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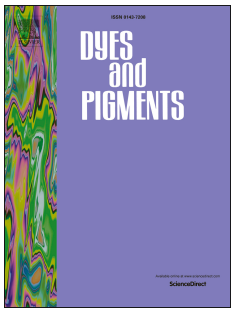

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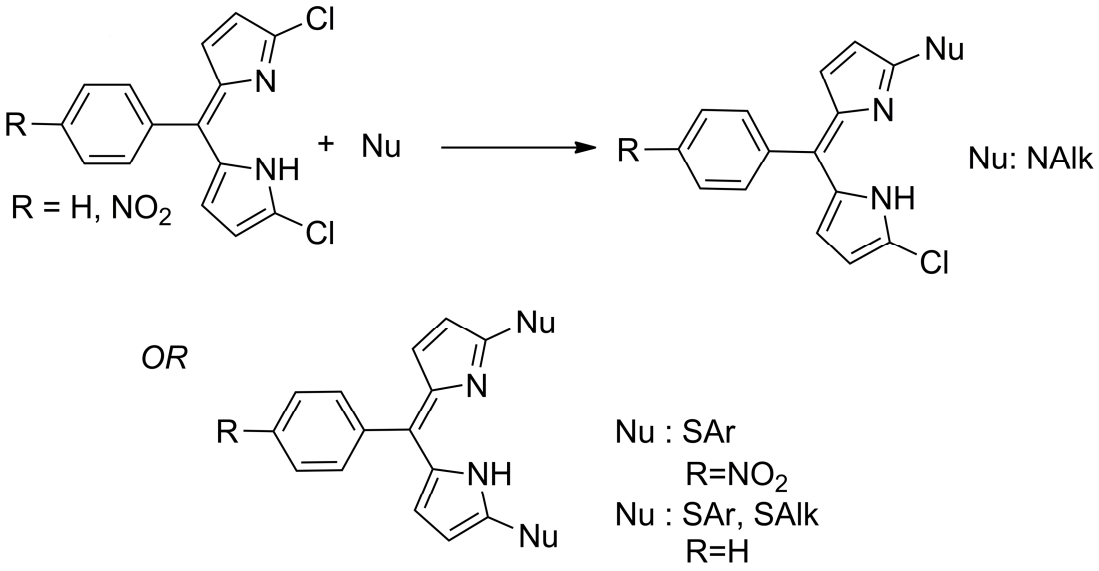

S_NAr Nucleophilic substitution of 1,9-dihalodipyrrins by S and N nucleophiles. Synthesis of new dipyrrins bearing pendant substituents.[1]

Evgenia Leushina, Ksenia Tikhomirova, Anastasiya Permyakova, Pavel Ilin, Maria Terenina, Alexander Anisimov, Andrey Khoroshutin*

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Abstract

5-Aryl-1,9-dichlorodipyrrins react with a series of S and N nucleophiles (both alkyl and aryl containing ones). Reagents with mercapto group yield product of double nucleophilic substitution of 5-pheny-1,9-dichlorodipyrrin, i.e. the respective 1,9-bis(alkyl- of arylthio)dipyrrin. On the contrary, 5-(4-nitrophenyl)-1,9-dichlorodipyrrin causes disulfides formation from the S-aliphatic substrates, whereas nucleophilic substitution remains the main path of the reaction for S-aryl ones. Reaction of N-Alkyl nucleophiles proceeds as mono-substitution. UV-Vis spectra feature batochromic shift for bis-S-substituted products and a hypsochromic shift for mono-N-substituted ones, with respect to the starting dichlrorides.

[1] Part of this work was reported at 6th EuCheMS Conference on Nitrogen Ligands in Coordination Chemistry, Metal-Organic Chemistry, Bioinorganic Chemistry, Materials and Catalysis, Beaune, France, September 13-17.

Keywords

1,9-dihalo-*H*-dipyrrins, nucleophilic substitution, S-nucleophiles, N-nucleophiles, UV-Vis spectra, NMR

Introduction

Dipyrrins (DPs) and their metal complexes [1, 2] are attracting much of researchers attention, in spite of being somewhat in the shade of their boron derivatives (BODIPY) [3-6]. DP-metal complexes have been studied for applications in dye-sensitized solar cells [7-9], catalysis[10] and as new fluorescent dyes.[11] They have been studied as prospective substance of anti-tumor activities[12-14] Besides, DP-metal complexes can govern the geometry and composition of supramolecular aggregates[15, 16] depending on both the mode of metal coordination and the geometry and steric demand of a DP ligand. [17-19] These factors also control the formation of metal-organic frameworks. [20, 21] Extensive studies focused on the substutients' influence on the energies of the ground and excited states manifested in their redox properties and optical spectra. .[22] Additional substituents at the periphery of DP bearing extra complexing groups had also been shown to drastically change complexes properties. [23, 24]

Known synthetic pathways to substituted DPs include condensation of substituted pyrroles. [25-32] Also, series of methods such as electrophilic substitution, oxidative couplings, a direct H-substitution and halogenation-Pd-catalyzed cross coupling sequences have been shown to work for BODIPY derivatization[33, 34] as well as conversion of a methyl group adjacent to the electronegative heterocycle to a double bond and nucleophilic substitution at the BODIPY core. [5] Some examples of these methods applied to non-borylated dipyrrins can be also found in the literature. [35] Research groups of Thompson, Ravikanth and Hao have developed synthetic methods leading to H-dipyrrins based on F-BODIPY deborylation by boron trihalides[36] or other Lewis acids[37], as well as by potassium tert-butoxide [38, 39]. However

the scope of these methods is rather limited, e.g. no dipyrrins possessing groups with substantial Lewis basicity are reported to stand these BF_2-removal conditions.

On the other hand no accounts on an aromatic nucleophilic substitution in free dipyrrins are found in the literature, although there are papers on the reactions of C-, S-, N- and O-nucleophiles with more electrophilic 1,9-dichloroBODIPY.[40] We were interested in the access to 1,9-disubstituted dipyrrins that possess additional pendant complexing substituents. 1,9-Modification of the dipyrrin framework was employed for the sterical encumbering to be used in catalysis[27, 41], the extension of a π-conjugation (regulated both by metal complexation[42] and hydrogen bonding[38]), used in photophysical applications.

This communication reveals first results of the study. It is aimed at filling this gap, being focused on the either bulky substrates or those possessing additional coordinating substituents. As there is an NH acidic proton in the dipyrrin, reaction of 5-aryl-1,9-dichlorodipyrrins **1** with C-nucleophiles is more difficult to study, so at first we limited the scope to N-, O- and S-nucleophiles

Materials and Methods

All solvents were distilled before use. Reagents were purchased from Aldrich and Acros companies, solvents were bought from Reakhim. CH_3CN and triethylamine have been distilled from CaH_2. 1,9-dichloro-5-(4-nitrophenyl)-dipyrromethene, 1,9-dichloro-5-phenyl-dipyrromethene [43], methyl 2-mercaptobenzoate [44], methyl mercaptoacetate [45], and methyl 3-mercaptopropanoate [46] were prepared according to the literature procedures.

NMR spectra, unless otherwise stated, were recorded on Bruker Avance 400 spectrometer, at 400.13 MHz for ^1H (standard – HMDS, 0.05 ppm) and 100.13 for ^{13}C (standard – ^{13}C signal of the solvent, 77.0 ppm for $CDCl_3$). For APT experiments, signals of secondary and quaternary atoms are marked with an asterisk.

LDI-TOF spectra have been collected on Bruker Daltonics Autoflex II spectrometer, samples were irradiated by N_2 laser (λ = 337 nm), accelerating voltage 19 kV. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI) [47]. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V); mass range from m/z 50 to m/z 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for solutions in methanol (flow rate 3 μL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180 °C.

TLC has been performed on DC-Alufolien Kieselgel 60 F254 plates (Merck). Kieselgel 60 0.063-0.200 мм (Merck) was used for column chromatography.

UV-Vis spectra were measured on Agilent-8453, in all cases a drop of Et_3N had been added to the sample before measurement. Extinction coefficients were reported for $5 \cdot 10^{-5}$ M concentrations, unless otherwise stated.

General procedure for nucleophilic substitution.

Dichlorodipyrrin (1 eq.) and dry acetonitrile were placed to three necked round bottom flask equipped with magnetic stirring bar, stoppered by rubber septa and flushed with argon *via* needles. Then a solution of the nucleophile (*ca.* 4 eq.) in CH_3CN and triethylamine (*ca.* 6 eq.) have been added by the syringe, reaction flask was immersed into an oil bath heated to 65^{o}C (unless otherwise specified). After a specified time period, the solvent was removed on rotary evaporator, the residue was dried on the vacuum line at $5*10^{-2}$ Torr at 80-90^{o}C to remove the base and one of the substrates and processed as cited below.

1,9-bis(methoxycarbonylmethylthia)-5-phenyl dipyrrin (**7**)**. 1a** (8.9 mg, 30.1 μmol) in 4 ml of CH_3CN and **3a** (13.1 mg, 124 μmol) in 6 ml of CH_3CN and Et_3N (17 μl, 12.4 mg, 122 μmol), rxn time 48 h, purified by TCL Al_2O_3 neutral, hexane/$CHCl_3$ 2:1 + 1% CH_3OH. **7**: (6.4 mg, 14.93 μmol, 49%). ^{1}H NMR ($CDCl_3$): δ = 3.79 (6H, s), 3.88 (4H , s), 6.38 (2H, d, *J* = 4.1 Hz),

6.44 (2H, d, *J* = 4.1 Hz), 7.36-7.44 (5H, m) ppm. ^{13}C NMR ($CDCl_3$) δ= 35.56, 52.76, 120.42, 127.60, 128.58, 128.79, 130.77, 134.41, 136.77, 141.76, 147.65, 170.02 ppm. LDI-TOF: m/z = 429 $[M+H]^+$, 467$[M+K]^+$. HRMS (ES): $C_{21}H_{21}N_2O_4S_2$ Found 429.0921 Calculated 429.0337. λ_{max} = 453 nm (ε=2.4×10^4 M^{-1}cm^{-1}).

1,9-bis(2-methoxycarbonylethylthia)-5-phenyl dipyrrin (**8**)**. 1a** (25.1 mg, 86.8 μmol) in 10 ml of CH_3CN and **3b** (41.7 mg, 347 μmol) in 4 ml of CH_3CN and Et_3N (48 μl, 35.2 mg, 348 μmol), rxn time 120 h, purified by TCL Al_2O_3 neutral, hexane/$CHCl_3$ 2:1 . **8**: (33.0 mg, 72.3 μmol, 83%). ^{1}H NMR ($CDCl_3$): δ = 2.73 (4H, t, *J* = 7.2 Hz), 2.91 (4H, t, *J* = 7.2 Hz), 3.69 (6H, s), 6.38 (2H, d, *J* = 4.1 Hz), 6.44 (2H, d, *J* = 4.1 Hz), 7.36-7.44 (5H, m) ppm. ^{13}C NMR ($CDCl_3$) δ= 28.87*, 34.42*, 51.88, 120.77, 127.72, 128.44, 128.64, 130.75, 133.61*, 136.63*, 141.91*, 148.24*, 172.06* ppm. LDI-TOF: m/z = 458 $[M]^+$. HRMS (ES): $C_{23}H_{25}N_2O_4S_2$ Found 457.1242 Calculated 457.1250. λ_{max} = 456 nm (ε=1.9×10^4 M^{-1}cm^{-1}).

Nucleophilic substitution of 1a with 3b – conversion and products distribution. All the experiments have been carried out according to the general procedure. After the evaporation and high vacuum drying reaction mixtures have been analyzed by NMR.

Methyl 3-({(2Z)-2-[(5-chloro-1H-pyrrol-2-yl)(phenyl)methylene]-2H-pyrrol-5-yl} thio)propanoate (7') 1a (30 mg, 104 μmol) in 8 ml of CH_3CN and **3b** (50.6 mg, 374 μmol) in 2 ml of CH_3CN and Et_3N (54 μl, 39.3 mg, 728 μmol), rxn time 17 h. Reaction mixture has been evaporated to dryness, then oily orange residue has been subjected to heating(95^{o}C, 40 min) at high vacuum (1·10^{-2-} Torr) for the nucleophile excess to be dried off. The product was isolated by column chromatography (SiO_2 neutral, petroleum ether/ethyl acetate 4:1). **7'**: (13.5 mg, 34.8 μmol, 33%).): ^{1}H NMR ($CDCl_3$) δ = 2.83 (2H, t, J = 7.2 Hz), 3.31 (2H, t, J = 7.2 Hz), 3.72 (3H, s), 6.33 (1H, d, J = 4.2 Hz), 6.48 (1H, d, J = 4.2 Hz), 6.25 (1H, d, J = 4.2 Hz), 6.54(1H, d, J = 4.2 Hz), 7.40 (5H, m). ppm. ^{13}C NMR ($CDCl_3$) δ= 28.63, 29.28, 33.92, 51.5 8, 117.53,

118.64, 127.36, 128.68, 130.37, 135.62, 171.51 ppm. LDI-TOF: m/z = 373 $[M]^+$. HRMS (ES): $C_{20}H_{20}ClN_2O_2S$ Found 373.0778 Calculated 373.0772. λ_{max} = 454 nm (ε=0.9×10^4 $M^{-1}cm^{-1}$).

1,9-bis(4-methylphenylthia)-5-phenyl dipyrrin (**9**)**. 1a** (14 mg, 48.4 μmol) in 8 ml of CH_3CN and **4** (24.1 mg, 194 μmol) in 2 ml of CH_3CN and Et_3N (27 μl, 19.7 mg, 194 μmol), rxn time 20 h (at 64^{o}C). Purified by column chromatography SiO_2, CCl_4. **9**: (21 mg, 45.2 μmol, 93%). ^{1}H NMR ($CDCl_3$): δ = 2.30 (6H, s) 6.27 (2H, d, *J* = 4.1 Hz), 6.44 (2H, d, *J* = 4.1 Hz), 7.13 (4H, d, *J* = 8.1 Hz), 7.33 (4H, d, *J* = 8.1 Hz), 7.37 – 7.41(5H, m), 12.2 (broad s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ= 21.23, 120.35, 127.64, 128.45, 128.57, 129.26*, 130.16, 130.75, 131.65, 134.46*, 136.66*, 136.66*, 138.14*, 141.91* ppm. LDI-TOF: m/z = 465 $[M+H]^+$. HRMS (ES): $[M+H]^+$ $C_{29}H_{24}N_2S_2$ Found 465.1464 Calculated 465.1454. λ_{max} = 462 nm (ε = 2.1×10^4 $M^{-1}cm^{-1}$).

1,9-bis(2-methoxycarbonylphenylthia)-5-phenyl dipyrrin (**10**)**. 1a** (14.6 mg, 50.5 μmol) in 8 ml of CH_3CN and **5** (43.8 mg, 260 μmol) and Et_3N (27 μl, 19.7 mg, 194 μmol), rxn time 72 h (at 76^{o}C). Purified by column chromatography SiO_2, hexane-EtOAc 4:1. Dried residue was chromatographed on Al_2O_3, hexane-EtOAc. **10**: (23 mg, 41.6 μmol, 82%). ^{1}H NMR ($CDCl_3$): δ = 3.91 (6H, s), 6.44 (2H, d, *J* = 4.4 Hz), 6.52 (2H, d, *J* = 4.4 Hz), 7.10-7.14 (2H, m), 7.21-7.27 (4H, m), 7.38-7.47 (5H, m), 7.85 (2H, dd, *J* = 7.8 Hz, 1.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ= 29.68, 52.25*, 122.60*, 126.50*, 127.73*, 128.65*, 128.79*, 129.55, 130.82*, 130.87*, 132.34*, 134.56, 136.54, 137.13, 147.03, 166.80 ppm. LDI-TOF: m/z = 465 $[M+H]^+$. HRMS (ES): $C_{29}H_{24}N_2S_2$ Found 465.1464 Calculated 465.1454. λ_{max} = 456 nm (ε = 2.1×10^3 $M^{-1}cm^{-1}$).

1,9-bis(4-methylphenylthia)-5-(4-nitrophenyl) dipyrrin (**15**)**. 1b** (33.3 mg, 100 μmol) in 16 ml of CH_3CN and **4** (50.7 mg, 408 μmol) and Et_3N (54 μl, 39 mg, 388 μmol), rxn time 48 h (at 65^{o}C). Washed by hot hexanes four times, removing this by decantation **15**: (19.6 mg, 38.4 μmol, 39%). ^{1}H NMR ($CDCl_3$): δ = 2.34 (3H, s), 6.27 (2H, d, *J* = 4.3 Hz), 6.33 (2H, d, *J* = 4.3 Hz), 7.16 (4H, d, *J* = 7.9 Hz), 7.35 (4H, d, *J* = 7.9 Hz), 7.58 (2H, d, *J* = 8.8 Hz), 8.27 (2H, d, *J* = 8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ= 21.26, 120.75, 122.99, 127.76, 128.62, 130.28, 131.61,

131.93, 138.55, 141.16, 143.47, 147.95, 150.59 ppm. LDI-TOF: m/z = 510.6 $[M+H]^+$. HRMS (ES): $C_{29}H_{23}N_3O_2S_2$ Found 510.1298 Calculated 510.1304 λ_{max} = 467 nm ($\varepsilon = 7.6\times10^3$ $M^{-1}cm^{-1}$).

1,9-bis(2-methoxycarbonylphenylthia)-5-(4-nitrophenyl)dipyrrin (**16**)**. 1b** (33.8 mg, 101 μmol) in 16 ml of CH_3CN and **5** (68 mg, 550 μmol) and Et_3N (54 μl, 40 mg, 380 μmol), rxn time 4 h (at 70°C).). Washed by hot hexanes four times, removing this by decantation. **16**: (47.4 mg, 79.2 μmol, 79%). ^1H NMR ($CDCl_3$): δ = 3.91 (6H, s), 6.41 (2H, d, *J* = 4.2 Hz), 6.46 (2H, d, *J* = 4.2 Hz), 7.12-7.16 (2H, m), 7.24 (the peak is overlaid by the $CDCl_3$ residual one, confirmed by COSY expt.), 7.63 (2H, d, *J* = 8.6 Hz), 7.87 (2H, d, *J* = 7.6 Hz), 8.30 (2H, d, *J* = 8.6 Hz), 11.92 (1H, br.s.) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.26, 123.05, 123.38, 126.70, 127.70, 129.59*, 130.88, 130.95, 131.68, 132.37,136.75*, 142.14*, 143.28*, 148.07*, 166.72* ppm. LDI-TOF: m/z = 598.1 $[M+H]^+$. HRMS (ES): $C_{31}H_{23}N_3O_6S_2$ Found 598.1051 Calculated 598.1101. λ_{max} = 461 nm ($\varepsilon=1.7\times10^4$ $M^{-1}cm^{-1}$).

