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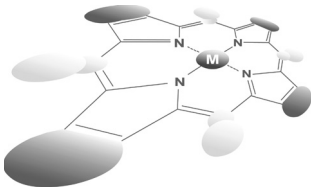

Synthesis and DNA photocleavage studies of novel porphyrin diarylthiazoles

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ABSTRACT: A convenient and regioselective synthesis of porphyrin diarylthiazoles is reported *via* the reactions of alkynyl(aryl)iodonium tosylates and porphyrin thioamides. Among the synthesized porphyrin diarylthiazoles, compounds **6d** and **6f** have shown significant interactions with ctDNA and exhibited efficient DNA photocleavage.

KEYWORDS: porphyrins, alkynyl(aryl)iodonium salts, thiazoles, porphyrin diarylthiazoles, DNA photocleavage.

INTRODUCTION

In recent years, there has been continuous upsurge of interest in the synthesis of porphyrin and its derivatives due to their wide variety of potential applications in both medicine and molecular materials [1]. A number of intermediates and synthetic strategies have been developed to constitute porphyrin systems. Their properties also make them useful in catalysis [2], drug delivery [3], nonlinear optics [4] and photodynamic therapy [5, 6]. Functionalizing the porphyrins has its challenges, inspite of the fact that it has been the main foundation for modulating various properties of the porphyrin moiety and further constructing new and useful porphyrins. Given the high significance of porphyrin heterocycles with extended π-conjugation as building blocks for constructing novel porphyrin systems, there is increasing need for the development of efficient and practical syntheses of novel porphyrins. Porphyrins with heterocyclic rings have proven to be valuable research tools and a fruitful area for the development of synthetic methodology. Numerous porphyrins have been synthesized and tested for their *in vitro* and *in vivo* phototoxicity, as existing photosensitizers have side-effects associated with their specificity for cancerous cells over normal cells and dosage [7]. They also exhibit varied interactions with DNA through intercalation, external groove binding and outside binding modes [8]. A large number of methods have been developed to overcome the problems mentioned earlier which have led to the modifications at peripheral positions of porphyrin ring [9]. Accordingly, it is very important to understand in detail how porphyrin heterocycles bind and cleave DNA.

Five-membered thiazole ring is among the most important classes of nitrogen containing heterocycles in medicinal chemistry owing to its unique biological activities including anti-inflammatory [10], anti-hypertensive [11], anti-bacterial [12], anti-HIV [13a] and anti-cancer [13b]. Further, thiazole ring is an integral part of several DNA photocleaving agents and anti-cancer antibiotics [13]. Because of the conjugated carbon nitrogen double bond in thiazole heterocycle, it is believed to produce the photo-excited $^3(n–\pi^*)$ and/or $^3(\pi–\pi^*)$ state (s) [13c, 13d].

Many methods for the preparation of the thiazole moiety are available, and among them, the Hantzsch thiazole synthesis employing lachrymatory α-haloketones and thioamides is one of the most common methods. Further, α-haloketones were replaced with α-tosyloxy ketones to prepare thiazoles and heterocyclic analogues [14, 15]. Alternate approach for the preparation of thiazoles utilizes the reaction of thioamides with alkynyl(aryl)-iodonium salts [16]. In the recent years, alkynyl(aryl)-iodonium salts have received much attention as useful and readily available starting materials in organic synthesis.

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The electron-withdrawing nature and powerful leaving ability of the phenyliodonium moiety has imparted unique reactivity to alkynyliodonium salts [17]. Recently, we have reported the synthesis of porphyrin-1,3,4-oxadiazoles by employing hypervalent iodine reagent, iodobenzene diacetate [18]. In continuation to our efforts in the synthesis of porphyrin appended heterocycles, we report herein a facile synthesis of novel porphyrin diarylthiazoles from readily available alkynyl(aryl)-iodonium tosylates and porphyrin thioamides.

