Synthesis of Novel Red-Shifted Phthalocyanines

Ph.D Thesis

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DECLARATION

I herby certify that this material, which I now submit for assessment on the programme of study leading to the award of Doctor of Philosophy, is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: Jianjun Yang Student Number: 50161458

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Date: 31/08/06

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ABBREVIATIONS

GENERAL ABBREVIATIONS

AIBN	α,α'-azobisisobutyronitrile
$AlPc(SO_3H)_4$	aluminum (III) phthalocyanine tetrasulfonate
Ar	aromatic
ATPase	adenosine triphosphatase
Bim	benzimidazole
Br	bromo
CCl_4	carbon tetrachloride
CD	cyclodextrin
Cl	chloro
CM	cytoplasmic membrane
$Co(OAc)_2$	cobalt acetate
CoPc	phthalocyaninato cobalt (II)
CQ	7-chloroquinoline
CuCN	copper (I) cyanide
CuI	copper (I) iodide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBN	1,8-diazabicyclonon-5-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAE	dimethylaminoethanol
DMAP	4-dimethylaminopyridine

DMF	dimethylformamide
DMSO	dimethyl sulphoxide
$(F_3CCO)_2O$	trifluoroacetic anhydride
H_2SO_4	sulphuric acid
H_3PO_4	phosphoric acid
HCl	hydrochloride acid
$HCONH_2$	formamide
HPLC	high performance liquid chromatography
I	iodo
IR	infra-red
KBr	potassium bromide
K_2CO_3	potassium carbonate
$KMnO_4$	potassium permanganate
KOH	potassium hydroxide
LiOH	lithium hydroxide
MAB	monoclonal antibodies
MALDI	matrix assisted laser desorption/ionization
$MgSO_4$	magnesium sulfate
MNc	metallo naphthalocyanine
MPc	metallo phthalocyanine
MS	mass spectra
NaI	sodium iodide
NaOAc	sodium acetate
$NaOCH_3$	sodium methoxide
NaOH	sodium hydroxide

Nap	naphthalene
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
NH_4OH	ammonium solution
NMR	nuclear magnetic resonance
Nc	naphthalocyanine
Pc	phthalocyanine
PCl_5	phosphorus pentachloride
Pd (II) $(OAc)_2$	palladium acetate
$PdCl_2(PPh_3)_2$	dichloro-bis(triphenylphosphine)-palladium (II)
PDT	photodynamic therapy
Ph_3P	triarylphosphines
PPA	poly phosphoric acid
PTC	phase transfer catalysis
$SOCl_2$	thionyl chloride
TEA	triethylamine
TEBA	triethylbenzylamine chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV/Vis	ultraviolet-visible
$Zn(OAc)_2$	zinc acetate
PcZn	phthalocyaninato zinc (II)

Abstract

We prepared four types of red-shift phthalocyanines: 2,9,16,23-tetra(hetp-*t*-1-enyl) phthalocyanine; 2,9,16,23-tetrachloro-3,10,17,24-tetra(3-methoxyprop-1-ynyl) phthalocyanine; 3,4,12,13,21,22,30,31–octa(alkynyl) and octa(alkenyl) naphthalocyanines. It was found that the each conjugated alkenyl group causes about 3nm red-shift on the Pc Q-band. We also demonstrated the π-conjugation of Ncs lead to a 3.5 ~ 4 nm red-shift for each alkynyl and a 3.5 nm red-shift for each alkenyl on the Q-bands.

In this thesis we also prepared the unsymmetrical substituted Pcs via both solid-support synthesis and liquid phase synthesis. Size-exclusion separation was used in the purification for the target Pc.

The one-step bromination to prepare 4-bromophthalonitrile was reported to produce a mixture containing up to three products, we found controlling the stiochiometric ratio of phthalonitrile to dibromoisocyanuric acid could give single product: 4-bromophthalonitrile in 33% yield.

In chapter 7, we introduced the preparations of benzimidazole-chloroquinoline complexes, a type of candidates for antimalaria and anti-HIV.

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Chapter 1: Literature review

1.1 Introduction

Phthalocyanine (Pc) **(1)** was first synthesized in 1907 and the structure was determined by Sir Linstead in the 1930s. The name "phthalocyanine" originates from Greek "naphtha" (rock oil) and "cyanine" (blue). (Figure 1.1)

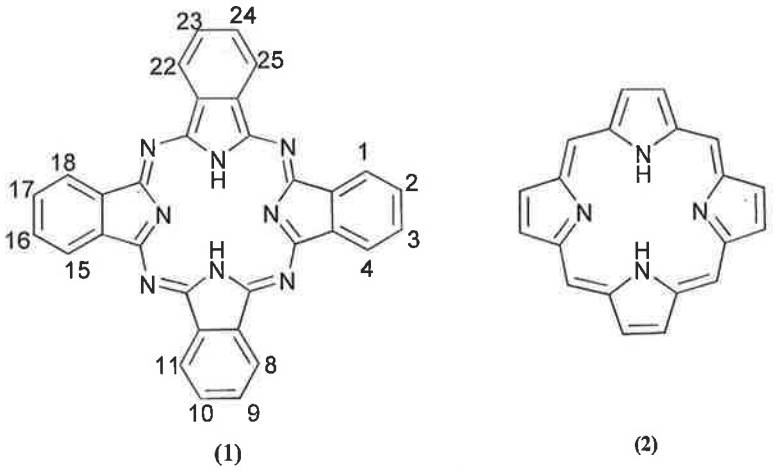


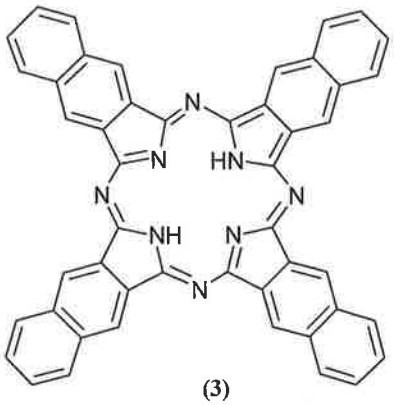
Figure 1.1 *The structures of Pc* ***(1)*** *and porphyrin* ***(2)***.

Pc is a tetramer macrocycle which is a planar conjugated array of 18-π electrons exhibiting aromatic behavior, formed from four isoindolines linked via azo-bridge. A comparison of Pcs with the natural porphyrin **(2)** (Figure 1.1), shows that Pcs have shorter diagonal N-N distance (396 pm) than in most porphyrins (402 pm).

Q-band of Pc is further red-shift at 680 nm compared to porphyrin (630nm), this is a result of the extended conjugation of the peripheral benzo groups in the Pc macrocycle.

Pcs have been used as dyes, [2] catalysts, [3] and optical data storage materials. [4] More recently Pcs have found potential as second generation photosensitisers in the photodynamic therapy (PDT) of cancer treatment. [5]

A related macrocycle to the Pcs is the family of naphthalocyanines (Ncs), these compounds possess an additional four benzo groups fused to the peripheral benzo groups of the Pc core. These molecules have also found applications in various areas: biological, electrochemistry, and optical data storage, etc. The absorption lambda (λmax) of Nc **(3)** is in the near infra-red region around 770 nm, an approximately 90 nm bathochromic shift versus Pc (680 nm). A typical Nc structure (2,3-naphthalocyanine (2,3-Nc) **(3)**), is outlined in Figure1.2.



(3)

Figure 1.2 *The structure of 2,3-Nc* ***(3)****.*

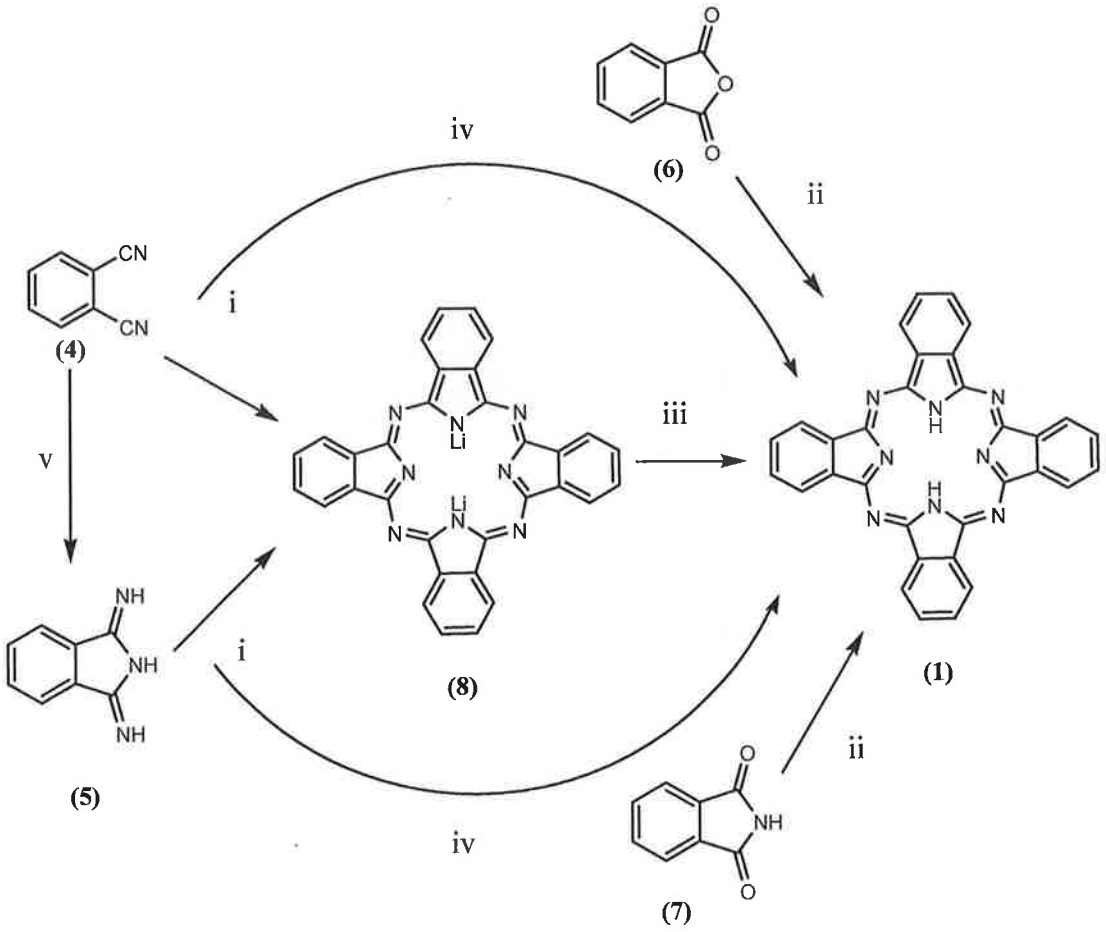
1.2 The synthesis of metal-free phthalocyanines and metallo phthalocyanines (PcM)

1.2.1 The preparation of unsubstituted metal-free phthalocyanines (PcH_2)

Pc can be prepared from a number of ortho-disubstituted benzene derivatives such as phthalonitrile, phthalimide, phthalic anhydride and 1,3-diiminoisoindoline. (Scheme 1.1)

Phthalonitrile **(4)** and 1,3-diiminoisoindoline **(5)** are two common types of starting materials used to prepare metal free Pcs (PcH_2). A typical synthetic procedure for preparing PcH_2 involves the condensation of phthalonitrile to dilithium Pc ($PcLi_2$) by

refluxing phthalonitrile and lithium metal in pentanol. $PcLi_2$ is then treated with dilute acid, to give PcH_2 in yields up to 60%.



Scheme 1.1 *The procedure for the cyclotetramerisation of phthalonitrile to form metal-free Pc (PcH_2). i Lithium, reflux; pentanol. ii Heat in a high boiling point solvent with urea. iii Treat with acid. iv Heat; 1,8-diazabicyclonon-5-ene (DBN); pentanol. (or dimethylaminoethanol (DMAE) and pentanol). v Sodium metal (Na); ammonium (NH_3); Methanol.*

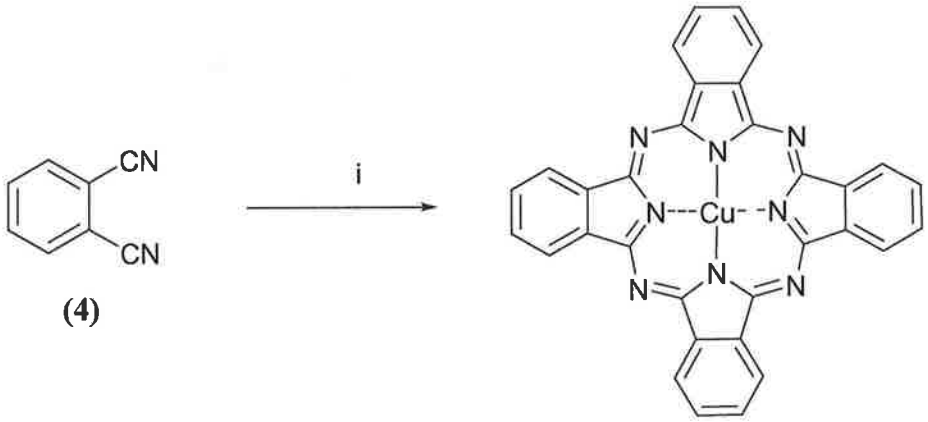
Alternatively, phthalonitrile can also be converted to 1,3-diiminoisoindoline **(5)**, by the reaction of phthalonitrile with ammonia and sodium metal in methanol under mild conditions (Scheme 1.1). The 1,3-diiminoisoindoline **(5)** is then condensed in a reducing solvent such as dimethylaminoethanol (DMAE), to produce PcH_2.

Non-nucleophilic hindered bases such as 1,8-diazabicyclonon-5-ene (DBN) and 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) can also be used for the preparation of metal-free Pcs from phthalonitriles in either a melt or in pentanol solution. [6]

1.2.2 The synthesis of unsubstituted metallo phthalocyanines (PcM)

Until the mid-1990s, about 70 elements (Cu^{2+}, Co^{2+}, Fe^{2+}, etc) have been incorporated as the central metal atoms in PcM complexes.

Most metallo Pcs (PcM) are prepared directly from the same starting materials as used for the preparation of PcH_2, except the condensations are carried out in the presence of the respective metal salts. (Scheme 1.2)

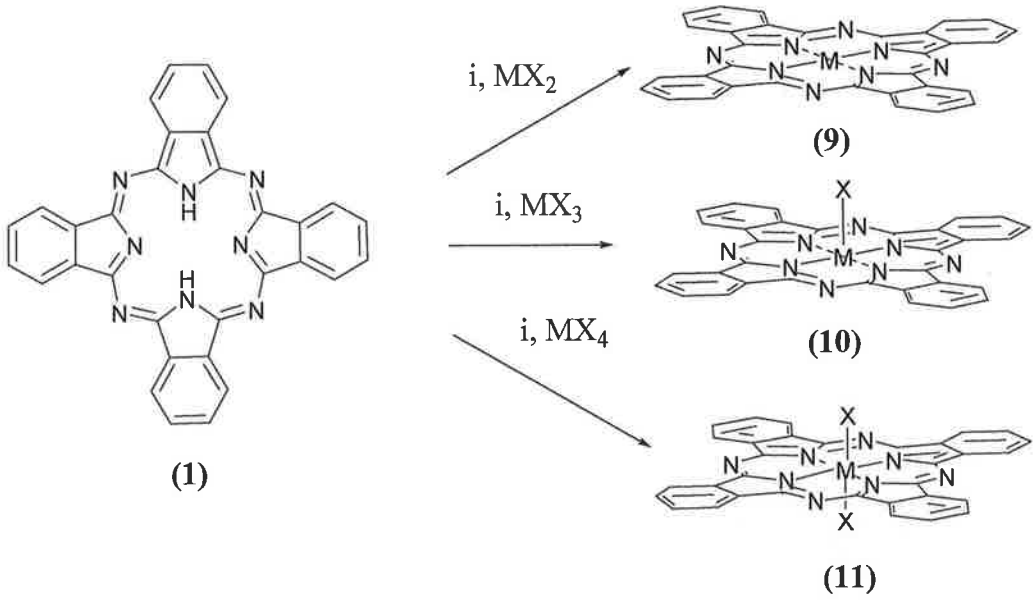


(4) **(9)**

M= Cu^{2+}; Zn^{2+}; Co^{2+}; etc.

Scheme 1.2 *The preparation of PcM. i. Heat; Li/Pentanol; metal salt.*

Alternatively, PcMs can also be prepared by treating PcH_2 with a metal salt (MXn), in a high boiling point solvent (Scheme 1.3).

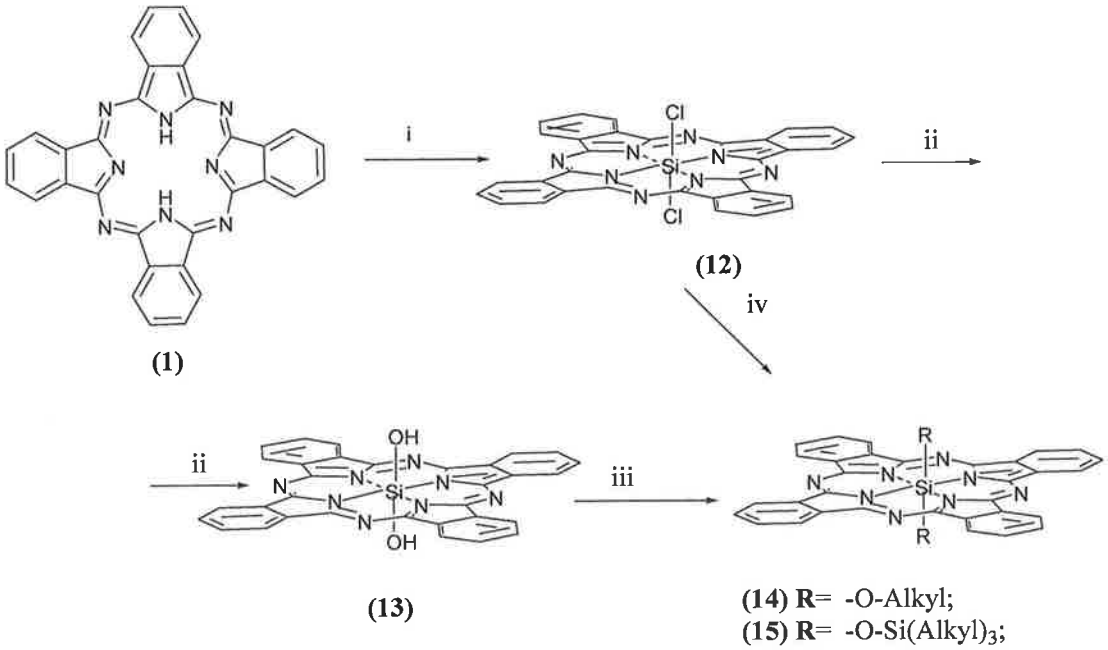


M= Cu^{2+}; Co^{2+};Zn^{2+}; Fe^{2+}; Al^{3+};Rh^{3+};
Si^{4+}; In^{3+}; etc.
X= Cl; I.

Scheme 1.3 *The synthesis of PcM i Heat; PcH_2; MX_n ; high boiling point solvent.*

Typically, most metals inserted into Pc are of a +2 oxidation state. PcM complexes containing the +3 or +4 metals in the center (such as Bi^{3+}; Rh^{3+}; Sn^{3+}; In^{3+}, Si^{4+}; etc,), can bind one or two axial ligands on the central metals. These PcM complexes have also drawn great interest since axial ligands can prevent aggregation through steric hindrance of the macrocycle.

An excellent example of such a Pc is the axial substituted silicon Pcs (α-$PcSiR_2$) which were prepared by Joyner et.al in 1962.[7] These complexes exhibit enhanced solubility in common organic solvents and display clear intermolecular edge-to-edge interactions in the solid state. [8] (Scheme 1.4)

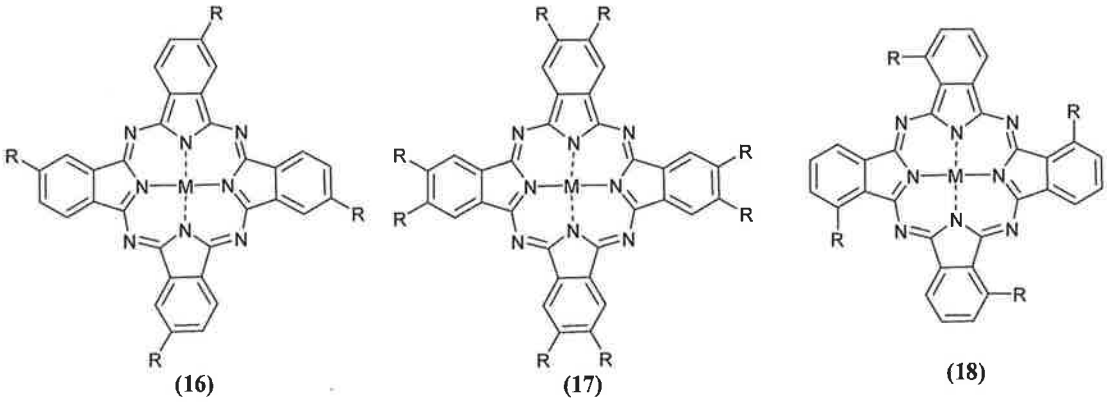


Scheme 1.4 *The synthesis of axial substituted silicon Pcs. i PcH_2; heat; silicon tetrachloride; high boiling point solvent. ii Hydrolysis using acidic or basic. iii Alcohol or silyl chloride; reflux; dry pyridine. iv Alcohol or silyl chloride; toluene; 80°C; base.*

1.2.3 Synthesis of benzo substituted phthalocyanines

There are 16 positions (marked on structure **(1)** in Figure 1.1) on the four peripheral benzo rings of the Pc (or PcM) core, which can be potentially functionalised.

If the substitution occurs at the 2,9,16,23 or 2,3,9,10,16,17,23,24 positions, it is usually referred to as a "peripheral substituted Pc", (eg. **(16)** and **(17)** in Figure 1.1). In contrast, a 1,8,15,22- tetra-substituted Pc **(18)** (or the substituents on 1,4,8,11,15, 18,22,25 positions) is referred to as a "non-peripheral substituted Pc". (Figure 1.3)

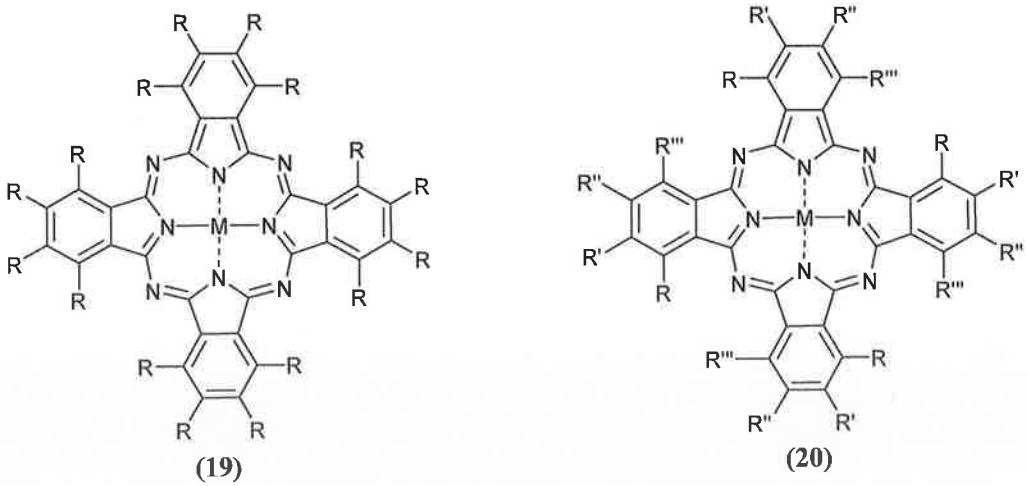


(16) **(17)** **(18)**

M= Cu^{2+}; Co^{2+}; Zn^{2+};Fe^{2+}; etc.
R= H; Alkyl;Alkoxyl.

Figure 1.3 *The structures of 2,9,16,23-tetra-substituted Pcs (or PcM)* ***(16)****, 2,3,9,10,16, 17,23,24-octa-substituted Pcs (or PcM)* ***(17)*** *and 1,8,15,22- tetra-substituted Pcs (or PcM)* ***(18)****.*

Depending on the substituents on the four benzo rings, the substituted Pcs (or PcM) can be separated into two different classes: symmetrical or unsymmetrical substituted Pcs (or PcM.). (Figure 1.4)



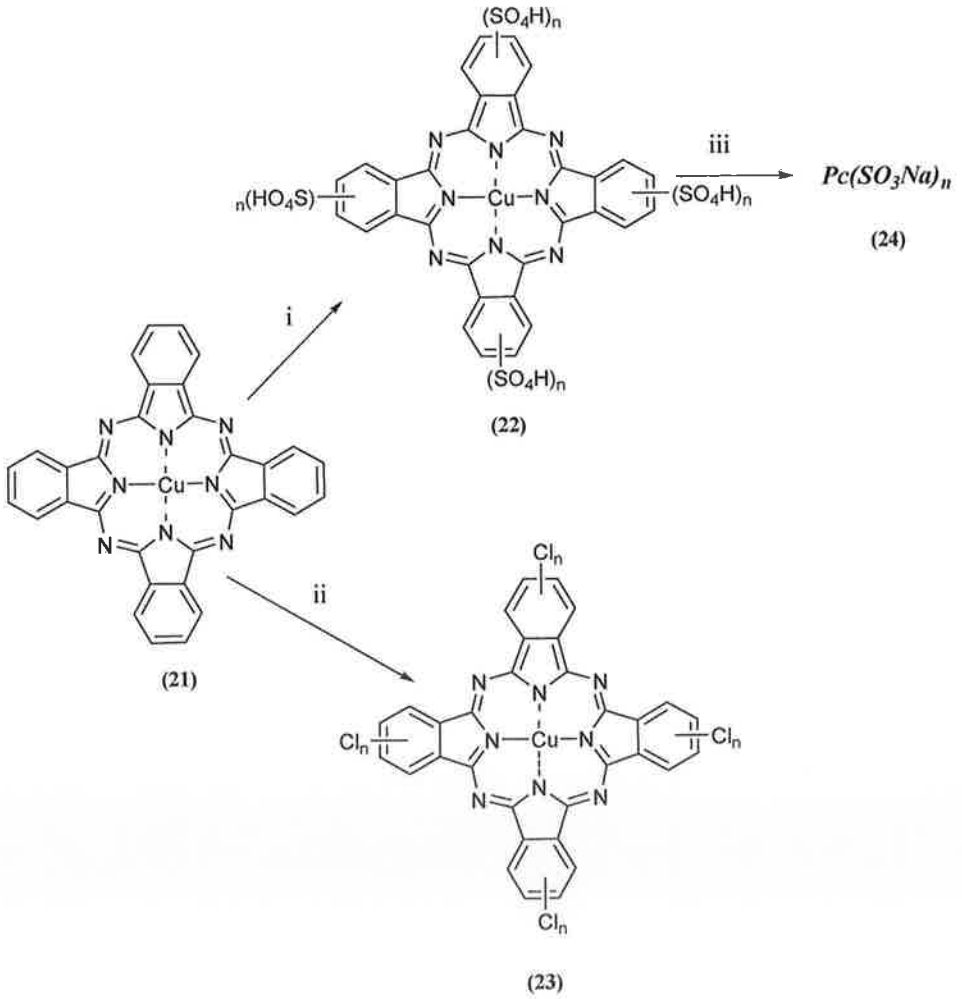
(19) **(20)**

M= Cu^{2+}; Co^{2+}; Zn^{2+}; Fe^{2+}; etc.
R= H; Alkyl;Alkoxyl. **R'**, **R"**, **R"** ≠ **R**= H; Alkyl;Alkoxyl. .

Figure 1.4 *The symmetrical* ***(19)*** *and unsymmetrical* ***(20)*** *-substituted Pcs (or PcM).*

1.2.3.1 Direct synthesis of substituted phthalocyanines

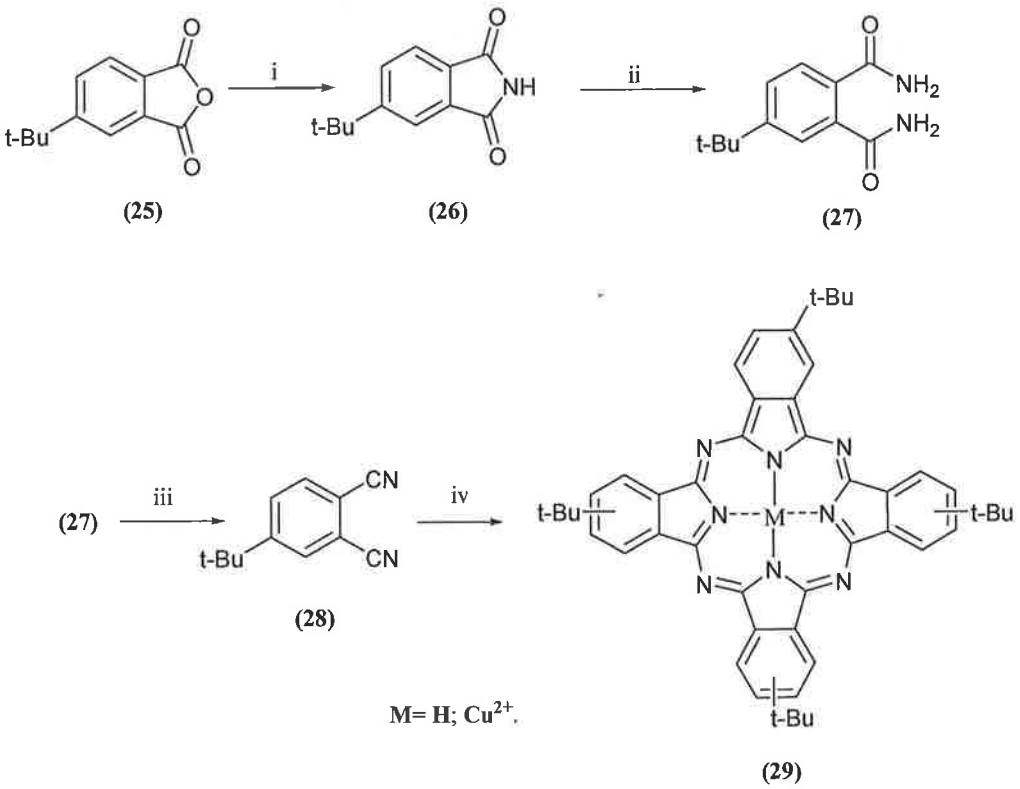
The initial methods used to prepare substituted Pcs involved direct electrophilic substitution which typically results in the formation of a mixture of substituted $PcCuX_n$ (n = 0, 1, 2, 3...16). (Scheme 1.5) This mixture could contain dozens of $PcCuX_n$ analogues including positional isomers. The separation of such mixtures has not been achieved. Some of these mixtures of $PcCuX_n$, which are produced by this route, are commonly used as color pigments in the dye industry.



Scheme 1.5 *The electrophilic substitution of PcCu forming $CuPcX_n$ (n = 0, 1, 2, 3, 4.). i H_2SO_4; SO_3. ii Cl_2; $FeCl_3$. iii NaOH.*

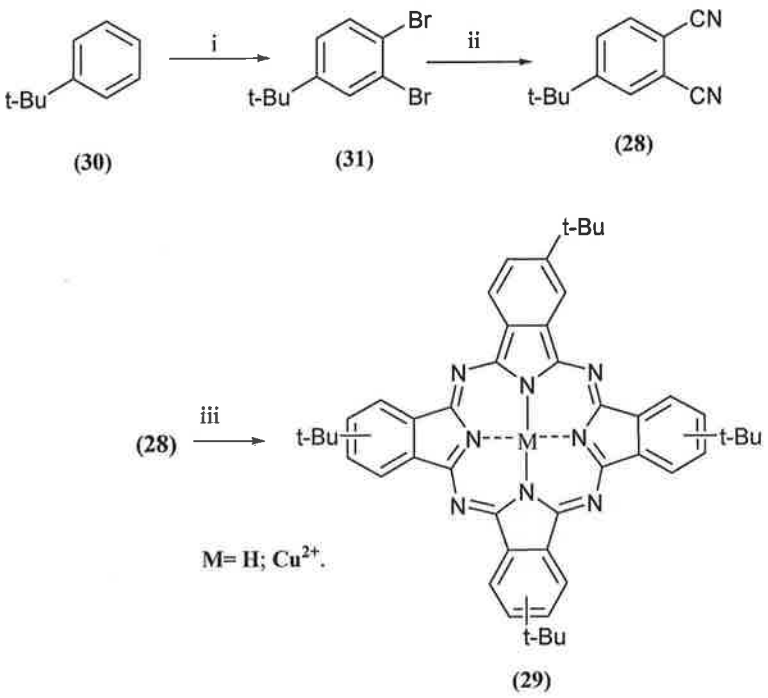
1.2.3.2 Synthesis of symmetrical substituted phthalocyanines

Since the direct electrophilic substitution failed to give a single pure substituted Pc, workers started to look for other synthetic strategies to obtain pure substituted Pcs. In 1976, tetra(*t*-butyl) Pc (Pc-*t*-tb) **(29)** was prepared by Koveshev et.al. (Scheme 1.6) [9] The preparation of this Pc started from 5-*t*-butyl-isobenzofuran-1,3-dione **(25)**, and after three steps gave the tetra(t-butyl) Pc **(29)**.



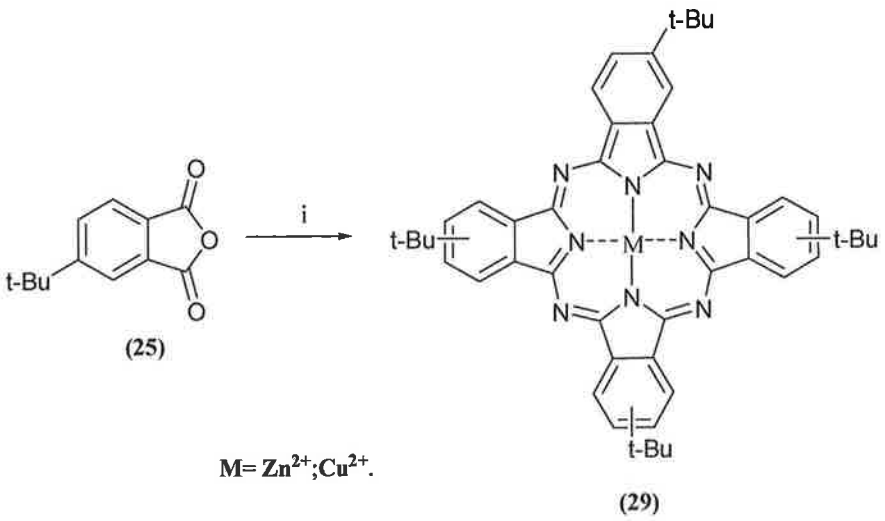
Scheme 1.6 *The preparation of tetra(t-butyl) Pc. i. Heat; Urea. ii. Ammonia. iii. Dehydration with PCl_5. iv. Condensation.*

An alternative synthesis of **(29)** was developed by the same group. [9] (Scheme 1.7) It included a bromination of *t*-butylbenzene **(30)** with bromine (Br_2), giving 1,2-dibromo-4-*t*-butylbenzene **(31)** and 1,2-dibromo-4-*t*-butylbenzene **(31)** which was treated with CuCN in dimethylformamide (DMF) to give 4-*t*-butylphthalonitrile **(28)**. This phthalonitrile **(28)** was used to prepare **(29)** by self-condensation.



Scheme 1.7 *The preparation of tetra(t-butyl) Pc. i. Br_2; iron. ii CuCN; DMF; reflux. iii. Condensation.*

It was also found that tetra(*t*-butyl) PcM **(29)** can be prepared in a single step via cyclo-tetramerisation of 5-*t*-butyl-isobenzylfur-an-1,3-dione **(25)** with metal salts and urea . [10] (Scheme 1.8)



Scheme 1.8 *The preparation of* ***(29)****. i metal (II) salt, hydroquinone and urea.*

Usually, the tetra-substituted Pcs **(29)** which are prepared from 4-substituted phthalonitriles give a mixture of four positional isomers with D_{2h}; D_{4h}; C_{2v} and C_s symmetries (Figure 1.5). Separation of these four isomers is extremely difficult. However, Hanack's group demonstrated that pure isomers of 2,9,16,23-tetra(substituted) Pcs could be isolated by high performance liquid chromatography (HPLC). [11]

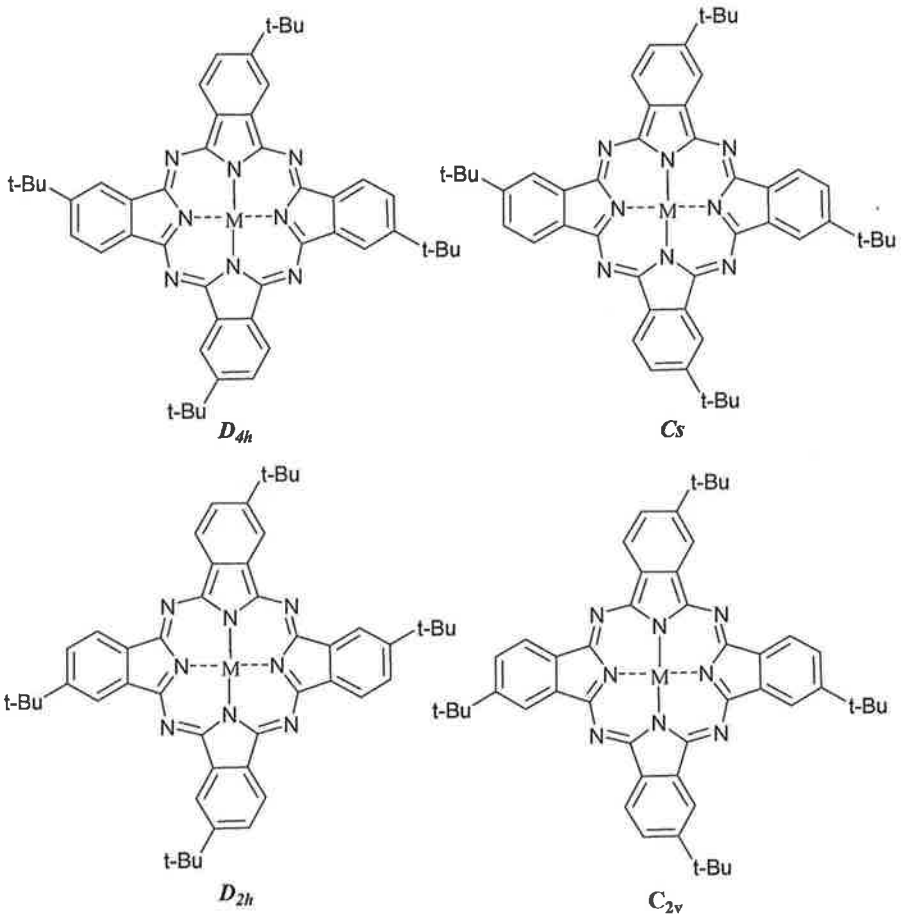
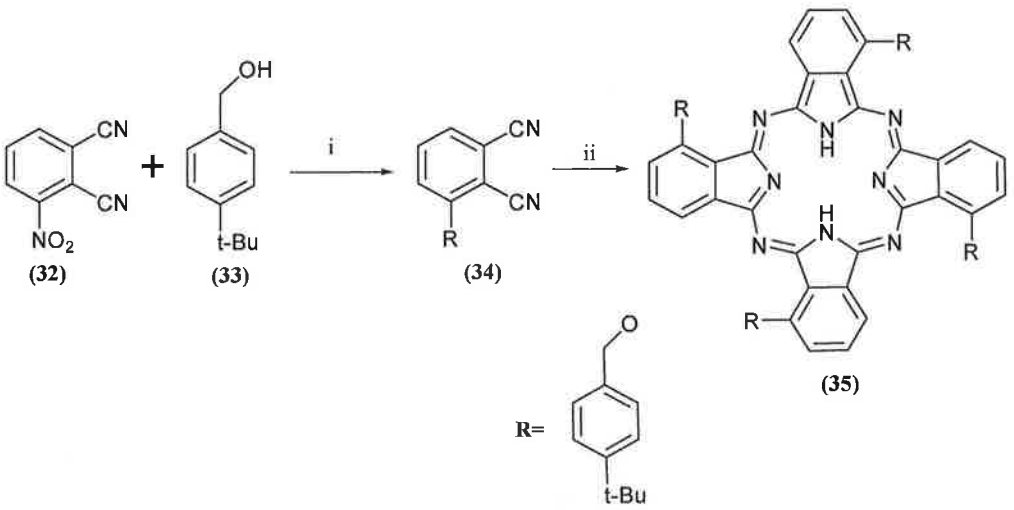


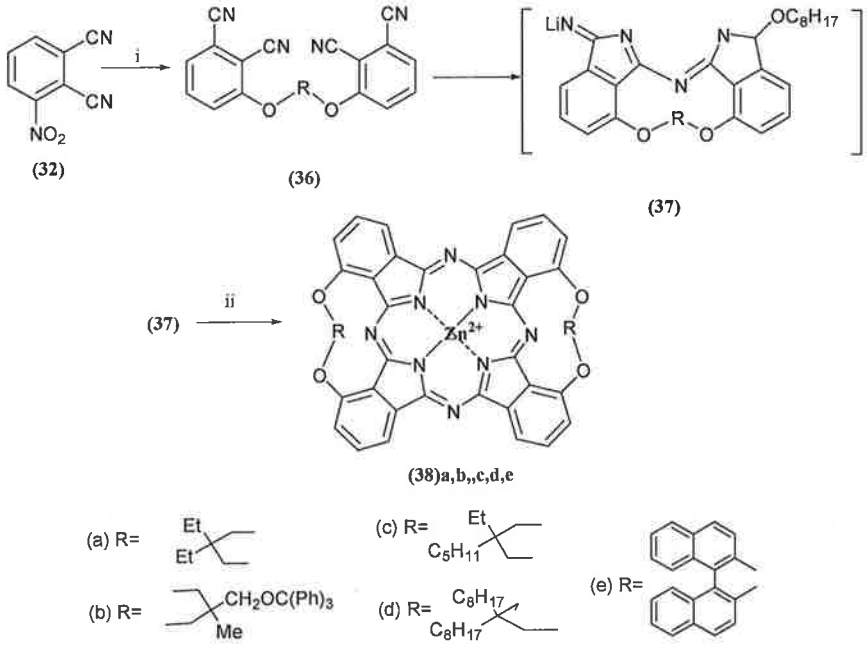
Figure 1.5 *The four positional isomers of tetra-substituted Pcs* ***(29)*** *(PcM-t-tb). Statistical ratio of the four isomers is:* $D_{4h} : D_{2h} : C_{2v} : C_s = 1 : 1 : 2 : 4$.

In 1994, the first successful synthesis of a single isomer tetra-substituted Pc (1,8,15, 22-tetra(benzyloxy) Pc) in 40% yield, was reported by Leznoff et. al. [12] (Scheme 1.9) The bulky groups (*p*-butylbenzyloxy) are suggested to cause steric hindrance during the condensation, which leads to the formation of a single tetra-substituted Pc isomer.



Scheme 1.9 *The preparation of 1,8,15,22-tetra-substituted Pc. i Potassium Carbonate (K_2CO_3); Dimethyl sulfoxide (DMSO). ii Lithium; octanol; followed by dilute acid.*

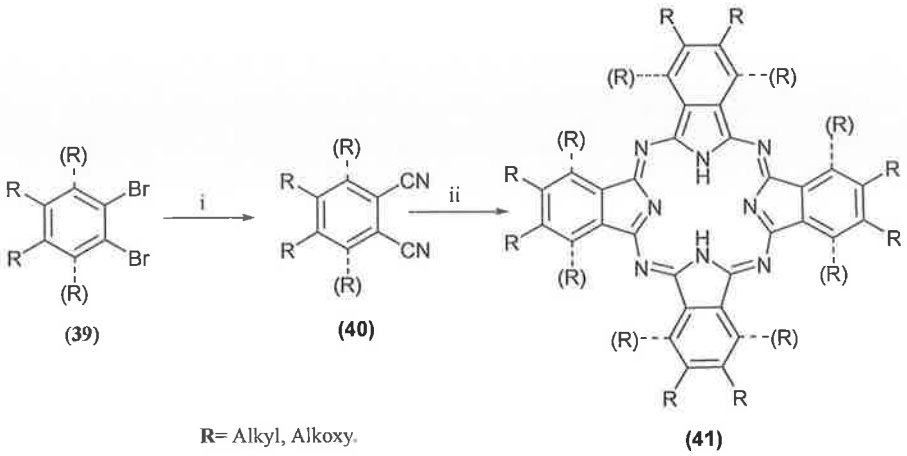
The preparation of pure 1,11,15,25-tetra(substituted) Pc as a single isomer was also reported by Leznoff in 1994 [13] (Scheme 1.10). 3-Nitrophthalonitrile **(32)** was treated with various 2,2-disubstituted-alkyl-1,3-diols to form an intermediate **(37)**. The short linkage of the bisphthalonitrile **(36)** forced a constrained condensation to give the single 1,11,15,25-tetra(substituted) Pc **(38 a~d)** (or its zinc complex) isomer only. Yields of these single isomers ranged from 7~20%. Kobayashi also reported a similar preparation of the single isomer (1,11,15,25-tetra(substituted) Pc) using [1,1'] binaphthalenoxy linked phthalonitrile **(38e)** in 1998, [14] giving the target Pc in 30~36% yield.



Scheme 1.10 *The synthesis of 1,11,15,25-tetra(substituted) Pcs. i K_2CO_3; DMSO. ii Lithium; octanol; $Zn(OAc)_2$.*

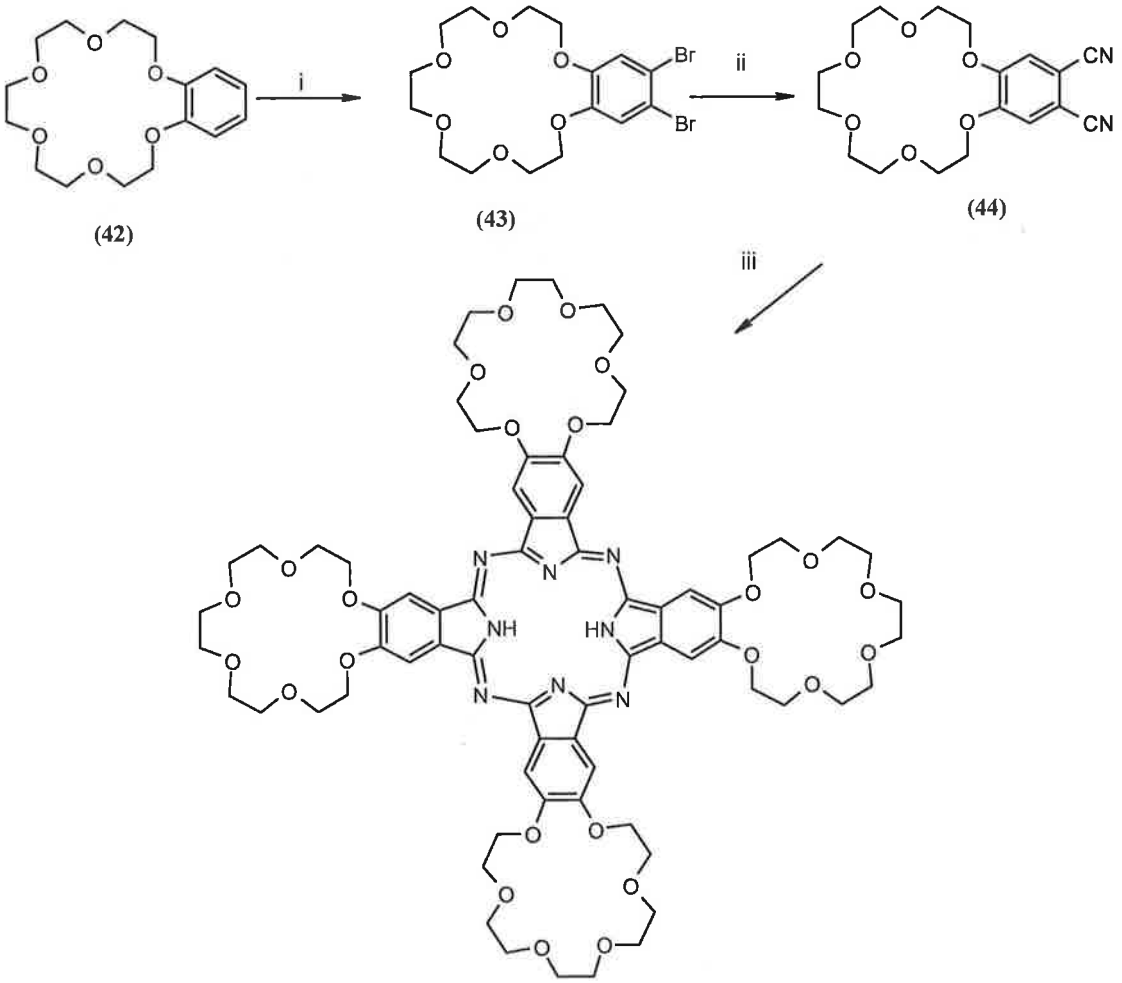
1.2.3.3 The preparation of octa-substituted phthalocyanines

Octa-substituted Pcs (or PcMs) will not form positional isomers, if prepared from a single phthalonitrile. They are typically prepared from 4,5-disubstituted phthalonitriles or 3,6-disubstituted phthalonitriles. [15] (Scheme 1.11)



Scheme 1.11 *Typical synthesis of symmetrical octa-substituted Pcs, i CuCN; DMF; reflux. ii Condensation; treat with acid.*

A route for the preparation of a novel Pc (or PcM) containing four 18-crown-6 rings was described in the 1980's. [16, 17] The reaction starts from **(42)** in three steps, giving the 18-crown-6-substituted Pc **(45)** at the yield of 23%. (Scheme 1.12)

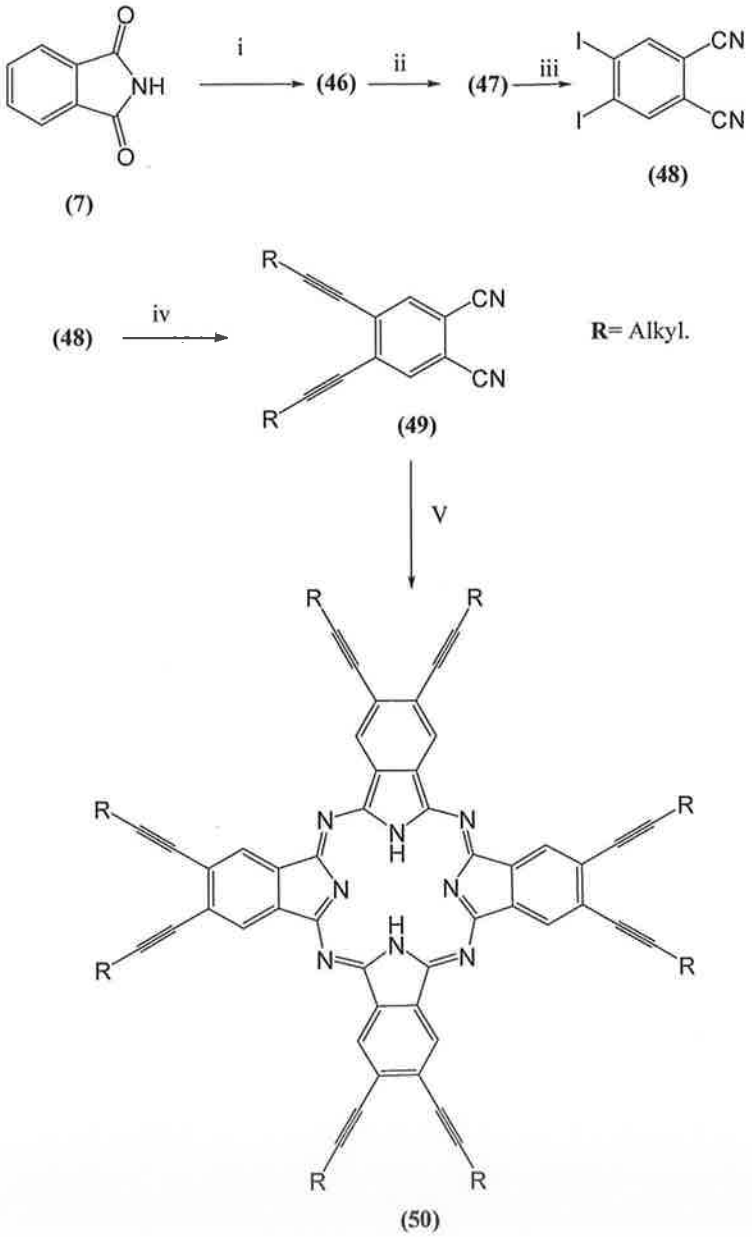


(42) **(43)** **(44)** **(45)**

Scheme 1.12 *The synthetic route used to prepare 18-crown-6 Pcs* ***(45)****. i* Br_2*; DCM; 0 °C. ii CuCN; DMF; reflux. iii Condensation; treat with acid.*

Octa(alkynyl) Pcs (or PcMs) were also prepared via a multiple step synthesis, [18] the synthetic route is outlined in Scheme 1.13. It started from the iodination of phthalimide **(7)** which was converted to 4,5-dialkynylphthalonitrile **(49)** after a

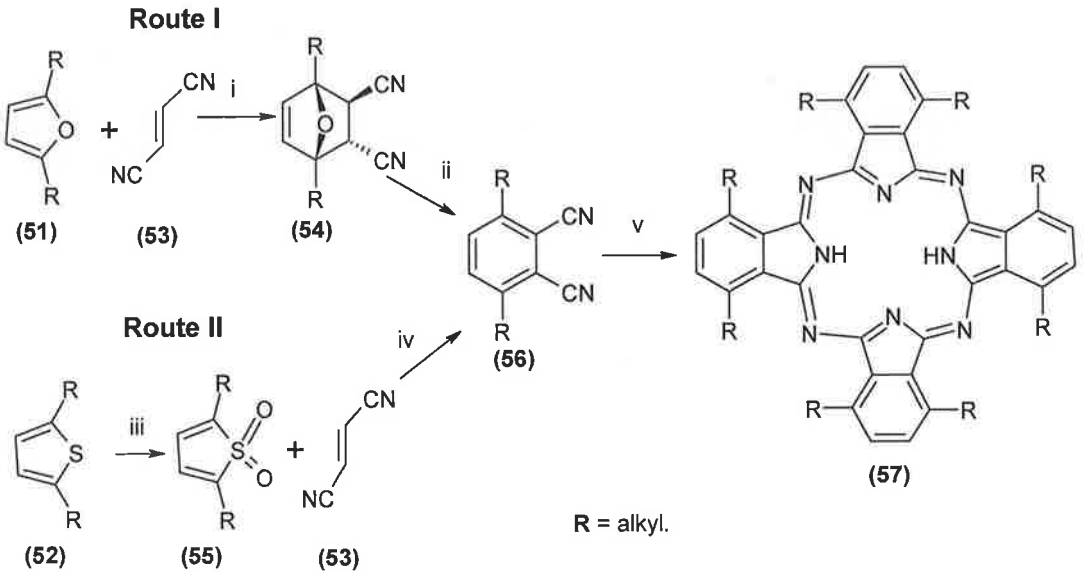
further three steps. Condensation was carried out by refluxing phthalonitrile **(49)** in Li/pentanol solution, to give the octa(alkynyl) Pcs **(50)** in 40% yield.



