Porphyrrins represent one of the most widely studied of all known macrocyclic ring systems [1]. Interest in these tetrapyrrolic macrocycles is broadly based on the multiple biological functions which includes electron transfer, oxygen transport and catalytic substrate oxidation. Porphyrrins and their reduced derivatives such as chlorins, bacteriochlorins, isobacteriochlorins and corrins are backbones of many important natural pigments of life, including heme, vitamin B_{12}, chlorophyll, bacteriochlorophyll etc [1]. Porphyrrin derivatives are also known for their ability to form wide variety of metal complexes. Apart from these, porphyrrins in their freebase as well as metallated state found applications in many scientific fields ranging from biology, electronics, material science, catalysis and medicine. This chemical richness has inspired the study of a whole range of porphyrrin analogues in past few decades [2, 3].

The term ‘porphyrrin analogue’ is used in broad sense in porphyrrin chemistry. In the most general sense, porphyrrin analogues may be defined as cyclic systems consisting of pyrrrolic units which are not naturally occurring [4]. These analogues were further classified in order to distinguish systems with no conjugation, partial conjugation and with complete electronic conjugation. The first and second type are represented as calixpyrrrole and calixphyrin respectively, while the last set represents systems with contracted, expanded and isomeric structures with respect to porphyrrin. A rearrangement of pyrrrole and methine bridges resulted in porphyrrin isomers, which have the same molecular formula, C_{20}H_{14}N_{4} and 18\pi electrons in their cyclic conjugated pathway. These porphyrrin isomers have been classified into two groups, ‘nitrogen in’ isomers and ‘nitrogen out’ isomers. The “nitrogen in” porphyrrin isomers include porphycene (2.0.2.0), corrphycene (2.1.0.1), hemiporphycene (2.1.1.0) and isoporphycene (3.0.1.0) [5-7].
On the other hand the ‘nitrogen out’ isomer includes a porphyrin isomer known as N-confused porphyrin (NCP), where one or more nitrogen atoms are outside the ring. NCP differs largely from the parent porphyrin in physical, chemical, structural, and coordination properties. The $\alpha\alpha'$-linkage in normal porphyrin is replaced with $\alpha\beta'$-linkage in NCP and are considered as the true isomer of porphyrin, where the meso-carbons are arranged in the same fashion (1.1.1.1) as in the case of normal porphyrin. The fascinating isomer of porphyrin was introduced in 1994 by two independent groups, Furuta and co-workers from Japan and Latos-Grażyński and co-workers from Poland [8, 9].

Since after the discovery of the isomer, research based on this molecule was preferentially targeting the structural modification as well as the versatile coordination ability of the molecule to stabilize various metal ions of usual and unusual oxidation states [10]. However, there are very few reports that explore properties like anion binding ability and applications in the area of biological and material science [11, 12]. Hence, the main objective of this thesis is to investigate the possible applications of various NCP derivatives in such areas. The thesis is organized into the following four chapters.

**Chapter 1: Introduction (N-Confused Porphyrin: Past and Present)**

A general introduction about NCP, which includes various synthetic methodologies, structural modifications and coordination chemistry is described in this chapter. Different synthetic methodologies were adopted for the synthesis of various NCP derivatives, starting from the first report of Furuta *et. al* and Latos-Grażyński *et. al* the modified procedure of Lindsey *et. al* [13] and multistep synthetic methodologies for doubly N-confused porphyrin, core-modified and expanded NCP. Apart from the structural and
synthetic modifications, NCP derivatives are known for their versatile coordination chemistry, which was elaborately studied and a significant number of metal complexes were reported [10]. The chapter reviews the metal complexes of NCP, where it stabilizes different unusual oxidation states of metals, which ranges from main group elements to late and early transition metal complexes. Also, applications of NCP derivatives are explained briefly, including anion binding studies and catalytic applications. Finally, the chapter ends with discussing the aim of the present thesis.

Chapter 2: meso-Tetrakis(3,5-dihydroxyphenyl)N-Confused Porphyrin: Tautomeric Existence, Exchange and Influence of Tautomerism and Anions on Morphological Features

Even though porphyrin based nanoarchitectures are well established, supramolecular assemblies of NCP and its derivatives are not explored much. This chapter describes the synthesis, spectral and structural characterization, solvent dependent tautomeric existence, exchange and aggregation behaviour of a novel octa-hydroxy N-confused porphyrin derivative; meso-tetrakis(3,5-dihydroxyphenyl)N-Confused porphyrin
(NCPH) [14]. The first part of the chapter investigates the tautomeric existence and exchange of NCPH in polar protic and aprotic solvents. The chapter demonstrates that the existence and switch over between the 3H and 2H tautomeric forms of NCP derivatives can be controlled exclusively by polar protic and aprotic solvents, rather than the established polar and non-polar nature of the solvent.

