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Inverse electron demand Diels–Alder reaction as the novel method of functionalization of natural chlorins

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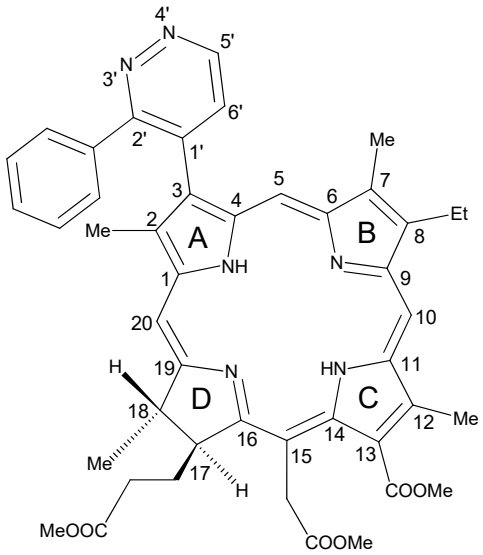

Figure S1. Atom numbering in chlorin macrocycle for compounds **2, 3** with letter symbols of pyrrole rings.

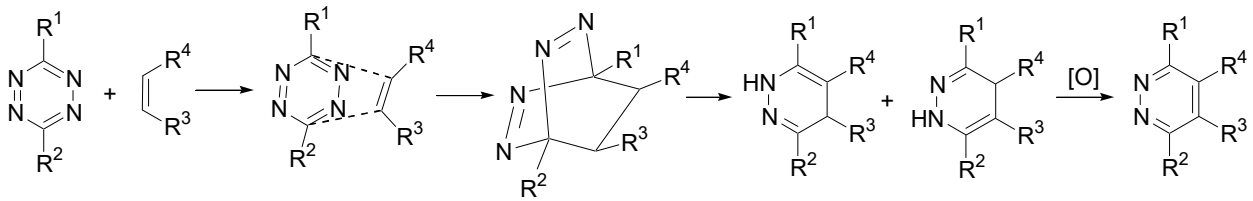

Figure S2. Schematic representation of IEEDA reaction mechanism between a dienophile and a tetrazine [S1,S2].

Experimental

Materials and methods. Tetrazines were obtained as previously described [S3]. Chlorin e_6 trimethyl ester **1** was obtained by extraction of chlorophyll *a* from *Spirulina Platensis* algae, followed by alkaline hydrolysis, methylation, and column chromatographic purification. Preparative column chromatography was performed on Merck 40/60 430 silica gel sorbent. Preparative TLC was performed on Merck TLC plates. All organic solvents were purified according to standard methods. NMR spectra were registered on Bruker DPX 300 and AVANCE-AV 600 spectrometers in $CDCl_3$. Signals of residual ^1H nuclei were used for scale calibrating. Bruker TopSpin 3.5 program was employed for NMR data processing. High resolution mass spectra were registered on Bruker micrOTOF II instrument using ESI ionization. Absorbance spectra were registered on Shimadzu UV1800 UV/VIS spectrometer in ethanol. Fluorescence spectra were recorded on CARY Eclipse spectrofluorimeter (Varian, USA). The fluorescence quantum yield was determined by the relative method. The solution of chlorin e_6 in ethanol was used as standard [S4].

General procedure for the synthesis of pyridazine–chlorin conjugates. Chlorin e_6 trimethyl ester **1** and tetrazine derivative were dissolved in DMF with stirring in a molar ratio of 1:1 at room temperature. After completion the reaction, the mixture was evaporated and dried under reduced pressure.

8-Ethyl-2,7,12,18-tetramethyl-13-methoxycarbonyl-15-(2-methoxy-2-oxoethyl)-17-(3-methoxy-3-oxopropyl)-3-(3-phenylpyridazin-4-yl)-17,18-dihydroporphyrin (**2**): Product was isolated using preparative TLC (CH_2Cl_2 : MeOH, 45:1, v/v). Yield 94%. ^1H NMR (600 MHz, $CDCl_3$, δ, ppm): 9.77 (H, s, 10-H), 9.60 (H, d, J = 4.7 Hz, 5'-H) ,9.20 (H, s, 5-H), 8.71+8.72 (H, s, 20-H), 8.07 + 8.06 (H, d, J = 4.7 Hz, 6'-H), 7.62 (2H, m, *o*-Phe), 7.12 (H, m, *p*-Phe), 7.02 (H, m, *m*-Phe), 5.42+5.40 (H, d, 18.8 Hz, 15^1-CH_2^a), 4.46 (2H, m, 18-H, 17-H), 4.30 (3H, s, 13^2-CH_3), 3.81 (3H, s, 15^3-CH_3), 3.80 (2H, q, J = 7.7 Hz, 8^1-CH_2), 3.71+3.65 (3H, s, 17^4-CH_3), 3.62 (3H, s, 12-CH_3), 3.20 (3H, s, 7-CH_3), 2.95 + 2.93 (3H, s, 2-CH_3), 2.60 (H, m, 17^2-CH_2^a), 2.28 (2H, m, 17^1-CH_2^a, 17^2-CH_2^b), 1.84 (H, m, 17^1-CH_2^b), 1.75 (3H, d, J = 18.1 Hz, 18-CH_3), 1.74 (3H, t, J = 7.7 Hz, 8^2-CH_3), -1.33(H, s, NH), -1.72 (H, s, NH). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 173.5, 172.9, 169.4, 169.2, 167.8, 162.0, 154.5, 149.6, 145.2, 138.2, 137.4, 136.3, 135.9, 134.3, 133.2, 133.1, 133.0, 131.7, 130.9, 129.5, 129.5, 128.9, 128.3, 124.4, 102.8, 102.8, 102.1, 99.4, 94.2, 94.1, 53.3, 52.1, 51.7, 49.3, 38.5, 31.9, 29.71, 23.1, 19.66, 17.64, 14.11, 12.43. ESI-HRMS: m/z calc. for $C_{45}H_{46}N_6O_6$ [M + H^+]: 767.3552, found: 767.3542, m/z calc. for [M + Na^+]: 789.3371,

found: 789,3357. UV/VIS (EtOH): λ_{max}, nm (ε, $M^{-1}sm^{-1}$): 395 (178000), 497 (17500), 524 (4500), 603 (5000), 665 (72000)