Scheme 1.13 *The preparation of octa(alkynyl) Pcs (or MPcs). i I_2/Oleum. ii Ammonium solution (NH_4OH). iii Trifluoroacetic anhydride ($(F_3CCO)_2O$); dry pyridine. iv 1-Alkyne; CuI; TEA; $PdCl_2(PPh_3)_2$. v Li/pentanol; heating; Followed by hydrolysis with acid.*

Two synthetic routes for the preparation of 1,4,8,11,15,18,22,25-octa(alkyl) Pcs were described by Chambrier et. al. [19] The route (I) started from 2,5-dialkylfuran **(51)**,

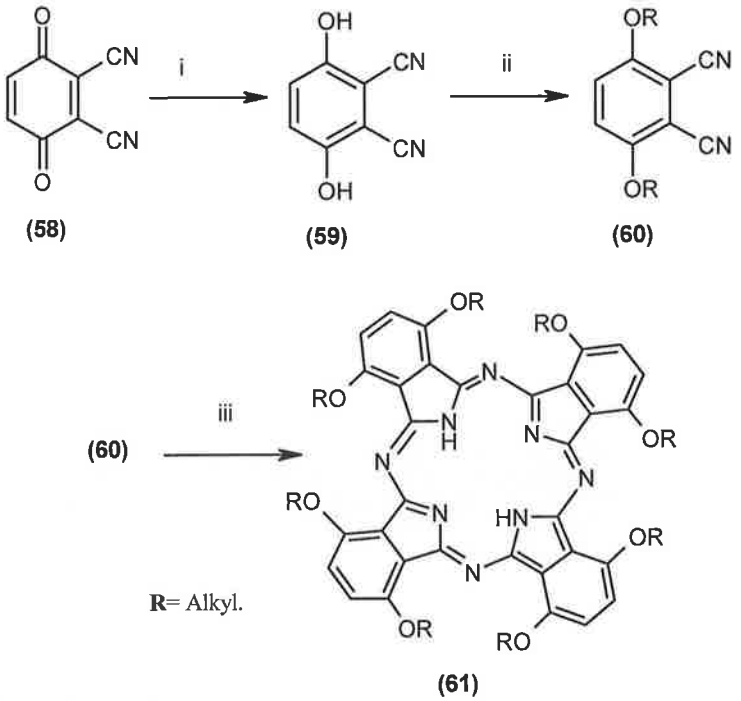
undergoing a Diels-Alder cycloaddition with fumaronitrile forming 3,6-dialky-lphthalonitriles **(56)**. The condensation was carried out under alkoxide conditions. The metal free Pcs were obtained by treating with dilute acid. (Scheme 1.14) Alternatively, the same Pc could be prepared from 2,5-dialkylthiophene **(52)**. (Route II) (Scheme 1.14)



Scheme 1.14 *The preparation of 1,4,8,11,15,18,22,25-octa(alkyl) Pcs. i Acetone; 0 °C. ii Lithium; bis(trimethylsilyl) amide; THF; -78 °C. iii 3-Chloroperbenzoic acid; DCM. iv 200 °C. v Li/pentanol; 100 °C; followed by aqueous hydrolysis.*

The thiophene route (II) was found to be more efficient than route I, and yields of 40% were obtained for some Pcs.

An improved synthetic route used to prepare 1,4,8,11,15,18,22,25-octa(alkoxy) Pcs is outlined in Scheme 1.15. The preparation started from 2,3-dicyanobenzo-quinone **(58)** which was reduced with sodium metabisulfite, to give 3,6-dihydroxyl-phthaloni-trile **(59)**. Then **(59)** was converted to the 3,6-alkoxyphthalonitrile **(60)** which was subsequently condensed to form Pc **(61)**.



Scheme 1.15 *Route for the preparation of non-peripheral octa-substituted Pcs. i Sodium metabisulfite. ii Alkyl halide; K_2CO_3; acetone. iii Li/pentanol/reflux; then hydrolysis with dilute acid.*

1.2.3.4 Synthesis of unsymmetrical substituted phthalocyanines

The unsymmetrical Pcs (or PcMs) are usually prepared by the cross-condensation of two different phthalonitriles. [20] The typical solution phase synthetic routes used to produce tetra-substituted and octa-substituted unsymmetrical Pcs are outlined in Scheme 1.16 and Scheme 1.17. Normally six different Pcs (or PcMs) are obtained in the product mixture. Control of the cross-condensation is usually achieved by using a stoichiometric excess of one phthalonitrile partner over the other. The separation of the resulting Pc mixtures is difficult and requires exhaustive purification, using silica gel column chromatography and size exclusion chromatography.

The postulated yields of these Pc isomers can be calculated by using the equations 1.1~1.5, and the results are outlined in table 1.1.

$P_a = m^4/(n+m)^4$ **(Equation 1.1)**

$P_b = n^4/(n+m)^4$ **(Equation 1.2)**

$P_c = n.m^3/(n+m)^4$ **(Equation 1.3)**

$P_d = m.n^3/(n+m)^4$ **(Equation 1.4)**

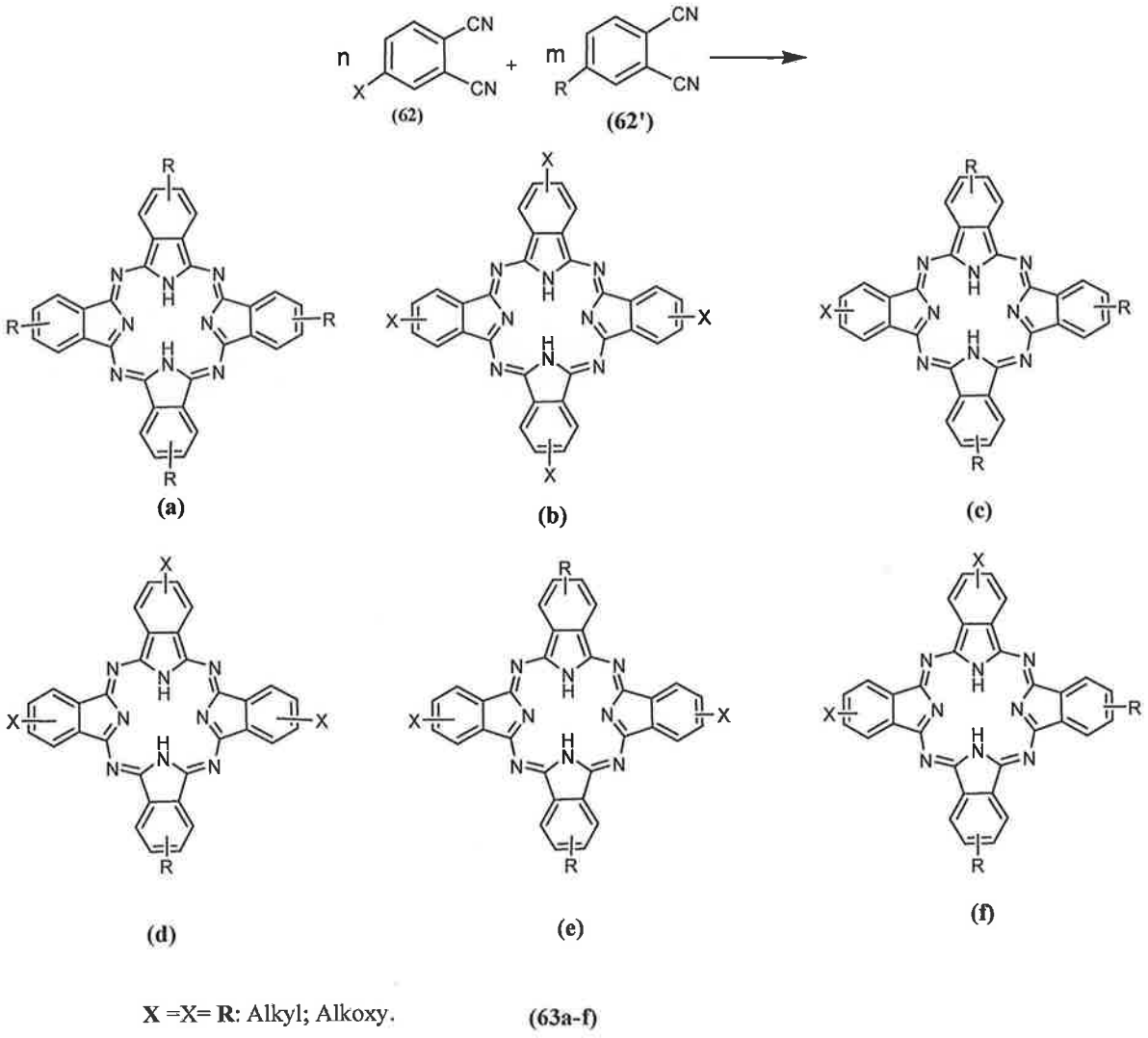
$P_{e+f} = 3m.n/(n+m)^2$ **(Equation 1.5)**

The P_a; P_b; P_c; P_d and P_{e+f} are the terms of the calculated yields of Pc **(a);** Pc **(b);** Pc **(c);** Pc **(d)** and Pc **(e, f)** respectively. The n and m are the stiochiometric ratio of **(62)** and **(62')**.

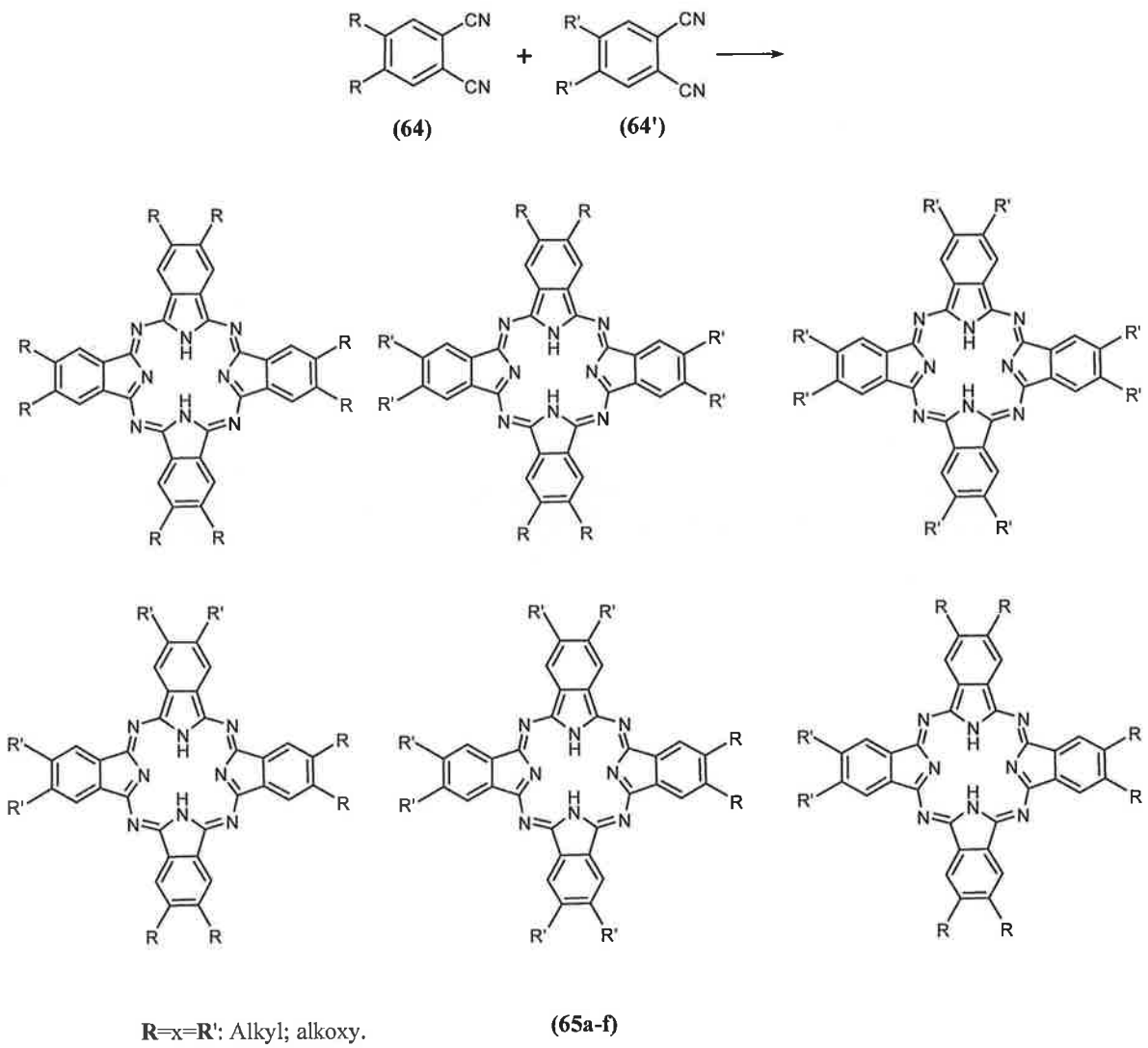
Phthalonitriles		The yields of Pcs (%)				
n	m	P_a	P_b	P_c	P_d	P_{e+f}
1	1	6.25	6.25	6.25	6.25	75
1	2	20	1.1	10	2.3	66.6
1	3	32	0.3	10.4	1.1	56.2
1	4	41.1	0.1	10.2	0.6	48
1	5	48.22	0.08	9.64	0.39	41.67
1	6	54	-	9	0.3	36.7

From the above table, we can tell the stiochiometric ratio of **(62)** and **(62')** have significantly effect on the yields of Pcs in the preparation of unsymmetrical Pcs by solution phase synthesis. When the stiochiometric ratio of **(62)** and **(62')** (n and m) is at 1:3, the Pc isomer **(c)** achieves the highest yields comparing with other

stiochiometric ratio. This will be a very important theory for the preparation of certain unsymmetrical Pcs.

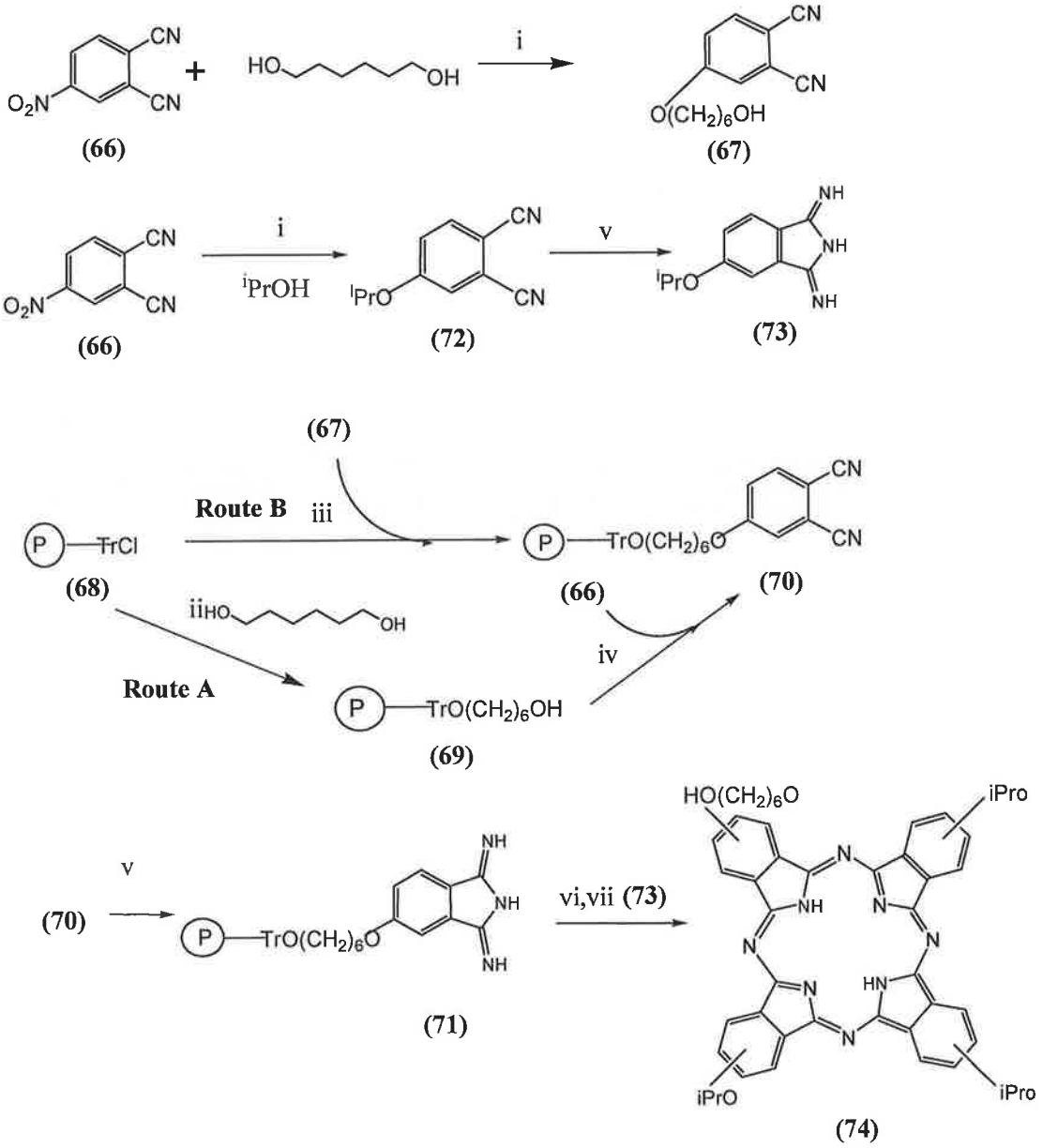


Scheme 1.16. *Possible products from the cross-condensation of two different mono-substituted phthalonitriles.*



Scheme 1.17 *The preparation for unsymmetrical octa-substituted Pcs.*

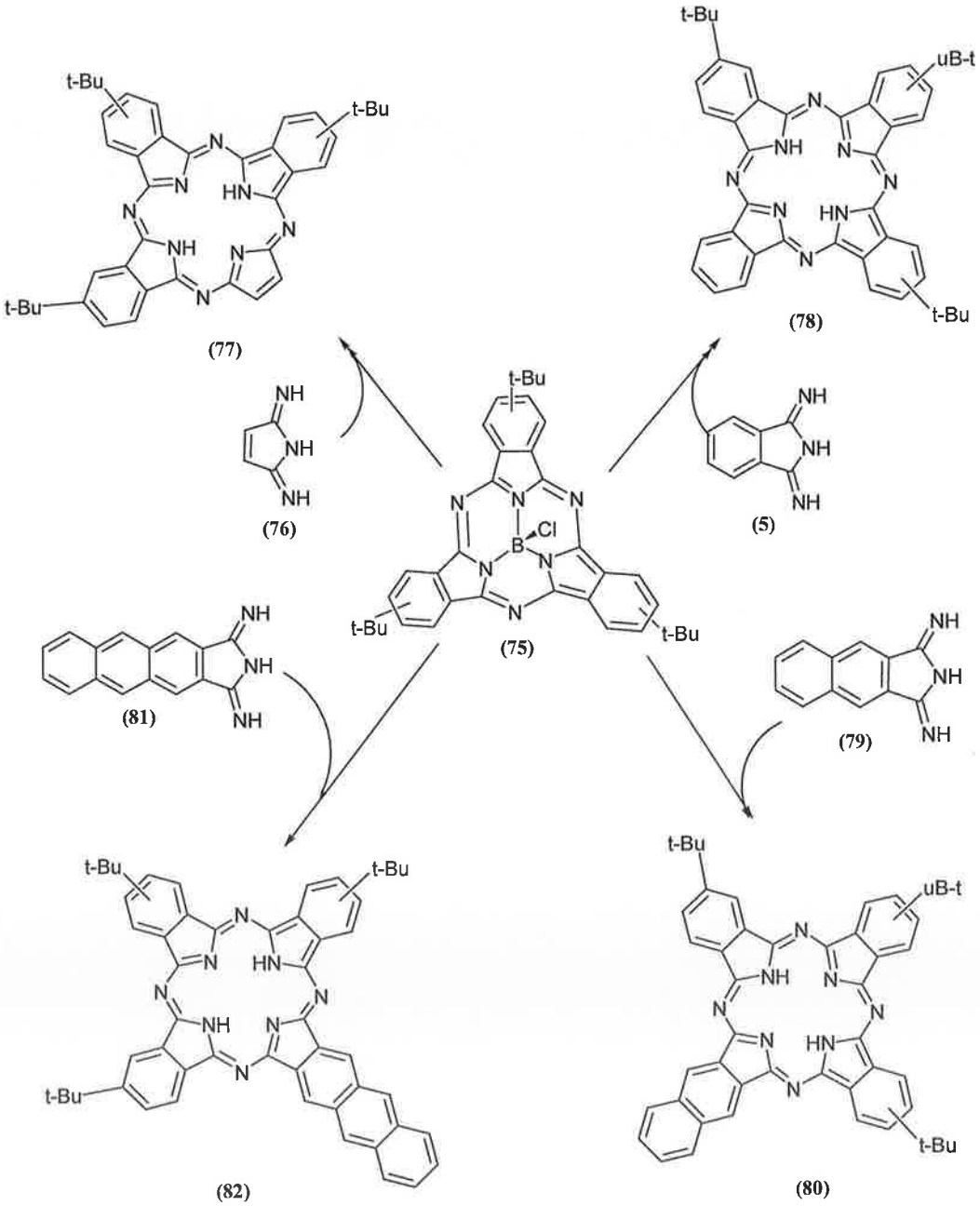
In 1982, Leznoff et.al used a solid-support approach for the preparation of unsymmetrical substituted Pcs. [21] The unsymmetrical Pc macrocycle was prepared on a cross-linked polymer resin. (Scheme 1.18) The advantage of the solid-support synthetic route is the target Pc is covalently bound to the polymer and isolated from the reaction mixture by filtration of the polymer, making purification simple.



Scheme 1.18 *The solid-support synthetic route for the preparation of* ***(74)****. i* K_2CO_3*; DMSO. ii Dry Pyridine. iii DCM; 4-dimethylaminopyridine (DMAP); dry pyridine. iv 25% potassium hydroxide (KOH); Adogen 464; nitrobenzene. v* NH_3H_2*; Methanol; THF. vi DMAE; DMF, Heat. vii Dilute acid.*

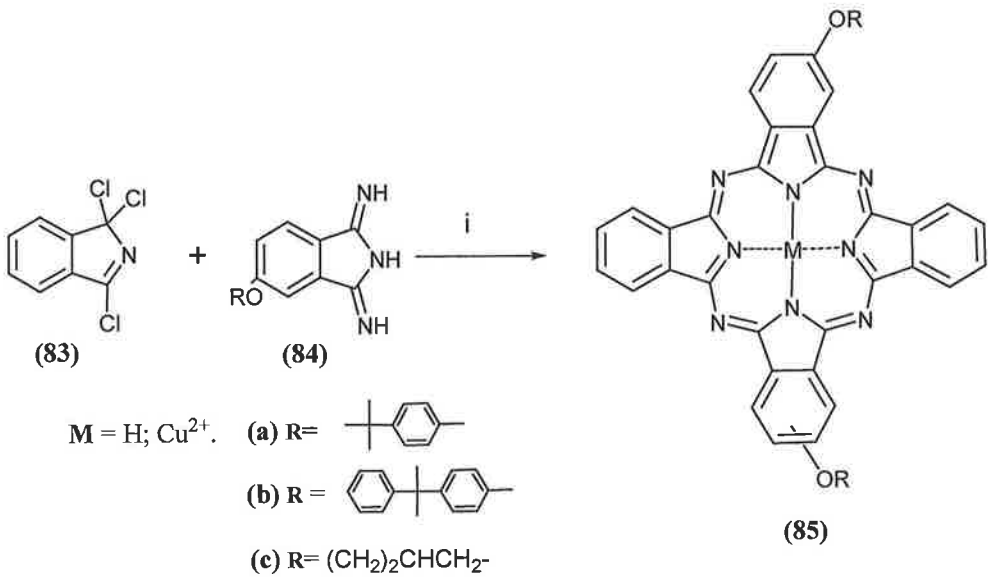
A new synthetic route for the preparation of both symmetrical and unsymmetrical substituted Pcs (or PcMs) was reported by Kobayashi et.al in the early 90's. This new route involves treating subphthalocyanine **(75)** with 1,3-diiminoisoindolines [22]. (Scheme 1.19) Compound **(75)** is prepared in 50% yield by mixing 4-*t*-butyl-phthalonitrile **(28)** and borane tribromide at 260 °C in 1-chloronaphthalene for 10

minutes. Unsymmetrical Pcs (or PcMs) could also be prepared by treating subphthalocyanine **(75)** with succinimidine **(76)** or 1,3-diiminoisoindoline analogues **(5)**, **(79)** and **(81)**. The unsymmetrical Pcs which were prepared by this synthetic route, were found to be a mixture obtaining at least ten different Pcs. As a result, this route has found limited application.



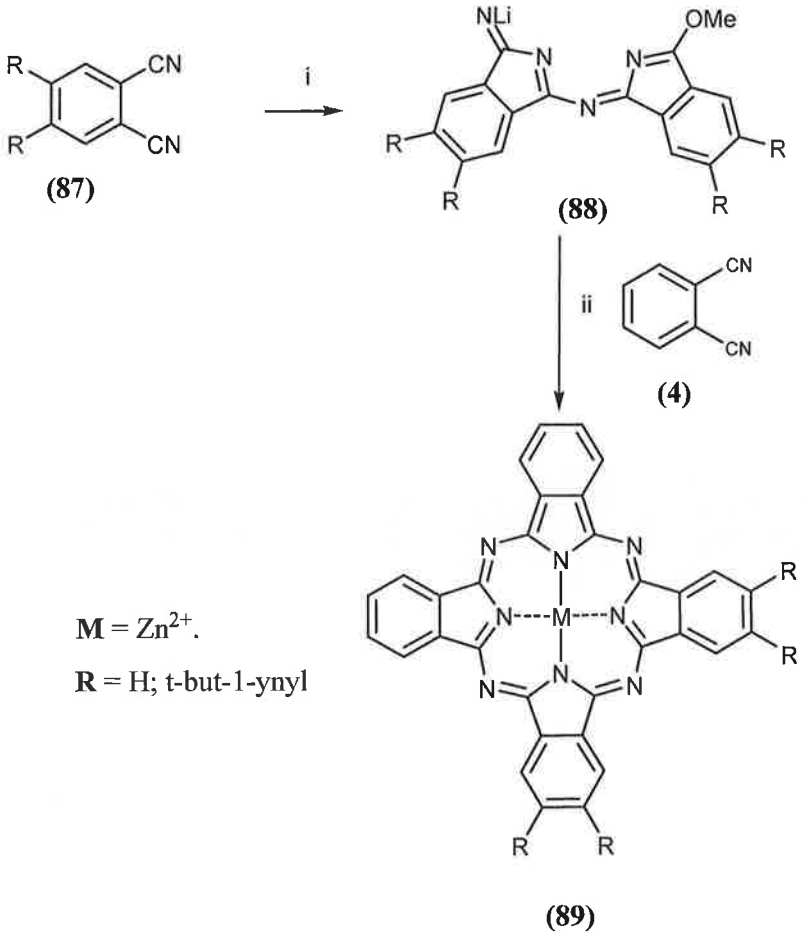
Scheme 1.19 *The preparation of Pcs (or PcMs) from subphthalocyanine* ***(75)****.*

The preparation of "opposite" di-disubstituted Pcs was first reported in the patent literature. [23] The opposite substituted Pcs were prepared in a yield of 5% without any other Pc by-product. (Scheme 1.20) The synthetic conditions employed to prepare opposite substituted Pcs are different from the normal preparation of Pcs. The reaction requires the treatment of 6-substituted-1,3-diimin-oisoindolines **(84 a~c)** with 1,3,3-trichloroisoindoline **(83)** in a THF and TEA solution. Pc formation occurs after the addition of hydroquinone at room temperature. This route was further modified by Young et.al in 1990 [24] by using 6-nitro-1,3,3-trichloroisoindoline with **(84)**, the opposite substituted Pc **(85a~c)** was obtained in yields up to 70%.



Scheme 1.20 *The new synthetic route used to prepare opposite-substituted Pcs (or MPcs)* ***(85a~c)****. i Sodium methoxide ($NaOCH_3$) and hydroquinone.*

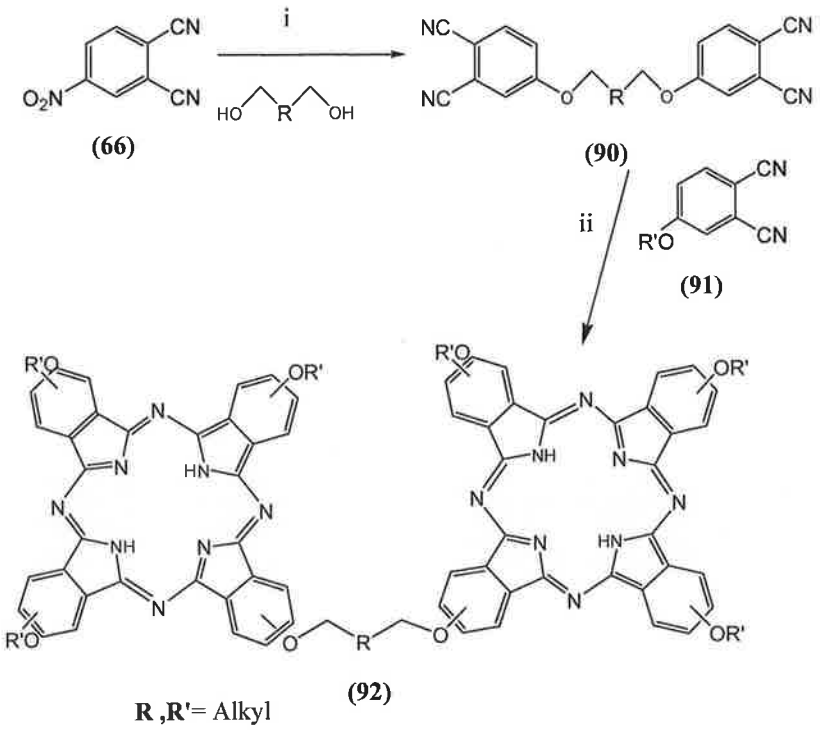
A direct route to the preparation of "adjacent" substituted Pcs was first reported in 1997. [25] (Scheme 1.21) An intermediate **(88)** was prepared by heating phthalonitrile in Li/methanol solution. The "adjacent" substituted Pcs were obtained by refluxing intermediate **(88)** with a substituted phthalonitrile partner in DMAE solution at 75 °C to give the "adjacent" Pc in 10~20% yield.



Scheme 1.21 *The synthesis of "adjacent" substituted Pcs. i Lithium; methanol. ii DMAE; 1-octanol; zinc acetate ($Zn(OAc)_2$).*

1.2.4 Multi-nuclear phthalocyanines

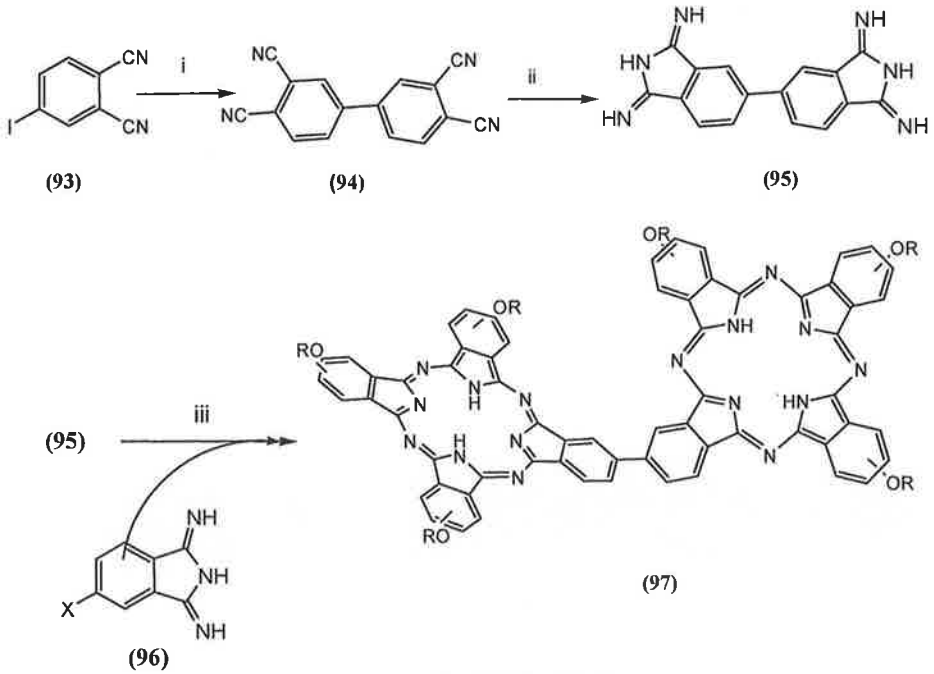
Face-to-face porphyrin dimers were first prepared in the late 70's. [26] These porphyrin dimers were able to catalyse the four-electron reduction of dioxygen to water, without forming free hydrogen peroxide. Unfortunately, the porphyrin dimer catalysts tend to decompose after 4-5 cycles. Since Pcs are both thermally and photochemically more stable than porphyrin, and since they possess similar electrochemical properties to porphyrin, a series of binuclear Pcs were prepared and assessed as catalysts for the $4e^-$ reduction of oxygen to water.



Scheme 1.22 *The preparation of binuclear Pc* ***(92)****. i DMSO;* K_2CO_3*. ii Condensation; Acetic acid (or HCl).*

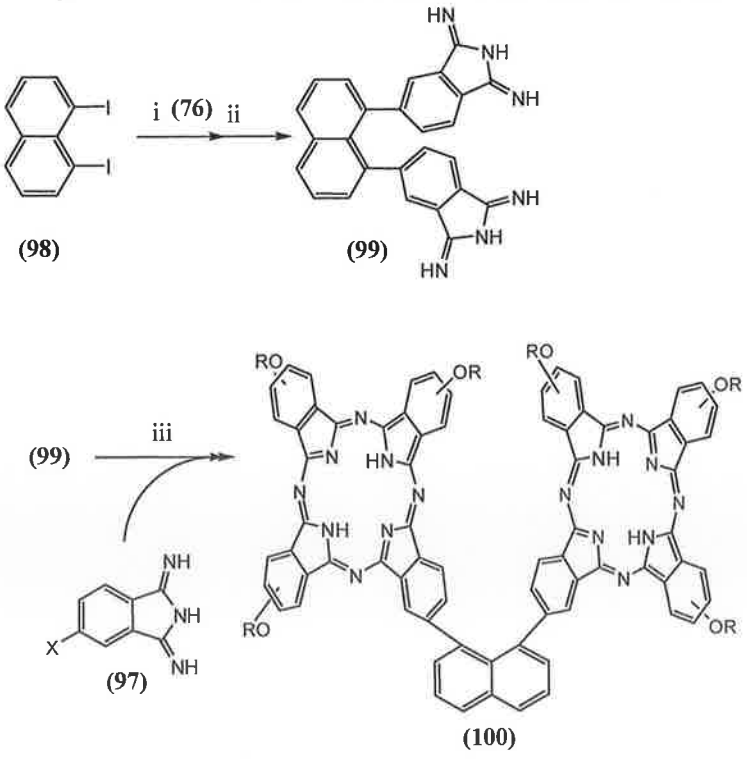
The first pure binuclear Pc **(92)** was prepared in 1984. [27] (Scheme 1.22) The preparation included treating 4-nitrophthalonitrile **(66)** with an alkyldiol to form the bisphthalonitrile **(90)**. The binuclear Pc **(92)** was produced via cross condensation with a partner phthalonitrile to give the binuclear Pc **(92)** in a 10% yield.

Binuclear Pcs (Scheme 1.23) linked by various bridges (Scheme 1.24) were also prepared using a similar route in 1988, giving Pcs **(97)** and **(100)** in 33% and 8.7% yields, respectively. [28]



X= Alkyl; alkoxy.
R = Alkyl.

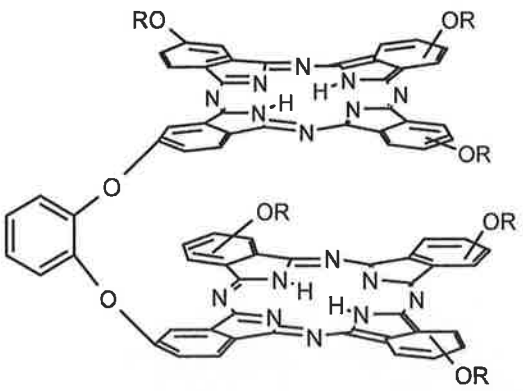
Scheme 1.23 *The preparation of binuclear Pc* ***(97)****. i Active nickel powder. ii Na; NH_3; Methanol. iii Condensation; Acetic acid (or HCl).*



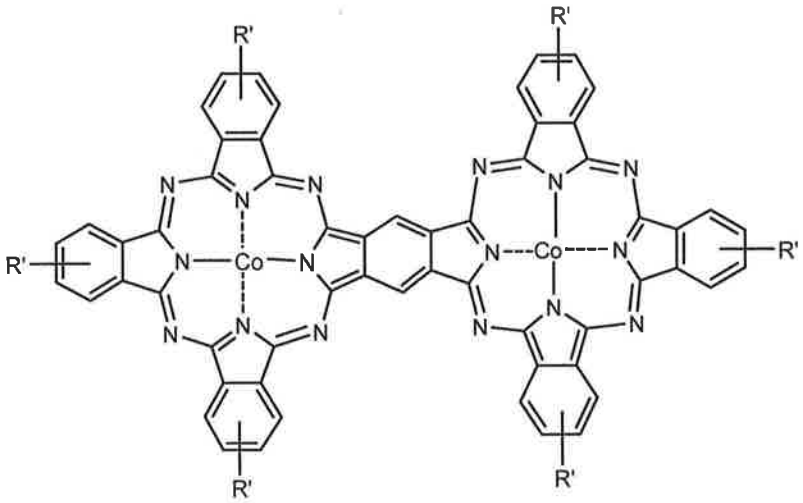
X= Alkyl; alkoxy.
R = Alkyl.

Scheme 1.24 *The preparation of aromatic bridged binuclear Pc* ***(100)****. i Active nickel powder. ii Na; NH_3; Methanol. iii Condensation; Acetic acid (or HCl).*

Using similar methods, other types of binuclear Pcs **(101)** and **(102)** were prepared. (Figure 1.6) [28, 29]



(101) **R** = Alkyl, Phenyl.



(102) **R'** = SO_3NH_4

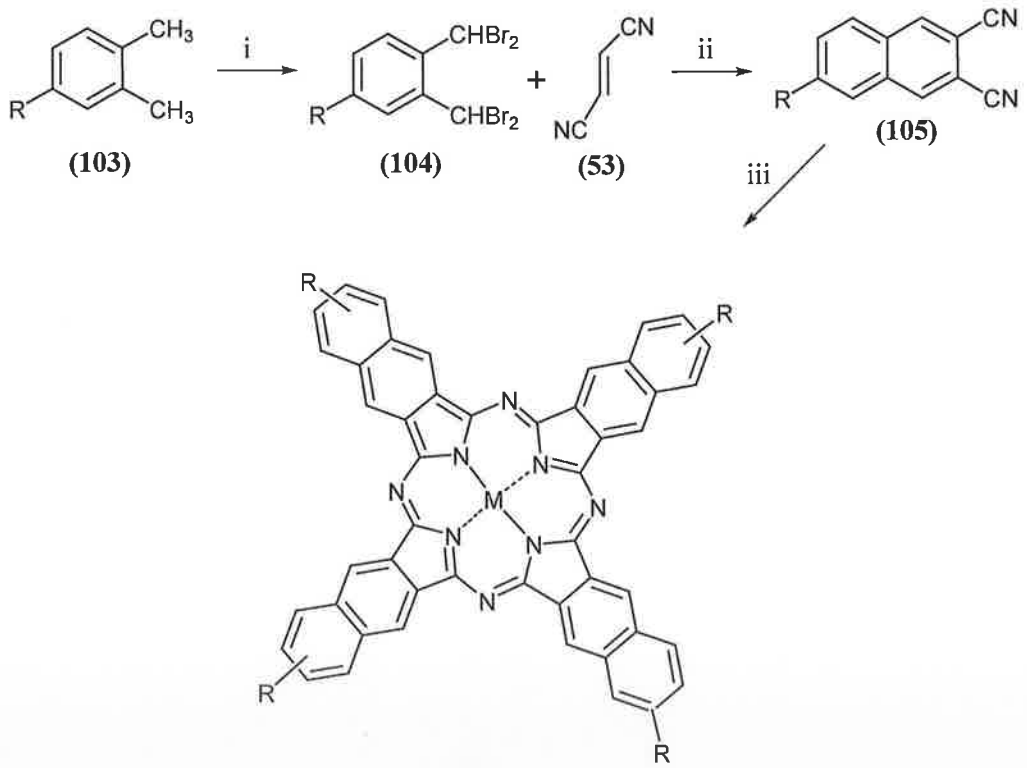
Figure 1.6 *The binuclear Pc (101) and (102).*

To date, there are several types of binuclear Pcs which have been prepared for different applications, such as catalysts: Pcs **(97)**, **(100)** and **(101)**; non-linear optical materials: Pc **(102)**.

Unfortunately, none of the multinuclear Pcs achieved the desired four-electron reduction of oxygen to water.

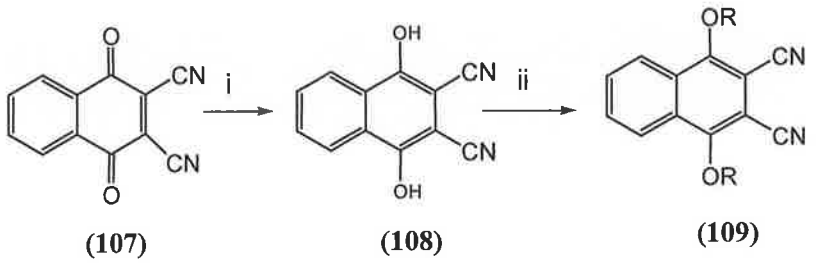
1.2.5 The synthesis of naphthalocyanines (Nc)

A synthetic route to prepare Ncs was described by Luk'yanets and co-workers in 1976. [30] (Scheme 1.25) The preparation started from substituted 3,4-dimethyl-benzene **(103)**, which was brominated to give substituted 1,2-bis(dibromomethyl) benzene **(104)**. Compound **(104)** was treated with fumaronitrile **(53)** and sodium iodide undergoing an elemination/Diels-Alder reaction to give the target substituted 2,3-dicyanonaphthalene **(105)**. Then Nc **(106)** was prepared by the self-condensation of **(105)**.

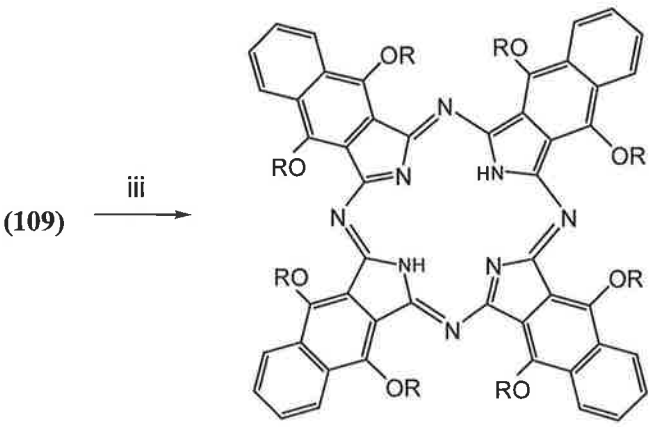


Scheme 1.25 *The synthetic route for the preparation of tetra-substituted Ncs. i N-Bromosuccinimide (NBS); hv; carbon tetrachloride. ii sodium iodide (NaI); DMF; 80 °C. iii Condensation.*

Octa-substituted Ncs **(110)** have also been prepared using the same route. An alternative route to prepare "non peripheral" octa-substituted Ncs involves converting 1,4-dioxo-2,3-dicyanonaphthalene **(107)** to 1,4-hydroxyl-2,3-dicyano-naphthalene **(108)** via reduction. The alcohol group can then be alkylated, forming 1,4-dialkoxy-2,3-dicyanonaphthalene **(109)**. The octa-substituted Ncs **(110)** were prepared directly from the self-condensation of compound **(109)**. (Scheme 1.26)



(107) **(108)** **(109)**



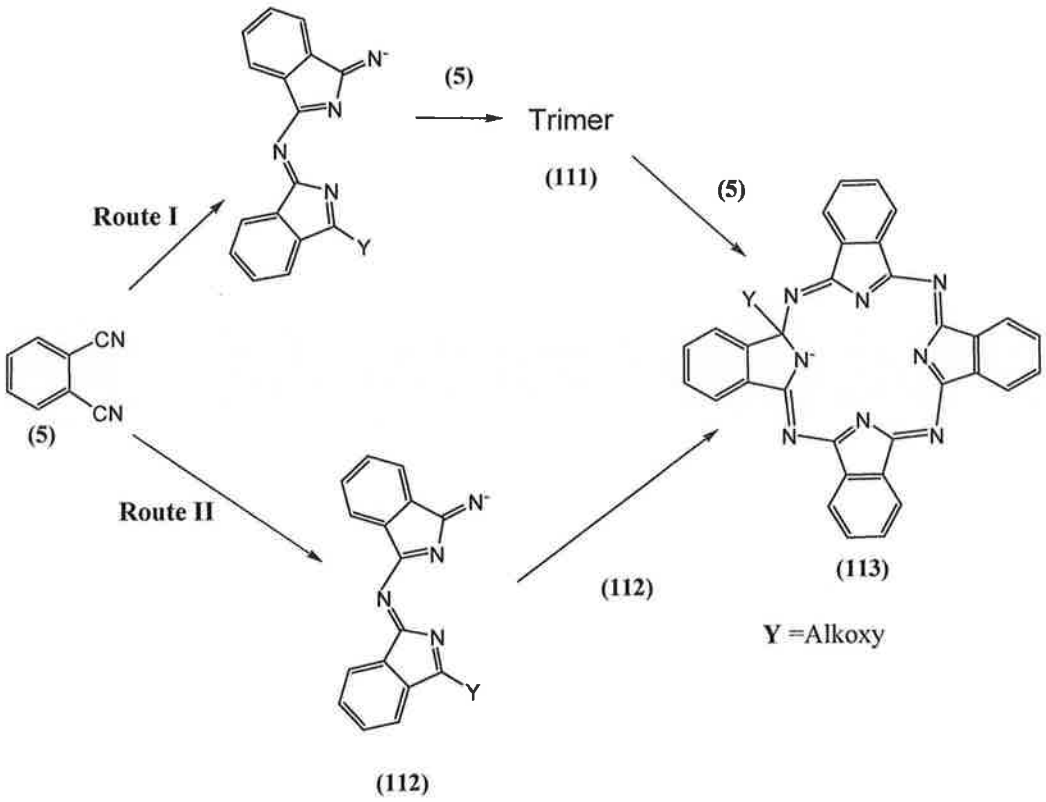
R = Alkyl **(110)**

Scheme 1.26 *The preparation of non-peripheral octa(alkoxy) Ncs. i sodium metabisulfite; ii Alkyl halide; K_2CO_3 ; acetone; reflux. iii Li/ pentanol/reflux; hydrolysis.*

1.2.6 Mechanism of phthalocyanine formation

To date, the mechanism of Pc cyclization has not been well defined. Two proposed mechanisms have been reported and are depicted in Scheme 1.27. [31] The first postulation proposes that the Pc macrocycle is formed by the sequential addition of **(5)** to generate **(111)**, forming intermediate **(113)**, which then condenses to the Pc

macrocycle. The second proposed mechanism involves the cyclization of two half Pc units **(112)**.



Scheme 1.27 *Two proposed mechanisms.*

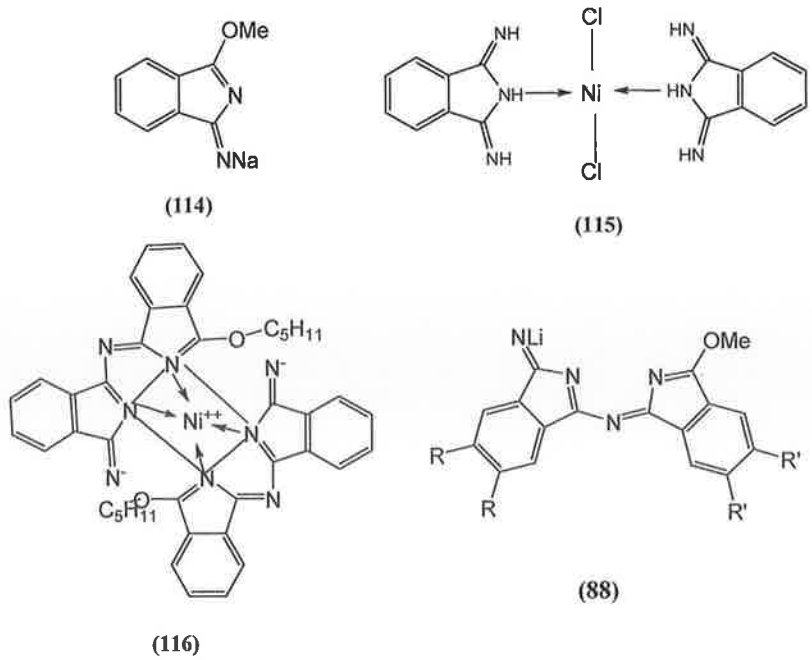
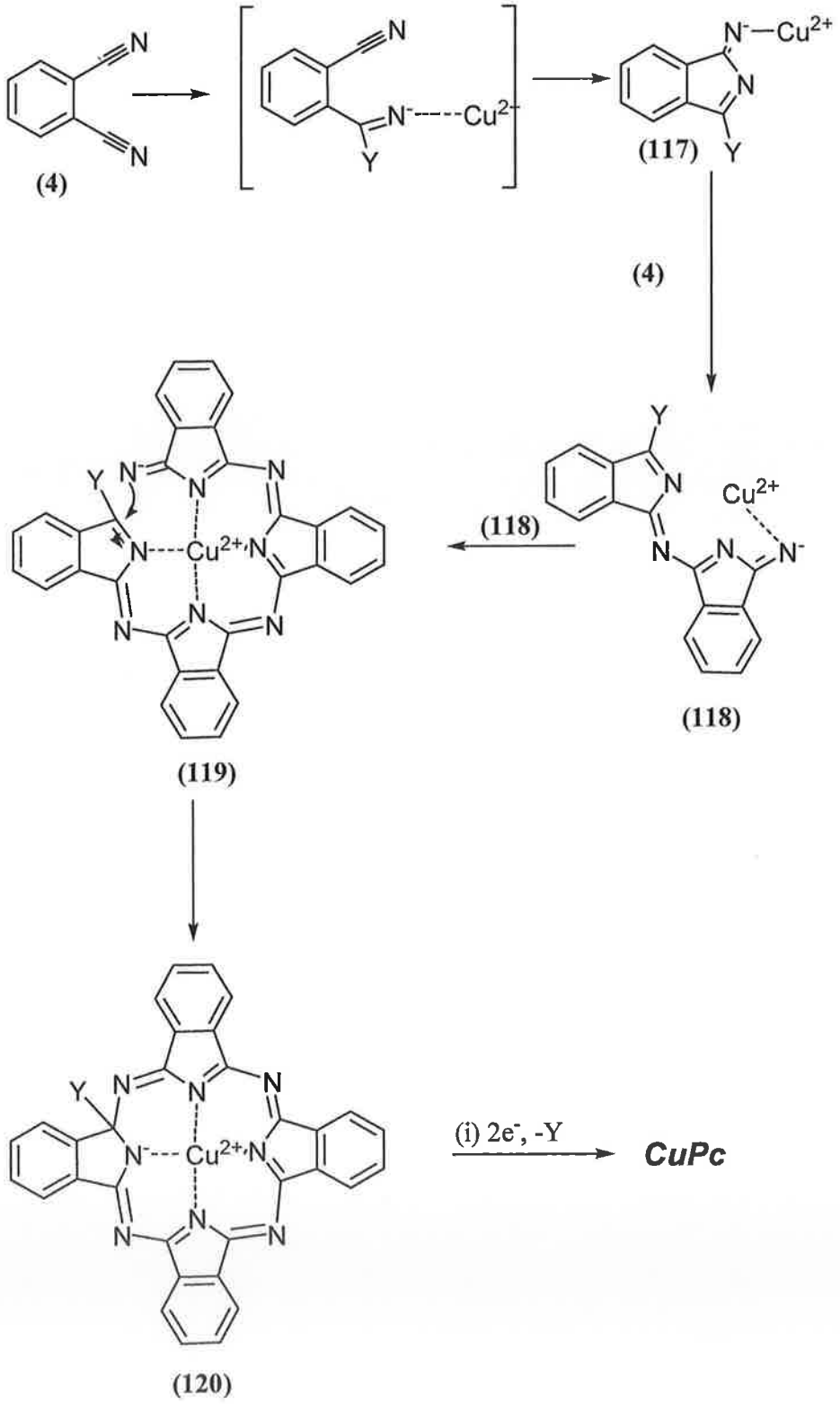


Figure 1.7 *The intermediates in Pc synthesis.*

Several intermediates which are produced during the synthesis of Pcs, have been isolated and identified, such as intermediate **(114)**, [32] nickel complexes **(115)** [33] and **(116)** [34] and the dimeric lithium salt **(88)** [25] (Figure 1.7).