1,9-bis(2-methoxycarbonylmethylthia)-5-(4-nitrophenyl)dipyrrin (**17**)**. 1b** (49.6 mg, 150 μmol) in 28 ml of CH_3CN and **3a** (63.6 mg, 600 μmol) and Et_3N (155 μl, 113 mg, 1.12 μmol), rxn time 21 h (at 70°C). **17**: (58,2 mg, 123 μmol, 82%). ^1H NMR ($CDCl_3$): δ = 3.75 (6H, s), 3.87 (4H, br.s.), 6.32 (2H, d, *J* = 4.2 Hz), 6.38 (2H, d, *J* = 4.2 Hz), 7.58 (2H, d, *J* = 8.6 Hz), 8.26 (2H, d, *J* = 8.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 35.35, 52.75, 120.89, 122.88, 128.06, 131.13, 131.60, 140.90, 143.48, 147.84, 148.99, 169.84 ppm. LDI-TOF: m/z = 474 $[M+H]^+$. HRMS (ES): $C_{21}H_{19}N_3O_6S_2$ Found 474.0783 Calculated 474.0794. λ_{max} = 458 nm ($\varepsilon = 1.9\times10^4$ $M^{-1}cm^{-1}$).

1,9-bis(2-methoxycarbonylethylthia)-5-(4-nitrophenyl)dipyrrin (**18**)**. 1b** (51.2 mg, 154 μmol) in 27 ml of CH_3CN and **3b** (72 mg, 600 μmol) and Et_3N (159 μl, 218 mg, 2.16 μmol), rxn time 21 h (at 70°C). **18**: (64,8 mg, 129,4 μmol, 84%). ^1H NMR ($CDCl_3$): δ = 2.83 (4H, t, *J* = 7.1 Hz), 3.32 (4H, t, *J* = 7.1 Hz), 3.70 (s, 6H), 6.37 (4H, t, *J* = 4.4 Hz), 7.60 (2H, d, *J* = 8.6 Hz), 8.28 (2H, d, *J* = 8.6 Hz), 12.42 (1H, br.s.) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.79, 34.23, 51.89, 121.25,

123.01, 127.75, 130.30, 131.59, 141.09, 143.36, 147.93, 149.61, 171.88 ppm. LDI-TOF: m/z = 502 $[M+H]^+$. HRMS (ES): $C_{23}H_{23}N_3O_6S_2$ Found 502.1096 Calculated 502.1107. λ_{max} = 463 nm (ε=2.1×10^4 M^{-1}cm^{-1}).

9-chloro-1-((2-hydroxyethyl)amino)-5-phenyldipyrrin (19) 1a (15 mg, 52 μmol) in 8 ml of CH_3CN and **6a** (16 mg, 262 μmol) and Et_3N (27 μl, 20 mg, 190 μmol), rxn time 163 h (at 70^{o}C). After the solvent removal on the vacuum line the reaction mixture was dissolved in 10 ml of CH_2Cl_2, washed with 0.1M HCl. Water phase was neutralized by an equal volume of saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic phases were dried over Na_2SO_4 and the solvent was removed on rotary evaporator. The residue was loaded onto silica gel column (hexane/EtOAc 1:3). Second fraction was collected giving dark orange crystals after drying. **19** (7 mg, 22 mol, 45%).

^{1}H NMR (CDCl3): = 3.69-3.72 (2H, m), 3.94-3.97 (2H, m), 6.00-6.02 (2H, m), 6.15 (1H, d, J = 4.7 Hz), 6.71 (1H, d, J = 4.7 Hz), 7.36-7.43 (5H, m) ppm. ^{13}C NMR ($CDCl_3$): = 45.7*, 62.3*, 108.19, 116.77, 117.72, 120.11*, 127.64, 127.74*, 128.03, 130.94, 132.29*, 137.04*, 137.92, 166.80* ppm. LDI-TOF: m/z = 314.1 $[M+H]^+$. HRMS (ES): $C_{17}H_{16}ClN_3O$ Found 314.1055 Calculated 314.1055. λ_{max} = 416 (ε=9.7×10^4 M^{-1}cm^{-1}); 521(ε=2.2×10^4 M^{-1}cm^{-1}) (c = 7.6×10^{-6} M).

9-chloro-1-((N-2-hydroxyethyl-N-methyl)amino)-5-phenyldipyrrin (20) 1a (15 mg, 52 μmol) in 8 ml of CH_3CN and **6b** (16 mg, 213 μmol) and Et_3N (27 μl, 20 mg, 190 μmol), rxn time 57 h (at 70^{o}C).). After the solvent removal on the vacuum line reaction mixture was dissolved in 10 ml of CH_2Cl_2, washed with brine and with water. Organic phase was dried over Na_2SO_4 and the solvent was removed on rotary evaporator. The dark orange solid of **20** were collected with the quantitative (17 mg, 52 μmol) yield. ^{1}H NMR ($CDCl_3$): = 3.27 (1H, s), 3.74-3.77 (2H, m), 3.94-3.97 (2H, m), 6.01 (2H, AB system, *J* = 3.9 Hz), 6.38 (2H, d, *J* = 4.76 Hz), 6.77 (2H, d, *J* = 4.76 Hz), 7.36-7.43 (5H, m) ppm. ^{13}C NMR (CDCl3): δ = 37.8, 54.0, 61.4, 108.1, 116.1, 116.3, 119.8, 127.1, 127.6, 127.9, 131.0, 132.7, 137.1, 138.2, 146.5, 168.4 ppm. LDI-TOF: m/z =327

[M], 328 $[M+H]^+$. HRMS (ES): $C_{17}H_{16}ClN_3O$ Found 328.1207 Calculated 328.1211 λ_{max} = 432 nm ($\varepsilon = 1.9\times10^4\ M^{-1}cm^{-1}$), 530 ($\varepsilon = 0.49\times10^4\ M^{-1}cm^{-1}$).

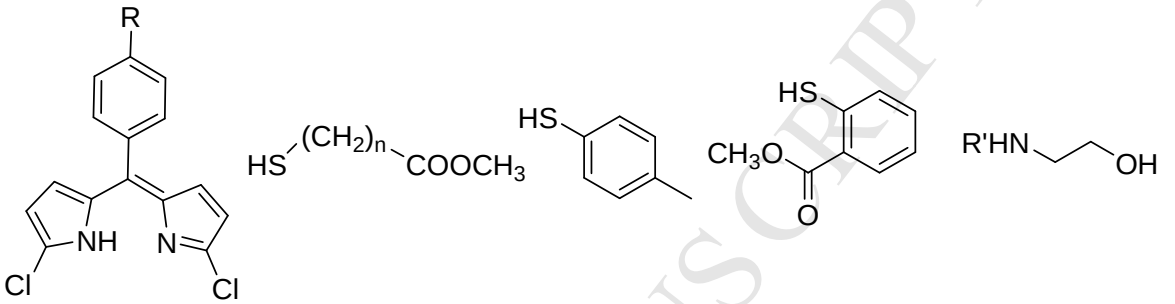
9-chloro-1-((2-hydroxyethyl)amino)-5-(4-nitrophenyl)-dipyrrin (21) 1b (19.4 mg, 61 μmol) in 10 ml of CH_3CN and **6a** (19 mg, 310 μmol) and Et_3N (32 μl, 23 mg, 230 μmol), rxn time 24 h (at 73°C). The solvent has been removed on the rotary evaporator, then the residue has been dried on high vacuum line (10^{-2} Torr) at 77°C for 40 min. **17**: (21.5 mg, 59.6 μmol, 96%). ^1H NMR ($CDCl_3$): δ = 3.68 (2H, m), 3.93 (m, 2H), 6.04 (1H, d, *J* = 4.0 Hz), 6.13 (1H, d, *J* = 4.0 Hz), 6.38 (1H, d, *J* = 5.1 Hz), 6.64 (1H, d, *J* = 5.1 Hz), 7.56 (2H, d, *J* = 8.8 Hz), 8.29 (2H, d, *J* = 8.8 Hz) ppm. ^{13}C ($CDCl_3$) 45.9, 61.8, 108.9, 116.5, 117.2, 118.5, 121.7, 123.1, 125.1, 130.6, 131.1, 131.8, 131.9, 137.4, 143.9, 147.8, 166.6 ppm. LDI-TOF: m/z = 358 $[M]^+$, 359 $[M+H]^+$. $C_{17}H_{15}ClN_4O_3$ $[M+H]^+$ Found 359.0895 Calculated 359.0905 λ_{max} = 424 nm (ε = $1.3\times10^4\ M^{-1}cm^{-1}$), 523($0.26\times10^4\ M^{-1}cm^{-1}$).

9-chloro-1-((N-2-hydroxyethyl-N-methyl)amino)-5-(4-nitrophenyl)-dipyrrin (22) 1b (23 mg, 73 μmol) in 11 ml of CH_3CN and **6b** (24.3 mg, 323 μmol) in 2ml of CH_3CN and Et_3N (38 μl, 28 mg, 270 μmol), rxn time 24 h (at 73°C). After the solvent removal on the vacuum line (40 min at 80°C). The dark orange solid of **22** were collected with 95% (26 mg, 70 μmol) yield. ^1H NMR ($CDCl_3$): = 3.31 (1H, s), 3.70-3.81 (2H, m), 3.96-3.98 (2H, m), 5.91 (1H, d, *J* = 3.9 Hz), 6.03 (1H, d, *J* = 3.9 Hz), 6.45 (1H, d, *J* = 4.8 Hz), 6.67 (1H, d, *J* = 4.8 Hz), 7.57(2H, d, *J* = 8.8 Hz), 8.25(2H, d, *J* = 8.8 Hz) ppm. ^{13}C NMR (CDCl3): δ = 38.06, 54.35*, 60.81*, 108.9, 116.6, 123.0, 132.0*, 131.8*, 131.9, 134.8*, 137.8, 144.2*, 147.7*, 167.0* ppm. LDI-TOF: m/z =372 [M], 323 $[M+H]^+$. HRMS (ES): $C_{18}H_{17}ClN4O_3$ Found 372.1001 Calculated 372.0989 λ_{max} = 441 nm ($\varepsilon = 1.4\times10^4\ M^{-1}cm^{-1}$); 530 nm ($\varepsilon = 3.4\times10^3\ M^{-1}cm^{-1}$) .

Results

Two dipyrrins differing in electrophilicity have been chosen to probe their substitution reactions, i.e. 5-phenyl-1,9-dichlorodipyrromethene (Ph-DP) **1a,** 5-(4-nitrophenyl)-1,9-dichlorodipyrromethene (NO_2Ph-DP) **1b**.

Figure 1. Starting compounds used in this study.



R = H, **1a**; NO_2, **1b**

3a n = 1; **3b** n = 2

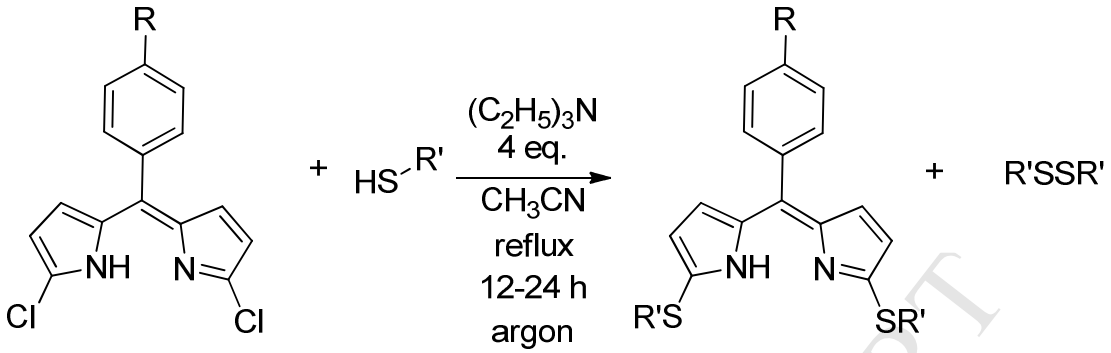
4

5

6a, R=H; **b**, R=CH_3

All reactions have been carried out as for the BODIPY[40] , i.e. in refluxing acetonitrile with triethylamine as the base. The reactions occurred at much slower rates than their *F*-BODIPY counterparts (*e.g.* 48 h for **7** *vs* 8h for its BF_2 counterpart[40]). Despite the oxygen-free conditions, formation of the disulfides **11-14** were detected along with disubstituted products in all cases, indicating that the DP also acts as an oxidant. The results are presented in the Scheme 1.

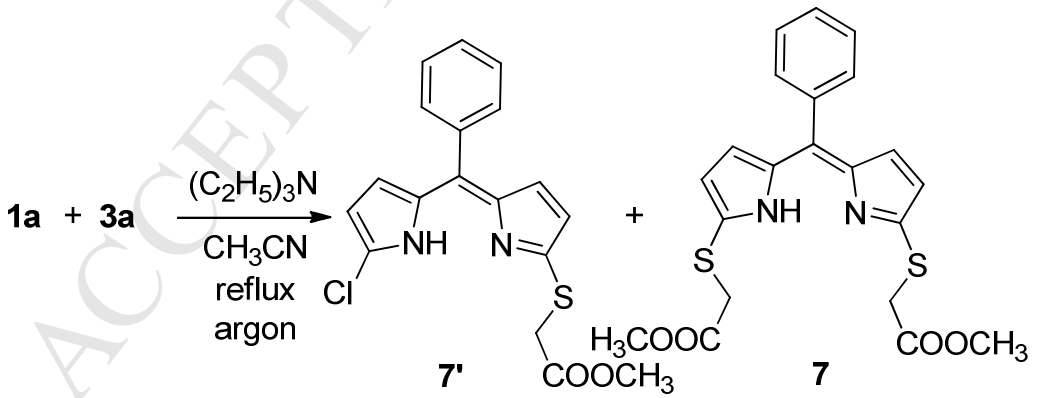
Scheme 1.



Entry	R	Nucleophile, R'	DP adduct	Disulfide
1	H	**3a**, SCH_2COOCH_3	**7**, 49%	**11**
2	H	**3b**, $S(CH_2)_2COOCH_3$	**8**, 83%	**12**
3	H	**4**, $S(C_6H_4$-*p*-$CH_3)$	**9**, 93%	**13**
4	H	**5**, $S(C_6H_4$-*o*-$COOCH_3)$	**10**, 84%	**14**
5	NO_2	**4**, $S(C_6H_4$-*p*-$CH_3)$	**15**, 58%	**13**
6	NO_2	**5**, $S(C_6H_4$-*o*-$COOCH_3)$	**16**, 78%	**14**
7	NO_2	**3a**, SCH_2COOCH_3	**17**, 82%	**11**
8	NO_2	**3b**, $S(CH_2)_2COOCH_3$	**18**, 84%	**12**

Both shorter reaction times and lower excess of **3a** give rise to either lower conversion or to the formation of the mixture of mono- and di-substitution products **7'** and **7** (Scheme 2). However no conditions can be found for selective formation of **7'**.

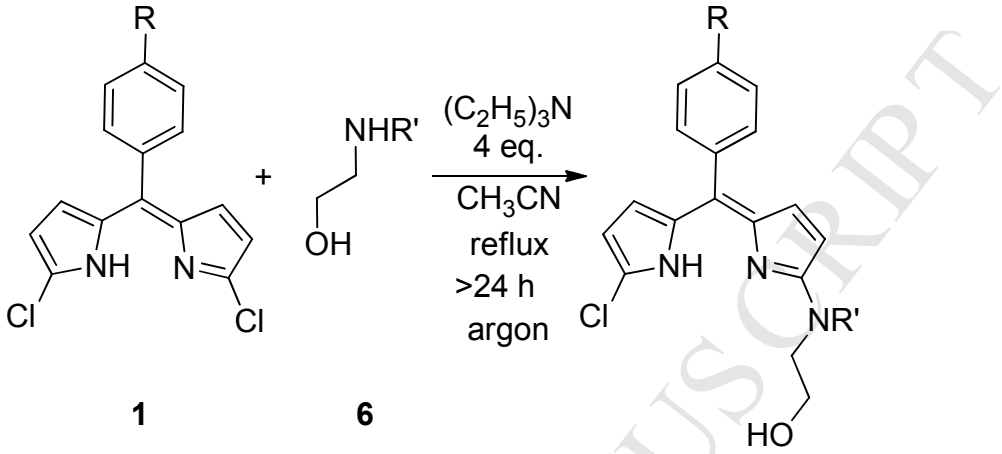
Scheme 2



Entry	**1a** : **3a**	rxn time, h	conversion, %	**7'** : **7**
1	1 : 4	29	100	0 : 100
2	1 : 4	16.5	100	2 : 3
3	1 : 2	29	85	2 : 3
	1 : 1	29	50	1 : 1

Nitrogen nucleophiles – react with **1a** and **1b** to yield mono-substitution product only. All attempts to effect disubstitution (severe conditions, long reaction time, solvent variation) failed (Scheme 3).

Scheme 3



1 **6**

Entry	R	Nucleophile, R'	DP adduct
1	H	6a, H	**19**, 45%
2	H	6b, CH3	**20**, 99%
3	NO2	6a, H	**21**, 99%
4	NO2	6b, CH3	**22**, 95%

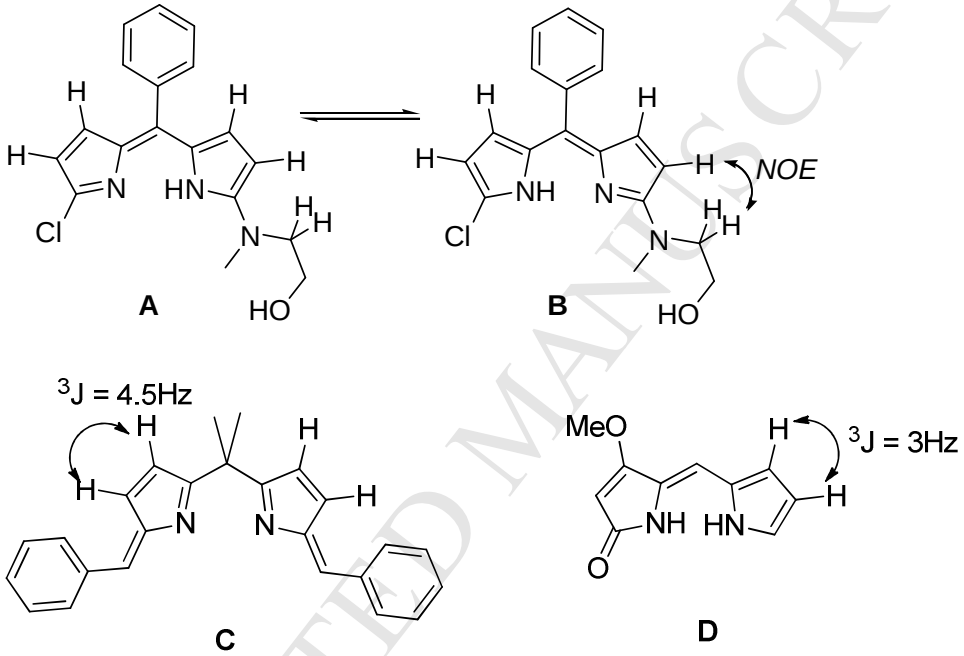
No products were observed when reacting **1** with EtOH in similar conditions.

