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Synthesis, spectroscopic characterization and singlet oxygen generation of 5,10,15,20-tetrakis(3,5-dimethoxyphenyl) porphyrin as a potential photosensitizer for photodynamic therapy

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ABSTRACT

Singlet oxygen is a valuable reactive oxygen species known for its effective action on the elimination of cancers and age-related eye disease such as macular degeneration. In this study, 5,10,15,20-tetrakis (3,5-dimethoxyphenyl) porphyrin was synthesized and characterized using various spectroscopic methods. The λ_{max} for the Soret and Q bands were 417 nm and 514, 547, 589 and 646 (nm) respectively. The estimated singlet oxygen yield (φ_Δ) for the porphyrin was higher than some literature reports, suggesting a stronger potential of the porphyrin for the photosensitizing photodynamic treatment of cancer and other related human disorders.

Capsule Summary: Synthesized and characterized 5,10,15,20-tetrakis (3,5-dimethoxyphenyl) porphyrin generated high quantum singlet oxygen value capable of effecting photo-inactivation of infective agents.

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INTRODUCTION

Porphyrins are a large class of deeply coloured, red or purple, fluorescent crystalline pigments, which are made up of substituted aromatic macrocyclic rings consisting of four pyrrole-type residues, linked together by four methine bridging groups (Amos-Tautua et al., 2019a). These tetrapyrrolic macrocycles have been used as promising photosensitizing drugs in photodynamic therapy (PDT) for some time (Huang et al., 2015; Pandey 2016; Amos-Tautua et al., 2019a). Several porphyrins are now recognized to be viable for the treatment of a variety of diseases such as cancers (McCormick et al., 2014; Chen et al., 2016; Broughton et al., 2016), bacterial infections (Sculean et al., 2015; Wikene et al., 2015; Vandresen et al., 2016; Amos-Tautua et al., 2019b) and age related macular degeneration (Neri et al., 2002; Das et al., 2011).

Porphyrins bearing methoxy substituents in the phenyl groups attached at the *meso*-positions have been shown to be effective photosensitizers because they have adequate photophysical properties that could be used for studies on the triplet state which are very important aspects of PDT (La Penna et al., 2001; Milanesio et al., 2001; Vilsinski et al., 2014).

During photodynamic therapy, as shown in Figure 1, a photosensitizer (PS) is irradiated with visible light of a wavelength which causes excitation of the PS to its singlet excited state which undergoes photochemical conversion to the triplet excited state. In the presence of molecular oxygen ($^3O_2$), the triplet state PS reacts with biomolecules in the cell through type II reaction pathway to produce the cytotoxic singlet oxygen ($^1O_2$). Research on singlet oxygen production and reactivity has developed with significance in numerous areas such as photodynamic applications in blood sterilization and sunlight-activated herbicides and insecticides (DeRosa and Crutchley, 2002).

Consequently, we report a simple and versatile method to evaluate the singlet oxygen generation of 5,10,15,20-tetrakis (3,5-dimethoxyphenyl) porphyrin (TdMPP) as a useful parameter to determine the potential phototherapeutic efficiency of the photosensitizer.

MATERIAL AND METHODS

Chemical and reagents

All reagents were analytical grades and were purchased from Sigma-Aldrich (Steinheim, Germany). They were used as received except for pyrrole which was vacuum distilled prior to use. Silica gel 60 (15–40 mesh) for column chromatography and aluminium-coated silica gel 60 F254 mm for thin layer chromatography (TLC) plates were purchased from Merck.

Synthesis of 5,10,15,20-tetrakis(3,5-dimethoxyphenyl) porphyrin (m-TdMPP)

Briefly, 3,5-dimethoxybenzaldehyde (2.493g, 15 mmol), and freshly distilled pyrrole (1.045ml, 15mmol) were dissolved in 100ml of DCM. Next, 3 drops of trifluoroboron etherate, $BF_3.O(Et)_2$) and trifluoroacetic acid (TFA) (35 mL, 0.45 mmol) were added and stirred for 60 min at room temperature in argon atmosphere. Then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.34 g, 1.5 mmol) was added and the mixture was stirred for additional 60 min, in an open atmosphere (Figure 1). The solvent was removed under reduced pressure and the black tarry product was re-dissolved in hot methanol and filtered to give purple crystalline crude product. The crude product was purified through column chromatography with 2:1 mixture of hexane-ethyl acetate as eluent.

