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Synthesis of Oxasmaragdyrin-Amino Acid Conjugates

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Abstract:

A series of covalently linked oxasmaragdyrin-amino acid and BF_2-oxasamaragdyrin-amino acid conjugates were synthesized by treating oxasmaragdyrin or its BF_2 complex containing benzylhydroxyl group at one of the meso position with appropriate Fmoc-protected amino acid in CH_2Cl_2 in the presence of EDC.HCl/HOBT under basic conditions at room temperature. The conjugates are stable, highly soluble in all organic solvents and confirmed by HR mass spectrometry. 1D and 2D NMR techniques were used to characterize the oxasmaragdyrin-amino acid conjuagtes. Absorption, fluorescence and electrochemical studies of conjugates indicated that the conjugates strongly absorb and emit in visible-NIR region with decent quantum yields, singlet state lifetimes and are stable under electrochemical conditions. Furthermore, the conjugates showed minimal change in their spectral and electrochemical properties compared to that of the unconjugated oxasmaragdyrin or its BF_2 complex suggesting that the characteristic features of the oxasmaragdyrin and its BF_2 complex is retained in the conjugates which will be useful feature for Near-IR fluorescence imaging and other applications.

Introduction

Smaragdyrins I are 22π aromatic expanded pentapyrrolic macrocycles in which the five pyrroles are connected via three meso-carbons and two direct pyrrole-pyrrole bonds.[1] Because of the presence of two direct pyrrole-pyrrole bonds, the smaragdyrin macrocycle is highly strained and not stable for further studies. Thus, to the best of our knowledge, there are no reports available on synthesis of stable smaragdyrin macrocycles containing five pyrrole rings. However, Chandrashekar and co-workers reported few years back the synthesis of meso-triaryl 25-oxasmaragdyrins II which are stable and exhibit interesting spectral and electrochemical properties.[2] The 25-oxasmaragdyrins were resulted by replacing one of the pyrrole group of smaragdyrin with furan ring and these macrocycles absorb and emit in 400-800 nm region with decent quantum yields and singlet state lifetimes. The spectral and electrochemical properties of 25-oxasamaragdyrins were further enhanced by BF_2-complexation of 25-oxasmaragdyrins.[3] For example, the BF_2-oxasmargdyrins III showed a strong band at 710 nm that is three times more intense than the absorption band of free base 25-oxasmaragdyrin and also the BF_2-smaragdyrins are more fluorescent than free base smaragdyrins with decent quantum yields and singlet state lifetimes. Thus, 25-oxasmaragdyrins and their BF_2-complexes are fluorescent expanded porphyrinoids unlike many other reported expanded porphyrinoids which are generally non-fluorescent.[4]

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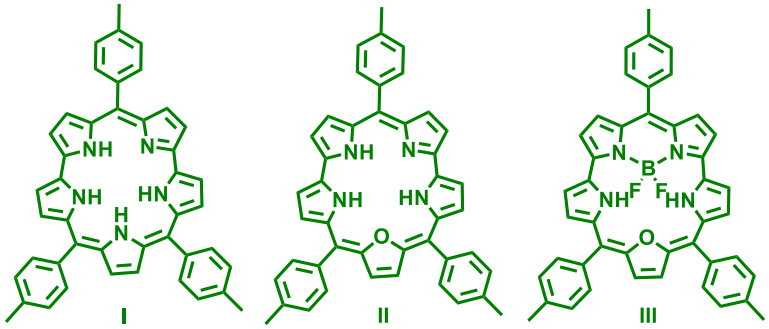


Chart 1: Structures of smaragdyrin analogues

Porphyrins, corroles and their peptide conjugates were previously used in various applications such as cellular imaging, PDT agents,[5] DSSC[6] due to their photophysical properties. As these molecules are fluorescent in the visible region, the signal to noise ratio of fluorescent signal in case of mammalian cells is very less due to auto fluorescence and scattering. It is known that the mammalian cells are quite transparent in the region of 650 nm to 900 nm. Therefore, the dyes in this region are very useful for Near Infrared Fluorescence Imaging (NIRF). Thus, there is a need for the dyes that can be easily prepared and absorbs and emits strongly in NIR region. However, to best of our knowledge, there are only handful of dyes which are fluorescent in this region like cyanine dyes,[7] squaraine dyes,[8] BODIPY analogues,[9] benzo[c]heterocycles,[10] xanthenes,[11] phthalocyanines and few porphyrin derivatives.[12] Although extensive literature is presently available on porphyrin-amino acid/peptide/protein conjugates,[13] only limited reports on contracted porphyrinoids such as corrole-amino acid conjugates,[14] and very few reports on expanded porphyrins[15] where the expanded porphyrins were linked to amino acids, peptides and proteins to form covalent conjugates which can be used for biological applications. We thought of using the fluorescent oxasmaragdyrins and their BF_2 complexes to link covalently with various amino acids to synthesize conjugates which can be used for NIR fluorescence imaging studies and other

applications. With this idea in mind, we attempted to synthesize oxasmaragdyrin/BF_2-smaragdyrin-amino acid conjugates using readily available precursors under simple reaction conditions. Herein, we report the synthesis of first examples of covalently linked meso-triaryl 25-oxasmaragdyrin-amino acid conjugates **1a-1d** and their BF_2 complexes **2a-2d** (Chart 2) and studied their photophysical and electrochemical properties. The studies indicated that the conjugates absorbs and emits strongly in visible-NIR region with decent quantum yields and singlet state lifetimes and exhibit reversible oxidation and reduction under electrochemical redox conditions.