RESULTS AND DISCUSSION

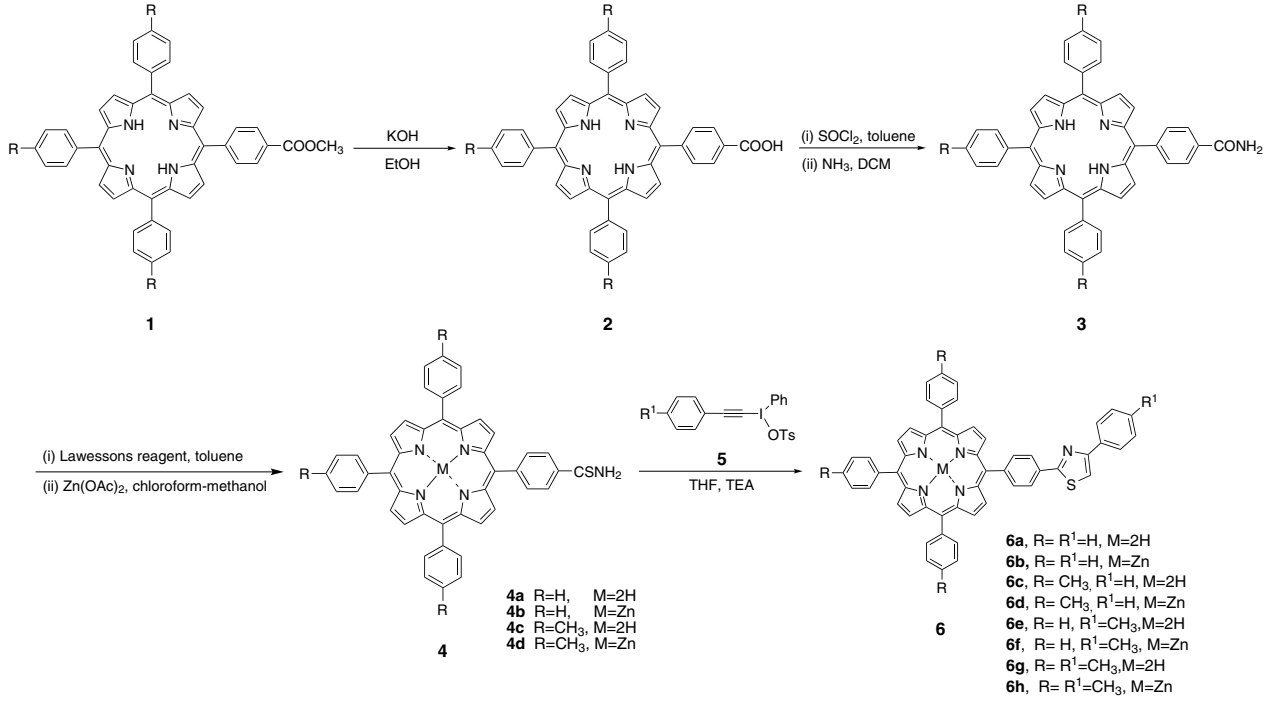
Synthesis and characterization

The synthesis of porphyrin diarylthiazoles **6a–6h** required *meso*-(4-thiocarboxamidophenyl)triphenyl porphyrins **4a–4d** which were prepared according to the procedure recently reported by our group [19]. Porphyrin **1**, prepared by the condensation of benzaldehyde, methyl-4-formylbenzoate and pyrrole under Adler-Longo conditions [20], was hydrolyzed to porphyrin **2** which upon reaction with thionyl chloride and ammonia afforded 5-(4-carboxamido-phenyl)-10,15,20-triphenylporphyrin **3**. The reaction of porphyrin **3** with Lawesson's reagent at 60 °C in toluene afforded porphyrin thioamides **4a** and **4c** in good yields. Finally, metalation with zinc acetate produced porphyrins **4b** and **4d**, respectively (Scheme 1). Alkynyl(aryl)iodonium tosylates **5** were prepared in quantitative yields by treating arylacetylenes with Koser's reagent, [hydroxy(tosyloxy)iodo] benzene (HTIB) in chloroform [21]. Our initial efforts to prepare porphyrin diarylthiazole **6a** from the reaction of thioamide **4a** with alkynyl(aryl)iodonium tosylate **5** in methanol showed poor conversion even after prolonging the reaction for 48 h. Subsequently, reaction in tetrahydrofuran furnished the desired porphyrins **6** in good yields. ^{1}H NMR spectrum of **6a** displayed a characteristic singlet for thiazole C5′-H at δ 7.56 ppm and a multiplet of the eight β-pyrrolic protons ranging δ 8.89–8.86 ppm. MALDI-TOF spectra of **6a–6h** showed corresponding molecular ion peaks. The structure of porphyrin 2,4-diarylthiazole **6a** was unambiguously assigned by its synthesis from an alternate method involving the reaction of porphyrin thioamide **4** and phenacyl bromide [19]. The porphyrin thiazole obtained from the alternate method was found to be identical in all respects to porphyrin thiazole **6a**. Also, 2,5-diarylthiazoles exhibited a characteristic singlet at δ 8.02 ppm for thiazole C4′-H [22] however, the proton NMR of **6a** was devoid of this singlet.