Characterization

Absorption (UV-VIS) and fluorescence (PL) spectra were recorded at room temperature using 1 cm path length cells on a UV/VIS Perkin Elmer LAMBDA 25 spectrometer and Shimadzu RF-6000 Spectro-fluorophotometer respectively. The FTIR spectrum was obtained on a Perkin-Elmer UATR Spectrum Two FT-IR spectrometer. Proton (^{1}H) and carbon-13 (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM500 Avance III spectrometer at 298K with $CDCl_3$ as the solvent. The chemical shifts (δ) were reported in parts per million. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26) and carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (the 3-line triplet signal near δ 77 ppm).

Determination of singlet oxygen quantum (φ_Δ) yield

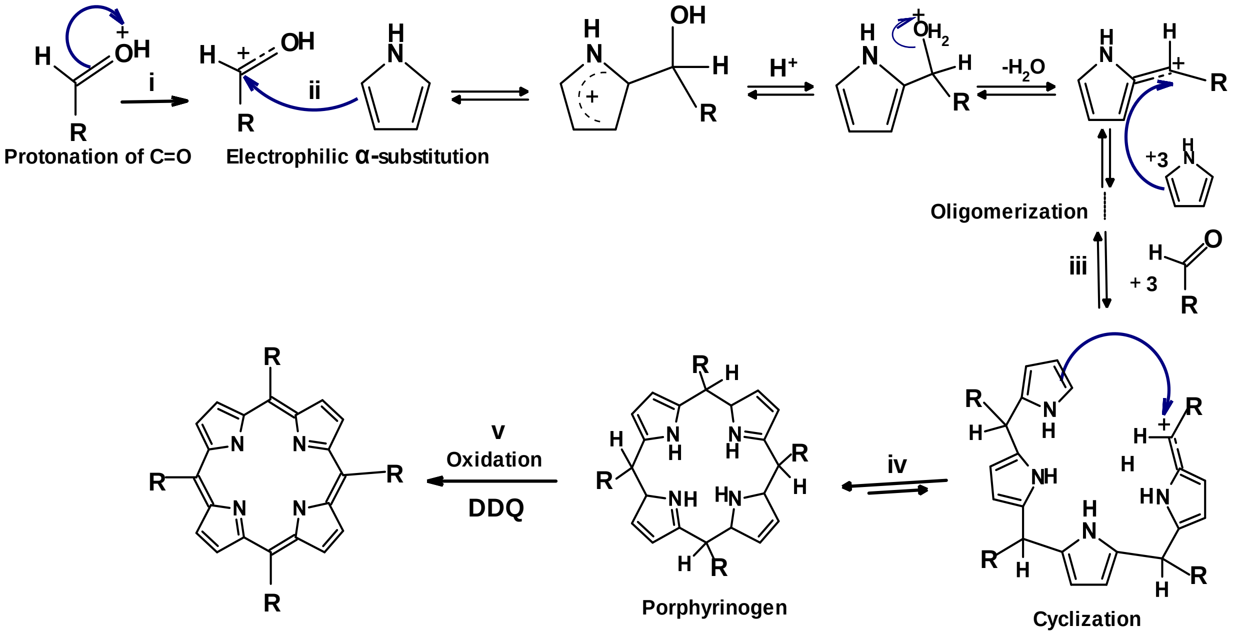
The method of Fakayode et al (2017) with slight modification was adopted to measure the singlet quantum oxygen yield of m-TdMPP using 1,3-diphenylisobenzofuran (DPBF) as the singlet oxygen acceptor (Amat-Guerri et al., 1996) and methylene blue (MB) as reference standard. Briefly, 1,3-diphenylbenzofuran solution (0.1 mL, 0.2 mg/10 mL DMSO) was diluted to 5.1 mL using dimethyl sulfoxide (DMSO). This solution (2 mL) was then added to 2 mL of the m-TdMPP solution (0.2 mg/3 mL DMSO) and the mixture irradiated at 670 nm using a spectrofluorophotometry laser light for 300 s. The decrease in the fluorescence intensity of DPBF was monitored at 461 nm. Similarly, 0.1 mL MB solution (0.2 mg/10 mL DMSO) was diluted to 10 mL with DMSO. 2 mL of this solution was then added to 2 mL of working DPBF solution and the mixture irradiated under light conditions as above. The singlet oxygen quantum φ_Δ was estimated by comparing the slope of the decrease in the fluorescence emission intensity versus irradiation time of DPBF solution containing porphyrin with that of the standard reference standard using the formula given in Eq. (1)(Adarsh et al., 2010).