3-[3-(4-Carboxyphenyl)pyridazin-4-yl]-8-ethyl-2,7,12,18-tetramethyl-13-methoxycarbonyl-15-(2-methoxy-2-oxoethyl)-17-(3-methoxy-3-oxopropyl)-17,18-dihydroporphyrin (**3**): Product was isolated using preparative TLC (CH_2Cl_2 : MeOH, 20:1, v/v). Yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 9.76 (H, s, 10-H), 9.63 (H, d, *J* = 4.6 Hz, 5'-H), 9.16 (H, s, 5-H), 8.69 (H, s, 20-H), 8.12 + 8.09 (H, d, *J* = 4.6 Hz, 6'-H), 7.68 (4H, m, Phe), 5.40+5.38 (H, d, 18.8 Hz, 15^1-CH_2^a), 4.43 (2H, m, 18-H, 17-H), 4.28 (3H, s, 13^2-CH_3), 3.79 (3H, s, 15^3-CH_3), 3.77 (2H, q, *J* = 7.7 Hz, 8^1-CH_2), 3.68+3.64 (3H, s, 17^4-CH_3), 3.61 (3H, s, 12-CH_3), 3.17 (3H, s, 7-CH_3), 2.91 + 2.89 (3H, s, 2-CH_3), 2.61 (H, m, 17^2-CH_2^a), 2.34 (2H, m, 17^1-CH_2^a, 17^2-CH_2^b), 1.83 (H, m, 17^1-CH_2^b), 1.72 (3H, d, *J* = 18.1 Hz, 18-CH_3), 1.72 (3H, t, *J* = 7.7 Hz, 8^2-CH_3), -1.76 (H, s, NH), -1.81 (H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 173.6, 173.0, 172.9, 169.8, 169.3, 168.2, 167.8, 161.1, 154.4, 149.9, 149.7, 145.3, 142.1, 137.8, 137.7, 136.4, 136.0, 133.9, 133.7, 132.1, 131.5, 131.4, 131.1, 130.4, 130.0, 129.6, 124.5, 102.9, 102.8, 102.0, 99.2, 94.4, 52.2, 51.7, 49.2, 38.5, 31.0, 29.7, 29.4, 23.1, 22.9, 19.6, 18.9, 17.7, 14.1, 12.4, 11.8, 11.3. ESI-HRMS: m/z calc. for $C_{46}H_{46}N_6O_8$ [M + H^+]: 811.3450, found: 811.3432, m/z calc. for [M + Na^+]: 833.3269, found: 811.3450, UV/VIS (EtOH): λ_{max}, nm (ε, $M^{-1}sm^{-1}$): 397 (154000), 498 (17500), 524 (5500), 605 (5000), 667 (59000)

References

S1. B. L. Oliveira, Z. Guo and G. J. L. Bernardes, *Chem. Soc. Rev.,* 2017, **46**, 4895.

S2. A. M. Prokhorov and D. N. Kozhevnikov, *Chem. Heterocycl. Compd.*, 2012, **48**, 1153 (*Khim*. *Geterotsikl. Soedin*., 2012, 1237).

S3. N. K. Devaraj, M. R. Karver, S. A. Hilderbrand and R. Weissleder, *Patent US 20150246893 A1*, 2015.

S4. A. Kay, R. Humphry-Baker and M. Graetzel, *J. Phys. Chem.*, 1994, **98**, 952.