Use of DMF as the solvent caused no substantially different results: all reactions have been accelerated *ca.* 1.5 times, no disubstitution in the case of N-nucleophiles has been observed, no substitution products by O-nucleophiles have been detected.

NMR of the disubstituted products feature much less difference between signals of pyrrolic protons (0.05 – 0.1 ppm) than in, *e.g.* **1a** (0.27 ppm [29]). Spectra of mono-substituted ones **19**-**22** exhibit two pairs of the pyrrolic protons: for pyrrole and pyrrolene units (see the Supporting Info). One may expect two possible tautomeric forms which distinctly differ in energy for such compounds (Fig.2). To get more insight to which form (**A** or **B**, Fig. 2) predominates we did the NOESY experiment **22**. Its results (see the Supporting Info) unambiguously indicate that N-methyl-N-(2-hydroxyethyl) group is attached to the doublet with the splitting of 4.8 Hz, not to the doublet with 3.8 Hz. Mono N-substituted BODIPY [48-51] and

O-substituted dipyrrins [52] do possess doublets with coupling constants that differ in their values for *ca.* 1 Hz. However, no authors appear to discuss this difference in terms of pyrrole-pyrrolene tautomerism. Analyzing the literature one can make the conclusion that, it's the pyrrolene ring in dipyrrins that has the constant 4.8 Hz (for instance, as in **C** [53]), and pyrrole ring features 3 Hz coupling constant (for instance, as in **D** [54])

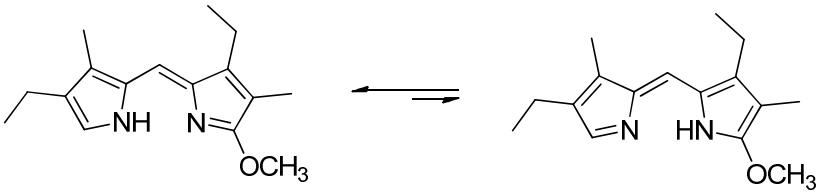
Figure 2. Possible tautomeric equilibrium (**A**, **B**) of **20** and *NOE* correlation (see Supplementraty Info); literature examples ^{3}J values in pyrrole and pyrrolene rings (**C**, **D**).



Thus we assume that 4.8 Hz doublet belongs to the ring existing predominantly in the pyrrolene form, whereas the residual chlorine substutuent is attached to a "pyrrole-character" ring. This hypothesis supports the observed complete inability of the chlorine atom to be substituted after the first reaction occurred.

Tautomerism in the dipyrrin series due to the migration of the inner proton is widely accepted phenomenon, [55] although there are few papers that discuss possible position of this equilibrium. For instance, Lightner and Datta [56] discuss the equilibrium in 1-methoxy-3,8-diethyl-2,7-dimethyldipyrrin (Fig 3). They point out that the equilibrium is shifted to the left, as judged by the bond lengths in the X-ray structure. Falk *et.al.* [57] also point out that the tautomeric form in which the pyrrolene ring is attached to the π-donor substituent predominates.

Figure 3. Tautomers of 9-methoxy-3,8-dimethyl-2,7-diethyldipyrrin [56]



UV-Vis spectra

UV-Vis spectra (for examples, see Figure 3) show the following trend. First, substitution of the S atoms for Cl (Table 1, entries **11**, **12**, **17**, **18**) yields a bathochromic shift of an absorption maximum that amounts *ca.* 30 nm if an additional π-substituent, i.e. *p*-tolyl group, is attached (entry **11**). On the contrary the introduction of a N-substituent yields a substantial hypsochromic shift (entries **21-24**).

Figure 4. Samples of the UV-Vis spectra (CH_3CN) of the starting compound **1a** (dashed line), bis-S-substituted **10** (grey line) and mono- N-substituted **20**(solid line).

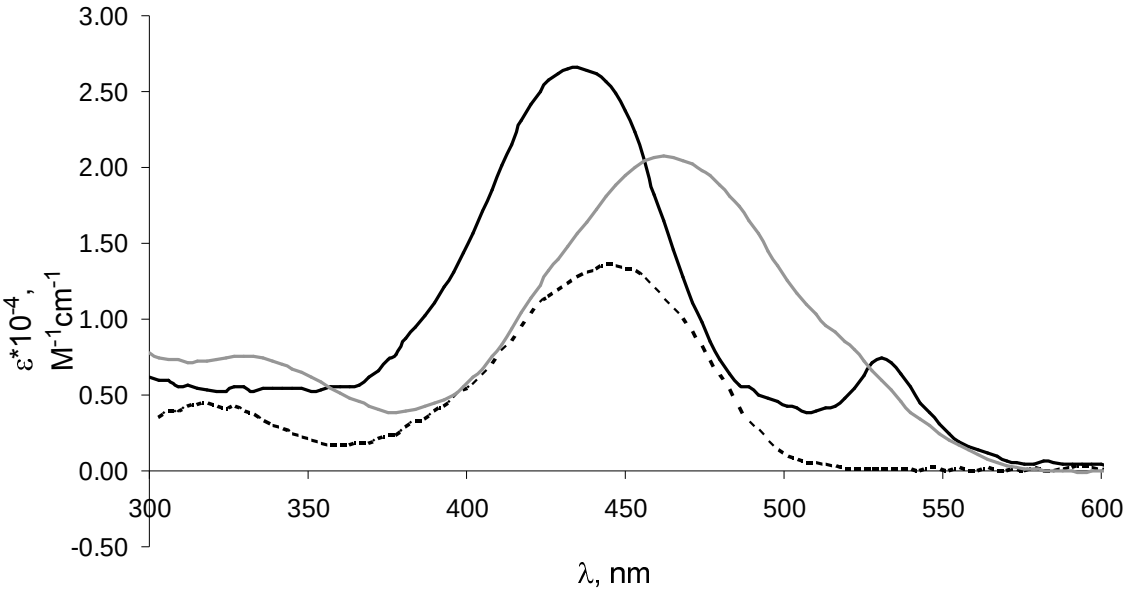


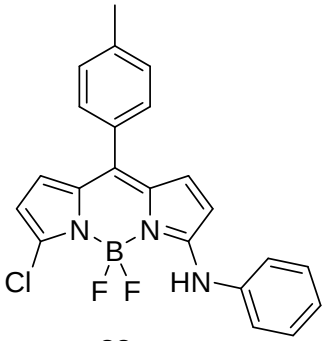
Table 1. UV-Vis spectral data of DPs in CH_3CN at r.t.

Cmpd	λ_{max} (ε)	Cmpd	λ_{max} (ε) (at 5×10^{-5}M)
1a	440($1.4\cdot10^4$)	**16**	461($1.7\cdot10^4$)
1b	448($2.4\cdot10^4$)	**17**	458($1.9\cdot10^4$)
7	453($2.4\cdot10^4$)	**18**	463($2.1\cdot10^4$)
8	456($1.9\cdot10^4$)	**19**	416($9.4\cdot10^4$) 521($2.2\cdot10^4$)*)
9	462($2.1\cdot10^4$)	**20**	432($1.9\cdot10^4$); 530($0.49\cdot10^4$)
10	456($2.1\cdot10^4$)	**21**	424($1.3\cdot10^4$) 523($0.26\cdot10^4$)
15	467($7.6\cdot10^3$)	**22**	441($1.4\cdot10^4$) 530($0.34\cdot10^4$)

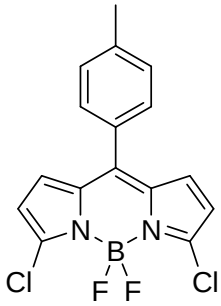
*) Measured at 7.6×10^{-6}M

This effect of a mono N-substitution has already been observed in the series of BODIPY dyes [40, 58-63] and reasons for it were comprehensively analyzed. Boens *et.al.* [50] carried out solvent-dependent UV-Vis and fluorescence studies of the dye **23**, as well as quantum chemical calculations of the ground and the excited state of the molecule. The authors suggested that the dipole moment of the exited state being lower than that of the ground state is responsible for the blue shift of the UV-Vis maximum of **23** with respect to **24**. On the other hand, mono S-substitution does not cause such an effect [40, 64, 65].

Figure 5. Mono-N-substituted BODIPY **23** [50] and its precursor **24**.



23



24

Besides, a low intensity bathochromically shifted band is observed in the UV-Vis spectra of mono-N-substituted products. However, we currently were are unable to make any plausible assignment of this band, although it is reproduced in all studied spectra. The analysis of more data will make it possible to attribute the band.

Conclusions

This study demonstrate that dihalo-*H*-dipyrrins can undergo the nucleophilic substitution reaction with S- and N-nucleophiles and are inert to O-nucleophiles. This relatively simple and mild method for substituted dipyrrins is complementary to the recently emerged "BODIPY nucleophilic substitution – deborylation" sequence. Also, the specific mono-N-substitution may be regarded as a reliable and clean procedure both for mono-N-substituted dipyrrins and for mono-N-substituted BODIPYs , eliminating the need to adjust the reaction conditions and/or the chromatography isolation of dyes [61, 66]. This work is in progress and will be reported in due course.

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[1] Wood TE, Thompson A. Advances in the chemistry of dipyrrins and their complexes. Chem. Rev. 2007; 107: 1831-1861.
[2] Wood TE, Uddin MI, Thompson A, The Synthesis and Properties of Dipyrrins. Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine, Vol 8: Open-Chain Oligopyrrole Systems *Vol. 8*. SIngapore: World Scientific Publishing Co; 2010; p. 235-291.
[3] Loudet A, Burgess K. BODIPY Dyes and Their Derivatives: Syntheses and Spectroscopic Properties. Chem. Rev. 2007; 107: 4891–4932.
[4] Ulrich G, Ziessel R, Harriman A. The chemistry of fluorescent bodipy dyes: Versatility unsurpassed. Angew. Chem. Int. Ed. 2008; 47: 1184-1201.
[5] Boens N, Leen V, Dehaen W. Fluorescent indicators based on BODIPY. Chem. Soc. Rev. 2012; 41: 1130-1172.
[6] Khan TK, Broering M, Mathur S, Ravikanth M. Boron dipyrrin-porphyrin conjugates. Coord. Chem. Rev. 2013; 257: 2348-2387.
[7] Djurovich PI, Kirlikovali KO, Thompson ME, Trinh C, Bartynski AN, Thompson ME, Tassone CJ, Toney MF, Burkhard GF, McGehee MD. Efficient energy sensitization of C60 and application to organic photovoltaics. JACS. 2013; 135: 11920 - 11928.
[8] Li G, Hu K, Yi C, Knappenberger KL, Jr., Meyer GJ, Gorelsky SI, Shatruk M. Panchromatic Light Harvesting and Hot Electron Injection by Ru(II) Dipyrrinates on a TiO2 Surface. J. Phys. Chem. C. 2013; 117: 17399-17411.
[9] Hewat TE, Yellowlees LJ, Robertson N. Neutral copper(i) dipyrrin complexes and their use as sensitizers in dye-sensitized solar cells. Dalton Trans. 2014; 43: 4127-4136.
[10] King ER, Sazama GT, Betley TA. Co(III) imidos exhibiting spin crossover and C-H bond activation. JACS. 2012; 134: 17858 - 17861.
[11] Baudron SA. Luminescent dipyrrin based metal complexes. Dalton Trans. 2013; 42: 7498-7509.
[12] Gupta RK, Pandey R, Sharma G, Prasad R, Koch B, Srikrishna S, Li P-Z, Xu Q, Pandey DS. DNA Binding and Anti-Cancer Activity of Redox-Active Heteroleptic Piano-Stool Ru(II), Rh(III), and Ir(III) Complexes Containing 4-(2-Methoxypyridyl)phenyldipyrromethene. Inorg. Chem. 2013; 52: 3687-3698.
[13] Paitandi RP, Gupta RK, Singh RS, Sharma G, Koch B, Pandey DS. Interaction of ferrocene appended Ru(II), Rh(III) and Ir(III) dipyrrinato complexes with DNA/protein, molecular docking and antitumor activity. Eur. J. Med. Chem. 2014; 84: 17-29.
[14] Gupta RK, Sharma G, Pandey R, Kumar A, Koch B, Li P-Z, Xu Q, Pandey DS. DNA/Protein Binding, Molecular Docking, and in Vitro Anticancer Activity of Some Thioether-Dipyrrinato Complexes. Inorg. Chem. 2013; 52: 13984-13996.
[15] Beziau A, Baudron SA, Hosseini MW. Heterometallic coordination polymers incorporating dipyrrin based heteroleptic copper and cobalt complexes: to Ag-pi or not? Dalton Trans. 2012; 41: 7227-7234.
[16] De S, Mahata K, Schmittel M. Metal-coordination-driven dynamic heteroleptic architectures. Chem. Soc. Rev. 2010; 39: 1555-1575.
[17] Ma L, Shin J-Y, Patrick BO, Dolphin D. Metal complexes of dipyrromethenes linked by rigid spacer arms. Crystengcomm. 2008; 10: 1539-1541.
[18] Antina LA, Guseva GB, V'Yugin AI, Antina EV, Berezin MB. meso-spacer influence on properties of zinc(II) complexes with 2,3'- and 3,3'-bis(dipyrrolylmethenes). Russ. J. Gen. Chem. 2013; 83: 1143-1150.

[19] Guseva GB, Dudina NA, Antina EV, V'Yugin AI. Coordination reactions of 3,3 '-bis(dipyrrolylmethene) with Co(II), Cu(II), and Zn(II) acetylacetonates, valinates, and dipyrrolylmethenates. Russ. J. Gen. Chem. 2013; 83: 731-737.

[20] Baudron SA. Dipyrrin based homo- and hetero-metallic infinite architectures. Crystengcomm. 2010; 12: 2288-2295.

[21] Béziau A, Baudron SA, Guenet A, Hosseini MW. Luminescent Coordination Polymers Based on Self-Assembled Cadmium Dipyrrin Complexes. Chem. Eur. J. 2013; 19: 3215-3223.

[22] Bröring M, Brandt Carsten D, Lex J, Humpf H-U, Bley-Escrich J, Gisselbrecht J-P. Molecular and Electronic Structure of (2,2′-Bidipyrrinato)nickel(II) Complexes. Eur. J. Inorg. Chem. 2001; 2001: 2549-2556.

[23] Sakamoto N, Ikeda C, Yamamura M, Nabeshima T. Structural Interconversion and Regulation of Optical Properties of Stable Hypercoordinate Dipyrrin−Silicon Complexes. JACS. 2011; 133: 4726-4729.

[24] Thoi VS, Stork JR, Niles ET, Depperman EC, Tierney DL, Cohen SM. Diamidodipyrrins: Versatile Bipyrrolic Ligands with Multiple Metal Binding Modes. Inorg. Chem. 2008; 47: 10533-10541.

[25] Ali AA-S, Cipot-Wechsler J, Crawford SM, Selim O, Stoddard RL, Cameron TS, Thompson A. The first series of alkali dipyrrinato complexes. Can. J. Chem. 2010; 88: 725-735.

[26] Guseva GB, Dudina NA, Antina EV, V'yugin AI, Semeikin AS. 3,3′-bis(dipyrrolylmethenes) as new chelating ligands: Synthesis and spectral properties. Russ. J. Gen. Chem. 2008; 78: 1215-1224.

[27] King ER, Betley TA. C-H bond amination from a ferrous dipyrromethene complex. Inorg. Chem. 2009; 48: 2361 - 2363.

[28] King ER, Hennessy ET, Betley TA. Catalytic C−H Bond Amination from High-Spin Iron Imido Complexes. JACS. 2011; 133: 4917-4923.

[29] Liu X, Sun W, Zhan M, Zou L, Xie Z, Li X, Cheng Y, Liu X, Nan H, Sun W, Zhang Q, Lu C. Synthesis and characterisation of neutral mononuclear cuprous complexes based on dipyrrin derivatives and phosphine mixed-ligands. Dalton Trans. 2012; 41: 10199 - 10210.

[30] Maeda H, Akuta R, Bando Y, Takaishi K, Uchiyama M, Muranaka A, Tohnai N, Seki S. Formation and Geometrical Control of Polygon-Like Metal-Coordination Assemblies. Chem. Eur. J. 2013; 19: 11676-11685.

[31] Miao Q, Shin J-Y, Patrick BO, Dolphin D. Self-assembly of oligomeric linear dipyrromethene metal complexes. Chem. Commun. 2009; 2541-2543.

[32] Wood TE, Berno B, Beshara CS, Thompson A. 15N NMR Chemical Shifts for the Identification of Dipyrrolic Structures. J. Org. Chem. 2006; 71: 2964-2971.

[33] Boens N, Verbelen B, Dehaen W. Postfunctionalization of the BODIPY Core: Synthesis and Spectroscopy. Eur. J. Org. Chem. 2015; 6577-6595.

[34] Bessette A, Hanan GS. Design, synthesis and photophysical studies of dipyrromethene-based materials: insights into their applications in organic photovoltaic devices. Chem. Soc. Rev. 2014; 43: 3342-3405.

[35] Ahrens J, Böker B, Brandhorst K, Funk M, Bröring M. Sulfur-Bridged BODIPY DYEmers. Chem. Eur. J. 2013; 19: 11382-11395.

[36] Lundrigan T, Cameron TS, Thompson A. Activation and deprotection of F-BODIPYs using boron trihalides. Chem. Commun. 2014; 50: 7028 - 7031.

[37] Lakshmi V, Chatterjee T, Ravikanth M. Lewis acid assisted decomplexation of F-BODIPYs to dipyrrins. Eur. J. Org. Chem. 2014; 2014: 2105 - 2110.

[38] Jiang T, Zhang P, Yu C, Yin J, Jiao L, Dai E, Wang J, Wei Y, Mu X, Hao E. Straightforward synthesis of oligopyrroles through a regioselective S NAr reaction of pyrroles and halogenated boron dipyrrins. Org. Lett. 2014; 16: 1952 - 1955.

