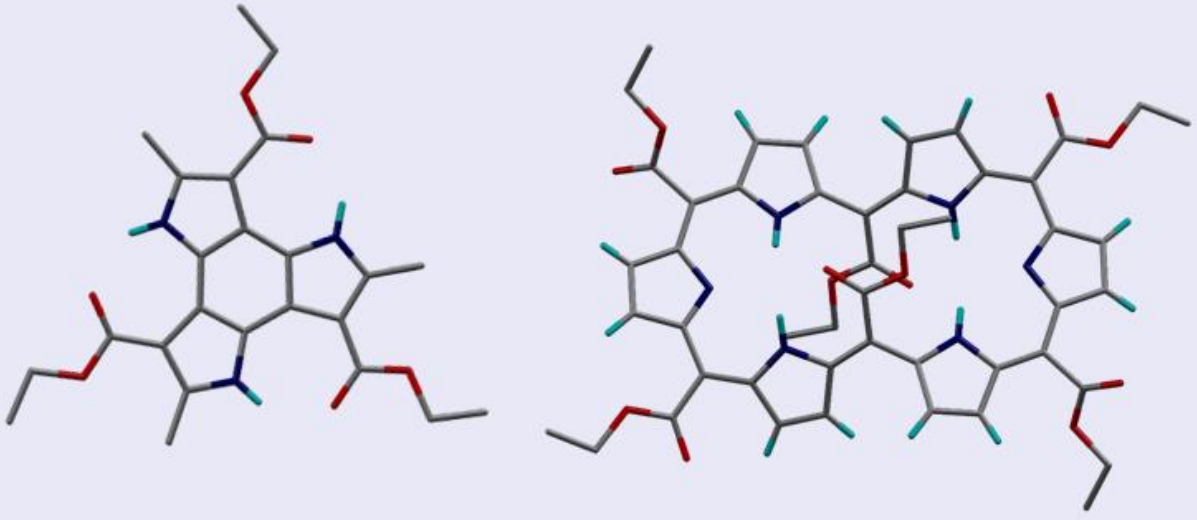
Exploration of Aromatic 1H-Benzotripyrrole And Antiaromatic Meso-Hexakis-(ethoxycarbonyl)[28]hexaphyrin(1.1.1.1.1.1)

A Thesis Submitted for the Degree of
DOCTOR OF PHILOSOPHY



By

Pandeeti Obaiah

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March 2021

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Dedicated

to

My beloved Parents and family

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DECLARATION

I hereby declare that the matter embodied in the thesis entitled ***"Exploration of Aromatic 1H-Benzotripyrrole and Antiaromatic Meso-Hexakis(ethoxycarbonyl)-[28]hexaphyrin(1.1.1.1.1.1)"*** is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India under the supervision of **Prof. Pradeepta K. Panda** and it has not been submitted elsewhere for the award of any degree or diploma or membership, etc. This work is also free from plagiarism. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET.

In keeping with the general practice of reporting scientific investigations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission or error that might have occurred by oversight or error is sincerely regretted.

P. Obaiah

March 2021 **Pandeeti Obaiah**

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CERTIFICATE

This is to certify that the work described in this thesis entitled "***Exploration of Aromatic 1H-Benzotripyrrole and Antiaromatic Meso-Hexakis(ethoxycarbonyl)[28]hexaphyrin (1.1.1.1.1.1)***" has been carried out by Mr. Pandeeti Obaiah, holding the Reg. No. 08CHPH43 under my supervision, for partial fulfilment for the award of Doctor of Philosophy in Chemistry and the same has not been submitted elsewhere for any degree, which is a plagiarism free thesis.

Part of thesis have been:

A. Published in following journal:

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B. Presented in the following conferences:

1. Oral and poster presented on "One pot synthesis of C_{3h} benzotripyrrole and its mechanistic studies", at the **15th Annual in-house Symposium (ChemFest-2018)**, School of Chemistry, University of Hyderabad, Hyderabad, India, March 9-10, **2018**. **P. Obaiah**, B. Satish Kumar and Pradeepta K. Panda. Chemfest-15, **2018**.
2. Poster presented on "Synthesis and characterization of C_{3h} benzotripyrroles", at the **21st CRSI National Symposium in Chemistry-2017**, CSIR-Indian Institute of Chemical Technology, Hyderabad, India, July 14-16, 2017. **P. Obaiah**, B. Satish Kumar and Pradeepta K. Panda. CRSI-21, **2017**.

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PREFACE

The present thesis entitled "**Exploration of Aromatic 1H-Benzotripyrrole and Antiaromatic *Meso*-Hexakis(ethoxycarbonyl)[28]hexaphyrin(1.1.1.1.1.1)**" consists of two parts. Part A contains two chapters, with the first chapter providing an elaborate introduction about C_3-symmetrc compounds. Chapter 2 deals with benzotripyrrole, a C_3-symmetric molecule, which once obtained in different isomeric forms in multiple steps can be attained in straightforward synthesis involving a single step. The reaction mechanistic studies and computational calculations were also performed to reveal its aromaticity and reactivity. Subsequently, part B contains two chapters with a brief introduction about antiaromatic compounds in the chapter 3. Chapter 4 describes the first stable symmetrically hexa-substituted [28]hexaphyrin displaying Hückle antiaromatic character with conformationally rigid dumbbell structure. These works are finally summarized in chapter 5. At the end, an appendix is provided regarding the materials used during the dissertation work and the methods followed to complete the thesis.

In **chapter 1,** a brief description about synthetic methods and few applications of benzo-fused polycyclic hetero aromatic compounds with C_3 symmetry are provided. In **Chapter 2,** we have developed an effective one pot synthesis of benzotripyrrole derivatives from 1*H*-pyrroles. In **chapter 3,** a brief introduction about antiaromatic compounds is elaborated. In **chapter 4**, we have successfully synthesized first stable symmetrically hexa-substituted [28]hexaphyrin displaying Hückle antiaromatic character. The **chapter 5** summarizes the findings of the present investigation. At the end, an appendix provides the information about the materials and methods used in the course of the investigation.

March 2021 **Pandeeti Obaiah**

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March 2021 **Pandeeti Obaiah**

University of Hyderabad

LIST OF ABBREVIATIONS

Abbreviation	Full Form
abs	Absorbance
AcOH	Acetic acid
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
anhyd	Anhydrous
aq.	Aqueous
atm	Atmosphere
Å	Angstrom
a.u.	arbitrary unit
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
Br_2	Bromine
bp	boiling point
***t*-Bu**	tertiary butyl
CCDC	Cambridge Crystallographic Data Centre
CMSD	Centre for Modelling, Simulation & Design
CIF	Crystallographic information file
cm	Centimeter (s)
conc.	Concentrated
CuCl	Copper(I)chloride
CuBr	Copper(I)bromide
CuI	Copper(I)iodide
$CHCl_3$	Chloroform
Cs_2CO_3	Cesium carbonate
CV	Cyclic voltammetry
d	Doublet
dd	Double doublet
δ	chemical shift in parts per million
°	Degree
°C	Degree Celsius
CCl_4	Tetrachloromethane

DCE	1,2-dichloroethane
DCM	Dichloromethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
diff.	Diffraction
DMF	Dimethylformamide
DFT	Density Functional Theory
DMAC	Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPA	Diisopropylamine
D_2O	Deuterium oxide
DPV	Differential pulse voltammetry
dt	Double triplet
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
E	Energy
ε	Epsilon (molar extinction coefficient)
e.g.	For example
eq.	Equivalent
Equiv.	Equivalent
eV	Electron volt
ESI	Electrospray Ionization
et al.	and others
etc	et cetera (and other similar things)
EtOH	Ethanol
fl	Fluorescence
FT	Fourier transform
$FeCl_3$	Ferric chloride
g	Gram
h	Hour (s)
H-bond	hydrogen bond
HBr	Hydrobromic acid
HCl	Hydrochloric acid

HOMA	Harmonic oscillator model of aromaticity
HOMO	Highest occupied molecular orbital
HRMS	High resolution-mass spectrometry
Hz	Hertz
I_2	Iodine
i.e.	that is
IPA	Isopropanol
IR	Infrared
J	coupling constant (in NMR)
KBr	Potassium bromide
K_2CO_3	Potassium carbonate
KH	Potassium hydride
KI	Potassium iodide
K_3PO_4	Potassium phosphate
KOH	Potassium hydroxide
L	Liter
LC	liquid chromatography
lit.	Literature
log	Logarithm
LUMO	Lowest unoccupied molecular orbital
µ	Micro
M	moles per litre
m	meta (structure); multiplet (NMR); milli (unit)
mA	milliAmpere
MeOH	Methanol
mg	milligram
$MgSO_4$	Magnesium sulfate
MHz	megahertz
min	Minute (s)
mL	milliLitre
mp	melting point
MnO_2	Manganese dioxide

MS	mass spectrometry
MSA	Methane sulfonic acid
m/z	mass to charge ratio (in mass spectrometry)
mCPBA	meta-Chloroperoxybenzoic acid
NMP	N-Methyl-2-pyrrolidone
NaOAc	Sodium acetate
NaCl	Sodium chloride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
Na_2S	Sodium sulfide
Na_2SO_4	Sodium sulfate
NIS	N-iodosuccinimide
NBS	N-bromosuccinimide
NH_4Cl	Ammonium chloride
$NaBH_4$	Sodium borohydride
NICS	Nucleus independent chemical shift
NLO	Nonlinear optical
nm	nanometer (s)
NMR	Nuclear magnetic resonance
ns	nanosecond (s)
o	ortho
ORTEP	Oak Ridge thermal ellipsoid Plot
p	para
Pd/C	Palladium(0) on activated carbon (charcoal)
***i*-Pr**	isopropyl
$POCl_3$	Phosphorous oxychloride
PPh_3	Triphenyl phosphene
ppm	parts per million
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
***p*-TSA**	*p*-Toluenesulfonic acid
q	quartet
rt	room temperature

s	singlet
sat.	saturated
t	triplet
TD-DFT	Time dependent density functional theory
TEA	triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TLC	Thin layer chromatography
TMS	tetramethylsilane
TMSBr	Bromotrimethylsilane
TPA	Two photon absorption
UV-vis-NIR	Ultraviolet-visible-near infrared
via	going through
viz.	namely
vs	versus (against)
w.r.t.	with respect to
XRD	X-ray diffraction
Z	Formula units in the unit cell
Zn	Zinc

PART A

CHAPTER 1

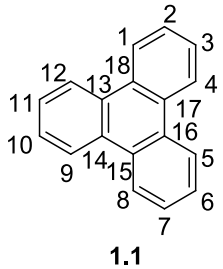
Introduction of C_3 Symmetric Molecules

1.1 General Introduction

An organic polycyclic compound contains several closed rings, which includes both aromatic and aliphatic type. They come in linkages that include fusing (edge-to-edge, like in steroids and anthracene), tethering (like in biaryls), etc. Among them polycyclic aromatic hydrocarbons (PAHs) are an important class of compounds endowed with multiple rings of pure aromatic compounds along with their heterocyclic analogues which contain nitrogen, sulfur, oxygen, or other non-carbon atoms. Not only the physical but also the biological properties of them are interesting. Some of the PAHs are inured as fluorescent probes by incorporating into polymer backbone [1] or connected to an amino acid or nucleobase framework [2-6] for the investigation of biological processes. Their enhanced aromaticity admits their applications in organic (photo) conductors,[7,8] conducting polymers,[9,10] and solar cell research.[11,12] In addition, their frequent uses are observed as dyes in pigments.[13,14] Overall, we can say that the focus of PAHs has long been in interdisciplinary research.[15-17] Benzo-fused heteroaromatic forms are common patterns in plenty of naturally-occurring compounds, having broad pharmaceutical applications like antibiotics and anti-microbial agents.[18] More importantly, C_3-symmetric forms[19] are matter of interest as effective materials for organic electronics devices viz. field-effect transistors[20] and for liquid crystals[21] as core units. Star-shaped molecules with conjugation have been employed in organic light-emitting diodes,[22] electroluminescent devices,[23] and photovoltaics.[20d,24] Some examples of benzo-fused polycyclic hetero aromatic compounds, in particular the C_3-symmetric systems will be discussed briefly as part of this thesis.

1.2 Triphenylenes

Triphenylene **1.1** is a flat structured PAH, made up of four fused benzene rings (Figure 1.1). Initially, **1.1** was separated from pyrolytic benzene products[25] and first discovered by Schultz. It is also a component of coal tar. However, **1.1** can also be produced using benzene chemistry synthetically *via* trimerization.



1.1

Figure 1.1: Structure and numbering of triphenylene **1.1.**

It's compounds display an array of properties, which make them alluring subjects for exploration and the major reason is triphenylene's potentiality to make mesophases of liquid crystals. It's derivatives are not only chemically but also thermally stable and notably, discotic liquid crystal study has been done for them than any different type.[26,27] Firstly, in 1981, mesophases of nematic discotic liquid crystals were illustrated with compounds **1.2** and **1.3** (Figure. 1.2).[28]

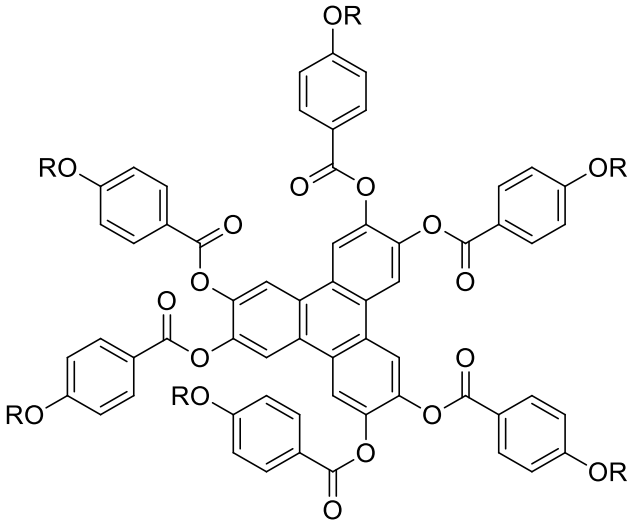


Figure 1.2: Structures of triphenylene-2,3,6,7,10,11-hexakis(4-n-alkoxybenzoate) **1.2** and **1.3**.

The frequently synthesized, extensively studied and structurally characterized analogues are hexaalkoxytriphenylenes (HATs) **1.4-1.6** (Figure 1.3) and makes them perfect building blocks for studying self-assembly properties as well as polymer unification properties for further investigation.[29]

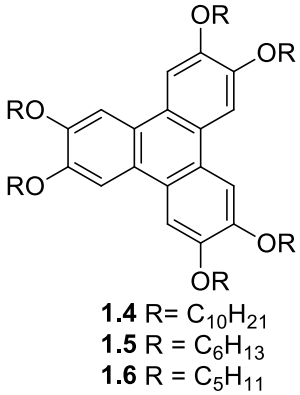
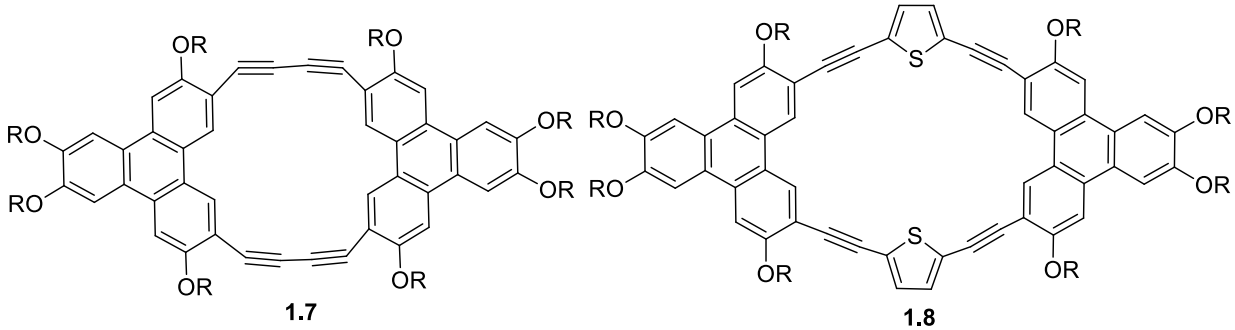


Figure 1.3: Structure of hexaalkoxytriphenylenes **1.4-1.6**.

Twinned triphenylene discogens **1.7**-**1.8** having rigid spacers showed nematic mesogen formation (Figure 1.4), as against the wider commonly originated columnar mesophase for the monomer.[30a] In addition, they have applications as components of functional polymers and as fluorescent labels.[30b]

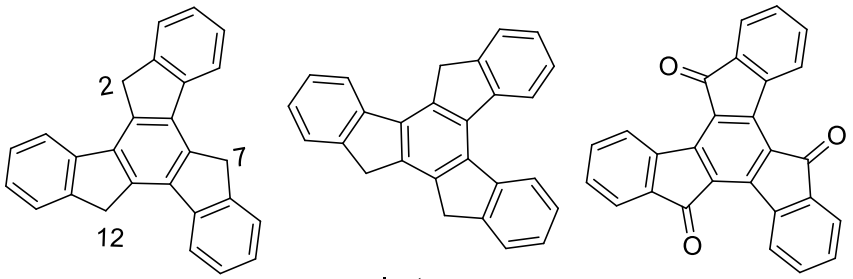


1.7 **1.8**

Figure 1.4: Synthetic twinned triphenylenes **1.7**-**1.8**.

1.3 Truxenes

Compound **1.9** is also come under PAHs. It has been studied quite elaborately for last several years due to its enhanced solubility. It has been inured for the fabrication of two-photon absorbers, non-linear optical materials, organic photovoltaics, transistors, lasers, molecular resistors, organic light emitting diodes, organogels, molecular wires, fluorescent probes, self-assembled systems and liquid crystals.[31] It exists as two feasible isomers: **1.9** and isotruxene **1.10** (Figure 1.5) having the difference in the way of arrangement of fluorene moieties.

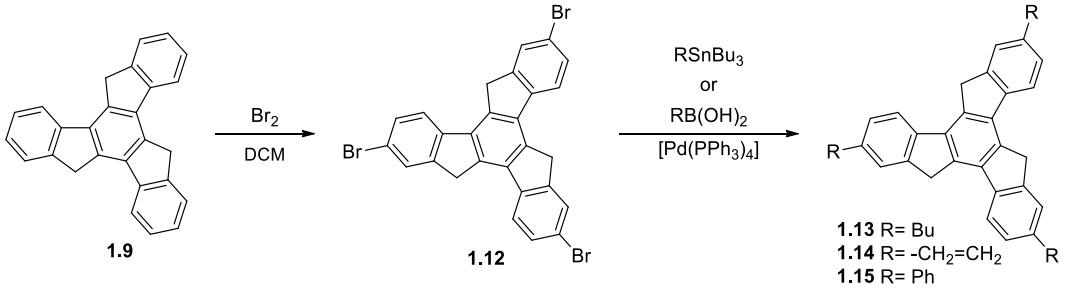


Truxene **1.9** Isotruxene **1.10** Truxenone **1.11**

Figure 1.5: Structures of truxene **1.9** isotruxene **1.10** and truxenone **1.11**.[31]

Compound **1.9** was initially reported as early as 1894 as a mixture of **1.10** and **1.9**.[32] It was first separated as only one isomer from (3-methylthio)indene[33] and subsequently from indan-1-one[34] after two years. Echavarren and co-workers made trialkylated truxene on the 2,7,12-positions[35] using KH or n-BuLi, and obtained *syn*- and *anti*- compounds as a mixture of products (1:1 or 3:1 ratios) upon addition with an alkyl halide. But, use of sodium[36] or

NaH produced completely the *anti*-derivative, which could be further isomerized, with *t*-BuOK, to the most stable *syn*-isomer.[37] To excavate more **1.9** based structures, electrophilic bromination was initially disclosed in 1894, and in 2001 revisited to accomplish the brominated compound **1.12** in 92% yield.[38] Subsequent Suzuki or Stille couplings employing [$Pd(PPh_3)_4$] with boronic acids or organostannanes procured in 30-40% yields of new truxene derivatives **1.13-1.15** (Scheme 1.1).[39,40]



Scheme 1.1: Synthesis of truxene derivatives **1.13-1.15.**

Owing to vast planar π-aromatic surface and the solvophobic effect, **1.9** exhibits strong π-stacking intermolecular interaction leading to aggregation. The supramolecular interaction is a general driving force[41-46] in these class of molecules and can be ascribed to enticing electrostatic interactions.[47-50] Liquid crystals based on compounds **1.9** have been probed in the 1980s.[51,52] Further development into liquid crystals[53] of compound **1.9** containing C_3-symmetric compounds **1.16-1.21** (Figure 1.6) was elucidated and this liquid crystalline nature shown by derivatives of **1.9** has been employed in organic electronics.[54]

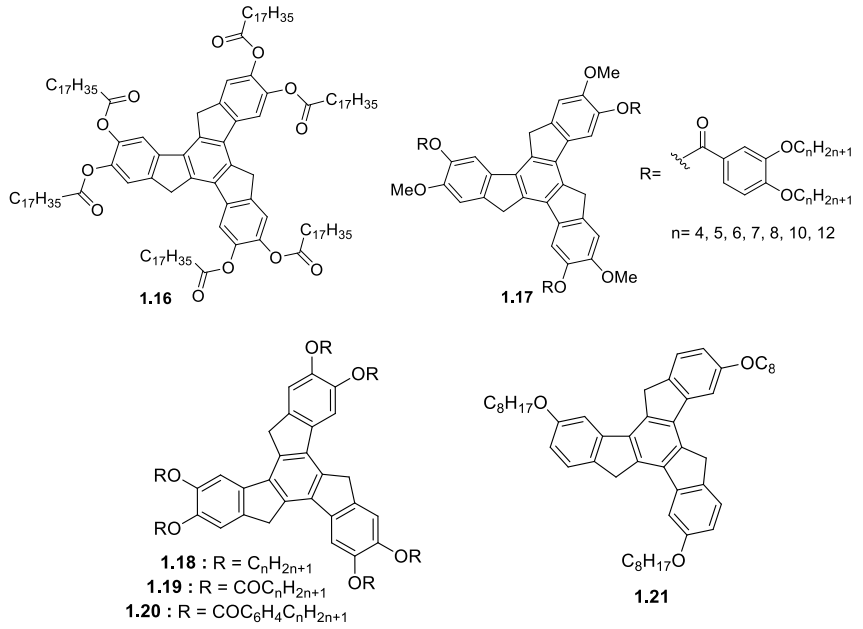


Figure 1.6: Structures of truxene derivatives **1.16-1.21**.

1.4 Triaazatruxenes

Triazatruxene **1.22** is a cyclic trimer of indole and considered as a C_3-symmetric planar conjugated structure with π-extension.[55-57] Formally, **1.22** is treated as three carbazoles with an overlapping framework and persist as an electron donating system.[57-60] This C_3-symmetric molecule has immense application in two-photon absorption,[61] fluorescent sensors,[55,62] non-linear optics,[63] organic lasers,[64] OLEDs,[65-68] OFETs, liquid crystal displays,[58,69,70] as well as OPVs.[71,72] It exists in two isomeric forms i.e. **1.22** and isotriazatruxene **1.23** in which the difference is in the way of arrangement of carbazole moieties (Figure 1.7).[73,74]

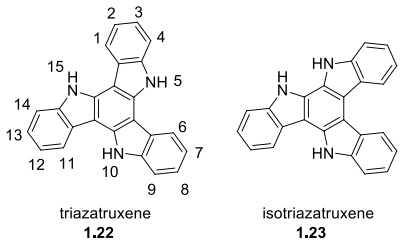
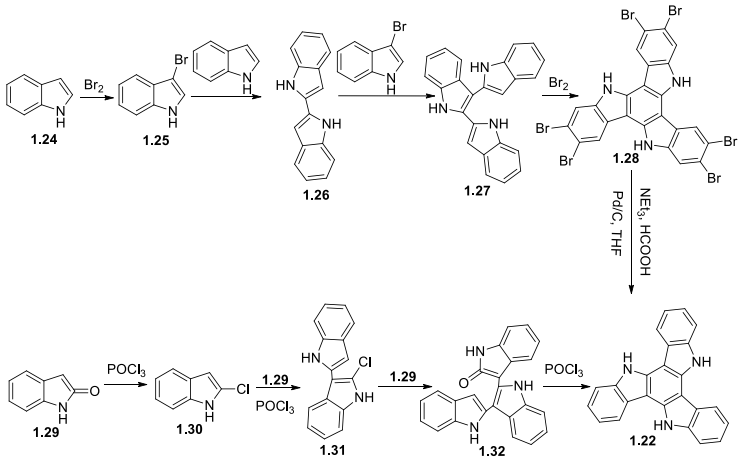


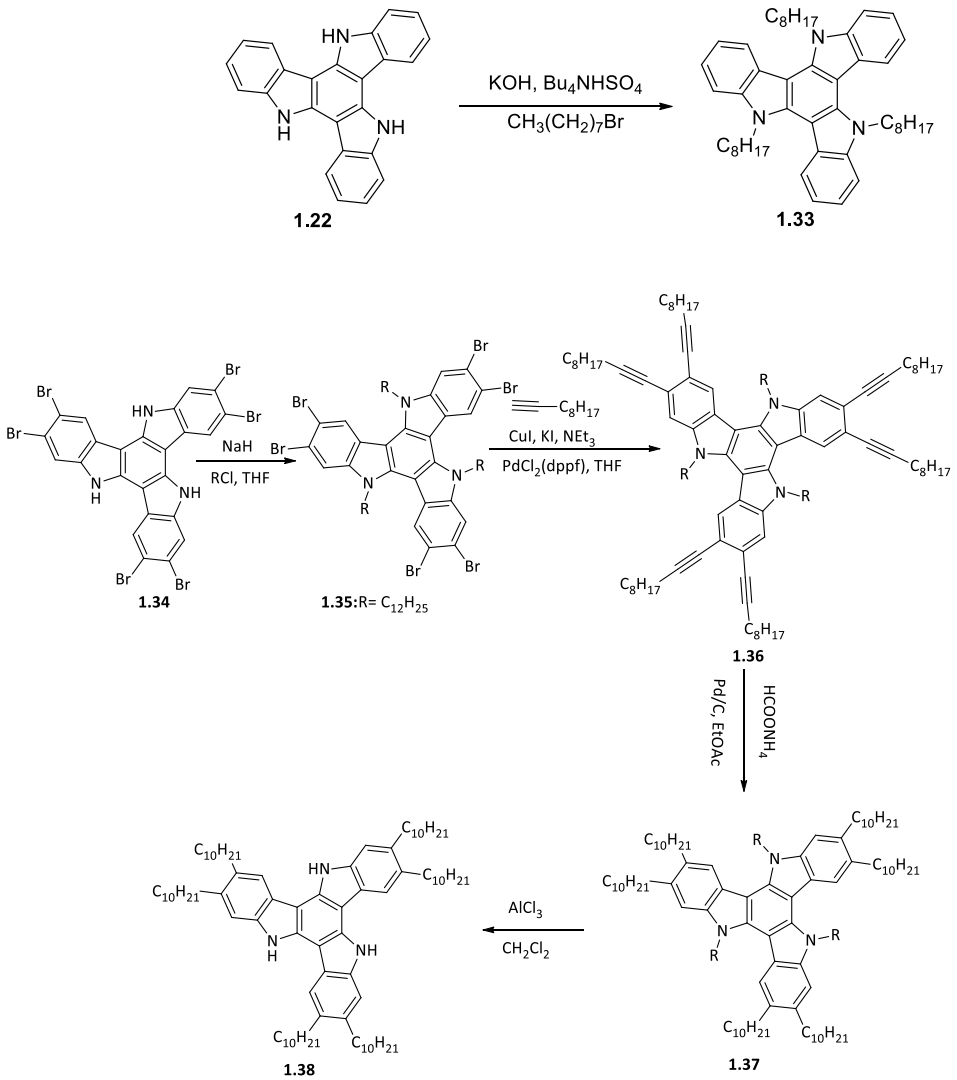
Figure 1.7: Structures of triazatuxene **1.22** and isotriazatruxene **1.23**.

Compounds **1.22** and **1.23** were first synthesized in 1980.[75,76] **1.22** was innovatively realized from indole derivative using copper.[75] At the same time, using *O*-acetate of indoxyl, asymmetric **1.23** was produced by cyclotrimerization.[76] Till now the symmetric unit has received more attention than the asymmetric system, even if their selective synthesis is known. Noticing triazatruxene **1.22**, Eissenstat *et al*. reported its synthesis beginning with $POCl_3$ from 2-indolone[77] in 1995 and afterwards in 2000, Robertson *et al*. obtained it using bromine from indole (Scheme 1.2).[78]

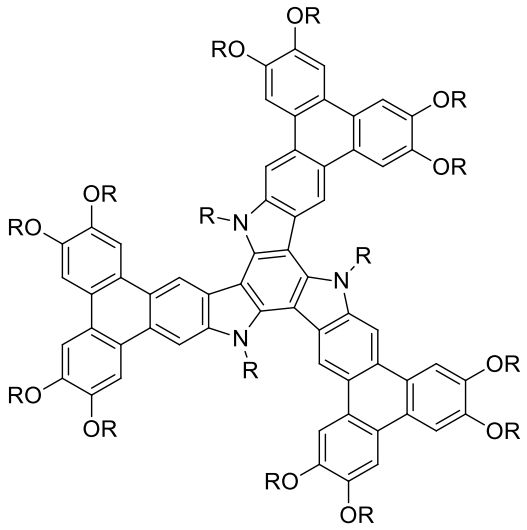


Scheme 1.2: Two possible reaction pathways of triazatruxene **1.22** formation.

Exploration of organic electronic materials having unique properties derived from functionalized triazatruxenes are mainly concentrated on the peripheral benzene rings and NH-sites.[57,58,79,80] Generally, N-alkylations are performed on compound **1.22** under basic conditions. Whereas, alkyl chains have been incorporated onto the benzene rings of peripheral positions of **1.22** by Sonogashira coupling (Scheme 1.3). Materials containing **1.22** moieties have been probed extensively since it consist of planar and C_3-symmetric structure, like C_3-symmetric starburst molecules,[81-83] dendrimers,[84,85] dumbell-shaped molecules,[86] conjugated microporous polymers,[87] D-π-A linear molecules,[88,89] and triazafullerene, etc.[60,90] Truxene-based star-shaped polycyclic aromatics were designed by applying a gorgeous method using $FeCl_3$, in which **1.22** and **1.1** were fused sharing the same benzene rings (Figure 1.8), which extends the π-conjugated plane and concurrently maintains the rigidity of the molecule.[91]



Scheme 1.3: Synthesis of functionalized triazatruxenes **1.33** and **1.38**.



1.39 : R= C_6H_{13}
1.40 : R= $C_{12}H_{25}$

Figure 1.8: Structures of star-shaped molecules **1.39-1.40**.

1.5 Benzotrithiophenes

Benzo[b]thiophene (BT), (Figure 1.9) and its derivatives are notable fused compounds of thiophene due to their vast array of biological characteristics[92,93] and material science applications.[94]

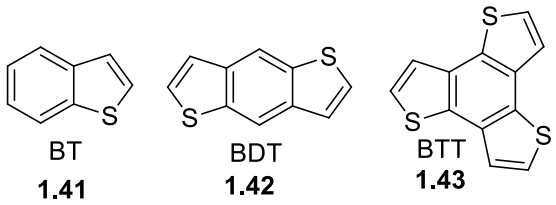
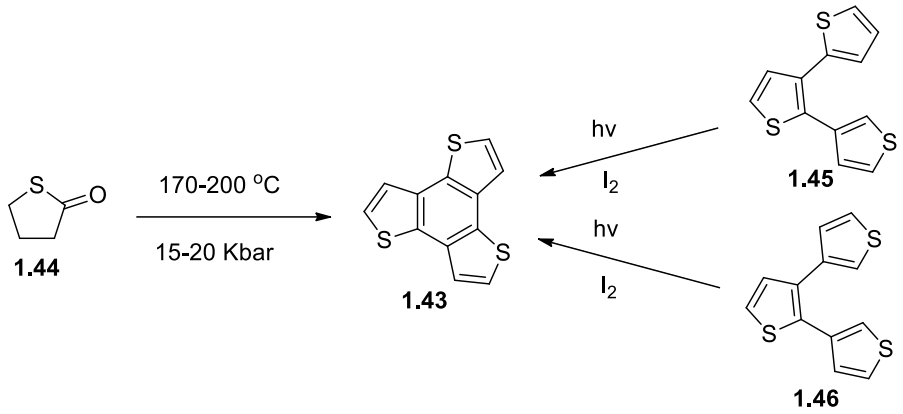


Figure 1.9: Fused thiophene compounds.

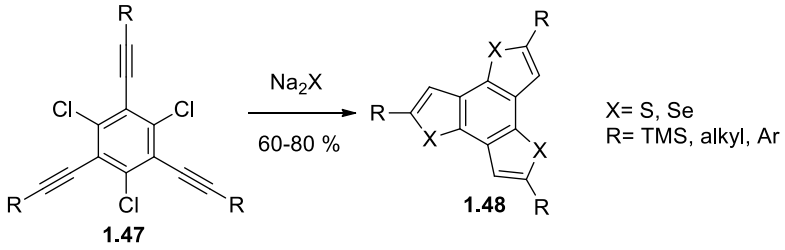
Mostly, fused (multi)thiophene aromatic compounds are marvelous optimistic electronic materials for organic field-effect transistors,[95] organic light-emitting diodes,[96] photovoltaic cells,[97] and organic conductors.[98] Compound **1.42** contains two identical thiophene units fused through a benzene moiety having C_{2h} symmetry that assist two dimensional molecular extensions and thus has been employed extensively as a semiconductor[99] and in solar cells as a building block.[100] Benzothiophene (BT) is a popular electron- accepting system that has been utilized to compose of the photovoltaic organic materials in high performance.[101,102] Fused trithiophene, namely benzotriphiophene (BTT) in which three thiophene units are fused in a cyclic fashion to provide an aromatic block with more extension (larger size) and a higher electron density.[103,104] For example, compound **1.43** is

a planar, sulfur-rich extended π-system.[105] Its characteristics support for potent π-π stacking and effective charge transport. Owing to its high coplanarity with extended π-conjugation, **1.43** is employed in the construction of materials like organic semiconductors.[106-109] In 1972, BTT **1.43** could be attained from γ-thiobutyrolactone at 170-200 ºC and 15-20 Kbar (Scheme 1.4).[110] Kagan and Perrine groups secured it by photocyclization method using a catalytic amount of iodine (Scheme 1.4).[103,111]



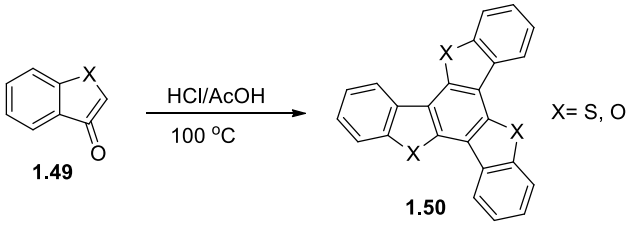
Scheme 1.4: Synthesis of benzotrithiophene **1.43** from **1.44**, **1.45** and **1.46**.

In a one-pot synthesis, Kashiki *et al*. produced a series of functionalized star-shaped molecules having both benzotrithiophenes and benzotriselenophenes (Scheme 1.5) in an efficient way.[112]



Scheme 1.5: Synthesis of benzotrithiophenes and benzotriselenophenes.

To build the star-shaped entities, benzothiophene and benzofuran derivatives have also been utilized (Scheme 1.6).[113]



Scheme 1.6: Synthesis of the derivatives of benzothiophene and benzofuran.

BTT exits in seven available isomers as depicted in fig 1.10.

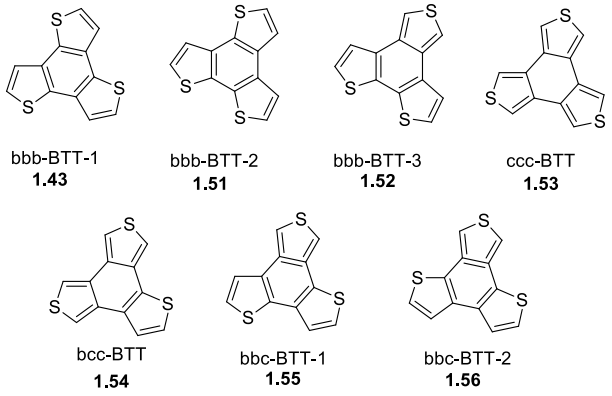


Figure 1.10: The seven possible BTT isomers.

Recently, compounds **1.57-1.59** containing BTT has been introduced (Figure 1.11), which are endowed with electron-donor groups, exhibiting efficiencies more than 18 % as a different HTM for PSCs.[114] The symmetrical **1.43** core is engaged in molecule 1.**57**,[103] which is envisaged to avail the intermolecular π-π interactions, pave the way for productive hole-transporting properties. Among the seven isomers, the asymmetrical compounds viz. **1.51** and **1.52** have been heavily utilized for PV applications,[107,115,116] while the compound 1.**56** has also been described basically for organic field-effect transistors.[106,117]

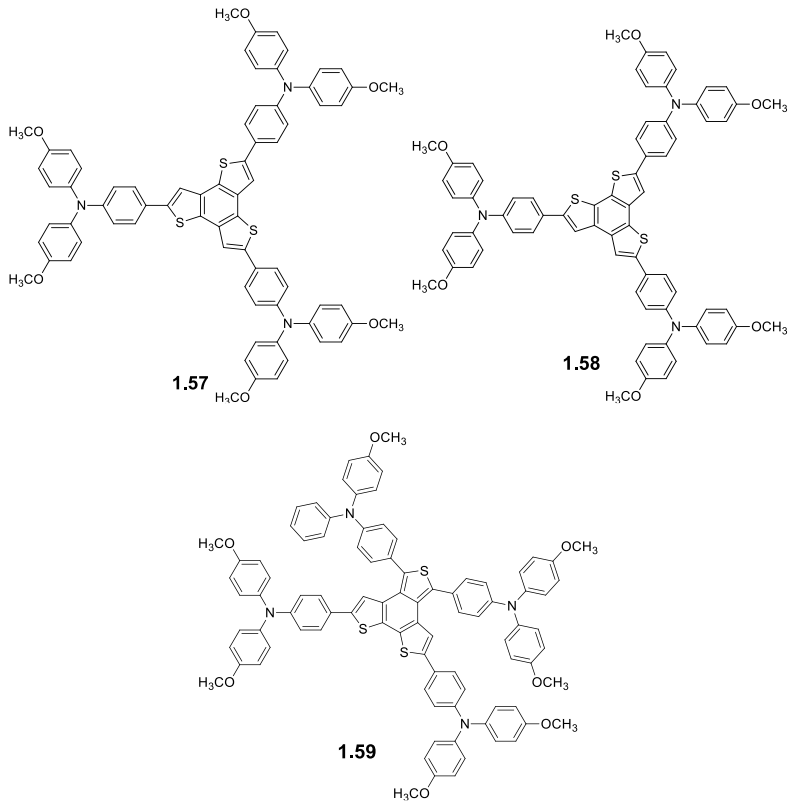
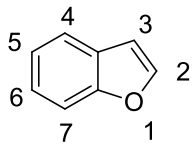


Figure 1.11: Molecular structures of HTMs containing isomeric BTT **1.57-1.59**.

BTT **1.43** has been widely utilized as a core for the design of star-shaped dendrimers and oligomers.[118] It's derivatives has been used in several patents for novel materials with semiconductor and liquid crystalline properties at industrially relevant levels.[119]

1.6 Benzotrifurans

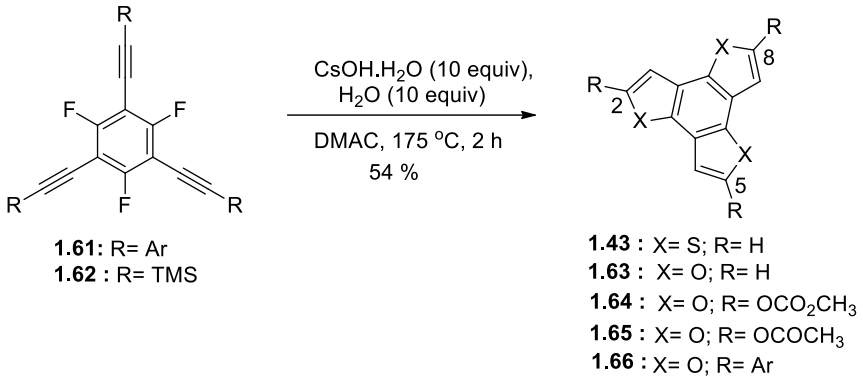
Complementary to thiophenes, π-conjugated building blocks containing furan-based entities have emerged as beneficial compounds,[120-124] to serve as agrochemicals, functional materials, biological active molecules, as well as helpful intermediates in organic synthesis,[125] and found in nature broadly as prominent type of heterocycles with polysubstitution.[126] These also act as an important scaffold in several pharmaceutical drugs.[127] Precisely, a lot of natural products have a broad spectrum of biological activities together with cytotoxic, antiproliferative, antisweet, antimicrobial, fungicidal, insecticidal, antioxidant properties.[128] In spite of HOMO with an often higher-lying and higher ability for air oxidation, in contrast to poly- and oligo- thiophenes, corresponding furans exhibit greater solubility and hence processing ability, sustainable admittance from biomass precursors, tighter packing in the solid phase and higher rigid planarity.[129-131] The simple benzofuran compound contains fused benzene and furan rings, which can be extracted from coal tar (Figure 1.12).



1.60

Figure 1.12: The basic motif of benzofuran **1.60**.

In 1886, hexafunctionalized BTFs were first reported by Lang from condensation reactions using phloroglucinol and later by other research groups.[132-136] While Castellano group introduced **1.64** and **1.65**, Nakamura and coworkers reported trifunctionalized π-conjugated derivatives **1.66**.[137] They exhibit an excellent 2D and 3D organization as well as better octopolar properties in the crystalline phase and on surfaces, respectively.[137]



Scheme 1.7: Structures of benzotrithiophene (BTT) and benzotrifuran (BTF) derivatives.

Recently, benzofurans have been utilized in optical applications in addition to two-photon singlet oxygen sensitizers,[138] and its derivatives has been examined for organic electroluminescence.[139] A new class of disc-like liquid crystal compound **1.67** realized comprising **1.63** as a central core (Figure 1.13).[140]

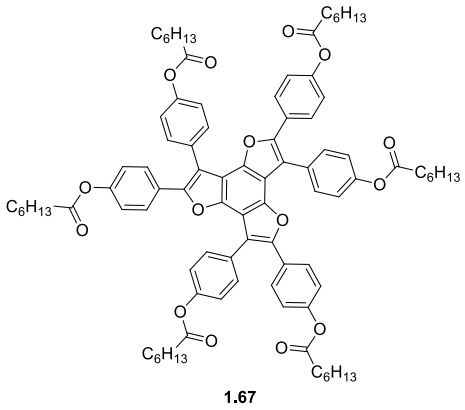
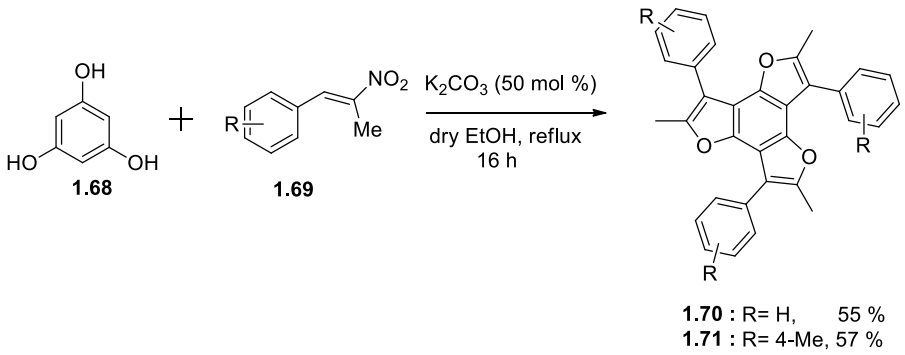


Figure 1.13: Structure of derivative of liquid crystalline benzotrifuran **1.67**.

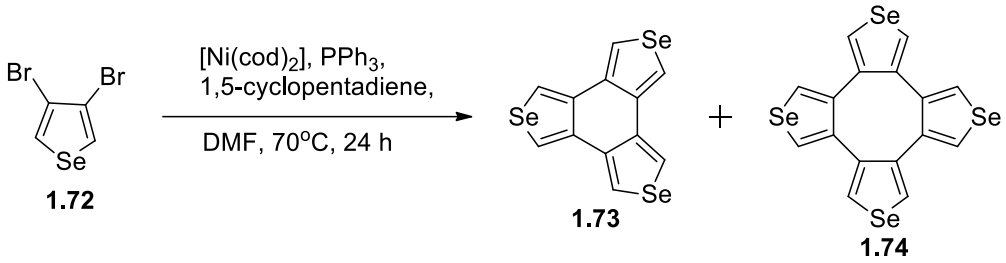
In 2015, in one-pot synthesis using phloroglucinol and nitroolefins, benzotrifurans were reported by A. Hajra and coworkers (Scheme 1.8).[135] These compounds are valuable hole-transporting materials.



Scheme 1.8: Synthesis of BTF derivatives as hole-transporting materials.

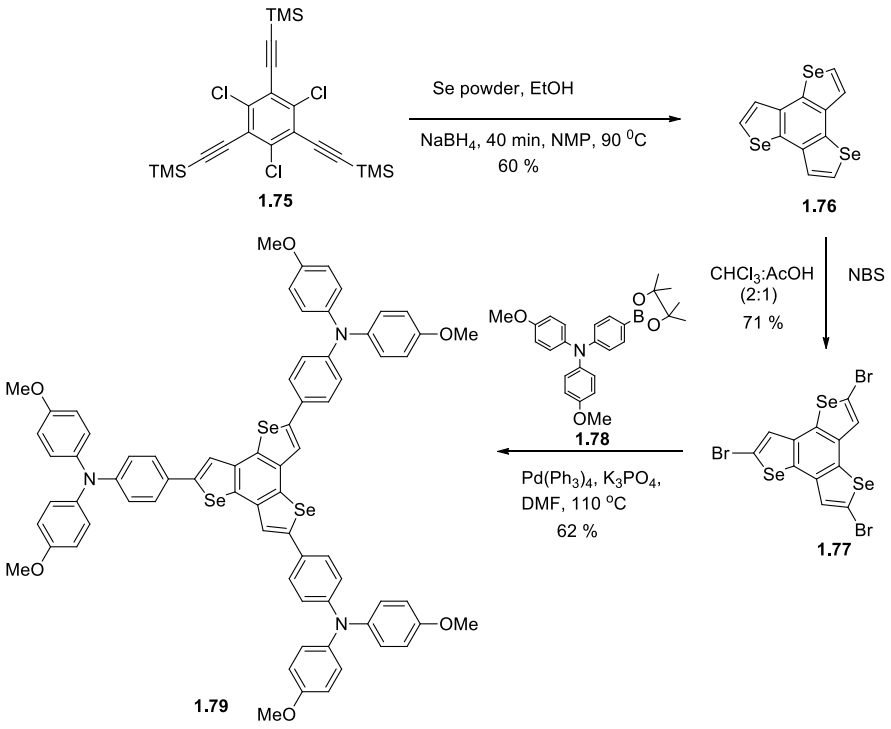
1.7 Benzotriselenophene

Bendikov group synthesized **1.73** with [Ni(cod)$_2$] from 3,4-dibromoselenophene **1.72** in the presence of PPh$_3$ and 1,5-cyclopentadiene in DMF in 40 % yield (Scheme 1.9).[141]



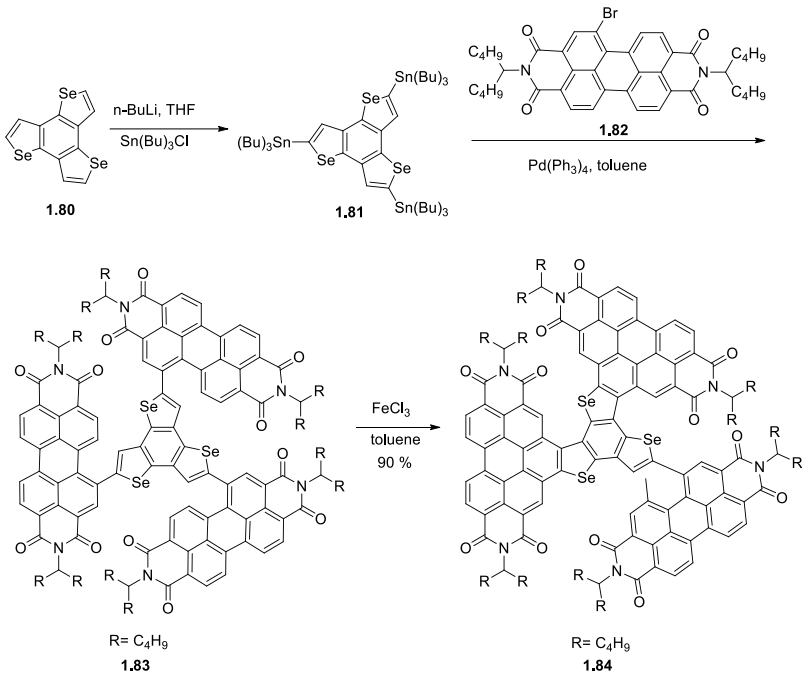
Scheme 1.9: Synthesis of benzotriselenophene **1.73**.

In 2018, Martin and Nazeeruddin groups made **1.76** from **1.75** using Se powder and NaBH$_4$ and further the triselenophene **1.76** was brominated with NBS to give **1.77**, which was then coupled with **1.78** using Suzuki protocol to form **1.79** for perovskite-based solar cells (Scheme 1.10).[142]



Scheme 1.10: Synthesis of benzotriselenophene derivative **1.79**.

