. This procedure reportedly results in a 48% yield of the desired product [27].
- Dissolving phthalonitrile in anhydrous tetrahydrofuran (THF). Lithium diisopropylamide is then added portion-wise to the mixture at room temperature. The resulting mixture is stirred for 3 hours under reflux, reportedly producing a 40% yield of the desired product [28].

- Heating a mixture of phthalonitrile and ammonium sulfate in a deep eutectic solvent based on chlorine chloride and urea at 150°C for 60 minutes. This procedure reportedly results in a 32% yield of the desired product [29].
- Adding lithium to dry 1-pentanol and stirring the mixture under an argon atmosphere at 140°C. Phthalonitrile is then added to the mixture once the lithium has dissolved. The reaction mixture is stirred at reflux overnight [30].
- Mixing gold powder and 1,3-diiminoisoindoline thoroughly by grinding them together with an agate mortar. The mixture is then allowed to sit for 5 minutes before being transferred to a quartz tube. The resulting mixture is heated to 240°C and allowed to react for 5 minutes [31].
- A glass tube is charged with phthalimide, p-toluenesulfonic acid, HMDS, and DMF under an argon atmosphere. The tube is subsequently sealed, and the mixture is subjected to heating at 150°C for a duration of 10 hours. It is reported that this process yields the desired product with a 58% efficiency [32].
- Grinding phthalic anhydride, urea, and ammonium heptamolybdate together. The resulting reaction mixture is then irradiated using a microwave [33].
- In this work, a new solid-state synthetic method for phthalocyanines has been developed. tetra-tert-butylphthalocyanine was selected as the model compound and 4-tert-Butylphthalonitrile was used as the precursor. The procedure was carried out with equimolar quantities of DMAE. The technique, which encompasses ball milling (also known as liquid-assisted grinding, LAG) and aging, leads to a decrease in solvent usage by up to 100 times compared to conventional methods, which are typically performed at around 0.2 M in DMAE reflux. The solid-state reaction that takes place at a lower temperature stands out from the harsh conditions used in molten-state reactions, which generally produce low yields. This method achieves a fourfold increase in Space–Time–Yield (STY) [34].

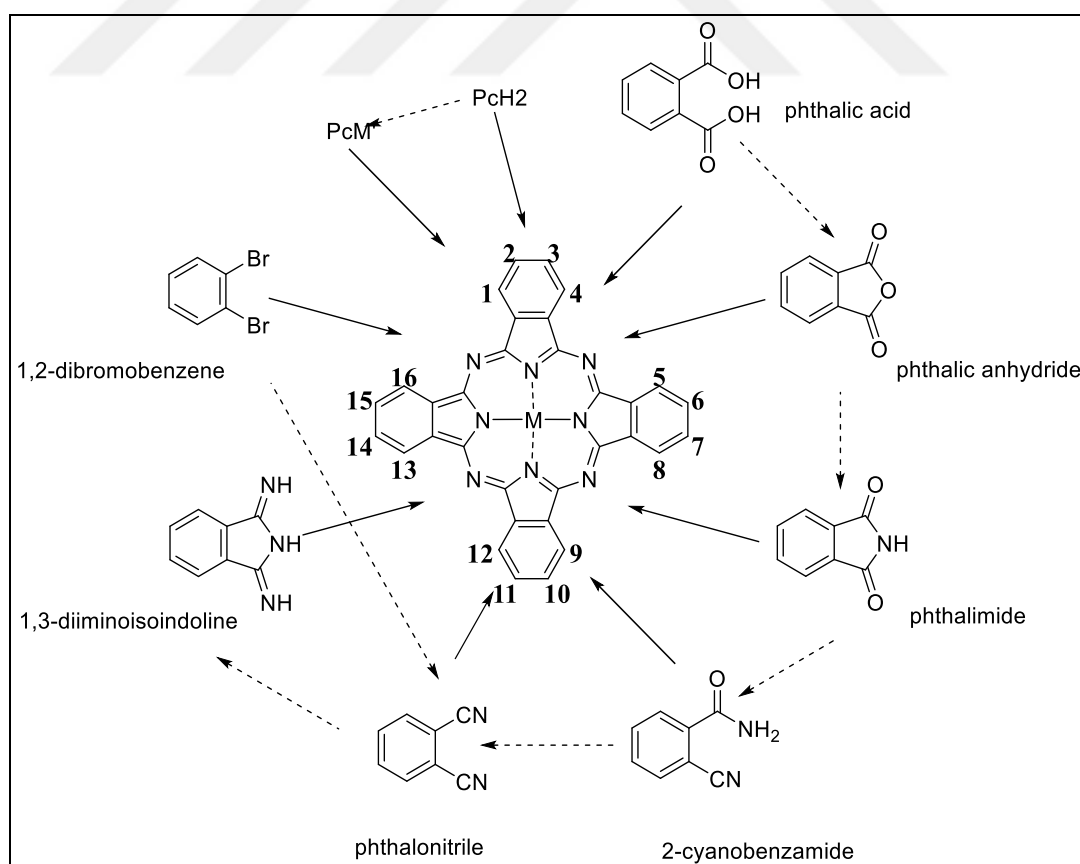
2.1.2.4. Synthesis of Metalated Phthalocyanines

Metalated phthalocyanines can be obtained by the cyclotrimerisation of precursors in the presence of a metal salt, or by the metalation of a free-base phthalocyanine.

Metalated phthalocyanines are commonly created through cyclotetramerization of phthalic acid, phthalic anhydride, phthalimide, 2-cyanobenzamide, phthalonitrile, or diiminoisoindoline, in the presence of a metal or metal salt.

- This reaction can be performed either in an appropriate solvent or in the melt at temperatures exceeding 200 °C. It's worth noting that employing a metal halide in the melt can lead to the formation of a mono halogenated phthalocyanine. Except for phthalonitrile and diiminoisoindoline, a source of nitrogen, usually urea, is essential to carry out cyclo-tetramerizations.
- The Rosenmund-von Braun reaction, involving in situ preparation and cyclotetramerization of phthalonitrile with copper(I) cyanide, allows 1,2-dibromobenzene to serve as a precursor to phthalocyanine copper (II). This method enhances the process efficiency, potentially improves the yield and purity of the phthalocyanine.

The preparation of metal complexes can be achieved by the addition of a metal ion to the free phthalocyanine or through trans metalation, which involves the use of labile complexes containing alkali-metal ions (e.g., Li or Na). The solubility of alkali-metal phthalocyanines in polar solvents is leveraged in the latter method [35]. Scheme 2.5 displays the synthetic map between these several precursors [36].



Scheme 2.5: The synthetic connectivity of metal-based phthalocyanine between various precursors.

2.1.3. Thioether-substituted Phthalocyanines

Thioether-substituted phthalocyanine refers to the compound where the phthalocyanine core is modified with thioether substituents at either peripheral or non-peripheral positions. These modifications can alter various characteristics of the phthalocyanine, such as its ability to donate electrons, its absorption spectrum, its performance in solar cells, and its photophysical and photochemical properties.

Thioether substituents are considered bulky electron-donating groups that donate electrons to the phthalocyanine core, affecting its electronic properties. The incorporation of sulfur atoms onto the phthalocyanine periphery by thioether substituents can result in a red shift of the absorption, allowing the phthalocyanine to absorb light at longer wavelengths. When it comes to solar cell performance, the use of sulfur atoms from thioether groups can lead to decreased quantum efficiency. This is possibly due to the symmetrical electronic structure and lower excited state level, causing lower injection efficiency [37].

The photophysical/photochemical properties of phthalocyanines were studied using fluorescence and UV/Vis absorption spectroscopies to examine how various thiophenic substituents affect them [38].

2.1.3.1. Synthesis of Thioether-substituted Phthalocyanines

The alkylthiophthalonitriles and arylthiophthalonitriles and their corresponding phthalocyanines are prepared through the alkylation on the phenols' hydroxyl group, aromatic nucleophilic substitution on phthalonitrile that bears either a nitro group or halogen atoms, the Rosenmund-von Braun reaction, and Diels-Alder reactions. A mixture of all possible isomeric forms is typically obtained when the cyclotetramerization reaction is performed using 3- and 4-substituted phthalonitriles [39].

For example, aromatic nucleophilic substitution reactions enable the creation of the desired 3-thioalkyl or 4-thioalkyl, as well as 4,5-dithioalkyl and 3,4,5,6-tetrathioalkyl or dithioarylphthalonitriles. These reactions take place between various thiols and thiophenols in DMF/K₂CO₃ and compounds such as 3-nitrophthalonitrile, 4-nitrophthalonitrile, 3,5-dinitrophthalonitrile, 4,5-dichlorophthalonitrile, 3,6-distosylated phthalonitrile, or tetrahalophthalonitrile. Following their formation, these

phthalonitriles can be transformed into the subsequent phthalocyanines through cyclotetramerization.

The process of forming thioalkylphthalonitriles and thioarylphthalonitriles through aromatic substitution reactions is more straightforward and efficient compared to the formation of their corresponding alkyloxy phthalonitriles and aryloxy phthalonitrile. This is primarily due to the superior nucleophilic properties of thiolates, which make them more reactive compared to alkoxides [39].

The formation of 3,6- and 4,5-thioalkyl or thioarylsubstituted phthalonitriles and their corresponding octathioalkyl(aryl)phthalocyanines is typically achieved through the alkylation on the phenols' hydroxyl group with appropriate alkyl/aryl halides. This can be performed either on its own or together with the Rosenmund-von Braun reaction. The alkylation reaction typically takes place under mildly basic conditions, utilizing a diverse set of alkyl/aryl halides, some of which have terminal functional groups. These terminal functional groups can later be used for various applications.

This includes applications like creating water-soluble salts for photodynamic therapy [40], building of macromolecular frameworks, and heterogeneous catalysis [41].

In 1980, it was reported that nitrophthalonitrile groups in 3- nitrophthalonitrile and 4-nitrophthalonitrile, as well as 4,5- and 3,5- dinitrophthalonitriles, could be substituted by thiophenols through aromatic nucleophilic substitution [42]. Thioarylphthalonitrile is produced in high yields through a reaction that is conducted smoothly in aprotic polar solvents (such as DMSO, DMF, acetonitrile etc.), with a large excess of potassium carbonate present as a base [13].

Tables 2.1, 2.2, 2.3, and 2.4 provide a comprehensive overview of the reported tetra or octa thioalkyl/aryl phthalocyanines.

Table 2.1: Tetra thio substituted phthalocyanines.

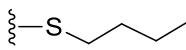
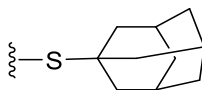
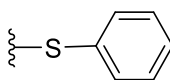
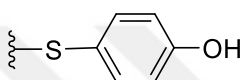
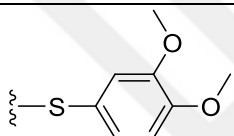
Substituents	Metal
	2H [43]
	2H, Zn [44]
	Zn [45]
	2H, Cu, Ni [46], Co [47], AlOH [48], TiO [49]
	Zn [50]
	Co [51]

Table 2.2: Octa non-peripheral thio alkyl substituted phthalocyanines.

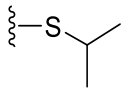
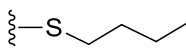
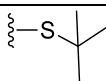
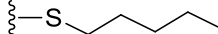
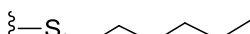
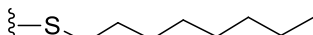
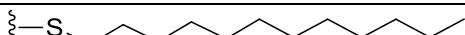
Substituents	Metal
	2H [43]
	Mn [52]
	2H, Mg [53], Zn [54]
	2H [54], Mg [53]
	2H, Pd [55], MnOAc, VO, TiO [56], Ta (OH) ₃ [57]
	Pb [38]
	Cu, Co, Ni, Pb [58] OV, OTi, MnAcO, TaOH [57] Pd [55]
	2H, SnCl ₂ [59], Pd [55], Zn [60]

Table 2.3: Octa non-peripheral thio aryl substituted phthalocyanines.

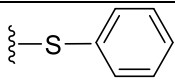
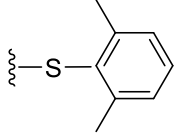
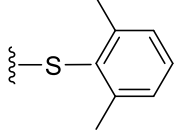
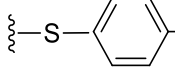
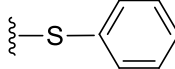
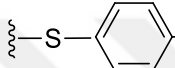
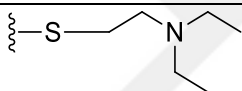
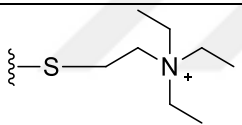
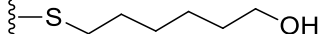
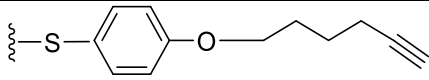
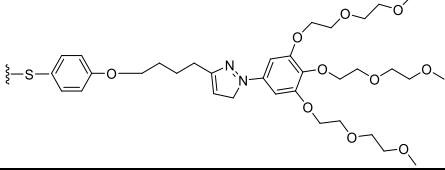
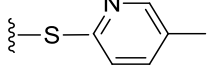
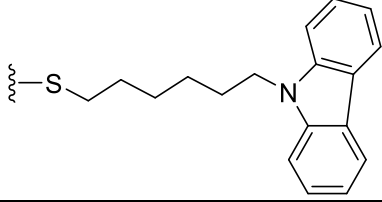
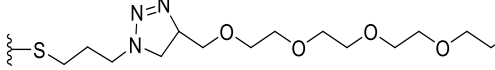
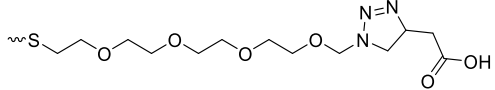
	2H [60], Mg [57], Zn [57], POME [60]
	Mg [57], Zn [57], 2H [57]
	SbOH [61], P(OMe) ₂ [61], Sb(OMe)OH [61]
	2H [58], Cu [58], Co [58], Ni [58], Zn [58], Pb [19]
	2H [58], Cu [58], Co [58], Ni [58], Zn [58], Pb [58]
	2H [58], Cu [58], Co [58], Ni [58], Zn [58], Pb [58]

Table 2.4: Octa non-peripheral thio aryl functionalised derivatives of phthalocyanines.

	2H [62], Zn [62], Mg [62],
	2H [62], Zn [62], Mg [62],
	Zn [37],[63]
	Zn [64]
	Zn [64]
	Ta(OH) [65]
	Zn [66]
	Zn [67]
	Zn [67]

2.1.3.2. Properties and Applications of Thio-substituted Phthalocyanines

Ultraviolet-visible absorption: Indeed, thio-substituted phthalocyanines, whether alkyl or aryl, are known to exhibit absorption in the UV-Vis region, specifically between 650-850 nm. The spectra of electronic absorption of thio-substituted phthalocyanine were measured in several solvents such as THF, DMF and water as presented in Figure 2.5 [53],[62].

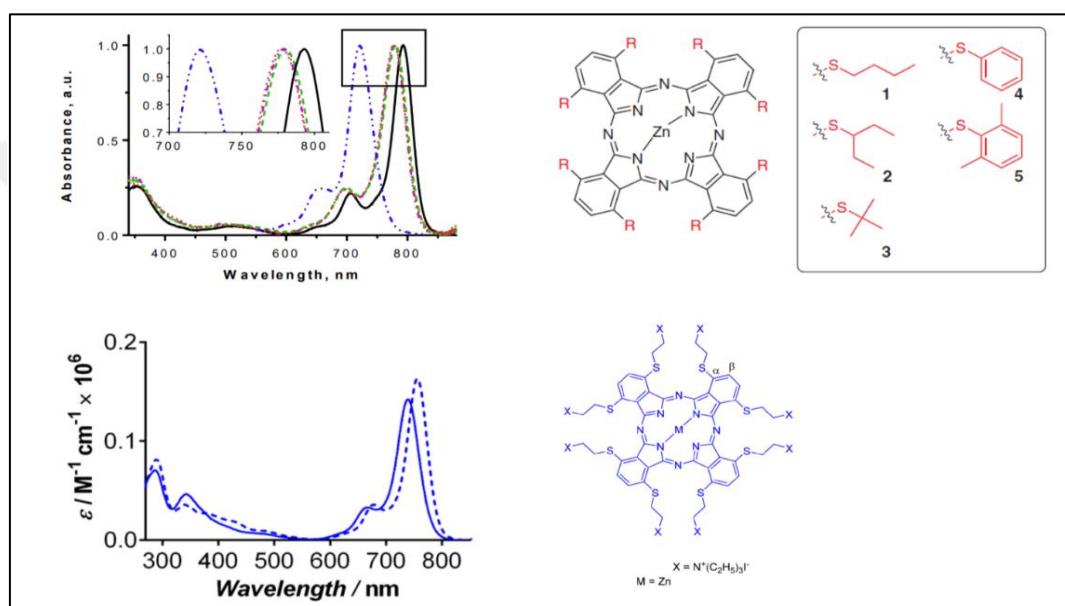


Figure 2.5: UV-vis absorption spectra of thio-substituted phthalocyanine [53],[62].

The metal complexes' absorption spectra displayed distinct B-bands, typically ranging from 340 nm to 430 nm. These bands are commonly linked with $\pi \rightarrow \pi^*$ transitions.

In addition to the B-bands, the spectra also displayed Q-bands within the range of 725 nm to 792 nm. These Q-bands are of particular importance as they are the primary bands for excitation in PDT.

The Q-bands of all the compounds under investigation were sharp and unsplit, indicating the presence of only monomeric species in the solution, with no aggregates. This is a significant observation as it suggests that the compounds are stable and do not form clusters in the solution.

Remarkably, a substantial redshift of the Q-band was observed when the substituents were moved from the peripheral to the non-peripheral positions on the phthalocyanine ring. This phenomenon, often referred to as a bathochromic shift, resulted in a shift of more than 50 nm. This shift is significant as it extends the absorption of the compounds into the near-infrared region, which is beneficial for applications such as PDT.

Emission of Fluorescence and Production of Singlet Oxygen: Studies were conducted on the emission of fluorescence and the production of singlet oxygen of thio-substituted phthalocyanines Figure 2.6 in a solvent that demonstrated good solubility and prevented aggregation of the compounds.

In comparative studies, unsubstituted zinc phthalocyanine is commonly utilized as a benchmark in the measurement of fluorescence and singlet oxygen's quantum yields.

The recorded excitation spectra perfectly match the absorption spectra, confirming the presence of lone monomeric forms of phthalocyanines in the solution, with no aggregates detected [53].

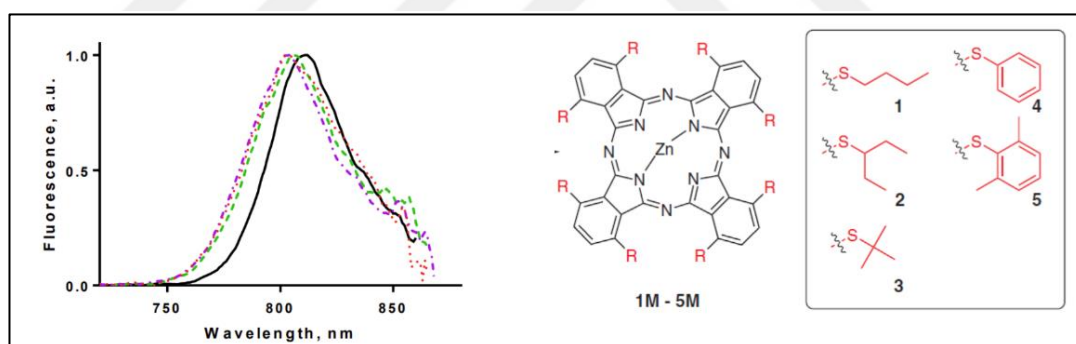


Figure 2.6: Normalized Emission Spectra in THF: 1 (Green Line), 2 (Red Line), 3 (Blue Line), 4 (Purple Line), and 5 (Black Line) [53].

In the series of thio-substituted phthalocyanine compounds, despite the variations in substitution, the photophysical properties remained largely unaffected. This suggests a remarkable stability in the photophysical behavior of these compounds, irrespective of the different substitutions.

The fluorescence and singlet oxygen's quantum yields, however, showed variations, but these were solely in relative to the central metal atom. This observation aligns with the well-established heavy atom effect. following to this principle, the likelihood of the compound undergoing intersystem crossing is increased by the presence of heavy

atoms in a molecule. This intersystem crossing, in turn, leads to an enhanced production of singlet oxygen. As a result, other competitive relaxation pathways, such as fluorescence emission, experience a corresponding reduction. This intricate interplay between the central metal atom and the photophysical properties underscores the complex nature of these thio-substituted phthalocyanine compounds.

When comparing with the corresponding peripherally zinc thio-substituted phthalocyanine, it was clear that moving the substituent to the non-peripheral positions led to a significant enhancement in the singlet oxygen production. This improvement, however, came at the expense of fluorescence emission. A trade-off between singlet oxygen production and fluorescence emission is suggested when the substituent is shifted to non-peripheral positions. Valuable insights into the photophysical behavior of these compounds are provided by this realistic observation, which can guide future design and synthesis strategies.

Dye-Sensitized Solar Cells (DSSCs) have been identified as a subject of intense research interest in both industrial and academic circles, attributed to their low embodied cost, ease of fabrication, and moderate sensitivity to temperature [69-73]. The capability to manufacture DSSCs on diverse platforms, such as glass or flexible substrates, has broadened the spectrum of photovoltaic solutions that are not only functionally effective but also aesthetically pleasing. This advancement has significant implications for the integration of solar technology into various architectural and design contexts.

DSSC is defined by a device in which a photosensitizing dye is chemically attached to a semiconductor with a wide bandgap. This dye, which is the key component of the device, absorbs solar photons and starts the process of charge separation by transferring electrons from its excited state to the conduction band of TiO_2 . The dyes that become oxidized in this process are then reduced again by the redox electrolyte. Among all the photosensitizers used in DSSCs, ruthenium complexes have been the front-runners. They've worked hand in hand with the standard I^-/I_3^- redox mediator to achieve a certified efficiency of 11.4%. However, the dream of mass-producing ruthenium complexes faces two major hurdles. First, ruthenium is a rare metal, which makes it difficult to source in large quantities. Second, these complexes don't absorb light in the near-infrared region, which limits their effectiveness. So, while ruthenium

complexes have shown great promise in the lab, their journey to widespread commercial use is still fraught with challenges [74-80].

The peak of DSSCs efficiency, surpassing the 12% mark, has been accomplished using a cocktail of Zn(II) porphyrin and organic dye [81]. This achievement underscores the potential of such combinations in enhancing the performance of DSSCs.

Phthalocyanines, another class of compounds, have got considerable attention in the scope of solar cell sensitizers [82]. These compounds are characterized by a large π -conjugated framework, which contributes to their ability to absorb light across a wide range of the solar spectrum.

In addition to their light-absorbing properties, phthalocyanines exhibit notable thermal and photostability. These characteristics play a crucial role in the long-term functioning of DSSCs, as they guarantee the solar cells' robustness and dependability under a range of conditions. The inherent stability of phthalocyanines, coupled with their effective light absorption, makes them promising candidates for future advancements in DSSC technology.

A unique molecular structure is possessed by the newly synthesized phthalocyanine sensitizer Figure 2.7, which has been introduced into DSSCs. It is characterized by six 4-tertbutyl benzenethiol groups, serving as electron-releasing ('push') entities. In addition, one carboxyl acceptor is contained, acting as an electron-withdrawing ('pull') component and an anchoring group [83].

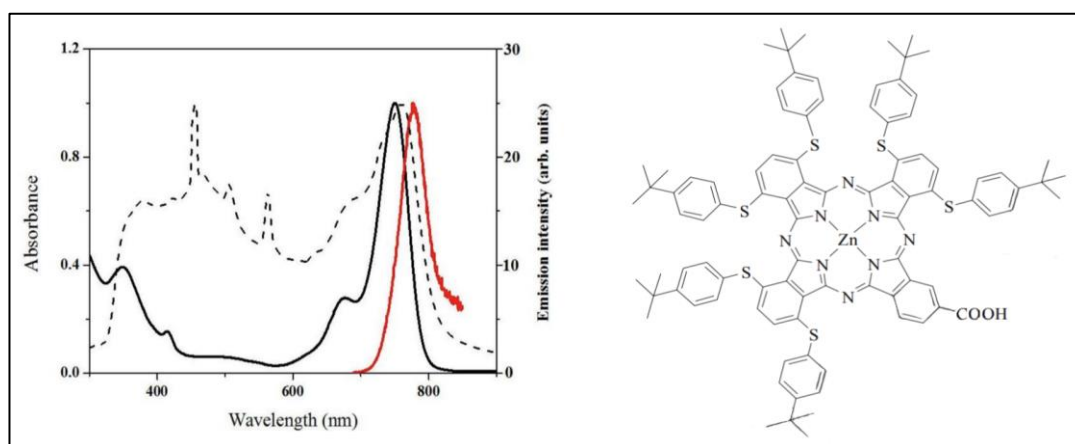


Figure 2.7: UV–Vis spectra of zinc thiophthalocyanine (black) in THF, (dotted black) adsorbed over a 2 μm thick TiO_2 film, (red) emission spectra in THF [83].

The photovoltaic potential of the DSSCs is aimed to be optimized by this innovative configuration of electron donating groups and electron withdrawing groups within the same molecule. An assessment is currently being conducted on the performance of this new phthalocyanine sensitizer in DSSC devices to determine its efficacy and potential for enhancing solar energy conversion. This could potentially pave the way for significant advancements in DSSC technology.

Photodynamic Therapy: The study being referred to involve the use of zinc octa peripheral thiosubstituted phthalocyanine, a photosensitizer (PS), in PDT on HeLa cells. The photosensitizer was used at a concentration equivalent to its IC₅₀ value. Cellular alterations were monitored using DIC and fluorescence microscopy, in conjunction with Lyso Tracker Blue and Mito Tracker Green Figure 2.8.

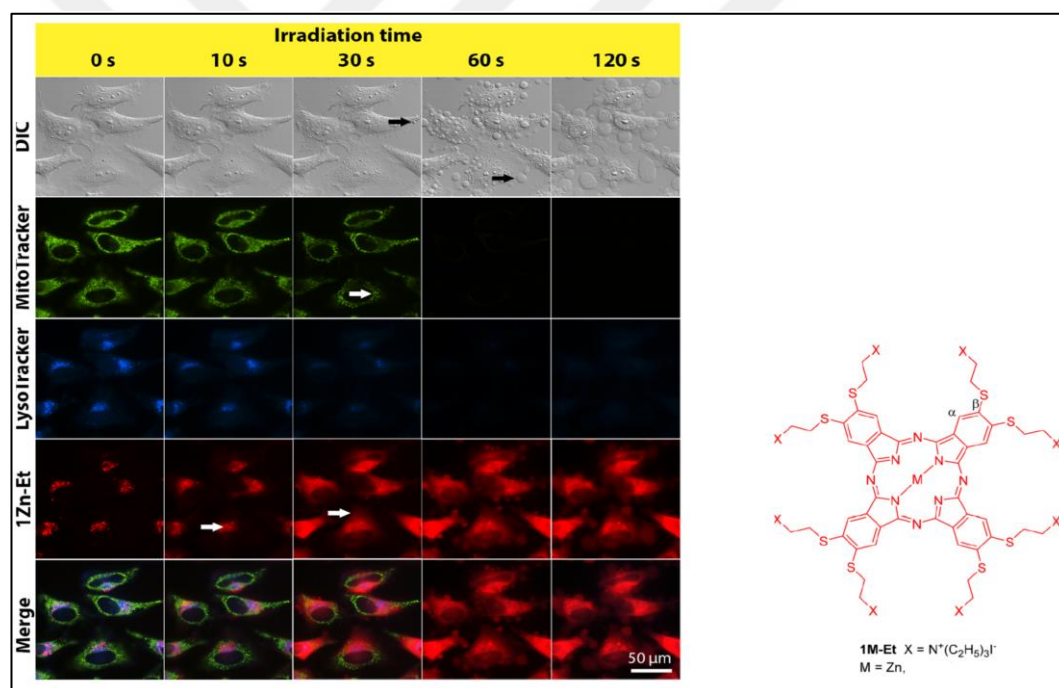


Figure 2.8: Observing changes in HeLa cells with 1Zn-Et under LED light source in a fluorescence microscope [62].

At the start the cells were normal, with blue spots (lysosomes) mainly around the nucleus and green, rod-shaped mitochondria. Everything looked as it should.

When the light hit in the first 10 seconds, the blue spots started to fade and disappear. The red glow from the PS, which was initially in the lysosomes, began to spread out into the rest of the cell. This took about 30 seconds.

Aftermath the spreading of the PS caused damage to different parts of the cell, including the mitochondria, which are important for cell life and death. The mitochondria changed shape and lost their green glow within 30 seconds, and by 120 seconds, it was completely gone.

The cells started to change shape almost immediately after the light hit. They stretched out, then pulled back in, changing from a spindle shape to a bag-like shape. After about 30 seconds, the cells started to break apart, a sign of cell death. But when the same light was used on cells without the PS, nothing happened.

2.2. Photodynamic Therapy

The total number of deaths worldwide in 2022 was approximately 69.16 million. If cancer accounted for approximately 13% of all deaths, that would equate to about 8.99 million cancer deaths worldwide in 2022 [84]. Annually, close to 13 million new cases of cancer are identified, and forecasts suggest that the number of fatalities may keep increasing, possibly hitting around 13.1 million by the year 2030. The most effective way to enhance outcomes and survival rates is through regular screening and monitoring programs, early diagnosis, and intervention. Therefore, it's crucial that we collectively strive to discover improved cancer treatment options that are acceptable to patients.

Traditional cancer treatments include chemotherapy, radiation therapy, and surgery. Lately, treatments involving small molecules and immunotherapy have been employed, frequently in conjunction with these conventional approaches. However, limitations are associated with each of these treatments: a high recurrence rate is associated with surgical tumour resection; the cumulative radiation dose limits radiation therapy; and systemic side effects often accompany chemotherapy.

Research is concentrated on creating alternative therapies that are secure, efficient, and cost-effective. Concurrently, there's an initiative to enhance traditional methods of cancer treatment. This two-pronged strategy is designed to offer patients the highest quality of care and results.

PDT serves as an alternative method for treating tumors, preserving function in the process. Having its roots in the early the twentieth century and first prominently demonstrated by Dougherty and his team in 1975 [85], PDT has evolved into a

treatment approach tailored to specific disease sites and employs a specific wavelength of visible light to destroy cells and tissues. This procedure is enabled by PSs, which produce reactive oxygen species (ROS) when molecular oxygen is present, resulting in oxidative harm and the death of cells [86]. Individually, each element involved in this process is safe, but when they come together, they cause considerable harm to the intended cells and tissues.

The mechanism principle of PDT is usually not specific, but its selectivity towards desired targets is improved by two mechanisms. The first one is the Enhanced Permeability and Retention (EPR) effect, which results in PSs being preferentially absorbed and accumulated in fast-growing cells and unhealthy tissues. The second one involves limiting the light exposure to a particular area or volume of tissue. Only the cells that are concurrently exposed to PS, light, and oxygen undergo the harmful ROS produced through PDT

In addition, healthy cells have a higher resistance to oxidative stress compared to cancerous cells. This, along with other factors, enables the eradication of tumour tissue while avoiding harm to nearby healthy cells. PDT usually harms the blood vessels around the area, thus depriving the tumour of nutrients. It might also stimulate an immune reaction against cancer cells.

2.2.1. Mechanism of Photodynamic Therapy

A PS takes in a photon and is stimulated from its ground state to a transiently excited singlet state (PS_{ex}) as shown in Figure 2.9. This excited PS can either go through intersystem crossing, where the spin of its excited electron flips to create a comparatively stable triplet state (PS_{Et}), or it can revert to the ground state by releasing phosphorescence. This property can be utilized medically for imaging and photodetection [87].

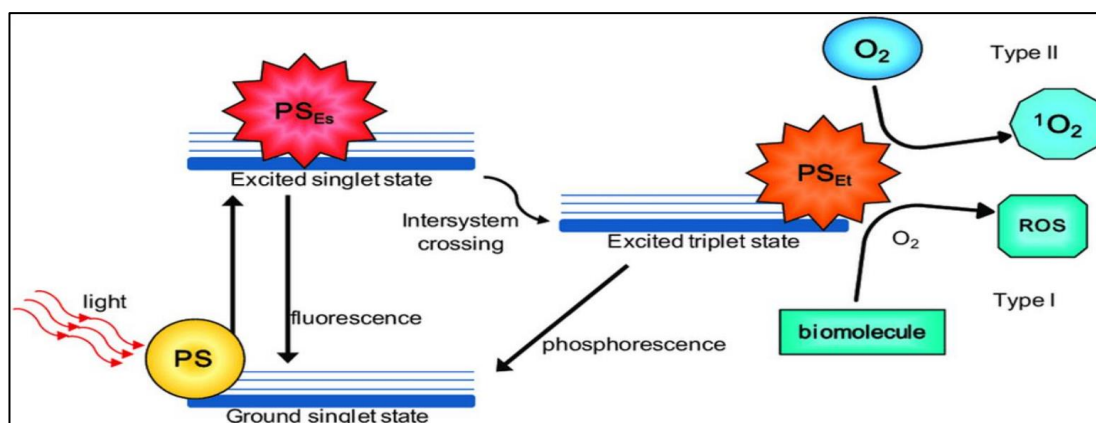


Figure 2.9: Diagrammatic representation of a standard photodynamic reaction [88].

A direct interaction can occur between the cell membrane and PS with a substrate, resulting in the transfer of a proton or an electron to form a radical anion or cation, respectively. Oxygen is then reacted with this radical anion or cation to produce oxygenated products like superoxide anion radicals, hydroxyl radicals, and hydrogen peroxides (type I reaction). As an alternative, The energy of the excited PS can be directly received by the oxygen molecule, which is a triplet in the ground state, resulting in the formation of $^1\text{O}_2$ (type II reaction). In order for oxygen to transition from its triplet ground state to its excited singlet state, it requires an expenditure of 22 kcal.mol^{-1} of energy, or an energy equivalent to a wavelength of 1274 nm [89]. Consequently, the formation of $^1\text{O}_2$ requires only a small amount of energy [90]. The by-products produced by the type I and type II reactions cause the therapeutic effects of PDT. The type of PS and the levels of molecular oxygen and substrate present determine the ratio between these processes. It's worth noting that type I and type II reactions can occur concurrently. The majority of studies, however, point to type II reactions, so $^1\text{O}_2$ plays a significant role in PDT [91].

2.2.2. Mechanism of Tumour Destruction

The elimination of the tumour through light therapy is influenced by various elements. These are determined by the type of PS, its concentration, and its site within the tumour or its intracellular location at the time of radiation. The time between the administration of PS and light exposure, the rate and total effect of light, the type of tumours, and their oxygen content are also factors that are taken into account [86],[92]. Not only tumour cells are targeted by PDT, but also the microvasculature of tumour and normal cells, along with the host's inflammatory and immune systems. The

irreversible damage to the microvasculature and tumour cells, which often leads to prolonged tumour control, is primarily attributed to the ROS generated by photodynamic reactions [92].

The diffusion of $^1\text{O}_2$ in biological systems is restricted to a radius of less than $0.02\ \mu\text{m}$ due to its notably brief half-life (0.03 to 0.18 ms) [93]. The location of photodamage is generally believed to align with the region of PS accumulation in tumor cells. The oxidation of biological molecules by $^1\text{O}_2$ results in unalterable photodamage to crucial subcellular targets like plasma membranes and organelles such as mitochondria, lysosomes, Golgi apparatus, and endoplasmic reticulum. Structural aspects such as the net charge, which can range from +4 to -4, the degree of hydrophobicity, and the degree of asymmetry within the PS molecule, determine the final location of the PS within the cell [87].

Hydrophobic PSs, having dual or fewer negative charges, are characterized by their ability to be absorbed intracellularly at the highest rate and to disperse throughout the plasma membrane. On the other hand, due to their excessive polarity, PSs are prevented from dispersing throughout the plasma membrane and are instead taken up through endocytosis [87]. Since the majority of PSs do not gather in cell nuclei, the likelihood of PDT causing mutations is extremely low [86].

Cell death induced by PDT can take place through apoptosis, necrosis, or autophagy, and it does not depend on the phase of the cell cycle [94]. When large amounts of PS and light dosages are employed, necrotic cell death, also known as unintentional cell death, is frequently induced. It is often characterized by cytoplasm enlargement, organelle destruction, and plasma membrane rupture, resulting in the discharge of intracellular materials and triggers an inflammatory response.

Following PDT, the preferred form of cell death is often apoptotic cell death, also referred to as automated cell death. This process is characterized by a series of events including cell disappearance, membrane blebbing, nuclear breakup, chromatin condensation, and chromosomal DNA fragmentation, leading to the formation of apoptotic bodies. These bodies are subsequently removed by phagocytes *in vivo*, thereby preventing an inflammatory response. The cell death mechanism is also influenced by the location of the PS within the cell. For example, if the PS is located in the endoplasmic reticulum or mitochondria, cell death proceeds via an apoptotic

pathway. Conversely, if the PS is found in the plasma membrane or lysosomes, the process of apoptosis may be delayed or prevented. This is when the cell dies by a different method, such as the autophagic or necrotic pathway [94].

2.2.3. Photosensitisers

A PS is a key component in PDT, a treatment modality used in various medical fields, including oncology. The ideal PS should possess certain characteristics to maximize its therapeutic potential and minimize side effects.

A key feature is the capacity of the PS to selectively accumulate in tumour tissue and quickly dissipate from ordinary tissue. This selective absorption is vital as it facilitates the targeted elimination of tumour cells while preserving healthful cells. A sequence of photochemical reactions that result in the formation of ROS is triggered once the PS is activated by light of a specific wavelength. These ROS can cause direct cytotoxicity, leading to cell death. Therefore, the cytotoxic effect is confined to the tumour due to the selective buildup of PS in tumour cells, which helps to minimize harm to the adjacent healthy tissues.

Another essential quality of a therapeutically relevant drug, including a PS, is amphiphilicity. Amphiphilic molecules have both hydrophilic (water-loving) and hydrophobic (water-hating) parts. This dual nature can improve the solubility of drugs, allowing them to dissolve in both aqueous and lipid environments. This is particularly important for drugs that need to be delivered through the bloodstream (which is aqueous) and then cross the lipid-rich cell membrane to reach their target.

When administering a substance systemically with the intention of reaching a specific tissue, such as a tumour, it is crucial that the substance is hydrophilic enough to move easily throughout the body and reach the intended target. Once it arrives at the target cells, it must also be lipophilic enough to bind to them. In order to create a significant amount of ROS, the substance must be minimally toxic in the absence of light, possess a high efficiency of creating a triplet-state, and have an adequate triplet lifetime to engage with ground-state oxygen [95]. It is crucial that the compound is activated using light wavelengths that exceed 700 nm, as this permit for deeper penetration into tissues. The effectual penetration of light into tissues is limited due to the stronger absorption of light below 700 nanometers by endogenous substances such as

haemoglobin. This makes it essential for the compound to be activated by light of longer wavelengths. Given the numerous specific requirements, identifying, or producing a substance that meets all of these criteria can prove challenging [96].

Despite not meeting all these criteria, many PSs have been authorized for clinical use, while others are under investigation in clinical trials as shown in Table 2.5. and figure 2.10.

Table 2.5: List of PSs that have received clinical approval or are currently undergoing clinical trials [96a].

	Class	Sensitizer	Trade name	Marketed by	Potential indications	Current status	Excipient formulation/ Mode of application	Typical maximum absorption (nm)	Extinction coefficient (M ⁻¹ cm ⁻¹)
1 st generation photosensitizer	Hematoporphyrin	HpD (partially purified), porfimer sodium	Photofrin	Axcan Pharma Inc. (QC, Canada)	Endobronchial non-small-cell lung cancer, esophageal cancers, bladder cancer, gastric cancer and cervical cancer	Canada (1993) Japan (1994) US FDA approved (1995), now approved in over 40 countries	Dextrose or NaCl injection	630	3 000
			Photogem	Moscow Research Oncological Institute (Moscow, Russia)					
2 nd generation photosensitizer	Protoporphyrin produgs	5-Aminolevulinic Acid (5- ALA)	Levulan	DUSA Pharmaceuticals, Inc. (MA, USA)	Treatment of actinic keratosis, basal-cell carcinoma, head and neck and gynaecological tumors as well as diagnosis of brain, head and neck, and bladder tumors	US FDA approved (1999), Europe (2001)	Topical cream	635	<10 000
		5-ALA-hexylester/ H-ALA	Hexvix	PhotoCure ASA (Oslo, Norway)	Diagnosis of bladder tumors	US FDA approved (2010)	Diluent for intravesical instillation	375 - 400	
			Cysview	Photocure Inc. (NJ, USA)					
		5-ALA-methylester/ M-ALA	Metvixia	Galderma Laboratories, L.P. (TX, USA)	Actinic keratosis, Bowen's disease and basal cell carcinoma	US FDA approved (2004) EU (2001) New Zealand (2002) Australia (2003)	Topical cream (includes cetostearyl alcohol and peanut oil)	635	
		5-ALA-benzylester	Benzvix	-	Gastrointestinal cancer	Not approved	-	635	
	Benzoporphyrin	Benzoporphyrin derivative monoacid, ring A (BPD-MA)/ Verteporfin	Visudyne	Valeant Pharmaceuticals International, Inc.(QC, Canada)	Treatment for wet age-related macular degeneration (AMD), pathologic myopia, histoplasmosis	US FDA approved (2000), Europe (2000),Canada (2000)	Liposomal formulation	689 - 693	35 000

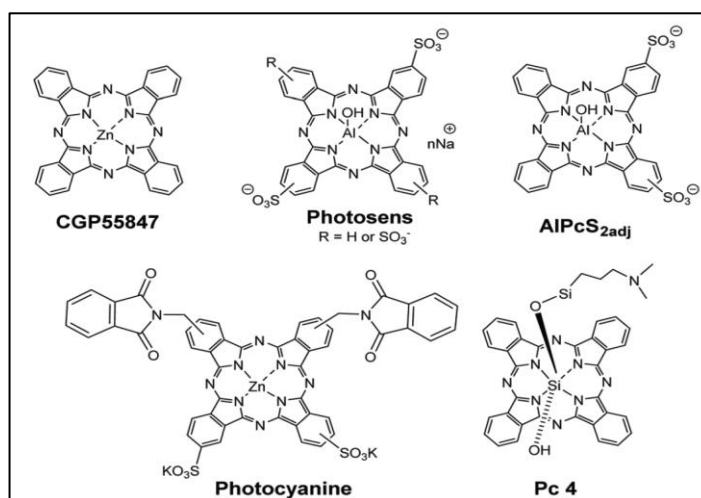


Figure 2.10: Structures of Pcs approved or having been or being enrolled in human clinical trials of cancer by PDT [96b].