NMR data

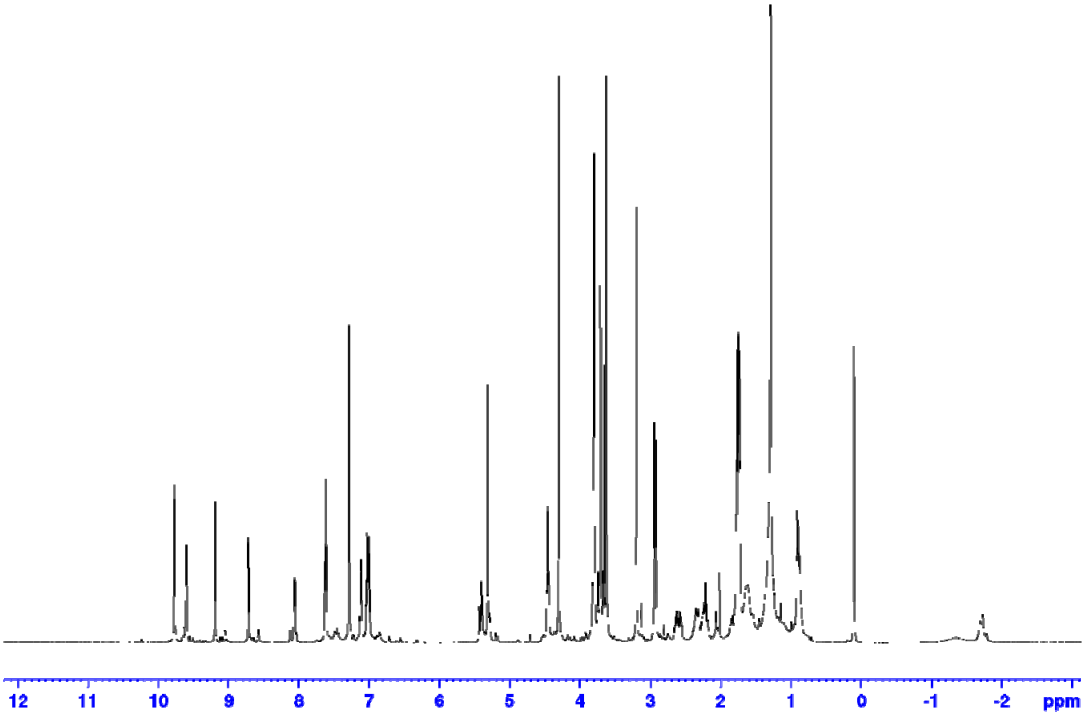

Figure S3. ^{1}H NMR for **2**.

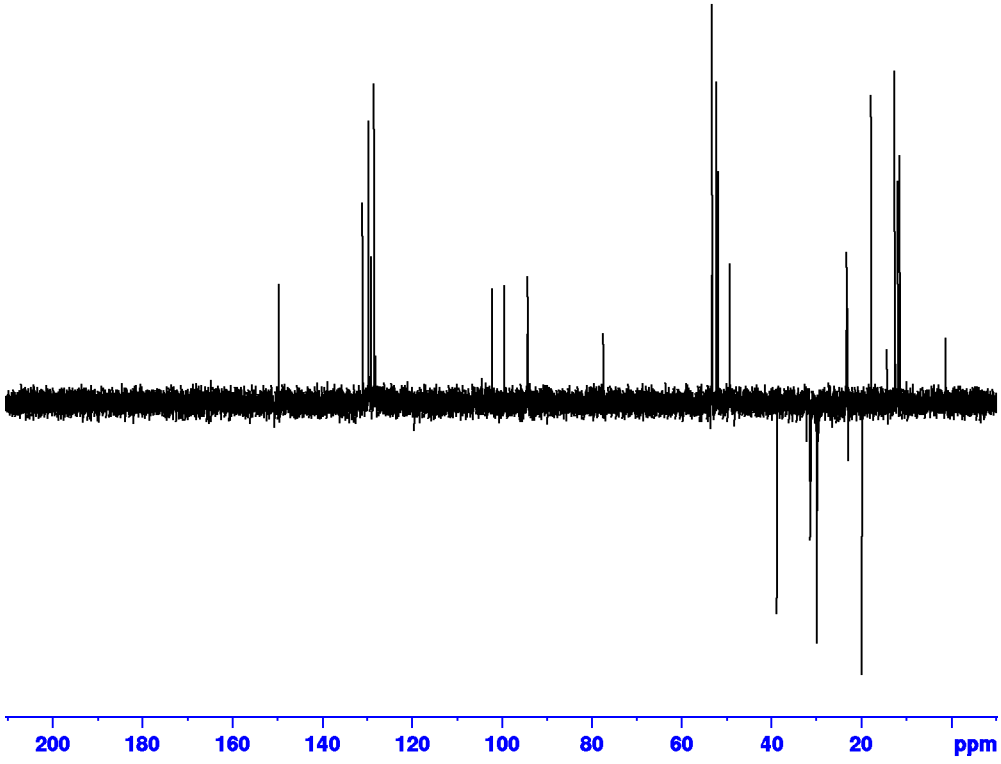

Figure S4. ^{13}C DEPT135 for **2**.