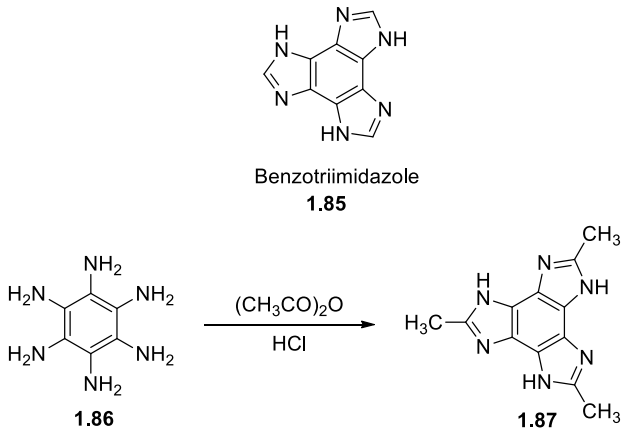
In 2020, Li *et al*. designed and synthesized propeller like **1.84** using different types of coupling reactions to obtain rigid fused linkages, which show flatter conformation and larger band gaps providing blue shifted absorption.[143]



Scheme 1.11: Synthesis of benzotriselenophene derivative **1.84**.

1.8 Benzotriimidazole

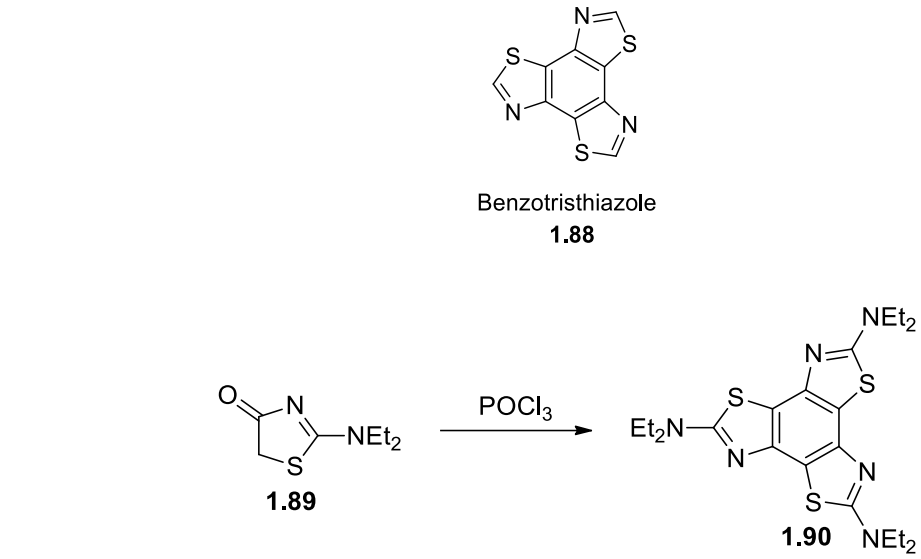
Benzotriimidazole **1.85** based compound i.e. **1.87** was synthesized by Novellino and coworkers by the reaction of **1.86** with acetic anhydride and acts as antagonist with higher affinity at A_1AR and/or A_3AR.[144]



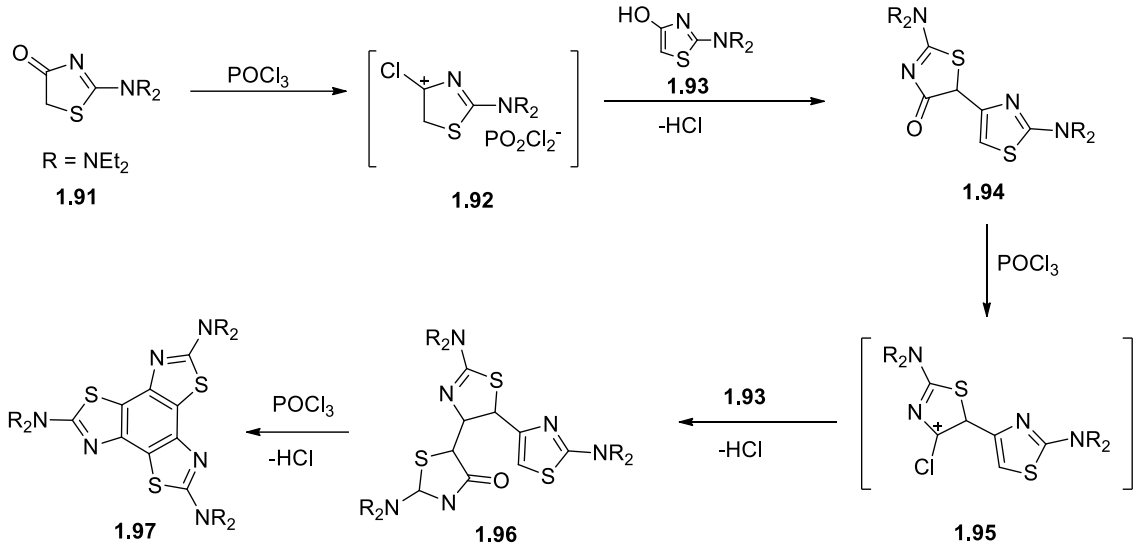
Scheme 1.12: Synthesis of benzotriimidazole derivative **1.87**.

1.9 Benzotristhiazole

Alexander Rossler and Peter Boldt synthesized **1.90**, a derivative of benzotristhiazole **1.88**, using $POCl_3$ by the transannulation of **1.89** in moderate yield (Scheme 1.13) and proposed a reasonable reaction mechanism (Scheme 1.14).[145] Its derivatives are promising candidates in the discotic liquid crystals field.



Scheme 1.13: Synthesis of benzotrithiazole derivative **1.90**.



Scheme 1.14: Proposed mechanism for benzotristhiazole derivative **1.97**.

In 2017, Danko group synthesized the compounds **1.98-1.100** (Figure 1.14), which act as donor-acceptor NLO-phores in polymer matrices and also have photon cellular imaging ability.[146]

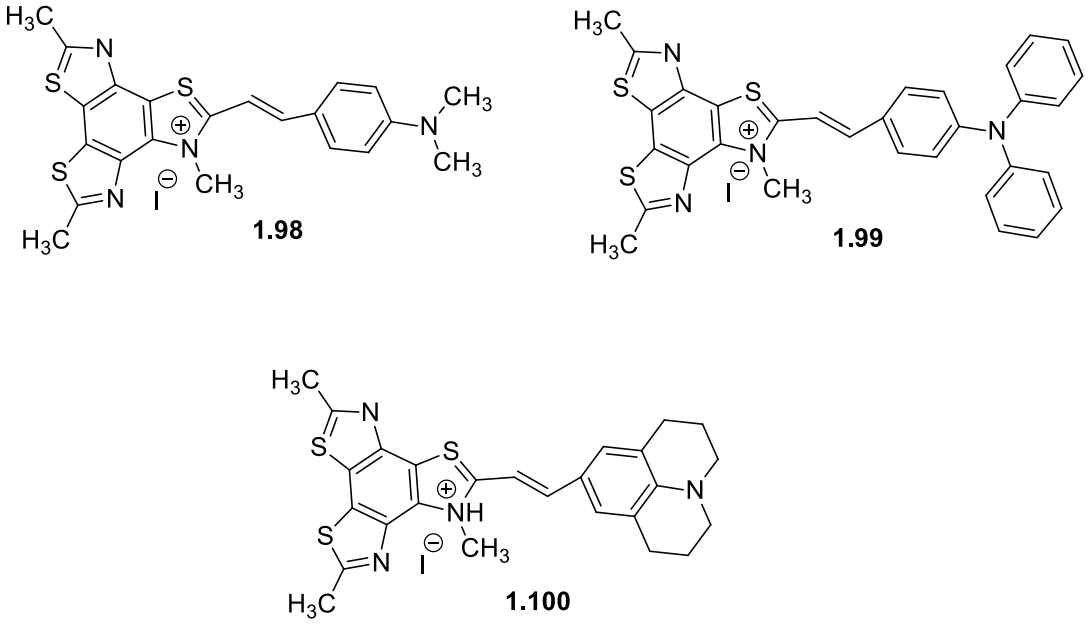
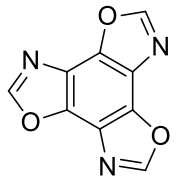


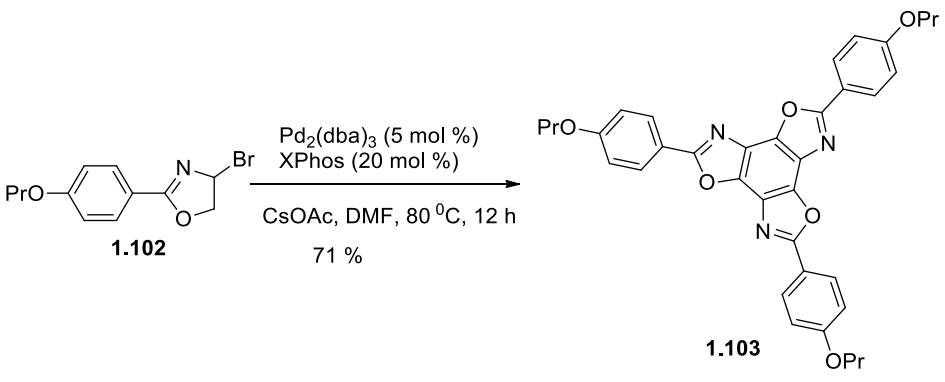
Figure 1.14: Structures of benzotristhiazole derivatives **1.98-1.100**.

1.10 Benzotrisoxazoles

In 2018, Jin group reported benzotrioxazole **1.101** based compound **1.103** (Scheme 1.15) from **1.102** using a Pd-catalyzed cyclotrimerization in excellent yield and further its derivatives can be explored as good candidates for optoelectronic material application with star-shaped discotic crystal structures and high fluorescence quantum yields.[147]



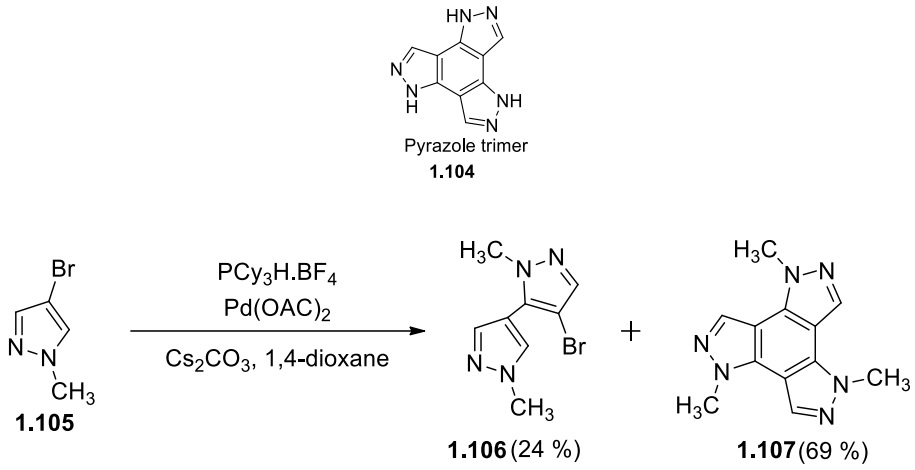
Benzotrisoxazole
1.101



Scheme 1.15: Synthesis of benzotrisoxazole derivative **1.103**.

1.11 Benzotripyrazoles

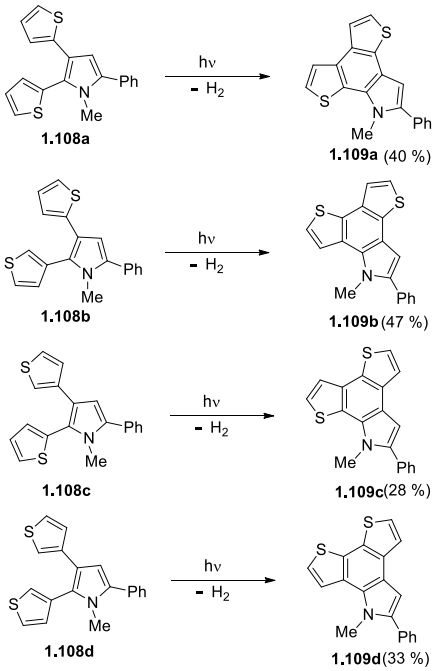
Recently, Joo group reported benzotripyrazole **1.104** based compound 1.**107** by cyclotrimerazation, using Pd catalyzed C-H annulation way from **1.105** in moderate yield (Scheme 1.16) and their compound may find uses in organic electrode materials.[148]



Scheme 1.16: Synthesis of pyrazole trimer derivative **1.107**.

1.12 Dithienoindoles

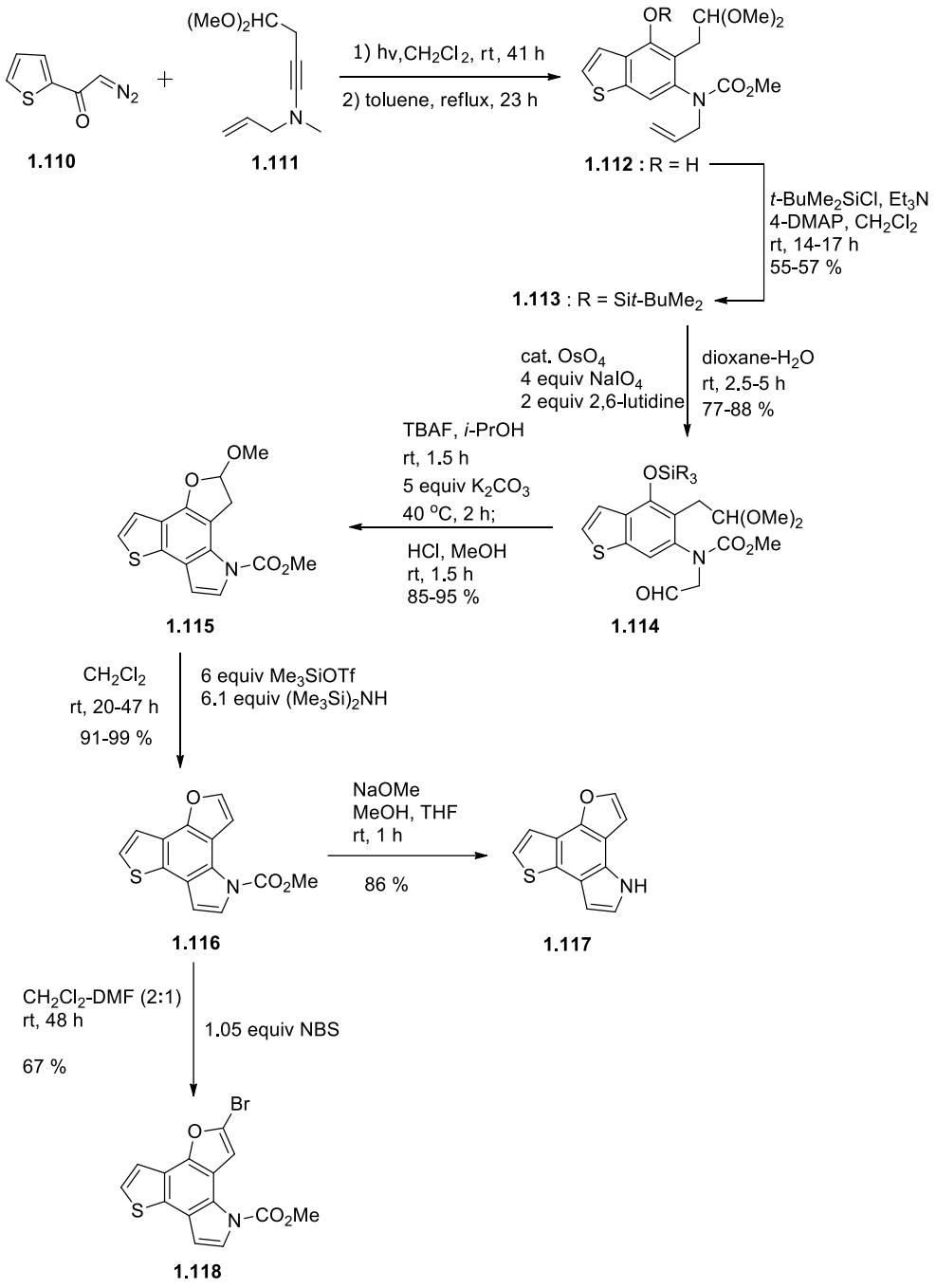
Isomeric 2,3-dithienyl-5-phenylpyrroles **1.108a-1.108d** yielded isomeric dithienoindoles **1.109a-1.109d** upon oxidative photocyclisation in a series in 28-47 % by Teo group in 1987 shown in scheme 1.17.[149]



Scheme 1.17: Synthesis of dithienoindoles **1.109a-1.109d**.

1.13 Furothienoindole

In 2018, Danheiser group synthesized **1.117** with three different heterocyclic rings for the first time, by photochemical benzannulation with ynamide-based systems in an efficient way and they have done bromination on **1.116** (Scheme 1.18).[150]



Scheme 1.18: Synthesis of furothienoindole **1.117**.

1.14 Benzo-fused pyrroles

1.14.1 Benzopyrroles

1.24 and **1.121** are heterocyclic aromatic compounds with bicyclic system in which pyrrole is fused at different positions with benzene.

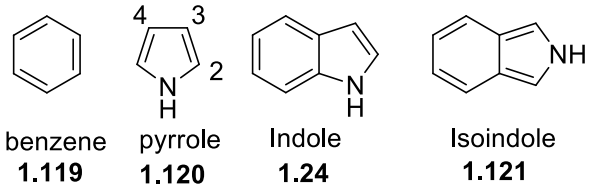
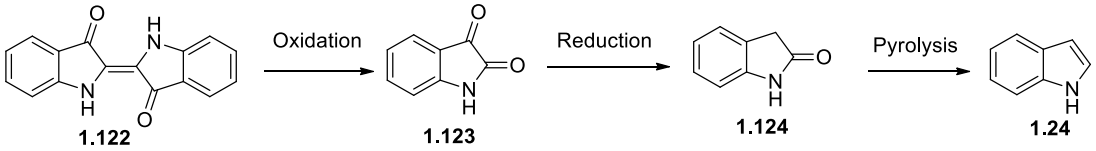


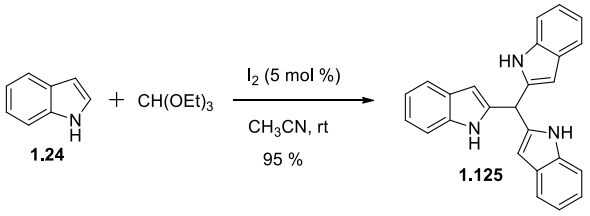
Figure 1.15: Structures of indole **1.24** and isoindole **1.121**.

In 1869, A. Baeyer proposed the formula for **1.24**[151] and it was obtained with zinc dust by pyrolysis of 2-oxiindole for the first time in 1866 (Scheme 1.19),[152] and its synthesis was followed by many different routes later. Next, Fischer indole synthesis opened further developments on **1.24** derivatives.[153]



Scheme 1.19: First synthesis of indole **1.24**.

Zhang and Lin group reported **1.125** from **1.24** using catalytic amount of iodine in acetonitrile at room temperature in high yield as shown in scheme 1.20.[154]



Scheme 1.20: Synthesis of triindolylmethane **1.125**.

1.14.2 Benzodipyrroles

These are heterocyclic systems consisting of two pyrroles fused with a benzene and can result in five isomers upon fusion through 2,3-pyrrolic positions (Figure 1.16).

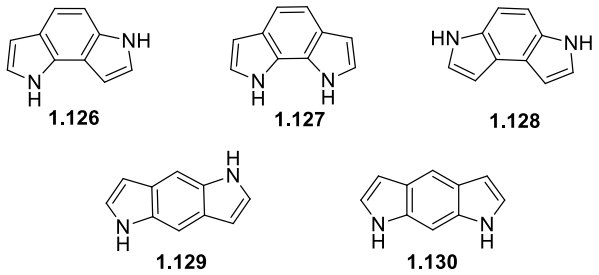
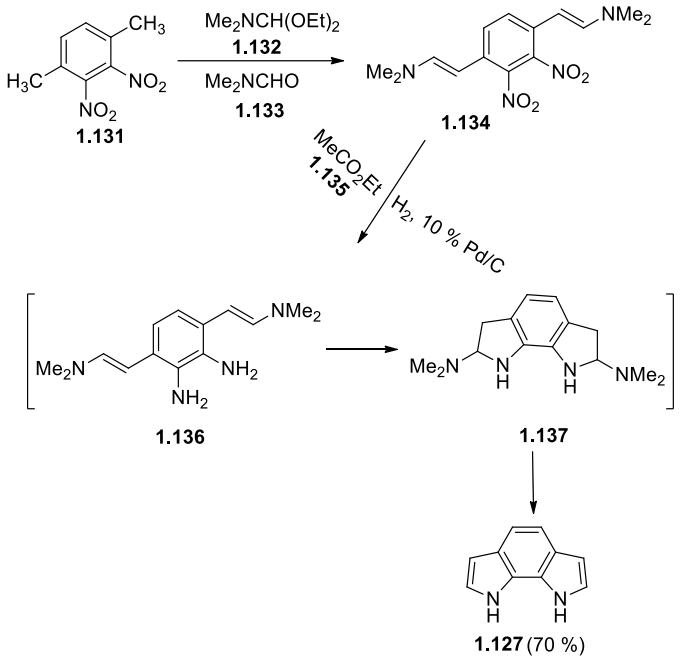


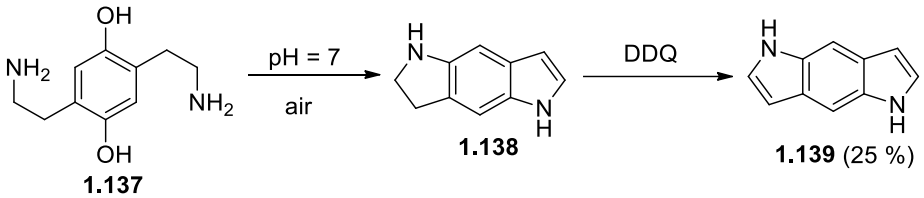
Figure 1.16: Isomers of benzodipyrroles **1.126-1.130**.

1.127 type of molecules were in gram scale first synthesized by Berlin *et al*. from **1.131**, using **1.132**, and **1.133** via condensation and followed by reduction (Scheme 1.21).[155]



Scheme 1.21: Synthesis of benzodipyrrole **1.127**.

Baxter and coworkers established the synthesis of **1.139** in 1973 by oxidative cyclization reaction from **1.137** in presence of air at pH = 7 and followed by oxidation of **1.138** with DDQ in 25 % yield (Scheme 1.22).[156]



Scheme 1.22: Synthesis of benzodipyrrole **1.139**.

These have evoked considerable interest in different fields of chemistry, like sensors for oxoanions in the development of ionophores,[157] semiconductor materials.[158,159] In the pursuit for the development of PDT efficacy, in 2005, Lee and coworkers reported a **1.127**-derived expanded porphyrin, namely sapphyrin **1.140** in 18 % yield (Figure 1.17), where **1.127** unit could furnish nice tuning of the macrocycle electronic properties.[160-161] On the other side, tetraalkylated dibenzoporphycenes **1.141-1.142** (Figure 1.17), have been synthesized for promising use in PDT applications.[155,162]

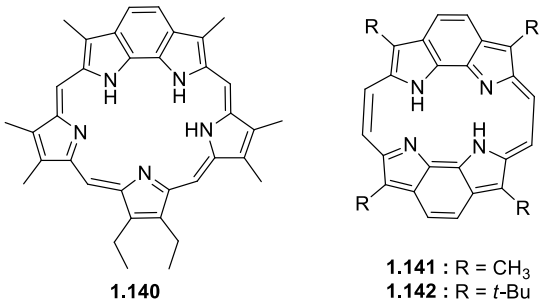


Figure 1.17: Benzodipyrrole-derived sapphyrin **1.140**, tetramethyldibenzoporphycene **1.141** and tetra-*tert*-butyldibenzoporphycene **1.142**.

Recently, Kuo group synthesized a new air stable BDPM derivatives **1.143-1.144** in good yields, which are useful as active materials for n-type organic field-effect transistors.[163]

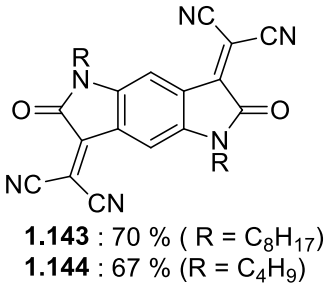


Figure 1.18: Structures of BDPM-based derivatives **1.143** and **1.144**.

1.14.3 Benzotripyrroles

Like the abovementioned benzotriheteroarenes, benzotripyrroles are expected to have interesting applications in various fields such as materials chemistry, biological chemistry, etc. It can exist in seven possible isomers **1.145-1.151**, which are depicted in figure 1.19.[164] In 1979, Gall et al. synthesized **1.152** and **1.153** (Figure 1.20) from hexakisbromomethylbenzene **1.154** with benzyl amine in nitromethane under argon atmosphere.[165]

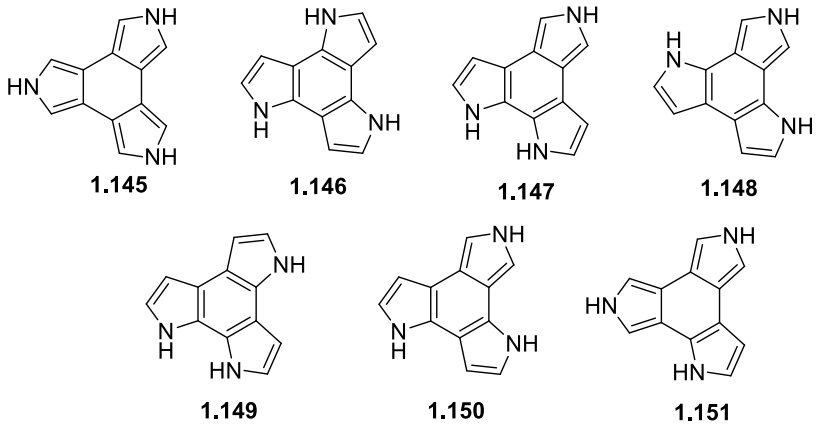


Figure 1.19: Seven possible isomers of benzotripyrrole **1.145-1.151**.

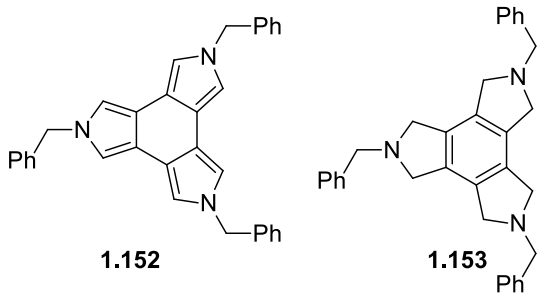
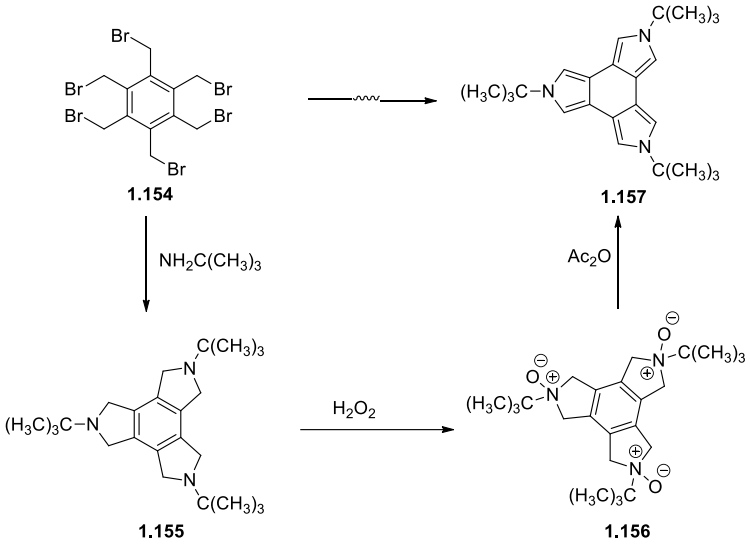


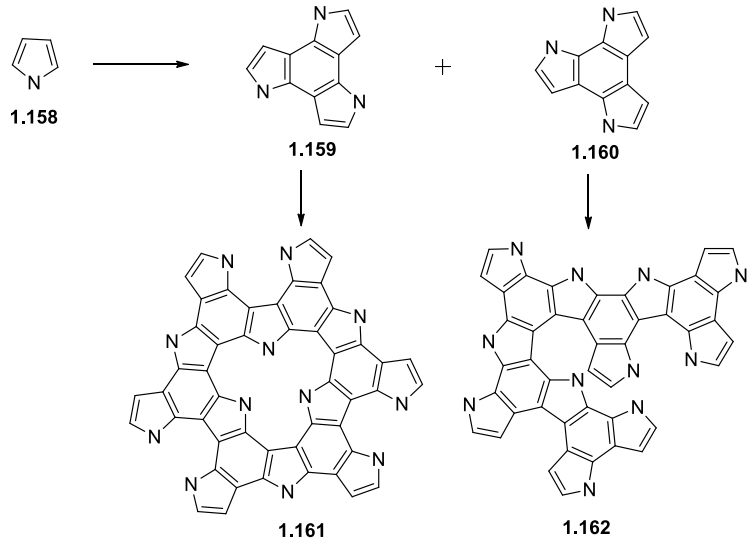
Figure 1.20: Structures of benzotripyrrole derivatives **1.152** and **1.153**.

In 1988, Kreher group also reported the synthesis of **1.157** from **1.154** via a cyclization using amines, oxidation with H_2O_2, and followed by acetolysis of the corresponding tricyclic N-oxides.[166] He also explained the structure and reactivity of isoannelated heterocyclic systems.



Scheme 1.23: Synthesis of tripyrrole derivative **1.157** from **1.154**.

In 1993, an electrochemical polymerization mechanism model of macrocyclic polypyrrole has been depicted (Scheme 1.24), whose conductivity can be used in advancement of various products such as polypyrrole electrode in rechargeable batteries, sensors for ELMI shielding, conductive coatings for plastic surfaces and in making of printed circuit boards.[167] The trimer units can also be used as a building block towards the proposed cyclic polypyrrole model **1.163** (Figure 1.21**)**. As they are very reactive towards the polymerization reaction, it is difficult to isolate the desired products.[167]



Scheme 1.24: Electropolymerization of pyrrole.

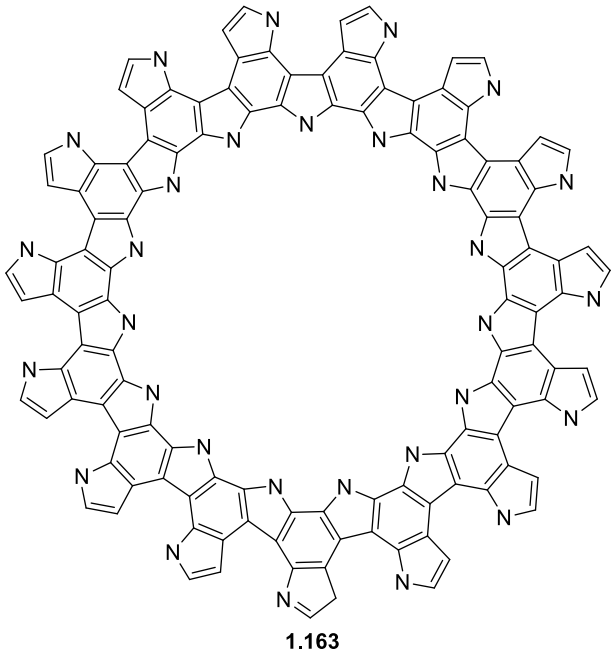
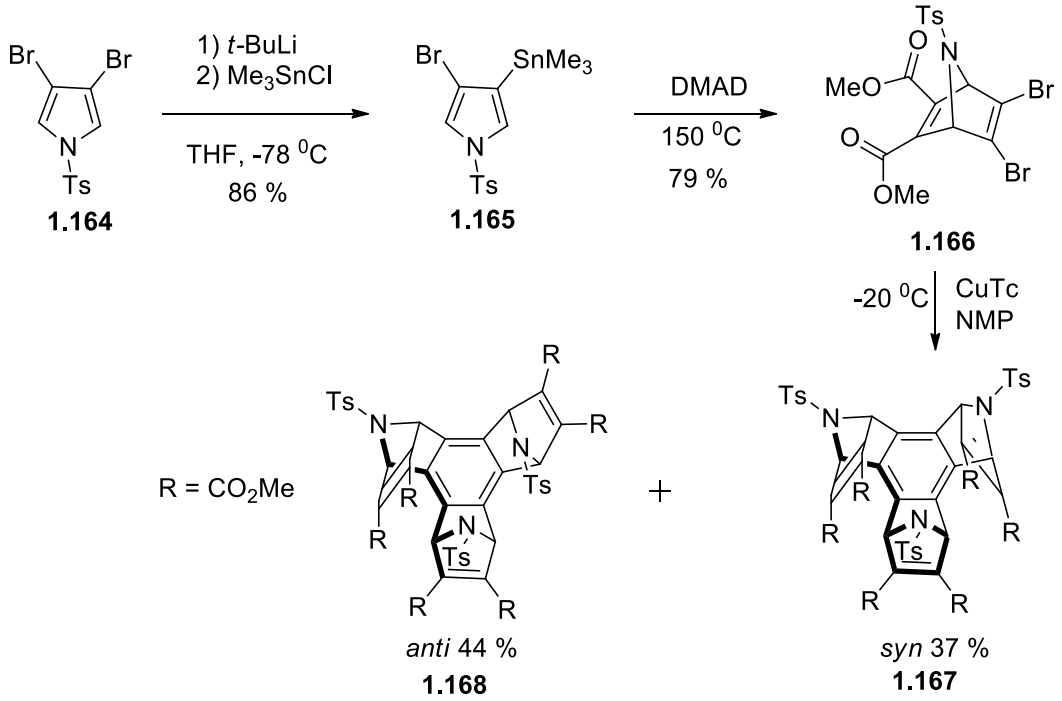


Figure 1.21: Structure of proposed cyclic polypyrrole model **1.163**.

In 2005, Zonta group synthesized fully functionalized cup-shaped cyclotrimers **1.167** and **1.168** from *β*-dibromo-substituted pyrrole **1.164** via metalation, cycloaddition and cyclotrimerization in good yield.[168]



Scheme 1.25: Synthesis of cup-shaped molecules **1.167** and **1.168**.

So far there are very few reports dealing with the synthesis of conjugated benzotripyrroles **1.146-1.150**.[164] This will be discussed in the subsequent working chapter.

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CHAPTER 2

One-pot synthesis of benzotripyrrole derivatives from 1H-pyrroles

2.1 Introduction

Porphyrins are a significant kind of aromatic compounds that are plentiful in nature and prime to all sorts of life. Sovereign examples include hemes, porphyrins containing iron that play mighty role in electron transport in ATP synthesis (cytochromes), oxygen storage (myoglobin), oxygen transport (hemoglobin).[1] Reduced porphyrins with magnesium complexes occur as photosynthetic bacteria (bacteriochlorophylls) and photosynthetic pigments of plants (chlorophylls) (Figure 2.1). As life hugely depends on these processes, porphyrins are called "pigments of life".[2] Porphyrin name comes from Greek word 'porphyros', which means purple. In addition to its biological functions, its emission and absorption properties, aromaticity and capability of binding with almost all metals in the periodic table accessed it as the extensively investigated macrocycle among all ring systems exist.[3]

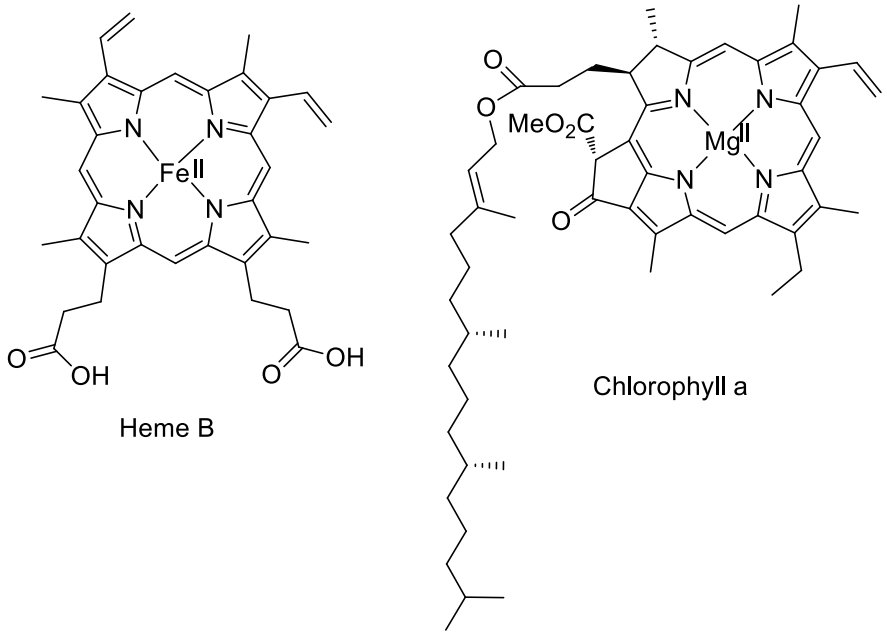


Figure 2.1: Structures of iron and magnesium porphyrins.

Generally, porphyrin (Figure 2.2) systems contain four pyrrole units connected through four "methine bridges" at their α-carbon atoms to give a square planar geometry in a coplanar fashion. The outer pyrrole carbon units are named as *β*-carbons while the "methine bridges" are quoted as *meso*-carbons. They contain 22π electrons of which 18π electrons are in conjugation, which makes it display an intense absorption band in near UV region designated as "Soret band".[4] Porphyrins aromaticity at times described as arising out of a

substructure of [18]-annulene system, even though theoretical calculations show a different picture engaging the entire π-system.[5]

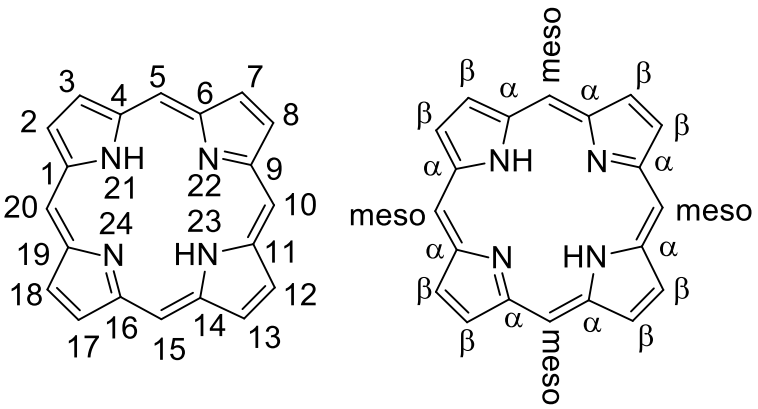


Figure 2.2: Structure of porphyrin and its numbering.

Understanding of porphyrins started as early as 1840s,[6] creating immense interest to investigate its biological, optical, photophysical, chemical properties involving broad areas such as catalysis, material chemistry, optoelectronics, as photosensitizers in photodynamic therapy etc. These types of significant and important roles led to a novel research field in advancing many synthetic systems like isomeric, expanded, contracted, confused, inverted, and core modified porphyrins which are nearly similar to macrocycles of naturally occurring but quite different chemically.[3]

Corroles are contracted porphyrins (Figure 2.3). They contain four pyrroles in which two pyrroles are directly connected by missing one meso carbon in the skeleton and maintaining the corrin skeletal structure. They are structurally similar to well-known porphyrin, while maintaining the aromaticity with 18π electrons in conjugation. With pyrrole-pyrrole linkage directly resulting in a smaller cavity, symmetry reduction, and capacity to aid higher oxidation states of various metal ions, such as Co(IV), Co(V), and Fe(IV). Unlike porphyrins, they are not available in nature but its close counterpart corrin ring present in naturally occurring vitamin B_{12} (Figure 2.3). It is reported as the first contracted porphyrins by Johnson and Kay in 1965.[7] An advance synthetic route is reported by two different research groups in 1999.[8-10] Vogel' group reported unanticipated corrole complexes by using metals with high oxidation states.[10] They are very different from porphyrins and corrins, which are dianionic and monoanionic ligands, respectively, as they are having in the inner core three amino and one imino nitrogen atoms and act as trianionic ligand with unique property. The anionic forms of them is obtained easily by addition of bases in organic solvents, since they are more acidic when compared to porphyrins.[11]

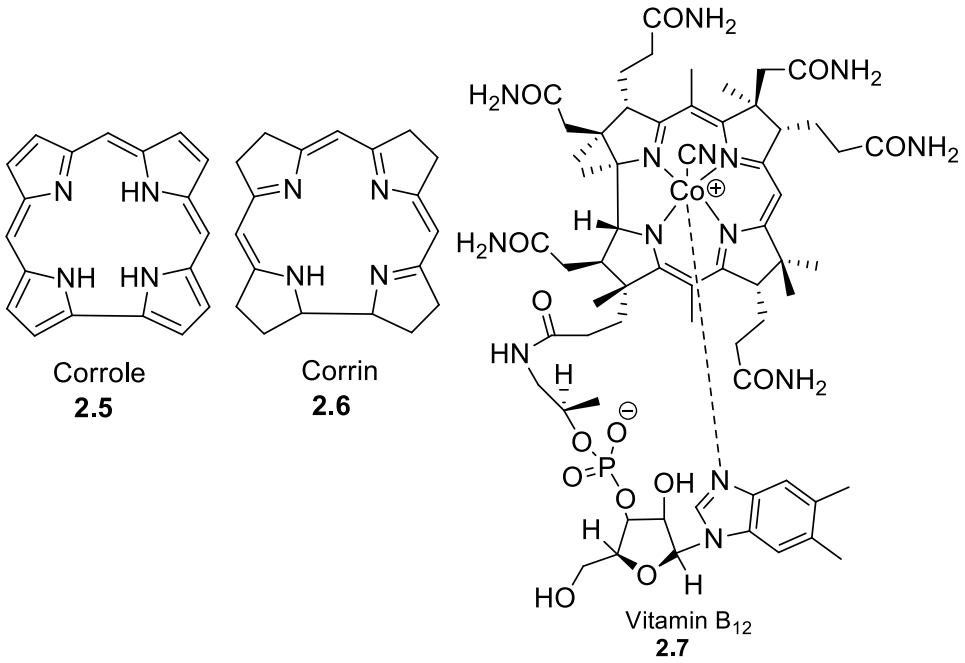


Figure 2.3: Structures of corrole, corrin, and vitamin B_{12}.

The properties of metallocorroles like stabilizing the metals such as Au^{III},[12] Fe^{IV},[13] Pt^{IV},[14] Th^{IV},[15] that allowed them having applications in various fields such as medicine,[16] sensors,[17] and catalysis.[18] Further, their freebases[19] with high luminescence quantum yields have been utilized in photoactive arrays,[20] imaging,[16a,21] to build sensors,[22] singlet oxygen sensitization.[19c,23] They have been broadly utilized in dye-sensitized solar cells.[24]

Sapphyrin is the first reported example of expanded porphyrins and also considered as one of the most extensively studied among them so far (Figure 2.4). It can be conventionally originated from porphyrin by exchanging one pyrrole moiety with a bipyrrole unit. Hence, it also consists of four meso carbons as porphyrin. It has 22 pi-electrons in conjugation in the shortest pathway, whereas, porphyrin possesses 18 pi-electrons and thus, it is aromatic like porphyrin.

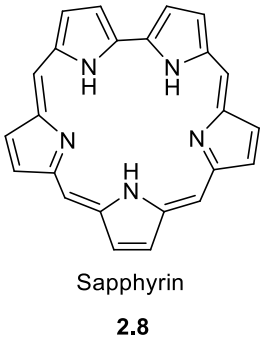
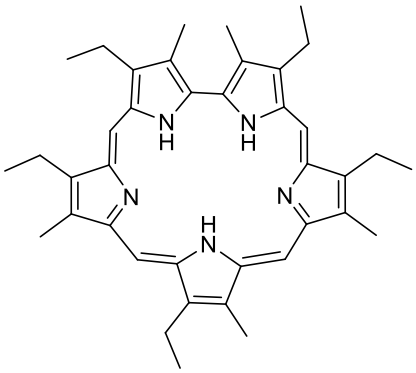


Figure 2.4: Structure of sapphyrin **2.8**.

They are a kind of "heterocycle-inserted" expanded porphyrins and consist of a (1.1.1.1.0) arrangement of meso carbons. It is discovered while trying to synthesize vitamin B_{12} by R. B. Woodward and coworkers.[25-27] He coined the name "sapphyrin" to this kind of macrocycle as it is intense green color in organic solution and deep blue in the solid state. As inferred above, its first synthesis was completely accidental and resulted from linear tetrapyrrolic unit with HBr, formic acid and followed by iodine as an unexpected macrocycle shown below in figure 2.5.[26] In 1969, Johnson and coworkers synthesized dioxasapphyrin derivative.[28]



2.9

Figure 2.5: Structure of first synthesized unexpected sapphyrin **2.9**.

Sessler's group first time reported in 1991 through crystallographic evidence that the diprotonated sapphyrin is capable of binding to anions.[29] This raised immense interest into the investigation of whether they could be utilized to transport and bind biologically active anions. Generally, sapphyrins in freebase form show an intense Soret-type absorbance band at 450 nm, which is approximately 50 nm red-shifted compared to that of porphyins and shows comparatively three weak Q-type bands in the visible region of spectrum at 620-710 nm range. These bands intensity increase and are blue shifted to 615-690 nm generally upon protonation and the number of noticed Q-bands varies from two to four in number for protonated sapphyrins depending upon which acid is utilized. The matter of fact is sapphyrins absorb light about the edge of the physiological "window of transparency"[30] which occurs in the 700- 900 nm range. This drives sapphyrins and their derivatives interesting candidates for PDT as photosensitizers.[30-35] Oligomeric sapphyrin systems were noticed as extremely good receptors of amino acids, nucleotide di- and triphosphates, and dicarboxylate anions.[36-38]

2.2 Motivation and objective of the present work:

Our major objective is to explore novel synthetic porphyrinoids as a special kind of macrocycles exhibiting unique coordinating ability, photophysical properties, variable aromaticity, and structural diversity.[39] Particularly, we are very eager to flourish new macrocycles provided with bipyrrolic moieties. 2,2'-bipyrroles are utilized as significant building blocks in the synthesis of various porphyrinoids, including porphycene, corrole, sapphyrin, cyclo[8]pyrrole, rosarin and octaphyrin.[40] Further, they are also crucial units in natural products like prodigiosin **2.10** (Figure 2.6).[41] It has motivated new researchers to investigate their structural variants, for example, Sessler and coworkers made an inverted sapphyrin **2.11** with *N*-protected 3,3'-bipyyrolic unit (Figure 2.6), which exhibited weak aromatic character.[42]

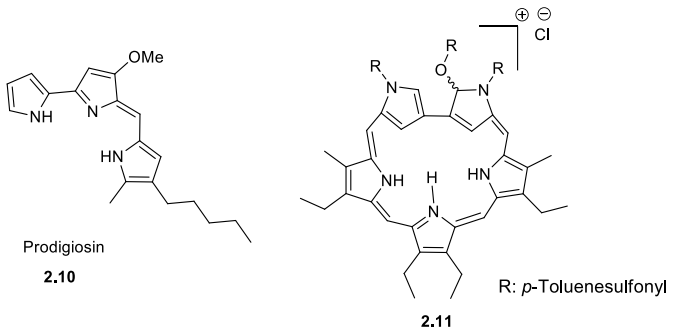


Figure 2.6: Structure of prodigiosin **2.10** and inverted sapphyrin **2.11**.

Thereafter, Ishida *et al*. and recently, Srinivasan's and Grazynski's groups individually utilized biphenyl and bipyridyl, phenanthrene, and 1,10-phenanthrolene as bipyrrole variants to synthesize different porphyrinoids **2.12-2.15** (Figure 2.7), which showed very interesting aromaticity, coordination chemistry, and metal sensing ability, and also produced a stable singlet biradical.[43]

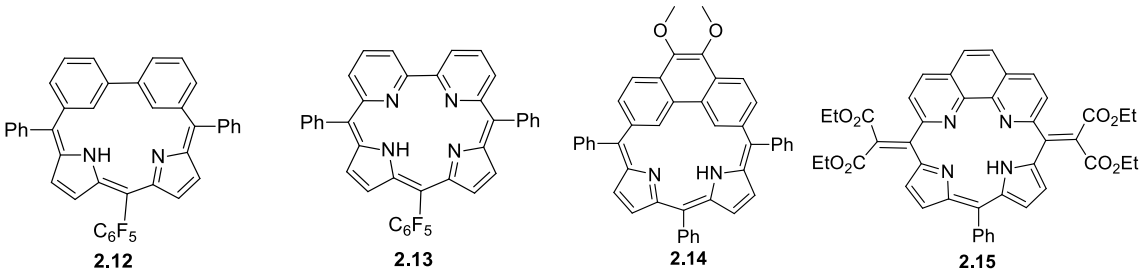
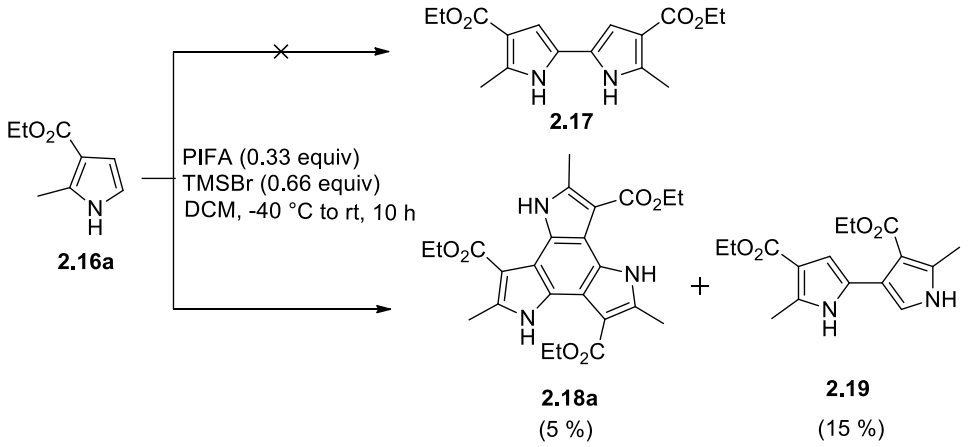


Figure 2.7: Structures of porphyrinoids **2.12-2.15**.