[39] Smithen DA, Baker AEG, Offman M, Crawford SM, Cameron TS, Thompson A. Use of F-BODIPYs as a protection strategy for dipyrrins: Optimization of BF2 removal. J. Org. Chem. 2012; 77: 3439 - 3453.
[40] Rohand T, Baruah M, Qin WW, Boens N, Dehaen W. Functionalisation of fluorescent BODIPY dyes by nucleophilic substitution. Chem. Commun. 2006; 266-268.
[41] King ER, Hennessy ET, Betley TA. Catalytic C-H bond amination from high-spin iron imido complexes. JACS. 2011; 133: 4917 - 4923.
[42] Ding Y, Li T, Xie Y, Zhu W, Li X. From nonconjugation to conjugation: Novel meso-OH substituted dipyrromethanes as fluorescence turn-on Zn2+ probes. Org. Biomol. Chem. 2013; 11: 2685 - 2692.
[43] Li L, Han J, Nguyen B, Burgess K. Syntheses and Spectral Properties of Functionalized, Water-Soluble BODIPY Derivatives. J. Org. Chem. 2008; 73: 1963-1970.
[44] Choi OK Novel intermediates of voriconazole and preparation method of voriconazole using the same. Patent (2012), EP 2444298 A2.
[45] Trofimov BA, Sobenina LN, Mikhaleva AI, Sergeeva MP, Nesterenko RN, Golovanova NI, Polovnikova PI. Addition of addition of methyl mercaptoacetate to n-vynilpyrroles. Chem. Heterocycl. Compd. 1992; 28: 403-405.
[46] Loccufier J, Schacht E. Convenient method for the preparation of 3-(2-pyridyl dithio) propionic acid N-hydroxy succinimid ester. Bull. Soc. Chim. Belg. 1988; 97: 535-539.
[47] Belyakov PA, Kadentsev VI, Chizhov AO, Kolotyrkina NyG, Shashkov AS, Ananikov VP. Mechanistic insight into organic and catalytic reactions by joint studies using mass spectrometry and NMR spectroscopy. Mendeleev Commun. 2010; 20: 125-131.
[48] Ganapathi E, Madhu S, Chatterjee T, Gonnade R, Ravikanth M. Synthesis, structure, spectral, electrochemical and sensing properties of 3-amino boron-dipyrromethene and its derivatives. Dyes Pigm. 2014; 102: 218-227.
[49] Huang J, Wang B, Ye J, Liu B, Qiu H, Yin S. A Highly Copper-Selective Ratiometric Fluorescent Sensor Based on BODIPY. Chin. J. Chem. 2012; 30: 1857-1861.
[50] Qin W, Leen V, Rohand T, Dehaen W, Dedecker P, Van der Auweraer M, Robeyns K, Van Meervelt L, Beljonne D, Van Averbeke B, Clifford JN, Driesen K, Binnemans K, Boens N. Synthesis, Spectroscopy, Crystal Structure, Electrochemistry, and Quantum Chemical and Molecular Dynamics Calculations of a 3-Anilino Difluoroboron Dipyrromethene Dye. J. Phys. Chem. A. 2009; 113: 439-447.
[51] Qin WW, Rohand TF, Dehaen W, Clifford JN, Driesen K, Beljonne D, Van Averbeke B, Van der Auweraer MD, Boens N. Boron dipyrromethene analogs with phenyl, styryl, and ethynylphenyl substituents: Synthesis, photophysics, electrochemistry, and quantum-chemical calculations. J. Phys. Chem. A. 2007; 111: 8588-8597.
[52] Halper SR, Stork JR, Cohen SM. Preparation and characterization of asymmetric alpha-alkoxy dipyrrin ligands and their metal complexes. Dalton Trans. 2007; 1067-1074.
[53] Setsune J-i, Tsukajima A, Watanabe J. Synthesis of isocorrole and the higher homologues. Tetrahedron Lett. 2006; 47: 1817-1820.
[54] Chepelev LL, Beshara CS, MacLean PD, Hatfield GL, Rand AA, Thompson A, Wright JS, Barclay LRC. Polypyrroles as antioxidants: Kinetic studies on reactions of bilirubin and biliverdin dimethyl esters and synthetic model compounds with peroxyl radicals in solution. Chemical calculations on selected typical structures. J. Org. Chem. 2006; 71: 22-30.
[55] Falk H. The Chemistry of Linear Oligopyrroles and Bile Pigments: Springer; 1989.
[56] Datta S, Lightner DA. Converting dipyrrinones to lactim ethers to fluorescent N,N '-difluoroboryl derivatives. Monatsh. Chem. 2008; 139: 1519-1529.
[57] Falk H, Gergely S, Grubmayr K, Hofer O. Beiträge zur Chemie der Pyrrolpigmente, XV. Die Lactam-Lactim-Tautomerie von Gallenpigmenten. Liebeg's Ann. Chem. 1977; 1977: 565-581.

[58] Dilek Ö, Bane SL. Synthesis of boron dipyrromethene fluorescent probes for bioorthogonal labeling. Tetrahedron Lett. 2008; 49: 1413-1416.

[59] Burgess K, Li L, Nguyen B. Functionalization of the 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) core. Bioorg. Med. Chem. Lett. 2008; 18: 3112 - 3116.

[60] Agarrabeitia AR, Maroto BL, Moreno F, Moya SDL, Ortiz MJ, Sanchez-Carnerero EM, Arbeloa T, Banuelos J, Lopez-Arbeloa I. Unprecedented induced axial chirality in a molecular BODIPY dye: Strongly bisignated electronic circular dichroism in the visible region. Chem. Commun. 2013; 49: 11641 - 11643.

[61] Brizet B, Denat F, Goze C, Volkova YA, Brizet B, Harvey PD, Averin AD. BODIPY dyes functionalized with pendant cyclic and acyclic polyamines. Eur. J. Org. Chem. 2013; 4270 - 4279.

[62] Cui J, Jia X, Liu W, Qin W, Tang X, Yang X, Yu X. A highly selective copper fluorescent indicator based on aminoquinoline substituted BODIPY. Dyes Pigm. 2013; 98: 195 - 200.

[63] Jia X, Liu W, Qin W, Yu X, Zhang G. Preparation of a fluorescent sensor based on BODIPY-functionalized hydroxyapatite nanoparticles and spectroscopic study of the Cd2+ and Zn2+ complex formation. J. Coord. Chem. 2013; 66: 662 - 670.

[64] Bane SL, Dilek O. Synthesis, spectroscopic properties and protein labeling of water soluble 3,5-disubstituted boron dipyrromethenes. Bioorg. Med. Chem. Lett. 2009; 19: 6911 - 6913.

[65] Niu L-Y, Guan Y-S, Chen Y-Z, Wu L-Z, Tung C-H, Yang Q-Z, Niu L-Y, Guan Y-S. BODIPY-based ratiometric fluorescent sensor for highly selective detection of glutathione over cysteine and homocysteine. JACS. 2012; 134: 18928 - 18931.

[66] Qin WW, Leen V, Rohand T, Dehaen W, Dedecker P, Van der Auweraer M, Robeyns K, Van Meervelt L, Beljonne D, Van Averbeke B, Clifford JN, Driesen K, Binnemans K, Boens N. Synthesis, Spectroscopy, Crystal Structure, Electrochemistry, and Quantum Chemical and Molecular Dynamics Calculations of a 3-Anilino Difluoroboron Dipyrromethene Dye. J. Phys. Chem. A. 2009; 113: 439-447.

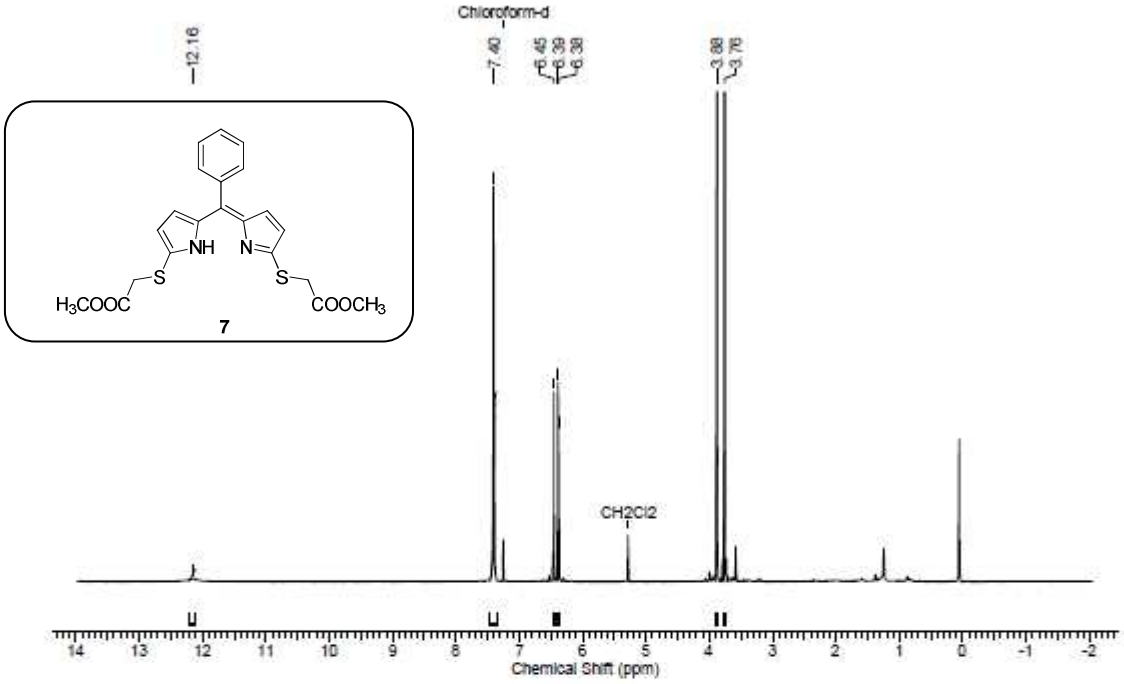
Supplementary Info

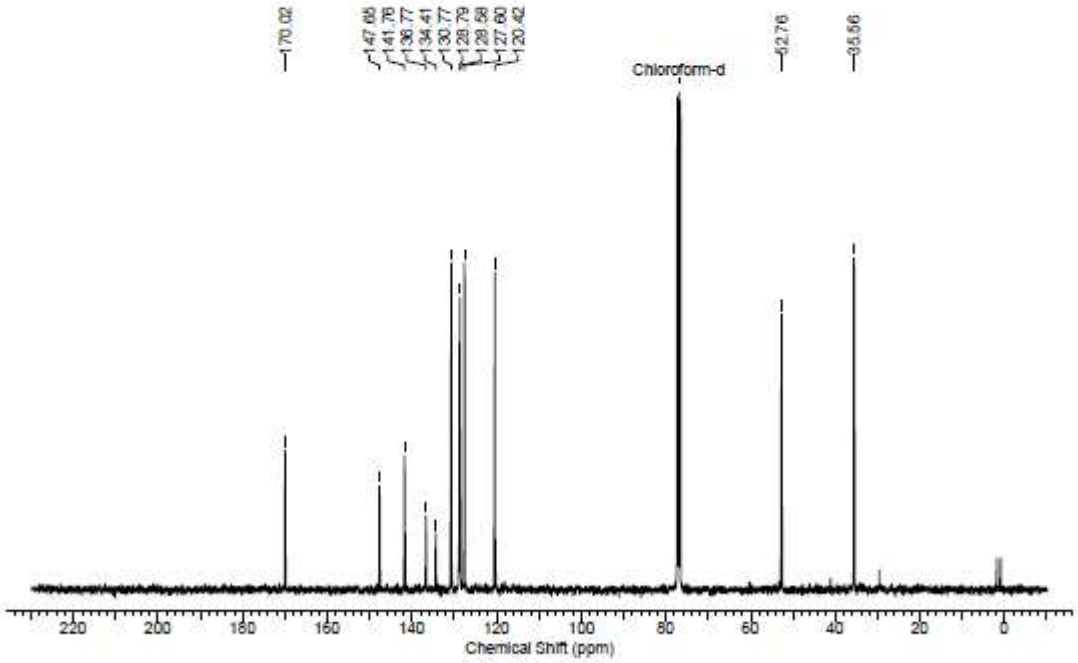
SNAr Nucleophilic substitution of 1,9-dihalodipyrrins by S and N nucleophiles. Synthesis of new dipyrrins bearing pendant substituents.

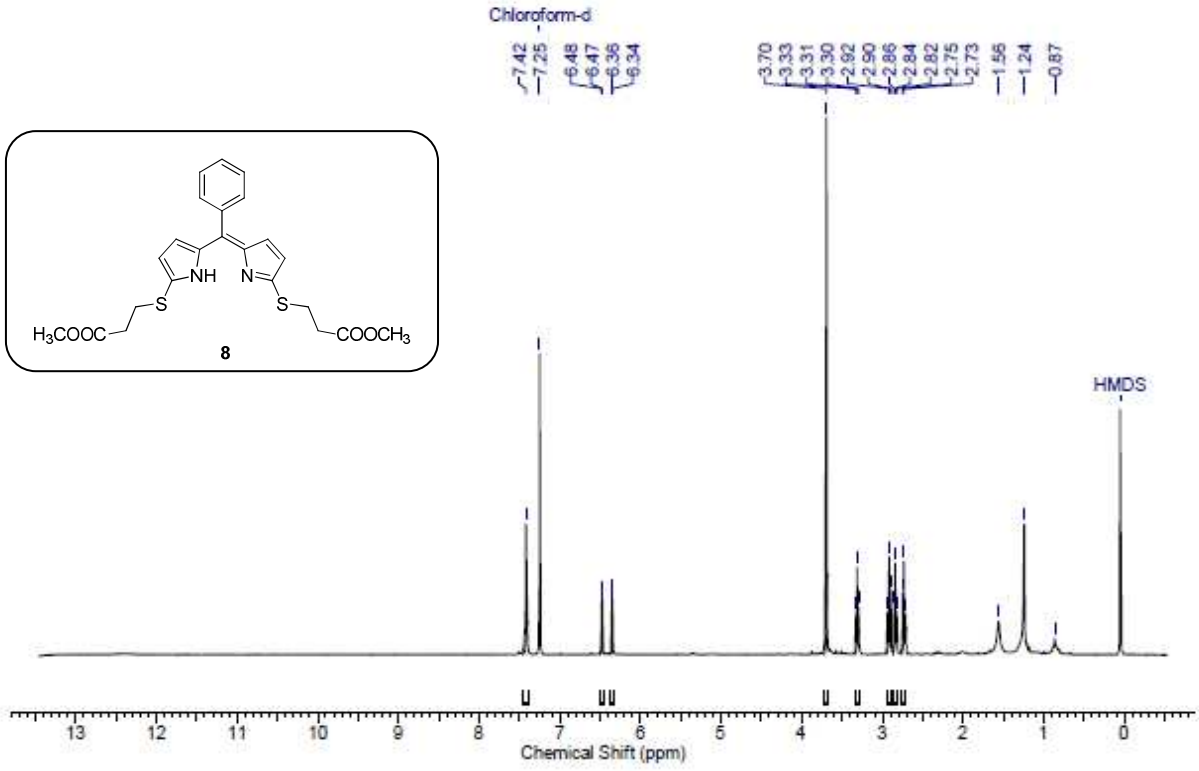
Evgenia Leushina, Ksenia Tikhomirova, Anastasiya Permyakova, Pavel Ilyin, Alexander Anisimov, Andrey Churakov, Andrey Khoroshutin *

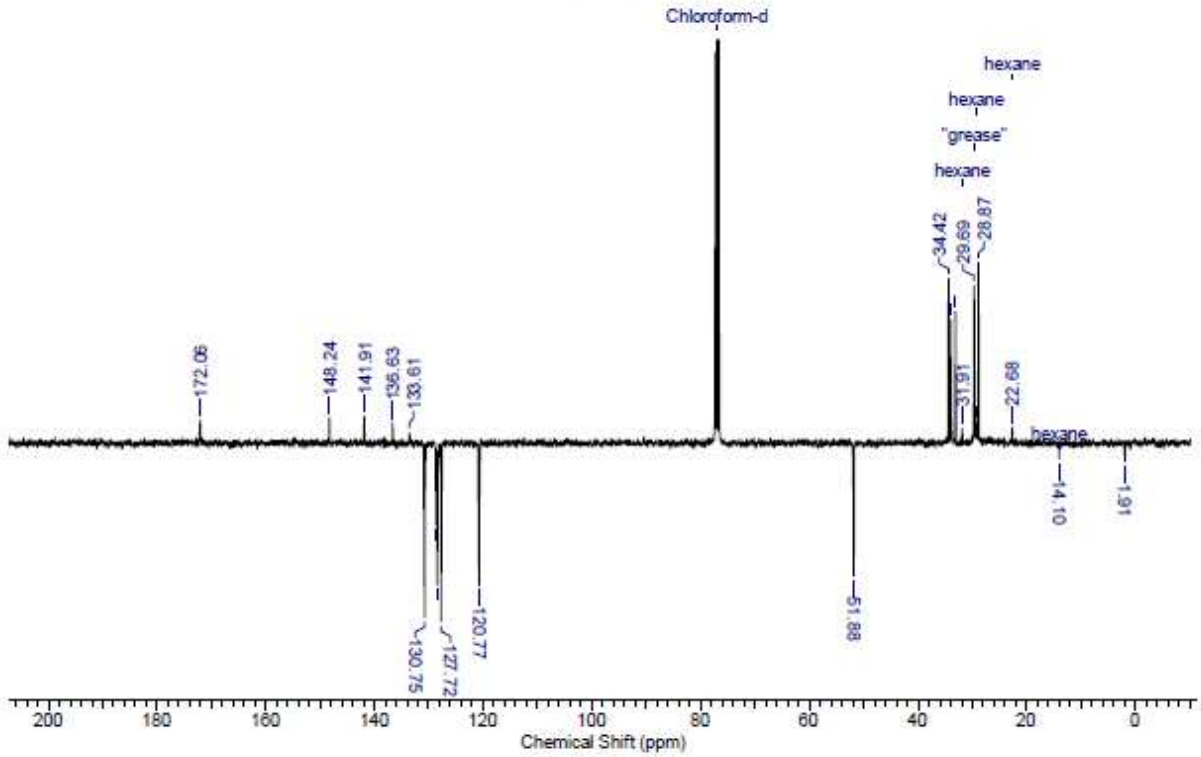
1.NMR spectra of S-substitution products