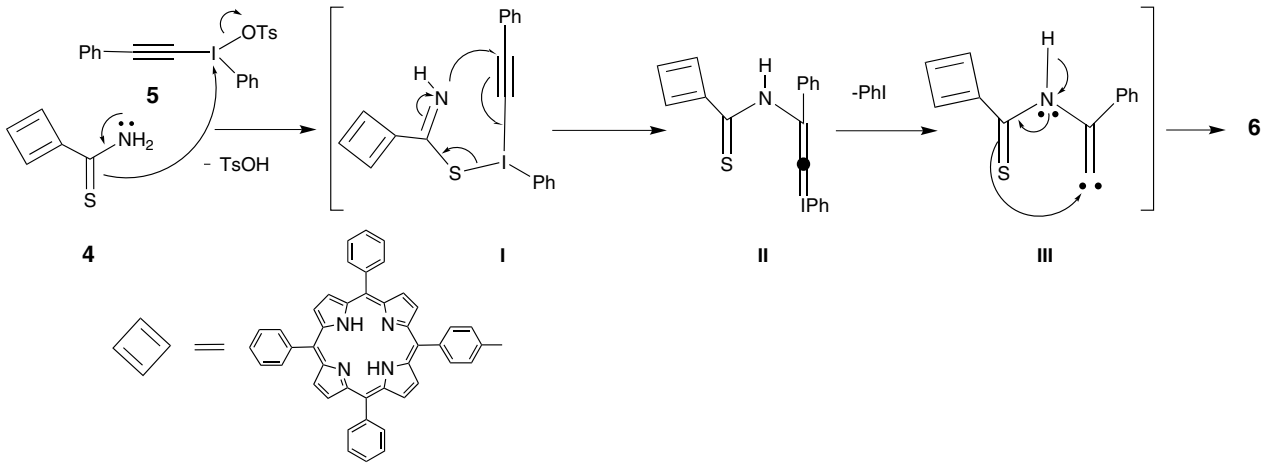
Formation of porphyrin diarylthiazoles **6a–6h** can be explained by a plausible mechanistic pathway as shown in Scheme 2. Initial nucleophilic displacement of tosylate in alkynyl(aryl)tosylate **5** by the thioamide **4a** probably generates an intermediate adduct **I** which rearranges to thioamide **II** [18, 23]. Subsequent loss of iodobenzene provides a reactive species **III**, which upon internal cyclization led the corresponding porphyrin thiazoles **6a–6h** [24].

DNA interaction studies

Interactions of porphyrin diarylthiazoles **6a–6h** with calf thymus DNA (ctDNA; Tris-HCl 5 mM, 0.1 M NaCl,



Scheme 1. Synthesis of porphyrin diarylthiazoles **6a–6h**



Scheme 2. A plausible pathway for the formation of porphyrin diarylthiazoles **6a–6h**

