SYNTHESIS AND CHARACTERIZATION OF *MESO*-SUBSTITUTED PORPHYRIN

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For the love one and his prophet. Alhamdulillah…

To my beloved Parents…

To my beloved wife …

Thank you for everything…

and to my cherish buddies…

Thanks for being my supporters

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ABSTRACT

Porphyrins and their analogs are a class of chemically and biologically important compounds that have found a variety of applications in different fields such as catalysis and medicine, especially for photodynamic cancer therapy (PDT). The physical, chemical, and biological dependence of the peripheral substituents of porphyrins on their properties has prompted great effort towards the synthesis of new porphyrins with different electronic, steric, and conformational environments. Significant improvement has been made to develop various synthetic methodologies in preparing the functionalised porphyrins. However, the challenges still remain especially to prepare asymmetrical type of porphyrin system which is useful for numerous applications. In this study, we have utilised three synthetic methods; condensation, bromination and Suzuki Cross Coupling reactions to synthesis porphyrins with different *meso*-substituents; A_2-, AB-, A_2B-, as well as ABC- type porphyrins. The synthetic strategy is developed based on dipyrromethane as the main precursor to prepare di-substituted porphyrin *via* Lindsey method, and followed by bromination reaction to obtain tri-substituted porphyrin. Eventually, the reaction was prolonged by using Suzuki- Cross coupling reaction to attain tri-substituted porphyrin. All of the compounds were characterized using Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon Magic Angle Spin Nuclear Magnetic Resonance (^{13}C-NMR), ultraviolet (UV) and infrared (IR) spectroscopies.

ABSTARK

Porfirin dan analognya adalah kelas bahan yang mempunyai kepentingan kimia dan biologi serta mempunyai pelbagai aplikasi dalam bidang seperti pemangkinan dan perubatan, khususnya dalam Terapi Kanser Fotodinamik (PDT). Pergantungan gantian peripheral pada porfirin secara kimia, fizik dan biologi terhadap sifat-sifatnya telah mendorong usaha untuk mensintesis porfirin baru dengan persekitaran elektronik, sterik, dan conformational yang berbeza. Penambahbaikan yang perlu telah dibuat untuk menghasilkan pelbagai kaedah sintetik dalam penyediaan porfirin dengan kumpulan berfungsi. Walau bagaimanapun, cabaran masih ada terutamanya dalam menyediakan sistem porfirin yang asimetri dan berguna untuk pelbagai aplikasi. Dalam kajian ini, tiga kaedah sintetik iaitu kondensasi, bromination dan tindak balas Suzuki Cross Coupling untuk telah digunakan mensintesis porfirin yang mempunyai *meso*-gantian yang berbeza; A_2-, AB-, A_2B, dan juga porfirin jenis ABC-. Strategi sintetik ini dihasilkan dengan menggunakan dipirometana sebagai reaktan utama dalam penyediaan porfirin dengan dua-pengganti porfirin melalui kaedah Lindsey, dan diikuti dengan reaksi bromination untuk mendapatkan porphyrin tiga diganti, tindak balas dilanjutkan dengan menggunakan tindak balas Suzuki Cross Coupling untuk mendapatkan porfirin dengan empat-penganti. Semua sebatian telah dicirikan menggunakan spektroskopi ^{1}H-NMR, ^{13}C-NMR, ultraungu (UV) dan inframerah (IR).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SCHEMES

LIST OF FIGURES

LIST OF ABBREVIATIONS

^{1}HNMR	Proton Nuclear Magnetic Resonance
^{13}CNMR	Carbon Magic Angle Spin Nuclear Magnetic Resonance
$CDCl_3$	Deuterated Chloroform-d1
FTIR	Fourier Transform Infrared
UV-Vis	Ultraviolet-visible
CC	Column Chromatography
$CHCl_3$	Chloroform
DCM	Dichloromethane
DDQ	2, 3 Dichloro-5,6-dicyano-1,4-benzoquinone
TFA	Trifluoroacetic acid
TEA	Triethylamine
THF	Tetrahydrofuran
EtOAc	Ethyl acetate
TLC	Thin Layer Chromatography
EtOH	Ethanol
PDT	Photodynamic Therapy
UV	Ultaviolet
G.S	Ground State
E.S	Exited State
HOMO	Highest occupied molecular orbitals
LUMO	Lowest unoccupied molecular orbitals
m.p	Melting Point
ca.	Circa (Approximately)
Ph	Phenyl
Ph-OH	Hydroxyphenyl
TPP	Tetraphenylporphyrin
Li	Lithium

R_f	Retention factor
BF_3	Boron trifluoride
OEP	Octaethylporphyrin
hr.	Hour

LIST OF SYMBLES

Hz	Hertz
J_{HH}	Coupling Constant
M	Molar
mL	Millilitre
mmol	Milimole
nm	Nanometer
°	Degree angle
℃	Celsius
ppm	Part per million
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
wt %	Weight percentage
v/v	Volume per volume
vol.	Volume
λ_{max}	Maximum absorption wavelength
δ	Chemical shift
B_o	Applied field
B	Soret band
ε	Molar absorptivity
α	Alpha
β	Beta
g	Gram
mg	Milligram
cm	Centimetre
π	Pi