A detailed explanation of the formation of copper Pc (PcCu) was reported by Christie et.al. [35] Their results are based on the thermal behaviour studies during the cyclization of PcCu. The mechanism is outlined in Scheme 1.28. It involves nucleophilic attack of the cyano group by alkoxide anion. This is followed by imine anion attack on a second phthalonitrile to give dimeric intermediate **(117)** which self-condenses to give **(118)**. To form the 18-π electron aromatic system, an oxidation occurs in the last step with the intermediate **(119)**, to give a stable 18-π electron system.



Scheme 1.28 *The detailed mechanism of PcCu formation.*

1.3 The ^{1}H NMR of phthalocyanines

1.3.1 The ^{1}H NMR studies of metal-free and metallo phthalocyanines

The ^{1}H NMR spectrum of the aromatic protons on PcZn is shown in Figure 1.8, the aromatic protons are present at 8.3 and 9.6 ppm respectively. The ^{1}H NMR studies carried out with oligomeric silicon Pc [36] demonstrated that the aromatic proton chemical shifts of Pc are significantly affected by aggregation interaction between the Pc macrocycles. The internal protons of substituted metal-free Pcs are normally found between –2 to –6 ppm, and the location of the proton chemical shifts are also relative to the amount of aggregation interaction between the Pc rings.

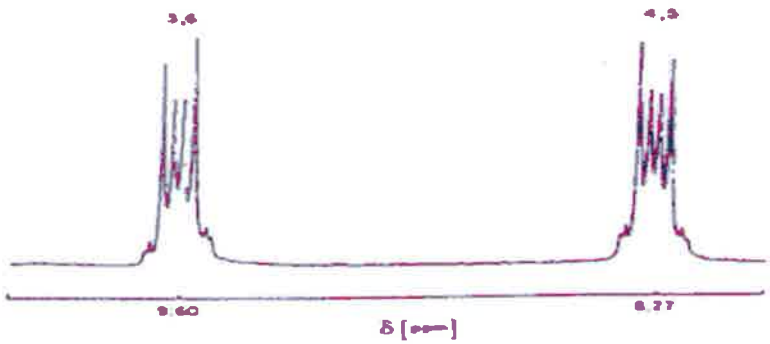
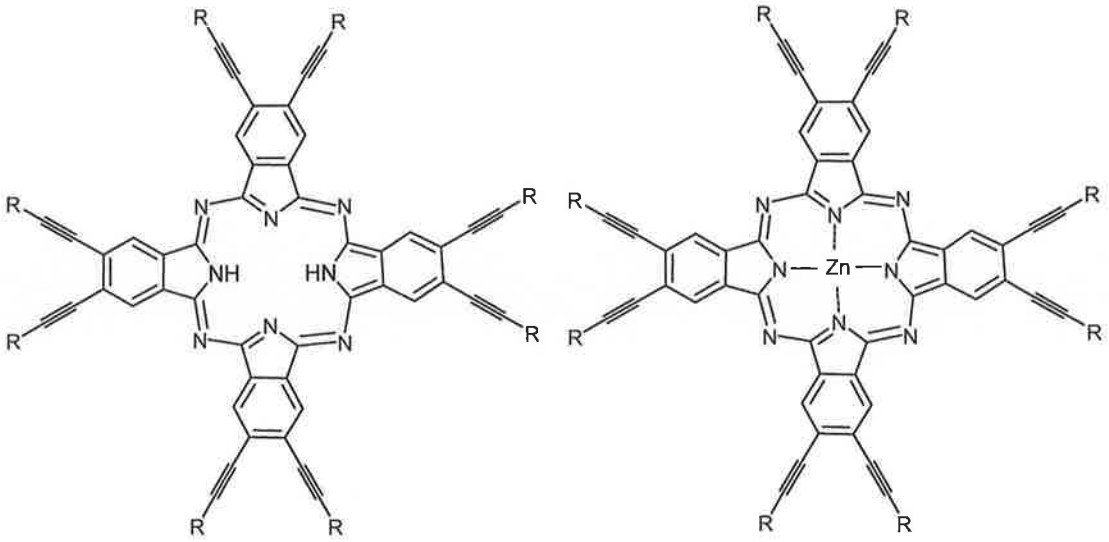


Figure 1.8 *The ^{1}H NMR spectrum of the aromatic protons of PcZn.*

1.3.2 The NMR studies of octa-substituted phthalocyanines

The ^{1}H NMR studies involving the effect of concentration and temperature were carried out on a series of octa-alkynyl Pcs (Figure 1.9). [18] The concentration studies were carried out a concentration range from 10^{-2} to 10^{-5} M in benzene-d_6. It was found that internal proton chemical shifts moved downfield by 2 ppm on dilution. These studies demonstrate that the aggregation between Pc macrocycles, has a significant effect on the ^{1}H NMR chemical shifts of the internal protons. It was also

found that the aromatic protons of these Pcs were also shifted downfield by 1 ppm upon dilution, which again is caused by the decreasing aggregation interaction between Pc macrocycles upon dilution.



(121) R = n-Hexyl
(122) R = n-Pentyl
(123) R= n-Butyl
(124) R = n-Propyl
(125) R = t-Butyl

(126) R = n-Hexyl
(127) R = n-Pentyl
(128) R = n-Butyl
(129) R = n-Propyl
(130) R = t-Butyl

Figure 1.9 *The octa-alkynyl Pcs.*

The ^{1}H NMR studies of the aromatic protons of the zinc octa(alkynyl) Pcs **(126~130)** also showed a 1 ppm (average) downfield shift on dilution, again demonstrating that the aromatic proton chemical shifts are concentration dependent.

The temperature (27 °C~160 °C) ^{1}H NMR studies of octa-substituted Pcs **(121~125)** were carried out in nitrobenzene-d_5, a high boiling point deuterated solvent. The results revealed that the aromatic protons of the metal free Pcs had a 0.2 ppm average downfield shift, but a downfield shift of 1 ppm was observed for the internal proton. The aromatic protons of metallo Pcs showed a 1 ppm downfield shift over the above temperature range. This temperature ^{1}H NMR study of octa(alkynyl) Pcs demonstrated that the high temperature also decreases the aggregation interaction between

Pc macrocycles, which cause a downfield shift of both the aromatic and internal protons og the Pc.

1.4 UV/Vis spectra of phthalocyanines and naphthalocyanines

1.4.1 The UV/Vis spectra of unsubstituted phthalocyanines and naphthalocyanines

The Pcs (or PcMs) have strong absorptions [37, 38] between 670 and 690 nm, (Figure 1.10) and Ncs have their maximum absorption at 770nm. This strong absorption is identified as the "Q-band", which is equivalent to the α–band in porphyrin. There is another strong absorption near the ultra-violet (UV) region (320~370nm), which is referred to as the "B-band" (equivalent to the porphyrin γ or Soret band). The Q-band is caused by a π-π* transition from the excited highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO).

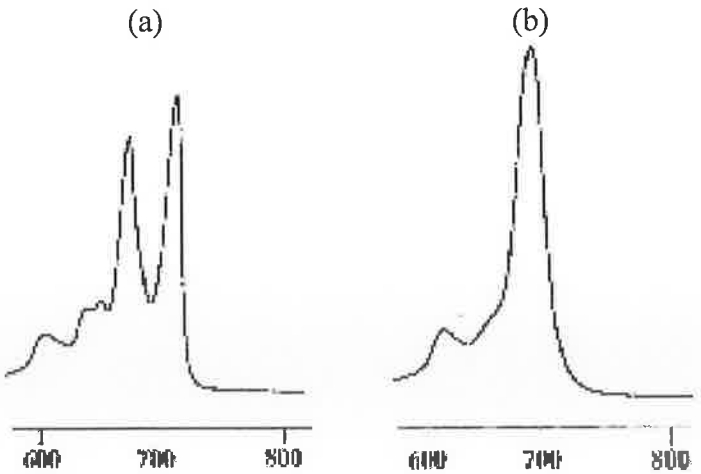


Figure 1.10 *The UV/Vis spectra of PcH_2 (a) and PcCu (b).*

Metallo Pcs and metal-free Pcs possess D_{4h} and D_{2h} symmetry respectively and the degeneracy of the lower-energy singlet state in the former is lifted in the latter by a

rhombic distortion. Unlike the spectra of metallo Pcs, the metal-free Pcs show a characteristic splitting of the Q-band into the Q_x and Q_y components.

1.4.2 The UV/Vis spectra of symmetrical and unsymmetrical substituted phthalocyanines

The Q-band absorption λ_{max} is particularly sensitive to both the central metals and the peripheral substitution of the Pc macrocycle. The Q-band absorptions of zinc Pc and copper Pc are at 670 nm and 680 nm respectively, but vanadium Pc has a maximum absorption at 710 nm, which is 40 nm red-shift.

Substituents that extend the conjugation of Pc also lead to a red-shift in the Q-band absorption. The UV/Vis spectral study of the alkynyl substituted Pcs **(121~130)** demonstrates this point, each conjugated alkynyl group on the peripheral benzo ring causes a 4 nm red-shift in the Q-band absorption at 700 nm.

Unsymmetrical substituted metallo Pcs containing substituents, which can perturb the molecular orbital (MO) of Pc, show uniquely split Q-band absorptions.

The Pcs **(131~136)** outlined in Figure 1.11, are unsymmetrical substituted Pcs, and their UV/Vis spectra are shown in Figure 1.12. [39, 40, 41] The perturbation caused by the substitution pattern and symmetry of the Pc splits the Q-band peaks of Pc **(131)** and **(135)**.

The Q-band peaks of Pc **(133)** and **(134)** do not show any splitting, although they are unsymmetrical substituted. It is suggested that the substituents of **(133)** and **(134)** do not cause a strong enough perturbation to effect the MO of these Pcs.

The perturbation leads to a significant change of the MO of Pc **(132)** and **(136)**. The Q-band absorption of Pc **(132)** is split into two peaks and the Q-band absorption of Pc **(136)** appears as a broadened peak.

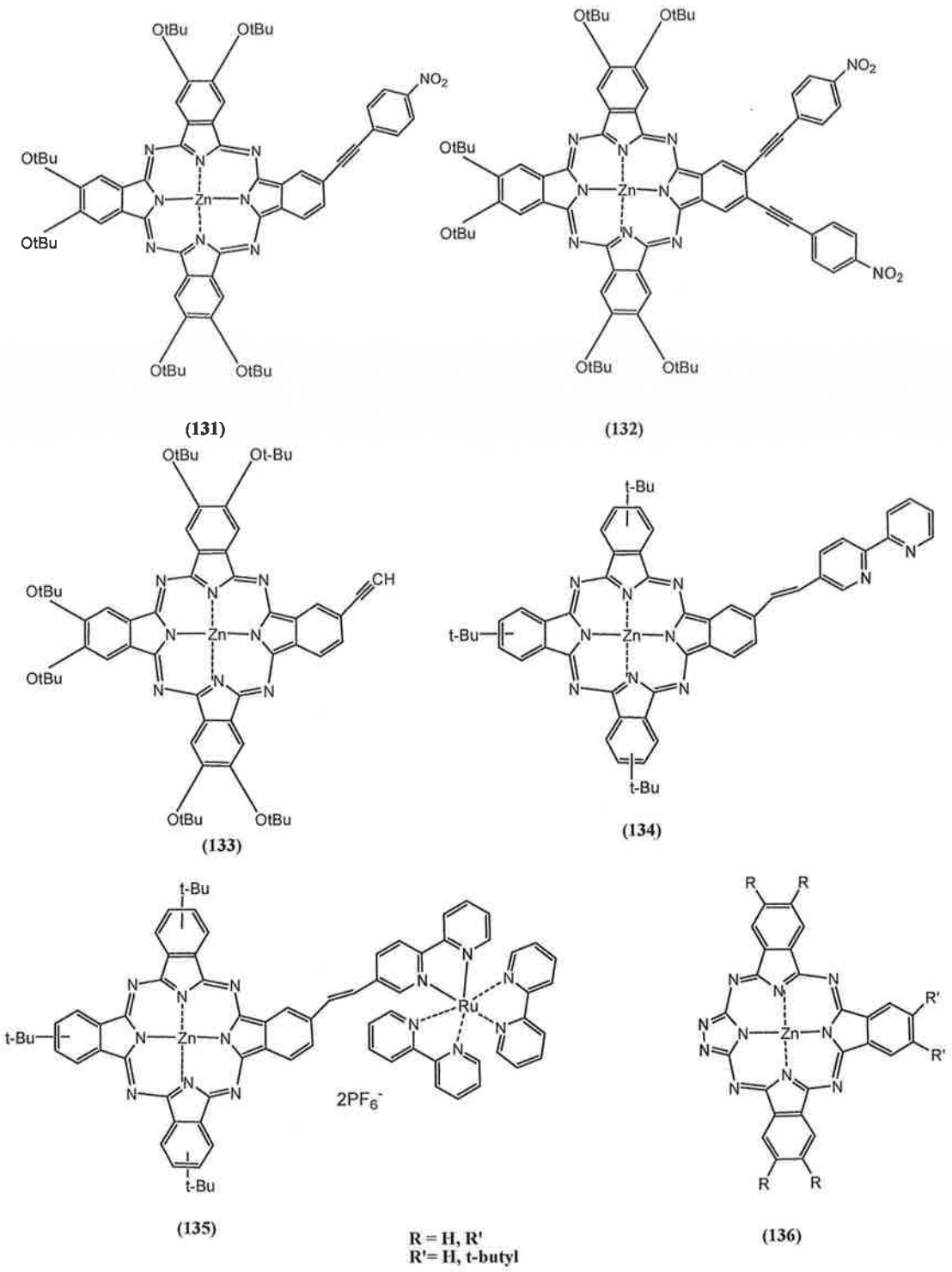


Figure 1.11 *The structures of unsymmetrical Pcs* ***(131~136)***.

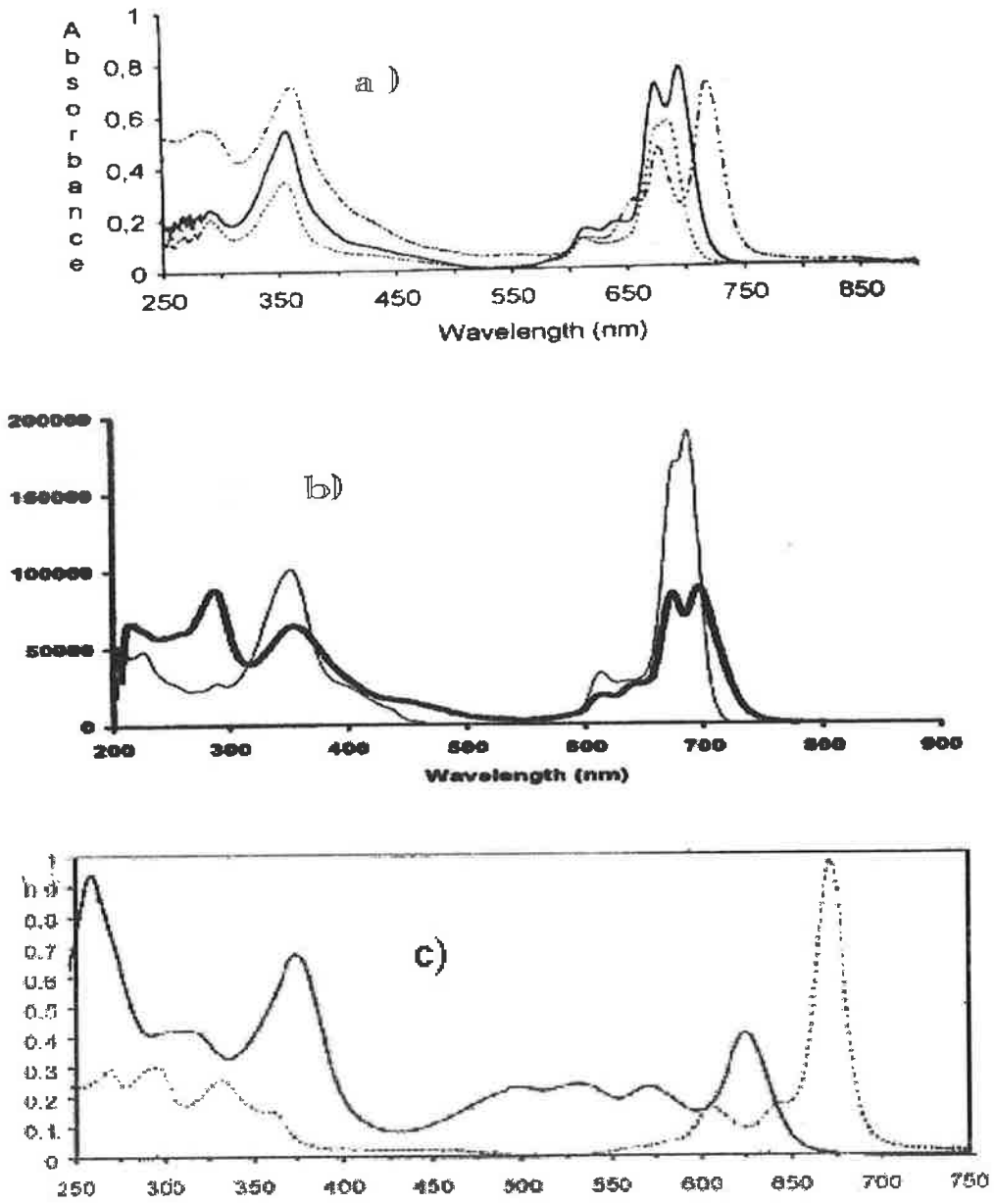


Figure 1.12 *The unsymmetrical substituted Pc* ***(131~136)****, structures are shown in Figure 1.11. a) the UV/Vis spectra of Pc* ***(131)*** *(solid line); Pc* ***(132)*** *(dotted-dashed line); Pc* ***(133)*** *(dotted line). b) the UV/Vis spectra of Pc* ***(134)*** *(thin line); Pc* ***(135)*** *(solid thick line). c) Pcs* ***(29)*** *(dotted-line) and Pc* ***(136)*** *(solid line).*

All the above phenomena is explained by "Symmetry-adapted perturbation theory" (SAPT). The Hamiltonian of a Pc can be described by the simple equation 1.6. [42]

$$H = H^{(0)} + V \qquad \textbf{(Equation 1.6)}$$

$H^{(0)}$ is the unperturbed Pc core Hamiltonian, unsubstitued Pc core of D_{4h} symmetry. V is the perturbation caused by the substituents. The V term is a sum of perturbations which span an irreducible representation for D_{4h} symmetry. (Equation 1.7)

$$V = V_{\Gamma 1} + V_{\Gamma 2} + \cdots\cdots \qquad \textbf{(Equation 1.7)}$$

$V_{\Gamma 1}$, $V_{\Gamma 2}$,...are the corresponding symmetry-adapted perturbations.

The V term can be described by symmetry elements: A_{1g}; B_{1g}; $E_{u,y}$ and B_{2g}. The presence of B_{1g} and B_{2g} will cause perturbation which results in the splitting of the Q-band absorption peaks. We can use a simple graphic to demonstrate the calculation of the perturbation, which is outlined in Figure 1.13.

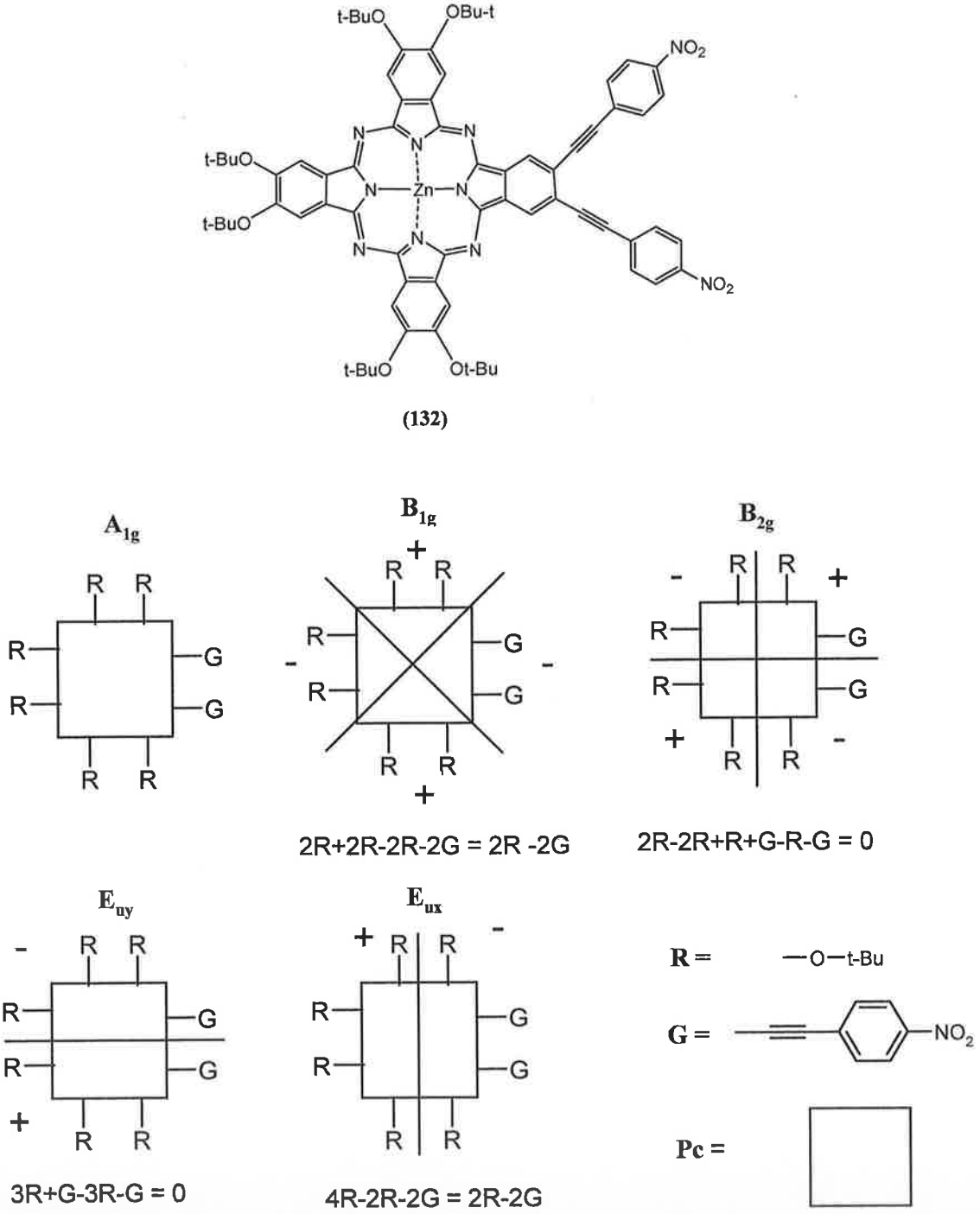


Figure 1.13 *SAPT analysis of Cs symmetry Pc(132).*

Based on the SAPT analysis study of Pc **(132)**, the Hamiltonian for Pc **(132)** is given by equation 1.8.

$$H = H^{(0)} + \{1/2A_{1g}+1/2B_{1g}+1/2E_{u,x}\} \quad \textbf{(Equation 1.8)}$$

Therefore, B_{1g} is present, so the Q-band absorption of this type of Pc should be split. This postulation is confirmed by the UV/Vis spectrum shown in Figure 1.12.

1.4.3 The energy of electronic excitation

According to the energy of the light wavelength, the required energy to excite an electron from HOMO to LUMO in Pc core can be calculated by Equation 1.9.

$$E = hC/\lambda \quad \textbf{(Equation 1.9)}$$

Where the E term is the quantum energy of light; the h term is Plank's constant; the C term is the speed of light in vacuum and the λ term is the wavelength of light. Equation 1.4 denoted that following the increase of the wavelength, the light energy is decreased. So it can be concluded that the Pc with a long wavelength absorption, should have a smaller electronic excitation energy gap between HOMO and LUMO than those Pcs which have the short wavelength absorptions. The difference (ΔE) of the electronic excitation energy between the red-shifted Pcs (E^{Red}) and the original Pcs (E^{Ori}), are described by Equation 1.10:

$$\Delta E = E^{Red} - E^{Ori} \quad \textbf{(Equation 1.10)}$$

A 4 nm red-shift for the Pc Q-band absorption caused by each conjugated alkynyl group at 700 nm, expresses 1 kJ decrease of the electronic excitation energy gap.

1.5 Biological applications of phthalocyanines

1.5.1 Phthalocyanines as second generation photosensitizers for Photodynamic Therapy (*PDT*) of cancer

PDT is a new clinical treatment for cancer. This new treatment requires three basic elements: photosensitizer, oxygen and visible light. None of these elements are harmful to cancer cells on their own, but the combination of these elements will generate singlet oxygen, a cytotoxic agent, which subsequently kills the cancer cells. The photochemistry and photophysics of PDT are outlined in Figure 1.14. [43]

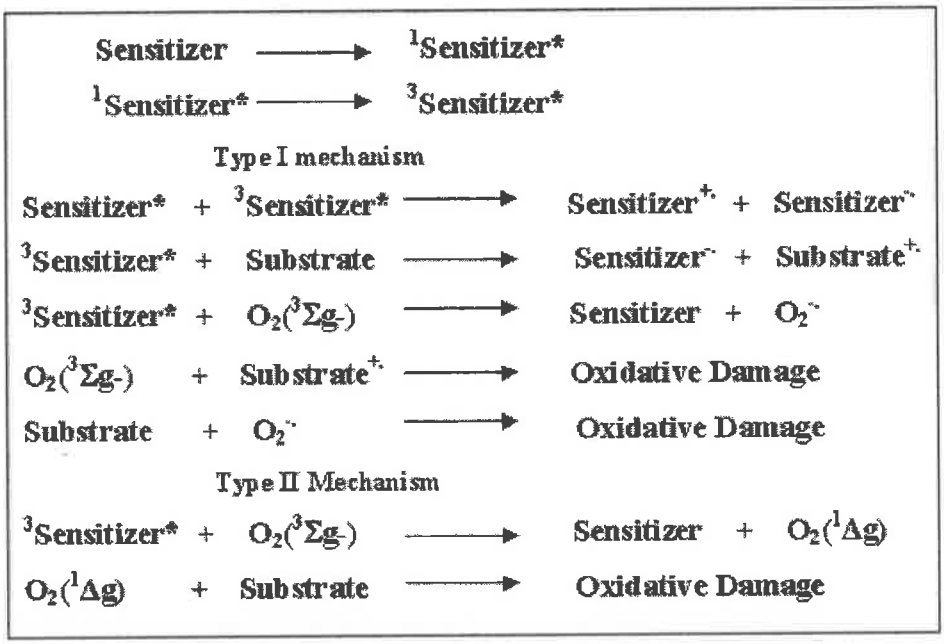


Figure 1.14 *Two proposed mechanisms for PDT.*

Two possible mechanisms for PDT have been postulated. The Type I mechanism involves hydrogen-atom abstraction or electron-transfer reactions between the excited state of the sensitizer and a substrate to create free radicals and radical ions. By contrast, the Type II mechanism has energy transferred between the excited

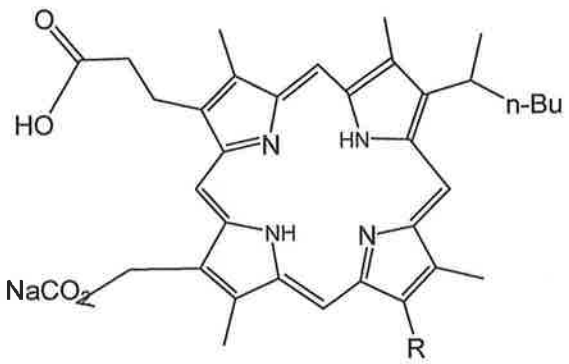
triplet state of the sensitizer and the ground-state of molecular oxygen, generating singlet oxygen. [44]

Thus, an ideal photosensitizer for PDT should have the following characteristics:

1. It should be pure and of known and constant composition.
2. The proposed photosensitizer must have a minimal dark toxicity and is cytotoxic in the presence of light.
3. The compound is selectively retained in the target tissue, but not normal tissue.
4. An ideal photosensitizer should have a high photochemical reactivity, with high triplet-state yields (ϕ_T) and long triplet-state lifetime (τ_T), and can effectively produce singlet oxygen and other reactive oxygen species.
5. Possess a strong absorption in the range of 600-800 nm with a high extinction coefficient (ε).

The photosensitizers, which are presently used in clinical trials for PDT of cancer, are listed in Table 1.1. Photofrin **(137)**: a type of haematoporphyrin (first generation photosensitizers), (Figure 1.15) is used clinically as a tumour-photosensitizing agent for PDT of lung, esophageal and bladder cancer in several countries. [44] Despite its apparent successes, haematoporphyrin derivatives have three important disadv-antages. First of all, these compounds are taken up and retained by cutaneous tissue for up to ten weeks. This causes a marked skin photosensitivity, patients are required to avoid bright sunlight. This is an obvious disadvantage especially for patients with late-stage malignancies. Secondly, photofrin^{TM} has a very low extinction coefficient ($\varepsilon = 3 \times 10^3$), [44] and thirdly haematoporphyrin used in the clinic, are a mixture of up to twelve compounds. These shortcoming have limited the application of photofrin^{TM}.

New types of photosensitizers with less photocytoxicity have been developed to replace photofrin^{TM} in photodynamic therapy, which are commonly known as "second generation phtotosensitizers". Three new photosensitisers are listed in Table 1.2.



(137)

R = CH_3CHOH
R = CH_2CH_3

Figure 1.15 *The structure of photofrin* ^{TM} *(137).*

Table 1.2

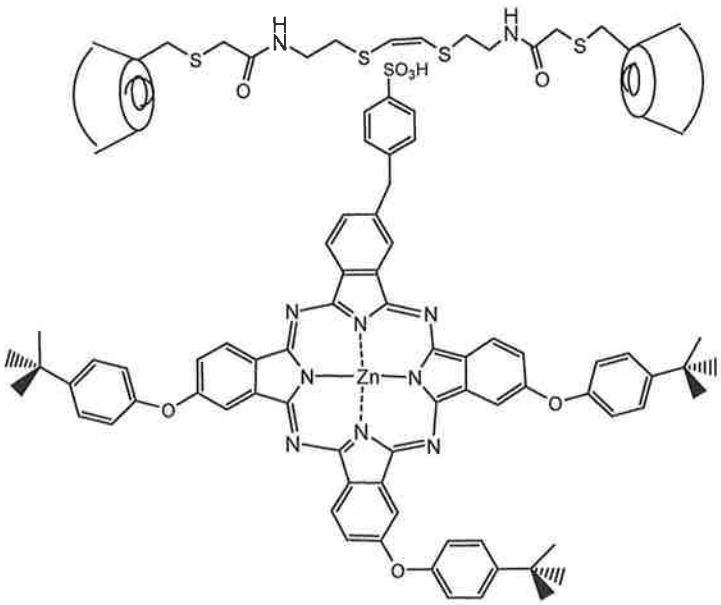
Photosensitizer	Type	Remarks	Absorption (nm)	Molar absorptivity ($M^{-1}scm^{-1}$)
Photofrin	1st	Contains mainlycovalent Hp oligo-mer, plus Hp, Pp and HVD	630	3200
Monoaprtyl-chlorin e_6	2nd	Fast clearance from tumour/skin	675	47000
Sn(VI)-etiopurin	2nd	Requires liposome delivery systems	660	28000
Zn(II)-Pc	2nd	Requires liposome delivery systems	675	243000

Pcs have been investigated as a second generation photosensitizer, because they possess strong absorptions at 680 nm, where tissue penetration of light is at a maximum while still being energetic enough to produce singlet oxygen. In addition, Pcs (or MPcs) possess higher extinction coefficients (normally, ε =, $2.5x10^5$ of Pcs) than porphyrins (ε = 10^3~10^5) and selectively accumulate in tumour cells. Unlike photofrin™, Pcs can be prepared pure.

1.5.2 Third generation sensitizer-drugs delivery in PDT of cancer treatment

Third generation photosensitizers are derivatives of second generation photosensitizers which have been incorporated into macromolecular delivery vehicles. This modification increases the biological specificity of the photosensitizers to a defined cell type. Complexes of Pcs conjugated to oncologically targeted antibodies have been recently prepared. [44] These systems enhance the localisation of photosensitizers at the targeted diseased tissue and eliminate unwanted side effects.

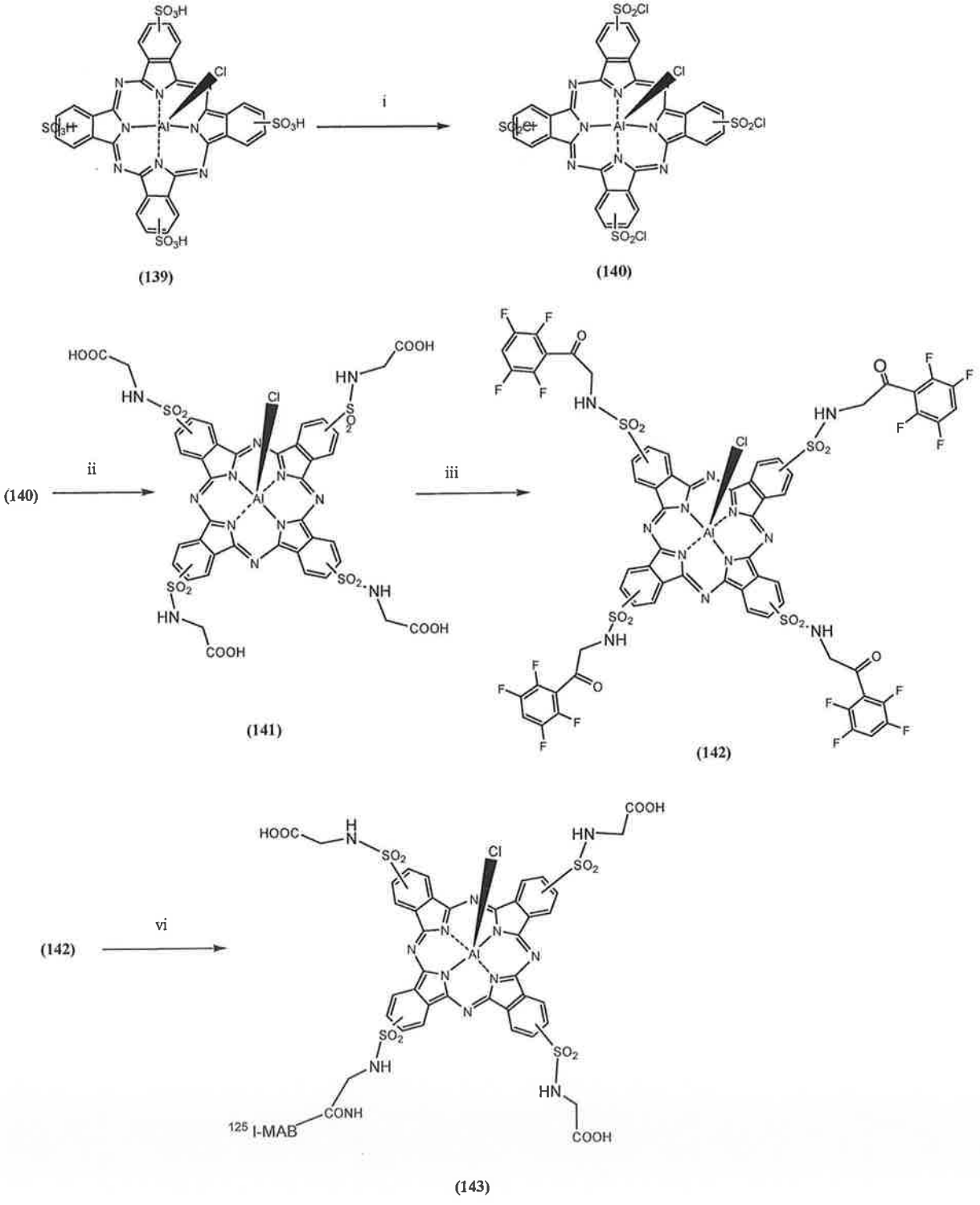
Pc has also been conjugated to a cyclodextrin (CD) dimer **(138)** (Figure 1.16) by an electron-rich carbon–carbon double bond. The CD dimer can be cleaved by singlet oxygen at the double bond linkage, resulting in the release of the Pc into surrounding tissue.[45, 46]



(138)

Figure 1.16 *Complex **(138)**: Pc bound to a cyclodextrin (CD) dimer.*

Using monoclonal antibodies (MAB) directed against tumour-associated antigens, is an interesting option to improve the selectivity of PDT in cancer treatment. Limited by the solubility, only hydrophilic photosensitizers are suitable for conjugation to MABs. Aluminum (III) Pc tetrasulfonate [$AlPc(SO_3H)_4$] has been conjugated to several different MABs (Scheme 1.29) by Van Dongen et.al. [47]



Scheme 1.29 *The preparation of $AlPc(SO_3H)_4$ conjugated to antibodies—^{125}IMAB. i. $SOCl_2$. ii. Glycine; BTA. iii. TFP; EDC; base. vi. ^{125}IMAB; NaCl (9%, pH 9.5).*

1.5.3 Phthalocyanines used in cancer diagnosis

As a result of their fluorescent properties, porphyrins were first used in tumour diagnosis in the early 80's. Unfortunately, porphyrin and its' analogues would accumulate in the patient's skin, which could cause "light-burn" with the irradiation of visible light. The patient who received the diagnostic treatment with porphyrins had to avoid bright light, especially sunlight, for 30 days. [48] As a result, porphyrins have had little application in cancer diagnosis.

Pcs and Ncs have strong fluorescent emissions between 650 nm and 770 nm. It has been found that if the absorption of the photosensitizers are over 770 nm, the yield of singlet O_2 is significantly reduced. This means these photosensitizers, which absorb beyond 770 nm, should show little or no phototoxic side effect, making them potential candidates for cancer diagnosis.

Chapter 2: Purpose and Goal of this project

To date much work has been carried out on the development of new red shifted Pcs. We were particularly interested in further developing this area by preparing a series of new red-shifted Ncs and unsymmetrical substituted red-shifted Pcs. Outlined in Figure 2.1 are the proposed structures that we wish to prepare. We believe that by introducing both alkynyl and alkenyl groups into the Pc and Nc peripheral benzo groups we could cause desirable red-shifts. We believe that these new Ncs should absorb beyond 770 nm and possess fluorescence beyond 800 nm. Such Ncs could find possible applications in cancer diagnostics.

We also wished to prepare some novel red shifted phthalocyanines that possess halo atoms in the peripheral benzo groups of the Pc ring **(146)** (Figure 2.1). The presence of these halo atoms may increase the rate of intersystem crossing of the photoexcited state of the Pc, increasing yields of the triplet state. If successful this might enhance the efficiency of the Pc as a photosensitiser in PDT.

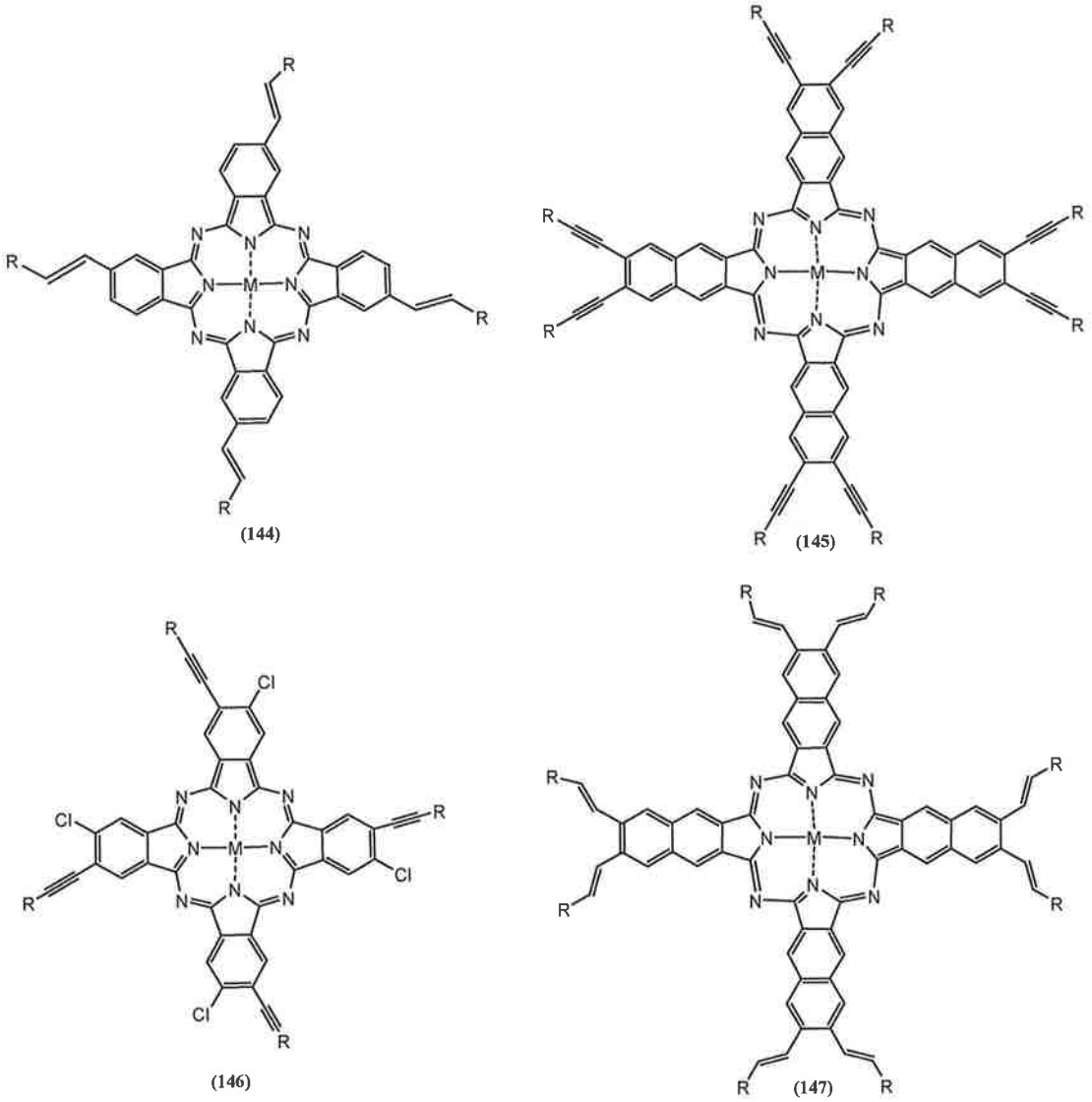
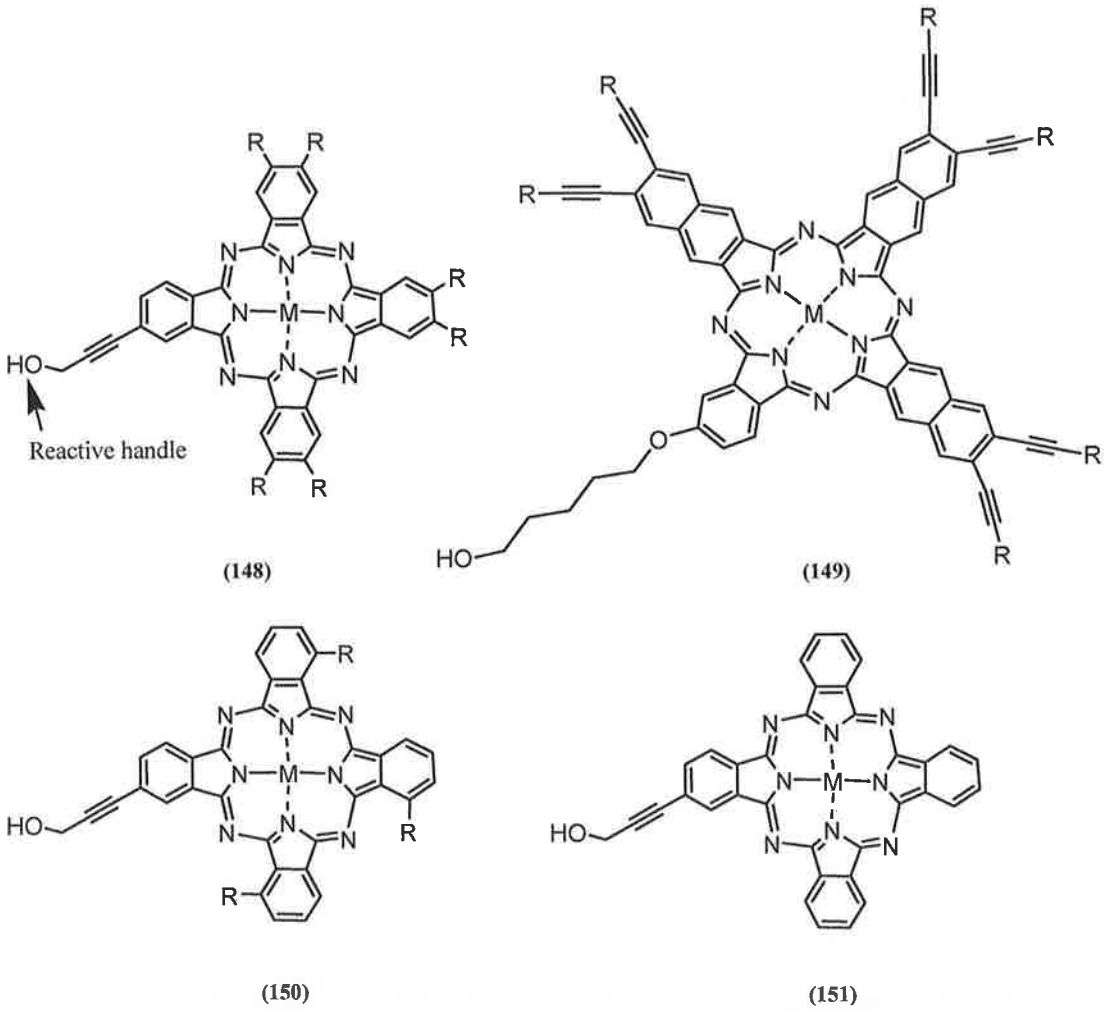


Figure 2.1 *The typical target Pcs and Ncs.*

We also desired to prepare a series of unsymmetrical Pcs and Ncs. We were interested in introducing both a 'reactive' handle, that could be possibly conjugated to antibodies, macromolecular drug carriers, or supramolecular structures (Figure 2.3). Outlined in Figure 2.2 are four examples of our new targets. To achieve this end, we need to try and develop an improved synthetic methods and/or more efficient purification methods of unsymmetrical Pcs, since existing methods to prepare these compounds are extremely time consuming as a result of exhaustive chromatography.

We planned to use both solid support and solution phase synthetic methods to determine whether the solid support methodology was more efficient. In the case of solution phase synthesis we would introduce the usage of size exclusion chromatography to determine whether this form of chromatography could be used to reduce purification times.



M = H; Co^{2+}; Zn^{2+}. **R** = Phenoxy; Benzyloxy.

Figure 2.2 *Unsymmetrical Pcs and Nc containing a reactive handle.*

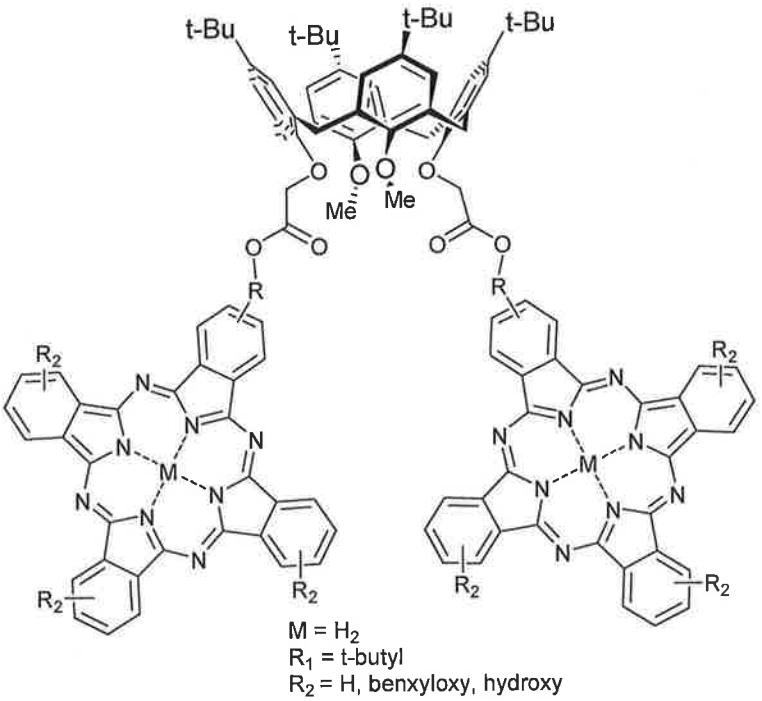
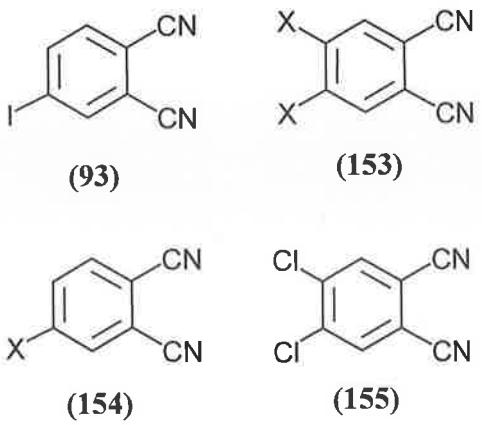


Figure 2.3 *New calix[4]arene binuclear phthalocyanine.*

Halo phthalonitriles are important starting materials in the preparation of various substituted Pcs. Unfortunately, only 4,5-dichlorophthalonitrile **(155)** and 4-iodo-pthalonitrile **(93)** are commercially available and they are extremely expensive, limiting their use. The third goal of this project was focused on developing new synthetic methods for the preparation of halophthalonitriles. (Figure 2.3)



(93) **(153)**

(154) **(155)**

X = I; Br; Cl.

