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Thieme

Supporting Information

Facile preparation of Λ-shaped building blocks: Hünlich-base derivatization

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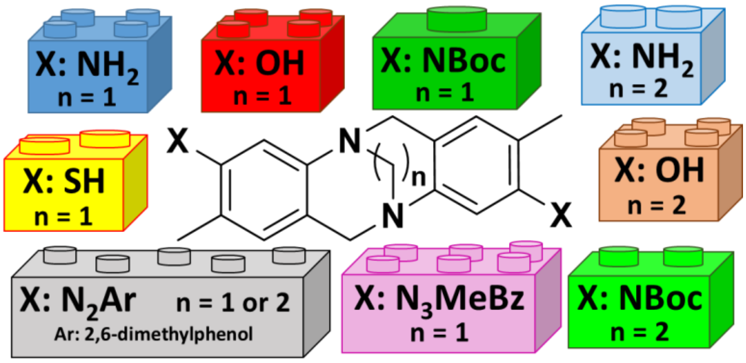

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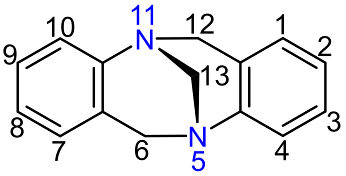
Materials and Methods:

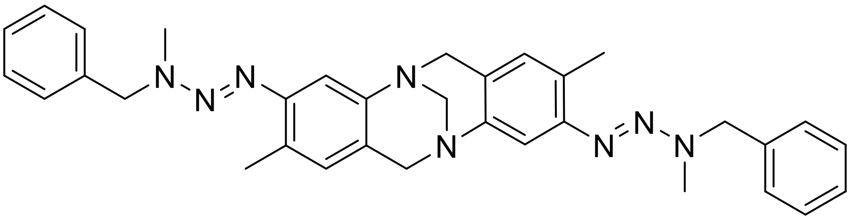
Except for Hünlich's base and 1,2-dibromoethane, all other chemicals were supplied by Sigma-Aldrich, Merck, BOC and Fluka companies. Agilent-6130 or Shimadzo-2010EV mass spectrometers, Varian-Cary-1 and Eppendorf-BioSpektrometer-kinetic spectrophotometers and Thermo-Scientific-Nicolet-iS5/ATR10 spectrophotometer recorded the MS, UV/Vis, and IR spectra. The reaction completion was checked by Thin Layer Chromatography (TLC) on UV-activate silica gel plates of 256nm. Chromatography columns were filled with silica gel (40–63 µm) and mobile phases are displayed by a retardation factor (R_f) for each product. Elemental analysers Vario-EL-Elementar and PerkinElmer-2400-series-II performed the micro-elemental analysis. Bruker-AVANCE-DRX NMR spectrometer and Topspin® software were used to obtain NMR spectra calibrated depending on the applied solvent and the chosen nucleon as follow: ^{1}H (400.0 MHz): 7.26 and 2.50 ppm, and ^{13}C (100.6 MHz): 77.16 and 39.52 ppm for $CDCl_3$ and DMSO-d_6, respectively. The NMR splitting, integrals, and coupling constants, are displayed by the common standards.



Numbering the atoms on Hünlich-base scaffold

1. Preparation and Purification of Compound (1)

3,9-bis((E)-3-benzyl-3-methyltriaz-1-en-1-yl)-2,8-dimethyl-6H,12H-5,11-methanodibenzo [b,f][1,5] diazocine



Hünlich's base (0.56 g, 2.0 mmol, 1.0 eq.) solution in H_2SO_4 (6.5%, 30 mL) was cooled down to -5°C. A sodium nitrite solution (0.30 g, 4.4 mmol, 2.2 eq. in 5 mL cold water) was dropped into the reaction flask and stirred for 30 min. The resulting yellowish solution was poured into a solution consisting *N*-benzylmethylamine (3 ml, excess), Na_2CO_3 (4.5 g), 60 mL of water, and 30ml of ACN chilled at -10°C. The stirring was continued for 3 h meanwhile the temperature was gradually raised to r.t.; afterward, a beige precipitate was extracted from the aqueous mixture by DCM (3x50 mL). The DCM layers were combined, dried over Na_2SO_4 and filtered. The evaporation of the DCM gave the crude product which was then purified by chromatography to furnish the purified bis-triazene compound **1** as a light-yellow solid.

Yield: 0.65 g (1.2 mmol, 60%); *R*$_f$: 0.3 (silica gel; MeOH–DCM, 2% v/v).

IR (neat): 3027, 2941, 2893, 2844, 1610, 1486, 1441, 1341, 1173, 1047, 921 and 697 cm^{-1}.

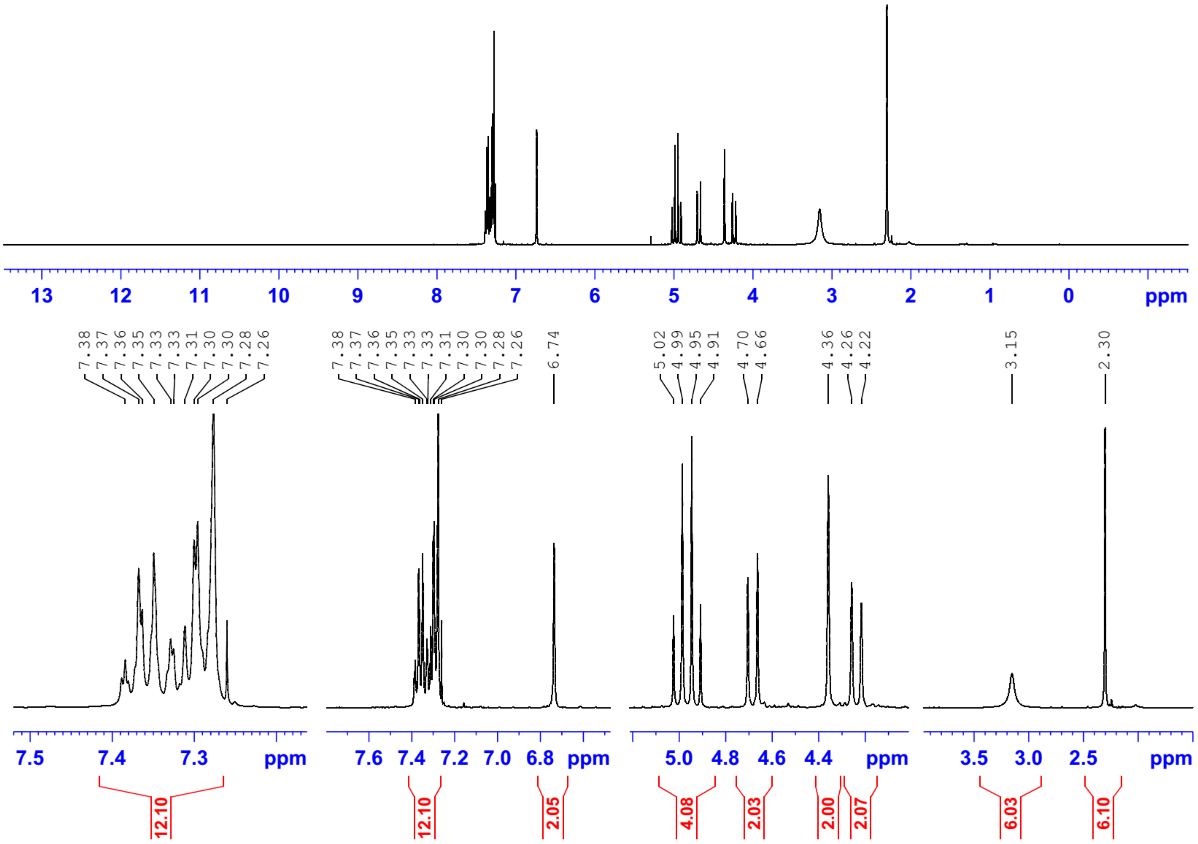
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28–7.38 (m, 12H, CH), 6.74 (s, 2H, CH), 4.91–5.02 (q, *J* = 16.1 Hz, 4H, NCH$_2$), 4.66–4.70 (d, *J* = 16.6 Hz, 2H, CH$_2$) , 4.36 (s, 2H, NCH$_2$N), 4.22–4.26 (d, *J* = 16.8 Hz, 2H, CH$_2$) , 3.15 (b, 6H, NCH$_3$), 2.30 (s, 6H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 147.9, 146.3, 137.1, 129.0, 128.7, 128.6, 128.0, 127.7, 125.1, 112.7, 67.3, 58.8, 34.4, 17.2.

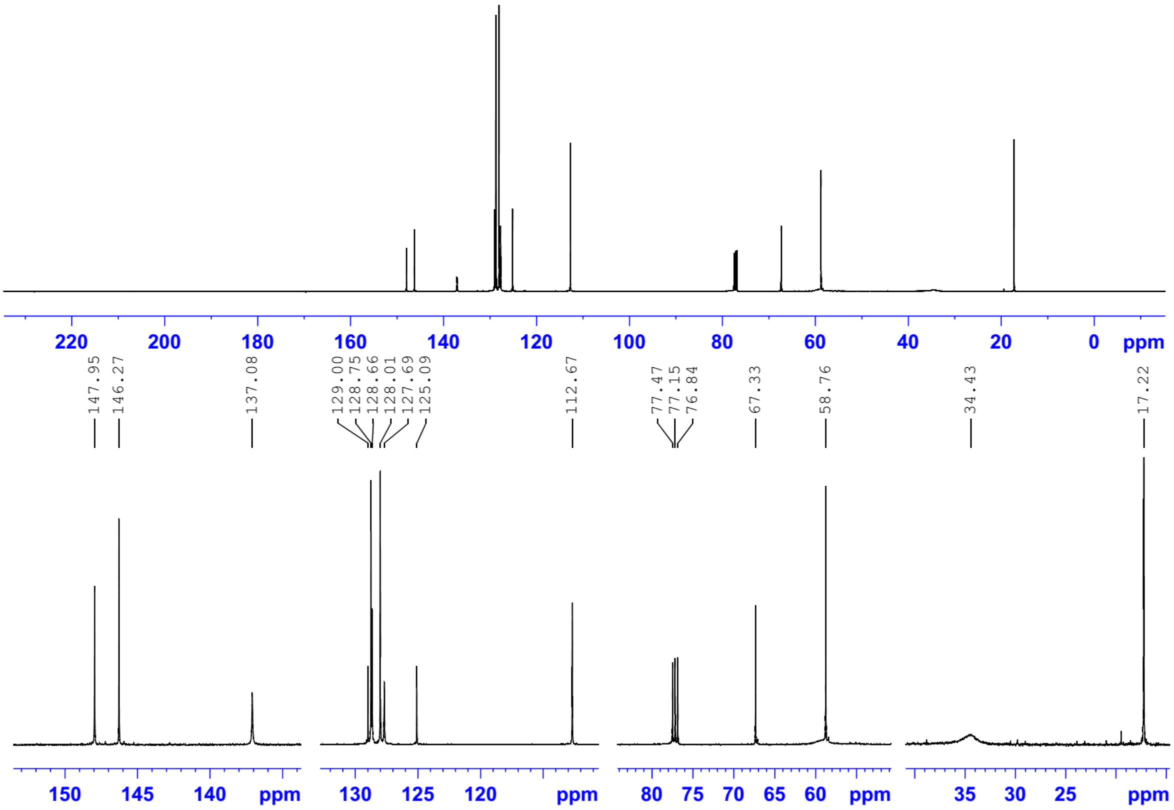
MS (ESI +; *i*-PrOH): *m/z* [M + H]$^+$ calcd for [C$_{33}$H$_{37}$N$_8$]$^+$: 545.31; found 545.2.

UV/Vis: (EtOAc): λ (lg ε) = 297 (4.465) nm.

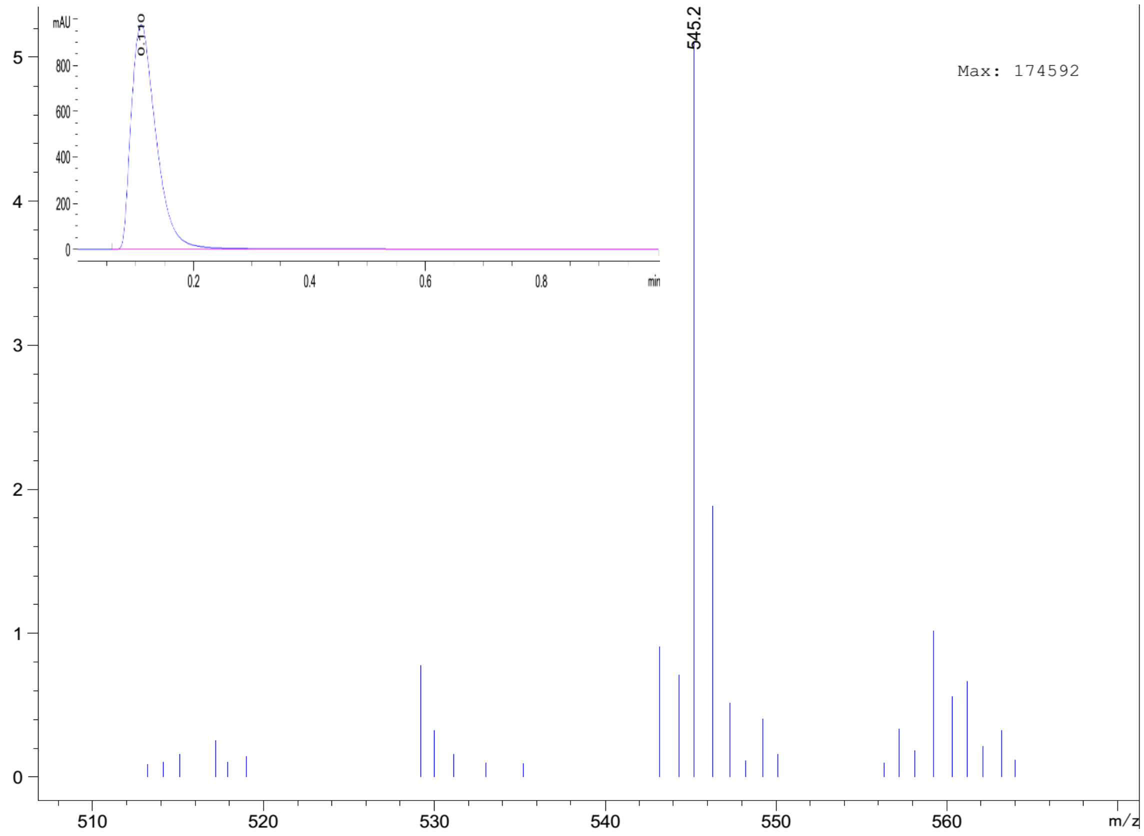
Anal. Calcd for C$_{33}$H$_{36}$N$_8$: C, 72.77; H, 6.66; N, 20.57. Found: C, 72.56; H, 6.85; N, 20.18.



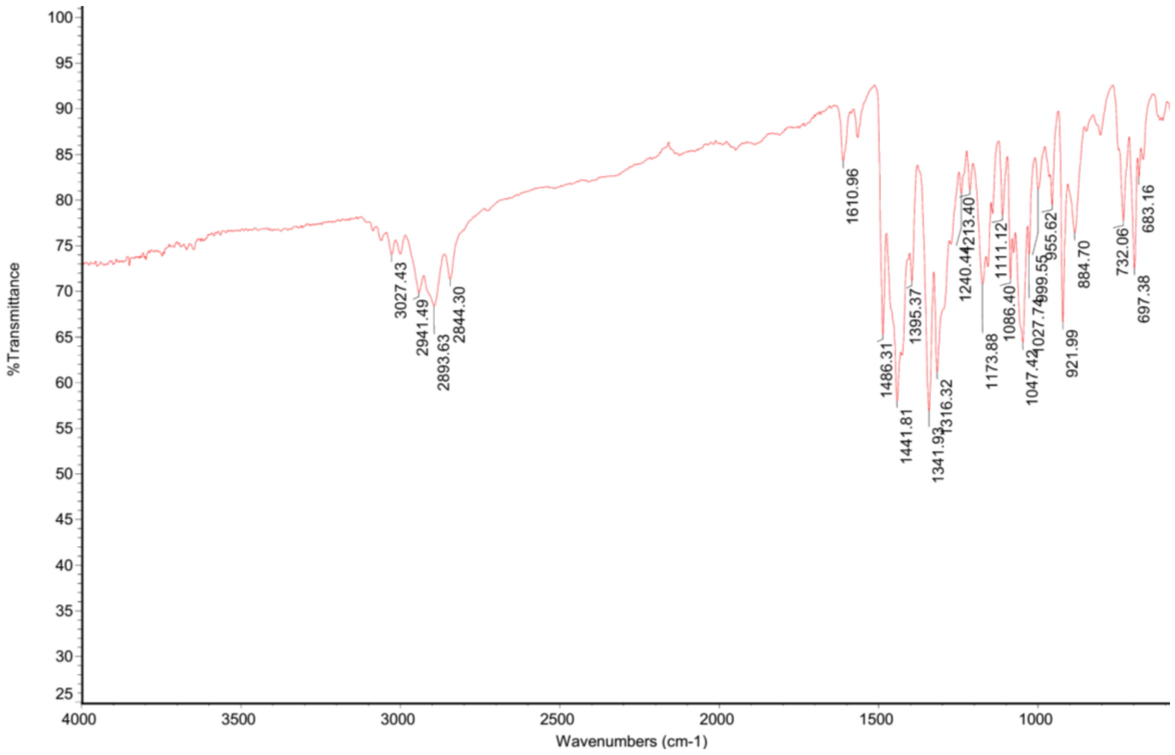
Compound 1, ^{1}H NMR (400 MHz, CDCl$_3$)



Compound 1, ^{13}C NMR (100 MHz, $CDCl_3$)



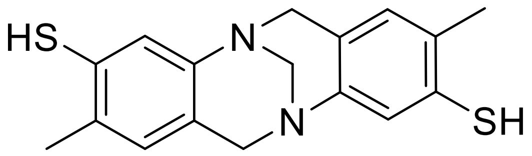
Compound 1, MS (ESI+)



Compound 1, IR transmittance (neat)

2. Preparation and Purification of Compound (2)

2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-3,9-dithiol



The bis-triazene compound **1** (0.54 g, 1.0 mmol, 1.0 eq.) was poured into a 50ml round-bottom flask containing DCM (20 mL). A solution of trichloroacetic acid (5.0 g, 30 mmol, excess, in DCM 20 mL) was added and stirred for 2 min. Afterward, Na_2S (0.70 g, 9 mmol, excess) was slowly added to the reaction flask, as shown in the following figure, and remained sealed when stirred for 2 hours at rt. The volume of the resulting yellowish suspension was then reduced to half by nitrogen gas flow and then refluxed for 30 min. The reaction mixture cooled down to rt and diluted with DCM (100 mL), and filtered. The DCM layer was rinsed with cold water (5 X 100 mL), dried over Mg_2SO_4 and filtered. The DCM was removed and the residue was purified by column chromatography to obtain a pale-lemon substance with a mild rotten-egg odour which was then stored under argon in darkness.

Yield: 0.06 g (0.19 mmol, 19 %); R_f = 0.2 (silica gel; MeOH–DCM, 4% v/v).

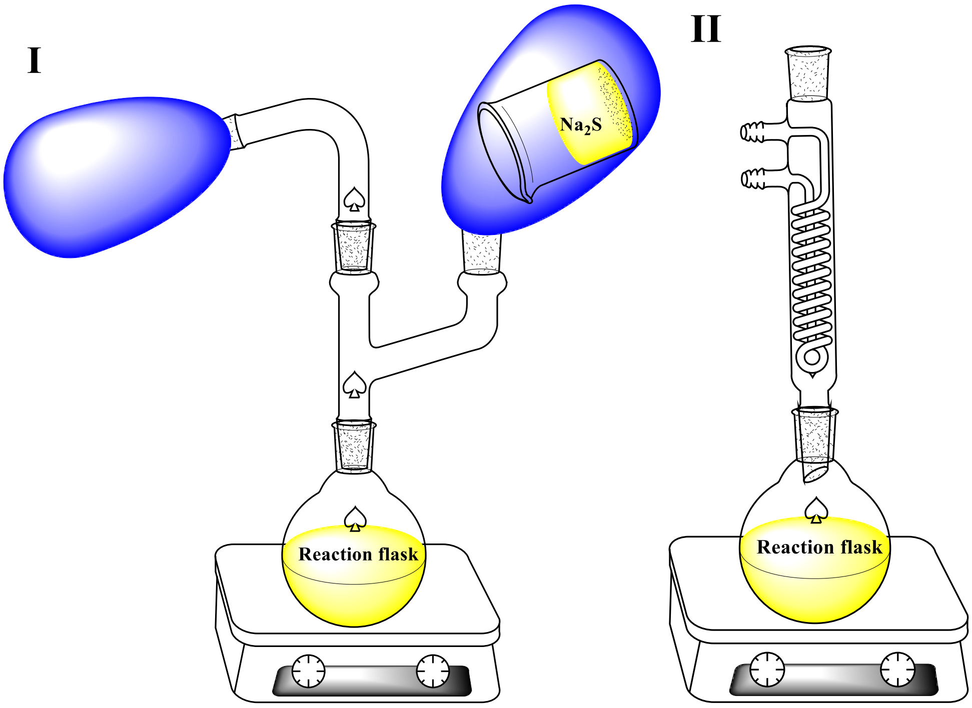
IR (neat): 2896, 2847, 2560, 1608, 1492, 1474, 1205, 1091, 1010, 811 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (br, 2 H, SH), 6.65 (s, 2 H, CH), 6.17 (s, 2 H, CH), 4.56–4.60 (d, *J* = 16.7 Hz, 2 H), 4.28 (s, 2 H, NCH_2N), 4.17–4.13 (d, *J* = 16.8 Hz, 2 H), 2.10 (s, 6 H, $2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 134.5, 128.6, 127.4, 126.8, 124.7, 67.1, 58.4, 20.9.

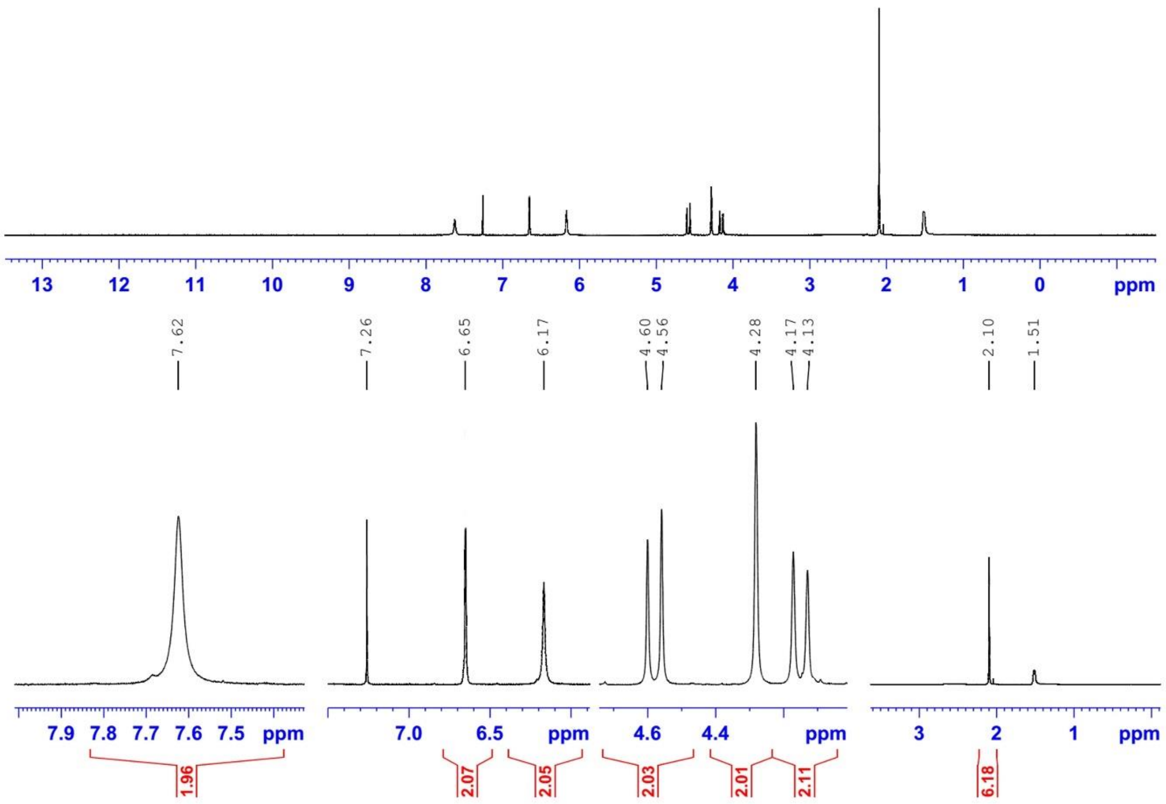
MS (ESI +; *i*-PrOH–EtOAc–H_2O/0.5% HCO_2Na, 90:5:5): *m/z* $[M + Na]^+$ calcd for $[C_{17}H_{18}N_2S_2Na]^+$: 337.08; found: 337.0. MS (ESI –): *m/z* $[M - H]^-$ calcd for $[C_{17}H_{17}N_2S_2]^-$: 313.09; found: 313.1. MS (ESI +; ACN/Δ): *m/z* $[M + 2ACN + H]^+$ calcd for $[C_{21}H_{25}N_4S_2]^+$: 397.14; found: 397.1.