2.2.4. Importance of Near Infrared (NIR) Excitation

NIR excitation finds its applications in diverse fields including medicine, biology, and chemistry. The technique involves the use of near-infrared light, which has a wavelength ranging from around 780 to 2500 nanometers. NIR excitation holds significance due to the following reasons:

- **Deeper Tissue Penetration:** Thanks to its ability to penetrate deeper into tissues, particularly in the phototherapeutic window, NIR light has become an indispensable tool in high-resolution imaging of in vivo structures. This makes it an ideal choice for researchers and medical professionals who require sharp and detailed images of biological samples [97].
- **Low Autofluorescence:** Biological samples often exhibit autofluorescence, which can interfere with imaging. However, the use of NIR excitation reduces this interference, resulting in clearer, more accurate images. This is especially useful in fields like medicine and biology research, where the detection of subtle differences can make a significant impact [98].
- **Reduced Tissue Scattering:** Compared to other forms of light, NIR light experiences less scattering in tissues. This means that the images produced using NIR excitation are of higher quality and provide better insights into the biological samples being studied [97].
- **Less Photodamage:** One of the biggest concerns when imaging biological samples is the potential for photodamage. However, using NIR light minimizes this risk, making it an ideal choice for live imaging and other applications that require minimal disruption to the biological samples being studied [98].
- **Low Water Absorption:** NIR light is minimally absorbed by water, which is a significant advantage when imaging biological samples. This is because water absorption can cause heating effects that may damage cells, leading to inaccurate results [97].
- **Time-Resolved Imaging:** With NIR excitation, researchers can use time-resolved imaging to collect luminescence signals after the relatively short-lived background signals. This reduces light scattering and autofluorescence, resulting in clearer

images that provide a more accurate representation of the biological samples being studied [97].

The unique properties of NIR excitation make it an invaluable tool for researchers and medical professionals in fields like medicine and biology research. Its ability to penetrate deeper into tissues, reduce autofluorescence, and minimize photodamage, along with its low water absorption and time-resolved imaging capabilities, make it an ideal choice for imaging biological samples with high accuracy and precision.

2.3. Nanomedicine and the Enhanced Permeability and Retention Effect

The EPR effect, an exceptional phenomenon, is utilized by nanocarriers to target cancer tissues. A process known as neovascularization, which involves the continuous formation of new blood vessels, supports cancerous growth. The vascular walls of these newly formed vessels are not fully developed and possess numerous slits or gaps, each spanning a width of several hundred nanometres as shown in Figure 2.11 [99].

EPR effect was initially identified by Maeda's team during inflammation research related to a bacterial infection. They discovered that the production of bradykinin, along with the concurrent activation of nitric oxide (NO) and superoxide anion, played a role in the EPR effect [100]. The EPR effect was noted in a study on the macromolecular anticancer agent SMANCS, which demonstrated a higher accumulation in tumor tissues and a longer plasma half-life compared to the unaltered neocarzinostatin (NCS) [101]. Over the past three decades, the EPR effect has been confirmed with various macromolecular drugs in both pre-clinical and clinical trials, thereby establishing it as a benchmark for the creation of tumor-targeted macromolecular anticancer drugs or nanomedicines.

The size dependency of the EPR effect was examined using nanomedicines. The EPR effect has a lower limit of 40-50 kDa, which corresponds to a nanomedicine size of 6-8 nm, the cut-off size for renal clearance [102]. These macromolecules circulate for an extended period, slowly infiltrate tumour tissue, and stay there for several days. Most nanomedicines, which typically have a diameter ranging from 10-100 nm, can

accumulate in tumors due to the EPR effect. Interestingly, even larger sizes, up to 1-2 μm - a size comparable to certain bacteria, can also gather in tumours [103].

The EPR effect of nanomedicines is influenced by several factors, not just size. Biocompatibility is crucial, as nanomedicines lacking it will be cleared by leukocytes, reducing their effectiveness. This issue is seen in antibody drugs, particularly those derived from mouse IgG, which are quickly cleared from human circulation due to anti-mouse antibody responses. To overcome this, humanized or human antibodies are used, despite their high cost. Other factors affecting biocompatibility include the nature of proteins and their modifications [104].

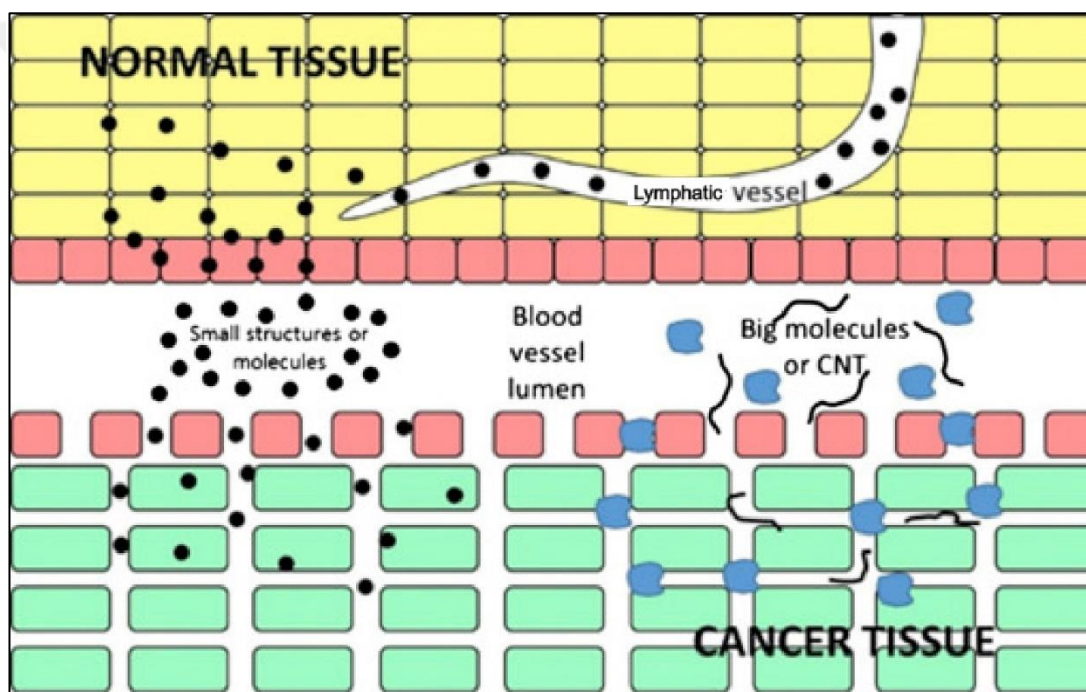


Figure 2.11: Diagram for the enhanced permeation and retention effect allowing to the big molecules to be introduced into tumoral tissue [99].

2.4. Nanoparticles with photosensitisers for PDT

2.4.1. Types of Organosilica and Their Preparations

In recent years, mesoporous materials have garnered considerable attention in research circles owing to their distinctive and intriguing characteristics. These materials possess high surface areas, which make them ideal for various applications such as catalysis, adsorption, and drug delivery. Additionally, they have large pore volumes that allow

for the efficient transport of molecules and ions. The uniform and ordered mesopores of these materials provide a well-defined structure that can be tailored to specific applications. Moreover, the plentiful structural compositions of mesoporous materials render them adaptable and appropriate for a broad spectrum of uses in diverse areas of science [105].

Consideration will be given to four unique types of organosilica nanoplateforms that have demonstrated significant potential in a variety of applications. These include mesoporous silica nanoparticles (MSNs), which, due to their extensive surface area and adjustable pore size, have been widely researched and employed within systems for drug delivering. Another type is mesoporous organosilica nanoparticles (MONs), which have similar properties to MSNs but with the added benefit of having organic functional groups incorporated into their structure, allowing for even greater control over their properties. Additionally, we will be looking at periodic mesoporous organosilica (PMO) NPs, which have a highly ordered pore structure and have been explored for use in catalysis and sensing applications. Finally, we will consider bridge silsesquioxanes NPs (BS NPs), which have a unique cage-like structure and have shown promise in areas such as drug delivery and visualization techniques [106].

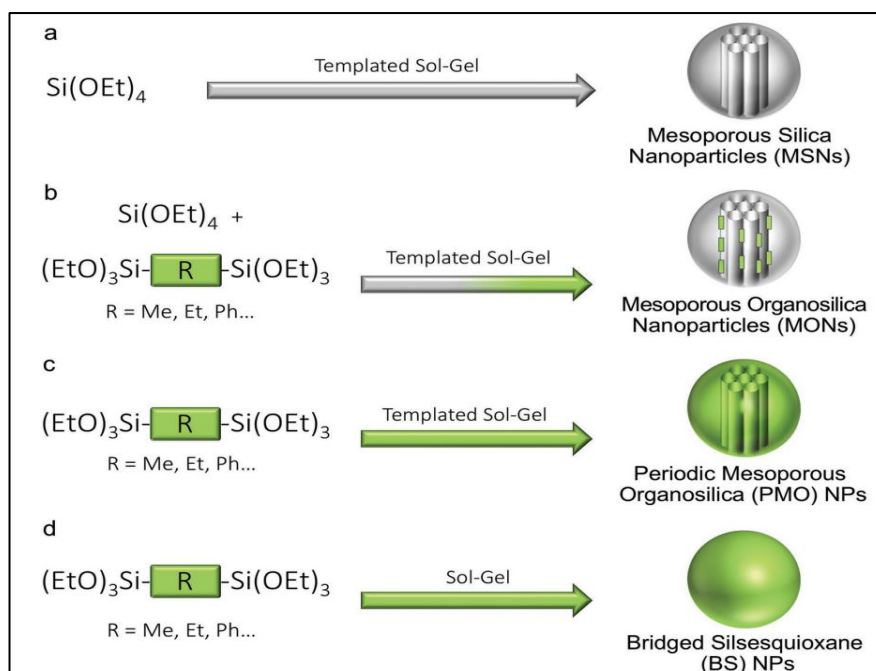
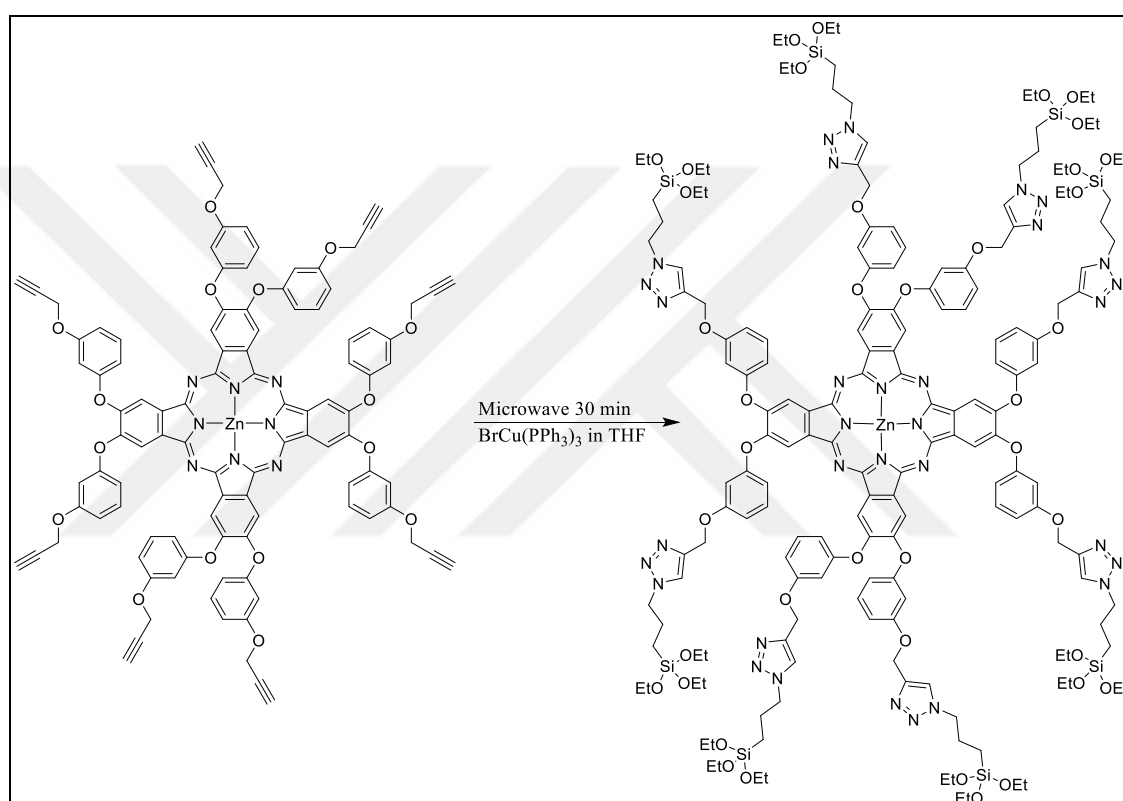


Figure 2.12: Depiction of the different types of silica (SiO_2) and silsesquioxanes ($\text{SiO}_{1.5}$) nanoparticles [106].

- Silica precursors such as tetraethoxysilane (TEOS) are used to obtain MSNs Figure 2.12 3a through the sol-gel process. This procedure entails fundamental catalysis in the presence of a water-based cetyltrimethylammonium bromide (CTAB) template. MSNs are a known characteristic for their high-level surface areas, which range from approximately 600 to 1200 m² g⁻¹. To serve various purposes, MSNs are typically post-functionalized with organic groups [107].
- To clarify, there are two types of silica particles: MONs (MSNs that are doped with organic materials) and MSNs (made purely of silica). MONs are produced via merging TEOS and organoalkoxysilanes, which leads to the incorporation of organic functions into the silica pore walls as shown in Figure 2.12 3b. This results in unique characteristics while preserving high porosity of the particles. When organoalkoxysilanes possess two or more condensing groups, their organic functions are located within the silica pore walls [108].
- PMO NPs are different from other nanoplateforms in that they are made only from bridged multi-organalkoxysilanes via templated sol-gel reactions Figure 2.12 3c [109]. High surface areas result from the pore walls being solely constituted by the organic groups of the organoalkoxysilanes. The properties of PMO NPs can be significantly altered by the design of their chemical structure, which allows them to bear a substantial load of up to 1200 mg for each gram of NPs[98]. The incorporation of certain chemical functions, which can be cleaved under biologically relevant conditions, into the internal structure allows for regulated biodegradability. This is exemplified by systems such as PMO NPs doped with disulfide and tetrasulfide, which undergo glutathione-mediated biodegradation in cells, and PMO NPs doped with degradable oxamide or lysine [106].
- Bridged multi-organalkoxysilanes can be used to create solid nonporous BS NPs, leading to the formation of intense NPs that have a high organic amount within the composite matrix. This occurs because there are no specific interactions between micelles and bridged organalkoxysilanes Figure 2.12 3d [110].

2.4.2. Organosilica Nanoparticles Based on Phthalocyanines

A group of researchers has successfully synthesized Mesoporous Organosilica Nanoparticles (PHT-PMO) using a starting material of octatriethoxysilylated zinc phthalocyanine. This material was synthesized from the corresponding propargylated phthalocyanine using a microwave for 30 mins, with bromo(tris(triphenylphosphine)copper(I) $\text{BrCu(PPh}_3)_3$ in THF (Scheme 2.6).



Scheme 2.6: Synthesis of octatriethoxysilylated zinc phthalocyanine [111].

These nanoparticles have been found to be non-toxic in the dark but exhibit high phototoxicity when exposed to 650 nm light. Additionally, they exhibit significant phototoxicity in the near-infrared range when stimulated at wavelengths of 760 and 810 nm. These findings hold great promise for the development of targeted photodynamic therapy for cancer treatment [111].

The toxicity of PHT-PMO on human breast cancer MCF-7 cells was tested by researchers. It was found that up to 40 μg per mL, there was no significant toxicity,

causing only 21% cell death. Even at 100 μg per mL, just 32% cell death was caused, demonstrating the biocompatibility of PHT-PMO.

The efficiency of PDT of PHT-PMO in killing cancer cells using light was also studied. Cells treated with PHT-PMO were exposed to light at 405 nm or 650 nm. Non-UV light (like 650 nm) is safer as it doesn't cause DNA mutations. It was found that PHT-PMO was most effective with 650 nm light. For instance, at 25 μg per mL, 51% cell death was caused by 405 nm light, but 71% cell death was caused by 650 nm light [122].

Another study has resulted in the creation of a mesoporous nanovehicle capable of transporting both photosensitizers and clinically related drugs for combined treatment. The nanovehicle is engineered to get into deeply into skin tissue, with the aid of microneedle technology to ease this process. The mesoporous structure of the nanovehicle allows for a high drug loading capacity, while the dual loading of photosensitizers and clinically relevant drugs enables a synergistic effect for enhanced therapeutic efficacy. The study demonstrates that microneedle technology is safe and effective for penetrating the skin, positioning it as a gifted method for delivering combination therapy in the treatment of skin conditions [112].

The synthesis of phthalocyanine with four silicate functional groups (Pc-Si) is capable of being stimulated by far-red light, which can easily access into the dermis of the skin, where melanoma penetrates. To synthesize phthalocyanine based on mesoporous organosilica (PcNP), Pc-Si was used via silane condensation and hydrolysis. The structure-directing agent CTAB, was used to form micelles in the existence of triethanolamine (TEOA), a basic catalyst [113] Instead of the frequently used tetraethyl orthosilicate (TEOS), tetramethyl orthosilicate (TMOS) was selected as the source of inorganic silica because it is more readily dissolved in water.

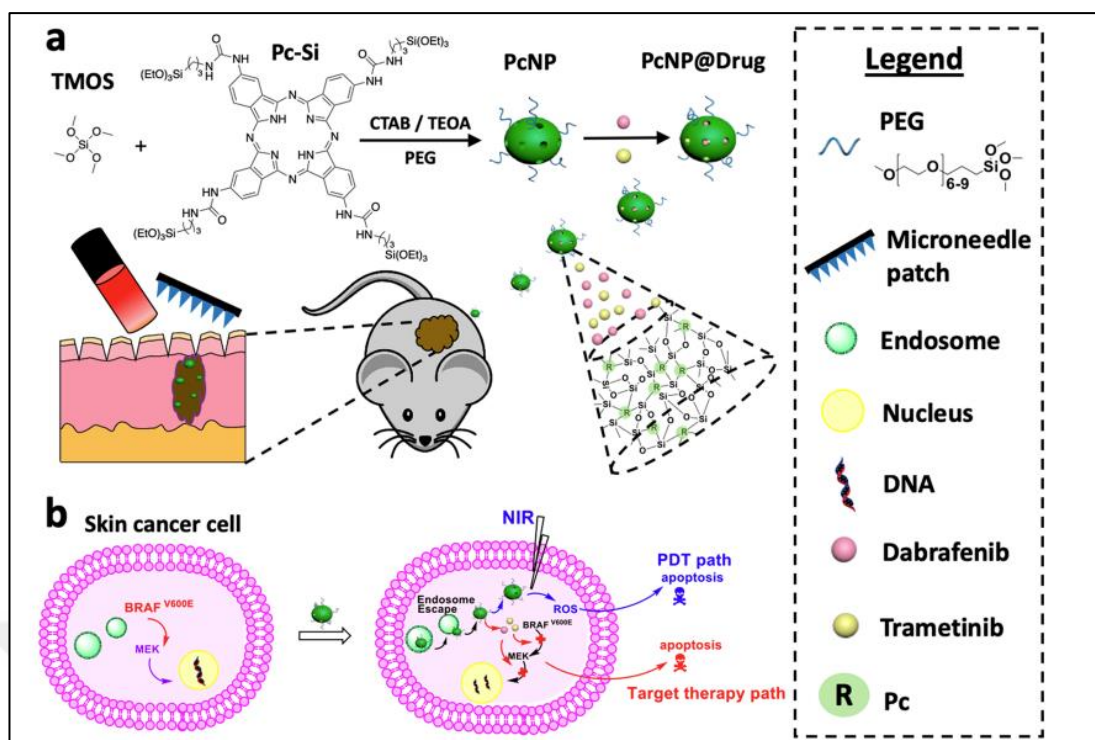


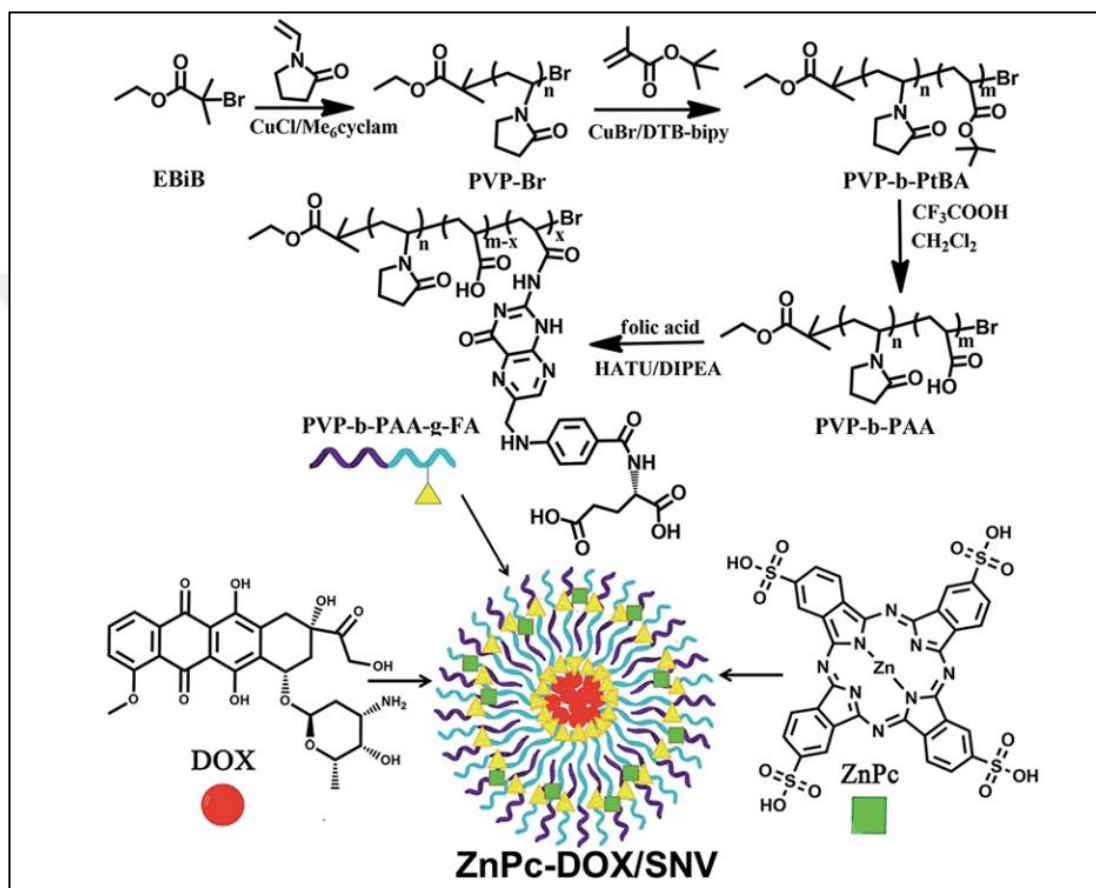
Figure 2.13: (a) The creation of PcNP@Drug and its infiltration into affected skin.
(b) The cellular process that enables PcNP@Drug to function [112].

The minor inhibitory medications, dabrafenib and trametinib, were integrated into the pores of PcNP, forming a drug based PcNP, known as PcNP@Drug Figure 2.13a. When administered to mice through a very small needle patch, PcNP@Drug could produce ROS in the body upon exposure to NIR light. Moreover, the medications discharged from PcNP@Drug have the potential to obstruct the distorted BRAF and the ensuing MEK pathway in cancerous cells [112].

In another research endeavour, a specially designed supramolecular nanovehicle (SNV) is introduced. This SNV is meticulously engineered for a systematic approach towards cancer therapy, which is targeted through a synergistic combination of chemotherapy and photodynamic therapy [113]. This involves a two-step process Scheme 2.7:

1. The development of a specific type of copolymer, known as polyvinylpyrrolidone-b-polyacrylic acid, which has been chemically altered with folic acid (PVP-b-PAA-g-FA). This specially designed copolymer has the unique ability to specifically target cancer cells.

2. Photosensitizer known as ZnPc, along with a chemotherapy drug called doxorubicin (DOX), are encapsulated within the structure of the copolymer. This leads to the formation of the final supramolecular nanovehicle (SNV) micelle, ZnPc-DOX/SNV. This micelle is designed to have targeted therapy delivered to cancer cells.



Scheme 2.7: Synthesis of the PVP-b-PAA-g-FA copolymer and a depiction of the structure of ZnPc-DOX/SNV [113].

The copolymer PVP-b-PAA-g-FA is made to function as a versatile SNV. The formation of the micelle's hydrophobic core is led by the addition of the acidic drug DOX, which counteracts the partially ionized folic acid (FA). The outer shell of the micelle is constituted by the remaining ionized FA, along with the terminal PVP, which is linked to ZnPc through hydrogen bond. An amphiphilic SNV, capable of targeted cancer treatment, is resulted from this configuration, leveraging the overexpression of FA in cancer cells. This unique structure and function are seen as a promising tool in the field of cancer treatment [113].

2.4.3. Organosilica Applications

Organosilica, specifically Periodic Mesoporous Organosilica nanoparticles, are utilized in a broad spectrum of intricate applications:

Nanomedicine: Periodic Mesoporous Organosilicas nanoparticles have garnered significant interest due to their potential in various biomedical applications. The diminutive size of PMO at the nanoscale plays a pivotal role in these applications, as it has a direct impact on their interactions with biological systems and their duration of effectiveness.

Crucial factors like the absorption into cells, distribution in the bloodstream, and accumulation in tumors are all determined by the dimensions of these nanoparticles. This means that the smaller the nanoparticle, the more efficiently it can be absorbed by cells, circulate in the blood, and accumulate in tumors [114].

Moreover, Incorporating particular organic groups into the PMO matrix can substantially change the rate at which the nanoparticles break down biologically. This is a crucial aspect as it can control how long the nanoparticles remain in the body before they are broken down and removed.

The organic composition of the pores in PMO nanoparticles presents an additional benefit. It enables the adjustment of their water-repelling properties and interactions between host and guest molecules, potentially resulting in increased loading capacities. This is particularly useful in drug delivery applications where a large amount of drug needs to be loaded onto the nanoparticles for effective treatment.

PMO nanoparticles are tiny particles that have a variety of uses. They can be used to make sure that they don't harm the body's cells or tissues, which is known as biocompatibility studies [115]. They can also be used to carry drugs straight to where the disease is, which can make the treatment more effective and reduce side effects. This is known as drug delivery [115]. In addition, they can carry proteins to specific parts of the body, which can be helpful in treating diseases caused by protein deficiencies or malfunctions. This is known as protein delivery. Because of their small size, ability to change how quickly they break down, and ability to carry a lot of drugs or proteins, PMO nanoparticles are a promising tool in medicine. They could be used in many different ways in the future[116].

Catalysis: PMO nanoparticles are used in catalysis because they can be made in many different ways, which makes them useful for many types of catalytic applications. They are being used more and more as catalysts for organic reactions. These tiny catalysts work better than their larger counterparts for a few reasons. They have a larger surface area compared to their volume, which means there is more space for reactions to happen. They also have shorter paths for reactants and products to move through, which makes the reactions happen faster. Some PMO nanoparticles can even act as tiny reactors. This special structure gives a specific space for reactions to happen, which can make the reactions more controlled and efficient. PMO materials can support many types of catalysts, like metallic salts, metal nanoparticles, or organocatalysts. These catalysts can help with many types of reactions, like acid/base catalysis, redox, or forming carbon-carbon bonds. PMO materials are used in many areas [114]. PMO materials find applications in several areas:

- **Organocatalysis:** PMO materials can support organocatalysts, which are organic compounds that can catalyse chemical reactions. This can be particularly useful in reactions where metal catalysts are not suitable [117].
- **Metal NPs Supported on PMO Nanoreactors:** Metal nanoparticles can be supported on PMO materials to create effective nanoreactors. These can enhance the catalytic activity of the metal nanoparticles and provide a robust and reusable catalyst system [118].
- **Metal Complexes Supported on PMO Nanoreactors:** Metal complexes can also be supported on PMO materials. These can offer unique catalytic properties and can be used in a variety of chemical transformations [119].
- The unique properties and versatility of PMO materials make them a promising candidate for use in various catalytic applications. Their potential to enhance reaction efficiency and control, coupled with their ability to support a wide range of catalysts, underscores their potential in the field of catalysis. Further research and development in this area could unlock even more applications and improvements in reaction efficiency.

2.5. Synthetic Methods, Properties and Applications of Poly- ϵ -caprolactone (PCL)

2.5.1. Synthetic Methods and Mechanism of Production of PCL

There are two main approaches to producing PCL. The first method involves the condensation of 6-hydroxycaproic acid. The second method employs the ring-opening polymerization (ROP) of ϵ -caprolactone cycle. This latter monomer is usually synthesised from the Baeyer-Villiger of oxocyclohexane using peroxyacetic acid [120].

Polycondensation is a process in which two distinct molecules with corresponding functional groups engage in a reaction, yielding a byproduct with a lower molecular weight. In the context of PCL's polycondensation reaction, the acid function of 6-hydroxyhexanoic acid or the growing polymer chain interacts with the alcoholic hydroxyl function group of another molecule. This interaction results in the formation of an ester bond and the release of water as a byproduct. The extraction of water tips the reaction equilibrium in favour of polymer formation, as per Le Chatelier's principle. While this synthesis route is reported for various aliphatic polyesters, it's seldom used in PCL synthesis [121-123].

Conversely, ROP produces polymers that have higher molecular weights while ensuring low variation in polydispersity [124],[125]. ROP is identified as a form of chain growing polymerization where the incorporation of cyclic monomers is facilitated by a reactive centre present at one terminal point of the polymer chain. The terminal groups of the polymer that results are determined by the initiator that is used and any termination reactions that occur. These polymerization reactions can be conducted either in bulk or in a solution [126].

In the ROP of lactones, the catalyst may not always be restored during the termination phase. This could lead to a polymer chain that remains reactive if there are still monomers available. The catalyst chosen can lead to one of four distinct ROP mechanisms, each with its own unique molecular polydispersities, weights, and terminal groups Figure 2.14 [126].

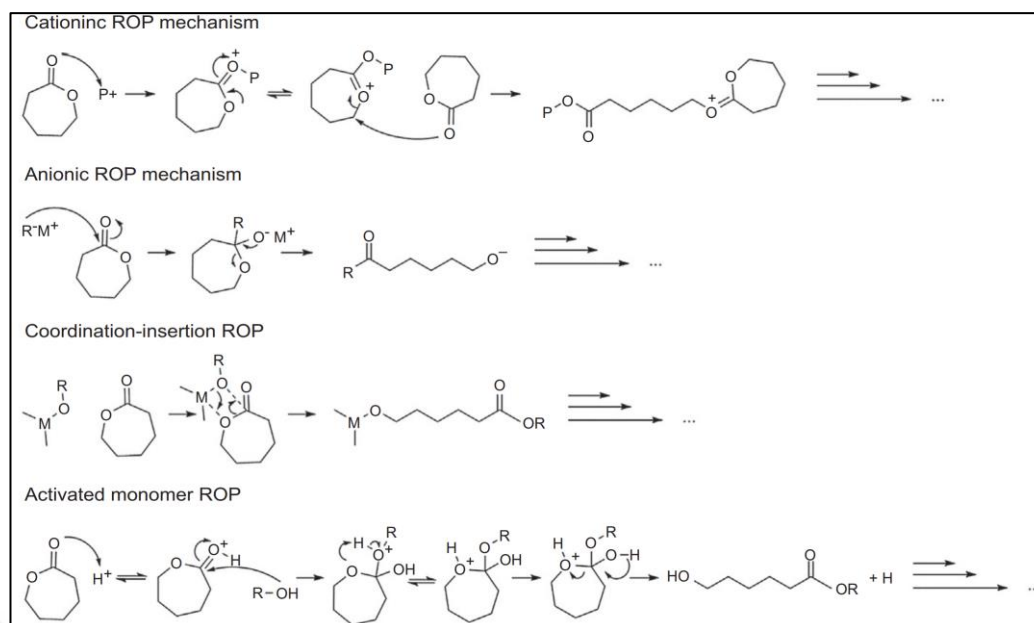


Figure 2.14: Mechanisms of various ring opening polymerization methods [126].

Cationic ROP: In this procedure, a positive charge is acquired by the caprolactone ring as a result of the interaction between an initiator and the monomer. The carbonyl oxygen of another monomer initiates a bimolecular nucleophilic substitution reaction (SN_2), causing the ring to open. The last monomer, which is now charged with positive, enables the continuation of the reaction. However, managing these polymerisation reactions can be difficult, and attaining high molecular weights can be challenging [127].

Anionic ROP: In this approach, the initiator focuses on carbon atom of the carbonyl group in the monomer, which results in the breaking the bond of oxygen atom of the acyl group. This allows the terminal alcoholate species which are negatively charged to continue the reaction. In the final stages of polymerization, this problem becomes more evident, and the polymerization process can be minimized by being halted prematurely which results in polymers that have lower molecular weights [128].

Coordination-Insertion ROP: This method is widely recognized as the most frequently used technique for chain growth polymerization. It employs a pseudo anionic ROP, a process where the monomer aligns itself with the active species, which are the reactive molecules in the system. In the next step, there is a rearrangement of electrons which allows the monomer to be incorporated into the metal-oxygen bond, a critical bond in the structure of the polymer.

The opening of the ring, a key step in the polymerization process, is brought about by the cleavage of the acyl-oxygen bond that when broken, allows for the continuation of the polymerization process. Following the cleavage of the bond, the polymer chain becomes connected to the metal. This connection is facilitated through an alkoxide coordination bond, and the polymerization reaction is able to proceed. This continuation is made possible by the insertion of another monomer. The addition of this new monomer allows the polymer chain to grow, further advancing the polymerization process. This cycle continues, leading to the formation of a long chain of polymers, which is the ultimate goal of the chain-growth [129].

Activated Monomer ROP: In the beginning of this process, the carboxyl oxygen undergoes protonation. The carbon atom attached to the protonated carboxyl oxygen acts as the electrophile. Following this, the hydroxyl end group of the polymer chain, which acts as the nucleophile, adds itself to the electrophilic carbon atom which leads to the opening of the ring structure in the polymer [130].

2.5.2. Typical catalysts and initiators used in ring opening polymerization

Several organometallic compounds have been utilized as catalyst initiators for the ROP. In this process, the metal ion acts as a catalyst such as tin (II), while one of the conjugate bases of an alcohol serves as an initiator such as 2-ethylhexanoate.

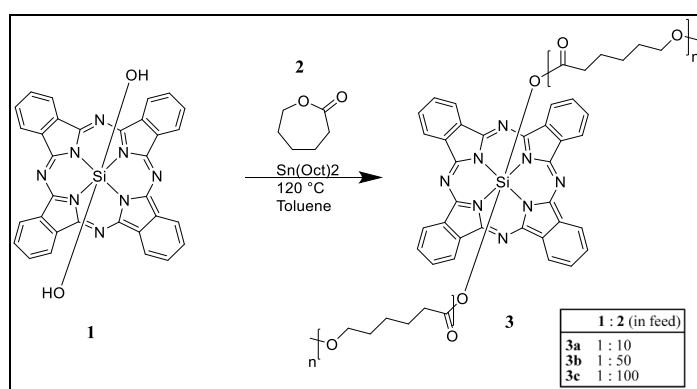
Tin(II) 2-ethylhexanoate ($\text{Sn}(\text{Oct})_2$) is a catalyst that is frequently utilized. It is known for its high efficiency, its ability to dissolve in a majority of organic solvents, and it is also found to be readily available commercially. While the precise mechanism of catalysis remains a mystery, it has been shown that the molecular weight does not rely on the concentration of $\text{Sn}(\text{Oct})_2$, suggesting that it doesn't serve as an initiator [138]. An enhancement in the rate of polymerization can be achieved when triphenyl phosphine is introduced in an amount that is equimolar to the alkoxide [131].

Aluminium isopropoxide is also a commonly used initiator-catalyst based on metal. Although compounds containing aluminium are not as reactive as other types of catalysts, they offer effective management of the polymerization process. This is accomplished via a process known as living polymerization. It's a type of chain polymerization where both chain transfer and chain termination do not occur, leading to the formation of well-structured polymers [132].

For the production of PCL for use in biomedical fields, catalysts like calcium and magnesium complexes are especially appealing because of their low toxicity and plentiful availability. Investigations into these metal complexes have demonstrated their high reactivity, leading to the synthesis of polymers with high molecular weight and a polydispersity index that varies from low to moderate [133]. Alternatively, lanthanide metals are also considered suitable options due to their lack of toxicity [134]. The activity and polydispersity of these catalysts depend on the ligands used. Scandium trifluoromethanesulfonate, a member of the lanthanide metal catalysts, has been found to be the most effective. When it is mixed with water and phenyl methanol, it leads to the formation of polymers with high molecular weights and low polydispersity [135]. Samarium, when coordinated with aryloxide ligands, is another effective option that has also produced positive outcomes [136].

2.5.3. Caprolactone polymers with phthalocyanines and their characterisations

A group of researchers embarked on a study to synthesize a new derivative of biodegradable PCLs, which incorporate phthalocyanine. The synthesis process was carried out through the polymerization which include opening the ring of ϵ -caprolactone. The reaction was initiated using silicon phthalocyanine dihydroxide and catalyzed by $\text{Sn}(\text{Oct})_2$ [137] as shown in scheme 2.8.



Scheme 2.8: The synthesis of PCLs [137].

The team characterized the resulting polymers using spectroscopic methods and determined their molecular weights via gel permeation chromatography (GPC). Interestingly, the observed molecular weights were significantly higher than theoretical

values, indicating a faster rate of propagation compared to initiation and the polymers exhibited relatively high polydispersities (PDI) [138].

The anticipated chemical shifts for the PCL [119] are exhibited by the ^1H NMR spectra of PCLs in CDCl_3 . Two signals with small intensity at δ 9.66 and 8.37 were identified in the case of 3a, which correspond to the protons of the phthalocyanine. In the enlarged spectrum, additional chemical shifts in the up field region (δ 0 to -1.5) were observed. These chemical shifts could be attributed to the segment of PCL situated in the shielding region of the phthalocyanine.

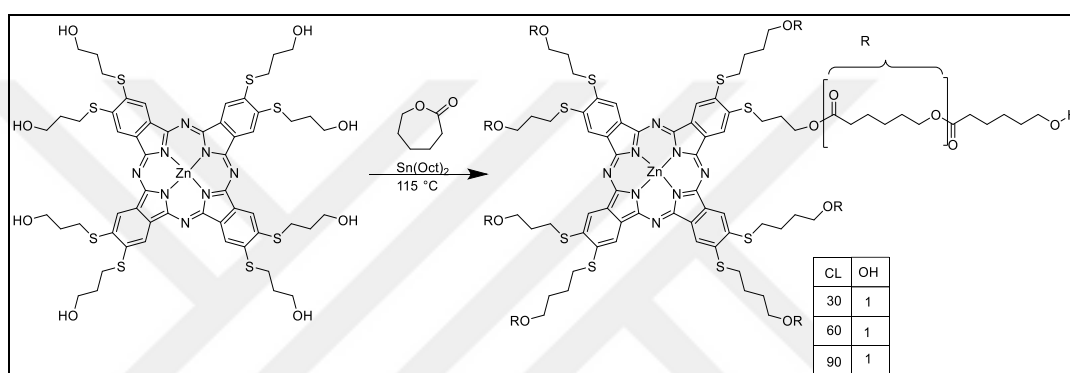
Spectroscopic analysis revealed typical electronic absorption characteristics for all polymers, including a distinct Q band at 677 nm, a B band at 357 nm, and two faint vibronic bands at 610 and 645 nm. These spectral characteristics were found to be consistent throughout the polymer series, indicating that the π system was not significantly affected by the length (the number of repeat units) and type of the polymeric substituents [137].

The researchers also found that the quantum yields of singlet oxygen from chosen polymers were marginally less than that of unsubstituted zinc phthalocyanine in DMF. Nanoparticles from the PCL were prepared by the team, with an average effective radius, also known as the hydrodynamic radius (R_h), of approximately 88 nm. This was accomplished using a microphase inversion method. The preparation of nanoparticles involved the gradual addition of a diluted solution of these synthesized polys(ϵ -caprolactone)s in THF into a large volume of aqueous solution, which contained CTAB as a stabilizing agent. The concentration of the surfactant was about twice its critical micelle concentration. Upon addition, the mixture was subjected to intense stirring, leading to the rapid diffusion, and blending of THF with water. The polymer chains, which repel water molecules, contracted, and gathered in water to form nanoparticles. These nanoparticles were subsequently stabilized by the surfactant molecules that were adsorbed onto the particle surfaces [137].

The photodynamic properties of polymers were evaluated against HepG2 human hepatocarcinoma cells. In the initial screening, the cells were exposed to approximately the same concentration of the polymers (around 0.05 mg per mL), which were prepared with Kolliphor EL. It was observed that all the polymers were essentially non-toxic in

the lack of light. However, when subjected to red light, all the polymers demonstrated significant photodynamic activity, with cell viability ranging from 85% to 97%[137].