$$O_2^1 = \frac{S1\ x\ Q2\ x\ A2}{S2\ x\ A1} \qquad (1)$$

Where, $^1O_2^*$ = Singlet oxygen quantum yield of sample, A1 = Absorbance of the sample at irradiation wavelength, S1 = Slope of sample; A2 = Absorbance of the reference at irradiation wavelength, Q2 = Quantum yield of the reference and S2 = Slope of the reference

RESULTS AND DISCUSSION

The purple solution eluted from the column was concentrated to dryness under vacuum to afford a shiny purple solid 125 mg (41%) of pure m-TdMPP (Figure 2A).



Scheme 1: Mechanism of the synthesis of 5,10,15,20-tetrakis(3,5-dimethoxyphenyl) porphyrin (m-TdMPP).

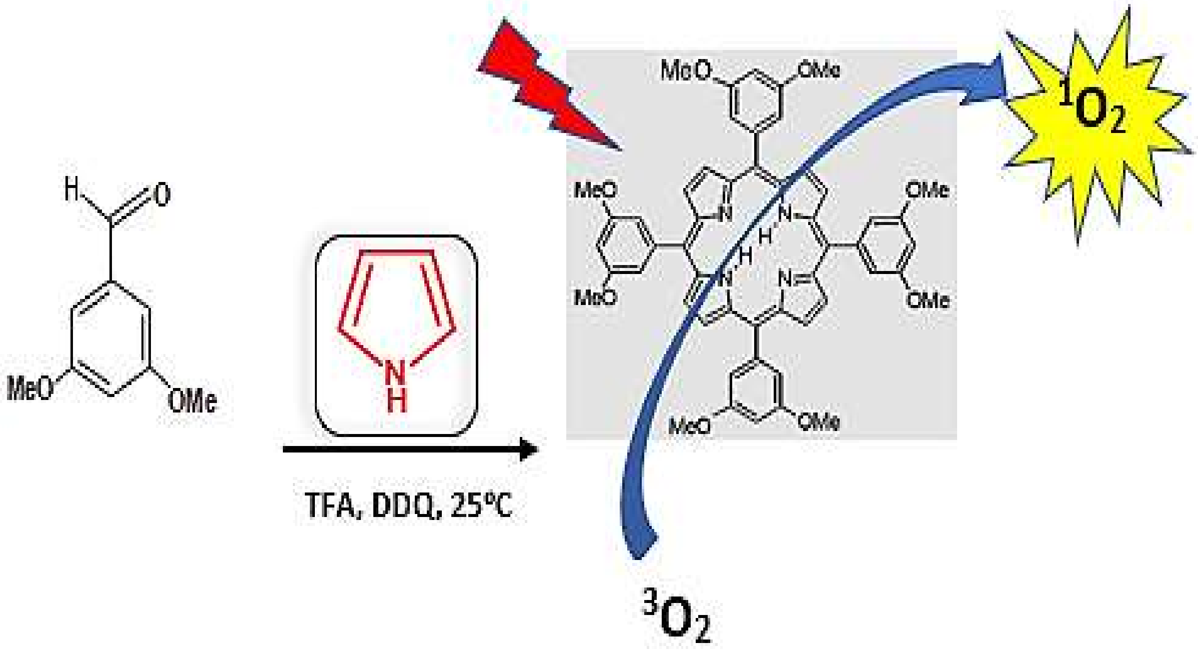


Fig. 1: Graphic illustration of photodynamic action of porphyrin

The solid was analysed by TLC (silica gel, hexane-EtOAc = 2:1) which showed a single spot with Rf = 0.64, and fluoresced bright orange light under a UV lamp at 350 nm (Figure 2B)

Reaction mechanism

A reaction mechanism involving five principal steps was proposed for the synthesis of the as-synthesized porphyrin as shown in scheme 1, viz:

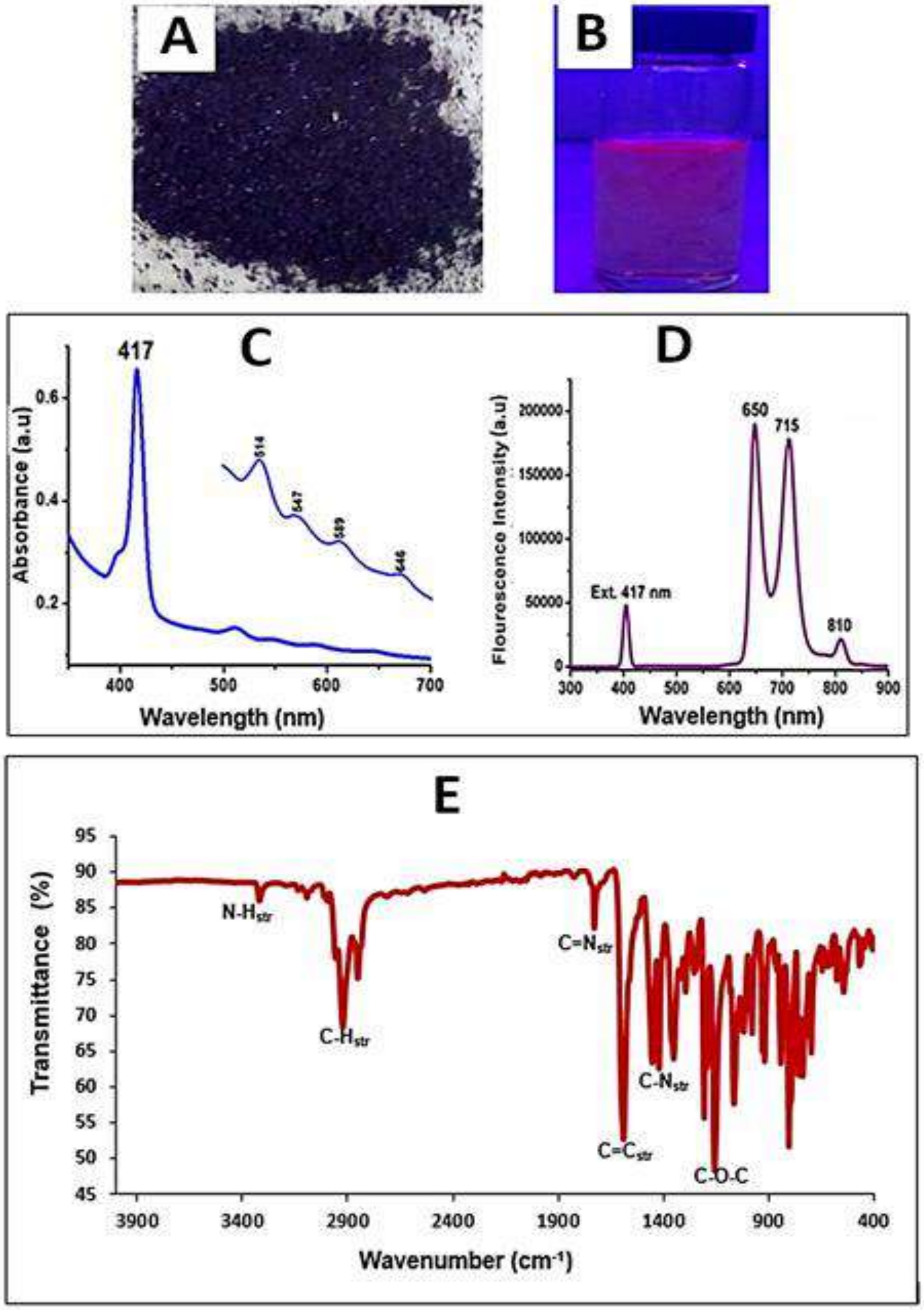


Fig. 2: Characterization of m-TdMPP. (A) Digital image of the purple crystals; (B) Digital image of the fluorescence solution ; (C) Absorption spectrum; (D) Emission spectrum and (E) FTIR spectrum

i. Protonation of the carbonyl O of the benzaldehyde by TFA.
ii. Electrophilic α-substitution of pyrrole by the protonated aldehyde
iii. Acid-catalyzed oligomerization which was initiated by trifluoroboron etherate, $BF_3.O(Et)_2$.
iv. Spontaneous non-template cyclization wherein 4 pyrrole units were combined.
v. Oxidation of the intermediate porphyrinogen to porphyrin