UV/Vis: (EtOAc): λ (lg ε) = 277 (3.583) nm.
Anal. Calcd for $C_{17}H_{18}N_2S_2$: C, 64.93; H, 5.77; N, 8.91; S, 20.39. Found: C, 65.08; H, 5.83; N, 9.22.

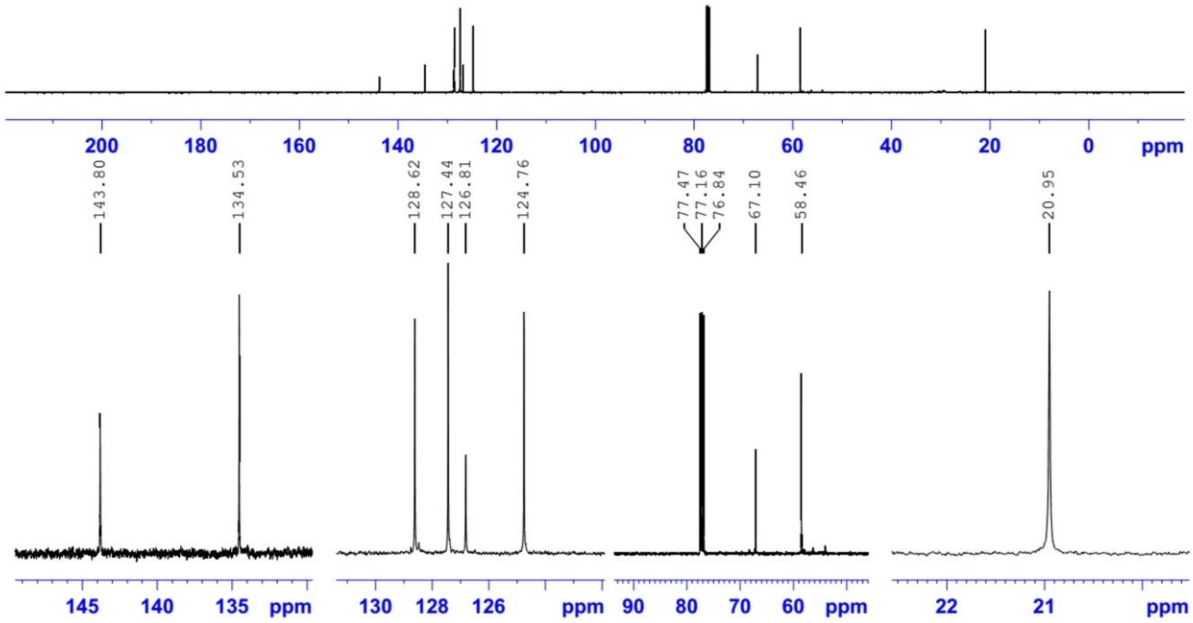


The apparatus used for compound 2 synthesis

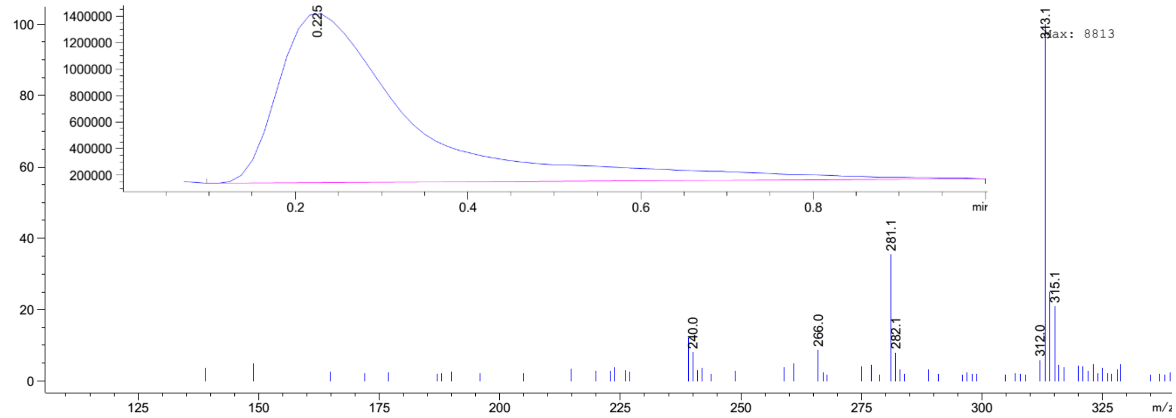
The balloons (shown in blue) prevent moisture/Na_2S contact as well as O_2/thiphenol contact, and stop H_2S escaping from the container and regulate H_2S/N_2 gases pressure



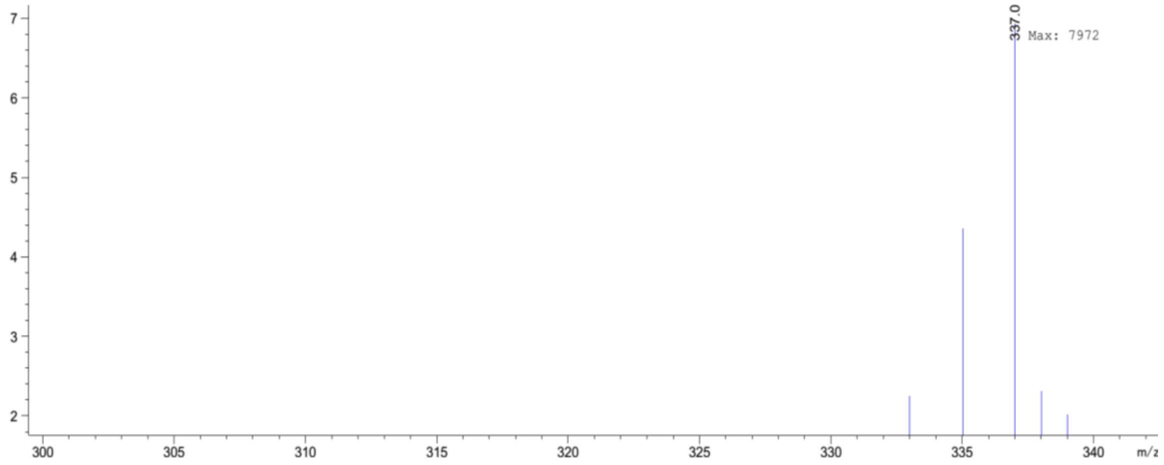
Compound 2, ^{1}H NMR (400 MHz, CDCl$_3$)



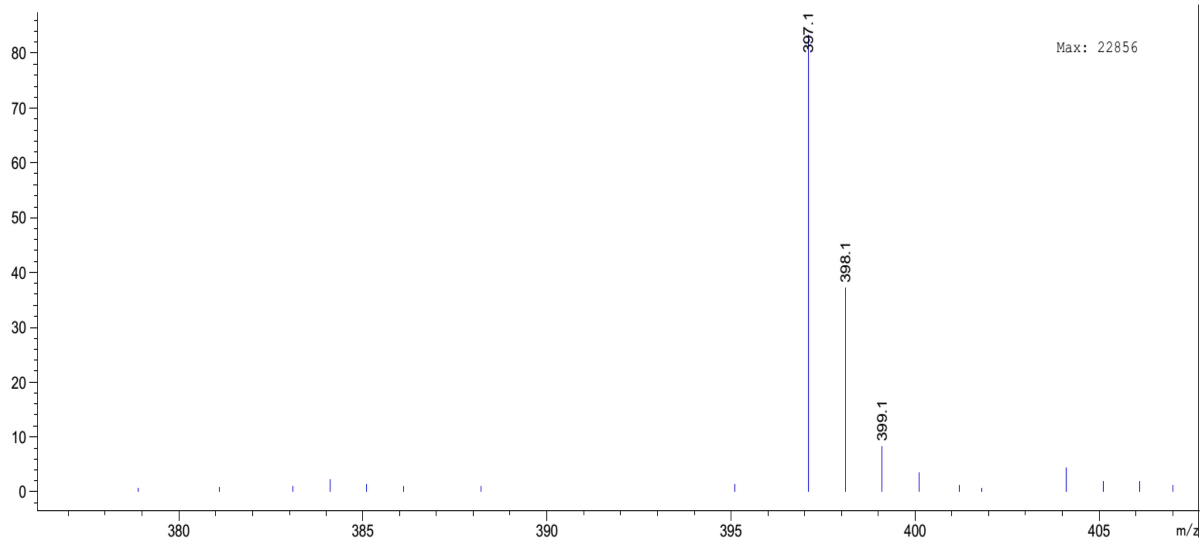
Compound 2, ^{13}C NMR (100 MHz, CDCl$_3$)



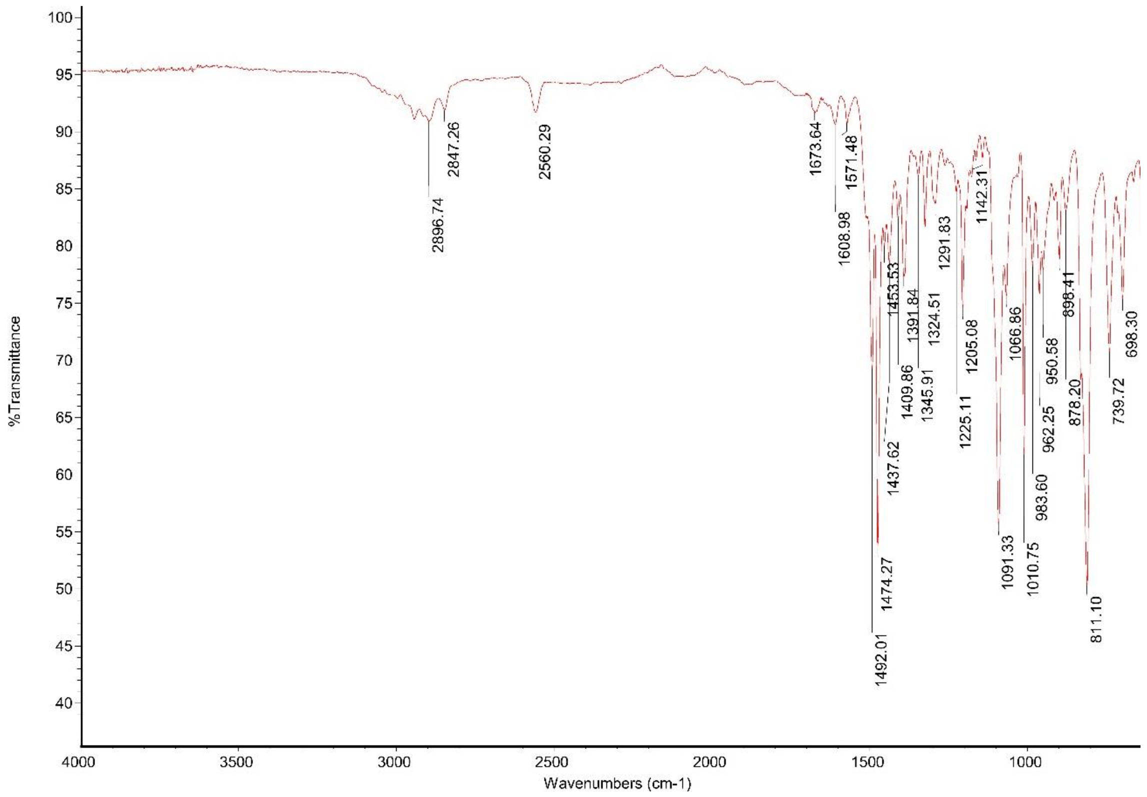
Compound 2, MS [M – H]



Compound 2, MS [M + Na]



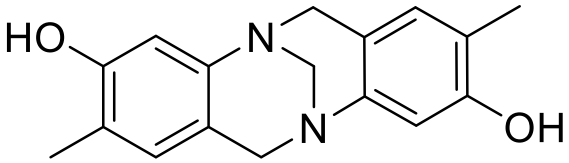
Compound 2, MS [M+ 2 ACN + H]



Compound 2, IR transmittance (neat)

3. Preparation and Purification of Compound (3)

2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-3,9-diol



Hünlich's base (0.56 g, 2.0 mmol, 1.0 eq.) was dissolved in H_2SO_4 (6.5%, 90 mL), then cooled down to –5°C. A sodium nitrite solution (0.30 g, 4.4 mmol, 2.2 eq.) in cold water (10 mL) was dropped into the reaction flask and stirred for 30 min. Afterward, the solution's temperature was gradually raised to boil, over two hours (Attention: this step releases nitrogen gas; hence, rapid heating and sealing the container may lead to explosion). The reaction mixture was cooled down to r.t. , its pH was adjusted to 5 (by adding Na_2CO_3 saturated solution) and extracted with EtOAc (30ml x 5), the organic layers were combined, dried over Na_2SO_4 and evaporated to dryness to obtain the product as a light-grey powder.

Yield: 0.54 g (1.9 mmol, 96%). R_f = 0.3 (silica gel; MeOH–DCM, 8% v/v).

IR (neat): 3649, 3549, 3012, 2948, 2904, 2857, 1620, 1508, 1368, 1081 and 910 cm^{-1}.

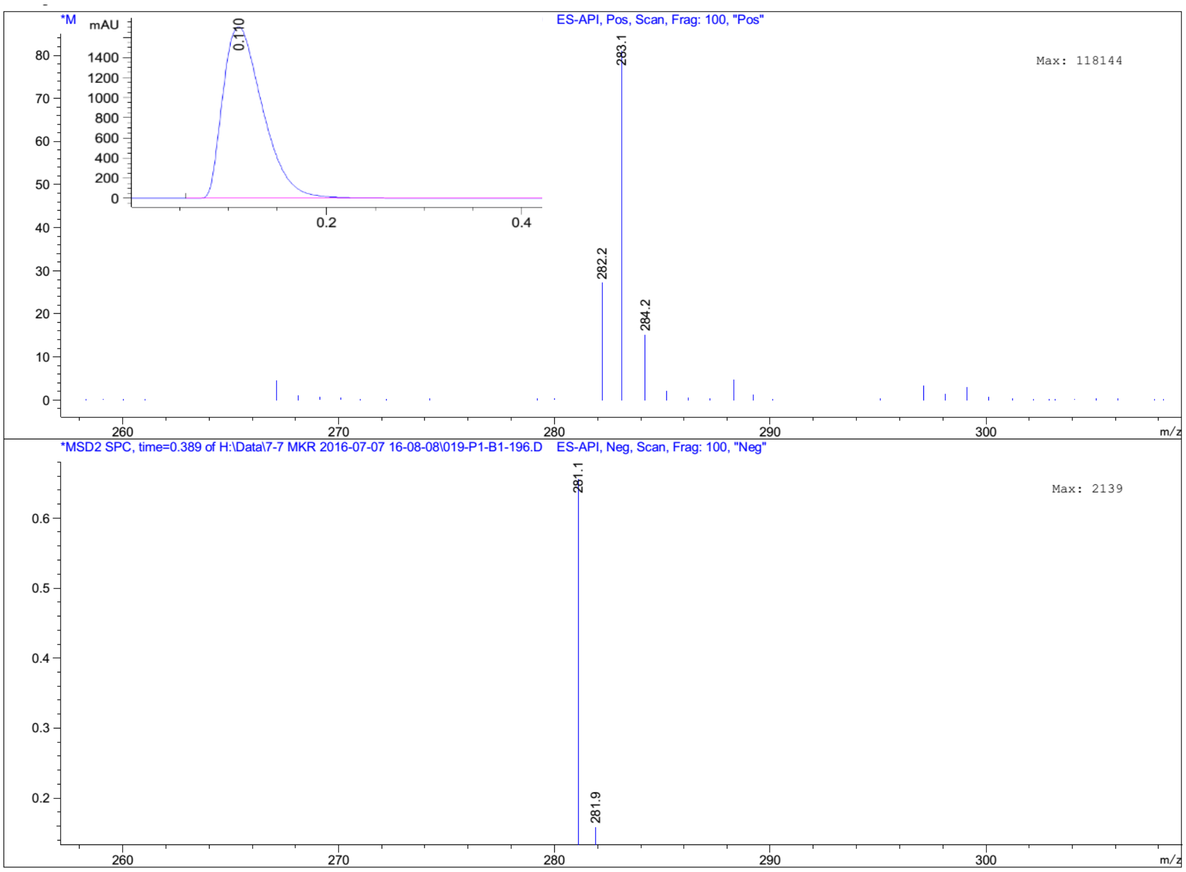
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.06 (s, 2H, OH), 6.56 (s, 2H, CH), 6.45 (s, 2H, CH), 4.39–4.43 (d, *J* = 16.4 Hz, 2H, CH$_2$) , 4.07 (s, 2H, NCH$_2$N), 3.81–3.85 (d, *J* = 16.4 Hz, 2H, CH$_2$), 1.97 (s, 6H, CH$_3$).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 154.1, 146.5, 128.2, 119.9, 117.9, 110.0, 66.5, 57.8, 15.5.

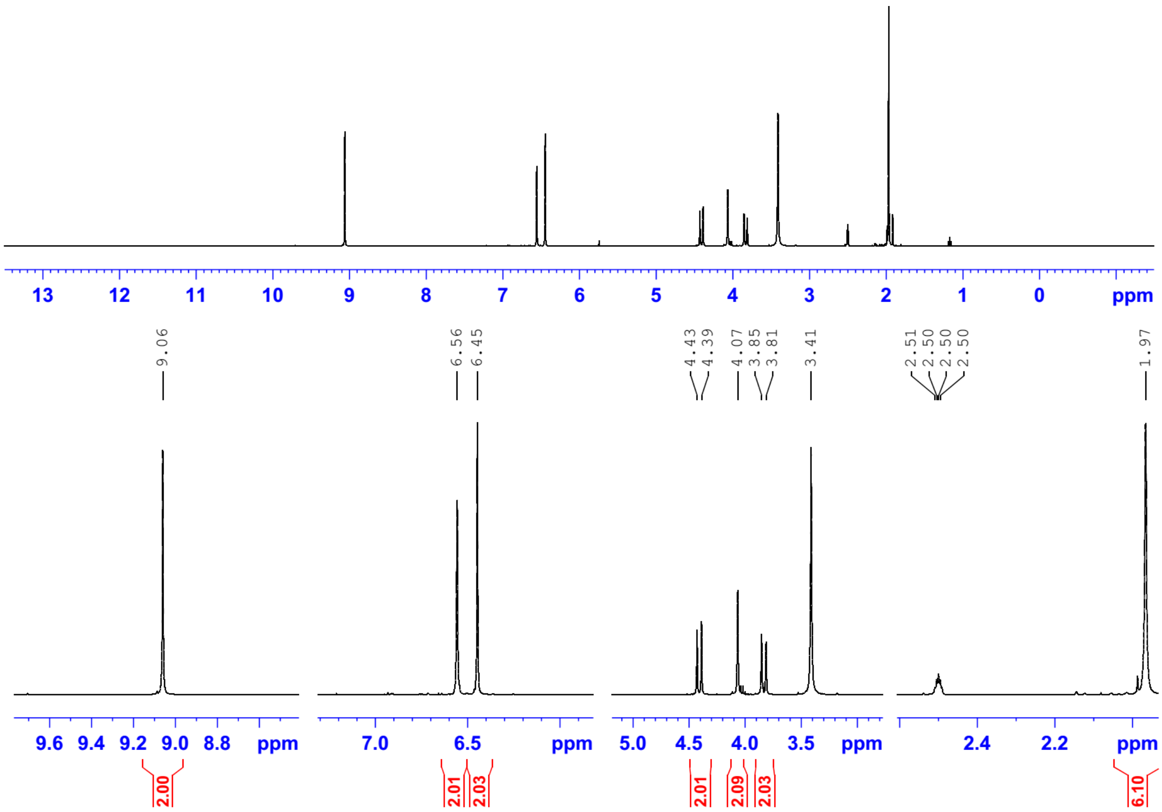
MS (ESI +; EtOH–EtOAc–H$_2$O, 90:5:5): *m/z* [M + H]$^+$ calcd for [C$_{17}$H$_{19}$N$_2$O$_2$]$^+$: 283.14; found 283.1. MS (ESI –): *m/z* [M – H]$^-$ calcd for [C$_{17}$H$_{17}$N$_2$O$_2$]$^-$: 281.14; found 281.1.

UV/Vis: (EtOAc): λ (lg ε) = 292 (3.643) nm.

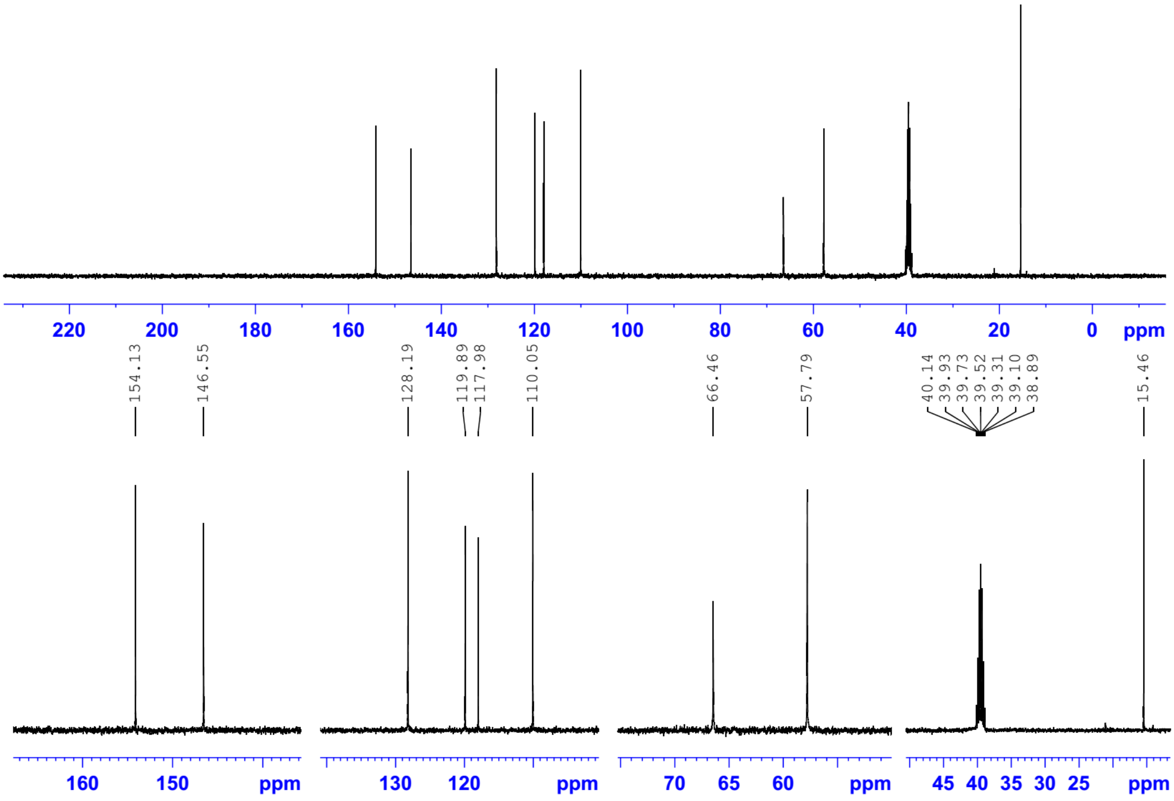
Anal. calcd for C$_{17}$H$_{18}$N$_2$O$_2$: C, 72.32; H, 6.43; N, 9.92; O, 11.33. Found: C, 72.21; H, 6.61; N, 9.74.