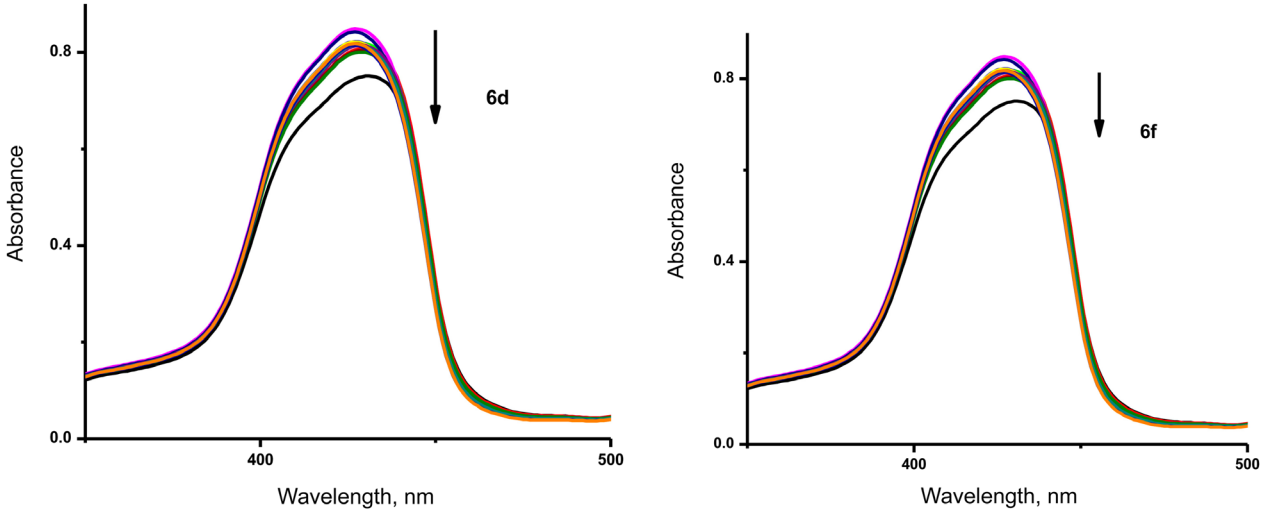


Fig. 1. Absorption spectra of porphyrins **6d** and **6f**. [Porphyrin] = 5 μM in (DMF), [ctDNA] = 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0 μM in 5 mM Tris–HCl buffer, 0.1 M NaCl, pH 7.4. Arrow indicates the decrease of absorbance with the increasing concentration of ctDNA

pH 7.4) were investigated by monitoring absorption changes in the Soret band near 420 nm. Porphyrin solutions (5×10^{-6} M) were titrated with increasing concentrations of DNA as shown in Fig. 1. Among the porphyrin diarylthiazoles studied, compounds **6a–6c**, **6e**, **6g–6h** did not show any significant changes in their UV-vis and fluorescence spectra, whereas porphyrins **6d** and **6f** displayed a relatively small red shift and hypochromicity of the Soret bands. At lower ctDNA concentrations (0–5 μM), porphyrin **6d** exhibited a small red shift (~3 nm) and hypochromicity (5%), whereas, porphyrin **6f** displayed only a five percent hypochromic shift in the Soret bands in absorption spectra. No change in the intensity of the Soret band was observed for compounds **6d** and **6f** upon further increasing ctDNA concentrations (5–10 μM). At lower DNA concentrations (0–5 μM), the observed changes in UV-vis spectra suggest that the porphyrin diarylthiazoles may interact with DNA in an outside binding mode. The binding modes of porphyrin to DNA depend on peripheral substituents and hydrophobicity of the molecule. Also, depending on the metal with one axial ligand Zn(II) and Fe(III); two axial ligands, Mn(III), Fe(III) and Co(III) and without any axial ligand, Ni(II), Cu(II) and Au(III), the binding interactions can alter from intercalation at GC sites to outside bound complexes at AT sites through electrostatic interactions or groove binding [25]. Thus, these Zn(II) porphyrins **6d** and **6f** bases can accommodate axial ligands which present steric barrier for intercalation. In view of observed interactions, the apparent binding constants of porphyrins **6d** and **6f** for ctDNA were determined using the following Equation 1:

$$\frac{[DNA]}{(\varepsilon_A - \varepsilon_F)} = \frac{[DNA]}{(\varepsilon_B - \varepsilon_F)} + \frac{1}{K_b(\varepsilon_B - \varepsilon_F)} \qquad (1)$$

where ε_F correspond to A_{obsd}/[porphyrin], the extinction coefficient for the free porphyrin, ε_A the extinction coefficient for the porphyrin complex of a given solution and ε_B is the extinction coefficient for fully bound form, respectively. A plot of [DNA]/($\varepsilon_A - \varepsilon_F$) *vs.* [DNA] will have a slope of 1/($\varepsilon_B - \varepsilon_F$) and a y-axis intercept equal to 1/K_b ($\varepsilon_B - \varepsilon_F$). The binding constant K_b was calculated from the ratio of the slope to y-axis intercept. The apparent binding constants (K_b) of **6d** (1.25×10^4 M^{-1}) and **6f** (2.4×10^4 M^{-1}) were derived to support their proposed electrostatic interactions with ctDNA [26]. It is to be noted that the equation for calculation of binding constant is valid only if we assume 1:1 stoichiometry for the porphyrin-DNA complex. To verify this proposition, we further analyzed the fluorescence titration data using Benesi–Hilderbrand Equation 2 [27].