Figure 2.3 *Halo phthalonitriles.*

The final aspect of this work was focused on the development of new benzimidazole-chloroquinoline compounds as potential candidates for malaria and HIV treatments. (Figure 2.4)

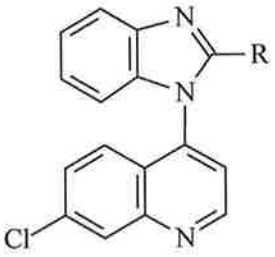
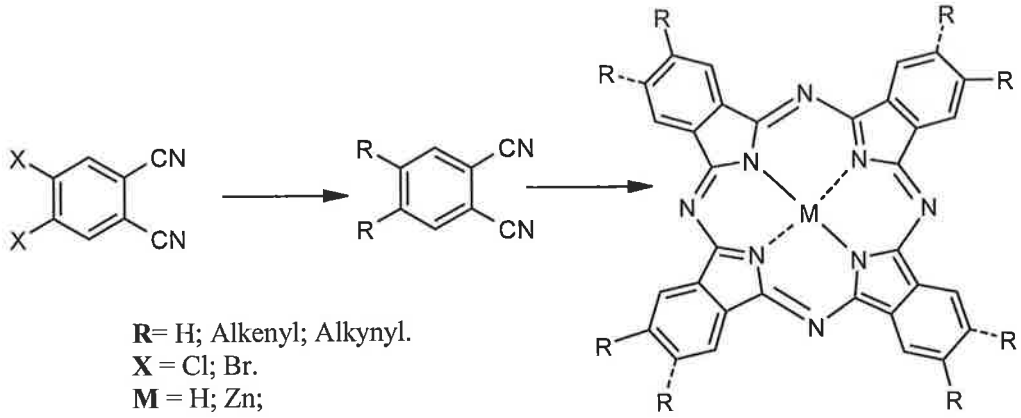


Figure 2.4 *The typical structure of benzimidazole-chloroquinoline complex.*

Chapter 3: The preparation of novel red shift symmetrical phthalocyanines and naphthalocyanines

The preparation of red-shift Pcs (Ncs) started from the substituted phthalonitriles, which were prepared from the cross-coupling reactions of halophthalonitriles with terminal alkynes and alkenes. (Scheme 3.1)



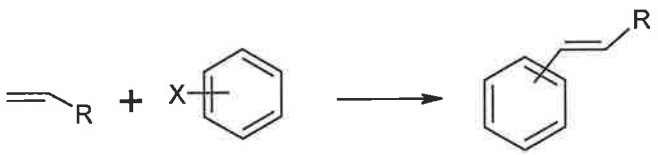
R= H; Alkenyl; Alkynyl.
X = Cl; Br.
M = H; Zn;

Scheme 3.1 *The general synthetic route used to prepare red-shift Pcs.*

3.1 The preparation of tetra(hept-1-enyl) phthalocyanine

3.1.1 The preparation of 4-hept-1-enyl phthalonitrile

The Heck reaction is a very efficient method for the arylation of olefins. [50] The Heck reaction is a palladium catalyzed coupling of aryl halides with olefins. (Scheme 3.2) Different aryl halides can be used in the Heck reaction, in general, the reactivity order for aryl halides is I>Br>>Cl. [51]

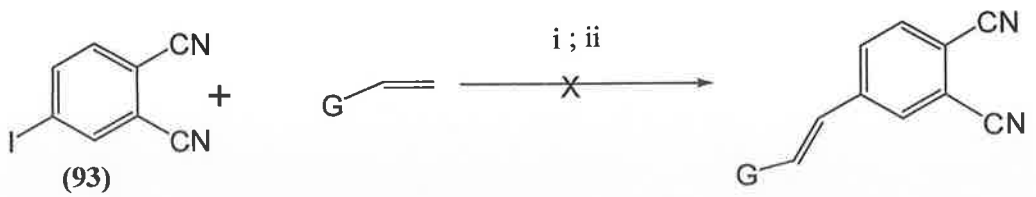


(156) (157) (158)

X = I; Br and Cl.
R= alkyl; phenyl.

Scheme 3.2 *Heck reaction.*

Our first attempts to prepare 4-alkyenyl phthalonitrile involved the coupling of 4-iodophthalonitrile **(93)** with three different vinylic compounds: styrene **(159)**; allyloxytrimethylsilane **(160)** and allyloxyethanol **(161)** in DMF. (Scheme 3.3) We believed that each of these substituents would impart good solubility in the final Pc product. The coupling conditions used palladium acetate (Pd (II) $(OAc)_2$) and triarylphosphines (Ph_3P) as the catalyst system and Et_3N (or sodium acetate (NaOAc)) as base. Unfortunately, the target products were not generated under these conditions. Even with the addition of silver nitrate [52] as a co-catalyst, the reactions still failed.

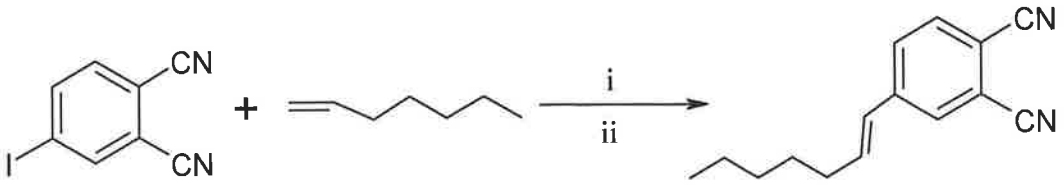


(93)

(159) G = Phenyl
(160) G = $CH_2OSi(CH_3)_3$
(161) G = $CH_2OCH_2CH_2OH$

Scheme 3.3 *The reaction of* ***(93)*** *with several vinylic compounds. i Pd (II)* $(OAc)_2$*;* Ph_3P*;* Et_3N *(or NaOAc). ii Pd (II)* $(OAc)_2$*;* Ph_3P*;* Et_3N *(or NaOAc); silver nitrate.*

We turned our attention to the preparation of 4-(hept-1-enyl) phthalonitrile **(163)**, the heptenyl substituents should significantly improve the solubility of the corresponding Pcs. The same reaction conditions as those employed above were tried with 1-heptene **(162)**, unfortunately the target product was not found in the reaction mixture. We decided to change the reaction conditions, by varying the catalyst, base, temperature, and reaction time. It was found after several reactions, that the cross-coupling reaction with Pd (II) $(OAc)_2$ and NaOAc, yielded small quantities of 4-hept-1-enylphthalonitrile **(163)**, at 6% of yield. The cross-coupling of alkene and halo phthalonitrile catalysed by $PdCl_2(PPh_3)_2$ and NaOAc, gave **(163)** in 52% yield after purification. (Scheme 3.4) It would appear that 4-iodophthalonitrile **(93)** requires a ligated palladium catalyst for the cross-coupling reaction to occur.



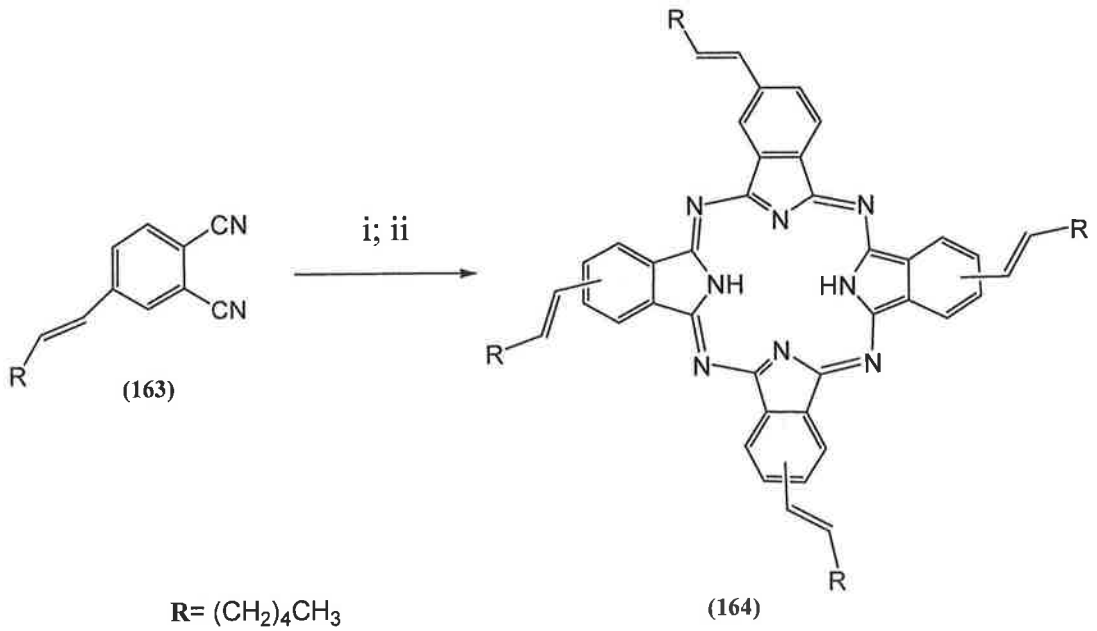
(93) **(162)** **(163)**

Scheme 3.4 *The Heck reaction carried out between* ***(162)*** *and* ***(93)****. i Pd (II)* $(OAc)_2$*; NaOAc. ii* $PdCl_2(PPh_3)_2$*; NaOAc.*

The ^1H NMR analysis of **(163)** shows two proton shifts at 6.5 and 6.9 ppm, which are characteristic for vinylic protons. The protons on the aromatic ring are found in the correct region, and the remaining 11 alkyl protons are present between 0.8~2.5 ppm. The ^{13}C NMR spectrum of **(163)** gave 5 carbon peaks in the alkyl region (14~35 ppm), and 10 carbon peaks between 113~144 ppm, which account for the phthalonitrile and the alkenyl carbons. The electrospray ionization (ESI) mass spectrum of **(163)** gave a parent ion peak at 263, which was the molecular mass of **(163)** combining K^+.

3.1.2 The preparation of 2,9,16,23-tetra(hept-1-enyl) phthalocyanine and spectrum study

The tetra(alkenyl) Pc **(164)** was prepared by the self-condensation of **(163)** with Li/pentanol under argon at 110°C.[18] (Scheme 3.5) The reaction mixture turned a lovely green color. The green sticky reaction mixture was diluted with ethanol, followed by acidification with dilute hydrochloric acid to give metal-free 2,9,16,23 tetra(hept-1-enyl) Pc **(164)**. The crude Pc **(164)** was collected by centrifuge and washed with methanol several times. The blue residue was purified with a silica gel column using THF as eluant to give tetra-alkenyl substituted Pc **(164)** in 22% yield.



(163) (164)

Scheme 3.5 *The synthesis of Pc* ***(164)****. i Condensation; ii Treat with dilute acid.*

The UV/Vis spectrum of 2,9,16,23-tetra(hetpt-1-enyl) Pc **(164)** gave the expected two peaks in the Q-band at 675 and 710 nm respectively. (Figure 3.1) It would appear that each alkenyl group causes an average 3 nm red shift at (700 nm) of the λ_{max} of the Pc Q-band by caculation. The red shift caused by the akenyl group is smaller than what has been reported for the alkynyl substitutents (4 nm caused by

each alkynyl group [18]). The actual energy change corresponds to 0.7 kJ by caculation of each alkenyl substitutents, which is 0.3 kJ smaller than that of the alkynyl substituents.

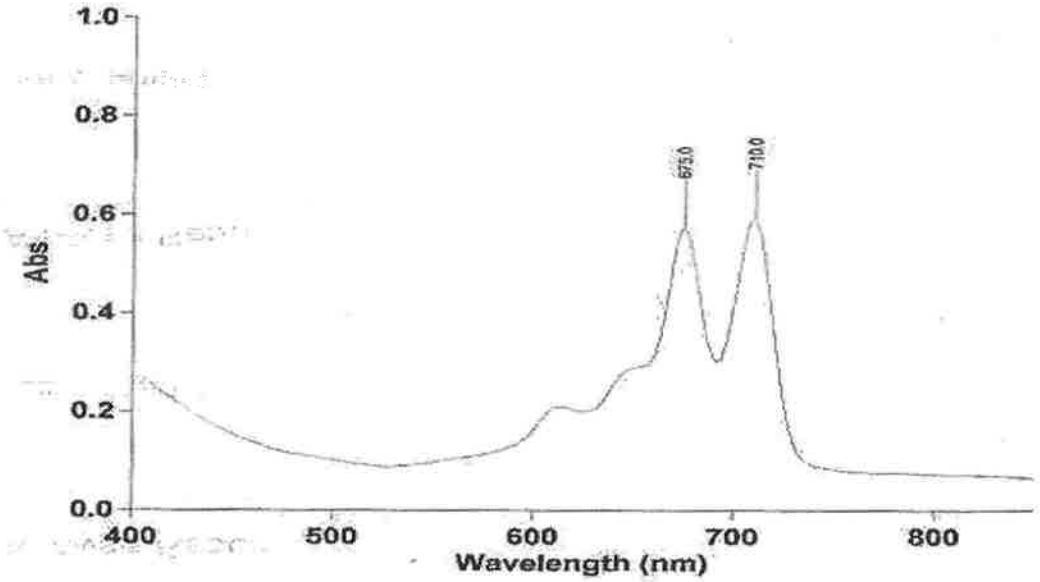


Figure 3.1 *The UV/Vis spectrum of Pc* ***(164)****, the sample solution is* $5x10^{-5}$*M, in THF.*

Since the product Pc **(164)** was a mixture of four position isomers, there was no good ^{1}H NMR spectra obtained, which the NMR experienments were carried out in Benzene-d_6 at both room temperature and 60°C. (Appendix 1 and 2.)

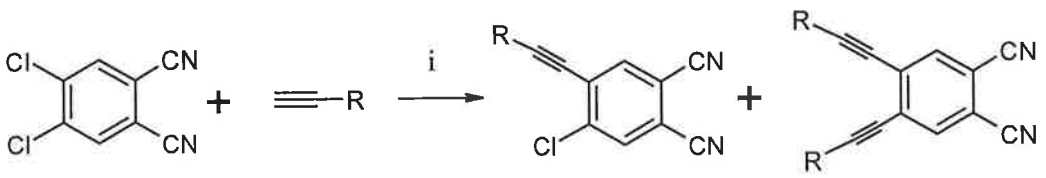
The molecular weight was measured by MALDI, a signal peak at 898 according to the Pc **(164)** cation was found on the spectrum.

3.2 The preparation of 2, 9,16,23-tetrachloro-3,10,17,24-tetra(3-methoxyprop-1-ynyl) phthalocyanine and 2,9,16,23-tetrachloro-3,10,17,24-tetra(3-methoxyprop-1-ynyl) phthalocyaninato Zinc (II)

3.2.1 The preparation of alkynyl substituted phthalonitriles

Since halide substituents on Pcs can increase the excited triplet yields, we attempted to prepare a new series of red-shifted Pcs that contain halide substituents.

The preparation of **(166)** and **(167)** is outlined in Scheme 3.6. [53] Normally, bromo or iodo are the preferred aryl halides for this class of reaction. Unfortunately neither iodo nor bromo di-substituted phthalonitrile are commercially available, 4,5-dichlorophthalonitrile **(155)** is the only aryl dihalide, which we could use for this reaction.



(155) **(165)** **(166)** **(167)**

R = CH_2OCH_3

Scheme 3.6 *The synthesis of 4-chloro-5-(3-methoxyprop-1-ynyl) phthalonitrile* ***(166)*** *and 4,5-bis(3-methoxyprop-1-ynyl) phthalonitrile* ***(167)****. i* $PdCl_2(PPh_3)_2$*; CuI; diisopropylamine* $(^iPro)_2NH$*.*

The procedure used involved treating compound **(155)** and 3-methoxypropyne **(165)** with $PdCl_2(PPh_3)_2$ and CuI in $(^iPro)_2NH$ at 60~70°C overnight. Two products **(166)** and **(167)** were isolated in 24% and 2% yield respectively. Other palladium catalysts, such as Pd (II) $(OAc)_2$ with Ph_3P were tried but the reactions failed to form the target product. Higher temperatures were also tried, but the 4,5-dichlorophthalonitrile **(155)**

was still recovered unreacted and no target product was found by silica thin layer chromatography (TLC) after 24 hrs.

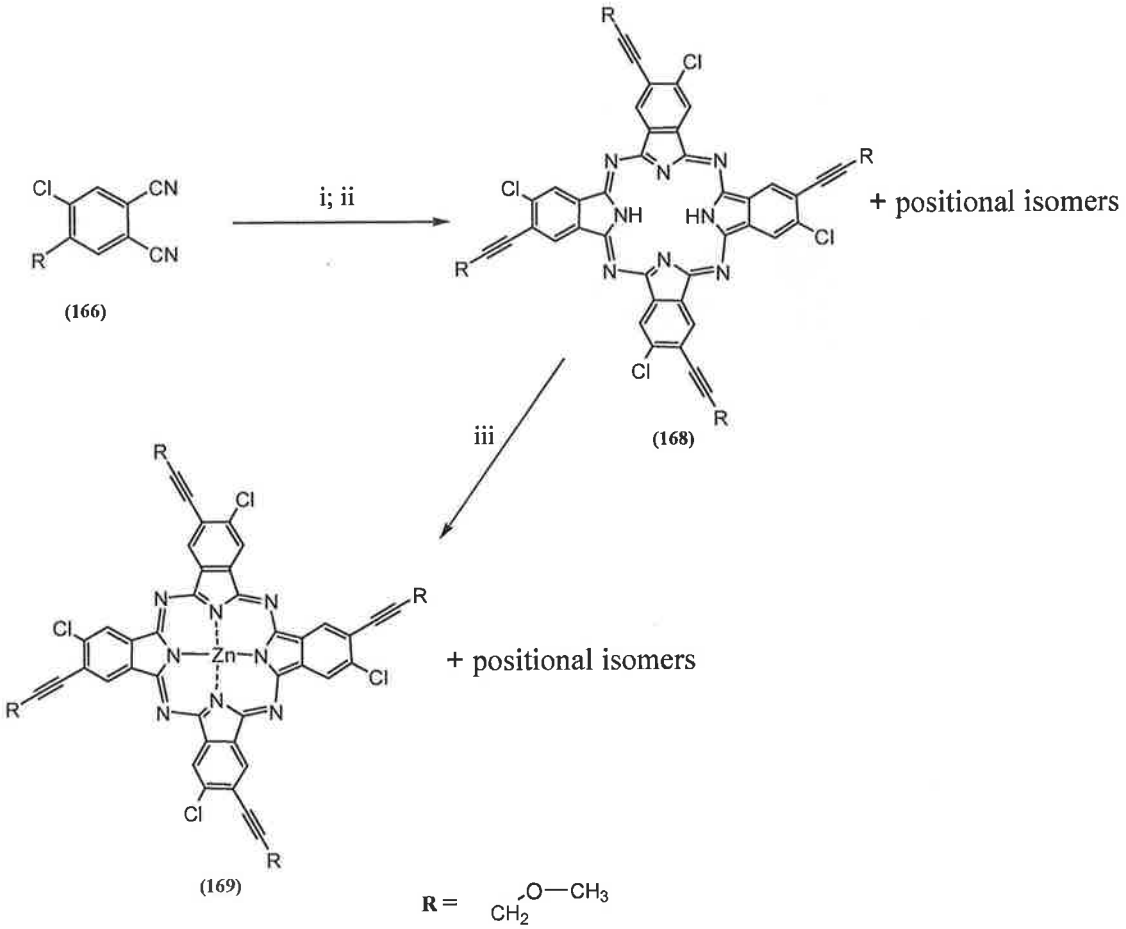
The ^{1}H NMR spectrum of **(155)** gave a single peak at 7.9 ppm for the aromatic protons. The ^{1}H NMR spectrum of **(166)** showed that two aromatic proton peaks were present in the correct region (7.7 and 7.8 ppm) and two singlets observed at 3.4 and 4.3 ppm could be assigned to the methylene and methyl protons respectively. In the ^{1}H NMR spectrum of **(167)**, a single peak for the two aromatic protons of **(167)** were observed at 7.8 ppm and two single peaks were still present at 3.4 ppm and 4.2 ppm, which were assigned to the methyl and methylene protons respectively.

3.2.2 The preparation of 2, 9,16,23-tetrachloro-3,10,17,24-tetra(3-methoxyprop-1-ynyl) phthalocyanine and 2,9,16,23-tetrachloro-3,10,17,24-tetra(3-methoxyprop-1-ynyl) phthalocyaninato Zinc (II)

Pc **(168)** was prepared by the self-condensation of **(166)** in refluxing Li/pentanol. The metal-free Pc **(168)** was obtained by adding dilute HCl into the cooled reaction mixture. The purification of Pc **(168)** was carried out by the same procedure as that used in the preparation of Pc **(168)**, which gave a mixture of positional isomers in 31% yield. (Scheme 3.7)

The conversion of Pc **(168)** into PcZn **(169)** was carried out by refluxing Pc **(168)** with $Zn(OAc)_2$ in DMF. The reaction mixture was cooled to room temperature and the crude PcZn **(169)** precipitated by the addition of water. After the liquid phase was removed by filtration, the blue residue was washed with plenty of water, followed by water/methanol solution, and dried under vacuum. This blue solid was then dissolved in a minimum volume of THF, and the solution was washed through a silica-gel column. The blue fraction was collected, the THF was removed under vacuum to

give a blue solid. We found that to completely remove all the insoluble impurities from the PcZn **(169)** product, a second silica-gel column with THF as eluant was required. PcZn **(169)** was obtained in 76% yield.



(166) (168) (169)

Scheme 3.7 *The synthesis of Pcs* ***(168)*** *and* ***(169)****. i Condensation; ii Treat with dilute acid; iii Reflux; Zn(OAc)$_2$; DMF.*

3.2.3 UV/Vis spectra discussion of Pc (168) and PcZn (169)

The UV/Vis spectrum of Pc **(168)** shows a broad Q-band absorption at 670~720nm. We believed that the broad absorption is caused by aggregation, suggesting that the chloro and methoxy propargyl groups are not effective at preventing the aggregation between Pc macrocycles. (Figure 3.2) To demonstrate this suggestion, a UV/Vis

concentration study was carried out, it showed that the strong aggregation was still existing even at very low concentration (10^{-7}M).

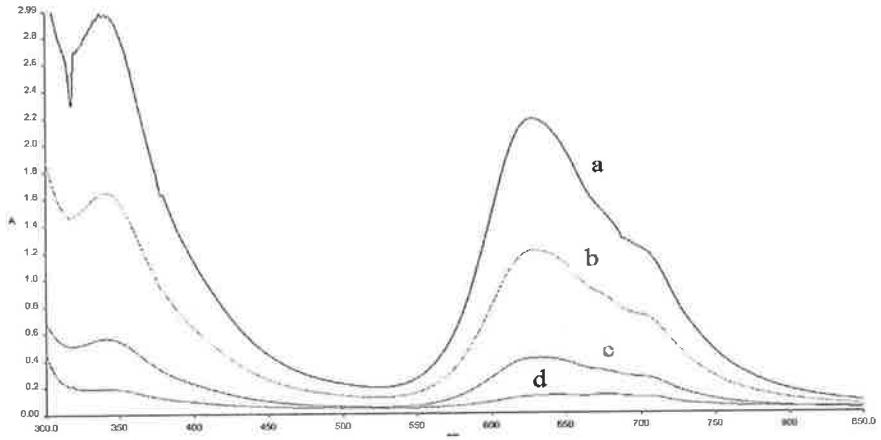


Figure 3.2 *The UV/Vis spectrum of Pc* ***(168)*** *at different concentrations (THF): (a) 1x10^{-4}M; (b) 1x10^{-5}M; (c) 1x10^{-6}M; (d) 1x10^{-7}M.*

The UV/Vis spectrum of PcZn **(169)** is outlined in Figure 3.3, which shows a single absorption peak at 690 nm. The aggregation interaction between PcZn **(169)** macrocycles is still very strong after metallation.

We added benzimidazole to decrease the aggregation between PcZn **(169)**, since the axial co-ordination between benzimidazole and the Zn center of PcZn **(169)** should occur, and this is evident from the resulting UV/Vis spectrum shown in Figure 3.4. The same experiment was run with PcH_2 **(168)**, but aggregation was unaffected.

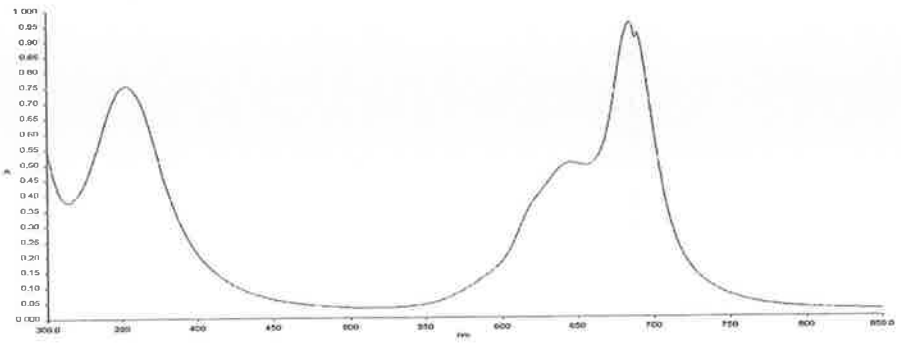


Figure 3.3 *The UV/Vis spectrum of PcZn* ***(169)****. Con 10^{-5}M in THF.*

a) *b)*

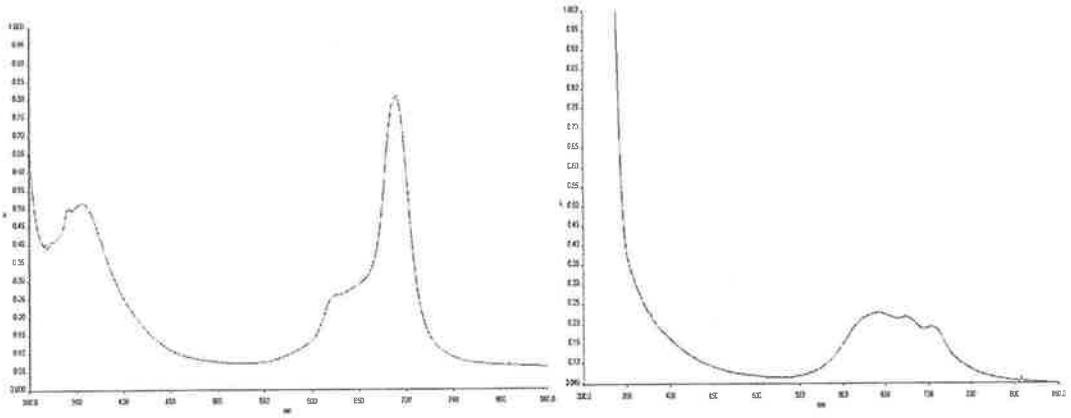


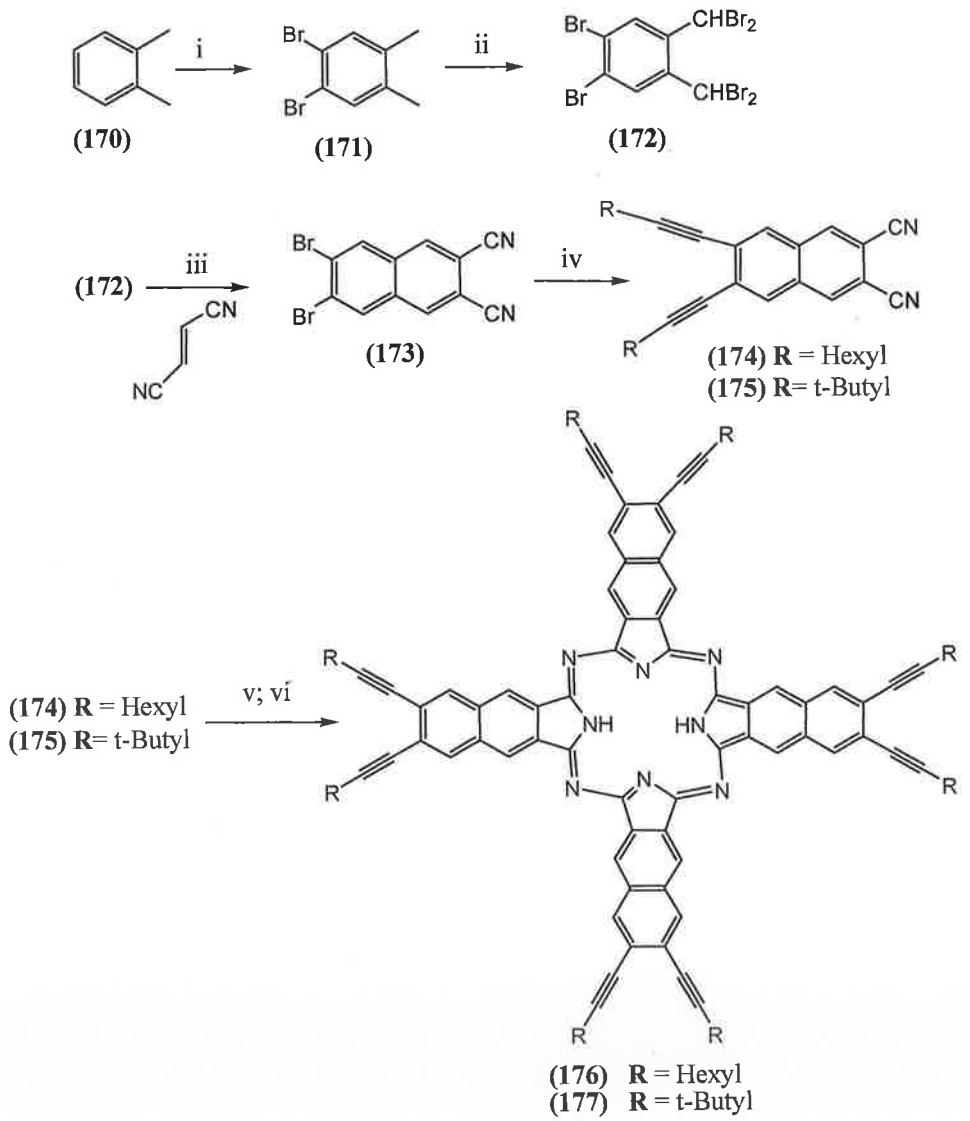
Figure 3.4 *The UV/Vis spectra of PcZn* ***(169)*** *(a) and* PcH_2 ***(168)*** *(b). At Con* 10^{-5}*M, in THF, Benzimidazole.*

3.3 The preparation of 3,4,12,13,21,22,30,31–octa(alkynyl) and octa(alkenyl) naphthalocyanines

3.3.1 The preparation of 6,7-di(alkynyl)-2,3-dicyanonaphthalene

The preparation of 3,4,12,13,21,22,30,31–octa(alkynyl) Ncs was accomplished from a five step synthesis as outlined in Scheme 3.8, beginning with the bromination of *o*-xylene **(170)** with bromine. Then, 1,2-dibromo-4,5-dimethylbenzene **(171)** was treated with NBS in carbon tetrachloride (CCl_4) to produce 1,2-dibromo-4,5-bisdibromomethylbenzene **(172)**. This reaction could be catalysed either by benzoyl peroxide irradiated with strong light irradation at room temperature, or refluxing with α,α'-azobisisobutyronitrile (AIBN) overnight. We found the reaction carried out by refluxing with AIBN, gave 1,2-dibromo-4,5-bisdibromomethylbenzene **(172)** in a higher yield, up to 70%, than these irradated by light with benzoyl peroxide in 30% of yield.

1,2-Dibromo-4,5-bisdibromomethylbenzene **(172)** was treated with fumaronitrile **(53)** and NaI in DMF to give 6,7-dibromo-2,3-dicyanonaphthalene **(173)** in a yield of 69%.



Scheme 3.8 *The synthetic route used to prepare octa(alkynyl) Ncs. i Br_2; Fe; I_2. ii N-Bromosuccinimide (NBS); AIBN; refluxing; carbon tetrachloride. iii sodium iodide (NaI); DMF; 80 °C. iv $PdCl_2(PPh_3)_2$; CuI; diisopropylamine $(^iPro)_2NH$. v Li/Pentanol/reflux. vi Dilute acid.*

The alkylation of 6,7-dibromo-2,3-dicyanonaphthalene **(173)** with 1-octyne to form 6,7-di(oct-1-ynyl)-2,3-dicyanonaphthalene **(174)**, was carried out using the same

palladium catalyst ($PdCl_2(PPh_3)_2$) and CuI in TEA. Compound **(174)** was obtained in 50% yield. Because of the low boiling point of 3,3'-dimethylbut-1-yne, 6,7-bis (3,3'-dimethylbut-1-ynyl)-2,3-dicyanonaphthalene **(175)** had to be prepared at low temperature (50 °C), this was accomplished using the same catalysts, to give **(175)** in 45% yield.

The ^1H NMR spectrum of **(175)** is shown in Figure 3.5. Two singlets at 8.1 and 7.9 ppm can be assigned to the naphthalene protons, and the single peak at 1.3 ppm can be assigned to the *t*-butyl protons.

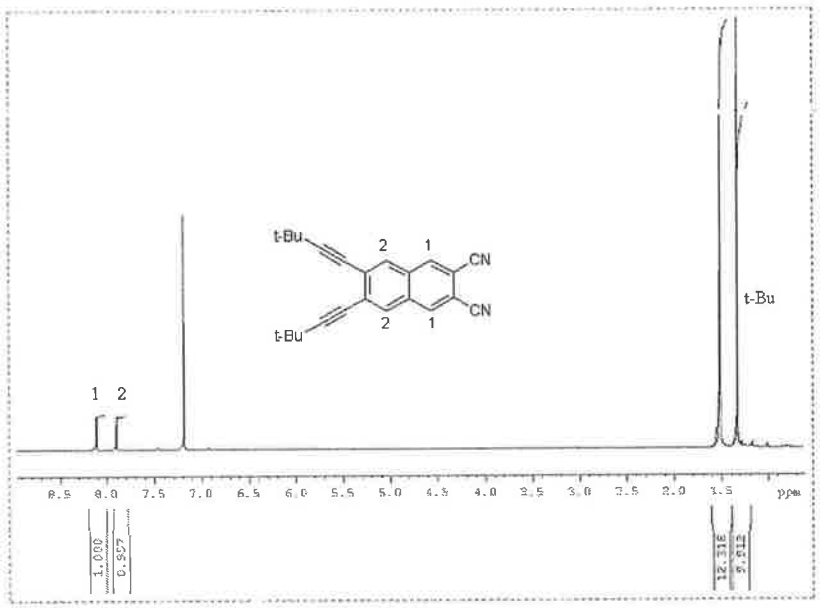


Figure 3.5 *The ^1H NMR spectrum of (175), in $CDCl_3$.*

3.3.2 The preparation of 3,4,12,13,21,22,30,31–octa(alkynyl) Nc (176) and (177)

The condensations of **(174)** and **(175)**, to give octa(alkynyl) Ncs were carried out in Li/pentanol solution. After the dilithium Ncs were treated with dilute acid, metal-free Nc **(176)** and **(177)** precipitated, which were collected by centrifuge. The crude blue solids obtained from the two reactions were further purified by silica-gel

chromatography using different eluants (chloroform; THF; Methanol/DCM). The pure Ncs **(176)** and **(177)** were obtained in 8% and 12% yields, respectively.

3.3.3 Spectra discussion of Nc (176) and (177)

The Q-band of unsubstituted Nc is typically at 770 nm. The Q-band of octa-alkynyl Ncs **(176)** and **(177)** are at 801 and 798 nm respectively. Each alkynyl group causes a 3.5~4.0 nm red-shift of the Q-band absorption at 770 nm. There is an approximate 0.75 kJ of energy decrease between the HOMO and LUMO energy gap, which is less than that found for the alkynyl Pcs. (Equation 1.5) This result is to be expected since the alkynyl groups lie further away from the Pc core for Nc **(176)** and **(177)** compared to the alkynyl Pcs.

On comparison of the UV/Vis-spectra of octa(alkynyl) Nc **(176)** and **(177)**, it would appear that the 3,3'-dimethylbut-1-ynyl substituents of Nc **(177)** are superior in preventing aggregation between the Nc macrocycles compared to the long alkyl chains of Nc **(176)**. The UV/Vis-spectra of **(176)** and **(177)** are outlined in Figure 3.6.

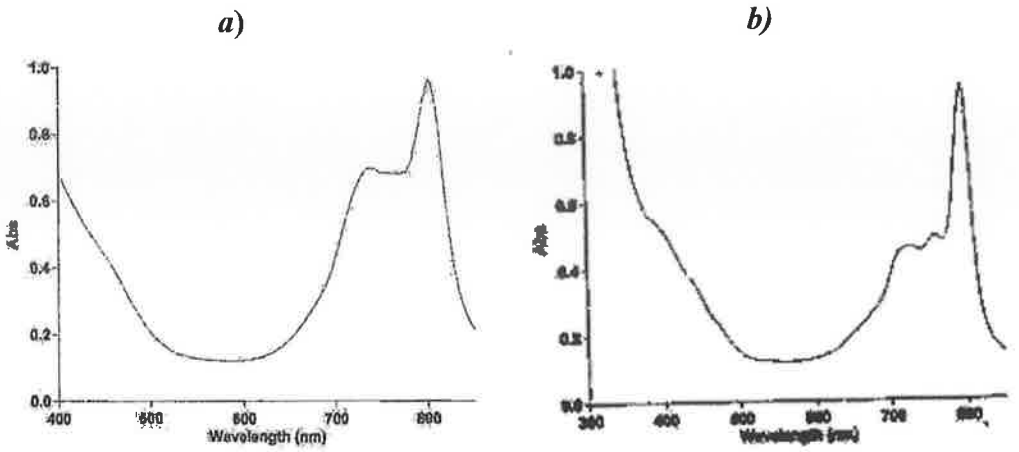


Figure 3.6 *The UV/Vis spectra of Ncs* ***(176)*** *(a) and* ***(177)*** *(b), at Con 1x10^{-5}M, in THF.*

To prove our suggestion, a UV/Vis concentration study (between 10^{-5}~10^{-7} M), was carried out on Nc **(177)**. (Figure 3.7) With increasing concentration, the absorption at 710 nm became more intense, (arrow pointed in Figure 3.7 A.) demonstrating the strong aggregation at high concentration. It also appears that when the concentration is at or below 10^{-6}M, a non-aggregated spectrum is observed. This is one of the few examples of a non-aggregated spectrum for a Nc system.

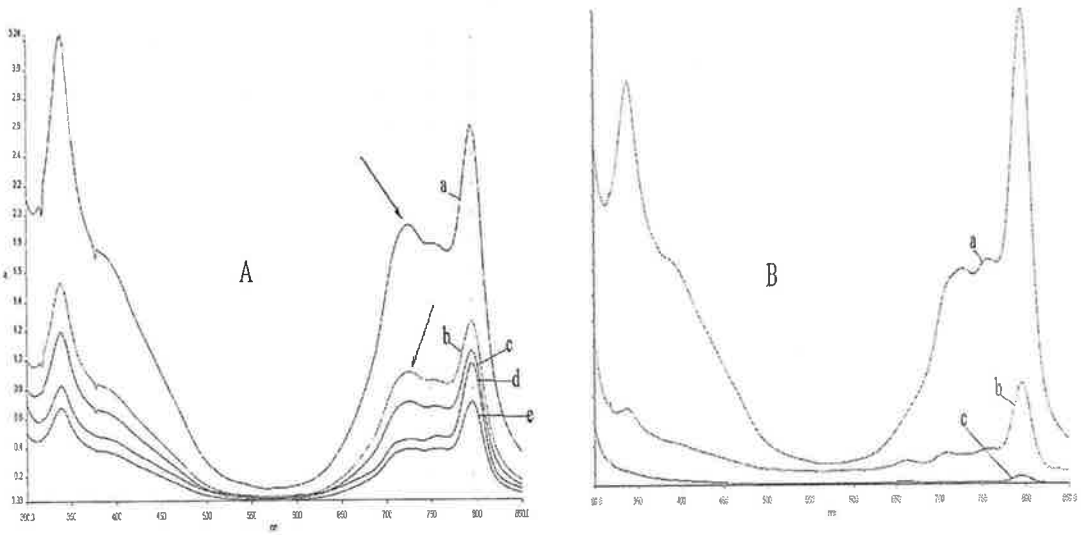


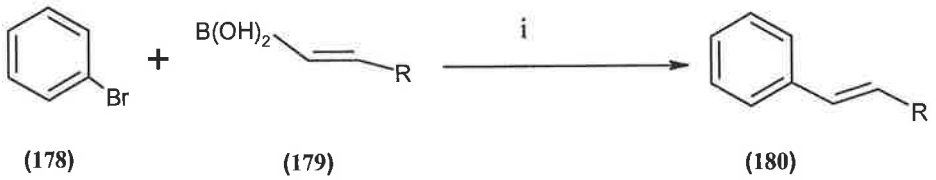
Figure 3.7 *The concentration study of Nc* ***(177)****, in THF. (A) a. 5x10^{-5}, b. 4.1x10^{-5}, c. 3.3x10^{-5}, d. 1.7x10^{-5} and e.1x10^{-5} M; (B) a. 5x 10^{-6}, b. 1x10^{-6} and c. 1x10^{-7} M.*

The ^{1}H NMR was run on both Nc **(176)** and **(177)** at 10^{-4}M. Unfortunately, no proper spectra could be obtained, which is common for Ncs.[54] The MALDI of Nc **(177)** gave a parent ion peak at 1354. (Appendix 3)

3.4 The synthesis of octa(alkenyl) Nc

3.4.1 The preparation of 6,7-dialkenyl-2,3-dicyanonaphthalene

The Heck reaction could not be used to prepare 6,7-dialkenyl-2,3-dicyanonaphthalene from 1-alkenes and **(173)**, since the reaction temperature required is 120 °C or higher. At this temperature, 2,3-dicyanonaphthalene would be converted to Nc. We used an alternative method involving the alkylation of aryl bromides with alkenylboronic acids and a "ligandless palladium catalyst" at 70 °C. (Scheme 3.9) This temperature is lower than the threshold used in Nc condensations.

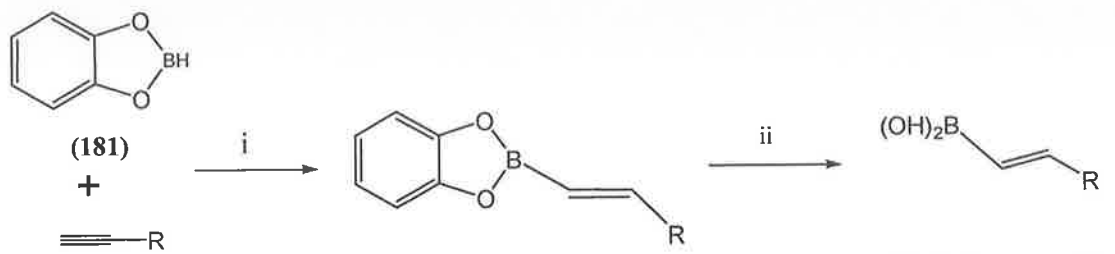


(178) **(179)** **(180)**

R= Alkanyl.

Scheme 3.9 *The reaction of aryl bromides and vinylic boronic acid. i N_2; 70 °C.*

Alkynes were converted to alkenylcatecholboranes by reaction with catecholborane, (Scheme 3.10) [55] and then rapidly hydrolysised to alkenylboronic acids upon stirring with excess water at room temperature. The alkenylboronic acids are solids which could be separated by filtration and purified by washing with water.



(181) + **(182)** **(183)**

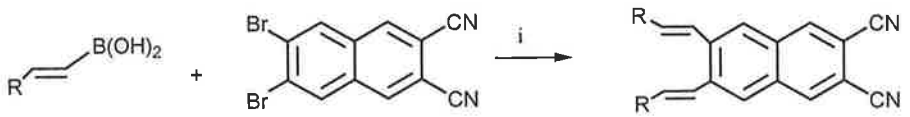
(184) **(185)**

(186) **R** = n-pentyl;
(187) **R** = t-butyl.

Scheme 3.10 *The preparation of alkenylboronic acid. i 70 °C; ii H_2O, r.t.*

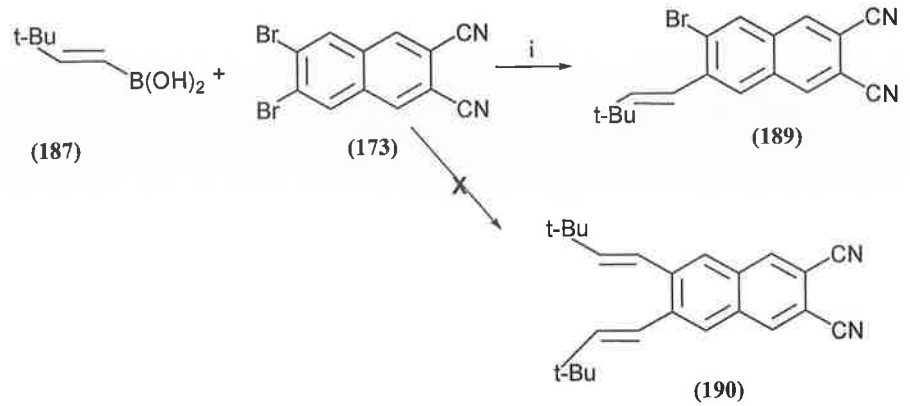
The "ligandless" Pd (II) $(OAc)_2$ catalysed reaction of aryl bromides with vinynyl-boronic acids is normally carried out in water in the absence of organic solvents. [56] We used similar conditions to prepare 6,7-dioct-1-enyl-2,3-dicyanonaphthalene **(188)** (Scheme 3.11) and 6-bromo-7-(3,3'-dimethylbut-1-ynyl)-2,3-dicyanonaphthalene **(189)** (Scheme 3.12). The yields of 6,7-di(oct-1-enyl)-2,3-dicyanonaphthalene **(188)** and 6-bromo-7-(3,3'-dimethylbut-1-ynyl)-2,3-dicyanonaphthalene **(189)** were 86% and 5% respectively, after purification.

To improve the yield of the cross-coupling reaction between **(186)** and **(173)**, the reaction temperature was raised to 90 °C, but it did not result in any improvement for the yield of **(188)**. Longer reaction times (up to two days) were also tried, but the yields were not improved. In addition, it was found that this reaction was air-sensitive, since if the reaction was carried out without argon, **(188)** would not be formed at all.



(186) **(173)** **(188)**

Scheme 3.11 *The preparation of* ***(188)****. i Heat; tetrabutylammonium bromide; water;* K_2CO_3.

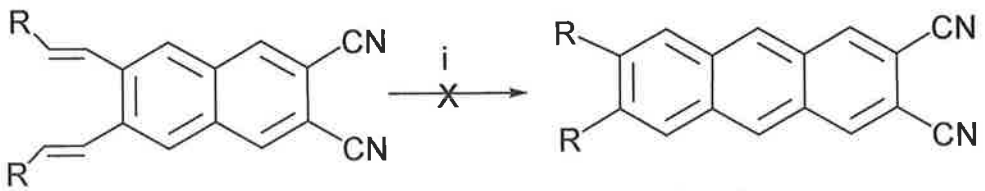


(187) **(173)** **(189)** **(190)**

Scheme 3.12 *The preparation of* ***(189)****. i Heat; tetrabutylammonium bromide; water;* K_2CO_3.

The two ^{1}H NMR spectra of **(188)** and **(189)** are outlined in Figure 3.8. In the ^{1}H NMR spectrum of **(188)**, there are two naphthalene proton peaks at 8.1 and 7.8 ppm and the two alkenyl protons appear between 6.6~6.2 ppm. The alkyl protons are present between 0.8~2.4 ppm. In the ^{1}H NMR spectrum of **(189)**, four naphthalene proton peaks are observed at 8.23, 8.18, 8.17 and 7.79 ppm, which is caused by the unsymmetrical substitution on the naphthalene ring. Two alkenyl proton chemical shifts appear between 6.6~6.2 ppm and the *t*-butyl proton shifts are found as a single peak at 1.21 ppm.

We also attempted to photocyclize **(188)** to **(190)**, which is a required starting material for anthralocyanine. This would be a new synthetic route to prepare alkylated anthralocyanines. (Scheme 3.13) The photocyclization of **(188)** was carried out in an iodine/hexane solution with irradiation by UV light at room temperature. Unfortunately, we could not find any target product to confirm that the photocyclization was successful.



(189) **(190)**

R = $(CH_2)_5CH_3$

Scheme 3.13 *The photocyclization of* ***(188)*** *to form* ***(190)****. i UV; Hexane;* I_2.

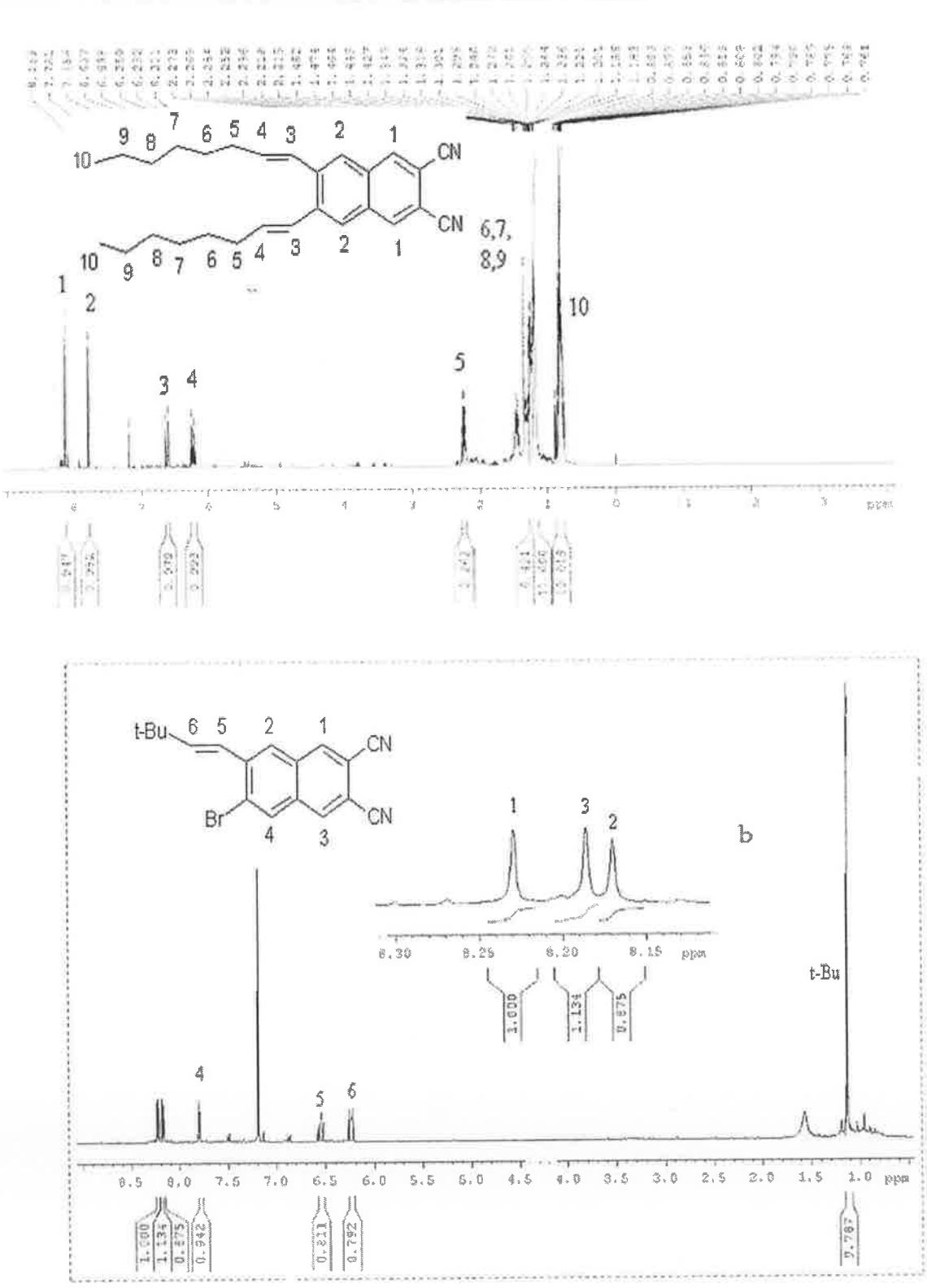
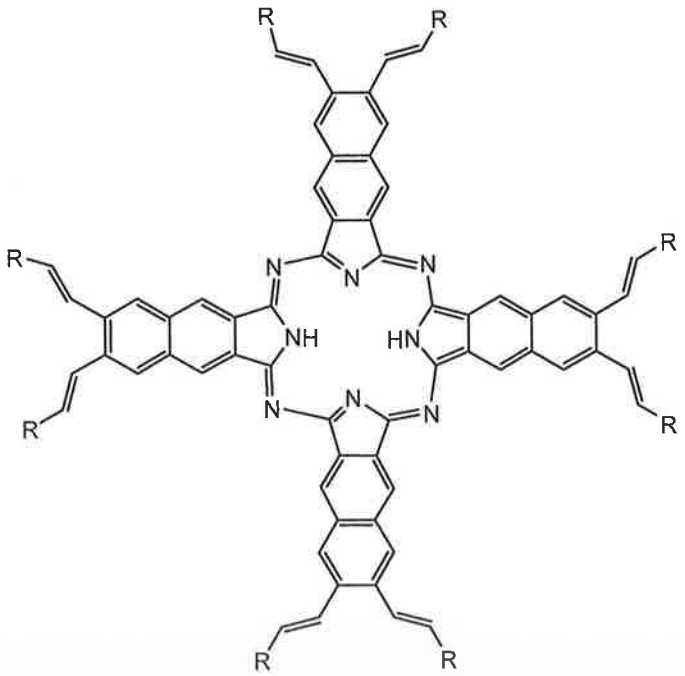


Figure 3.8 *The ^{1}H NMR spectra of* ***(188)*** *(a) and* ***(189)*** *(b), in $CDCl_3$.*

3.4.2 The synthesis of 3,4,12,13,21,22,30,31– octa(oct-1-enyl) Nc (191)

3,4,12,13,21,22,30,31–Octa(oct-1-enyl) Nc **(191)** (Figure 3.9) was prepared using the same condensation method reported earlier. The purification of 3,4,12,13,21,22, 30,31–octa(oct-1-enyl) Nc **(191)** involves removing the insoluble impurities by washing the crude product twice through a silica gel column with chloroform and THF respectively. The blue product was collected and solvents were removed under vacuum, giving a green residue. The green residue was then dissolved into a minimum volume of THF and pure 3,4,12,13,21,22,30,31–octa(oct-1-enyl) Nc **(191)**, was precipitated by the addition of methanol, the yield was 8%.