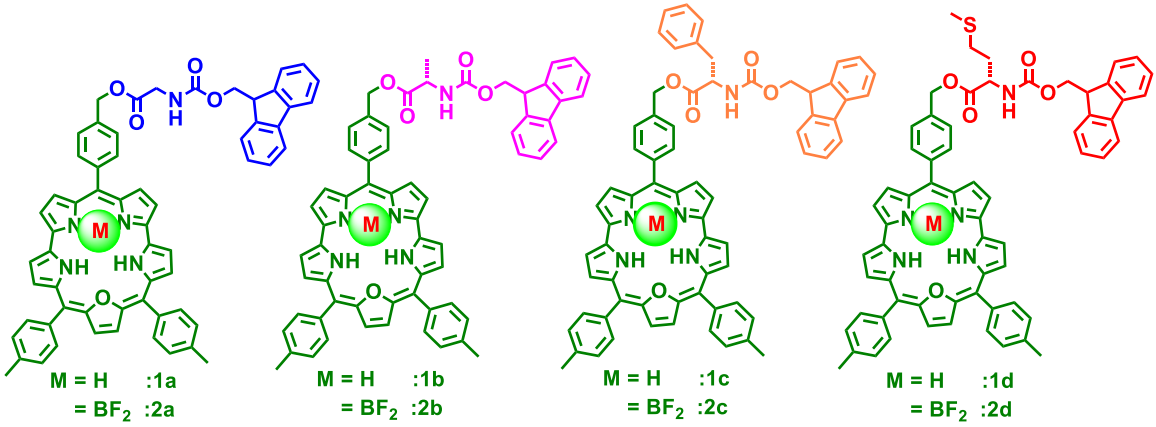


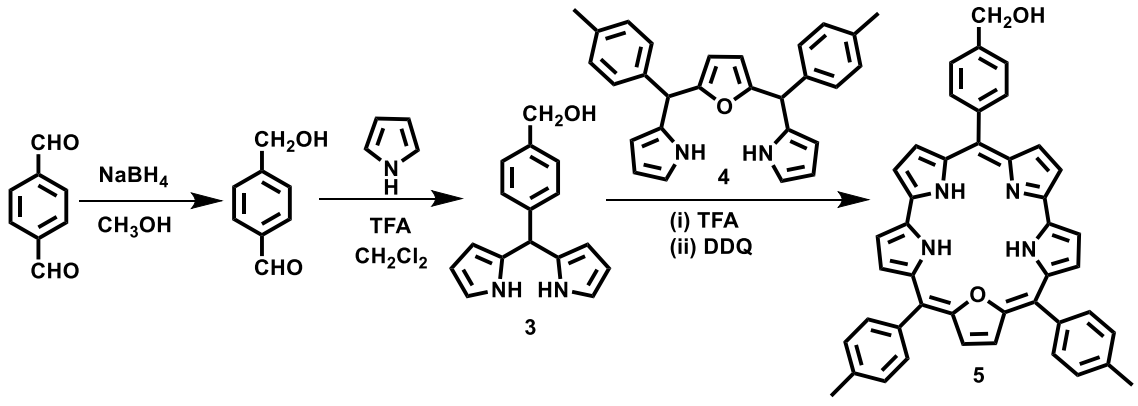
Chart 2: Smaragdyrin-amino acid conjugates and their corresponding BF_2 complexes.

Results and Discussion

Synthesis and Characterization

The required *meso*-(4-hydroxymethyl)phenyl dipyrromethane **3** was synthesized in two steps starting from commercially available 1,4-terephthalaldehyde as shown in Scheme 1. The 1,4-terephthalaldehyde was selectively reduced by treating with 0.25 equivalent of $NaBH_4$ in CH_3OH to afford 4-(hydroxymethyl)benzaldehyde in 80% yield. The 4-(hydroxymethyl)benzaldehyde was reacted with excess of pyrrole in the presence of catalytic amount of TFA in CH_2Cl_2 followed by work-up and column chromatographic

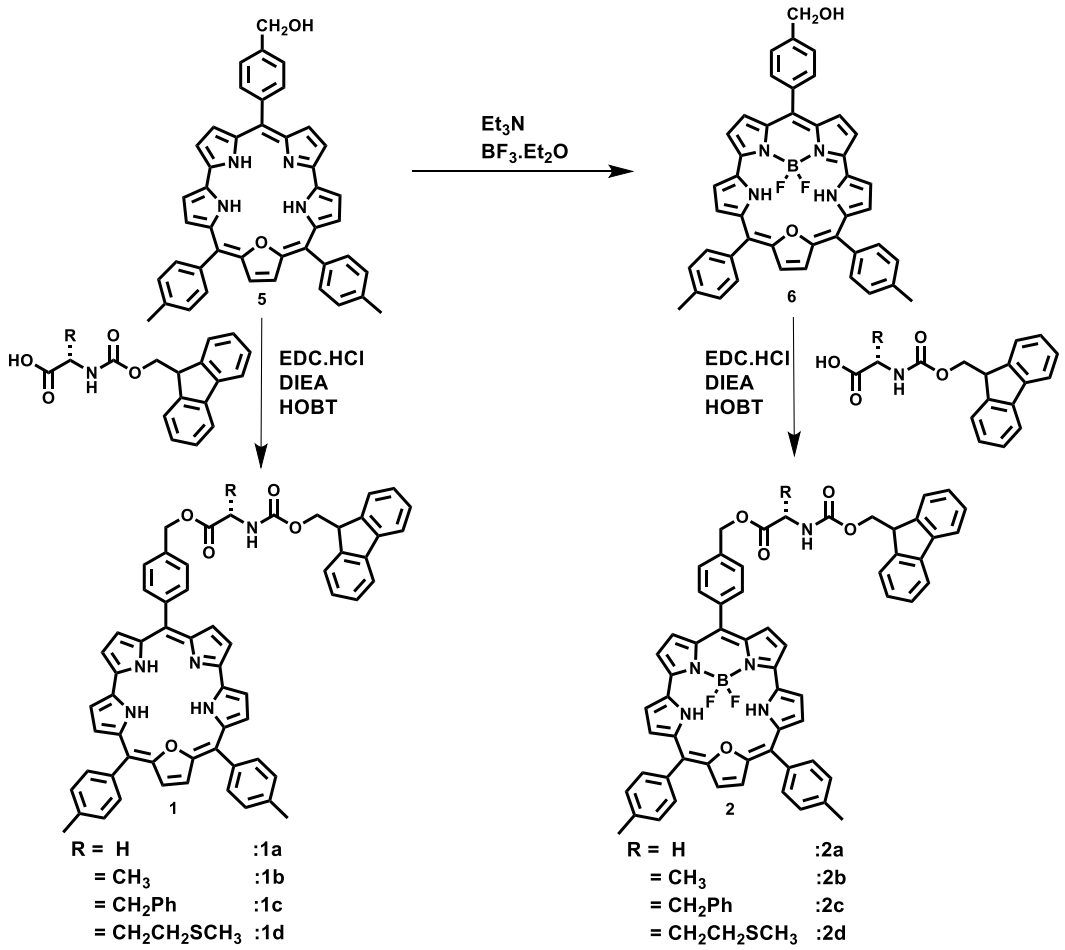
purification afforded *meso*(4-hydroxymethyl)phenyl dipyrromethane as white solid in 40% yield.[16] The other desired 16-oxatripyrrane **4** was synthesized by following the reported procedure.[17] The 25-oxasmaragdyrin **5** containing benzylhydroxyl group at one of the *meso* position was synthesized by condensing one equivalent of dipyrromethene **3** with one equivalent of 16-oxatripyrrane **4** in CH_2Cl_2 in the presence of catalytic amount of TFA for 1 h under inert atmosphere followed by oxidation with DDQ in open air for additional 1 h. The formation of the 25-oxasmaragdyrin **5** was followed by tlc analysis and absorption spectroscopy. The crude compound was purified by basic alumina column chromatography and afforded the desired functionalized 25-oxasmaragdyrin **5** in 25% yield. The formation of 25-oxasmaragdyrin **5** was confirmed by HR-MS and NMR spectroscopy. The compound **5** was treated with excess $BF_3{\cdot}OEt_2$ in CH_2Cl_2 in the presence of triethylamine for 15 min and purified the crude compound by basic alumina column chromatography to afford pure BF_2 complex of functionalized 25-oxasmaragdyrin **6** as green crystalline solid in 80% yield. The BF_2-smaragdyrin complex **6** was confirmed by HR-MS, ^1H, ^{19}F and ^{11}B NMR spectroscopy.