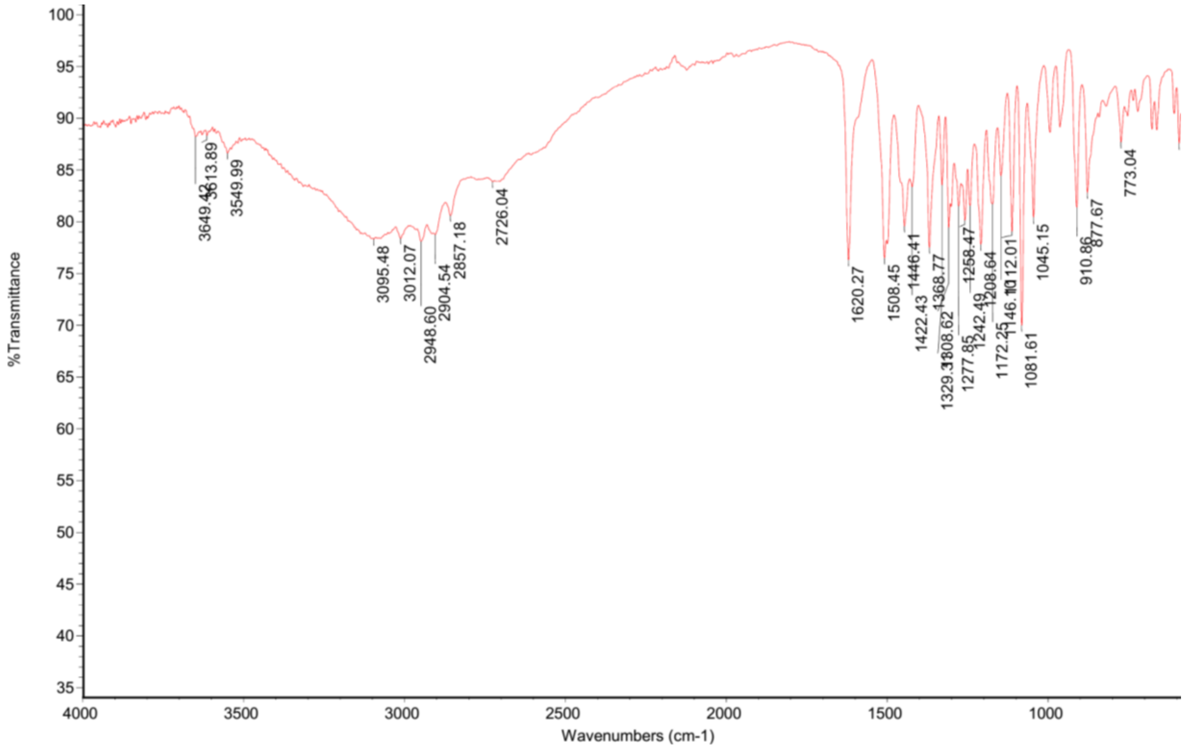
Compound 3, MS (ESI + and ESI –)



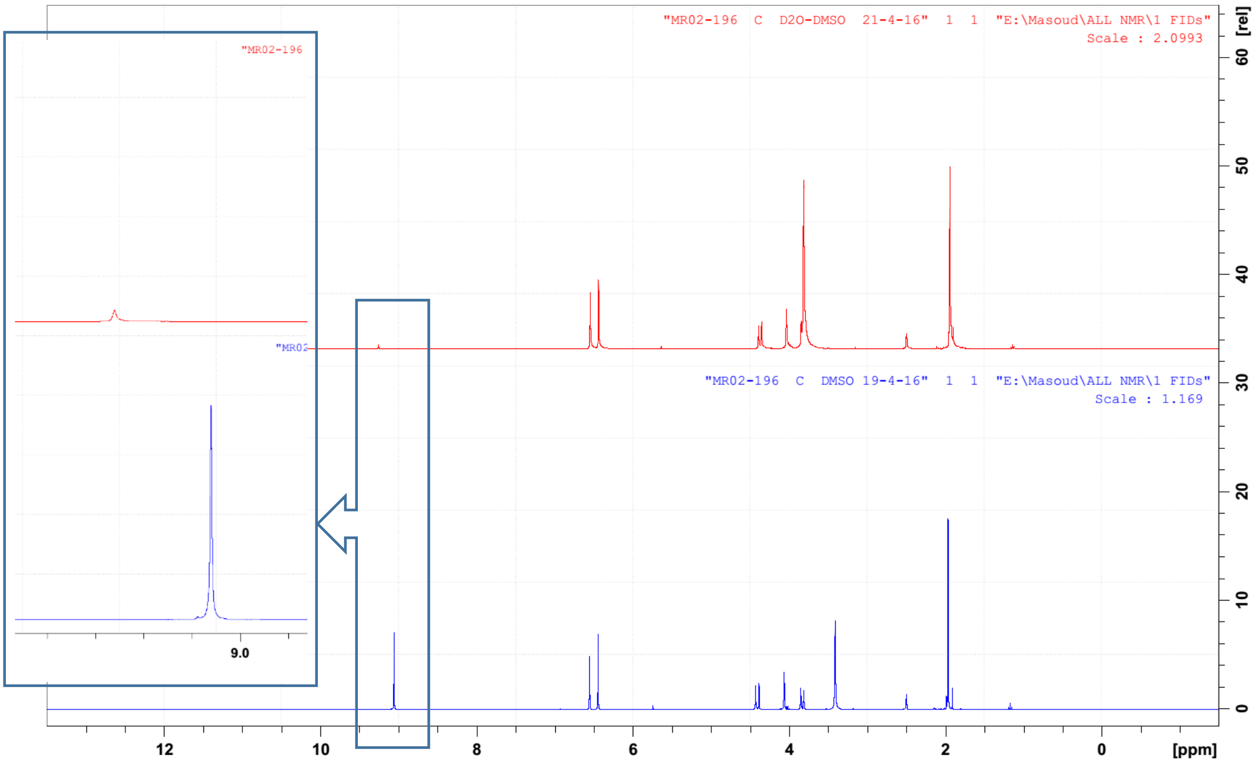
Compound 3, ^{1}H NMR (400 MHz, DMSO-d_6)



Compound 3, ^{13}C NMR (100 MHz, DMSO-d_6)



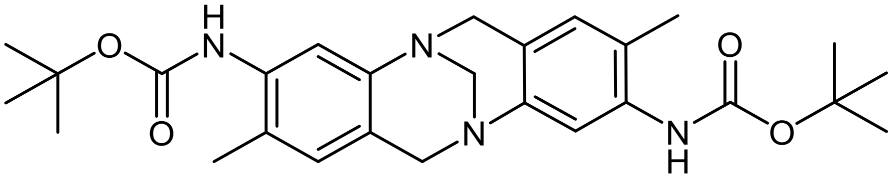
Compound 3, IR transmittance (neat)



Compound 3, ^{1}H NMR 400 MHz, DMSO-d_6 (in blue) and D_2O/DMSO-d_6 (in red)

4. Preparation and Purification of Compound (4)

di-tert-butyl (2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-3,9-diyl) dicarbamate



Hünlich's base (0.28 g, 1 mmol, 1eq.) and di-tert-butyl dicarbonate (0.458 g, 2.1 mmol, 1.05eq.) were dissolved in MeOH (7 mL) then a catalytic amount of iodine (0.025 g, 0.1 mmol, 0.1eq.) was added to the solution and stirred at room temperature in darkness for 6 hours (Attention: This step releases CO_2 gas and the container should not be tightly sealed). Finally, the suspension was filtered by paper and its filtrate was neutralized by sodium thiosulfate before discarding. The obtained white precipitate was washed with few drops of cold MeOH and then desiccated under high-vacuum to obtain neat **4**.

The catalytic role of iodine is proven within the literature. [1]

Yield: 0.44 g (0.92 mmol, 92%); R_f: 0.5 (silica gel; EtOAc–DCM= 40% v/v).

IR: (neat): 3232, 2976, 1645, 1515, 1248, 1069 and 593 cm^{-1}.

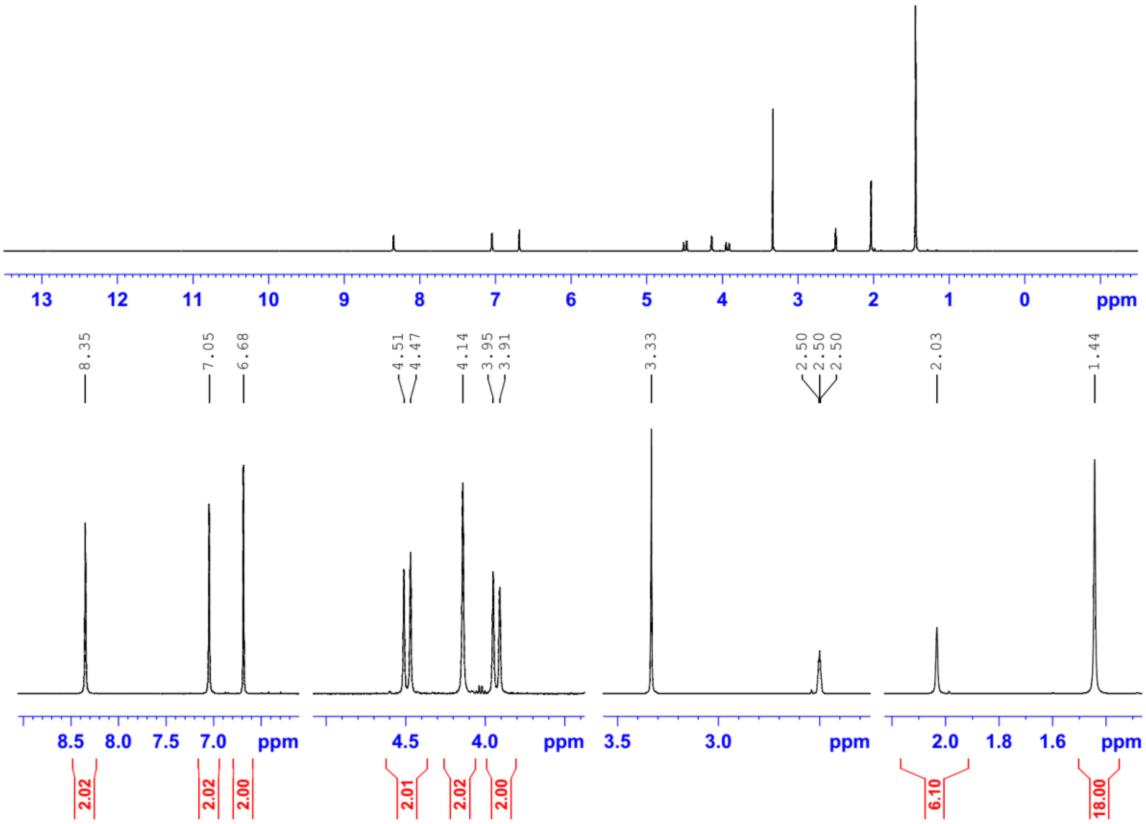
^{1}H NMR (400 MHz, DMSO-*d6*): δ = 8.35 (s, 2H, NH) ,7.05 (s, 2H, CH) , 6.68 (s, 2H, CH), 4.47–4.51 (d, *J* = 16.6 Hz, 2H, CH_2), 4.14 (s, 2H, NCH_2N), 3.91–3.95 (d, *J* = 16.8 Hz, 2H, CH_2) , 2.03 (s, 6H, CH_3), 1.44 (s, 18H, CH_3).

^{13}C NMR (100 MHz, DMSO-*d6*): δ = 153.4, 145.8, 135.4, 127.9, 126.6, 123.8, 120.0, 78.6, 66.4, 57.9, 28.1, 17.2.

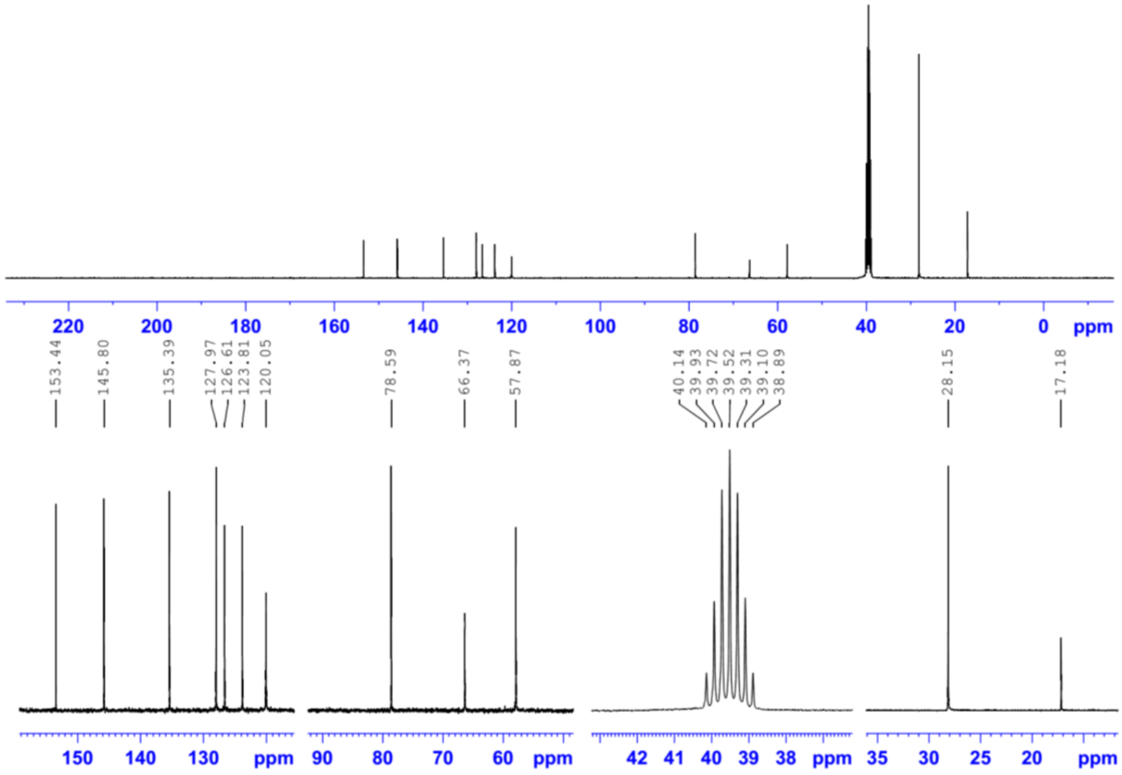
MS (ESI +; EtOH): *m/z* $[M + H]^+$ calcd for $[C_{27}H_{37}N_4O_4]^+$: 481.27; found 481.3.

UV/Vis: (EtOAc): λ (lg ε) = 296 (3.647) nm.

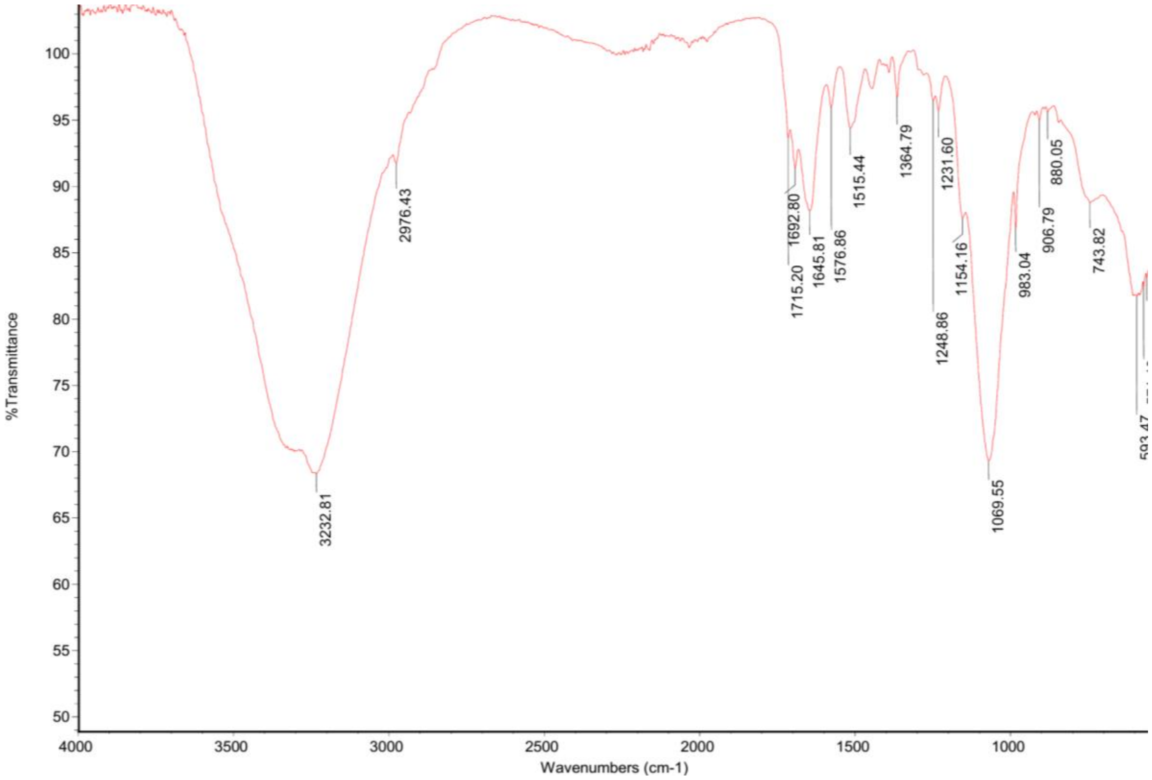
Anal. calcd for $C_{27}H_{36}N_4O_4$: C, 67.48; H, 7.55; N, 11.66; O, 13.32. Found: C, 67.57; H, 7.60; N, 11.84.



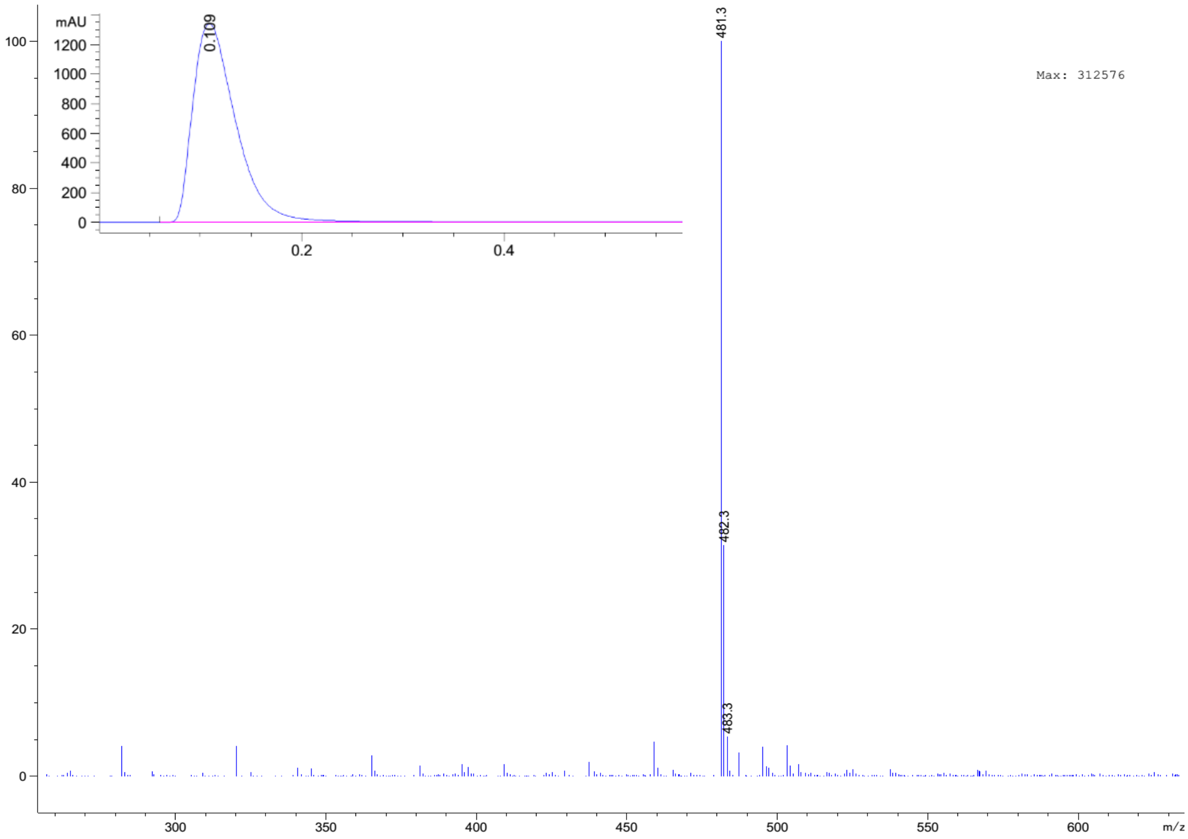
Compound 4, ^{1}H NMR (400 MHz, DMSO-d_6)



Compound 4, ^{13}C NMR (100 MHz, DMSO-d_6)



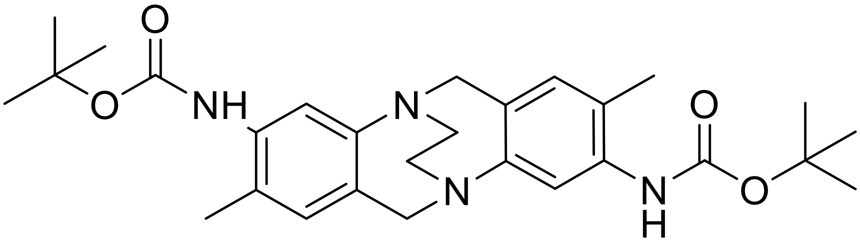
Compound 4, IR transmittance (neat)



Compound 4, MS (ESI +)

5. Preparation and Purification of Compound (5)

di-tert-butyl (2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-3,9-diyl)dicarbamate



Compound **4** (0.24 g, 0.5 mmol, 1.0 eq.), 1,2-dibromoethane (0.47 g, 2.5 mmol, excess) and Li_2CO_3 (0.37 g, 5.0 mmol, excess) were mixed in DMF (1.5 mL) and heated at 105°C for 12 hours under argon atmosphere in darkness. Afterwards, the reaction mixture was added to 100ml of cold water containing 8 g of NaCl; then the obtained suspension was filtered by sintered funnel and vacuum pump. The collected light-brown precipitate was rinsed with few more drops of cold water and purified by column chromatography to obtain an extra-pure white product. (The reaction rescaled tenfold, gave 80% yield)

Yield: 0.19 g (0.39 mmol, 77%); R_f: 0.3 (silica gel; EtOAc–DCM= 30% v/v).

IR (neat): 3242, 2976, 1692, 1648, 1515, 1364, 1232, 1154, 1069 and 601 cm^{-1}.

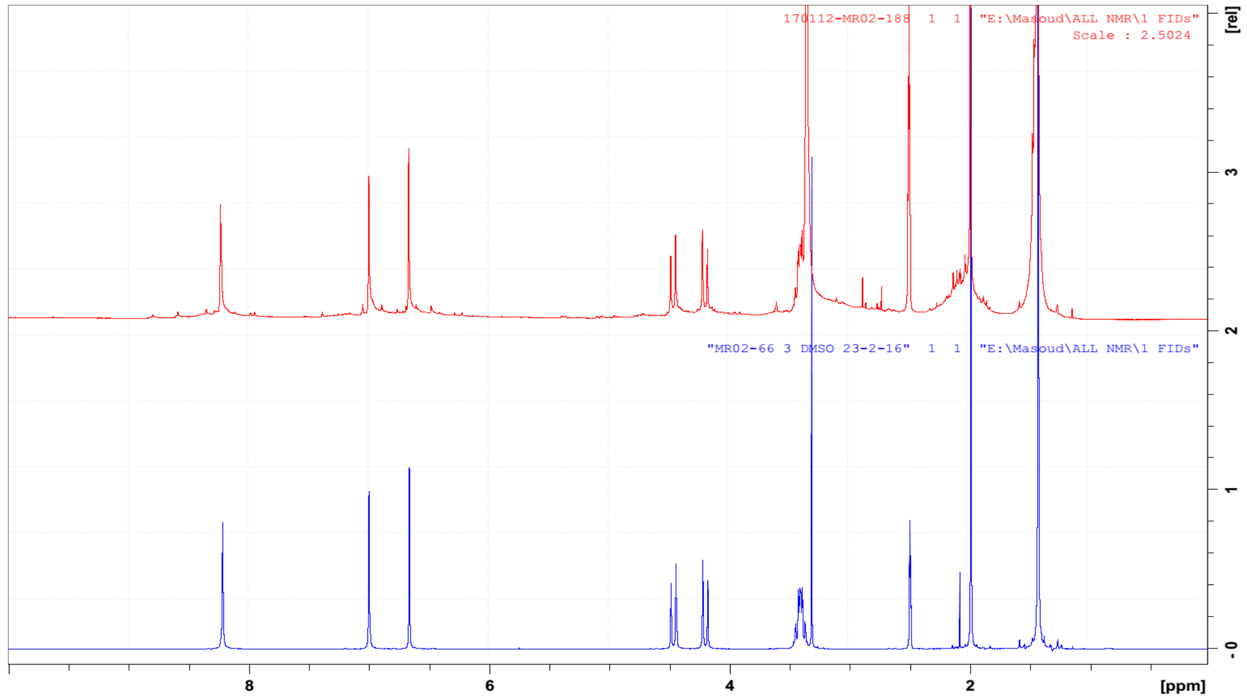
^{1}H NMR (400 MHz, DMSO-*d6*): δ = 8.22 (s, 2H, NH), 7.00 (s, 2H, CH), 6.67 (s, 2H, CH), 4.45–4.49 (d, *J* = 17.2 Hz, CH_2) , 4.18–4.22 (d, *J* = 17.2 Hz, CH_2) , 3.36–3.47 (m, 4H, CH_2) , 1.99 (s, 6H, CH_3), 1.43 (s, 18H, CH_3).