A series of PCLs that terminated with hydroxyl groups was successfully synthesized by another group of researchers. This type of polymer is known as a star-shaped polymer with eight arms. The synthesis of these polymers was achieved by using an initiator core of octakis(3-hydroxypropylmercapto)phthalocyaninato zinc(II) Scheme 2.9. This was achieved through the opening of the ring of ϵ -caprolactone which was catalysed by $\text{Sn}(\text{Oct})_2$ [139].



Scheme 2.9: Synthesis of octaarmed starshaped poly(ϵ -caprolactone)s [139].

A strong, wide absorption band was shown in the polymers' FT-IR spectrums, which is associated with the hydroxyl group stretching at 3320 cm^{-1} . As the polymer's molecular weight was increased by the polymerization process, the distinguished absorption peaks of the carbonyl group at 1730 cm^{-1} also intensified. These peaks are due to the formation of the ester linkage. This implies that the ϵ -caprolactone molecule polymerisation is facilitated by hydroxyl groups. The characteristic vibration bands of the phthalocyanine skeleton at 1650 cm^{-1} ($-\text{C}=\text{N}-$) and 1590 cm^{-1} ($-\text{C}=\text{C}-$) were also detected as faint peaks, indicating the inclusion of the initiator and the PCL units[152].

The ^1H NMR spectrum of one of the polymers, when observed in CDCl_3 , indicated a decrease in the peak at 4.97 ppm, which is associated with the protons of the primary hydroxyl groups, in comparison to the ^1H -NMR spectrum of the initiator. However, the $-\text{OH}$ protons signal, corresponding to the hydroxyl end groups of the polymer, could not be detected [139].

High-resolution detection revealed the resonance peaks of the recurring methylene groups at 2.30 ppm and 4.05 ppm. Meanwhile, the protons of the phthalocyanine were observed as a faint signal at 7.62 ppm. The polymer's molecular weight, as deduced from the ^1H NMR spectra, closely matched the theoretical value. In addition, the integral ratio of the proton signal from the hydroxymethylene terminal group to the methyleneoxy groups was found to be 1.19, a value that is nearly identical to the theoretical prediction. These findings suggest that the synthesis of the eight-armed star-shaped polymers was successful [139].

Symmetrical and single-peak GPC chromatograms were displayed by all the star-shaped polymers, which experienced a shift towards a down elution time region as the lengths of the arms increased. Relatively higher polydispersities were observed in the polymers, potentially due to the intramolecular cross esterification reactions that occur at great conversions.

The number average molecular weight ($M_{n,\text{GPC}}$) by GPC of one of the polymers was determined to be 15406 g mol^{-1} . A higher discrepancy from the theoretical result was observed in GPC, a common occurrence when determining the molecular weights of branched polymers. This could be attributed to the compacted spherical structure of the star-shaped PCL [139].

The polymers' UV-vis absorption spectrums, together with the starting hydroxylated zinc phthalocyanine initiator in DMF. Distinguishing electronic spectra with two absorption regions are exhibited by Phthalocyanines. One is in the visible region at around 600–700 nm, attributed to the $\pi \Rightarrow \pi^*$ transition from the HOMO to LUMO of the phthalocyanine core, and the other is in the visible region at around 300–400 nm, attributed to deeper $\pi \Rightarrow \pi^*$ transitions. For the entire series of ZnPc-containing star polymers, it was observed that the Q-band absorption values did not change considerably. This observation suggests that the π -electron system is not significantly disturbed by the length of the polymeric substituent [139].

2.5.4. PCL based Nanoparticles for Biomedical Applications

PCL is characterized by its safety for use with living systems, causing no harm or unwanted reactions. Its ability to be naturally decomposed by organisms in an ecosystem and its formation of structures that naturally dissolve and are removed from the body over time are also notable features. These characteristics have positioned PCL as a subject of significant research in recent years, particularly due to its potential uses in drug delivery and nanomedicine.

The potential of PCL is especially noteworthy in the formation of nanomedicines for treating cancer, a prevalent health issue in today's society. The unique properties of PCL, such as its biocompatibility and biodegradability, make it an ideal material for creating microparticles and scaffolds, which are widely used in pharmaceutical and biomedical applications [140].

Treatment of brain cancer using nanoparticles based on PCL: PCL is prominently used in managing glioblastoma, an extremely aggressive form of brain cancer. There have been substantial attempts to enhance the treatment results for this disease using drug delivery systems based on PCL. The nanoparticulated systems have shown promising results, enhancing the effectiveness of several types of drugs used in the treatment of glioblastoma.

Using the emulsion-evaporation method, PCL nanospheres loaded with 5-fluorouracil were created and an in vitro evaluation was conducted to assess their toxicity against medulloblastoma cells. After approximately 70 hours of exposure, greater toxicity was caused by these drug-loaded nanospheres than by free 5-fluorouracil [141].

Nanospheres were also fabricated using blends of poly(lactide-co-caprolactone-co-glycolide) (PLA-PCL-PGA) and poly(lactide-co-caprolactone) (PLA-PCL), and their properties were analyzed in comparison. PCL led to the minimum diameter and the most gradual drug release, but it also exhibited modest encapsulation efficiency. Conversely, block copolymers showed better efficiency, although they displayed diverse and more rapid drug release patterns [141].

Treatment of breast cancer using nanoparticles based on PCL: Globally, breast cancer is identified as the primary cause of deaths related to cancer among women, accounting

for 14.6% of the total 3.5 million fatalities [142]. Given these statistics, it is understandable that extensive exploration has been conducted into nanotechnology and various types of nanoparticles to improve more efficient medications for this multiplex disease. Nanoparticles based on polymers, particularly those made with PCLs, have been the subject of widespread investigation. This adaptable polymer has attracted a considerable amount of research interest [140]. It should be noted that these efforts are not surprising considering the global impact of breast cancer. PCL nanoparticles loaded with Paclitaxel, a chemotherapy drug, with a size of approximately 0.946 μm , were synthesized using a spray-drying, which involves the conversion of a liquid into dry particles, achieved by spraying the substance into a heated drying medium, method. These nanoparticles, which had a spherical form and a smooth surface, showed almost total in vitro release of paclitaxel after a period of 36 days. Upon exposure to MCF-7 cells, these nanoparticles resulted in a substantial rise in the count of cells halted in the G2/M phase, in a comparison to the paclitaxel solution, afterwards a day of exposure [143]. PCL-based nanoparticles for lung cancer treatment In addition to brain and breast cancer, the use of PCL-based nanoparticles for drug delivery in the treatment of other types of cancer has been extensively investigated. Lung cancer, being the most prevalent cancer worldwide with 1.8 million new cases, and also having the highest mortality rate with 1.6 million deaths has been a particular focus. With the aim of enhancing treatments for this type of cancer, several drug-loaded polymeric nanoparticles have been developed using PCL [142]. Among the various types of PCL-based nanoparticles, it was discovered that micellar nanoparticles loaded with doxorubicin and modified with PCL-g-chondroitin sulfate were more efficiently absorbed by NCI-H358 non-small lung cancer cells. This resulted in a lower IC₅₀, indicating a higher potency compared to the free drug. This outcome aligns with the observation that these micelles preferentially enter the nuclei of NCI-H358 cells, which is where doxorubicin, the active drug, exerts its therapeutic effect. Further in vivo studies conducted on mice bearing tumors (induced with NCI-H358 cells) revealed that PCL-g-chondroitin micelles primarily accumulated in the liver and kidneys. However, despite this distribution, a superior anti-tumour efficacy was observed for the drug-loaded micelles compared to both the free drug and PBS when administered intravenously [144]. This suggests that the use of PCL-g-chondroitin sulfate micellar nanoparticles as a delivery system enhances the therapeutic effectiveness of doxorubicin in the treatment

of non-small cell lung cancer [144]. PCL-based nanoparticles for colon cancer: Nanoparticles loaded with drugs, specifically designed for the treatment of colon cancer, have been extensively studied. One such example includes doxorubicin-loaded poly (caprolactone) -poly (ethylene glycol) -poly (caprolactone) (PCL-PEG- PCL) nanoparticles. These nanoparticles were initially evaluated in vitro and subsequently in vivo using mice bearing subcutaneous C-26 murine colon carcinoma. The doxorubicin-loaded nanoparticles demonstrated enhanced cytotoxicity against C-26 cells in vitro and exhibited superior anti-cancer activity compared to free doxorubicin when evaluated in vivo [145]. In addition, polymers such as methoxypoly(ethylene glycol) poly(caprolactone) (MPEG-PCL) and (PCL-PEG-PCL), with varying block molecular weights, were examined for their physicochemical characteristics. Their efficacy against LoVo human colon adenocarcinoma cells was assessed in vitro, and their anti-tumour potency was evaluated through the Histo-culture Drug Response Assay. Among these, the most effective drug carrier was found to be the MPEG-PCL copolymer with a 4000/20000 MPEG/PCL ratio. This particular formulation demonstrated an improved effect both in vitro and in the Histo-culture Drug Response Assay[146]. These findings underscore the potential of PCL-based nanoparticles in enhancing the effectiveness of drug delivery systems for the treatment of colon cancer.

PCL-based nanoparticles for liver cancer: Nanoparticles loaded with 5-fluorouracil, prepared from PCL and PCL copolymers, demonstrated an enhancement in cytotoxicity against HepG2 (human hepatocellular carcinoma), especially when block copolymers were utilized [141]. Oridonin, a diterpenoid known for its significant anti-proliferative activity and potential in cancer treatment, was incorporated into PCL-PEG-PCL nanoparticles. This approach aimed to overcome the poor aqueous solubility of Oridonin and to establish an effective delivery system for its application [147]. In vivo evaluations conducted on mice bearing tumors induced by H22 cells (hepatocellular mouse carcinoma) revealed that the longest survival time and highest survival rate were observed when the mice were treated with drug-loaded nanoparticles [147]. There are two primary methods for synthesizing PCL. The first involves the condensation of 6-hydroxycaproic acid, while the second uses the ROP of cyclic ϵ -caprolactone. The latter monomer is typically obtained through the Baeyer-Villiger oxidation of cyclohexanone using acetyl hydroxyperoxide.

3. RESULTS AND DISCUSSION

3.1. NIR-absorbing Propargylated Phthalocyanine

Phthalocyanines, specifically those incorporating propargyl moieties, have emerged as a focal point in scientific research. These compounds exhibit a rigid and linear structure, which is primarily attributed to the presence of propargyl group. Propargyl group contain a carbon-carbon triple bond, which is inherently linear and contributes to the overall rigidity of the molecule.

This structural rigidity and linearity are crucial in facilitating high exciton and electron coupling between chromophore units, and in the case of phthalocyanines, these units absorb light in the NIR region of the spectrum [37].

Exciton coupling refers to the interaction between two electronic excited states. In phthalocyanines, this coupling allows for efficient energy transfer between chromophore units. The ability of these propargylated phthalocyanines to absorb light in the NIR region is particularly valuable in various applications, including photodynamic therapy and other biomedical applications [13]. This is due to the fact that NIR light can penetrate deeper into tissues compared to light in the visible spectrum, making it ideal for medical applications [13].

In addition, zinc-phthalocyanines are considered among the most effective metal phthalocyanine complexes for photosensitizing [37]. They exhibit high triplet and singlet oxygen quantum yields, making them potential Type II photosensitizers [149].

Phthalocyanines substituted at non-peripheral positions, such as those with di thioalkyl/thioaryl octa or tetra groups and four propargyl groups, induce a red-shifted maximum electronic absorption. This shift is beneficial as it results in the absorption of the NIR region extending up to 800 nm [37].

The combination of factors that mentioned indeed contributes significantly to the potential of the study on phthalocyanines, particularly those containing propargyl group.

3.1.1. Design and Synthetic strategy of Octa-thiosubstituted Non-Peripheral Tetra or Octa Propargylated Phthalocyanines

The objective of this work, described in a more detailed manner, is the synthesis of octa substituted non-peripheral tetra or octa propargylated phthalocyanines. These compounds, which bear terminal propargyl groups at non-peripheral positions, are intended to serve as building blocks for organosilica nanoparticles. The ultimate aim is to apply these nanoparticles in biocompatible photodynamic therapy applications.

In general, two different approaches have been designed to obtain the desired phthalocyanines bearing four or eight propargyl groups

Route A:

- Grafting of propargyl group on the phthalocyanine precursor: The propargyl is grafted to the hydroxylated phthalonitrile.
- Cyclotetramerization of the propargylated phthalonitrile

Route B:

- Synthesis of hydroxylated phthalocyanine: The phthalocyanine is directly synthesized from the hydroxylated phthalonitrile.
- Grafting of propargyl moiety: The propargyl molecule is then grafted to the synthesized phthalocyanine.

All the synthetic pathways have been comprehensively detailed in both Figure 3.1 and Scheme 3.1.

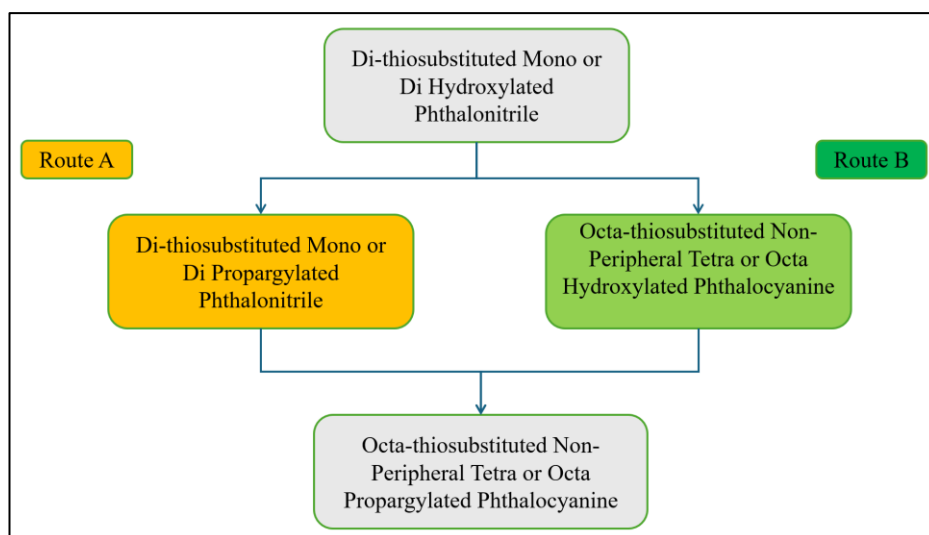
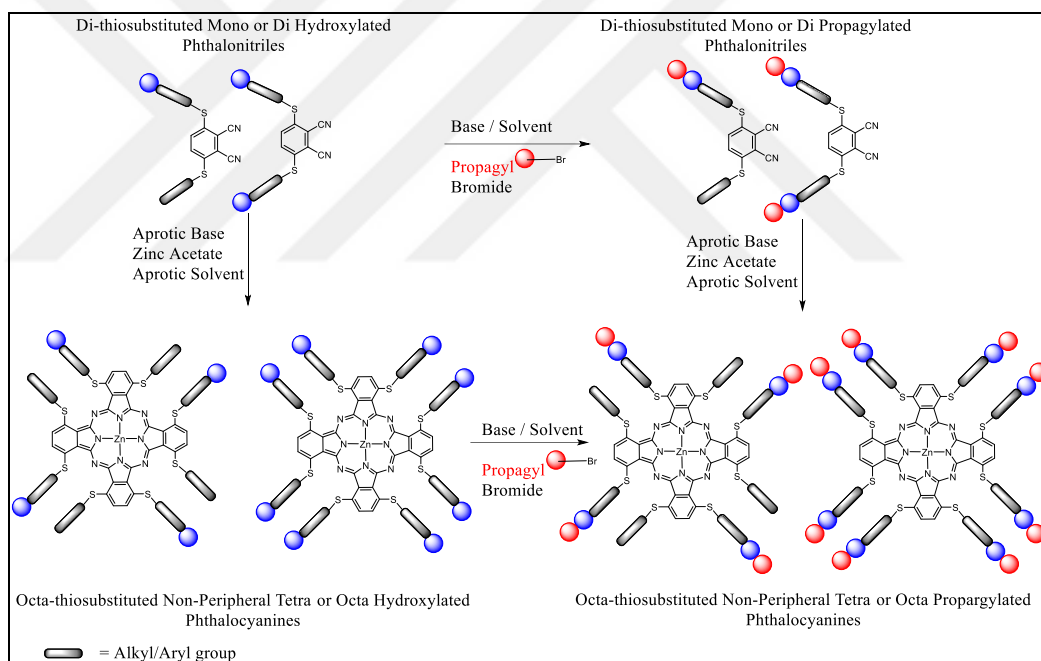


Figure 3.1: The two possible synthetic routes of octa-thiosubstituted non-peripheral tetra or octa propargylated phthalocyanines.



Scheme 3.1: Synthesis design routes octa-thiosubstituted non-peripheral tetra or octa propargylated phthalocyanines.

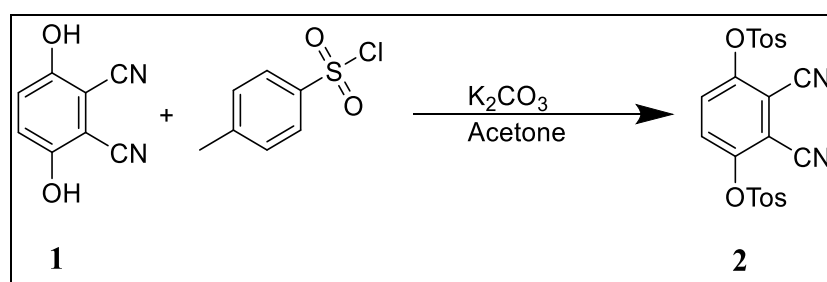
3.1.2. Synthesis and Characterization of Phthalonitriles

3.1.2.1. Synthesis and Characterization of Di-hydroxylated Phthalonitriles

In this work, the precursors for 3,6-dithiubstituted phthalonitriles can be synthesized through two methods: by treating dicyanohydroquinone **1** with either trifluoromethanesulfonic anhydride[58] or 4-methylbenzenesulfonyl chloride [150]. Given its relative ease of use, the method involving 4-methylbenzenesulfonyl chloride is generally preferred.

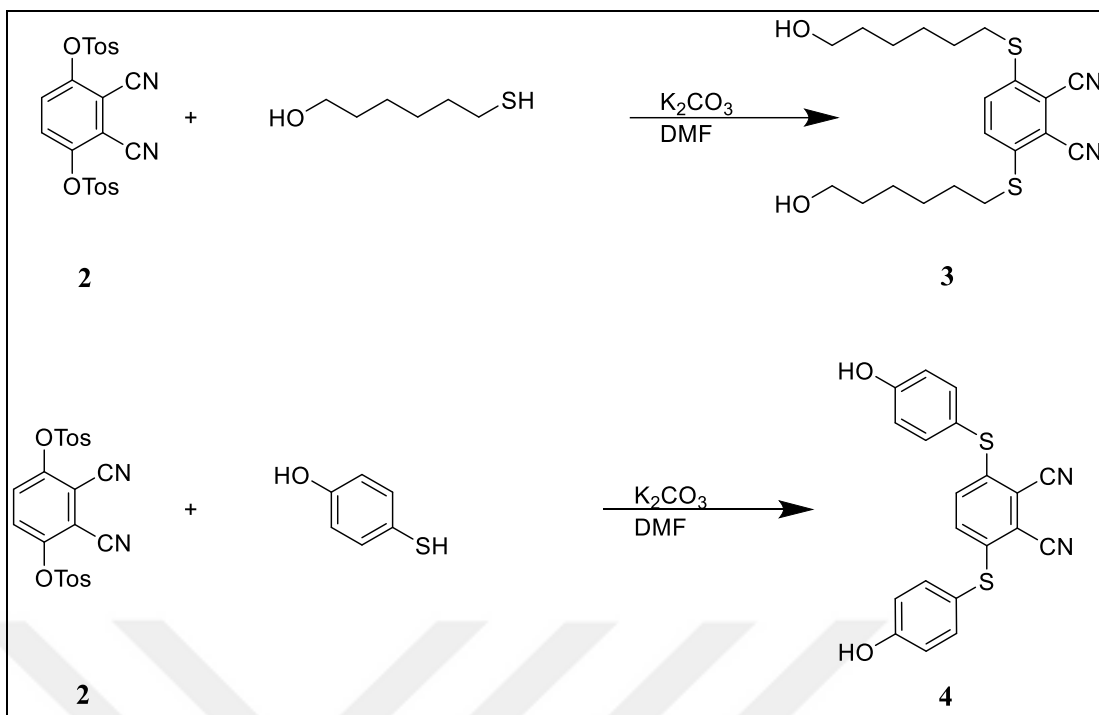
The synthesis of ditosylated phthalonitrile **2** was successfully carried out through the tosylation of dicyanohydroquinone **1** (1 equiv.) by 4-methylbenzenesulfonyl chloride (2 equiv.). Importantly, this synthesis was completed in a single step, as depicted in Scheme 3.2. The consumption of dicyanohydroquinone **1** was verified by thin layer chromatography (TLC). Following the reaction, the mixture was cooled, then poured into water, stirred for 1 hour, and ultimately filtered, resulting in a high yield of 92%.

The precise structure of the ditosylated phthalonitrile **2** has been confirmed by FT-IR, ^1H NMR and ^{13}C NMR spectroscopies and all the results were matching the reported values [151].



Scheme 3.2: Synthesis of 3,6-bis (4'-methylbenzenesulfonyloxy) phthalonitrile **2** [151].

The objective of employing ditosylated phthalonitrile **2** in the synthesis of dehydroxylated phthalonitriles **3** and **4** is to make the nucleophilic substitution process more efficient with 6-mercaptohexan-1-ol and 4-mercaptophenol separately Scheme 3.3. This is primarily due to the tosyl group's excellent leaving group properties.



Scheme 3.3: Synthesis of dihydroxylated phthalonitriles **3** and **4** in DMF.

The synthesis of **3** and **4** was conducted in DMF and by using 2 equivalents of 6-mercaptohexan-1-ol and 4-mercaptophenol separately, utilizing anhydrous potassium carbonate as a base. The choice of anhydrous potassium carbonate as a base was for two reasons. Firstly, it reacts with the thiol group, a weak acid, to produce a thiolate ion. This ion, being a stronger nucleophile, facilitates the nucleophilic substitution with tosylated phthalonitrile. Secondly, it neutralizes the by-product, tosylic acid, thereby maintaining the reaction conditions.

The purification procedure for **3** and **4** phthalonitriles was straightforward, primarily due to the high polarity of the target product. This characteristic facilitated the efficient removal of the impurities through the use of a silica gel column. The inherent polarity of the desired product thus simplified the purification process, ensuring a clean and uncontaminated final product with moderate yield Table 3.1. It is observed that the difference in the thiols used does not impact the yield of the final hydroxylated phthalonitriles **3** and **4**.

The exact structures of both final products were clearly confirmed by comparing the obtained spectral data with previously reported values [149],[153].

Table 3.1: Experimental yields of di-hydroxylated phthalonitriles **3** and **4**.

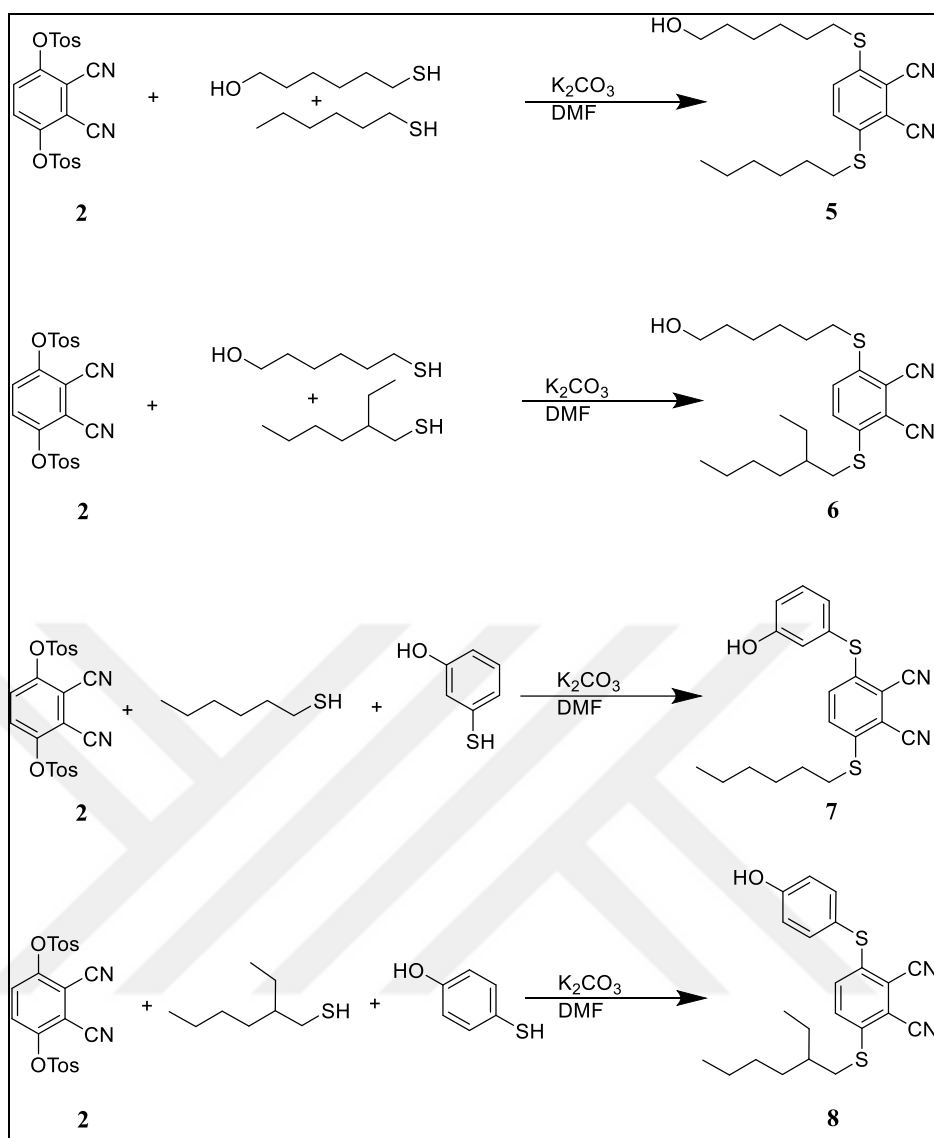
Compound	Yield (%)
3	42
4	44

3.1.2.2. Synthesis and Characterization of Di-substituted Mono-hydroxylated Phthalonitriles

The objective of this study is to synthesize disubstituted mono-hydroxylated phthalonitrile. A variety of thiols, including 1-hexanethiol, 6-mercaptohexan-1-ol, 2-ethylhexane-1-thiol, 3-mercaptophenol, and 4-mercaptophenol, are employed to achieve this goal. To ensure the synthesis of the di-substituted mono-hydroxylated phthalonitriles and minimize the possibility of producing other phthalonitriles, the equivalent ratio was adjusted as ditosylated phthalonitrile: non hydroxylated thiol: hydroxylated thiol ratio of 1:1.5:0.5. This ratio is chosen on the assumption that the two thiols, assuming they have same reactivity, and ditosylated phthalonitrile, when mixed in a 1:1:1 mole ratio theoretically would give 25% dihydroxylated phthalonitrile, 25% non-hydroxylated phthalonitrile, and 50% mono-hydroxylated phthalonitrile yield. The synthetic process conditions were applied completely the same as the ones applied in the synthesis of dihydroxylated phthalonitriles, and for the same reasons too.

The synthesis of di-substituted mono-hydroxylated phthalonitriles **5-8** results in a low yield, specifically between 7-11% (Table 3.1) regardless the difference of the used thiols. The low yield is due to the formation of two other possible phthalonitriles: di-thiosubstituted phthalonitrile and di-thiosubstituted di-hydroxylated phthalonitrile. These additional compounds complicate the reaction and reduce the overall yield of the desired product. Furthermore, the purification process of these compounds presents significant challenges and even requires more than three separate silica gel columns.

The synthesis of phthalonitriles **5-8** is illustrated in Scheme 3.4, and their respective yields are presented in Table 3.2.



Scheme 3.4: Synthesis of di-substituted mono-hydroxylated Phthalonitriles **5-8** in DMF.

Table 3.2: Experimental yields of monohydroxylated phthalonitriles.

Compound	Yield (%)
5	11
6	7
7	8
8	7

The characterization of the phthalonitriles **5-8** was accomplished through various techniques such as FT-IR and $^1\text{H}/^{13}\text{C}$ NMR.

FT-IR spectra corresponding to di-substituted mono-hydroxylated phthalonitriles **5-8** are depicted in figure 3.2. Each spectrum exhibits characteristic peaks indicative of various bond types.

In each spectrum, $\text{C}\equiv\text{N}$ bonds (around 2223 cm^{-1}), aliphatic C-H bonds (between $2960\text{--}2860\text{ cm}^{-1}$), aromatic C-H bonds (around 3050 cm^{-1}), C=C bonds (around 1580 cm^{-1}) and -OH bonds as broad peaks (between $3425\text{--}3330\text{ cm}^{-1}$) can be seen clearly.

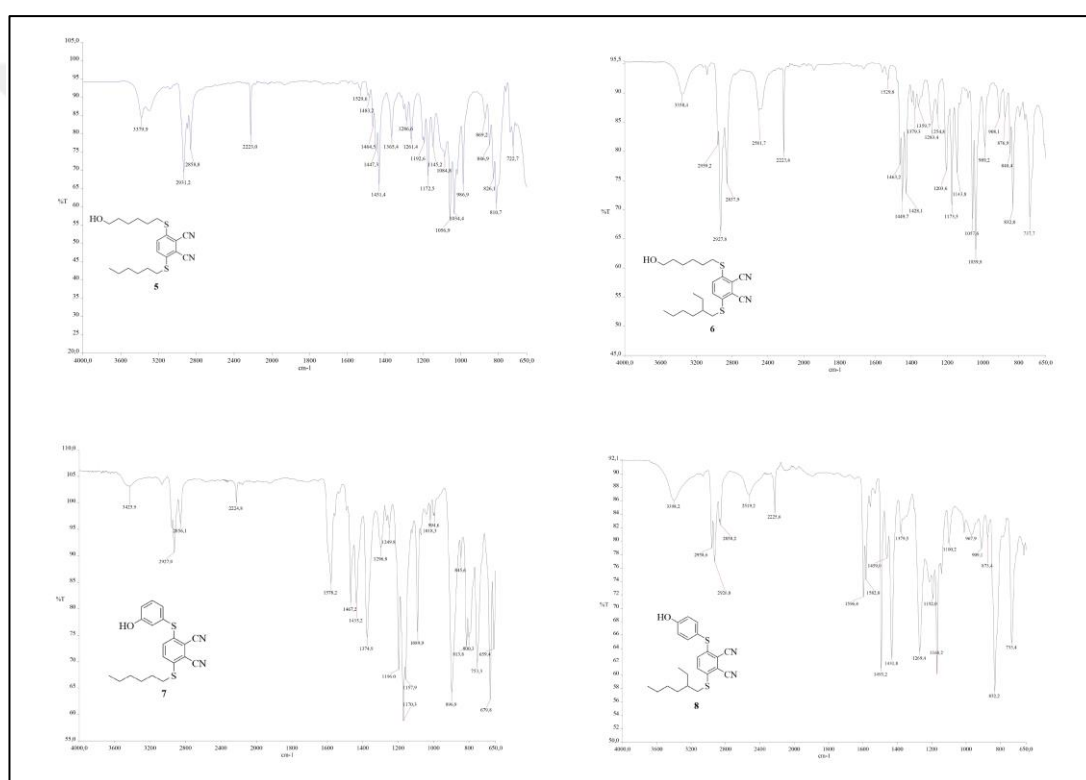


Figure 3.2: FT-IR spectrum of di-substituted mono-hydroxylated phthalonitrile **5-8**.

Figure 3.3 present the $^1\text{H}/^{13}\text{C}$ NMR spectra of di-substituted mono-hydroxylated phthalonitrile **5**. The ^1H NMR spectrum shows the presence of aliphatic protons - CH_2CH_3 , - $\text{S-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-OH}$ and - $\text{S-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, which are part of hexyl groups. The methyl protons are observed at $\delta = 0.82\text{ ppm}$ and the methylene protons are observed at $\delta = 1.23\text{--}1.65\text{ ppm}$. The spectrum also shows clearly the - $\text{S-CH}_2\text{CH}_2\text{-}$ protons at $\delta = 2.974\text{ ppm}$ (t, - $\text{S-CH}_2\text{CH}_2\text{-}$) and $\text{CH}_2\text{CH}_2\text{-OH}$

protons at $\delta = 3.58$ ppm (t, $\text{CH}_2\text{CH}_2\text{-OH}$). While both of hydroxyl group and the aromatic protons can be seen at $\delta = 1.18$ and 7.43 ppm respectively.

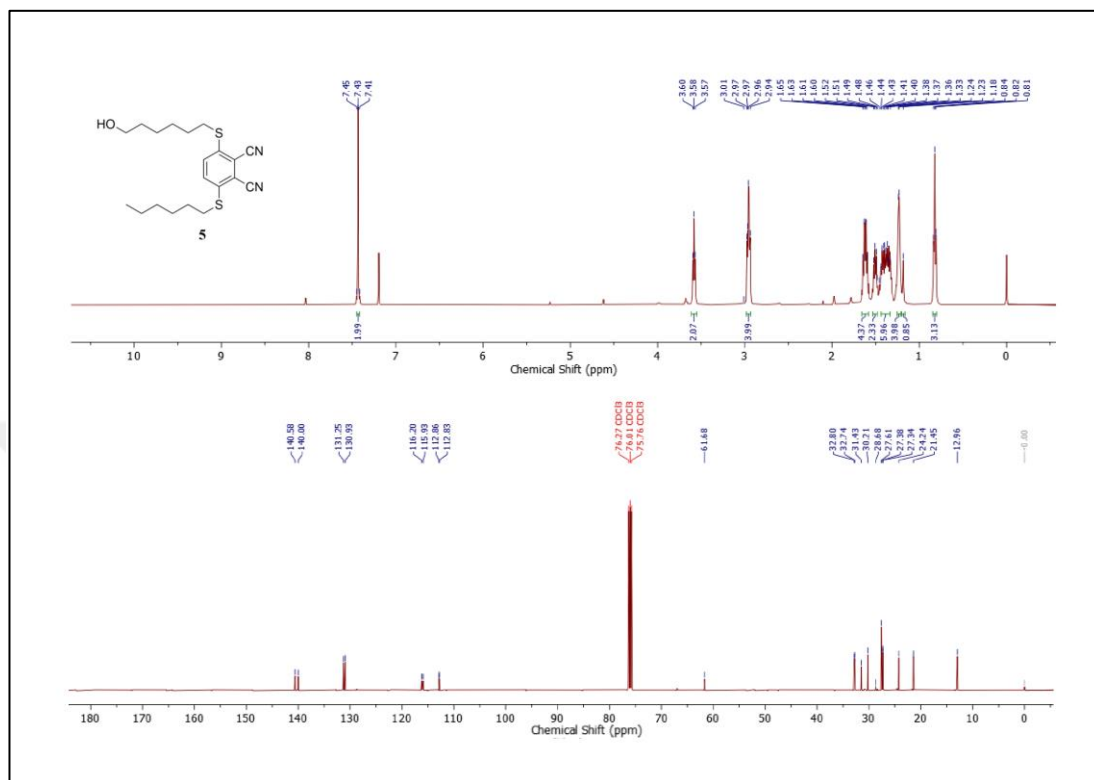


Figure 3.3: $^1\text{H}/^{13}\text{C}$ NMR spectra of di-substituted mono-hydroxylated phthalonitrile **5** in CDCl_3 .

The $^1\text{H}/^{13}\text{C}$ NMR spectra of di-substituted mono-hydroxylated phthalonitrile **6** are presented in Figure 3.4. The presence of aliphatic protons CH_2CH_3 , $-\text{S-CH}_2\text{CH}(\text{CH}_2\text{CH}_3)-$, $-\text{S-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-OH}$ and $-\text{S-CH}_2\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, which are part of hexyl groups, is shown by the ^1H NMR spectrum. Observations are made of the methyl protons at $\delta = 0.88$ ppm and the methylene protons at $\delta = 1.27\text{-}1.69$ ppm. The $-\text{S-CH}_2\text{CH}_2-$ protons at $\delta = 2.99$ ppm (t, $-\text{S-CH}_2\text{CH}_2-$) and $\text{CH}_2\text{CH}_2\text{-OH}$ protons at $\delta = 3.66$ ppm (t, $\text{CH}_2\text{CH}_2\text{-OH}$). The presence of hydroxyl group proton could not be observed clearly, as it overlapped with the aliphatic protons. While the aromatic protons can be seen as singlet peak at 7.50 ppm.

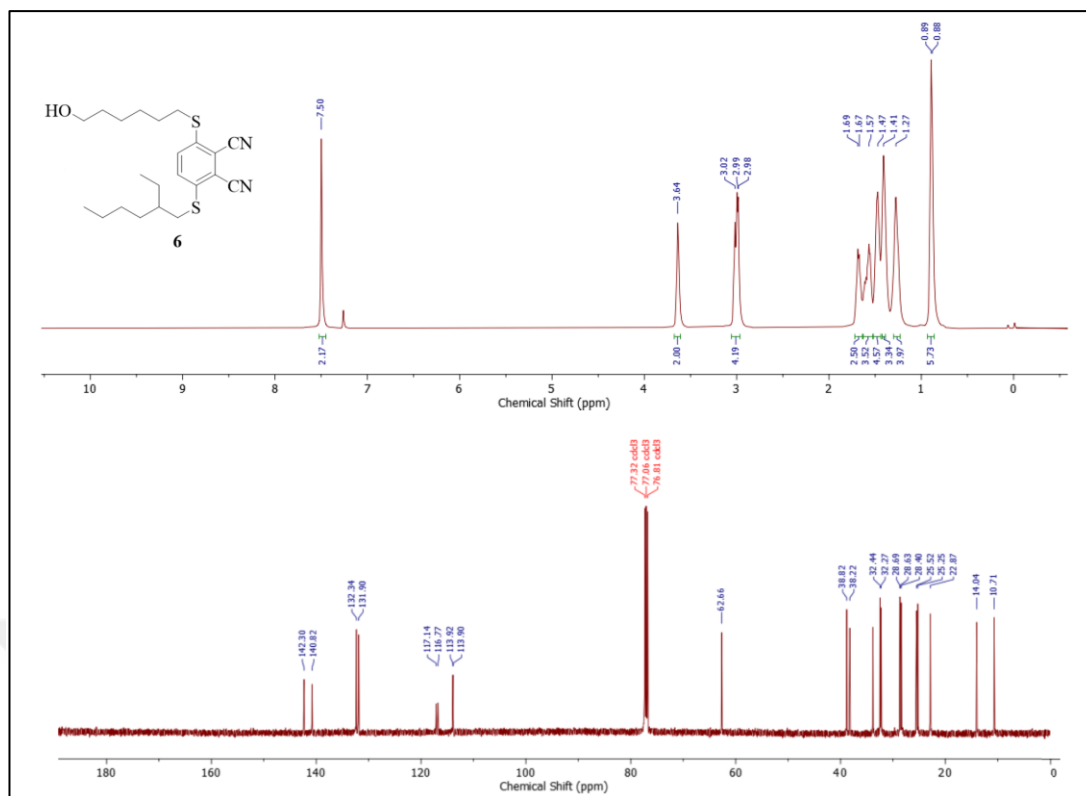


Figure 3.4: ¹H/¹³C NMR spectra of di-substituted mono-hydroxylated phthalonitrile **6** in CDCl₃.

The ¹H/¹³C NMR spectra of di-substituted mono-hydroxylated phthalonitrile **8** are presented in Figure 3.5. The ¹H NMR spectrum shows the presence of the methyl and methylene groups protons -S-CH₂CH(CH₂CH₃)CH₂CH₂CH₂CH₃, at δ= 0.88 ppm and at δ= 1.27-1.60 ppm respectively. The -S-CH₂CH- protons at δ= 2.96 ppm (d, -S-CH₂CH-). The presence of the hydroxyl group proton is observed at δ= 6.44 ppm and the aromatic protons can be seen as in the range 6.98-7.40 ppm.