(191) R = $(CH_2)_5CH_3$

Figure 3.9 *The structure of Nc (191).*

3.4.3 The spectra discussion of Nc (191)

The λ_{max} absorption of the Q-bands of Nc **(191)** appears at 798 nm in the UV/Vis spectrum. (Figure 3.10) A 3.5 nm red shift for the Q-band absorption is caused by each alkenyl group, leading to a 0.7 kJ decrease in the HOMO-LUMO energy gap, which is similar to the effect of an alkynyl substituent on Ncs.

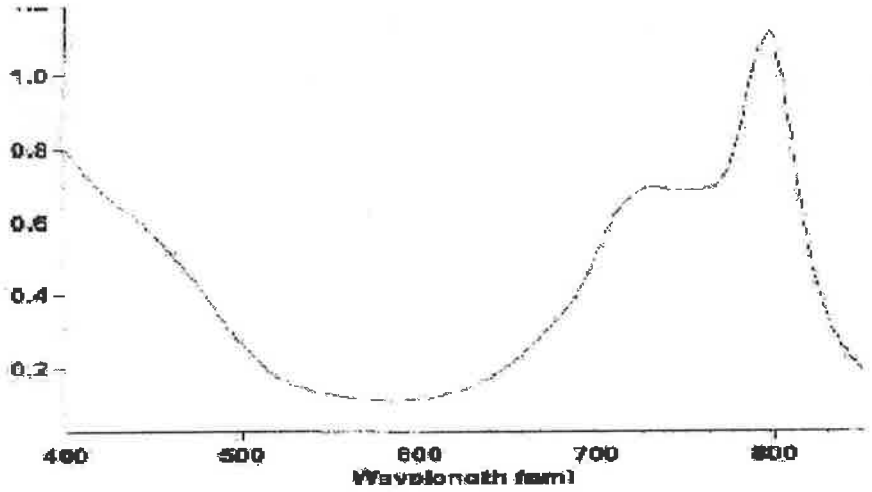


Figure 3.10 *The UV/Vis spectrum of Nc* ***(191)****, con* 10^{-5}*M, in THF.*

The MALDI mass spectrum of **(191)** gave a cluster at 1594, which corresponds to the molecular weight of **(191)**.

We could not obtain a ^{1}H NMR spectrum of **(191)** as a result of the strong aggregation interaction between the Nc macrocycles.[54] It is very normal for Ncs macrocycles.

3.5 Conclusion

In this chapter, we successfully prepared and performed UV/Vis spectra studies of new tetra-alkenyl substituted Pc **(164)**, tetra(alkynyl)-tetra(chloro) Pc **(168)**, octa(alkenyl) Nc **(191)** and octa(alknyl) Ncs **(176)** and **(177)**. The UV/Vis spectrum

of tetra(alkenyl) Pc **(164)**, showed that a 3 nm red-shift was caused by each conjugated alkenylgroup, which is 1 nm shorter than the red-shift caused by a single alkynylgroup. The Pc **(168)** and its zinc derivative showed strong aggregation in solution. The UV/Vis studies carried out on both the alkynyl and alkenyl substituted Nc **(191)**, revealed that both the alkenyl and alkynyl substituents could induce the same red-shift on Nc as on Pc. We were delighted to find that the degree of aggregation of Nc **(177)** in solution was much less than the other two Ncs **(176)** and **(191)** demonstrating that the eight bulky *t*-butyl groups on Nc **(177)** are quite effective in decreasing the aggregation interaction between the Nc macrocycles.

Unfortunately, these Pcs, because all of these Pcs are the mixtures of position isomers.

No ^{1}H NMR datas were obtained for Ncs, which is very normal for Ncs macrocycles and this has been mentioned in the previous paper. [54]

Micro-analysis measurements were carried out on all the Pcs and Ncs in University College Dunlin, unfortunately no decent results were feedback. It could be caused by either the no-efficient burning of these macrocycles, or the purities of these compounds.

Chapter 4: The preparation of unsymmetrical phthalocyanines and naphthalocyanines by solid-support synthesis

4.1 Introduction

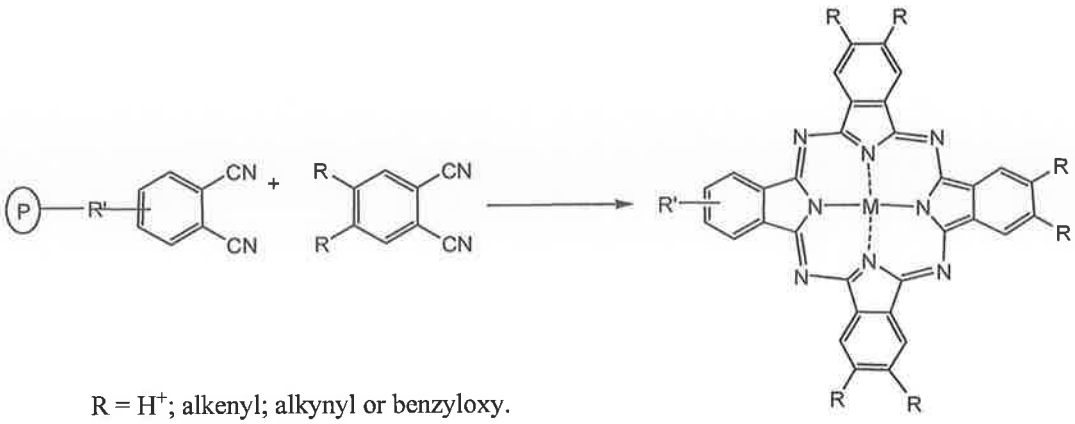
As we introduced in Chapter 1, unsymmetrical Pcs can be prepared via three different methods:

a) solid-support synthesis;

b) liquid solution phase synthesis and

c) from subphthalocyanines.

We attempted to prepare a series of unsymmetrical substituted Pcs and Ncs, which possess a hydroxyl handle. The preparations of these Pcs and Ncs could be achieved by either solid-support synthesis or solution phase synthesis. This chapter deals with the solid-support synthesis of unsymmetrical Pcs and Ncs. The target Pcs and Ncs were prepared in two steps: first Pcs and Ncs were condensed with polymer-bound phthalonitriles and partner phthalonitriles; then they were cleaved from the polymer resin.



R = H^+; alkenyl; alkynyl or benzyloxy.
R' = alkoxy; alkyl alcohol; alkynyl alcohol.

Scheme 4.1 *The solid-support synthesis of unsymmetrical Pcs (Ncs).*

4.2 The synthesis of polymer-bound phthalonitriles

Lenznoff had earlier reported the preparation of unsymmetrical Pcs using tritylated 2% cross-linked polystyrene. [21] We adopted this procedure in our work to prepare the following target Pcs **(202)** and **(205)** from polymer-bound phthalonitriles, which are outlined in Figure 4.1.

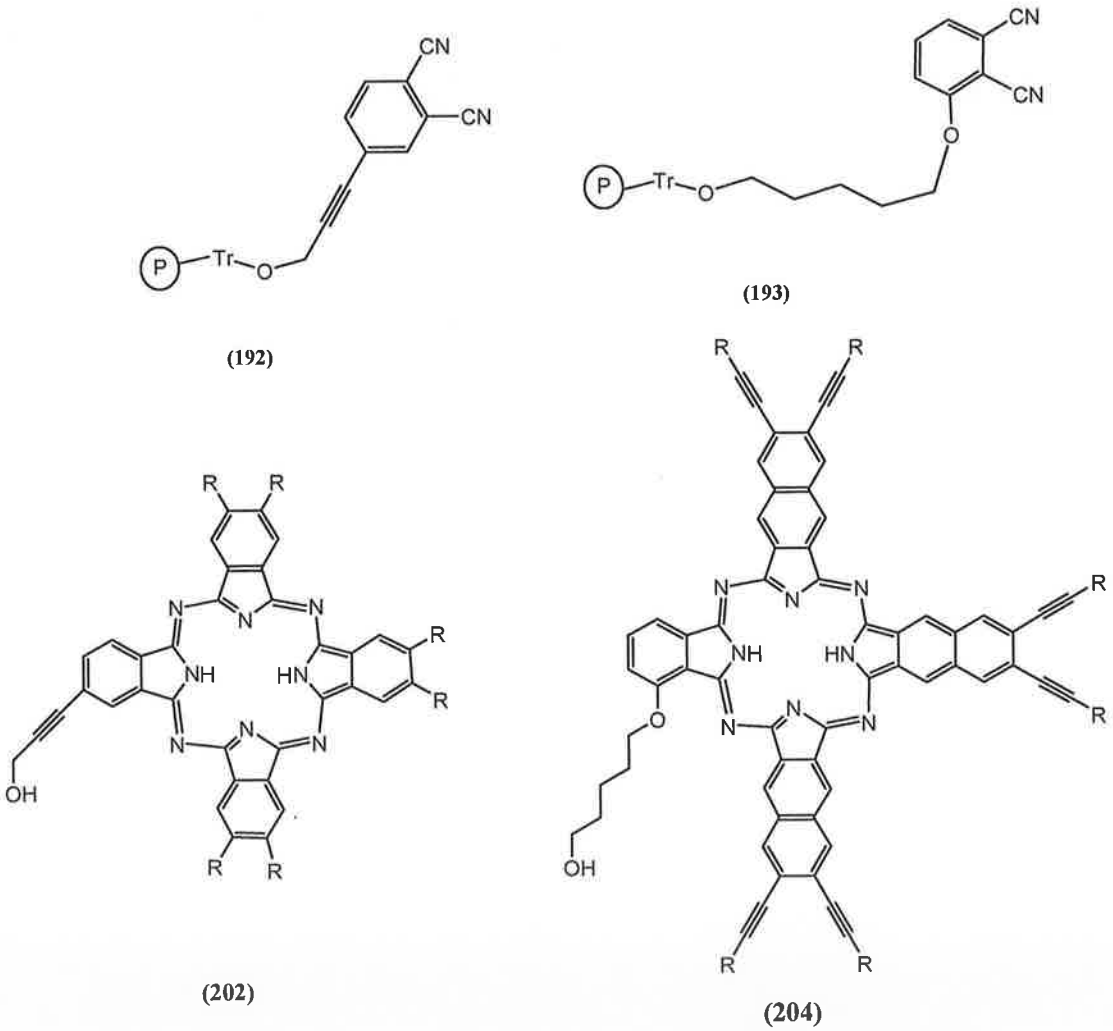
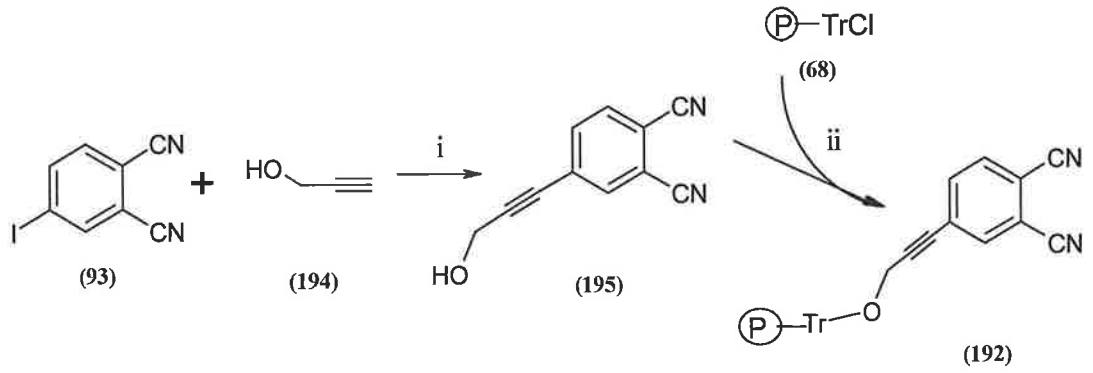


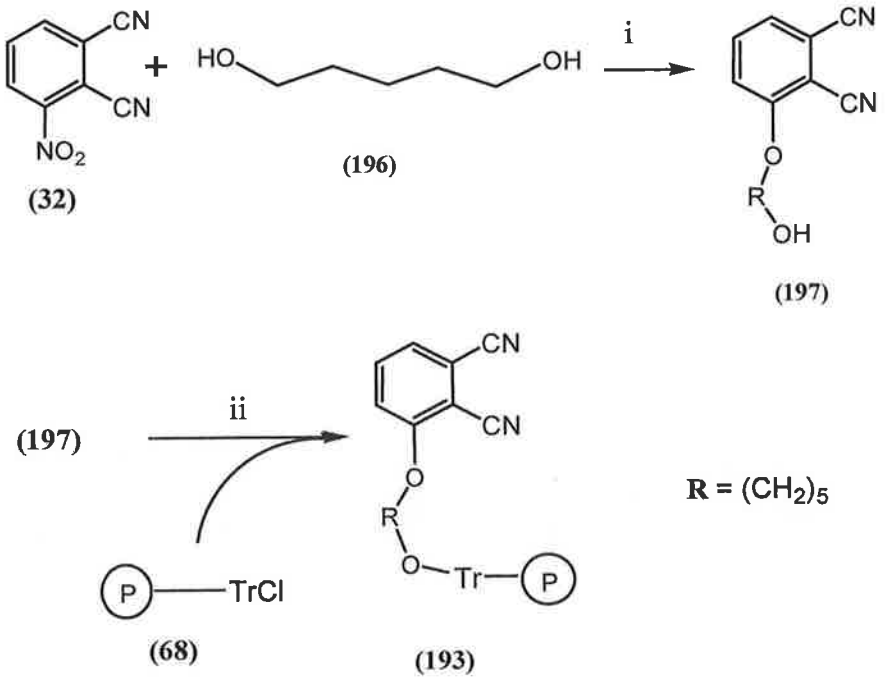
Figure 4.1 *Two polymer-bound phthalonitriles **(192)** and **(193)** and two unsymmytrical Pc, prepared via solid-support synthesis.*

The preparation of polymer-bound phthalonitrile **(192)** is outlined in Scheme 4.2. The conversion of 4-(3-hydroxylprop-1-ynyl) phthalonitrile **(195)** was accomplished by the coupling of 4-iodophthalonitrile **(93)** and 1-propargyl alcohol **(194)** in dry DMF with TEA. The 4-(3-hydroxylprop-1-ynyl) phthalonitrile **(195)** was obtained in 45% yield. Loading of 4-(3-hydroxylprop-1-ynyl) phthalonitrile **(195)** onto the polymer resin was carried out by treating **(195)** and trityl chloride polymer resin with TEA and DMAP in DCM. The polymer resin was then washed several times with different organic solvents (chloroform, DCM, methanol, and THF) to remove the unreacted **(195)** and impurities.



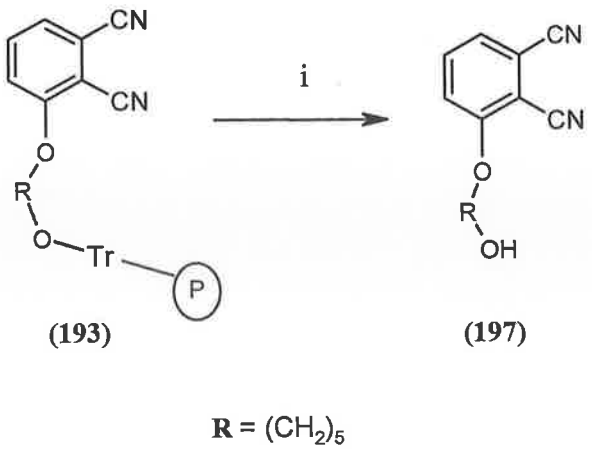
Scheme 4.2 *The preparation of one of the polymer-bounded phthalonitrile (192). i* $PdCl_2(PPh_3)_2$*; CuI;* $(^iPro)_2NH$*. ii DCM; DMAP; TEA.*

To prepare the second polymer-bound phthalonitrile **(193)**, we need to prepare the intermediate **(197)**, which was achieved by treating 3-nitrophthalonitrile **(32)** with pentane-1,5-diol **(196)** and K_2CO_3 in DMSO. (Scheme 4.3) The yield of **(197)** was 58%. Compound **(197)** was then loaded onto the polymer-resin by the same procedure as that used to prepare **(192)**.



Scheme 4.3 *The preparation of polymer-bound phthalonitrile* ***(193)****. i* K_2CO_3*; DMSO. ii DMAP; TEA; Dry DCM.*

The loading capacities of these two polymer-bound phthalonitriles were obtained by cleavage of the phthalonitriles from the polymer. TFA was found to be the most efficient acid for this cleavage reaction. (Scheme 4.4)



Scheme 4.4 *The cleavage of polymer-bound* ***(193)****. i dry chloroform; TFA.*

The two phthalonitriles were cleaved from the polymer resin in one gram scales. The loading capacity was 0.56 mmol of **(195)** per gram for polymer-bound phthalonitrile **(192)** and 0.46 mmol of **(197)** per gram of polymer-bound phthalonitrile **(193)** which are similar to the loading capacity reported previously [21] (0.53 mmol per gram) for tritylated resins.

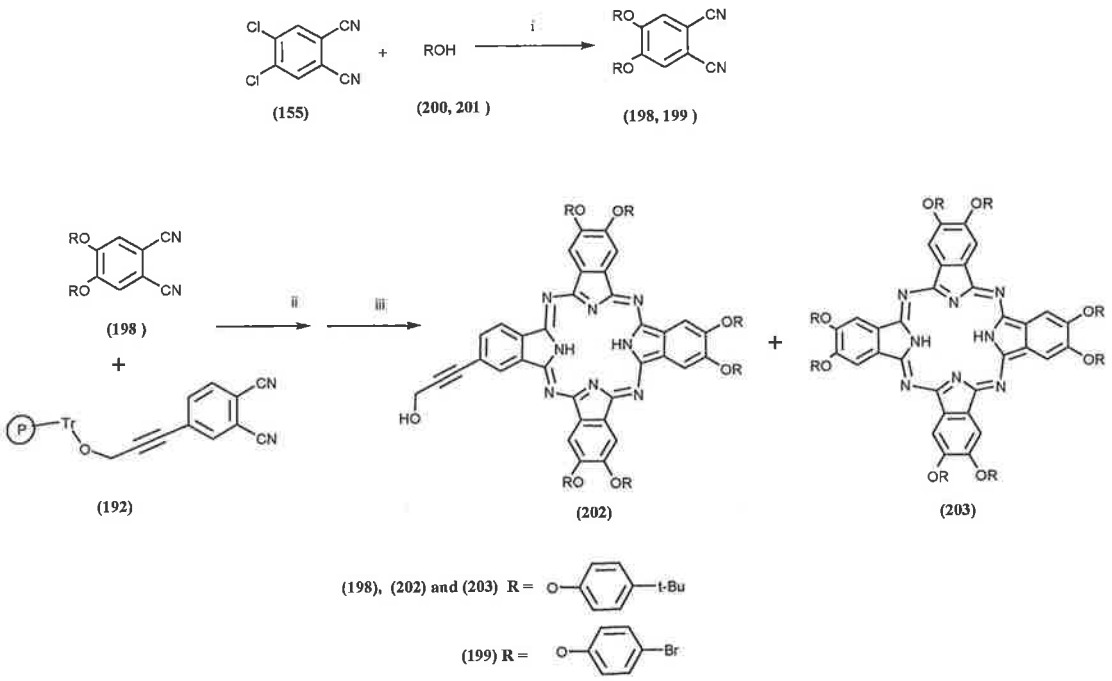
4.3 The synthesis of unsymmetrical phthalocyanines and naphthalocyanines

In the work carried out by Leznoff et. al, polymer-bound phthalonitriles were first converted into polymer-bound 1,3-diiminoisoindolines, and then cross-condensed with a partner 1,3-diiminoisoindoline to give the target Pcs. Herein, we decided to use the polymer-bound phthalonitriles directly in the Pc preparation.

A typical preparation involves the suspension of polymer-bound phthalonitrile **(192)** preswollen in pentanol for several hours. To this solution, an excess (normally 3~6 times excess) of phthalonitrile **(198)** and lithium metal were added. Then, this mixture was refluxed overnight under argon. To remove most of the symmetrical substituted Pc by-product, the blue-green polymer was washed several times with chloroform, methanol and THF. The unsymmetrical Pc was then cleaved from the polymer resin by treating with TFA in dry chloroform. Most of the Pc **(202)** could be separated by washing the polymer with THF until the filtrate was colourless.

It was found that after cleavage, a trace of symmetrical Pc was still present in the product. To remove this symmetrical Pc, a silica gel column using DCM/methanol as eluant was needed. (Scheme 4.5) The yield of pure unsymmetrical substituted Pc **(202)** was 8%. Compared to the yield of 24% obtained by Lenznoff et.al for the condensation of polymer-bound 1,3-diiminoisoindolines. [21] The yield of unsymmetrical substituted Pc via phthalonitrile in Li/pentanol is lower, but this could also

result from steric hindrance caused by the bulky groups on **(198)**, which are not present in Leznoff's work.



Scheme 4.5 *The solid-support synthesis of Pc* ***(202)****. i Condensation ;treat with dilute acid. ii Li/Pentanol, refluxing. iii TFA; dry chloroform.*

4.4. The UV/Vis spectrum study of Pc (202)

The UV/Vis spectrum of the unsymmetrical substituted Pc **(202)** is shown in Figure 4.2. The Q-bands are found at 670 and 703 nm respectively. Comparing with the UV/Vis spectrum of octa-substituted Pc **(203)** (two Q-bands at 668 and 700 nm), the λ_{max} absorption of the Q-bands of the unsymmetrical substituted Pc **(202)** shows a 3 nm red shift, which is caused by the presence of a single alkynyl group.

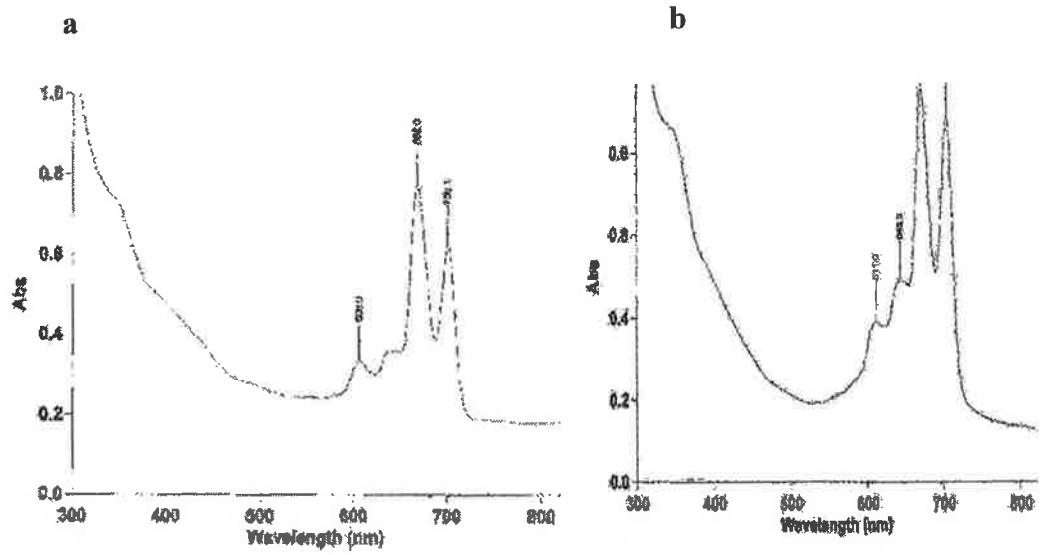
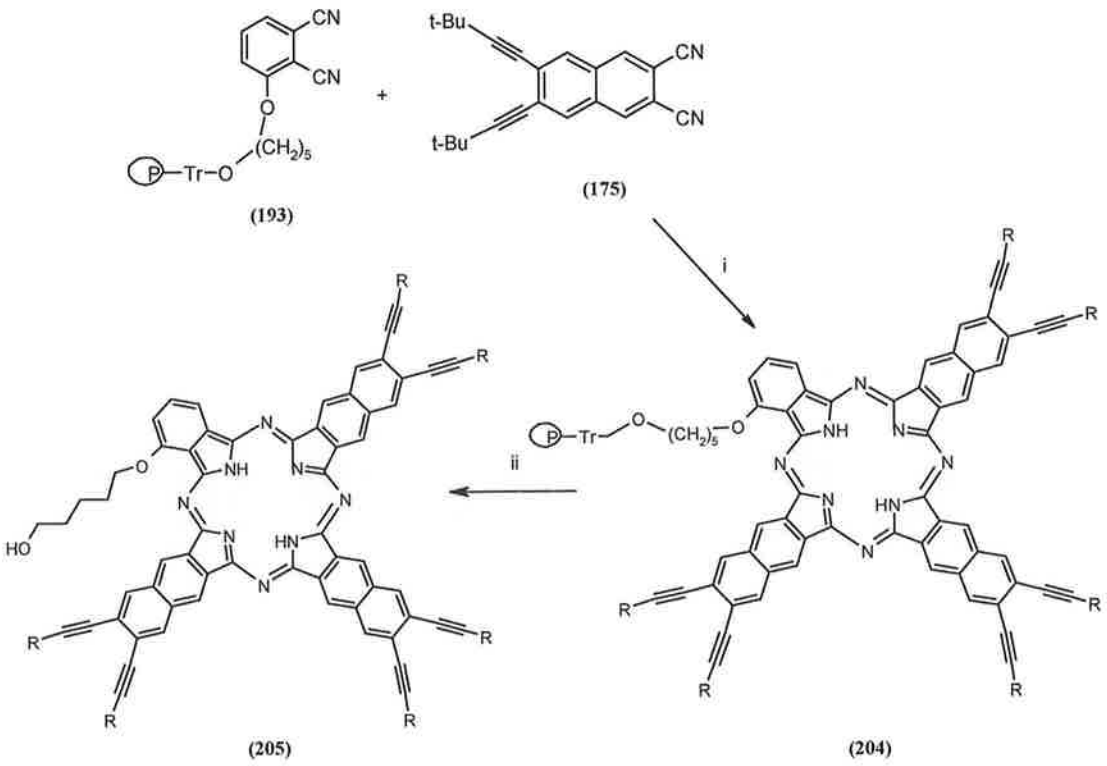


Figure 4.2 *Two UV/Vis spectra of the two Pc a)* ***(202)*** *and b)* ***(203)****, both concentrations are* $10^{-5}M$.

4.5 The preparation and UV/Vis study of Nc (205)

The unsymmetrical Nc **(205)** was prepared by treatment of **(193)** with **(175)**. The preparation procedure of Nc **(205)** was the same as described above for the preparation of Pc **(202)**. (Scheme 4.6) The UV/Vis spectrum of Nc **(205)** is outlined in Figure 4.3. A broad peak appears between 704 and 746 nm, which could be caused by both aggregation and unsymmetrical perturbation. Since the UV/Vis spectrum of Nc **(177)** showed the 3,3'-dimethylbut-1-ynyl groups significantly decreased the aggregation in dilute solution, we believed that six 3,3'-dimethylbut-1-ynyl groups in Nc **(205)** macrocycle should also prevent aggregation at low concentration. But, even at very low concentration the Q-band of **(205)** (10^{-7} M), is still a broad absorption peak, suggesting a strong perturbation exists for Nc **(205)**.



Scheme 4.6 *The solid-support synthesis of unsymmetrical Nc* ***(205)****. i Condensation; treat with dilute acid; ii TFA; dry chloroform.*

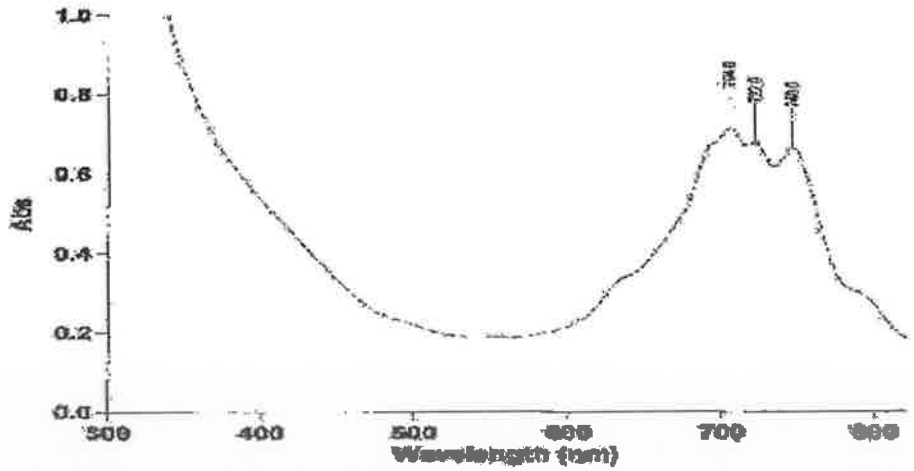


Figure 4.3 *The UV/Vis spectrum of Nc* ***(205)****, con 10^{-5}M, in THF.*

4.6 Conclusion

In this chapter, we found solid-support synthesis is still a convenient way to prepare unsymmetrical substituted Pcs. This method can avoid the exhaustive separation of Pc mixtures. However we did find some disadvantages to this synthetic strategy:

(1) Only suitable for microscale preparations, our two preparations only gave a trace amount of products,

(2) Removal of the Pc by-product requires exhaustive washing, even then there remains traces of by-product Pc,

(3) The preparation procedure of solid-support synthesis is complicated by the need to prepare mono-hydroxyl substituted phthalonitriles, this limits the scope of the classes of phthalonitriles that can be used.

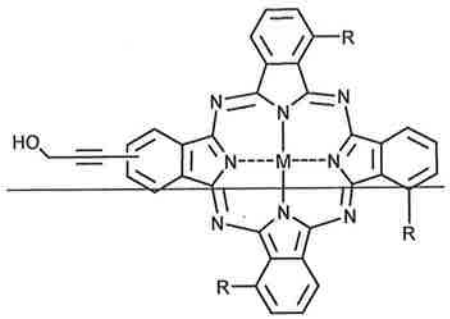
(4) As the results indicate, it is necessary to find a new type of "solid" support (either insoluble or soluble), which possesses a higher loading capacity, good product yields and a simple preparation procedure.

(5) Since this synthetic method only gave trace of products, and it failed to enlarge the reaction scale, no furthure measurement, such as ^{1}H NMR and mass spectra, was carried out.

Chapter 5 The preparation of unsymmetrical phthalocyanines by solution phase synthesis

5.1 Introduction

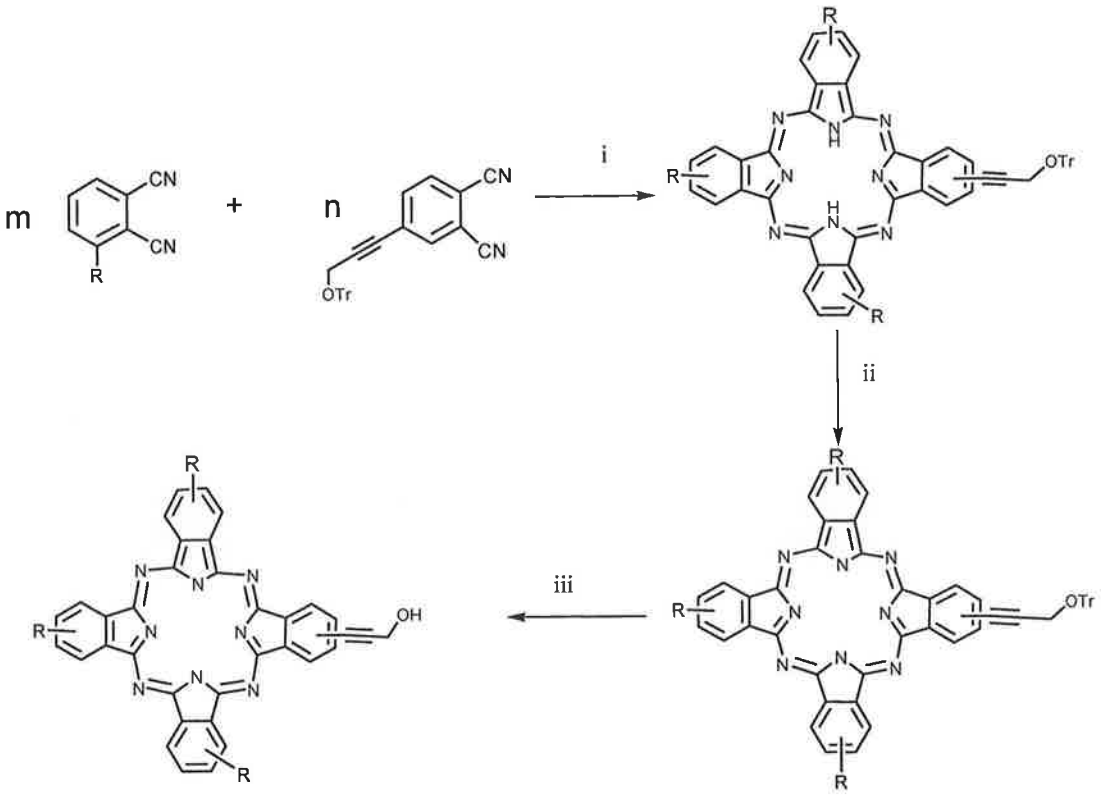
In this chapter, we employed solution phase synthesis for the preparation of mono-hydroxyl substituted Pcs. (Figure 5.1)



R = H; Alkyl; Benzyloxy.

Figure 5.1 The *structure of unsymmetrical mono-hydroxyl substituted Pc.*

The advantage of liquid phase synthesis of unsymmetrical Pcs, is that we can prepare unsymmetrical Pcs on a larger scale, unfortunately the product mixture normally contains several different Pcs, leading to difficult separations. A general preparation procedure of these unsymmetrical Pcs is outlined in Scheme 5.1. The preparation includes cross-condensation of two phthalonitirles, conversation of the metal-free Pc to metal PcM, separation of the target PcM from the mixture and removing the protection groups.

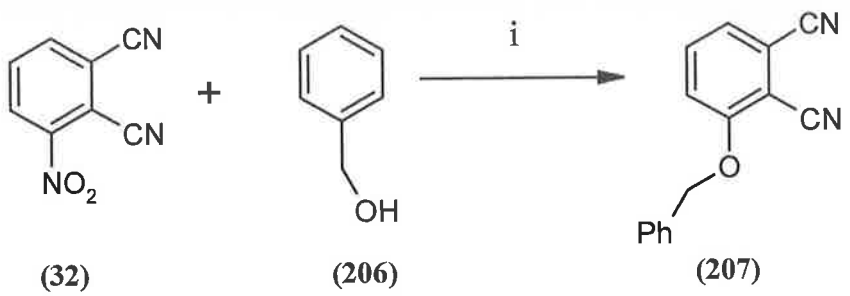


R= H; Alkyl; Benzoxyl;
M= H; Zn^{2+}; Co^{2+}.

Scheme 5.1 *The typical liquid-phase synthesis of unsymmetrical Pcs. i Pc Condensation; ii Pc metallation. iii Cleavage with acid.*

5.2 The preparation of partner phthalonitriles

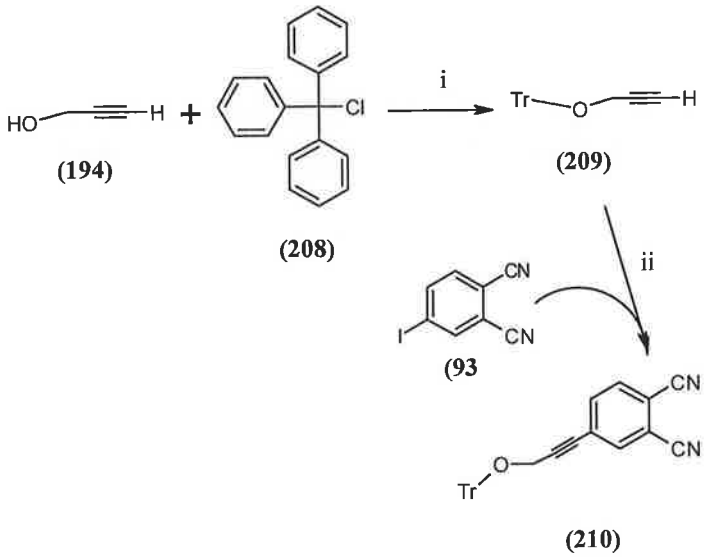
The preparation of 3-benzyloxyphthalonitrile **(207)** is outlined in Scheme 5.2. The yield of **(207)** was 92%.



(32) **(206)** **(207)**

Scheme 5.2 *The preparation of* ***(207)****. i* K_2CO_3*; DMSO; Under vacuum.*

4-(3-Tritoxyprop-1-ynyl)-phthalonitrile **(210)** was prepared under similar conditions used to prepare compound **(195)**, except 3-tritoxyprop-1-yne **(209)** was used instead of propargyl alcohol. **(209)** was prepared by the reaction of trityl chloride and propargyl alcohol **(208)** with TEA catalysed by DMAP in DCM. (Scheme 5.3) The yield of **(210)** was 56%.



Scheme 5.3 *The preparation of* ***(210)****. i DCM; DMAP; TEA. ii* $PdCl_2(PPh_3)_2$*; CuI;* $(^iPro)_2NH$.

5.3 The preparation of unsymmetrical metallo phthalocyanines

The metallo Pcs have much better solubilities in organic solvents and easier to purify than these metal free Pcs. Thus, we converted all the metal free Pcs to their metallo complexes.

The preparation of the target unsymmetrical metallo Pcs, requires the cross-condensation of two different phthalonitriles **(207)** and **(210)** in Li/pentanol. (Scheme 5.4) Then, to this reaction mixture was added $Zn(OAc)_2$, and left to reflux for a further 3 hours.

The purification of the target unsymmetrical PcZn **(212)** required two steps: silica gel chromatography and size-exclusion chromatography (Cross-linked polystyrene Bio-beads SX-3).

The first step involved washing the mixture through a silica gel column to remove all the insoluble impurities with different mobile phases (ethyl acetate : DCM = 1: 6~10; methanol : DCM = 1: 6~20).

The second purification step involved size-exclusion column chromatography using THF as eluant. By using this separation technique, the high weight molecules would come out before the small weight molecules. So the tetra-,tri- and di-(3-tritoxyprop-1-ynyl) substituted PcZns, which have bigger molecular weights than the mono(tritoxyprop-1-ynyl) substituted Pc, would come out before the target PcZn. (Figure 5.2)

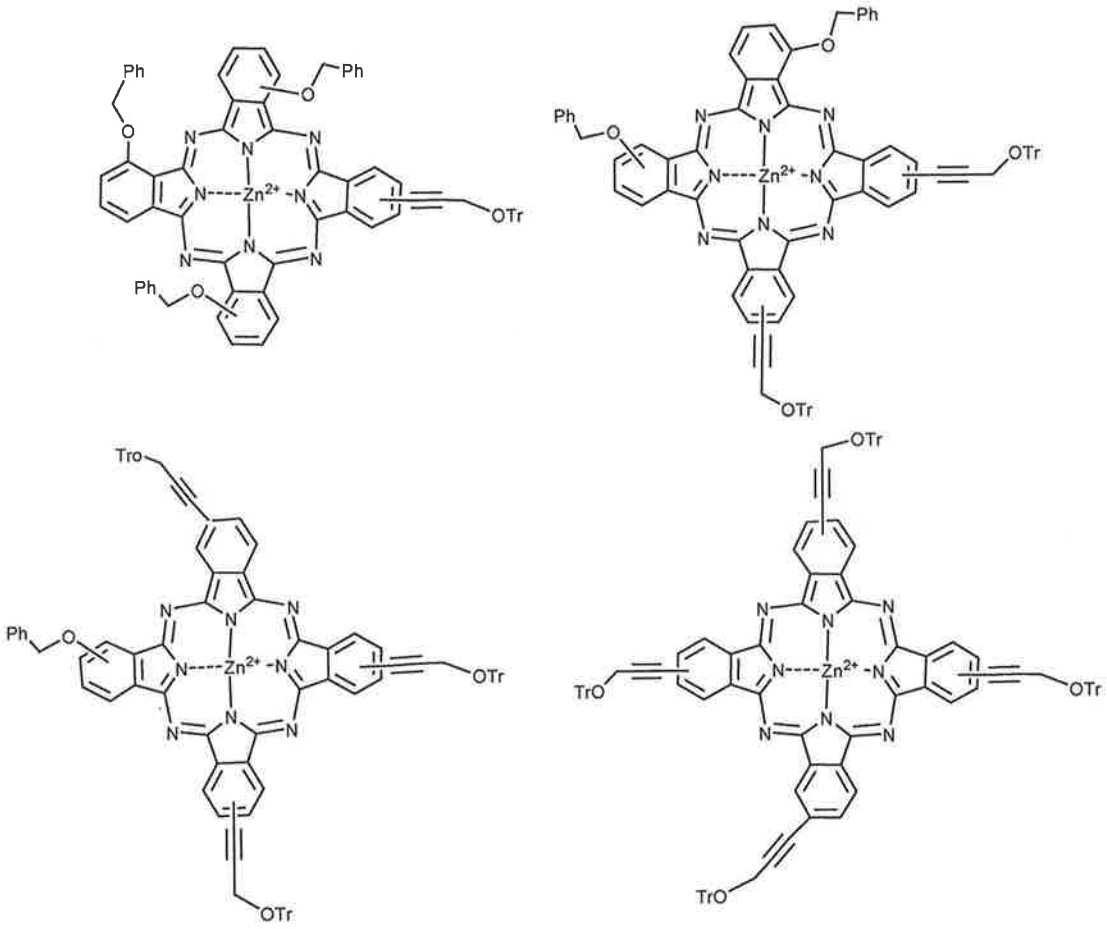


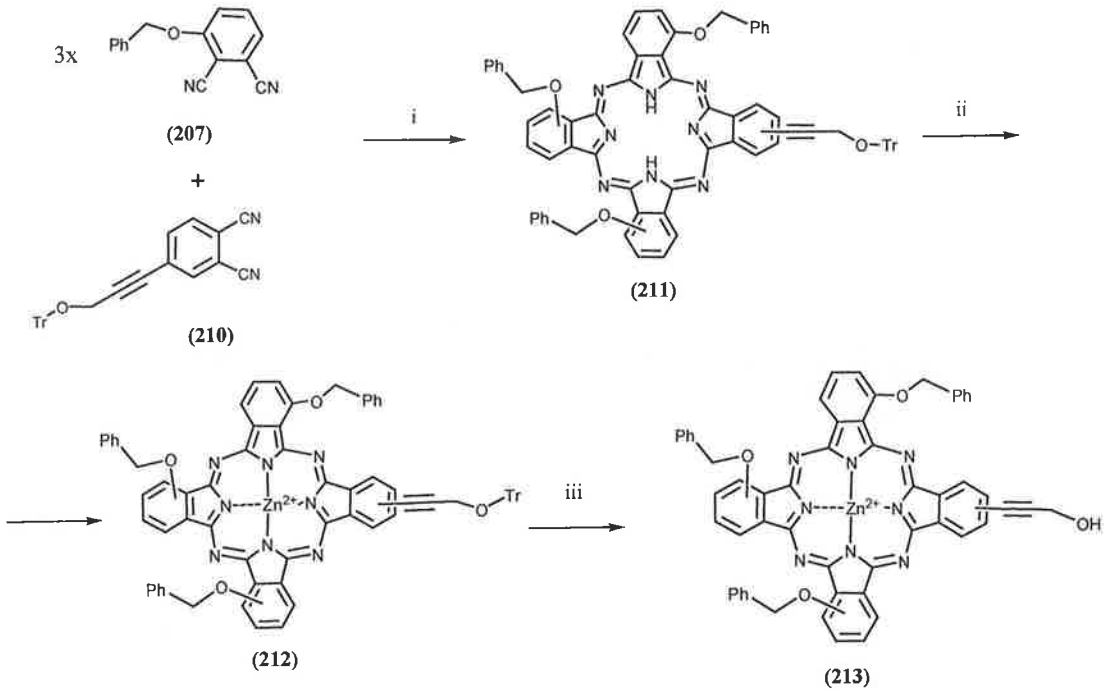
Figure 5.2 *The mono-, di-, tri- and tetra(3-tritoxyprop-1-ynyl) unsymmetrical substituted PcZns, formed during the liquid synthesis with* ***(207)*** *and* ***(210)****.*

The blue product obtained from the above silica columns was put onto a size-exclusion column and separated into two bands. The second band was collected, containing the target product PcZn **(212)**. The first band was a mixture of tetra-, tri- and di-phenyl substituted PcZn products.

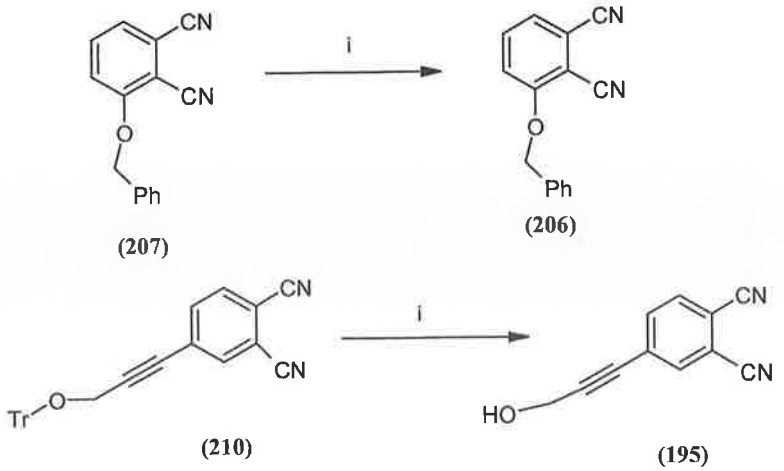
Then, PcZn **(212)** was dissolved in a minimum volume of THF, and was precipitated by the addition of methanol. The PcZn **(212)** was collected by centrifuge, the yield was at 20%, which is higher than the theoretical yield by calculation.

To remove the trityl group, it was necessary to run a series of reactions to determine, which cleavage conditions could be used to selectively cleave the trityl group over the benzyloxy group. These test reactions were carried out using **(207)** and **(210)** (Scheme 5.5) and the results are shown in Table 5.1. It was found that TFA in

chloroform/THF gave the best results, and PcZn **(212)** was converted to **(213)** using these conditions, yield of **(213)** at 95%.



Scheme 5.4 *The preparation of unsymmetrical Pcs* ***(211~213),*** *which including it's position isomer (dot). i Condensation to forma Pcs; ii $Zn(OAc)_2$; DMF; reflux. iii Chloroform; THF; TFA; r.t.*



Scheme 5.5 *Cleavage reactions of* ***(207)*** *and* ***(210).*** *i Conditions see Table 5.2.*

TABLE 5.2

	Conditions	Protection Group	
		Benzyloxy	Trityl
1	Acetic Acid; Dry Chloroform (20%); r.t; 12 hs.	N	N
2	HCl; THF (20%); r.t; 12 hs.	N	N
3	HCl; THF (20%); 50 °C; 12 hs.	N	N
4	Acetic Acid; Dry Chloroform (20%); 50 °C; 12 hs	N	N
5	TFA; Dry chloroform (20%); r.t;0.5~3 hours	N	100%
6	TFA; THF (20%); r.t; overnight.	N	100%
7	TFA; THF/chloroform (4~6:1) (30%); r.t; 12 hs.	N	100%

Since PcZn **(213)** has more than two possible positional isomers (Figure 5.3), we prepared a second PcCo **(216)**, which possesses a single hydroxyl group handle, and exists as a desirable single isomer. (Scheme 5.6)

The preparation of Pc **(214)**, **(215)** and **(216)** were similar to the procedure we used to prepare Pcs **(211~213)**.

Due to the absence of the three benzyloxy groups, the PcCo **(215)** and **(216)** were much less soluble in most organic solvents than **(212)** and **(213)**.

PcCo **(215)** has lower solubility than PcZn **(212)**, which even shows a poor solubility in THF. Thus THF was only solvent used as the eluant for both silica gel chromatography and size-exclusion chromatography. The reaction crude was flashed through a silica gel column with a large volume of THF. Insoluble impurities and unsubstituted PcCo were left on the top of the column. Comparing the purification procedures of PcZn **(212)** and PcCo **(215)**, the latter was much harder than the first, as a result of the solubility of **(215)**. Two bands were also observed, when the Pc mixture was washed through the size-exclusion column. The second band contained the PcCo **(215)**, the organic solvent (THF) was removed under vacuum; the collected

blue residue was then dissolved in a minimum amount of THF and precipitated by the addition of methanol. The pure PcCo **(215)** was collected by centrifuge.

After the purification of PcCo **(215)**, PcCo **(215)** was obtained in 28% yield, which was a little higher than the yield of PcZn **(212)**.

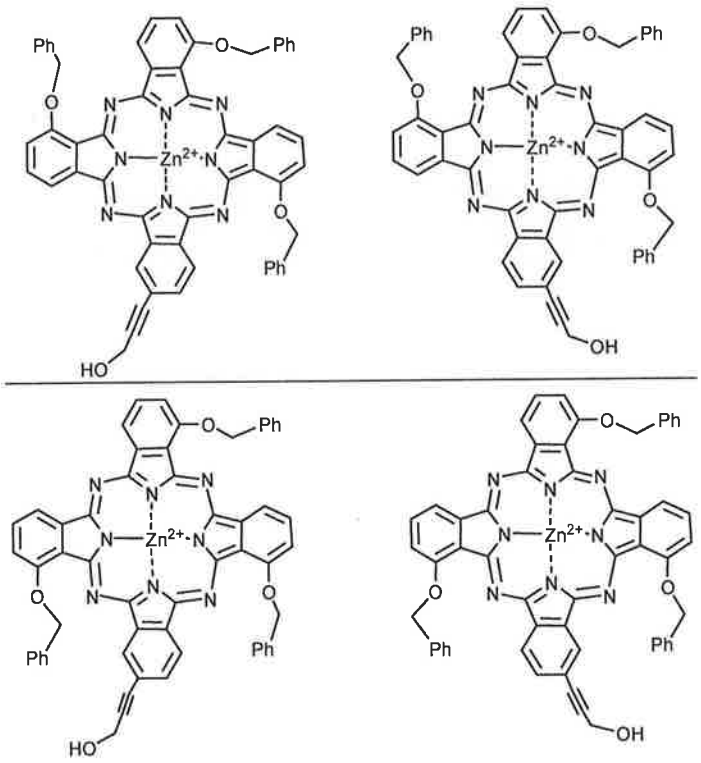
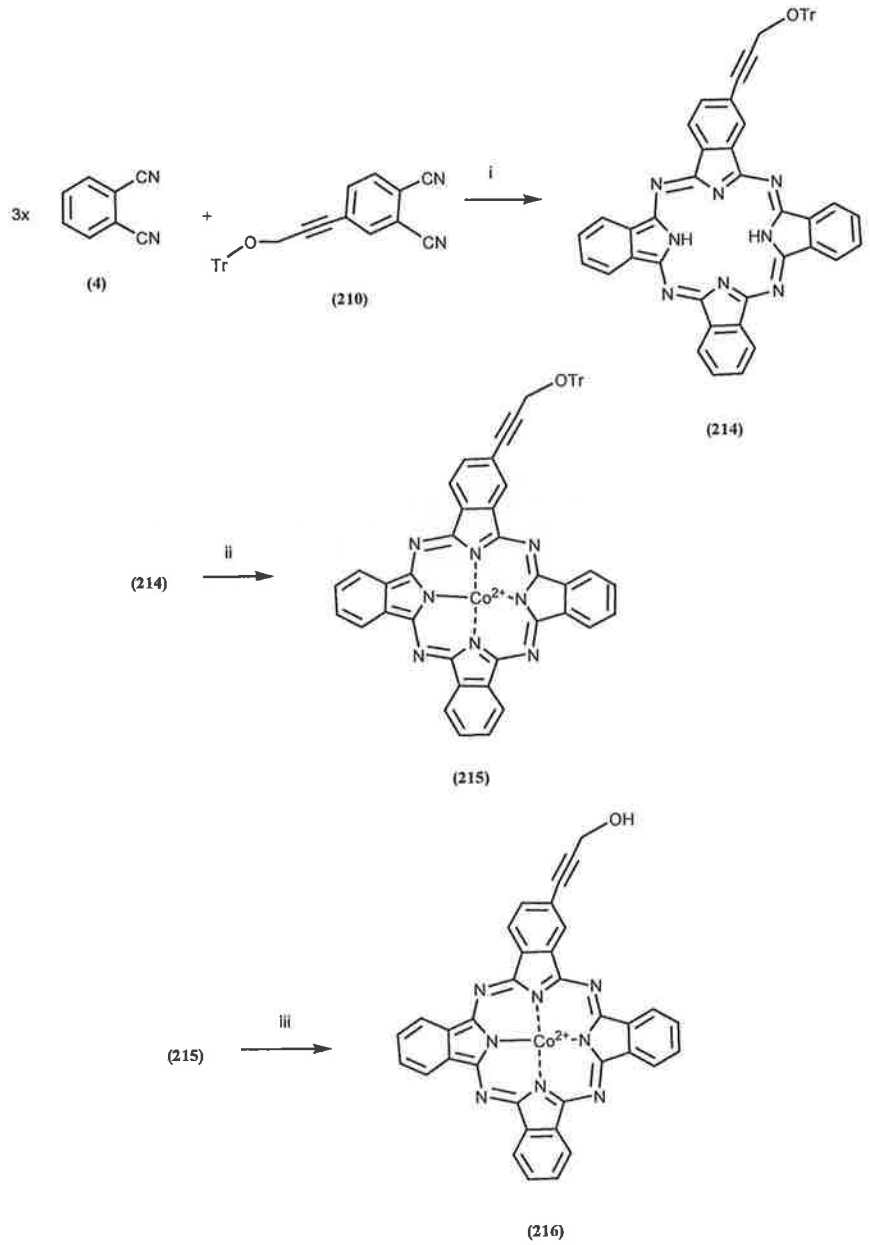


Figure 5.3 *The positional isomers of Pc (213).*

The cleavage of the trityl group was carried out under the same conditions as that described above. After the trityl group was removed the pure PcCo **(216)** was obtained by washing the crude product with different organic solvents (chloroform, methanol, ethyl acetate), to give **(216)** in 90% of yield, which was slightly less than the conversion yield from **(212)** to **(213)**.