^{13}C NMR (100 MHz, DMSO-*d6*): δ = 153.4, 148.2, 135.0, 132.9, 129.8, 127.2, 123.3, 78.5, 57.9, 54.3, 28.1, 17.1.

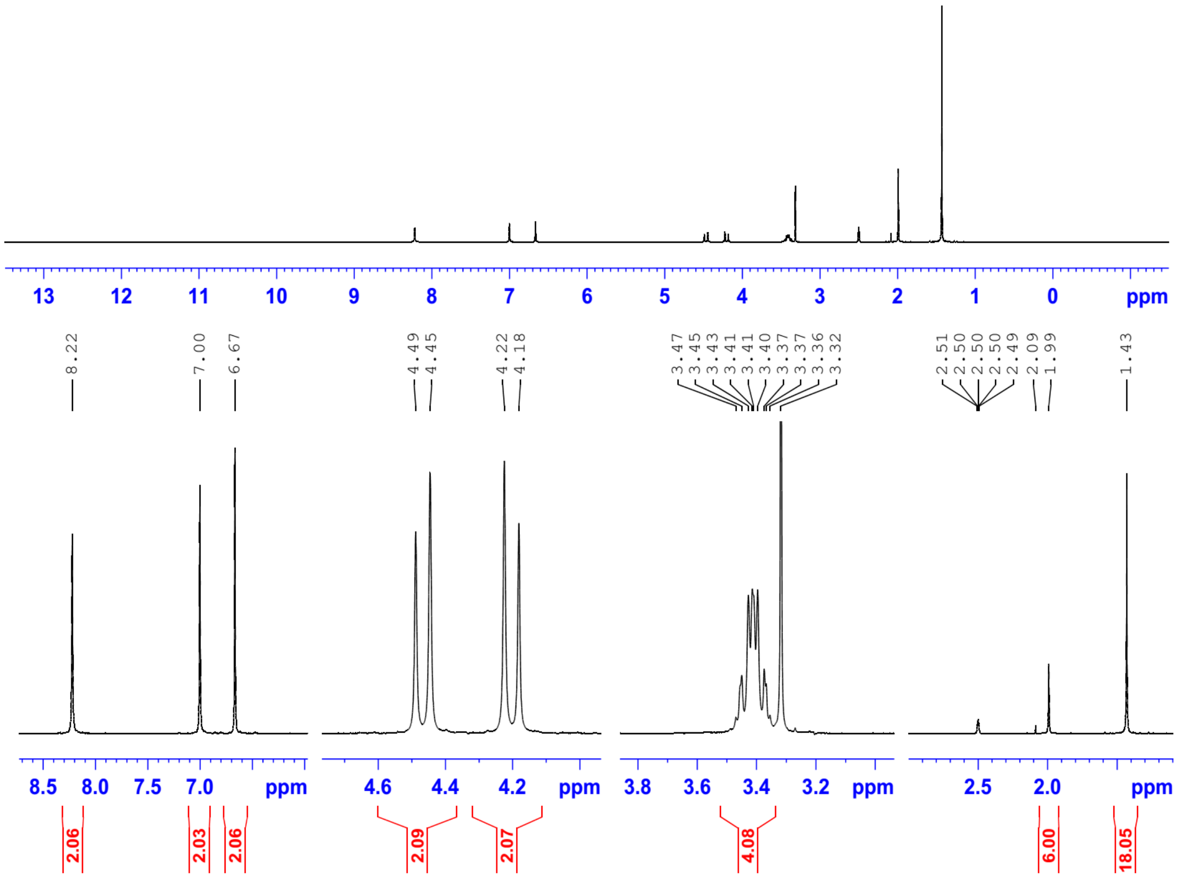
MS (ESI +; EtOH): *m/z* $[M + H]^+$ calcd for $[C_{28}H_{39}N_4O_4]^+$: 495.29; found 495.3.

UV/Vis: (EtOAc): λ (lg ε) = 295 (3.597) nm.

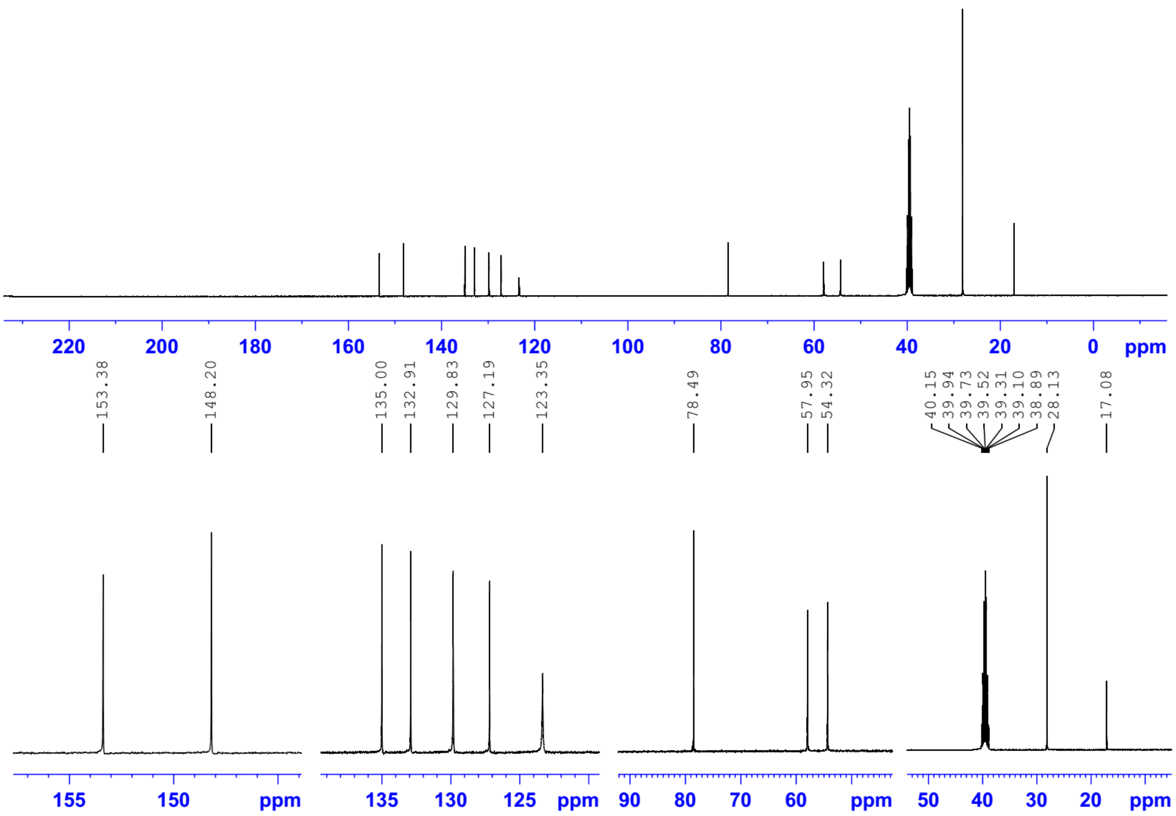
Anal. Calcd for $C_{28}H_{38}N_4O_4$: C, 67.99; H, 7.74; N, 11.33; O, 12.94. Found: C, 67.86; H, 7.53; N, 11.21.



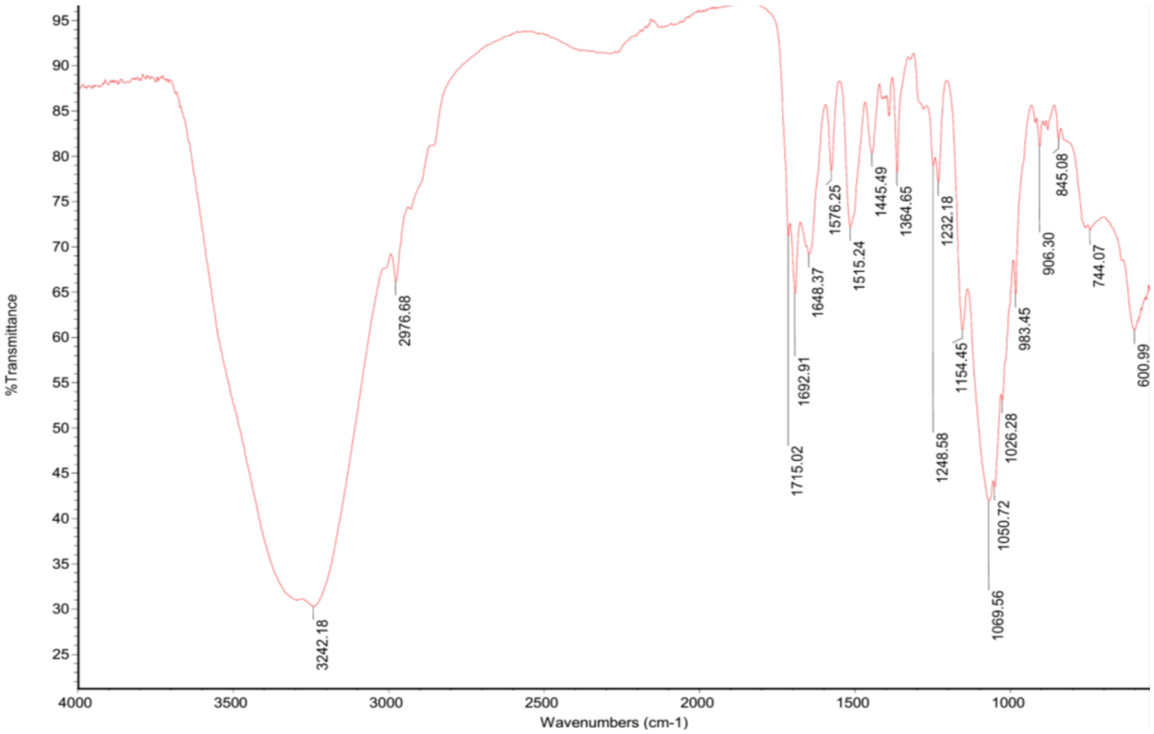
Compound 5 crude (top) and pure (bottom), ^{1}H NMR (400 MHz, DMSO-d_6)



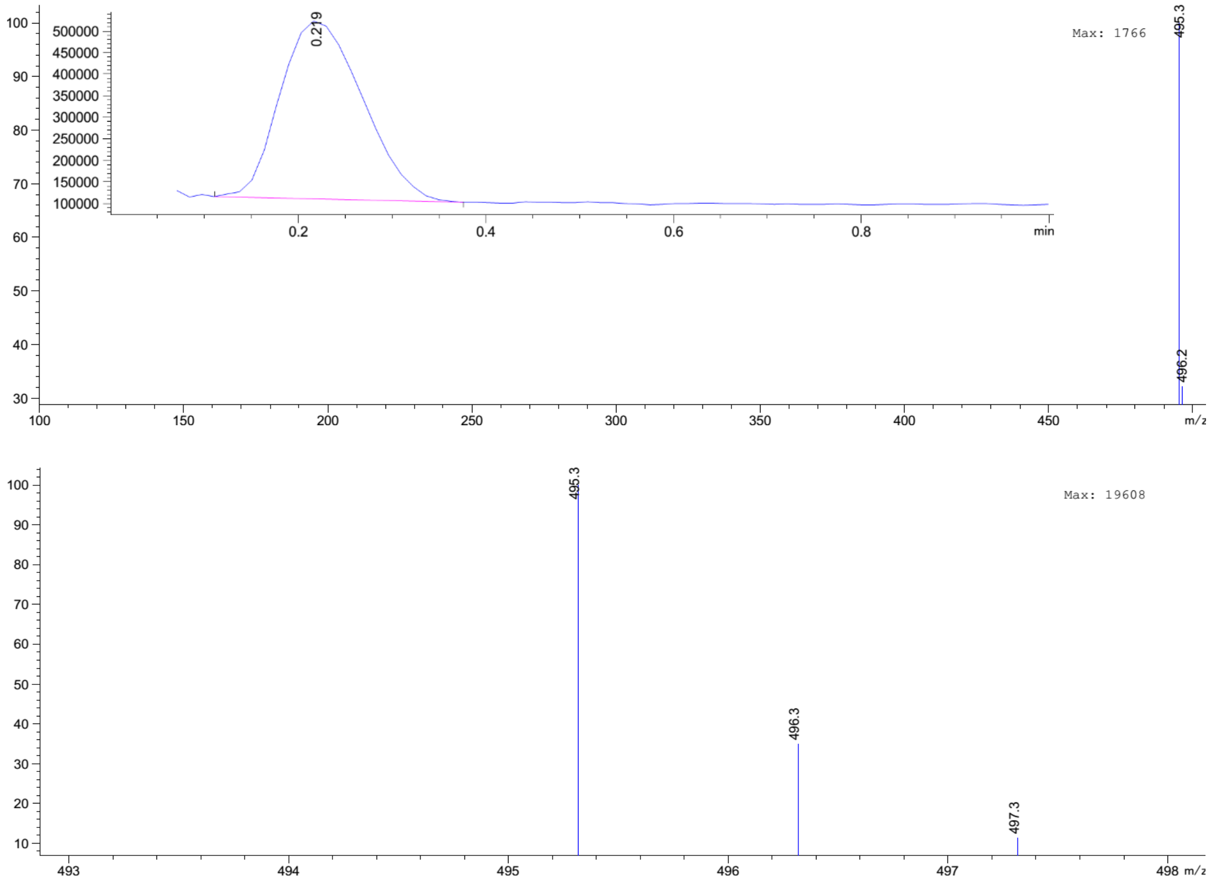
Compound 5, ^{1}H NMR (400 MHz, DMSO-d_6)



Compound 5, ^{13}C NMR (100 MHz, DMSO-d_6)



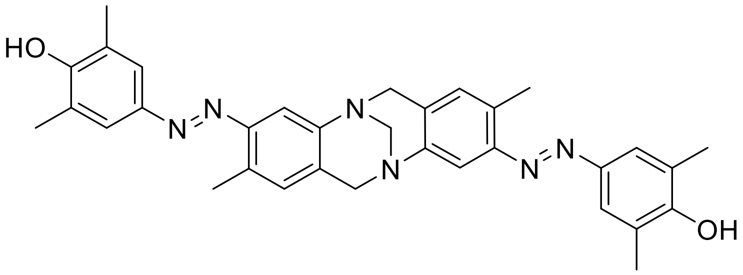
Compound 5, IR (neat)



Compound 5, MS (ESI +)

6. Preparation and Purification of Compound (6)

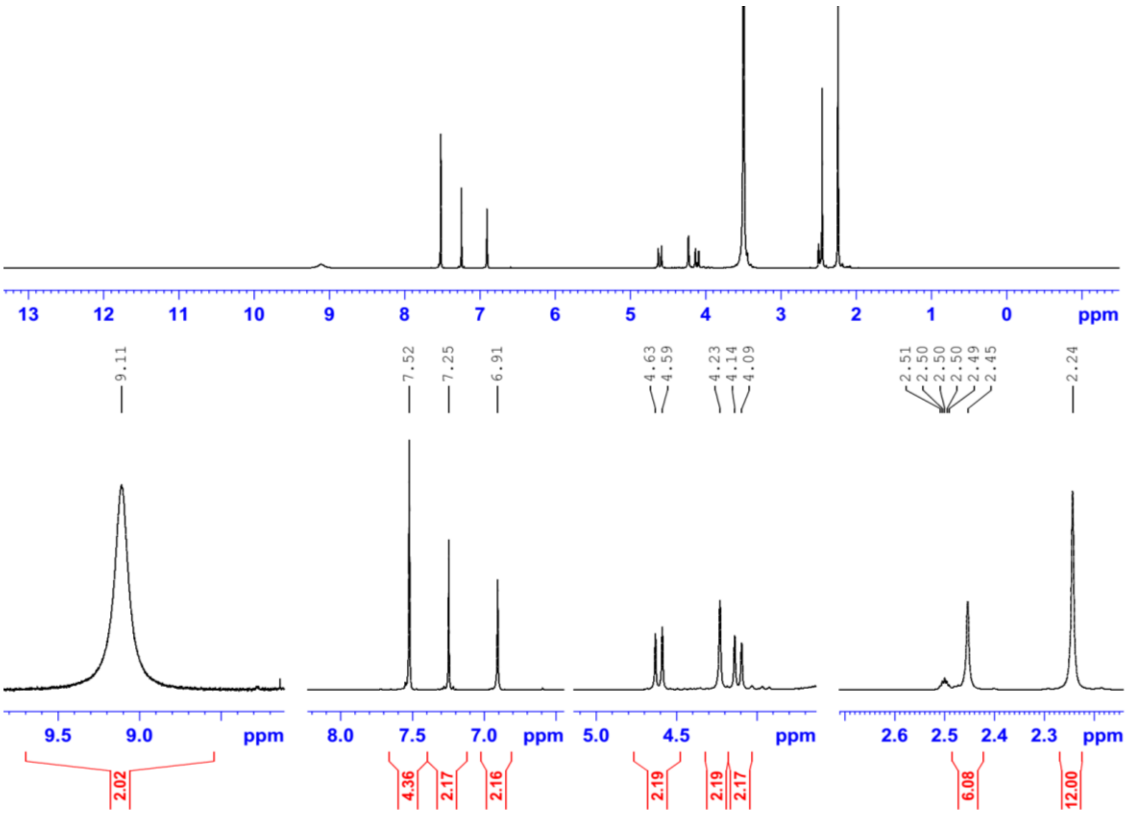
4,4'-((1E,1'E)-(2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-3,9-diyl) bis (diazene-2,1-diyl)) bis (2,6-dimethylphenol)



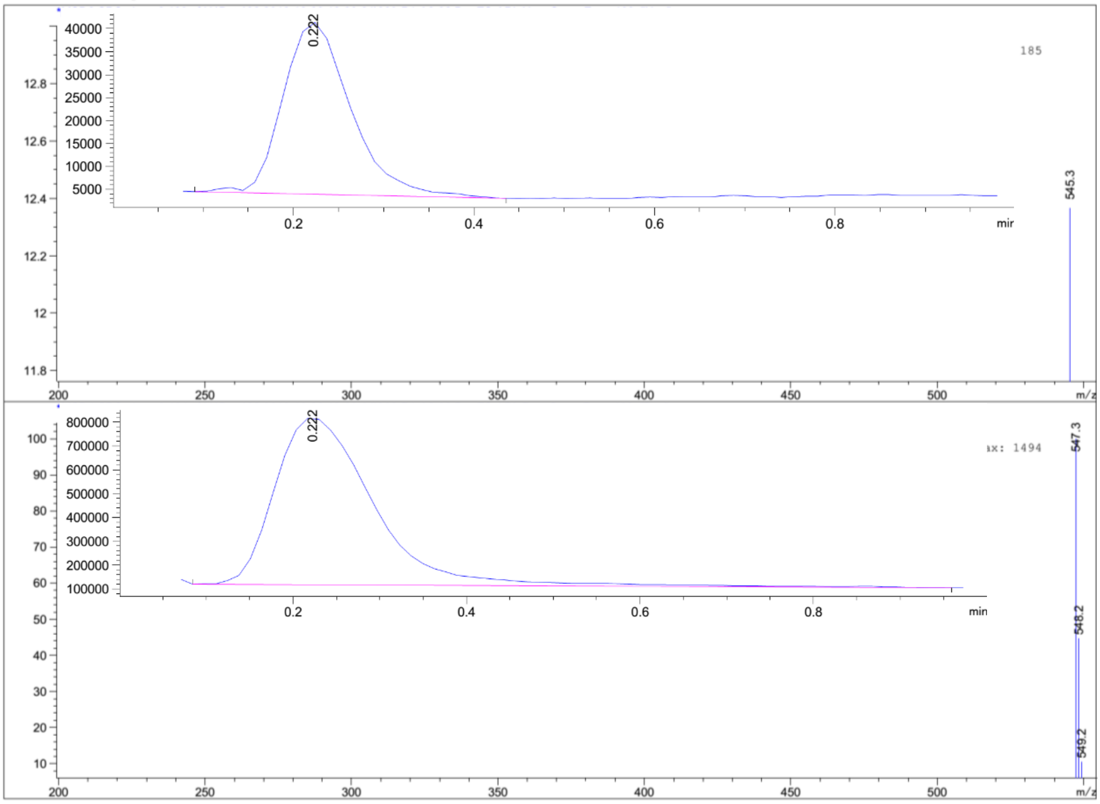
Prepared according to the literature. [2]

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 9.11 (br, 2H, OH) , 7.52 (s, 4H, CH), 7.25 (s, 2H, CH), 6.91 (s, 2H, CH), 4.59–4.63 (d, *J* = 17.2 Hz, 2H, CH_2), 4.23 (s, 2H, NCH_2N), 4.09–4.14 (d, *J* = 17.3 Hz, 2H, CH_2) , 2.45 (s, 6H, CH_3), 2.24 (s, 12H, CH_3).

MS (ESI +; EtOAc): *m/z* $[M+H]^+$ calcd for $[C_{33}H_{35}N_6O_2]^+$: 547.27; found: 547.3. MS (ESI –): *m/z* $[M-H]^-$calcd for $[C_{33}H_{33}N_6O_2]^-$: 545.27; found: 545.3.