$$\frac{1}{I - I_0} = \frac{1}{I_\alpha - I_0} + \frac{1}{K(I_\alpha - I_0)} \times \frac{1}{[DNA]} \qquad (2)$$

where I is the porphyrin fluorescence intensity at a particular DNA concentration; I_0 and I_α indicate the intensity in absence and in presence of highest DNA concentration, respectively. K indicated the binding constant. The plot of 1/($I–I_0$) against 1/[DNA] for both **6d** and **6f** are shown in Fig. 2. The linear nature double reciprocal plot confirms the 1:1 binding stoichiometry [27, 28]. The K values calculated from the slope of the linear plot (for **6d**, $K = 0.15 \times 10^4$ M^{-1} and for **6f**, $K = 0.61 \times 10^4$ M^{-1}) are in agreement with the corresponding values obtained from the absorption data.

The fluorescence spectra of **6d** and **6f** are shown in Fig. 3. The stronger emission band at 726 nm was assigned to the porphyrin transition. A systematic increase in the emission intensity was observed at lower (0–5 μM) and higher (5–10 μM) concentrations of ctDNA. The luminescence spectra were consistent with the observed changes in the UV-vis spectra as a function of ctDNA concentration, supporting the occurrence of outside binding mode in the porphyrin appended thiazole system. This type of behavior has also been reported for a number of systems and suggests switching of binding modes with the increasing concentrations of ctDNA [29]. Analogous to porphyrin derivatives containing bulky substituents, porphyrins **6d** and **6f** were not expected to intercalate between the DNA base pairs. This implies that the predominant interaction of porphyrin diarylthiazoles could be through outside binding with ctDNA.

DNA photocleavage assay

The photocleavage abilities of porphyrin diarylthiazoles **6a–6h** were initially investigated at higher concentrations (50 μM) by mixing plasmid DNA (pBR 322 in Tris-HCl buffer (20 mM, pH 7.2) in the presence and absence of UV and visible light (Fig. S1 in Supporting information). The stock solutions for **6a–6h** (10^{-4} M) were prepared in DMF and final test solutions were achieved by appropriate dilution in Tris-HCl buffer (20 mM). The cleavage of supercoiled plasmid DNA was determined quantitatively by the effective conversion of supercoiled form I to nicked circular form II. Porphyrins **6b**, **6d** and **6f** showed photocleavage of pBR 322 DNA at 50 μM in presence of UV light, which was further studied at lower concentrations by increasing the irradiation time. Control experiments did not show any apparent DNA cleavage; lanes 1 and 5 (Fig. 4a), and lane 1 (Fig. 4b); however, there was degradation of plasmid DNA under UV light when irradiated for 1.5 h (lanes 6–8, Fig. 4a). Similarly, no change was observed in the plasmid DNA when compounds **6b**, **6d** and **6f** were exposed to visible light for 1–2 h, (Figure not shown). The irradiation time was increased for **6b**, **6d** and **6f** as shown in lanes