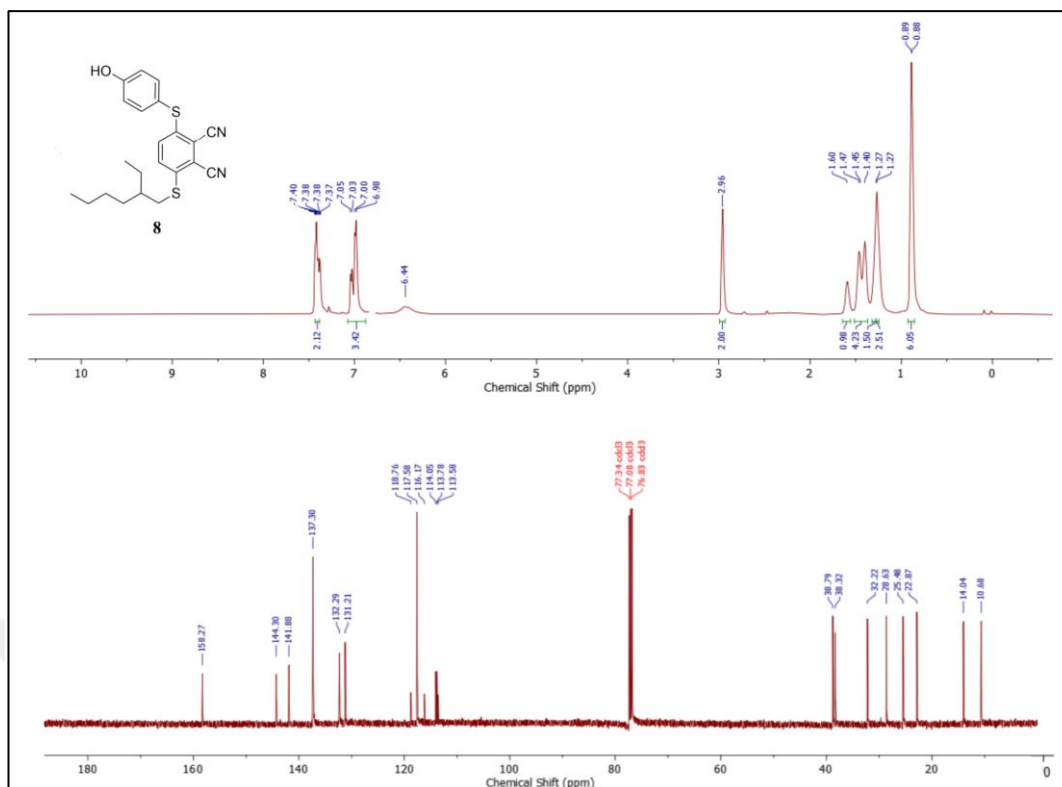


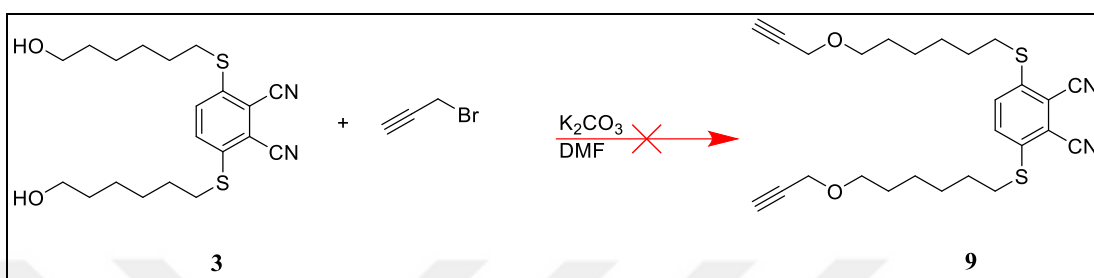
Figure 3.5: $^1\text{H}/^{13}\text{C}$ NMR spectra of di-substituted mono-hydroxylated phthalonitrile **8** in CDCl_3 .

3.1.2.3. Synthesis and Characterization of Propargylated Phthalonitriles

All phthalocyanines bear propargyl groups, making it crucial to graft the propargyl group onto hydroxylated phthalonitriles following Route A in Figure 3.1. This can be achieved by reacting the hydroxylated phthalonitriles **3**, **6**, and **8** directly with propargyl bromide in DMF as a solvent, in the presence of anhydrous potassium carbonate or sodium hydride.

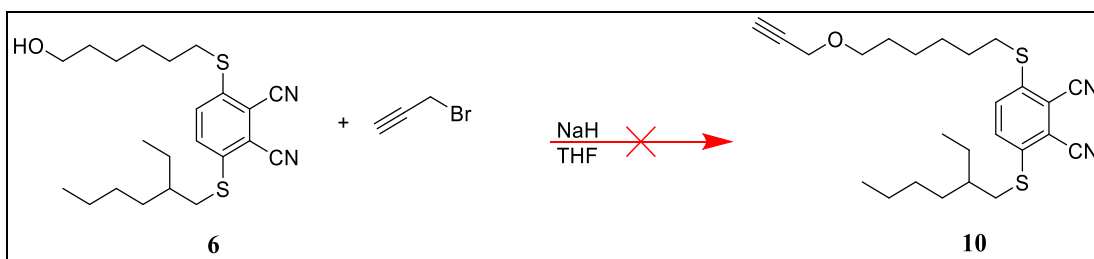
Dipropargylated phthalonitrile 9: The synthesis of dipropargylated phthalonitrile **9** was attempted using dihydroxylated phthalonitrile **3** (1 equiv.) and propargyl bromide (2 equiv.) in DMF as a solvent, in the presence of anhydrous potassium carbonate Scheme 3.5. The mixture was stirred overnight at room temperature. The completion of the reaction was monitored by TLC, which confirmed the consumption of dihydroxylated phthalonitrile **3**. The reaction mixture was then poured into water and filtered. The crude product was purified using a silica gel column, and the collected

fractions were checked by MALDI-TOF MS, and none of them showed the corresponding molecular mass of the dipropargylated phthalonitrile **9**. Meanwhile, the FT-IR spectra showed a peak at (3280 cm^{-1}), which indicates the propargyl group $\text{C}\equiv\text{C}-\text{H}$, and an unexpected sharp peak at (1774 cm^{-1}), which made the analysis of the structure more challenging.



Scheme 3.5: Synthesis of dipropargylated phthalonitrile **9** in DMF.

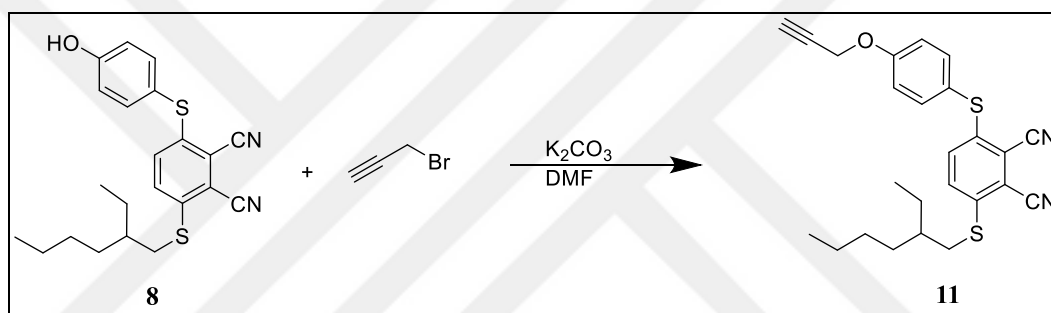
Mono propargylated phthalonitrile 10: An alternative approach was explored for the synthesis of mono propargylated phthalonitrile **10** from mono hydroxylated phthalonitrile **6**. This method involved the use of sodium hydride in THF as a solvent, instead of potassium carbonate in DMF as it shown in Scheme 3.6. The reaction was allowed to stir at room temperature overnight, and the completion of mono hydroxylated phthalonitrile **6** was verified using TLC. The reaction was then terminated by adding it to crushed ice, and the resulting crude product was filtered out. The crude product was found to be insoluble in most organic solvents, including ethanol, DMSO, and DCM, and its insolubility prevented any further purification and characterization. The unexpected insolubility of **10**, coupled with the presence of the sensitive propargyl group, resulted in self-polymerization.



Scheme 3.6: Synthesis of mono propargylated phthalonitrile **10** in THF.

Propargylation of dihydroxylated phthalonitrile **3** and mono hydroxylated phthalonitrile **6** aimed to achieve, but these attempts gave negative results due to the presence of the alkyl chains that reduced the reactivity of the hydroxyl group. Therefore, it was decided to apply the same procedure to mono hydroxylated phthalonitrile **8**, which bears a phenyl group.

Mono propargylated phthalonitrile 11: The attempt to synthesize mono propargylated phthalonitrile **11** from mono hydroxylated phthalonitrile **8** gave a positive outcome. Mono hydroxylated phthalonitrile **8** (1 equiv.) was used along with propargyl bromide (1 equiv.) in DMF as a solvent, in the presence of anhydrous potassium carbonate Scheme 3.7.



Scheme 3.7: Synthesis of propargylated phthalonitrile **11** in DMF.

The consumption of mono hydroxylated phthalonitrile **8** was verified by TLC. Subsequently, the reaction mixture was added to water and the crude product was filtered out. The crude product was then purified using a silica gel column and yielded 73%. The collected fraction was analysed by FT-IR Figure 3.6, which clearly showed the expected values, confirming the presence of propargyl group -C≡C-H bond (3292.4 cm⁻¹) and cyano groups -C≡N bond (2223.7 cm⁻¹).

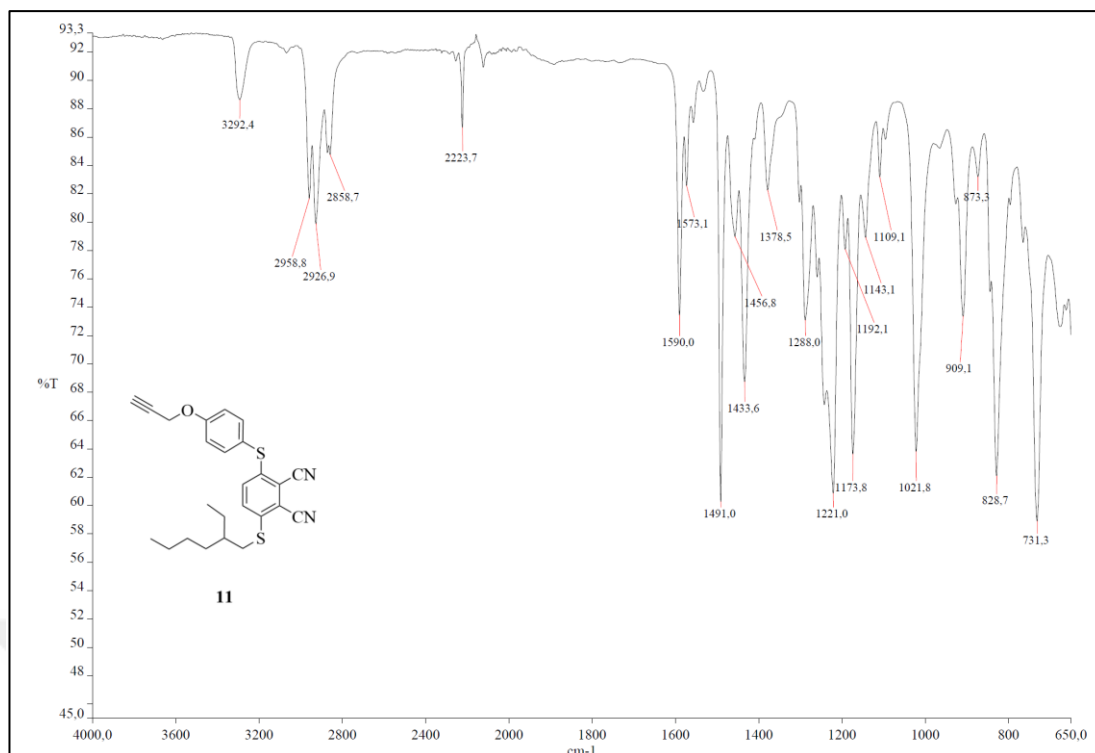


Figure 3.6: FT-IR spectrum of propargylated phthalonitrile **11**.

The exact structure of mono propargylated phthalonitrile **11** is doubly confirmed by ^1H and ^{13}C NMR as it shown in Figure 3.7.

The presence of aliphatic protons CH_2CH_3 , $-\text{S}-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)-$, and $-\text{S}-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, which are part of alkyl group, is shown by the ^1H NMR spectrum. Observations are made of the methyl protons at $\delta = 0.89$ ppm and the methylene protons at $\delta = 1.27$ - 1.59 ppm. The $-\text{S}-\text{CH}_2\text{CH}-$ protons are observed at $\delta = 2.96$ ppm (d, $-\text{S}-\text{CH}_2\text{CH}_2-$) and $\text{CH}\equiv\text{CCH}_2\text{-O-}$ protons are observed at $\delta = 2.58$ ppm (s, $\text{CH}\equiv\text{CCH}_2\text{-O-}$) and at $\delta = 4.76$ ppm (s, $\text{CH}\equiv\text{CCH}_2\text{-O-}$). While the aromatic protons can be observed at 7.04 - 7.51 ppm.

The successful synthesise of mono propargylated phthalonitrile **11** was due to the phenol exhibits greater acidity than alcohols because the phenoxide ion is stabilised through resonance. The acidity of phenol is enhanced by the presence of an electron-withdrawing group, which stabilises the phenoxide ion. Conversely, the presence of an electron-donating group reduces the acidity of phenol by destabilising the phenoxide ion.

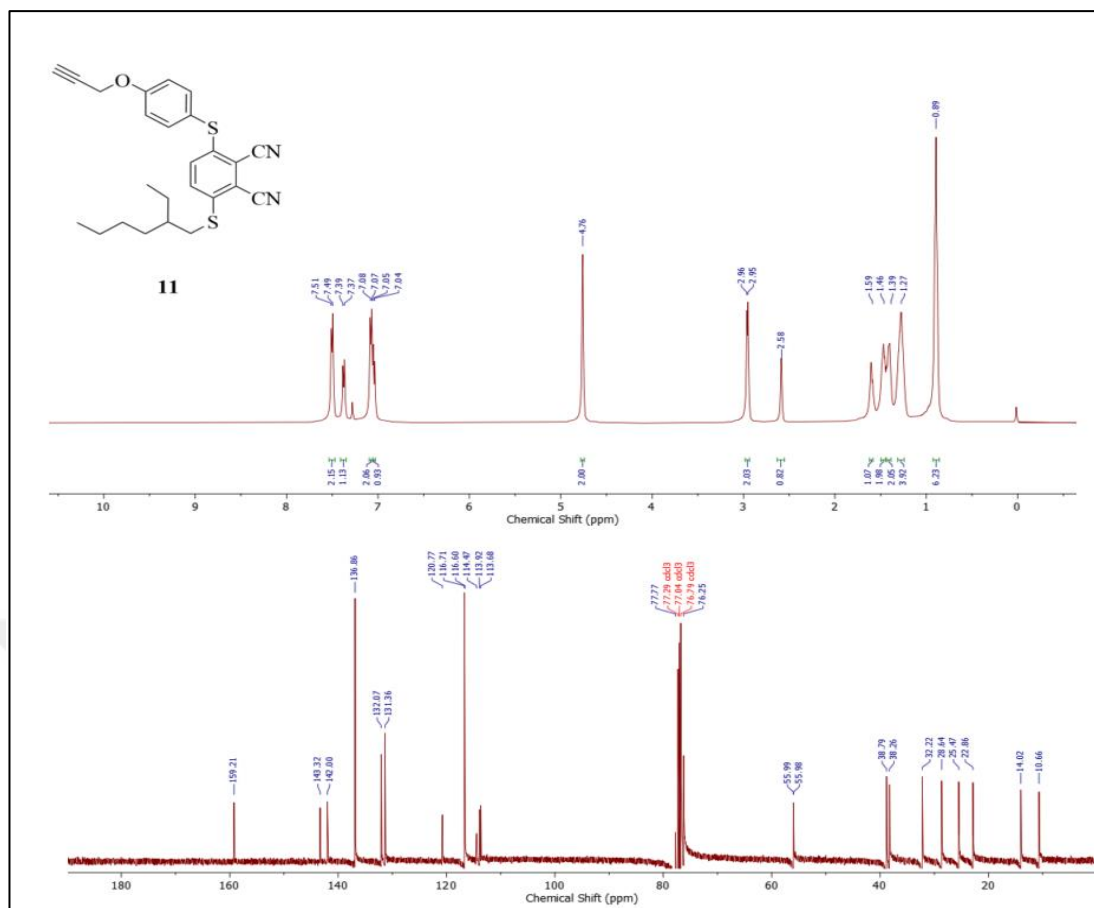
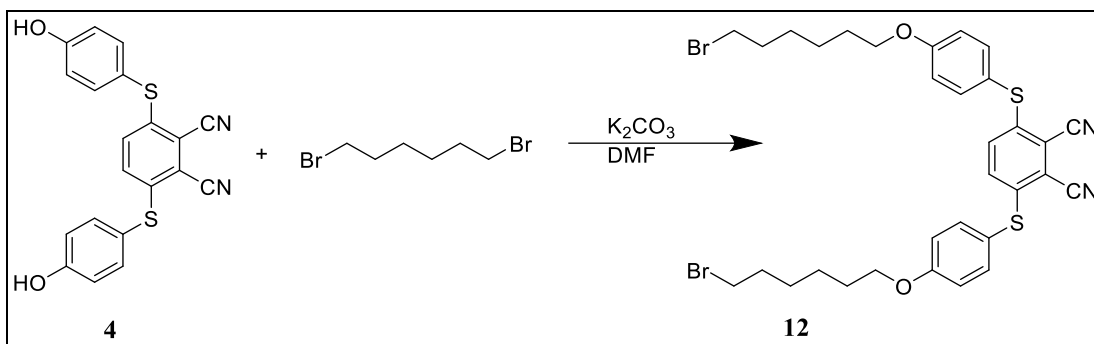


Figure 3.7: ¹H and ¹³C NMR spectra of propargylated phthalonitrile **11** in CDCl₃.

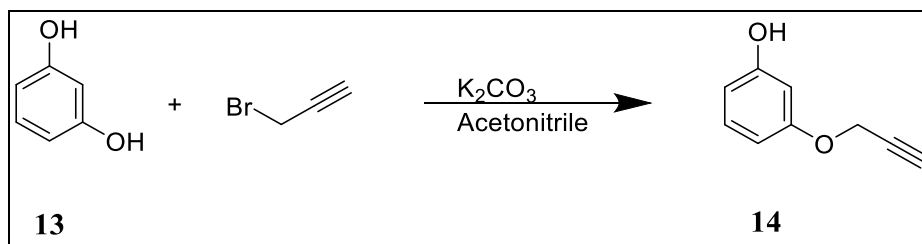
Dipropargylated phthalonitrile 15: The dihydroxylated phthalonitrile **4** (1 equiv.) was first reacted with 1,6-dibromohexane (4 equiv.) to ensure that the substitution occur on side of 1,6-dibromohexane. The reaction was done in the presence of anhydrous potassium carbonate in DMF as a solvent. This mixture was stirred at room temperature overnight Scheme 3.8. The consumption of dihydroxylated phthalonitrile **4** was verified by TLC. Subsequently, the reaction mixture was poured into water and filtered. The resulting crude product of dibromohexyl phthalonitrile **12** was used in the subsequent step without any additional purification.

The objective of this step is to extend the alkyl chain length, which could enhance the solubility of the associated propargylated phthalocyanine. It was reported that the propargylated phthalocyanine, synthesised from dipropargylated phenylthiophthalonitrile, exhibits low solubility in common organic solvents such as THF, DCM, chloroform, dimethylacetamide (DMAC), and N-methylpyrrolidone (NMP) [153].



Scheme 3.8: Synthesis of phthalonitrile **12** in DMF.

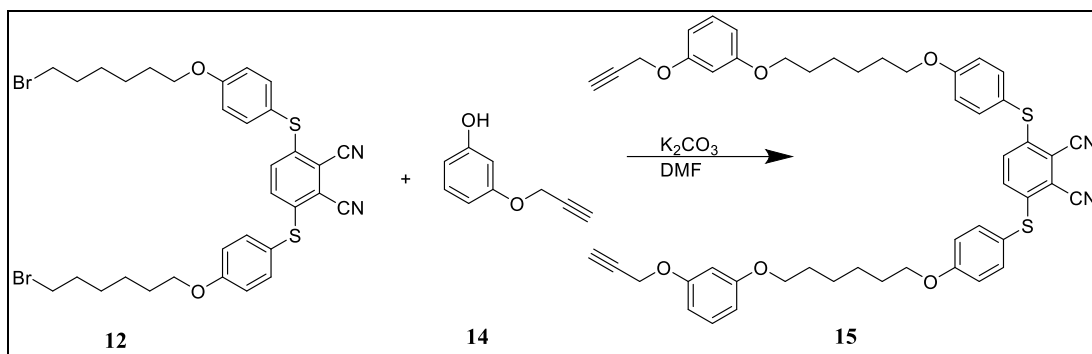
The propargylation reagent, mono propargylated resorcinol **14**, which is intended to react with dibromohexyl phthalonitrile **12**, was synthesized in a single-step reaction. This reaction began with resorcinol **13** (1 equiv.) and propargyl bromide (1 equiv.) and was facilitated by potassium carbonate in acetonitrile as a solvent Scheme 3.9. The reaction mixture was refluxed for 5 hours at 82°C. The reaction was then terminated by pouring it into water, and the crude product was purified with a silica gel column. The collected product was an oily yellow substance with a yield of 28%. The structure of the final product, mono propargylated resorcinol **14**, was confirmed by FT-IR and $^1\text{H}/^{13}\text{C}$ NMR and all the spectrums were matching the reported values [154].



Scheme 3.9: Synthesis of mono propargylated resorcinol **14** in acetonitrile.

The propargylated phthalonitrile **15** was finally synthesized by reacting dibromohexyl phthalonitrile **12** (1 equiv.) and mono propargylated resorcinol **14** (4 equiv.) in the presence of anhydrous potassium carbonate in DMF as a solvent Scheme 3.10. The reaction mixture was stirred overnight at room temperature. The consumption of dibromophthalonitrile **12** was monitored by TLC. After that, the reaction mixture was poured into water and filtered. The crude product was purified using a silica gel

column, yielding the final propargylated phthalonitrile **15** with a yield of 73%. The structure was confirmed by FT-IR and $^1\text{H}/^{13}\text{C}$ NMR.



Scheme 3.10: Synthesis of propargylated phthalonitriles **15** in DMF.

FT-IR spectrum corresponding to propargylated phthalonitrile **16** is depicted in Figure 3.8 exhibits characteristic peaks indicative of various bond types. $\text{-C}\equiv\text{N}$ bonds (around 2223 cm^{-1}), aliphatic C-H bonds (between $2930\text{--}2860\text{ cm}^{-1}$), aromatic C-H bonds (around 2960 cm^{-1}), C=C bonds (around 1590 cm^{-1}) and $\text{-C}\equiv\text{C-H}$ bonds (around 3295 cm^{-1}) can be seen clearly.

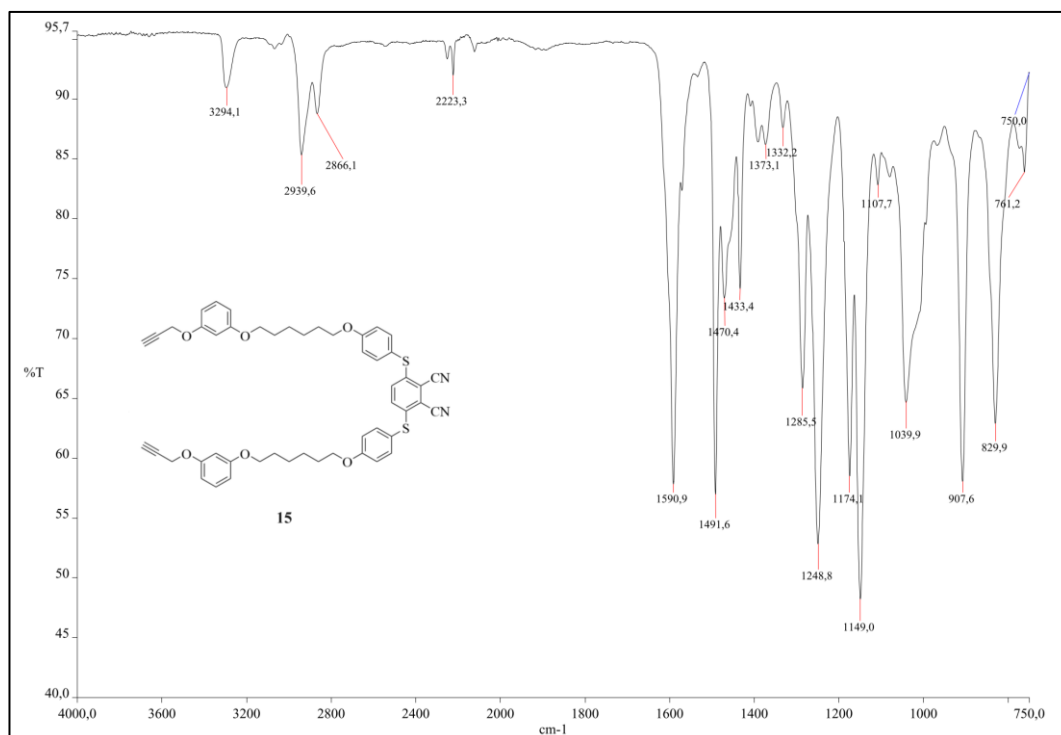


Figure 3.8: FT-IR spectrum of propargylated phthalonitrile **15**.

The $^1\text{H}/^{13}\text{C}$ NMR spectra of dipropargylated phthalonitrile **15** are presented in Figure 3.9. The ^1H NMR spectrum shows the presence of the methylene groups protons $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-$, at $\delta = 0.10$ - 1.83 ppm, $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-$ at $\delta = 3.97$ ppm and $\text{CH}\equiv\text{CCH}_2-\text{O}-$ at $\delta = 4.69$ ppm. The $\text{CH}\equiv\text{CCH}_2-\text{O}-$ proton was clearly observed at $\delta = 2.54$ ppm while the aromatic protons can be observed at the range between 6.55 - 7.42 ppm.

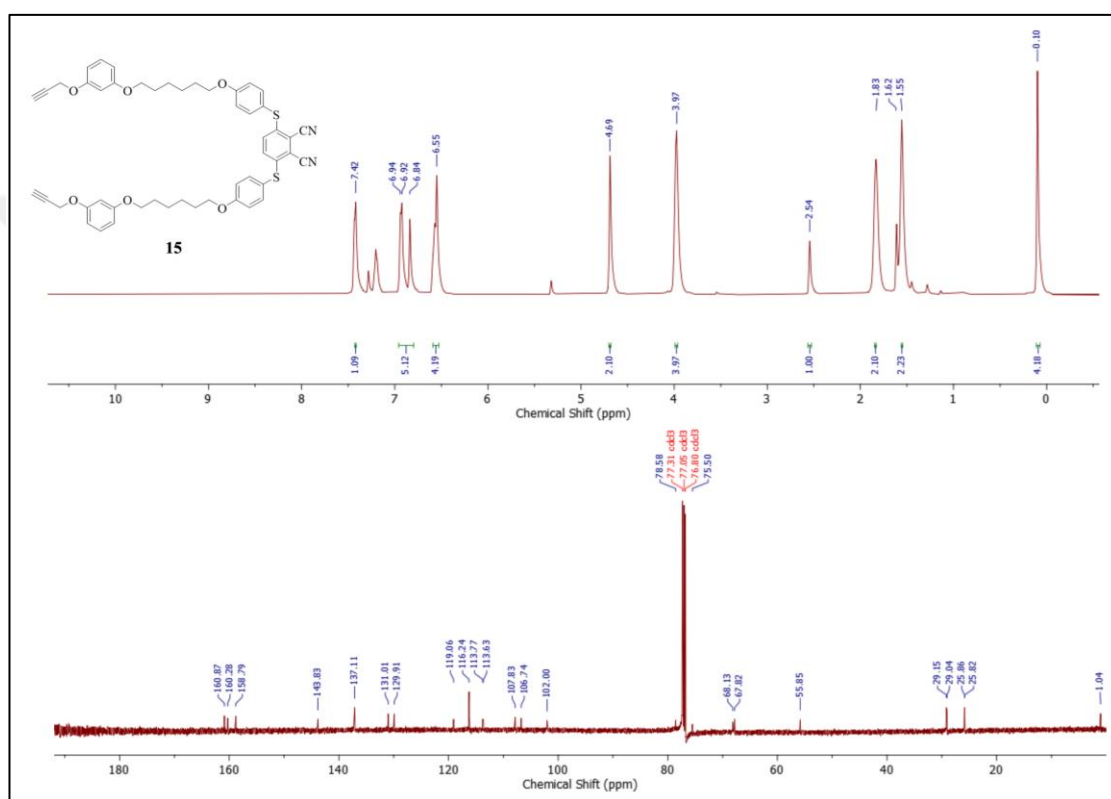


Figure 3.9: ^1H and ^{13}C NMR spectra of propargylated phthalonitrile **15** in CDCl_3 .

3.1.3. Synthesis and Characterization of Phthalocyanines

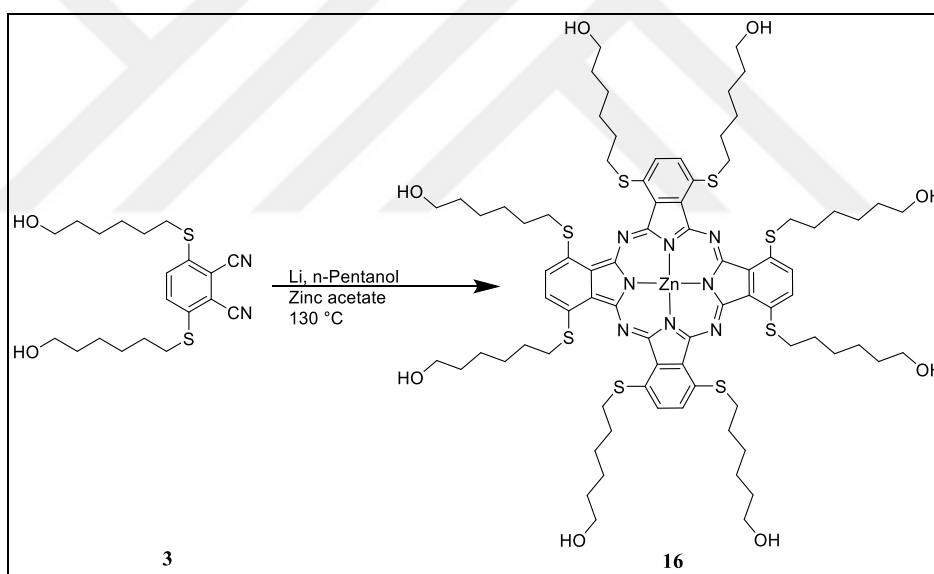
3.1.3.1. Synthesis and Characterization of Hydroxylated Phthalocyanines

Hydroxylated phthalocyanines **16**, **17**, and **18** are produced from their corresponding hydroxylated phthalonitriles **3**, **5**, and **6** respectively. The reaction involves the use of zinc acetate (4 equiv.) and lithium/n-pentanol (Scheme 3.11-13). The production of hydrogen gas, observed at the start of the reaction, indicates the formation of lithium

pentanoate, which acts as a base. A colour changes to green, observed approximately 2 minutes later in the reaction flask, signifies the cyclotetramerization and the creation of phthalocyanine. Zinc acetate is then added to the reaction mixture and left to reflux for 2 hours. All the reactions were terminated by pouring the reaction mixture into water and filtering out the precipitated crude product.

Hydroxylated phthalocyanines 16: The purification of octa hydroxylated phthalocyanine **17** was done by using a Soxhlet extractor. Initially, the compound was washed with DCM, followed by ethyl acetate. Finally, the purified octa hydroxylated phthalocyanine **16** was collected using ethanol and yielded of 35%

The structure of octa hydroxylated phthalocyanine **16**, which has been reported by Dumoulin and coll. [155], was verified solely through MALDI-TOF. The spectrum distinctly displayed the molecular peak of the phthalocyanine as shown in Figure 3.10.



Scheme 3.11: Synthesis of hydroxylated phthalocyanine **16** in n-pentanol.

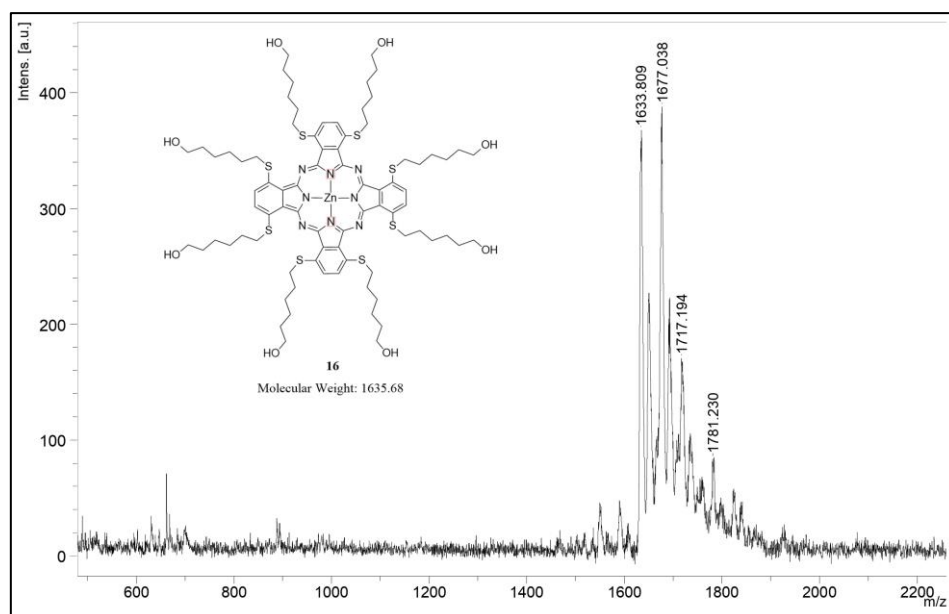
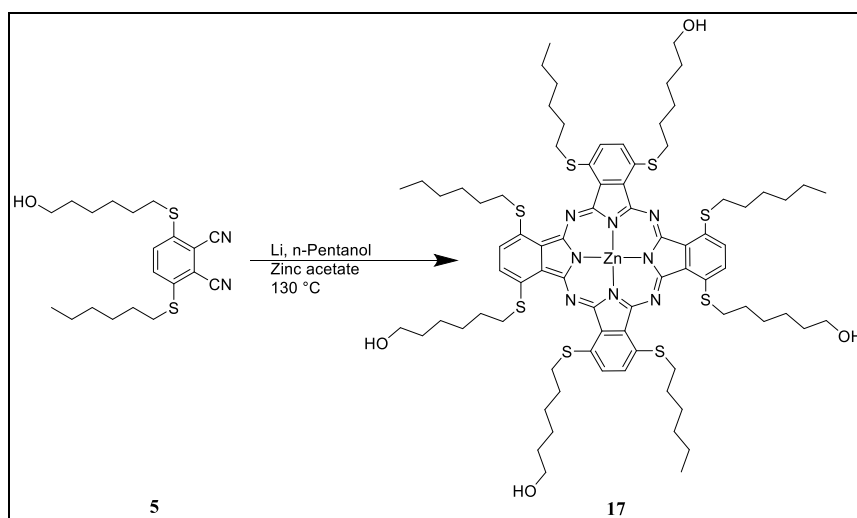


Figure 3.10: MALDI-TOF (Matrix: DIT) mass spectra of hydroxylated phthalocyanine **16**.

Hydroxylated phthalocyanines 17: The purification of tetra hydroxylated phthalocyanine **17** was carried out using a silica gel column, beginning with hexane as the eluent. The polarity was gradually increased by using DCM then ethanol due to the presence of four hydroxyl groups, extending the purification process to two weeks and its yielded 3%. The purified tetra hydroxylated phthalocyanine **17** was then characterized using MALDI-TOF as it is shown in Figure 3.11.



Scheme 3.12: Synthesis of hydroxylated phthalocyanine **17** in n-pentanol.

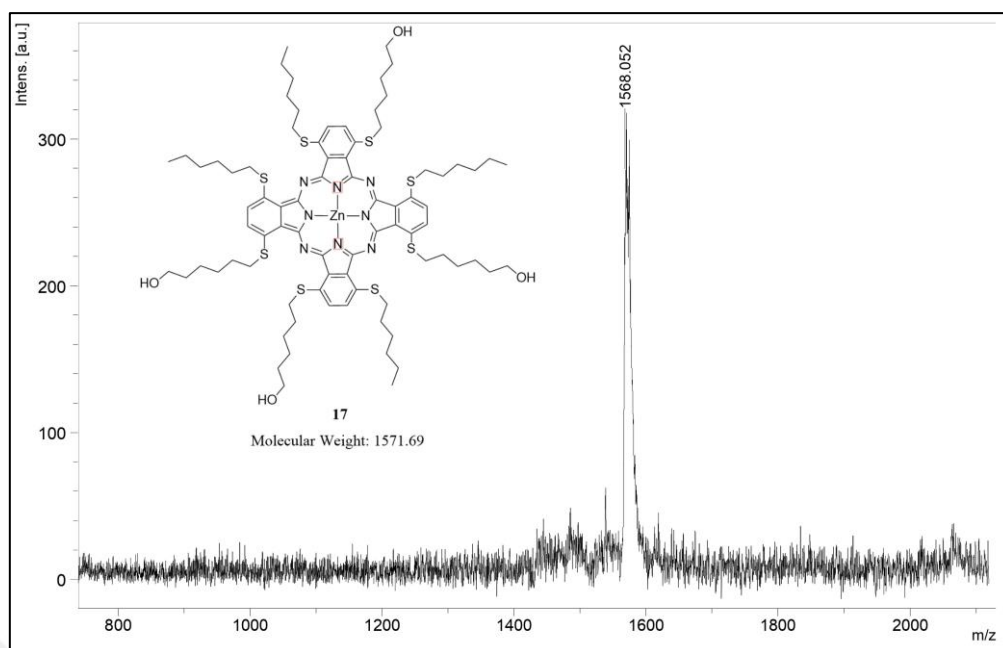


Figure 3.11: MALDI-TOF (Matrix: DHB) mass spectra of hydroxylated phthalocyanine **17**.

FT-IR spectra, as depicted in Figure 3.12, provide insights into the structure of the di-substituted mono-hydroxylated phthalonitrile **5**, and hydroxylated phthalocyanine **17**.

What can be observed clearly from FT-IR spectra is the hydroxyl stretching vibration frequency at 3322.9 cm^{-1} , associated with the phthalocyanine, with significant increase in the intensity and its width which indicates an increasing in the number of hydroxyl groups. While the peak of the $\text{-C}\equiv\text{N}$ groups at 2223 cm^{-1} , associated with the phthalonitrile, completely disappeared indicating that the cyclotrimerization process is facilitated through $\text{-C}\equiv\text{N}$ groups. The characteristic peaks of phthalocyanine ($\text{-C}=\text{C-}$ at 1640 cm^{-1} and -C=N- at 1690.7 cm^{-1}) can be observed clearly too. These observations affirm the successful cyclotrimerization process and the expected structure of the resulting hydroxylated phthalocyanine **17**.

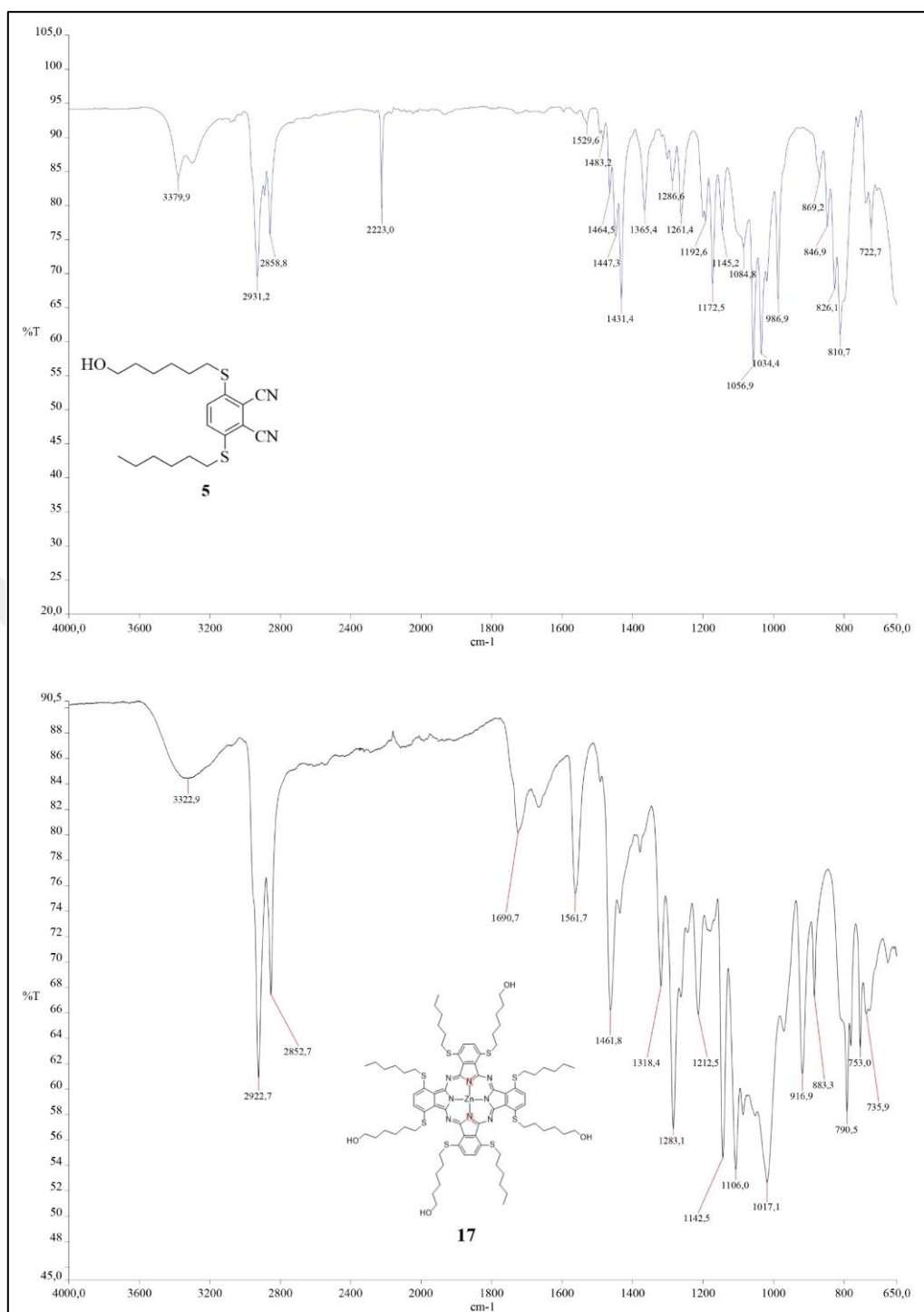


Figure 3.12: FT-IR spectrum of di-substituted mono-hydroxylated phthalonitrile **5**, and hydroxylated phthalocyanine **17**.