This motivated us to proceed in this direction, to flourish new basic units like bipyrrole **2.17**. However, we isolated benzotripyrrole (BTP) (**2.18a**) during our effort to synthesize **2.17** (Scheme 2.1).



Scheme 2.1: PIFA-mediated synthesis of BTP **2.18a**.

For example, we treated ethyl 2-methyl-1H-pyrrole-3-carboxylate **2.16a** with an acid catalyst like PIFA and TMSBr at -40 ^{0}C by oxidative coupling to synthesize **2.17**,[44] but the Thin layer chromatography result was difficult to analyze. A clear nonpolar spot **2.18a**, accompanied by **2.19** and some more extra polar spots were observed. Seperation and subsequent ^{1}H NMR analysis of above mentioned nonpolar spot disclosed no proton resonance correspond to *β*-pyrrolic position as predicted for an intended bipyrrole (Figure 2.8).

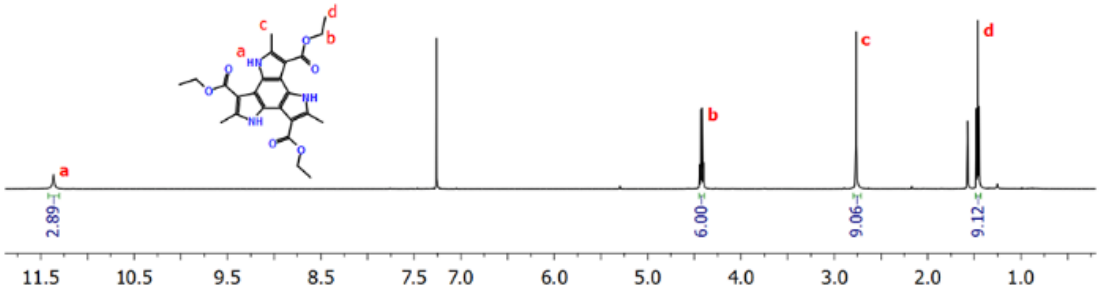


Figure 2.8: ^{1}H NMR spectrum of BTP **2.18a** in $CDCl_3$ (δ-scale in ppm).

Similarly, ester CH_2 and CH_3, as well as α-methyl protons showed at 4.41 (q), 1.47 (t) and 2.76 (s) ppm, respectively. In addition, the pyrrolic NH appeared as a broad peak at 11.36 ppm denoted presence of very strong hydrogen bonding. This guided us to conclude the formation of either 4,5-dibromopyrrole derivative or the formation of a cyclized product. Subsequently, the HRMS spectrum disclosed a molecular ion peak at 454.1978 (Figure

2.9), which ruled out the chance of formation of the dibromo compound and further led us to assume it as a trimeric cyclic analogue of the pyrrole derivative **2.16a**.

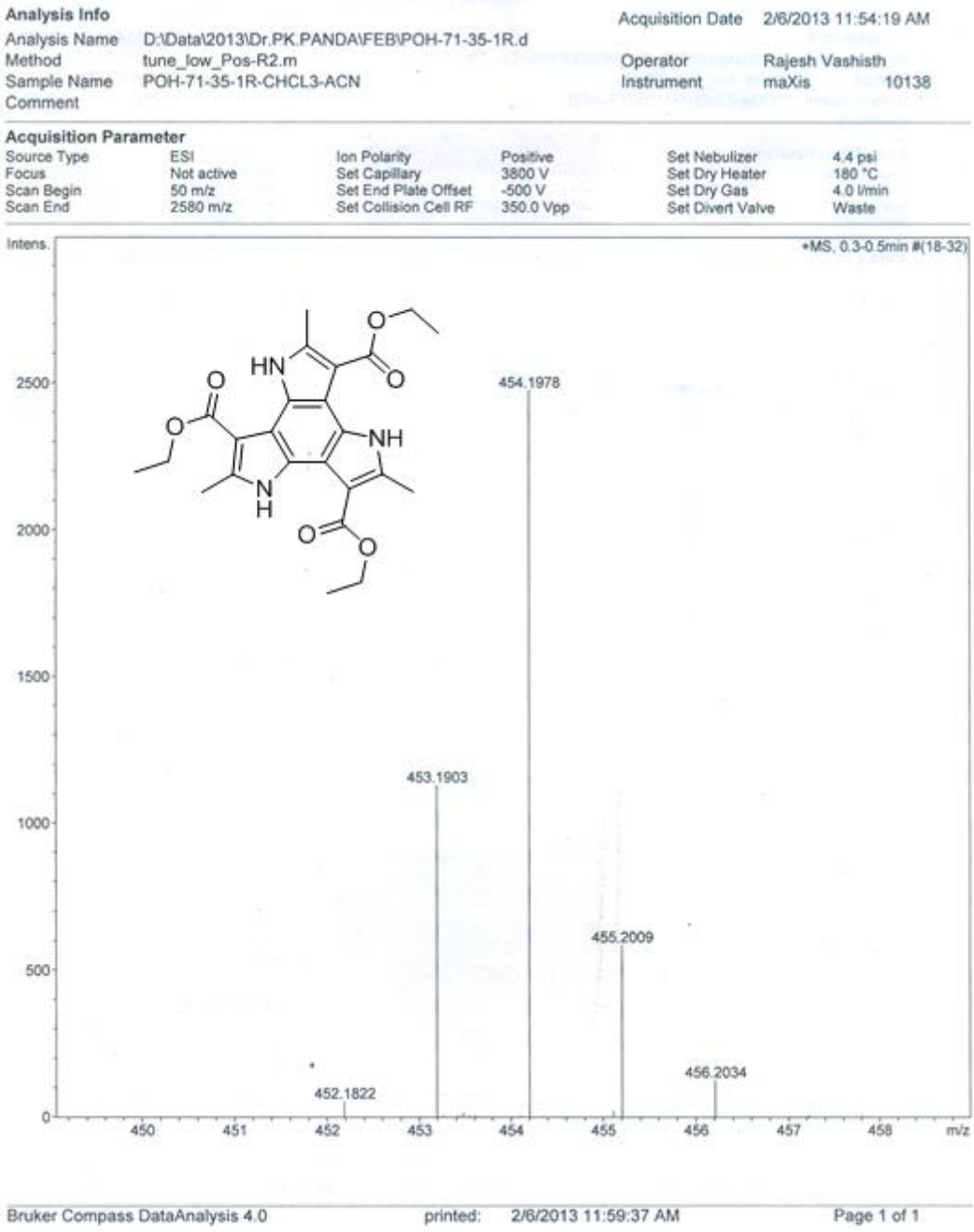
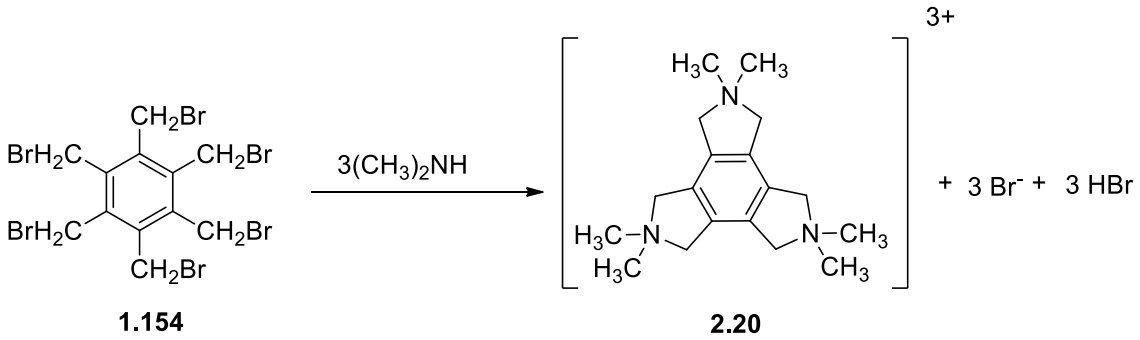


Figure 2.9: HRMS data of **2.18a** $(M+H)^+$; Calculated for $C_{24}H_{28}N_3O_6$: 454.1978; found: 454.1978.

Finally, the compound's structure was unequivocally confirmed as **2.18a** by single crystal XRD analysis (the crystals were obtained from very slow evaporation of hexane-chloroform solution).

2.3 Relavence of benzotripyrroles:

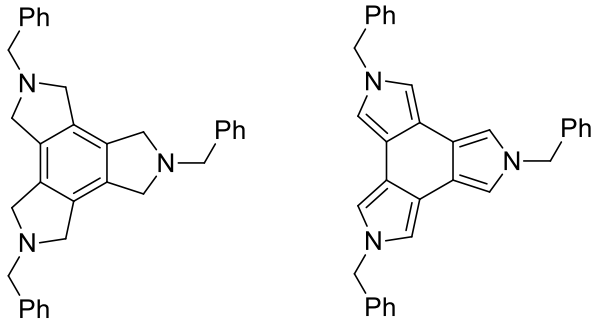
In literature, we found similar type of compounds like BTP. For example, in 1978, Ciric et al. hoped to synthesize the tri-*N*-methylated BTP with D_{3h} symmetry but could be able to obtain **2.20** only from **1.154** in nitromethane upon heating with dimethylamine (Scheme 2.2).[45]



1.154 **2.20**

Scheme 2.2: Synthesis of **2.20**.

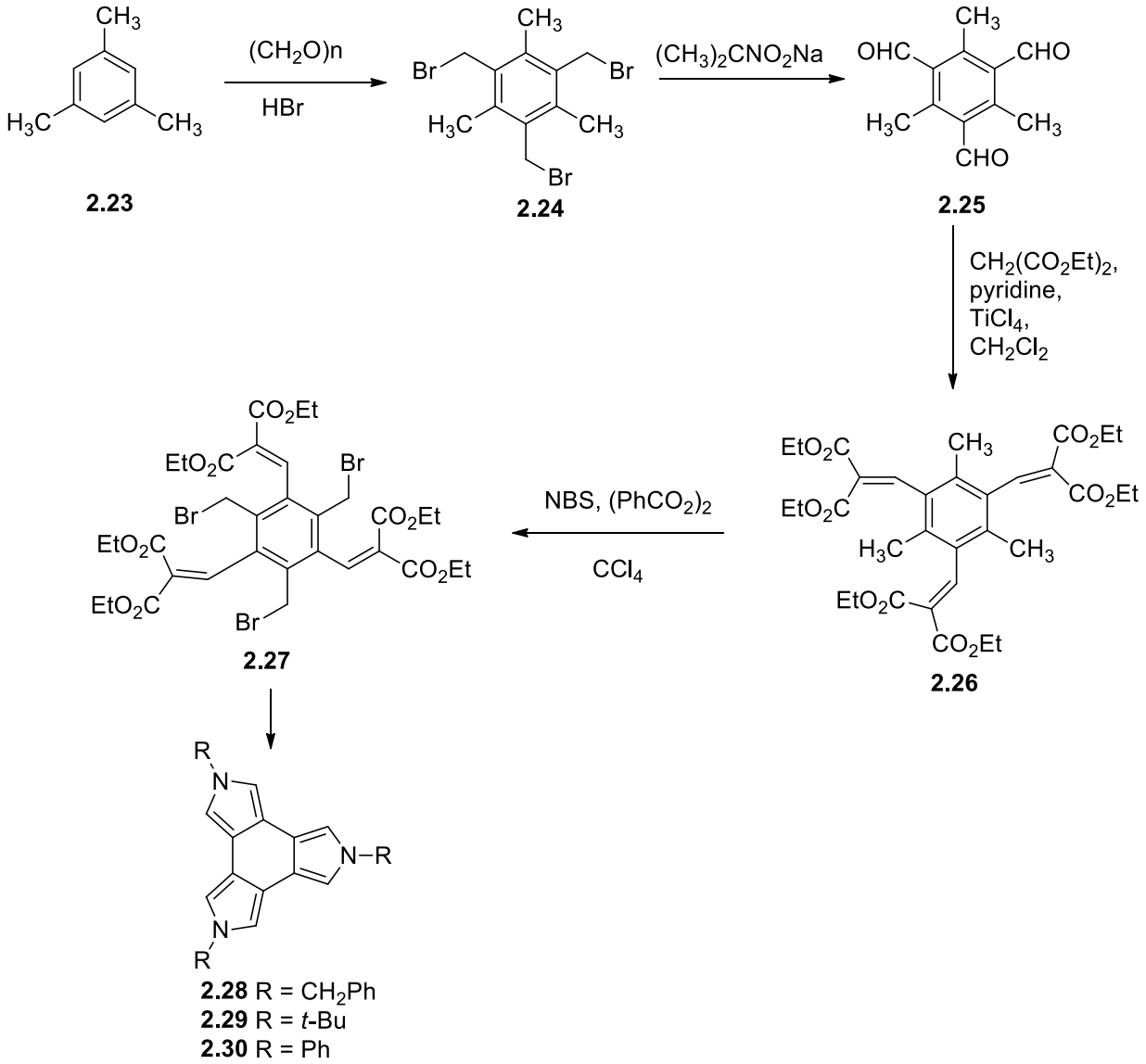
In 1979, **2.21** was obtained from **1.154** and benzylamine, whose structure was confirmed by single crystal X-ray analysis and further converted into **2.22** using *m*-chloroperbenzoic acid and acetic anhydride.[46]



2.21 **2.22**

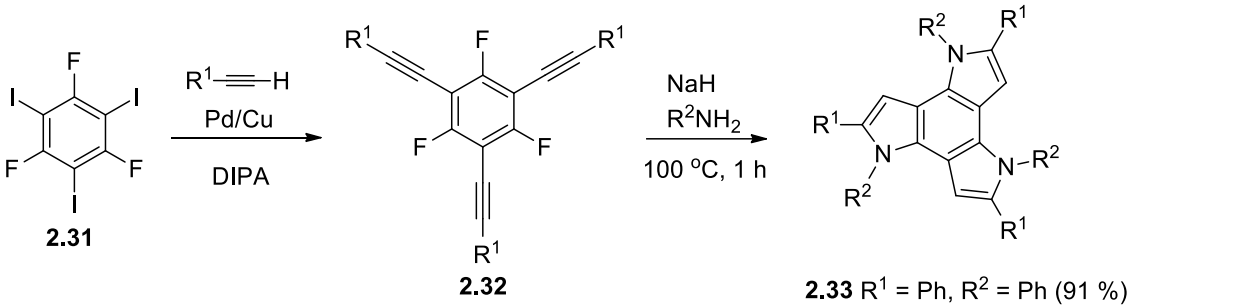
Figure 2.10: Structures of **2.21** and **2.22**.

In 1992, Sha's group synthesized iso-condensed heteroaromatic pyrroles efficiently (Scheme 2.3).[47]



Scheme 2.3: Synthesis of iso-condensed heteroaromatic pyrroles **2.28**-**2.30**.

Recently, Nakamura and Tsuji's group reported the successful synthesis of BTPs with C_{3h} symmetry, starting with **2.31** in two steps (Scheme 2.4).[48] They reported several BTPs whose α-positions and pyrrolic Ns are protected. Thus, once these BTPs are synthesized, there is no possibility of further modifications like those observed in the case of TAT and BTT derivatives for the evolution of desired compounds for various material science applications. In addition to that, high cost Palladium catalyst has been used in this methodology.



2.33 R^1 = Ph, R^2 = Ph (91 %)
2.34 R^1 = Ph, R^2 = C8H17 (91 %)
2.35 R^1 = Ph, R^2 = Cy (82 %)
2.36 R^1 = 2-Me-C6H4, R^2 = Ph (90 %)
2.37 R^1 = 4-CF3-C6H4, R^2 = Ph (97 %)

Scheme 2.4: Synthesis of BTPs **2.33-2.37**.

2.4 Results and discussion

The planar nature of BTP was observed from the solid state structure with very strong H-bonding between the pyrrolic NH and adjacent pyrrolic carbonyl oxygen (∠N-H···O = 141˚; N-H···O = 2.766 (2) Å, Figure 2.11a), which agrees well with the NH proton resonance observed in the ^{1}H NMR spectrum. Strong π-π stacking was noticed between the BTPs from the packing diagrams (d = 3.35 Å) (Figure 2.11b and 2.11c).

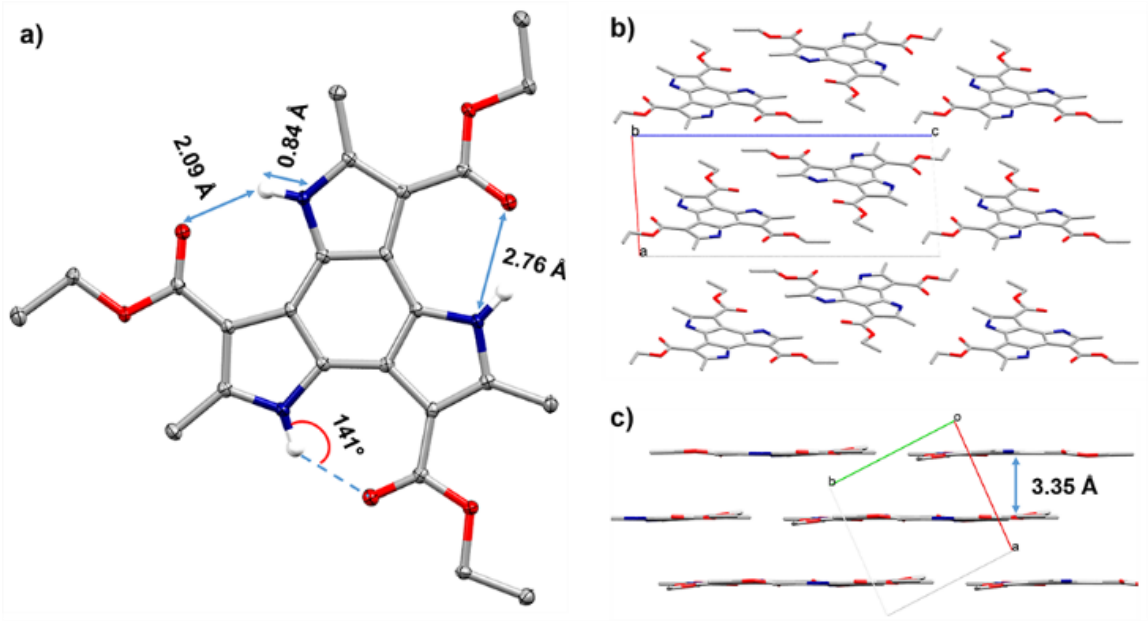
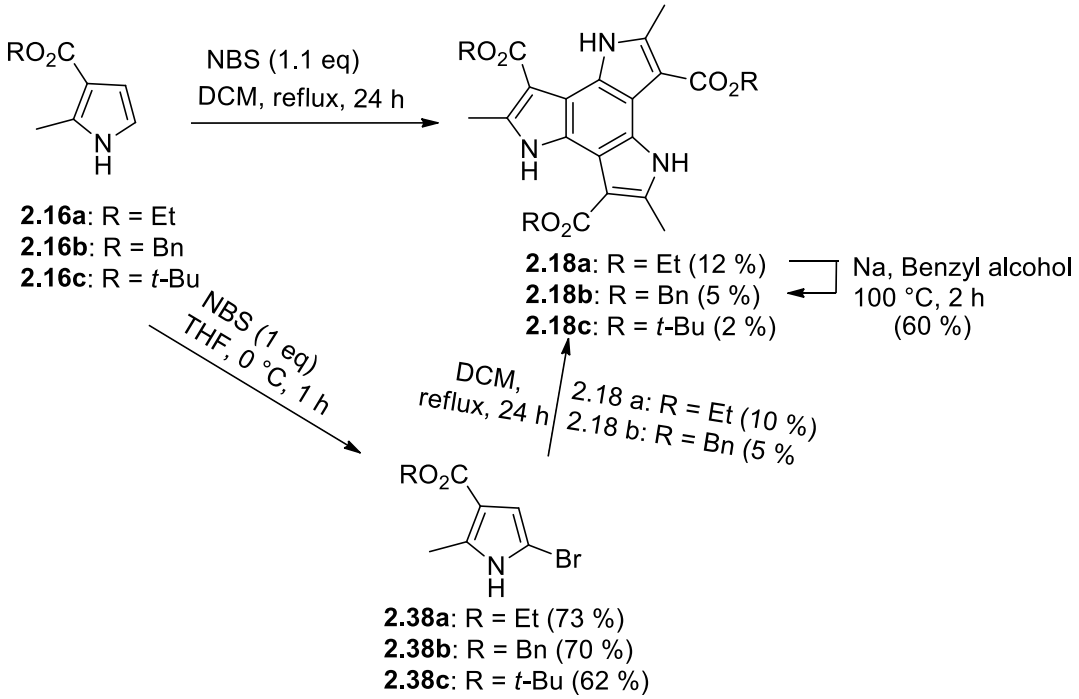


Figure 2.11: X-ray crystal structure of BTP **2.18a** and its packing diagrams viewed along the b- and c-axis. All hydrogen atoms bound with carbon atoms are omitted for clarity. Colour code: grey: C, blue: N, red: O and white: H.

Very careful investigation of these reaction conditions indicated another spot formation at low temperature, which later disappeared during the work up to form **2.18a** and followed by chromatographic purification. Very careful workup and further purification led to

separation of intermediate **2.38a** (Scheme 2.5) and its immediate and consequent proton NMR analysis confirmed the presence of one proton at *β*-pyrrolic position. This we assumed as the mono-bromo derivative **2.16a**. Then we carried out bromination with NBS on **2.16a** at low temperature to gather further evidence and observed same type of result. From this we concluded that the cyclization does not happen at low temperature and reaction proceeds via mono-bromination, which was consequently confirmed ^{1}H NMR spectroscopy by monitoring the reaction progress by at 25 ˚C using $CDCl_3$ (Figure 2.12).



Scheme 2.5: Synthetic approaches towards BTPs **2.38a-c**.

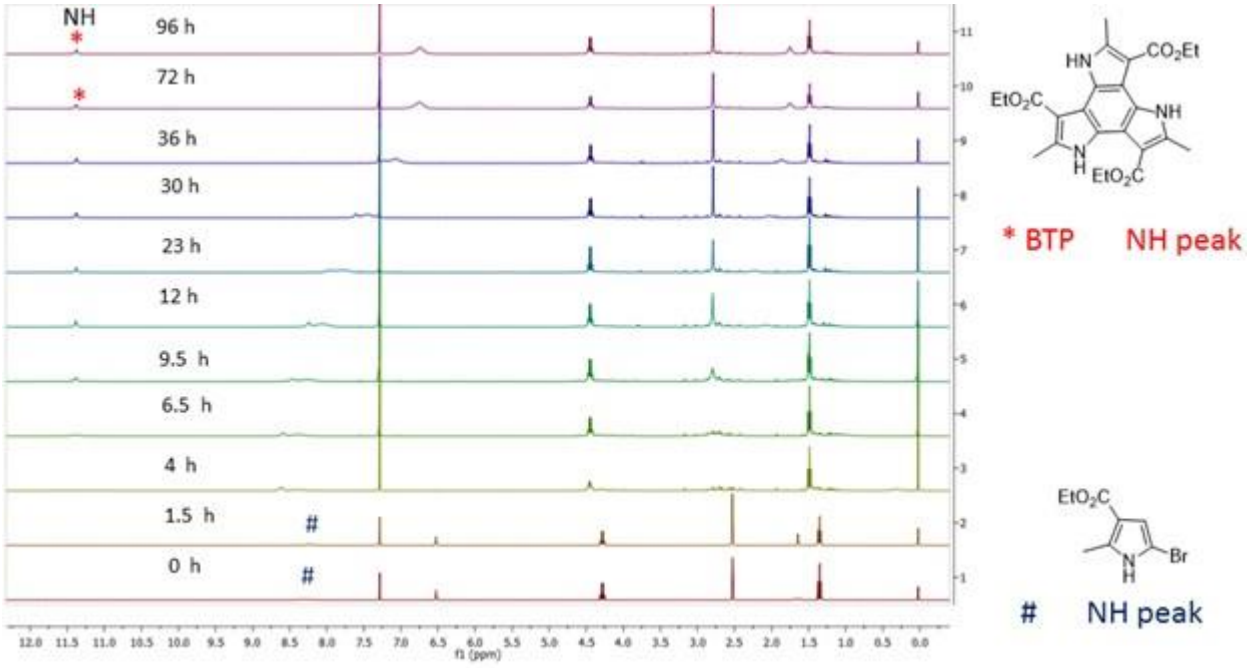
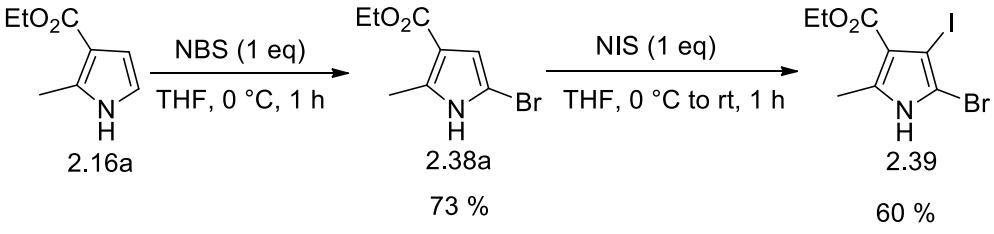


Figure 2.12: Reaction monitoring of BTP **2.18a** in $CDCl_3$.

However, the separation of this mono-bromo compound became a nightmare as it kept getting converted to **2.18a** under ambient conditions, even sometimes during removal of solvent in rotary evaporation, and consequently, it is degraded in neat conditions.[49]

Our further exploration of solvent effect preceded us to find that this process is more easy in halogenated solvents like 1,2-dichloroethane (DCE), chloroform ($CHCl_3$), dichloromethane (DCM), and **2.38a** was found to be reasonably more stable in THF in the solution state. Hence, this compound which is in the THF solution was dried and immediately subjected to iodination using NIS to isolate the bromoiodo compound **2.39** to confirm the bromine position on the pyrrole (Scheme 2.6). This product **2.39** was characterized unequivocally by ^{1}H and ^{13}C NMR spectroscopy, HRMS and also single crystal X-ray diffraction analysis (Figure 2.13).



Scheme 2.6: Synthesis of bromoiodo derivative **2.39**.

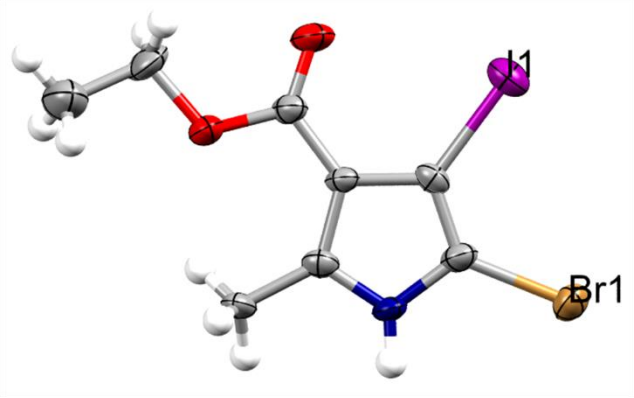
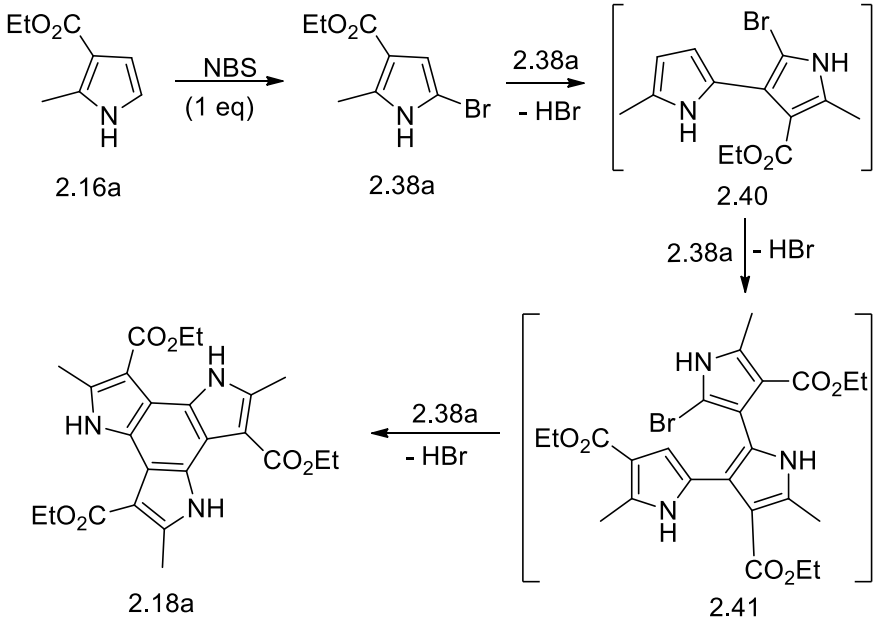


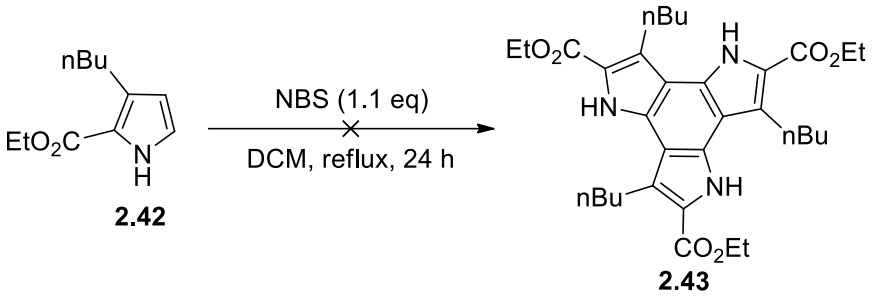
Figure 2.13: ORTEP Pov-ray diagram of compound **2.39**; Thermal ellipsoids are scaled upto 35% probability level; Color code: grey: C, Blue: N, Red: O, Brown: Br, Violet: I and White: H.

The formation of **2.39** revealed clearly that the reaction mechanism of synthesis of BTP involves formation of the 5-bromo derivative as first step and then subsequent dehydrobromination to obtain the cyclic product (Scheme 2.7).[50]



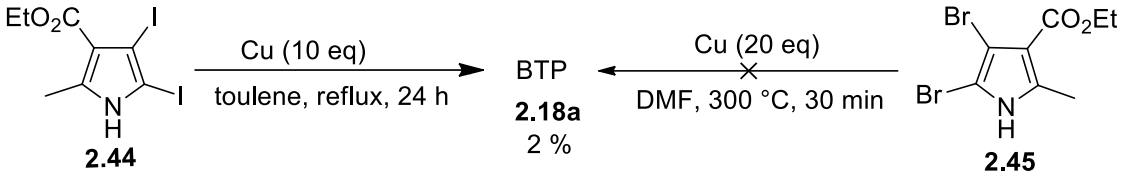
Scheme 2.7: Plausible mechanism for the synthesis of BTP.

This dehydrobromination is very specific to hydrogen atom at the *β*- and bromine atom at α-pyrrolic positions of this compound, as our curious effort with another pyrrole derivative **2.42**,[51] where their positions are exchanged, did not give the corresponding BTP (Scheme 2.8).



Scheme 2.8: Attempted synthesis towards BTP **2.43**.

Further, we have also tried to synthesize the BTP **2.18a** by Ullmann coupling of the 4,5-dibromo and 4,5-diiodo derivatives of pyrrole **2.45** and **2.44**, respectively (Scheme 2.9).[52] While the former (**2.44**) yielded only 2%, the latter (**2.45**) did not result in any product.



Scheme 2.9: Synthetic approaches towards BTP **2.18a**.

Solvent screening showed the reaction is workable only in halogenated solvents in general and not in solvents like tetrahydrofuran, methanol and acetonitrile (Table 2.1).

Table 2.1: Optimization of reaction conditions for BTPs formation.

entry	**substrate**	**Reagent (equiv)**	**solvent**	**Time (h)**	**Temp**	**compound**	**Yield (%)**
1	**2.16a**	NBS (1.1)	DCM	24	reflux	**2.18a**	12
2	**2.16a**	NBS (1.1)	$CHCl_3$	24	reflux	**2.18a**	10
3	**2.16a**	NBS (1.1)	DCE	24	reflux	**2.18a**	10
4	**2.16a**	NBS (1.1)	CCl_4	24	reflux	**2.18a**	2
5	**2.16b**	NBS (1.1)	DCM	24	reflux	**2.18b**	5
6	**2.16c**	NBS (1.1)	DCM	24	reflux	**2.18c**	2
7	**2.38a**	-	DCM	24	reflux	**2.18a**	10
8	**2.38b**	-	DCM	24	reflux	**2.18b**	5
9	**2.38c**	-	DCM	24	reflux	**2.18c**	Trace

However, the cyclization reaction was found to be dependent on the reaction temperature among the halogenated solvents. For example, the reaction performed in dichloromethane (DCM) for 24 h under reflux condition, obtained the BTP **2.18a** in 12% yield (Scheme 2.5). In chloroform ($CHCl_3$), refluxing for 24 h provided in 10% yield of the product BTP **2.18a** (Table 2.1). On the other hand, refluxing the reaction mixture in CCl_4 and DCE solvents resulted 2 and 10 % yields, respectively (Table 2.1). This shows that an increase in the reaction temperature, possibly enhanced side reactions leading to lessen the yield of BTP and was reflected in increased difficulty in chromatographic seperation of the desired product. It is noteworthy to mention here that during the reaction several close lying polar spots are found, which could not be isolated owing to their very similar polarity. Mass spectra analysis of the crude product indicated formation of higher cyclic products like tetramer and pentamer (Figure 2.14).

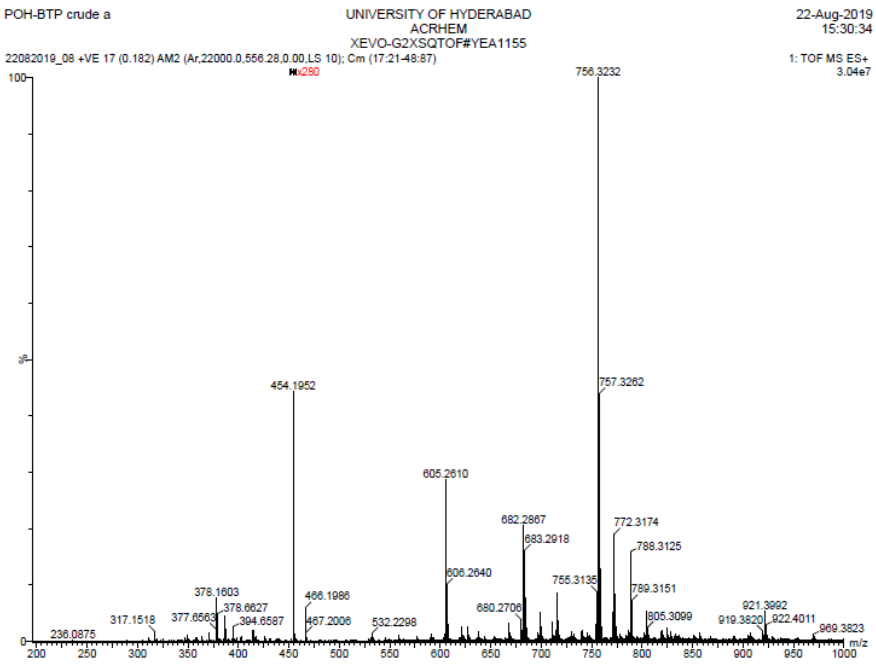


Figure 2.14: HRMS spectrum of crude reaction mixture: Calculated mass $[M+H]^+$ for trimer BTP (**2.18a**), $C_{24}H_{28}N_3O_6$: 454.1978; found: 454.1978; calculated mass $[M+H]^+$ for Tetramer, $C_{32}H_{37}N_4O_8$: 605.2611; found: 605.2610; calculated mass $[M+H]^+$ for Pentamer, $C_{40}H_{46}N_5O_{10}$: 756.3245; found: 756.3232.

We further examined about the BTP formation in case of the corresponding *t*-butyl and benzyl esters **2.16c** and **2.16b** respectively and found that while benzyl analogue **2.18b** obtained in 5%, the *t*-butyl derivative **2.18c** resulted in 2% only (Scheme 2.5). The very low yield in case of the latter (**2.18c)** may be ascribed to its poor stability as it decomposed

much before melting unlike the other two BTP derivatives which are quite stable (more than 300 °C) as reflected in their thermogravimetric analysis (Figure 2.15-2.16).

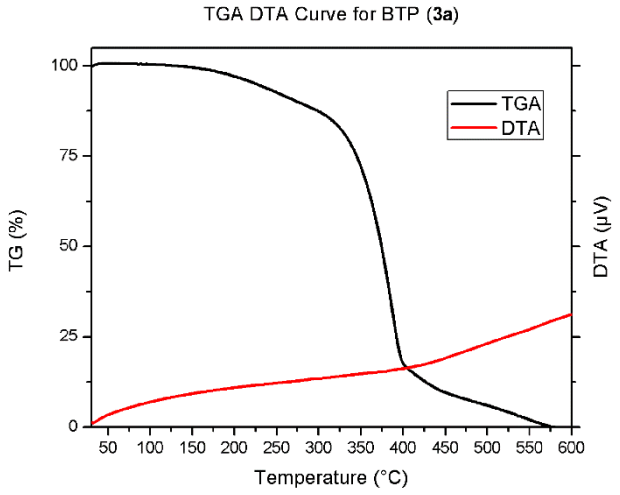


Figure 2.15: TGA profile for BTP **2.18a**.

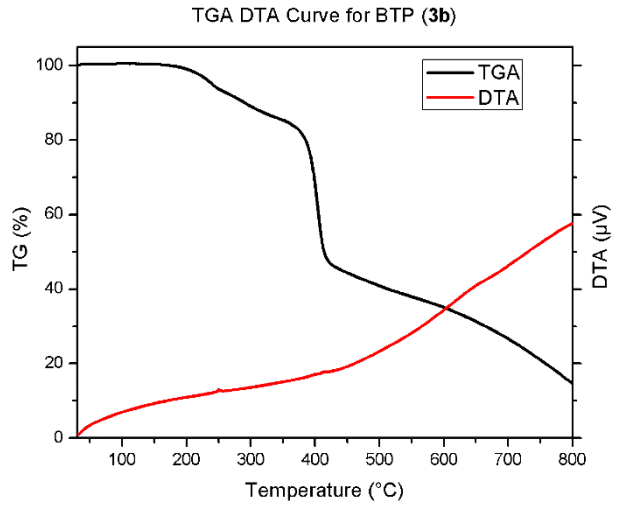


Figure 2.16: TGA profile for BTP **2.18b**.

Further, we could also able to synthesize the BTPs (**2.18a**-**2.18c**) from their isolated intermediate bromo compounds by refluxing in DCM (Scheme 2.5; Table 2.1 entry 7-9). Trans-esterification reaction of **2.18a** in presence of benzyl alcohol/Na provided in 60% yield of **2.18b,** but in presence of *t*-BuOH/Na could not produce any BTP **2.18c** (Scheme 2.5). The latter result may be ascribed to the lack of **2.18c** stability.

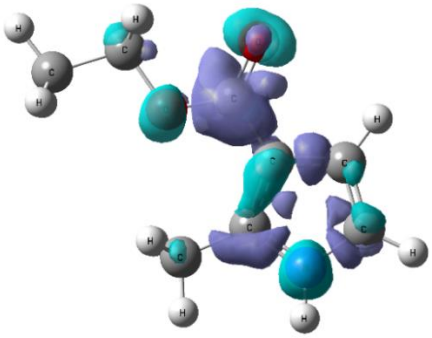
In order to know about the reactivity of pyrroles **2.16a, 2.38a, 2.40, 2.41, 2.42, 2.42a** and **2.42b**, we have performed the DFT calculations to understand the reactive sites (nucleophilic and electrophilic centers) by Multiwfn program by using condensed dual descriptor analysis.[53] The results revealed that nucleophilic centers (less electron density)

are readily available among the brominated compounds on vacant position of every brominated compound **2.38a**, **2.41** and **2.42** than for other compounds **2.42a** and **2.42b**. This shows that above mentioned brominated compounds, remained more reactive, except **2.42a** and **2.42b**, and thus probably transformed to form cyclized BTP.

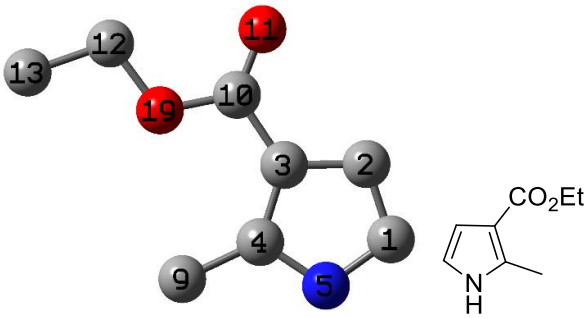
2.5 Exact evaluation of dual descriptors based on electron density:[53]

Electron densities were calculated for the electron systems N, N+1 and N-1; f^- = for electrophilic attack, f^+ = for nucleophilic attack. Visualization of iso-surface of dual descriptors of the compounds: where the cyan colored mesh (negative), which indicates about the more electron density (favorable for the electrophilic attack) and the violet colored mesh (positive) indicates the less electron density (favorable for nucleophilic attack).

Compound 2.16a:



Electron density surfaces

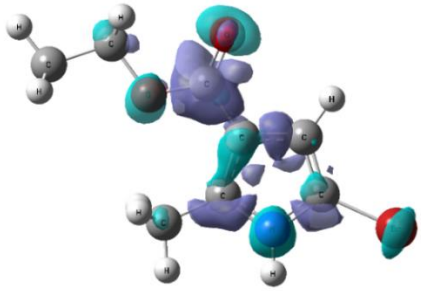


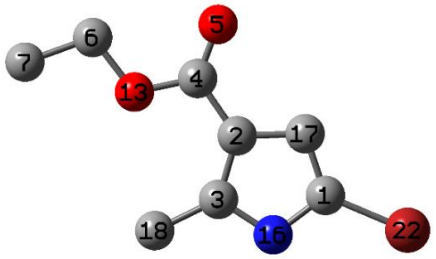
Corresponding atomic labels

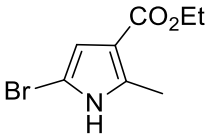
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.019486	0.132634	-0.093563	**0.113148**	0.113049	-0.00010
C	2	-0.002637	0.013405	-0.12303	**0.016042**	0.120393	0.10435

Compound 2.38a:





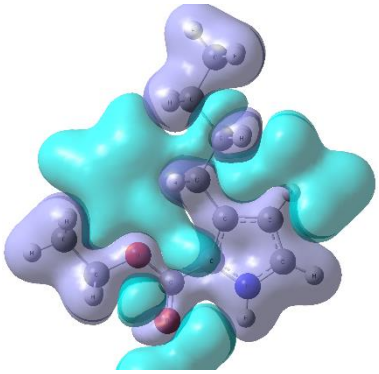


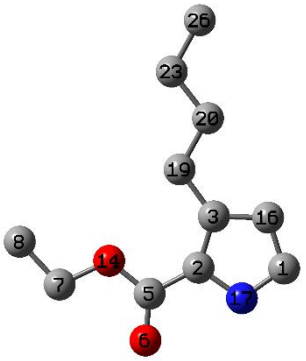
Electron density surfaces **Corresponding atomic labels**

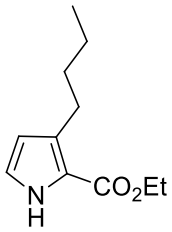
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.106572	0.109011	-0.033854	0.002439	0.140426	0.13799
C	17	0.027139	0.004871	-0.112539	-0.022268	**0.139678**	0.16195
Br	22	-0.101502	0.2037	-0.151827	**0.305202**	0.050325	-0.25488

Compound 2.42:





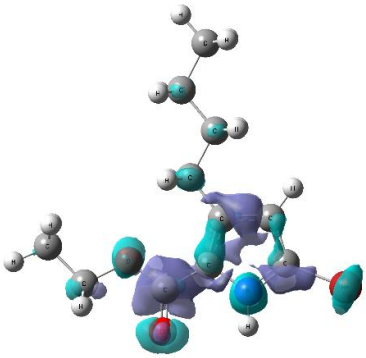


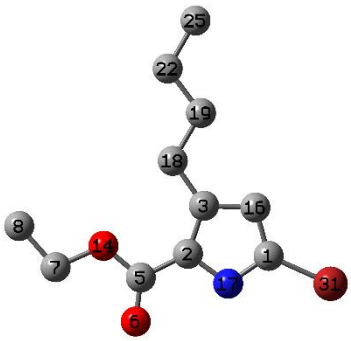
Electron density surfaces **Corresponding atomic labels**

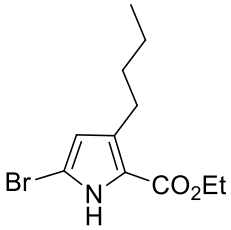
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.054083	0.135465	-0.114745	**0.081382**	**0.168828**	0.08745
C	16	-0.032076	-0.016716	-0.142837	**0.015360**	**0.110761**	0.09540

Compound 2.42a:





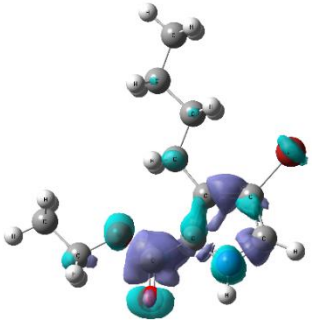


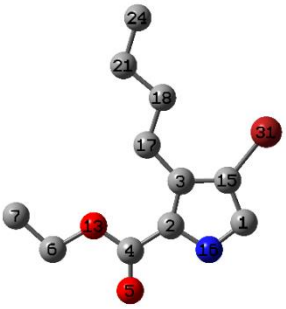
Electron density surfaces **Corresponding atomic labels**

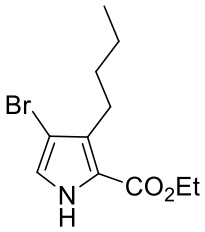
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.136565	0.114857	-0.051147	**-0.021708**	**0.187712**	0.20942
C	16	0.00299	-0.022647	-0.133547	**-0.025637**	**0.136537**	0.16217
Br	31	-0.096586	0.198358	-0.152781	**0.294944**	**0.056195**	-0.23875

Compound 2.42b:





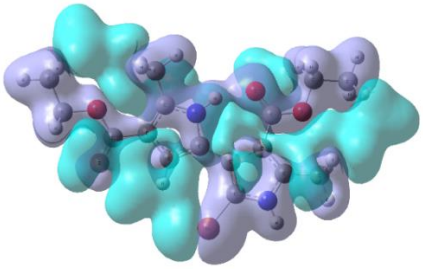


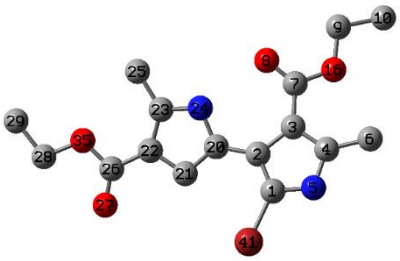
Electron density surfaces **Corresponding atomic labels**

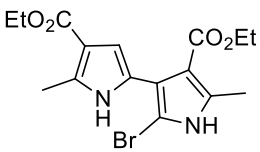
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.08926	0.126615	-0.106996	**0.037355**	**0.196256**	0.15890
C	15	0.059488	0.021465	-0.076607	**-0.038023**	**0.136095**	0.17412
Br	31	-0.098893	0.175836	-0.131365	**0.274729**	**0.032472**	-0.24226

Compound 2.40:





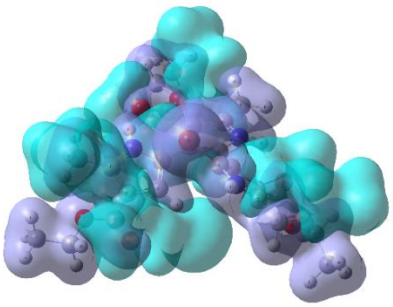


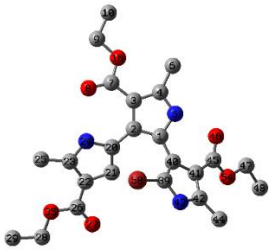
Electron density surfaces **Corresponding atomic labels**

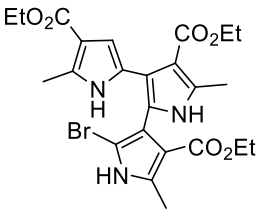
Mesh color (cyan = - ve; violet = + ve)

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	1	0.08926	0.126615	-0.106996	**0.037355**	**0.196256**	0.15890
C	15	0.059488	0.021465	-0.076607	**-0.038023**	**0.136095**	0.17412
Br	31	-0.098893	0.175836	-0.131365	**0.274729**	**0.032472**	-0.24226

Compound 2.41:







Electron density surfaces **Corresponding atomic labels**

Mesh color (cyan = - ve; violet = + ve

Symbol	Label	N	N-1	N+1	f^-	f^+	Δf
C	21	-0.013466	-0.029369	-0.102527	**-0.015903**	**0.089061**	0.10496
C	39	0.125477	0.038207	-0.005638	**-0.087270**	**0.131115**	0.21839
Br	58	-0.081544	0.043173	-0.060569	**0.124717**	**-0.020975**	-0.14569

UV-vis absorption spectrum of **2.18a** showed two well separated absorption bands at 230 and 288 nm (Figure 2.17).