Scheme1: Synthesis oxasmaragdyrin **5**.

The smaragdyrin-amino acid **1** as well as BF_2 smaragdyrin-amino acid **2** conjugates were synthesized as shown in the Scheme 2. The oxasmaragdyrin **5** or its BF_2

complex **6** was reacted with appropriate Fmoc (Fluorenylmethyloxycarbonyl)-protected amino acid in CH_2Cl_2 in the presence of 1 equivalent of EDC.HCl (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride), 0.1 equivalent HOBt (Hydroxybenzotriazole) and 1 equivalent DIEA (diisopropylethylamine) at room temperature for 3 h. The tlc analysis showed the disappearance of the more polar spot corresponding to the starting material **5** or **6** and appearance of less polar spot corresponding to the desired conjugate. The crude mixture after standard work-up was purified by silica gel column chromatography and afforded the desired smaragdyrin-amino acid conjugates in 25% yields and BF_2 smaragdyrin-amino acid conjugates in 30% yields. The conjugates **1** and **2** are freely soluble in all common organic solvents and their identities were confirmed by corresponding molecular ion peak in HR-MS.



Scheme2: Synthesis of oxasmaragdyrin-amino acid conjugates **1a-d** and BF_2 complex of oxasmaragdyrin-amino acid conjugates **2a-d**.

The conjuagates **1** and **2** were characterized in detail by 1D and 2D NMR spectroscopy, absorption, fluorescence and electrochemical techniques. The representative ^{1}H NMR and ^{1}H-^{1}H COSY spectra of **2c** are presented in Figure 1. In general, covalently linked smaragdyrin-amino acid conjugates showed five sets of resonances for 10 protons corresponding to eight pyrrole and two furan protons in the region of 9 – 10.5 ppm which were identified by their location, integration, coupling constant and cross-peak connectivity in COSY NMR. The protons corresponding to amino acid moiety appeared in the region of 1.5 – 6 ppm which were also easily

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identified based on their cross peak correlations in COSY spectra. The inner NH protons of BF_2 smaragdyrin-amino acid conjugates **2** were appeared at upfield region of -3.5 ppm which were not observed in smaragdyrin-amino acid conjugates due to their involvement in rapid tautomerism. The conjugates **2** were also characterized by ^{19}F and ^{11}B NMR spectroscopy.

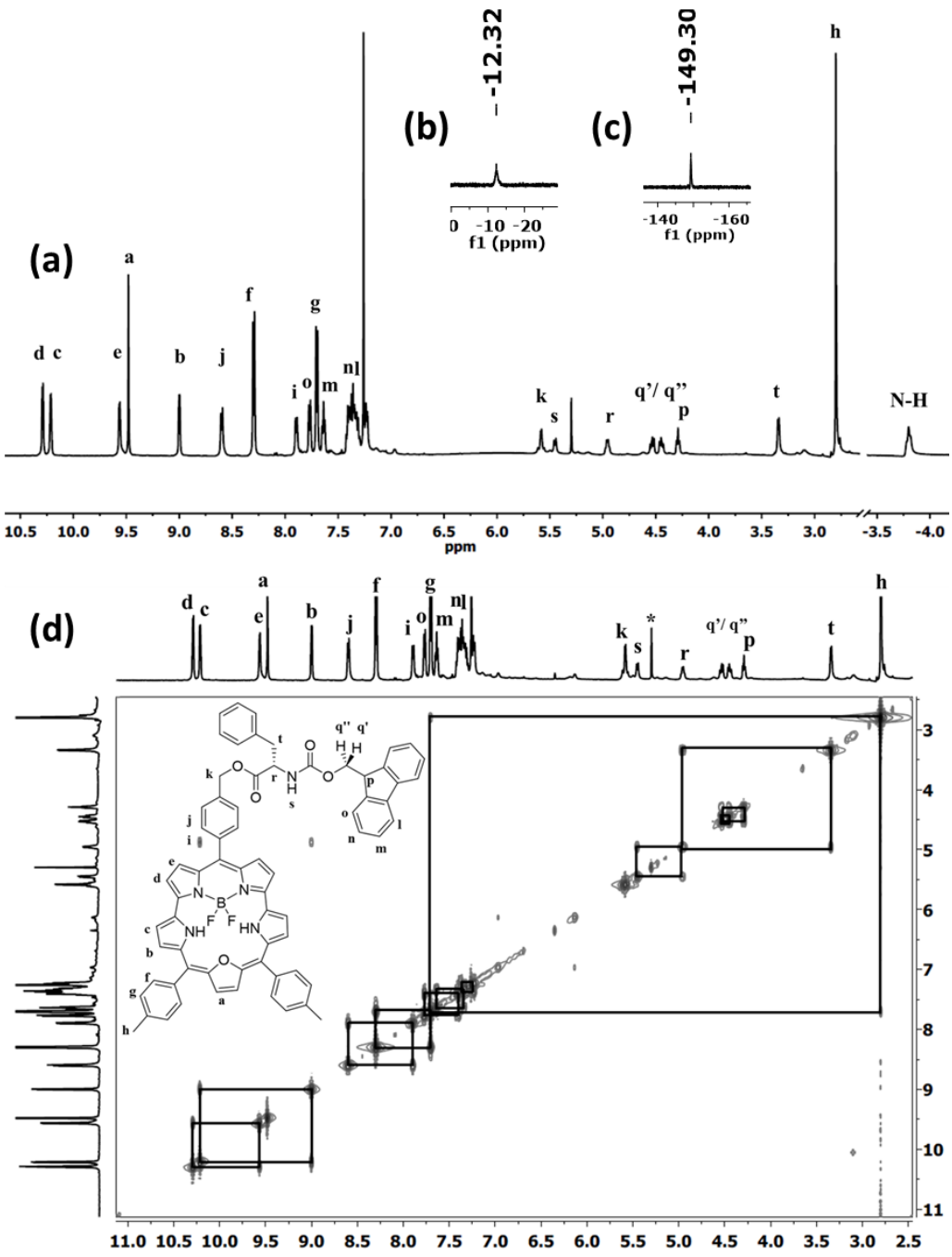

Figure 1: (a) ^{1}H, (b) ^{11}B, (c) ^{19}F, (d) ^{1}H-^{1}H COSY NMR of **2c** recorded in $CDCl_3$.