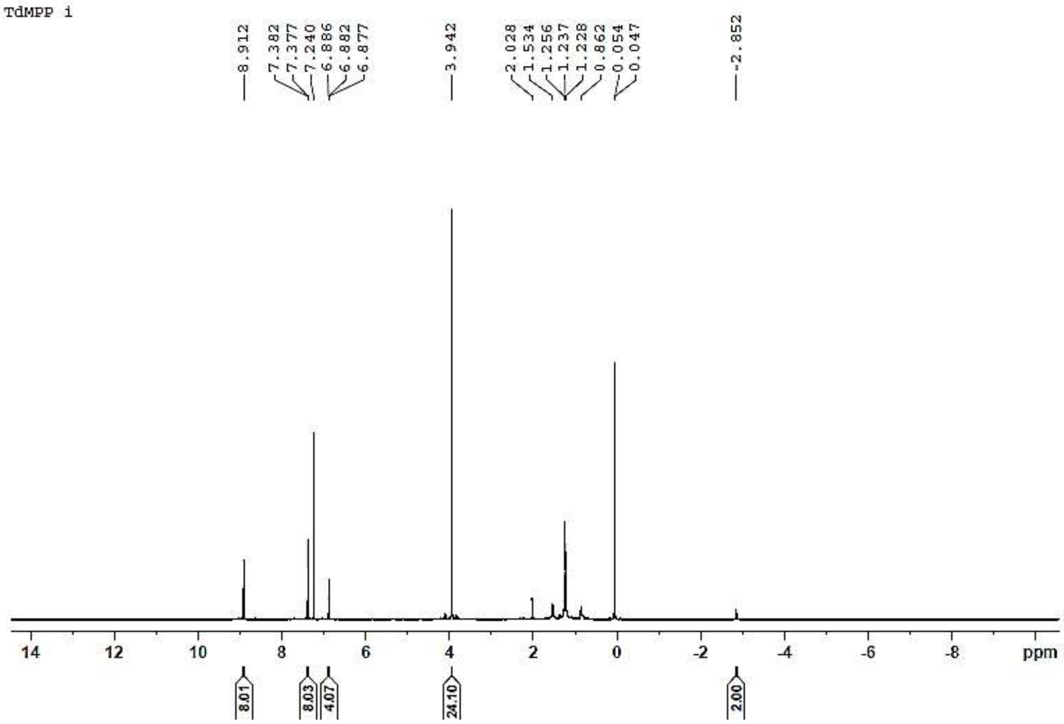


Fig. 3: ^{1}H NMR ($CDCl_3$) spectrum of m-TdMPP (Chemical shifts (δ) in ppm: -2.844 (s, 2H, inner pyrrole N-H); 3.947 (s, 24H, Ar-OCH3), 7.385 - 7.390 (d, 8H, J=2.5, 5,10,15,20-Ar 2’,6’-H); 6.883 - 6.892 (t, 4H, J=2.0, 10,15,20-Ar 4’-H); 8.921 (s, 8Hβ, pyrrole)).