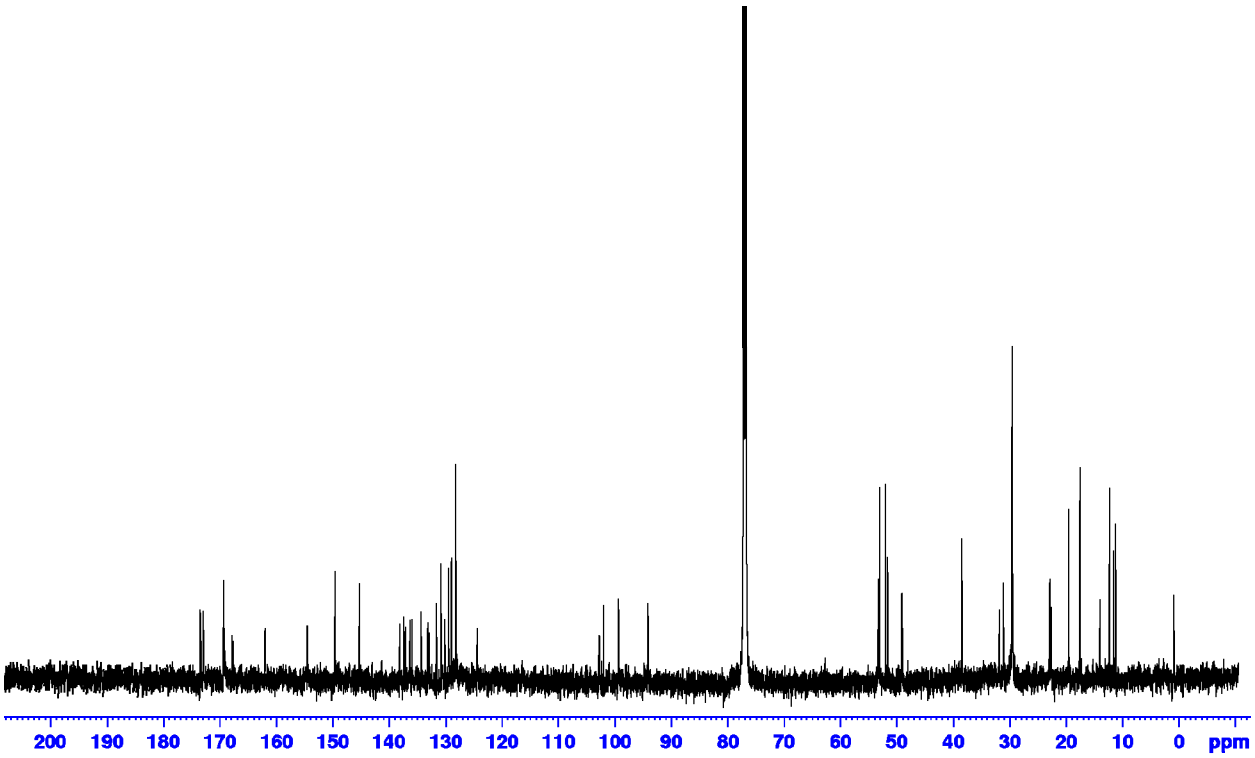

Figure S5. ^{13}C NMR for **2**.

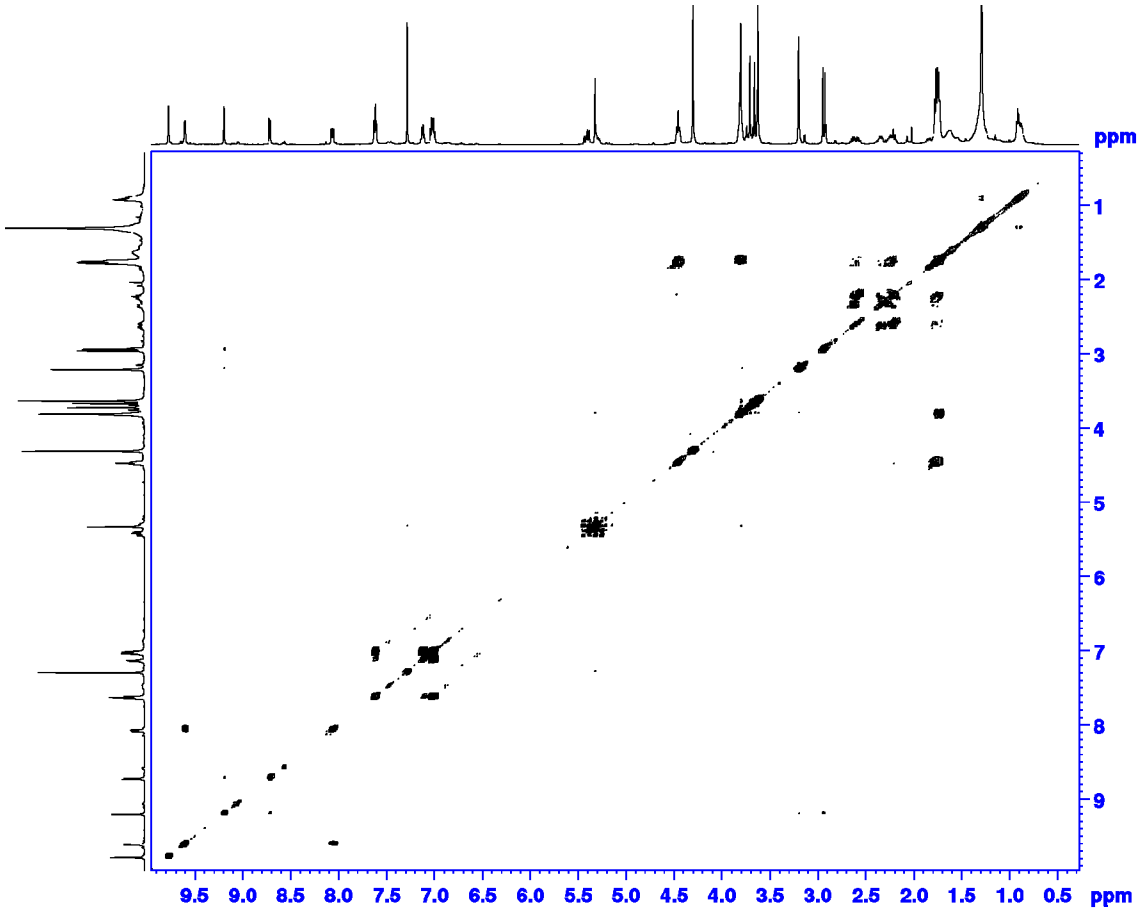

Figure S6. ^{1}H,^{1}H COSY for **2**.