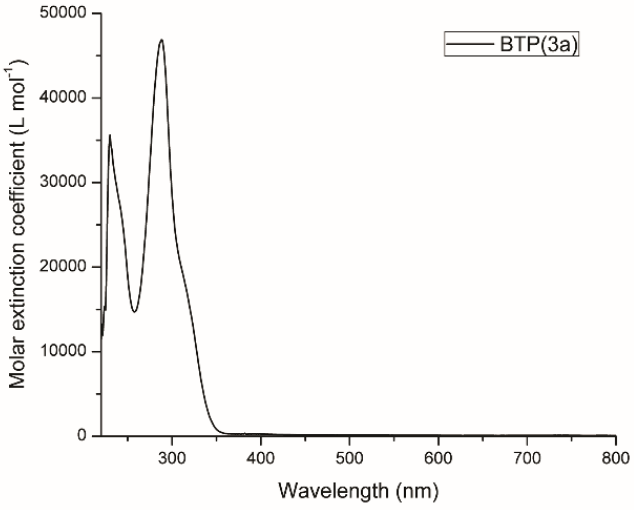


Figure 2.17: UV -Vis absorption spectrum of BTP **2.18a** in DCM.

To get further understanding we have done TD-DFT calculations and simulated the absorption spectrum of **2.18a** theoretically (Figure 2.18) (Table 2.2). The steady state absorption spectrum and vertical electronic transitions were found to be very alike and the energy level diagram involving the four frontier orbitals obviously shows almost degenerate nature of HOMO-1 and HOMO, and also LUMO and LUMO+1 (Figure 2.19).

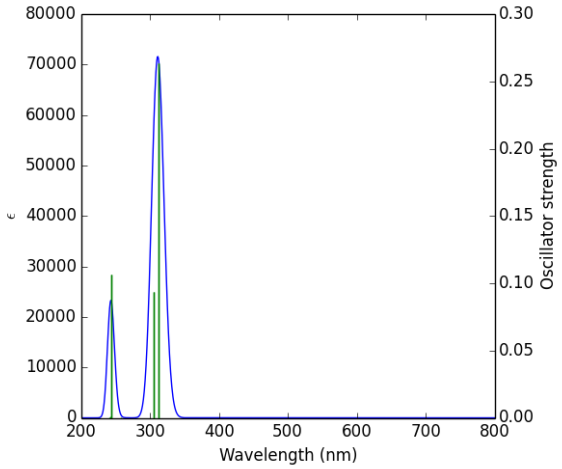


Figure 2.18: Theoretical absorption spectrum (by TD-DFT) of BTP **2.18a**.

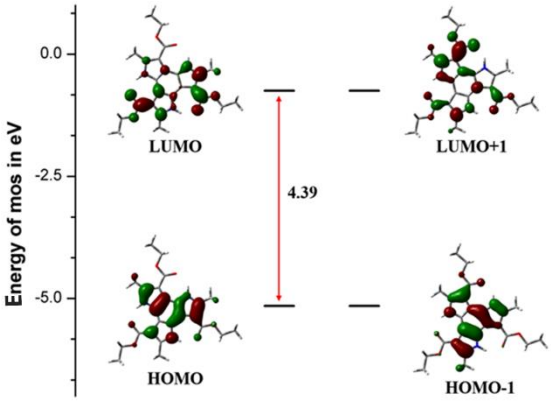


Figure 2.19: Selected molecular orbital diagram of the optimized structure of BTP **2.18a**.

Table 2.2: Summary of theoretical excitation energies of BTP **2.18a**

Sl. No.	Wavelength (nm)	Oscillator Strength	Major contributions
1	312.87	0.2631	H-1 —> L+1 (22%), H-1 —> L+2 (16%), HOMO —> LUMO (21%), HOMO —> L+2 (20%)
2	312.84	0.2636	H-1 —> LUMO (22%), H-1 —> L+2 (20%), HOMO —> L+1 (22%), HOMO —> L+2 (16%)
3	305.27	0.0932	H-1 —> LUMO (10%), H-1 —> L+2 (25%), HOMO —> L+1 (10%), HOMO —> L+2 (38%)
4	305.25	0.0935	H-1 —> L+1 (10%), H-1 —> L+2 (38%), HOMO —> LUMO (10%), HOMO —> L+2 (25%)
5	243.22	0.1063	H-2 —> LUMO (91%), H-1 —> L+10 (2%), HOMO —> L+9 (2%)
6	243.21	0.1064	H-2 —> L+1 (91%), H-1 —> L+9 (2%), HOMO —> L+10 (2%)

Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) of **2.18a** by the electrochemical study revealed to have a reversible reduction peak at -0.94 V and multiple oxidation peaks, with a reversible peak coming at 0.90 V and three quasi reversible peaks at 1.48 V, 1.63 V and 1.84 V, with an electrochemical HOMO-LUMO energy gap of 1.84 V (Figure 2.20).

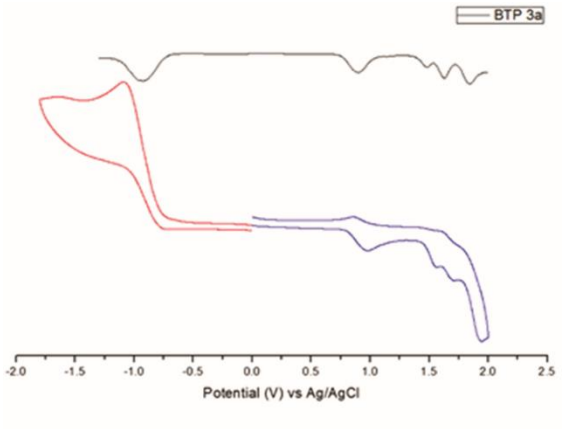
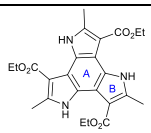


Figure 2.20: CV and DPV of BTP **2.18a** vs Ag/AgCl at scan rate of 0.1 V/sec in DCM**.**

Further, we studied the nature of aromaticity of the BTP **2.18a** and compared with free BTP, benzene, pyrrole, and indole moieties, via HOMA (Harmonic Oscillator Model of Aromaticity) and nucleus independent chemical shift NICS(1) method on their corresponding optimized geometries and the values are depicted in (Table 2.3).[54-55] The study disclosed ring fusion led to reduced aromaticity of both the pyrrole and benzene units that in case of the unsubstituted BTP unlike in indole, where aromaticity of both rings

enhanced. On the other hand, in case of BTP **2.18a**, the benzene ring aromaticity increases upon substitution at the expense of the pyrrole moities. Moreover, the results indicate greater reactivity (or lack of stability) of unsubstituted BTP, perhaps indicating the reason behind its so far evasive synthesis.

Table 2.3: Summary of calculated NICS(1) and HOMA values.

Compounds		**NICS(1)**	**HOMA**
BTP (3a)		A = - 10.45 B = - 9.21	A = 0.847 B = 0.484
BTP free		C = -9.85 D = -9.38	C = 0.767 D = 0.534
Benzene		E = -10.20 *	E = 0.972
Pyrrole		F = -10.09 *	F = 0.693
Indole		G = -10.83 * H = -10.18 *	G = 0.894 H = 0.422

NICS values were calculated by using B3LYP/6-311+G(d,p) by NMR GIAO method in Gaussian 09.[56]

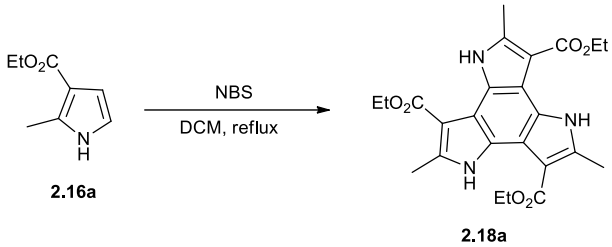
2.6 Summary

We have reported the synthesis of BTPs with unprotected pyrrolic nitrogens from 2,3-disubstituted pyrroles (**2.16**) in a single step as the first example and explored the reaction mechanism. Additionally, these BTPs at their pyrrolic β- and α-positions provided with simple functionalizable substituents. The obtained BTPs are a result of serendipity. Although the obtained yield is modest, however, the facile synthetic approach more than compensate for it. NICS(1) study revealed lesser stability of free benzotripyrrole, which could be stabilized through functionalization. Computational calculations using condensed dual descriptor analysis further supports the greater reactivity of pyrrole derivatives. Further, our study obviously indicates in order to explore this chemistry, the pyrrole unit must be stabilized or appropriately functionalized towards possible transformations. For example, in our reported functionalized BTPs, the substituents at their α- and *β*- positions can be easily transformed towards material science applications including trisBODIPY and our present efforts are aimed in this direction.

2.7 Experimental details:

Synthesis of Triethyl 2,5,8-trimethyl-4,7-dihyro-1H-dipyrrolo[2,3-e:2',3'-g]indole-3,6,9-tricarboxylate (2.18a):

Protocol 1:

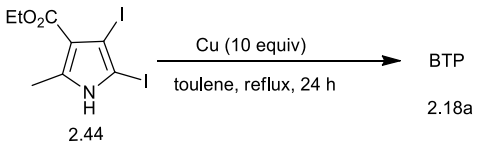


2.16a **2.18a**

To ethyl 2-methyl-1H-pyrrole-3-carboxylate (**2.16a**)[57] (100 mg, 0.65 mmol) in DCM (5 mL), NBS (128 mg, 0.72 mmol) solution in DCM (10 mL) was added under N_2 atmosphere at room temperature and was refluxed for 24 h. The reaction mixture was cooled to room temperature and quenched by addition of aq. $NaHCO_3$ solution. Then the organic layer was separated and the aq. layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated in rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography using EtOAc: hexane (5:95) as an eluent to obtain the desired product **2.18a** as white color solid after drying (12 mg, 12 %).

Melting point: 260-262 ^oC; IR (KBr) (cm^{-1}): 3320, 2956, 1659, 1431; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 11.36 (s, 3H), 4.42 (q, *J* = 7.1 Hz, 6H), 2.77 (s, 9H), 1.46 (t, *J* = 7.1 Hz, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 168.1, 137.8, 124.5, 109.1, 103.4, 15.3, 14.6; HRMS- (ESI+) m/z: calculated for $C_{24}H_{28}N_3O_6$ $[M+H]^+$: 454.1978; found: 454.1978.

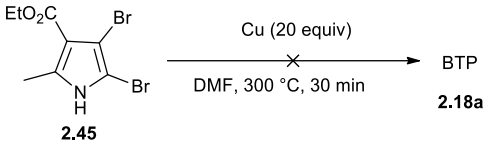
Protocol 2:



2.44

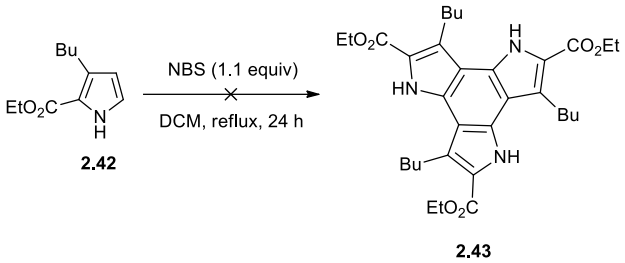
To ethyl 4,5-diiodo-2-methyl-1H-pyrrole-3-carboxylate (**2.44**)[58] (100 mg, 0.25 mmol) in toluene (15 mL), Cu (157 mg, 2.47 mmol) was added under N_2 atmosphere at room temperature and was refluxed for 24 h. After complete consumption of starting material, the reaction mixture was cooled to room temperature. The organic layer was separated and the residue was washed with DCM (2 x 10 mL). The combined organic layers were concentrated in rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography by using EtOAc: hexane (5:95) as an eluent, which resulted the product as white solid (2 mg, 2 %).

Protocol 3:



To ethyl 4,5-dibromo-2-methyl-1H-pyrrole-3-carboxylate (**2.45**)[59] (100 mg, 0.25 mmol) in DMF (1 mL), Cu (255 mg, 4.02 mmol) was added under N_2 atmosphere at room temperature and was heated for 30 min at 300 °C . The reaction mixture was cooled to room temperature and TLC confirmed the complete consumption of starting material, but there was no desired BTP **2.18a**.

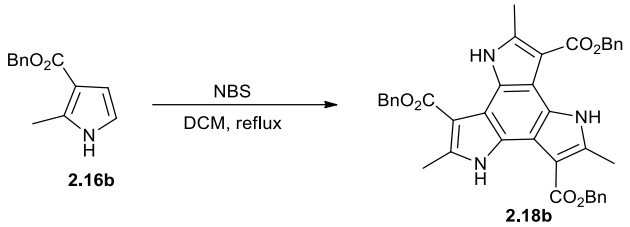
Attempted synthesis of Triethyl 3,6,9-tributyl-4,7-dihydro-1H-dipyrrolo[2,3-e:2',3'-g]indole-2,5,8-tricarboxylate (2.43):



To ethyl 3-butyl-1H-pyrrole-2-carboxylate (**242**)[51] (100 mg, 0.51 mmol) in DCM (5 mL), NBS (128 mg, 0.72 mmol) solution in DCM (10 mL) was added under N_2 atmosphere at room temperature and was refluxed for 24 h. The reaction mixture was cooled to room temperature and quenched by addition of aq.$NaHCO_3$. TLC showed complete consumption of the starting material but there was no formation of desired BTP **2.43**.

Synthesis of Tribenzyl 2,5,8-trimethyl-4,7-dihydrodipyrrolo[2,3-e:2',3'-g]indole-3,6,9-tricarboxylate (2.18b):

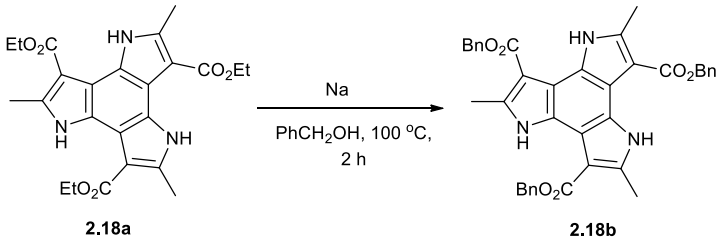
Protocol 1:



The same synthetic procedure for **2.18a** was followed; 5 mg product (**2.18b**) was obtained from 100 mg starting material (**2.16b**) [57] with 5% yield (white solid).

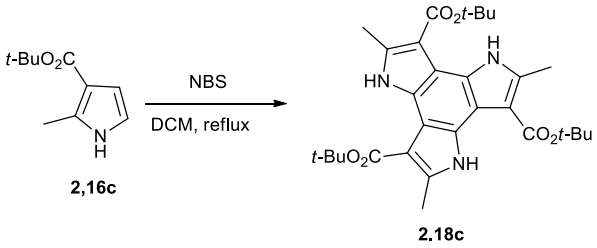
Melting point: 201-203 ^{o}C; IR (KBr) (cm^{-1}): 3345, 2929, 1671, 1424; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm):11.25 (s, 3H), 7.49 (d, *J* = 7 Hz, 2H), 7.42 (t, *J* = 7 Hz, 3H), 7.37 (d, *J* = 7 Hz, 2H), 5.43 (s, 6H), 2.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm):167.60, 138.7, 136.6, 128.8, 128.3, 128.2, 103.2, 66.2, 15.4; HRMS (ESI+) : m/z : calculated for $C_{39}H_{34}N_3O_6$ $[M+H]^+$: 640.2447; found: 640.2430.

Protocol 2:



To sodium metal (25 mg) in benzyl alcohol (2 mL), BTP **2.18a** (100 mg, 0.22 mmol) in benzyl alcohol (3 mL) was added under N_2 atmosphere at room temperature and was stirred at 100 °C for 2 h under ~10 mmHg pressure. Subsequently benzyl alcohol was removedunder reduced pressure and residue was dissolved in DCM. The DCM layer was washed with water, passed through anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. Crude product was purified by silica-gel column chromatography by using EtOAc: hexane (3:7) as an eluent, which resulted the desired product as white solid (85 mg, 60 %).

Synthesis of Tri-tert-butyl 2,5,8-trimethyl-4,7-dihydro-1H-dipyrrolo[2,3-e:2', 3;-g]indole-3,6,9-tricarboxylate (2.18c):

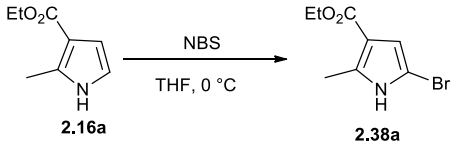


The same synthetic procedure for **2.18a** was followed; 2 mg product (**2.18c**) was obtained from 100 mg of starting material **2.16c** [57] with 2% yield (white solid).

IR (KBr) (cm^{-1}): 3312, 2921, 1666, 1462; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm):11.39 (s, 3H), 2.75 (s, 9H), 1.67 (s, 27H); HRMS (ESI+) : m/z : calculated for $C_{30}H_{40}N_3O_6$ $[M+H]^+$: 538.2917; found: 538.2918.

Synthesis of Ethyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate (2.38a):[60]

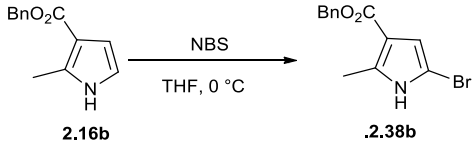
(**[60] =** The product **2.38a** was reported recently by different procedure).



To ethyl 2-methyl-1H-pyrrole-3-carboxylate **2.16a** (100 mg, 0.65 mmol) in THF (50 mL), NBS (116 mg, 0.65 mmol) was added under N_2 atmosphere at 0 ^oC and stirred for 1 h. After complete consumption of starting material, the reaction was quenched by addition of aq. $NaHCO_3$ solution. Then the organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layers were combined, dried over anhyd. Na_2SO_4, and concentrated using the rotary evaporator under reduced pressure. Finally, the crude product was purified by silica gel column chromatography by using EtOAc: hexane (15:85) as an eluent, which resulted the desired product as white solid (110 mg, 73 %).

IR (KBr) (cm^{-1}): 3256, 2980, 1673, 1445; ^1H NMR (500 MHz, CD_3CN δ in ppm): 9.68 (s, 1H), 6.38 (s, 1H), 4.18 (q, *J* = 7 Hz, 2H), 2.42 (s, 3H), 1.27 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN, δ in ppm): 164.0, 137.7, 114.1, 112.1, 96.9, 60.2, 14.7, 12.8; HRMS (ESI+) : m/z : calculated for $C_8H_{11}BrNO_2$ $[M+H]^+$: 231.9973; found: 231.9984.

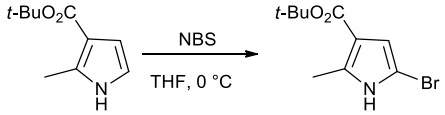
Synthesis of Benzyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate (2.38b):



The same synthetic procedure for **2.38a** was followed; 95 mg product (**2.38b**) was obtained from 100 mg starting material (**2.16b**) with 70% yield (white solid).

IR (KBr) (cm^{-1}): 3269, 3030, 1667, 1431; ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm): 8.34 (s, 1H), 7.4 (d, *J* = 7.2 Hz, 2H), 7.4 (t, *J* = 7 Hz, 3H), 7.3 (d, *J* = 7 Hz, 2H), 6.54 (d, *J* = 2.8 Hz, 1H), 5.27 (s, 2H), 2.5 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 164.4, 136.8, 136.7, 128.6, 128.1, 128.0, 113.4, 112.3, 96.5, 65.6, 13.2; HRMS (ESI+): m/z: calculated for $C_{13}H_{13}BrNO_2$ $[M+H]^+$: 294.0129; found: 294.0129.

Synthesis of *t*ert-butyl 5-bromo-2-methyl-1H-pyrrole-3-carboxylate (2.38c):

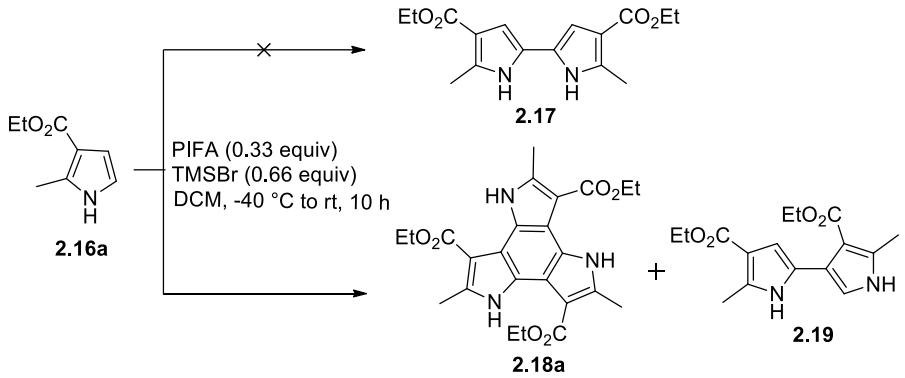


2.16c **2.38c**

The same synthetic procedure for **2.38a** was followed; 90 mg product (**2.38c**) was obtained from 100 mg starting material (**2.16c**) with 70% yield (white solid).

IR (KBr) (cm^{-1}): 3176, 2969, 1649, 1453; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 8.35 (s, 1H), 6.44 (d, *J* = 2.9 Hz, 1H), 2.46 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ in ppm): 164.2, 135.8, 115.3, 112.3, 86.0, 79.9, 28.6, 13.4; HRMS (ESI+): m/z: calculated for $C_{10}H_{14}BrNNaO_2$ $[M+Na]^+$: 282.0105; found: 282.0100.

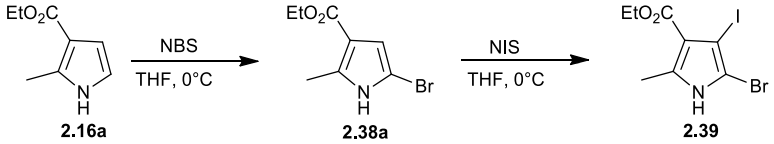
Attempted synthesis of bipyrrole 2.17:



To ethyl 2-methyl-1H-pyrrole- 3-carboxylate **2.16a** (100 mg, 0.65 mmol) in DCM (20 mL), PIFA (200 mg, 1.30 mmol) and TMSBr (0.11 mL, 0.87 mmol) were added under N_2 atmosphere at low temperature i.e. -40 ^oC and was stirred overnight. After complete consumption of starting material, the reaction was stopped by addition of aq.$NaHCO_3$ solution. Then the organic layer was separated and the remaining crude compound was extracted with DCM (2 x 10 mL). Then the organic layers were combined, dried over anhyd. Na_2SO_4, and concentrated using rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography using EtOAc: hexane (1:9) as an eluent, which resulted the 1st fraction as BTP **2.18a** 5 mg (5 %), along with the 2nd fraction as compound **2.19**, a white solid 60 mg (15 %).

Compound **2.19**: Melting point 266-267 ^oC; IR (KBr), (cm^{-1}): 3213, 2979, 1652, 1441; ^1H NMR (500 MHz, $CDCl_3$, δ in ppm): 11.51 (s, 1H), 8.30 (s, 1H), 6.90 (d, *J* = 2.15Hz, 1H), 6.64 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.6 (s, 3H), 2.5 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm): 167.6, 166.2, 136.4, 133.9, 125, 118.8, 113.7, 111.9, 105.8, 60.5, 59.3, 15.5, 14.7, 14.6, 13.7; HRMS (ESI+) : m/z : calculated for $C_{16}H_{21}N_2O_4$ $[M+H]^+$: 305.1501; found 305.1502.

Synthesis of 5-bromo-4-iodo-2-methyl-1H-pyrrole-3-carboxylate (2.39):



To ethyl 2-methyl-1H-pyrrole-3-carboxylate **2.16a** (100 mg, 0.65 mmol), NBS (116 mg, 0.65 mmol) in THF (30 mL) was added at 0 ^oC under N_2 atmosphere and then stirred for 1 h. Subsequently, to the same reaction mixture, NIS (146 mg, 0.65 mmol) was added, and stirred for additional 2 h. Then the reaction was quenched with aq. $NaHCO_3$ solution. The organic layer was separated and the aq. layer was extracted with EtOAc (2 x 10 mL). The

combined organic layer was dried over anhyd. Na_2SO_4, and concentrated using rotary evaporator under reduced pressure. Finally the crude product was purified on silica gel column using EtOAc : Hexane (1:9) as an eluent, which resulted the product as white solid (150 mg, 60 %).

IR (cm^{-1}): 3213, 2984, 1671, 1436; ^1H NMR data (500 MHz , $CDCl_3$, δ in ppm): 8.54 (s, 1H), 4.3 (q, *J* = 9 Hz, 2H), 2.5 (s, 3H), 1.37 (t, *J* = 9 Hz, 3H); ^{13}C NMR Data (500 MHz, $CDCl_3$, δ in ppm): 163.3, 137.8, 114.9, 105.8, 68.5, 60.2, 14.6, 14.6, 14.4; HRMS (ESI+) m/z: calculated for $C_8H_{10}BrINO_2[M+H]^+$: 357.8939; found: 357.8938.

2.8 Crystallographic details:

Table 2.4: Crystallographic data of compound **2.39**:

Identification code : **2.39**

Empirical formula : C_8 H_9 Br I N O_2

Formula weight : 357.97

Temperature : 299(2) K

Wavelength : 0.71073 Å

Crystal system : Monoclinic

Space group : P c

Unit cell dimensions : a = 9.9046(5) Å ; α = 90°.

b = 8.2466(4) Å ; β = 105.4160(10)°.

c = 14.0533(6) Å ; γ = 90°.

Volume = 1106.56(9) $Å^3$

Z = 4

Density (calculated) = 2.149 Mg/m^3

Absorption coefficient = 6.475 mm^{-1}

F(000) = 672

Crystal size : 0.18 x 0.12 x 0.10 mm^3

Theta range for data collection : 3.825 to 25.108°.

Index ranges : -11<=h<=11, -9<=k<=9, -15<=l<=16

Reflections collected = 18333

Independent reflections = 3616 [R(int) = 0.0455]

Completeness to theta = 25.108° ; 96.2 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission : 0.7459 and 0.7158

Refinement method : Full-matrix least-squares on F2

Data / restraints / parameters : 3616 / 2 / 239

Goodness-of-fit on F2 : 1.185

Final R indices [I>2sigma(I)] : R1 = 0.0424, wR2 = 0.1360

R indices (all data) : R1 = 0.0432, wR2 = 0.1371

Absolute structure parameter : 0.5

Extinction coefficient : n/a

Largest diff. peak and hole : 1.015 and -0.914 e.Å-3

Table 2.5: Crystallographic data of compound **2.18a**:

Identification code : **2.18a**

Empirical formula : $C_{24}H_{27}N_3O_6$

Formula weight : 453.48

Temperature : 100(2) K

Wavelength : 0.71073 Å

Crystal system : Triclinic

Space group : *P* -1

Unit cell dimensions : a = 7.5562(3) Å α = 80.335(2)°.

b = 7.5770(3) Å β = 85.586(2)°.

c = 19.0345(8) Å γ = 86.0240(10)°.

Volume = 1069.37(8) $Å^3$

Z = 2

Density (calculated) = 1.408 Mg/m^3

Absorption coefficient = 0.102 mm^{-1}

F(000) = 480

Crystal size = 0.28 x 0.24 x 0.18 mm^3

Theta range for data collection : 2.708 to 27.565°.

Index ranges : -9<=h<=9, -9<=k<=9, -24<=l<=24

Reflections collected : 53415

Independent reflections : 4943 [R(int) = 0.0471]

Completeness to theta = 25.242° ; 99.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission : 0.7459 and 0.7158

Refinement method : Full-matrix least-squares on F2

Data / restraints / parameters : 4943 / 0 / 316

Goodness-of-fit on F2 : 0.810

Final R indices [I>2sigma(I)] : R1 = 0.0419, wR2 = 0.1150

R indices (all data) : R1 = 0.0535, wR2 = 0.1259

Extinction coefficient : n/a

Largest diff. peak and hole : 0.409 and -0.317 e.Å-3

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2.10 ^{1}H, ^{13}C NMR spectra and HRMS data:

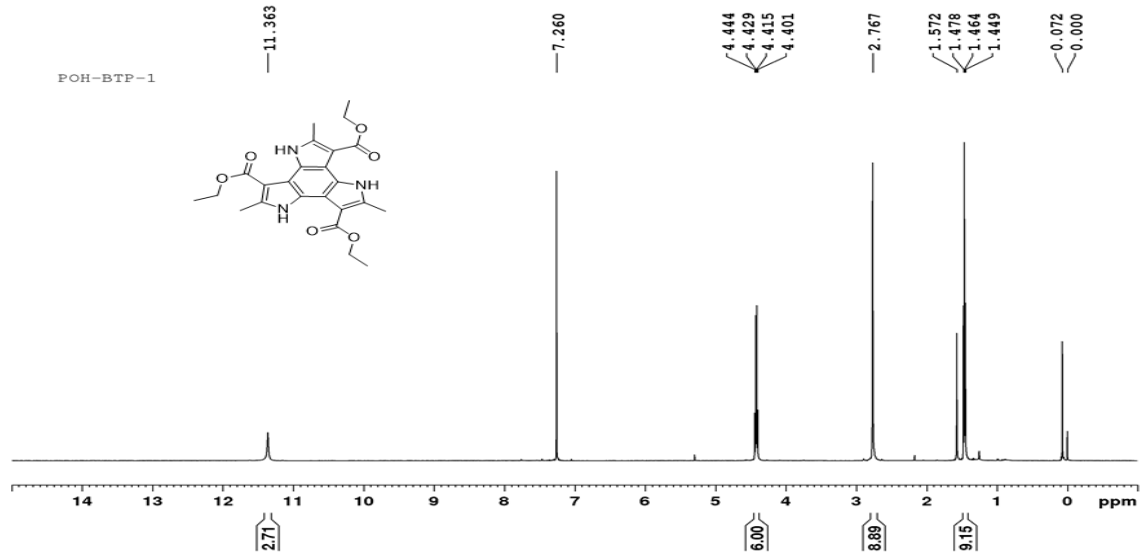


Figure 2.21: ^{1}H NMR spectrum of **2.18a** in $CDCl_3$.

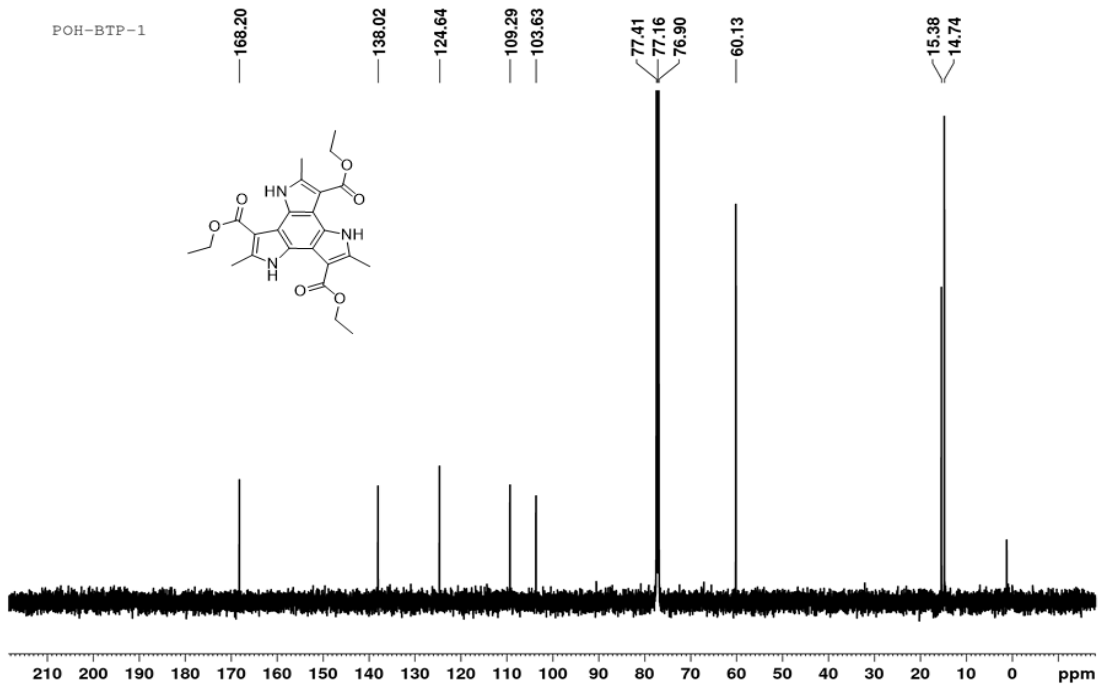


Figure 2.22: ^{13}C NMR spectrum of **2.18a** in $CDCl_3$.

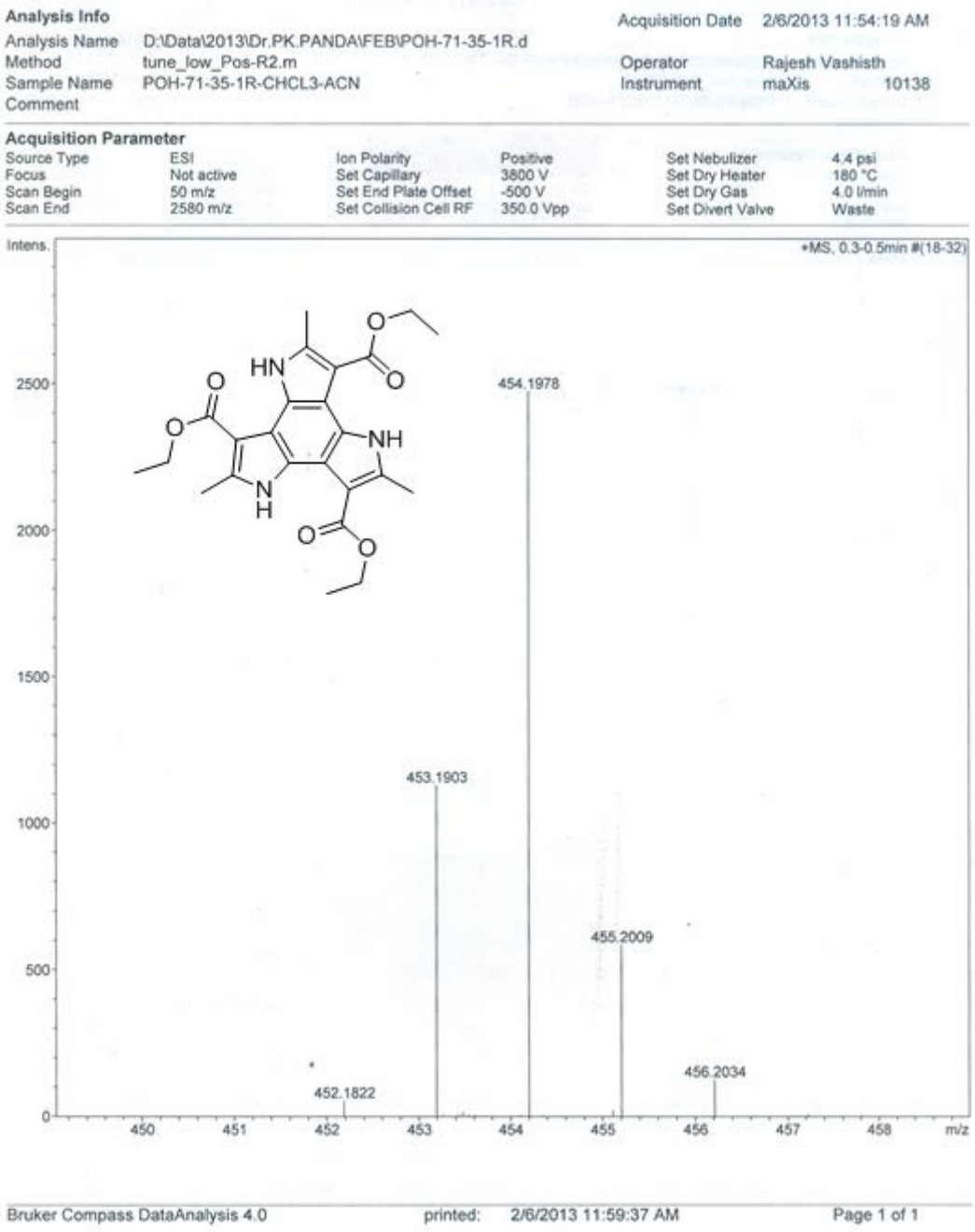


Figure 2.23: HRMS data of **2.18a** $(M+H)^+$; Calculated for $C_{24}H_{28}N_3O_6$: 454.1978; found: 454.1978.

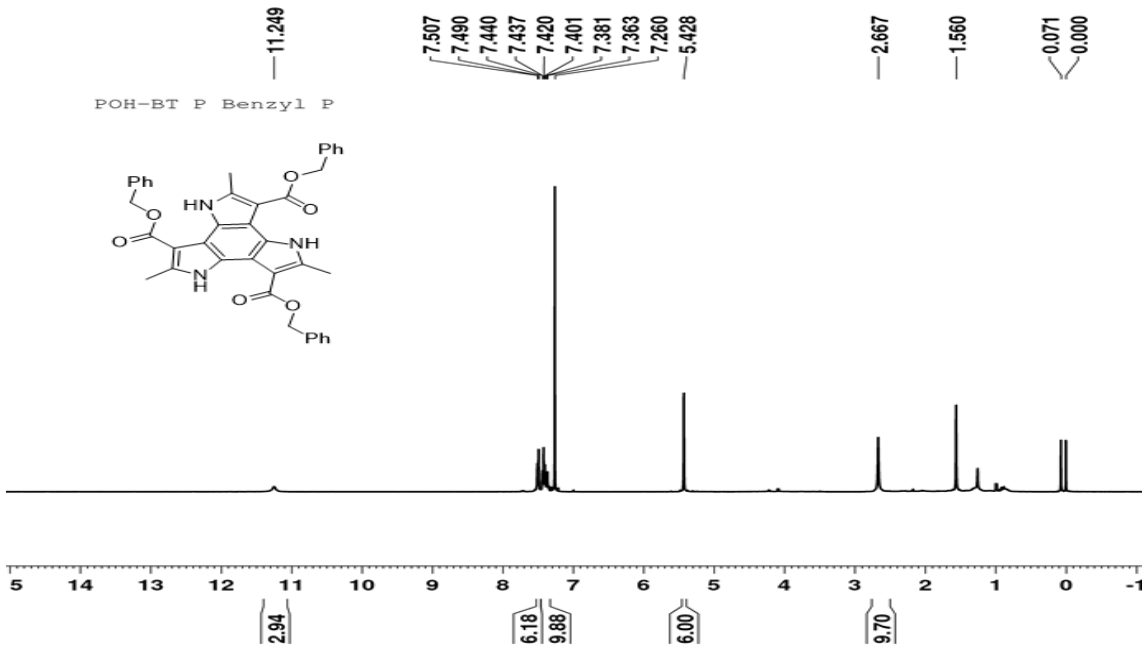


Figure 2.24: ^{1}H NMR spectrum of **2.18b** in $CDCl_3$.

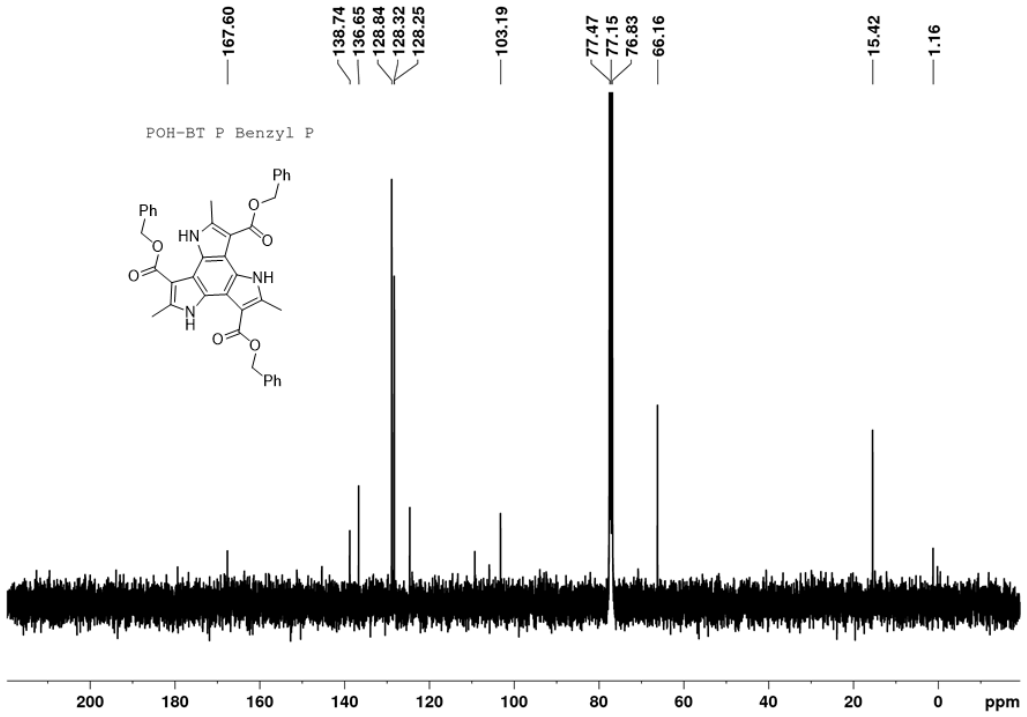


Figure 2.25: ^{13}C NMR spectrum of **2.18b** in $CDCl_3$.

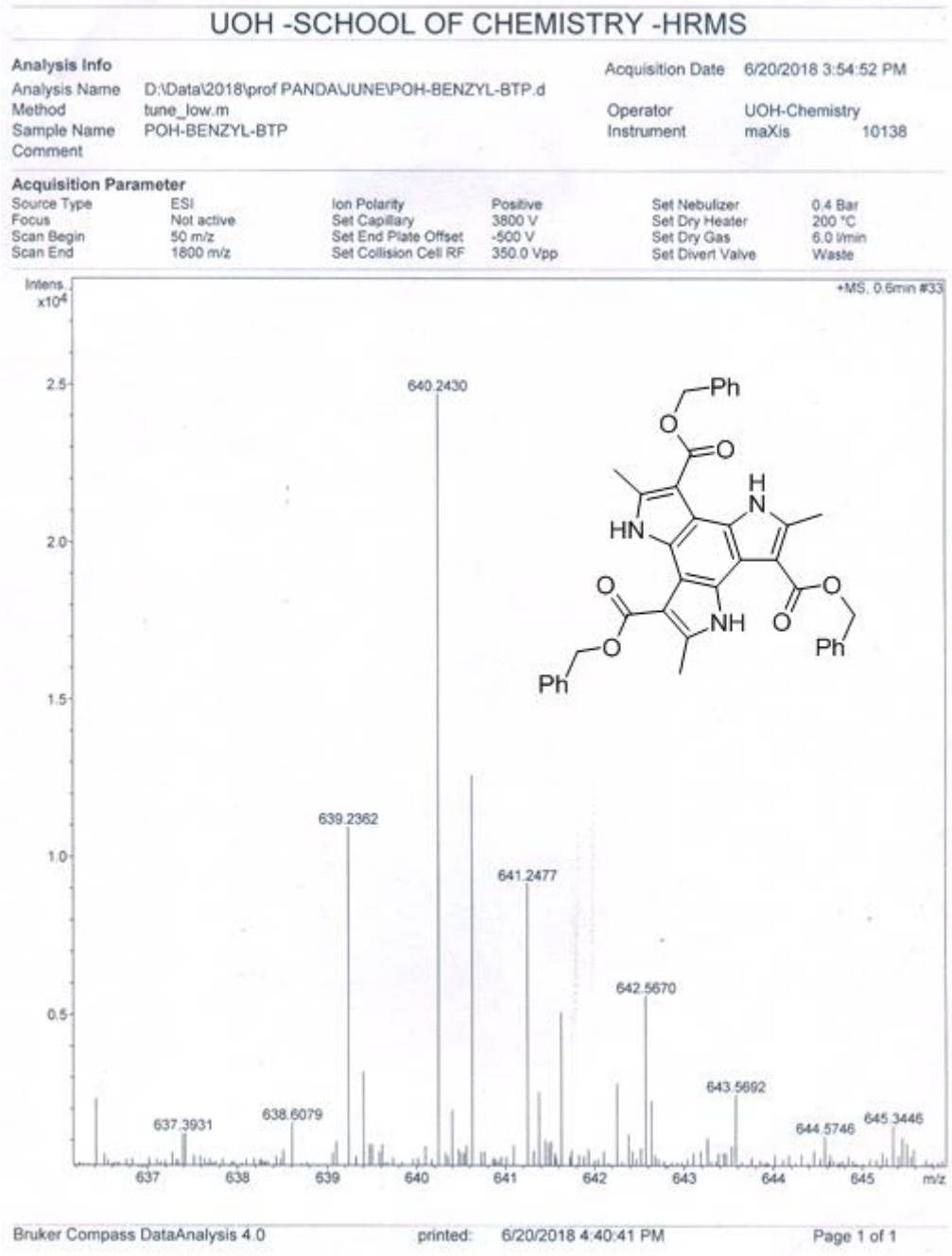


Figure 2.26 HRMS data of **2.18b** $(M+H)^+$; Calculated for $C_{39}H_{34}N_3O_6$ $[M+H]^+$: 640.2447; found: 640.2430.

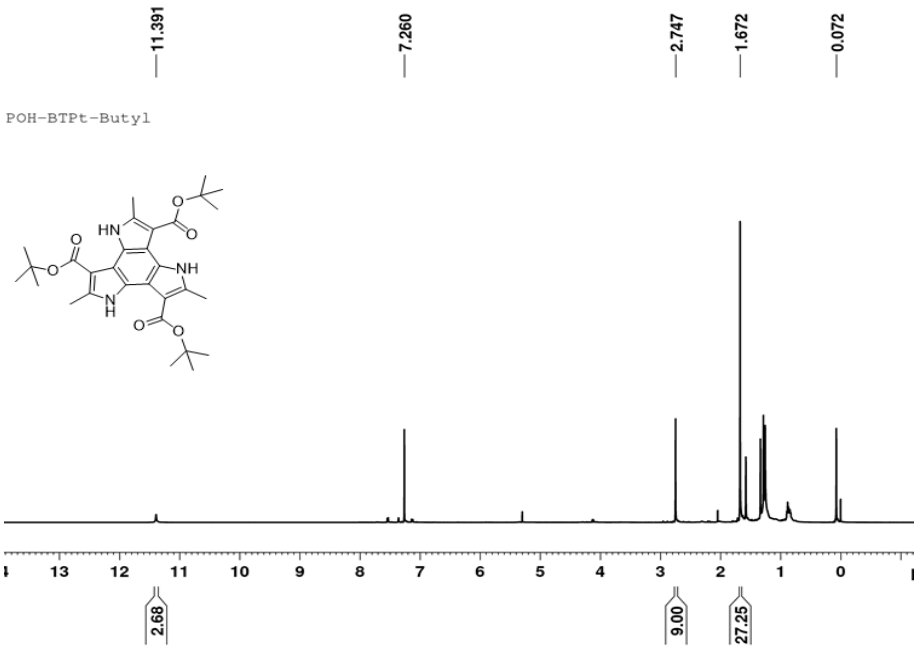


Figure 2.27: ^{1}H NMR spectrum of **2.18c** in $CDCl_3$ (^{13}C NMR data could not be recorded due to lack of stability).