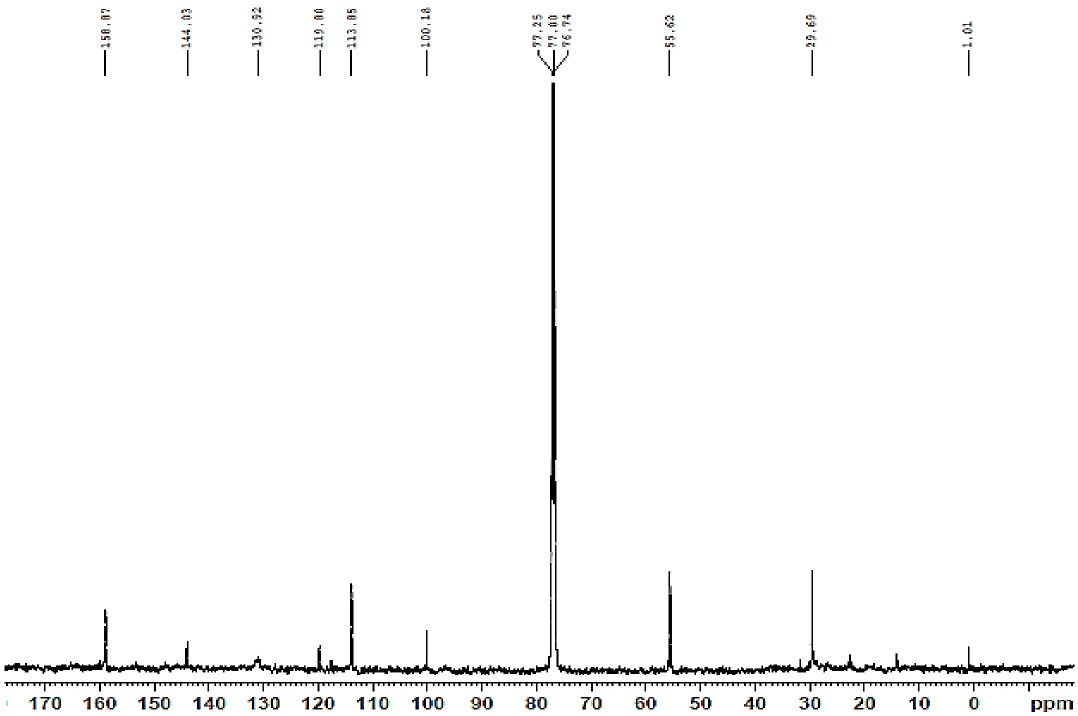


Fig. 4. ^{13}C NMR ($CDCl_3$) spectrum of m-TdMPP

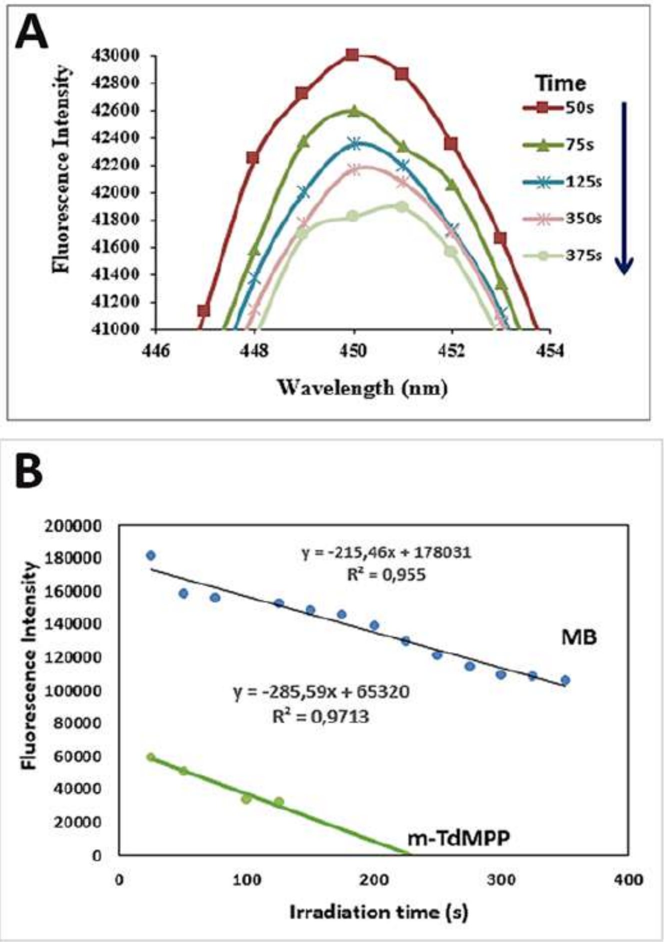


Fig. 5: Singlet oxygen characterization. (A) Fluorescence emission intensity of DPBF at 451 nm for different times in the presence of TdMPP; (B) Comparative linear plots of the fluorescence emission intensity of DPBF vs. irradiation time for methylene blue (MB) and m-TdMPP.

Spectroscopic characterization of 5,10,15,20-tetrakis(3,5-dimethoxyphenyl)porphyrin

Due to extensive electron delocalization, porphyrins are intensely coloured and absorb light in the visible part of the electromagnetic spectrum. The absorption spectrum of TdMPP (Figure 2C) showed a characteristic phyllo-type spectral pattern which are typical of meso-substituted porphyrins. There was an intense absorption at 417 nm, the Soret band which was due to the transition of a_{1u} (π) → e_g*(π), or the $S_2 \leftarrow S_0$. The four other weaker satellite absorption maxima at 514, 547, 589 and 646 nm called the Q bands which also correspond to a_{2u} (π) → e_g* (π) transitions or $S_1 \leftarrow S_0$ transitions have been assigned Qy(1,0), Qy(0,0), Qx(1,0) and Qx(0,0) respectively. (Fagadar-Cosma et al., 2007; Uttamlal and Holmes-Smith, 2008).