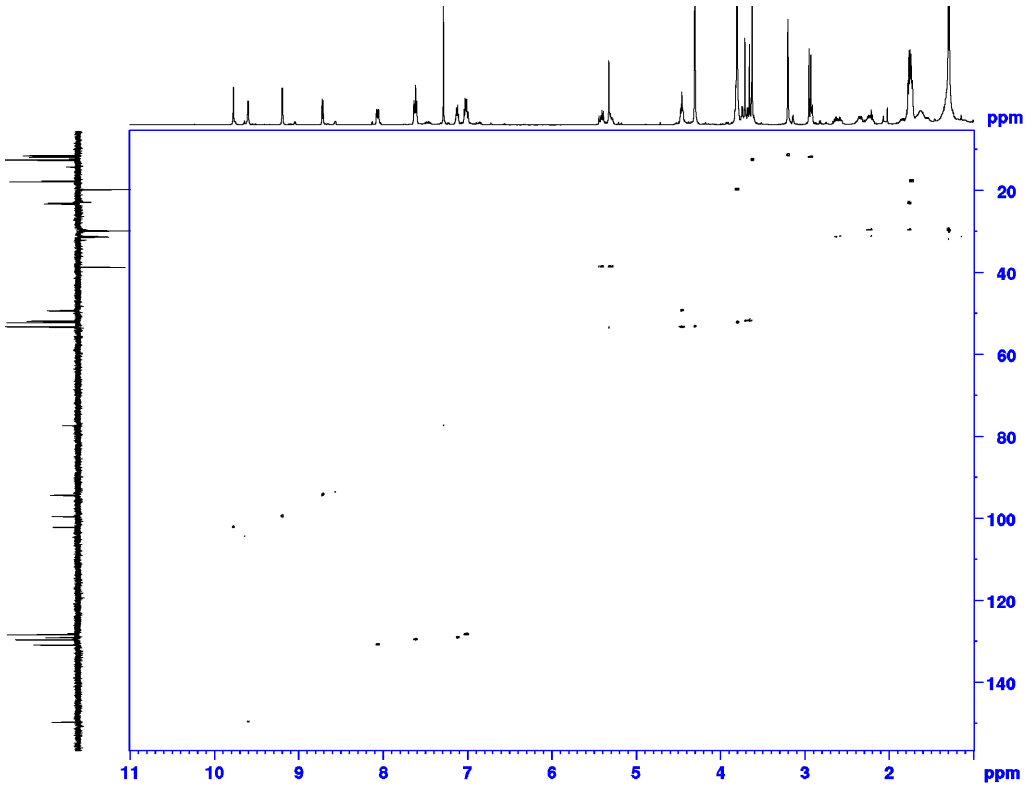

Figure S7. $^{1}H,^{13}C$-HSQC for **2**.

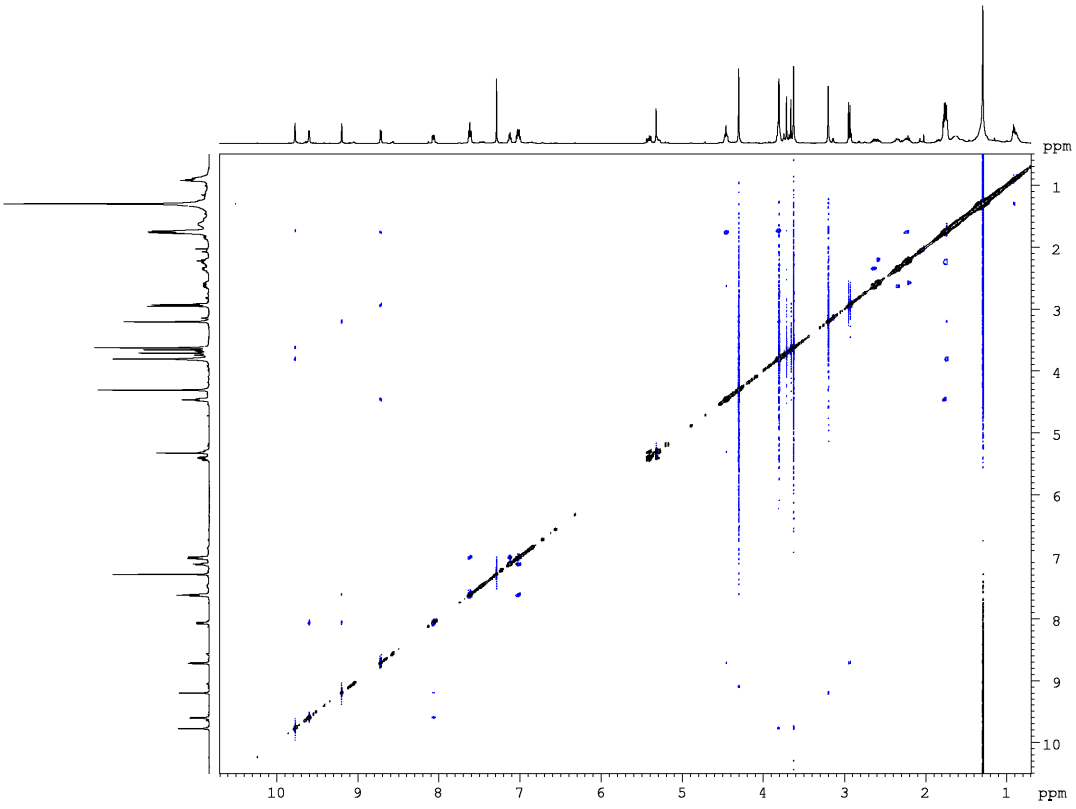

Figure S8. $^{1}H,^{1}H$-NOESY for **2**.