Scheme 5.6 *The preparation of unsymmetrical Pcs (214), (215) and (216). i Condensation. ii $Co(OAc)_2$; reflux. iii Chloroform; THF; TFA; r.t.*

5.4 The UV/Vis and ^{1}H NMR spectra study of Pc (212), (213), (215), and (216)

The UV/Vis spectra of Pc **(212)**, **(213)**, **(215)** and **(216)** are outlined in Figure 5.4. The UV/Vis spectrum of Pc **(213)** gives a broad absorption peak at 690 nm, which suggests strong aggregation interaction between the Pc macrocycles.

For Pc **(212)**, **(215)** and **(216)**, a sharp Q-band is observed in the UV/Vis spectra, confirming the purity of these Pcs. If other Pcs were present, we believe a more complicated spectrum would be observed. (Figure 5.4)

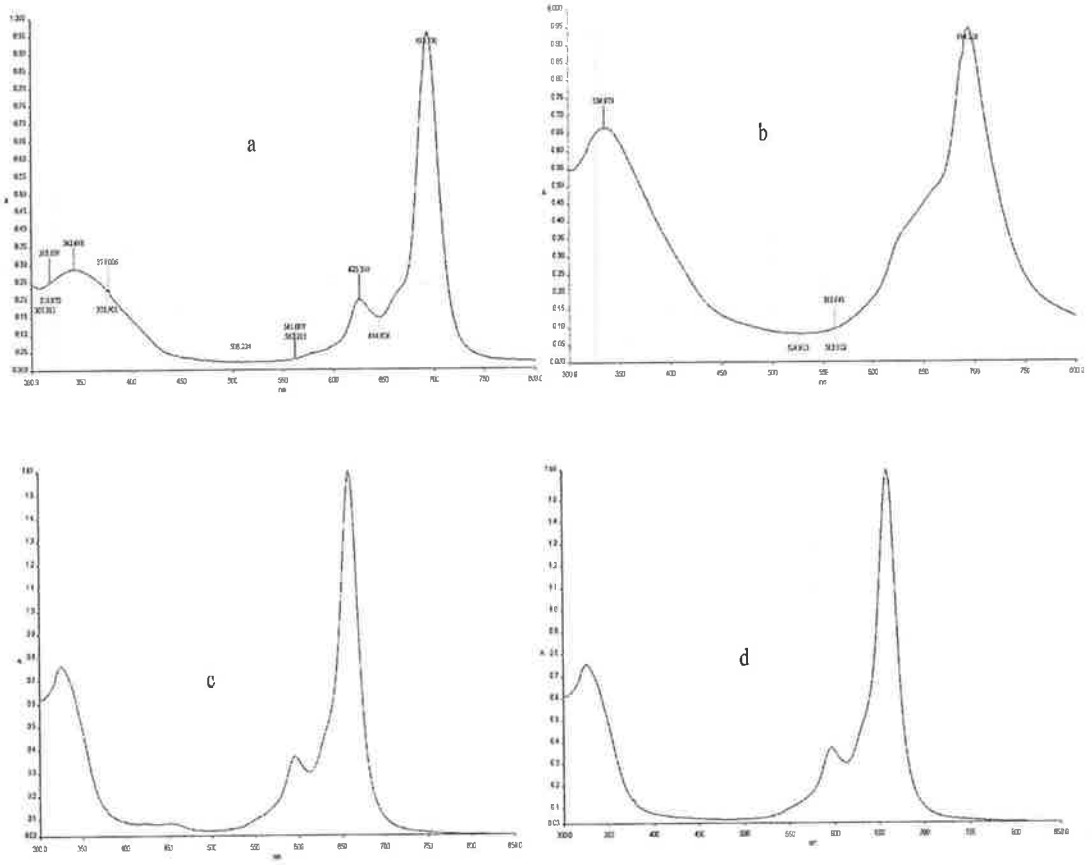


Figure 5.4 *The UV/Vis spectra of Pc* ***(212)*** *(a),* ***(213)*** *(b),* ***(215)*** *(c) and* ***(216)*** *(d), con* 10^{-5}*M, in THF.*

The ^{1}H NMR spectra of Pc **(212)** (Appendix 4) and **(213)** also show the disappearance of the trityl group proton signals. Before the cleavage forty-two aromatic protons are observed between 8~10 ppm, which are assigned to the aromatic protons on benzyloxy and the trityl groups. Eight methylene protons are present around 7 ppm and 5 ppm respectively, which involve six benzyloxy protons and two prop-1-ynyl protons. After the cleavage, only twenty-seven aromatic protons are found between 8.5~7.1 ppm. The six methylene protons from benzyloxy groups

are still present, but the prop-1-ynyl methylene proton signal is moved upfield by 0.4 ppm, which is caused by the removal of the trityl group.

The ^{1}H NMR spectrum of Pc **(215)** was obtained in pyridine-d_5. Fifteen aromatic protons on the Pc core are observed at 8.0 ppm and the trityl protons are observed between 6.8~7.1 ppm. Due to the poor solubility of Pc **(216)** in normal organic solvents, we failed to obtain a decent ^{1}H NMR spectrum.

5.5 Discussion

From the cross-condensation of **(207)** and **(210)**, we would expect six different PcZn's in the product (as discussed in the Chapter 1).

The order of the weights of these PcZns is: tetra(3-tritoxyprop-1-ynyl) PcZn>tri(3-tritoxyprop-1-ynyl)-benzolxy PcZn>bis(3-tritoxyprop-1-ynyl)-bis(benzyloxy) PcZn> tri(benzyloxy)-(3-tritoxyprop-1-ynyl) PcZn>tetra(benzyloxy) PcZn.

Based on the mechanism of size-exclusion separation, the high weight molecules should come out from the column before the low weight molecules. So the order of these PcZns washed out from the column, should be the same order as their molecular weights. Two bands were present during the separation by size-exclusion chromatography. The second band was collected, which should contain the low weight PcZn **(212)** molecules.

To confirm the presence of PcZn **(212)**, a UV/Vis study was carried out. We used the Q-band absorption of 1,8,15,22-tetra(benzyloxy) PcZn **(269)** as the standard (λmax at 696 nm).[12] There is a 2 nm shift difference between PcZn **(269)** and PcZn **(212)** (λmax at 693.7 nm). We could deterine that the isolated product was PcZn **(212)** and not tetra(benzyloxy) PcZn.

We also believed if the obtained product is a mixture of bis(3-tritoxyprop-1-ynyl)-bis(benzyloxy) PcZn, it would show a more complicated UV/Vis spectrum than the spectrum outlined in Figure 5.4.

Therefore, based on; 1) elution order, 2) the Q-band absorption and 3) theoretical calculated yields of the tetra(3-tritoxyprop-1-ynyl) PcZn and tri(3-tritoxyprop-1-ynyl) benzolxy PcZn, we believe that the isolated product is PcZn **(212)**.

In addition, we also compared the ^{1}H NMR spectra of PcZn **(212)** and **(269)**, which were separated from the PcZn mixture by silica column chromatography. (Appendix 5) The methylene proton signal of the benzyloxy groups of the two PcZn's are present in the same region as a single peak (around 7 ppm), the integration of the methylene peak confirms the presence of six protons in the spectrum of PcZn **(212)**. (note:The aromatic proton peaks of PcZn **(212)** are more complicated than PcZn **(269)**).

The NMR spectrum confirms that the product PcZn should be the target product (tri(benzyloxy)-3-tritoxyprop-1-ynyl PcZn **(212)**).

The PcZn **(213)** was prepared by removing the trityl group from PcZn **(212)**. The PcCo **(215)** and **(216)** were obtained by the same method as used to prepare **(212)** and **(213)**, however we cannot confirm the purity or presence of these two Pcs at this time and therefore they will not be further discussed.

To determine the purity of these Pcs, both MALDI and HPLC methods need to be carried out.

5.6 Conclusion

The solution synthesis is more suitable for the large scale preparation of unsymmetrical substituted Pcs compared to solid-support synthesis. The preparation of unsymmetrical substituted Pcs could obtain in yields up to 28%, which was even higher than the reported yield obtained via solid-support synthesis by Leznoff et. al. We also demonstrated that size-exclusion chromatagraphy using 2% cross-linked polystyrene is a very efficient method to separate these Pc mixtures. We believe that the separation mechanism involves both separation based on molecular wieght and π-π interactions between the Pcs and the aromatic groups of the stationary phase.

Chapter 6: Developing new routes toward the preparation of halo phthalonitriles

6.1 Introduction

Due to the lack of commercially available halo phthalonitriles, we decided to develop a cost-effective route which could be used to prepare specific halophthalonitriles. The preparations of 4-bromophthalonitrile and 4,5-dibromophthalonitrile in a single step has been reported by Leznoff. [57] Unfortunately, these reactions gave a mixture containing more than three types of brominated phthalonitriles, and the separation of these three phthalonitriles required exhaustive column chromatography.

In our work, we reproduced this reaction, and found that by controlling the stiochiometric ratio of the starting materials, we could prepare the 4-bromophthalonitrile as a single product. (Figure 6.1)

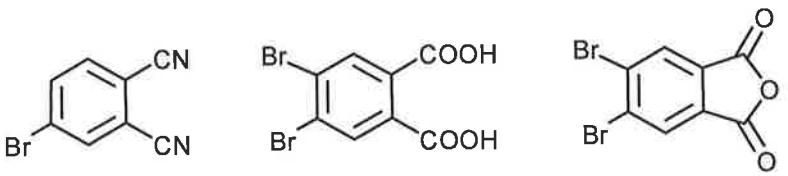
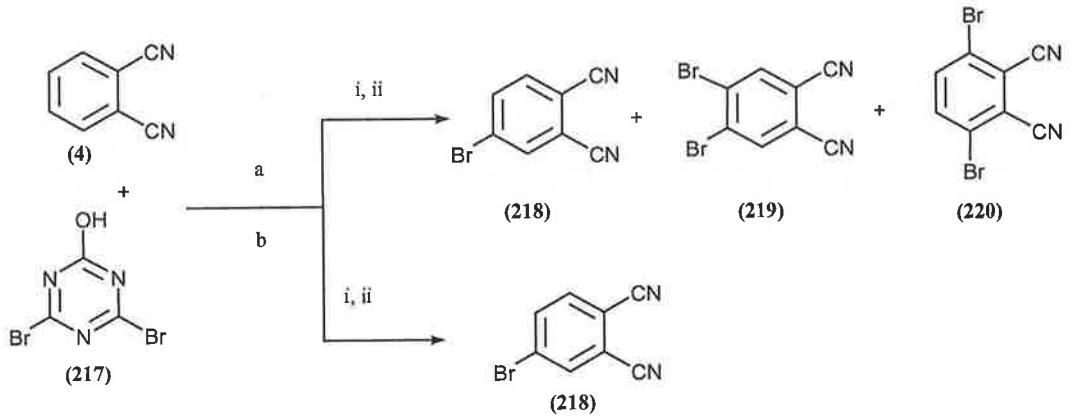


Figure 6.1 *Halogenated starting materials for the preparation of Pc.*

We were also interested in developing a clean route to prepare 4,5-dibromophthalonitrile.

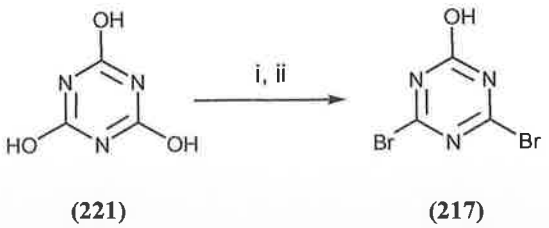
6.2 The preparation of bromo phthalonitriles

The preparation of 4-bromophthalonitrile **(218)**; 4,5-dibromophthalonitrile **(219)** and 3,6-dibrormopthalonitrile **(220)** from phthalonitrile **(4)** was reported in 1998 with yields of 45%, 6% and 7% respectively. [57] (route a in Scheme 6.1)



Scheme 6.1 *The preparation of compounds (218), (219) and (220) using different stiochiometric ratios of (4) and (217) a) (217) was in large excess b) the stiochiometric ratio of (4) and (217) was 1:1~1.2. i con H_2SO_4; ii Ice.*

We reproduced this reaction. Dibromoisocyanuric acid **(217)** was prepared by a literature method. [58] (Scheme 6.2) The bromination of phthalonitrile **(4)** with **(217)**, gave **(218)** in 35% yield and 3% of **(219)**, with no evidence of **(220)** being formed.

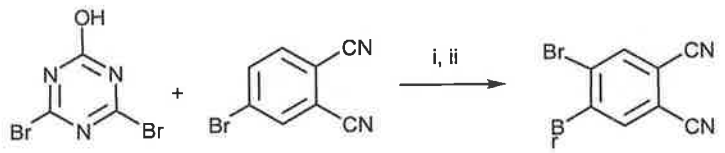


Scheme 6.2 *The preparation of (217). i LiOH; ii Br_2.*

It was found that different stiochiometric ratios of phthalonitrile **(4)** to **(217)** could make a significant difference in this reaction. If using a stiochiometric ratio of **(4)** to **(217)** of 1:1~1.2, only **(218)** would be obtained in 33% yield. (route b in Scheme 6.1) In contrast, using a large excess of **(217)**, (the stiochiometric ratio of **(4)** to **(217)** at

1:2~5,) improved the yield of **(218)** to 42%, but **(219)** was still generated in yields at 5%, again **(220)** was absent.

Since the 4-bromophthalonitrile **(218)** could be prepared in a good yield, we attempted to prepare **(219)** from **(218)** directly in a single step, by the same bormination condition used above. (Scheme 6.3) The TLC showed the reaction only gave **(219)**.



(217) (218) (219)

Scheme 6.3 *The bromination of* ***(218)*** *with* ***(217)*** *to prepare* ***(219)****, i con* H_2SO_4*; ii Ice.*

Unfortunately, the yield of **(219)** was only at 6%, which was not significantly improved, comparing with the yields obtained by direct bromination of **(4)** with **(217)**.

6.3 The discussion of the bromination of phthalonitrile

We also tried different bromination systems, such as bromine with CCl_4 and bromine with acetic acid. Bromination in CCl_4 did not react at all, and we found that in acetic acid all the phthalonitrile was converted into phthalic acid. It should be noted that we also found that some of the phthalonitrile was converted into phthalic acid when using dibromoisocyanuric acid in concentrate H_2SO_4, however the yield of 4-bromophthalonitrile at 33%, was acceptable, and this synthetic route avoids further purification by column chromatography.

A postulated mechanism for the reaction of dibromoisocyanuric acid in concentrated H_2SO_4 is outlined in Figure 6.2. We believe it starts with the protonation of the nitrogen atom in dibromoisocyanuric acid, generating a positive charge on a bromine which then subsequently acts as an electrophile.

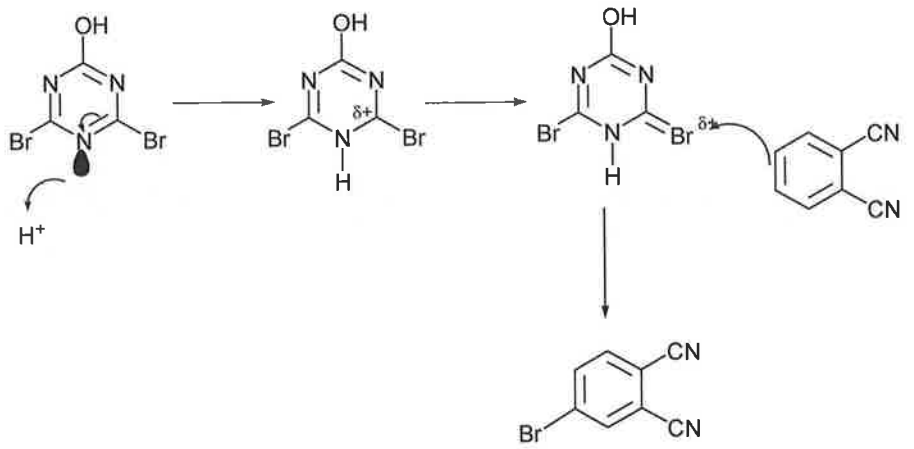


Figure 6.2 *The postulated mechanisum of bromination of phthalonitrile with dibromoisocyanuric acid in concentrated* H_2SO_4.

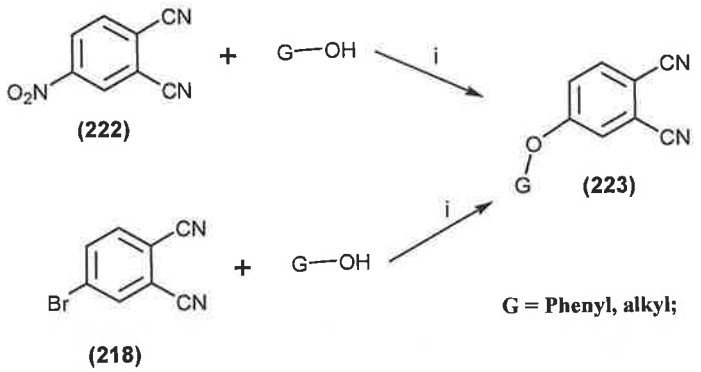
6.4 Attempted nucleophilic displacement of 4-nitrophthalonitrile

Since 4-bromophthalonitrile **(218)** could be prepared via a low cost method, we attempted to use **(218)** instead of 4-nitrophthalonitrile **(222)** in the S_{Naryl} substitution for the preparation of alkoxy or benzyloxy phthalonitriles. (Scheme 6.4)

The **(218)** and p-(*t*-butyl)-phenol with base were room temperature in DMF/Et_3N for overnight. No target product was found by TLC. At high reaction temperature, up to 60°C, there was still no target product found. We also use K_2CO_3 as base with palladium catalyst by refluxing the reaction mixture in benzene, and again no target product was found.

The only few of reactions obtained the product **(223)**, were carried out by using LiOH as base at room tempereature. The higher temperature reaction was not allowed to carry out, since at the high temperature in the present of LiOH, the cyano

groups of phthalonitrile would be destroyed. The brief conditions and yields are listed in Table 6.1.



Scheme 6.4 *The S_{Naryl} substitution for the preparation of alkoxy or benzyloxy phthalonitriles. i For conditions see Table 6.1.*

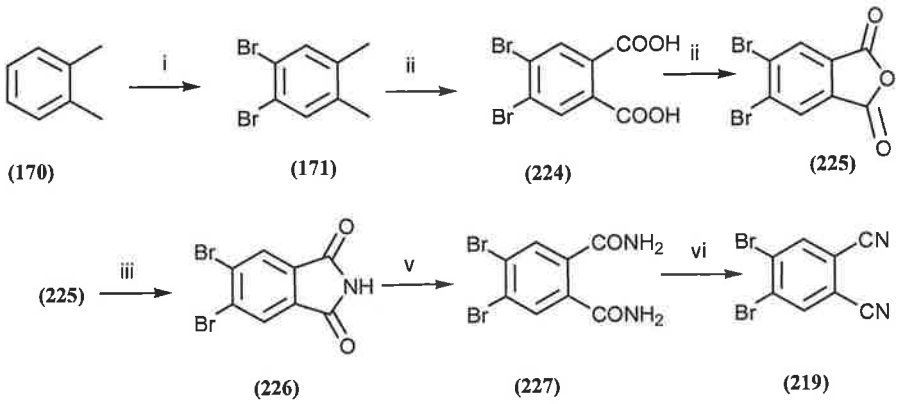
TABLE 6.1

	Conditions	**Yields**
p-(*t*-butyl)-phenol	DMF,Et_3N, r.t, overnight	No reaction
p-(*t*-butyl)-phenol	DMF,Et_3N, 60~65 °C, 4~5 hs	No reaction
p-(*t*-butyl)-phenol	DMSO, LiOH, r.t, overnight	3%
p-(*t*-butyl)-phenol	Pd; Benzene, K_2CO_3, refluxing	No reaction
Benzyl alcohol	DMF,Et_3N, r.t, overnight	No reaction
Benzyl alcohol	DMSO, LiOH, r.t, overnight	4%

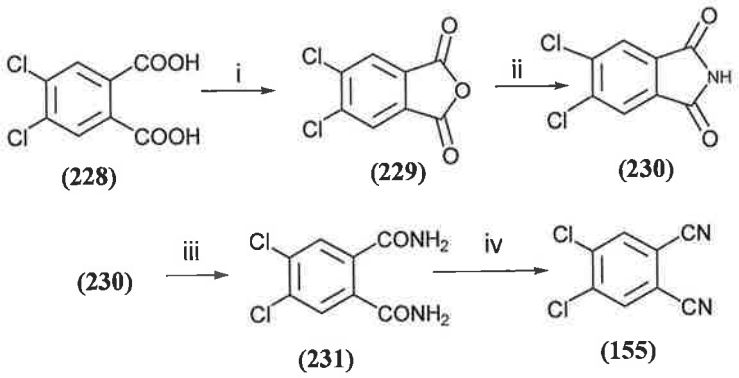
The results demonstrated that the bromo substituent is ineffective for S_{Naryl} substitution reactions.

6.5 Alternative route to the preparation of (219)

Due to the low yield of 4,5-dibromophthalonitrile **(219)** obtained by direct bromination of phthalonitrile **(4)**, an alternative synthetic route was designed to prepare **(219)** and is outlined in Scheme 6.5. This route is similar to the preparation of 4,5-dichlorophthalonitrile **(155)** described by Yamada et.al in 1993. [59] (Scheme 6.6)



Scheme 6.5 *The synthetic route for the preparation of* ***(219)****. i* Br_2*;* I_2*; Fe. ii* $KMnO_4$*; KOH; reflux. iii* $(OAc)_2O$*; reflux. iv* $HCONH_2$*; reflux. v con* NH_3H_2O*. vi* $SOCl_2$*; DMF.*



Scheme 6.6 *The synthetic route for the preparation of* ***(155)****. i* $(OAc)_2O$*; reflux. ii* $HCONH_2$*; reflux. iii conc* NH_3H_2O*. iv* $SOCl_2$*; DMF.*

The preparation of 4,5-dibromophthalonitrile **(219)** began with the bromination of o-xylene **(170)** with bromine to give **(171)** in 67% yield. 1,2-Dibromo-4,5-dimethyl-benzene **(171)** was then converted to 4,5-dibromophthalic acid **(224)** by oxidation with potassium permanganate ($KMnO_4$) and potassium hydroxide (KOH). The methyl peak of compound **(171)** disappeared in the ^1H NMR spectrum of compound **(224)**, [60] after the oxidation. The yield of **(224)** was 95%. Dehydration of **(224)** was carried out by refluxing in fresh distilled acetic anhydride, and **(225)** was obtained in 67% yield.

Both **(224)** and **(225)** can be used as starting materials for the preparation of Pcs. Unfortunately, we did not achieve the last stage of this preparation, as a result of time

constraints, but we believe that the remaining preparation of 4,5-dibromophthalonitrile would be quite straightforward and high yielding.

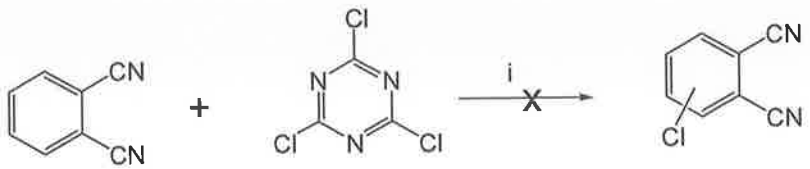
6.6 Attempted iodination and chlorination of phthalonitrile (4)

Due to the successful preparation of 4-bromophthalonitrile, we also attempted direct chlorination and iodination of phthalonitrile **(4)** in a single step procedure in an attempt to prepare the respective halo substituted phthalonitriles.

Chloro atom is a good leaving group for aryl nucleophilic substitution. Unfortuantely, the preparation of mono(chloro) substituted phthalonitrile has not been reported so far.

Iodo atom is good functional group in croos-coupling reactions, such as Heck reaction, Suzuki reaction, etc. But both the preparations of 4-iodo and 3-iodo phthalonitrile start from expensive nitrophthalonitriles and require multiple step reactions and as a result are expensive to make.

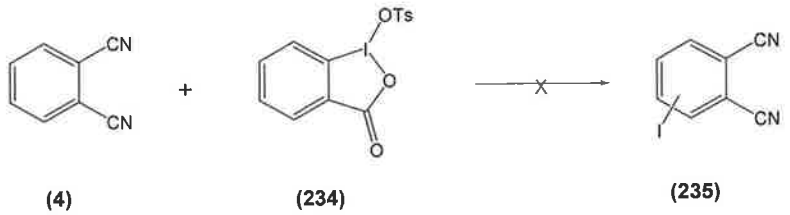
The attempted chlorination of **(4)** was carried out using cyanuric trichloride **(232)** under the same conditions for the preparation of 4-bromophthalonitrile. The target product **(233)** was not found, and all of phthalonitrile **(4)** was converted into phthalic acid. (Scheme 6.7)



(4) **(232)** **(233)**

Scheme 6.7 *The direct chlorination of* ***(4)*** *with* ***(232)****. i conc.* H_2SO_4.

The direct iodination of **(4)** with 1-(*p*-toluenesulfonyloxy)-1,2-benziodoxol-3-(H)-one **(234)** to form mono-iodo phthalonitrile **(235)**, which is a good iodination reagent for aryl compounds, also failed to produce any iodophthalonitriles. [61, 62] (Scheme 6.8)



(4) **(234)** **(235)**

Scheme 6.8 *The attempted direct iodination of* ***(4)*** *with* ***(234)***.

6.7 Conclusion

We found that by using stiochiometric control in the bromonation of phthalonitrile with bromocyanuric acid we could obtain 4-bromophthalonitrile in around 33% yield in the absence of any other brominated products. By increasing the stiochiometric ratio between of bromocyanuric acid to phthalonitrile we could improve the yields of 4-bromophthalonitrile, however 4,5-dibromophthalonitrile was also generated in 5% yield. The preparation of 4,5-dibromophthalonitrile from 4-bromophthalonitrile using bromocyanuric acid yielded the target compound in 6% yield, most of the starting material was recovered as 4-bromophthalic acid.

We designed an alternative synthetic strategy to prepare 4,5-dibromophthalonitrile starting with o-xylene.

Chapter 7 Benzimidazole-chloroquiniline complexes

7.1 Introduction

Benzimidazole itself and its derivatives have been used in various biological applications such as antifungal, [63, 64, 65] antimalarial, [66] anti-HIV, [67] and anticancer agents. [68] We prepared a new series of benzimidazole-chloroquinoline complexes (Figure 7.1), which contain a 7-chloroquinoline on the 1-position of benzimidazole (benzimidazolium iodide salts). We believed these benzimidazole-chloroquinoline complexes could be potential candidates for the treatment of malaria, cancer, and HIV.

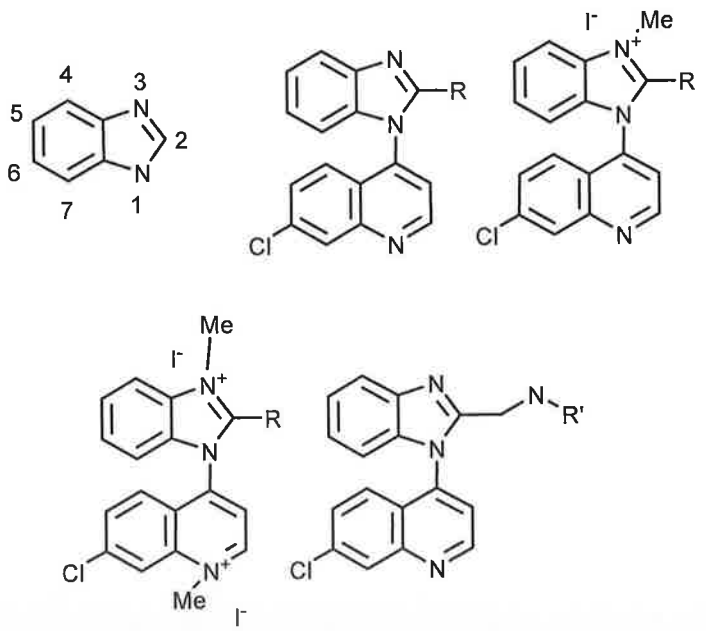
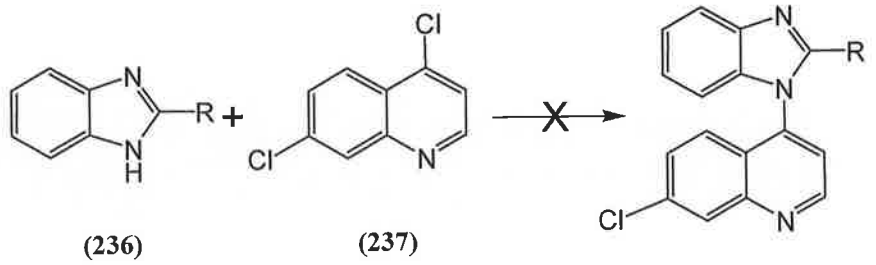


Figure 7. 1 *The typical benzimidazole-chloroquinoline complexes structures. R and R' group see Table 7.1.*

7.2 The synthesis of benzimidazole-chloroquinoline complexes

We desired to prepare these structures from the direct conversion of 2-substituted benzimidazoles **(236)** and 4,7-dichloroquinoline **(237)** via a phase transfer catalysis reaction. This synthesis did not generate any of the target products. (Scheme 7. 1)



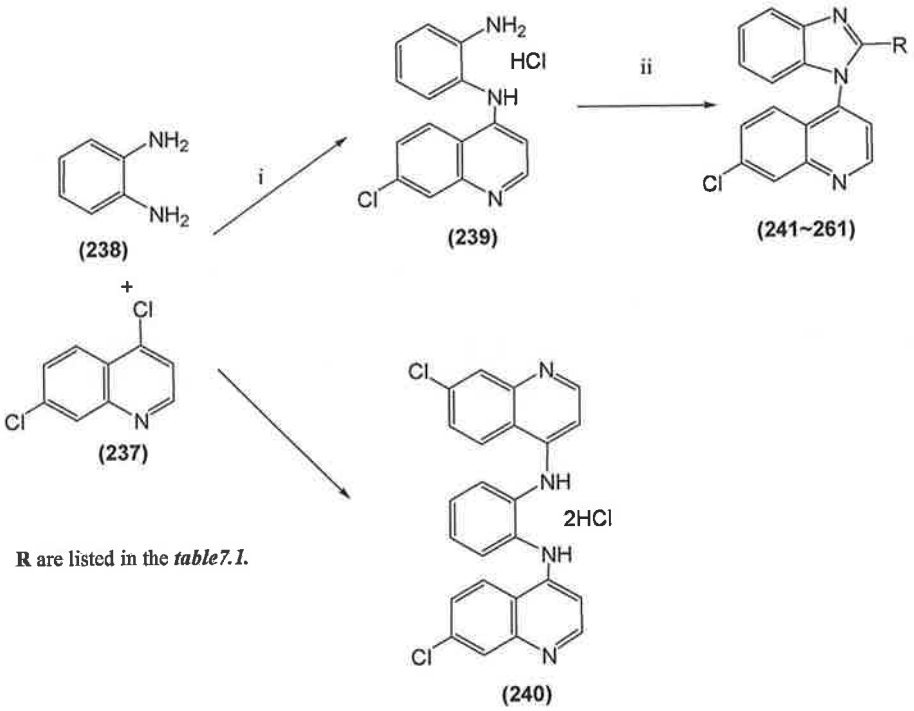
(236) **(237)**

R = Alkyl, Phenyl, etc

Scheme 7.1 *The synthesis of N-(7-chloroquinolin-4-yl)-2-substituted benzimidazole by PTC failed to form the target compounds.*

We then decided to prepare the target products from the intermediate **(239)** by a two-step reaction. [69] (Scheme 7. 2) A typical procedure of the synthesis of **(241~261)** included: the preparation of intermediate **(239)** from o-phenylenediamine **(238)** and 4,7-dichloroquinoline **(237)** in ethanol. A bright yellow solid **(239)** precipitated after one hour refluxing. The suspension was left standing overnight at room temperature, and the crude **(239)** was collected by filtration. The unreacted **(237)** and **(238)** was removed by washing the crude product with plenty of ethanol. In this preparation, we found that the starting material **(238)** must be used in excess. If the excess of **(237)** exists, N, N'-bis(7-chloroquinolin-4-yl)-o-phenylenediamine dihydrochloride **(240)** will be produced. When the stiochiometric ratio of **(237)** to **(238)** is changed to 2:1, the main product isolated was **(240)**. (Scheme 7. 2) The cyclizations of **(239)** to form benzimidazole-chloroquinoline complexes were carried out with different organic

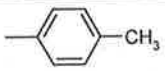
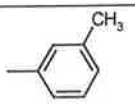
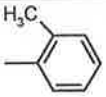
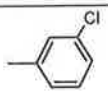
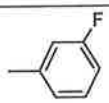
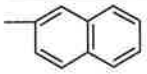
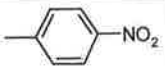
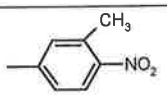
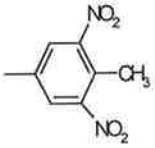
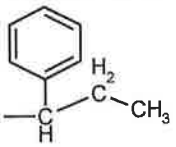
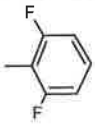
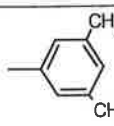
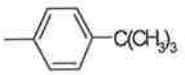
acids in polyphosphoric (PPA) at 180 °C. [70] The yields range of **(241~261)** were between 10~90% (Table 7. 1).



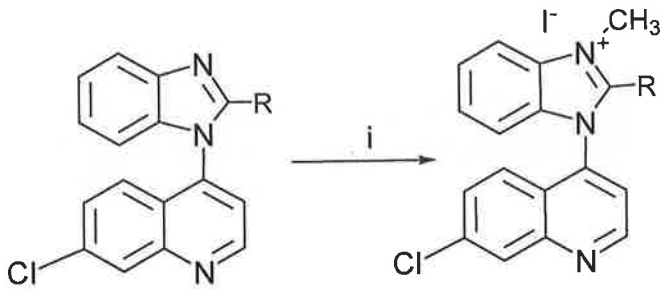
R are listed in the *table7.1.*

Scheme 7. 2 *The synthetic route to prepare N-(7-chloroquinolin-4-yl)-2-substituted benzimidazoles* ***(241~261)****,R are listed in Table 7.1. i Reflux; ethanol; stand overnight. ii >180 °C; different organic acids; PPA.*

Table 7.1

	Group (G)	Reaction Time (h)	Yield (%)		Group (G)	Reaction Time (h)	Yield (%)
(241)	$-CH_3$	2	53	(242)	$-CH_2CH_3$	2	60
(243)	$-CH_2CH_2CH_3$	2	60	(244)	$-CH(CH_3)_2$	2	15
(245)	$-CH_2CH_2CH_2CH_3$	2	50	(246)	$-CH_2CH(CH_3)_2$	2	60
(247)		2.5	75	(248)		2.5	15
(249)		2.5	17	(250)		3	33
(251)		3	31	(252)		3	26
(253)		3.5	50	(254)		3	60
(255)		4	60	(256)		2.5	15
(257)		4	27	(258)		3	32
(259)		4	8	(260)		3	43
(261)		3	33				

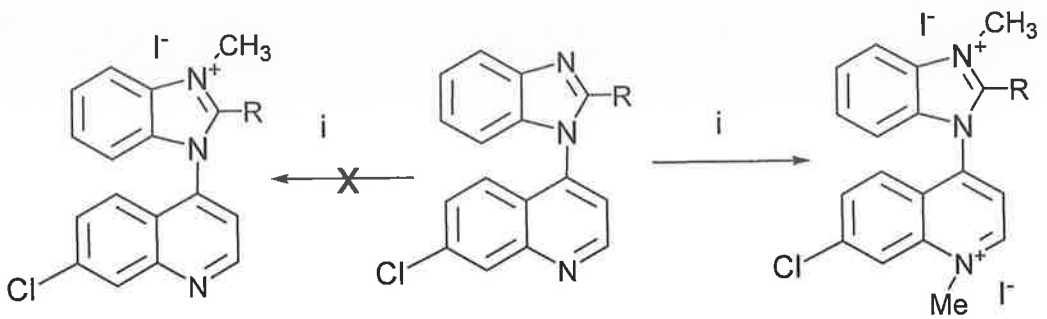
N-(7-Chloroquinolin-4-yl)-N'-methyl-2-(substituted) benzimidazolium iodide salts **(262)**, **(263)** and **(264)** were prepared from their benzimidazole-chloroquinoline complexes by refluxing in the presence of excess iodomethane. [71] (Scheme 7. 3) Compounds **(262)**, **(263)** and **(264)** are reddish powders, yields were between 90~95%.



(241), (257), (258) **(262), (263), (264)**

Scheme 7.3 *The preparation of* ***(262)***, ***(263)*** *and* ***(264)***, *R see table 7.2. i Reflux; Iodomethane.*

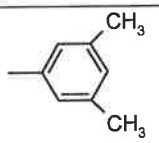
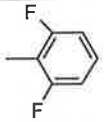
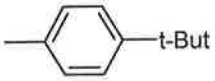
Using the same procedure but a longer reaction time, we also produced the di(iodide) salt. If the reaction time is long enough (over 5 hours), the conversion of benzimidazole-chloroquinoline complexes will only produce the di(iodide) salt complexes. For example, **(260)** was refluxed in iodomethane for 5 hours, to give **(265)** in a yield of 90%, and no **(266)** was obtained in the product from this reaction. (Scheme 7.4)



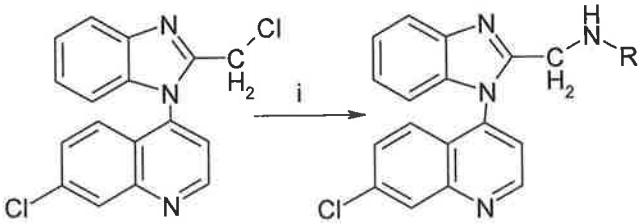
(266) **(260)** **(265)**

Scheme 7.4 *The preparation of di(iodide) benzimidazole-chloroquinoline salts. i Refluxing; Iodomethane.*

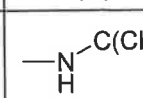
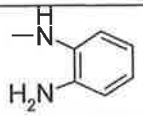
TABLE 7.2

	Group R	Time (h)		Group R	Time (h)
(262)	—CH_3	2.5	(264)		2.5
(263)		2.5	(265)		5

N-(7-Chloroquinolin-4-yl)-2-((amine substituted)-methyl)-benzimidazoles **(267)** and **(268)** were prepared by refluxing **(261)** with a primary amine in TEA/ethanol, the yields for **(267)** and **(268)** were 70% and 35% respectively. (Scheme 7.5) The crude products **(267)** and **(268)** were brown-reddish sticky liquids, which were purified with a silica gel column using ethyl acetate/hexane as eluant, to give the pure products **(267)** and **(268)** as brown powders.



(261)

	Group (R)	Yield (%)
(267)		70
(268)		35

Scheme 7.5 *The synthesis of (267) and (268). i Primary amine; TEA; Ethanol; Reflux.*

7.3 The NMR study of benzimidazole-chloroquinoline complexes

^{1}H NMR spectrum of 4,7-dichloroquinoline **(237)** has 5 aromatic proton signals between 6.8~9.2 ppm. The ^{1}H NMR spectrum of **(239)** has 11 proton signals in the

region between 5.9 to 8.6 ppm including nine aromatic protons and two amino protons. In the ^{1}H NMR spectrum of **(241)**, nine aromatic proton signals are present and a sharp single peak for the methyl protons at 2.44 ppm is also observed.

The ^{13}C NMR spectrum of compound **(241)** reveals seventeen carbon signals, which includes 16 aromatic carbon peaks from 110 to 152 ppm, and one methyl carbon signal at 14 ppm.

The ^{1}H NMR spectrum of **(262)** has two methyl proton peaks at 2.69 ppm and 4.2 ppm. The nine aromatic protons of the benzimidazole and chloroquinoline rings are present in the aromatic region between 7.0 to 9.5 ppm.

The ^{13}C NMR spectrum of **(262)** gave a signal at 32 ppm for the methyl carbon on the 3-position of benzimidazole ring, and the carbon peak observed at 11 ppm is the remaining methyl carbon linked to the 2-position of benzimidazole. Sixteen aromatic carbon peaks are present in the region between 110~153 ppm.

The ^{1}H NMR spectra of **(260)** and **(265)**, are outlined in Figure 7.2. In the ^{1}H NMR spectrum of **(265)**, thirteen aromatic proton signals are present and they have been shifted downfield by 1 ppm, and the two single peaks observed at 4.1 and 4.7 ppm, can be assigned to the two methyl group protons.

In the ^{1}H NMR spectrum of **(267)**, a sharp single *t*-butyl proton peak is observed at 0.87 ppm, and another single methylene proton peak is present at 3.7 ppm. Nine aromatic proton peaks are present between 6.7~9.0 ppm.

In the ^{13}C NMR spectrum of **(267)**, three peaks for the alkyl carbons are present between 29~51 ppm, and sixteen aromatic carbon peaks appear in the region from 110 ppm to 155 ppm.

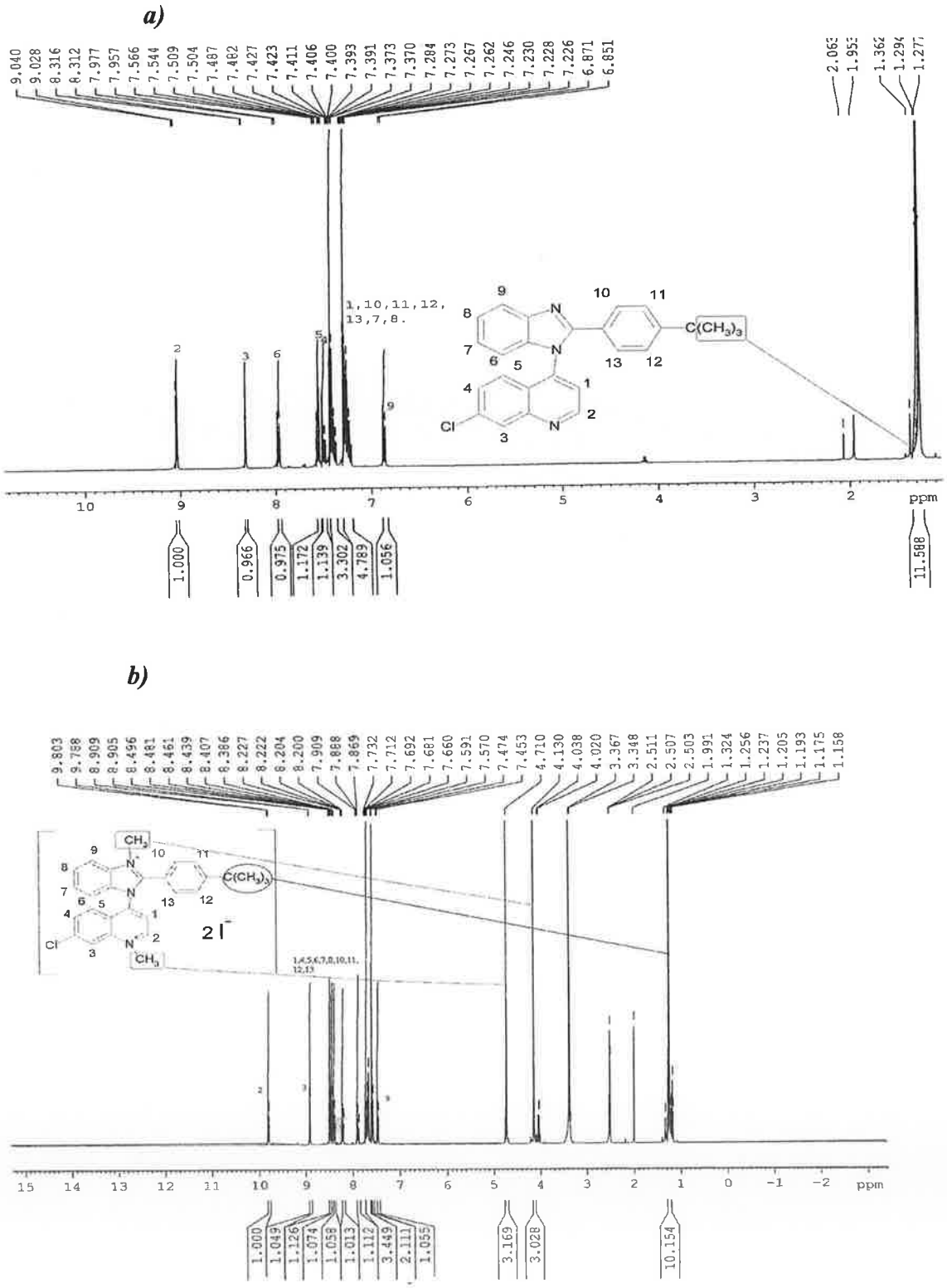


Figure 7. 2 *The ^{1}H NMR spectra of* ***(262)*** *(a) and* ***(265)*** *(b).*

7.4 Conclusion

There were three types of benzimidazole-chloroquinoline complexes prepared. The yield for the cyclization of **(241~261)** were obtained in good yields. The conversion of benzimidazole-chloroquinoline to their respective iodide salts was unsatifactory . Alkylation of benzimidazole-chloroquinoline complexes with primary amines gave N-(7-chloroquinolin-4-yl)-2-((amine substituted)-methyl)-benzimidazoles **(267)** and **(268)** in good yields of up to 70%.

Experimental

All reactions were carried out with standard glassware and solvents. All chemicals were purchased from Sigma Aldrich. Melting point determinations were done with a Griffin melting point apparatus. Infra-red (IR) spectra were recorded using a Nicolet 405 FT-IR spectrophotometer. All the UV/Vis spectra were recorded using a UV/Vis/NIR spectrometer Lambda 900. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker AC 400 instrument operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. All chemical shifts (δ) are recorded in parts per million (ppm) and coupling constants (J) in Hz. The silica gel used for column chromatography was 70~230 mesh, 60 Å. Size exclusion chromatography was carried out using SX-3 biobeads purchased from Biorad. Mass spectra (MS) were recorded using an Esquire LC_00050 MS instrument and all the spectra were carried out with an ESI source. All the Mass spectra of phthalocyanines and napthalocyanines were recorded by MALDI technique in the Department of Chemistry, National University of Ireland, Maynooth.

4-Hept-1-enylphthalonitrile (163)

4-Iodophthalonitrile (1.2 g; 4.7 mmol), 1-heptene (15 mls, 10.5 mmol), $PdCl_2(PPh_3)_2$ (0.03 g; 0.005 mmol) and NaOAc were dissolved in DMF (25 mls). This mixture was heated to 94°C with stirring under N_2 overnight. The reaction mixture was cooled to room temperature and poured into 100 ml of water. The product was extracted with ethyl acetate. The organic phase was washed with water and dried over $MgSO_4$. The pure product **(163)** was purified through a silica gel column (Hexane:Diethyl ether/1:1), giving 0.55g of product **(163)**: a green liquid in 52% yield.

R_f = 0.84 Hexane :Diethyl ether = 1 : 1

IR: ($CHCl_3$) ν_{max} 3061; 2928; 2235; 1612; 1316; 1267; 743 cm^{-1}

NMR: (Acetone-d_6)

^1H $\delta_{(ppm)}$: 8.10 (1 H; s; Ar-H); 7.96 (1 H; d, J= 7.2 Hz; Ar-H); 7.92 (1 H; d, J = 7.2 Hz; Ar-H); 6.77 (1 H; d, J = 16 Hz; =C-H); 6.60-6.56 (1 H; m; =C-H), 2.30 (2 H; d, J = 7.6 Hz; =C-CH_2); 1.38~1.31 (6 H; m; -CH_2-); 0.90 (3 H; t, J = 8 Hz; -CH_3). (Appendix 6)

^{13}C $\delta_{(ppm)}$: 14.71; 23.57; 28.86; 34.19; 35.42; 113.77; 116.93; 117.06; 117.96; 128.22; 131.22; 132.05; 135.31; 139.67; 144.73.

MS: $[M + K]^+$ found: 263 **$C_{15}H_{16}N_2$ required:** 224

The general precedure used for the preparation of symmetrical metal-free phthalocyanines.

To a 50 ml round-bottom flask was placed 2 ml of pentanol and 0.2~0.3 g of lithium metal, this reaction mixture was stirred under argon. After all of the Li had reacted, 0.2 g of phthalonitrile was quickly added into this sticky solution. The reaction mixture was heated to 110~120 °C under argon, and kept at this temperature overnight. The reaction mixture was cooled to room temperature and 5~10 ml of ethanol (or methanol) was added. Dilute acid (HCl) was added dropwise to this solution, and metal-free Pc precipitated and was collected by centrifuge (or filtration). To remove the insoluble impurities, the crude Pc was washed through a silica gel column with an appropriate solvent (for different Pcs, various solvents can be used, such as chloroform, THF or DCM). The Pc removed from the silica gel column, was dissolved in a minimum volume of THF and precipitated by the addition of methanol. Pure Pc precipitated and was collected by centrifuge.

2,9,16,23-Tetra(hept-1-enyl) phthalocyanine (164)

The synthetic procedure used was the same as the general procedure, self-condensation of 4-(hept-1-enyl) phthalonitrile **(163)** (0.224g; 1mmol) gave 0.05g of Pc **(164)**, yield: 22%. The solvents used for silica gel chromatography were chloroform and THF.

IR: (KBr) ν_{max} 3288; 2921; 2846; 2355; 1612; 1502; 1341; 1096; 1010; 962; 892; 744 cm^{-1}.

UV/Vis λ_{max} **(nm) (*in THF* $5x10^{-5}$M): (log ε)** 710 (5.049); 676 (5.048); 614 (4.458); 361 (4.309).

MS (MALDI): $[M^+]$ 898 **$C_{60}H_{66}N_8$ required:** 898

4-Chloro-5-(3-methoxyprop-1-ynyl) phthalonitrile (166) and 4,5-bis(3-methoxy-prop-1-ynyl) phthalonitrile (167)

To a 50-ml, two necked, round-bottomed flask wrapped with tin foil, was added 0.985 g (5 mmol) of 4,5-dichlorophthalonitrile, 0.18 g (0.06 mmol) of $PdCl_2(PPh_3)_2$, 0.98 g (24 mmol) of 3-methoxypropyne in 20 ml of $(^iPr)_2NH$ and 0.01 g (0.5 mmol) of CuI. This solution was stirred at 65~70 °C under a nitrogen atmosphere for 3~4 hours. The reaction solution was allowed to cool to room temperature. Then, it was gravity filtered, and the collected solid was washed with DCM. The filtrate was concentrated by rotary evaporation to give a crude product, which was purified with a silica gel column using hexane/ethyl acetate as eluant to give 0.28 g of the pure product **(166)** (an orange powder) and 0.03 g of **(167)**, were obtained in 24% and 2% yields respectively.

1. **4-Chloro-5-(3-methoxyprop-1-ynyl) phthalonitrile (166):**

Melting Point : 86~88 °C

R_f= 0.46 Hexane : Ethyl acetate = 5 :1

IR: (KBr) ν_{max} 3106; 3037; 2925; 2298; 1590; 1478; 907 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.81 (1H; s; Ar-H); 7.78 (1H; s; Ar-H); 4.34 (2H; s; $-CH_2-$); 3.42 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 58.58; 60.57; 80.63; 98.61; 114.38; 114.47; 114.58; 115.89; 128.99; 134.46; 137.84; 141.80.

MS: $[M+Na]^+$ found: 253 **$C_{12}H_7ON_2Cl$ required:** 230

2. 4,5-Bis(3-methoxyprop-1-ynyl) phthalonitrile (167)

Melting Point : 98~99°C

R_f= 0.43 Ethyl acetate : Hexane = 1 : 1.5

IR: (KBr) ν_{max} 3104; 2929; 2234; 1590; 1489; 1377; 907 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.76 (2H; s; Ar-H); 4.32 (4H; s; $-CH_2-$); 3.40 (6H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 57.00; 59.16; 80.99; 95.46; 113.43; 113.58; 129.38; 135.47

MS: $[M+H]^+$ found: 265 **$C_{16}H_{12}O_2N_2$ required:** 264

2,9,16,23-Tetrachloro-3,10,17,24-tetra(3-methoxypro-1-ynyl) phthalocyanine (168)

The synthetic procedure was the same as the general procedure, self-condensation of 4-chloro-5-(3-methoxyprop-1-ynyl) phthalonitrile **(176)** gave Pc **(178)**, yield was 31%. The solvent used for silica gel chromatography was THF.