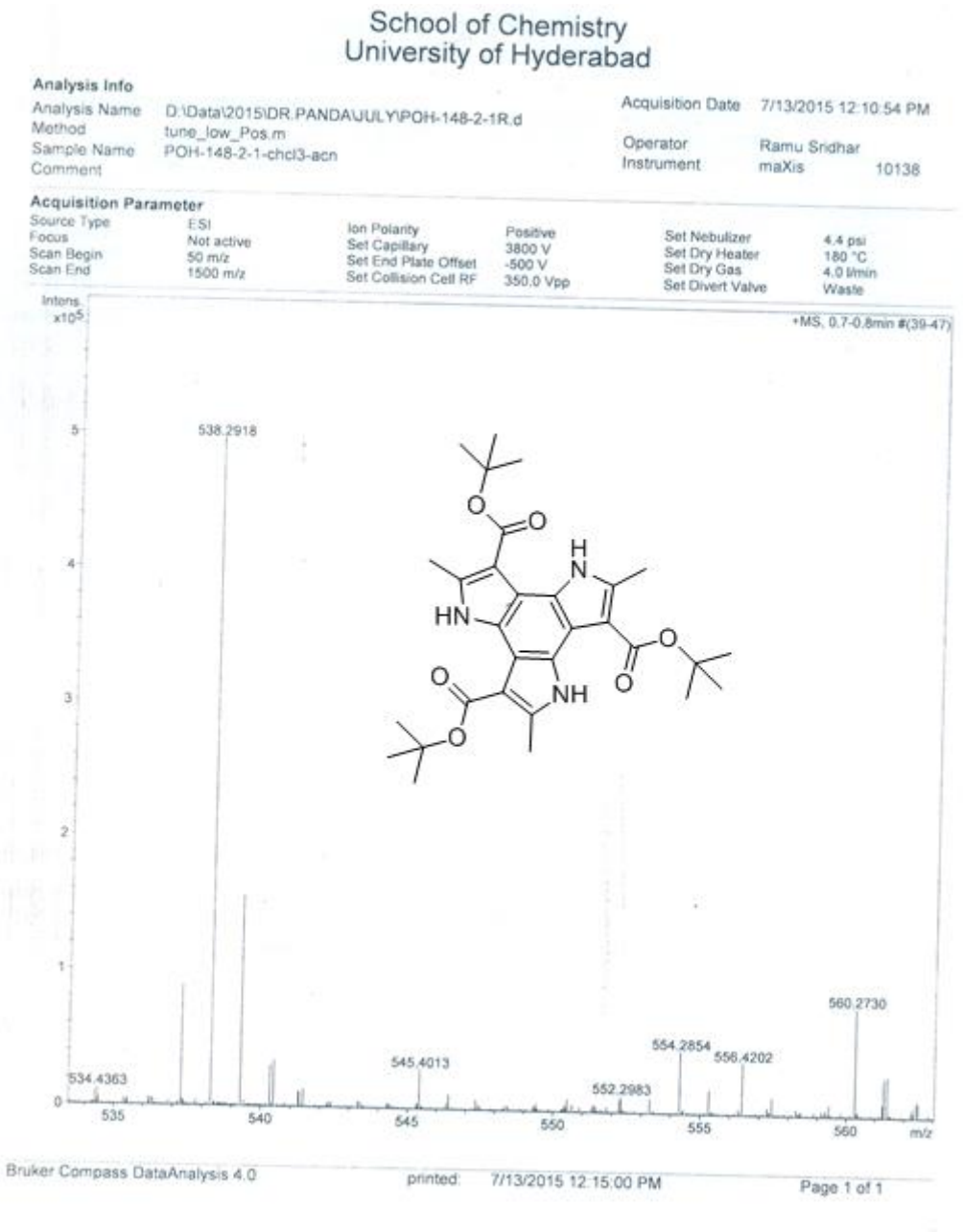


Figure 2.28: HRMS data of **2.18c** $(M+H)^+$; Calculated for $C_{30}H_{40}N_3O_6$ $[M+H]^+$: 538.2917; found: 538.2918.

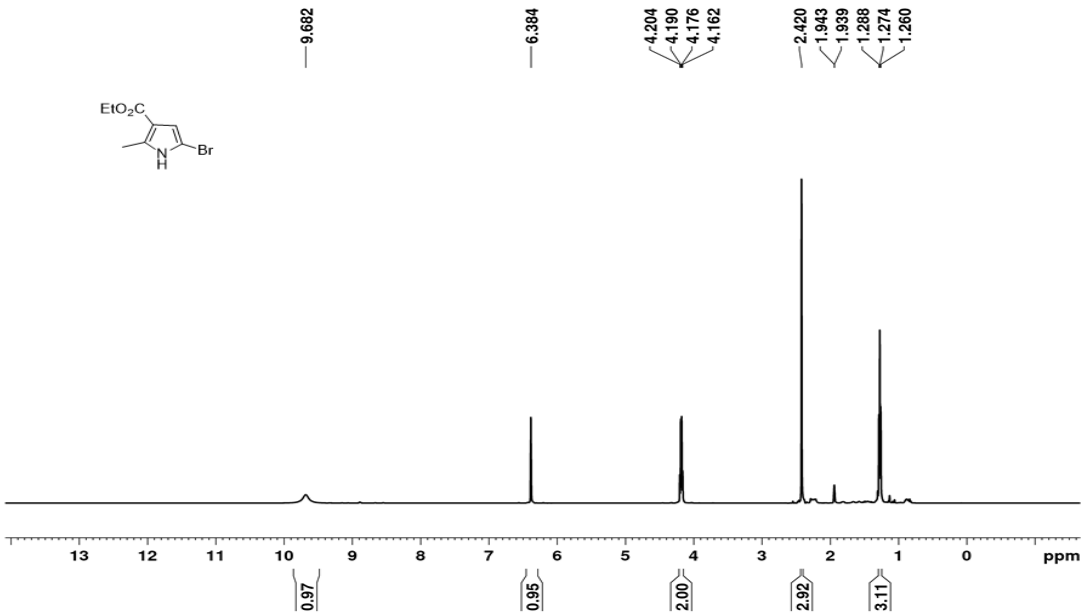


Figure 2.29: ^{1}H NMR spectrum of **2.38a** in CD_3CN.

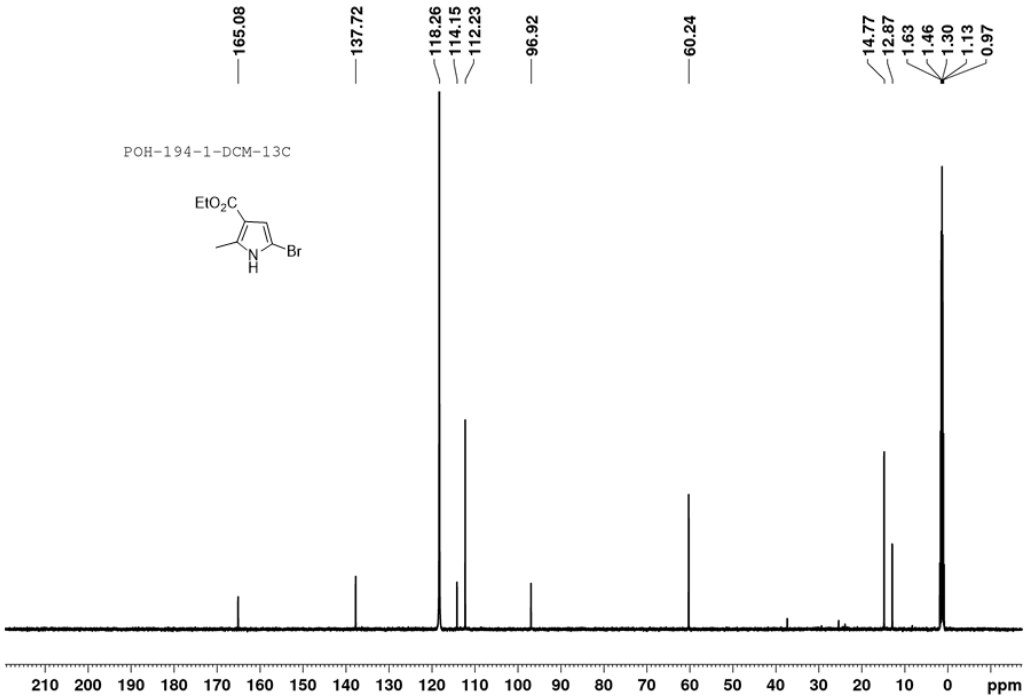


Figure 2.30: ^{13}C NMR spectrum of **2.38a** in CD_3CN.

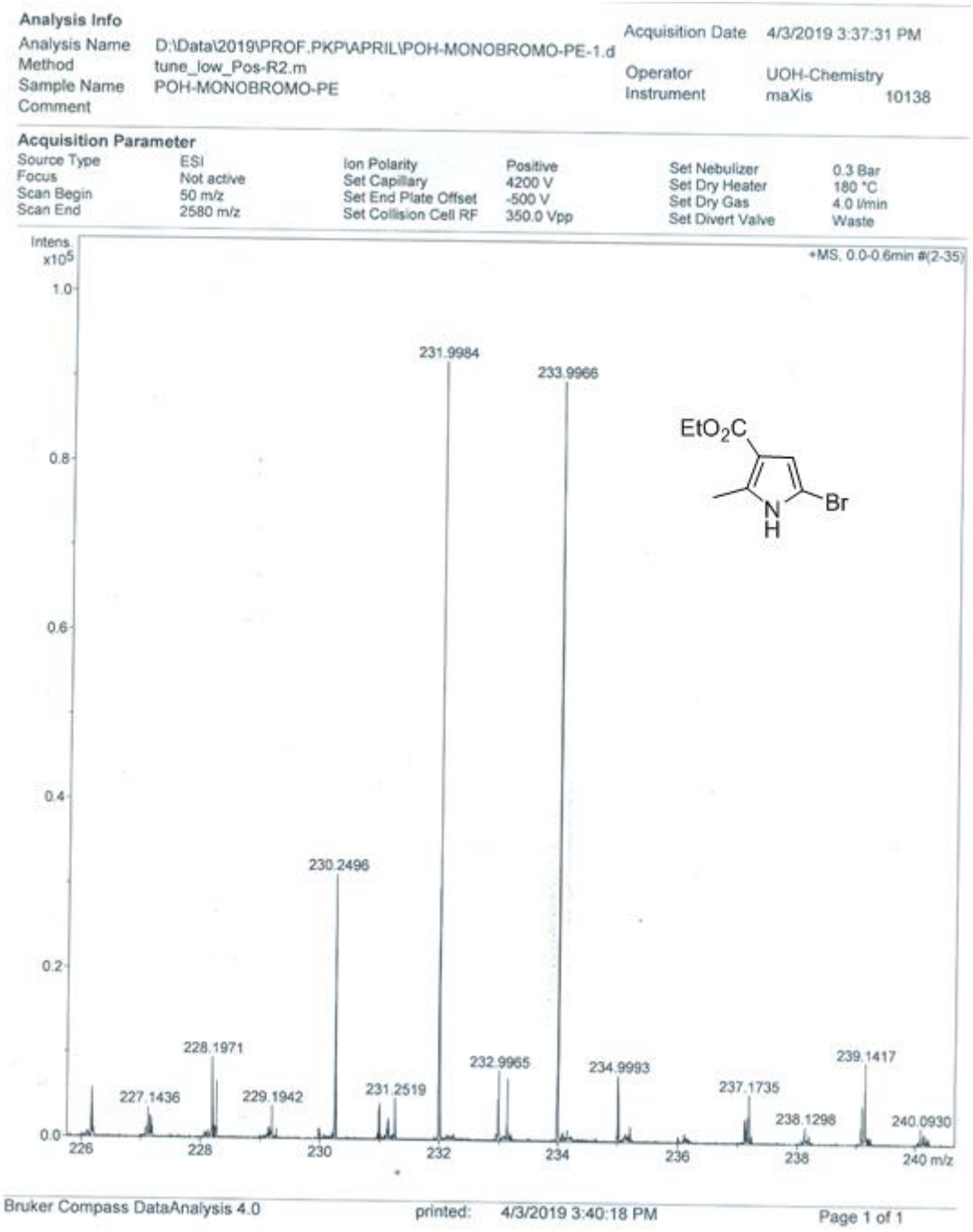


Figure 2.31: HRMS data of **2.38a** $(M+H)^+$; Calculated for $C_8H_{11}BrNO_2$ $[M+H]^+$: 231.9973; found: 231.9984.

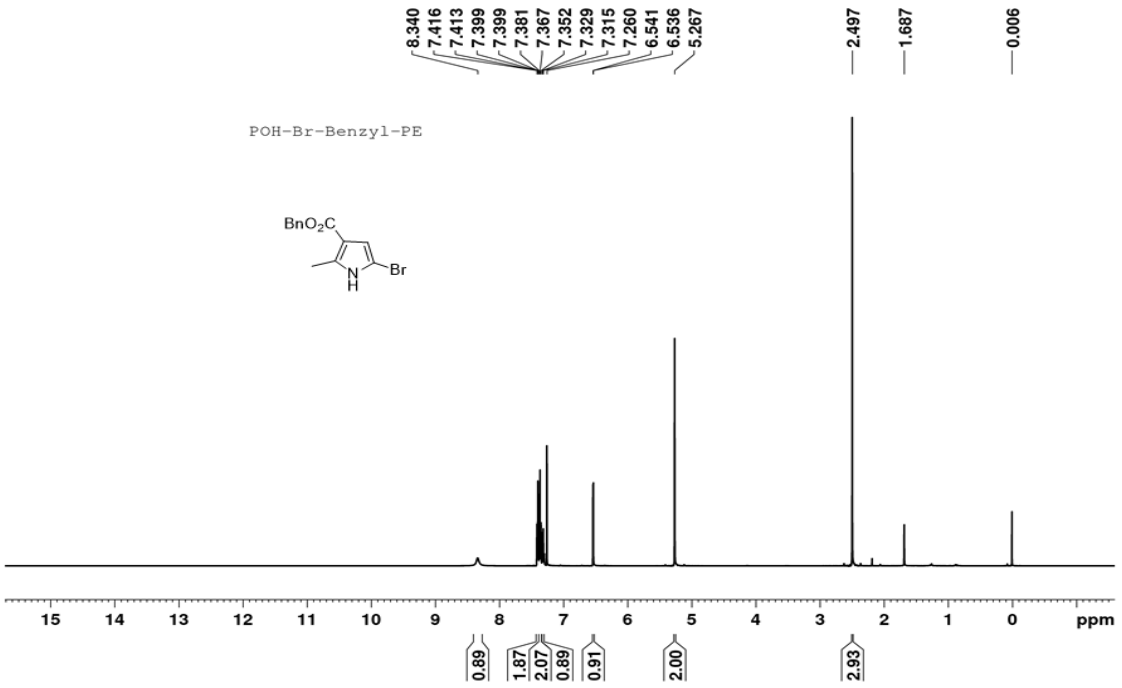


Figure 2.32: ^{1}H NMR spectrum of **2.38b** in $CDCl_3$.

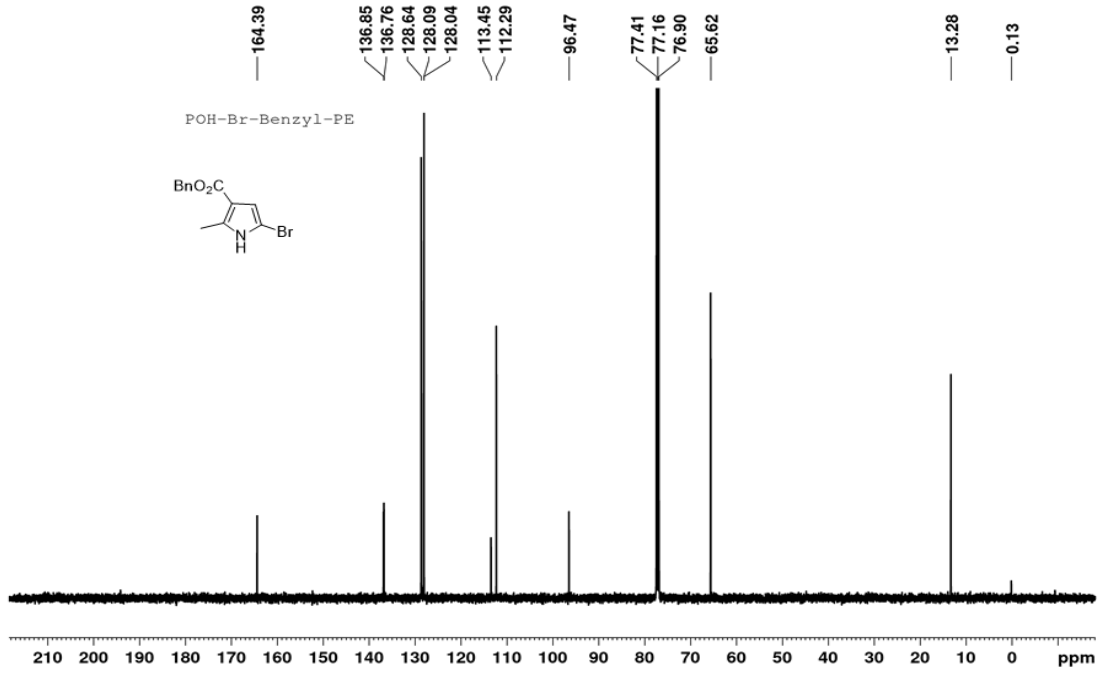


Figure 2.33: ^{13}C NMR spectrum of **2.38b** in $CDCl_3$.

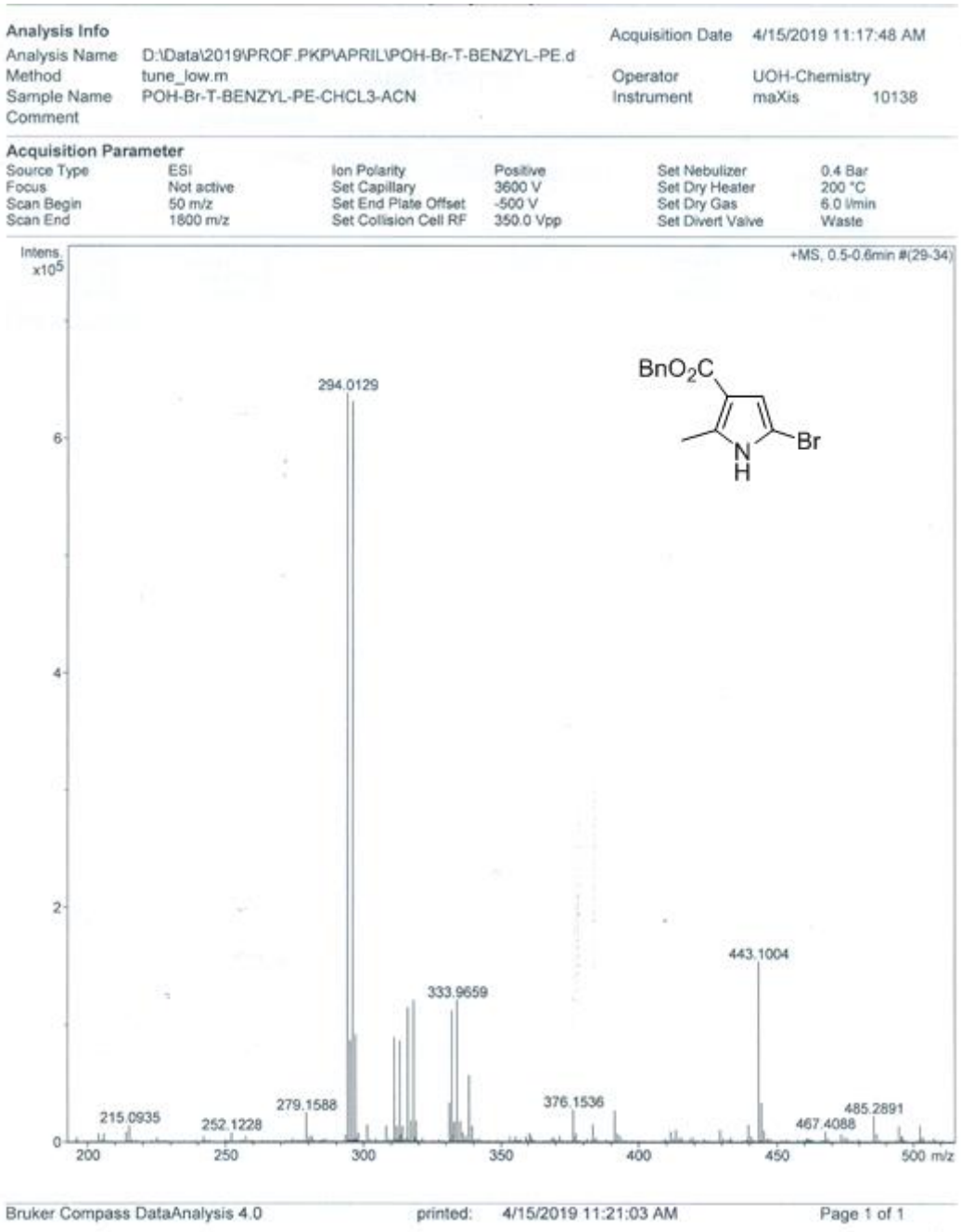


Figure 2.34: HRMS data of **2.38b** $(M+H)^+$; Calculated for $C_{13}H_{13}BrNO_2$ $[M+H]^+$: 294.0129; found: 294.0129.

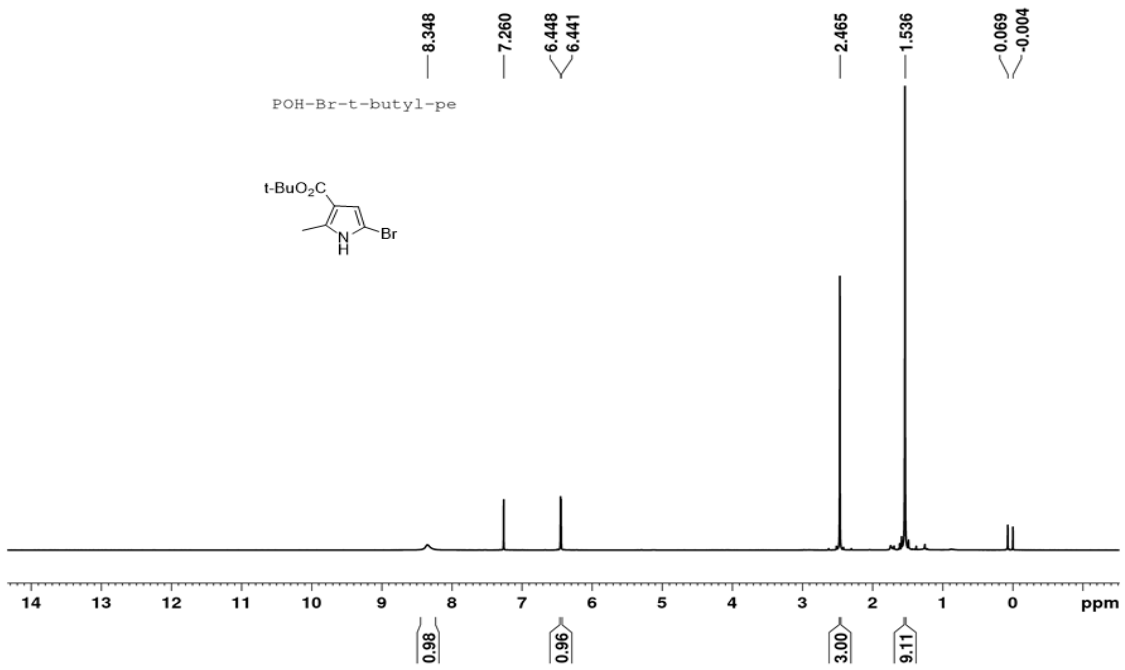


Figure 2.35: ^{1}H NMR spectrum of **2.38c** in $CDCl_3$.

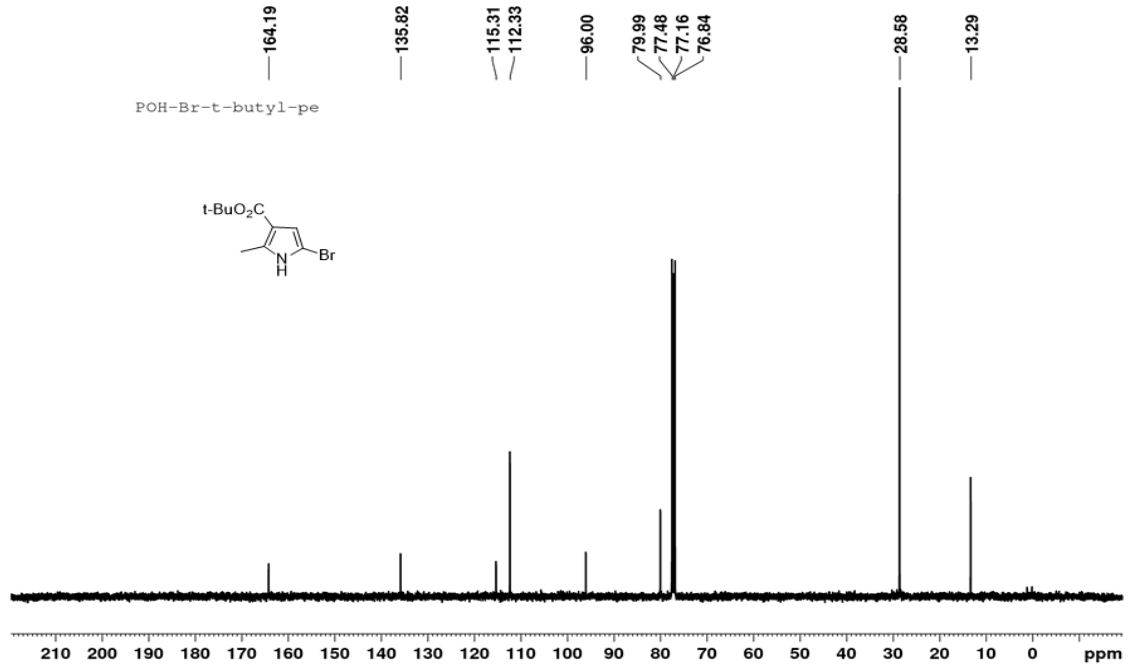


Figure 2.36: ^{13}C NMR spectrum of **2.38c** in $CDCl_3$.

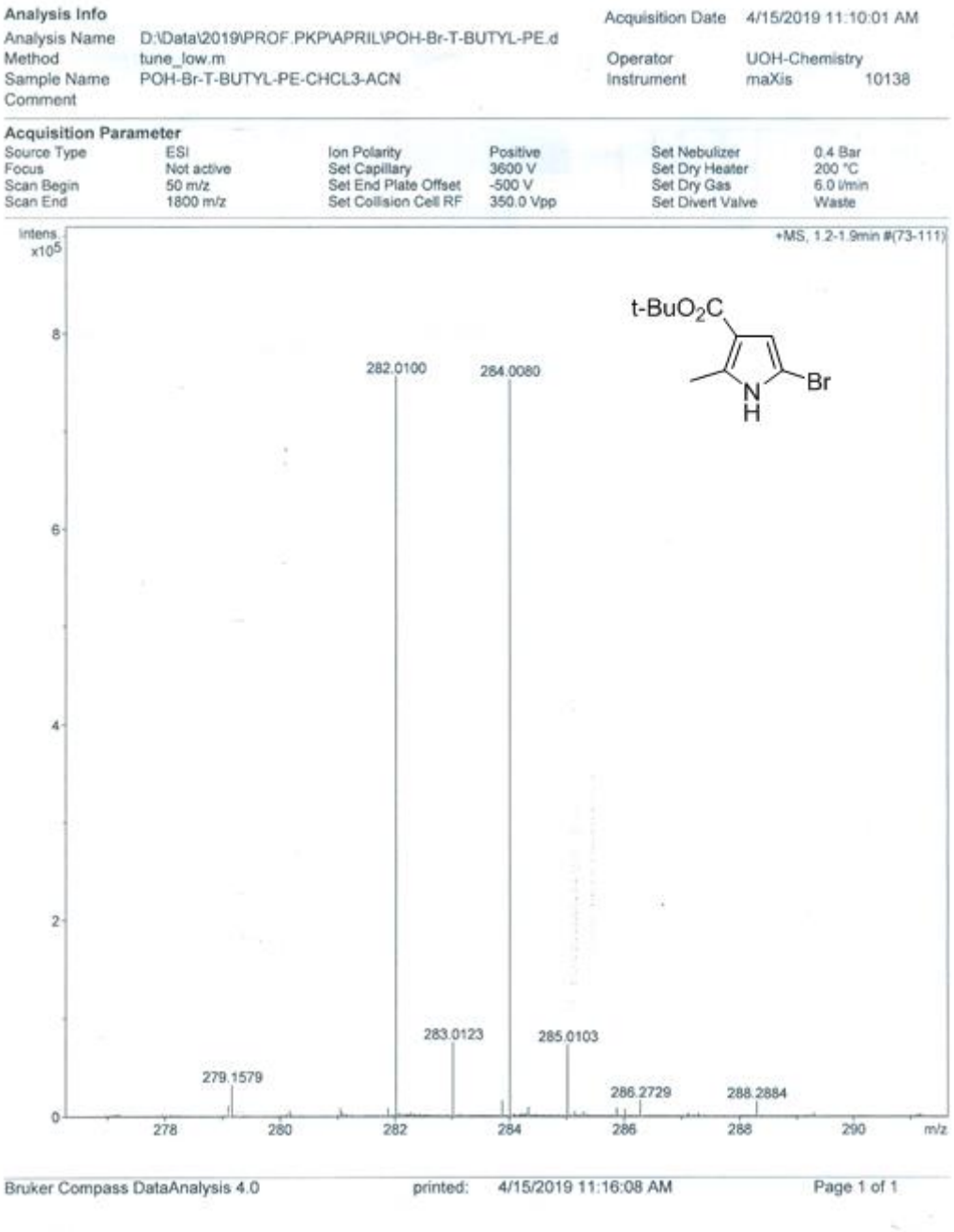


Figure 2.37: HRMS data of **2.38c** $[M+Na]^+$; Calculated for $C_{10}H_{14}BrNaNO_2$ $[M+Na]^+$: 282.0105; found: 282.0100.

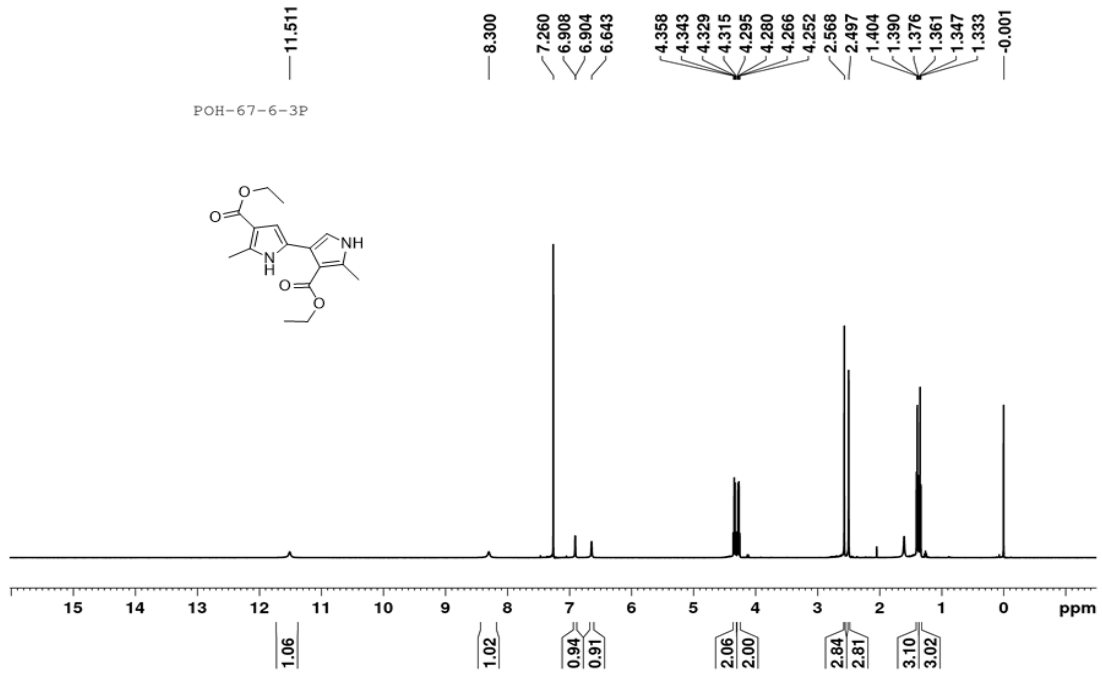


Figure 2.38: ^{1}H NMR spectrum of **2.19** in $CDCl_3$.

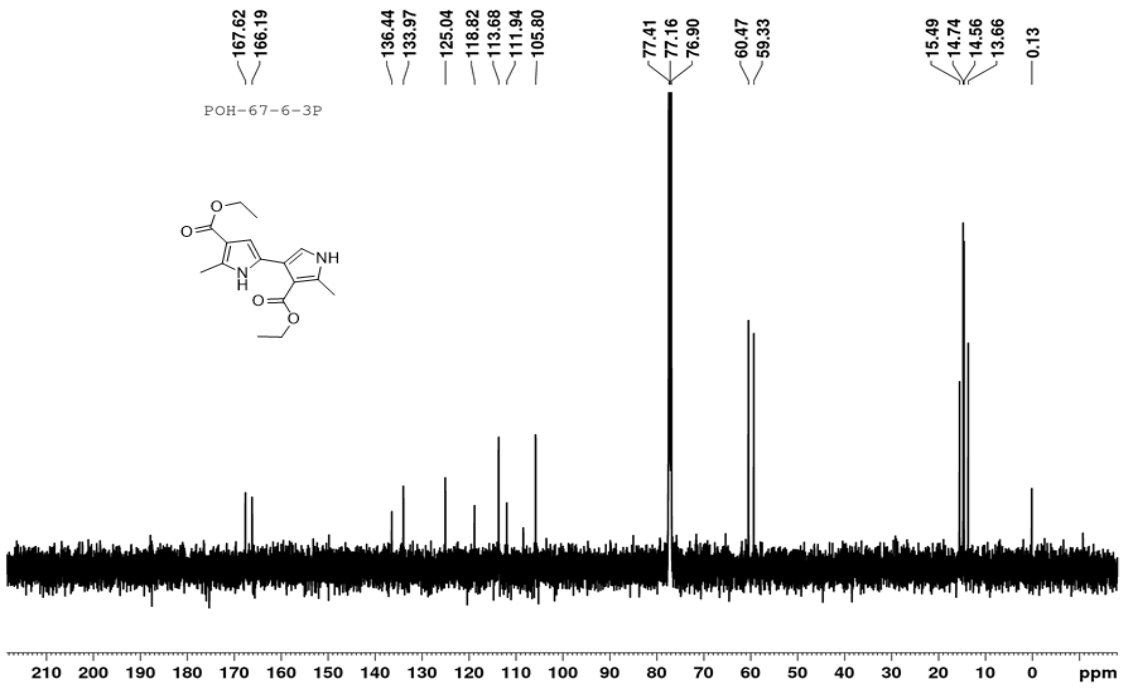


Figure 2.39 ^{13}C NMR spectrum of **2.19** in $CDCl_3$.

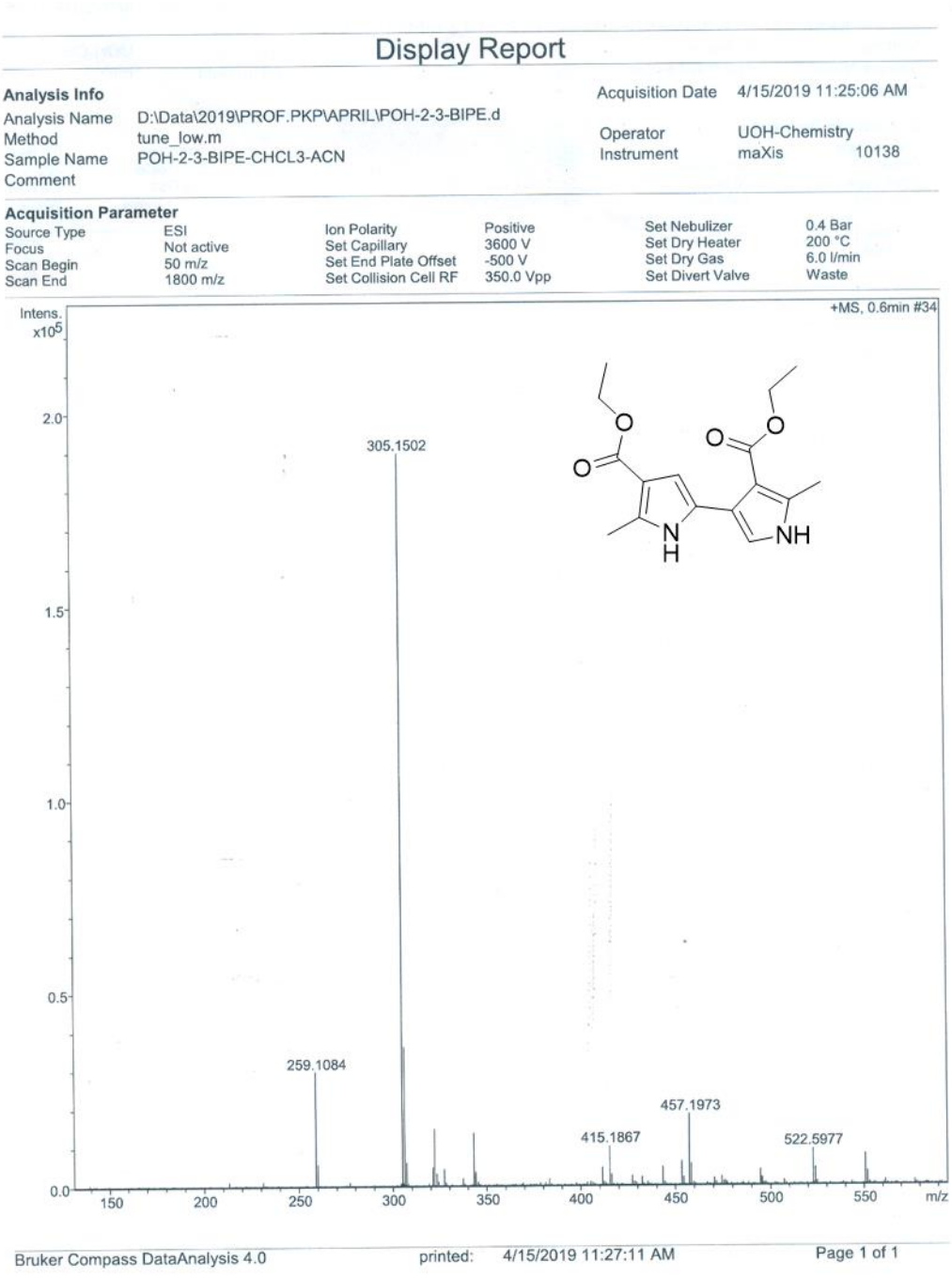


Figure 2.40: HRMS data of **2.19** $(M+H)^+$; Calculated for $C_{16}H_{21}N_2O_4$ $[M+H]^+$: 305.1501; found: 305.1502.

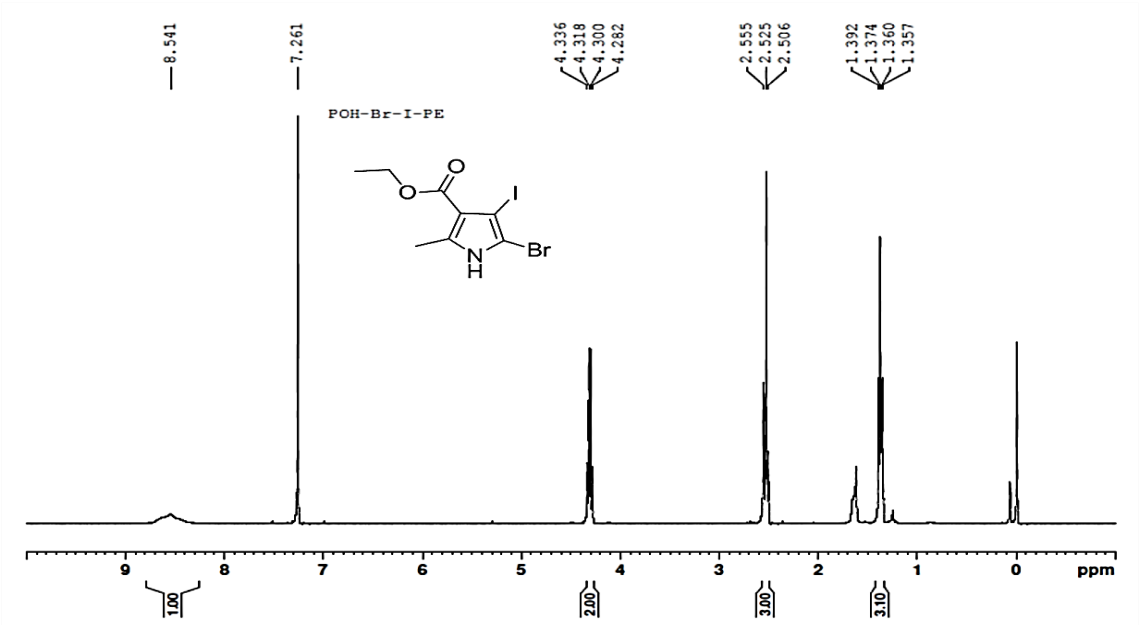


Figure 2.41 ^{1}H NMR spectrum of **2.44** in $CDCl_3$.

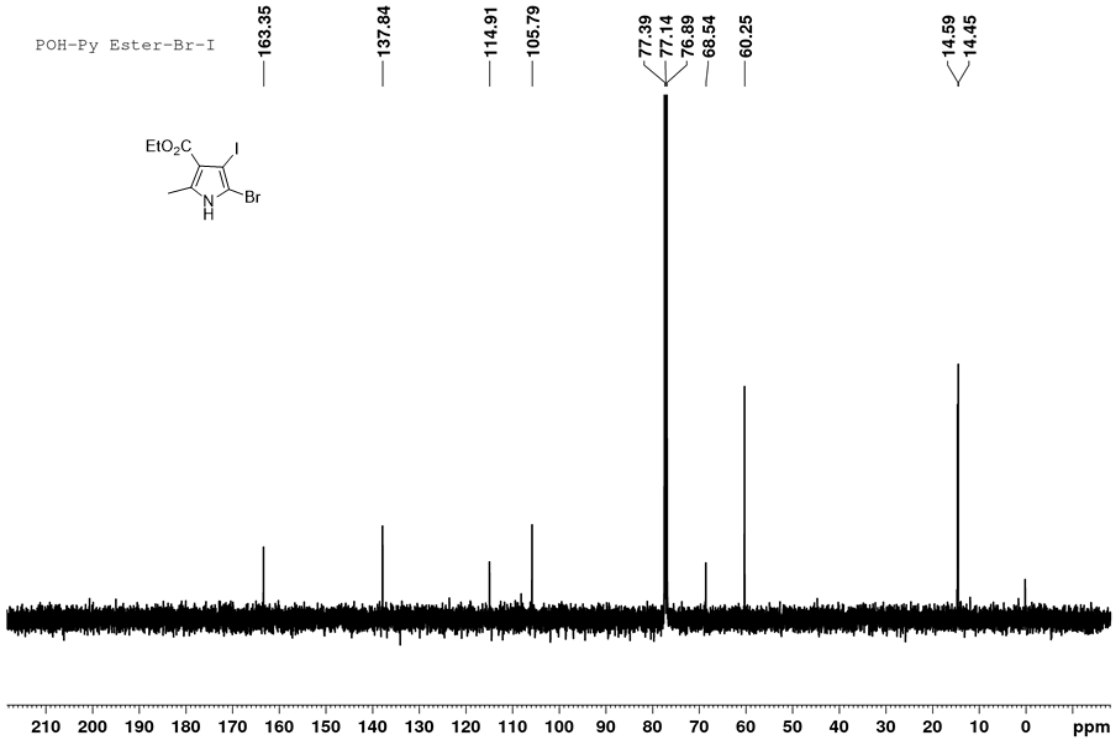


Figure 2.42: ^{13}C NMR spectrum of **2.44** in $CDCl_3$.

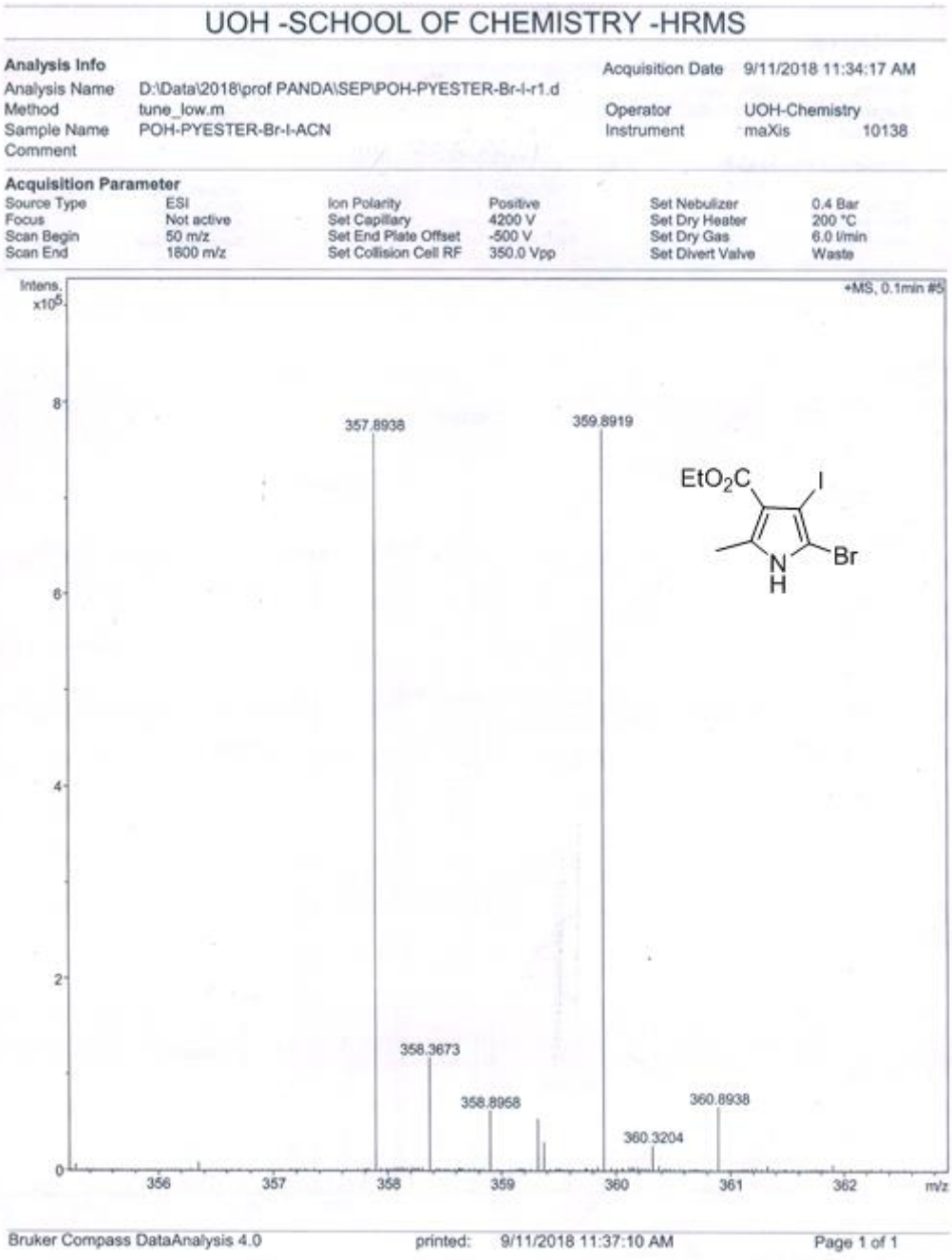


Figure 2.43: HRMS data of **2.44** $(M+H)^+$; Calculated for $C_8H_{10}BrINO_2$ $[M+H]^+$: 357.8939; found: 357.8938.

PART B

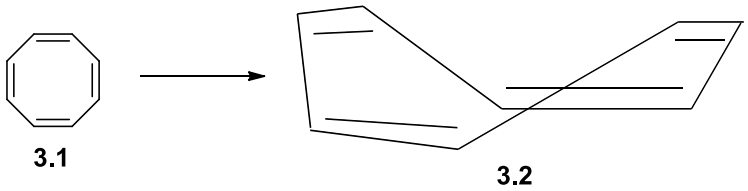
CHAPTER 3

Introduction of Antiaromatic Compounds

3.1 Introduction

Aromaticity has been a matter of immense interest to study for decades.[1-2] In 1825, Michael Faraday discovered the benzene which is a classic example of an aromatic compound.[3-4] In chemistry, aromaticity was introduced by Friedrich August Kekulé[5-6] to characterize low reactivity derivatives of benzene in particular. Procuring of aromaticity furnishes a driving force for various reactions viz electrophilic substitution reactions.[7-8] This concept is widely applied for an assessment of the reactions and properties in the electronic ground state (S_0). In 1931, the German physicist Erich Hückel issued a rule for aromaticity. According to it; a monocyclic, planar and conjugated system with 4n+2 π-electrons in the electronic S_0 state is aromatic.[9-10]

In 1967, the antiaromaticity concept was introduced by Breslow and it can be illustrated as the destabilization attained by delocalization of 4n π-electrons.[11] He also introduced antiaromatic compound examples, viz. cyclooctatetraene (COT) **3.1** and cyclobutadiene (CBD) **3.3**. But, COTs prone to endorse a tub-shaped conformation **3.2** to escape antiaromaticity according to crystallographic results (Scheme 3.1).[12]



Scheme 3.1: Conversion of COT from planar antiaromatic conformation to tub-shape.

According to Hückel molecular orbital (HMO) theory, in comparison to CBD **3.3**, benzene is stabilized due to occupancy of all π-electrons in filled orbitals (Figure 3.1). Based on the heat of hydrogenation of benzene, the stabilization energy of benzene is about 36.0 kcal/mol in comparison to the hypothetical cyclohexatriene with localized bonds.[13] On the other hand, relative to 1,3-butadiene, the destabilization of antiaromatic CBD **3.3** is 42.0 kcal/mol.[14]

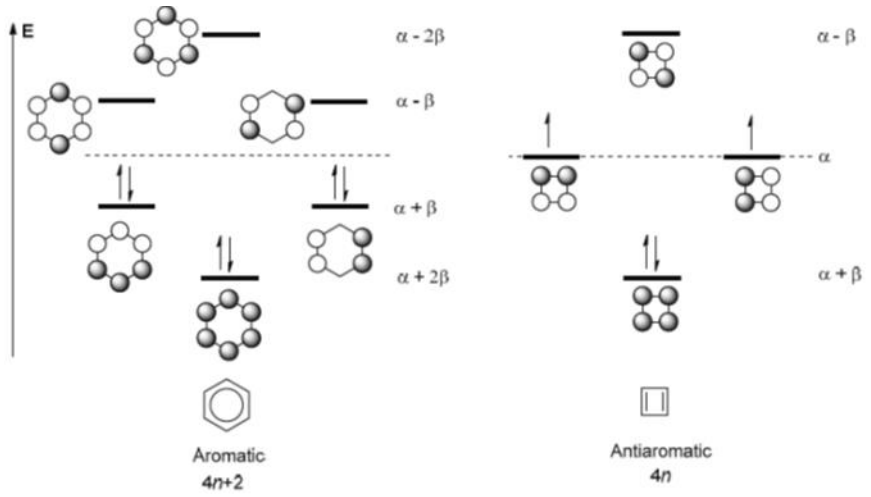


Figure 3.1: Benzene and cyclobutadiene in the S_0 state according to HMO theory. The parameter α is the coulomb integral and β is the resonance integral.