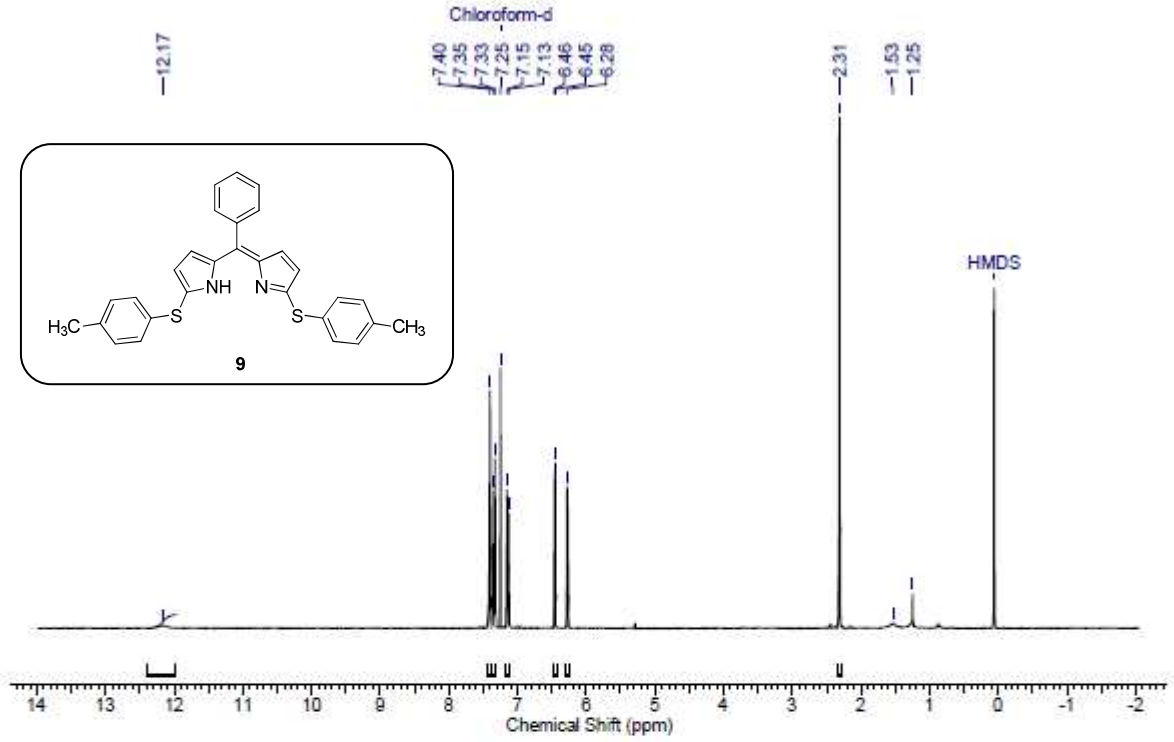
1H and 13C NMR spectra of products:

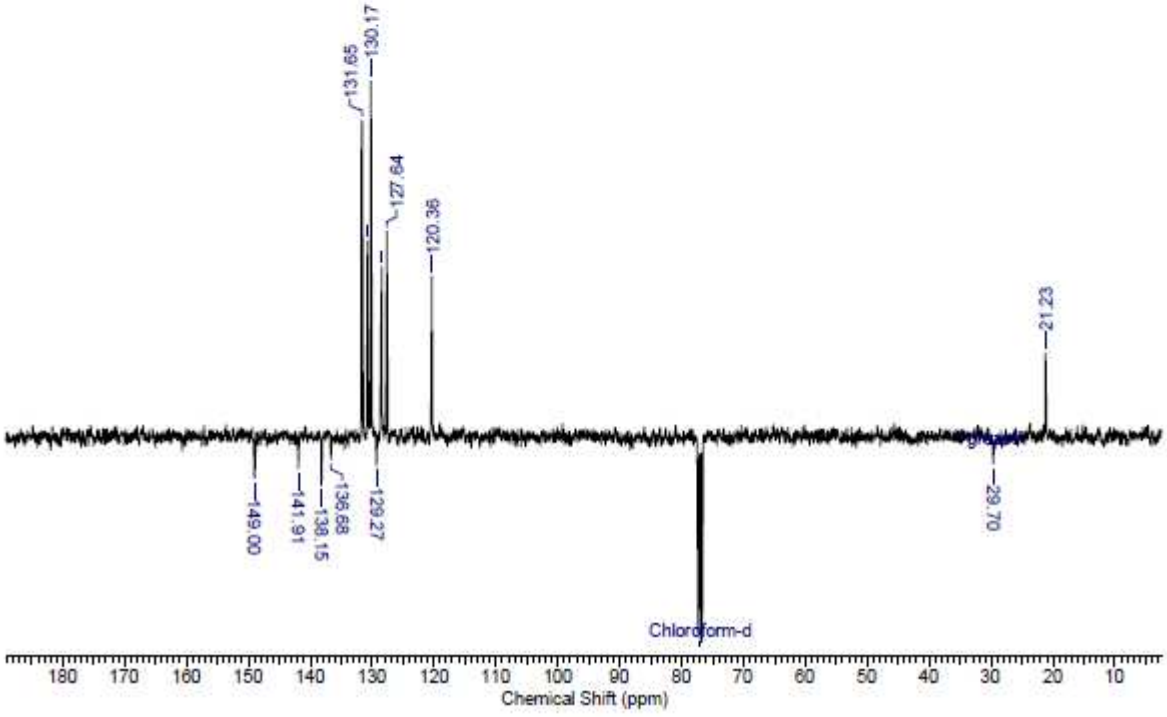


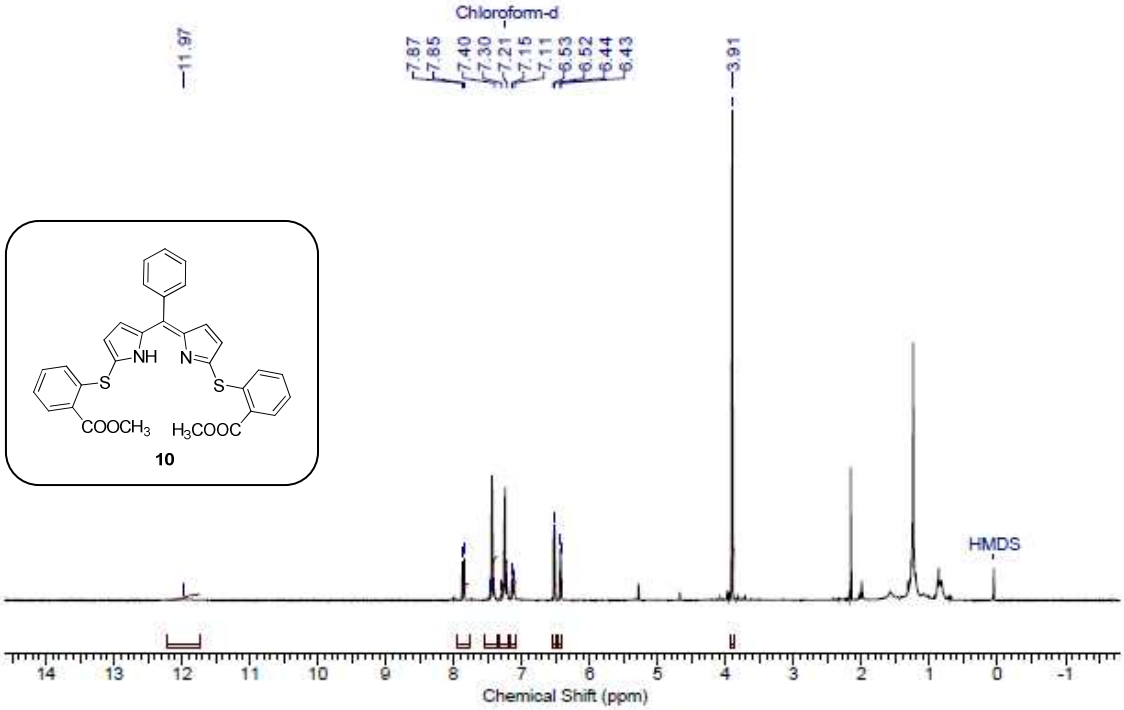


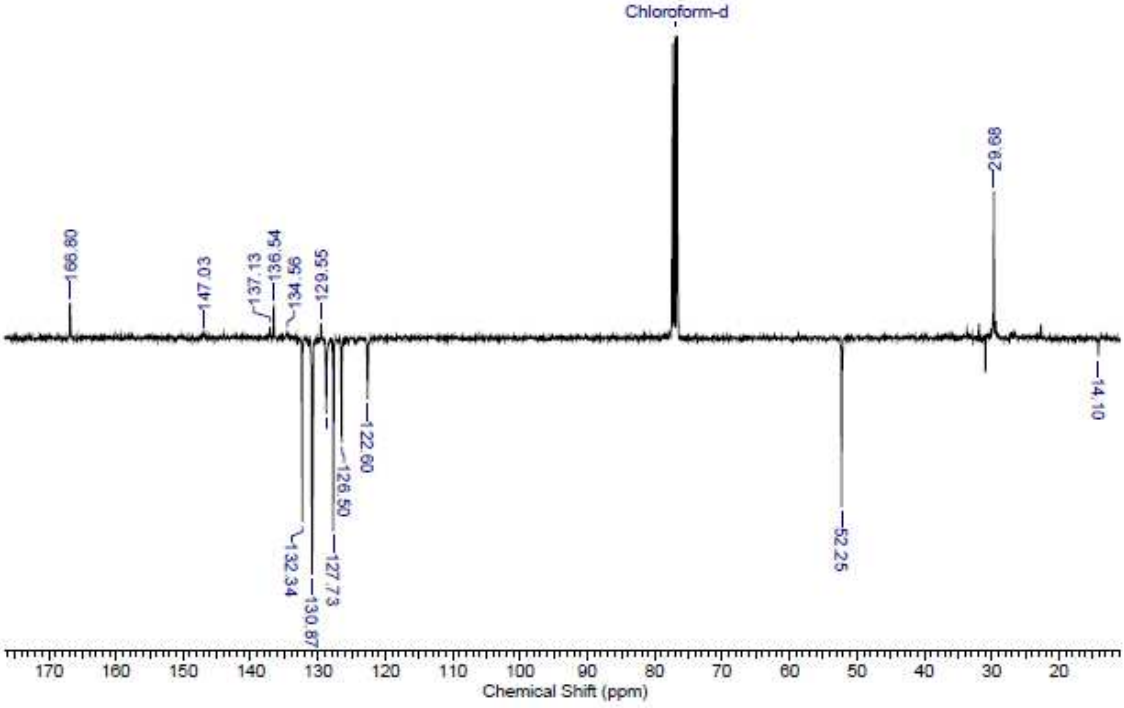

Chloroform-d
7.42
7.25
6.48
6.47
6.36
6.34
3.70
3.33
3.31
3.30
2.92
2.90
2.86
2.84
2.82
2.75
2.73
1.56
1.24
0.87
HMDS
NH
N
S
S
H3COOC
COOCH3
8
Chemical Shift (ppm)

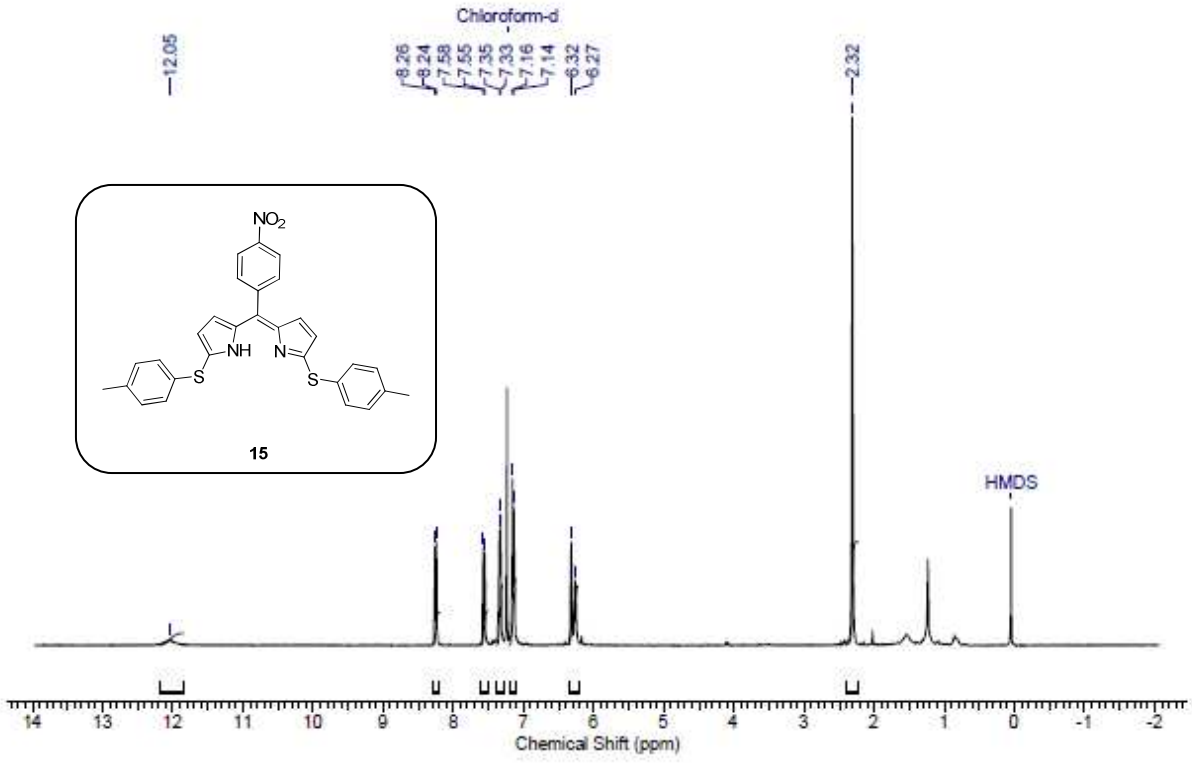

Chloroform-d
hexane
hexane
"grease"
hexane
34.42
29.69
28.87
31.91
22.68
hexane
14.10
13.91
172.06
148.24
141.91
136.63
133.61
130.75
127.72
120.77
51.88
Chemical Shift (ppm)

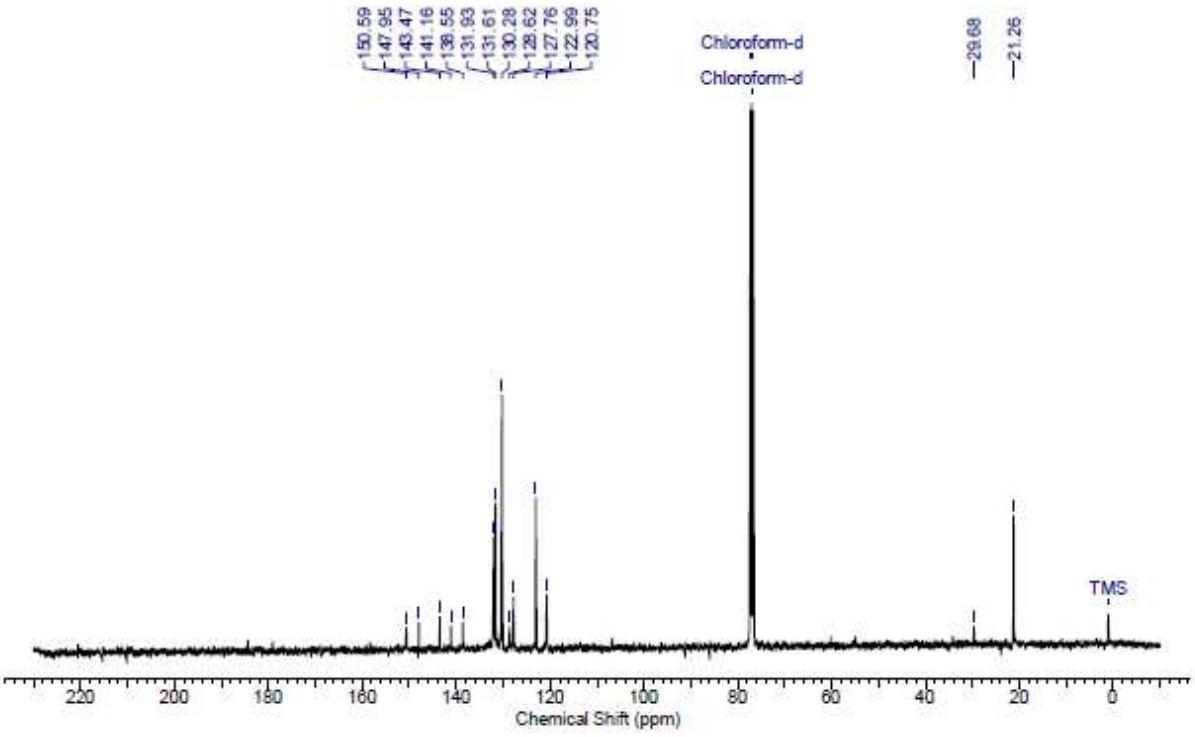

Chloroform-d
12.17
7.40
7.35
7.33
7.25
7.15
7.13
6.46
6.45
6.28
2.31
1.53
1.25
HMDS
NH
N
S
S
H3C
CH3
9
Chemical Shift (ppm)

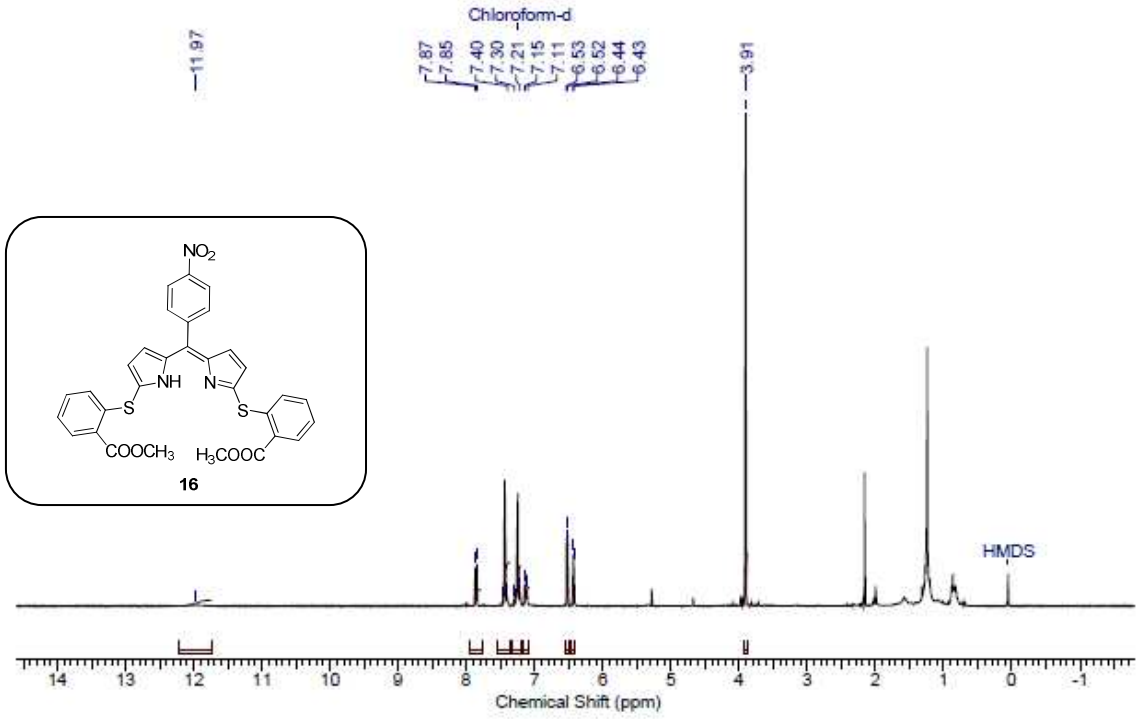

131.65
130.17
127.64
120.36
21.23
149.00
141.91
138.15
136.68
129.27
29.70
Chloroform-d
Chemical Shift (ppm)