![Figure A](image.png)

**Figure A.** Change in the emission characteristics of NCPH in (a) DMSO/ACN, (b) DMSO/H$_2$O, (c) MeOH/ACN and (d) MeOH/H$_2$O with increasing amount of ACN and H$_2$O.
The tautomeric existence and exchange were investigated in solvent combinations such as (a) DMSO/ACN, (b) DMSO/H₂O (c) MeOH/ACN and (d) MeOH/H₂O by various spectroscopic techniques. Figure A shows change in the emission spectra of NCPH during aggregation, which proves tautomeric existence and exchange of NCPH in the mixture of solvents, depending upon their protic and aprotic nature facilitated by the hydrogen bonding formation in the particular solvent as shown here. The solvent driven aggregation were also monitored through scanning electron microscopy (SEM) and atom force microscopy (AFM) analysis. The different morphological features observed in the different solvent combinations were explained on the basis of change in the planarity of the tautomeric forms and there by difference in the intermolecular hydrogen bonding formation possible in the two tautomers in the particular medium.

The second part of the chapter demonstrates the anion induced aggregation of NCPH, where the peripheral hydroxyl and NH protons participate in hydrogen bonding with anions to facilitate the formation of aggregated structures. In addition to routine spectral analyses, the anion induced aggregation was monitored by ITC, SEM and DLS analysis. Upon addition of initial 4 equiv of fluoride (F⁻) ions resulted in gradual decrease in the absorbance of Soret (450 nm) and Q-bands of NCPH. Further addition (up to 20 equivalents) of F⁻ ions accompanied with the appearance of red-shifted Soret band at 472 nm, corresponds to the J-aggregates which were formed by the complexation. Interestingly, the emission maximum of NCPH experienced a prominent blue-shift of about 30 nm by the addition of F⁻ ions with significance increase in the fluorescence quantum yield. This can be attributed to the enhanced rigidity, which can be expected
during aggregation by intermolecular hydrogen bonding. Further, the involvement of peripheral hydroxyl and NH protons in the hydrogen bonding formation with anions is confirmed by $^1$H NMR, IR and ITC analysis. Formation of nanospheres during aggregation was observed by SEM analysis and the size of nanostructure by DLS analysis.

Chapter 3: *meso*-Tetrakis(3-alkoxyphenyl)N-Confused Porphyrins and Their Ag(III) Complexes; Synthesis, Characterization and Aggregation Behaviour

Porphyrins substituted with alkyl chains are found suitable in different areas such as liquid crystalline material and self assembled nanostructures [15]. The synthesis of porphyrins with alkyl chains at $\beta$-positions is difficult due to the high steric hindrance induced by the alkyl substituents, where insertions of alkyl chains on the *meso*-aryl rings are comparatively easy. Usually, alkyl substitution to the porphyrin fragment increases the solubility of the porphyrin in organic solvents. This chapter describes the synthesis, structural, spectral characterization and aggregation behaviour of long chain substituted


**NCP derivatives, meso-tetrakis(3-alkoxyphenyl)N-confused porphyrins and their Ag(III) complexes.** The number of carbon atoms in the alkyl side chain varies from 6 to 18 in the free base NCP. Ag(III) complexes of NCP derivatives were synthesized for the 6, 8 and 10 derivatives and the formation of desired compounds were confirmed by different spectral analyses. This chapter further describes the influence of metellation on the morphological features during aggregation, where aggregation in each case was achieved by increasing the amount of H$_2$O in a THF solution of compounds. Both in the case of free base and metallated forms, as the H$_2$O concentration increases from 50% to 90%, due to extended hydrophobic interaction the morphology of aggregated structures deforms continuously to attain cubic and flower like structures at 10:90 (THF/H$_2$O) ratio of solvents respectively. The different morphological features exhibited by the free base and metalled NCP is explained on the basis of structural changes occurred to the free base structure on metellation.

**Chapter 4: N-Confused Porphyrin Derivatives as PDT Sensitizers**

In recent years, photodynamic therapy (PDT) has emerged as a promising and noninvasive treatment for various types of cancer. The technique involves controlled generation of short-lived cytotoxic agents within a cell on irradiation of a prodrug or
photosensitizer, which in turn destroys the affected cells. This chapter describes the PDT application of two NCP derivatives, meso-hydroxy (NCPH) and p-sulfonato-phenyl substituted (NCPS) derivatives [16], which have better molar extinction coefficient in the red region of visible light compared with normal porphyrin derivatives. The chapter documents photophysical studies of these molecules, which give promising values for parameters required for PDT such as triplet and singlet oxygen quantum yield. The results encouraged us to investigate in vitro anticancer studies with both NCP derivatives. The photodynamic activity of NCPS was evaluated against eight different cell lines, namely, human colon cancer cells (HCT-116), human breast cancer cells (MCF7-ER, PR positive, and MDA-MB-231-ER, PR negative), human pancreatic cancer cells (MIA-PaCa-2), human cervical cancer cells (HeLa and SiHa), and human oral cancer cells (SCC-172 and SCC-131), where NCPS exhibited more photocytotoxicity to adenocarcinomas than the other epithelial cell lines, and maximum activity has been attributed toward breast adenocarcinoma MDA-MB-231 cells, with an IC_{50} value as low as 6 µM, where corresponding value for NCPH was 12 µM. Upon illumination, generation of reactive oxygen species and apoptosis induced pathway of cell death was also described in the chapter. Apoptosis mediated cell death was established by a set of experiments, which proves cell membrane asymmetry, chromatin condensation, mitochondrial potential change and PARP [poly(ADP-ribose)polymerase] cleavage.

Over all, the thesis exhibits different NCP derivatives and reveal their properties and applications, which were not explored till date.
References