3.2 Rules of aromaticity

3.2.1 Clar's rule:

In 1972, Clar extended Huckel's rule to PAHs[15] and in his book given the rule as ''The Aromatic Sextet,'' and it describes as ''for illustrating the properties of a PAH, the resonance structure having more number of disjointed aromatic π-sextets is the most important.'' This rule is also extended to non-benzenoid hydrocarbons,[16] heterocyclic systems,[17] and excited states[18] (together with Baird's rule). Compared to the other rings in a PAH, the ring with Clar's π-sextet is more aromatic. In addition to that, the isomer of a series of isomeric PAHs which can host the more number of disjointed aromatic π-sextets is also most stable. The anthracene structure represented in three ways in Figure 3.2. Phenanthrene is thermodynamically 4-8 kcal/mol is more stable than anthracene (Figure 3.2).[19-20]

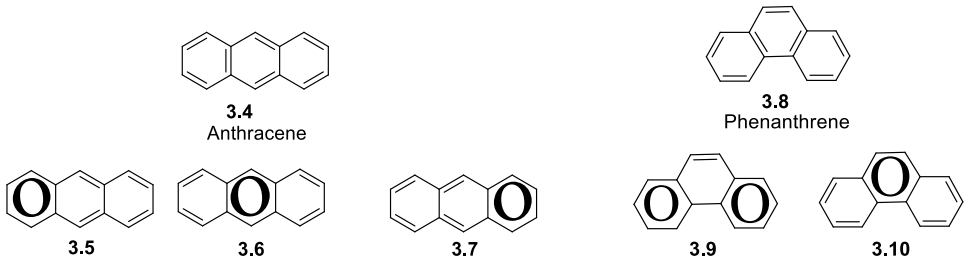


Figure 3.2: Clar's representation structures of anthracene and phenanthrene.

3.2.2 Baird's rule:

In 1972, Baird continued on the Dewar's perturbation molecular orbital approach in the ππ* triplet state to reveal the reversal of Huckel's aromaticity.[21] The Baird's rule is ''The

ring having 4n π-electrons exhibit aromaticity and ring having 4n+2 π-electrons show antiaromaticity.'' He explained that [4n+2] annulenes are destabilized and [4n] annulenes are stabilized in the state T_1. Splitting of an annulene into two separate polyenyl monoradical fragments will occur with odd number of carbon atoms and combining these fragments to obtain the triplet diradical annulene. The net energy loss or gain on combining these fragments provided destabilization or stabilization, indicative of antiaromaticity or aromaticity. According to symmetry and orbital considerations, type I and type II orbital interactions occur when combining these fragments. For CBD, interaction of type I is zero because of having mismatch symmetry orbitals while the stabilization is greater than zero due to type II interaction. In case of benzene, type II interaction is zero while type I interaction is less than zero. In conclusion, on combining these separated fragments, benzene is destabilized while CBD is stabilized in their T_1 states (Figure 3.3).

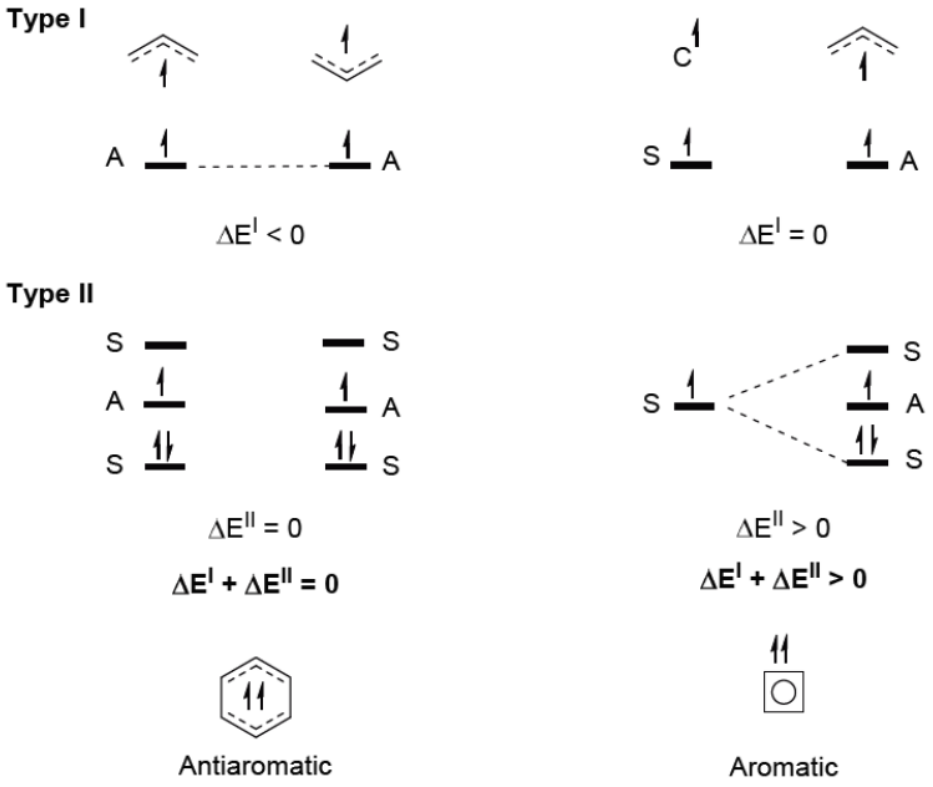


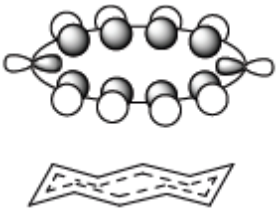
Figure 3.3: Formation of T_1 states of benzene and CBD. The labels S and A represent the symmetries of π-molecular orbitals as symmetric and antisymmetric.

3.3 Types of aromaticity:

Schleyer has developed the aromaticity concept not only restricted to Huckel aromaticity but also to various types of aromaticites.[22-23] Aromaticity types are described as given below:

a) Excited state aromaticity: In the ππ* T_1 state, rings having 4n+2 π-electrons are antiaromatic and 4n π-electrons are aromatic, according to it.[21,24]

b) In-plane aromaticity: When pi-electrons delocalization occur as in n-transannulenes in the cyclic ring plane follows this.[25-26]

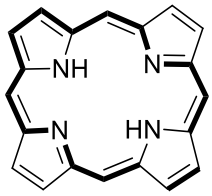


In-plane aromaticity

c) Hückel aromaticity: A planar complete pi-conjugated monocycle with 4n+2 π-electrons follows it.[9-10]

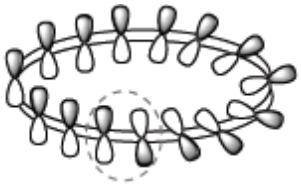
Hückel aromaticity

d) Macrocyclic aromaticity: A macrocycle can have many conjugation path ways but the 4n+2 π-electrons path way follows aromaticity or super aromaticity,[21] as in the porphyrin ring.[27]



Macrocyclic aromaticity

e) Möbius aromaticity: According to it, in the S_0 state, [4n+2] annulenes are antiaromatic and [4n] annulenes are aromatic. It is observed when P_π atomic orbitals arranged in cyclic with a single half-twist for which the orbital symmetry and aromaticity of Huckel's rule is reversed.[28]



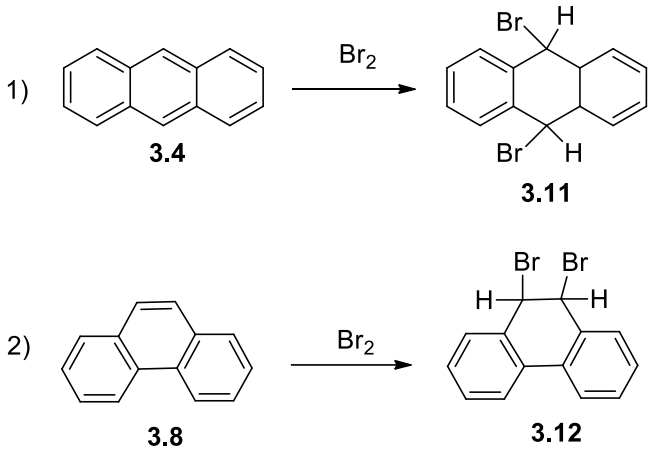
Möbius aromaticity

In addition, metallobenzenes[29] and transition-metal sandwich complexes (for example, ferrocene)[30] are also follow aromaticity.

3.4 Criteria for aromaticity characterization

Over the years five criteria were developed based on physicochemical properties to characterize the molecules as being nonaromatic, aromatic and antiaromatic[22-23,31] and details are given below.

1) **Reactivity**: In general, aromatic compounds reactivity is very less compared to nonaromatic systems and according to Labarre and Crasnier.[32] They undergo substitution reactions in contrast to olefinic systems, which undergo addition reactions instead. But, there are few exceptions, for example, anthracene and phenanthrene undergo addition reactions with bromine (Scheme 3.2).[33] Antiaromatic compounds reactivity is very high.



Scheme 3.2: Addition reactions of anthracene and phenanthrene.

1) **Energetic**: Cyclic π-electron delocalization causes the energy of (de)stabilization is called as aromatic stabilization energy.[34] The net (de)stabilization energy calculated from the aromatic stabilization energy or resonance energy based on homodesmotic or isodesmic reactions are employed as criteria to quantify (anti)aromaticity.

2) **Structural**: Bond length equalization due to planarity as well as delocalization of π-electrons determines a molecule's aromaticity while localized pi-bonds shows antiaromiticity. For example, borazine is isoelectronic with benzene as it has equalized bond lengths in addition to six π-electrons. But, the pi-electrons are heavily localized on the nitrogen atoms for which it show scarcely a pi-ring current and it is weakly aromatic.[35]

3) **Magnetic**: The well-verified ring model[36] tells that in the presence of an external magnetic field aromatic compounds exhibit a diatropic ring current (Figure 3.4). In response to applied external magnetic field, π-electrons circulation creates ring-currents. Molecule's magnetic properties are dependent on the ring currents. Using ring currents and magnetic properties, various methods, e.g., magnetic susceptibility exaltation, ^{1}H NMR chemical shift and NICS, have been developed for the estimation of (anti)aromaticity.[35]

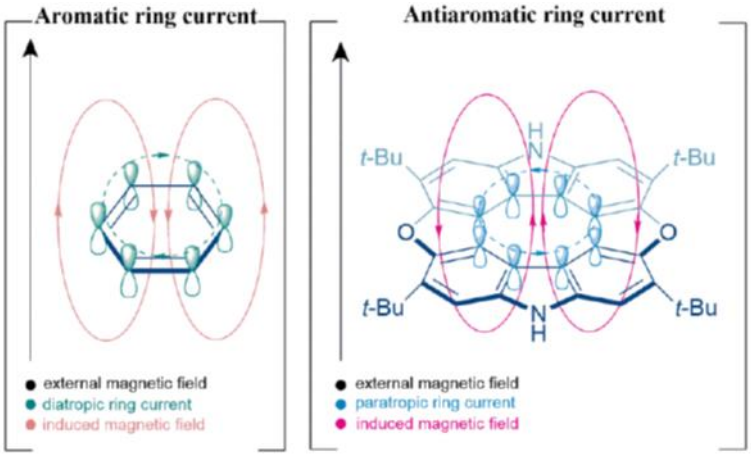


Figure 3.4: Ring current in aromatic and antiaromatic compounds.

4) **Electron delocalization**: The electron (de)localization degree of uniformity furnishes another measure to assessment the (anti)aromaticity. Bader and coworkers explained that electron (de)localization depends on the Fermi hole density localization.[37] The integration of Fermi hole density provides the percentage of (de)localization[38] and several methods have been flourished based on the electron density topology, for example, the *para*-delocalization index (PDI), delocalization index (DI), aromatic fluctuation index (FLU) and aromatic multicenter index (MCI). FLU estimates in a ring the fluctuation of electronic charges while MCI illustrates an electron sharing between centers of a ring. Higher values corresponds

to higher aromaticity for MCI while lower values related to higher aromaticity for FLU.[39]

In conclusion, the compounds which fulfill only one or two criteria are termed partly or weakly aromatic whereas the compounds which satisfy all the given above criteria of aromaticity is named as fully aromatic. Based on electron delocalization, Sola and coworkers illustrated that indices among all of the above criteria are the best to assess the aromaticity.[40]

3.5 Computational methods for aromaticity analyzation

3.5.1 Harmonic oscillator model of aromaticity (HOMA): It is a geometric index. It depends on the degree of delocalization of π-electrons. The formula to calculate HOMA with n bonds for a system is

HOMA $= 1 - \frac{\alpha}{n}\sum_{i=1}^{n}(R_{opt} - R_i)^2$ (equation 1)

Where 'α' is an empirical normalization constant, R_i is the experimental or computed bond length of *i*th bond and R_{opt} is the optimal aromatic bond length.

An antiaromatic compound has a negative HOMA value, a nonaromatic compound has close to zero HOMA value and an aromatic compound has a HOMA value, which approaches to one (Figure 3.5). The HOMA value can be utilized to estimate both global and local aromaticity of polycyclic compounds.[41] Further, Krygowski utilized this value for triplet states of 4n π-electrons.[42]

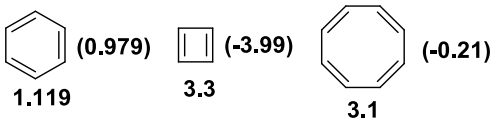


Figure 3.5: HOMA values of benzene, CBD **3.3** and COT **3.1**.[41b,42]

3.5.2 Nucleus independent chemical shifts (NICS): It is an aromaticity index depend on the molecular magnetic properties. Positive NICS values indicate antiaromaticity while negative NICS values denote aromaticity (Figure 3.6).

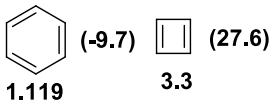
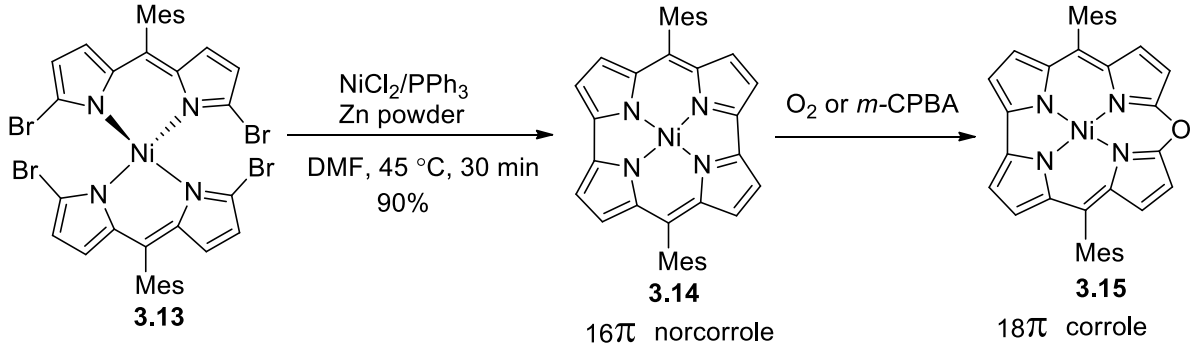


Figure 3.6: NICS values of benzene and CBD **3.3**.[43]

In recent times, antiaromatic compounds chemistry has enticed huge attention in their planar conjugation cyclic path ways with 4n π-electrons since they exhibit enhanced and unique reactivity along with their noticeable physical properties.[44] They unequivocally show variety of properties for standard aromatic compounds, like stable redox processes,[45] smaller HOMO-LUMO energy gaps,[46] increased bond length alterations and decreased delocalization.[1,47] They exhibit positive NICS values and paratropic ^{1}H NMR chemical shifts with larger values.[48] They have been attracted and explored by chemist's with theoretical interest and their material science applications[49] viz. conductivity,[50] nonlinear optical studies,[51] optoelectronics[44e] and energy storage[52] even though having quite rare experimental examples. Recently, Anderson and coworkers designed these type of compounds as semiconductor material applications.[53] This led to have immense interest in developing stable antiaromatic compounds.[54] Annulenes and porphyrins are few among the classical probes to study basic aromatic and antiaromatic properties.[55] Some of examples for antiaromatic compounds will be briefly described as given below as part of this thesis with some details.

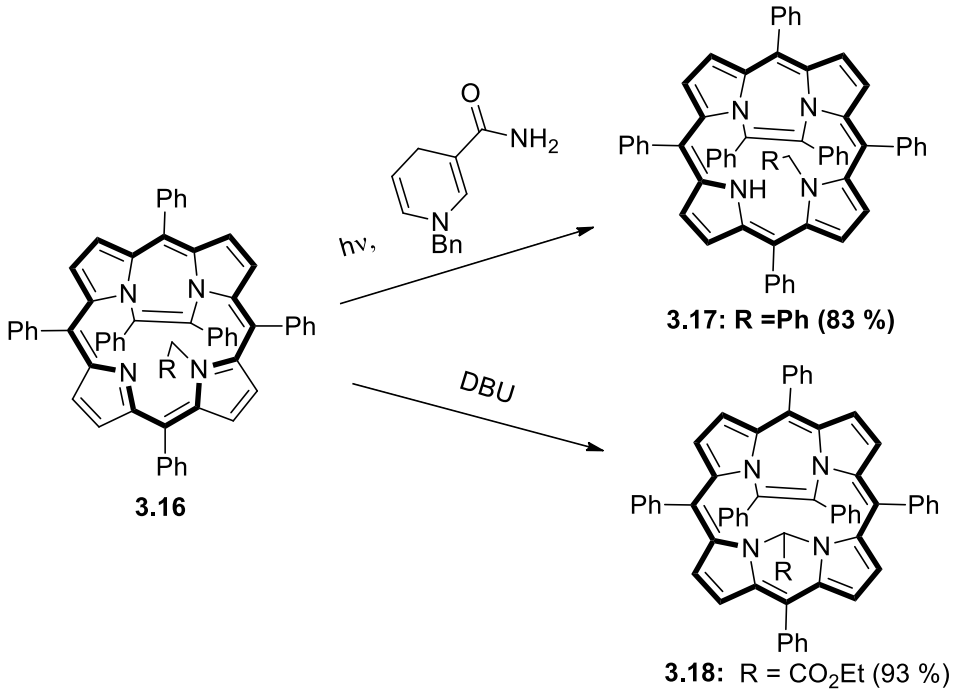
3.6 Antiaromatic porphyrinoids

In 2012, Shinokubo group synthesized norcorrole complex **3.14** by a strategy of nickel-template using nickel dichloride, triphenylphosphine and zinc powder in presence of dimethyl sulfoxide solvent. For the first time, Ni^{II} norcorrole revealed a marked antiaromatic character with highly planar structure as a stable molecule at room temperature (Scheme 3.3).[56] This norcorrole complex upon oxidation at high temperature gives oxocorrole complex **3.15** which displays 18π aromatic character.



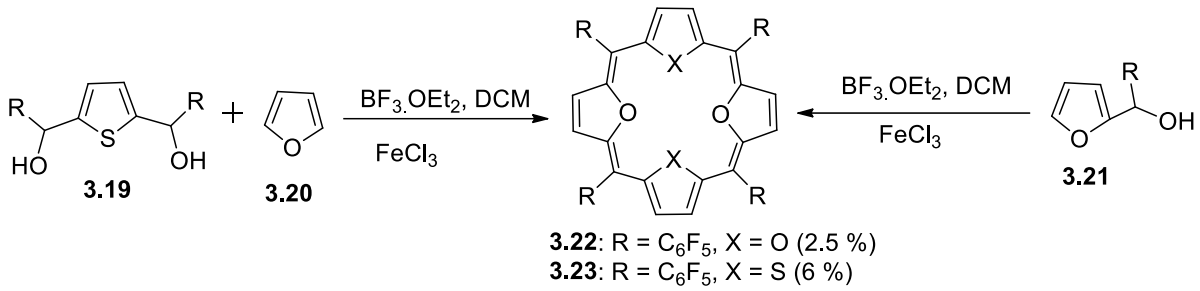
Scheme 3.3: Synthesis of norcorrole complex **3.14**.

Sestune *et al*. prepared *N,N',N''*-trisubstituted isophlorin **3.17** from *N,N'*-diphenylethano-bridged porphyrin **3.16** by photochemical reduction with *N*-benzyl-1,4-dihydronicotinamide (BNAH) in 83 % yield and **3.18** made from **3.16** upon treatment with DBU in 93 % yield (Scheme 3.4).[57] These 20π porphyrins are having planar conformations due to the ethylene bridge to show paratropic ring current.



Scheme 3.4: Synthesis of etheno-bridged isophlorins **3.17** and **3.18**.

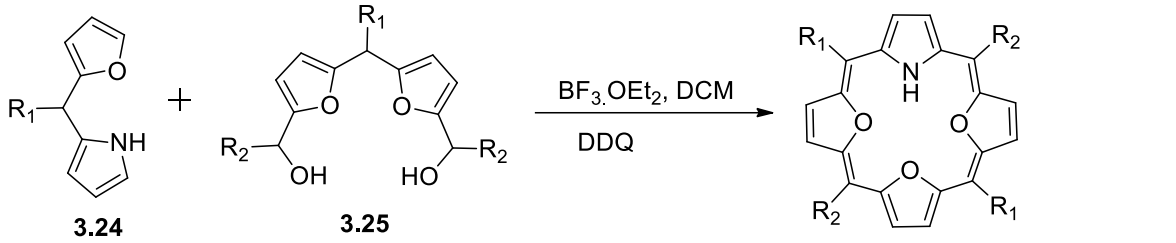
In 2007, V. G. Anand group obtained isophlorin **3.22** from **3.21** by acid-catalyzed self - condensation reaction using $BF_3.OEt_2$, followed by oxidation with $FeCl_3$ and also made **3.23** using **3.19** and **3.20** (Scheme 3.5).[58] These macrocycles did not undergo further oxidation with DDQ, trifluoroacetic acid, or iodine reveals their stability may be due to the presence of strong electron withdrawing pentafluorophenyl groups on the macrocycle *meso*-positions. Upfield chemical shift value from ^{1}H NMR spectra indicates the paratropic ring current effect.



3.22: R = C_6F_5, X = O (2.5 %)
3.23: R = C_6F_5, X = S (6 %)

Scheme 3.5: Synthesis of isophlorins **3.22** and **3.23**.

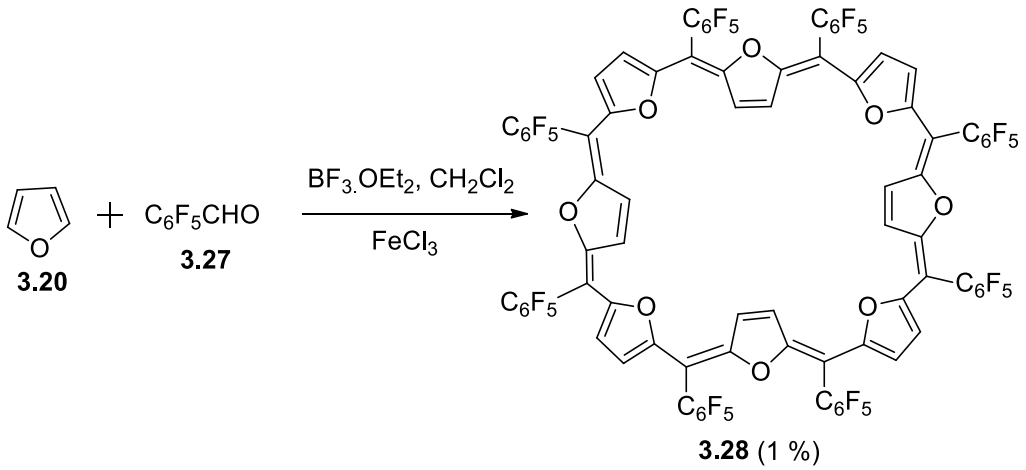
Core-modified antiaromatic 20π isophlorin **3.26** was obtained from **3.24** and **3.25** by MacDonald-type condensation under acidic condition followed by oxidation using DDQ by V. G. Anand group (Scheme 3.6).[59]



3.26: R_1 = C_6H_5, R_2 = C_6F_5 (10 %)

Scheme 3.6: Synthesis of 20π antiaromatic isophlorin **3.26**.

The 40π expanded isophlorin **3.28** was achieved from condensation of furan **3.20** and pentafluorobenzaldehyde **3.27** and its antiaromatic character displayed from ^{1}H NMR, Uv-vis absorption spectrum and cyclic voltammetric studies (Scheme 3.7).[60]

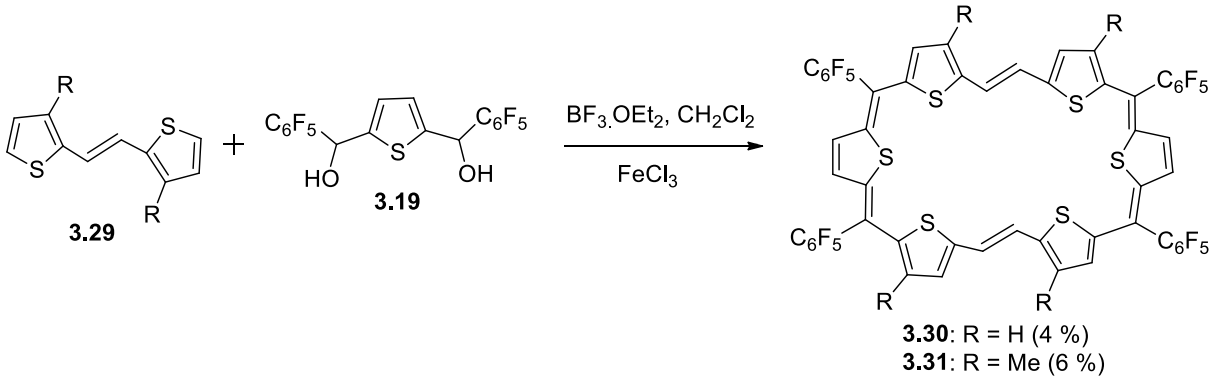


3.28 (1 %)

Scheme 3.7: Synthesis of 40π antiaromatic expanded isophlorin **3.28**.

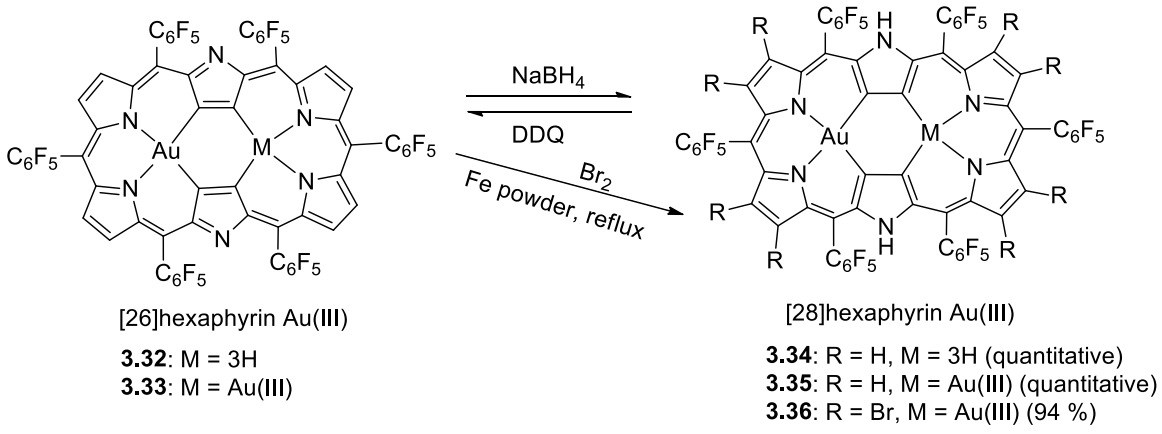
Ethylene bridged antiaromatic 32π expanded isophlorin **3.30** synthesis was realized by acid catalyzed condensation of dithienylethylene **3.29** with thiophene diol **3.19** followed by

oxidation with ferric chloride in presence of DCM (Scheme 3.8)[61] and its paratropic ring current effect was observed at low temperature only.



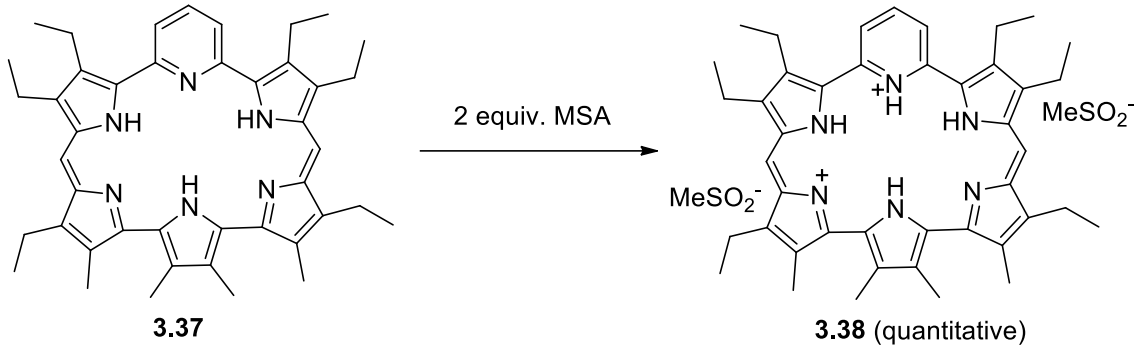
Scheme 3.8: Synthesis of ethylene bridged 32π antiaromatic expanded isophlorins **3.30-3.31**.

Osuka group obtained the [28]hexaphyrin mono- and bis-Au(III) complexes **3.34** and **3.35** by reduction of [26]hexaphyrins **3.32** and **3.33** with sodium borohydride. In addition to that they afforded fully β-brominated [28]hexaphyrin **3.36** from **3.33** upon treatment with neat bromine and iron powder in reflux condition (Scheme 3.9).[62] ^{1}H NMR spectra of **3.34** and **3.35** display paratropic ring current.



Sheme 3.9: Interconversion between aromatic [26]hexaphyrin and [28]hexaphyrin.

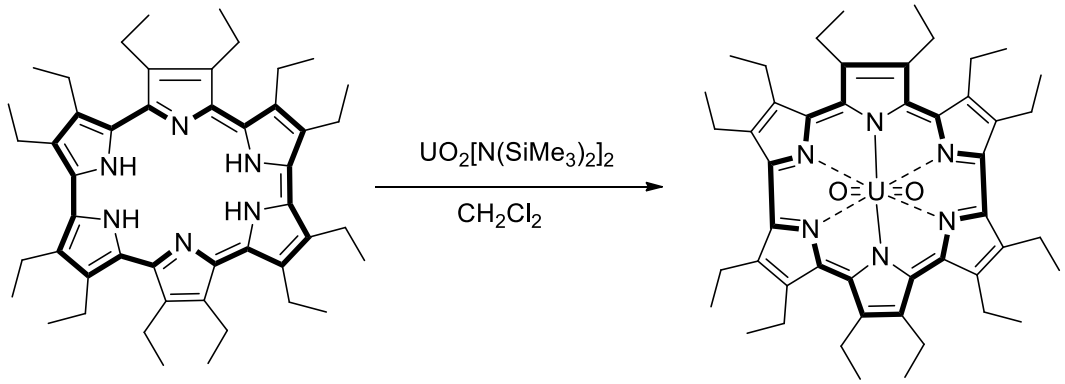
Recently, Sessler *et al*. prepared the diprotonated antiaromatic compound **3.38**, upon treatment of **3.37** with methanesulfonic acid (Scheme 3.10).[63] Protonation increases π-conjugation and yields antiaromatic character.



3.37 **3.38** (quantitative)

Scheme 3.10: Prepararion of antiaromatic species **3.38**.

Uranyl complex **3.40** was achieved by Sessler *et al*. upon treatment of cyclo[6]pyrrole **3.39** with $UO_2[N(SiMe_3)_2]_2$ in dichloromethane as an antiaromatic species in 2007 (Scheme 3.11).[64] Both X-ray crystal structure displaying high planarity and chemical shifts of ^1H NMR spectrum **3.40** indicating a paratropic ring current.

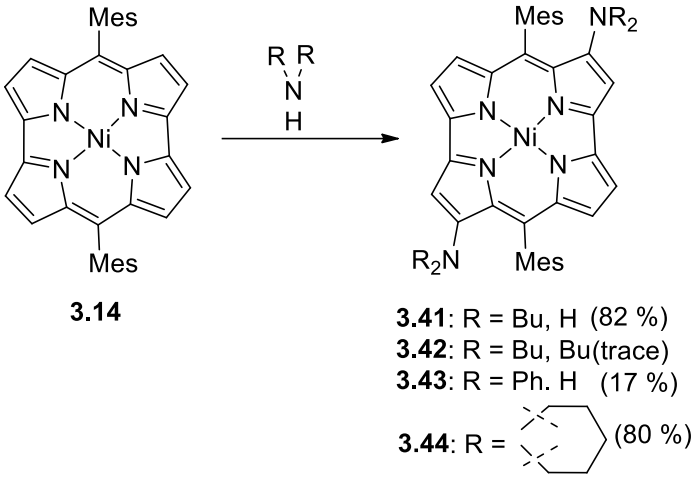


3.39 **3.40** (25 %)

Scheme 3.11: Uranium insertion into cyclo[6]pyrrole **3.40**.

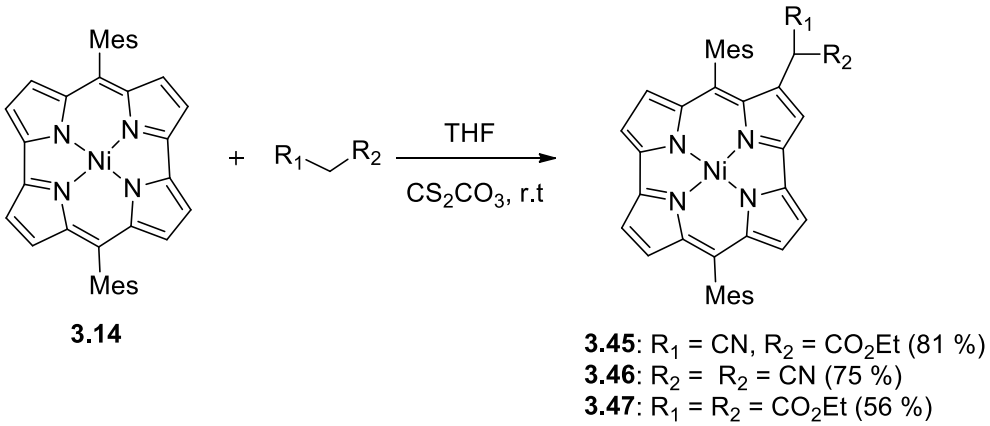
3.7 Applications of antiaromatic compounds

Antiaromatic compounds high reactivity is very useful for selective further manipulation via functionalization towards future applications.[56] Details of some examples are briefly given below. In 2017, Shinokubo group achieved successfully bis-aminonorcorrole complex **3.41** from Ni^{II} dimesitylnorcorrole complex **3.14** using amine in 82% yield without catalyst (Scheme 3.12) and other derivatives were also made.[65] This type of aminonocorroles can be useful in material science applications due to introduction of electron donor amino groups.



Scheme 3.12: Synthesis of aminonorcorroles **3.41-3.44**.

New types of norcorrole derivatives **3.45-3.47** were obtained from **3.14** with active methylene compounds at room temperature in tetrahydrofuran solvent in presence of cesium carbonate in moderate to nice yields by Chmielewski group in 2019 (Scheme 3.13).[66] These derivatives can be used in coordination chemistry in future.



Scheme 3.13: Preparation of derivatives of norcorroles **3.45-3.47**.

[28]hexaphyrins antiaromaticity will be explained in next working chapter 4 with some examples in detail.

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CHAPTER 4

Meso-Hexakis(ethoxycarbonyl)[28]Hexaphyrin-(1.1.1.1.1.1): A Symmetrically Substituted Intramolecular Hydrogen Bond Stabilized Conformationally Rigid Hückel Antiaromatic

4.1 Introduction

Hexaphyrins are most versatile and broadly explored among the expanded porphyrinoids.[1] Their chemistry started with the synthesis of rosarin,[2] rubyrin,[3] hexaphyrin,[4] amethyrin,[5] and bronzaphyrin[6] in early 1990s and subsequently cyclo[6]pyrrole[7] in 2003. These macrocycles were systematically named based on the varied number of *meso*-methine bridges between the pyrrolic units according to Franck and Nonn's nomenclature[8] as [24]hexaphyrin(1.0.1.0.1.0), [26]hexaphyrin(1.0.1.1.0.1), [26]hexaphyrin(1.1.1.1.1.1), [24]hexaphyrin(1.0.0.1.0.0), [26]hexaphyrin(2.0.0.2.0.0) and [22]hexaphyrin(0.0.0.0.0.0), respectively (Figure 4.1).

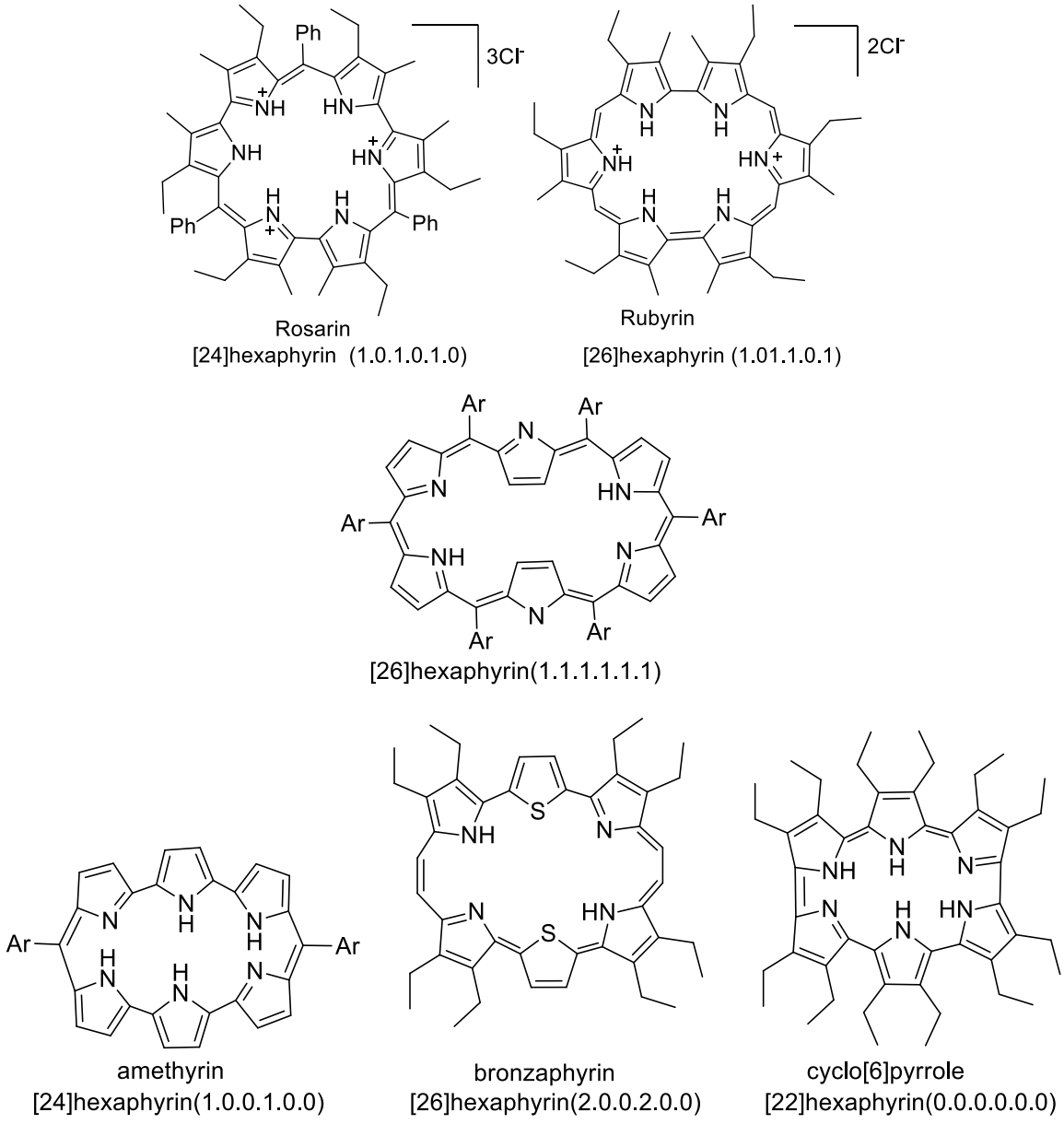
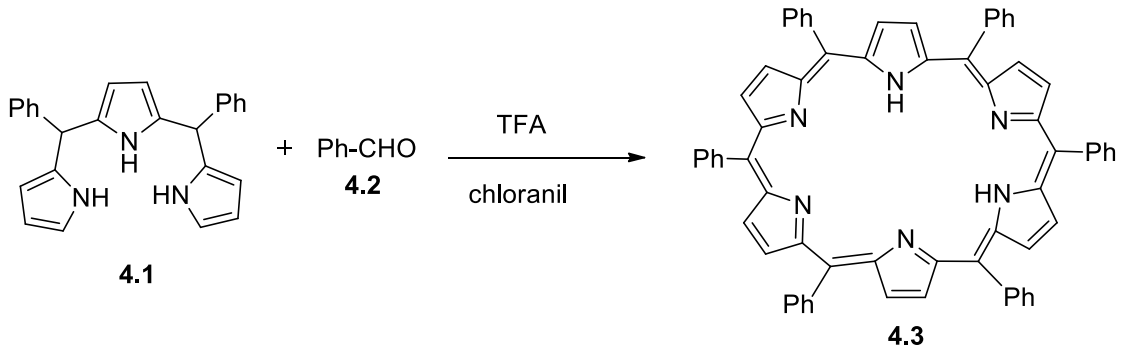


Figure 4.1: Structures of different types of hexaphyrins.

They are found to be of immense importance to explore many fields viz. bimetallic coordination,[4,9] proton coupled reactions,[10] nonlinear optical properties,[11] stable organic radicals,[12] structural diversity,[13] probe for near infrared absorption and emission.[14] Among various expanded porphyrinoids, hexaphyrin(1.1.1.1.1.1) derivatives were of great research interest due to their engrossing physico-chemical properties, in particular, in view of aromaticity and antiaromaticity switch between [26]hexaphyrins(1.1.1.1.1.1) and [28]hexaphyrins(1.1.1.1.1.1). Further, they can display different conformations viz. dumbbell,[15] figure-of-eight,[16] twisted figure-of-eight,[17] rectangular,[18] triangular,[19] spectacles-shaped,[20] twisted möbius strip shapes.[21] Although, [26]hexaphyrin systems exhibit Hückel aromaticity with a double-sided ring conformation, [28]hexaphyrin systems adopt a single-sided twisted ring conformation having Möbius aromaticity.[22] These conformational tunability help hexaphyrins emerge as ideal systems to address the classical Hückel *vs* Mobius aromaticity, making them excellent probes for studying variable aromaticity.[23] Their oxidation state has a vital impact on the properties of its light-absorption and emission.[24] Their unique absorption and emission properties furnish very useful nonlinear optical properties like two-photon absorption,[24a] which make them more potential for a broad range of applications viz. microscopy, microfabrication, up- converted lasing, three-dimensional data storage, optical power limiting, photodynamic therapy.[25] In addition to that, their cavities are very suitable for the consequent coordination of two identical or different metal centers.[26]

4.2 Synthesis of [26] and [28]hexaphyrins:

The first synthesis of hexaphyrin was reported as its *β*-substituted analogue by Gossauer in 1993.[27] In 1997, Dolphin and coworkers reported regarding unstable nature of *meso*-phenyl hexaphyrin (Scheme 4.1).[28]



Scheme 4.1: Structure of *meso*-phenyl hexaphyrin.

In 1999, Cavaleiro group achieved the first stable fully characterized *meso*-aryl hexaphyrins by introduction of electron deficient groups like pentafluorophenyl at its *meso*-positions (Figure 4.2).[29]

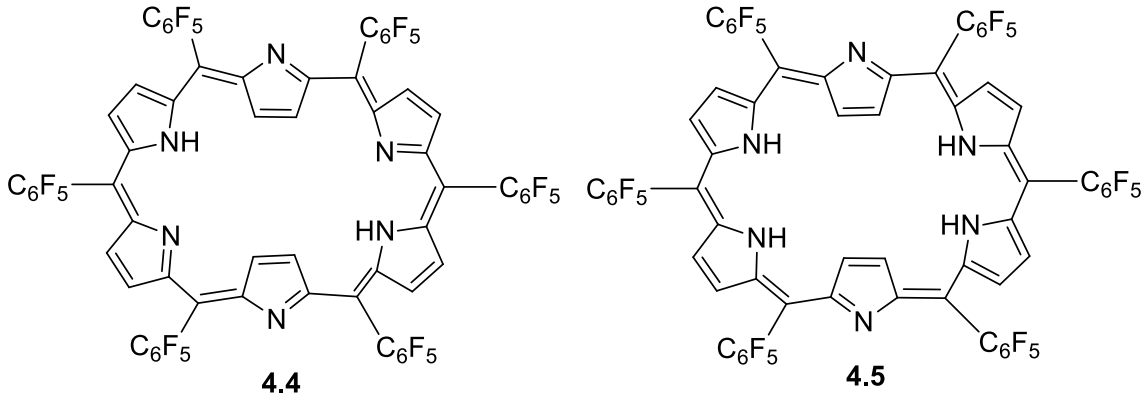
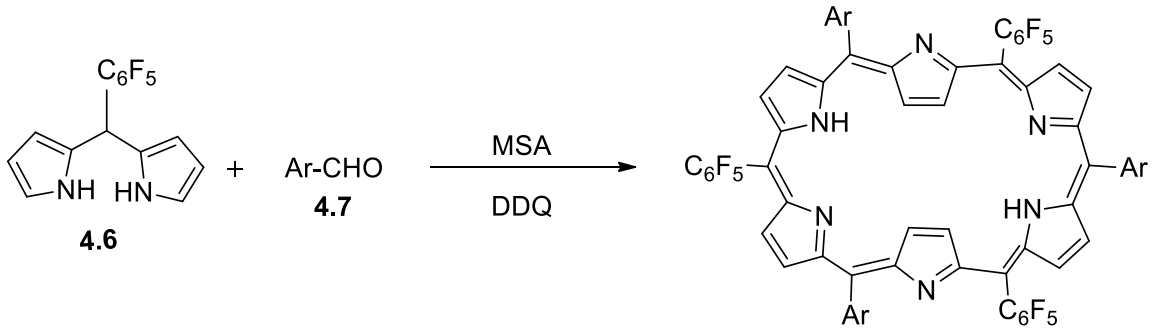


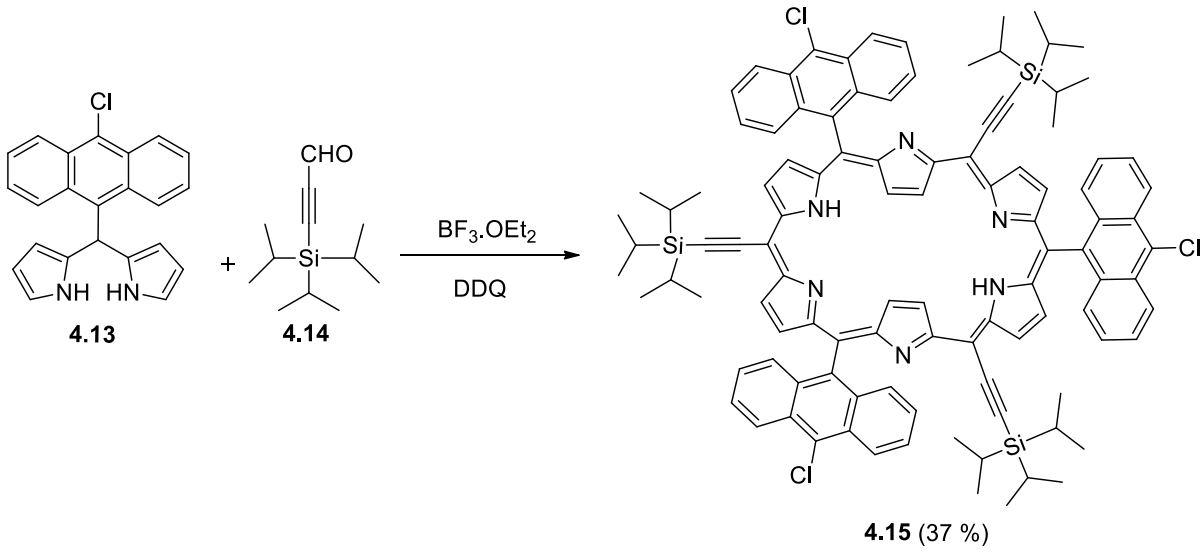
Figure 4.2: Structures of *meso*-pentafluorophenyl hexaphyrins.