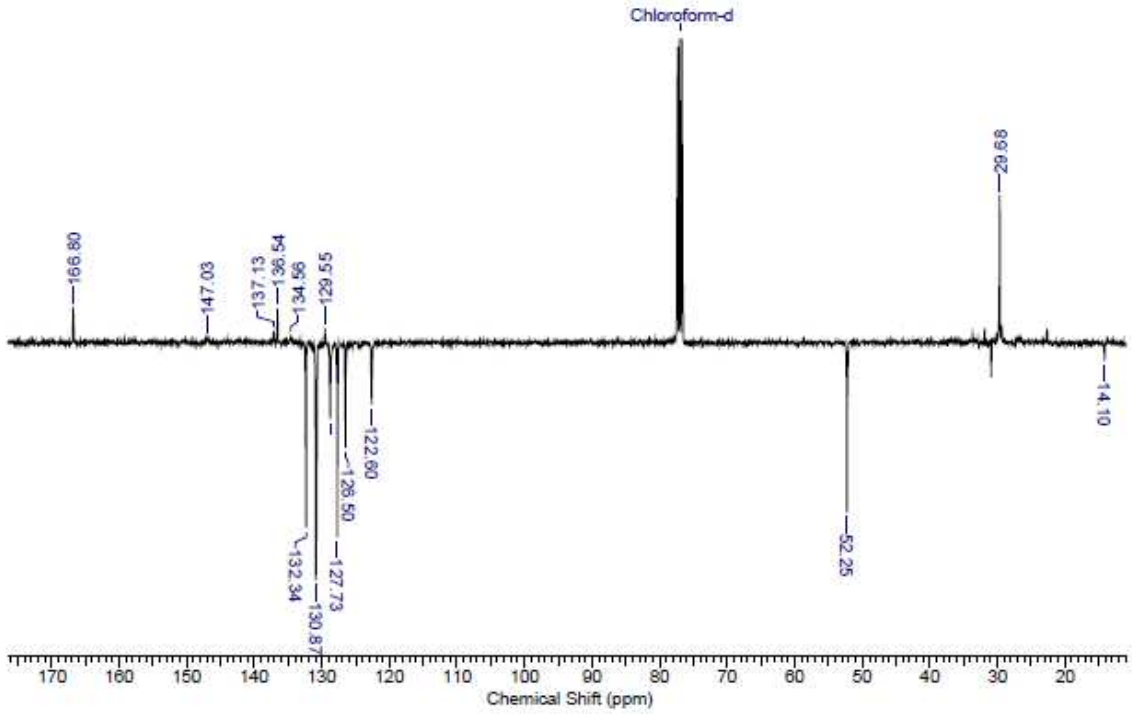

Chloroform-d
11.97
7.87
7.85
7.40
7.30
7.21
7.15
7.11
6.53
6.52
6.44
6.43
3.91
HMDS
NH
N
S
S
COOCH3
H3COOC
10
Chemical Shift (ppm)


Chloroform-d
166.80
147.03
137.13
136.54
134.56
129.55
122.60
126.50
127.73
132.34
130.87
52.25
29.68
14.10
Chemical Shift (ppm)

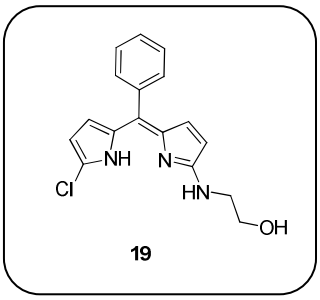

Chloroform-d
12.05
8.26
8.24
7.58
7.55
7.35
7.33
7.16
7.14
6.32
6.27
2.32
HMDS
NO2
NH
N
S
S
15
Chemical Shift (ppm)


150.59
147.95
143.47
141.16
138.55
131.93
131.61
130.28
129.62
127.76
122.99
120.75
Chloroform-d
Chloroform-d
29.68
21.25
TMS
Chemical Shift (ppm)

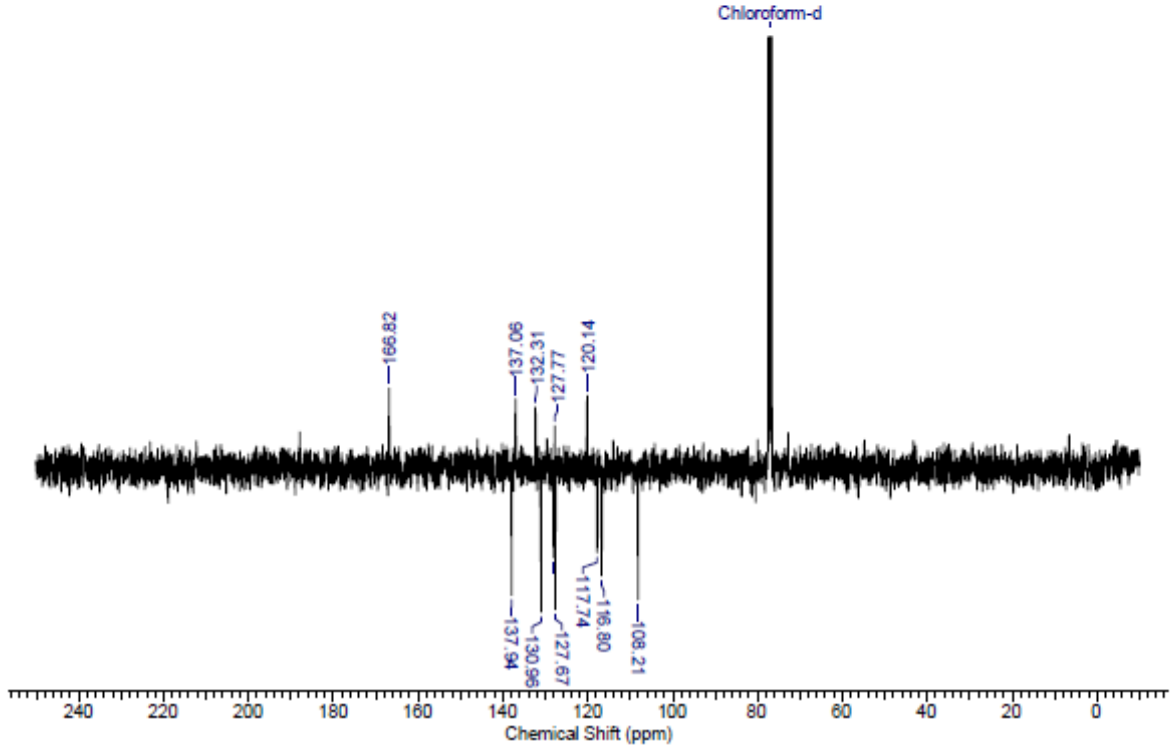

Chloroform-d
11.97
7.87
7.85
7.40
7.30
7.21
7.15
7.11
6.53
6.52
6.44
6.43
3.91
HMDS
NO2
NH
N
S
S
COOCH3
H3COOC
16
Chemical Shift (ppm)

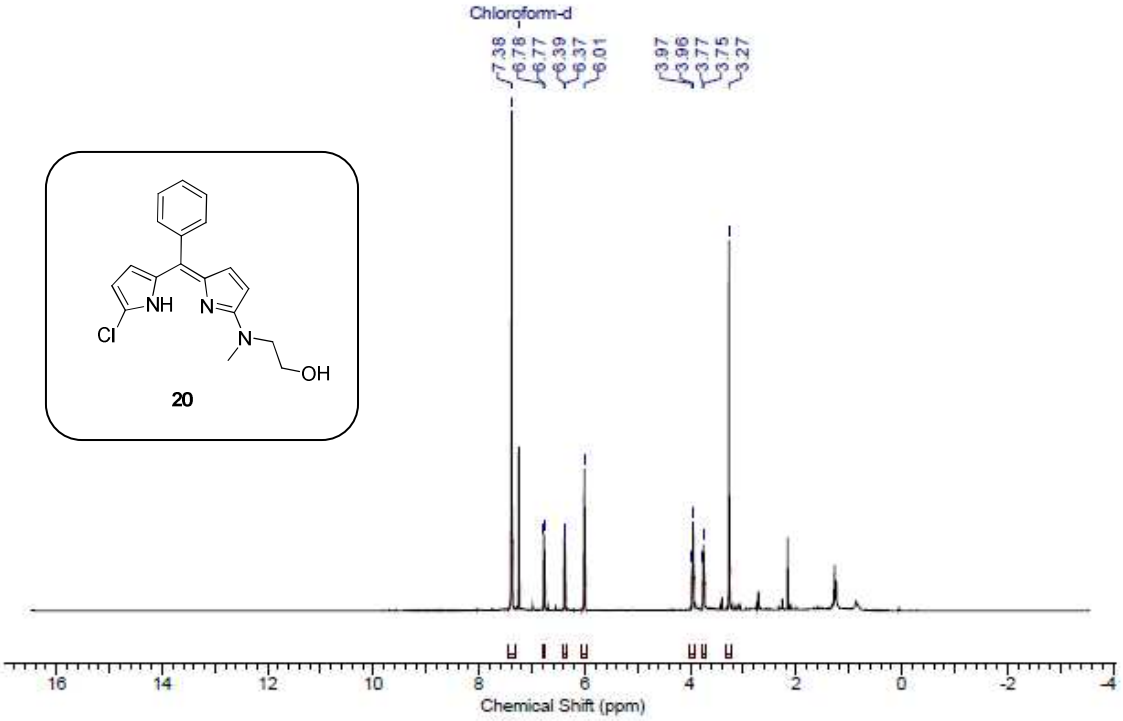

Chloroform-d
166.80
147.03
137.13
136.54
134.56
129.55
122.60
132.34
130.87
128.50
127.73
52.25
29.68
14.10
Chemical Shift (ppm)

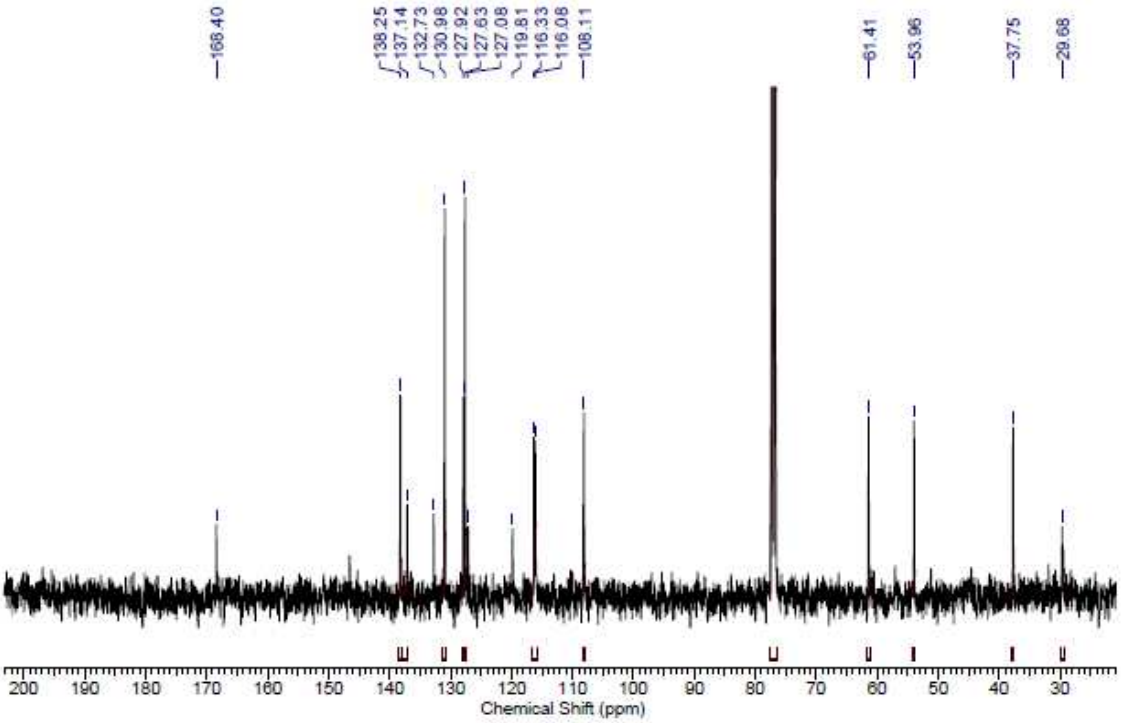
2.NMR spectra of N-substitution products