The ^1H NMR spectrum of hydroxylated phthalocyanine **17** is presented in Figure 3.13. The spectrum shows the presence of the aliphatic protons at $\delta = 0.50\text{--}2.00$ ppm and the $-\text{S}-\text{CH}_2\text{CH}_2$ protons at $\delta = 4.41$ ppm. The intensity of the aliphatic protons is significant

that it reduces the visibility of hydroxyl protons in the spectrum. While the aromatic protons can be seen clearly at $\delta = 7.42$ - 8.37 ppm.

An attempt was made to record ^{13}C NMR, but the low solubility of tetra hydroxylated phthalocyanine **17** prevented the addition of a sufficient amount to obtain a good spectrum.

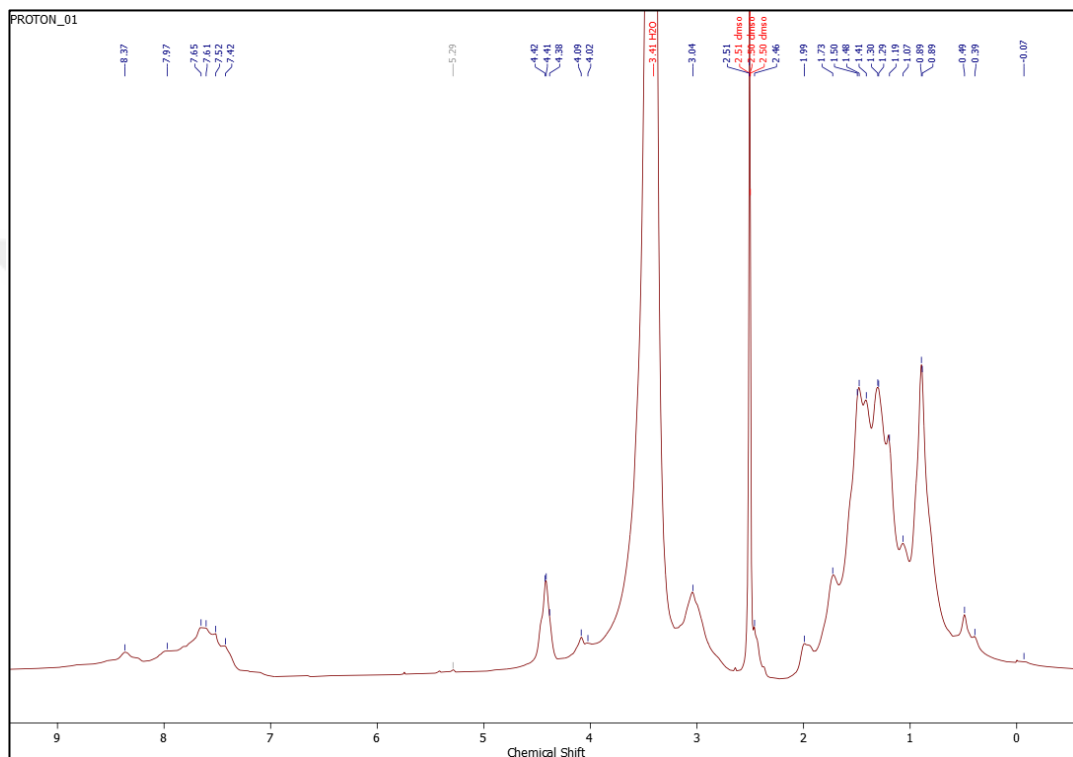
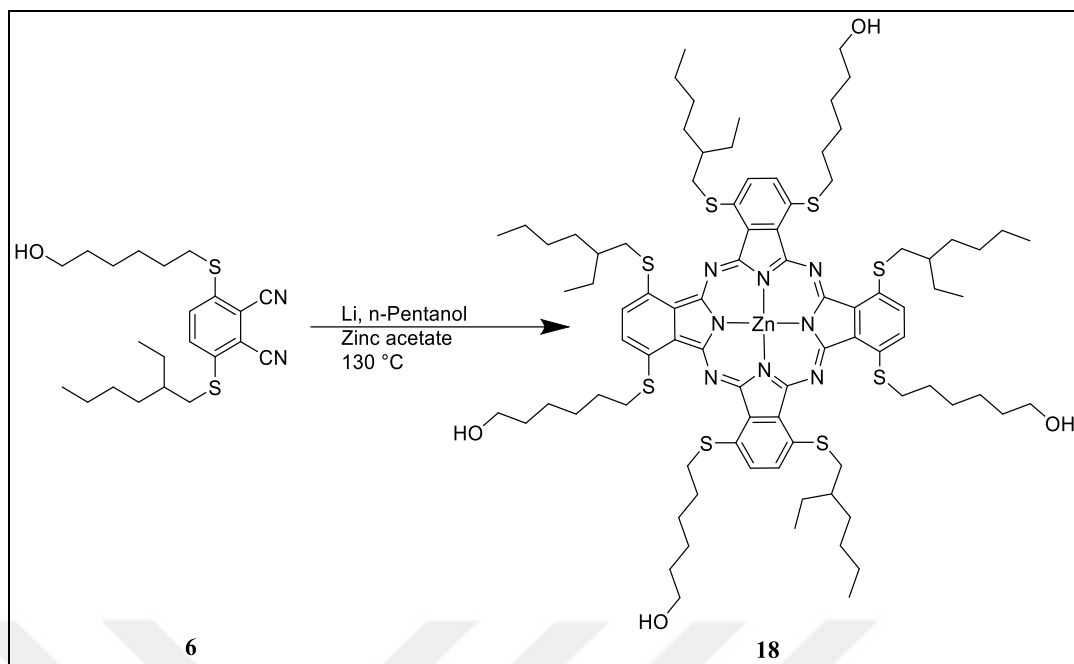


Figure 3.13: ^1H NMR spectrum of hydroxylated phthalocyanine **17** in $\text{DMSO-}d_6$.

Hydroxylated phthalocyanine 18: Tetra hydroxylated phthalocyanine **18** was purified using a silica gel column, but only 35 mg was collected, yielding 10%. The limited quantity prevented us from characterizing it via NMR, as it requires dissolving in $\text{DMSO-}d_6$ solvent and recovery would result in loss. Therefore, it was characterized by MALDI-TOF (Figure 3.14), which clearly showed the molecular peak of the corresponding phthalocyanine.



Scheme 3.13: Synthesis of hydroxylated phthalocyanine **18** in n-pentanol.

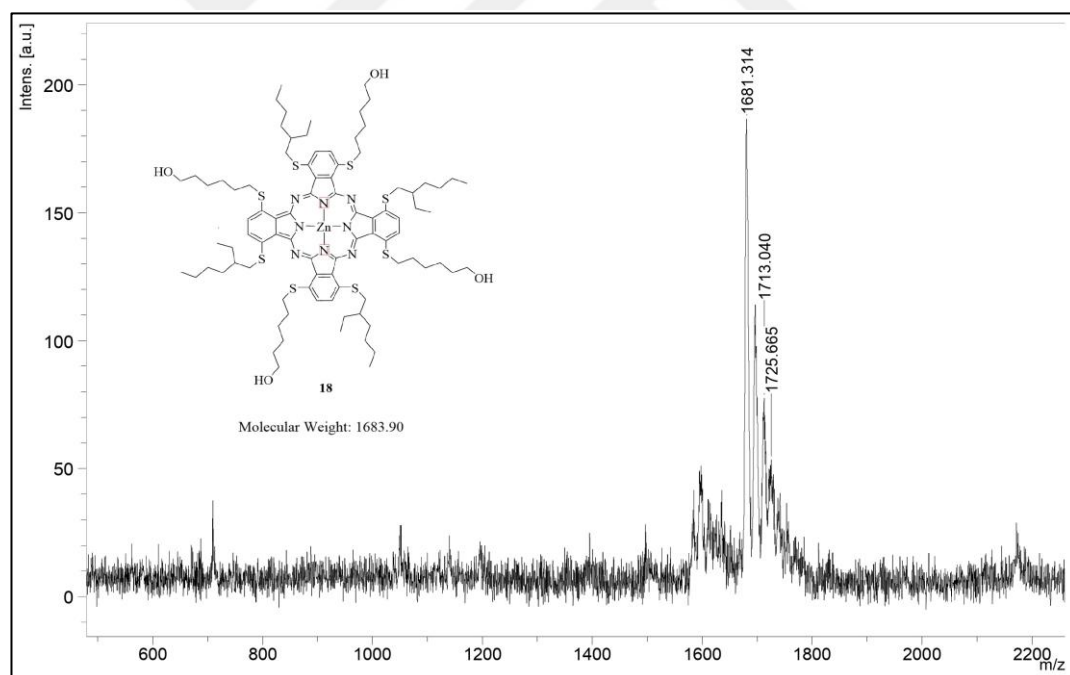


Figure 3.14: MALDI-TOF (Matrix: DIT) mass spectra of hydroxylated phthalocyanine **18**.

The FT-IR spectra, illustrated in Figure 3.15, shed light on the structure of the di-substituted mono-hydroxylated phthalonitrile **6** and hydroxylated phthalocyanine

18. From the FT-IR spectra, the hydroxyl stretching vibration frequency at 3406.2 cm^{-1} , linked to the phthalocyanine, is clearly visible. There is a notable increase in its intensity and width, suggesting an increase in the number of hydroxyl groups.

Conversely, the peak of the $\text{-C}\equiv\text{N}$ groups at (2223.6 cm^{-1}), related to the phthalonitrile, shows a decrease in intensity. This implies that the cyclotrimerization process is facilitated through $\text{-C}\equiv\text{N}$ groups.

The characteristic peaks of phthalocyanine (-C=C- and -C=N- at 1658.1 cm^{-1}) are also clearly visible. These observations confirm the successful cyclotrimerization process and the anticipated structure of the resulting hydroxylated phthalocyanine **18**.



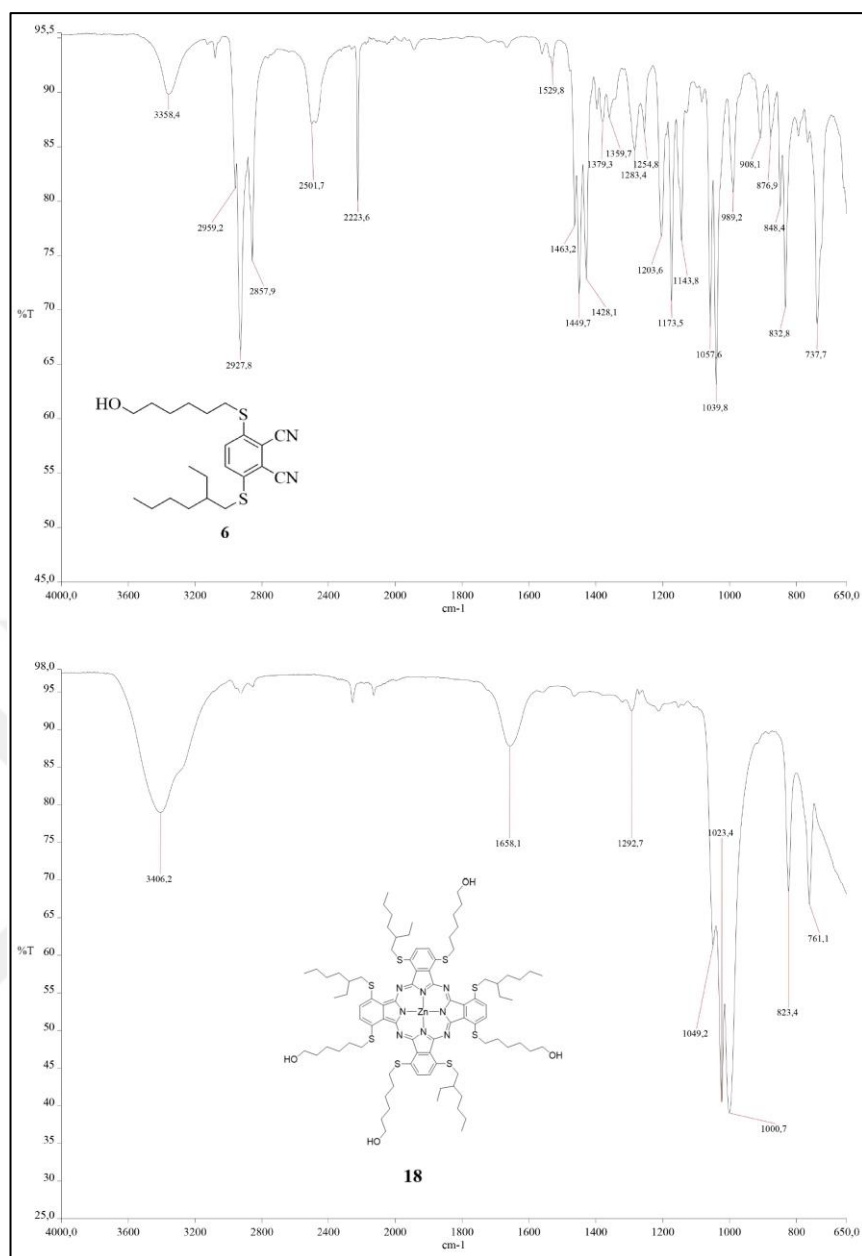


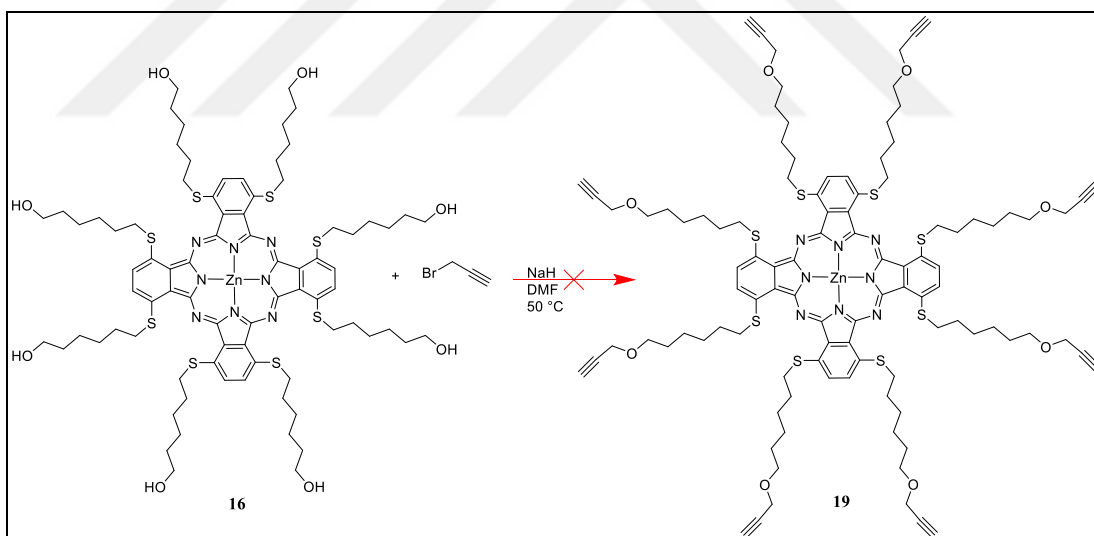
Figure 3.15: FT-IR spectrum of di-substituted mono-hydroxylated phthalonitrile **6** and hydroxylated phthalocyanine **18**.

3.1.3.2. Synthesis and Characterization of Propargylated Phthalocyanines

Since the objective of this study is to synthesize propargylated phthalocyanine and this attempted to be achieved via three different routes, each with its own unique process and intermediates.

Direct Propargylation of Hydroxylated Phthalocyanine: This method involves the direct propargylation of hydroxylated phthalocyanine **16** and **18**. In this approach, the hydroxyl group of the phthalocyanine is directly reacted with a propargyl bromide in the presence of a base, leading to the formation of the propargylated phthalocyanines **19** and **20**.

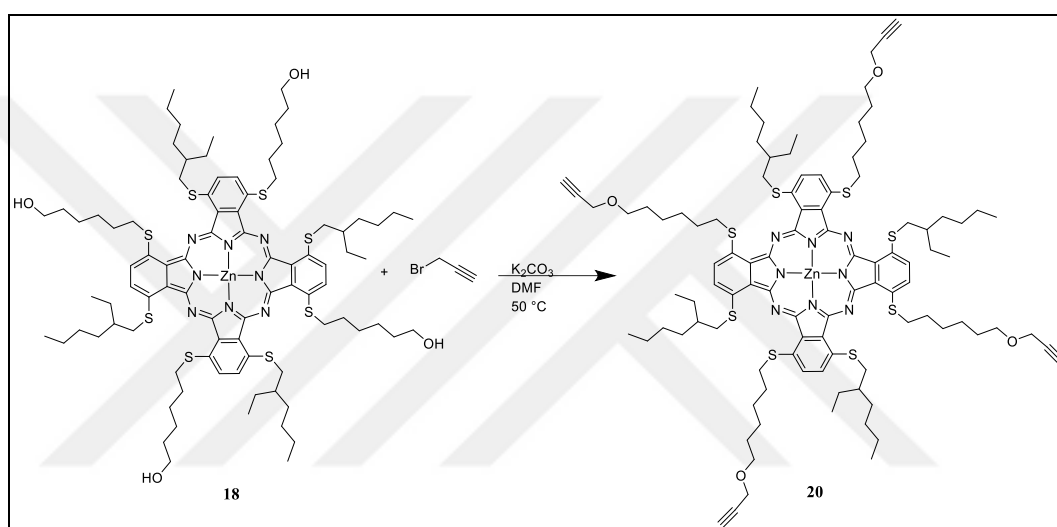
Octa propargylated phthalocyanine 19: An attempt was made to synthesize octa propargylated phthalocyanine **19** by dissolving octa hydroxylated phthalocyanine **16** (1 equiv.) in DMF. This was done in the presence of sodium hydride (16 equiv.), after which propargyl bromide (16 equiv.) was added to the reaction mixture. The mixture was then heated at 50 °C and left to stir overnight Scheme 3.14. The following day, the reaction mixture had solidified. The reaction was terminated by adding ethanol, after which it was found to be completely insoluble in most organic solvents. The crude quantity was recorded and found to be significantly more than the hydroxylated phthalocyanine **16** itself, indicating that polymerization likely occurred.



Scheme 3.14: Synthesis of propargylated phthalocyanine **19** in DMF.

Tetra propargylated phthalocyanine 20: A synthesis attempt was made for tetra propargylated phthalocyanine **20**, starting with the corresponding tetra hydroxylated phthalocyanine **18** (1 equiv. 35 mg). This was done in DMF with propargyl bromide (4 equiv.), in the presence of anhydrous potassium carbonate (4 equiv.). The reaction

was stirred at 50 °C overnight Scheme 3.15. The reaction was then terminated by adding water, and the crude product was filtered out. It was found that the quantity was just a few milligrams. The crude tetra propargylated phthalocyanine **20** was sent to MALDI-TOF before the purification, and the resulting spectrum clearly showed its molecular mass (Figure 3.16) along with other peaks which are corresponding to approximately the molecular weights of mono and tri propargylated phthalocyanines. The low yield obtained from tetra propargylated phthalocyanine **20**, along with the low quantity of the tetra hydroxylated phthalonitrile **18**, has posed challenges for this route.



Scheme 3.15: Synthesis of propargylated phthalocyanine **20** in DMF.

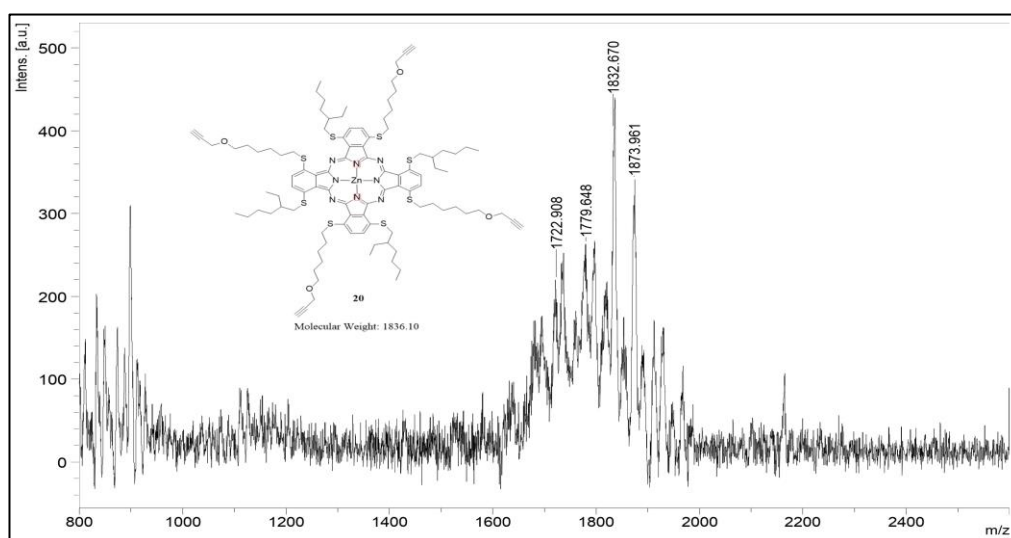
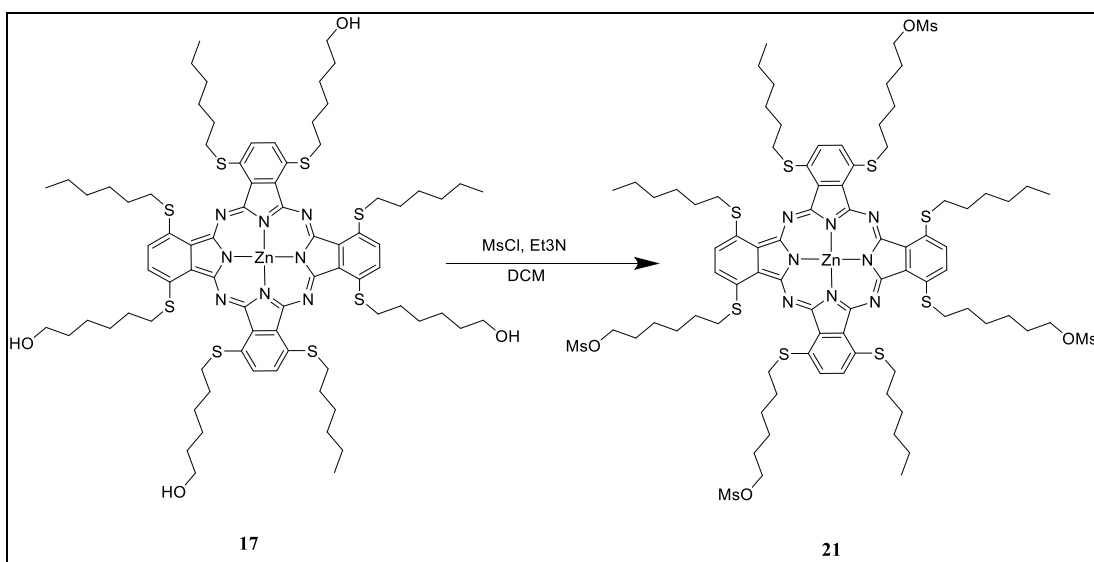


Figure 3.16: MALDI-TOF (Matrix: DIT) mass spectra of propargylated phthalocyanine **20**.

Mesylation Followed by Propargylation: This method involves an initial mesylation of the tetra hydroxylated phthalocyanine **17**. Mesylation, which involves the conversion of a hydroxyl group into a mesylate, serves as a preparatory step for the subsequent propargylation. The mesylate is a better leaving group than the hydroxyl, which can facilitate the propargylation reaction. After mesylation, the tetra mesylated phthalocyanine **21** is then reacted with a propargylated mono resorcinol to give the targeted tetra propargylated phthalocyanine **22** which has increased the length of the substituents, and this may affect formation and the yield of the propargylated phthalocyanine.

Tetra mesylated phthalocyanine **21** was synthesized by reacting tetra hydroxylated phthalocyanine **17** with methanesulfonyl chloride. This reaction was carried out in the presence of triethyl amine as a base and DCM as a solvent Scheme 3.16. The reaction mixture was stirred at room temperature overnight, after which it was terminated by adding water and filtering out the mixture. The crude product was collected, dried, and sent to MALDI-TOF, which clearly displayed the molecular weight of tetra mesylated phthalocyanine **21** Figure 3.17. The crude product was then used in the subsequent reaction without any additional purification.



Scheme 3.16: Synthesis of mesylated phthalocyanine **21** in DMF.

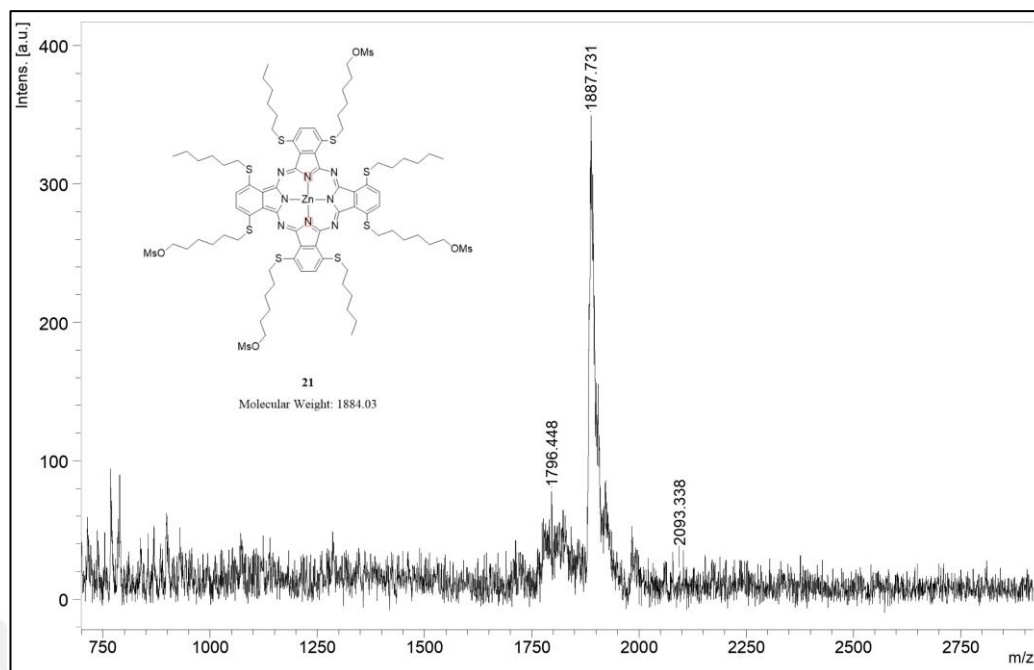
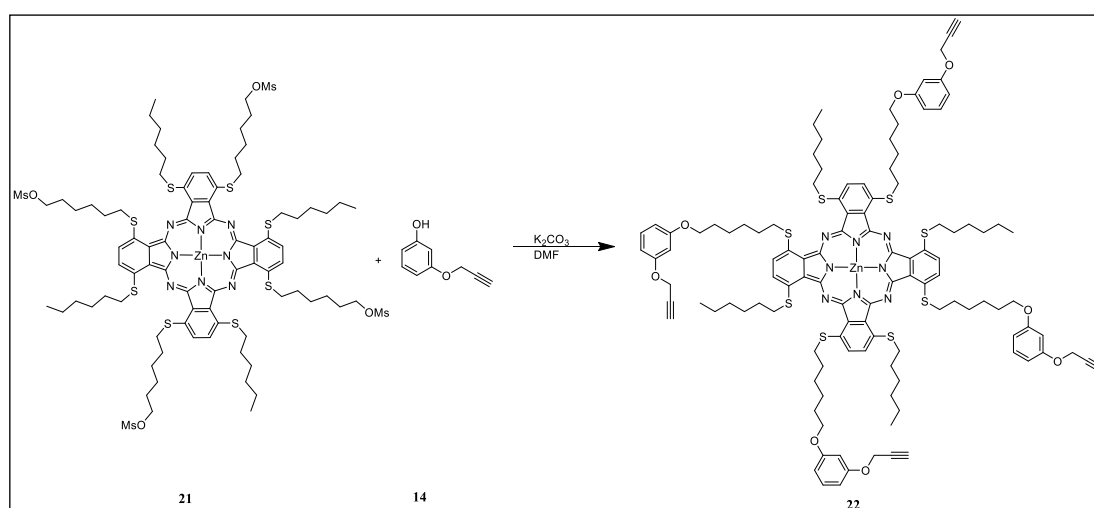


Figure 3.17: MALDI-TOF (Matrix: DIT) mass spectra of mesylated phthalocyanine **21**.

The mesylated phthalocyanine **21** (1 equiv.) was subjected to a reaction with mono propargylated resorcinol **14** (4 equiv.). This reaction was facilitated by anhydrous potassium carbonate in DMF, which served as the solvent. The reaction mixture was allowed to stir at room temperature overnight Scheme 3.17.



Scheme 3.17: Synthesis of propargylated phthalocyanine **22** in DMF.

The consumption of tetra mesylated phthalocyanine **22** was confirmed by TLC then a sample was extracted from the reaction mixture and analysed using MALDI-TOF. The spectrum shows the molecular peak of the formation of tetra propargylated phthalocyanine **22**, Figure 3.18 along with many peaks which are corresponding to the mono, di and tri propargylated phthalocyanines. This led to the belief that the substitution had not occurred on all the mesylate groups.

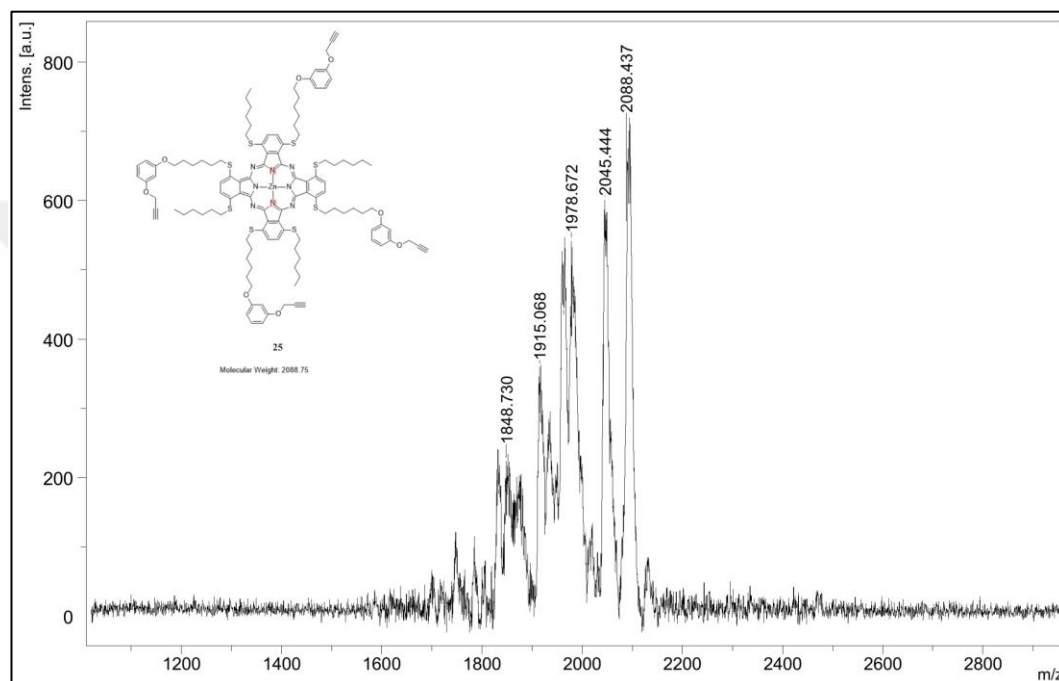
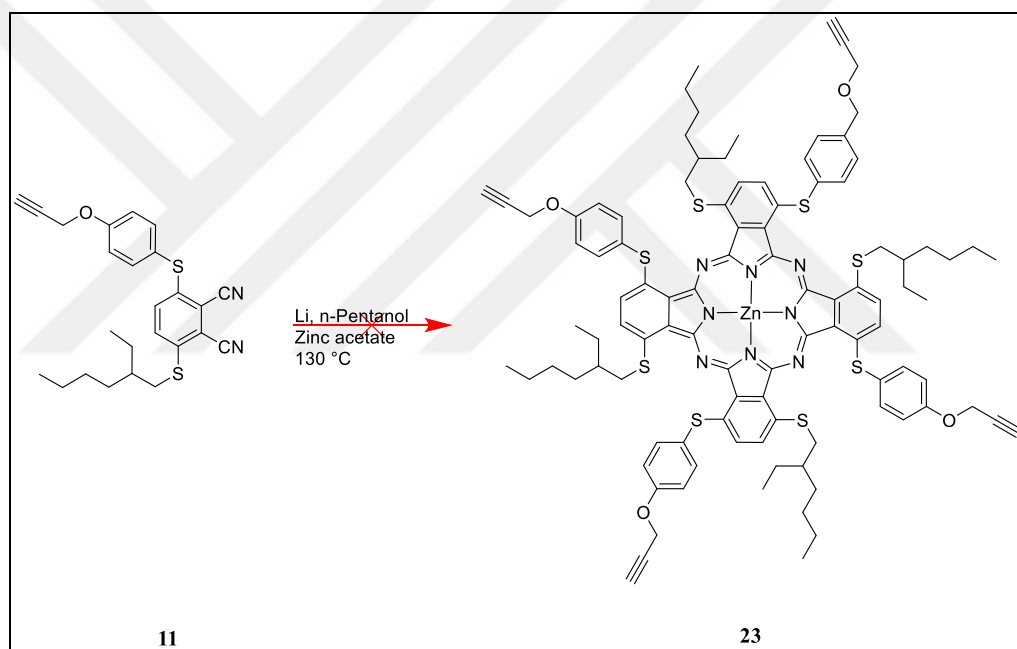


Figure 3.18: MALDI-TOF (Matrix: DIT) mass spectra of mesylated phthalocyanine **22**.

To address this, an additional amount of mono propargylated resorcinol **14** was introduced to the reaction mixture. The mixture was then stirred overnight. Despite these efforts, a subsequent sample analysis using MALDI-TOF showed no significant improvements.

From Propargylated Phthalonitriles: The third method involves the synthesis of propargylated phthalocyanine from propargylated phthalonitriles. This route involves the initial propargylated phthalonitriles **11** and **15**, followed by their cyclotetramerization to form the propargylated phthalocyanine **23** and **24** respectively. This method, while potentially more complex, might offer better control over the substitution pattern on the phthalocyanine ring.

Tetra propargylated phthalocyanine 23: An attempt was made to produce tetra propargylated phthalocyanine **23**. This reaction began with the dissolving mono propargylated phthalonitrile **11** (1 equiv.) in 10 mL of pentanol. Lithium metal was then introduced, and the mixture was stirred at 130 °C under an argon gas atmosphere. The formation of lithium pentanoate was confirmed by the release of hydrogen gas, then zinc acetate (2 equiv.) was added to the reaction mixture, which was then refluxed for an additional 2 hours. Finally, water was added to the reaction mixture after it had cooled. The formation of a yellow precipitate in the reaction mixture indicated that phthalocyanine had not formed. while TLC has confirmed that all the initial phthalonitrile had been completely consumed Scheme 3.18.



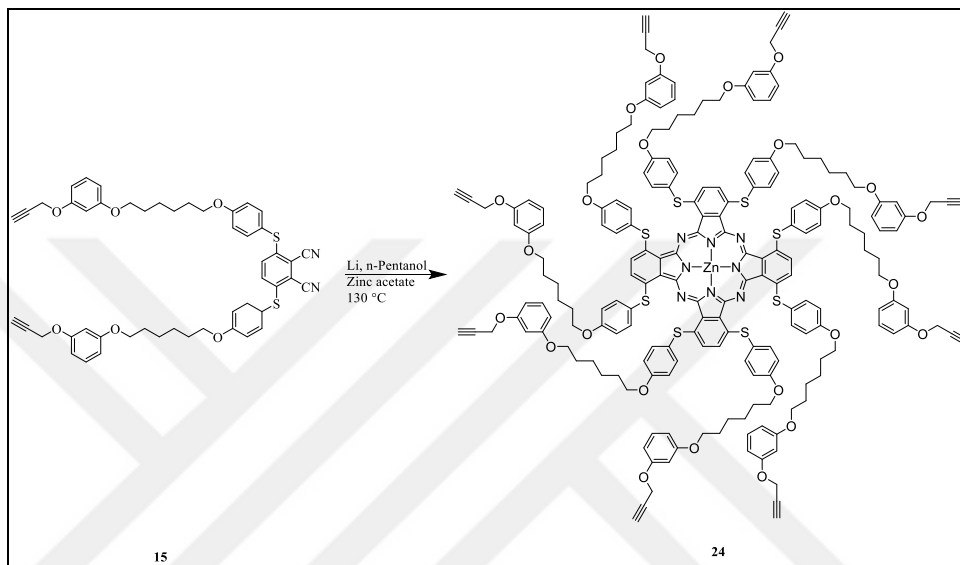
Scheme 3.18: Synthesis of propargylated phthalocyanine **23** in DMF.

Octa propargylated phthalocyanine 24: An attempt was made to synthesize octa propargylated phthalocyanine **24**, starting with dipropargylated phthalonitrile **15**. The synthesis was carried out in n -pentanol, using lithium pentanoate as a base. Zinc acetate was added to the reaction, which was then refluxed for a brief period of 15 mins to prevent polymerization via the highly sensitive propargyl group.

The reaction mixture was allowed to cool to room temperature and was then terminated by the addition of ethanol. The resulting dark precipitate was filtered out. A sample of

the crude product was sent for MALDI-TOF analysis, which confirmed the molecular weight of the octa propargylated phthalocyanine **24**.

Extending the length of the substituent chain and the short refluxing time were found to be optimal conditions for obtaining octa propargylated phthalocyanine. The process of purification and further characterization is still ongoing.



Scheme 3.19: Synthesis of propargylated phthalocyanine **24** in n-pentanol.

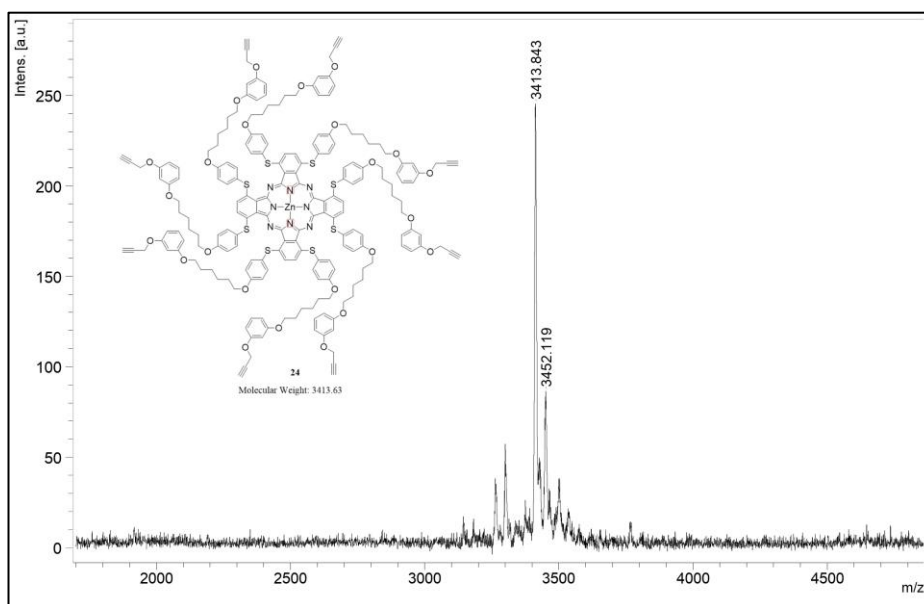


Figure 3.19: MALDI-TOF (Matrix: DIT) mass spectra of hydroxylated phthalocyanine **24**.

3.2. NIR-absorbing Phthalocyanine-centred Caprolactone Star Polymers

In the pursuit of synthesizing propargylated phthalocyanines, numerous obstacles were encountered despite extensive efforts. These challenges include the purification of the corresponding phthalonitrile, a low yield, and the sensitivity of the propargyl group, all of which culminated in unsuccessful results.

As a result, the decision was made to employ the successfully synthesized octa-thiosubstituted non-peripheral hydroxylated phthalocyanines. The hydroxyl group in these compounds was utilized as an initiator to open the ring of ϵ -caprolactone, with the aim of synthesizing star-shaped polycaprolactones while keeping the primary objective of this study which was to achieve a successfully synthesised molecules that absorb light in NIR region of the spectrum, equal or longer than 780 nm, which is preferred for PDT.

3.2.1. Synthesis and Characterization of Poly(ϵ -caprolactone) Star Polymers

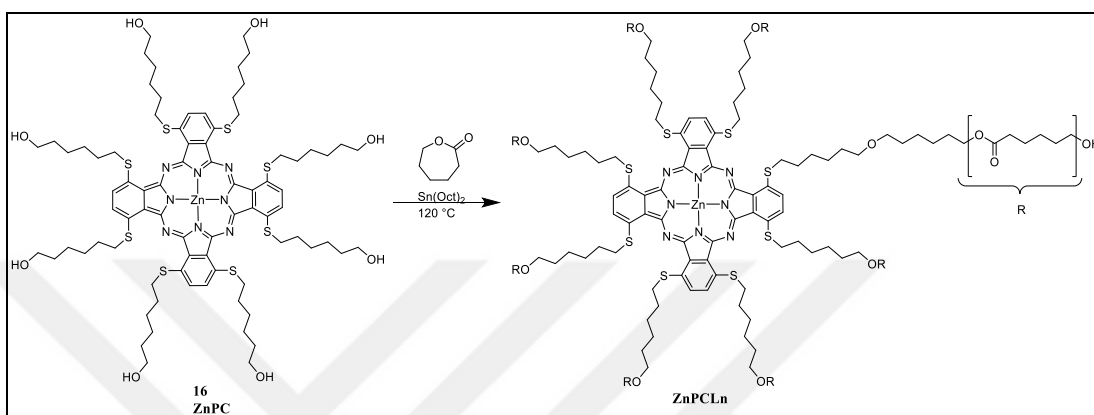
3.2.1.1. Synthesis of Poly(ϵ -caprolactone) Polymers

The ring-opening polymerization of the ϵ -caprolactone monomer was catalysed by SnOct₂ at a temperature of 115 °C, utilizing octa-thiosubstituted non-peripheral octa hydroxylated phthalocyanines zinc(II) **ZnPc** [156] as an initiator. The reaction was carried out at three distinct monomer-to-initiator ratios: 20, 30, and 40 Scheme 3.20 [156],[157].