Thereafter hexaphyrins chemistry obtained a new life with their *meso*-aryl derivatives, due to excellent works of Osuka and coworkers. In 2003, They synthesized *meso*-aryl [26]hexaphyrin derivatives (Scheme 4.2).[30]



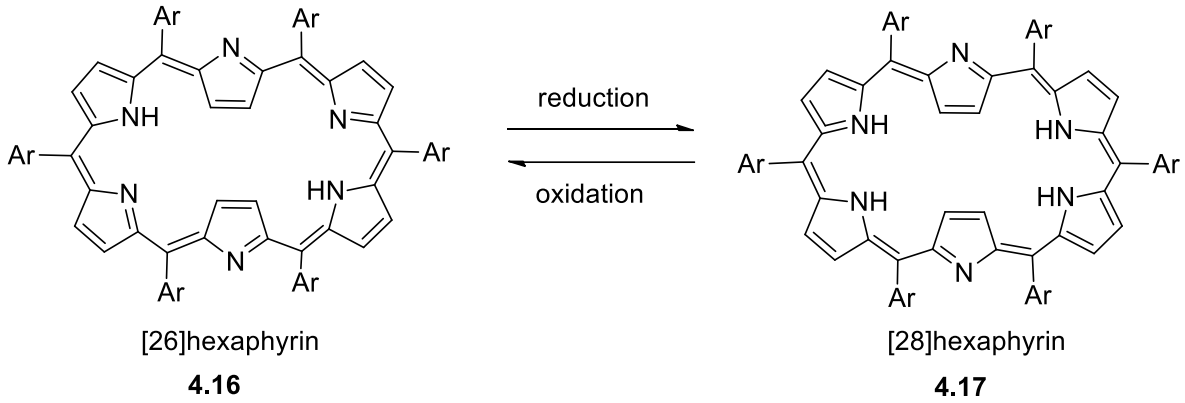
Scheme 4.2: Synthesis of hexaphyrin derivatives **4.8**-**4.12**.

Anderson group obtained **4.15** as a stable molecule in 37 % yield (Scheme 4.3).[31]



Scheme 4.3: Synthesis of [28]hexaphyrin derivative **4.15**.

Subsequently, it was showed that aromatic [26]hexaphyrin systems could be converted easily to [28]hexaphyrin systems by reduction with sodiumborohydride ($NaBH_4$) or tosylhydrazide (Scheme 4.4).[29,32] However, the obtained reduced systems were observed to be unstable under ambient conditions.



Scheme 4.4: Interconversion of [26]hexaphyrin and [28]hexaphyrin.

4.3 Motivation and objective of the research work:

Recently, Osuka group could be able to synthesize the stable antiaromatic [28]hexaphyrins by applying a strategy through introduction of intramolecular hydrogen bonding route by substitution of two of the *meso*-positions (at 5- and 20-) with *o*-pyridyl **4.18**, imidazolyl **4.19**, ethoxycarbonyl **4.20** and benzoyl **4.21** groups (Figure 4.3). Except imidazolyl substituted compound, remaining other compounds were found to undergo oxidation to

with PbO_2 or MnO_2.[33] However, there is no report on stable antiaromatic [28]hexaphyrins containing all symmetrical *meso*-substituents so far.

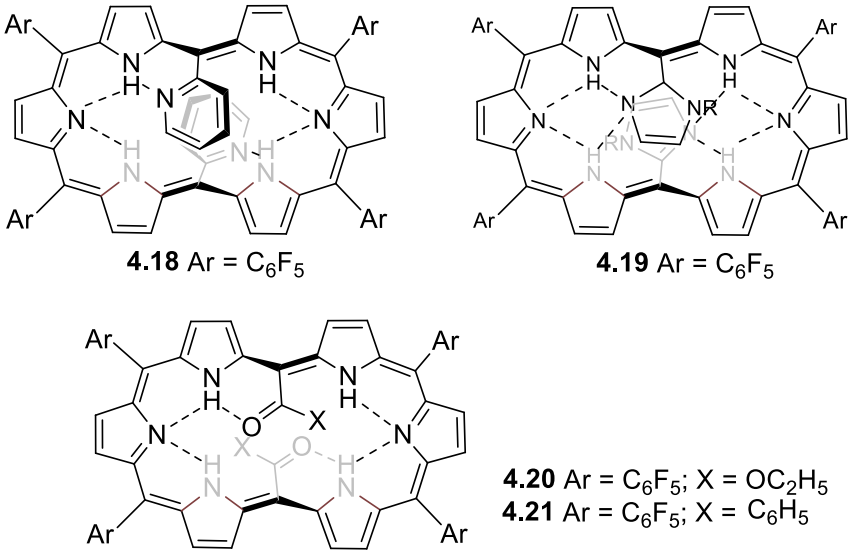


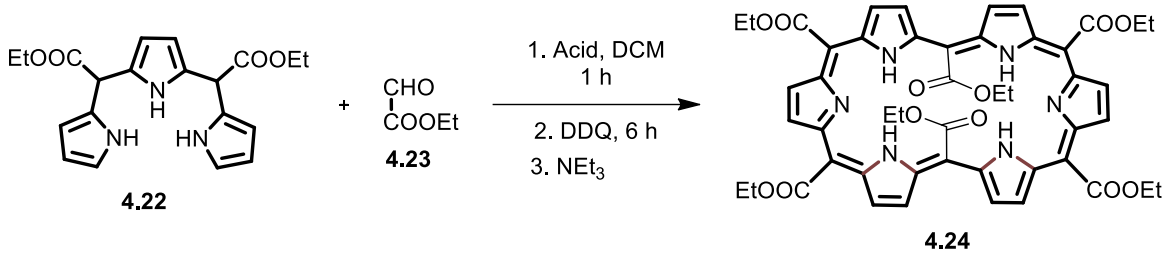
Figure 4.3: Structures of hexaphyrin derivatives **4.18-4.21**.

We anticipated the [28]hexaphyrins can be stabilized by introducing strong electron deficient groups which are capable of forming additional hydrogen bond and should not create much steric repulsion on macrocyclic periphery. Towards this direction, we chose *meso*-diester tripyrrane as an interesting building block,[34] which can be used for synthesis of a symmetrically substituted hexaphyrin in which ester groups satisfy all our requirements. In this direction, we herein report the first stable antiaromatic [28]hexaphyrin with ethoxycarbonyl moities at its six *meso*-positions. Introduction of these ethoxycarbonyl groups not only expected to rigidify the hexaphyrin macrocyclic system through intramolecular hydrogen bonding but also help in decreasing the conformational possibilities in the obtained macrocycle due to its symmetrical substitution pattern. In addition, our synthetic method should also decrease the scrambling in acid catalyzed condensation reactions.[35]

4.4 Results and discussion:

[28]Hexaphyrin **4.24** was synthesized in a one-pot via acid catalyzed condensation of *meso*-diester tripyrrane **4.22** with ethylglyoxalate **4.23** by a modified Lindsey approach under dark conditions and the formed porphyrinogen in the reaction mixture was oxidized with DDQ (Scheme 4.5). In this reaction the oxidation process needed more time. The formation of the product was observed after 2 h only and completed in 6 h. Subsequently, the reaction was quenched with triethylamine (NEt_3) and purified by column chromatography using

neutral alumina. Further, the product could be purified by recrystallization method in dichloromethane-hexane solvent mixture under ambient condition. Only $BF_3.OEt_2$ provides the product in about 6 % yield among acid catalysts (Table 4.1).



Scheme 4.5: One-pot synthesis of [28]hexaphyrin **4.24**.

Table 4.1: Influence of different acid catalysts in the synthesis of **4.24**.

Acid	**Conc. in eq.**	**% Yield of 4.24**	**Scrambling level**
TFA	0.1	2%	5 major spots
$BF_3.OEt_2$	0.1	6%	2 spots (minor spot is corrole as per absorption spectrum)
p-TSA	0.1	Trace	Very less
MSA	0.1	Nil	No product
$BF_3.OEt_2$	0.5	3%	3 major spots (corrole and porphyrin as the additional products)

Hexaphyrin **4.24** was found to be quite stable under ambient condition in solid state (for several weeks) and characterized by high-resolution mass spectrometry at m/z 898.3174 (calcd m/z 898.3174 for $C_{48}H_{46}N_6O_{12}$, $[M]^+$) with the parent ion peak. ^1H NMR spectrum of **4.24** showed paratropic characteristics at room temperature (Figure 4.4). This was concluded based on the sharp deshielded singlet for core NH protons at 19.20 ppm which was confirmed by deuterium exchange study (Figure 4.5) along with concomitant upfield shifted *β*-pyrrolic protons appearing as a broad signal in the range of 5.4-6 ppm. This paratropic ring current further noticed in two different types of *meso* ester peaks. The relatively downfielded ethoxycarbonyl CH_2 quartet peak at 6.4 ppm could be assigned for the methylene protons of the two meso esters directed towards the hexaphyrin core,

whereas, the multiplet peak at 4.1 ppm could account for the methylene protons for the remaining four ethoxycarbonyl moieties staying at the periphery of the hexaphyrin core.

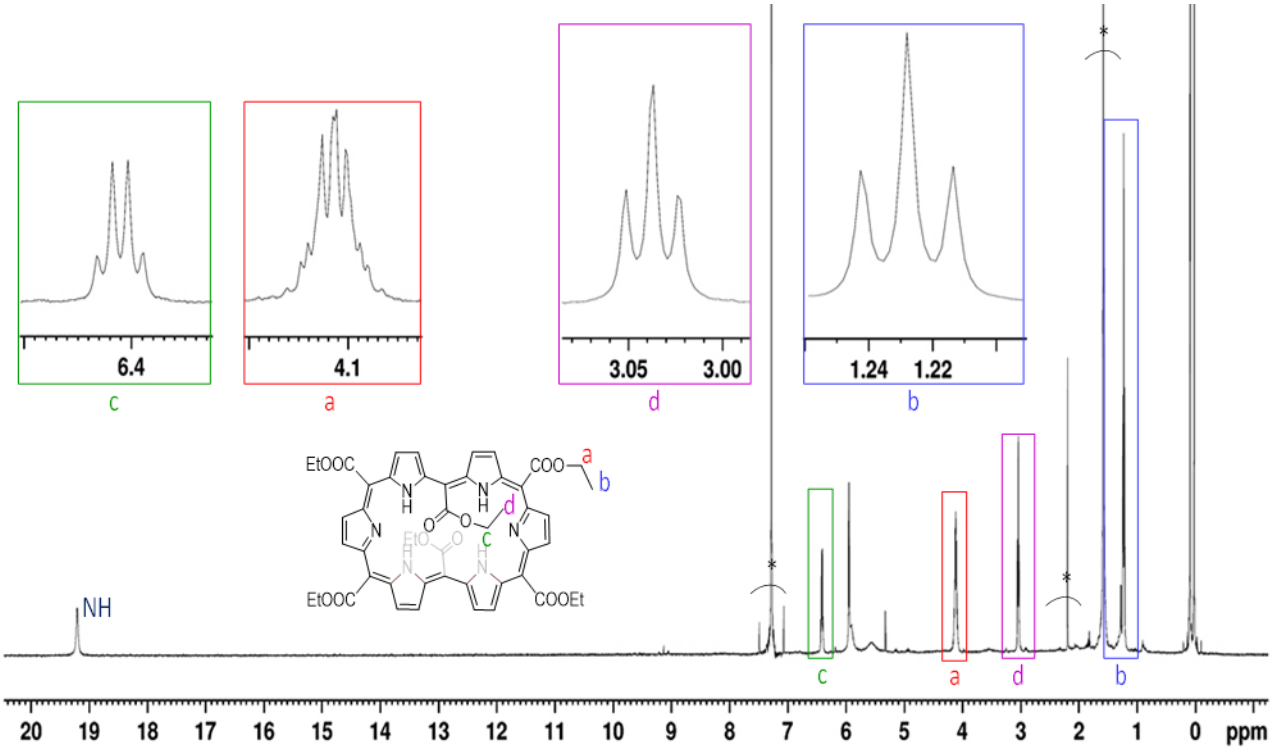


Figure 4.4: ^{1}H NMR spectrum of **4.24** in $CDCl_3$ at 25 °C (* is due to residual solvents).

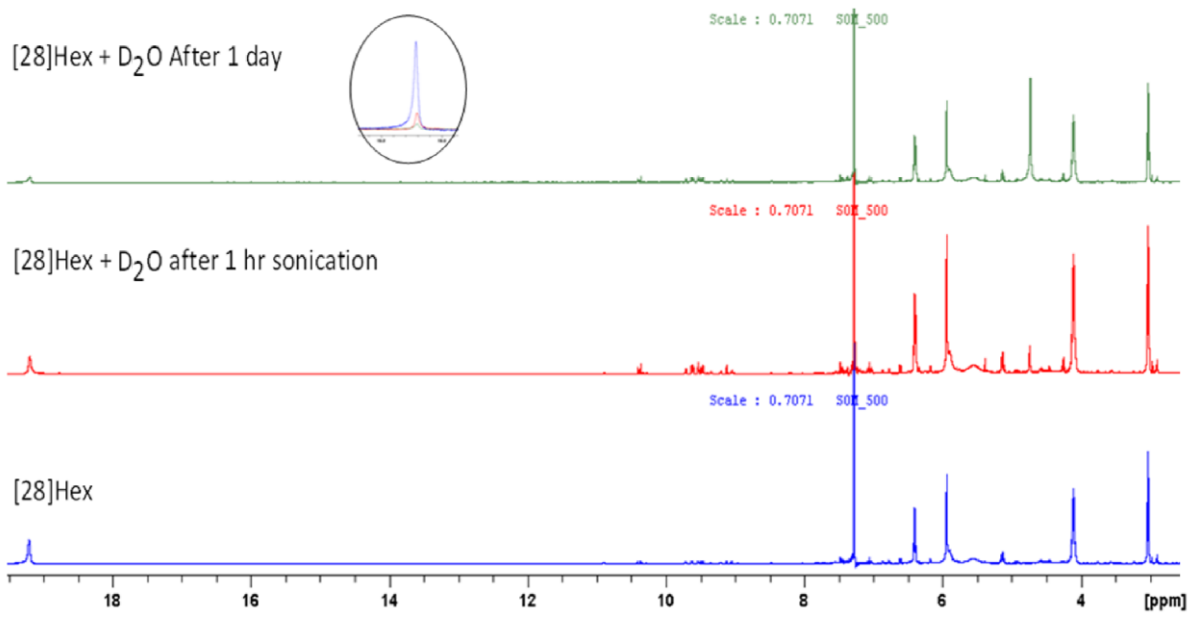


Figure 4.5: Deuterium exchange experiment, ^{1}H NMR spectra of [28]Hexaphyrin **4.24** in $CDCl_3$ + D_2O.

The *β*-pyrrolic protons could be resolved to six different signals between 4.00 to 6.44 ppm, whereas, the NHs split into two resonances at 19.05 and 19.82 ppm upon lowering the temperature, revealing a C_2 symmetric pattern (Figure 4.6).

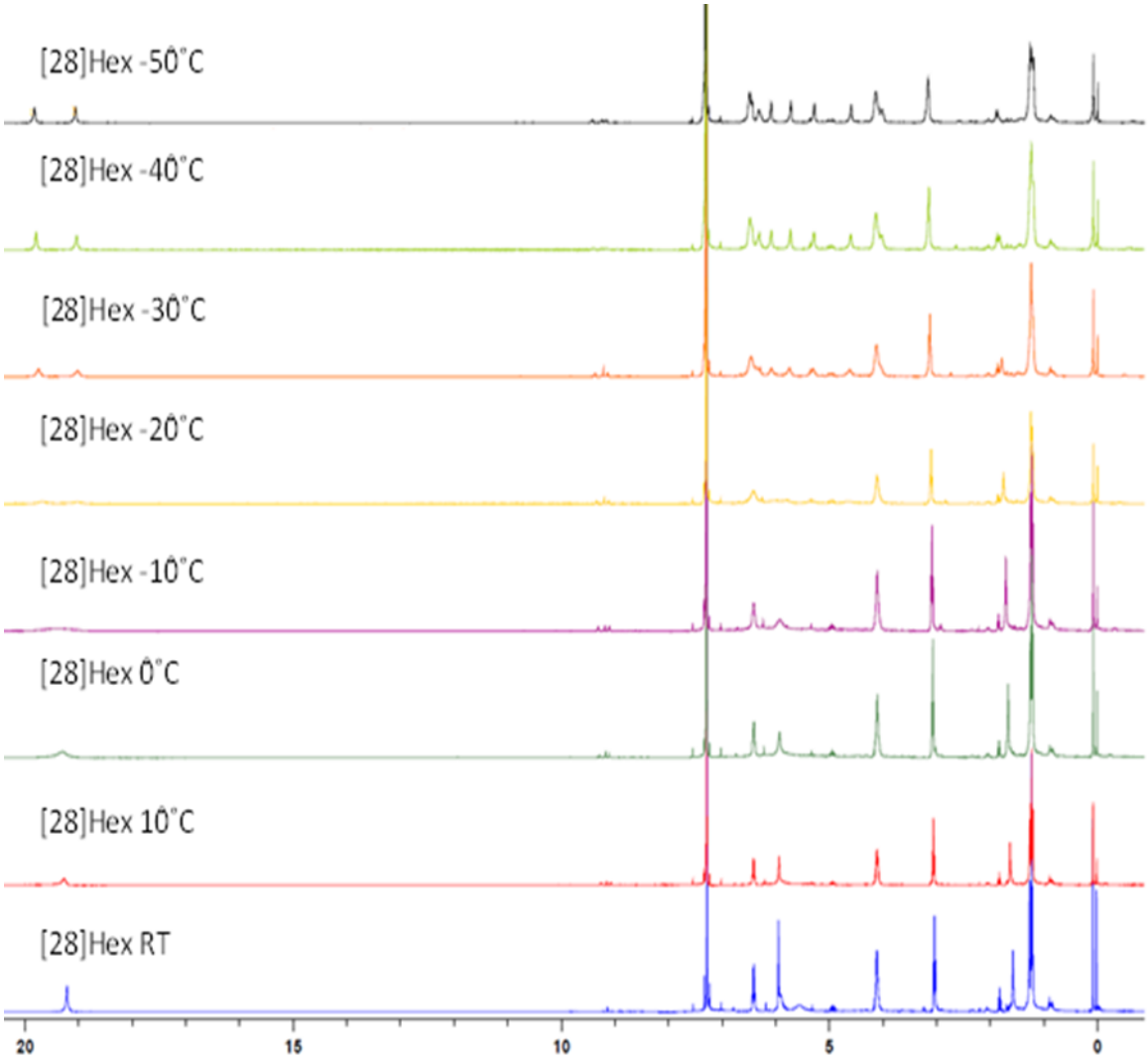
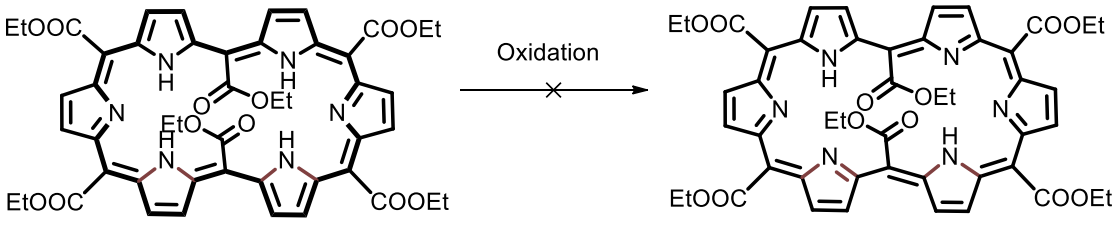


Figure 4.6: Variable temperature ^{1}H NMR spectra of [28]hexaphyrin **4.24** in $CDCl_3$.

Further, for the first time the ethoxycarbonyl groups different magnetic environment on the macrocyclic periphery allowed us to correlate the antiaromatic character of hexaphyrin with the ^{13}C NMR spectrum. For example, the methylene carbons at the core found to resonate at 63.4 ppm, which is much deshielded than those at the periphery (53.4 ppm).

Our attempts to convert this antiaromatic [28]hexaphyrin to the corresponding [26]hexaphyrin resulted in failure so far. Unlike reported [28]hexaphyrins **4.18, 4.20 and 4.21**, macrocycle **4.24** slowly degrades when treated with MnO_2 and PbO_2.[33] Even stronger oxidising agent like DDQ could not oxidize it to the corresponding aromatic analogue (Scheme 4.6).



Scheme 4.6: Interconversion of [28]hexaphyrin and [26]hexaphyrin.

The absorption spectrum (Figure 4.7) of **4.24** showed a broad soret like band at 511 nm and a very weak absorption band at 758 nm, accompanied with a very broad absoption band in the near infrared region, typical of antiaromatic hexaphyrins and are in good agreement with hexaphyrin **4.20**.[33]

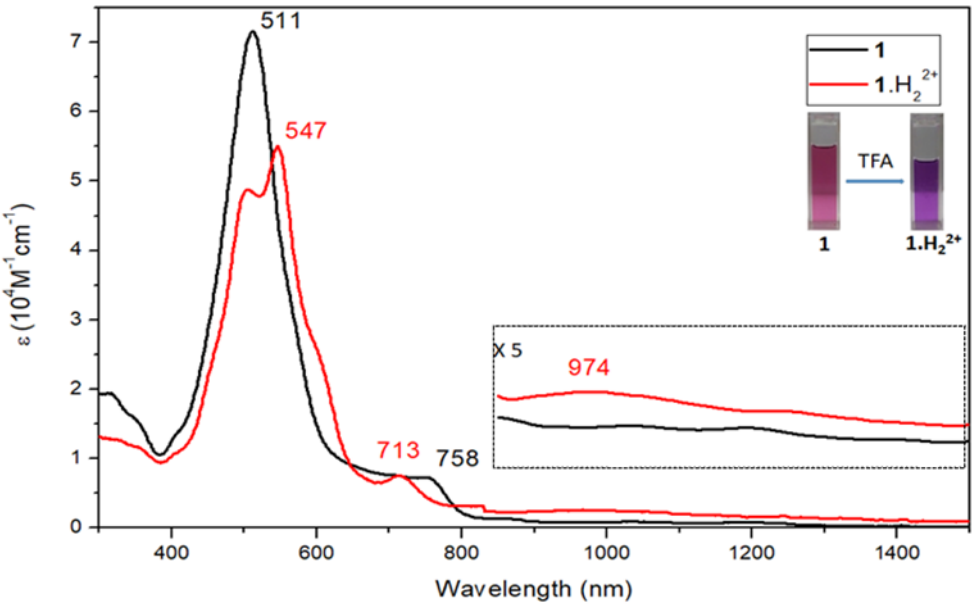


Figure 4.7: UV-Vis-NIR absorption spectra of freebase **4.24** (black line) and its protonated form with TFA (red line) in CH_2Cl_2 at 25 °C and very weak NIR absorption region (x 5) pinned inside dotted box.

Protonation with excess TFA shows slight splitting in the Soret like band with coming of a new red shifted band at 547 nm in absorption spectrum (Figure 4.7), accompanied with blue shift of the 758 nm band to 713 nm. This indicates increase in the symmetry of the molecule upon protonation due to lack of NH-tautomerism.

On the other hand, enhancement in the intensity of the near IR band around 974 nm indicates possible increase in the antiaromatic character of **4.24** upon protonation, which was corroborated by downfield shift of the NH proton to 25.38 ppm in ^{1}H NMR spectrum (Figure 4.8). Lack of conformational change upon protonation, indicates structural rigidity that can be ascribed to possible increase in number of hydrogen bonding interactions between the NHs and the inwardly directed ethoxycarbonyl moieties.

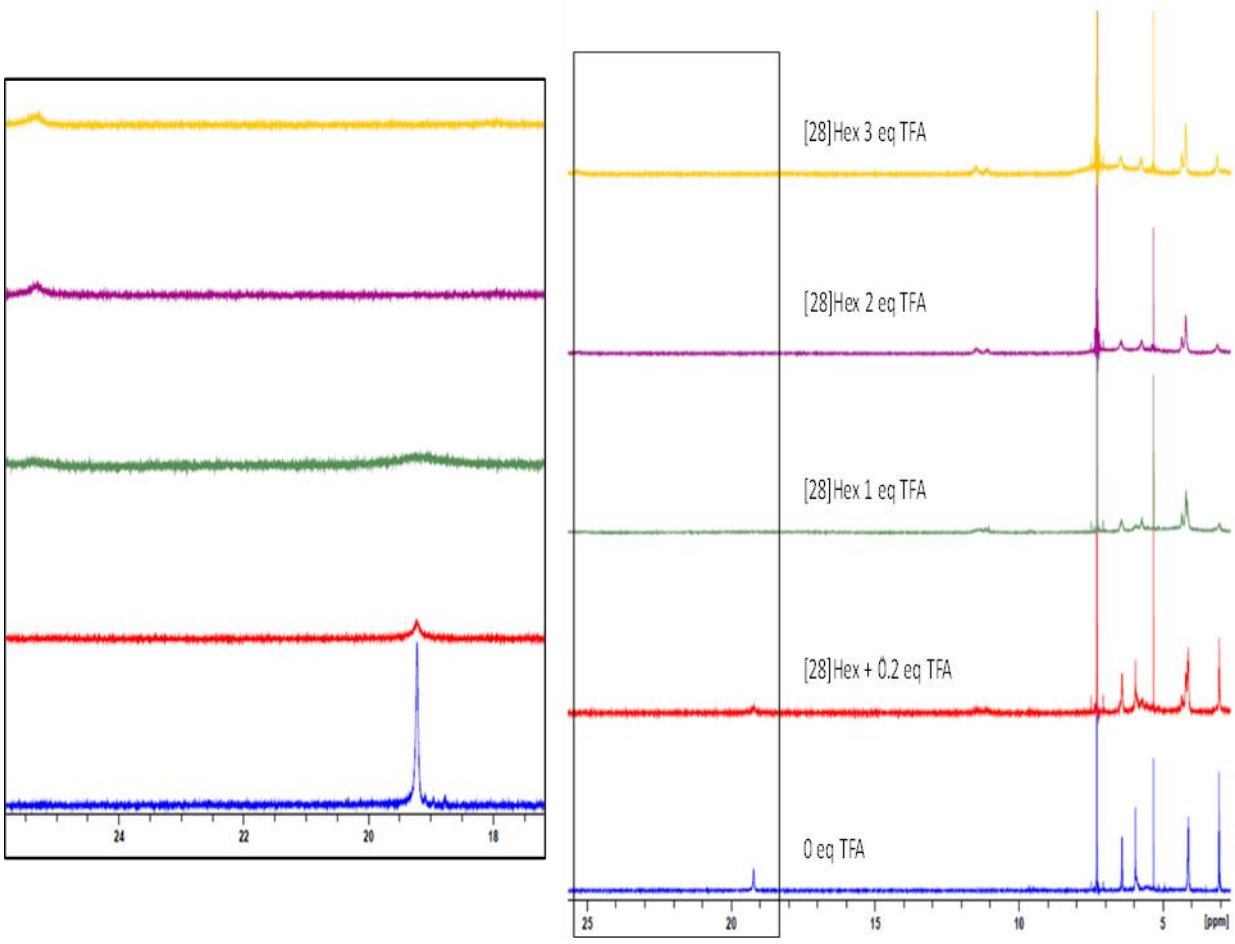
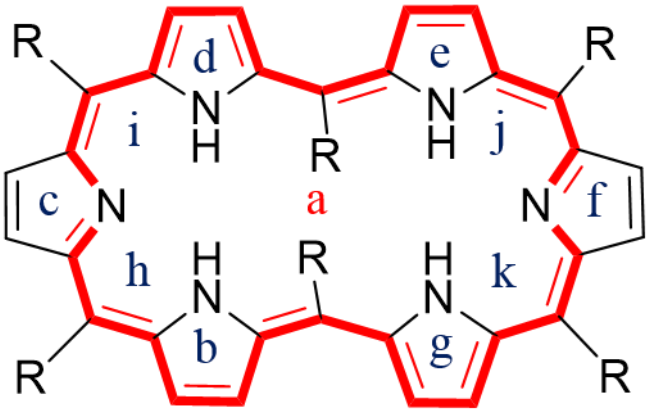


Figure 4.8: ^{1}H NMR spectroscopic titration of [28]hexaphyrin **4.24** *vs* TFA in $CDCl_3$.

Antiaromatic character of this 28π electron macrocycle **4.24** is further supported by nucleus-independent chemical shift (NICS)[36a] (Table 4.2) and HOMA[36b] calculations. The NICS value calculated at the B3LYP/6-31G(d) level by GIAO method at the center of gravity (conjugation path along the 28π) of **4.24** is 9.44 ppm and the HOMA value was

found to be 0.319 and these values are similar with those of reported antiaromatic hexaphyrins.[33a] The molecular orbitals were visualized using Gauss view 4.1 (Figure 4.9).

Table 4.2: Summary of NICS values at selected positions of [28]hexaphyrin **4.24**.



Sl. No.	Label	NICS value
1	**A**	**9.44**
2	B	-0.99
3	C	-2.49
4	D	-6.00
5	E	-0.99
6	F	-2.49
7	G	-6.00
8	H	13.23
9	I	15.39
10	J	13.23
11	K	15.39

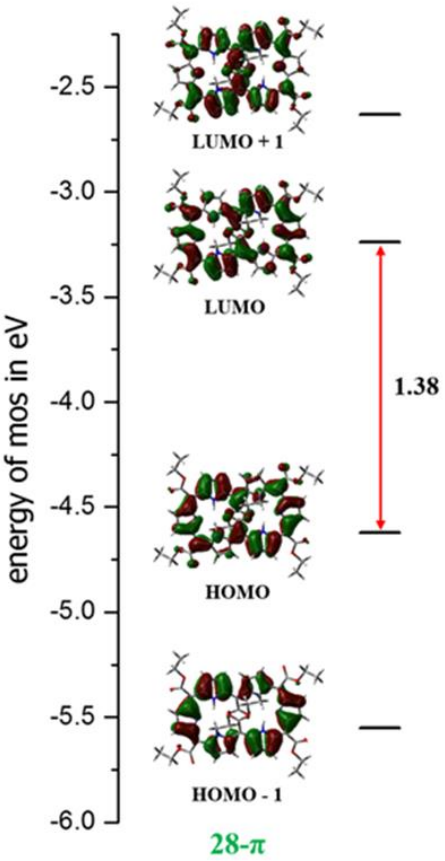


Figure 4.9: Selected molecular orbital diagram for the optimized structure of [28]hexaphyrin **4.24**.

X-ray crystals were obtained from hexane and dichloromethane solution of the hexaphyrin under ambient condition by slow vapor diffusion. XRD analysis revealed that **4.24** adopts a dumbell like conformation. The structure was stabilized by strong intramolecular hydrogen bonding between the four pyrrolic NH protons with oxygens of two *meso* ester groups directed towards the hexaphyrin core, whereas, the other four *meso* ester groups residing away from the macrocyclic core, complying with our ^{1}H NMR interpretation (Figure 4.11). In spite of its symmetric substitution pattern, hexaphyrin **4.24** displays unsymmetrical intramolecular hydrogen bonding pattern. For example, proton on N3′ forms strong hydrogen bond with ester carbonyl O2 (1.958 Å) directed towards the hexaphyrin core, that on N1 forms relatively weaker hydrogen bonds with N2 (2.291 Å) and ethoxy O1 (2.365 Å) and can be seen from their corresponding elongation of NH bond length (Figure 10 and Table 3). This type of unsymmetrical hydrogen bonding pattern has not been noticed for the reported [28]hexaphyrins so far. The mean plane displacements (Figure 4.12) and its packing diagram shown in figure 4.13.

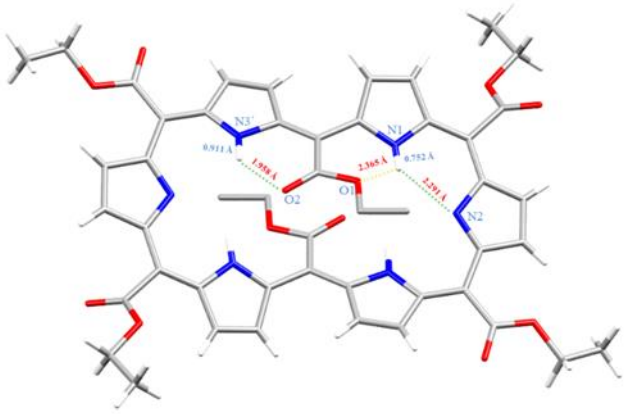
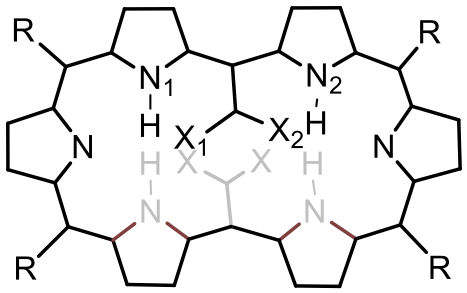


Figure 4.10: X-ray crystal structure of **4.24** shown in stick representation indicating different hydrogen bonding pattern (green dotted lines) of NHs.

Table 4.3: Comparison of crystal structure analysis and intramolecular hydrogen bonding in reported [28]hexaphyrin vs **4.24**.



		Bond distance (Å)		H bond distance (Å)		Bond Angle (°)	
		N_1-H	N_2-H	*NH⋯X₁*	*NH⋯X₂*	*NH⋯X₁*	*NH⋯X₂*
1[a]	X_1, X_2 = O_{Ester}	0.911	0.753	1.958	2.365	134.25	108.70
2[b]	X_1, X_2 = $N_{imidazolyl}$	0.880	0.881	2.173	2.923	120.69	99.51
3[c]	X_1 = $N_{Pyridyl}$	0.879	0.880	2.109	--	122.84	--
4[d]	X_1 = $O_{benzoyl}$	0.880	0.880	2.063	--	121.16	--
5[e]	X_1, X_2 = O_{Ester}	0.880	0.880	2.047	2.364	122.61	104.64

[a] Conditions for **4.24** [b] *Angew. Chem. Int. Ed*. **2012,** *51*, 12459 [c] *J. Org. Chem*. **2015**, *80*, 11726 [d] *Angew. Chem. Int. Ed*. **2018**, *57*, 13640 [e] *Chem. Asian J.* **2019** *14*, 968:

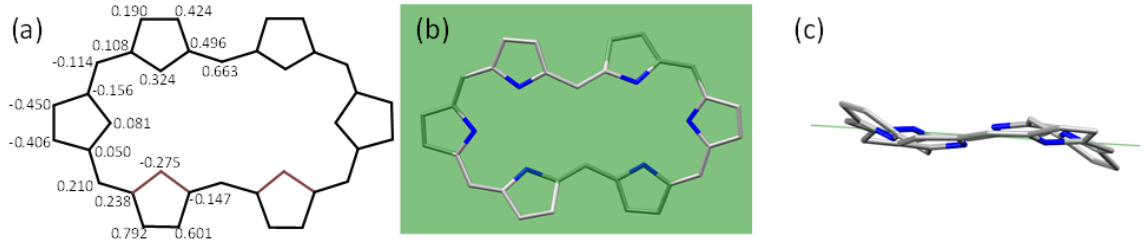


Figure 4.11: (a) The mean plane displacement of the macrocycle asymmetric unit (18-atoms) in Å, (b) Plane drawn with respect to [28]hexaphyrin core atoms below the plane represented in green shade, (c) side on view with respect to mean plane.

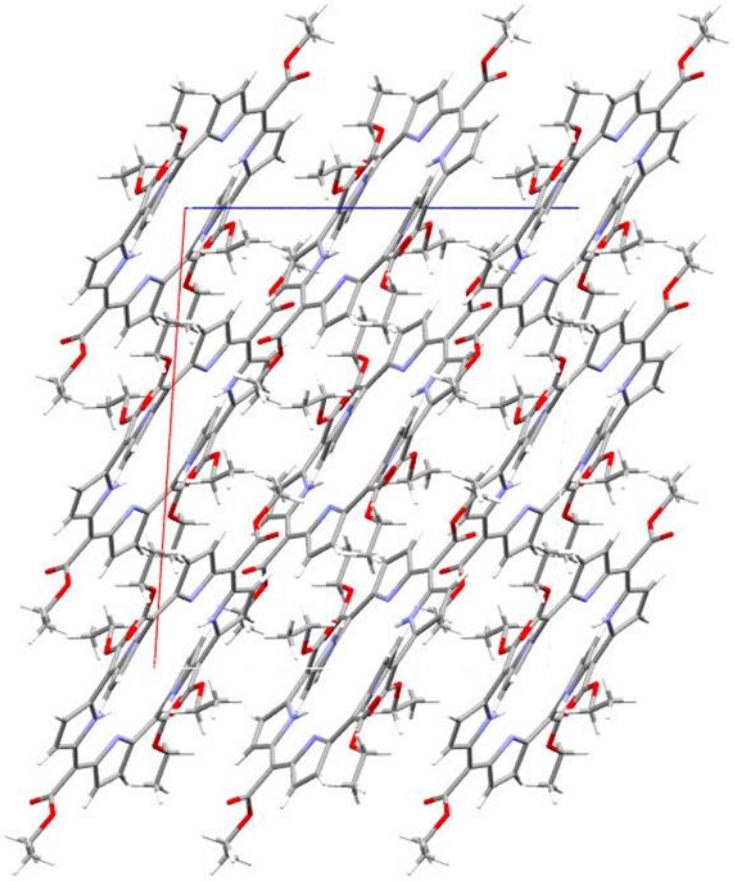


Figure 4.12: [28]Hexaphyrin crystal packing diagram (viewed through b axis).

Cyclic voltammogram revealed the reason behind stability of the macrocycle **4.24**, where four reversible waves were observed at 0.37, 0.08, –0.95, and –1.09 V versus ferrocene/ferrocenium couple in dichloromethane (Figure 4.13). While comparing with the oxidation potential of reported stable [28]hexaphyrins (Table 4.4), compound **4.24** showed relatively higher oxidation potentials and lower reduction potentials. This can be attributed

to the presence of six strong electron withdrawing ester groups on the macrocyclic periphery.

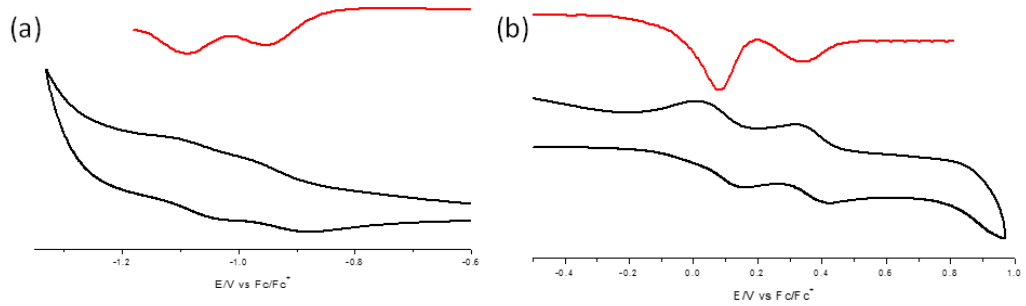


Figure 4.13: Cyclic and differential pulse voltammograms of [28]hexaphyrin **4.24** in CH_2Cl_2 containing $TBAPF_6$ as supporting electrolyte.

The electrochemical HOMO–LUMO gap for **4.24** has been determined to be 1.03 eV. On the other hand, that calculated using DFT calculation is found to be 1.34 eV (Figure 4.9), which is similar to that obtained for the diester analogue **4.20** reported by Osuka[33d] and these reduced HOMO-LUMO gaps are typical of antiaromatic compounds.

Table 4.4. Oxidation potentials ($E_{1/2}^{ox}$), reduction potentials ($E_{1/2}^{red}$) *vs* Fc/Fc^+ in V, and electrochemical HOMO-LUMO gaps (ΔE) for reported [28]hexaphyrins and **4.24**.

Comp.	$E_{1/2}^{ox1}$	$E_{1/2}^{ox2}$	$E_{1/2}^{Red1}$	$E_{1/2}^{Red2}$	ΔE [eV]
4.24 [a]	0.08	0.37	-0.95	-1.09	1.03
4.18 [b]	−0.05	0.15	−1.18	−1.44	1.13
4.21 [c]	0.06	0.37	-0.89	--	0.95

[a] Conditions for **4.24**: solvent CH_2Cl_2, scan rate 0.05 V s^{-1}, working electrode glassy carbon, counter electrode Pt wire, reference electrode Ag/AgCl, supporting electrolyte $TBAPF_6$. [b] Ref. 33b, [c] Ref. 33c [d] $\boldsymbol{\Delta E = E_{1/2}^{ox1} - E_{1/2}^{red1}}$.

4.5 Conclusion:

In conclusion, we have synthesized the first stable A_6 Hückel antiaromatic hexaphyrin bearing six ethoxycarbonyl groups at its *meso*-positions. Unlike reported [28]hexaphyrins with two benzoyls/ ethoxycarbonyls, presence of the six electron withdrawing *meso*-substituents viz. ethoxycarbonyl groups make the molecule electron deficient, thereby stabilizing the 28π system, which did not undergo further oxidation with common oxidizing

agents. The macrocycle showed a dumbbell like conformation, which was resistant to conformational change even upon protonation and the rigidity may be attributed to resultant additional hydrogen bonding interactions. This indicates presence of appropriate strong electron withdrawing moieties at the [28]hexaphyrin periphery not only stabilizes the macrocycle but also controls in conformational tunability.

4.6 Experimental section:

4.6.1 Synthesis of *meso*-Hexakis(ethoxycarbonyl) [28]Hexaphyrins(1.1.1.1.1.1) (4.24):

In a dry 500 mL two neck round bottom flask covered with aluminium foil, *meso*-diester TPM **4.22** (0.5 g, 1.35 mmol) was taken and dissolved in dichloromethane (350 mL) under N_2 atmosphere. To this a solution of 50% ethyl glyoxalate in toluene (277 μL, 1.35 mmol)) was added and stirred for 10 min. The acid catalyst was dissolved in dichloromethane was added to it and allowed to stir for 1 h. DDQ (922 mg, 4.06 mmol) was added and the reaction was stirred for another 6 h. The reaction mixture was quenched with excess triethylamine. The compound was purified using neutral alumina. Further, recrystallization of the compound from dichloromethane/hexane resulted the pure product as red plate like crystals. ^{1}HNMR (500 MHz, $CDCl_3$) δ (ppm) 19.20 (s, 4H, NH), 6.41 (q, 4H, *J*=7.0 Hz, CH_2 inner ester), 5.94 (s, b, 8H, β-CH), 4.11 (m, 8H, CH_2 outer ester), 3.03 (t, 6H, *J*=7.0 Hz, CH_3 inner ester), 1.22 (t, 12H, *J*=7.0 Hz, CH_3 outer ester); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.14, 170.43, 132.63, 132.58, 131.30, 131.06, 130.55, 111.33, 110.47, 107.41, 63.31, 53.44, 14.85, 14.82; HRMS (ESI+): m/z: calculated for $C_{48}H_{46}N_6O_{12}$ (M+): 898.3174; found: 898.3174.

4.7 Crystallographic details:

Table 4.5: Crystal data table for [28]hexaphyrin.

Compound code	**4.24**
Empirical formula	C_{48} H_{46} N_6 O_{12}
Formula weight	898.91
Temperature	100.01(11) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*C*2/*c*

Unit cell dimensions	a = 18.345(2) Å; α= 90°; b = 14.2576(15) Å; β= 93.783(10)°; c = 15.6723(16) Å; γ = 90°;	Volume: 4090.2(8) Å^3.
Z	4	
Density (calculated)	1.460 g/cm^3	
Radiation	Mo Kα (λ = 0.71073)	
2θ range for data collection	4.374 to 50.038 °	
Index ranges	-21 ≤ h ≤ 21, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18	
Reflections collected	14679	
Independent reflections	3483 [R(int) = 0.1641]	
Data / restraints / parameters	3483/0/309	
Goodness-of-fit on F^2	0.949	
Final R indices [I>2σ (I)]	R_1 = 0.0997, wR_2 = 0.1964	
R indices (all data)	R_1 = 0.2551, wR_2 = 0.2658	
Largest diff. peak and hole	0.35/-0.31 e Å^{-3}	

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4.9 ^{13}C NMR spectrum and HRMS data:

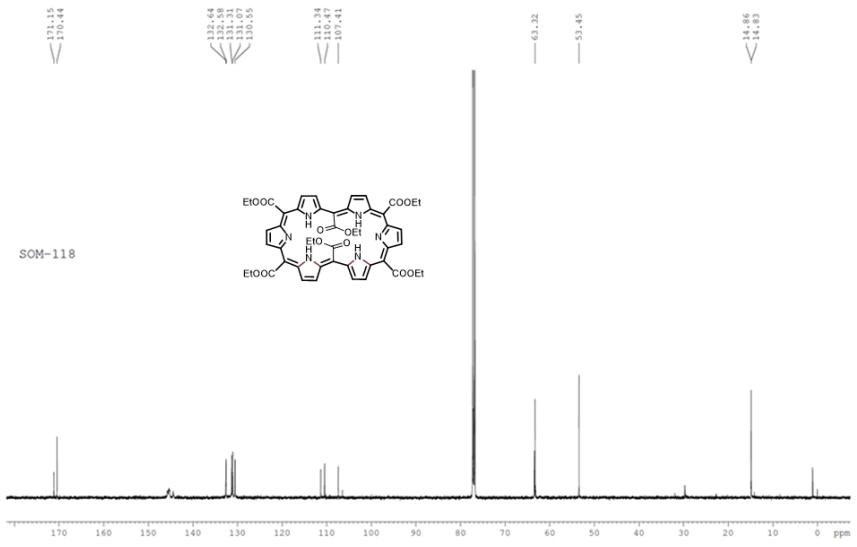

Figure 4.14: ^{13}C NMR spectrum of [28]Hexaphyrin **4.24** in $CDCl_3$.

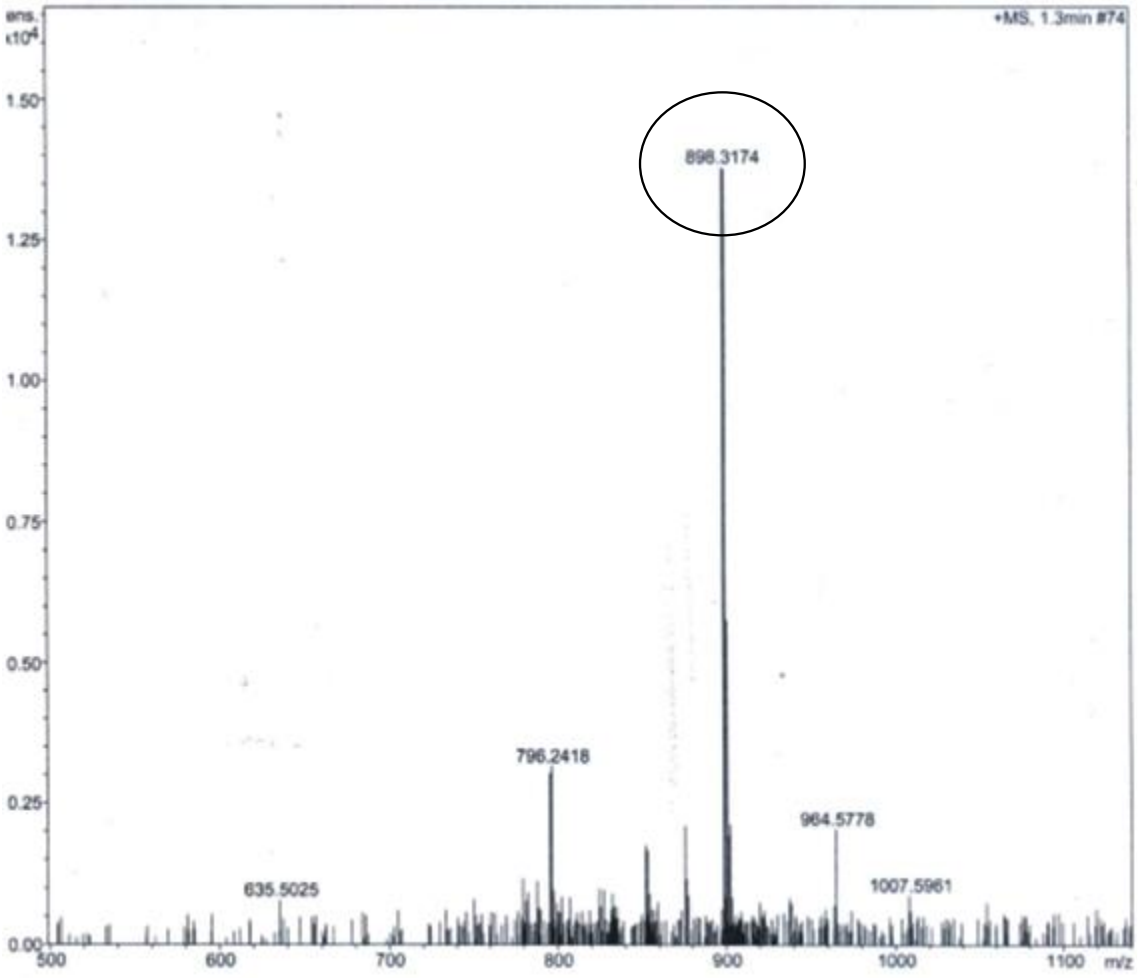

Figure 4.15: HRMS data of [28]Hexaphyrin **4.24** (calcd m/z for $C_{48}H_{46}N_6O_{12}$: 898.3174).