IR: (KBr) ν_{max} 2355; 1112; 961; 836 cm^{-1}.

UV/Vis λ_{max} (nm) (*in THF* $1x10^{-5}$M): (log ε) 710 (4.782); 671 (4.804); 651 (4.775); 370 (4.978).

1,2-Dibromo-4,5-dimethylbenzene (171)

In a three-necked round-bottomed flask was placed 5.3 g (50 mmol) of *o*-xylene, 0.12 g of clean iron fillings and 0.5 g of crystal iodine. The mixture was cooled in an ice-water bath, and 16 g (100 mmol) of bromine was added dropwise over 30 minutes. The temperature was allowed to rise to 0~5 °C. After the addition of bromine, the liquid solution became a red wax. It was dried under vacuum, giving 8.8 g of the product, in 67% yield. (Ref 30)

NMR: ($CDCl_3$)

^{1}H $\delta_{(ppm)}$: 7.22 (2H; s; Ar-H); 2.04 (6H; s; -CH_3).

^{13}C $\delta_{(ppm)}$: 19.51; 121.50; 134.56; 138.03.

1,2-Dibromo-4,5-bis(dibromomethyl) benzene (172)

To a mixture of 5 g of **(171)** and 0.5g of AIBN was added 12 g of NBS in 30 ml of carbon tetrachloride. An orange colour could be seen after this mixture was refluxed for 1 hour. This suspension was allowed to reflux overnight. The hot mixture was filtered, and the organic solvent was removed under vacuum, giving 7.7 g of crude product **(172)** in 70% yield, and was used in the next step without any further purification. (Ref 30)

6,7-Dibromo-2,3-dicyanonaphthalene (173)

A solution of 1.37 g of **(172)** in 5 ml of DMF was added with 0.2g (0.25 mmol) of fumaronitrile **(53)** and 3.0 g (0.02 mmol) of NaI. The mixture was kept at 75~80 °C

for 7 hours. The colour of this solution became red. The mixture was poured into an aqueous sodium sulphate (Na_2SO_4) solution. The precipitate was collected by filtration, washed with water, then DCM several times, and dried under vacuum, giving 0.58g of **(173)** (yellow powder), in 69% yield. (Ref 30)

Melting point: > 300 °C

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.62 (2H; s; Nap-H); 8.48 (2H; s; Nap-H).

^{13}C $\delta_{(ppm)}$: 110.47; 116.44; 127.25; 132.73; 133.54; 135.93.

MS: $[M+H]^+$ found: 337 **$C_{12}H_4N_2Br_2$ required:** 336

6,7-Di(oct-1-ynyl)-2,3-dicyanonaphthalene (174)

To a solution of 1.0g (3 mmol) of **(173)** in 5 ml DMF was treated 2 ml of 1-octyne, 0.36 g (0.06 mmol) of $PdCl_2(PPh_3)_2$, 0.019 g (1 mmol) of CuI, and 3 ml of TEA. The mixture was kept at 60 °C under nitrogen for 3 hours. Then it was cooled to room temperature, and poured into 20 ml of water. A brown oil was formed, and 20 ml of ethyl acetate was used to extract this oil. The organic layer was separated and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified using a silica gel column with hexane/benzene as eluants. 0.6 g of product **(174)** was isolated. Yield: 50%.

Meltin Point: 76~80 °C.

R_f = 0.29 Hexane : Benzene = 3 :2

IR: (KBr) ν_{max} 3018; 2919; 2851; 2227; 1449; 1208; 738 cm^{-1}

NMR: ($CDCl_3$)

^{1}H $\delta_{(ppm)}$: 8.10 (2H; s; Nap-H); 7.86 (2H; s; Nap-H); 2.45 (4H; t, J= 6.4 Hz; -CH_2-); 1.60 (4H; t, J = 6.4 Hz; -CH_2-); 1.44 (4H; m; -CH_2-); 1.29~1.24 (8H; m; -CH_2-); 0.84 (6H; t, J = 6 Hz; -CH_3).

^{13}C $\delta_{(ppm)}$: 14.50; 20.22; 22.98; 28.94; 29.07; 31.81; 99.21; 110.82; 116.17; 129.27; 131.75; 131.95; 135.33.

MS: $[M+K]^+$ found: 433 **$C_{28}H_{30}N_2$ required:** 394

6,7-Bis (3,3'-dimethylbut-1-ynyl)-2,3-dicyanonaphthalene (175)

The procedure is similar to that used above for **(174)**, except 3,3'-dimethyl-1-butyne (2 ml) was used instead of 1-octyne (2 ml) and the reaction temperature was 40 °C, giving 0.46g of **(175)**. Yield: 45%.

Melting Point : 222~224°C

R_f= 0.32 Hexane : Benzene = 3 :2

IR: (KBr)ν_{max} 3206; 3067; 2964; 2229; 1596; 1358; 1261; 755cm^{-1}

NMR: ($CDCl_3$)

^{1}H $\delta_{(ppm)}$: 8.10 (2H; s; Nap-H); 7.89 (2H; s; Nap-H); 1.31 (18H; s; -CH_3).

^{13}C $\delta_{(ppm)}$: 28.81; 31.28; 106.60; 110.77; 116.21; 128.73; 129.05; 131.92; 131.98; 135.33.

MS: $[M+K]^+$ found: 377 **$C_{24}H_{22}N_2$ required:** 338 (Appendix 7)

3,4,12,13,21,22,30,31–Octa(oct-1-ynyl) naphthalocyanine (176)

The synthetic procedure used was the general procedure, using 0.394g (1mmol) of 6,7-di(oct-1-ynyl)-2,3-dicyanonaphthalene **(174)**, which gave Nc **(176)** (0.016g) in a 8% yield. The solvent used in the silica gel chromatography was THF.

IR: (KBr) ν_{max} 3288; 2954; 2916; 2857; 2355; 1658; 1456; 1346; 1177; 1091; 1018; 959; 908; 760; 717 cm^{-1}.

UV/Vis λ_{max}**(nm)(*in THF* 1x10^{-5}M):(log ε)** 801(4.98);7.34(4.83);336(4.78).

3,4,12,13,21,22,30,31–Octa(t-but-1-ynyl) naphthalocyanine (177)

The synthetic procedure used was the general procedure, using 0.338g (1 mmol) of 6,7-bis (3,3'-dimethylbut-1-ynyl)-2,3-dicyanonaphthalene **(175)**, which gave Nc **(177)** (0.04g) in 12% yield. The solvent used in the silica gel chromatography was THF.

IR: (KBr) ν_{max} 3644; 3288; 2959; 2355; 2226; 1725; 1602; 1467; 1387; 1338; 1263; 1158; 1091; 1016; 908; 801; 755; 706 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF* 1x10^{-5}M): (log ε)** 798 (4.95); 756 (4.43); 725 (4.38) 341 (4.67).

MS (MALDI): $[M]^+$ 1354. **$C_{96}H_{90}N_8$ Require: 1354**

Octenylboronic acid (186)

A well mixed solution of 1 ml of 1-octyne (97%) and 1.05 ml of catecholborane (98%) was placed in a 50 ml round bottom flask with a magnetic stirring bar. This flask was flushed with argon for five minutes, before it was sealed. This solution was then heated to 70 °C and kept stirring for four hours. After the mixture was cooled to room temperature, 10 ml of water was injected and the mixture was stirred for another hour. A brown sticky solid precipitated, which was collected by filtration and dried under vacuum to give 1.79 g of white solid **(186)**, in 97% yield.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 5.78~5.69 (1H; m; B-CH=); 5.14 (1H; d, J = 1.84 Hz; =CH-); 2.01~1.98 (2H; m; $-CH_2-$); 1.28~1.14 (8H; m; $-CH_2$); 0.80 (3H; t, J = 8.0 Hz; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 14.42; 22.68; 29.42; 30.49; 32.12; 36.76; 116.16; 152.23.

***t*-Butenylboronic acid (187)**

The procedure for the preparation of **(187)** was the same as that used to prepare **(186)**, except 3,3-dimethylbutyne (2 ml) was used instead of 1-octyne (1 ml), giving 1.1 g of **(187)**. Yield was 5%.

NMR: (Acetone-d_6)

^1H $\delta_{(ppm)}$: 6.58 (1H; d, J = 1.84 Hz; -CH=CH-); 5.34 (1H; d, J = 1.84 Hz; -CH=CH-); 1.012 (9H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 29.67; 35.36; 118.67; 161.98.

6,7-Di(oct-1-enyl)-2,3-dicyanonaphthalene (188)

To a suspension of 1.35 g (4 mmol) of (186); 1.4 g (9 mmol) of (172); 2.9 g (9 mmol) of tetrabutylammonium bromide (Bu_4NBr) and 3.0 g (21 mmol) of K_2CO_3 in 10 ml of water was added 0.3 g of Pd $(OAc)_2$. This mixture was stirred at 70 °C for one hour. When all of the **(172)** disappeared, the reaction mixture was cooled to room temperature. This reaction mixture was extracted with ethyl acetate several times. The organic phase was collected, washed with water and dried over $MgSO_4$. The ethyl acetate was removed under vacuum. The crude product was purified through a silica gel column with hexane/diethyl ether as eluants, giving a gray product **(188)** 1.37 g, in 86% yield.

Melting Point : 42°C.

R_f = 0.87 Diethyl ether : Hexane = 1 : 1.5

IR: (KBr) ν_{max} 3212; 2928; 2229; 454; 1267; 966; 719 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.13 (2 H; s; Nap-H); 7.78 ppm (2 H; s; Nap-H); 6.62 (2 H; d, J = 15.6 Hz; CH=CH); 6.25~6.21 (2 H; m; CH=CH); 2.25 (4 H; q, J = 7.2 Hz, =C-CH_2); 1.48 (4 H; q, J = 8.0 Hz; -CH_2-) 1.31~1.18 (12 H; m; -CH_2-); 0.82 (6 H; t, J = 8.0 Hz; -CH_3).

^{13}C $\delta_{(ppm)}$: 14.51; 23.05; 29.45; 32.00; 32.12; 33.84; 109.50; 116.61; 125.58; 127.07; 132.63; 135.72; 137.97; 140.71.

MS: $[M+H]^+$ found: 399 **$C_{28}H_{34}N_2$ required:** 398

6-Bromo-7-(3,3'-dimethylbut-1-enyl)-2,3-dicyanonaphthalene (189)

The procedure used was the same as used for the preparation of **(188)**, except **(187)** (1.5g) was used in 1.2 equivalents to **(172)** (1.4 g; 9 mmol). This reaction gave **(189)** (0.15 g) in 5% yield.

Melting Point : 198~202°C

R_f = 0.87 Ethyl Acetate : Hexane = 1 : 3

IR: (KBr) ν_{max} 3058; 2952; 2233; 1479; 974 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.23 (1 H; s; Nap-H); 8.18 (1 H; s; Nap-H); 8.17 (1 H; s; Nap-H); 7.79 (1 H; s; Nap-H); 6.55 (1H; d, J = 16 Hz; -CH=); 6.24 (1H; d, J = 16 Hz; =CH-); 1.21 (9 H; s; -CH_3).

^{13}C $\delta_{(ppm)}$: 29.82; 34.53; 116.88; 118.87; 121.34; 121.97; 122.44; 125.77; 129.06; 132.63; 133.15; 135.06; 135.73; 137.42; 137.42; 141.18; 148.37.

3,4,12,13,21,22,30,31–Octa(oct-1-enyl) naphthalocyanine (191)

The synthetic procedure used was the general procedure, self-condensation of 6,7-dioct-1-enyl-2,3-dicyanonaphthalene **(188)** (0.398) gave Nc **(191)** (0.03g) in a 8% yield. The solvent used for silica gel chromatogarphy was THF.

IR: (KBr) ν_{max} 3396; 2952; 2857; 2355; 1333; 1220; 1139; 1094; 905; 741 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF*** $1x10^{-5}$M**): (log ε)** 797 (5.08), 724 (4.87); 344 (4.84).

MS (MALDI): $[M^+]$ 1594 $C_{112}H_{138}N_8$ **required:** 1594

4-(3-Hydroxylprop-1-ynyl) phthalonitrile (195)

To 5 ml of TEA was added 1g (4 mmol) of 4-iodophthalonitrile, 0.12 g of $PdCl_2(PPh_3)_2$, 0.006 g of CuI and 1 g (10 mmol) of propargyl alcohol. This mixture was stirred at 60 °C for 1 hour. The reaction was monitored by TLC. The solution was poured into 20 ml of water. The precipitate was filtered and the filtrate collected. The solvent was then removed under vacuum. The product was purified by a silica gel column with hexane/ethyl acetate as eluants, giving 0.33 g of **(195)**, yield: 45%.

Melting Point : 40±1 °C.

R_f= 0.32 Hexane : Ethyl acetate = 2 :5

IR: (KBr) ν_{max} 3407; 2919; 2851; 2233; 1591; 1029; 738 cm^{-1}

NMR: ($CDCl_3$)

^{1}**H** $\delta_{(ppm)}$: 7.75 (1H; s; Ar-H); 7.70~7.69 (2H; m; Ar-H); 4.47 (2H; s; $-CH_2-$).

^{13}**C** $\delta_{(ppm)}$: 51.59; 82.25; 95.45; 114.96; 115.15; 115.52; 116.52; 129.16; 133.99; 136.31; 136.52.

MS: $[M+Na]^+$ **found:** 205 $C_{11}H_6ON_2$ **required:** 182

4-(5-Hydroxylpentoxy) phthalonitrile (197)

To a solution of 0.52 g (2.0 mmol) of 3-nitrophthalonitrile in 10 ml of DMSO was added 1.04 g (10 mmol) of pentane-1,5-diol and 0.25 g (1.88 mmol) of finely ground K_2CO_3. The flask was evacuated by vacuum and stirred for 4 days. Another three 0.25g portions of potassium carbonate were added to this mixture at 24-hour intervals during the reaction. The orange solution was then poured into cold water, and the solid was collected by filtration. The solid was washed with water several times and dried under vacuum to obtain the pure product **(197)** 0.27 g, yield: 58%.

Melting Point : 118~19°C.

IR: (KBr) ν_{max} 3356; 2934; 1297; 1047; 725 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.73 (1H; t, J = 8 Hz; Ar-H); 7.51 (1H; d, J = 8.8 Hz; Ar-H); 7.44 (1H; d, J = 8 Hz; Ar-H); 4.16 (2H; t, J = 6.8 Hz; Ph-O-CH_2-); 3.45 (2H; d, J = 5.2 Hz; -CH_2-OH); 1.76 (2H; t, J = 6.8 Hz; -CH_2-); 1.48~1.45 (4H; m; -CH_2-).

^{13}C $\delta_{(ppm)}$: 23.37; 29.67; 33.62; 62.64; 71.15; 105.22; 114.48; 116.82; 117.59; 119.17; 126.53; 136.63; 162.82.

MS: $[M + Na]^+$ found: 253 **$C_{13}H_{14}O_2N_2$ required:** 230

4,5-Bis(*t*-butylphenoxy) phthalonitrile (198)

A solution of 1.97 g (10 mmol) of 4,5-dichloropthalonitrile and 20 g of *p*-*t*-butyl-phenol in 40 ml of DMSO was heated to 90 °C. K_2CO_3 was added in portions (9 x 2.76g, 180 mmol) at 30 minute intervals. After the addition was complete, this mixture was stirred at 90 °C under nitrogen for one hour. The mixture was cooled to room temperature, then it was poured into 200 ml ice-water, filtered and dried under vacuum to give **(198)** 3.8 g, in 90% yield. (Ref. 59)

IR: (KBr) ν_{max} 3234; 2964; 2225; 1583; 1503; 1016; 828 cm^{-1}.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.49 (4H; d, J = 8.8 Hz; Ar-H); 7.15 (2H; s; Ar-H); 7.04 (4H; d, J = 8.8 Hz; Ar-H); 1.38 (18H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 31.82; 35.01; 110.17; 115.65; 120.04; 121.66; 127.85; 149.53; 151.91; 152.65.

4,5-Bis(*p*-bromophenoxy) phthalonitrile (199)

The method used was the same as the procedure used to prepare **(199)**, except 4-bromophenol was used instead of *p-t*-butylphenol. The product **(199)** (3.6 g) was recrystallised from methanol, in 78% yield. (Ref. 59)

IR: (KBr) ν_{max} 3224; 2225; 1597; 1576; 1503; 1484; 1394; 1305; 1012; 733 cm^{-1}.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.56 (4H; d, J = 8.4 Hz; Ar-H); 7.34 (2H; s; Ar-H); 7.13 (4H; d, J = 8.4 Hz; Ar-H).

^{13}C $\delta_{(ppm)}$: 111.21; 114.73; 118.94; 121.43; 122.61; 133.73; 151.43; 153.32.

The general procedure used for the preparation of polymer-bound phthalonitriles.

The solid support, tritylated 2% cross-linked polystyrene (1g), was swollen in DCM for one hour. Then, DMAP and TEA were added with the phthalonitriles **(195)** 1g (or **(197)**). The solution was stirred at room temperature overnight. The polymer was filtered and washed with methanol, DCM, chloroform, and ethyl acetate several times. The polymer was then dried under vacuum.

The measurement of the loading capacity of polymer-bound phthalonitriles by the cleavage of phthalonitriles from the polymer resin.

The polymer-bound phthalonitriles were allowed to swell in dry chloroform for an hour, a few of drops of triflouroacetic acid was added. The mixture was stirred for 30 minutes. The suspension was filtered and washed with several solvents until all the cleaved phthalonitrile were collected. The organic phase was dried over $MgSO_4$, and the solvent was removed under vacuum, giving 0.102 g of **(195)** and 0.106 g of **(197)**. The loading capacities were 0.56 mmol/gram for **(209)** and 0.46 mmol/gram for **(210)**.

The general procedure used for the preparation of unsymmetrical phthalocyanine (naphthalocyanine) using a solid-support.

Polymer-bound phthalonitrile (1.0 g) was preswollen in 5 ml of pentanol for 3~6 hours at room temperature before the partener phthalonitrile and lithium metal (0.3~0.5 g) was added. The reaction mixture was heated to 110~120 °C under Argon overnight with vigorous stirring. The reaction mixture was cooled to room temperature and methanol (30 ml) was added. The blue (green) polymer resin was filtered and washed with various solvents several times until the filtrates were colorless. The blue (green) polymer was then swollen in 30 ml of dry chloroform for 6 hours, and 2~4 ml of TFA was added dropwise. The mixture was kept stirring for one hour. The polymer was filtered and the filtrate which contained Pcs, was collected. The organic solution was dried over $MgSO_4$ and chloroform was removed under vacuum, giving unsymmetrical Pcs.

The general procedure used for the cleavage of polymer-bound phthalocyanine (naphthalocyanine).

To a solution of 1.0 g of polymer-bound phthalocyanine in 10 ml of dry chloroform/THF mixture (10:1), was added 2 ml of TFA dropwise. The mixture was stirred at room temperature for 2 hours. The organic solvents were then removed under vacuum, 10 ml of water and 10 ml of ethyl acetate were added to the residue. The organic layer was separated and washed three times with water, and then it was dried over $MgSO_4$. The target Pc was purified by silica gel chromatography with THF, or DCM:Methanol (10~50:1).

2-(3-Hydroxylprop-1-ynyl)-9,10,16,17,23,24-hexa(*t*-butylphenoxy) phthalocyanine (202).

The procedure used was the same as the general procedure. Polymer-bound phthalonitirle **(192)** (1g) and **(198)** (1g) were used in this reaction. After cleavage and purification, the target Pc **(202)** (0.06g) was obtained in 8% yield.

UV/Vis λ_{max} (nm) (*in THF* $1x10^{-5}$M): (log ε) 703 (4.998); 670(5.024); 643 (4.662); 611 (4.506); 346 (4.864).

1-(5-Hydroxylpentoxy)-10,11,19,20,28,29-hexa(3,3'-dimethylbut-1-ynyl) naphthalocyanine (204)

The procedure used was the same as the general procedure. Polymer-bound phthalonitirle **(193)** (1g) and **(175)** (1g) were used in this reaction. After cleavage and purification, the target Pc **(202)** (0.002g) was obtained in 2% yield.

UV/Vis λ_{max} (nm) (*in THF* $1x10^{-5}$M): (log ε) 744 (5.236); 718 (5.289); 704 (5.324); 379 (5.149).

3-Benzyloxyphthalonitrile (207.)

The procedure was the same as we employed to prepare **(197)**, except using benzyl alcohol instead of pentane-1,5-diol. Pure product **(207)** (0.43 g) was obtained in 92% yield. (Ref. 21)

Melting Point : 158~60 °C.

R_f= 0.69 Hexane : Ethyl Acetate = 1 :2

IR: (KBr) ν_{max} 3091; 2958; 2223; 1300; 924; 794 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.54 (1H; t, J = 8 Hz; Ar-H); 7.37~7.26 (6H; m; Ar-H); 7.21 (1H; d, J = 8.8 Hz; Ar-H); 5.20 (2H; s; $-CH_2$).

^{13}C $\delta_{(ppm)}$: 71.76; 105.72; 113.45; 117.51; 117.88; 125.80; 127.47; 129.09; 129.35; 134.92; 134.97; 161.34.

MS: $[M + Na]^+$ found: 257 **$C_{15}H_{10}ON_2$ required:** 234

3-Trityloxyprop-1-yne (209).

A mixture of 5.6 g (10 mmol) of propargyl alcohol, 2.78g (10 mmol) of trityl chloride and 0.5 g of DMAP were dissolved in 40 ml of dry DCM. This reaction mixture were stirred for about 15 minutes, after which time 10 ml of TEA was added. This clear solution was kept stirring at room temperature overnight. The organic solvents were removed under reduced pressure, and the product **(209)** was crystallized in hexane and ether, giving 2.6g of **(209)**. Yield: 87%.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.40~7.37 (6H; m; Ar-H); 7.24~7.20 (6H; m; Ar-H); 7.17~7.13 (3H; m; Ar-H); 3.67 (2H; s; $-CH_2-$); 2.29 (3H; s; $-CH_3$). (Appendix 8)

^{13}C $\delta_{(ppm)}$: 53.35; 73.92; 80.82; 127.65; 128.40; 129.01; 143.80.

4-(3-Tritoxyprop-1-ynyl) phthalonitrile (210)

To a solution of 1g (4 mmol) of 4-iodophthalonitrile, 0.01 g of $PdCl_2(PPh_3)_2$ and 0.01g of CuI in 20 ml of TEA/DMF (1:3) was added 1.8 g (6 mmol) of **(209)**. This mixture was let stir at 60 °C for 1 hour. The reaction mixture was monitored by TLC. After 3~4 hours, all the 4-iodophthalonitrile disappeared. The solution was poured into 50 ml of water, and extracted with three portions of 30 ml ethyl acetate. The extractions were combined and the solvent was removed under vacuum. The product was purified through a silica gel column with hexane/ethyl acetate as eluants, to give 0.95g of **(210)**. Yield: 56%.

Melting Point: 148~150 °C

R_f = 0.45 Ethyl acetate: Hexane = 1:3

IR: (KBr) ν_{max} 3049; 2931; 2234; 1541; 1148; 1214; 1053 cm^{-1}.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 7.65 (2H; t, J = 4 Hz ; Ar-H); 7.68 (1H; d,d, J = 8.4 ,1.6 Hz; Ar-H); 7.42 (6H; d, J = 7.2 Hz; Ar-H), 7.26 (6H; t, J = 7.2 Hz; Ar-H), 7.19 (3H; t, J = 7.2 Hz; Ar-H); 4.01 (2H; s; $-CH_2-$).

^{13}C $\delta_{(ppm)}$: 53.74; 82.17; 88.32; 94.30; 114.87; 115.11; 116.55; 127.67; 128.33; 128.46; 129.00; 129.32; 133.76; 136.16; 136.64; 143.56.

MS: $[M+Na]^+$ found: 447 **$C_{30}H_{20}ON_2$ required:** 424

The preparation of unsymmetrical phthalocyanines by solution phase synthesis.

To 5 ml of pentanol was added 0.5g of lithium metal under argon at room temperature with vigorous stirring. Two different phthalonitriles (stiochiometric ratio 1:3) were added and the reaction mixture was kept at 110~120 °C under argon overnight. A metal salt was added and the mixture was kept at the same temperature

for an additional 5~6 hours. After the reaction mixture was cooled to room temperature, methanol (30 ml) was poured into the reaction mixture. The unsymmetrical Pcs precipitated and the crude product was first purified through a silica gel column with different mobile phases (THF or methanol: DCM = 1: 6~20), and then the blue product obtained from the above silica columns was put onto a size-exclusion column using THF as the eluant. Two bands were separated on the column, the second band was collected, and it contained the target unsymmetrical PcM. To obtain high purity of the target Pc, the product was further purified by dissolving it into a minimum of THF, and precipitated by adding methanol. The blue solid was then collected by centrifuge in 20~28% yield.

General procedure for the deprotection of trytilated Pcs.

Unsymmetrical Pcs were dissolved in dry chloroform (if the Pc could not be dissolved in chloroform, THF should be added.). To the solution was added 1 ml of TFA and this reaction mixture was let stir for 30 minutes. The organic solvents and TFA were removed under vacuum. The purification of the unsymmetrical Pcs was achieved by column chromatography or by methanol extraction.

2-(3-Tritoxyprop-1-ynyl)-8,15,22-tri(benzyloxy) phthalocyaninato Zinc (II) (212).

The synthetic procedure was the same as that described above, condensation of two phthalonitriles **(206)** (0.8g; 3mmol) and **(210)** (0.424g; 1mmol) with $Zn(OAc)_2$, gave PcZn **(212)** (0.23g), yield: 20%. THF was used as the mobile phase in silica gel chromatography and size-exclusion chromatography.

IR: (KBr) ν_{max} 2921; 2857; 2361; 1717; 1394; 1489; 1456; 1338; 1266; 1231; 1088; 1040; 741; 693 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF*** $1x10^{-5}$M**): (log ε)** 694 (4.60), 631 (4.24); 377 (4.38); 338 (4.50).

NMR: (Pyridine-d_5)

^{1}H $\delta_{(ppm)}$: 9.26~9.24 (4H; m broad; Ar-H); 9.05~8.78 (24H; m; Ar-H); 8.59~8.38 (10H; m; Ar-H); 8.36~8.16 (2H; m; Ar-H); 8.10 (2H; s; Ar-H); 6.98 (6H; s, broad; -O-CH_2-); 5.20 (2H; t, J= 6.8 Hz; -CH_2-OTr).

2-(3-Hydroxyprop-1-ynyl)-8,15,22-tri(benzyloxy) phthalocyaninato Zinc (II) (213)

The synthetic procedure was the same as the general procedure. The purification of PcZn **(213)** was first by silica-gel chromatography with methanol/DCM (1: 6~20) as the eluants. The sample was further purified by a size-exclusion column with THF as eluant to give highly pure PcZn **(213)**, in 95% yield.

Melting point: >240 °C.

IR: (KBr) ν_{max} 2366; 1685; 1594; 1486; 1330; 1266; 1131; 1033; 1040; 798; 693 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF*** $1x10^{-5}$M**): (log ε)** 693 (4.72); 686 (4.59); 662 (4.07); 625 (4.03) 346 (4.19).

NMR: (Pyridine-d_5)

^{1}H $\delta_{(ppm)}$: 8.49 (4H; s; Ar-H); 8.20~8.12 (3H; m; Ar-H); 7.98 (1H; s, broad; Ar-H); 7.90~7.55 (10H; m; Ar-H); 7.47~7.38 (5H; m; Ar-H); 7.14 (2H; m; Ar-H); 7.01 (2H; s; Ar-H)6.89 (6H; s, broad; -O-CH_2-); 4.87 (2H; s; -CH_2-OH).

2-(3-Tritoxyprop-1-ynyl) phthalocyaninato Cobalt (II) (215).

The synthetic procedure was the same as that described above, cross-condensation of two phthalonitriles **(5)** (0.4g; 3mmol) and **(210)** (0.424g; 1mmol) with $Co(OAc)_2$ (1.0g), gave PcCo **(215)** (0.22g), yield: 28%. THF was used as the mobile phase in silica gel chromatography and size-exclusion chromatography.

Melting point: >340 °C.

IR: (KBr) ν_{max} 2954; 1607; 1518; 1424; 1336; 1290; 1161; 1120; 1094; 911; 733 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF*** $1x10^{-5}$M**): (log ε)** 658 (4.90); 596 (4.28); 326 (4.59).

NMR: (Pyridine-d_5)

^{1}H $\delta_{(ppm)}$: 8.0 (15H; s broad; Ar-H); 7.1~6.8 (15H; m; Ar-H); 5.92 (2H; s, broad; $-CH_2$-OTr).

2-(3-Hydroxyprop-1-ynyl) phthalocyaninato Cobalt (II) (216).

The synthetic procedure used was the same as the general procedure. The purification of **(216)** was carried out by washing the crude blue residue with plenty of methanol, giving PcCo **(216)** 0.2g in 90% yield.

Melting point: >340 °C.

IR: (KBr) ν_{max} 1518; 1424; 1330; 1290; 1163; 1118; 1088; 913; 752; 733 cm^{-1}

UV/Vis λ_{max} **(nm) (*in THF*** $1x10^{-5}$M**): (log ε)** 659 (4.86); 596 (4.22); 326 (4.33).

4-Bromophthalonitrile (218).

To concentrated H_2SO_4 (98%) was added 5.0 g of **(217)** at room temperature. The solution was then cooled in an ice-water bath for 30 mins with stirring, before 2 g of phthalonitrile **(4)** was added. After addition, the mixture was poured onto ice

immediately. The target product was collected by filtration, giving 1.13 g of **(218)** in 35% yield. (Ref. 57)

NMR: (Acetone-d_6)

^{1}H $\delta_{(ppm)}$: 7.90 (1H; s; Ar-H); 7.83 (1H; d, J = 8.4 Hz; Ar-H); 7.62 (1H; d, J = 8.4 Hz; Ar-H).

^{13}C $\delta_{(ppm)}$: 114.42; 115.03; 117.77; 128.58; 134.83; 136.80; 137.06; 138.15.

MS: $[M+K]^+$ found: 246 **$C_8H_3N_2Br$ required:** 207

4,5-Dibromophthalonitrile (219).

Compound **(219)** was prepared via the same procedure as that used to prepare **(218)**, except a large excess (about 2~3 times) of **(217)** was used. This reaction produced a mixture of **(218)** and **(219)**. The product **(219)** was purified by a silica gel column with hexane and ethyl acetate as eluants, to give 0.1 g of **(219)**. Yield was 3%.

NMR: (Acetone-d_6)

^{1}H $\delta_{(ppm)}$: 7.98 (1H; s; Ar-H).

^{13}C $\delta_{(ppm)}$: 114.02; 115.79; 131.93; 138.16.

MS: $[M+K]^+$ found: 325 **$C_8H_2N_2Br_2$ required:** 286

1,2-Dibromophthalic acid (224)

A mixture of 1.3 g (5 mmol) of 1,2-dibromo-4,5-dimethylbenzene, 9.0 g (5 mmol) of $KMnO_4$ and 1g of KOH were added to 70 ml of water, and this reaction mixture was refluxed overnight and was then filtered. To the filtrate was added 100 ml of dilute HCl. A white solid precipitated. The solid was collected by filtration, washed with water and dried under vacuum to give 1.5 g of pure product **(224)**, in 95 % yield.

NMR: (DMSO-d_6)

^{1}H $\delta_{(ppm)}$: 8.15 (2H; s; Ar-H).

4,5-Dibromophthalic anhydride (225).

A solution of 3.24 g of **(224)** in the minimum volume of hot redistilled acetic anhydride, was refluxed for 4 hours. On cooling, brown crystals of **(225)** precipitated. The crystals were filtered to give 2 g of **(225)**. Yield: 67%.

NMR: (Acetone-d_6)

^{1}H $\delta_{(ppm)}$: 8.32 (2H; s; Ar-H).

^{13}C $\delta_{(ppm)}$:131.50; 133.13; 134.26; 162.56.

MS: $[M+H]^+$ found: 307 **$C_8H_2O_3Br_2$ required:** 306

N-(-7-Cloroquinolin-4-yl) benzenediamine hydrochloride acid (239).

o-Phenylenediamine (1.08 g; 10 mmol) and 4,7-dichloroquine (1.97 g; 10 mmol) were dissolved in 100 ml ethanol, and this solution was refluxed with stirring for one hour. The yellow solid **(239)** precipitated, and this suspension was cooled to room temperature. The crude product **(239)** was collected by filtration. The yellow solid **(239)** was then washed with fresh ethanol several times, and dried under vacuum. (2.8 g) Yield: 93%

Melting Point : 250~254 °C

IR (KBr) : ν_{max} 3234; 3127; 3029; 2797; 1607; 1542; 1497; 1325; 906; 744 cm^{-1}.

NMR: ($CDCl_3$)

^{1}H $\delta_{(ppm)}$: 8.58~8.56 (1H; d, J = 9.2 Hz; CQ-H); 8.23~8.21 (1H; d, J = 6.8 Hz; CQ-H); 7.91 (1H; s; CQ-H); 7.59~7.56 (1H; d, J = 9.2 Hz; CQ-H); 6.95~6.90 (1H; t, J = 8 Hz; Ar-H); 6.88~6.87 (1H; d; J = 8 Hz; Ar-H); 6.66~6.64 (1H; d, J = 8.4 Hz; Ar-

H); 6.45~6.41 (1H; t, J = 6.8 Hz; Ar-H); 6.38~6.35 (1H; m; $-NH_2$); 6.25~6.23 (1H; m; $-NH_2$); 6.00~5.98 (1H; d, J = 6.8 Hz; CQ-H).

^{13}C $\delta_{(ppm)}$: 100.78; 106.96; 116.22; 116.65; 117.95; 120.17; 120.97; 126.80; 128.22; 129.41; 134.12; 137.82; 140.39; 140.70; 145.17.

MS: $[M+H]^+$ Found: 270 **$[C_{15}H_{12}N_3Cl+HCl]$ Requires:** 305

$C_{15}H_{12}N_3Cl$ Requires: 269

N-(7-Cloroquinolin-4-yl)-2-methylbenzimidazole (241)

A mixture of 1.53g of **(239)** (5 mmol) and 0.36g of acetic acid (6 mmol) were heated to over 180 °C in 5g PPA, for 3 hours with stirring. This sticky solution was allowed to cool to room temperature. An excess amount of aqueous 1N ammonium solution was added into the reaction mixture, this solution was cooled in an ice-water bath. When the pH value of the reaction mixture was alkaline, a brown solid **(241)** precipitated. This mixture was then extracted with DCM several times. The organic layer was combined and washed with dilute ammonium solution, followed by water. DCM was removed under vacuum, giving a brown-reddish solid **(241)**. This crude brown-reddish solid was purified through a silica gel column (ethyl acetate : hexane = 5:1), giving the orange powder **(241)** 0.79g. Yield was 53%.

Melting point: 147~149 °C

R_f = 0.40 Ethyl acetate : Diethyl ether = 5 : 1

IR (KBr): ν_{max} : 3034; 1608; 1423; 744 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.15 (1H; d, J= 4.8 Hz; CQ-H); 8.31 (1H; s; CQ-H); 7.83 (1H; d, J= 8 Hz; Bim-H); 7.49 (1H; d, J= 9.2 Hz; CQ-H); 7.45 (1H; d, J= 4.4 Hz; CQ-H); 7.35~7.31

(1H; t, J= 7.2 Hz; Bim-H); 7.29 (1H; d, J= 8.8 Hz; CQ-H); 7.21~7.17 (1H; t, J= 7.2 Hz; Bim-H); 6.86 (1H; d, J= 8 Hz; Bim-H); 2.43 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 14.69; 110.22; 119.87; 120.71; 123.47; 123.71; 123.97; 124.52; 129.66; 129.77; 137.03; 137,36; 141.56; 143.17; 150.72; 151.82; 152.43

MS: $[M+Na]^+$ Found: 316 **$C_{17}H_{12}N_3Cl$ Requires:** 293

N-(7-Cloroquinolin-4-yl)-2-ethylbenzimidazole (242)

The synthetic procedure used was the same as that used to prepare **(241)**, except propionic acid was used instead of acetic acid, giving a light yellow powder **(242)** 0.92 g. Yield was 60%.

Melting Point: 203~206 °C

R_f = 0.34 Ethyl acetate : Hexane = 1 : 1

IR: (KBr) υ_{max}: 3045 ; 2985 ; 1594 ; 1422 ; 746 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.15 (1H; d, J = 4.8 Hz; CQ-H); 8.31 (1H; s; CQ-H); 7.87 (1H; d, J = 8.0 Hz; Bim-H); 7.48 (1H; d, J = 8.8 Hz; CQ-H); 7.45 (1H; d, J = 4.4 Hz; CQ-H); 7.35~7.31 (1H; t, J = 7.6 Hz; Bim-H); 7.27 (1H; d, J = 8.8 Hz; CQ-H); 7.21~7.16 (1H; t, J = 7.6 Hz; Bim-H); 6.85~6.83 (1H; d, J = 4.4 Hz; Bim-H); 2.72~2.66 (2H; m; $-CH_2-$); 1.34~1.30 (3H; t, J = 7.2 Hz; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 12.34; 21.71; 110.17; 120.00; 120.86; 123.39; 123.70; 124.13; 124.50; 129.63; 129.77; 137.03; 137.34; 141.61; 143.11; 150.70; 152.43; 156.57.

MS: $[M+Na]^+$ found: 330 **$C_{18}H_{14}N_3Cl$ required:** 307

N-(7-Cloroquinolin-4-yl)-2-propylbenzimidazole (243)

The synthetic procedure used was the same as that used to prepare **(241)**, except *n*-butyric acid was used instead of acetic acid, giving a brown powder **(243)** 0.96 g. Yield was 60%.

Melting Point: 192~194 °C

R_f = 0.43 Ethyl acetate : Hexane = 2 : 3

IR: (KBr) ν_{max} 3045 ; 2981 ; 1594 ; 1425 ; 742 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.06 (1H; d, J = 4.4 Hz; CQ-H); 8.22 (1H; s; CQ-H); 7.77 (1H; d, J = 8.0 Hz; Bim-H); 7.39 (1H; d, J = 8.8 Hz; CQ-H); 7.36 (1H; d, J = 4.8 Hz; CQ-H); 7.26~7.22 (1H; t, J = 7.6 Hz; Bim-H); 7.17 (1H; d, J = 8.8 Hz; CQ-H); 7.11~7.07 (1H; t, J = 7.6 Hz; Bim-H); 6.74 (1H; d, J = 8.0 Hz; Bim-H); 2.58~2.53 (2H; t, J = 7.6 Hz; Bim-CH_2-); 1.70~1.65 (2H; q, J = 7.6 Hz; -CH_2-); 0.82~0.78 (3H; t, J = 7.6 Hz; -CH_3).

^{13}C $\delta_{(ppm)}$: 14.19; 21.52; 30.10; 110.21; 119.97; 120.90; 123.39; 123.65; 124.15; 124.52; 129.63; 129.75; 136.95; 137.34; 141.65; 143.15; 150.686; 152.43; 155.47.

MS: $[M+Na]^+$ found: 344 **$C_{19}H_{16}N_3Cl$ required:** 321

N-(7-Chloroquinolin-4-yl)-2-(*iso*-propyl) benzimidazole (244)

The synthetic procedure was used the same as that used to prepare **(241)**, except *iso*-butyric acid was used instead of acetic acid, giving a brown powder **(244)** 0.24 g. Yield was 15%.

Melting Point: 197~198 °C

R_f = 0.45 Ethyl acetate : Hexane = 2 : 3

IR: (KBr) ν_{max} 3041; 2977; 1590; 1421; 746 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.16 (1H; d, J = 4.8 Hz; CQ-H); 8.31 (1H; s; CQ-H) 7.79 (1H; d, J = 8.0 Hz; Bim-H); 7.49~7.46 (2H; m; CQ-H); 7.34~7.31 (1H; t, J = 7.6 Hz; Bim-H); 7.24 (1H; d, J = 9.2 Hz; CQ-H); 7.19~7.15 (1H; t, J = 7.6 Hz; Bim-H); 6.79 (1H; d, J = 8.0 Hz; Bim-H); 2.91~2.84 (1H; q, J = 7.8 Hz; -CH-); 1.38 (3H; d, J = 7.8 Hz; $-CH_3$); 1.25 (3H; d, J = 7.8 Hz; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 21.98; 22.37; 27.44; 110.22; 120.07; 121.06; 123.39; 123.66; 124.33; 124.41; 129.64; 129.82; 136.83; 137.35; 141.73; 143.02; 150.69; 152.45; 160.49.

MS: $[M+Na]^+$ found: 344 **$C_{19}H_{16}N_3Cl$ required:** 321

N-(7-Chloroquinolin-4-yl)-2-butylbenzimidazole (245)

The synthetic procedure used was the same as that used to prepare **(241)**, except *n*-pentanoic acid was used instead of acetic acid, giving a light brown product **(245)** 0.84 g. Yield was 50%.

Melting Point: 172~174 °C

R_f = 0.44 Hexane : Ethyl acetate = 2 : 1

IR: (KBr) υ_{max} 3045; 2963; 1596; 1401; 747 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.15 (1H; d, J = 4.4 Hz; CQ-H); 8.31 (1H; s; CQ-H); 7.86 (1H; d, J = 8 Hz; Bim-H); 7.48 (1H; d, J = 9.2 Hz; CQ-H); 7.44 (1H; d, J = 4.8 Hz; CQ-H); 7.34~7.30 (1H; t, J = 7.6 Hz; Bim-H); 7.27 (1H; d, J = 9.2 Hz; CQ-H); 7.20~7.16 (1H; t, J = 7.6 Hz; Bim-H); 6.82 (1H; d, J = 8 Hz; Bim-H); 2.69~2.65 (2H; t, J = 8 Hz; $-CH_2-$); 1.74~1.70 (2H; t, J = 8 Hz; $-CH_2-$); 1.31~1.26 (2H; q, J = 7.2 Hz; $-CH_2$); 0.82~0.79 (3H; t, J = 7.2 Hz; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 14.04; 22.68; 27.92; 30.17; 110.19; 119.97; 120.88; 123.38; 123.63; 124.15; 124.52; 129.64; 129.73; 136.95; 137.33; 141.66; 143.16; 150.69; 152.42; 155.66.

MS: $[M+Na]^+$ found: 358 **$C_{20}H_{18}N_3Cl$ required:** 335

N-(7-Chloroquinolin-4-yl)-2-(*iso*-butyl) benzimidazole (246)

The synthetic procedure used was the same as that used to prepare **(241)**, except *iso*-pentanoic acid was used instead of acetic acid, giving a off-white powder **(246)** 1g. Yield was 60%.

Melting Point: 176~178 °C

R_f = 0.39 Ethyl acetate : Hexane = 1 : 2

IR: (KBr) ν_{max} 3045; 2958; 1596; 1401; 747 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.07 (1H; d, J = 4.4 Hz; CQ-H); 8.22 (1H; s; CQ-H); 7.78 (1H; d, J = 8.0 Hz; Bim-H); 7.39 (1H; d, J = 8.8 Hz; CQ-H); 7.34 (1H; d, J = 8.8 Hz; CQ-H); 7.27~7.23 (1H; t, J = 7.6 Hz; Bim-H); 7.17 (1H; d, J = 8.8 Hz; CQ-H); 7.11~7.07 (1H; t, J = 7.6 Hz; Bim-H); 6.73 (1H; d, J = 8.0 Hz; Bim-H); 2.56~2.50 (1H; q, J = 6.8 Hz; $-CH_2-$); 2.45~2.40 (1H; q, J = 6.8 Hz; $-CH_2-$); 2.06~2.30 (1H; m; -CH); 0.80~0.76 (6H; t, J = 6.8 Hz; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 22.74; 22.88; 28.29; 37.07; 110.26; 120.00; 120.99; 123.41; 123.62; 124.16; 124.57; 129.64; 129.73; 136.85; 137.34; 141.69; 143.21; 150.69; 152.40; 154.91.

MS: $[M+Na]^+$ found: 358 **$C_{20}H_{18}N_3Cl$ required:** 335

N-(7-Chloroquinolin-4-yl)-2-(*p*-methylbenzyl) benzimidazole (247)

The synthetic procedure used was the same as that used to prepare (241), except *p*-tuloic acid was used instead of acetic acid. The pure (247): a white powder 1.4 g, was obtained by filtration and washing with water several times. Yield was 75%.

Melting point: 238~249 °C

IR: (KBr) δ_{max} 3034; 1557; 1448; 739 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.94 (1H; d, J= 4.8 Hz; CQ-H); 8.20 (1H; s; CQ-H); 7.87 (1H; d, J= 8.4 Hz; Bim-H); 7.45~7.37 (2H; m; CQ-H); 7.40~7.37 (3H; m; Ar-H, CQ-H and Bim-H); 7.19~7.12 (2H; m; Ar-H and Bim-H); 6.95 (2H; d, J= 8 Hz; Ar-H); 6.79 (1H; d, J= 8Hz; Bim-H); 2.22 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 21.76; 110.80; 120.56; 121.16; 123.84; 124.00; 124.22; 124.92; 126.60; 129.07; 129.62; 129.65; 129.77; 137.24; 137.68; 140.75; 142.93; 143.62; 150.66; 152.45; 152.56

MS: $[M+Na]^+$ Found: 392 **$C_{23}H_{16}N_3Cl$ Requires:** 369

N-(7-Chloroquinolin-4-yl)-2-(*m*-methylbenzyl) benzimidazole (248)

The synthetic procedure used was the same as that used to prepare **(241)**, except *m*-tuloic acid was used instead of acetic acid, giving a light yellow powder **(248)** 0.27 g. Yield was 15%.

Melting Point: 170~173 °C

R_f = 0.43 Ethyl acetate : Hexane = 1 : 3

IR: (KBr) υ_{max} 3045; 2925; 1594; 1361; 745 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.90 (1H; d, J = 4.4 Hz; CQ-H); 8.18 (1H; s; CQ-H); 7.86 (1H; d, J = 8.4 Hz; Bim-H); 7.48 (1H; s; Ar-H); 7.40 (1H; d, J = 9.2 Hz; CQ-H); 7.35 (1H; d, J = 9.2 Hz; CQ-H); 7.30~7.26 (1H; t, J = 7.6 Hz; Bim-H); 7.16 (1H; d, J = 4.4 Hz; CQ-H); 7.14~7.10 (1H; t, J = 7.6 Hz; Bim-H); 7.02 (1H; d, J = 6.8 Hz; Ar-H); 6.94~6.90 (2H; d, J = 7.6 Hz; Ar-H); 6.79~6.77 (1H; d, J = 8.4 Hz; Bim-H); 2.17 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 21.70; 110.86; 120.64; 121.15; 123.80; 124.05; 124.38; 124.87; 125.94; 128.70129.35; 129.60; 129.67; 130.12; 131.28; 137.22; 137.66; 139.06; 142.84; 143.56; 150.61; 152.40; 153.55.

MS: $[M+Na]^+$ found: 392 **$C_{23}H_{16}N_3Cl$ required:** 369

N-(7-Chloroquinolin-4-yl)-2-(*o*-methylbenzyl) benzimidazole (249)

The synthetic procedure used was the same as that used to prepare **(241)**, except *o*-tuloic acid was used instead of acetic acid, giving a light yellow powder **(249)** 0.31 g. Yield was 17%.

Melting Point: 190~192 °C

R_f = 0.46 Ethyl acetate : Hexane = 1 : 3

IR: (KBr) υ_{max} 3049; 2929; 1610; 1390; 745 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.90 (1H; d, J = 4.4 Hz; CQ-H); 8.23 (1H; s; CQ-H); 7.98 (1H; d, J = 8.0 Hz; Bim-H); 7.56 (1H; d, J = 8.8 Hz; CQ-H); 7.49 (1H; d, J = 8.8 Hz; CQ-H); 7.43~7.39 (1H; t, J = 7.6 Hz; Bim-H); 7.28~7.25 (1H; t, J = 7.6 Hz; Bim-H); 7.22~7.10 (2H; m; Ar-H); 7.12~7.10 (2H; m; CQ-H and Ar-H); 7.01~6.98 (1H; m, Ar-H); 6.94 (1H; d, J = 8.0 Hz; Bim-H); 2.35 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 20.69; 111.08; 120.82; 120.88; 123.46; 123.89; 124.30; 124.97; 125.93; 129.29; 129.33; 129.60; 130.28; 130.59; 131.17; 136.51; 137.01; 138.35; 141.95; 143.50; 150.46; 152.11; 153.53.

MS: $[M+Na]^+$ found: 392 **$C_{23}H_{16}N_3Cl$ required:** 369

N-(7-Chloroquinolin-4-yl)-2-(*m*-chlorobenzyl) benzimidazole (250)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3-chlorobenzoic acid was used instead of acetic acid, giving a yellow powder **(250)** 0.64 g. Yield was 33%.

Melting point: 184~187 °C

R_f = 0.36 Ethyl acetate : Hexane = 3 : 1

IR (KBr): υ_{max} 3046; 1586; 1450; 740 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.04 (1H; d, J= 4.4 Hz; CQ-H); 8.30 (1H; s; CQ-H); 7.96 (1H; d, J= 8 Hz; Bim-H); 7.74 (1H; s; Ar-H); 7.48~7.47 (2H; m; CQ-H); 7.43~7.38 (1H; t, J= 8.0 Hz; Bim-H); 7.35~7.30 (3H; m; CQ-H, Ar-H, and Bim-H); 7.14~7.10 (2H; m; Ar-H); 6.91 (1H; d, J= 8 Hz; Bim-H).

^{13}C $\delta_{(ppm)}$: 110.98; 120.85; 121.05; 123.62; 124.34; 124.60; 124.83; 126.79; 129.48; 129.74; 129.89; 130.15; 130.56; 131.25; 135.28; 137.43; 137.70; 142.35; 143.42; 150.69; 151.75; 152.43.

MS: $[M+Na]^+$ Found: 412 **$C_{22}H_{13}N_3Cl_2$ Requires:** 389

N-(7-Chloroquinolin-4-yl)-2-(*m*-fluorobenzyl) benzimidazole (251)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3-flourobenzoic acid was used instead of acetic acid, giving a light yellow powder **(251)** 0.58g. Yield was 31%.

Melting point: 181~183 °C

R_f = 0.32 Ethyl acetate : Hexane = 3 : 1

IR: (KBr) υ_{max} 3063; 1590; 1450; 744 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.01 (1H; d, J= 4.4Hz; CQ-H); 8.26 (1H; t, J= 0.8Hz; CQ-H); 7.93 (1H; d, J= 8Hz; Bim-H); 7.44~7.43 (2H; m; CQ-H); 7.44~7.40 (1H; t, J= 7.2Hz; Bim-H); 7.29~7.24 (3H; m; Bim-H, CQ-H and Ar-H); 7.15~7.09 (2H; m; Ar-H); 6.98~6.94 (1H; m; Ar-H); 6.86 (1H; d, J= 8 Hz; Bim-H).

^{13}C $\delta_{(ppm)}$: 110.97; 116.31; 117.54; 120.86; 121.03; 123.66; 124.32; 124.61; 124.69; 124.80; 129.75; 129.88; 130.65; 131.63; 137.44; 137.72; 142.42; 143.42; 150.70; 151.91; 152.44; 161.68.

MS: $[M+Na]^+$ Found: 396 **$C_{22}H_{13}N_3ClF$ Requires:** 373

N-(7-Chloroquinolin-4-yl)-2-naphthylbenzimidazole (252)

The synthetic procedure used was the same as that used to prepare **(241)**, except 2-naphthalenecarboxylic acid was used instead of acetic acid, giving a light yellow powder **(252)** 0.53 g. Yield was 26%.

Melting point: 191~194 °C

R_f = 0.36 Ethyl acetate : Hexane = 2 : 5

IR (KBr): υ_{max} 3051; 1553; 1444; 1451; 740 cm^{-1}

NMR: ($CDCl_3$)

^{1}H $\delta_{(ppm)}$: 9.10 (1H; d, J= 4.8 Hz; CQ-H); 8.31 (1H; s; CQ-H); 8.10 (1H; s; Nap-H); 8.02 (1H; d, J= 8 Hz; Bim-H); 7.77 (1H; d, J= 7.6 Hz; Nap-H); 7.68 (2H; d, J= 8.4 Hz; Nap-H); 7.60 (1H; d, J= 8.8 Hz; Nap-H); 7.51~7.41 (5H; m; CQ-H, Bim-H, and Nap-H); 7.31~7.28 (2H; m; Bim-H and CQ-H); 6.94 (1H; d, J= 8 Hz; Bim-H).

^{13}C $\delta_{(ppm)}$: 110.92; 120.72; 121.20; 123.80; 124.18; 124.49; 124.88; 125.57; 126.81; 127.16; 127.86; 128.08; 128.79; 128.98; 129.61; 129.70; 129.78; 133.16; 134.01; 137.33; 137.81; 142.86; 143.71; 150.69; 152.45; 152.44.