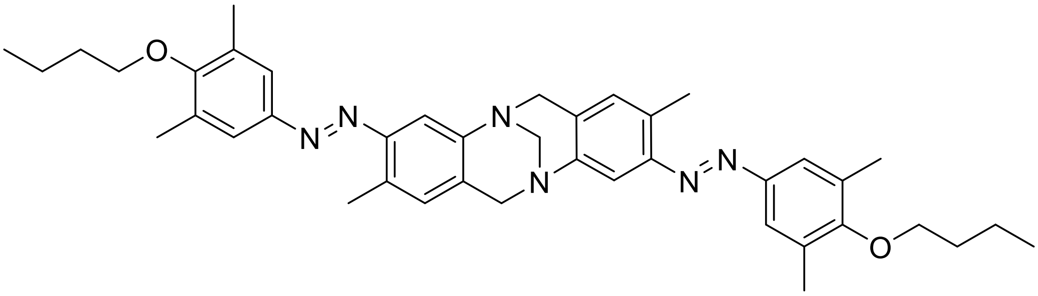
Compound 6, ^{1}H NMR (400 MHz, DMSO-d_6)



Compound 6, MS (ESI + and ESI –)

7. Preparation and Purification of Compound (7)

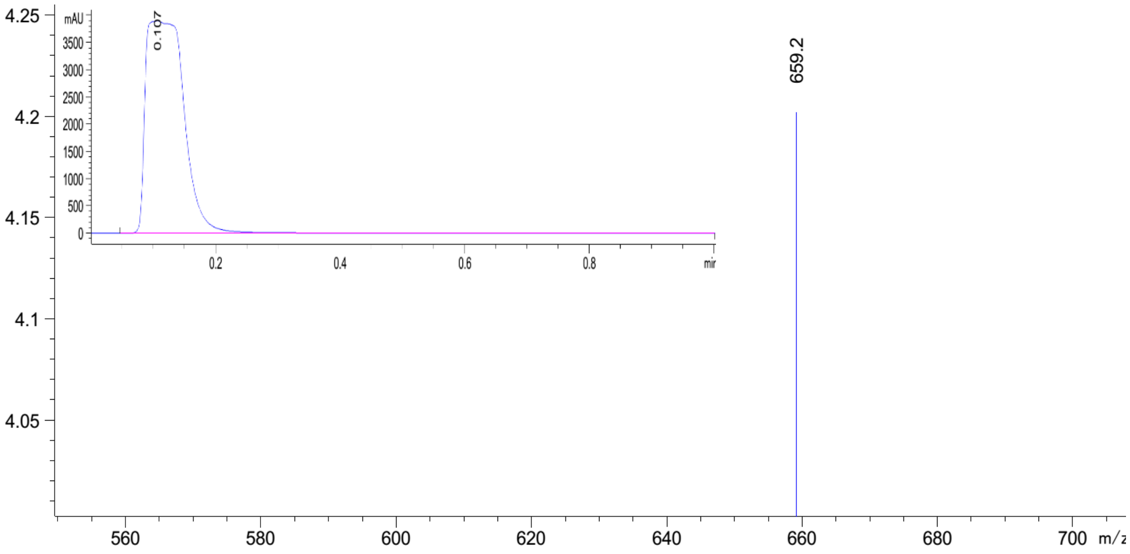
3,9-bis((E)-(4-butoxy-3,5-dimethylphenyl)diazenyl)-2,8-dimethyl-6H,12H-5,11-methanodibenzo [b,f][1,5]diazocine



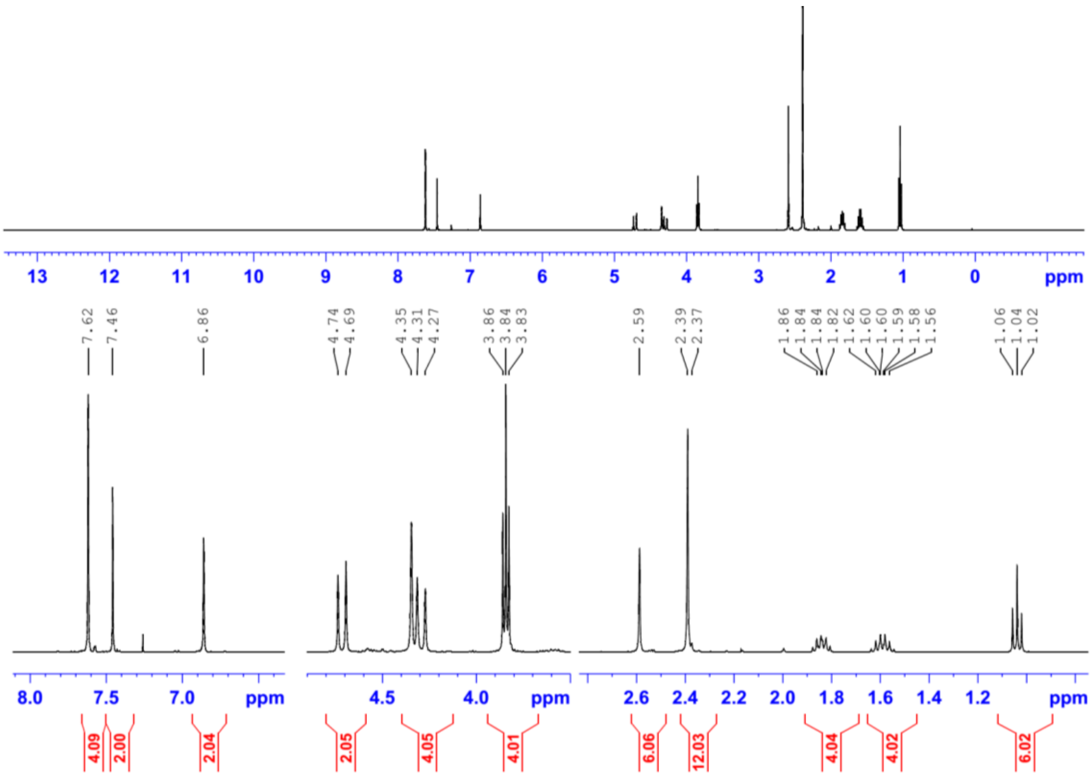
Prepared according to the literature. [2]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (s, 4 H, CH), 7.46 (s, 2 H, CH), 6.86 (s, 2 H, CH), 4.69–4.74 (d, *J* = 17.1 Hz, 2 H, CH_2), 4.35 (s, 2 H, NCH_2N), 4.27–4.31 (d, *J* = 17.2 Hz, 2 H, CH_2), 3.83–3.86 (t, *J* = 8.1 Hz, 4 H, CH_2), 2.59 (s, 6 H, CH_3), 2.39 (s, 12 H, CH_3), 1.81–1.86 (m, 4 H, CH_2), 1.54–1.62 (m, 4 H, CH_2), 1.02–1.06 (t, *J* =8.1 Hz, 6 H, CH_3).

MS (ESI +; MeCN–EtOAc–H_2O, 90:5:5): *m/z* $[M + H]^+$ calcd for$[C_{41}H_{51}N_6O_2]^+$: 659.40; found: 659.2.



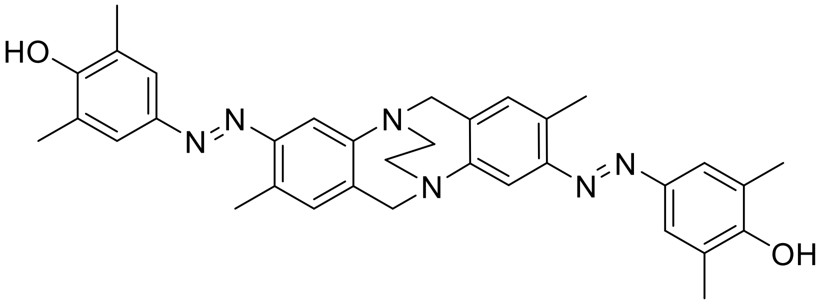
Compound 7, MS (ESI +)



Compound 7, ^{1}H NMR (400 MHz, $CDCl_3$)

8. Preparation and Purification of Compound (8)

4,4'-((1E,1'E)-(2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-3,9-diyl)bis(diazene-2,1-diyl))bis(2,6-dimethylphenol)



Compound **5** (0.49 g, 1.0 mmol, 1.0 eq.) was sonicated and dissolved in H_2SO_4 (6.5%, 30 mL) at 95°C, then cooled down to -5°C by placing the reaction container in ice/acetone bath. A sodium nitrite solution (0.30 g, 4.4 mmol, excess, in 5 mL of cold water) was dropped into the reaction flask and stirred for 15 minutes. The resulting solution was poured into a solution consisting 2,6-dimethylphenol (0.25 g, 2.1 mmol, 1.0 eq), Na_2CO_3 (4.0 g, 38 mmol) and 50 mL of ice-cold water and stirred for 8 h. The crude was extracted by EtOAc (30 mL x 3), the organic layers were combined, dried over $MgSO_4$ and filtered. After solvent removal under reduced pressure, the solid residue was chromatographed (silica gel in dark) to obtain a shiny orange solid.

Yield: 0.44 g (0.78 mmol, 78%); R_f: 0.4 (silica gel; EtOAc–*n*-hexane, 40% v/v). IR (neat): 3331, 2917, 2849, 1719, 1674, 1595, 1490, 1287, 1183, 1113, 1017, 825 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.16 (s, 2H, OH), 7.55 (s, 4H, CH), 7.42 (s, 2H, CH), 7.05 (s, 2H, CH),

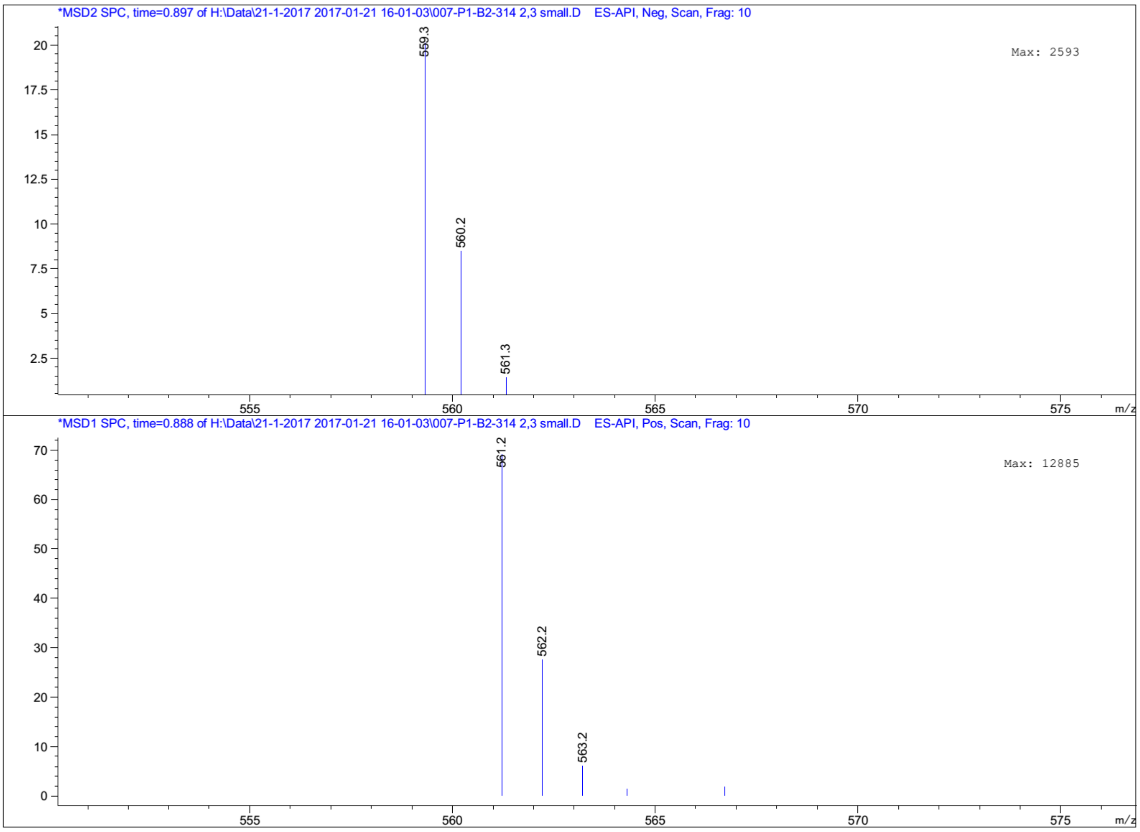
4.50–4.55 (d, *J* = 17.2, 2H, CH$_2$), 4.75–4.79 (d, *J* = 17.3, 2H, CH$_2$), 3.59–3.71 (br, 4H, NCH$_2$CH$_2$N), 2.47 (s, 6H, CH$_3$), 2.30 (s, 12H, CH$_3$).

^{13}C NMR (100 MHz, CDCl$_3$) δ [ppm]: 156.6, 149.2, 146.4, 142.1, 131.9, 129.2, 126.7, 124.8, 123.3, 110.4, 58.4, 53.9, 16.6, 16.4.

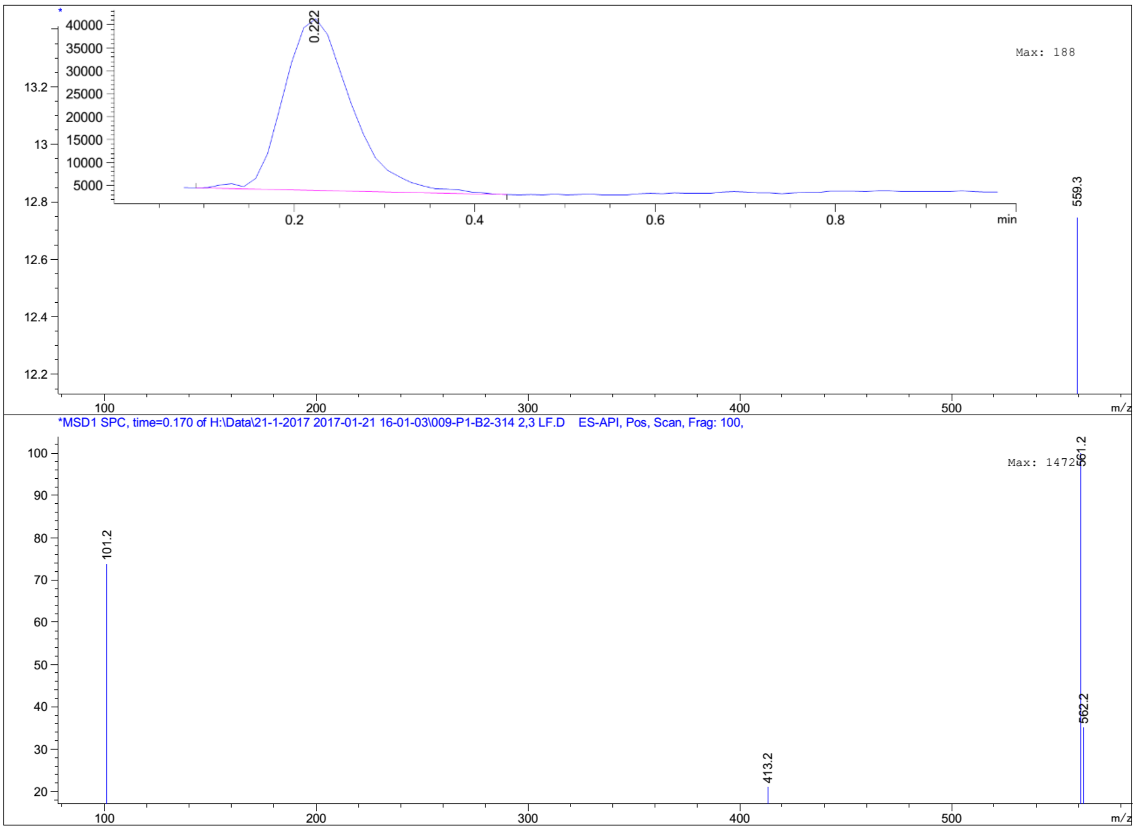
MS (ESI +; EtOAc): *m/z* [M + H]$^+$ calcd for [$C_{34}H_{37}N_6O_2$]$^+$: 561.29, found 561.2. (ESI –): *m/z* [M – H]$^-$ calcd for [$C_{34}H_{35}N_6O_2$]$^+$: 559.29, found 559.3.

UV/Vis: (EtOAc): λ (lg ε) = 349 (4.619) nm.

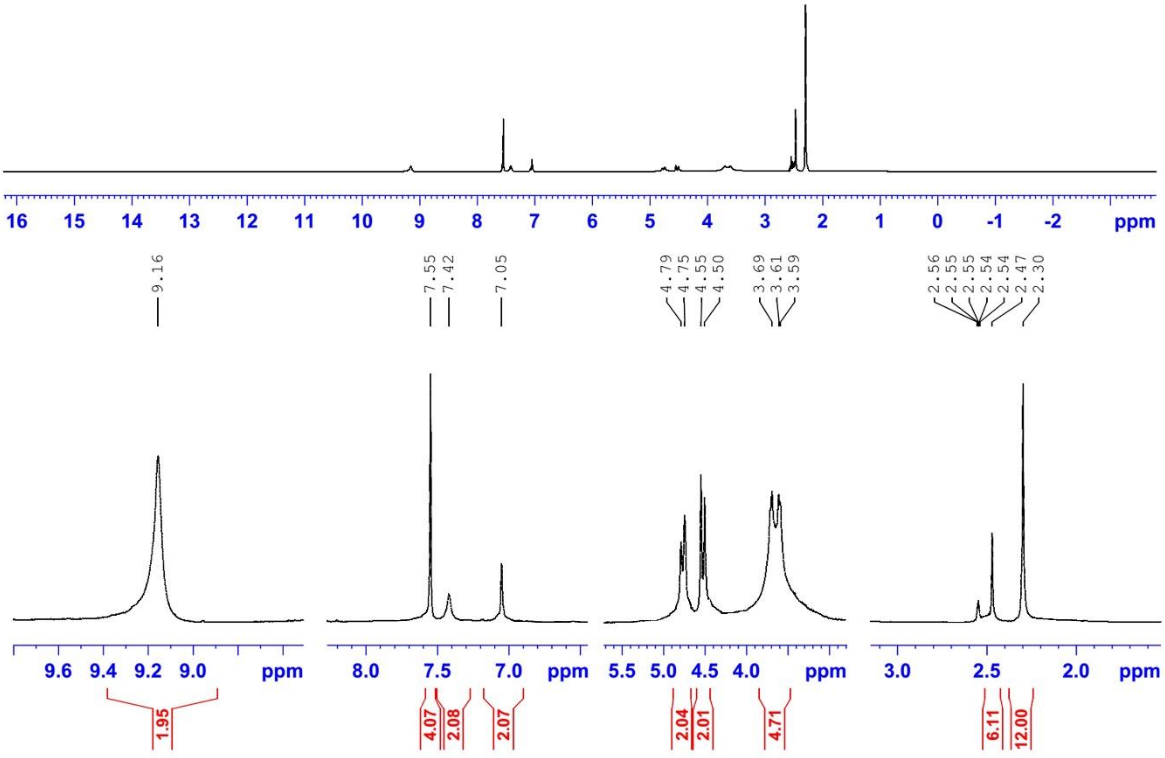
Anal. Calcd for $C_{34}H_{36}N_6O_2$: C, 72.83; H, 6.47; N, 14.99; O, 5.71. Found: C, 72.69; H, 6.81; N, 15.13.



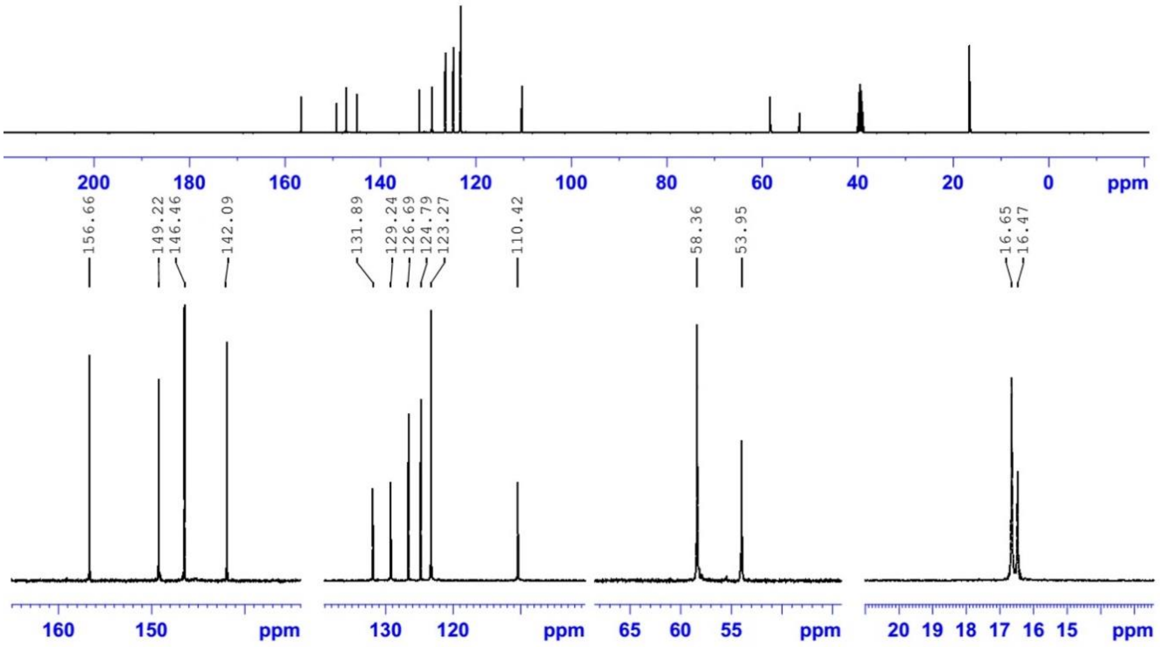
Compound 8, MS ESI + (bottom) and ESI – (top)



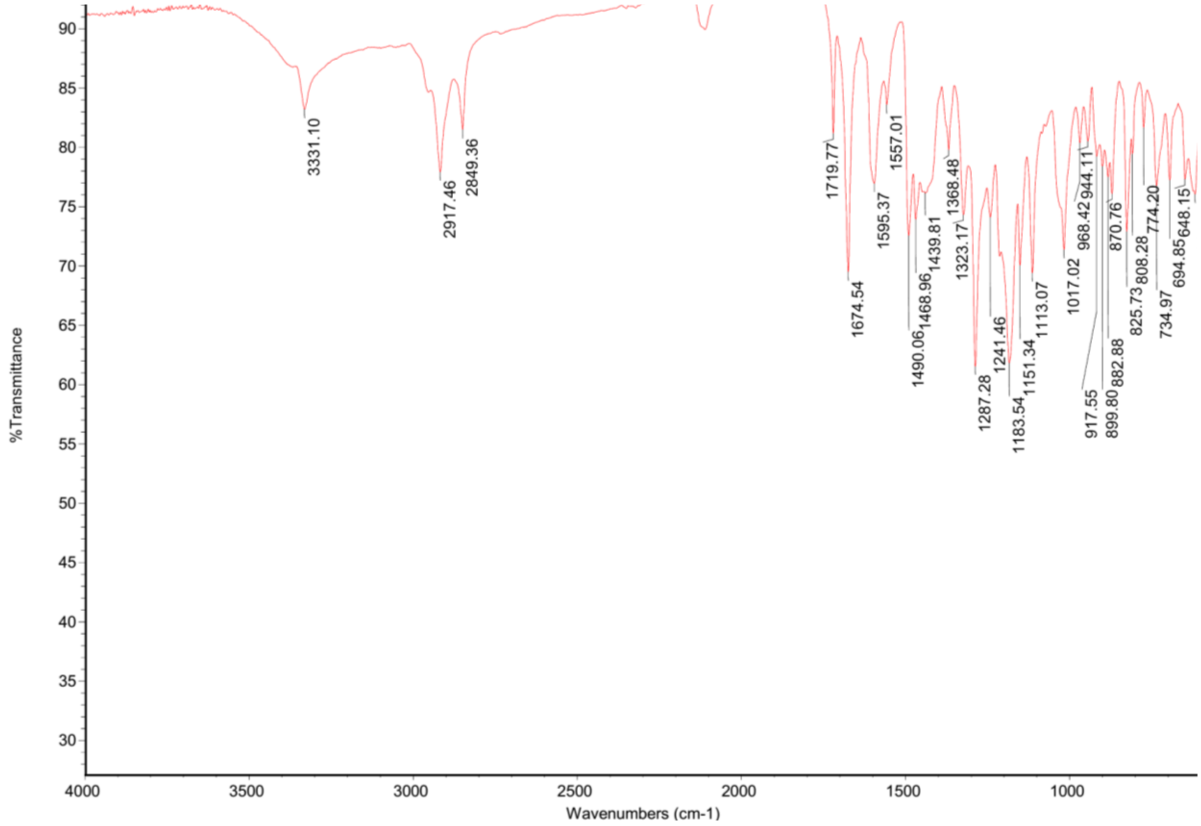
Compound 8, MS ESI + (bottom) and ESI – (top)



Compound 8, ^{1}H NMR (400 MHz, DMSO-d_6)



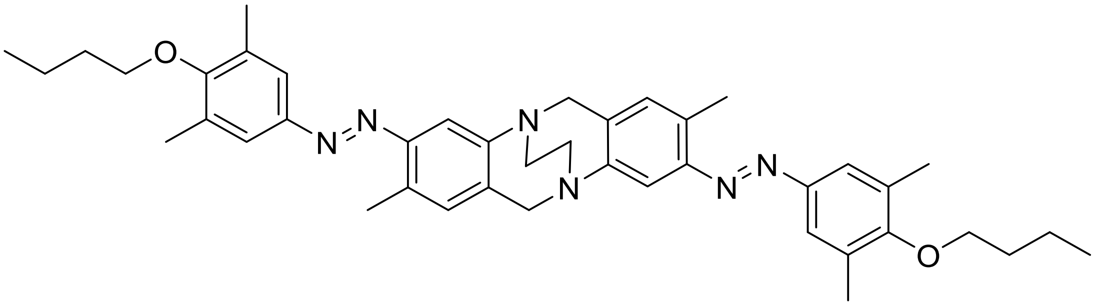
Compound 8, ^{13}C NMR (100 MHz, DMSO-d_6)



Compound 8, IR transmittance (neat)

9. Preparation and Purification of Compound (9)

3,9-bis((E)-(4-butoxy-3,5-dimethylphenyl)diazenyl)-2,8-dimethyl-6H,12H-5,11-ethanodibenzo [b,f][1,5]diazocine



Compound **7** (1.31 g, 2.0 mmol, 1.0 eq.), 1,2-dibromoethane (0.75 g, 4.0 mmol, 2.0 eq.) and Li_2CO_3 (0.59 g, 8.0 mmol) were mixed in dried DMF (10 mL) and refluxed for 24 hours at 110°C under nitrogen atmosphere in darkness and then the reaction mixture was poured into cold water and the crude was extracted by EtOAc (50 mL x 3). The organic layer was collected, dried over $MgSO_4$ and filtered. After solvent removal under reduced pressure, the solid residue was chromatographed (silica gel in dark) to obtain a shiny orange solid.