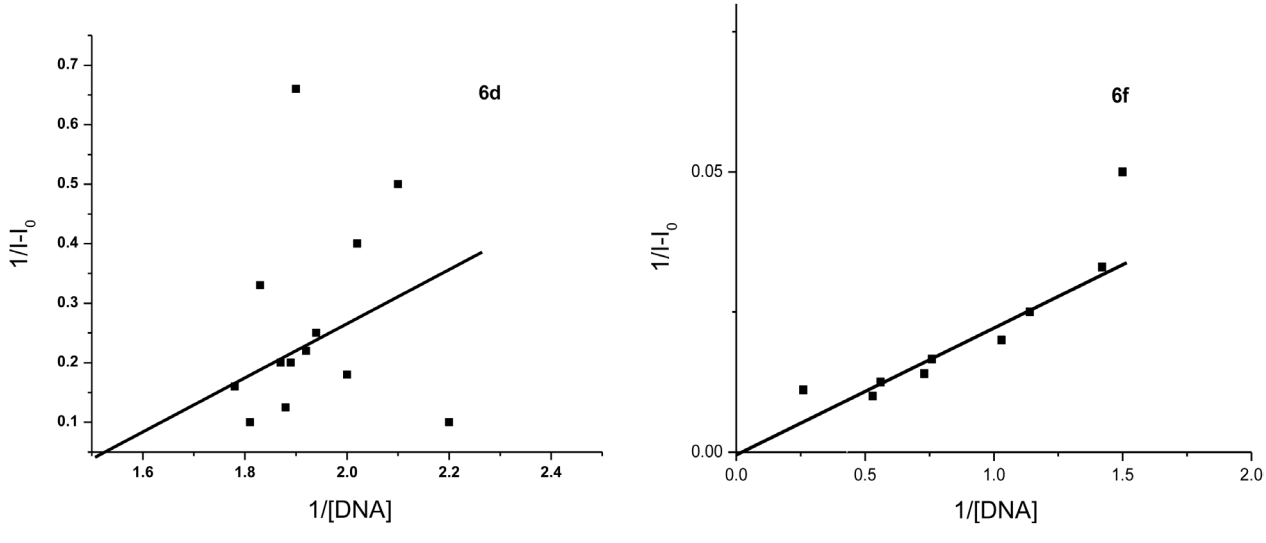


Fig. 2. Plots of 1/($I–I_0$) against 1/[DNA] for porphyrins **6d** and **6f**

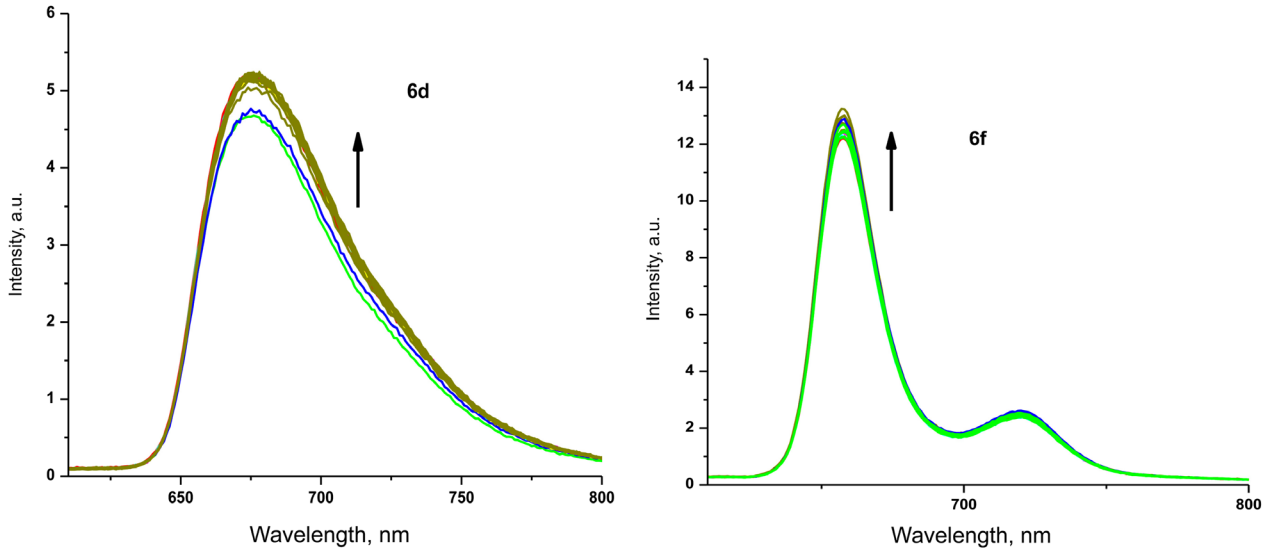


Fig. 3. Fluorescence spectra of porphyrins **6d** and **6f**. [Porphyrin] = 5 μM, [ctDNA] = 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0 μM in 5 mM Tris–HCl buffer, 0.1 M NaCl, pH 7.4. Arrow indicates the increase in intensity with the increasing concentration of ctDNA (λ_{Exc}-429 nm)

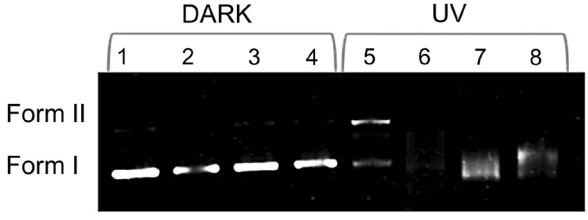


Fig. 4a. Photoinduced DNA cleavage by porphyrins **6b**, **6d** and **6f**. pBR 322 supercoiled DNA (0.1 μg) was incubated with the porphyrins (25 μM) in Tris–HCl (20 mM, pH 7.2), DMF (2.5 vol%) at ambient temperature in the dark for 3 h, and UV-irradiated (310–390 nm) for 1.5 h. Lane 1: Control DNA alone, Lane 2: DNA + **6b** (dark), Lane 3: DNA + **6d** (dark), Lane 4: DNA + **6f** (dark), Lane 5: DNA alone (UV), Lane 6: DNA + **6b** (UV), Lane 7: DNA + **6d** (UV), Lane 8: DNA + **6f** (UV)