The absorption, fluorescence and electrochemical properties of free base/BF_2-smaragdyrin-amino acid conjugates **1**/**2** were studied. The comparison of absorption

spectra of smaragdyrin-phenylalanine conjugate **1c** with meso-triaryl smaragdyrin **5** is presented in Figure 2a and comparison of their corresponding BF_2- complexes is presented in Figure 2b. As clear from Figures 2a & 2b, the conjugates showed similar absorption features like smaragdyrin precursors **5** & **6** with almost no shifts in their peak maxima. However, the extinction coefficients of absorption bands of conjugates were slightly altered compared to corresponding precursors **5** & **6**.

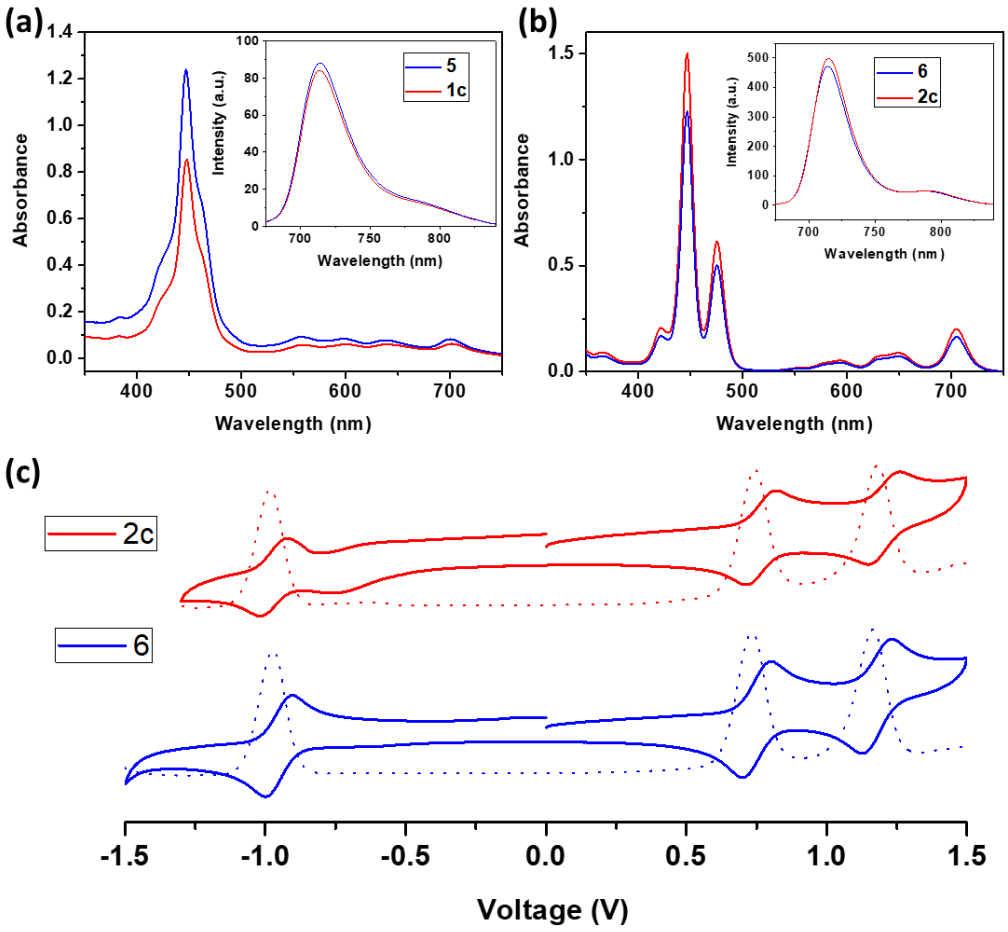

Figure 2: (a) Comparison of absorption and fluorescence (inset) spectra of **1c** and **5** recorded in $CHCl_3$; (b) Comparison of absorption and fluorescence (inset) spectra of **2c** and **6** recorded in $CHCl_3$; (c) Comparison of cyclic Voltammograms and Differential

Pulse Voltammograms of **2c** and **6** in CH_2Cl_2 containing 0.1M TBAP as supporting electrolyte using scan rate of 50 mV/sec.

The comparison of fluorescence spectra of smaragdyrin and conjugate shown as an inset in Figure 2a and comparison of fluorescence spectra of BF_2-smaragdyrin and conjugate shown as inset in Figure 2b also indicate that the linking of amino acids to smaragdyrin/BF_2-smaragdyrin did not modify the fluorescence properties of smaragdyrin/BF_2-smaragdyrin moiety supporting weak interaction between the smaragdyrin/BF_2-smaragdyrin and amiono acid moieties in conjugates.

Table 1: Absorption and fluorescence data of oxasmaragdyrin, BF_2 complexed oxasmargdyrin and their amino acid conjugates recorded in $CHCl_3$.

Compound	Wavelength (nm) (ε in $mol^{-1}L^{-1}cm^{-1}$ x10^4)						λ_f (nm)	Φ_f	τ (ns)
5	447 (12.3)	--	558 (9.2)	599 (9.3)	638 (7.7)	700 (8.1)	714	0.029	--
1c	447 (8.5)	--	558 (5.7)	599 (5.9)	638 (5.9)	700 (6.1)	714	0.026	--
6	447 (28.4)	475 (12.7)	592 (11.3)	631 (15.5)	649 (18.3)	705 (39.9)	714	0.143	4.05
2c	447 (29.9)	475 (12.2)	592 (10.5)	631 (14.8)	649 (17.8)	705 (40.4)	715	0.167	4.10

Table 2: Cyclic voltammogram data of oxasmaragdyrin, BF_2 complexed oxasmargdyrin and their amino acid conjugates recorded in CH_2Cl_2 containing 0.1M TBAP as supporting electrolyte using scan rate of 50 mV/sec with BAS electrochemical system utilizing the three electrode configuration consisting of a glassy carbon (working electrode), platinum wire (auxillary electrode) and saturated calomel (reference electrode) electrodes. All potentials were calibrated versus saturated calomel electrode by the addition of ferrocene as an internal standard, taking E1/2 (Fc/Fc+) = 0.42 V vs SCE.