The ratio of monomer to initiator during polymerization plays a crucial role in determining the characteristics of the final polymer. Specifically, for PCL, this ratio can guide the linearity of the polymer, which subsequently influences its chemical and physical attributes. Importantly, the linearity of PCL has a significant impact on its biocompatibility, a key aspect for its use in biomedical applications.

All polymerization reactions took place in an argon environment. The reactions were performed without a solvent, as both caprolactone and the catalyst used are liquid. The reaction mixture was stirred for 15 hours under an oil bath. Following this, the reaction mixture solidified, indicating the formation of the polymer. DCM was then added to the crude polymer to dissolve it. This solution was slowly added drop by drop to 500

mL of methanol under stirring. This process precipitated the polymer and helped avoid the entrapment of the catalyst used within the polymer structure. The mixture was then transferred to a freezer to enhance the precipitation. The next day, the precipitated polymer was filtered and left to dry, yielding high results. These results are presented in Table 3.3.



Scheme 3.20: Synthesis of the three star polymers **ZnPc-PCL20**, **ZnPc-PCL30** and **ZnPc-PCL40**.

Table 3.3: Characteristics of the phthalocyanine-core **ZnPc-PCLn** star polymers

Polymer	[M]/[I] ^a	$M_{n, \text{theo}}^b$ (g/mol)	$M_{n, \text{NMR}}$ (g/mol)	$M_{n, \text{GPC}}^c$ (g/mol)	PDI^c	Conversion ^d (%)
ZnPc-PCL20	20	19 898	20 272	11 700	1.28	90
ZnPc-PCL30	30	29 029	29 102	19 500	1.18	88
ZnPc-PCL40	40	38 160	38 671	31 200	1.08	89

^aM=ε-CL, I= initiator, [M]/[I]=The molar ratio of ε-CL to **ZnPcOH8** core initiator.

^b $M_{n, \text{theo}}$ = the theoretical number-average molecular weight of **ZnPc-PCLn**, $M_{n, \text{theo}} = m_{\text{monomer}} \times [M]_0/[I]_0 \times \text{conversion} + M_{\text{initiator}}$ ($M_{\epsilon\text{-CL}} = 114.14$ g/mol and $M_{\text{ZnPc}} = 1635.68$ g/mol).

^c $M_{n, \text{GPC}}$ and PDI were determined by GPC analysis.

^dConversion = $m_{\text{yield}} - m_{\text{multiinitiator}} / m_{\epsilon\text{-CL}}$.

3.2.1.2. FT-IR Spectra of Poly-(ϵ -caprolactone) Polymers

FT-IR spectra, as depicted in Figure 3.20, provide insights into the structure of the PCL polymers **ZnPc-PCL20**, **ZnPc-PCL30**, and **ZnPc-PCL40** and octa-thiosubstituted non-peripheral octa hydroxylated phthalocyanines zinc(II) **Zn-Pc** which was used as an initiator.

What can be observed clearly from FT-IR spectra is the hydroxyl stretching vibration frequency at (3274 cm^{-1}), associated with the initiator, and the carbonyl stretching vibration frequency at (1721 cm^{-1}) which is confirming the structure of the PCL polymers. The C=O peak intensities at (1721 cm^{-1}) show an increase, suggesting an increase in ϵ -CL units in the structure. While the peak intensities of the hydroxyl groups at (3274 cm^{-1}) show a decrease, indicating that the polymerization process is facilitated through -OH groups. As the length of the polymer chains increases, there is a corresponding decrease in the relative intensity of the characteristic peaks of phthalocyanine (-C=C- at 1608 cm^{-1} and -C=N- at 1647 cm^{-1}). These observations affirm the successful polymerization process and the expected structure of the resulting **ZnPc-PCL_n** polymers.

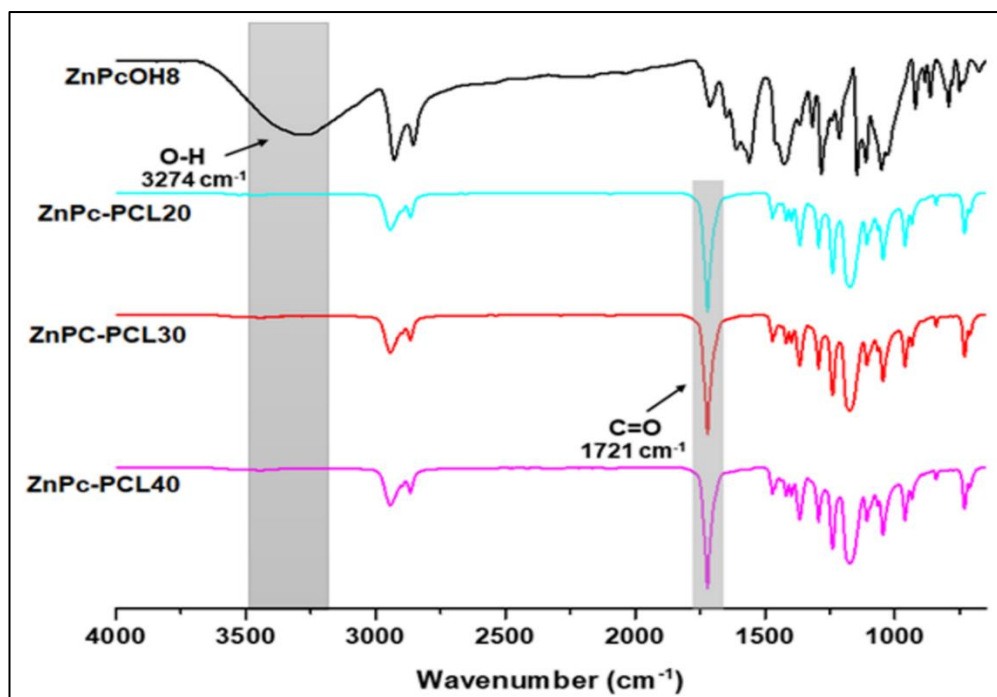


Figure 3.20: FT-IR spectrum of hydroxylated phthalocyanine and polycaprolactones.

3.2.1.3. ^1H NMR Spectra of Poly-(ϵ -caprolactone) Polymers

Figure 3.21 presents the ^1H NMR spectrum of the PCL polymers, specifically **ZnPc-PCL20**, **ZnPc-PCL30**, and **ZnPc-PCL40**. The spectra show the presence of aliphatic protons, which are part of the repeating methylene groups in the PCL polymers. These protons are observed at $\delta = 4.04$ ppm (t, $\text{O}=\text{C}-\text{CH}_2\text{CH}_2-$, H_b) and the $-\text{CH}_2\text{CH}_2-\text{OH}$ proton, which is located at the end of the chain, is observed at $\delta = 3.63$ ppm (t, $-\text{CH}_2\text{CH}_2-\text{OH}$, H_a).

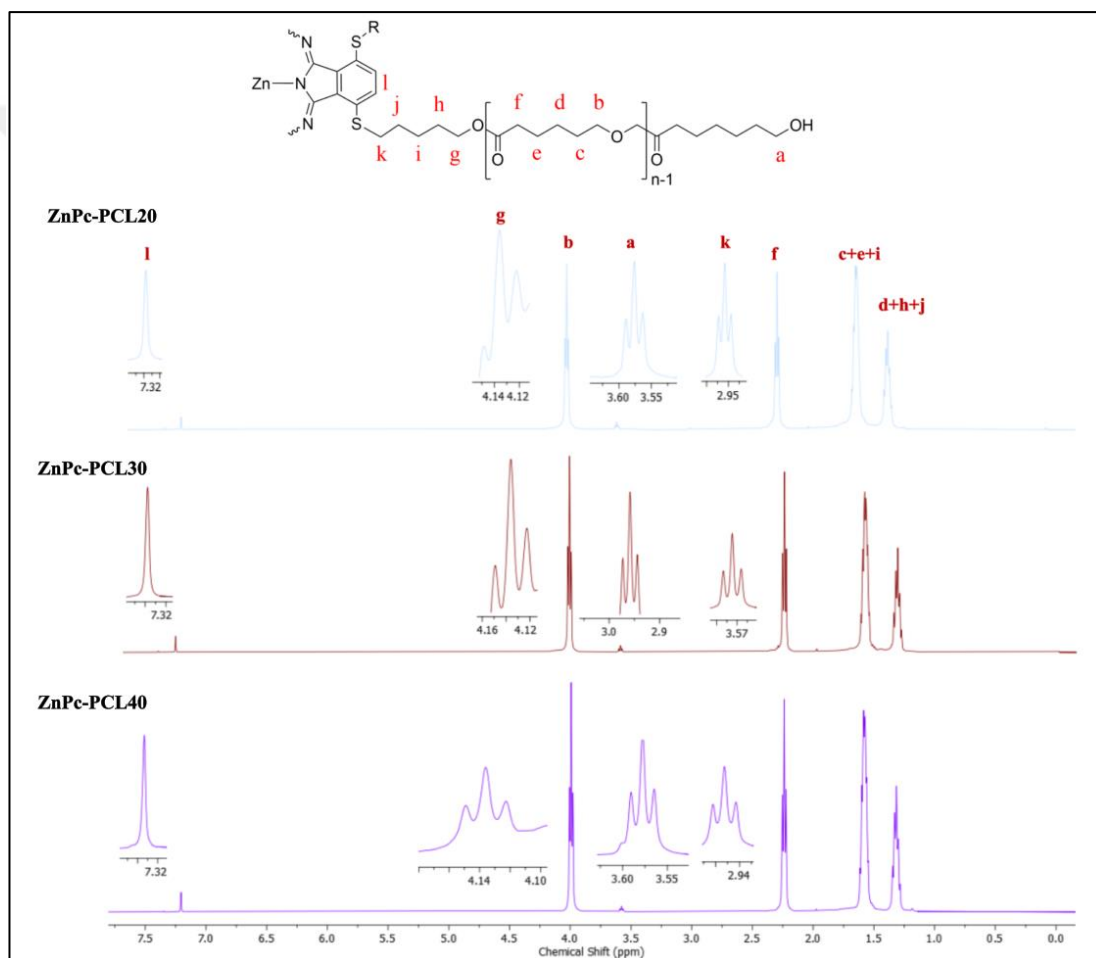


Figure 3.21: ^1H NMR spectrum of **ZnPc-PCL20**, **ZnPc-PCL30** and **ZnPc-PCL40** in CDCl_3 .

The intensity of the methylene protons is so significant that it obscures the visibility of both aromatic and hydroxyl protons in the spectrum, however the protons of the aromatic can be seen in the expanded spectrum at $\delta = 7.32$ ppm. The number-average

molecular weight ($M_{n,NMR}$) of each polymer, as determined by NMR, was computed using the integral ratio of the methylene protons ($O=C-CH_2CH_2-$, H_b) to the terminal protons ($-CH_2CH_2-OH$, H_a). The $M_{n,NMR}$ values show a strong correlation with the theoretical values ($M_{n,theo}$), as outlined in Table 3.3. This agreement validates the accuracy of the NMR measurements and the theoretical calculations.

3.2.1.4. Gel Permeation Chromatography Characterization

The molecular weights of the **ZnPc-PCLn** polymers, both number-average (M_n) and weight-average, were determined using GPC at different monomer-to-initiator ($[M]/[I]$) ratios [158]. The M_n values obtained from GPC ($M_{n,GPC}$) were found to be lower. This is a common observation and is attributed to the unique star-shaped architecture of the polymers.

Star polymers have lower hydrodynamic volumes compared to linear polystyrene standards of the same molecular weight. As a result, when GPC analysis is performed using refractive index (RI) or UV detection, the molecular weight of star-shaped polymers is invariably underestimated. This is due to the fact that these detection methods are sensitive to the physical size of the polymers in solution, which is smaller for star polymers compared to linear ones of the same molecular weight [158].

Given this inherent limitation of GPC analysis for star-shaped polymers, data obtained from ^1H NMR spectroscopy is often considered more reliable for determining the molecular weight of these polymers. The ^1H NMR technique is not influenced by the physical size or shape of the polymers, making it a more accurate method for molecular weight determination in this context. Therefore, in studies involving star-shaped polymers like **ZnPc-PCLn**, ^1H NMR data is typically given more weight than those established by GPC analysis.

3.2.1.5. Polydispersity Index

The **ZnPc-PCLn** star polymers exhibit significant polydispersity, as indicated by their Polydispersity Index (M_w/M_n) values, which are in the range of 2.3. The PDI is a measure of the distribution of molecular mass in a given polymer sample. A PDI value of 2.3 suggests a broad distribution of polymer chain lengths, indicating a high degree of polydispersity [152].

This high PDI value has been previously observed in polymers that are structurally similar to **ZnPc-PCLn**. The reason for this high polydispersity can be attributed to the unique structure of these polymers. Specifically, each **ZnPc-PCLn** polymer molecule consists of a core from which eight polymer chains emanate, giving it a star-like structure.

This star-shaped structure inherently leads to a higher degree of polydispersity. This is because the multiple chains on the same core can have varying lengths, leading to a broad distribution of molecular weights within the polymer sample. Therefore, the high PDI values observed for **ZnPc-PCLn** star polymers are a direct consequence of their unique structural configuration.

3.2.1.6. Thermal Properties

The thermal characteristics of **ZnPc-PCLn** polymers were examined using differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA), and the results were compared with those of linear PCL (LPCL).

The DSC experiments, Table 3.4 and Figure. 3.22, revealed that both **ZnPc-PCLn** star polymers and **LPCL** exhibit a singular melting peak (T_{m1}) ranging from 57.19 to 62.10 °C during the initial heating cycle, a cold crystallization peak (T_c) between 28.20 and 33.29 °C during the cooling cycle, and a singular endothermic peak (T_{m2}) from 51.54 to 54.69 °C during the second heating cycle.

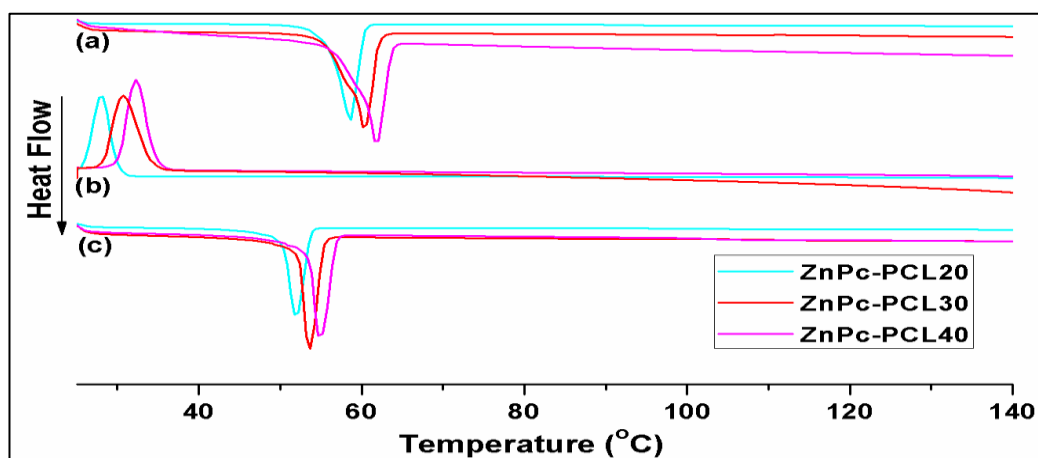


Figure 3.22: DSC thermograms of the cored star-shaped **ZnPc-PCLn** polymers in (a) the first heating run, (b) cooling run, and (c) second heating run.

Table 3.4: T_m , T_c , ΔH and crystallinity (%) values obtained from DSC analysis for LPCL and ZnPc-PCLn star polymers.

Sample	T_{m1} (°C) ^a	T_{m2} (°C) ^a	T_c (°C) ^b	ΔH_{m1} (J/g) ^c	X_{c1} (%) ^d	ΔH_{m2} (J/g) ^c	X_{c2} (%) ^d
LPCL [158]	57.19	51.54	33.29	122.52	87.78	85.42	61.19
ZnPc-PCL20	58.68	51.75	28.20	-96.22	68.93	-66.79	47.84
ZnPc-PCL30	60.15	53.65	30.71	-103.58	74.20	-69.56	49.83
ZnPc-PCL40	62.10	54.69	32.25	-112.26	80.42	-73.75	52.83

^a T_{m1} and T_{m2} denote the maximal melting temperature of **ZnPc-PCLn** in the first and second heating run in turn.

^b T_c denotes the crystallization temperature of the polymer in the cooling run.

^c ΔH_{m1} and ΔH_{m2} are the fusion enthalpy of the polymers in the first and second heating run, respectively.

^d $X_{c1} = \Delta H_{m1} / \Delta H_m^0$ and $X_{c2} = \Delta H_{m2} / \Delta H_m^0$, ΔH_m^0 is the enthalpy of fusion for perfectly crystalline PCL. $\Delta H_m^0 = 139.6$ J/g [15].

Interestingly, the maximum melting points (T_{m1} and T_{m2}) of **LPCL** are lower than those of the **ZnPc-PCLn** star polymers. Conversely, the cold crystallization temperature (T_c), crystallinity (X_c), and fusion enthalpies (ΔH_m) of all **ZnPc-PCLn** star polymers are lower than those of **LPCL**. This is likely due to the star-shaped architecture and ZnPc core of the polymers, which reduce the motion of the PCL arms and consequently decrease their crystallinity.

As the PCL chain length increases, there is a corresponding enhancement in T_c , the maximum melting points (T_{m1} and T_{m2}), ΔH_m , and the corresponding X_c of the **ZnPc-PCLn**. In terms of thermal stability, an increase in the molecular weight of **ZnPc-PCLn** leads to an increase in their onset temperature (T_{onset}) and maximum temperature (T_{max}), thereby enhancing their stability. This is because the number of terminal -OH groups per gram of the polymer sample decreases, which aligns with the hypothesis that the thermal degradation of PCL is triggered by the presence of thermally unstable end-capped hydroxyl groups [159] (Figure 3.23 and Table 3.5).

The phthalocyanine core is significantly more stable than the PCL chains, which explains why the char yield value decreases as the PCL chain length increases.

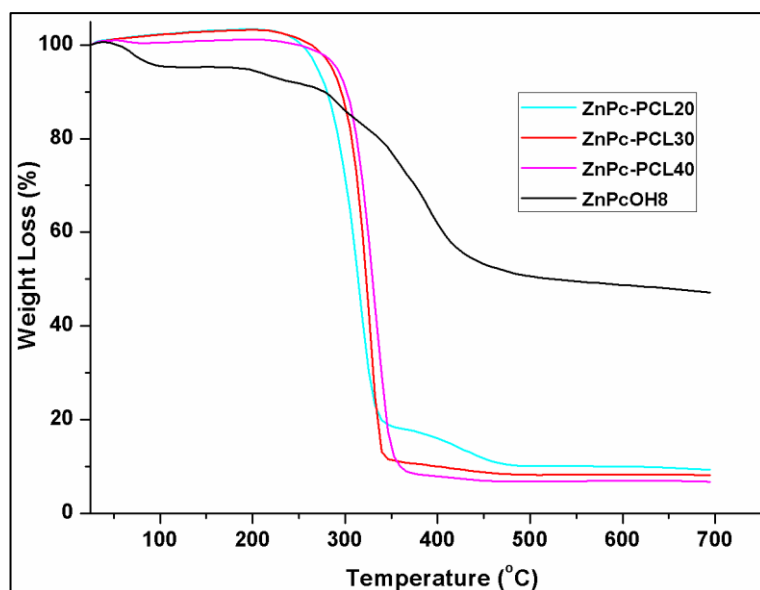


Figure 3.23: TGA thermograms of **ZnPc-OH8**, **ZnPc-PCL20**, **ZnPc-PCL30** and **ZnPc-PCL40**

Table 3.5: T_{onset} , T_{max} and residue (%) values obtained from TGA analysis for **ZnPc-OH8**, **LPCL**, and star-shaped **ZnPc-PCLn**.

Sample	T_{onset} (°C) ^d	T_{max} (°C) ^e	Char Yield (%) ^f
ZnPcOH8	182	391	47.09
LPCL [158]	313	352	4.46
ZnPc-PCL20	271	314	9.26
ZnPc-PCL30	286	326	8.10
ZnPc-PCL40	290	333	6.73

^a T_{onset} is the onset decomposition temperature of the polymers in TGA experiments.

^b T_{max} is the temperature corresponding to the maximum rate of weight loss in TGA experiments.

^cThe percent of char yield at 700 °C in TGA experiments.

3.2.1.7. UV-Vis Spectra of Poly-(ϵ -caprolactone) Polymers

All **ZnPc-PCLn** star polymers exhibit solubility in two solvents: dichloromethane and tetrahydrofuran, as detailed in Table 3.6 and illustrated in Figures 24-29. When compared to non-functionalized core phthalocyanine **ZnPc-Hex8** [156], the introduction of PCL chains into the polymer structure does not influence the maximum absorption in THF.

Furthermore, the logarithmic extinction coefficient ($\log \epsilon$), a measure of how strongly a chemical species absorbs light at a particular wavelength, exhibits lower values for the star polymers compared to the non-functionalised **ZnPc-Hex8**. This suggests that the presence of PCL chains in the star polymers affects their light absorption properties, making them less absorbent than their non-functionalised counterparts.

Table 3.6: Uv-vis data for **ZnPc-PCL20**, **ZnPc-PCL30**, **ZnPc-PCL40**, **ZnPc-OH8** [158] and **ZnPc-Hex8** [156]: Maximum absorption wavelength (nm) and logarithm extinction coefficient $\log \epsilon$.

	ZnPc-PCL20	ZnPc-PCL30	ZnPc-PCL40	ZnPc-OH8	ZnPc-Hex8
DCM	787 (3.1)	784 (3.1)	786 (3.1)	-	800 (4.3)
THF	779 (3.1)	779 (3.1)	779 (3.1)	780 (3.6)	779 (5.1)

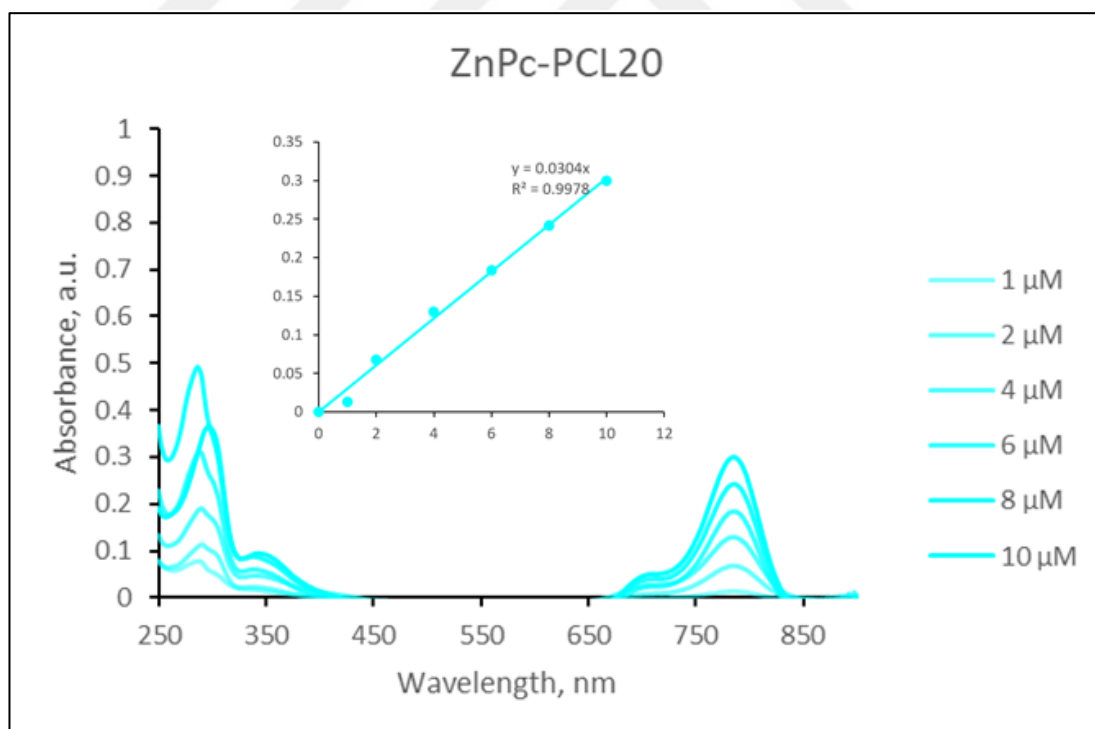


Figure 3.24: UV-Vis spectra of **ZnPc-PCL20** (inset: plot of absorbance vs concentration) (DCM, 1-10 μM).

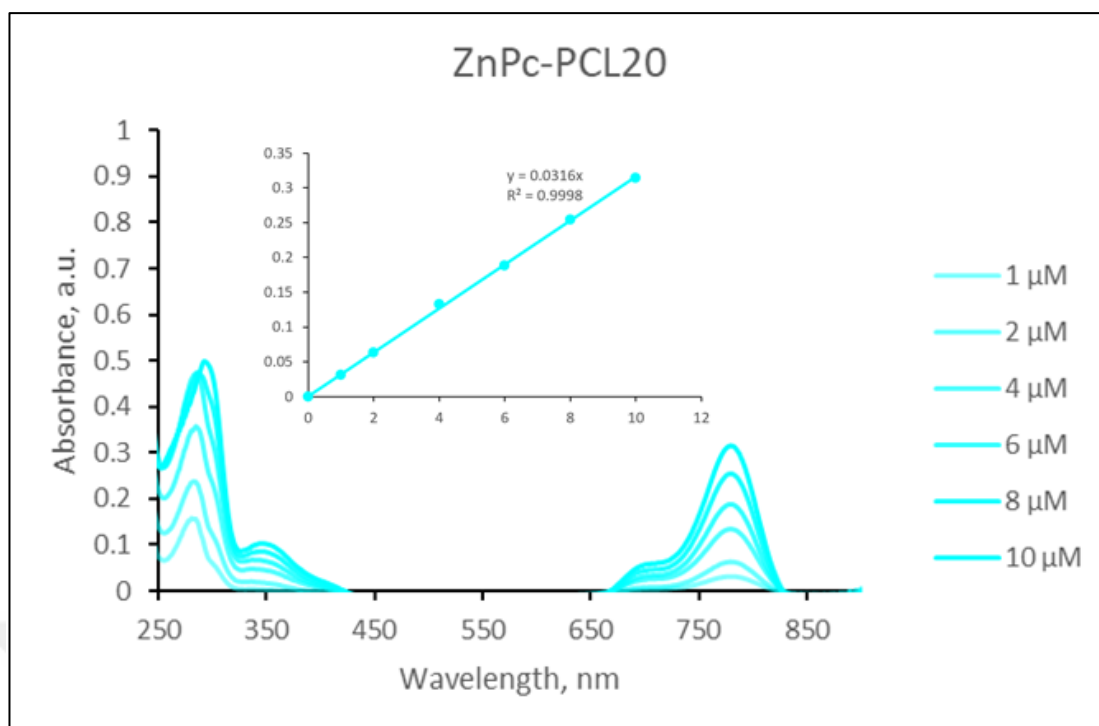


Figure 3.25: UV-Vis spectra of **ZnPc-PCL20** (inset: plot of absorbance vs concentration) (THF, 1-10 μM).

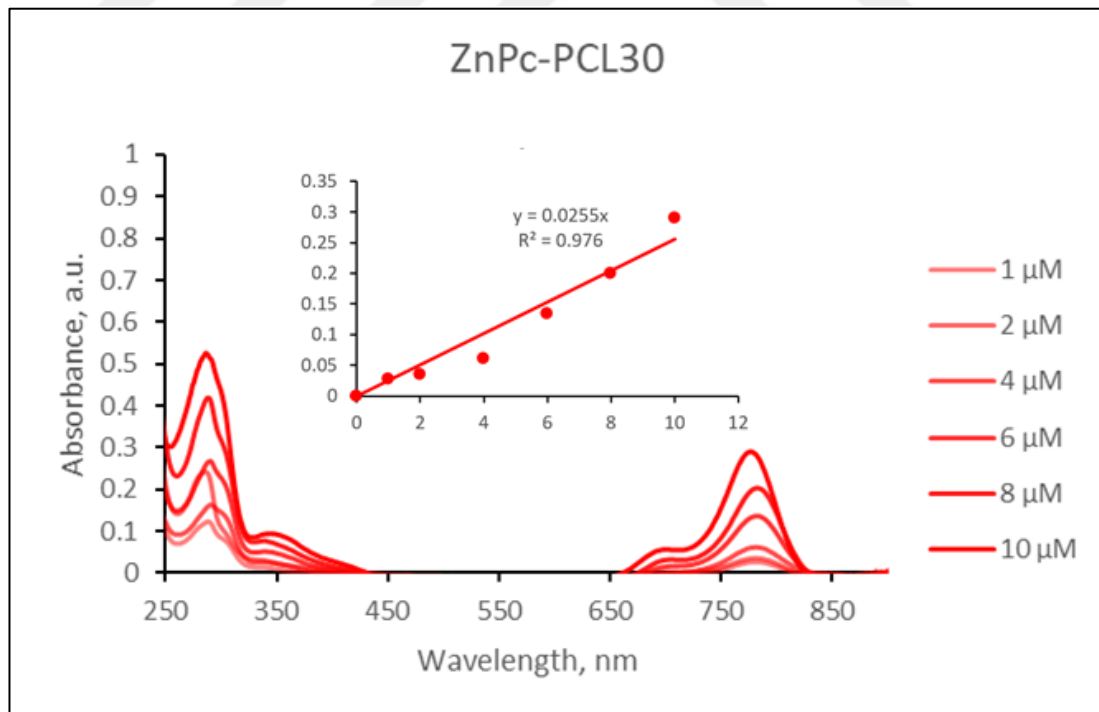


Figure 3.26: UV-Vis spectra of **ZnPc-PCL30** (inset: plot of absorbance vs concentration) (DCM, 1-10 μM).

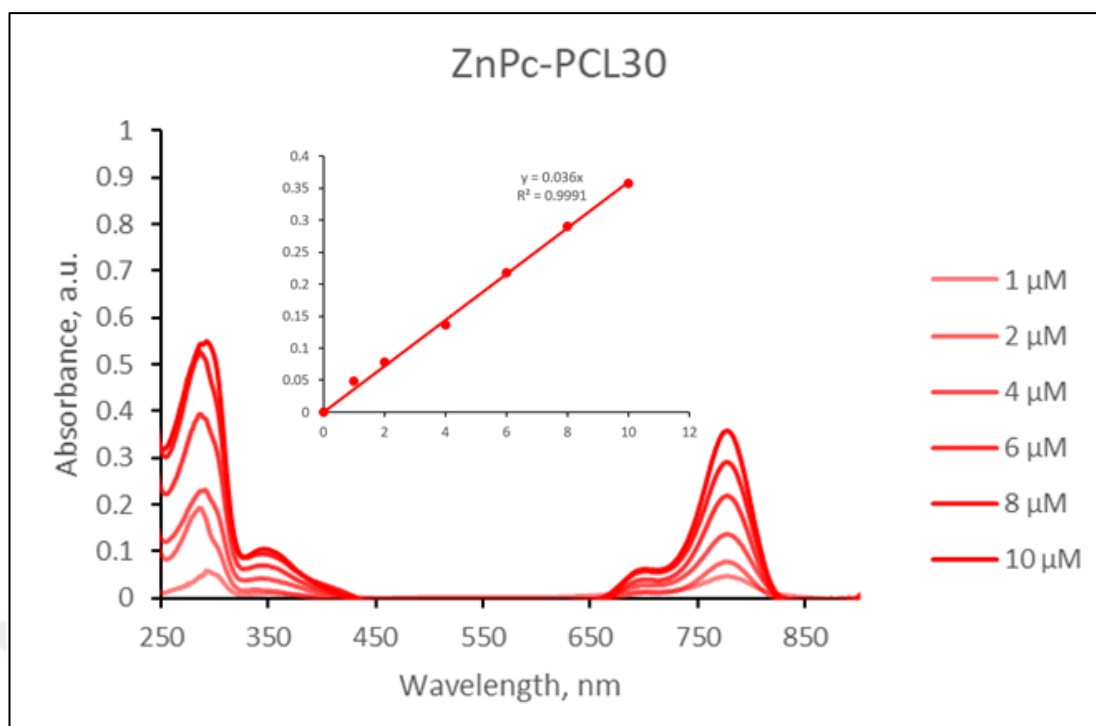


Figure 3.27: UV-Vis spectra of **ZnPc-PCL30** (inset: plot of absorbance vs concentration) (THF, 1-10 μM).

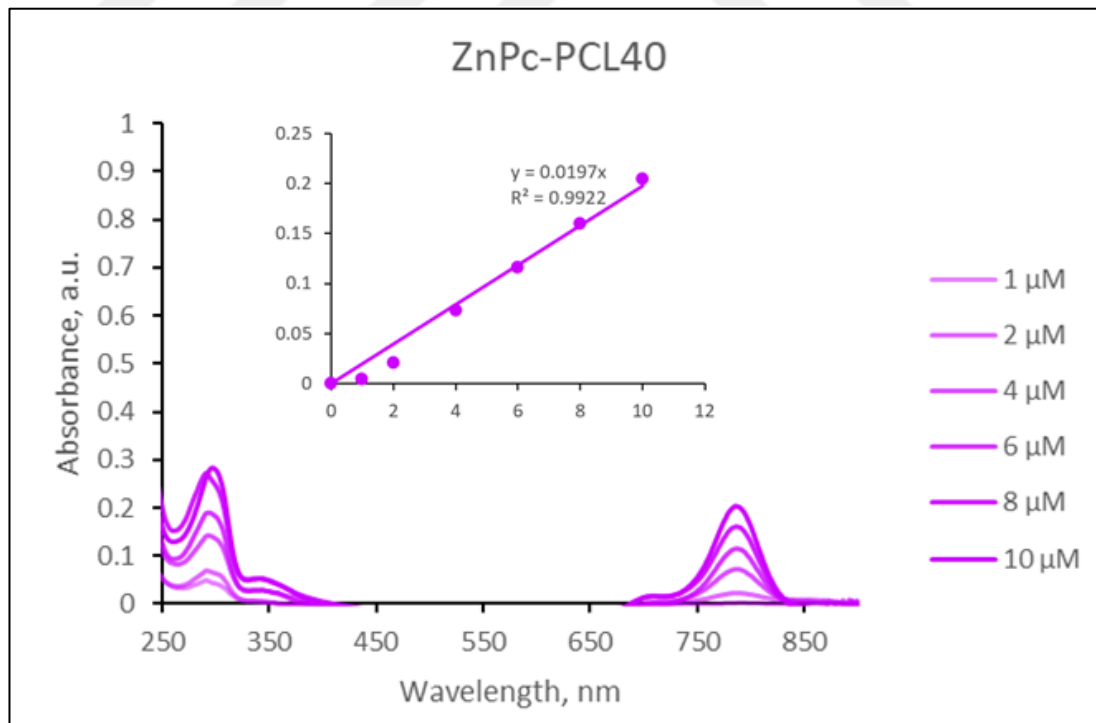


Figure 3.28: UV-Vis spectra of **ZnPc-PCL40** (inset: plot of absorbance vs concentration) (DCM, 1-10 μM).

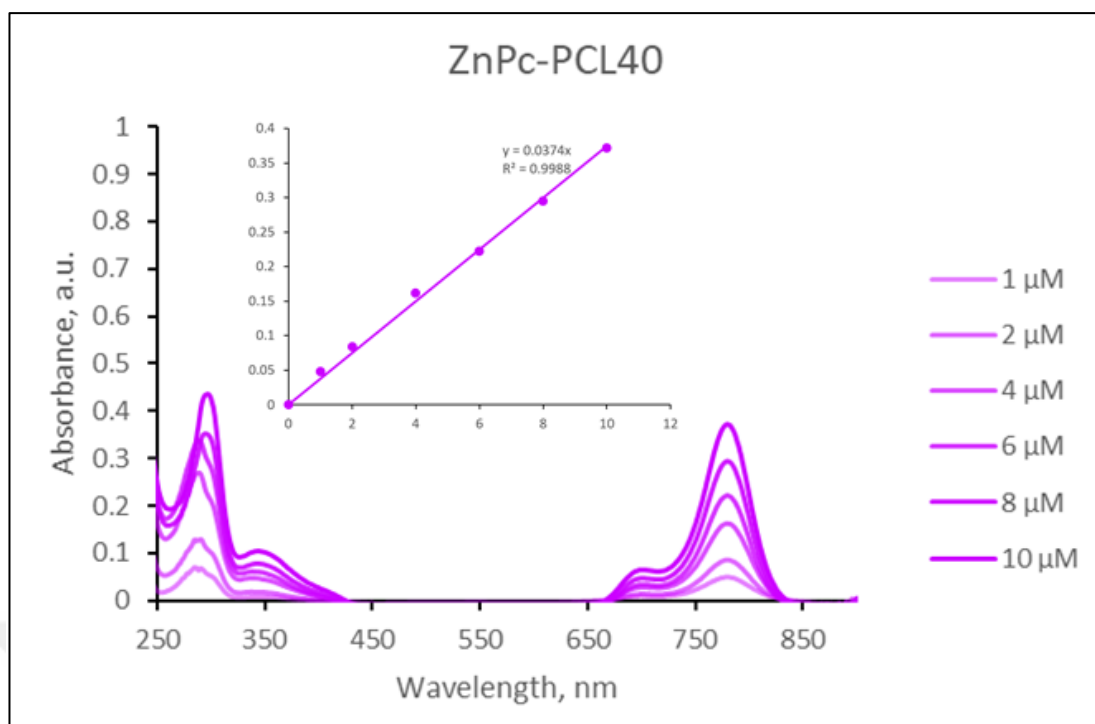


Figure 3.29: UV-Vis spectra of **ZnPc-PCL40** (inset: plot of absorbance vs concentration) (THF, 1-10 μM).

3.2.2. Nanoparticles Formation by Nanoprecipitation

In order to benefit from the maximum near-infrared absorption of the **ZnPc-PCL_n** star polymers for potential biomedical applications, a process of nanoprecipitation was employed to form nanoparticles from these polymers. The phthalocyanines were self-encapsulated into the arms of their respective PCL polymers under two distinct conditions.

Initially, solutions of the **ZnPc-PCL_n** star polymers were prepared in THF at concentrations of 10 and 100 micromolar. A volume of 1 mL from each of these solutions was then added by using syringe to 2 mL of water under very fast stirring and left under stirring for 10 min. Following this, the THF was allowed to evaporate using vacuumed evaporator for 15 min, which triggered the formation of nanoparticles via a process known as nanoprecipitation.

In case where the water volume had also partially reduced due to evaporation alongside the THF, adjustments were made to ensure that the final water volume was maintained

at 2 mL. As a result of this process, two stock solutions were obtained for each polymer, with concentrations set at 5 and 50 micromolar.

3.2.2.1. Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM) Studies

The length of the PCL arms has a minimal impact on the size of the nanoparticles. Through DLS experiments Figure 3.30, it was found that the size of the nanoparticles was approximately 140 nm for **NP-ZnPc-PCL20** (PDI, of 0.111) and around 180 nm for **NP-ZnPc-PCL40** (PDI of 0.206).

The nanoparticles, **NP-ZnPc-PCL_n**, exhibit a spherical shape, as revealed by TEM studies. The sizes observed in the TEM studies were in agreement with those determined by the DLS experiments. This consistency in size across different measurement techniques further validates the nanoparticle formation process.

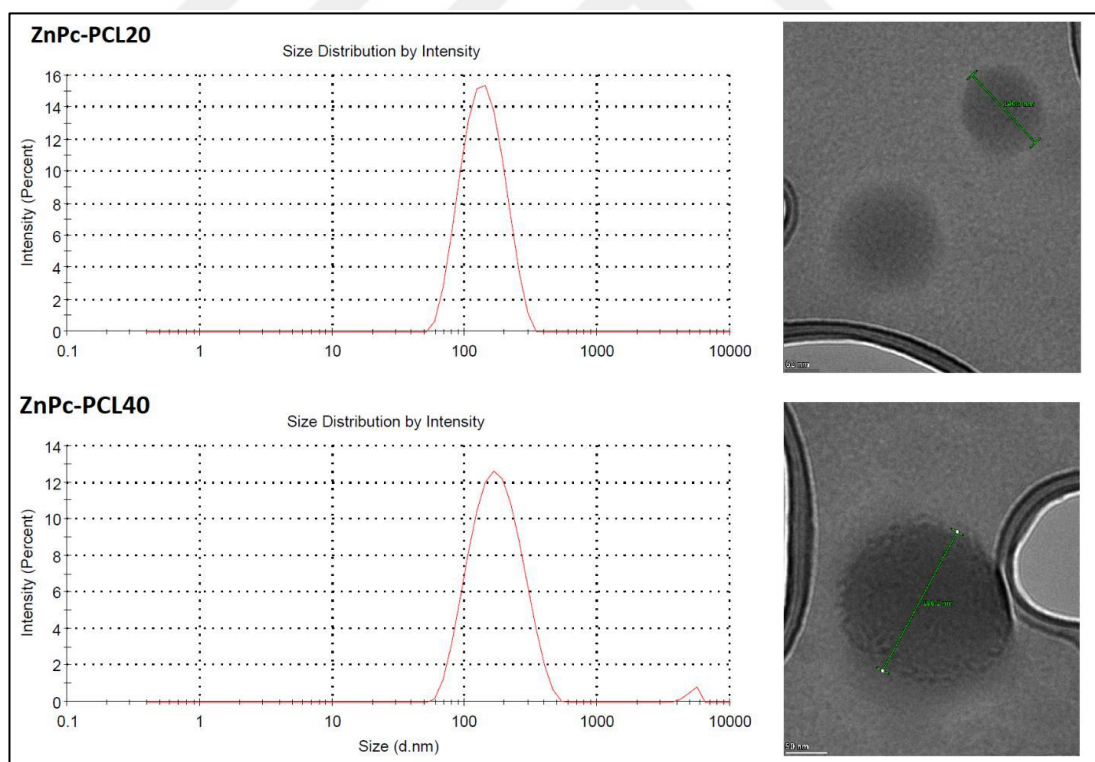


Figure 3.30: DLS (left) and TEM characterisation of **ZnPc-PCL20** and **ZnPcPCL40**

3.2.2.2. UV-Vis Spectra of Nanoparticles based on Poly-(ϵ -caprolactone) Polymers

The UV-vis spectra of each **NP-ZnPc-PCLn** were recorded in water at various concentrations. For the **NP-ZnPc-PCLn** derived from the 50 μM stock solution, spectra were obtained at concentrations of 2.5, 5, 10, and 20 μM . Additionally, UV-vis spectra were recorded at concentrations of 2.5 and 5 μM from the 5 μM stock solution.