Yield: 0.29 g (0.44 mmol, 22%); R_f: 0.45 (silica gel; MeOH–DCM = 2% v/v).

IR (neat): 2956, 2927, 2868, 1589, 1480, 1208, 1115, 956 and 890 cm^{-1}.

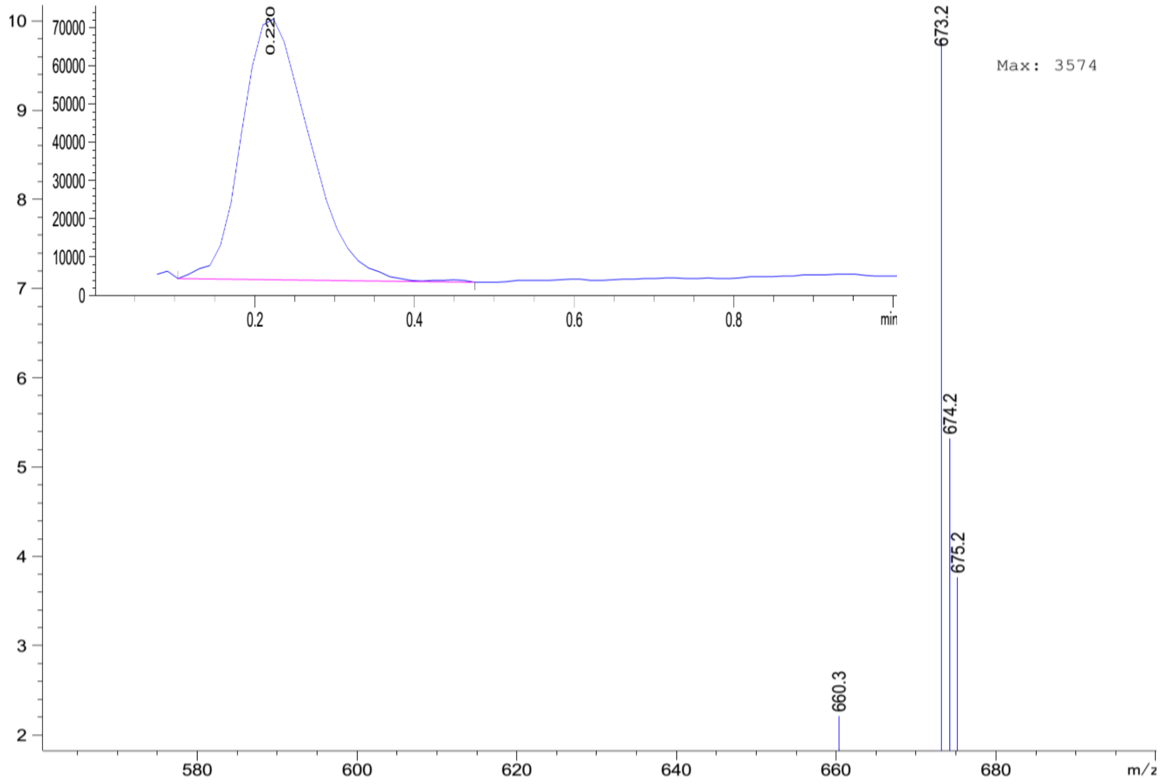
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 4H, CH), 7.43 (s, 2H, CH), 6.86 (s, 2H, CH), 4.51–4.65 (m, 4H, CH_2), 3.81-3.84 (t, 4H, CH_2), 3.55–3.65 (m, 4H, CH_2), 2.52 (s, 6H, CH_3), 2.37 (s, 12H, CH_3), 1.79–1.83 (m, 4H, CH_2), 1.53–1.62 (m, 4H, CH_2), 1.01–1.04 (t, J = 8.2, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm]: 158.6, 150.0, 149.0, 148.7, 139.7, 134.3, 131.7, 131.4, 123.5, 114.6, 72.3, 59.0, 54.8, 32.6, 19.5, 17.0, 16.6, 14.1.

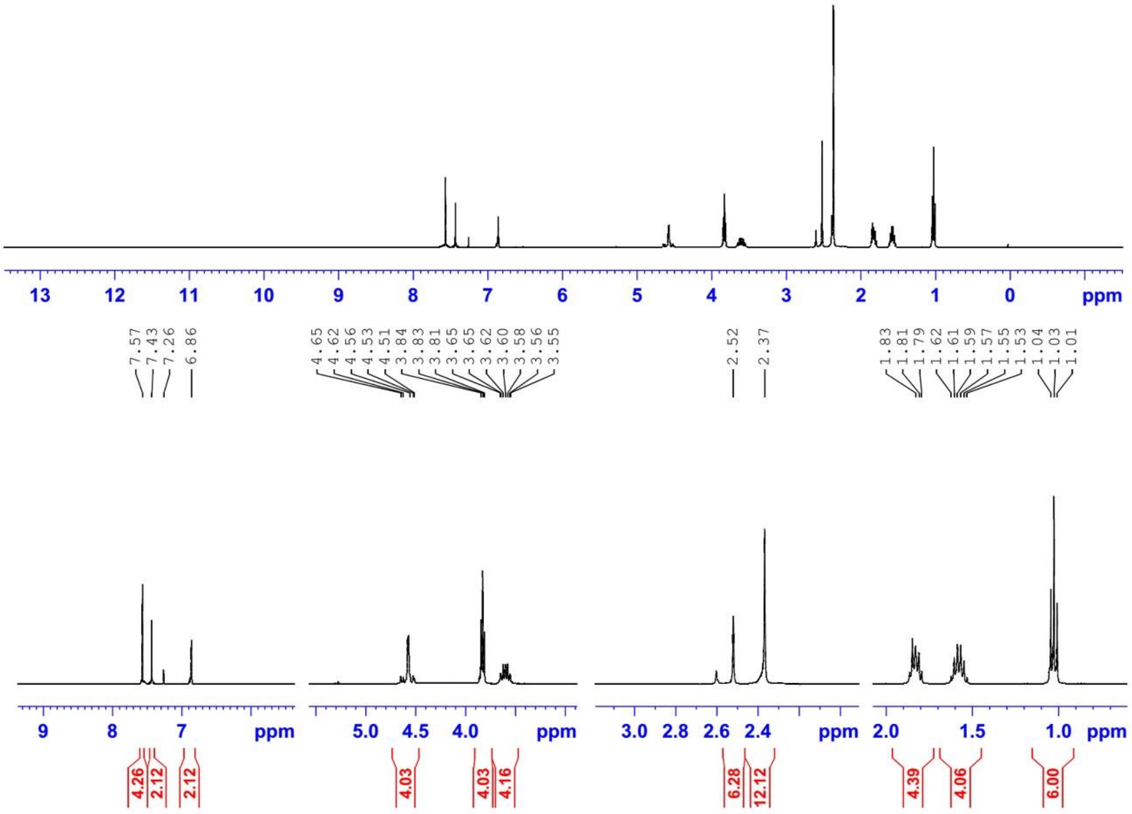
MS (ESI +; ACN–EtOAc–H_2O/HCO_2H, 90:5:5): m/z $[M + H]^+$ calcd for $[C_{42}H_{53}N_6O_2]^+$: 673.42, found 673.2.

UV/Vis: (EtOAc): λ (lg ε) = 349 (4.569) nm.

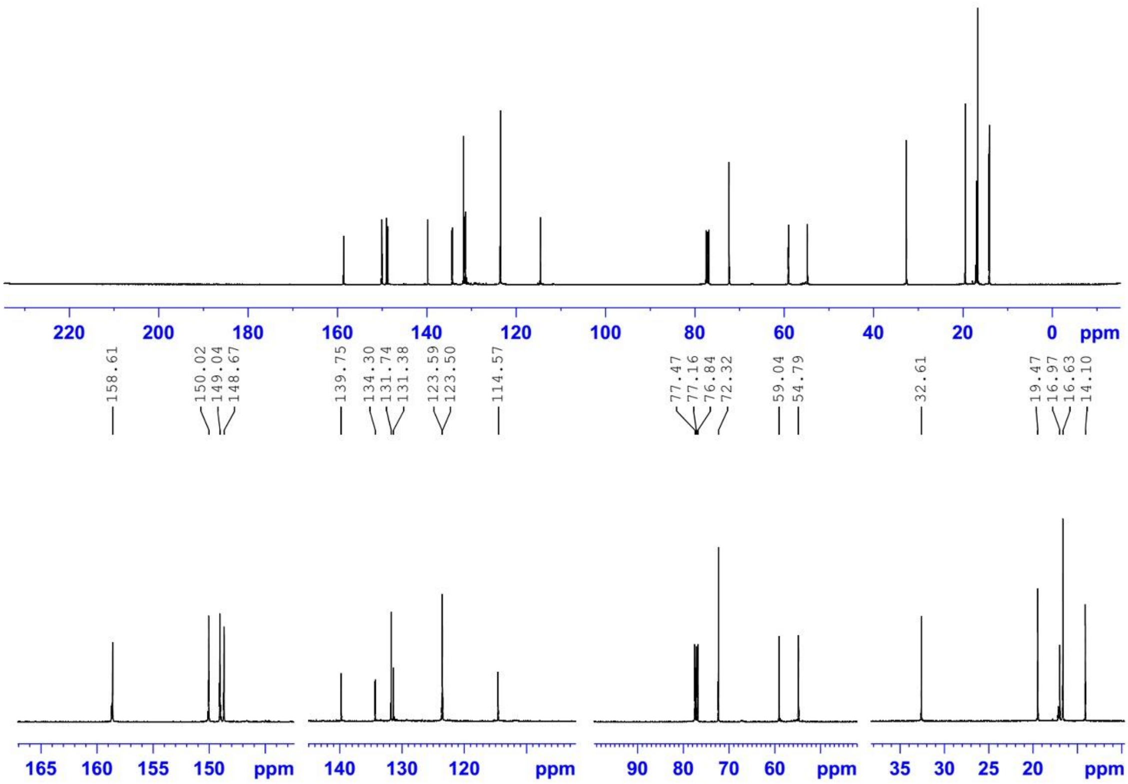
Anal. Calcd for $C_{42}H_{52}N_6O_2$: C, 74.97; H, 7.79; N, 12.49; O, 4.76. Found: C, 74.75; H, 7.91; N, 12.68.



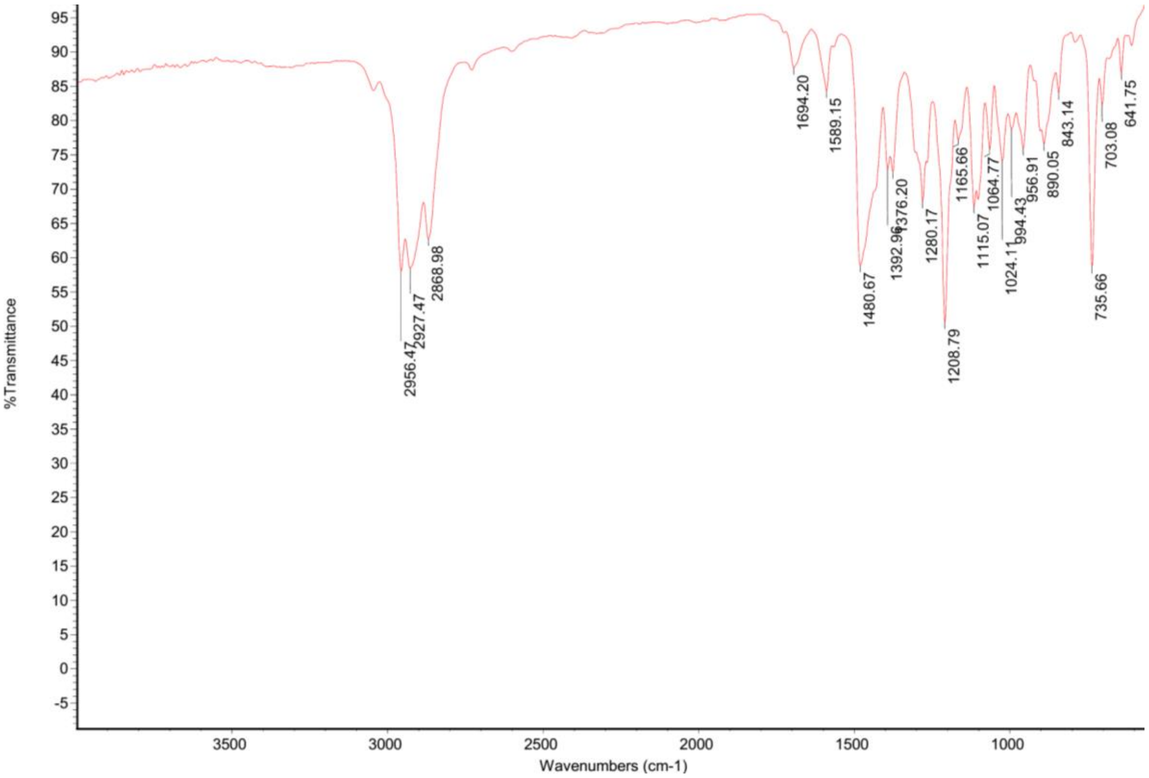
Compound 9, MS (ESI +)



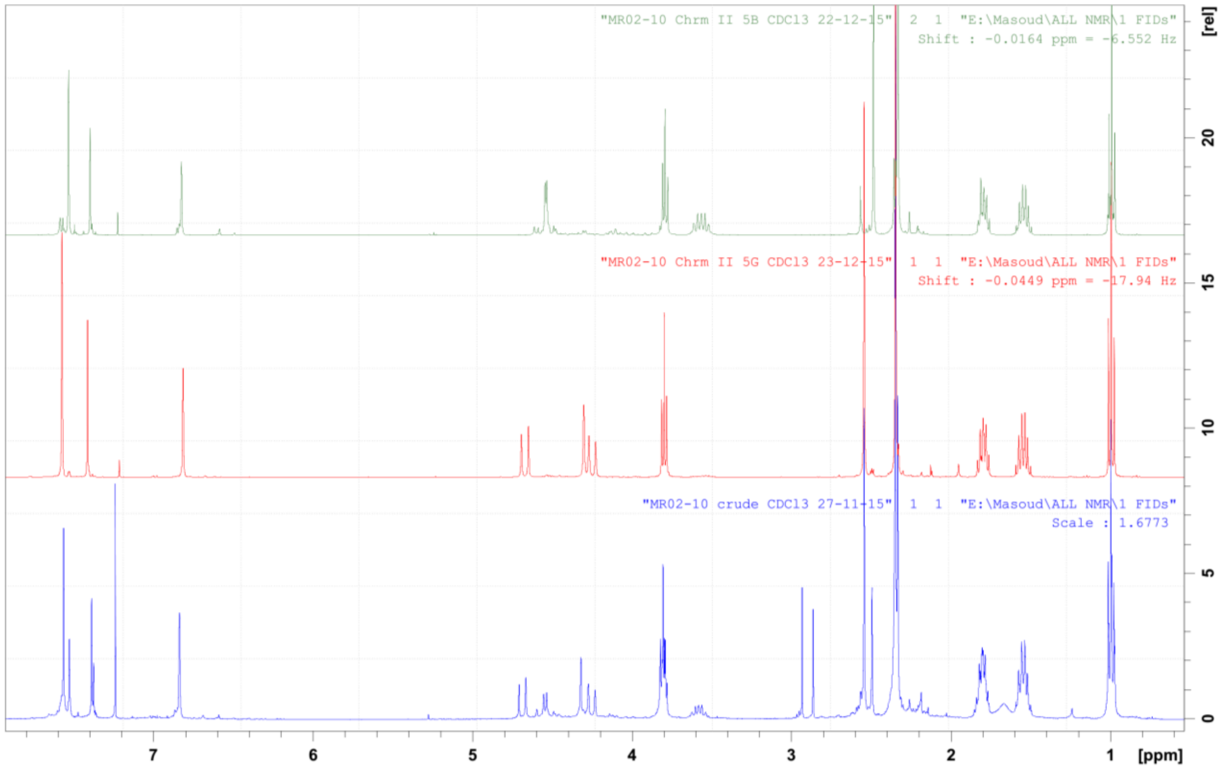
Compound 9, ^{1}H NMR (400 MHz, $CDCl_3$)



Compound 9, ^{13}C NMR (100 MHz, $CDCl_3$)



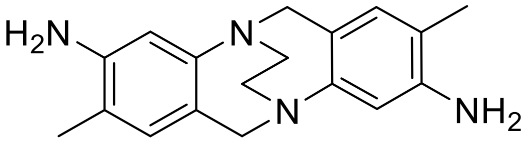
Compound 9, IR transmittance (neat)



^{1}H NMR (400 MHz, $CDCl_3$), 9 (ethano-strap, in green), 7 (methano strap, in red), reaction mixture containing 7 and 9 (in blue)

10. Preparation and Purification of Compound (10)

2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-3,9-diamine



Method G: Sonicating compound **5** (0.49 g, 1.0 mmol in H_2SO_4 12%, 15 mL) gave a milky suspension; which was then heated (80°C, 15-20 min) under argon atmosphere until turned to a clear colourless solution. Afterwards, the solution was neutralized by Na_2CO_3 (3.5 g) and basified by adding ammonium solution (28%, 5 mL) and was then extracted by DCM (30 mL x 5). DCM layers were combined and washed with brine, dried over Na_2SO_4 and filtered. DCM was removed under reduced pressure at 15°C in darkness to obtain pure **10** as a cream-coloured solid. Yield: 0.28 g (0.96 mmol, 96%).

Method H: Compound **9** (0.67 g, 1 mmol, 1eq.), was dissolved in boiling MeOH (30 mL). Then, sodium dithionite ($Na_2S_2O_4$, 4 g, excess) was gradually added. The suspension was refluxed until obtaining a total discoloration from orange to milky white (3-4 h). The suspension was cooled down to r.t., DCM (120 mL) was added and the suspension was filtered off. The solvents were removed under reduced pressure and the remaining residue was chromatographed to obtain purified **10**. (This product has to be stored under inert atmosphere in dark and cold otherwise darkens fast). Yield: 0.18 g (0.62 mmol, 62%); R_f: 0.6 (silica gel; MeOH–DCM = 10% v/v).

IR (neat): 3338, 3227, 2894, 2855, 1619, 1501, 1440, 1287, 1117, 876 cm^{-1}.

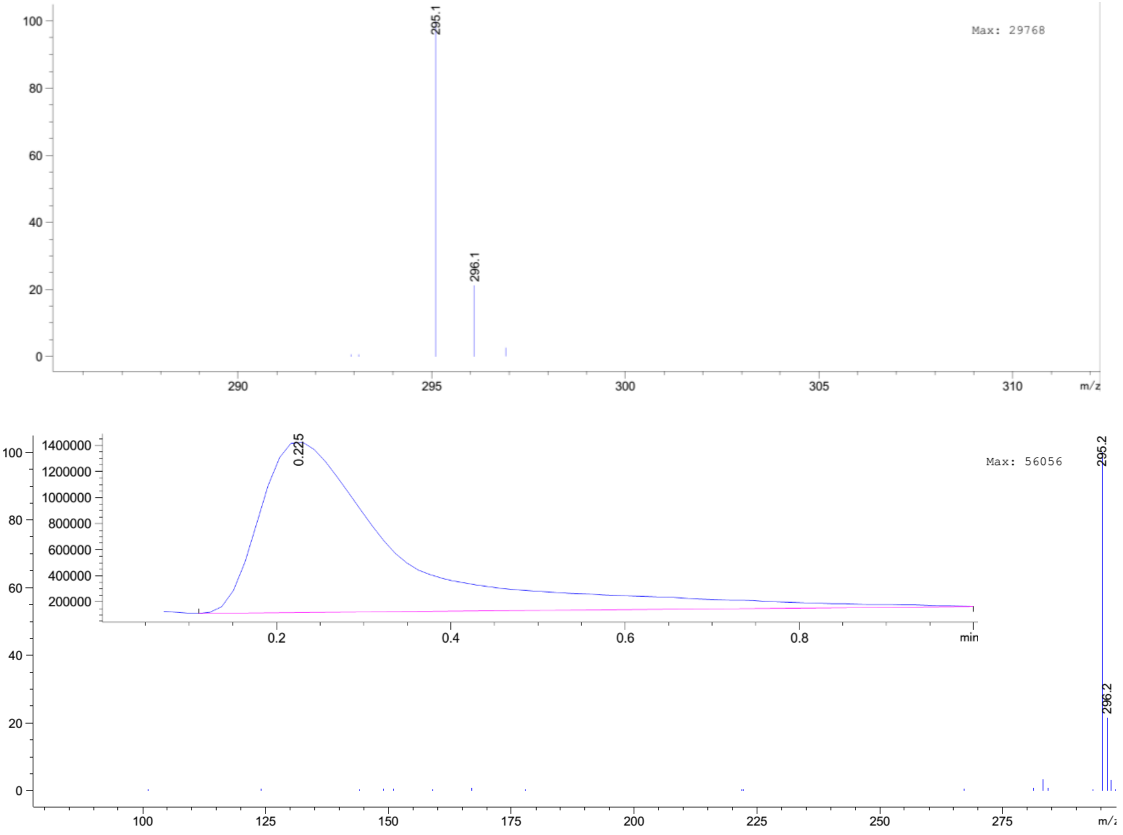
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.40 (s, 2H, CH), 6.27 (s, 2H, CH), 4.47 (br, 4H, NH), 4.30–4.34 (d, J = 16.6 Hz, 2H, CH_2), 4.01–4.05 (d, J = 16.7 Hz, 2H, CH_2), 3.34 (br, 4H, $N(CH_2)_2N$), 1.86 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.0, 144.8, 129.6, 124.3, 117.4, 112.8, 58.2, 54.44, 16.7.

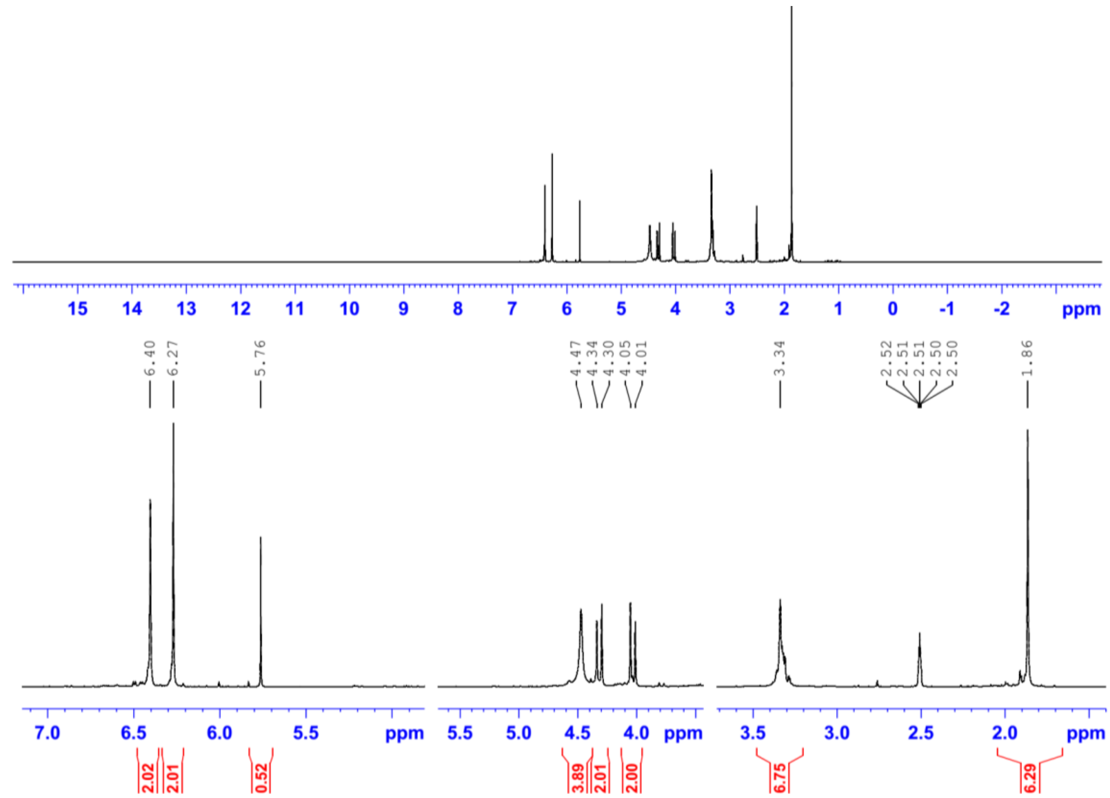
MS (ESI +; MeOH): m/z $[M + H]^+$ calcd for $[C_{18}H_{23}N_4]^+$: 295.18, found 295.1.