Compound	Oxidation (V)		Reduction (V)	
	I	II	I	II
5	0.49	0.82	-1.32	-1.66
1c	0.46	0.77	-1.27	-1.64
6	0.73	1.16	-0.97	--
2c	0.74	1.18	-0.98	--

The electrochemical properties of conjugates **1** and **2** along with their corresponding precursors were studied in CH_2Cl_2 by cyclic voltammetry at a scan rate of 50 mV/s using tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte. The conjugates **1** and **2** also showed two reversible oxidations and one or two reversible/irreversible reduction(s) like their precursor smaragdyrin **5** and BF_2-

smaragdyrin **6** with negligible shifts in their peak potentials indicating that the rich redox chemistry of smaragdyrin/BF_2-smaragdyrin did not alter significantly by linking them with various amino acids. Thus, the spectral and electrochemical properties indicate that the smaragdyrin/BF_2-smaragdyrin and amino acid moieties did not interact strongly and the individual properties of the moieties retained in conjugates.

Conclusions

In summary, we successfully synthesized a series smaragdyrin-amino acid conjugates and BF_2-smaragdyrin-amino acid conjugates using readily available building blocks under simple reaction conditions. The conjugates were easily isolated by column chromatography and characterized in detail by HR-MS, 1D and 2D NMR spectroscopy. The spectral and electrochemical properties indicated that the conjugates showed similar rich spectral and redox properties like unconjugated smaragdyrins/BF_2-smaragdyrins without significant alteration which are very useful for their potential applications as NIR fluorescent probes in biology and medicine. The biological studies on these conjugates are currently under investigation in our laboratory.

General Experimental:

All chemicals were used as received unless otherwise noted. All solvents were of at least reagent grade and dried if necessary. The ^{1}H, ^{11}B, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 400 or 500 MHz instrument. The frequency of 101 and 126 MHz is used for ^{13}C nucleus. Tetramethylsilane [$Si(CH_3)_4$] was used as an internal standard for ^{1}H and ^{13}C NMR, tetrafluorotoluene as an external standard for ^{19}F NMR

and boric acid as an external standard for ^{11}B NMR. Absorption and steady state fluorescence spectra were obtained with Cary series UV-Vis-NIR sectrophotometer and Varian-Cary Eclipse spectrofluorometer respectively. The fluorescence quantum yield (Φ_f) were estimated from emission and absorption spectra by comparative method at the excitation wavelength of 440 nm using H_2TTP (Φ_f = 0.11) as the standard.[18] Cyclic voltammetric studies were carried out with BAS electrochemical system utilizing the three electrode configuration consisting of a glassy carbon (working electrode), platinum wire (auxillary electrode) and saturated calomel (reference electrode) electrodes. The experiments were done in dry CH_2Cl_2 using 0.1 M tetrabutylammonium perchlorate (TBAP) as supporting electrolyte. Half wave potentials were measured using DPV (differential pulse voltammetry) and also calculated manually by taking the average of the cathodic and anodic peak potentials. All potentials were calibrated versus saturated calomel electrode by the addition of ferrocene as an internal standard, taking E1/2 (Fc/Fc^+) = 0.42 V vs SCE. All the solutions were purged prior to electrochemical and spectral measurements with argon gas. The high resolution mass spectra (HRMS) were recorded with a Bruker maxis Impact and Q-Tof micro mass spectrometer. For UV-vis and fluorescence titrations, the stock solution of all compounds (1×10^{-3} M) were prepared by using HPLC grade chloroform solvent. IR spectra were recorded on a Nicolet Impact-400 FT-IR spectrometer using CsBr plates and analysed.

Synthesis of 4-(hydroxymethyl)benzaldehyde:[15]

To 1,4-terephthalaldehyde (1.0 g, 7.46 mmol) in methanol, sodiumborohydride (70.51 mg, 1.86 mmol) was added at 0 ºC and the reaction mixture was stirred at room

temperature for 3 hours. The completion of the reaction was monitored by the formation of more polar spot on TLC. After the completion of reaction, the solvent was evaporated to get crude solid. The crude solid was extracted in dichloromethane and organic layer was washed with water (3 × 25 mL). The organic layer was dried over anhydrous sodium sulphate and evaporated to give product as colourless liquid in 80% yield.

Synthesis of compound 3:[15]

To a mixture of 4-(hydroxymethyl) benzaldehyde (1.0 g, 7.34 mmol) and pyrrole (10 mL, 146.90 mmol) in dichloromethane under nitrogen atmosphere, TFA (73 µL, 0.73 mmol) was added. The resulting mixture was stirred for 10 min at room temperature and the mixture was quenched by 10% aqueous NaOH solution. The organic layer was washed with water (3 × 50 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure to give crude product which was further purified by silica gel column chromatography (petroleum ether/ethyl acetate) to give pure compound as crystalline solid (0.750 g) in 40% yield. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.98 (s, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 1.5 Hz, 1H), 6.16 (d, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 1.0 Hz, 1H), 5.46 (s, 1H), 4.66 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.80, 139.64, 132.58, 128.77, 127.53, 117.44, 108.57, 107.37, 65.20, 43.87.

Synthesis of compound 5:

To a mixture of *meso*-(4-hydroxymethyl)phenyl dipyrromethane **3** (0.310 g, 1.23 mmol), oxatripyrrane **4** (0.500 g, 1.23 mmol) in dichloromethane solvent, 0.1 equivalents of TFA (10 µL, 0.123 mmol) was added and stirred at room temperature for 1.5 hours. Then

DDQ (0.836 g, 3.69 mmol) was added to above mixture and stirred for further 1.5 hours. The reaction mixture was evaporated under reduced pressure and the crude solid was subjected to basic-alumina column chromatography using dichloromethane/petroleum ether as solvent to give pure compound as dark green solid in 25% yield. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.41 (d, *J* = 4.2 Hz, 2H), 9.34 (d, *J* = 4.3 Hz, 2H), 8.91 (d, *J* = 4.3 Hz, 2H), 8.75 (s, 2H), 8.40 (d, *J* = 4.2 Hz, 2H), 8.33 (d, *J* = 7.7 Hz, 2H), 8.08 (d, *J* = 7.8 Hz, 4H), 7.77 – 7.64 (d, *J* = 7.7 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 4H), 4.86 (s, 2H), 2.72 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 143.7, 139.6, 138.1, 137.8, 136.0, 134.7, 133.8, 131.0, 129.9, 129.3, 128.9, 128.5, 128.3, 127.9, 126.5, 126.3, 126.0, 125.2, 124.4, 119.5, 118.6, 117.7, 115.5, 108.2, 105.5, 65.1, 21.7. IR (ν cm^{-1}, $CHCl_3$) 3393, 2918, 2861, 1715, 1600, 1512, 1463, 1463, 1271, 1044, 785, 756. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (123600), 558 (9200), 599 (8321), 638 (7708), 700 (8177). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.029) Calculated mass: m/z = 651.2755, measured mass: m/z = 651.2756 $[M+H]^+$.