The fluorescence emission spectrum of TdMPP was measured in MeOH. The values of λem (maximum emission wavelength) were obtained by exciting TdMPP at the wavelength of the maximum absorption of the Soret band (417 nm). The spectrum exhibited two strong fluorescence bands at 650 nm and 715 nm as observed in other meso-substituted porphyrins and had been assigned Q*x(0,0) and Q*x(0,1) transitions respectively. Also, a weaker emission band around 810 nm was observed as shown in Figure 2D. The emission intensity of the free base porphyrins has been shown to be influenced by the stereo-electronic effects of the meso substituents (Gentemann et al., 1995). Accordingly, the presence of electron-rich OMe groups at the meso position of TdMPP gave rise to an increase in the aryl-porphyrin π – π resonance interactions. This had been attributed to the smaller dihedral angle between the aryl groups and the porphyrin mean plane in the excited state of porphyrins (S_1) with respect to that in the ground state (S_0) (Lee et al., 2009; Zakavi and Hoseini, 2015). Furthermore, the stokes shift of the porphyrin which describes the energy gap between the emission Q*x(0,0) and absorption Qx(0,0) bands is 4 nm which was an additional indication of minor structural changes of the porphyrin macrocycle in the ground and excited states (Ha et al., 2001).

The FTIR spectrum of TdMPP is shown in Figure 2E. A weak band due to the asymmetrical N-H stretching vibration of the pyrrole group was observed at - 3327 cm^{-1}. The C-H stretching in pyrrole was responsible for the peaks between 3132- 3138 cm^{-1}. The weak 3093 cm^{-1} peak showed the presence of the aryl C-H stretching. The bands observed at 2973, 2916, and 2851 cm^{-1} were assigned to the asymmetric and symmetric C-H stretching vibrations of the $-CH_3$ groups, while those at 1380, 1261, 1020 and 1013 cm^{-1} were for the asymmetric and symmetric C-O-C stretching vibrations of the 3,5-dimethoxy groups in the phenyl moiety. The C=N stretching was responsible for the 1671-1743 cm^{-1} peaks. The 1589 cm^{-1} peak was due to the presence of conjugated C=Cstr of aromatic rings in the fractions. The peaks at 1450 and 1418 cm^{-1} were due to the C-N stretching in the pyrrole. The peaks at 1013-1380 cm^{-1} (4 bands) were due to the presence of C-O and C-N stretching. The C-H bending out-of-plane for 1,3,5 tri-substituted benzene ring (-Ar-3,5 diMeO) was found between 950 and 850 cm^{-1}.

Nuclear magnetic resonance (NMR) characterization

The ^1H-NMR spectrum and data of the m-TdMPP obtained in $CDCl_3$ are shown in Figure 3. The diamagnetic ring current of porphyrin de-shielded the peripheral protons on the outside of the macrocycle thus the *meso* and β-protons were shifted further downfield than the protons on the inside of the macrocycle. Thus, the inner N-H protons were shifted up-field and they appeared as a singlet at δ = -2.852 ppm (Zhang et al., 2016). The protons of 3,5-dimethoxygroups on the phenyl substituents exhibited one intense singlet at δ = 3.942 ppm. The β-protons signals from pyrrole resonate as a singlet at δ = 8.912 ppm. The singlet signal at 7.240 ppm was due to $CDCl_3$ in which the sample was dissolved. The remaining signals (0.062 to 1.274 ppm) were due to the solvent impurities. Since the existence of the methoxy groups may distort the porphyrin core from planarity, some of the expected singlet proton signals of the meso-attached phenyl groups were detected as doublet and triplet (Fagadar-Cosma et al., 2007). The doublet appearing at δ = 7.377-7.382 ppm were attributed to the *ortho*- protons on the phenyl substituents, while the triplet observed at δ = 6.877-6.889 ppm were due to the *para*- aromatic protons.

The ^{13}C-NMR spectrum of m-TdMPP obtained in $CDCl_3$ is shown in Figure 4. The signals at 158.86 ppm were assigned to the phenylic carbons. The β- pyrrolic carbons resonated at 130.92 ppm while the α- pyrrolic appeared at 144.02. The signals between 100 and 119.80 were assigned to the meso carbons whereas signal at 55.62 ppm was due to the $-OCH_3$ groups. The 3-line triplet signals near 77 ppm was due to the $CDCl_3$ in which the sample was dissolved.