UV/Vis: (ACN): λ (lg ε) = 225 (4.569), 304 (4.009) nm.

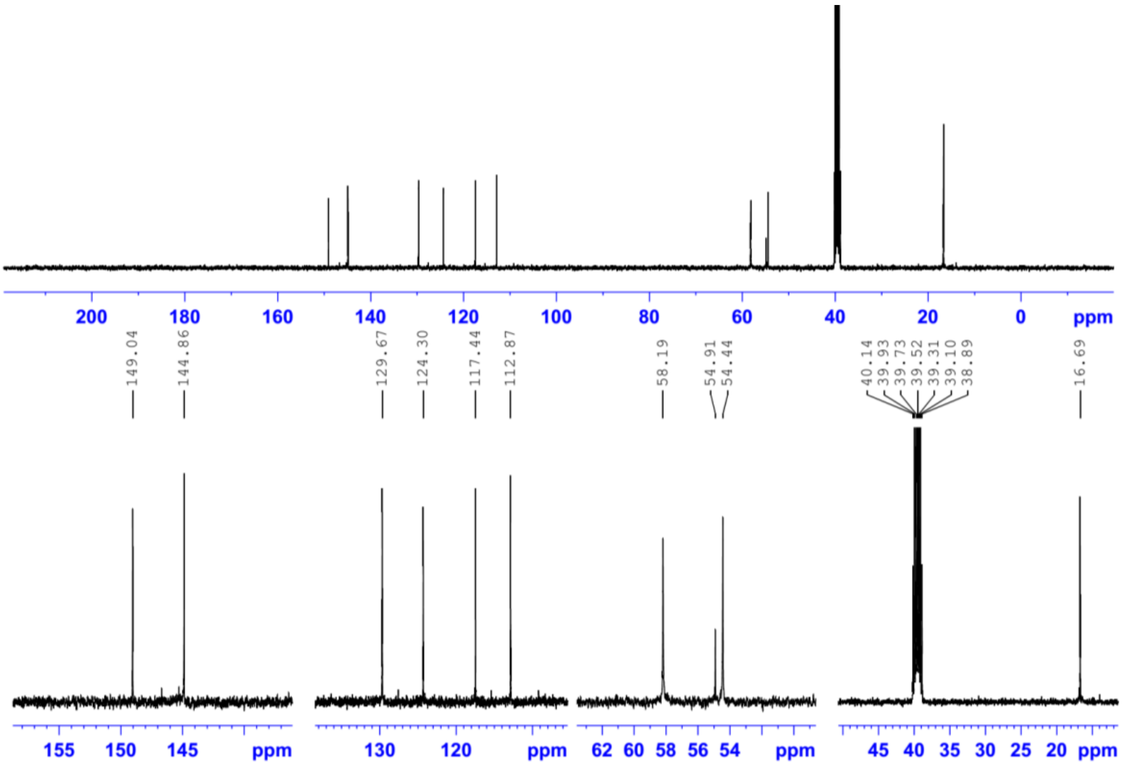
Anal. Calcd for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.23; H, 7.70; N, 19.14.



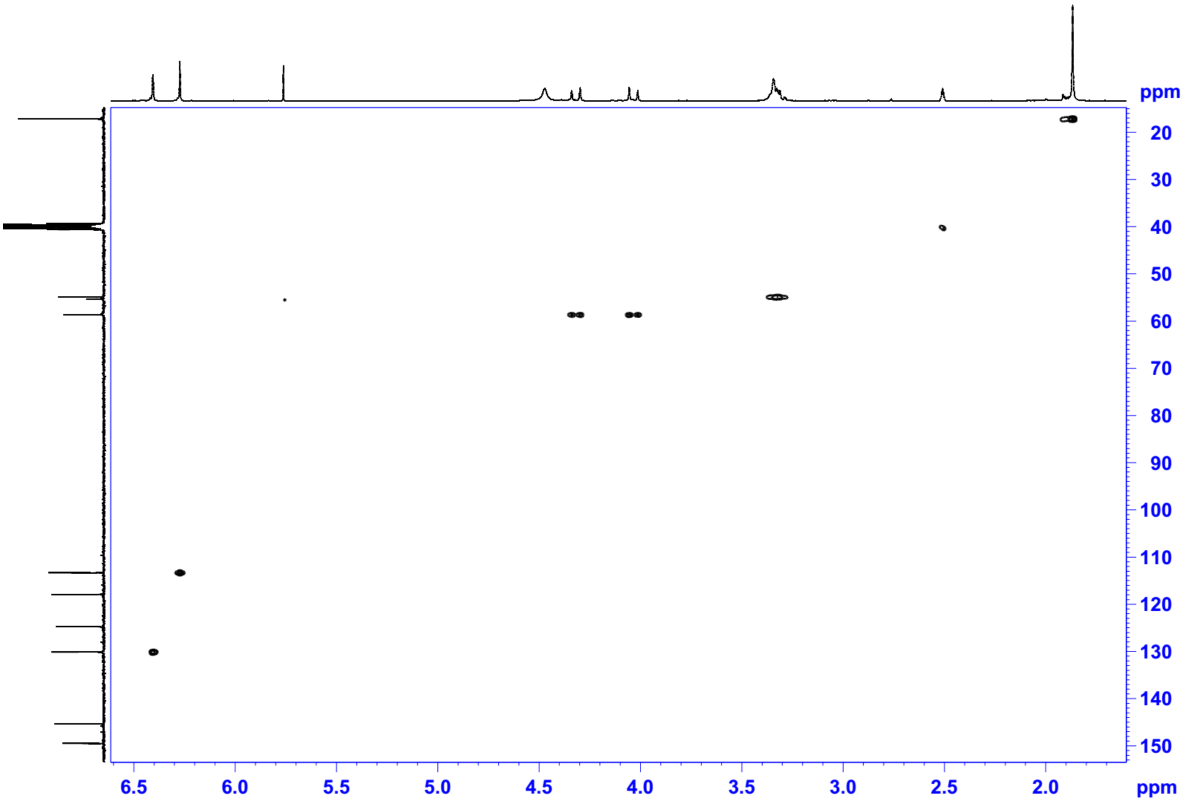
Compound 10, MS (ESI +)



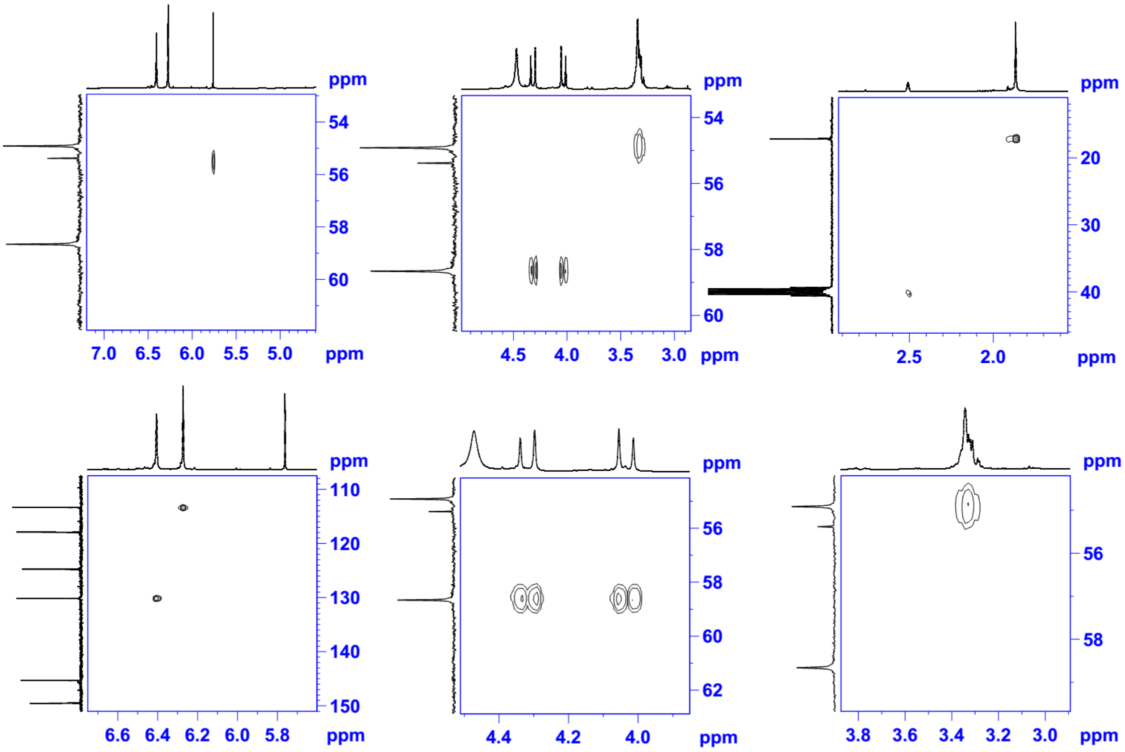
Compound 10, ^{1}H NMR (400 MHz, DMSO-d_6)



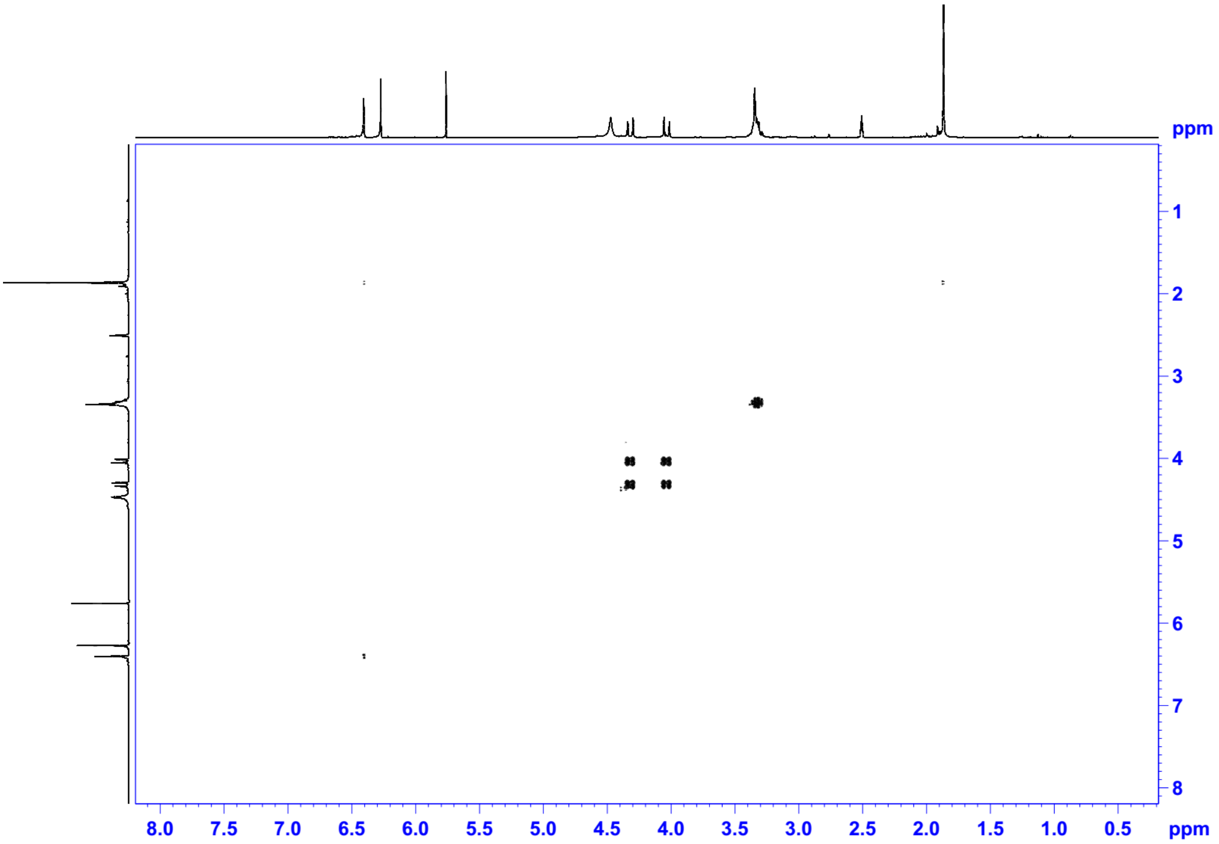
Compound 10, ^{13}C NMR (100 MHz, DMSO-d_6)



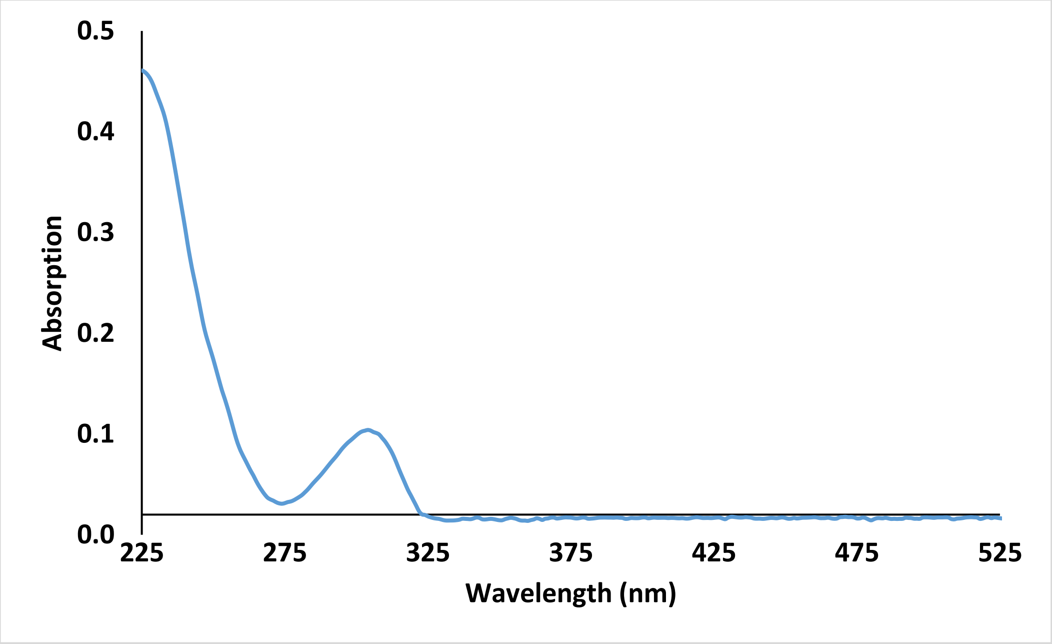
Compound 10, HSQC (DMSO-d_6)



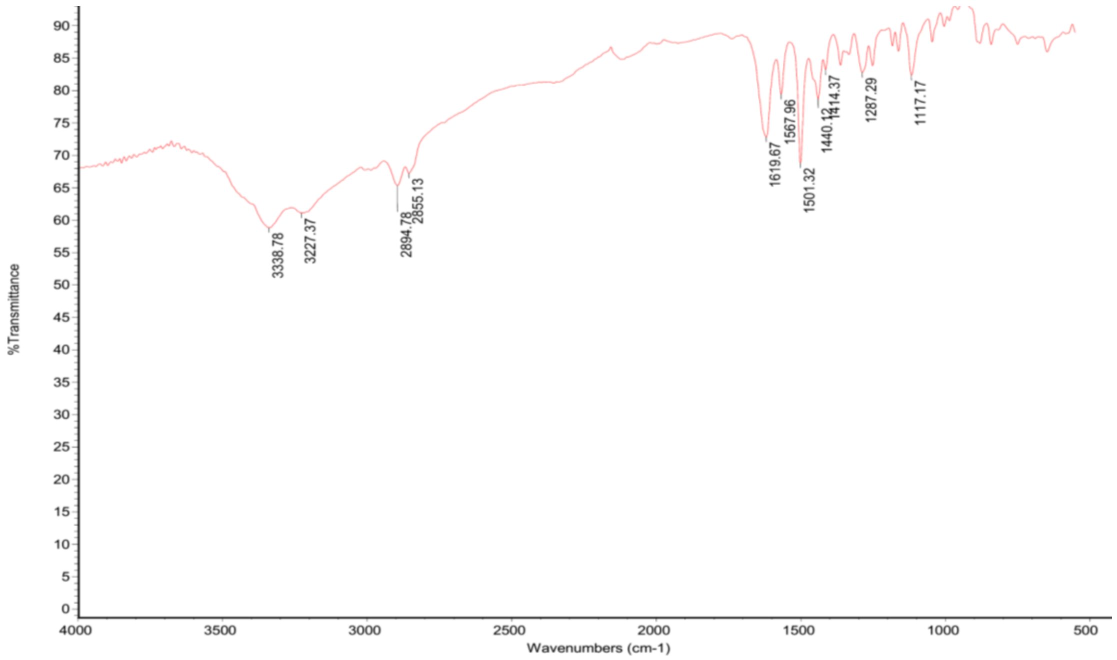
Compound 10, HSQC (DMSO-d_6)



Compound 10, COSY (DMSO-d_6)



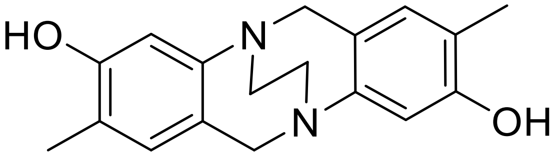
Compound 10, UV/Vis (ACN, r.t.)



Compound 10, IR transmittance (neat)

11. Preparation and Purification of Compound (11)

2,8-dimethyl-6H,12H-5,11-ethanodibenzo[b,f][1,5]diazocine-3,9-diol



Compound **5** (0.49 g, 1 mmol, 1eq.) was dispersed in H_2SO_4 (6.5%, 30 mL) by sonication for 5 min. Then, the obtained milky suspension was refluxed under nitrogen atmosphere in darkness until turned to a clear colourless solution. The solution was cooled down to -5°C and sodium nitrite solution (0.3 g, 4.4 mmol, 2.2 eq.) in cold water (10 mL) was added dropwise and stirring continued for 30 min at -5°C. Afterwards, the solution's temperature was gradually raised until boil over two hours (Attention: this step releases nitrogen gas; hence, rapid heating of a sealed container may lead to explosion). The reaction mixture was cooled down to r.t. , its pH was adjusted to 5 (by adding Na_2CO_3 saturated solution) and extracted by EtOAc (30ml x 5), the organic layers were combined, dried over Na_2SO_4 and evaporated until dryness to obtain the pure product as an off-white powder.

Yield: 0.27 g (0.91 mmol, 91%). R_f = 0.4 (silica gel; MeOH–DCM, 8% v/v).

IR (neat): 3190, 2949, 2914, 1704, 1616, 1500, 1440, 1220, 1042, 879, 716 cm^{-1}.

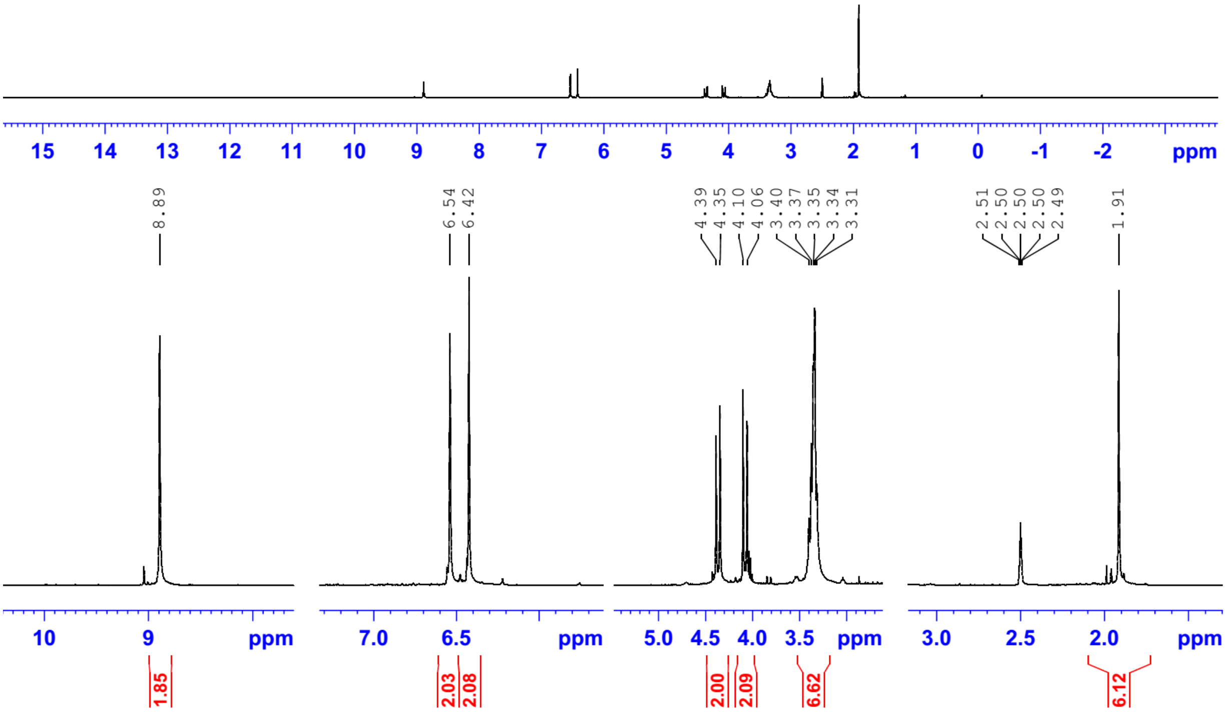
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.89 (s, 2H, OH), 6.54 (s, 2H, CH), 6.42 (s, 2H, CH), 4.34–4.38 (d, *J* = 16.7 Hz, 2H, CH_2), 4.05–4.10 (d, *J* = 16.8 Hz, 2H, CH_2), 3.29–3.39 (m, 4H, CH_2), 1.91 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.7, 148.8, 130.1, 126.8, 119.8, 113.4, 58.0, 54.4, 15.3.