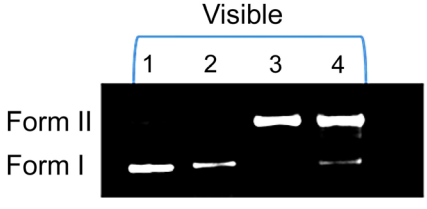


Fig. 4b. Photoinduced DNA cleavage by porphyrins **6b**, **6d** and **6f**. pBR 322 supercoiled DNA (0.1 μg) was incubated with the porphyrins (25 μM) in Tris–HCl (20 mM, pH 7.2), DMF (2.5 vol%) and exposed to visible light for 3 h. Lane 1: Control DNA alone (vis), Lane 2: DNA + **6b** (vis), Lane 3: DNA + **6d** (vis), Lane 4: DNA + **6f** (vis)

2–4 (Fig. 4b), where the amount of form I of pBR 322 DNA diminished gradually and form II increased. Under experimental conditions, porphyrins **6d** and **6f** exhibited more effective DNA cleavage under visible light when compared to UV light.

EXPERIMENTAL

General

All chemicals were procured from Sigma-Aldrich, India and Spectrochem Pvt Ltd., were of analytical grade and used as such unless indicated. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker-avance 400 MHz instrument using TMS as an internal standard. Mass spectra were obtained on a Bruker ProFLEX III MALDI-TOF mass spectrometer using DHB as the matrix. The UV-vis spectroscopy was carried out on Hitachi U-2900 spectrophotometer and fluorescence spectra were recorded on Horiba Jobin Yvon Fluoro max-4-scanning fluorimeter. Quartz cuvettes were used with 1-cm path length.

Synthesis

Preparation of porphyrin diarylthiazoles 6. To a stirred solution of porphyrin thioamide **4** (0.1 g, 0.148 mmol), alkynyl(aryl)iodonium tosylate **5** (0.074 g, 0.178 mmol) in tetrahydrofuran (15 mL) at 0 °C was added triethylamine (15 μL, 0.148 mmol) and the reaction mixture was allowed to heat up to 50 °C for 4–6 h. After completion of the reaction, the contents were diluted with water and then basified to pH ~ 8 with 10% sodium carbonate solution (20 mL). The crude product was extracted with chloroform (3 × 15 mL) and the combined organic layer was dried over anhydrous sodium sulphate. Excess solvent was distilled off and the crude product obtained was chromatographed using chloroform/hexane (3:7 *v/v*) as eluent to afford **6** as purple solid.

5-{4′-(4″-Phenyl)-2″-thiazolyl}-10,15,20-triphenylporphyrin (6a). Yield 61 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm -2.95 (s, 2H), 7.33 (t, J = 7.4 Hz, 1H),

7.44 (t, J = 7.6 Hz, 2H), 7.56 (s, 1H), 7.63–7.75 (m, 9H), 8.05 (d, J = 7.2 Hz, 2H), 8.16–8.19 (m, 6H), 8.26 (d, J = 6.2 Hz, 2H), 8.37 (d, J = 8.2 Hz, 2H), 8.85–8.89 (m, 8H). MS (MALDI-TOF): *m/z* 774.2909 (calcd. for $[M + H]^+$ 774.2691).

5-{4′-(4″-Phenyl)-2″-thiazolyl}-10,15,20-triphenylporphyrinato zinc(II) (6b). Yield 65 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 7.33 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.56 (s, 1H), 7.66–7.73 (m, 9H), 8.06 (d, J = 7.4 Hz, 2H), 8.15–8.17 (m, 6H), 8.27 (d, J = 6.2 Hz, 2H), 8.38 (d, J = 8.2 Hz, 2H), 8.88–8.95 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 114.86, 117.84, 118.54, 124.63, 125.38, 126.29, 129.35, 129.70, 130.02, 135.95, 140.64, 141.33, 145.97, 148.89, 149.55, 152.23, 168.73. MS (MALDI-TOF): *m/z* 835.2504 (calcd. for $[M]^+$ 835.1748).