When comparing the UV-spectra of the same nanoparticle prepared at a concentration of 5 μM , either directly or by diluting the 50 μM stock solution, a distinct behaviour was observed. The absorption was found to be superior for the 5 μM solution that was prepared by diluting the 50 μM solution. This was particularly noticeable for **NP-ZnPc-PCL40** as it is shown in Figure 31-33.

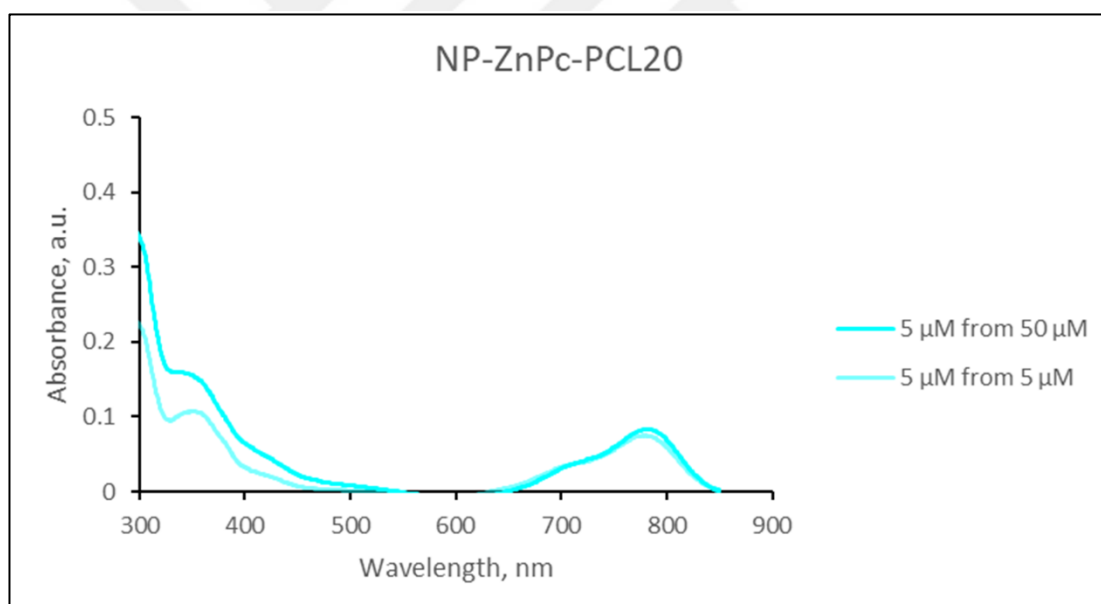


Figure 3.31: UV-Vis spectra of **NP-ZnPc-PCL20** in water at 5 μM are prepared from 5 or 50 μM stock solutions.

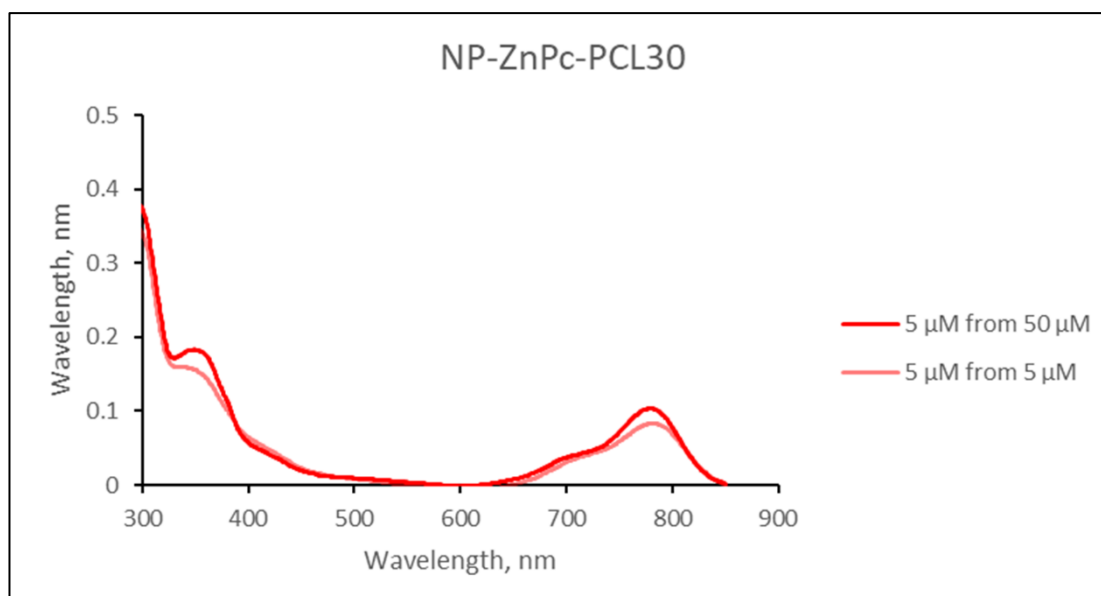


Figure 3.32: UV-Vis spectra of **NP-ZnPc-PCL30** in water at 5 μM are prepared from 5 or 50 μM stock solutions.

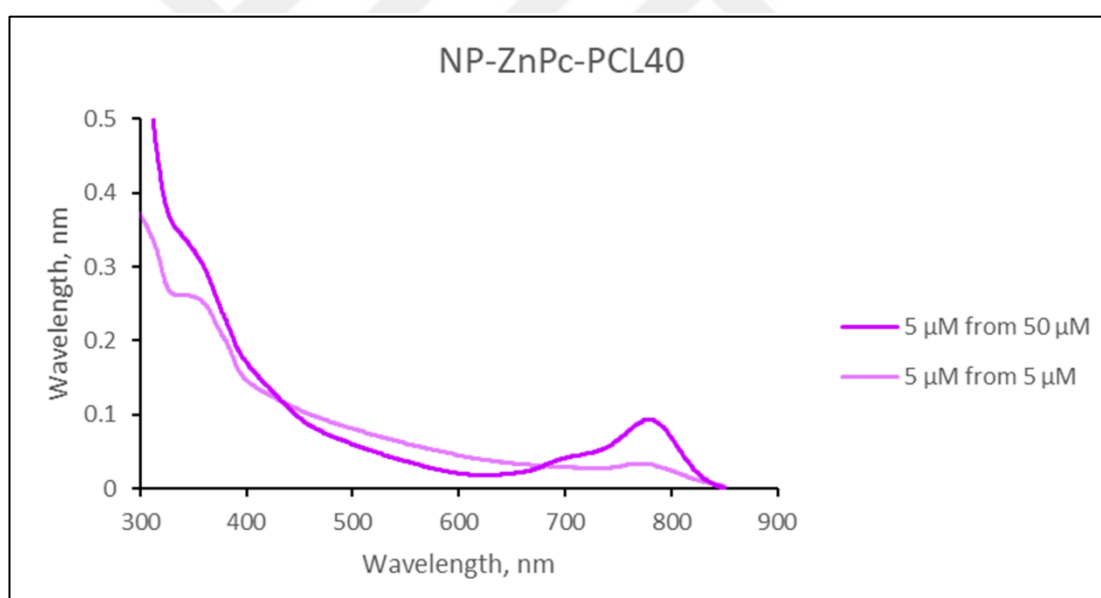


Figure 3.33: UV-Vis spectra of **NP-ZnPc-PCL40** in water at 5 μM are prepared from 5 or 50 μM stock solutions.

All the nanoparticles that were prepared from the 50 μM stock solutions demonstrated a strong absorption at 782 nm when suspended in water (Figure 3.34-3.36). This absorption corresponds to the Q band of the phthalocyanine core. The ability of these nanoparticles to exhibit such strong absorption in water at these specific concentrations

and wavelengths is quite remarkable. This characteristic in this micromolar range makes them potentially useful for various applications such as PDT.

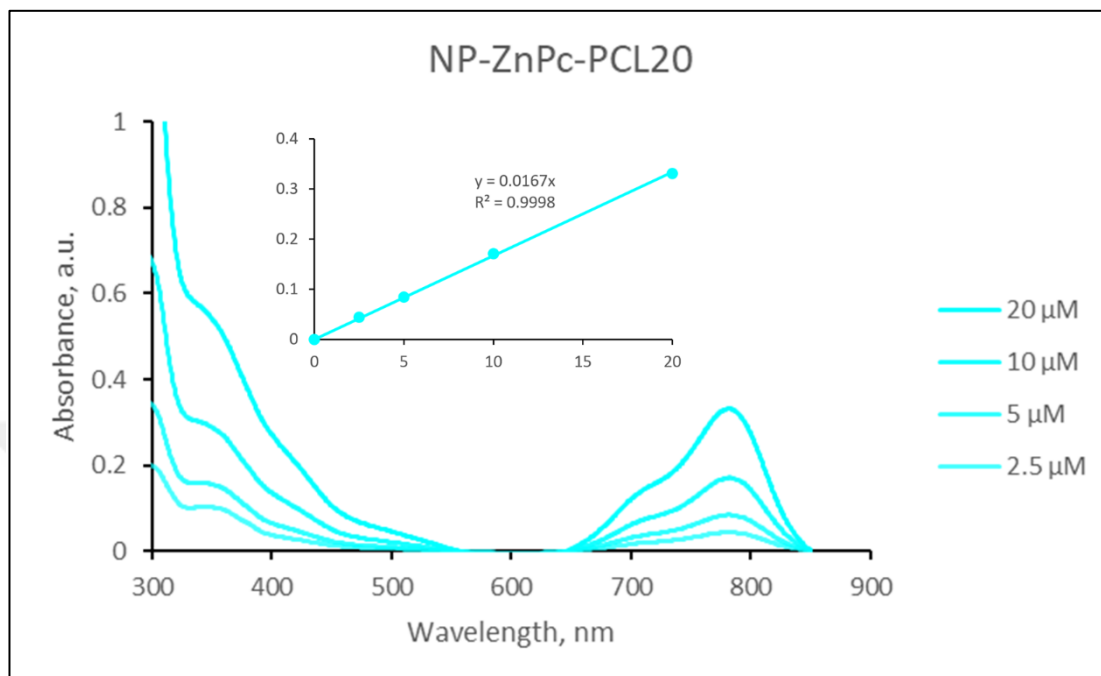


Figure 3.34: UV-Vis spectra of NP-ZnPc-PCL20 (inset: plot of absorbance vs concentration) (Water, 2.5-20 μM).

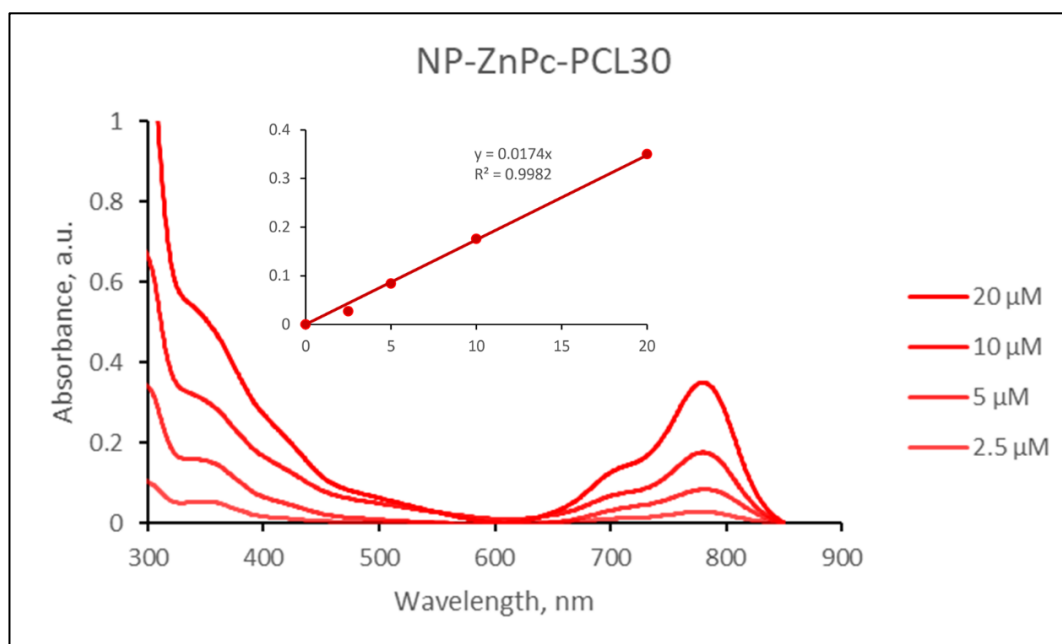


Figure 3.35: UV-Vis spectra of NP-ZnPc-PCL30 (inset: plot of absorbance vs concentration) (Water, 2.5-20 μM).

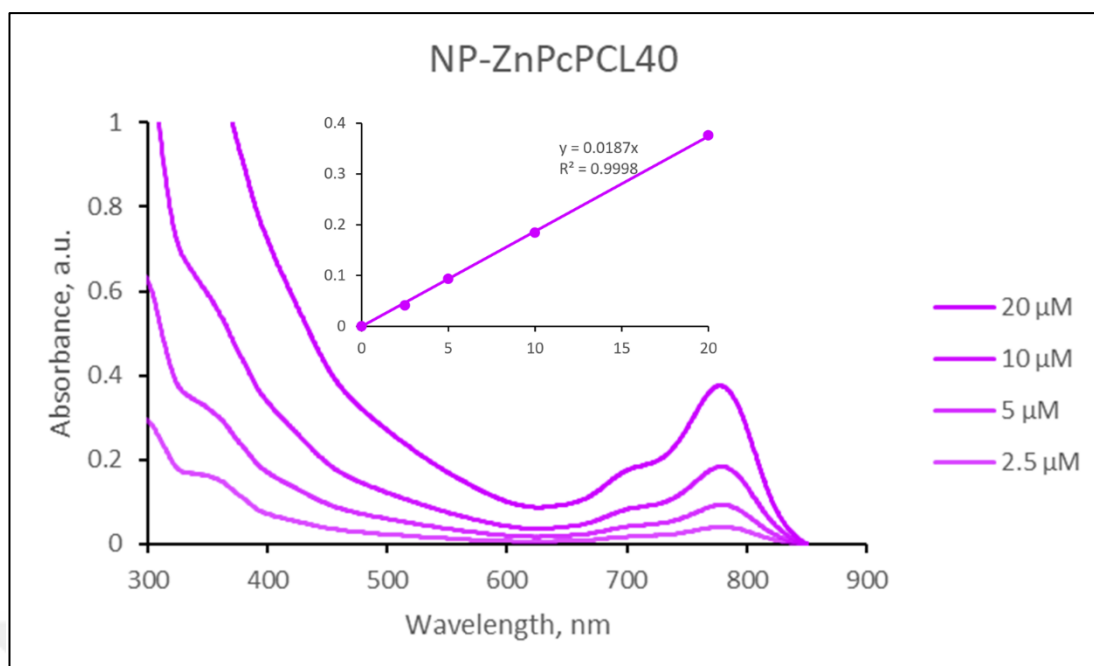


Figure 3.36: UV-Vis spectra of NP-ZnPc-PCL40 (inset: plot of absorbance vs concentration) (Water, 2.5-20 μM).

4. EXPERIMENTAL PART

4.1. Numbering of Synthesised Compounds

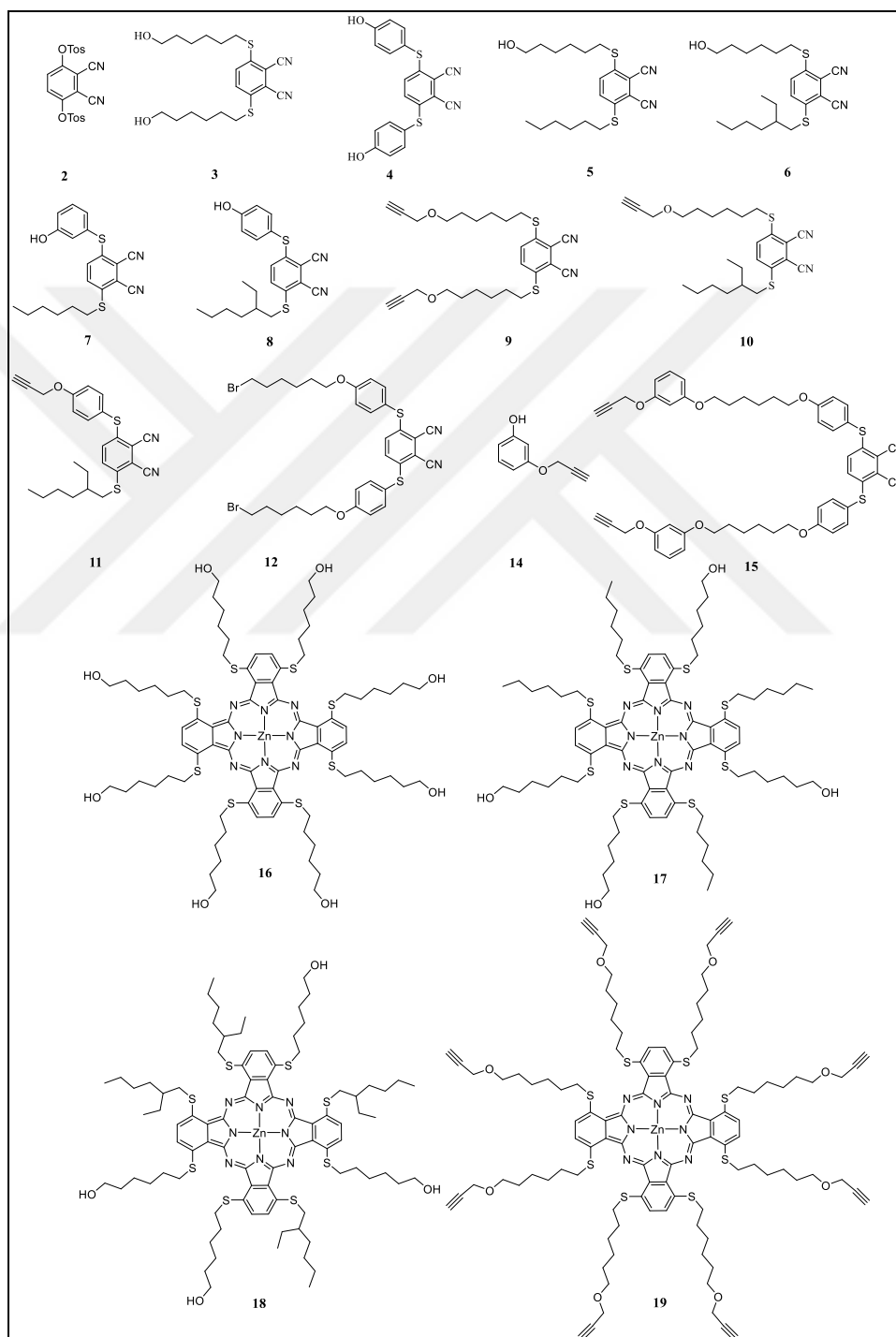


Figure 4.1: Numbering of Synthesised Compounds.

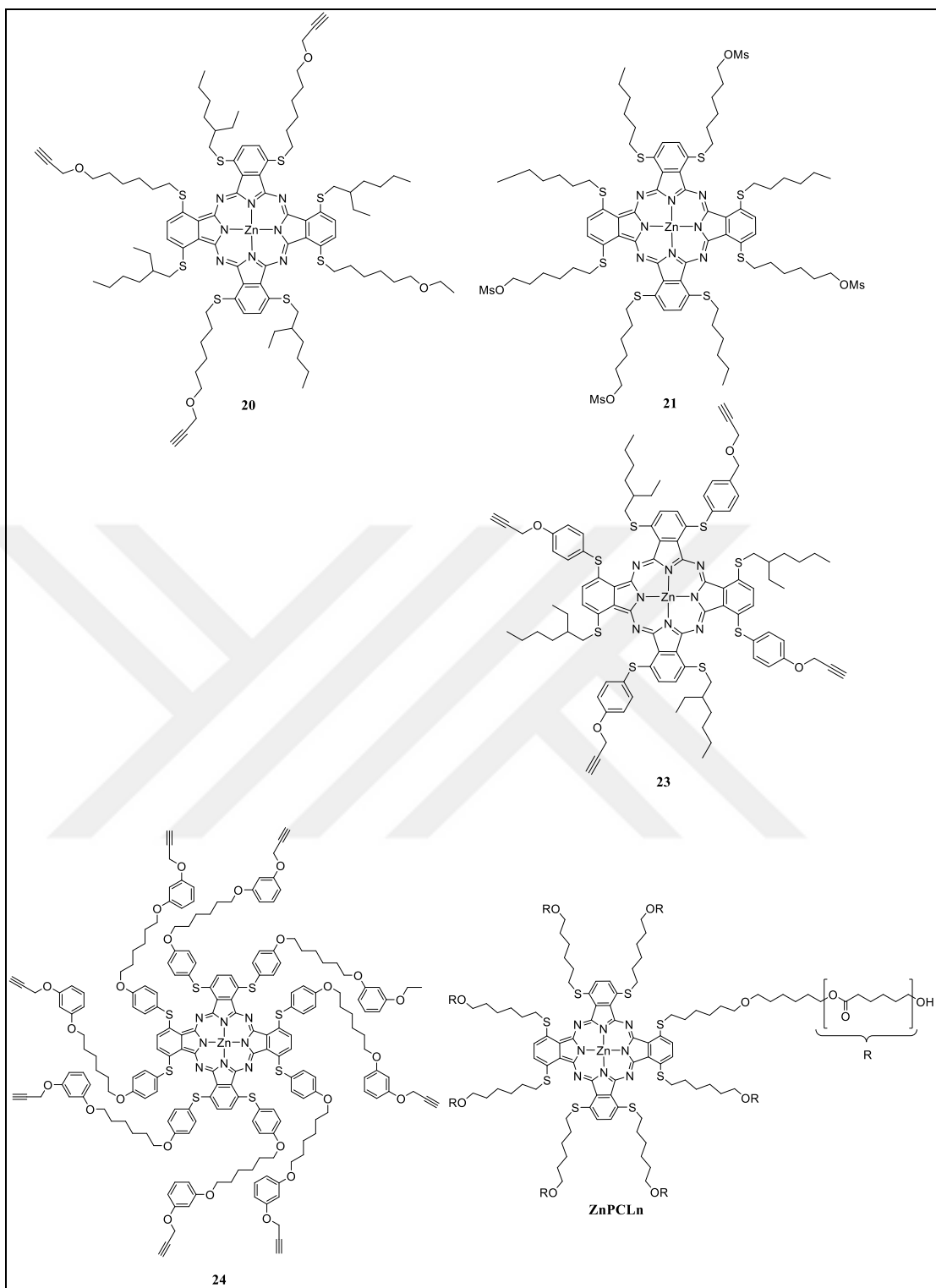


Figure 4.2: Numbering of Synthesised Compounds.

4.2. Materials and Instruments

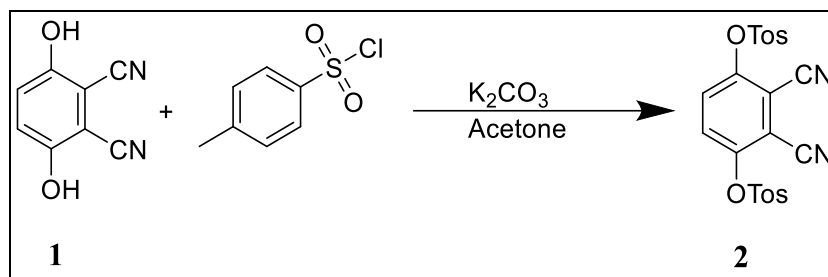
Table 4.1: Chemicals utilized for synthesis, purification, and separation processes.

Name	Manufacturer
Acetone	
Acetonitrile	
Dichloromethane	99.8%, Merck
Dicyanohydroquinone	
Dimethylformamide	
Hexane-1-thiol	
Lithium	
Methanesulfonyl chloride	
Methanol	≥99.8%, Sigma-Aldrich
N-Pentanol	
Potassium carbonate	
Propargyl bromide	
Resorcinol	
Sodium hydride	
Tetrahydrofuran	
Tin(II) 2-ethylhexanoate	95%, Aldrich
Triethylamine	
Zincacetate	
ε-caprolactone	97%, Aldrich
1,6-dibromohexane	
2-ethylhexane-1-thiol	
3-mercaptophenol	
4-mercaptophenol	
4-methylbenzenesulfonyl chloride	
6-mercaptohexan-1-ol	

Table 4.2: Instruments employed for characterization

Name	Model	Place
MALDI-TOF Mass Spectrometry	Bruker Microflex LT	GTU
NMR Spectrometry		GTU
FT-IR infrared Spectrometry	Perkin Elmer Spectrum 100	GTU
NMR Spectrometry	Bruker BioSpin AG Avance 500 MHz	KOU
Viscotek RI	Viscotek, VE3580	KOU
Differential Scanning Calorimetry	Mettler Toledo DSC 1 Star System	KOU
Thermogravimetric Analyzer	Mettler Toledo TGA 1 Star System	KOU
Dynamic Light Scattering	Zetasizer Nano ZS (Malvern Instruments)	Acibadem
Transmissive Electron Microscopy	Transmissive Electron Microscope TALOS L120C TEM	Acibadem
UV-Vis Spectrometry	Shimadzu UV-2600	Acibadem

4.3. Synthesis of 3,6-bis (4'-methylbenzenesulfonyloxy) phthalonitrile (2)

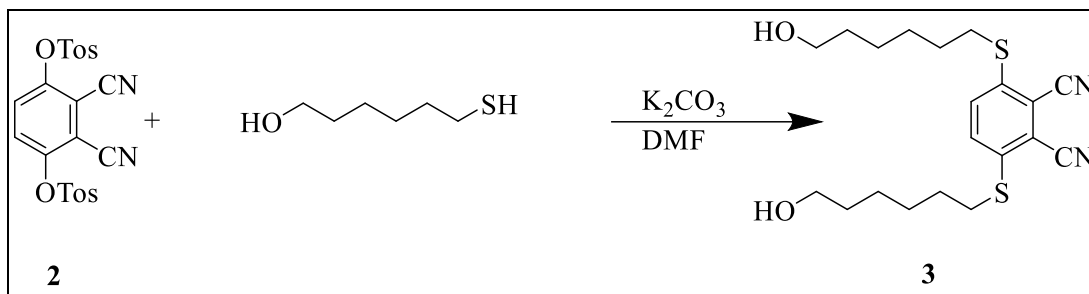


Scheme 4.1: Synthesis of 3,6-bis (4'-methylbenzenesulfonyloxy) phthalonitrile 2.

4-methylbenzenesulfonyl chloride (26.0 g, 135.0 mmol, 2 equiv.) was added to a mixture of dicyanohydroquinone **1** (10.0 g, 65.0 mmol, 1 equiv.) and potassium carbonate (36.0 g, 260.0 mmol, 4 equiv.) in dry acetone (75 mL). The final mixture was heated to reflux for 2 hours, then checked by TLC to ensure that **1** had reacted completely. Afterward, the mixture was cooled down to room temperature, poured into 200 mL of water, and stirred for 1 hour. The reaction mixture was then filtered, and the final product was collected. Yield: 58.0 g (92%).

- C₂₂H₁₆N₂O₆S₂, MW: 468.50 g/mol.
- Melting Point: 181 °C.
- FT-IR (cm⁻¹): 3102, 3098, 3053, 2241 (CN), 1932, 1713, 1655, 1594, 1464, 1388, 1378, 1313, 1296, 1237, 1192, 1177, 1159, 1123, 1088, 1018, 938, 851, 812, 706, 652, 513.
- ¹H NMR (CDCl₃, δ, ppm): 7.80 (d, 4H), 7.77 (s, 2H), 7.44 (d, 4H), 2.55 (s, 6H).
- ¹³C NMR (CDCl₃, δ, ppm): 149.05, 147.41, 130.74, 130.50, 129.44, 128.85, 112.09, 110.60, 21.92.

4.4. Synthesis of 3,6-bis((6-hydroxyhexyl)thio)phthalonitrile (3)

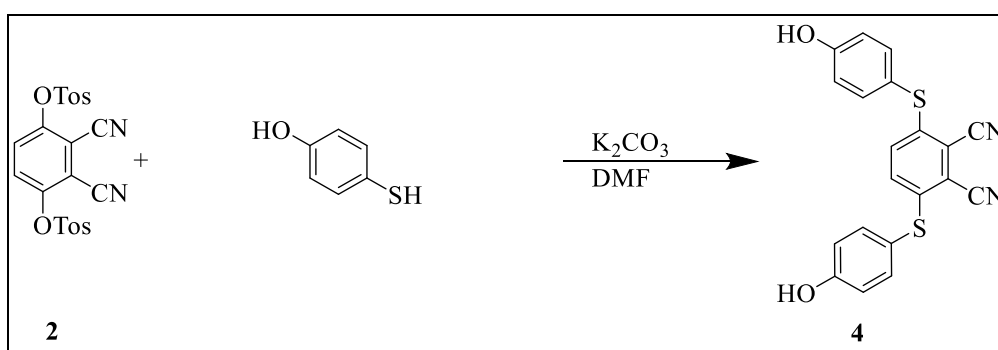


Scheme 4.2: Synthesis of 3,6-bis((6-hydroxyhexyl)thio)phthalonitrile 3.

Ditosylated phthalonitrile **2** (2.5 g, 5.3 mmol, 1 equiv.) was dissolved in DMF (20 mL) which contains potassium carbonate (6.0 g, 42.4 mmol, 8 equiv.), then 6-mercaptohexan-1-ol (1.4 mL, 10.6 mmol, 2 equiv.) was added to the mixture, and heated overnight at 60°C. The mixture was then cooled down to room temperature, and crushed ice was added to precipitate the product. After 30 minutes, the mixture was filtered and dissolved in dichloromethane, then evaporated to obtain the crude product which was purified by column chromatography (silica gel), eluting with hexane and then a hexane/dichloromethane mixture. Yield: 1.0 g (49 %).

- C₂₀H₂₈N₂O₂S₂, MW: 392.58 g/mol.

4.5. Synthesis of 3,6-bis((4-hydroxyphenyl)thio)phthalonitrile (4)

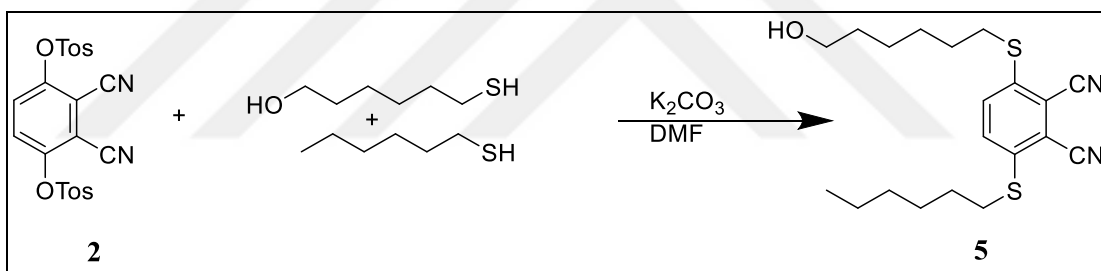


Scheme 4.3: Synthesis of 3,6-bis((4-hydroxyphenyl)thio)phthalonitrile 4.

Ditosylated phthalonitrile **2** (1.7 g, 3.6 mmol, 1 equiv.) was dissolved in DMF (20 mL) which contains potassium carbonate (4.0 g, 28.8 mmol, 8 equiv.), then 4-mercaptophenol (1.0 g, 8.0 mmol, 2.2 equiv.) was added to the mixture, and heated overnight at 60°C. The mixture was then cooled down to room temperature, and crushed ice was added to precipitate the product. After 30 minutes, the mixture was filtered and dissolved in dichloromethane, then evaporated to obtain the crude product which was purified by column chromatography (silica gel), eluting with hexane and then a hexane/dichloromethane mixture. Yield: 0.6 g (44 %).

- $C_{20}H_{12}N_2O_2S_2$, MW: 376.45 g/mol.

4.6. Synthesis of 3-(hexylthio)-6-((6-hydroxyhexyl)thio)phthalonitrile (**5**)

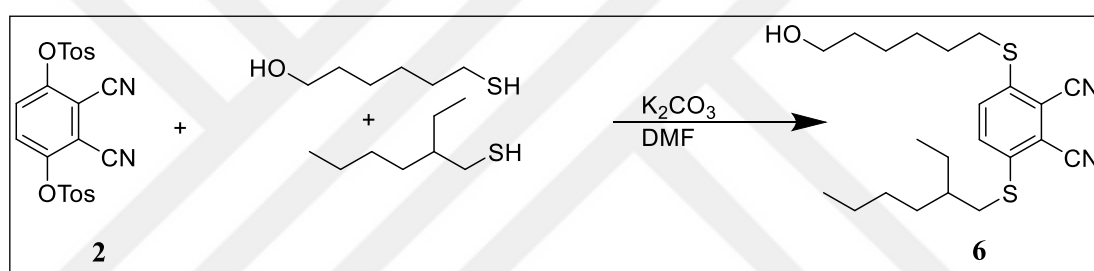


Scheme 4.4: Synthesis of 3-(hexylthio)-6-((6-hydroxyhexyl)thio)phthalonitrile **5**.

Ditosylated phthalonitrile **2** (10.0 g, 22.0 mmol, 1 equiv.) was dissolved in DMF (50 mL) containing potassium carbonate (23.0 g, 176.0 mmol, 8 equiv.). Then, both hexane-1-thiol (4.5 mL, 3.7 g, 33.0 mmol, 1.5 equiv.) and 6-mercaptohexan-1-ol (1.5 mL, 1.5 g, 11.5 mmol, 0.5 equiv.) were added to the mixture and heated for overnight at 60°C. The mixture was then cooled down to room temperature and crushed ice was added to precipitate the product. After 30 minutes, the mixture was filtered and dissolved in dichloromethane, then evaporated to obtain the crude product. The final product was purified by column chromatography (silica gel), eluting with hexane and then a hexane/dichloromethane mixture. Yield: 0.9 g (11 %).

- $C_{20}H_{28}N_2OS_2$, MW: 376.58 g/mol.
- FT-IR (cm^{-1}): 3379 (OH), 2931, 2858, 2223 (CN), 1529, 1464, 1447, 1431, 1365, 1286, 1261, 1192, 1172, 1056, 1034, 986, 810, 722.
- ^1H NMR ($CDCl_3$, δ , ppm): 7.45-7.41 (s, 2H), 3.60-3.57 (t, 2H), 3.01-2.94 (m, 4H), 1.18 (s, 1H), 1.65-1.23 (m, 16H), 0.84-0.81 (t, 3H).
- ^{13}C NMR ($CDCl_3$, δ , ppm): 140.58, 140.00, 131.25, 130.93, 114.20, 115.93, 112.86, 112.83, 61.68, 32.80, 32.74, 31.43, 30.21, 28.68, 27.61, 27.38, 27.34, 24.24, 21.45, 12.69.

4.7. Synthesis of 3-((2-ethylhexyl)thio)-6-((6-hydroxyhexyl)thio)phthalonitrile (6)



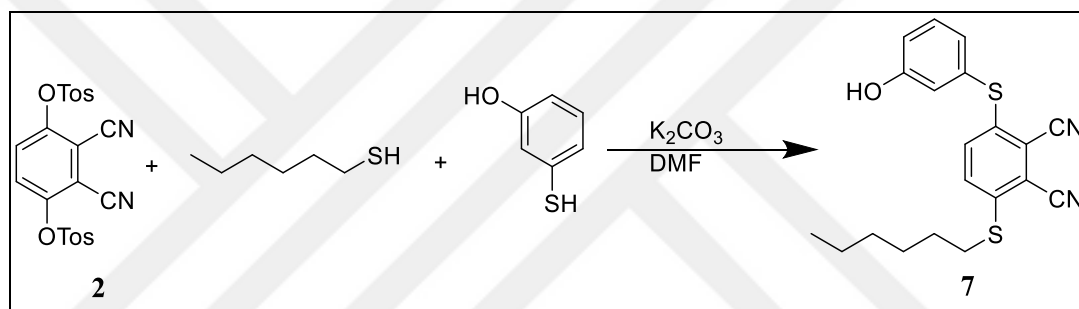
Scheme 4.5: Synthesis of 3-((2-ethylhexyl)thio)-6-((6-hydroxyhexyl)thio)phthalonitrile **6**.

Ditosylated phthalonitrile **2** (5.0 g, 11.0 mmol, 1 equiv.) was dissolved in DMF (50 mL) which contains potassium carbonate (11.5 g, 88.0 mmol, 8 equiv.). Then both 2-ethylhexane-1-thiol (2.8 mL, 2.4 g, 16.5 mmol, 1.5 equiv.) and 6-mercaptohexan-1-ol (0.8 mL, 1.3 g, 5.5 mmol, 0.5 equiv.) were added to the mixture and heated for 24 hours at 60 °C. The mixture then cooled down to room temperature and crushed ice was added to precipitate the product. The oily product was extracted using dichloromethane, then purified by column chromatography (silica gel), eluting with hexane and then hexane/dichloromethane. Yield: 0.3 g (7 %).

- $C_{22}H_{32}N_2OS_2$, MW: 404.63 g/mol.

- FT-IR (cm^{-1}): 3358 (OH), 2959, 2927, 2857, 2501, 2223 (CN), 1529, 1463, 1449, 1428, 1379, 1254, 1203, 1173, 1143, 1057, 1039, 989, 832, 737.
- ^1H NMR (CDCl_3 , δ , ppm): 7.53-7.51 (s, 2H), 3.68 (s, 1H), 3.04-3.00 (m, 4H), 1.51-0.90 (m, 25H).
- ^{13}C NMR (CDCl_3 , δ , ppm): 142.30, 140.82, 132.34, 131.90, 117.14, 116.77, 113.92, 113.90, 62.66, 38.82, 38.22, 32.44, 32.27, 28.69, 28.63, 28.40, 25.52, 25.25, 22.87, 14.04, 10.71.

4.8. Synthesis of 3-(hexylthio)-6-((3-hydroxyphenyl)thio)phthalonitrile (7)

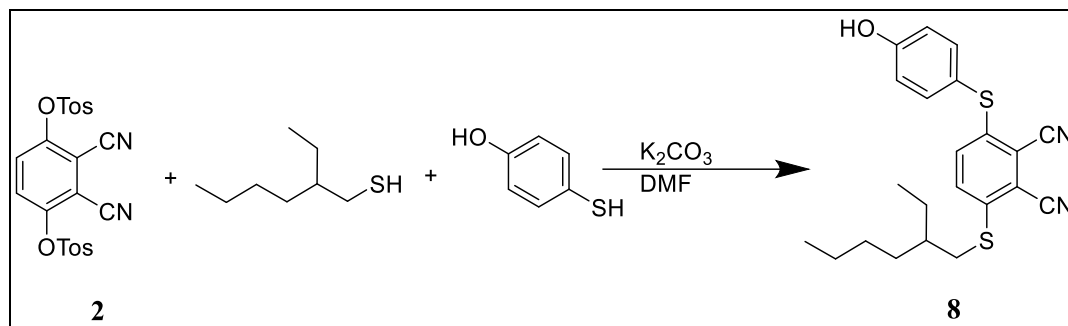


Scheme 4.6: Synthesis of 3-(hexylthio)-6-((3-hydroxyphenyl)thio)phthalonitrile 7.

Ditosylated phthalonitrile **2** (5.7 g, 12.0 mmol, 1 equiv.) was dissolved in DMF (20 mL) which contains potassium carbonate (13.5 g, 98.0 mmol, 8 equiv.). Then both hexane-1-thiol (2.6 mL, 2.2 g 18 mmol, 1.5 equiv.) and 3-mercaptophenol (0.6 mL, 0.8 g, 6.0 mmol, 0.5 equiv.) were added to the mixture and heated overnight at 60 °C. The mixture then cooled down to room temperature and crushed ice was added, then extracted by ethyl acetate. After 30 min, the mixture was filtered and dissolved in dichloromethane, then evaporated to obtain the crude product. The product was purified by column chromatography (silica gel), eluting with hexane and then hexane/dichloromethane. Yield: 0.35 g (8 %).

- $\text{C}_{20}\text{H}_{20}\text{N}_2\text{OS}_2$, MW: 368.51 g/mol.
- FT-IR (cm^{-1}): 3425 (OH), 2927, 2856, 2224 (CN), 1578, 1467, 1374, 1196, 1170, 1157, 1089, 896, 780, 753, 679.