Synthesis of compound 1:

To the mixture of (4-(methylhydroxy)phenyl) oxasmaragdyrin **5** (50 mg, 0.077 mmol) and N-Fmoc protected amino acid (0.23 mmol) in dry CH_2Cl_2, diisopropylethylamine (60 µL, 0.346 mmol) and HOBT (37.4 mg, 0.277 mmol) were added under nitrogen atmosphere, followed by addition of EDC.HCl (54 mg, 0.277 mmol) at 0 ºC. The mixture was stirred for 12 hr. The reaction was monitored by thin layer chromatography which showed formation of less polar spot. Upon completion of reaction, the mixture was washed with 10% $NaHCO_3$ (3 × 50 mL). The organic layer was collected, dried over

anhydrous Na_2SO_4 and the solvent was evaporated to give crude product. The crude product was purified using silica gel column chromatography by EtOAc/Petroleum ether (15%) as eluent to give amino acid conjugate as green solid in 20-25% yield.

Compound 1a

Yield = 22%; ^{1}H NMR (500 MHz, Chloroform-d) δ 9.51 (d, *J* = 4.3 Hz, 2H), 9.41 (d, *J* = 4.3 Hz, 2H), 8.97 (d, *J* = 4.2 Hz, 2H), 8.81 (s, 2H), 8.50 (d, *J* = 4.2 Hz, 2H), 8.43 (d, *J* = 7.7 Hz, 2H), 8.12 (d, *J* = 7.5 Hz, 4H), 7.92 – 7.82 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 9.1 Hz, 6H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 5.58 (s, 2H), 5.41 (s, 1H), 4.44 (d, *J* = 7.1 Hz, 2H), 4.30 (d, *J* = 7.3 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 2H), 2.76 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.29, 149.2, 143.9, 141.4, 139.6, 137.9, 135.9, 134.8, 133.8, 128.6, 127.9, 127.2, 125.2, 124.4, 120.1, 119.7, 118.8, 115.7, 105.5, 67.4, 67.3, 60.5, 47.2, 43.0, 21.8. IR (ν cm^{-1}, $CHCl_3$) 2925, 2854, 2111, 1664, 1512, 1451, 1273, 1217, 1186, 1054, 782, 758. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (71900), 558 (5300), 599 (5251), 638 (5066), 700 (5363). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.015) Calculated mass: m/z = 929.3572, measured mass: m/z = 929.3579 $[M+H]^+$.

Compound 1b

Yield = 24%; ^{1}H NMR (500 MHz, Chloroform-d) δ 9.66 (d, *J* = 4.3 Hz, 2H), 9.54 (d, *J* = 4.4 Hz, 2H), 9.15 (s, 2H), 9.09 (s, 2H), 8.67 (d, *J* = 4.2 Hz, 2H), 8.56 (d, *J* = 7.6 Hz, 2H), 8.22 (s, 4H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 4H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 3H), 7.35 (t, *J* = 7.5 Hz, 2H), 5.62 (s, 2H),

5.51 (d, *J* = 7.9 Hz, 2H), 4.66 (s, 1H), 4.47 (t, *J* = 7.8 Hz, 2H), 4.30 (s, 1H), 2.78 (s, 6H), 1.66 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 156.2, 149.0, 143.7, 141.3, 139.4, 137.7, 135.7, 134.6, 133.6, 130.8, 130.3, 129.6, 128.4, 127.7, 127.1, 125.0, 124.2, 119.9, 119.6, 118.6, 115.5, 105.3, 67.3, 47.0, 42.8, 29.7, 21.6. IR (ν cm^{-1}, $CHCl_3$) 2925, 2850, 1718, 1601, 1510, 1451, 1271, 1053, 787, 758, 737. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (71900), 558 (5300), 599 (5251), 638 (5066), 700 (5363). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.015). Calculated mass: m/z = 944.3806, measured mass: m/z = 944.3802 $[M+H]^+$.

Compound 1c

Yield = 25%; ^{1}H NMR (500 MHz, Chloroform-d) δ 9.51 (d, *J* = 4.3 Hz, 2H), 9.41 (d, *J* = 4.3 Hz, 2H), 8.97 (d, *J* = 4.2 Hz, 2H), 8.81 (s, 2H), 8.50 (d, *J* = 4.2 Hz, 2H), 8.43 (d, *J* = 7.7 Hz, 2H), 8.12 (d, *J* = 7.5 Hz, 4H), 7.92 – 7.82 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 9.1 Hz, 6H), 7.41 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.38 – 7.32 (m, 8H), 7.25 (s, 2H), 5.58 (d, *J* = 5.1 Hz, 2H), 5.45 (d, *J* = 8.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.53 (dd, *J* = 10.7, 7.2 Hz, 1H), 4.45 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.29 (t, *J* = 7.0 Hz, 2H), 3.34 (d, *J* = 5.9 Hz, 2H), 2.80 (s, 6H), -3.81 (d, *J* = 10.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 155.7, 150.8, 144.0, 141.7, 141.3, 140.1, 138.9, 138.1, 136.5, 134.8, 133.2, 132.8, 131.7, 129.4, 128.5, 128.4, 127.7, 127.1, 127.0, 126.8, 126.6, 126.4, 125.3, 125.2, 125.0, 122.3, 120.6, 120.0, 118.2, 117.2, 107.8, 66.8, 65.3, 63.0, 55.0, 52.8, 47.2, 37.7, 29.8, 22.0, 21.8, 7.9, 7.8. IR (ν cm^{-1}, $CHCl_3$) 2925, 2854, 1720, 1605, 1512, 1449, 1395, 1274, 1251, 1053, 912, 793, 761, 739, 700. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (85100), 558 (5700), 599 (5967), 638 (5945), 700 (6164). Fluorescence (in chloroform)

λ_f (Φ_f) 714 nm (0.026). Calculated mass: m/z = 1020.4119, measured mass: m/z = 1020.4104 $[M+H]^+$.