Singlet quantum (φ_Δ) yield of m-TdMPP

Table 1: Singlet oxygen characteristics of the m-TdMPP

Photosensitizer	λabs* Soret-band (nm)	λabs* Q-bands (nm)	λexc** Q-bands (nm)	λem*** (nm)	*$^1O_2$* Quantum yield
m-TdMPP	417	514,547, 589, 646	670	650, 715	0.62

**abs = maximum absorption; **exc = maximum excitation; ***em = maximum emission*

Table 2: Singlet oxygen characteristics of the m-TdMPP

Photosensitizer	Solvents	$^1O_2$ yield	Reference
P2.2	$CHCl_3$	0.16	Boscencu et al. (2017)
Zn(II)2.2	$CHCl_3$	0.17	Boscencu et al. (2017)
Phthalocyanine	CH_3OD	0.16	Darwent et al. (1982)
m-T-2PyP	H_2O	0.18	Rapozzi et al. (2014)
Photofrin	Toluene	0.32	Redmond and Gamlin (1999)
Foscan	CH_3OH	0.43	Bonnett et al. (1999)
Porphycene	DMSO	0.31	Szeimies et al. (1996)
m-TdMPP	DMSO	0.65	Present work

m-T-2PyP = *meso*-5,10,15,20-tetra(N-methyl-2-pyridyl)porphyrin, P2.2= 5-(4-hydroxy-3-methoxyphenyl)-10,15,20-tris-(4-acetoxy-3-methoxyphenyl)porphyrin and Zn(II)2.2=Zn(II)-5-(4-hydroxy-3-methoxyphenyl)-10,15,20-tris-(4-acetoxy-3-methoxyphenyl)porphyrin

The singlet oxygen quantum yield (φ_Δ) is a quantitative measurement of the efficiency in which photosensitizers can use energy, in the form of light, to convert oxygen in the ground state to the reactive singlet oxygen species, $^1O_2(^1\Delta_g)$, useful in photodynamic therapy (Bonacin et al., 2009). Table 1 shows the singlet oxygen parameters of m-TdMPP. In this study, the singlet oxygen generated by TdMPP was trapped by DPBF, causing a decrease in the oxygen concentration in solution. This decrease in oxygen concentration as reflected in the decrease in the fluorescent emission intensity of DPBF at 451 nm with time is presented in Figure 5. Subsequently, the singlet oxygen quantum yield (φΔ) of m-TdMPP was estimated by comparing the slope of the decrease in fluorescence emission intensity at 451 nm versus irradiation time of DPBF solution containing porphyrin with that of the standard reference, MB as presented in Figure 5A-B. The R^2 values (0.9551 and 0.9713) of the plots show the linearity of the curves for both the MB standard and m-TdMPP sample respectively. The slopes for MB, and porphyrin m-TdMPP were -215.46, and -285.59 respectively (Fig. 5B). In the absence of dimerization, the value of (φΔ) for MB measured in several media was 0.52 (Severino et al., 2003; Wetzler et al., 2006).

The singlet oxygen quantum yield was measured as shown in Eq. 1.

$$\frac{-285.59\ x\ 0.52\ x\ 0.131365}{-2.15.46\ x\ 0.142541} = 0.64$$

It is worthy of note that the estimated singlet oxygen quantum yield for m-TdMPP was higher than that of the reference standard MB (0.52) and some photosensitizing materials reported in the literature (Table 2). High singlet oxygen quantum yield is required for wastewater treatment, fine chemical synthesis, and photodynamic applications.

CONCLUSIONS

Meso-5,10,15,20-tetrakis(3,5-dimethoxyphenyl)porphyrin (m-TdMPP) was successfully synthesized and its structure confirmed by UV-Vis, FTIR, PL, NMR spectroscopic methods. The porphyrin has higher singlet oxygen ($^1O_2$) quantum yield than methylene blue and other photosensitizers reported in literature. Hence, the *meso*-5,10,15,20-tetrakis(3,5-dimethoxyphenyl)porphyrin is considered a good candidate as photosensitizer in PDT. The effectiveness of the as-synthetized porphyrin in biological application could be enhanced by further conjugation to biocompatible and hydrophilic molecules.

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