5-{4′-(4″-Phenyl)-2″-thiazolyl}-10,15,20-tritolylporphyrin (6c). Yield 55 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm -2.85 (s, 1H), 2.61 (s, 9H), 7.46 (d, J = 8.0 Hz, 8H), 7.99–8.02 (m, 8H), 8.22 (d, J = 8.0 Hz, 2H), 8.33–8.36 (m, 2H), 8.68 (d, J = 4.8 Hz, 2H), 8.75–8.80 (m, 8H). MS (MALDI-TOF): *m/z* 815.3083 (calcd. for $[M]^+$ 815.3376).

5-{4′-(4″-Phenyl)-2″-thiazolyl}-10,15,20-tritolylporphyrinato zinc(II) (6d). Yield 52 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 2.73 (s, 9H), 7.46 (d, J = 8.0 Hz, 8H), 7.96–8.02 (m, 8H), 8.22 (d, J = 8.0 Hz, 2H), 8.33–8.36 (m, 2H), 8.68 (d, J = 4.8 Hz, 2H), 8.72–8.80 (m, 8H). MS (MALDI-TOF): *m/z* 877.2448 (calcd. for $[M]^+$ 877.2218).

5-{4′-(4″-Tolyl)-2″-thiazolyl}-10,15,20-triphenylporphyrin (6e). Yield 62 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm -2.83 (s, 2H), 2.50 (s, 3H), 7.51 (s, 1H), 7.66–7.72 (m, 9H), 8.11–8.16 (m, 10H), 8.38 (d, J = 6.4 Hz, 2H), 8.66 (d, J = 8.4 Hz, 2H), 8.78–8.86 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 21.12, 116.97, 119.95, 120.65, 126.68, 126.79, 127.49, 127.71, 128.40, 131.46, 131.74, 131.81, 132.13, 138.06, 142.75, 143.44, 148.08, 151.00, 151.66, 154.34, 167.84. MS (MALDI-TOF): *m/z* 788.3203 (calcd. for $[M + H]^+$ 788.2770).

5-{4′-(4″-Tolyl)-2″-thiazolyl}-10,15,20-triphenylporphyrinato zinc(II) (6f). Yield 60 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 2.51 (s, 3H), 7.51 (s, 1H), 7.67–7.74 (m, 9H), 7.95–7.99 (m, 4H), 8.14–8.19 (m, 6H), 8.36 (d, J = 6.4 Hz, 2H), 8.69 (d, J = 8.4 Hz, 2H), 8.78–8.86 (m, 8H). MS (MALDI-TOF): *m/z* 849.2061 (calcd. for $[M]^+$ 849.1905).

5-{4′-(4″-Tolyl)-2″-thiazolyl}-10,15,20-tritolylporphyrin (6g). Yield 54 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm -2.87 (s, 2H), 2.48 (s, 3H), 2.73 (s, 9H), 7.40–7.43 (m, 3H), 7.50–7.57 (m, 12H), 7.62–7.66 (m, 4H), 7.71 (d, J = 8.4 Hz, 2H), 8.29–8.36 (m, 8H). MS (MALDI-TOF): *m/z* 829.3619 (calcd. for $[M]^+$ 829.3083).

5-{4′-(4″-Tolyl)-2″-thiazolyl}-10,15,20-tritolylporphyrinato zinc(II) (6h). Yield 52 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm 2.49 (s, 3H), 2.73 (s, 9H), 7.40–7.43 (m, 3H), 7.49–7.57 (m, 12H), 7.64–7.69 (m, 4H), 7.73 (d, J = 8.4 Hz, 2H), 8.25–8.37 (m, 8H). MS (MALDI-TOF): *m/z* 891.2951 (calcd. for $[M]^+$ 891.2218).

CONCLUSION

In conclusion, we have developed a facile, efficient and regioselective synthesis of porphyrin appended diarylthiazoles from easily accessible alkynyl(aryl)iodonium tosylates and porphyrin thioamides. The porphyrin diarylthiazoles **6d** and **6f** showed binding affinity (1.25×10^4 M^{-1} and 2.4×10^4 M^{-1}) towards ctDNA probably through outside binding mode and quantitative plasmid DNA photocleavage upon exposure to visible light. Further, detailed mechanistic studies are currently underway.

Acknowledgements

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Supporting information

Supplementary material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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