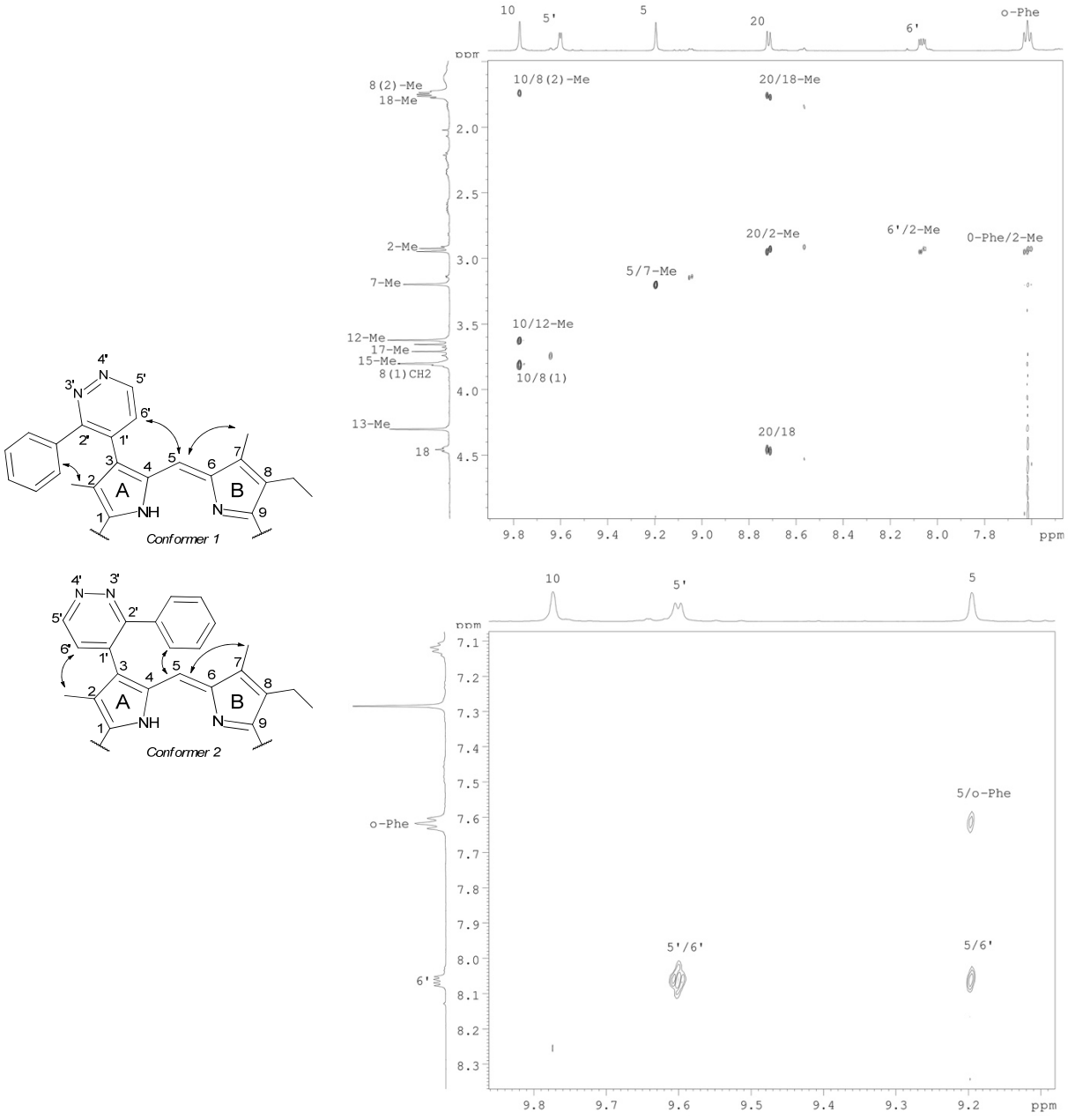

Figure S9. Fragment of the structures of conformers of compound **2** (the arrows show the NOE effects) and ^{1}H,^{1}H-NOESY fragments with assignment.