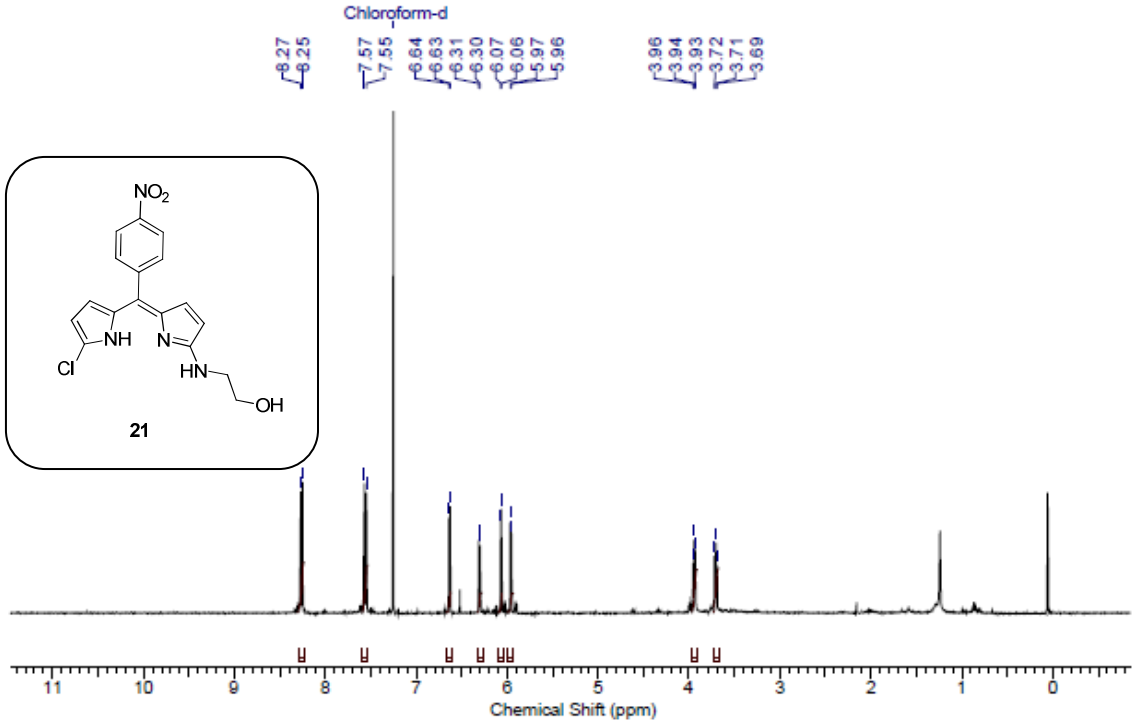


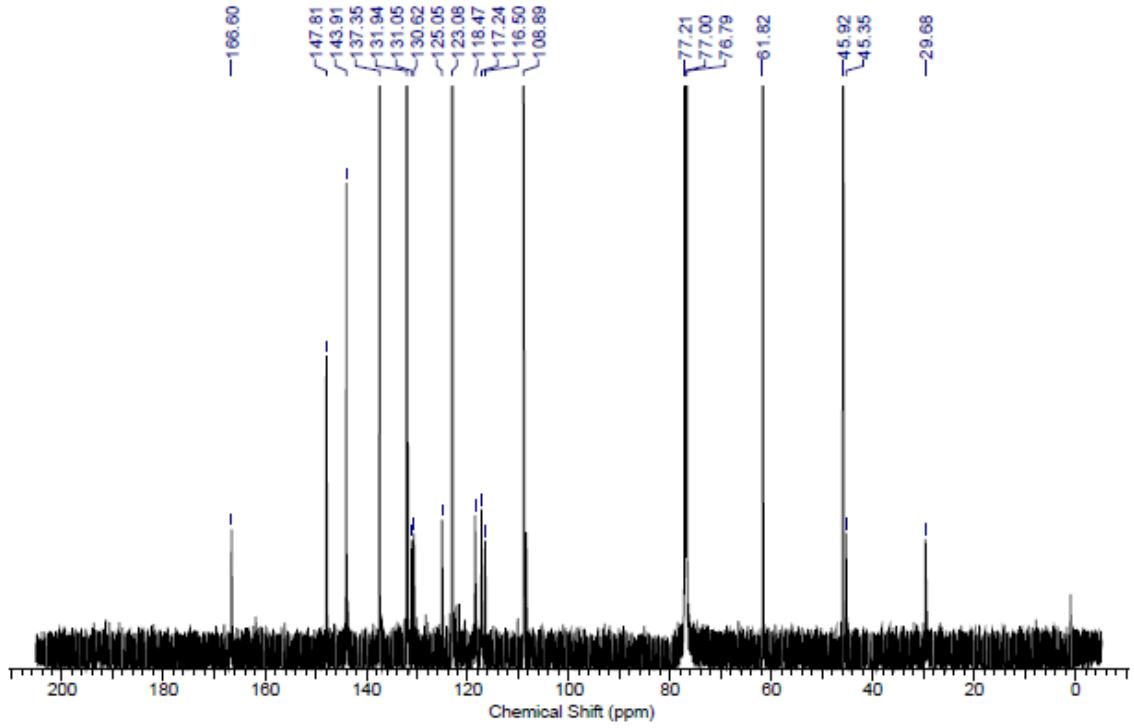
19

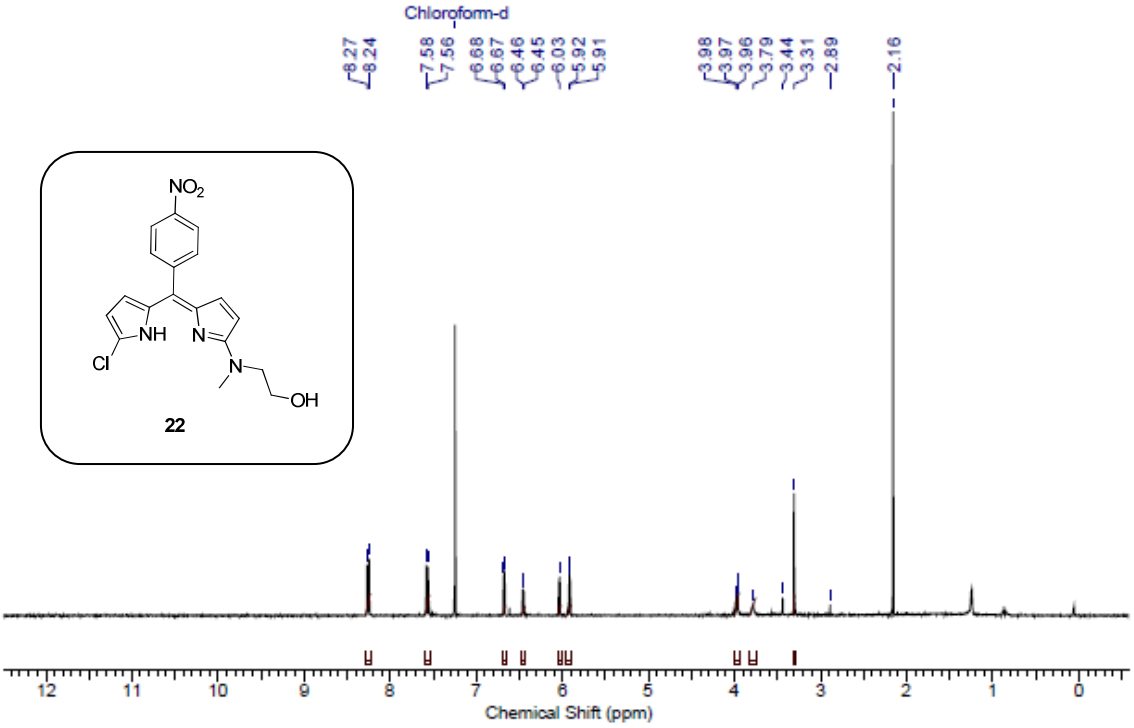


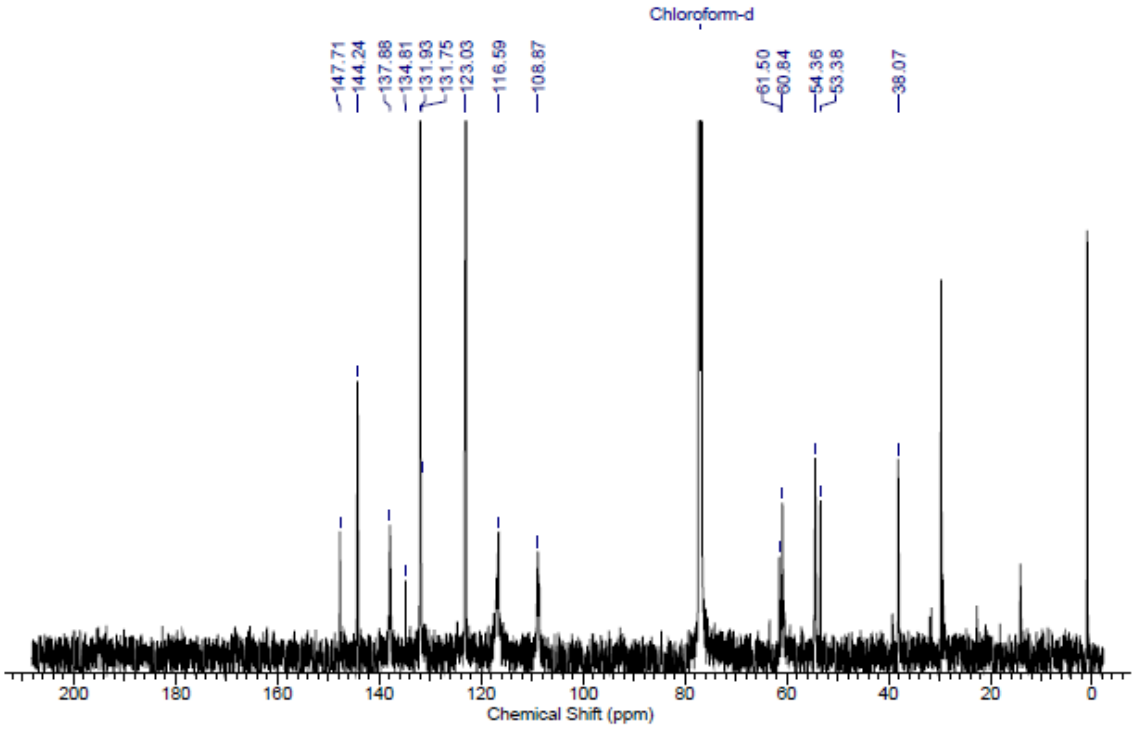

Chloroform-d
7.38
6.78
6.77
6.39
6.37
6.01
3.97
3.96
3.77
3.75
3.27
NH
N
Cl
N
OH
20
Chemical Shift (ppm)


166.40
138.25
137.14
132.73
130.98
127.92
127.63
127.08
119.81
116.33
116.08
108.11
61.41
53.96
37.75
29.68
Chemical Shift (ppm)

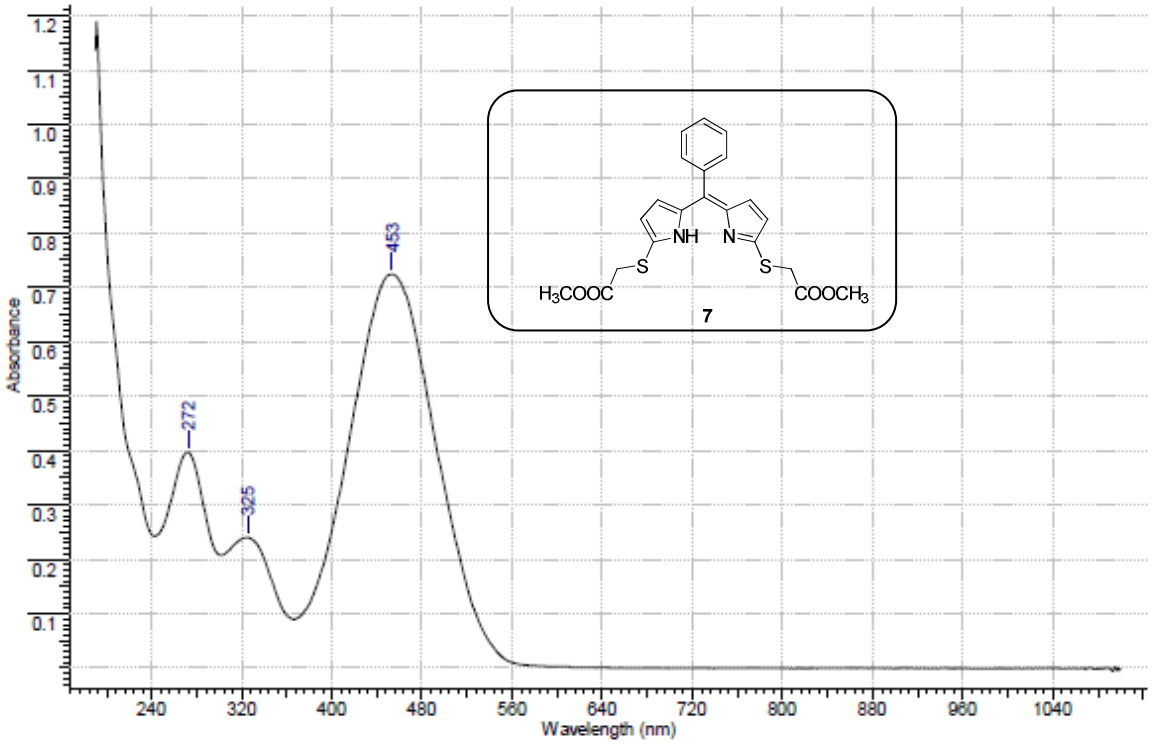

Chloroform-d
8.27
8.25
7.57
7.55
6.64
6.63
6.31
6.30
6.07
6.06
5.97
5.96
3.96
3.94
3.93
3.72
3.71
3.69
NO2
NH
N
Cl
HN
OH
21
Chemical Shift (ppm)

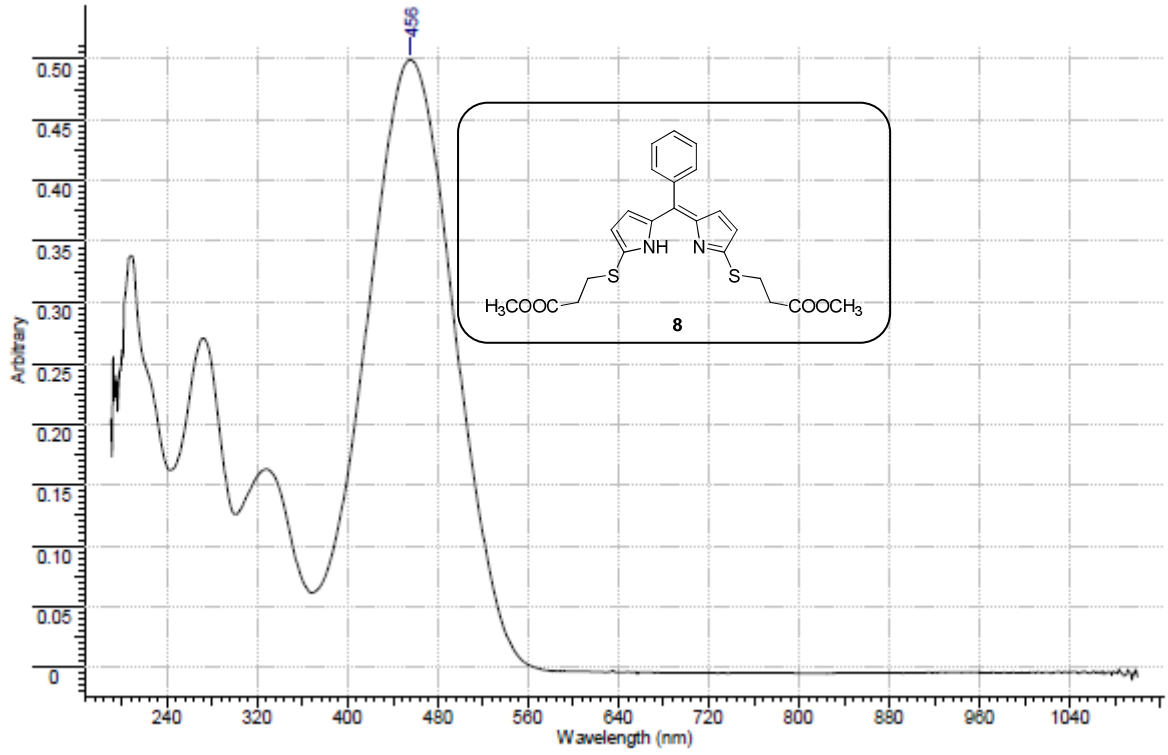

166.60
147.81
143.91
137.35
131.94
131.05
130.62
125.05
123.08
118.47
117.24
116.50
108.89
77.21
77.00
76.79
61.82
45.92
45.35
29.68
Chemical Shift (ppm)

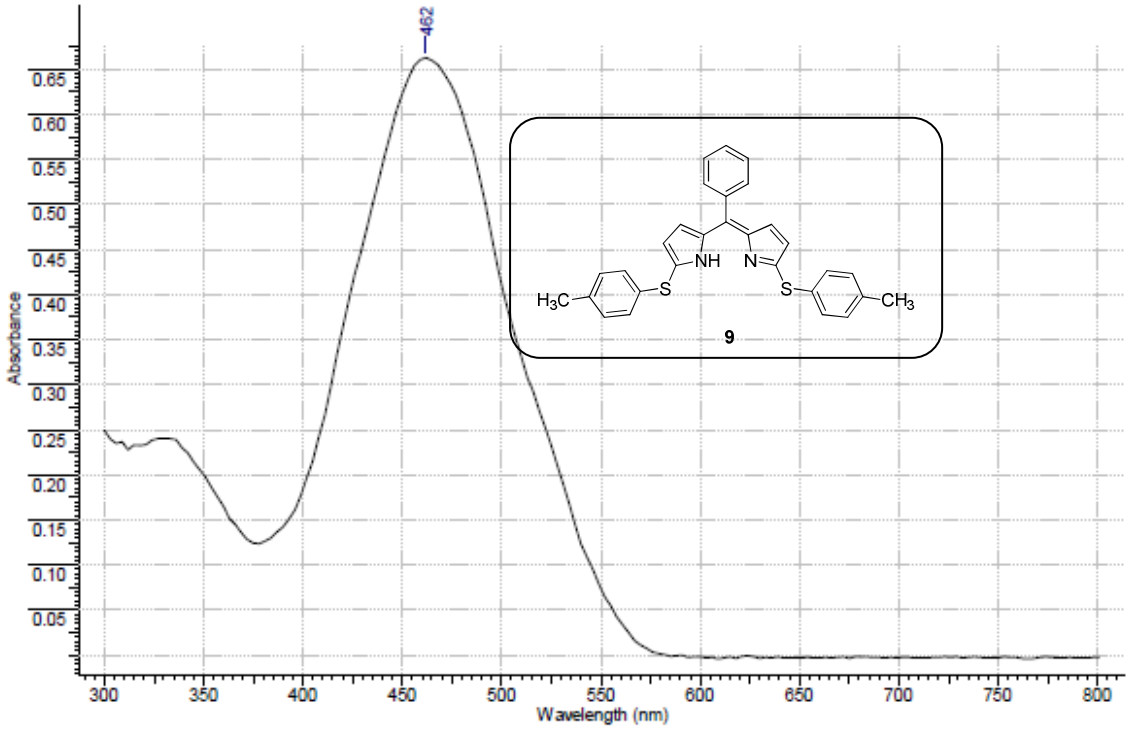

Chloroform-d
8.27
8.24
7.58
7.56
6.68
6.67
6.46
6.45
6.03
5.92
5.91
3.98
3.97
3.96
3.79
3.44
3.31
2.89
2.16
NO2
NH
N
N
Cl
OH
22
Chemical Shift (ppm)

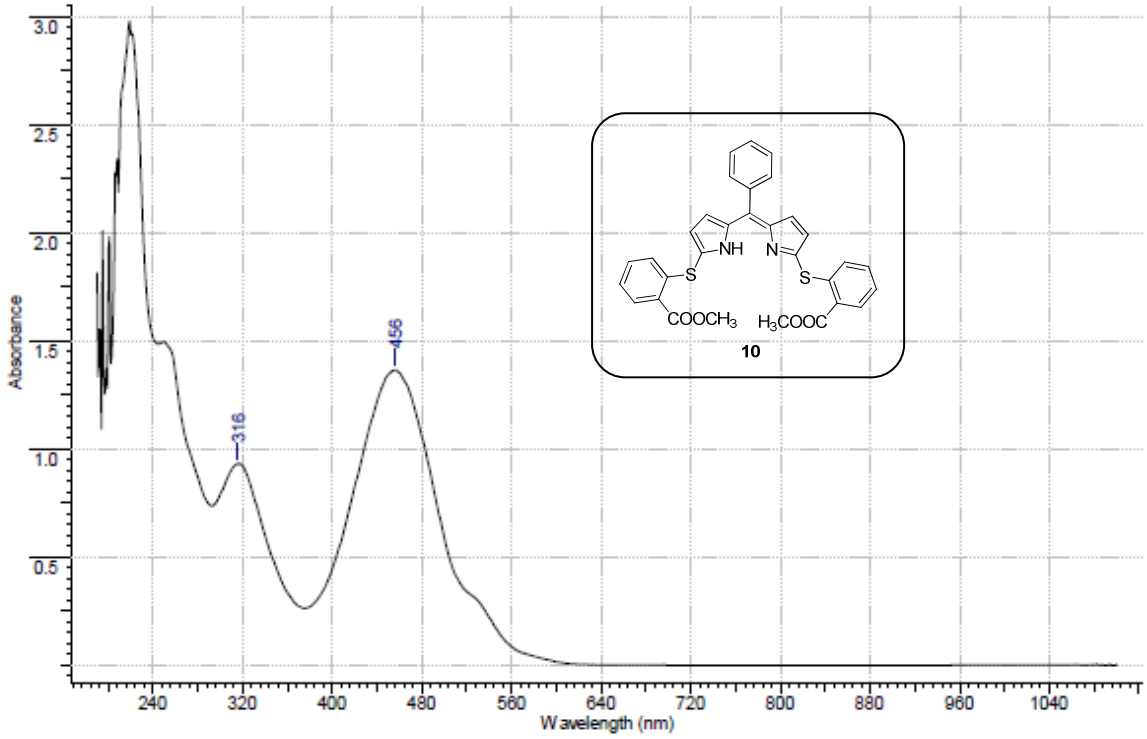

Chloroform-d
147.71
144.24
137.88
134.81
131.93
131.75
123.03
116.59
108.87
61.50
60.84
54.36
53.38
38.07
Chemical Shift (ppm)

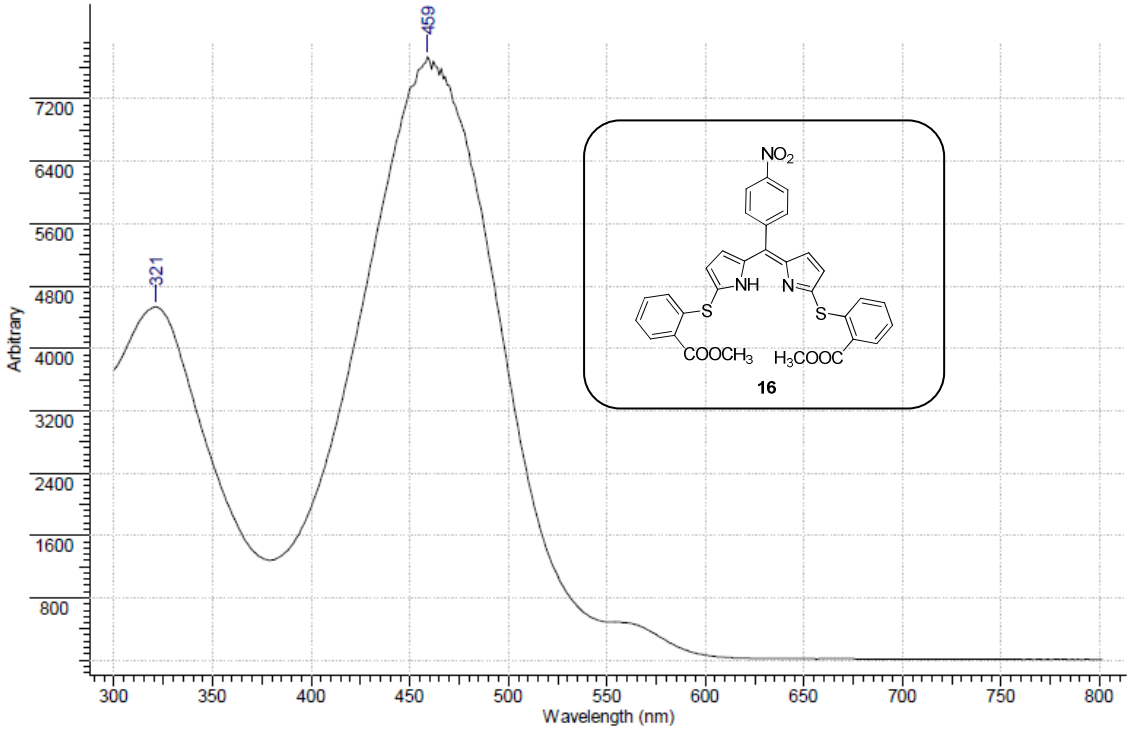
3.UV-Vis spectra of S-substitution products