4.9. Synthesis of 3-((2-ethylhexyl)thio)-6-((4-hydroxyphenyl)thio)phthalonitrile (8)

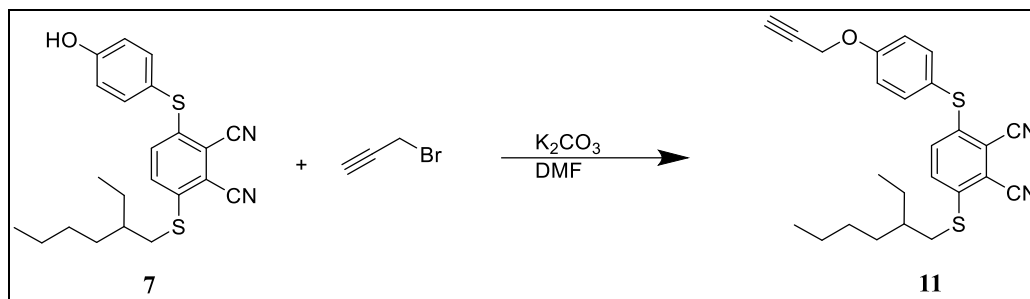


Scheme 4.7: Synthesis of 3-((2-ethylhexyl)thio)-6-((4-hydroxyphenyl)thio) phthalonitrile **8**.

Ditosylated phthalonitrile **2** (5 g, 11 mmol, 1 equiv.) was dissolved in DMF (50 mL) which contains potassium carbonate (12.0 g, 88 mmol, 8 equiv.). Then both 2-ethylhexane-1-thiol (2.8 mL, 2.4 g, 16.5 mmol, 1.5 equiv.) and 4-mercaptoethanol (0.6 mL, 0.7 g, 5.5 mmol, 0.5 equiv.) were added to the mixture and heated for 24 hours at 60 °C. The mixture then cooled down to room temperature and crushed ice was added to precipitate the product. The oily product was extracted using dichloromethane, then purified by column chromatography (silica gel), eluting with hexane and then hexane/dichloromethane. Yield: 0.3 g (7 %).

- $C_{22}H_{24}N_2OS_2$, MW: 396.57 g/mol.
- FT-IR (cm^{-1}): 3398 (OH), 2958, 2926, 2858, 2519, 2225 (CN), 2596, 1582, 1493, 1431, 1269, 1168, 1100, 832.
- ^1H NMR ($CDCl_3$, δ , ppm): 7.40-6.98 (d, 4H), 6.44 (s, 1H), 2.96 (d, 2H), 1.60-1.27 (m, 7H), 0.89-0.80 (t, 6H).
- ^{13}C NMR ($CDCl_3$, δ , ppm): 158.27, 144.30, 141.88, 137.30, 132.29, 131.21, 118.76, 117.58, 116.17, 114.05, 113.78, 113.58, 38.79, 38.32, 32.22, 28.63, 25.48, 22.87, 14.04, 10.68.

4.10. Synthesis of 3-((2-ethylhexyl)thio)-6-(4-hydroxyphenyl)thio)phthalonitrile (**11**)

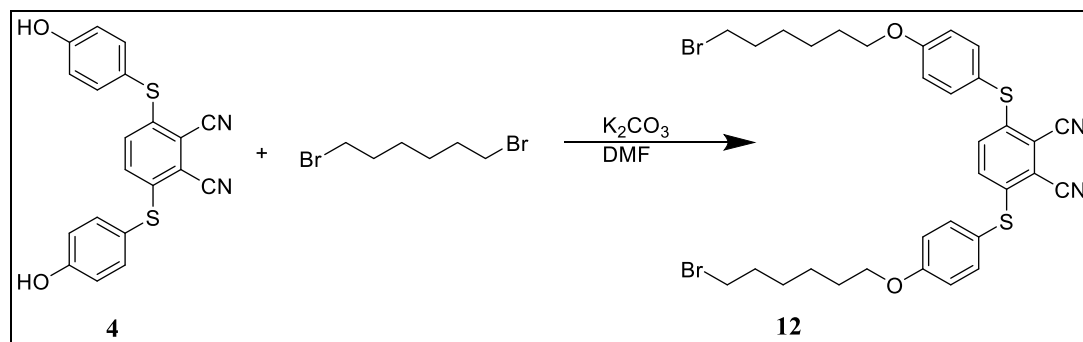


Scheme 4.8: Synthesis of 3-((2-ethylhexyl)thio)-6-((4-hydroxyphenyl)thio)phthalonitrile **11**.

Mono hydroxylated phthalonitrile **7** (0.5 g, 1.26 mmol, 1 equiv.) was dissolved in DMF (10 mL) which contains potassium carbonate (1.3 g, 10.1 mmol, 8 equiv.). Then, propargyl bromide (0.15 g, 1.26 mmol, 1 equiv.) was added to the mixture and left overnight at room temperature under stirring. Then, water was added to the mixture to precipitate the product, but an oily product was formed. The product was filtered, then the crude product was purified by column chromatography (silica gel), eluting with hexane and then hexane/dichloromethane. Yield: 0.4 g (73 %).

- $C_{25}H_{26}N_2OS_2$, MW: 434.62 g/mol.
- FT-IR (cm^{-1}): 3292 (OH), 2958, 2926, 2858, 2223 (CN), 1590, 1491, 1433, 1221 1173, 1021, 909, 828, 731.
- ^1H NMR ($CDCl_3$, δ , ppm): 7.51-7.04 (d, 6H), 4.76 (s, 2H), 2.96 (d, 2H), 2.58 (s, 1H), 1.59-1.27 (m, 9H), 0.89 (t, 6H).
- ^{13}C NMR ($CDCl_3$, δ , ppm): 159.21, 143.32, 142.00, 136.86, 120.77, 116.71, 116.60, 114.47, 113.92, 113.68, 77.77, 76.25, 55.99, 55.98, 38.79, 38.26, 32.22, 28.64, 25.47, 22.86, 14.02, 10.66.

4.11. Synthesis of 3,6-bis((4-((6-bromohexyl)oxy)phenyl)thio)phthalonitrile (**12**)

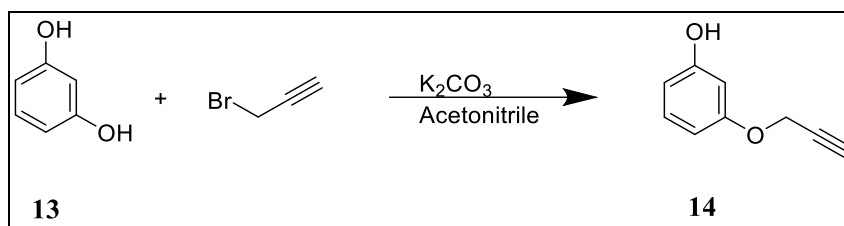


Scheme 4.9: Synthesis of 3,6-bis((4-((6-bromohexyl)oxy)phenyl)thio)phthalonitrile **12**.

Dihydroxylated phthalonitrile **4** (0.6 g, 1.6 mmol, 1 equiv.) was dissolved in DMF (10 mL) which contained potassium carbonate (2.20 g, 16.0 mmol, 10 equiv.). Then 1,6-dibromohexane (1.55 g, 6.4 mmol, 4 equiv.) was added to the reaction and left under stirring at room temperature overnight. The reaction was checked by TLC to ensure that **4** had reacted completely. Then, the reaction mixture was poured into 200 mL of water, filtered, and the crude product was used for the next reaction without further purifications.

- $\text{C}_{32}\text{H}_{34}\text{Br}_2\text{N}_2\text{O}_2\text{S}_2$, MW: 702.56 g/mol.

4.12. Synthesis of 3-(prop-2-yn-1-yloxy)phenol (**14**)

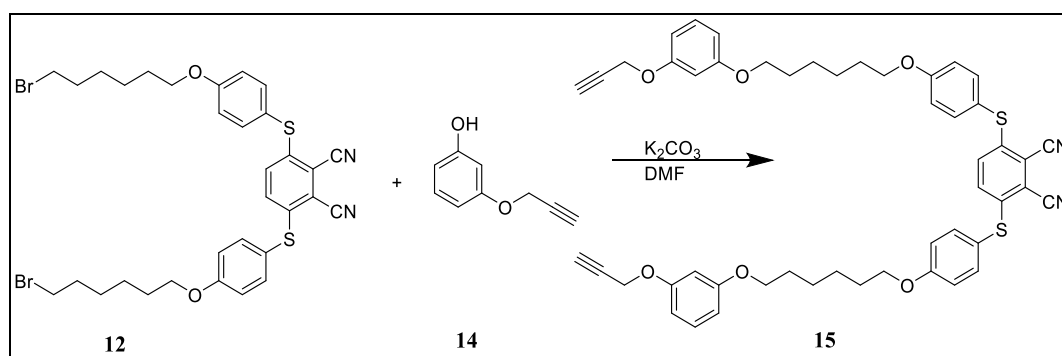


Scheme 4.10: Synthesis of 3-(prop-2-yn-1-yloxy)phenol **14**.

Propargyl bromide (4.1 mL, 45 mmol, 1 equiv.) was added to a mixture of resorcinol **13** (5 g, 45 mmol, 1 equiv.) and potassium carbonate (62 g, 448 mmol, 10 equiv.) in acetonitrile (200 mL). The mixture was heated to reflux for 5 h at 82 °C, then checked by TLC to ensure that **12** had completely reacted. After that, the mixture was cooled down to room temperature. The reaction mixture was then filtered, and a yellow oily product was obtained. The crude product was purified by column chromatography (silica gel), eluting with hexane and then hexane/dichloromethane. Yield: 1.9 g (28 %).

- $C_9H_8O_2$, MW: 148.16 g/mol.
- FT-IR (cm^{-1}): 3287 (OH), 2123, 1594, 1489, 1457, 1372, 1280, 1171, 1143, 1031, 761, 681.
- ^1H NMR ($CDCl_3$, δ , ppm): 7.19-6.49 (m, 4H), 5.38 (s, 1H), 4.68 (s, 2H), 2.54 (s, 1H).
- ^{13}C NMR ($CDCl_3$, δ , ppm): 158.73, 156.69, 130.44, 109.19, 107.36, 102.86, 78.59, 76.10, 56.02.

4.13. Synthesis of 3,6-bis((4-((6-(3-(prop-2-yn-1-yloxy)phenoxy)hexyl)oxy)phenyl)thio)phthalonitrile (**15**)



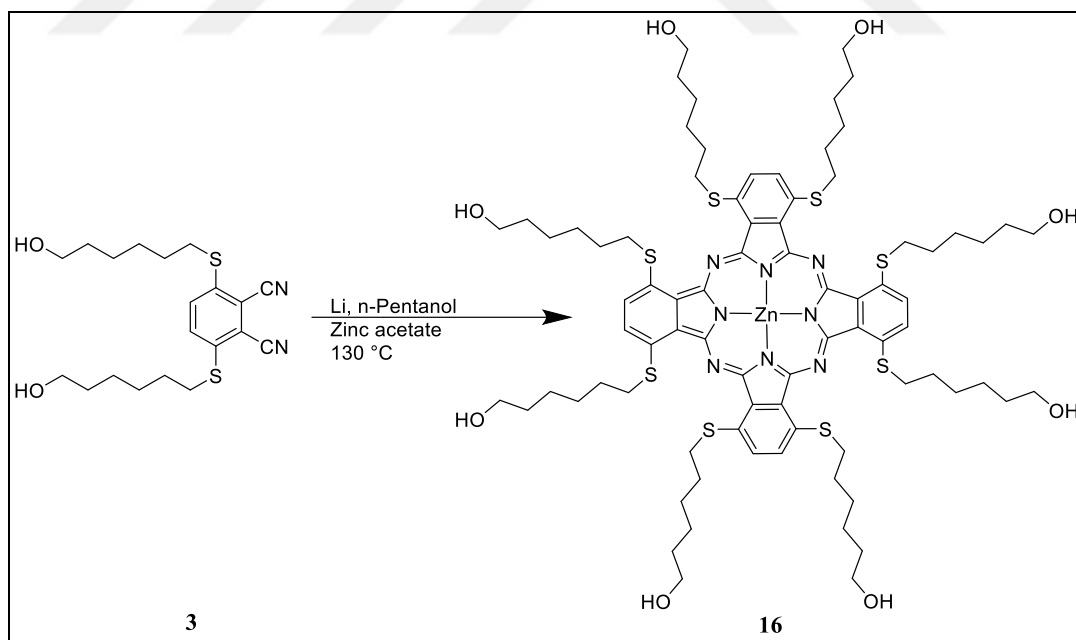
Scheme 4.11: Synthesis of 3,6-bis((4-((6-(3-(prop-2-yn-1-yloxy)phenoxy)hexyl)oxy)phenyl)thio)phthalonitrile **15**.

Dibromohexyl phthalonitrile **12** (0.45 g, 0.64 mmol, 1 equiv.) was dissolved in DMF (20 mL) which contained potassium carbonate (0.70 g, 5.2 mmol, 8 equiv.). Then, monopropagylated resorcinol **14** (0.28 g, 1.9 mmol) was added to the reaction and left under stirring at room temperature overnight. The reaction was checked by TLC to

ensure that the compound **12** had reacted completely. Then, the reaction mixture was poured into 200 mL of water, filtered, and the crude product was purified by column chromatography (silica gel), eluting with hexane/dichloromethane. Yield: 0.4 g (73 %)

- $C_{50}H_{48}N_2O_6S_2$, MW: 837.06 g/mol.
- FT-IR (cm^{-1}): 3292, 2939, 2866, 2223, 1590, 1491, 1470, 1433, 1258, 1248, 1174, 1149, 1039, 907, 829.
- ^1H NMR ($CDCl_3$, δ , ppm): 7.42-6.55 (m, 9H), 4.69 (s, 2H), 3.97 (t, 4H), 2.58 (s, 1H), 1.83-0.10 (m, 8H).
- ^{13}C NMR ($CDCl_3$, δ , ppm): 160.87, 160.28, 158.79, 143.83, 137.11, 131.01, 129.91, 119.06, 116.24, 113.77, 113.63, 107.83, 106.74, 102.00, 68.13, 67.82, 55.85, 29.15, 29.04, 25.86, 25.82, 1.04.

4.14. Synthesis of Hydroxylated Phthalocyanine (**16**)



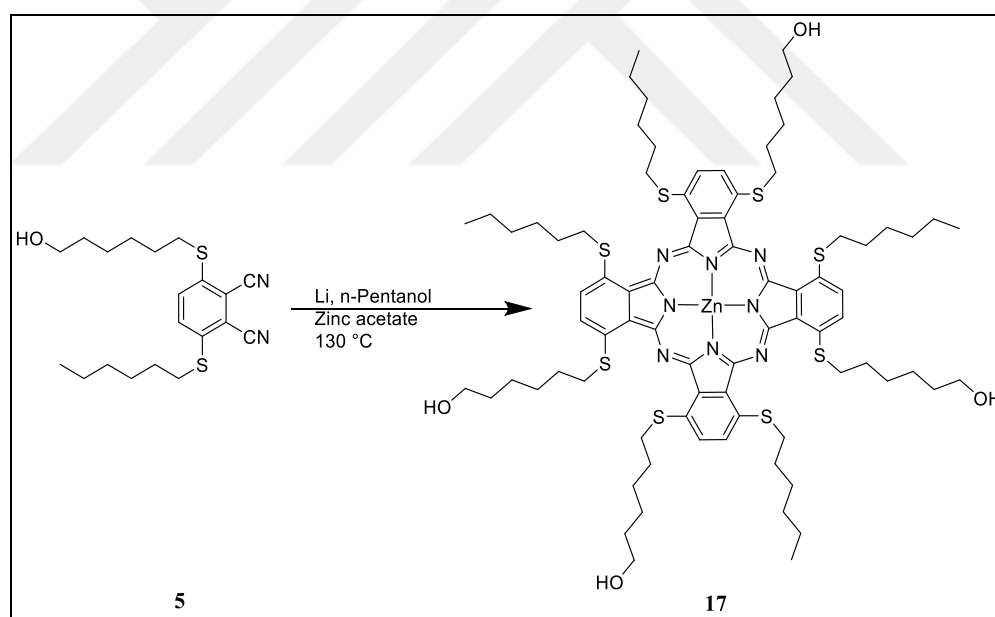
Scheme 4.12: Synthesis of hydroxylated phthalocyanine **16**.

Dihydroxylated phthalonitrile **3** (0.50 g, 1.26 mmol, 1 equiv.) was dissolved in pentanol (5 mL) in a round-bottom flask. Then, lithium metal was added under argon

gas, with stirring at 130 °C. The formation of lithium pentanoate was evidenced by the evolution of hydrogen gas. Meanwhile, the colour gradually changed from yellow to dark green. Then, zinc acetate (1.00 g, 5.10 mmol, 4 equiv.) was added, and the reaction mixture was refluxed for a further 2 hours. After that, water was added to the cooled reaction mixture, followed by ethanol. A very dark precipitate formed, which was then filtered. The crude product was purified by column chromatography (silica gel), eluting with dichloromethane and then a mixture of dichloromethane/ethanol. Yield: 0.2 g (35 %).

- $C_{80}H_{112}N_8O_8S_8Zn$, MW: 1635.68 g/mol.

4.15. Synthesis of Hydroxylated phthalocyanine (17)



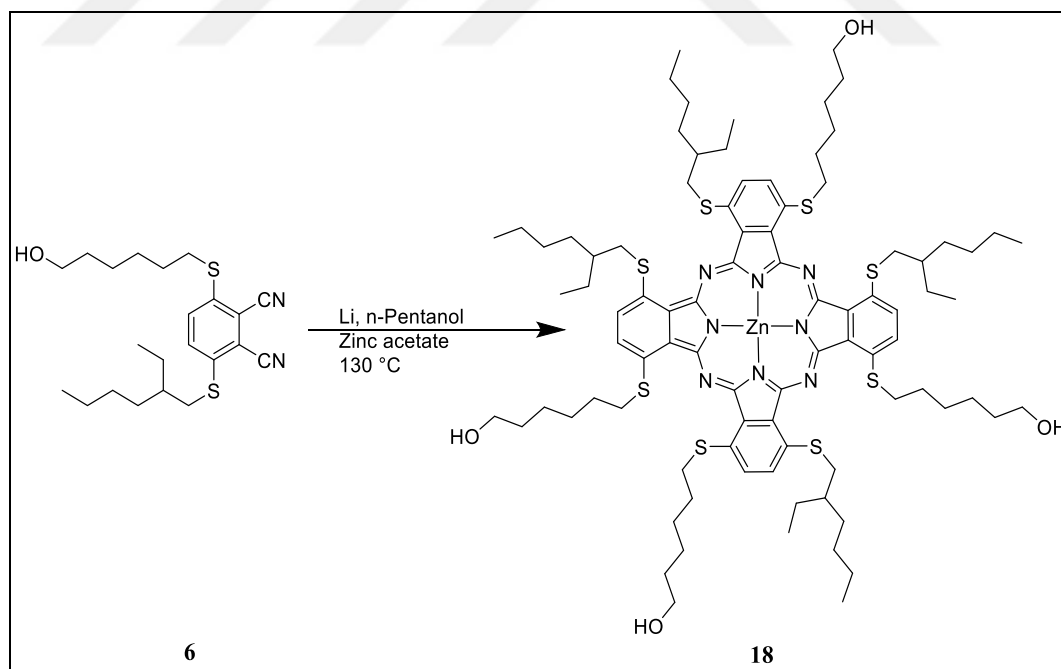
Scheme 4.15: Synthesis of hydroxylated phthalocyanine **17**.

Monohydroxylated phthalonitrile **5** (0.85 g, 2.26 mmol, 1 equiv.) was dissolved in pentanol (10 mL) in a round-bottom flask. Then, lithium metal was added under argon gas, with stirring at 130 °C. The formation of lithium pentanoate was evidenced by the evolution of hydrogen gas. Meanwhile, the colour gradually changed from yellow to dark green. Then, zinc acetate (3.31 g, 18.1 mmol, 8 equiv.) was added, and the

reaction mixture was refluxed for a further 2 hours. After that, water was added to the cooled reaction mixture, followed by ethanol. A very dark green precipitate formed, which was then filtered. The crude product was purified by column chromatography (silica gel), eluting with dichloromethane and then a mixture of dichloromethane/ethanol. Yield: 0.03g (3 %).

- $C_{80}H_{112}N_8O_4S_8Zn$, MW: 1571.69 g/mol.
- FT-IR (cm^{-1}): 3322 (OH), 2922, 2852, 1690, 1561, 1461, 1318, 1283, 1212, 1142, 1106, 1017, 916, 883, 790, 735.
- ^1H NMR ($DMSO-d_6$, δ , ppm): 8.37-7.42 (m, aromatic H), 4.42 (t), 3.04-0.39 (m).
- MS-MALDI-TOF (m/z): 1568.052 $[M]^+$ (Matrix: DIT)

4.16. Synthesis of Hydroxylated phthalocyanine (18)



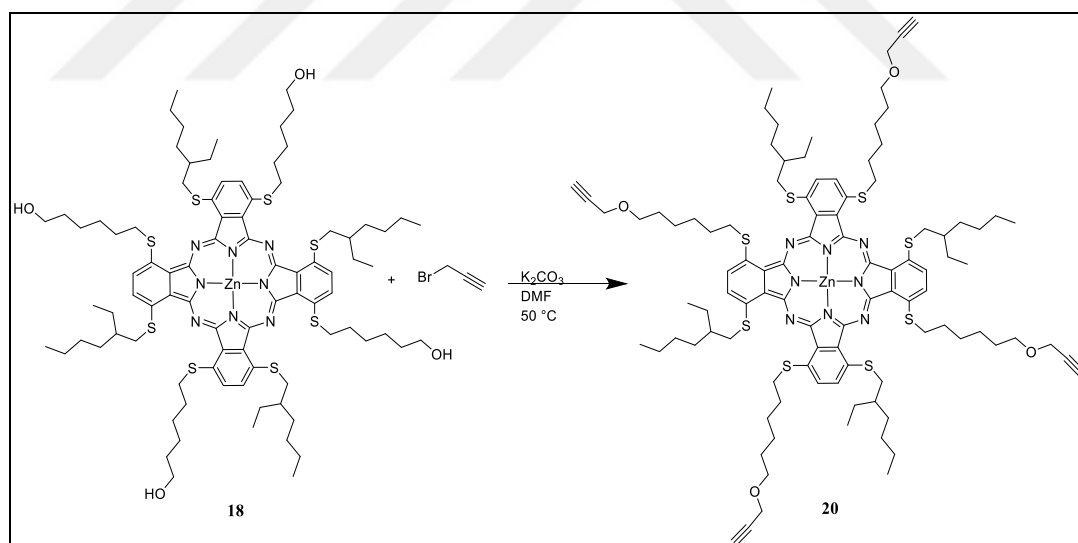
Scheme 4.14: Synthesis of hydroxylated phthalocyanine **18**.

Monohydroxylated phthalonitrile **6** (0.32 g, 0.76 mmol, 1 equiv.) was dissolved in pentanol (10 mL) in a round-bottom flask, then lithium metal was added under argon

gas, with stirring at 130 °C. The formation of pentanoate lithium was evidenced by the degassing of hydrogen. Meanwhile, the colour gradually changed from yellow to dark green. Then, zinc acetate (1.11 g, 6.10 mmol, 8 equiv.) was added, and the reaction mixture was refluxed for a further 2 hours. After that, water was added to the cooled reaction mixture, followed by ethanol. A very dark green precipitate formed, which was filtered out. The crude product was then purified by column chromatography (silica gel), eluting with dichloromethane and then a mixture of dichloromethane/ethanol. Yield: 0.03 g (10 %).

- $C_{88}H_{128}N_8O_4S_8Zn$, MW: 1683.90 g/mol.
- FT-IR (cm^{-1}): 3406 (OH), 1658(CN), 1292, 1049, 1000, 823, 761
- MS-MALDI-TOF (m/z): 1681.314 $[M]^+$ (Matrix: DIT).

4.17. Synthesis of Propargylated Phthalocyanine (20)



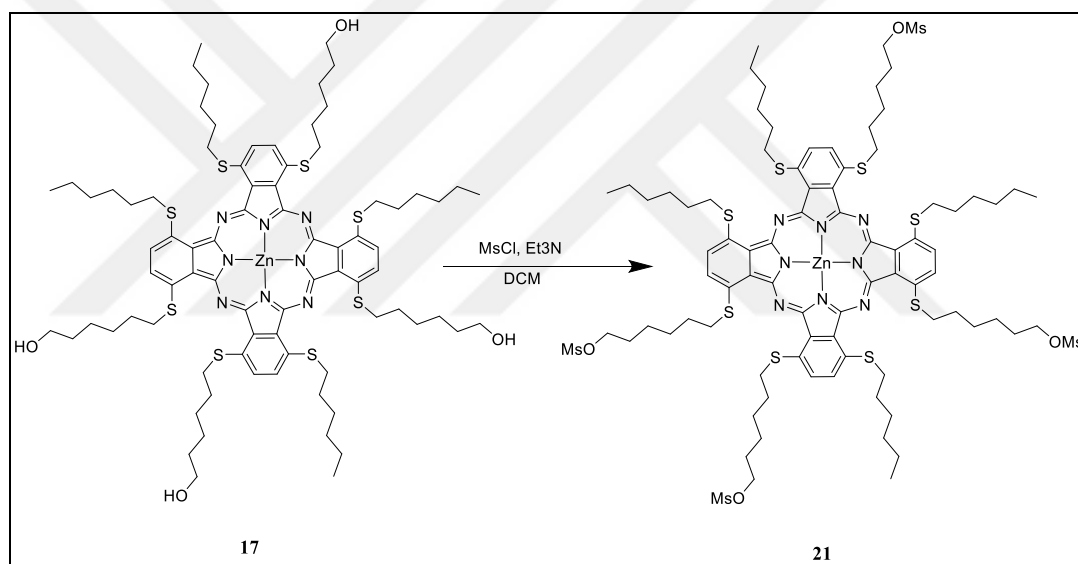
Scheme 4.15: Synthesis of propargylated phthalocyanine **20**.

Hydroxylated phthalocyanine **18** (0.035 g, 0.02 mmol, 1 equiv.) was dissolved in DMF (10 mL) which contains potassium carbonate (0.0140 g, 0.10 mmol, 5 equiv.). Then, propargyl bromide (0.010 g, 0.08 mmol, 4 equiv.) was added to the mixture and left

overnight at room temperature under stirring. Then, water was added to the mixture to precipitate the product. Yield: --- %

- $C_{100}H_{136}N_8O_4S_8Zn$, MW: 1836.10 g/mol.
- MS-MALDI-TOF (m/z): 1832.961 $[M]^+$ (Matrix: DIT).

4.18. Synthesis of Mesylated phthalocyanine (21)



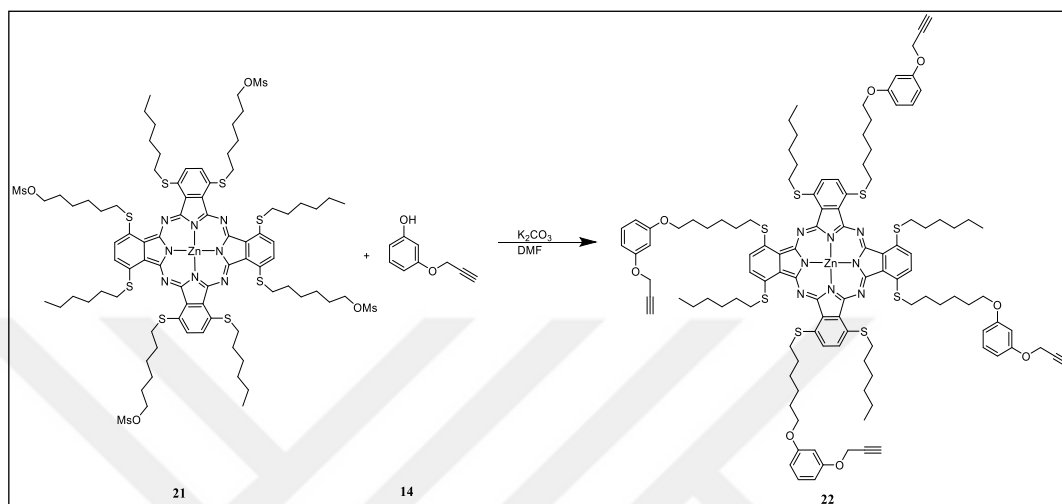
Scheme 4.16: Synthesis of mesylated phthalocyanine **21**.

Hydroxylated phthalocyanine **17** (0.30 g, 0.2 mmol, 1 equiv.) was dissolved in DCM (50 mL) containing triethylamine (20 mL) under stirring in an ice bath. Then, methanesulfonyl chloride ($MsCl$) (1.5 mL, 2.1 g, 20 mmol, 10 equiv.) was added dropwise. The reaction mixture was left under stirring for 3 hours. After that, the reaction was poured into water and filtered. The precipitate was dried and used directly without any further purification. Yield: 0.34 g (90 %).

- $C_{84}H_{120}N_8O_{12}S_{12}Zn$, MW: 1884.03 g/mol.

- MS-MALDI-TOF (m/z): 1887.731 $[M]^+$ (Matrix: DIT)

4.19. Synthesis of Propargylated phthalocyanine (22)

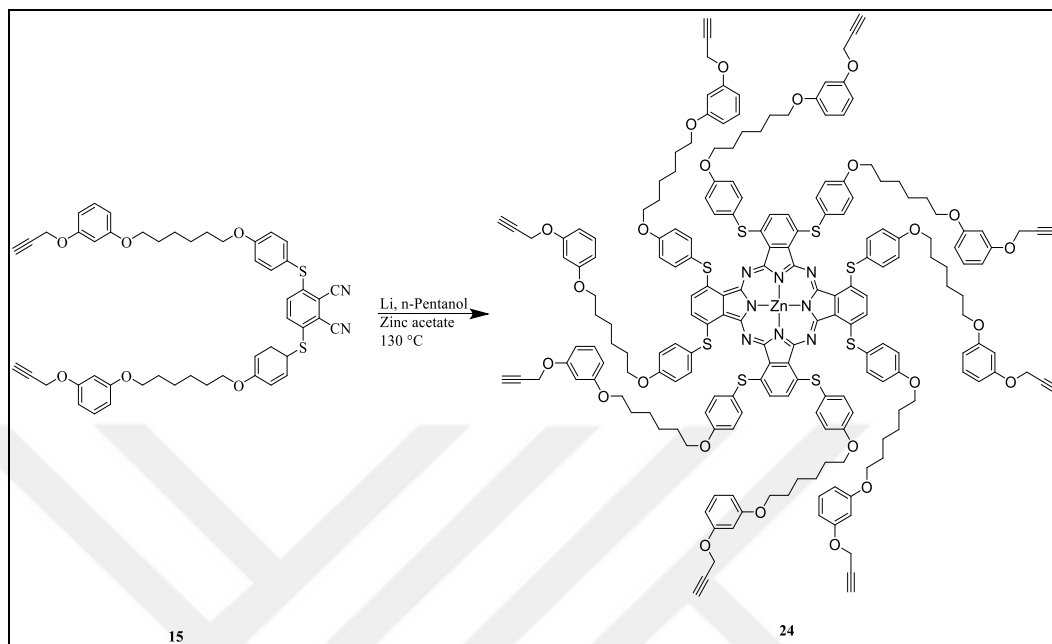


Scheme 4.17: Synthesis of propargylated phthalocyanine **22**.

Mesyalted phthalocyanine **21** (0.33 g, 0.18 mmol, 1 equiv.) was dissolved in DMF (20 mL), which contained potassium carbonate (0.10 g, 0.72 mmol, 4 equiv.). Then, monopropargylated resorcinol **14** (0.13 g, 0.90 mmol) was added to the reaction and left under stirring at room temperature overnight. The reaction was checked by TLC to ensure that the **21** had reacted completely. Then, the reaction mixture was poured into 150 mL of water, filtered, and the crude product was dried.

- $C_{116}H_{136}N_8O_8S_8Zn$, MW: 2092.27 g/mol.
- MS-MALDI-TOF (m/z): 2088.437 $[M]^+$ (Matrix: DIT)

4.20. Synthesis of Propargylated phthalocyanine (24)



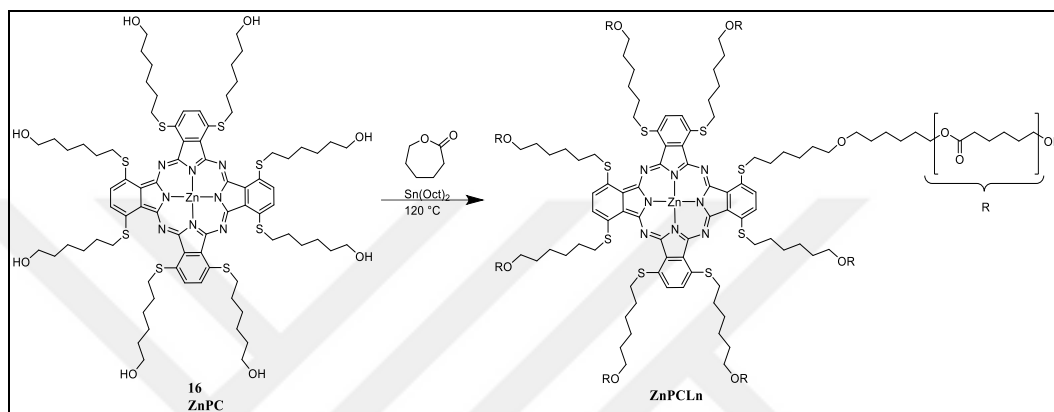
Scheme 4.18: Synthesis of propargylated phthalocyanine **24**.

Propargylated phthalonitrile **15** (0.25 g, 0.30 mmol, 1 equiv.) was dissolved in pentanol (10 mL) in a round-bottom flask. Then, lithium metal was added under argon gas, with stirring at 130 °C. The formation of lithium pentanoate was evidenced by the evolution of hydrogen gas. Meanwhile, the colour gradually changed from yellow to dark green. Then, zinc acetate (0.22 g, 1.20 mmol, 4 equiv.) was added, and the reaction mixture was refluxed for a 15 min. After that, water was added to the cooled reaction mixture, followed by ethanol. A dark precipitate formed, which was then filtered.

- $\text{C}_{200}\text{H}_{192}\text{N}_8\text{O}_{24}\text{S}_8\text{Zn}$, MW: 3413.63 g/mol.
- MS-MALDI-TOF (m/z): 3413.843 $[\text{M}]^+$ (Matrix: DIT).

4.21. Synthesis of Poly-(ϵ -caprolactone) Star Polymers (ZnPc-PCLn)

The ϵ -caprolactone monomer was subjected to ring-opening polymerization, with octahydroxylated phthalocyanine zinc(II) **ZnPc** acting as the initiator. $\text{Sn}(\text{Oct})_2$ was employed as a catalyst at three different monomer/initiator ratios: $[\text{M}]/[\text{I}] = 20, 30$, and 40 . The polymerization reactions were carried out in an argon atmosphere. The synthesis of PCL polymers using **ZnPc** is illustrated in Figure 4.23.



Scheme 4.19: Synthesis of the three star polymers **ZnPc-PCL20**, **ZnPc-PCL30** and **ZnPc-PCL40**.

4.21.1. Synthesis of Poly-(ϵ -caprolactone) Star Polymer (ZnPc-PCL20)

Hydroxylated phthalocyanine ZnPc (0.04 g, 0.025 mmol, 1 equiv.) was added as an initiator into a dried round-bottom flask. This was followed by the addition of $\text{Sn}(\text{Oct})_2$ (0.008 g, 0.020 mmol, 1 equiv.) and ϵ -caprolactone (0.451 g, 3.952 mmol, 160 equiv.). The reaction mixture was then deoxygenated with argon for 10 minutes. The flask was immersed in an oil bath pre-set to 120 °C and stirring was applied vigorously. An increase in viscosity was observed as the reaction proceeded.

After 24 hours, a dark viscous substance had formed. The reaction mixture was allowed to cool down, during which time the reaction crude solidified. Approximately (5 mL) of DCM was added to remove the remaining unreacted monomer and catalyst. The dissolved crude was then taken with a pasture pipette and transferred dropwise into vigorously stirred cold methanol (500 mL) to precipitate it. The precipitated crude was filtered through a sintered glass filter (G4) and dried under reduced pressure at ambient temperature until a constant weight was achieved. Yield: 0.45 g (91%).

- The theoretical number-average molecular weight ($M_{n, \text{theo}}$): 19898 g/mol.
- The number-average molecular weight according to NMR ($M_{n, \text{NMR}}$): 20272 g/mol.
- The number-average molecular weight according to GPC ($M_{n, \text{GPC}}$): 11700 g/mol.
- The PDI: 1.28.
- FT-IR (cm^{-1}): 3442 (O-H, broad), 2942 and 2867 (C-H), 1721 (C=O), 1471 (C-H), 1240 ((C=O)-O), 1044 (C-O-C).
- ^1H NMR (CDCl_3 , δ , ppm): 4.03 (m, $-\text{CH}_2\text{O}(\text{C}=\text{O})-$); 3.63 (m, terminal CH_2OH); 2.29 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2$); 1.63 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$); 1.37 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$)

4.21.2. Synthesis of Poly-(ϵ -caprolactone) Star Polymer (ZnPc-PCL30)

Hydroxylated phthalocyanine ZnPc (0.025 g, 0.015 mmol, 1 equiv.) was added as an initiator into a dried round-bottom flask. This was followed by the addition of $\text{Sn}(\text{Oct})_2$ (0.009 g, 0.021 mmol, 1 equiv.) and ϵ -caprolactone (0.488 g, 4.280 mmol, 285 equiv.). The reaction mixture was then deoxygenated with argon for 10 minutes. The flask was immersed in an oil bath pre-set to 120 °C and stirring was applied vigorously. An increase in viscosity was observed as the reaction proceeded.

After 24 hours, a dark viscous substance had formed. The reaction mixture was allowed to cool down, during which time the reaction crude solidified. Approximately (5 mL) of DCM was added to remove the remaining unreacted monomer and catalyst. The dissolved crude was then taken with a pasture pipette and transferred dropwise into vigorously stirred cold methanol (500 mL) to precipitate it. The precipitated crude was filtered through a sintered glass filter (G4) and dried under reduced pressure at ambient temperature until a constant weight was achieved. Yield: 0.45 g (88%).

- The theoretical number-average molecular weight ($M_{n, \text{theo}}$): 29029 g/mol.
- The number-average molecular weight according to NMR ($M_{n, \text{NMR}}$): 29102 g/mol.
- The number-average molecular weight according to GPC ($M_{n, \text{GPC}}$): 19500 g/mol.
- The PDI: 1.18.
- FT-IR (cm^{-1}): 3440 (O-H, broad); 2945 and 2867 (C-H); 1721 (C=O); 1471 (C-H); 1239 ((C=O)-O); 1045 (C-O-C).

- ^1H NMR (CDCl_3 , δ , ppm): 4.04 (m, $-\text{CH}_2\text{O}(\text{C}=\text{O})-$); 3.63 (m, terminal CH_2OH); 2.29 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2$); 1.64 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$); 1.37 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$).

4.21.3. Synthesis of Poly-(ϵ -caprolactone) Star Polymer (ZnPc-PCL40)

Hydroxylated phthalocyanine ZnPc (0.020 g, 0.012 mmol, 1 equiv.) was added as an initiator into a dried round-bottom flask. This was followed by the addition of $\text{Sn}(\text{Oct})_2$ (0.009 g, 0.021 mmol, 1 equiv.) and ϵ -caprolactone (0.502 g, 4.402 mmol, 367 equiv.). The reaction mixture was then deoxygenated with argon for 10 minutes. The flask was immersed in an oil bath pre-set to 120 °C and stirring was applied vigorously. An increase in viscosity was observed as the reaction proceeded.

After 24 hours, a dark viscous substance had formed. The reaction mixture was allowed to cool down, during which time the reaction crude solidified. Approximately (5 mL) of DCM was added to remove the remaining unreacted monomer and catalyst. The dissolved crude was then taken with a pasture pipette and transferred dropwise into vigorously stirred cold methanol (500 mL) to precipitate it. The precipitated crude was filtered through a sintered glass filter (G4) and dried under reduced pressure at ambient temperature until a constant weight was achieved. Yield: 0.46 g (89%).

- The theoretical number-average molecular weight ($M_{n, \text{theo}}$): 38160 g/mol.
- The number-average molecular weight according to NMR ($M_{n, \text{NMR}}$): 38671 g/mol.
- The number-average molecular weight according to GPC ($M_{n, \text{GPC}}$): 31200 g/mol.
- The PDI: 1.08.
- FT-IR (cm^{-1}): 3437 (O-H, broad); 2946 and 2868 (C-H); 1721 (C=O), 1471 (C-H), 1240 ((C=O)-O); 1045 (C-O-C).
- ^1H NMR (CDCl_3 , δ , ppm): 4.05 (m, $-\text{CH}_2\text{O}(\text{C}=\text{O})-$); 3.63 (m, terminal CH_2OH); 2.29 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2$); 1.63 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$); 1.38 (m, $\text{O}(\text{C}=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{O}(\text{C}=\text{O})$).

5. CONCLUSIONS

Biocompatible star polymers with a core of zinc phthalocyanine have been successfully synthesized and thoroughly characterized. These polymers are unique due to their core structure, which is a phthalocyanine with an octa-SR non-peripheral substitution pattern. This specific structure gives the nanoparticles some interesting properties.

One of the most notable properties of these nanoparticles is their strong absorption at near-infrared wavelengths. This is particularly significant because this absorption remains strong even when the nanoparticles are in water. This characteristic is crucial for many applications, especially in the field of photodynamic therapy.

It's important to note that while these initial results are promising, further testing is needed to fully understand the potential of these nanoparticles. Biological experiments are currently underway and will provide more insight into the practical applications of these nanoparticles. The results of these experiments will be reported in the near future.

This research represents an exciting development in the field of nanotechnology and has the potential to significantly advance photodynamic therapy treatments. As we continue to explore and understand the properties of these nanoparticles, we may discover even more applications for this versatile material. The future certainly looks bright for zinc phthalocyanine-cored PCL star polymers.

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BIOGRAPHY

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PUBLICATIONS AND PRESENTATIONS FROM THE THESIS

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