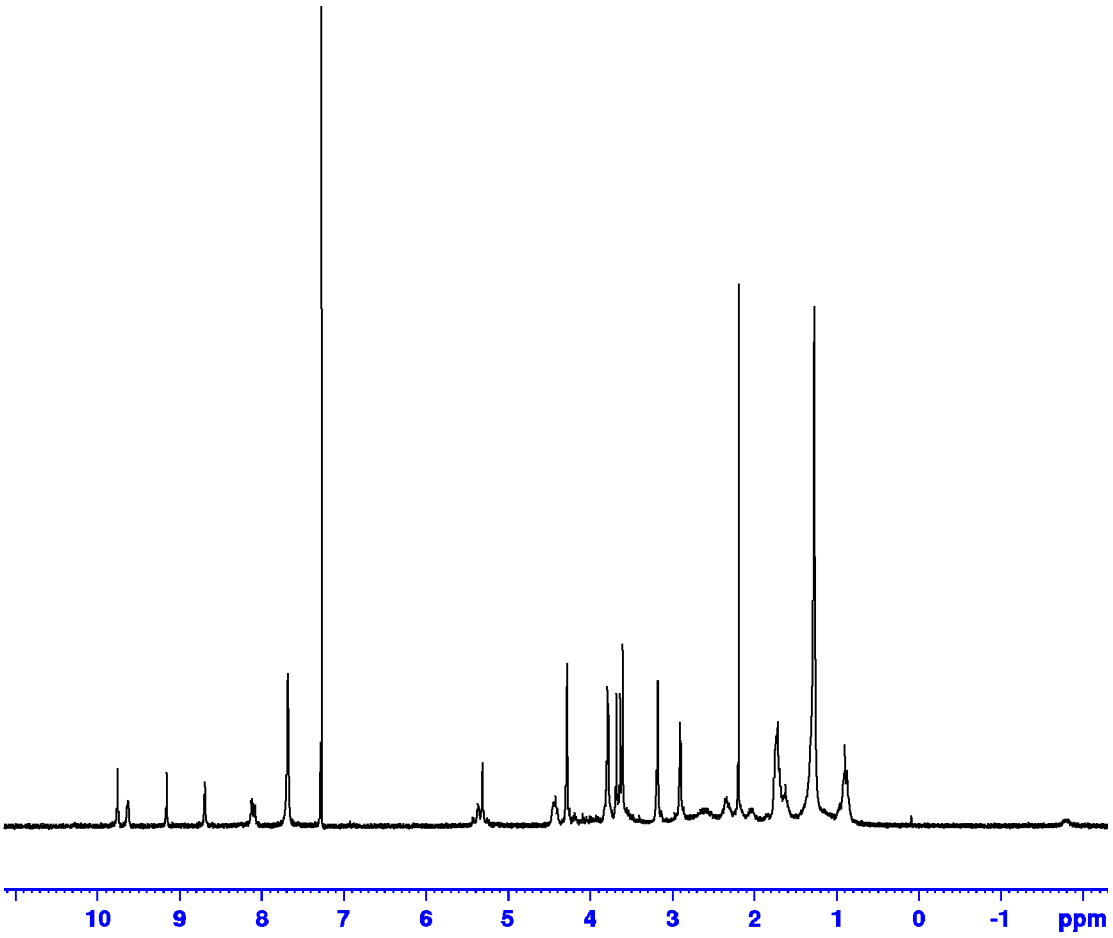

Figure S10. ^{1}H NMR for **3**.

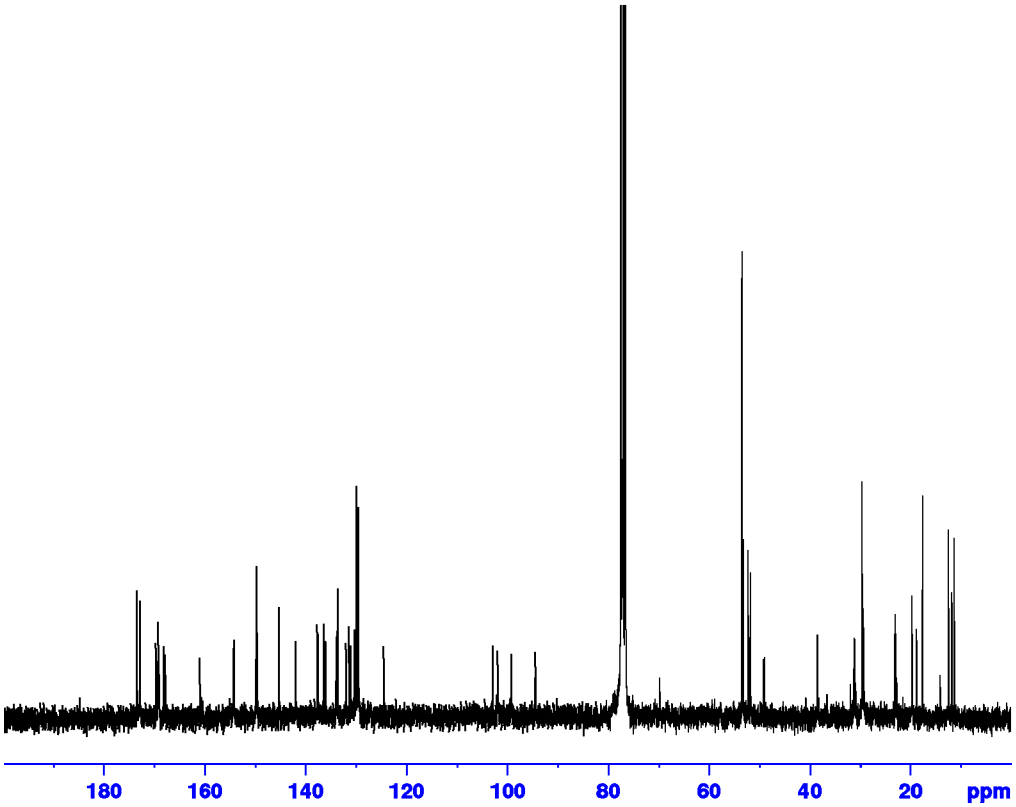

Figure S11. ^{13}C NMR for **3**.