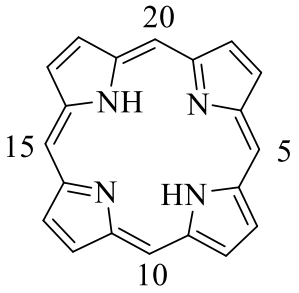
LIST OF APPENDIXES

CHAPTER ONE

INTRODUCTION

1.0 Background of Study

Porphyrins are the most widespread of highly prosthetic organizations present in environment. They are coloured tetrapyrrolic pigments which have crucial role within nature ranging from electron transfer, oxygen transportation, photosynthetic procedures as well as catalytic substrate oxidation, therefore they are appropriately referred to as 'pigments associated with life'[1]. Pophyrins have 22π electron frameworks whose primary conjugation pathway holds 18 π electrons, which illustrates the aromatic nature from which their correlated compelling colour stems. The guardian type of these tetrapyrrolic macrocycles has structure **(1)**, known as "porphyrin". The omnipresence of its capacities in nature led scientists around the globe to focus their research on these macrocycles, such as to prepare altered porphyrins that contrasted from the naturally occurring porphyrins and related the system in various ways [2].



(1)

The metal ions are easily coordinated with these macrocycles, which achieved functions such as transportation of oxygen and storage (hemoglobin and myoglobin), electron and energy transfer (cytochromes and chlorophylls) and biocatalysis (coenzyme B12 cytochrome P-450). The metal-free porphyrins additionally are generally present in organisms as precursors of metalloporphyrins and are accumulated and excreted in certain physiological disorders such as porphyrias [3].

Under the influence of the large planar π-conjugated structure, porphyrin derivatives display good energy balance, powerful two-photon assimilation, effective electron move, as well as fascinating photo-electrochemical attributes. For that reason porphyrins happen to be regularly used in a few fields for example biomimetic catalysis, chemical substance and natural receptors, natural light-emitting diodes, area effect diffusion and solar panels [4].

Among the great variation of porphyrins with a specific pattern of substituents, the most widely studied synthetic porphyrin group encompasses the symmetrical 5,10,15,20-tetraarylporphyrins like 5,10,15,20-tetraphenylporphyrin (TPP) (A_4-type porphyrin), because of their potential applications in materials chemistry. *Meso* Substituted trans-A_2B_2-tetraarylporphyrins are also important components found in many applications of biomimetic and materials chemistry [5].

In some cases, porphyrins with fused aromatic units show strongly red shifted absorptions, a property that could result in the development of superior photosensitizers for photodynamic therapy (PDT). In PDT, the porphyrin 'drug' is excited by visible light and transfers energy to generate singlet oxygen. As porphyrins commonly show an affinity for tumor cells over normal tissues, the highly toxic effects of singlet oxygen are localized to the malignant tissues [6]. All tissues strongly absorb light through most of the visible region, but red light in the region of 650–800 nm gives much better penetration while providing the necessary energy for singlet oxygen production. Unfortunately, porphyrins usually only have weak absorptions above 600 nm, and for this reason modified chromophores are attracting considerable interest.

1.1 Statement of Problem

There are several methods that have been developed to access the unsymmetrical type porphyrin compounds. Among the methods is the disconnection into any combination of pyrrole building blocks that can be used in [2+2] or [3+1] condensation reactions. It is also theoretically possible to perform a mixed condensation using pyrrole and various aldehydes. However, the number of regioisomers formed is too large and the necessary purification and separation workup is too cumbersome if possible at all. It is noted that most of these reactions involve acid-catalyzed condensation reactions, often resulting in significant scrambling of the pyrrole units thus limiting the type of substituents that can be used. Therefore, alternative synthetic strategy is needed especially to introduce different residues into porphyrin macrocyclic core.

1.1 Objective of Study

The objectives of the study are:-

a) To synthesize symmetrical type of porphyrins.
b) To synthesize unsymmetrical type of porphyrins.

1.2 Scope of Study

This research focused on the synthesis of the *meso*-substituted porphyrin and aims to evaluate the applicability and limitations of the synthetic methods for the preparation of symmetrical and unsymmetrical type of porphyrins. We also report on the synthesis of new functionalized derivatives for some of the different porphyrin classes. In this research, several methods were utilized based on condensation, bromination and Suzuki Cross Coupling reactions. In almost all cases, optimum amounts of reactants are required to obtain high yields. The products were characterized by Fourier transform infrared spectroscopy (FTIR), UV-Vis Spectrometer, melting point, and Nuclear magnetic resonance (NMR).

1.4 Significant of the study

We have taken an alternative approach focusing on partial synthesis starting with preformed porphyrins. The last decades have seen a surge in novel functionalization reactions of porphyrins, many based on C–C coupling reactions

which have put this approach within possibility. By now many A_2BC- and A_3B-type porphyrins have been prepared starting with the easily accessible 5,15-disubstituted porphyrins and from brominated precursor compounds often based on Heck-type reactions. In this context we have developed the use of different reagents for the synthesis of various tetrapyrrole classes.

Unsymmetrical type porphyrin compounds are a broad spectrum of biological activities and apply for photodynamic cancer therapy (PDT) and optical applications. This combination of methods is also suited for preparing unsymmetrically substituted porphyrins for other application protocols, for example, push–pull porphyrins for nonlinear optics and chiral oxidation catalysts. We here present a comprehensive analysis of the application of the currently available synthetic strategies for the meso functionalization of porphyrins.

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