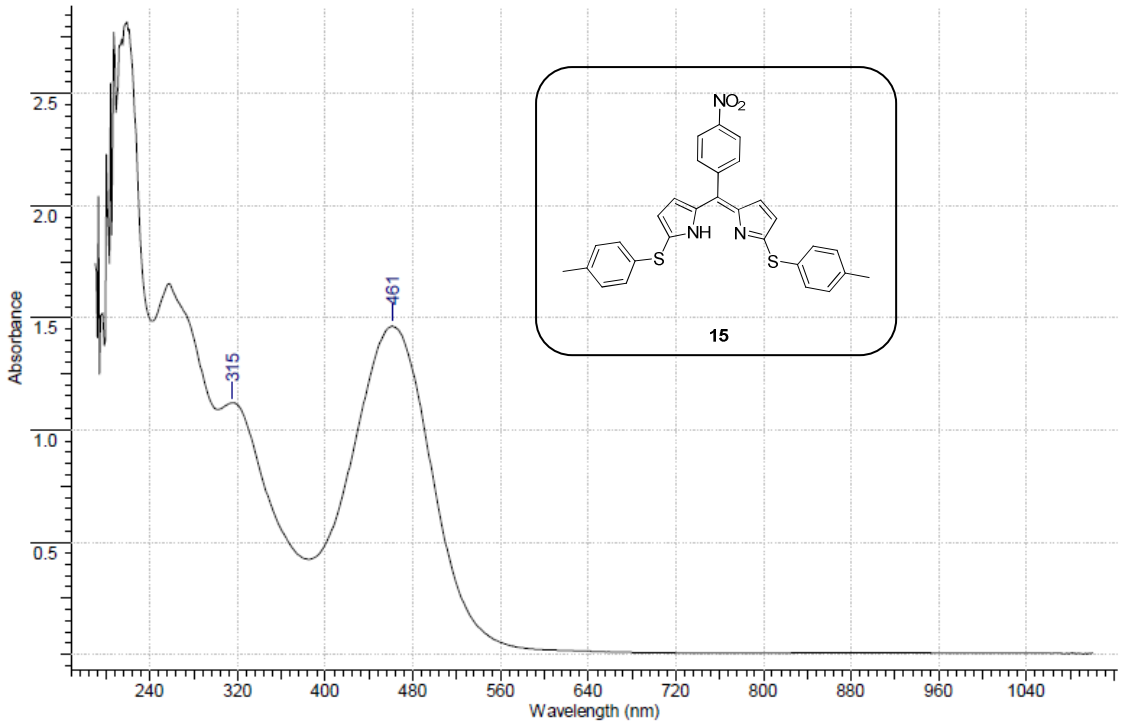


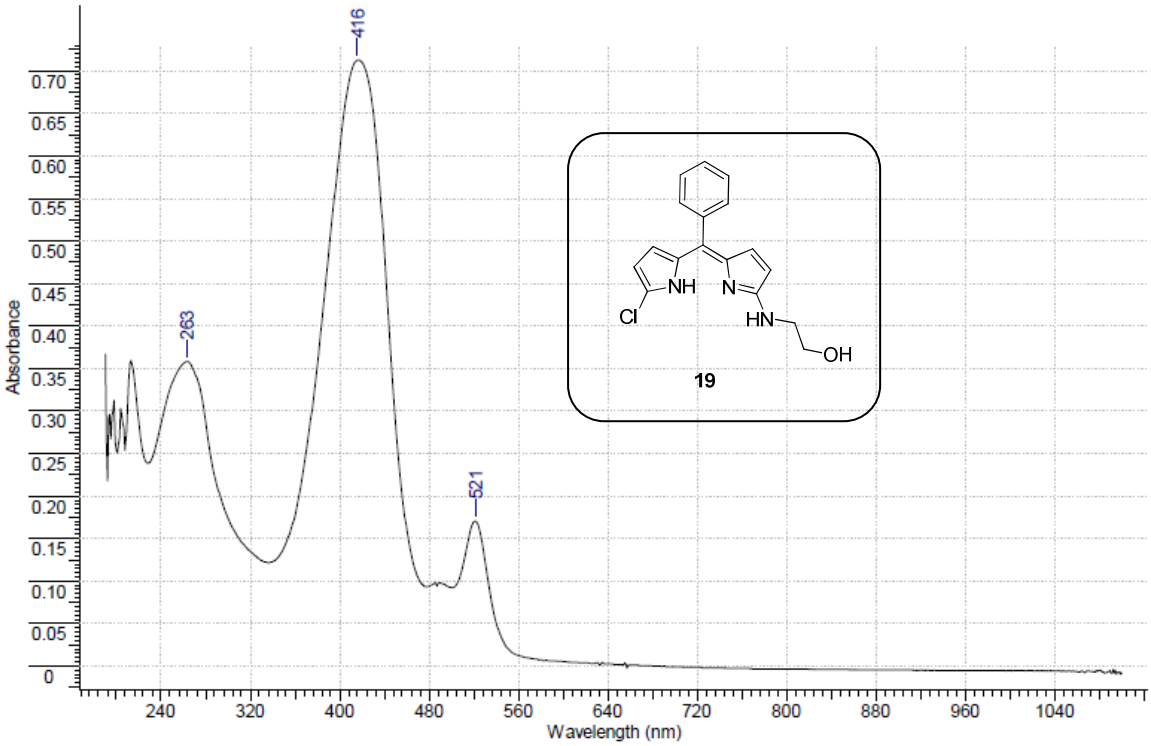


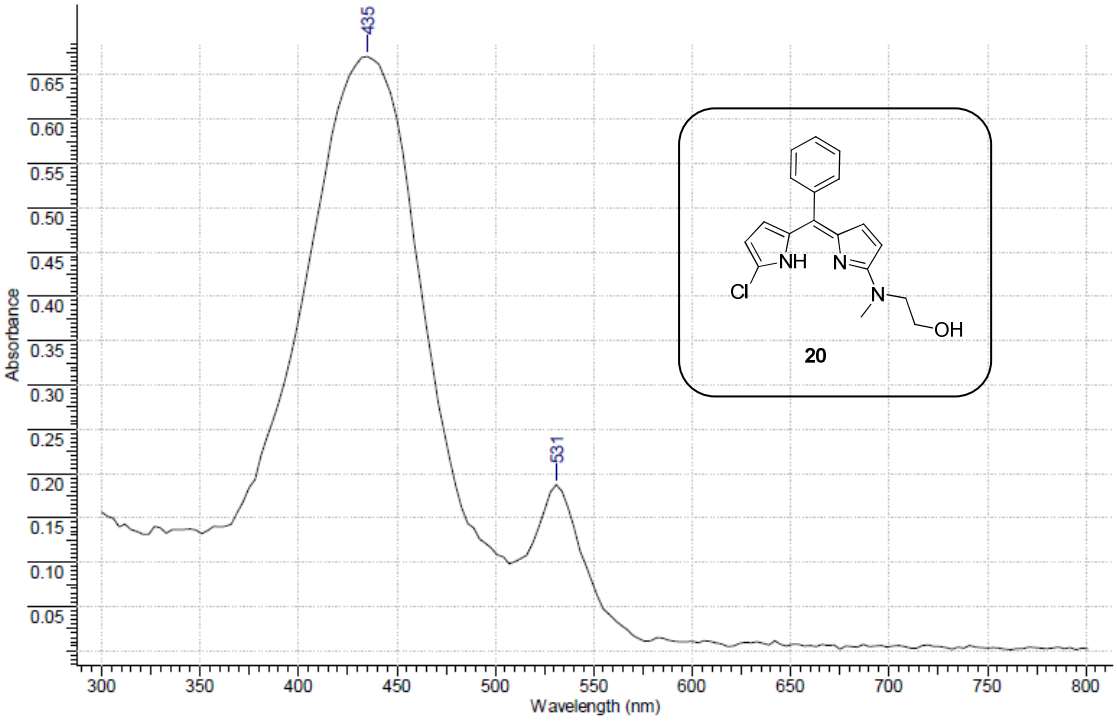

462
Absorbance
Wavelength (nm)
NH
N
S
S
H3C
CH3
9

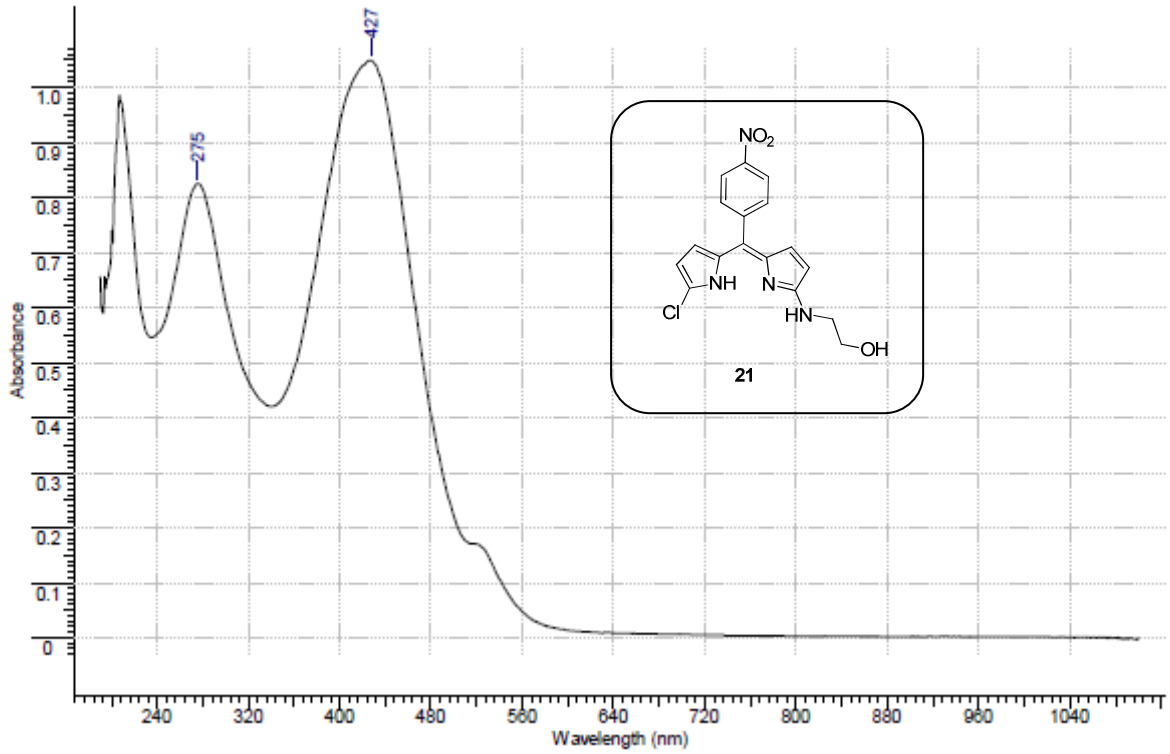

316
456
Absorbance
Wavelength (nm)
NH
N
S
S
COOCH3
H3COOC
10

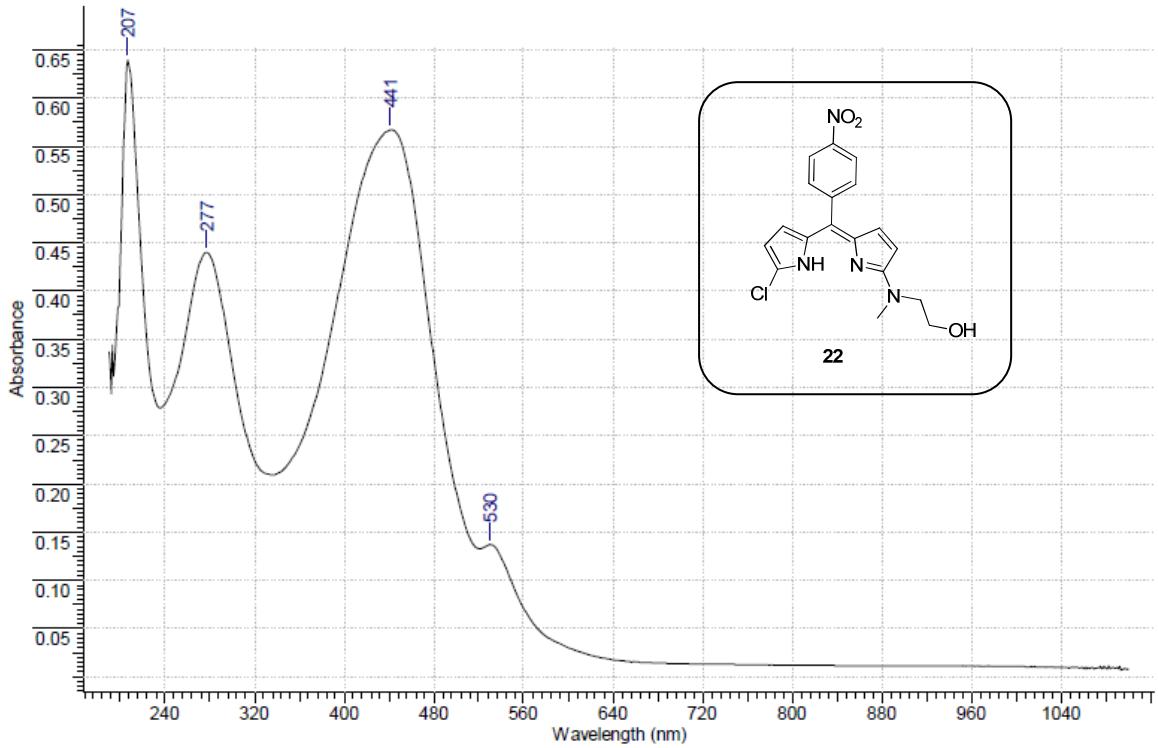

459
321
Arbitrary
7200
6400
5600
4800
4000
3200
2400
1600
800
300
350
400
450
500
550
600
650
700
750
800
Wavelength (nm)
NO2
NH
N
S
S
COOCH3
H3COOC
16


461
315
Absorbance
2.5
2.0
1.5
1.0
0.5
240
320
400
480
560
640
720
800
880
960
1040
Wavelength (nm)
NO2
NH
N
S
S
15


416
263
521
Absorbance
Wavelength (nm)
NH
N
Cl
HN
OH
19

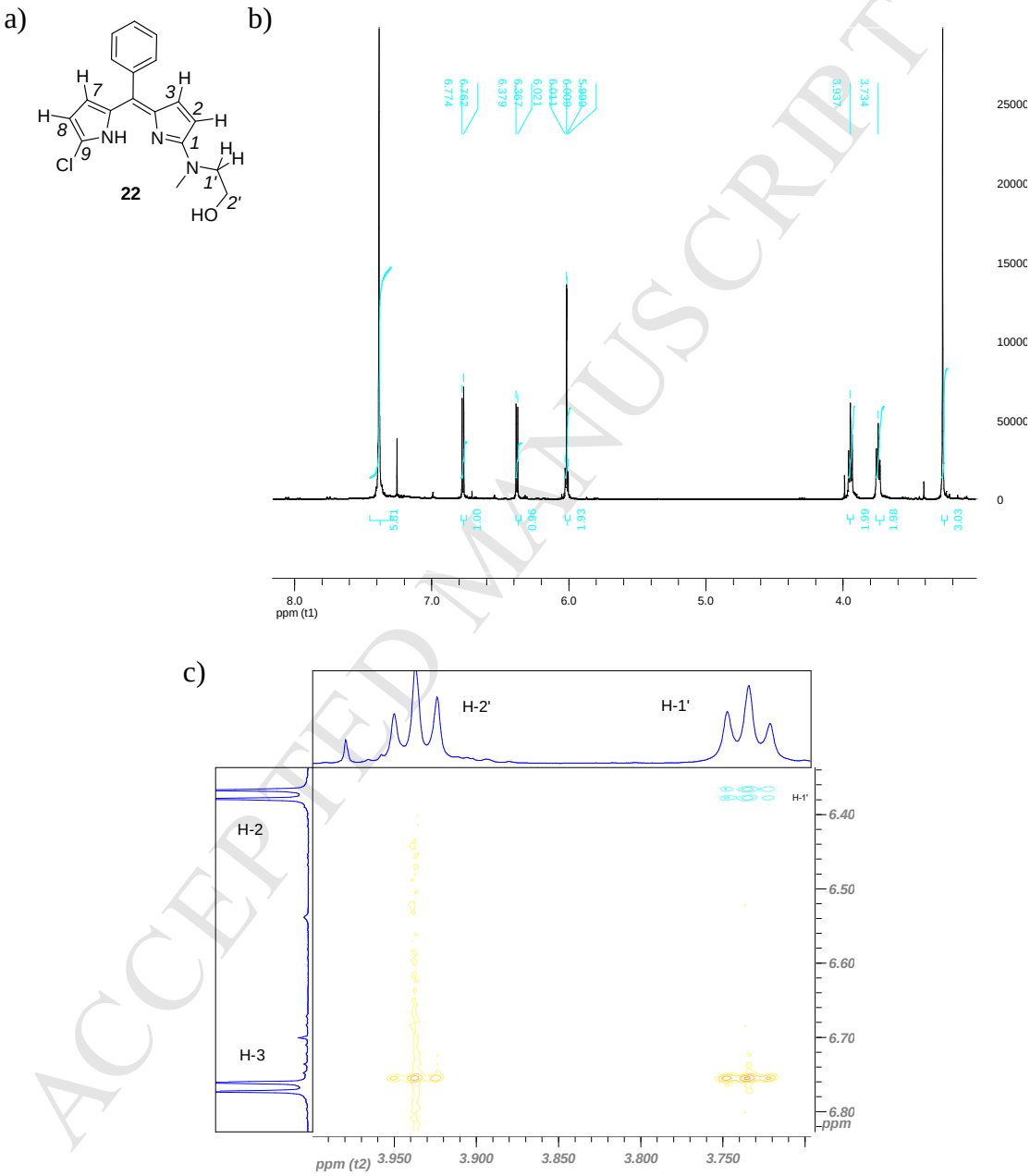

435
531
Absorbance
Wavelength (nm)
NH
N
Cl
N
OH
20


427
275
Absorbance
Wavelength (nm)
NO2
NH
N
Cl
HN
OH
21


207
277
441
530
Absorbance
Wavelength (nm)
NO2
NH
N
Cl
N
OH
22

4.NOESY data of 20 spectra of S-substitution products

Figure S1. a) Structure, b) ^{1}H NMR and c) part of the NOESY experiment of **22** confirming the predominant position of the pyrrole ring.



- Free 1,9-Dichlorodipyrrins indergo nucleophilic substitution by S- and N-nucleophiles
- S-Nucleophiles yield disubstition resulting in 1,9-dithiadipyrrins
- N-Nucleophiles quantitatively substitute only one chlorine atom
- UV-Vis spectra of bis-S-substituted products shift bathochromically as to that of dichlorides
- Mono-N-substituted products with H-bonding group feature two bands in the UV-Vis spectra