Mass spectrometry data

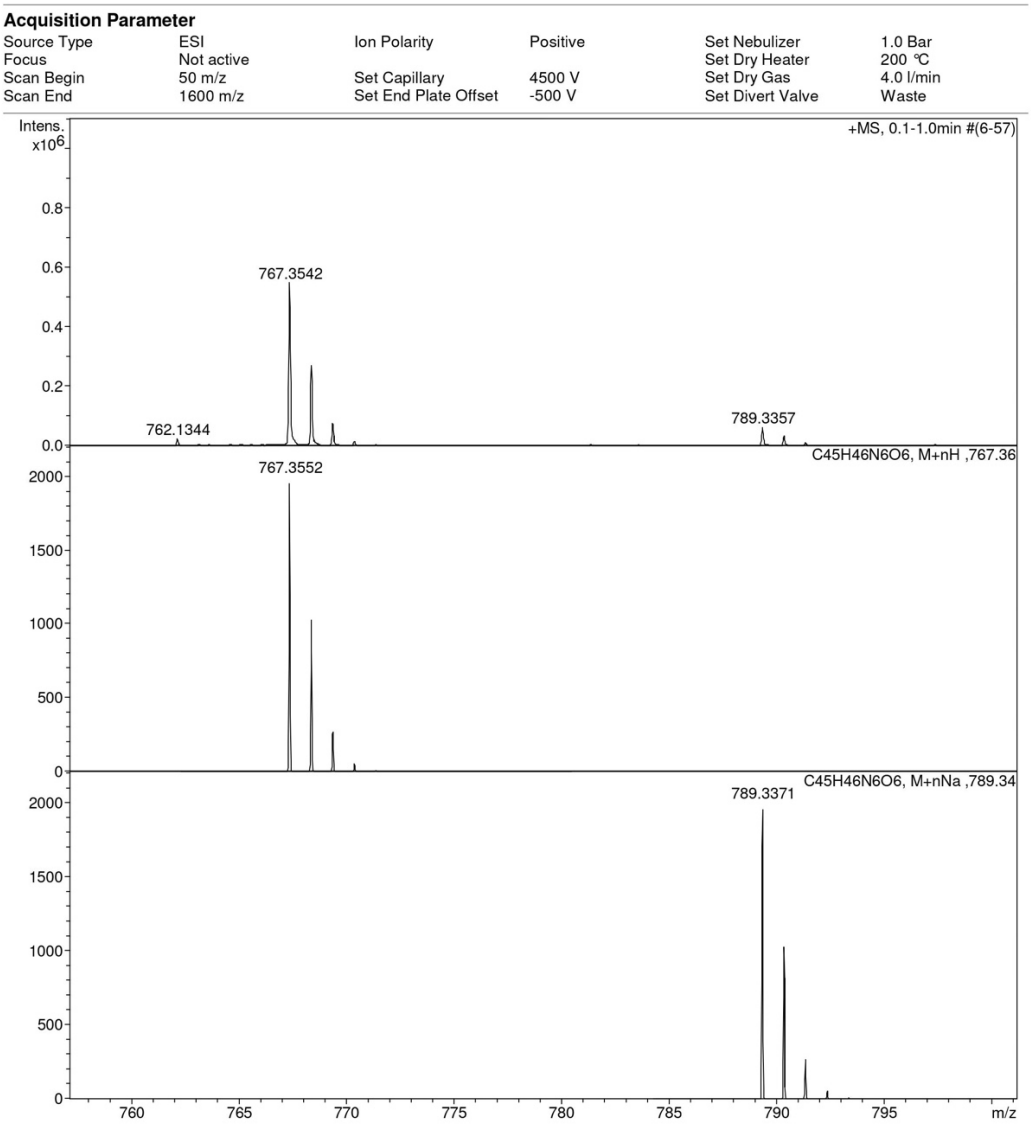

Figure S12. ESI-HRMS of compound **2**.

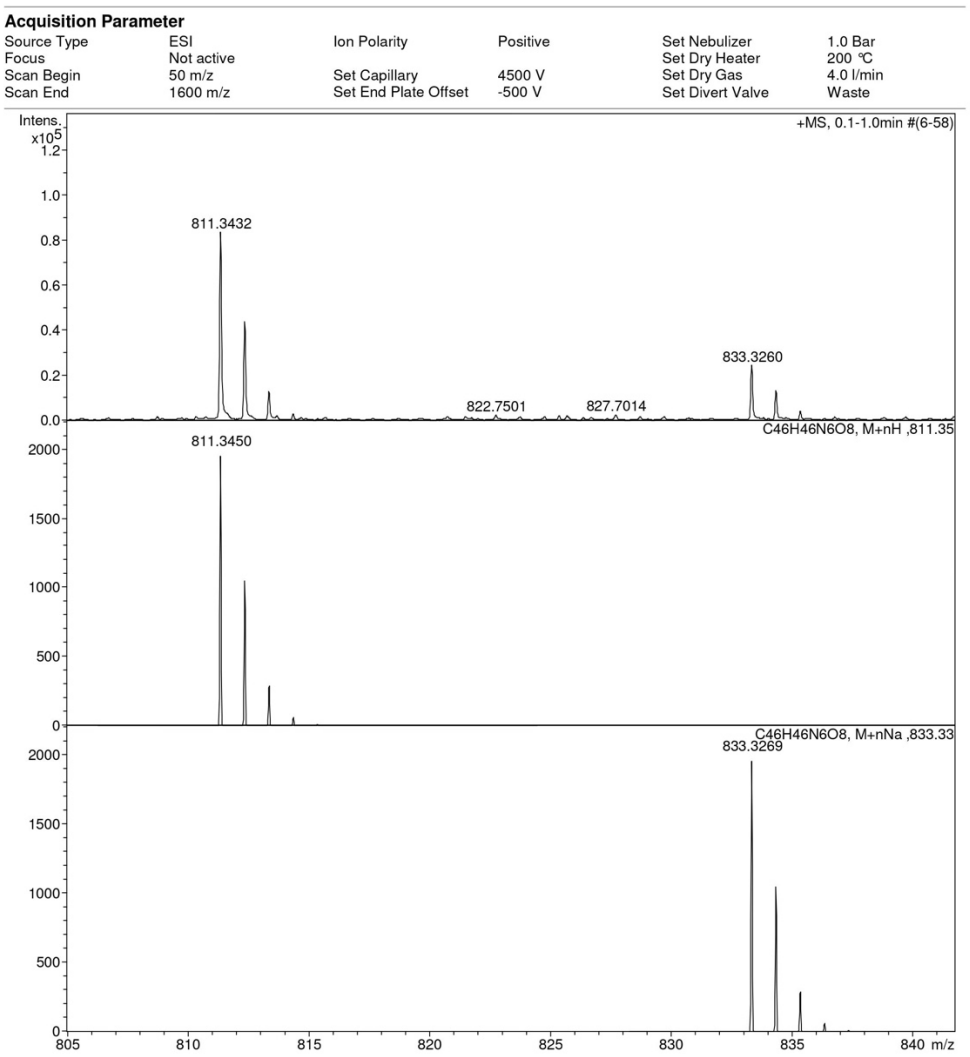

Figure S13. ESI-HRMS of compound **3**.