Compound 1d

Yield = 20%; ^{1}H NMR (500 MHz, Chloroform-d) δ 9.51 (d, *J* = 4.3 Hz, 2H), 9.41 (d, *J* = 4.3 Hz, 2H), 8.97 (d, *J* = 4.2 Hz, 2H), 8.81 (s, 2H), 8.50 (d, *J* = 4.2 Hz, 2H), 8.43 (d, *J* = 7.7 Hz, 2H), 8.12 (d, *J* = 7.5 Hz, 4H), 7.92 – 7.82 (m, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 9.1 Hz, 6H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 5.58 (s, 2H), 5.41 (s, 1H), 4.44 (d, *J* = 7.1 Hz, 2H), 4.30 (d, *J* = 7.3 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 2H), 2.76 (s, 6H), 2.19 (s, 3H), 1.26 (d, *J* = 1.3 Hz, 2H), 0.89 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 155.7, 149.4, 144.0, 143.8, 141.4, 140.6, 139.7, 137.9, 135.6, 135.0, 134.0, 131.0, 130.4, 130.0, 129.5, 128.9, 128.5, 127.8, 127.6, 127.2, 125.2, 124.7, 120.1, 118.5, 116.0, 105.9, 67.3, 67.1, 49.9, 49.5, 47.2, 32.1, 30.2, 29.8, 29.6, 29.5, 29.1, 22.8, 21.7, 21.4, 18.9, 14.3. IR (ν cm^{-1}, $CHCl_3$) 2972, 2854, 1718, 1605, 1512, 1452, 1407, 1376, 1342, 1269, 1213, 1166, 1047, 959, 910, 787, 758, 736. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (71400), 558 (5500), 599 (5416), 638 (5267), 700 (5424). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.018).

Synthesis of compound 6:

To a mixture of oxasmaragdyrin **5** (100 mg, 0.153 mmol) and triethylamine (0.850 ml, 6.15 mmol) in dichloromethane solvent, $BF_3.OEt_2$ (1.1 ml, 8.0 mmol) was added and stirred for 30 minutes. The formation of product was checked through TLC. Upon completion of reaction, the solvent was evaporated and crude solid was subjected to

basic-alumina column chromatography using dichloromethane/petroleum ether as solvent to give pure compound as light green solid in 80% yield. ^{1}H NMR (500 MHz, Chloroform-d) δ 10.30 (d, *J* = 4.4 Hz, 2H), 10.21 (dd, *J* = 4.4, 1.9 Hz, 2H), 9.59 (d, *J* = 4.4 Hz, 2H), 9.48 (s, 2H), 9.00 (d, *J* = 3.7 Hz, 2H), 8.63 (d, *J* = 7.6 Hz, 2H), 8.32 (d, *J* = 7.7 Hz, 4H), 8.00 (d, *J* = 7.7 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 4H), 5.16 (s, 2H), 2.82 (s, 6H), -3.70 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 147.3, 144.2, 143.9, 140.8, 139.7, 138.6, 138.0, 135.1, 134.4, 133.1, 131.9, 131.6, 130.9, 130.7, 128.4, 127.1, 126.8, 125.1, 124.5, 123.7, 121.9, 120.7, 120.3, 119.0, 118.7, 107.0, 65.5, 64.7, 29.8, 21.8. ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.39. ^{19}F NMR (471 MHz, $CDCl_3$) δ -149.43. IR (ν cm^{-1}, $CHCl_3$) 3430, 2925, 2857, 1727, 1574, 1471, 1457, 1413, 1390, 1263, 1114, 1075, 1031, 760, 715, 666. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (284700), 475 (127000), 592 (11300), 631 (15500), 649 (18300), 705 (39900). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.143). Calculated mass: m/z = 698.2667, measured mass: m/z: 698.2695 [M^+].

Synthesis of compound 2:

To the mixture of BF_2-(4-(methylhydroxy)phenyl) oxasmaragdyrin **6** (30 mg, 0.04 mmol) and N-Fmoc proected amino acid (0.126 mmol) in dry CH_2Cl_2, diisopropylethylamine (33µL, 0.19 mmol) and HOBT (20.5 mg, 0.152 mmol) was added under nitrogen atmosphere. Followed by addition of EDC.HCl (29 mg, 0.152 mmol) was added at 0 ºC. The mixture was stirred for 12 hr. The reaction was monitored by thin layer chromatography which showed formation of less polar spot. Upon completion of reaction, the mixture was washed with 10% $NaHCO_3$ (3 × 50 mL). The

organic layer was collected, dried over anhydrous Na_2SO_4 and the solvent was evaporated to give crude product. The crude product was purified using silica gel column chromatography by EtOAc/Petroleum ether (15%) as eluent to give amioacid conjugate as green solid in 25-30% yield.

Compound 2a:

Yield = 28%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.28 (d, *J* = 4.5 Hz, 2H), 10.21 (dd, *J* = 4.5, 2.0 Hz, 2H), 9.56 (d, *J* = 4.5 Hz, 2H), 9.48 (s, 2H), 9.00 (dd, *J* = 4.5, 1.8 Hz, 2H), 8.60 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 8.0 Hz, 4H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 8.5 Hz, 6H), 7.41 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.37 (dd, *J* = 7.4, 1.3 Hz, 2H), 5.62 (s, 2H), 5.45 (s, 1H), 4.52 (d, *J* = 7.1 Hz, 2H), 4.33 (t, *J* = 7.2 Hz, 1H), 4.27 (d, *J* = 5.6 Hz, 2H), 2.80 (s, 6H), -3.79 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 149.9, 143.8, 143.8, 141.5, 139.7, 138.0, 135.4, 134.4, 131.9, 130.9, 130.7, 128.9, 128.4, 128.0, 127.4, 127.2, 125.2, 125.1, 124.5, 123.7, 121.9, 121.1, 120.6, 120.3, 120.2, 120.1, 119.9, 118.8, 107.0, 67.6, 58.5, 47.3, 45.9, 29.8, 29.5, 21.8, 18.2, 8.8, 8.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.28. ^{19}F NMR (471 MHz, $CDCl_3$) δ -149.32. IR (ν cm^{-1}, $CHCl_3$) 2922, 2406, 2315, 1725, 1515, 1454, 1380, 1276, 1181, 1053, 907, 780, 760, 732, 616. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (175600), 475 (75600), 592 (5890), 631 (8730), 649 (10350), 705 (23400). Fluorescence (in chloroform) λ_f (Φ_f) 716 nm (0.156). Calculated mass: m/z = 977.3565, measured mass: m/z = 977.3566 [M^+].