MS: $[M+Na]^+$ Found: 428 **$C_{26}H_{16}N_3Cl$ Requires:** 405

N-(7-Chloroquinolin-4-yl)-2-(*p*-nitrobenzyl) benzimidazole (253)

The synthetic procedure used was the same as that used to prepare **(241)**, except *p*-nitrobenzoic acid was used instead of acetic acid, giving a yellow powder **(253)** 1g. Yield was 50%.

Melting Point: 245~248 °C

R_f = 0.43 Ethyl acetate : Hexane = 2 : 5

IR: (KBr) υ_{max} 3049; 1450; 1361; 807; 738 cm^{-1}

NMR: (CDCl3)

^{1}H $\delta_{(ppm)}$: 9.00 (1H; d, J = 4.8 Hz; CQ-H); 8.24 (1H; s; CQ-H); 8.02 (2H; d, J = 9.2 Hz; Ar-H); 7.92 (1H; d, J = 8.0 Hz; Bim-H); 7.60 (2H; d, J = 8.8 Hz; Ar-H); 7.42 (1H; d, J = 8.8 Hz; CQ-H); 7.39~7.34 (2H; m; CQ-H and Bim-H); 7.25~7.22 (2H; m; CQ-H and Bim-H); 6.86 (1H; d, J = 8.4 Hz; Bim-H).

^{13}C $\delta_{(ppm)}$: 111.14; 120.92; 121.20; 123.47; 124.28; 124.33; 124.74; 125.52; 129.87; 129.94; 130.18; 135,55; 137.73; 137.90; 142.08; 143.49; 148.73; 150.62; 150.78; 152.48.

MS: $[M+Na]^+$ found: 423 **$C_{22}H_{13}N_4O_2Cl$ required:** 400

N-(7-Chloroquinolin-4-yl)-2-(3-methyl-4-nitrobenzyl) benzimidazole (254)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3-methyl-4-nitrobenzoic acid was used instead of acetic acid, giving a light yellow powder **(254)** 1.24 g. Yield was 60%.

Melting Point: 170~174 °C

R_f = 0.43 Ethyl acetate : Hexane = 2 : 5

IR: (KBr) υ_{max} 3091; 1592; 1418; 880; 838; 743 cm^{-1}

NMR: (CDCl3)

^1H $\delta_{(ppm)}$: 9.06 (1H; d, J = 4.4 Hz; CQ-H); 8.30 (1H; s; CQ-H); 7.97 (1H; d, J = 8.0 Hz;Bim-H); 7.79 (1H; s; Ar-H); 7.73 (1H; d, J = 8.4 Hz; Ar-H); 7.49 (1H; d, J = 9.2 Hz; CQ-H); 7.46~7.40 (2H; m; Bim-H and CQ-H); 7.32 (1H; d, J = 4.4 Hz; CQ-H); 7.31~7.27 (1H; t, J = 8.0 Hz; Bim-H); 7.16 (1H; d, J = 8.0 Hz; Ar-H); 6.92 (1H; d, J = 8.4 Hz; Bim-H); 2.51 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 20.86; 111.01; 120.98; 121.05; 123.52; 124.38; 124.62; 125.30; 125.34; 126.81; 129.86; 130.11; 133.70; 133.89; 134.82; 137.61; 137.85; 142.13; 143.41; 149.82; 150.72; 150.73; 152.47.

MS: $[M+Na]^+$ found: 437 **$C_{23}H_{15}N_4O_2Cl$ required:** 414

N-(7-Chloroquinolin-4-yl)-2-(4-methyl-3, 5-dinitrobenzyl) benzimidazole (255)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3,5-nitro-*p*-tuloic acid was used instead of acetic acid, giving a gray powder **(255)** 1.38 g. Yield was 60%.

Melting Point: 178~182 °C

R_f = 0.47 Ethyl acetate : Hexane = 1 : 2

IR: (KBr) ν_{max} 3049; 1592; 1418; 1199; 838; 743 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.89 (1H; d, J = 4.4 Hz; CQ-H); 8.49 (1H; s; Ar-H); 8.21 (1H; s; Ar-H); 8.10 (1H; s; CQ-H); 7.88 (1H; d, J = 8.4 Hz; Bim-H); 7.44 (1H; d, J = 8.8 Hz; CQ-H); 7.40~734 (2H; m; Bim-H and CQ-H); 7.28~7.25 (1H; t, J = 8 Hz; Bim-H); 7.16 (1H; d, J = 4.8 Hz; CQ-H); 6.92 (1H; d, J = 8.0 Hz; on Bim-H); 2.47 (3H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 18.16; 111.35; 120.74; 121.12; 121.32; 123.08; 123.90; 124.82; 125.79; 128.87; 130.02; 130.13; 134.50; 136.65; 137.69; 140.58; 143.07; 145.58; 148.74; 150.61; 152.21 .

MS: [M / Na^+] found: 482 **$C_{23}H_{14}N_5O_4Cl$ required:** 459

N-(7-Chlroquinolin-4-yl)-2-((2-phenyl)-butyl) benzimidazole (256)

The synthetic procedure used was the same as that used to prepare **(241)**, except 2-phenylbutyric acid was used instead of acetic acid, giving a light yellow powder **(256)** 0.31 g, yield was 15%.

Melting Point: 195~197 °C

R_f= 0.58 Hexane : Ethyl acetate = 3:1

IR: (KBr) υ_{max} 3033; 2963; 1596; 1418; 875; 743 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.75 (1H; d, J = 4.4 Hz; CQ-H); 8.21 (1H; s; CQ-H); 7.88 (1H; d, J = 8 Hz; Bim-H); 7.40 (1H; d, J = 9.2 Hz; CQ-H); 7.26~7.22 (1H; t, J = 7.6 Hz; Bim-H); 7.16 (1H; d, J = 9.2 Hz; CQ-H); 7.08~7.04 (4H; m; Bim-H and Ar-H); 6.85~6.83 (2H; m; Ar-H); 6.66 (1H; d, J = 8 Hz; Bim-H); 6.00 (1H; d, J = 4.4 Hz; CQ-H); 3.37~3.47 (1H; t, J = 7.6 Hz; Ph-CH-); 2.42~2.41 (1H; m; $-CH_2-$); 1.98~1.93 (1H; m; $-CH_2-$); 0.78~0.75 (3H; t, J = 7.2 ; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 12.97; 29.44; 47.22; 110.16; 120.36; 121.87; 123.34; 123.82; 124.27; 124.36; 127.42; 128.18; 128.98; 129.64; 129.80; 137.06; 137.20; 141.12; 141.70; 143.12; 150.48; 152.10; 156.53

MS: $[M+Na]^+$ found: 434 **$C_{26}H_{22}N_3Cl$ required:** 411

N-(7-Chloroquinolin-4-yl)-2-(*o,o*-difluorobenzyl) benzimidazole (257)

The synthetic procedure used was the same as that used to prepare **(241)**, except 2,6-difluorobenzoic acid was used instead of acetic acid, giving a bright yellow powder **(257)** 0.53 g. Yield was 27%.

Melting point: 184~188 °C

R_f = 0.65 Ethyl acetate : Hexane = 1 : 1

IR: (KBr) υ_{max} 3051; 1553; 1302; 740 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.97 (1H; d, J= 4.4Hz; CQ-H); 8.22 (1H; s; CQ-H); 8.02 (1H; d, J= 8 Hz; Bim-H); 7.48~7.24 (3H; m; CQ-H and Bim-H); 7.35~7.29 (3H; m; on CQ-H, Ar-H, and Bim-H); 7.11 (1H; d, J= 8 Hz; Bim-H); 6.87~6.83 (2H; d, J= 8 Hz; Ar-H).

^{13}C $\delta_{(ppm)}$: 108.40; 110.01; 112.06; 112.31; 120.27; 121.21; 123.52; 124.07; 124.88; 129.37; 133.07; 136.71; 137.11; 141.17; 143.23; 143.66; 150.44; 152.06; 159.95; 162.47.

MS: $[M+Na]^+$ Found: 414 **$C_{22}H_{12}N_3ClF_2$ Requires:** 391

N-(7-Chloroquinolin-4-yl)-2-(*m,m*-dimethylbenzyl) benzimidazole (258)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3,5-dimethylbenzoic acid was used instead of acetic acid, giving a white powder **(258)** 0.61 g. Yield was 32%.

Melting point: 172~176 °C

R_f= 0.36 Ethyl acetate : Hexane = 2 : 7

IR: (KBr) υ_{max} 3033; 2917; 1591; 1451; 738 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.01 (1H; d, J= 4.4 Hz; CQ-H); 8.27 (1H; s; CQ-H); 7.95 (1H; d, J= 8 Hz; Bim-H); 7.49 (2H; d, J= 8.8 Hz; CQ-H); 7.48 (1H; d, J= 9.2 Hz; CQ-H); 7.39~7.35 (1H; t, J= 7.6; Bim-H); 7.27 (1H; d; J= 4.8Hz; CQ-H); 7.23~7.19 (1H; t, J= 7.6Hz; Bim-H); 7.09 (2H; s; Ar-H); 6.95 (1H; s; Ar-H); 6.87 (1H; d, J= 8 Hz; Bim-H); 2.13 (6H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 21.55; 110.84; 120.60; 121.13; 123.80; 123.98; 124.24; 124.90; 126.96; 129.30; 129.56; 129.59; 132.20; 137.15; 137.63; 138.61; 142.90; 143.57; 150.58; 152.36; 153.72.

MS: $[M+Na]^+$ Found: 406 **$C_{24}H_{18}N_3Cl$ Requires:** 383

N-(7-Chloroquinolin-4yl)-2-thiophenylbenzimidazole (259)

The synthetic procedure used was the same as that used to prepare **(241)**, except 2-thiophenecarboxylic acid was used instead of acetic acid, giving a brown powder **(259)** 0.14 g. Yield was 8%.

Melting point: 207~209 °C

R_f= 0.4 Ethyl acetate : Hexane = 1 : 1

IR: (KBr) υ_{max} 3046; 1590; 1456; 736 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.07 (1H; d, J= 4.4 Hz; CQ-H); 8.23 (1H; s; CQ-H); 7.84 (1H; d, J= 8.4 Hz; Bim-H); 7.43 (1H; d J= 4.4 Hz; on CQ-H); 7.36 (1H; d, J= 8.8 Hz; CQ-H);

7.31~7.24 (3H; m; Bim-H, CQ, and Thi-H); 7.16~7.12 (1H; t, J= 8 Hz; Bim-H); 6.76~6.72 (2H; m; Bim-H and Thi-H); 6.61 (1H; d, J= 3.6 Hz; Thi-H).

^{13}C $\delta_{(ppm)}$: 110.37; 120.36; 121.65; 124.19; 124.30; 124.48; 124.58; 128.17; 128.58; 129.38; 129.64; 129.98; 131.92; 137.48; 137.83; 142.21; 143.45; 147.84; 150.77; 152.60

MS: $[M+Na]^+$ Found: 384 **$C_{20}H_{12}N_3ClS$ Requires:** 361

N-(7-Chloroquinolin-4-yl)-2-(*p*-(*t*-butyl) benzyl) benzimidaz-ole (260)

The synthetic procedure used was the same as that used to prepare **(241),** except *p*-butylbenzoic acid was used instead of acetic acid, giving a white powder **(260)** 0.88 g. Yield was 43%.

Melting point: 202~204 °C

R_f = 0.40 Ethyl acetate : Hexane = 2 : 7

IR: (KBr) υ_{max} 3057; 2962; 1591; 1451; 743 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.03 (1H; d, J= 4.8 Hz; CQ-H); 8.31 (1H; s; CQ-H); 7.96 (1H; d, J= 8 Hz; Bim-H); 7.55 (1H; d, J= 8.8 Hz; CQ-H); 7.50 (1H; d, J= 8.8 Hz; CQ-H); 7.42~7.22 (7H; m; Bim-H, CQ-H, and Ar-H); 6.86 (1H; d, J= 8 Hz; Bim-H); 1.28 (9H; d, J= 2.8 Hz; -*t*-butyl).

^{13}C $\delta_{(ppm)}$: 31.45; 35.17; 11.0.80; 120.55; 121.30; 123.96; 124.19; 124.95; 126.03; 126.47; 128.87; 129.62; 129.69; 137.25; 137.77; 140.74; 143.01; 143.63; 150.65; 152.53; 153.45; 153.81

MS: $[M+Na]^+$ Found: 434 **$C_{26}H_{22}N_3Cl$ Requires:** 411

N-(7-Chloroquinolin-4yl)-2-(*m*-chlorobenzyl) benzimidazole (261)

The synthetic procedure used was the same as that used to prepare **(241)**, except 3-chlorobenzoic acid was used instead of acetic acid, giving a yellow powder **(261)** 0.64 g. Yield was 33%.

Melting point: 167~169 °C

R_f = 0.39 Ethyl acetate : Hexane = 3 : 1

IR (KBr): υ_{max} 3046; 1586; 1450; 740 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.09 (1H; d, J= 4.4 Hz; CQ-H); 8.22 (1H; s; CQ-H); 7.84~7.82 (1H; d, J= 8 Hz; Bim-H); 7.50~7.49 (1H; d, J= 4.4 Hz; CQ-H); 7.40~7.37 (1H; d,d, J = 8.8, 2 Hz; CQ-H); 7.32~7.29 (1H; t, J= 8.0 Hz; Bim-H); 7.20~7.16 (3H; m; CQ-H and Bim-H); 6.77 (1H; d, J= 8 Hz; Bim-H); 4.67 (1H; d, J = 12.8 Hz; $-CH_2-$); 4.44 (1H; d, J = 12.4 Hz; $-CH_2-$).

^{13}C $\delta_{(ppm)}$: 19.76; 36.76; 110.84; 120.97; 121.14; 123.79; 124.38; 125.29; 129.72; 129.92; 137.21; 137.49; 140.58; 142.66; 149.60; 150.68; 152.42.

MS: $[M+Na]^+$ Found: 351 **$C_{17}H_{11}N_3Cl_2$ Requires**: 328

N-(7-Chloroquinolin-4-yl)-2,3-dimethylbenzimidazolium iodide (262)

A solution of 0.3g of **(241)** (1mmol) in 2g iodomethane was refluxed for one hour with stirring. A violet-reddish solid precipitated. The reaction suspension was then kept refluxing for other 1.5 hours. The solid was collected by filtration, washed with ethanol and dried under vacuum; giving a violet-reddish solid **(262)** 0.41 g. Yield was 95%.

Melting point: 253~254 °C

IR: (KBr) υ_{max} 3455 ; 3037 ; 1617 ; 1471 ; 826 ; 751 cm^{-1}

NMR: (DMSO-d_6)

^{1}H $\delta_{(ppm)}$: 9.30 (1H; d, J = 4.4 Hz; CQ-H), 8.41 (1H; s; CQ-H), 8.20 (1H; d, J = 8.4 Hz; Bim-H), 7.99 (1H; d, J = 4.4 Hz; CQ-H), 7.77~7.72 (3H; m; CQ-H and Bim-H), 7.56~7.54 (1H; t, J = 7.6 Hz; Bim-H), 7.30 (1H; d, J = 8Hz; Bim-H), 4.16 (3H; s; N-CH_3), 2.69 (3H; s; -CH_3).

^{13}C $\delta_{(ppm)}$: 11.79; 32.62; 113.05; 113.68; 122.15; 122.68; 125.05; 126.99; 127.32; 128.91; 129.73; 132.11; 132.23; 136.32; 137.23; 149.98; 153.43; 153.62.

MS: $[M]^+$ Found: 308 **$[C_{18}H_{15}N_3Cl+I^-]$Requires:** 436

$[C_{18}H_{15}N_3Cl]^+$ Requires: 308

N-(7-Chloroquinolin-4-yl)-3-methyl-2-(2,6-difluorobenz-1-yl) benzimidazolium iodide (263)

The preparation used was the same as that used for the preparation of **(262)**, except **(257)** was instead of **(241)**, giving a red solid **(263)** 0.48 g. Yield was 90%.

Melting point: 222~224 °C

IR: (KBr) υ_{max} 3435; 3029; 1607; 1414; 784 cm^{-1}

NMR : (DMSO-d_6)

^{1}H $\delta_{(ppm)}$: 9.15 (1H; d, J = 4.4 Hz; CQ-H), 8.40 (1H; d, J = 8.4 Hz; Bim-H), 8.35 (1H; s; CQ-H), 7.95~7.70 (6H; m; CQ-H, Bim-H and Ar-H), 7.52 (2H; d, J = 8.8 Hz; Ar-H), 7.28~7.23 (1H; t, J = 8.8 Hz; Bim-H); 4.14 (3H, s; -CH_3).

^{13}C $\delta_{(ppm)}$: 34.42; 113.38; 113.60; 113.80; 114.04; 115.01; 121.44; 122.01; 124.72; 128.36; 128.91; 129.01; 129.80; 133.12; 133.16; 136.36; 137.13; 138.78; 141.62; 149.70; 153.01.

MS: $[M]^+$ Found: 406 **$[C_{23}H_{15}N_3ClF_2+I^-]$ Requires:** 534

$[C_{23}H_{15}N_3ClF_2]^+$ Requires: 406

N-(-7-Chloroquinolin-4-yl)-3-methyl-2-(3,5-dimethylbenzyl) benzimidazolium iodide (264)

The preparation used was the same as that used for the preparation of **(262)**, except **(258)** was used instead of **(241)**, giving a red solid **(264)** 0.47 g. Yield was 90%.

Melting point: 257~258 °C

IR (KBr): υ_{max} 3439; 3016; 1600; 1464; 863; 756 cm^{-1}

NMR: (DMSO-d_6)

^1H $\delta_{(ppm)}$: 9.18 (1H; d, J = 4.8 Hz; on CQ-H), 8.36 (1H; d, J = 8.4Hz; Bim-H), 8.30 (1H; s; CQ-H), 7.96~7.94 (2H; m; CQ-H), 7.87~7.84 (1H; t, J = 7.6 Hz; Bim-H), 7.78~7.77 (1H; d, J = 9.2 Hz; CQ-H), 7.68~7.64 (1H; t, J = 7.6 Hz; Bim-H), 7.40 (1H; d, J = 8.4 Hz; Bim-H), 7.31 (2H; s; Ar-H), 7.22 (1H; s; Ar-H), 3.36 (3H; s; N-CH_3), 2.18 (6H; s; -CH_3).

^{13}C $\delta_{(ppm)}$: 21.03; 33.75; 113.47; 114.46; 120.96; 122.59; 122.75; 125.06; 127.62; 128.09; 128.15; 128.78; 129.72; 132.53; 132.80; 134.79; 136.32; 137.80; 138.87; 149.58; 151.45; 153.10.

MS: $[M]^+$ Found: 398 **$[C_{25}H_{21}N_3Cl+I^-]$ Requires:** 526

$[C_{25}H_{21}N_3Cl]^+$ Requires: 398

N-((1-(7-Chloroquinolin-4-yl) bezimidazol-2-yl) methyl)-2-methyl-propan-2-amine (267)

To a mixture of 1 ml of TEA in 15 ml of ethanol was added 0.4 g (1 mmol) of **(261)** and 0.2 g of tetra-butylamine (99%). This solution was refluxed overnight under N_2. The solvent was removed under vacuum. A brown-reddish sticky liquid was left and to this was added 30 ml DCM. This solution was washed with water several times. The DCM was then removed under vacuum. The orange solid product **(267)** (0.25 g)

was obtained by using a silica gel column with ethyl acetate and hexane as eluants. Yield was 70%.

Melting Point: 174~175 °C

R_f = 0.39 Ethyl acetate : Hexane = 1 : 1

IR: (KBr) ν_{max} 3045; 2963; 1596; 1464; 1186; 739 cm^{-1}

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 9.02 (1H; d, J = 4.4 Hz; CQ-H); 8.19 (1H; s; CQ-H); 7.76 (1H; d, J = 8.0 Hz; Bim-H); 7.48 (1H; d, J = 4.4 Hz; CQ-H); 7.35 (1H; d, J = 9.2 Hz; CQ-H); 7.25~7.21 (2H; m; Bim-H and CQ-H); 7.11~7.07 (1H; t, J = 7.6 Hz; Bim-H); 6.75 (1H; d, J = 8.0 Hz; Bim-H); 3.75~3.64 (2H; q, J = 9.6 Hz; $-CH_2-$); 0.81 (9H; s; $-CH_3$).

^{13}C $\delta_{(ppm)}$: 28.91; 40.24; 50.93; 110.43; 120.21; 120.85; 123.44; 123.98; 124.00; 124.88; 129.36; 129.45; 137.00; 137.06; 141.50; 142.85; 150.53; 152.27; 154.36.

MS: $[M + H^+]$ found: 365 **$C_{21}H_{21}N_4Cl$ required:** 364

N-((1-(7-Cloroquinolin-4-yl) bezimidazol-2-yl) methyl) benzene-1,2-diamine (268)

The synthetic procedure was the same as that used to prepare **(267)**, except *o*-phenylenediamine was used instead of *t*-butylamine. The brown product **(268)** (0.14 g) was obtained in 35% yield.

Melting Point: 189~193 °C

R_f = 0.61 DCM : Methanol= 20 : 1

IR: (KBr) ν_{max} 3654; 3098; 1530; 1357; 776 cm^{-1}.

NMR: ($CDCl_3$)

^1H $\delta_{(ppm)}$: 8.94 (1H; d, J = 4.8 Hz; CQ-H); 8.16 (1H; s; CQ-H); 7.77 (1H; d, J = 8.0

Hz; Bim-H); 7.16~7.19 (3H; m; Bim-H and CQ-H); 7.12~7.08 (1H; t, J = 7.6 Hz; Bim-H); 7.01 (1H; d, J = 8.8 Hz; CQ-H); 6.72 (1H; d, J = 8.0 Hz; Bim-H); 6.59~6.50 (2H; m; Ar-H); 6.45~6.39 (2H; m; Ar-H); 4.31 (2H; s; -CH_2-).

^{13}C $\delta_{(ppm)}$: 42.53; 110.49; 113.49; 117.00; 117.09; 120.34; 120.52; 120.61; 120.70; 123.74; 123.91; 124.31; 129.45; 129.53; 135.55; 136.16; 137.15; 137.26; 141.30; 142.76; 150.46; 152.42; 152.87.

MS: $[M+H]^+$ found: 400 **$C_{23}H_{18}N_5Cl$ required:** 399

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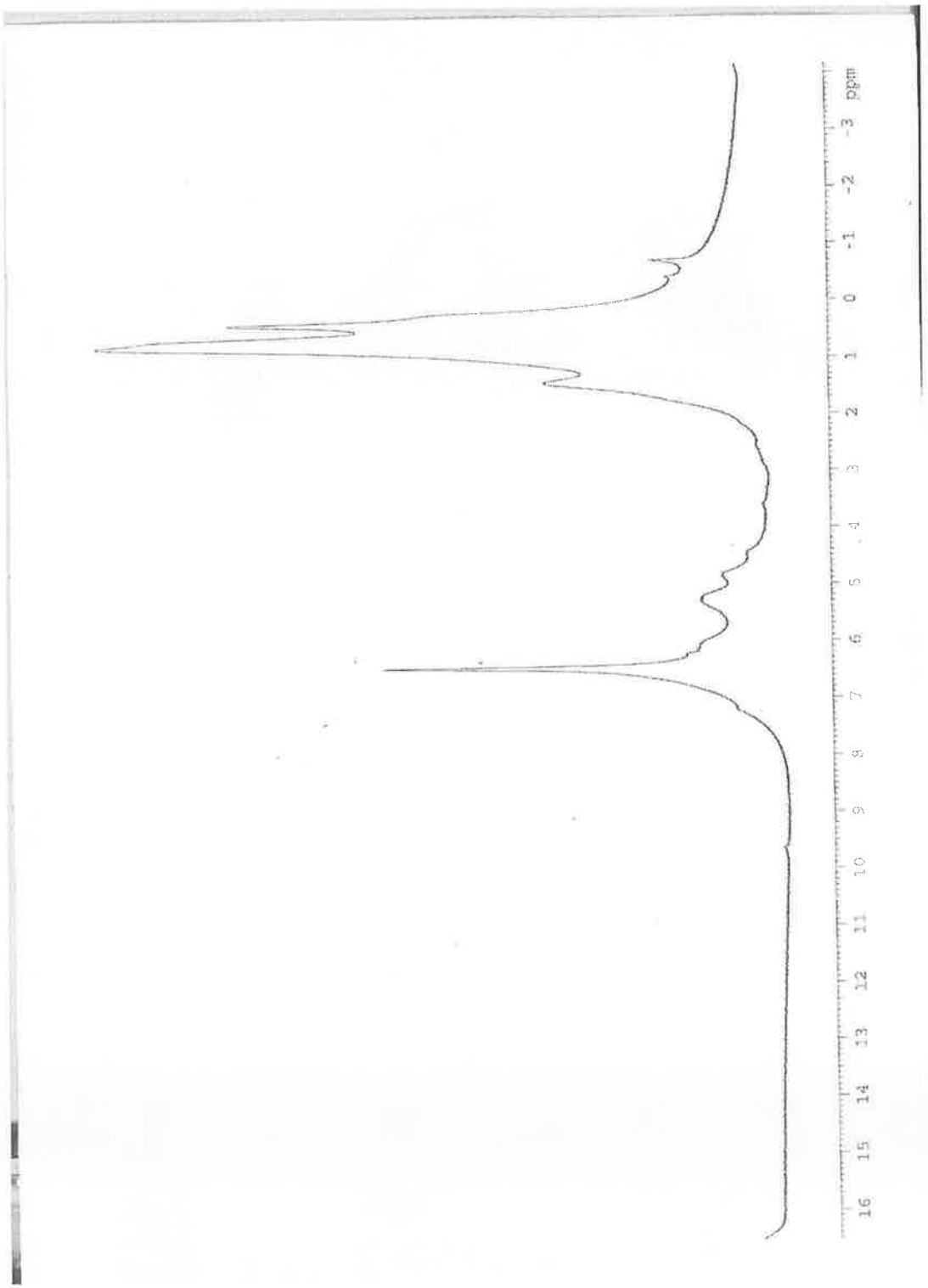
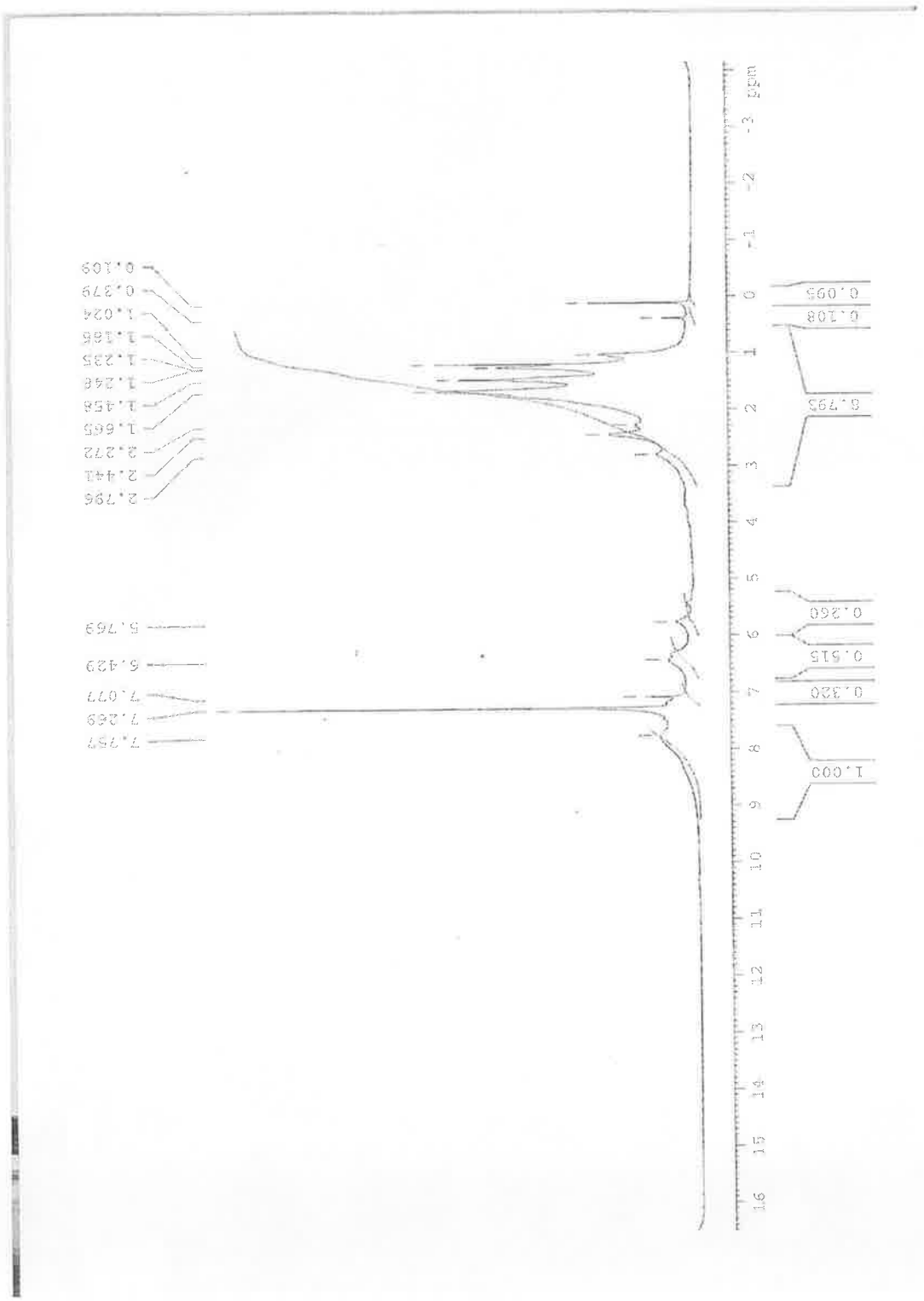
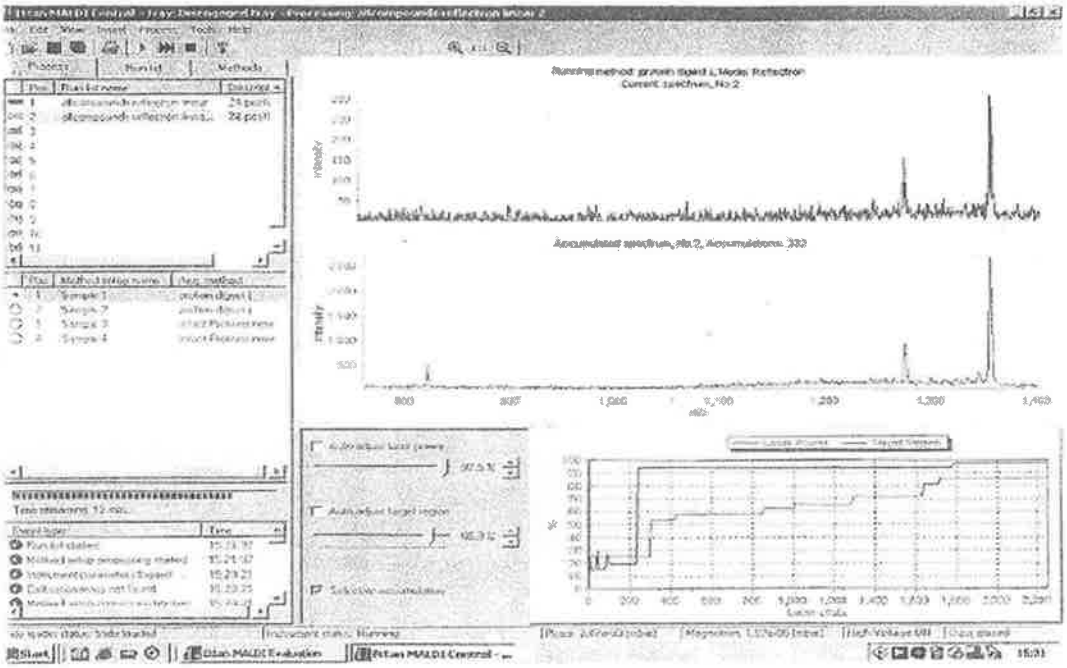
Appendix:

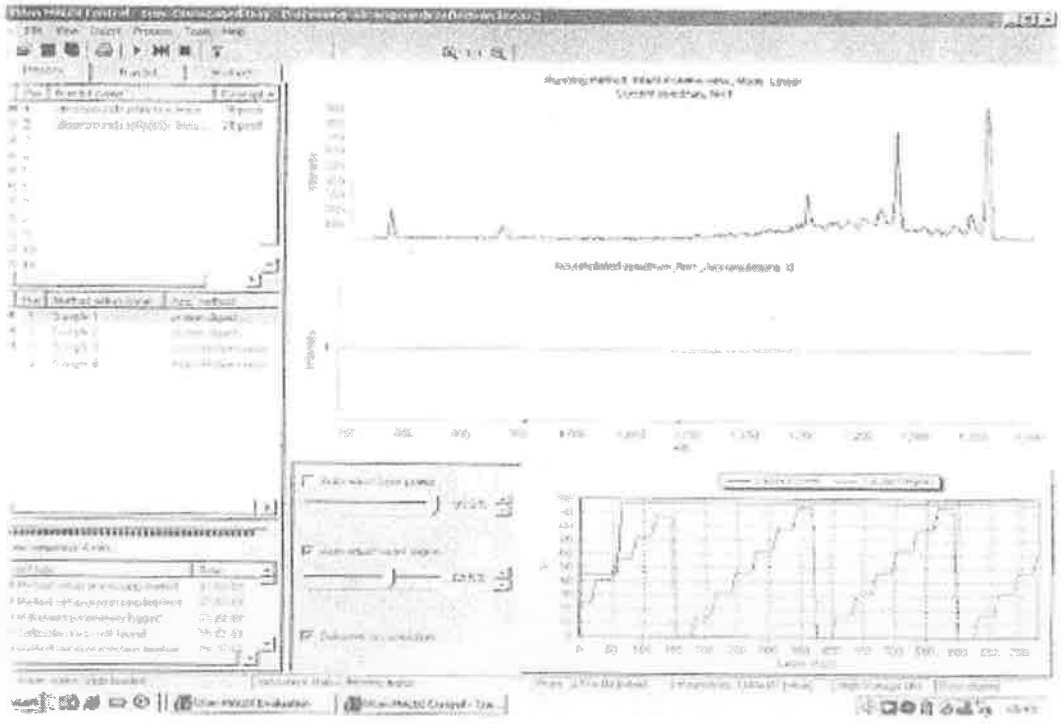


Appendix 1 *The* ^{1}H *NMR of Pc* ***(164)*** *in Benzene-d6, carried out at r. tem.*

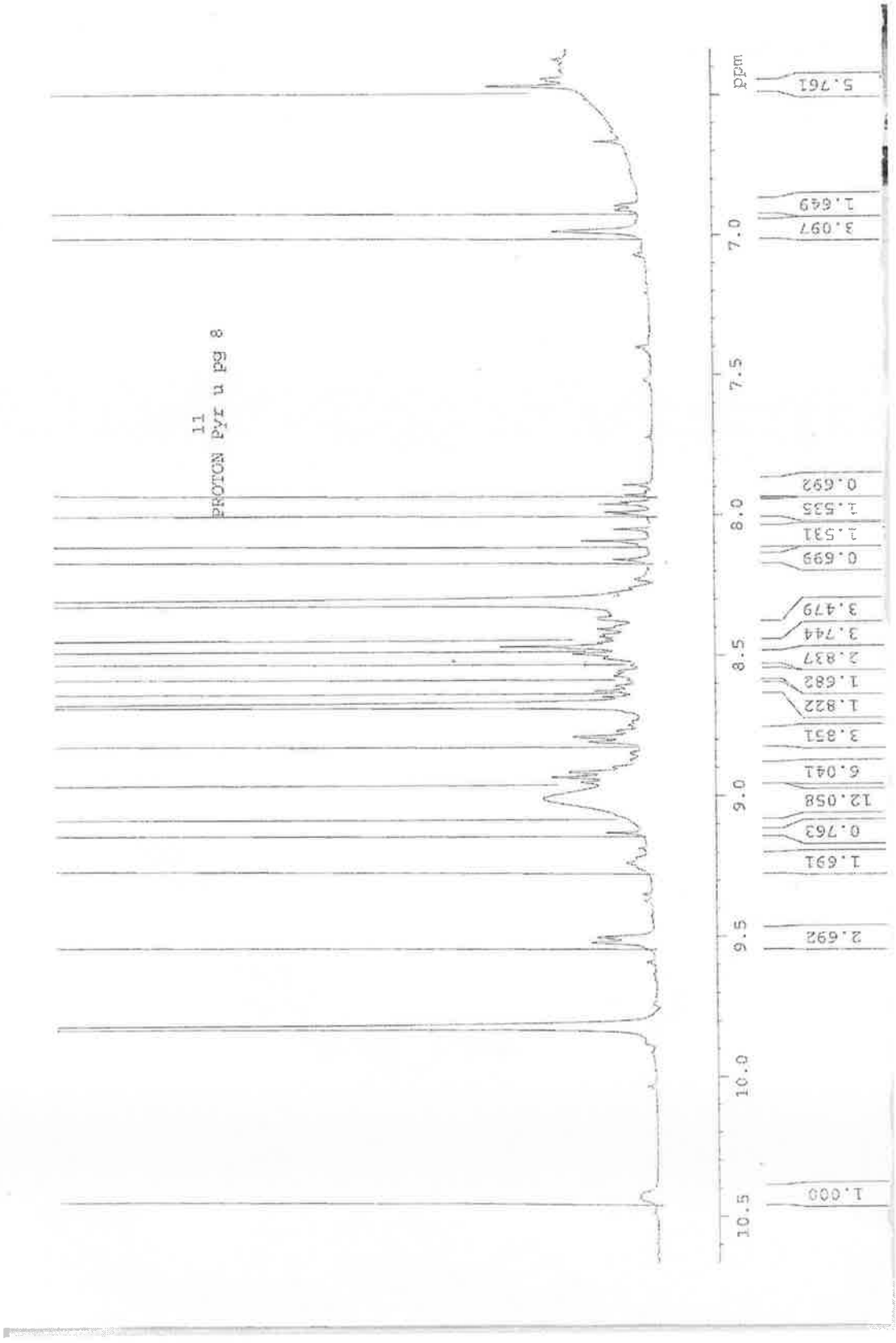


Appendix 2 *The* ^{1}H *NMR of Pc* ***(164)*** *in Benzene-d6, carried out at60 ºC.*

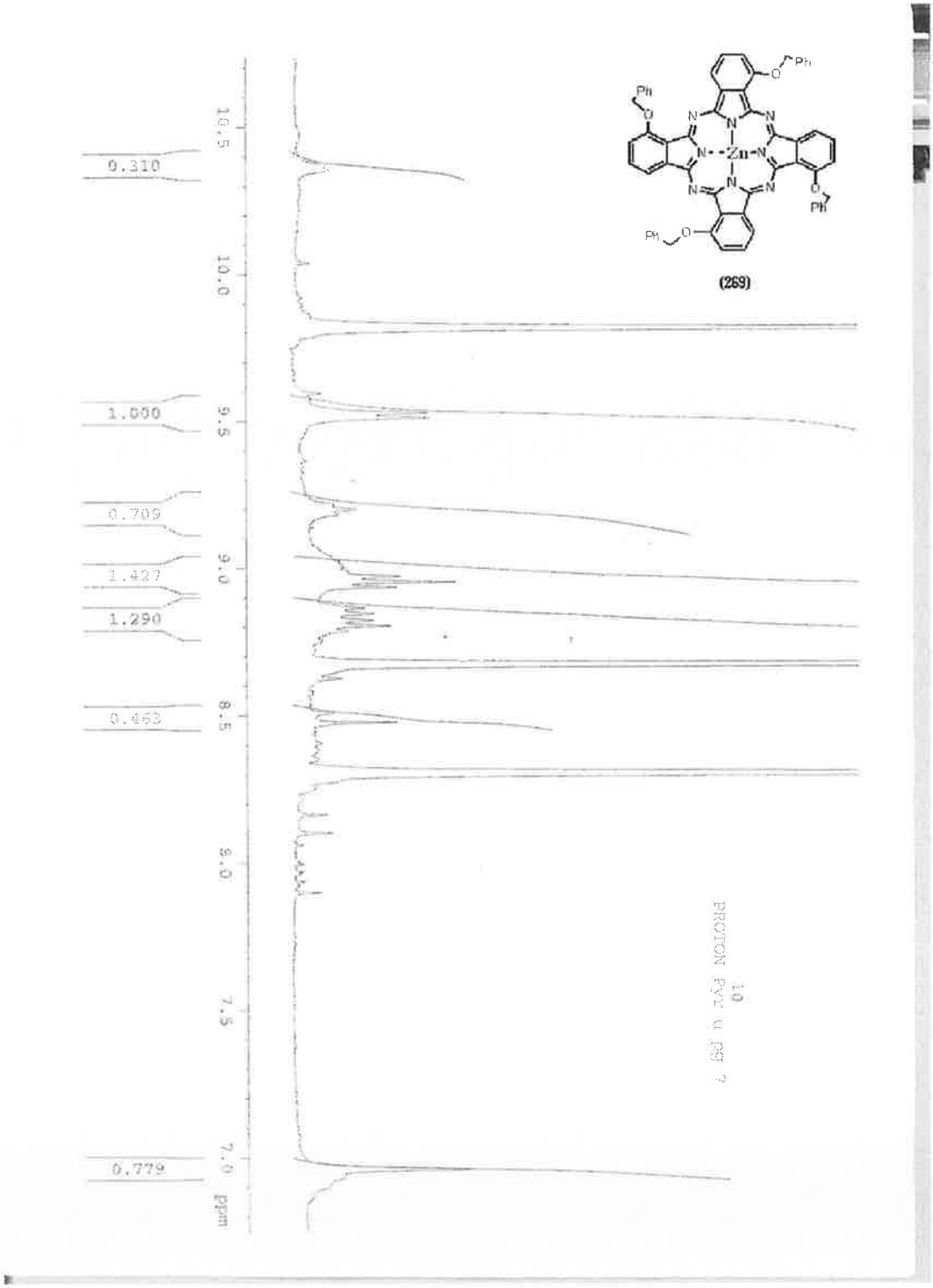




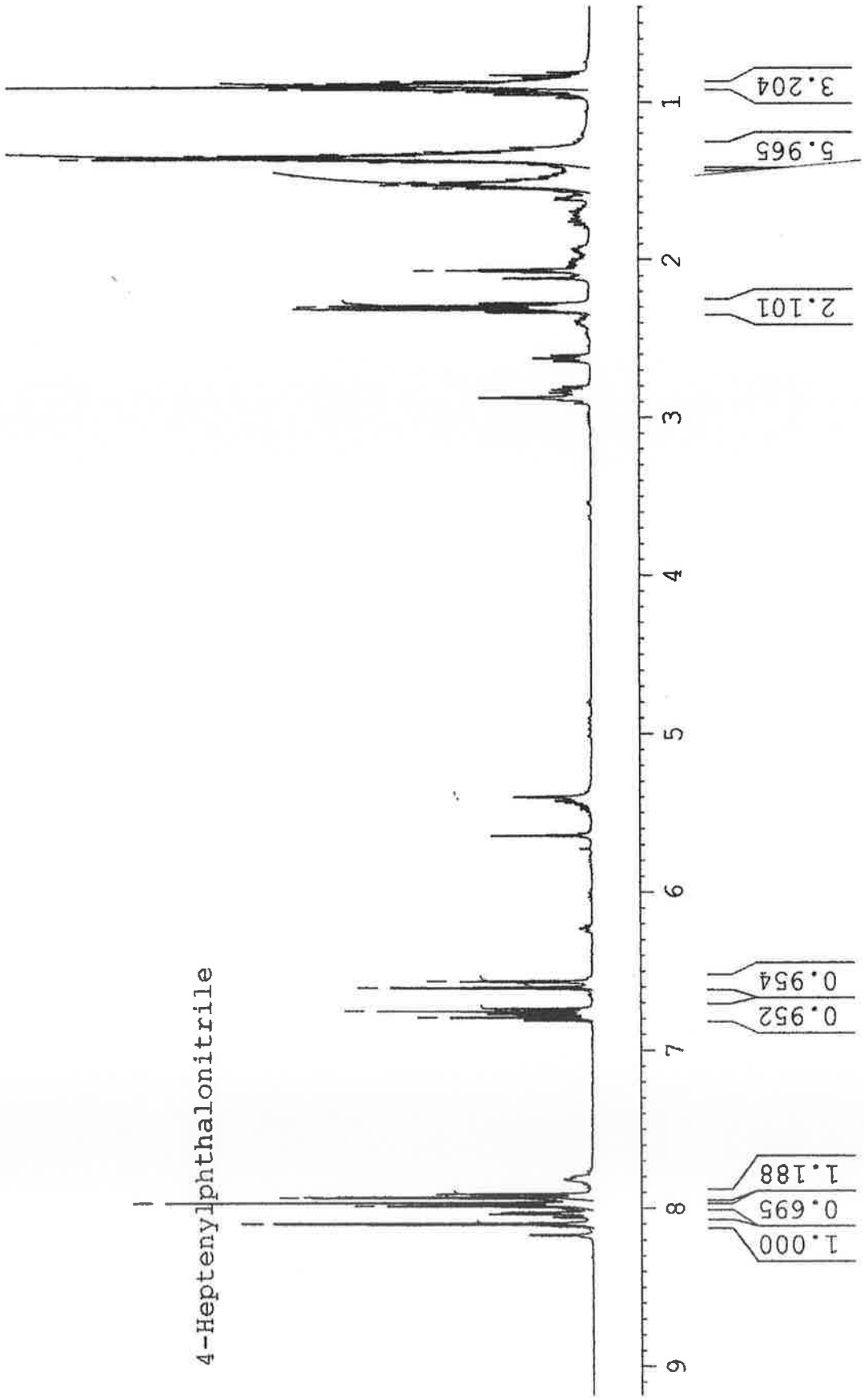
Appendix 3 *The MALDI spectra of* ***Nc (177)****, which was run by National University of Ireland,. Maynooth.*



Appendix 4 *The* ^{1}H *NMR of Pc* ***(212)***.



Appendix 5 *The* ^{1}H *NMR of Pc* ***(269)***.



Appendix 6 *The* ^{1}H *NMR spectrum of* ***(163)***.

Display Report

Analysis Info

FileName	D:\Data\yang\dibutnap.d\Analysis.yep		
Acquisition Date	Thursday, 11/20/03, 14:19:09 UTC	Print Date	Thursday, 20.November.2003, 14:19
Method	XO Defaultms	Operator	Stephen Carey
Comment	sample 6,7-dibutyl-naphthalonnitirle	Instrument	Esquire-LC 00050

Acquisition Parameter

Ion Source Type	ESI	Ion Polarity	Positive	Alternating Ion Polarity	
Mass Range Mode	Std/Normal	Scan Begin	100.00 m/z	Scan End	400.00 m/z
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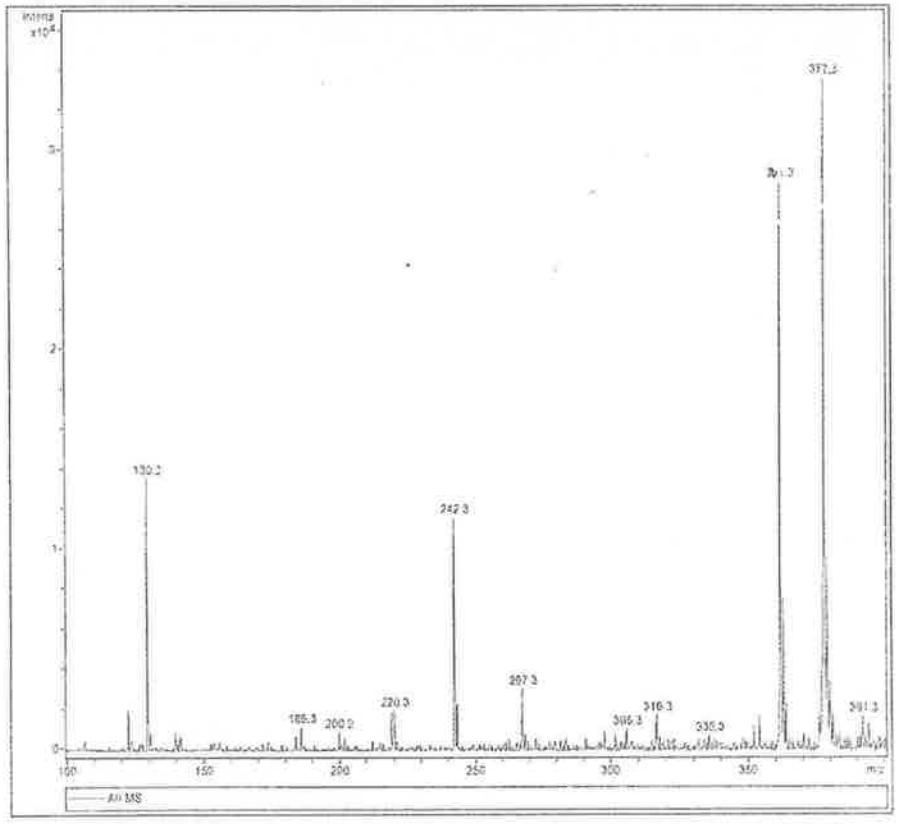
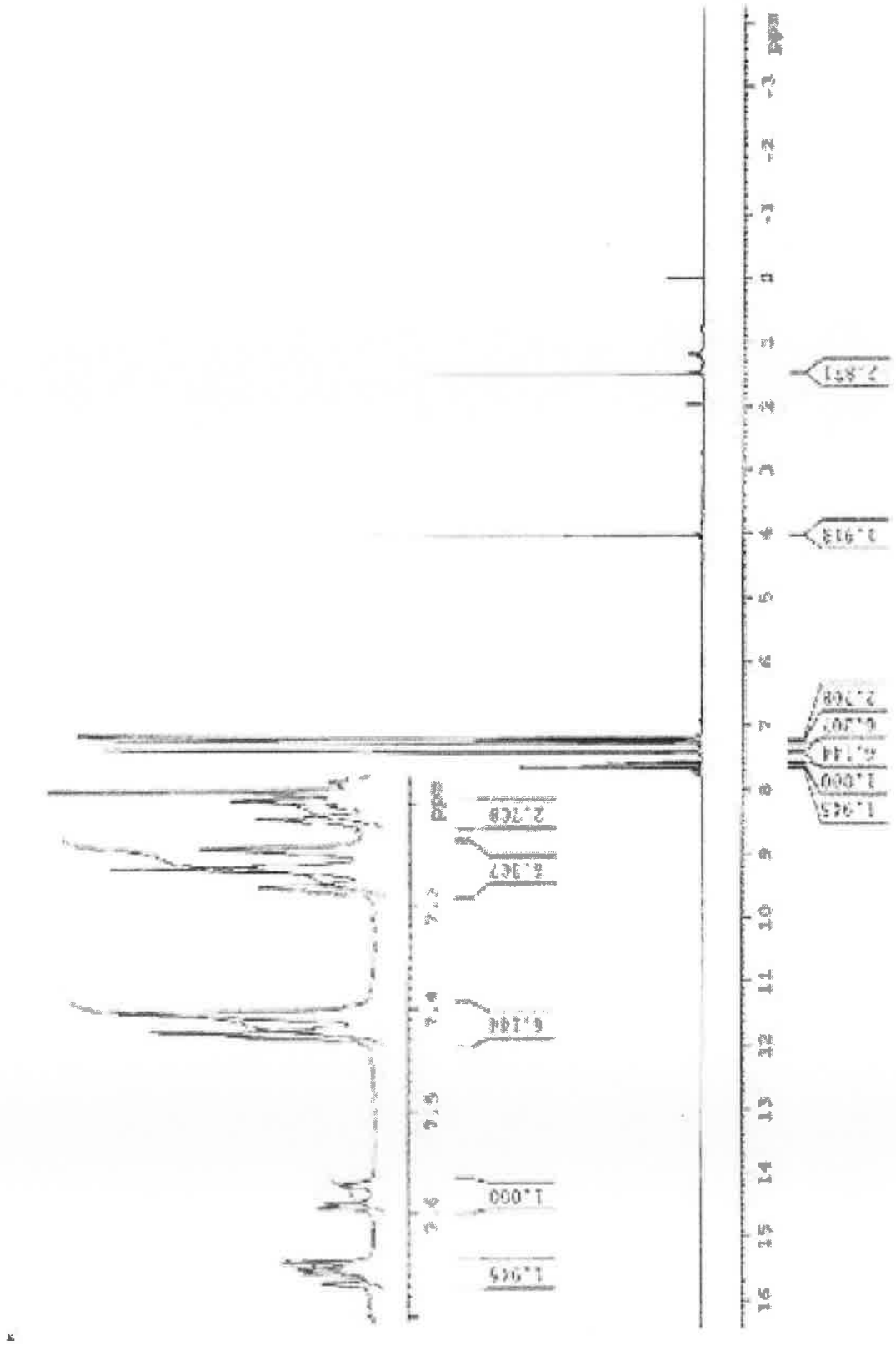
Accumulation Time	11616 µs	Averages	30 Spectra	Auto MS/MS	Off



Bruker Daltonics DataAnalysis 2.0

Appendix 7 *The mass spectrum of* ***(175)****.*



Appendix 8 *The* ^{1}H *NMR spectrum of* ***(210)***.