CHAPTER 5

Conclusion

5.1 Summary

The thesis entitled "**Synthesis and characterization of 1*H*-benzotripyrrole and *Meso*-Hexakis(ethoxycarbonyl)[28]hexaphyrin**" consists of two parts. Part A contains two chapters, with the first Chapter providing an elaborate introduction about C_3-symmetric compounds. Chapter 2 deals with benzotripyrrole, a C_3-symmetric molecule, which once obtained in different isomeric forms in multiple steps can be attained in a straightforward synthesis involving a single step. The reaction mechanistic studies and computational calculations were also performed to study its aromaticity and reactivity. Subsequently, the part B contains two chapters with a brief introduction about antiaromatic compounds in the chapter 3. Chapter 4 describes the first stable symmetrically substituted [28]hexaphyrin displaying Hückel antiaromatic character with conformationally rigid dumbbell structure. These works are finally summarized in chapter five, i.e. the present one along with their future scope, followed by appendix chapter which deals with materials and methods employed during the course of the research work at the end and the procedure for synthesis of known compounds used during the investigation.

5.1.1 Introduction

C_3-symmetric benzo-fused polycyclic hetero aromatic star-shaped compounds have a broad range of applications ranging from pharmaceutical to material to optoelectronics. Even though different kinds of C_3-symmetric systems containing various hetero aromatics are explored, there is still much scope, particularly, in fused systems containing pyrroles and in their effective synthesis, analyzing photophysical aspects, and investigating their applications in various fields. In the same way, there is also much scope in exploring hexaphyrins, which are having wide range applications in different fields, in their effective synthesis, understanding structural diversities, analyzing photophysical aspects and investigating their optoelectronics applications. This chapter highlights the synthesis of benzotripyrroles and *meso*-hexakis(ethoxycarbonyl)[28]hexaphyrin along with major findings regarding reactivity of substituted pyrroles, which are used for synthesis of benzotripyrroles, its computational calculations and proton NMR studies and photophysical aspects of [28]hexaphyrin.

5.1.2 Synthetic achievements

We have demonstrated a simple one-pot approach in synthesizing benzotripyrroles from 1*H*-pyrrole derivatives with less costly reagents and also succeeded in isolating the

intermediates.[1] We have also synthesized stable antiaromatic meso-hexakis(ethoxycarbonyl)[28]hexaphyrin in a single step.[2]

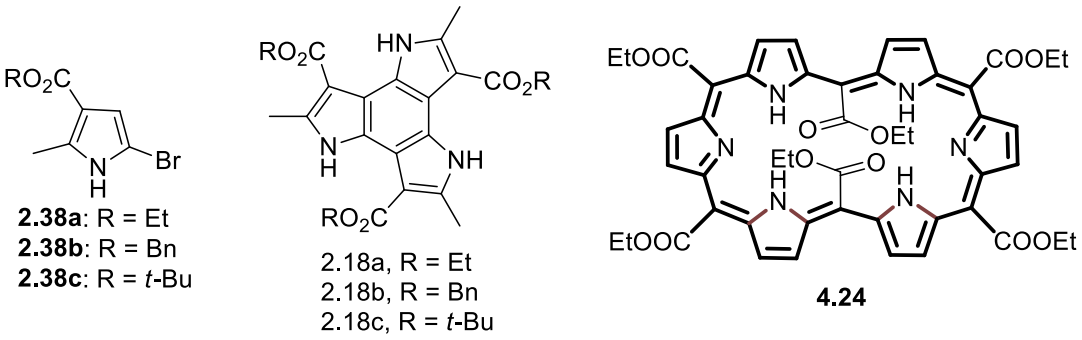

Figure 5.1: Structures of compounds **2.38a-c**, **2.18a-c** and **4.24.**

5.1.3 ^{1}H NMR studies

5.1.3.1 Reaction monitoring of BTP

The cyclization of benzotripyrrole from 1*H*-pyrrole derivatives does not happen at low temperature and advances via mono-bromination, which was consequently confirmed by monitoring the reaction progress by ^{1}H NMR spectroscopy at 25 ˚C using $CDCl_3$.

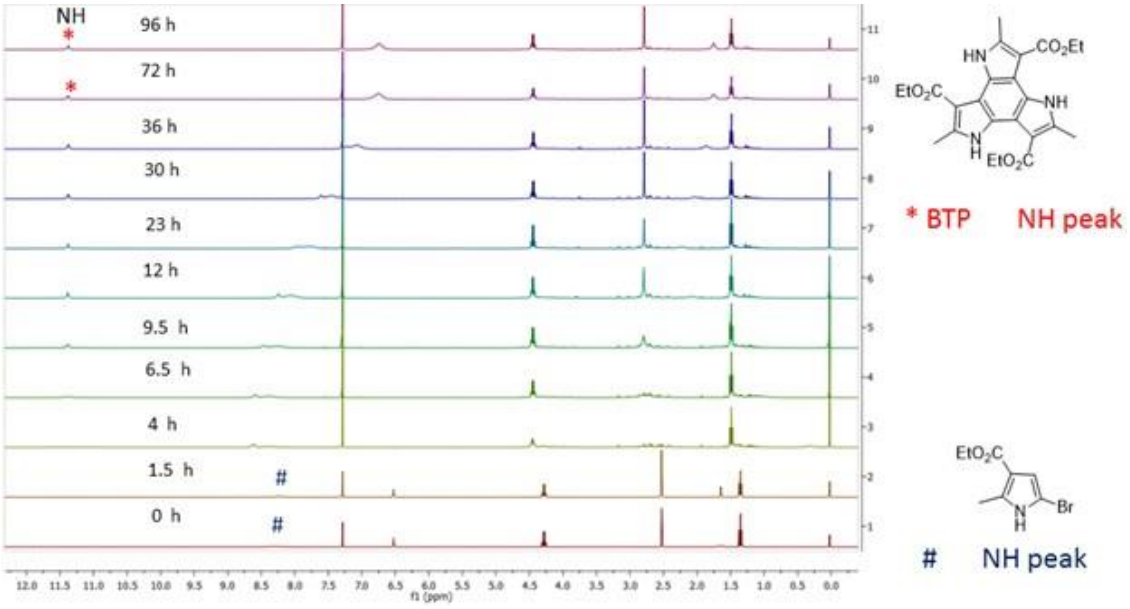

Figure 5.1: Reaction monitoring of BTP **2.18a** in $CDCl_3$.

5.1.3.2 Variable temperature ^{1}H NMR spectra of [28]Hexaphyrin

The *β*-pyrrolic protons could be resolved to six different signals between 4.00 to 6.44 ppm, whereas, the NHs split into two resonances at 19.05 and 19.82 ppm upon lowering the temperature, revealing a C_2 symmetric pattern.

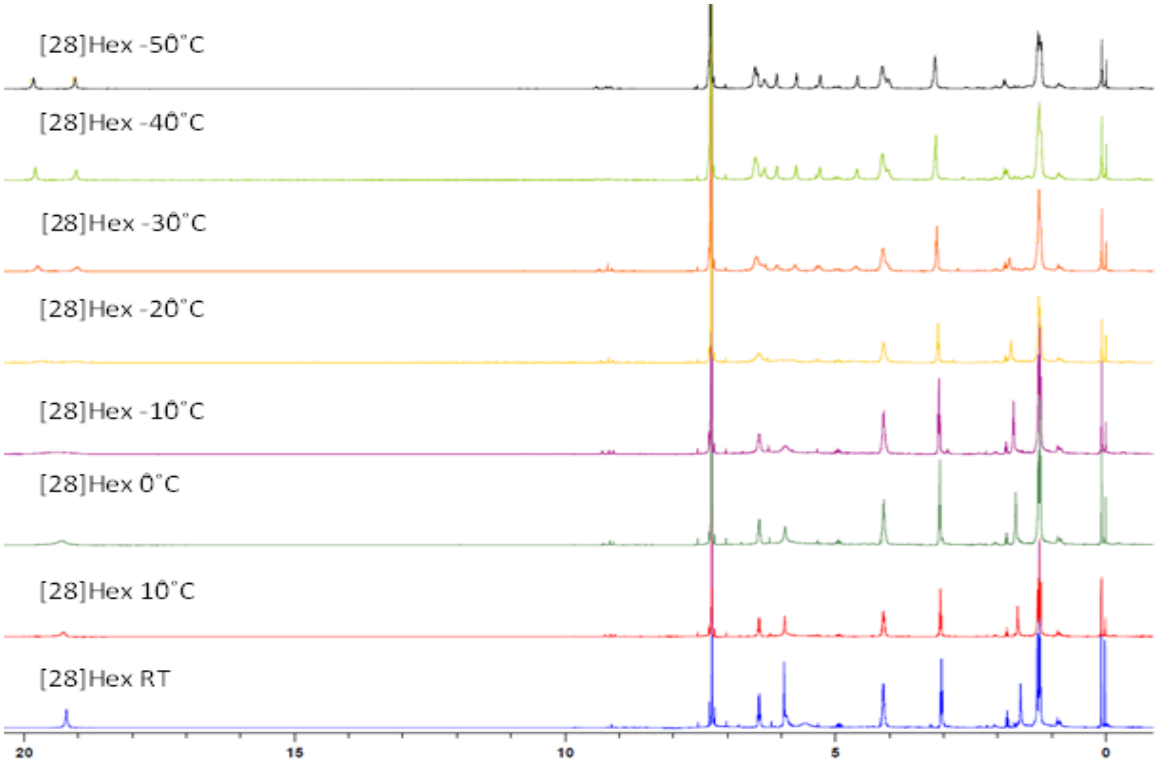

Figure 5.2: Variable temperature ^{1}H NMR spectra of [28]Hexaphyrin **4.24** in $CDCl_3$.

5.1.3.3 ^{1}H NMR spectroscopic titration of [28]Hexaphyrin

The increase in the antiaromatic character of [28]hexaphyrin **4.24** upon protonation was confirmed by downfield shift of the NH proton to 25.38 ppm in ^{1}H NMR spectrum.

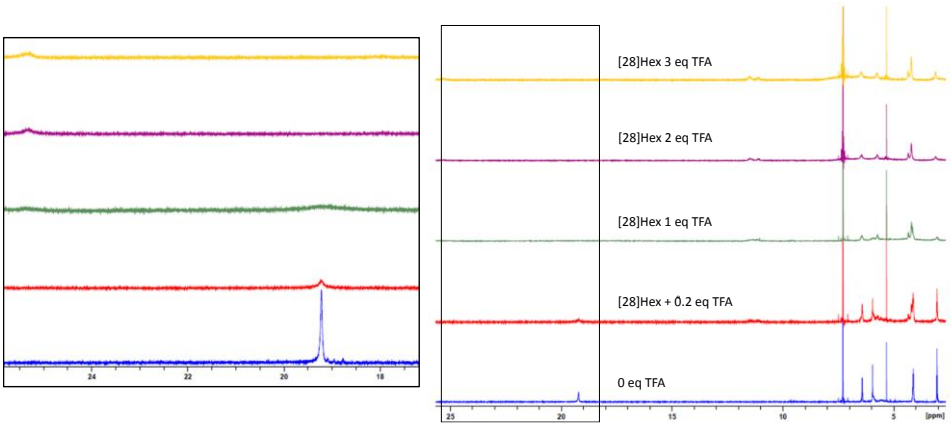

Figure 5.3: ^{1}H NMR spectroscopic titration of [28]Hexaphyrin **4.24** *vs* TFA in $CDCl_3$.

5.1.4 Absorption studies

The absorption spectrum of **4.24** showed a broad soret like band at 511 nm and a very weak absorption band at 758 nm, accompanied with a very broad absoption band in the near infrared region, typical of antiaromatic hexaphyrins. Protonation with excess TFA shows slight splitting in the Soret like band with appearance of a new red shifted band at 547 nm

in absorption spectrum, accompanied with blue shift of the 758 nm band to 713 nm. This indicates increase in the symmetry of the molecule upon protonation due to lack of NH-tautomerism. On the other hand, enhancement in the intensity of the near IR band around 974 nm indicates possible increase in the antiaromatic character of **4.24** upon protonation.

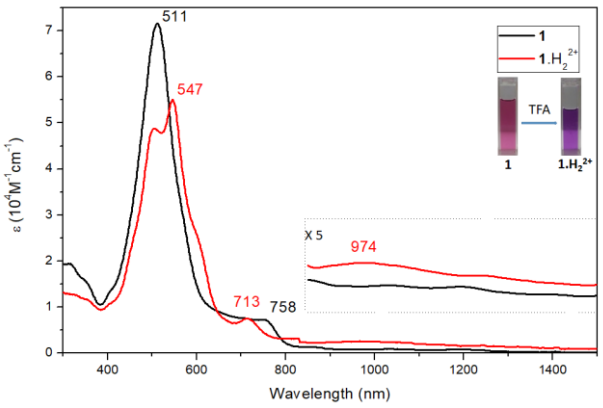

Figure 5.4: UV-Vis-NIR absorption spectra of freebase **4.24** (black line) and its protonated form with TFA (red line) in CH_2Cl_2 at 25 °C and very weak NIR absorption region (x 5) pinned inside dotted box.

5.1.5 DFT studies

The DFT results revealed that nucleophilic centers (less electron density) are readily available among the brominated compounds on vacant position of every brominated compound **2.38a**, **2.40** and **2.41** than for other compounds **2.42a** and **2.42b**. This shows that above mentioned brominated compounds, remained more reactive, except **2.42a** and **2.42b**, and thus probably transformed to form cyclized BTP moiety with greater stability.

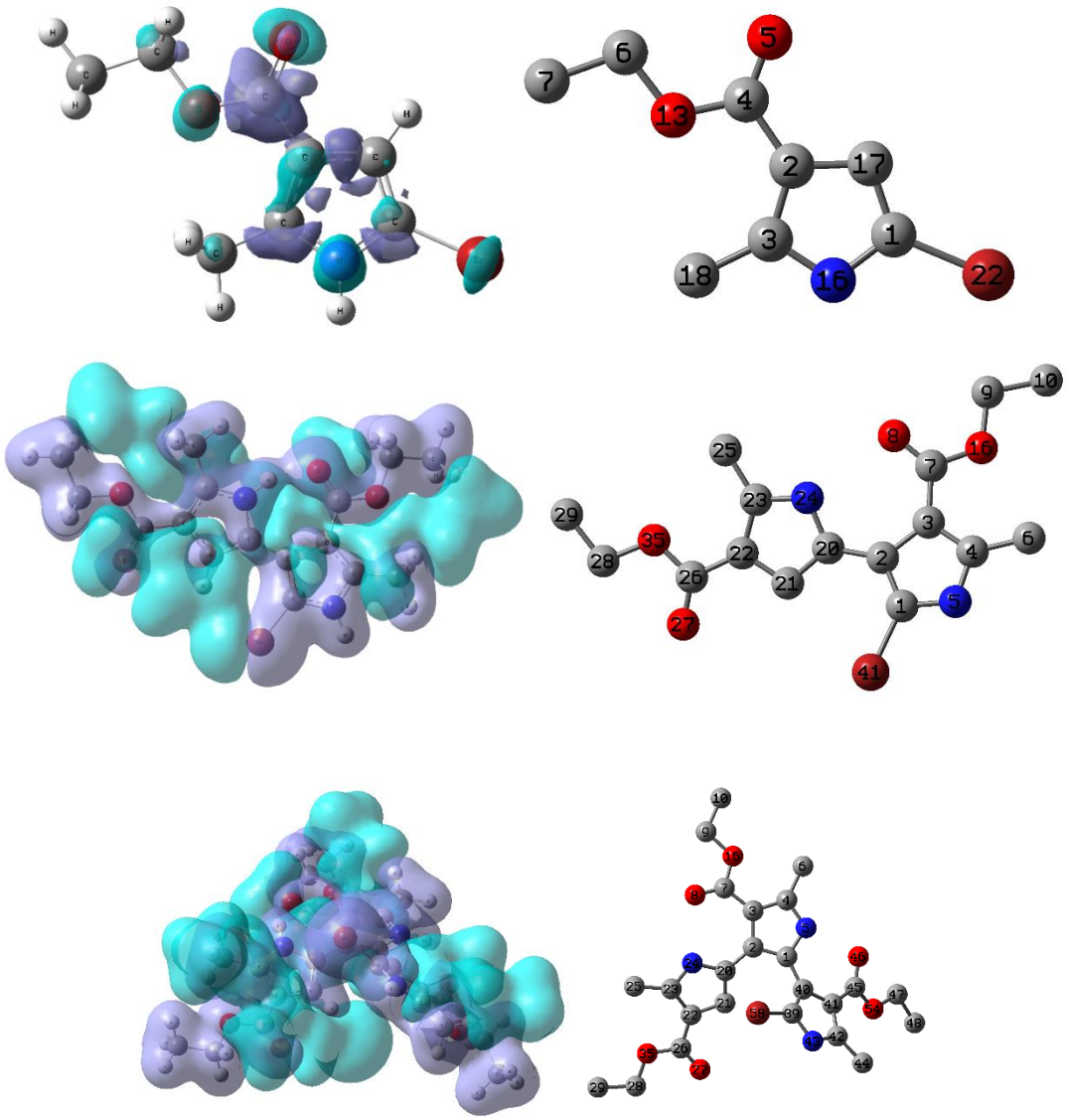

Figure 5.5: Electron density surfaces of **2.38a**, **2.40** and **2.41**.

Further, the aromaticity of BTP **2.18a** and antiaromaticity of [28]hexaphyrin **4.24** was confirmed by NICS and HOMA calculations.

We believe, the facile synthesis routes of BTPs and [28]hexaphyrin will allure other researchers in developing this type of other new compounds. Hopefully, we have created a huge scope and enthusiasm with this work in this type of compounds and our efforts are directed to extend their scope and applications further.

5.2 References

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APPENDIX

Materials and Methods

This chapter furnishes a detailed record of the chemicals used, methods and instrumentation followed for various studies and also the procedures used for the purification of chemicals and solvents are illustrated. Further, we have elaborated about the synthetic procedures of known compounds employed during the course of our investigations.

6.1 General experimental

6.1.1 Solvents

6.1.1.1 Solvents for reactions[1]

Chloroform, DCE, DCM, acetonitrile and DMF were dried first over calcium hydride and then followed by distillation. THF was dried by passing through an activated alumina column, next followed by distillation over sodium metal in presence of benzophenone as an indicator. Methanol was dried with I_2 by using activated magnesium turnings. Toluene and benzyl alcohol were dried with sodium and distilled before use. Triethylamine was dried over potassium hydroxide (KOH) and distilled before use.

6.1.1.2 NMR solvents

Chloroform-*d* and D_2O were purchased from Sigma Aldrich/ Acros Organics/ Cambridge Isotope Inc. and used for spectroscopic purpose directly.

6.1.1.3 Solvents for optical measurement

Dichloromethane (spectroscope grade) was purchased from Merck and utilized as such.

6.1.2 Reagents

Calcium hydride, copper, *p*-TSA, DDQ, $BF_3.OEt_2$ were purchased from Sigma-Aldrich and utilized as such. Triethylamine, THF, benzyl alcohol were bought from Finar chemicals. NBS, NIS, MeOH, DMF, methanesulfonic acid, DCM, $CHCl_3$, DCE and CCl_4 were purchased from SRL / Merck / Avra / Finar. Ethyl glyoxalate was bought from TCI chemicals. All the inorganic salts, KOH, Na_2SO_4, $NaHCO_3$, NaOH and solvents utilized for the laboratory work, were bought from Merck, India.

6.2 Chromatography

Thin layer chromatography was done on pre-coated TLC Silica gel 60 F_{254} on aluminum sheet which was purchased from Merck, India. Column chromatography was performed on silica gel (100-200 mesh) which was bought from SRL / Merck / Dessica, India.

6.3 Characterization and instrumentation

All the instrumentation facilities have been provided by School of Chemistry and ACRHEM at University of Hyderabad, Hyderabad, India for the thesis work. Nuclear magnetic resonance (NMR) spectra were recorded on 500 MHz and 400 MHz FT-NMR spectrometer operating at ambient temperature. TMS (δ = 0 ppm) was utilized as internal standard in $CDCl_3$ for ^1H NMR spectra and for other deuterated solvents, solvent residual peak was taken as standard. Solvent peak was taken as standard for ^{13}C NMR spectra likewise. Mass spectral data were recorded by Bruker Maxis HRMS by ESI techniques and LCMS data were collected by Shimadzu-LCMS-2010 mass spectrometer both by negative and positive ionization method. Melting points were determined by a Lab India MR-VIS$^+$ visual melting point apparatus. IR spectra were recorded by either using KBr pellet or neat sample on NICOLET 5700 FT-IR spectrometer. Uv-vis spectral analysis were performed on Perkin Elmer Lambda-35 and UV-3600 UV-Vis-NIR Spectrophotometer by Shimadzu Scientific Instruments Inc. Spectroscopic grade solvent were used for absorbance measurement. Cyclic Voltammetry (CV) and differential pulse voltammetry (DPV) measurements were performed using CH Instruments Electrochemical Analyzer and electrodes were purchased from CH Instruments Inc. All measurements were recorded in dichloromethane under flow of nitrogen and 0.1M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) used as a supporting electrolyte. Platinum disc as working electrode, platinum wire as counter electrode and Ag/AgCl in (1M) KCl as reference electrode were used. Ferrocenium/Ferrocene, Fc^+/Fc couple was used as external reference for calibration. All cyclic voltammetry data were recorded at 100 mV/s scan rate.

Crystallographic data for **2.18a** and **2.39** were collected on BRUKER APEX-II CCD microfocus diffractometer, Mo-K_α (λ = 0.71073 Å) radiation was used to collect X-ray reflections from their single crystals. Data reduction was performed using Bruker SAINT software.[2] Intensities for absorption were corrected using and SADABS 2014/5,[3] refined using SHELXL-2014/7[4] with anisotropic displacement parameters for non-H atoms. Hydrogen atoms on O and N were experimentally located in difference electron density maps. All C−H atoms were fixed geometrically using HFIX command in SHELX-TL. A check of the final CIF file using PLATON[5] did not show any missed symmetry. DTA-TG analysis was done on Perkin Elmer STA-6000. Crystallographic data for **4.24** was collected on Rigaku XtaLAB Synergy Synergy diffractometer with a HyPix3000 detector, using Mo Kα (λ = 0.71073 Å) radiation. Data reduction was performed using CrysAlisPro 171.40.35a

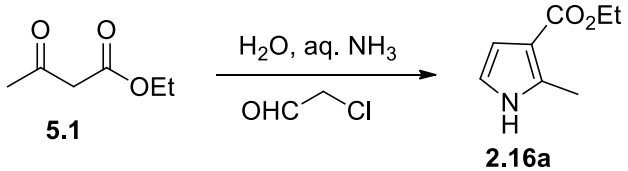
software.[6] Structure was solved by using Olex2-1.0 with anisotropic displacement parameters for non-H atoms and final refinement was done by SHELXL-2018/3.[7] Hydrogen atoms on O and N were experimentally located in difference electron density maps. All C−H atoms were fixed geometrically using HFIX command in SHELX-TL. A check of the final CIF file using PLATON did not show any missed symmetry.

6.4 Computational studies

Quantum mechanical calculations were performed with Gaussian 09 program[8] provided by CMSD, University of Hyderabad. All calculations were carried out by density functional theory (DFT) with Becke's three-parameter hybrid exchange functional and the Lee-Yang-Parr correlation functional (B3LYP) and the 6-311+G(d,p) basis set was used. The molecular orbitals were visualized using Gauss view 4.1 software. The theoretical excitation energies are obtained for the compound BTP **2.18a** by applying the TD-SCF method, which are visualized and tabulated by using GaussSum 3.0 software. The nucleus independent chemical shift, NICS(1) values were obtained with gauge independent atomic orbital (GIAO) method based on the optimized geometries.[9] HOMA (Harmonic Oscillator Model of Aromaticity) was calculated by using R_{opt} (C-C) = 1.388 Å and R_{opt} (C-N) = 1.334 Å.[10] Fukui function[11] and dual descriptor study[12] have been carried out by Multiwfn program,[13] to generate electron density surfaces to understand the electrophilic and nucleophilic centers, and the corresponding electron density cubes were visualized by using the GaussView 4.1 software. Visualization of iso-surface of dual descriptors of the compounds: where the cyan colored mesh (negative), which indicates about the more electron density (favorable for the electrophilic attack) and the violet colored mesh (positive) indicates the less electron density (favorable for nucleophilic attack). Electron densities were calculated for the electron systems N, N+1 and N-1; $\boldsymbol{f}^-$ = for electrophilic attack, $\boldsymbol{f}^+$ = for nucleophilic attack.

6.5 Preparation of starting materials

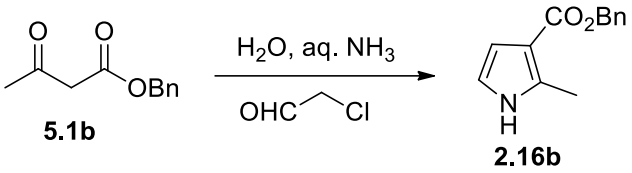
6.5.1 Synthesis of ethyl 2-methyl-1H-pyrrole-3-carboxylate[14]



Scheme 6.1: Synthesis of **2.16a**.

To a vigorously stirred ethyl acetoacetate solution (2.60 g, 20.0 mmol) in H_2O (10 mL) was added chloroacetaldehyde (2.80 mL of a 50 wt% in H_2O solution, 22.0 mmol) and followed instantaneously by aq. NH_3 (10 mL of a 28 wt% H_2O solution, 144 mmol). The reaction mixture was stirred for overnight at room temperature, providing an oily globular precipitate. Then the organic layer was separated and the aq. layer was extracted with ethylacetate (2 x 10 mL). The combined organic layers were washed sequentially with 10% NaOH (10 mL), H_2O (10 mL) and 5% HCl (10 mL). Further, the solution was dried over anhyd. Na_2SO_4 and concentrated in rotary evaporator under reduced pressure. Hexane (10 mL) was added to resultant mixture and was stirred for 30 min in an ice bath to grind the product. The cold reaction mixture was filtered and the filtrate was washed with a few mL of cold hexane, which provided a slightly off-white, pinkish powder, which was dried in vacuum to obtain **2.16a** (Obtained yield 1.0 g, 32.6%; Reported yield 33%).

6.5.2 Synthesis of benzyl 2-methyl-1H-pyrrole-3-carboxylate[14a]



Scheme 6.2: Synthesis of **2.16b**.

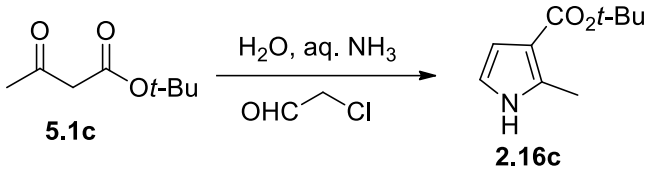
Protocol A:

The same synthetic procedure for **2.16a** was followed; 187 mg product (**2.16b**) was obtained from 2.60 g starting material (**5.2**) as a white solid (Obtained yield 7%; Reported yield 25%).

Protocol B:

To a prior dried benzyl alcohol (7 mL, 1.480 mmol) was added sodium (60 mg, 2.60 mmol) and compound **2.16a** (500 mg, 3.26 mmol). The reaction set up was connected to high vacuum pump and was heated at 100 ^oC for 2 h. Then the reaction mixture was cooled to room temperature. The organic layer was separated and the residue was washed with DCM (2 x 10 mL). The combined organic layers were concentrated in rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography by using EtOAc: hexane (5:95) as an eluent, which resulted the product as white solid (540 mg, 77 %).

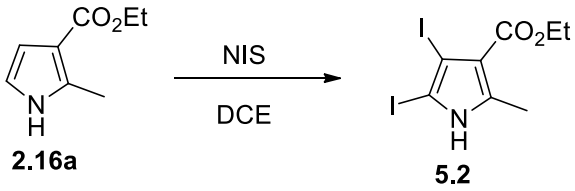
6.5.3 Synthesis of tert-butyl 2-methyl-1H-pyrrole-3-carboxylate[14a]



Scheme 6.3: Synthesis of **2.16c**.

The same synthetic procedure for **2.16a** was followed; 580 mg product (**2.16c**) was obtained from 2.60 g starting material (**5.1c**) as a white solid (Obtained yield 19%; Reported yield 12%).

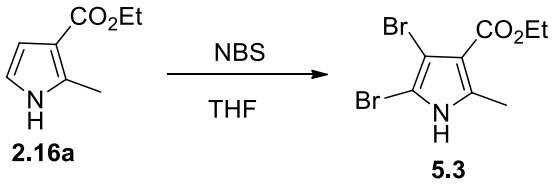
6.5.4 Synthesis of ethyl 4,5-diiodo-2-methyl-1H-pyrrole-3-carboxylate[15]



Scheme 6.4: Synthesis of **5.2**.

To ethyl 2-methyl-1H-pyrrole-3-carboxylate (**2.16a**) (100 mg, 0.6528 mmol) in DCE (15 mL) was added N-Iodosuccinimide (NIS) (367 mg, 1.632 mmol) was added under N_2 atmosphere at room temperature and was stirred for 2 h. The reaction mixture was quenched by addition of H_2O. The organic layer was separated and the residue was washed with DCM (2 x 10 mL). The combined organic layers were concentrated in rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography by using EtOAc: hexane (5:95) as an eluent, which resulted the product as white solid (Obtained yield 210 mg, 79 %; Reported yield 94%).

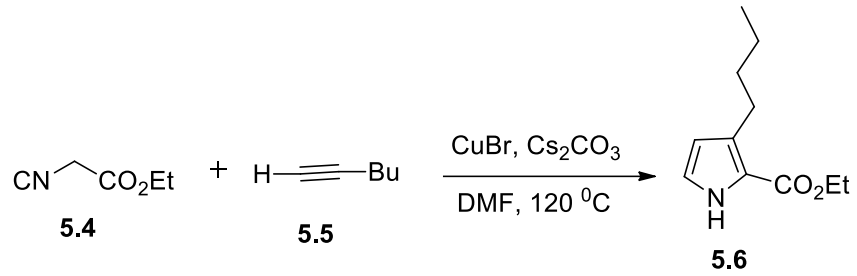
6.5.5 Synthesis of ethyl 4,5-dibromo-2-methyl-1H-pyrrole-3-carboxylate[16]



Scheme 6.5: Synthesis of **5.3**.

The same synthetic procedure for **5.2** was followed; 370 mg product (**5.3**) was obtained from 200 mg starting material (**2.16a**) as a white solid (Obtained yield 90%).

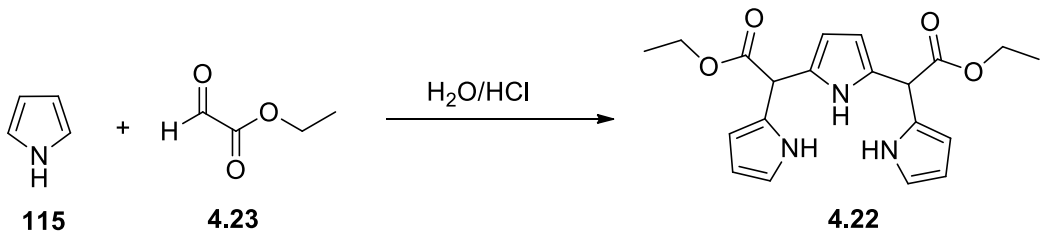
6.5.6 Synthesis of ethyl 3-butyl-1H-pyrrole-2-carboxylate[17]



Scheme 6.6: Synthesis of **5.6**.

To hex-1-yne (0.7 ml, 6.087 mmol) was added CuBr (0.873 g, 6.087 mmol) and Cs_2CO_3 (1.983 g, 6.087 mmol) and DMF (30 mL). The reaction mixture was evacuated using high vacuum, refilled with nitrogen and was heated at 120 ^{0}C for 10 min. Then solutions of the ethyl 2-isocyanoacetate (**5.4**) and 1-hexyne (**5.5**) in DMF (30 mL) were injected to the mixture over a period of 2 h, after that the reaction mixture was stirred at 120 ^{0}C for another 1 h. The reaction mixture was cooled to room temperature. The organic layer was separated and the residue was washed with DCM (2 x 10 mL). The combined organic layers were concentrated in rotary evaporator under reduced pressure. Finally the crude product was purified by silica gel column chromatography by using EtOAc: hexane (5:95) as an eluent, which resulted the product as a colorless oil (Obtained yield 100 mg, 5%; Reported yield 64%).

6.5.7 Synthesis of meso-diester tripyromethane[18]



Scheme 6.7: Synthesis of **4.22**.

Pyrrole (1.7 mL, 24.50 mmol) and 50% ethylglyoxalate in toluene (2.4 mL, 12.10 mmol) were added in a 2 L round bottomed flask containing deionized water (1.7 L) and conc. HCl (35%) (10.0 mL). The reaction mixture was stirred at room temperature for 24 h, followed by quenching with aqueous ammonia till the reaction mixture become neutral. The aqueous layer was extracted with dichloromethane, and the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed in vacuuo. The crude product was loaded on silica gel column and TPM **6** was eluted with hexane/ethyl

acetate (15%) as an off-white pasty solid in its pure form (Obtained yield 750 mg, 17%; Reported yield 17%).

6.6 Summary

A brief account of various solvents and chemicals utilized in the synthesis and different techniques and other physical and computational methods employed for characterization in our investigation, is given in this chapter. All the compounds are synthesized and characterized by following reported procedure, which are employed as starting materials for the dissertation work, were also described here.

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6.8 ^{1}H NMR spectra

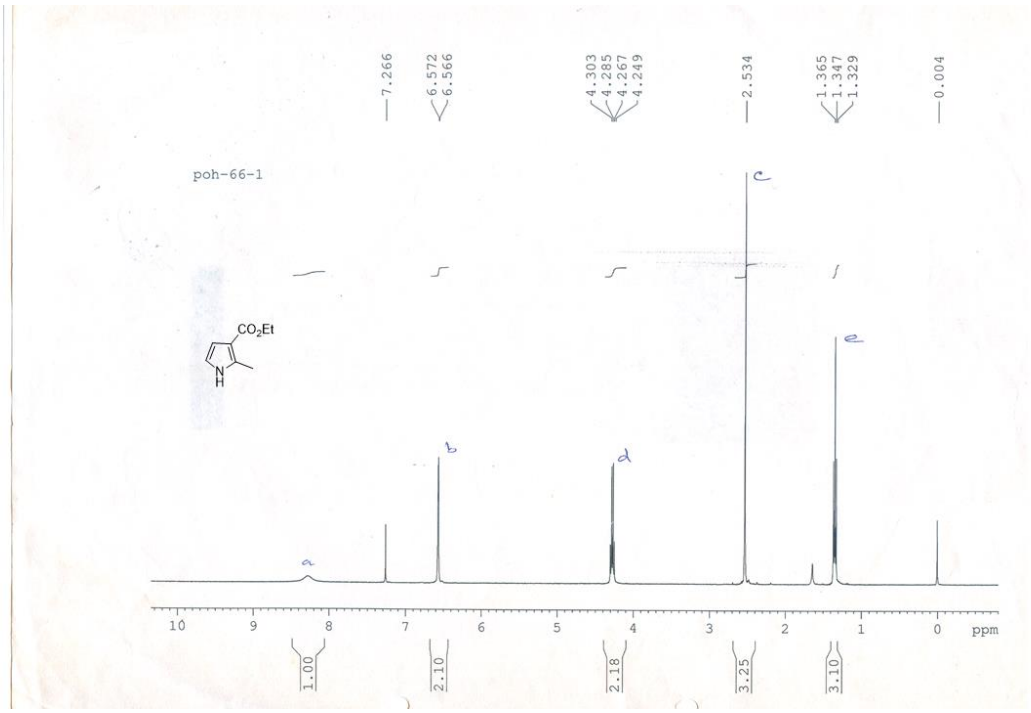

Figure 6.1: ^{1}H NMR spectrum of **2.16a** in $CDCl_3$.

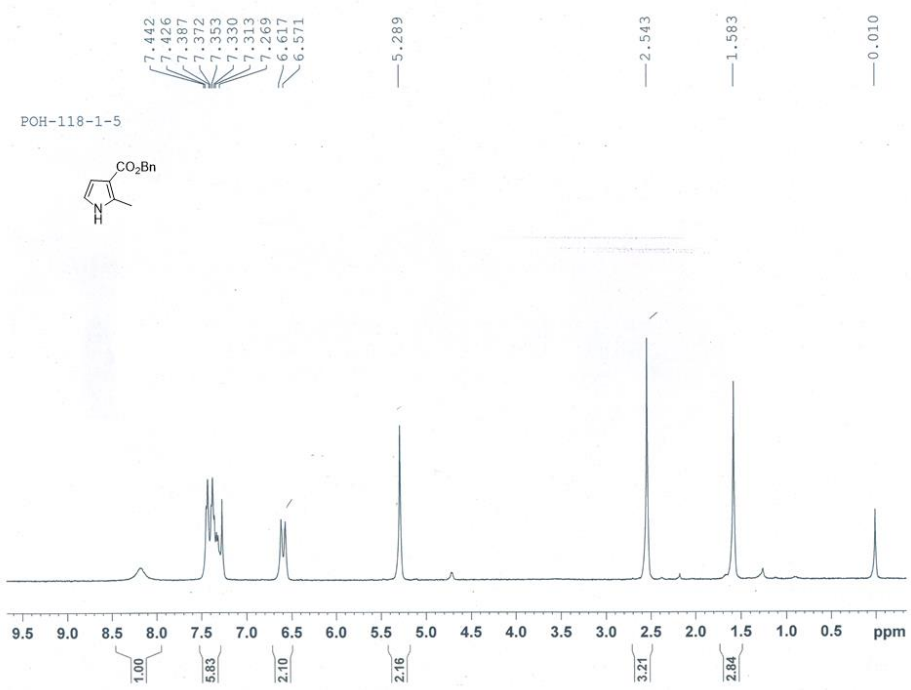

Figure 6.2: ^{1}H NMR spectrum of **2.16b** in $CDCl_3$.

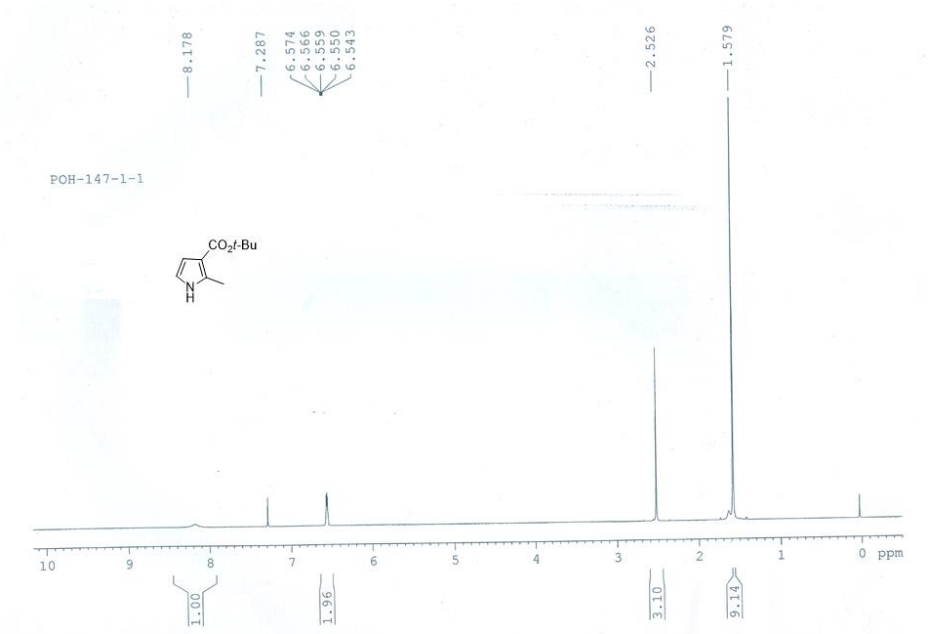

Figure 6.3: ^{1}H NMR spectrum of **2.16c** in $CDCl_3$.

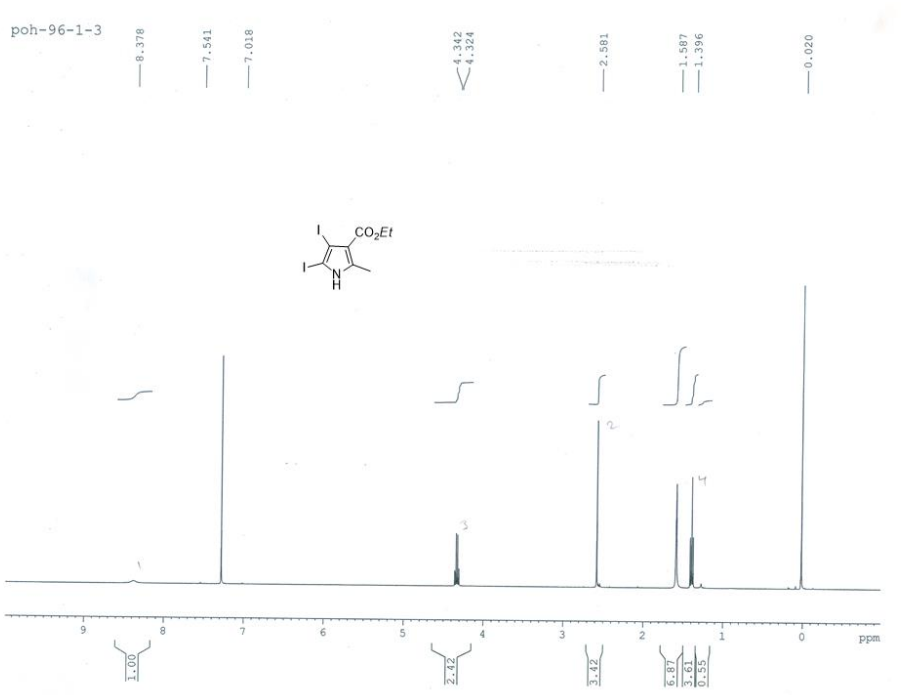

Figure 6.4: ^{1}H NMR spectrum of **5.2** in $CDCl_3$.

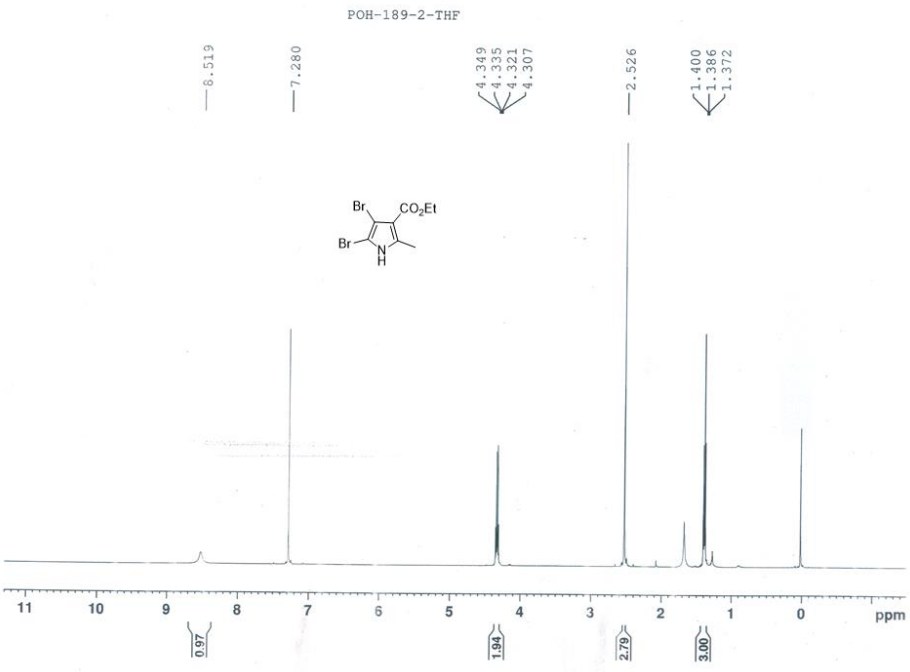

Figure 6.5: ^{1}H NMR spectrum of **5.3** in $CDCl_3$.

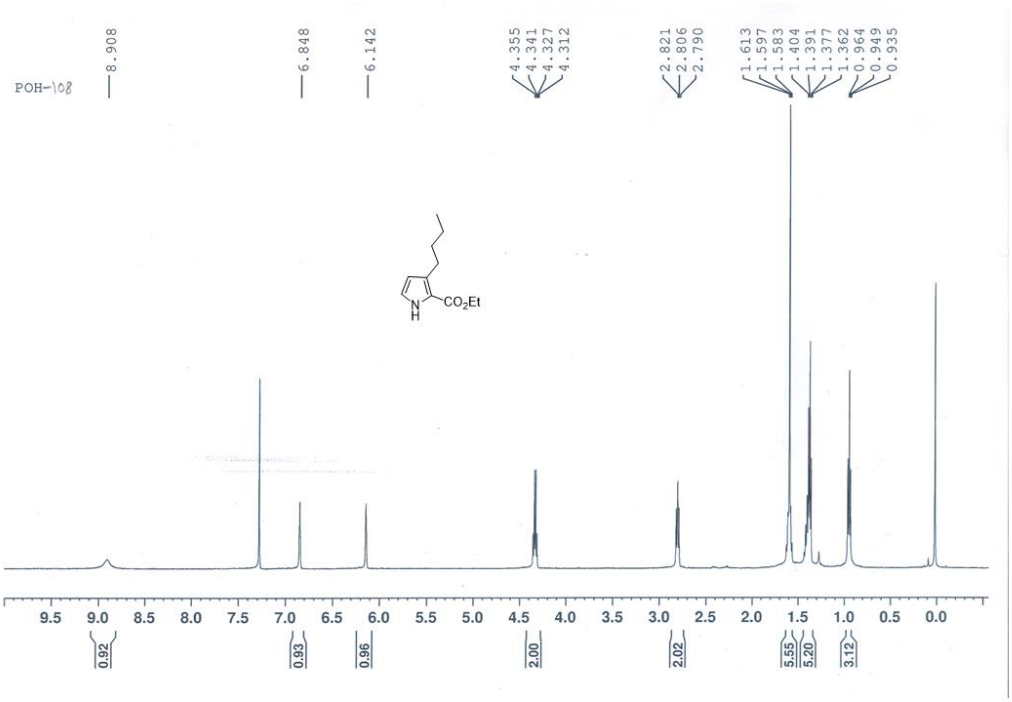

Figure 6.6: ^{1}H NMR spectrum of **5.6** in $CDCl_3$.

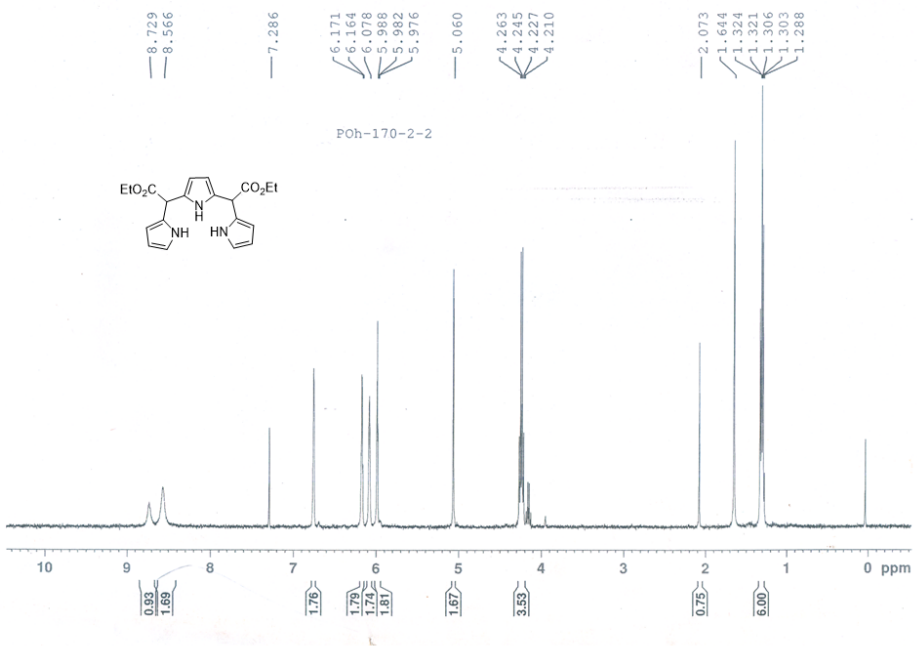

Figure 6.7: ^{1}H NMR spectrum of **4.22** in $CDCl_3$.

Research Publications (Thesis)

1. One-pot synthesis of benzotripyrrole derivatives from 1H-pyrroles, **Obaiah, P.**; Kumar, B. S.; Panda, P. K. *New J. Chem.* **2019**, *43*, 18437.
2. *Meso*-Hexakis(ethoxycarbonyl)[28]Hexaphyrin-(1.1.1.1.1.1): A Symmetrically Substituted Intramolecular Hydrogen Bond Stabilized Conformationally Rigid Hückel Antiaromatic Macrocycle, Soman, R.; **Obaiah, P.**; Sahoo, S.; Panda, P. K. (manuscript under preparation).

Conference presentations

1. Oral and poster presented on "One pot synthesis of C_{3h} benzotripyrrole and its mechanistic studies", **15th Annual in house symposium (ChemFest-2018),** School of Chemistry, University of Hyderabad, Hyderabad, India, March 9-10, **2018**.
   P. Obaiah, B. Satish Kumar and Pradeepta K. Panda. Chemfest-15, **2018**.
2. Poster presented on "Synthesis and characterization of C_{3h} benzotripyrroles", **21st CRSI National Symposium in Chemistry-2017**, CSIR-Indian Institute of Chemical Technology, Hyderabad, India, July 14-16, **2017**.
   P. Obaiah, B. Satish Kumar and Pradeepta K. Panda. CRSI-21, **2017**.

Exploration of Aromatic 1H-Benzotripyrrole And Antiaromatic Meso-Hexakis-(ethoxycarbonyl) [28]hexaphyrin(1.1.1.1.1.1)

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