Compound 2b

Yield = 27%; ^{1}H NMR (500 MHz, Chloroform-d) δ 10.31 (d, *J* = 4.4 Hz, 2H), 10.23 (dd, *J* = 4.4, 2.0 Hz, 2H), 9.58 (d, *J* = 4.4 Hz, 2H), 9.50 (s, 2H), 9.02 (s, 2H), 8.63 (d, *J* = 7.7 Hz, 2H), 8.32 (d, *J* = 7.8 Hz, 4H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.78 (dd, *J* = 7.6, 3.8 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 7.0 Hz, 4H), 5.65 (s, 2H), 5.55 (d, *J* = 7.9 Hz, 1H), 4.79 – 4.62 (m, 1H), 4.51 (dt, *J* = 17.9, 9.0 Hz, 2H), 4.34 (t, *J* = 7.0 Hz, 1H), 2.82 (s, 6H), 1.69 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 149.9, 143.8, 143.8, 141.5, 139.7, 138.0, 135.4, 134.4, 131.9, 130.9, 130.7, 128.9, 128.4, 128.0, 127.4, 127.2, 125.2, 125.1, 124.5, 123.7, 121.9, 121.1, 120.6, 120.3, 120.2, 120.1, 119.9, 118.8, 107.0, 67.6, 58.5, 47.3, 45.9, 29.8, 29.5, 21.8, 18.2, 8.8, 8.3. ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.29. ^{19}F NMR (471 MHz, $CDCl_3$) δ -149.45. IR (ν cm^{-1}, $CHCl_3$) 2922, 2857, 1690, 1601, 1523, 1513, 1454, 1378, 1344, 1290, 1249, 1183, 1092, 1066, 1017, 997, 927, 909, 782, 732. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (175645), 475 (75652), 592 (6000), 631 (9000), 649 (11200), 705 (24400). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.165). Calculated mass: m/z = 943.3728, measured mass: m/z = 943.3725 [M^+].

Compound 2c

Yield = 30%; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.29 (d, *J* = 4.4 Hz, 2H), 10.21 (dd, *J* = 4.5, 2.0 Hz, 2H), 9.56 (d, *J* = 4.4 Hz, 2H), 9.48 (s, 2H), 9.00 (dd, *J* = 4.4, 1.9 Hz, 2H), 8.60 (d, *J* = 7.6 Hz, 2H), 8.30 (d, *J* = 7.5 Hz, 4H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 4H), 7.64 (t, *J* = 6.8 Hz, 2H), 7.46 – 7.32 (m, 8H), 7.26 (s, 2H), 5.58 (d, *J* = 5.1 Hz, 2H), 5.45 (d, *J* = 8.3 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.53 (dd, *J* = 10.7, 7.2 Hz, 1H), 4.45 (dd, *J* = 10.7, 7.0 Hz, 1H), 4.29 (t, *J* = 7.0 Hz, 2H),

3.34 (d, *J* = 5.9 Hz, 2H), 2.80 (s, 6H), -3.81 (d, *J* = 10.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 155.7, 149.8, 143.7, 141.3, 139.5, 137.9, 134.9, 134.2, 131.6, 130.6, 129.5, 128.7, 128.5, 128.3, 127.7, 127.3, 127.1, 125.1, 124.9, 124.2, 123.6, 121.8, 120.6, 120.2, 120.0, 106.9, 67.3, 67.1, 55.0, 47.2, 38.4, 21.6. ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.32. ^{19}F NMR (471 MHz, $CDCl_3$) δ -149.30. IR (ν cm^{-1}, $CHCl_3$) 2928, 2854, 2355, 2325, 1725, 1515, 1454, 1378, 1349, 1276, 1254, 1185, 1095, 1053, 1022, 780, 758, 739, 580. UV/Vis (Chloroform) (λ_{max}/nm, **ε** $mol^{-1}dm^3cm^{-1}$) 447 (299200), 475 (122400), 592 (105200), 631 (14800), 649 (17800), 705 (40400). Fluorescence (in chloroform) λ_f (Φ_f) 715 nm (0.167). Calculated mass: m/z = 1067.4035, measured mass: m/z = 1067.4037 [M^+].

Compound 2d:

Yield = 25%; ^{1}H NMR (400 MHz, Chloroform-d) δ 10.29 (d, *J* = 4.4 Hz, 2H), 10.21 (dd, *J* = 4.4, 1.9 Hz, 2H), 9.56 (d, *J* = 4.5 Hz, 2H), 9.48 (s, 2H), 9.00 (dd, *J* = 4.4, 1.8 Hz, 2H), 8.60 (d, *J* = 7.8 Hz, 2H), 8.30 (d, *J* = 7.9 Hz, 4H), 7.95 (d, *J* = 7.6 Hz, 4H), 7.76 (d, *J* = 5.7 Hz, 2H), 7.72 – 7.65 (m, 6H), 7.46 – 7.32 (m, 4H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 2H), 4.79 (d, *J* = 6.4 Hz, 1H), 4.52 (d, *J* = 7.0 Hz, 2H), 4.31 (t, *J* = 6.7 Hz, 1H), 2.80 (s, 6H), 2.19 (s, 3H), 1.26 (d, *J* = 1.3 Hz, 2H), 0.89 (s, 2H), -3.82 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 156.2, 150.0, 144.0, 143.8, 141.5, 139.7, 138.1, 137.6, 135.1, 134.8, 134.4, 132.1, 131.8, 131.0, 130.8, 128.6, 128.4, 127.9, 127.3, 125.2, 125.1, 124.4, 123.8, 122.0, 120.8, 120.4, 120.2, 118.2, 107.1, 67.9, 67.6, 67.3, 53.6, 53.3, 47.4, 38.9, 32.2, 32.1, 30.1, 29.8, 29.5, 22.8, 21.8, 15.8, 14.7, 14.2. ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.26. ^{19}F NMR (376 MHz, $CDCl_3$) δ -149.36. IR (ν cm^{-1}, $CHCl_3$) 2922, 2850, 2322,

1900, 1810, 1723, 1601, 1512, 1454, 1378, 1344, 1252, 1181, 1095, 1070, 1017, 758, 712. UV/Vis (Chloroform) (λ_{max}/nm, $\boldsymbol{\varepsilon}$ $mol^{-1}dm^3cm^{-1}$) 447 (244200), 475 (100200), 592 (83000), 631 (12000), 649 (14400), 705 (32800). Fluorescence (in chloroform) λ_f (Φ_f) 714 nm (0.159). Calculated mass: m/z = 1051.3755, measured mass: m/z = 1051.3766 [M^+].

Keywords: Oxasmaragdyrin, Oxasmaragdyrin-Amino Acid Conjugates, Expanded porphyrins, NIR Fluorophores

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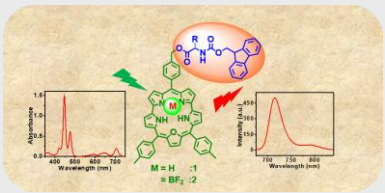

Oxasmaragdyrin-Amino Acid Conjugates

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Synthesis of Oxasmaragdyrin-Ar Acid Conjugates