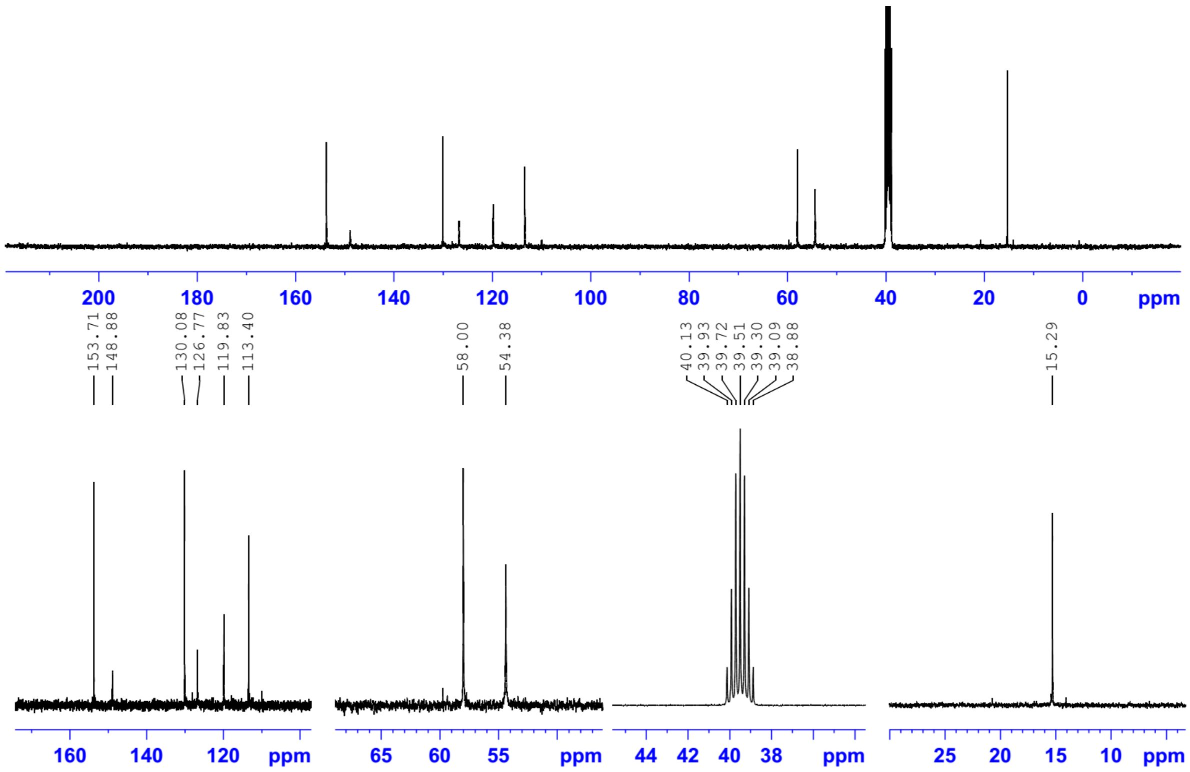
MS (ESI +; EtOH–EtOAc–H_2O, 90:5:5): *m/z* [M + H]$^+$ calcd for $[C_{18}H_{21}N_2O_2]^+$: 297.15; found 297.1. MS (ESI –): *m/z* [M – H]$^-$ calcd for $[C_{18}H_{19}N_2O_2]^-$: 295.15; found 295.1.

UV/Vis: (EtOAc): λ (lg ε) = 294 (3.655) nm.

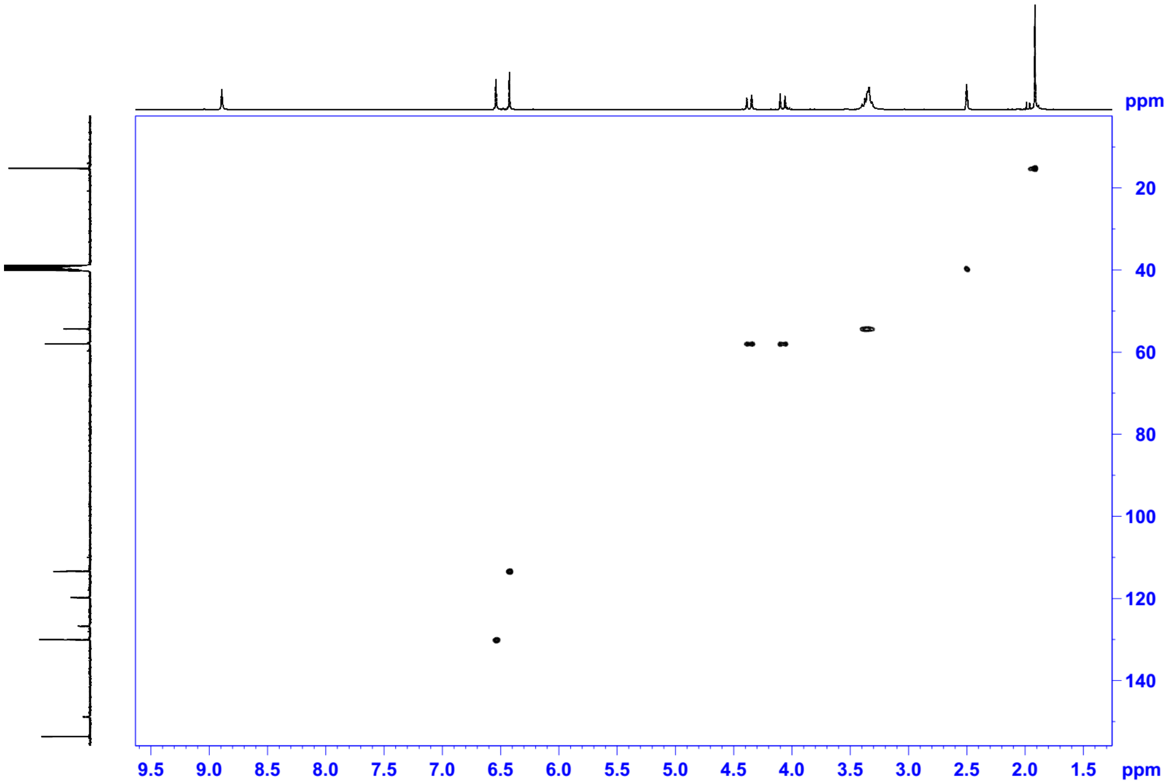
Anal. calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45; O, 10.80. Found: C, 72.67; H, 6.64; N, 9.83.



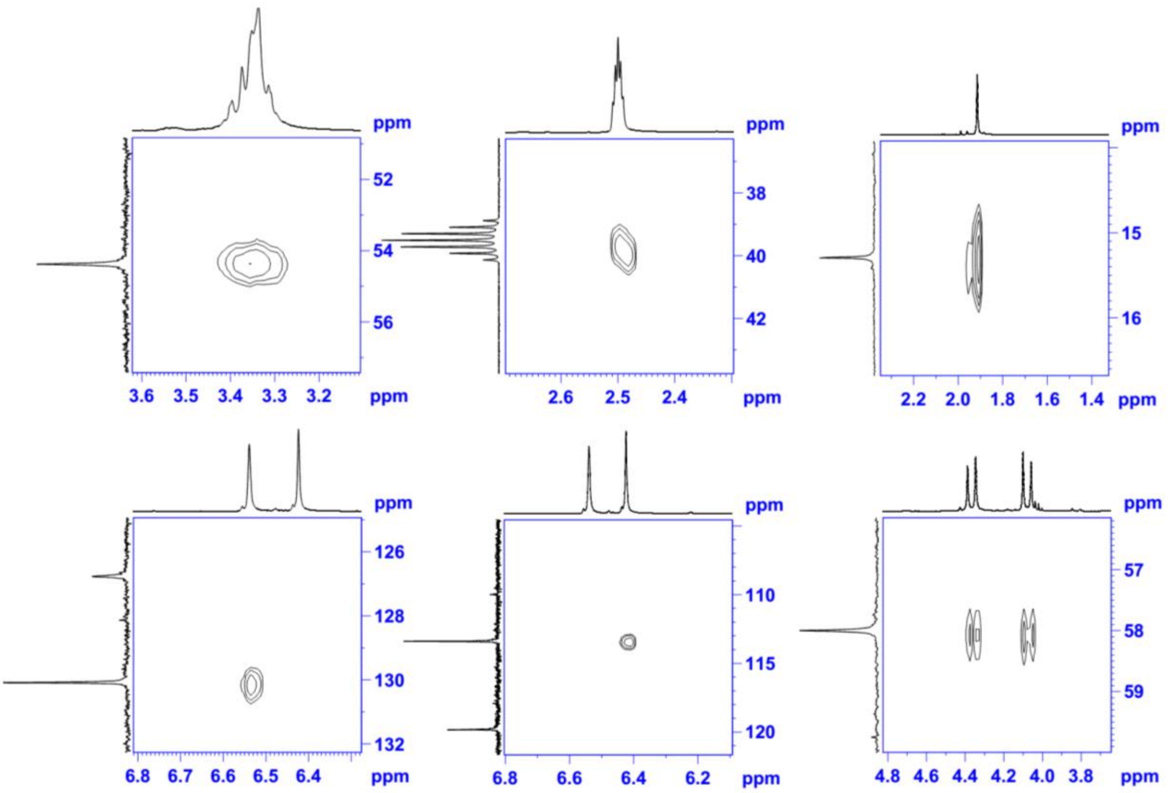
Compound 11, ^{1}H NMR (400 MHz, DMSO-d_6)



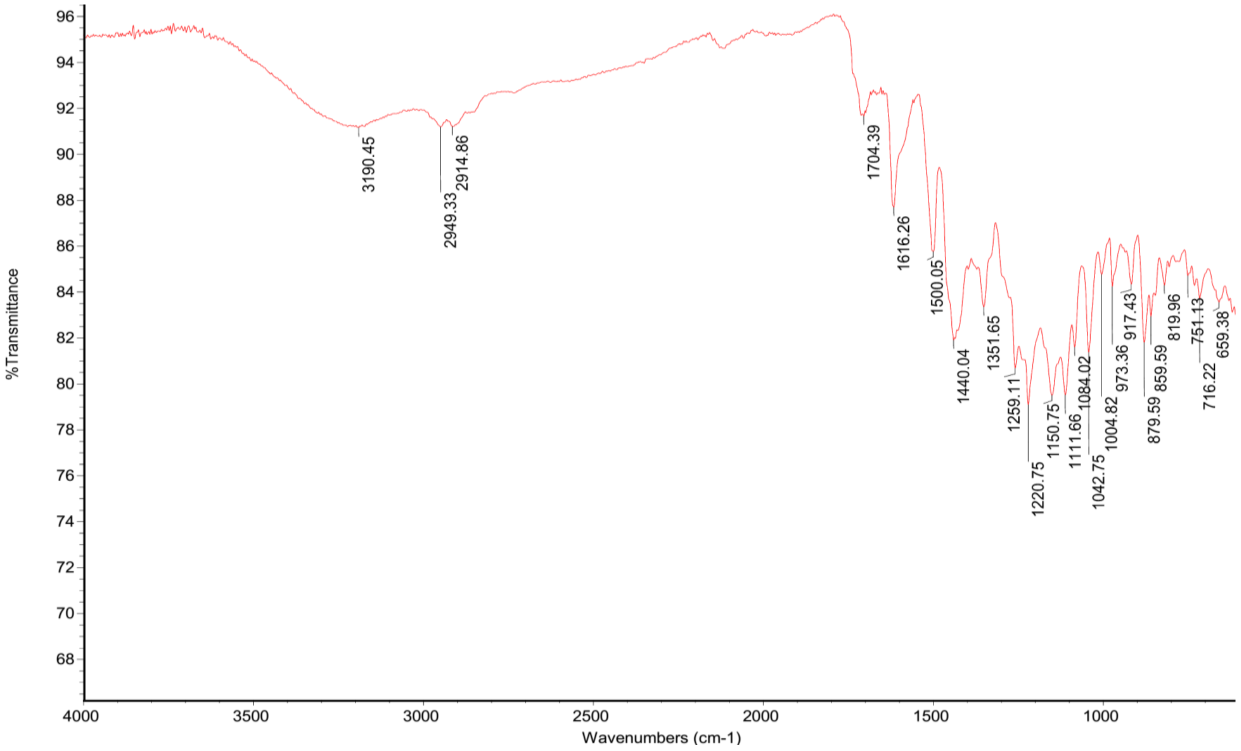
Compound 11, ^{13}C NMR (100 MHz, DMSO-d_6)



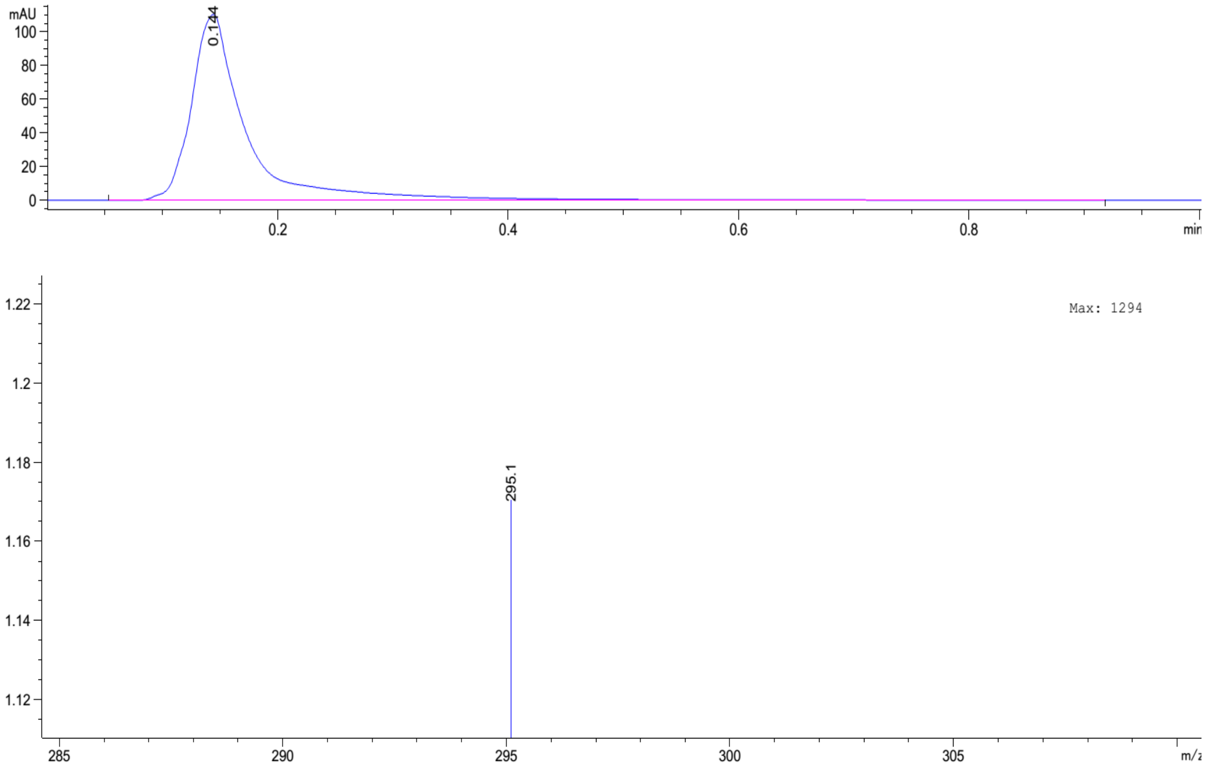
Compound 11 (HSQC, DMSO-d_6)



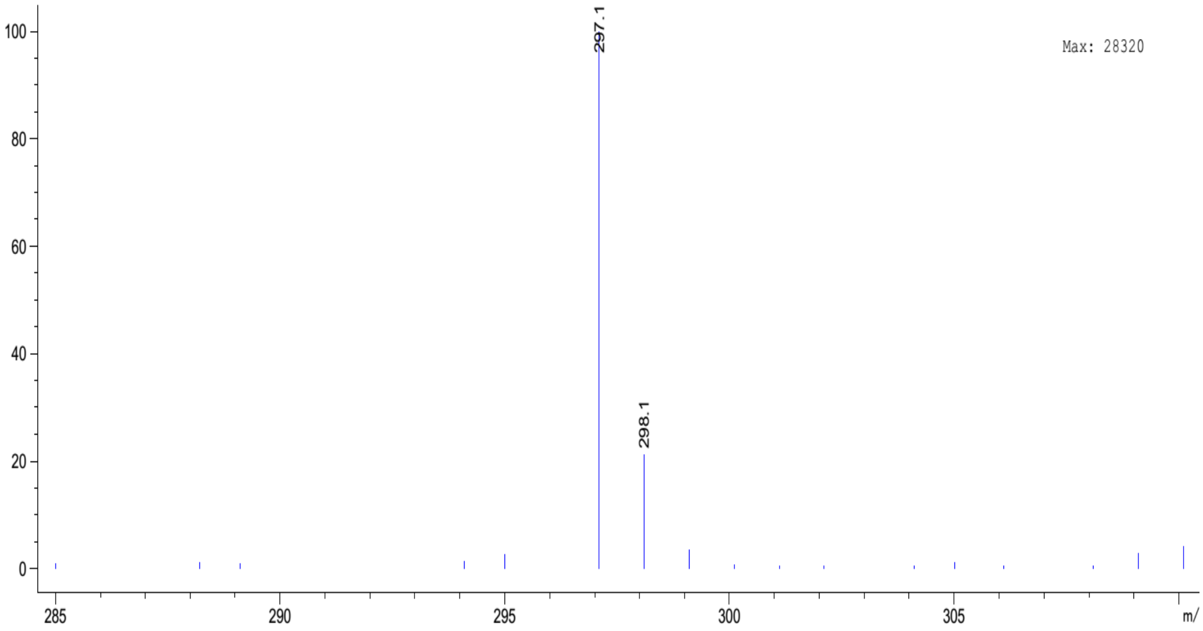
Compound 11 (HSQC, DMSO-d_6)



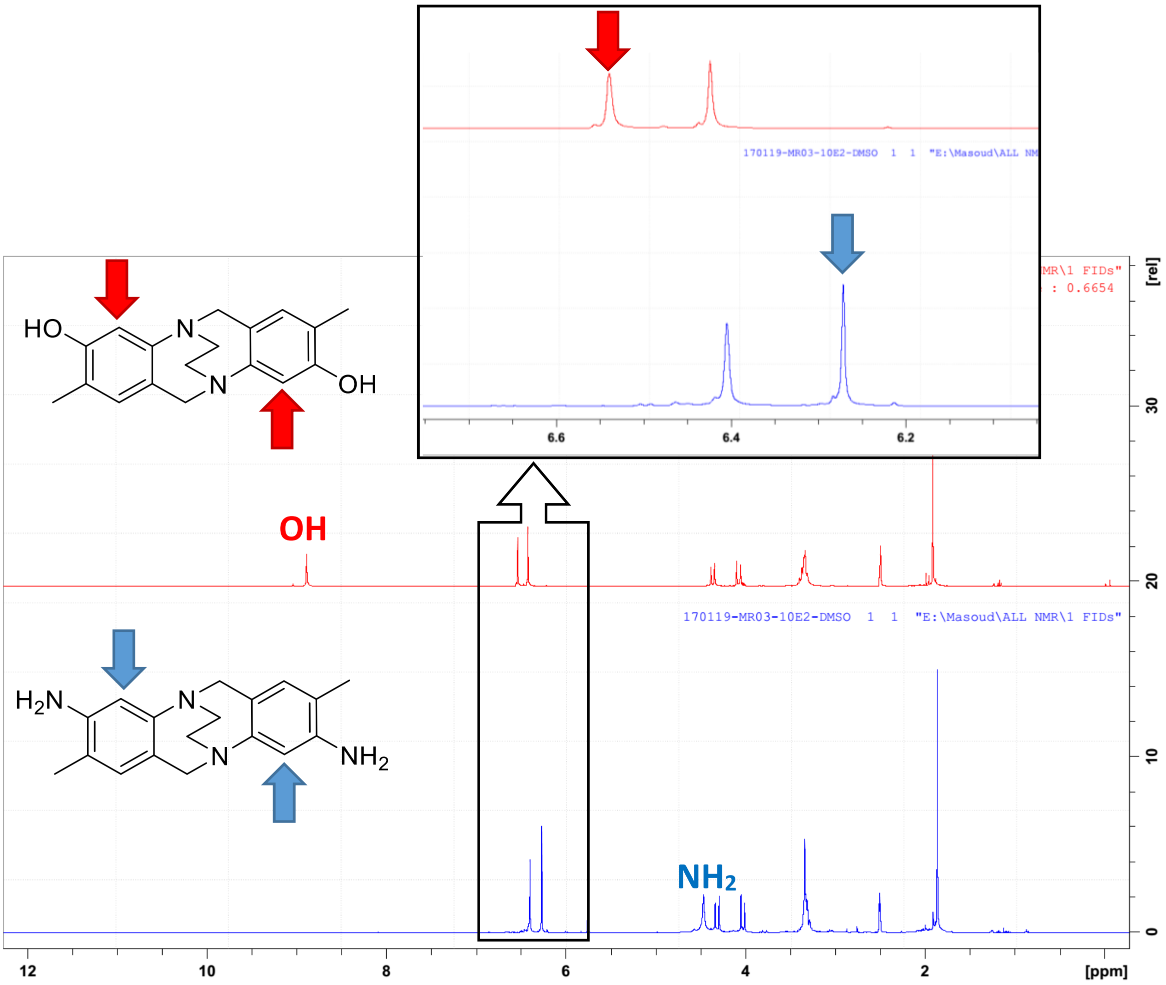
Compound 11, IR (neat)



Compound 11, MS (ESI –)



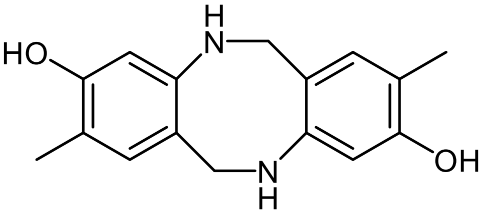
Compound 11, MS (ESI +)



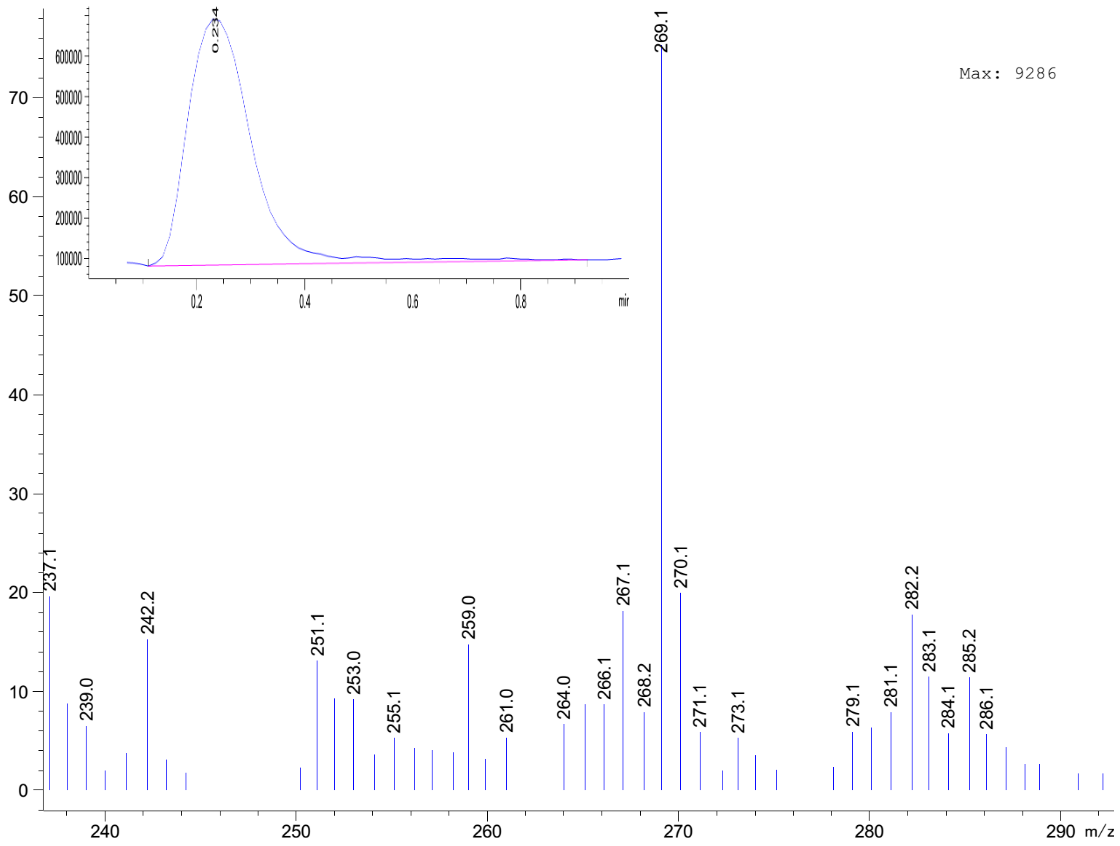
Comparative ^{1}H NMR spectra of 10 and 11, DMSO-*d*$_6$

12. Preparation and Purification of Compound (12)

2,8-dimethyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine-3,9-diol



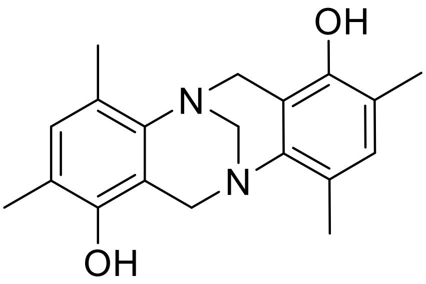
Hünlich's base was subjected to the method described in the literature. [3] The amount of obtained product was not sufficient to be properly characterized, despite scaling up the reaction tenfold. Yield: trace. MS (ESI +; ACN–MeOH, 90:10): *m/z* [M − H]$^-$ calcd for [$C_{16}H_{17}N_2O_2$]$^-$: 269.14; Found: 269.1.



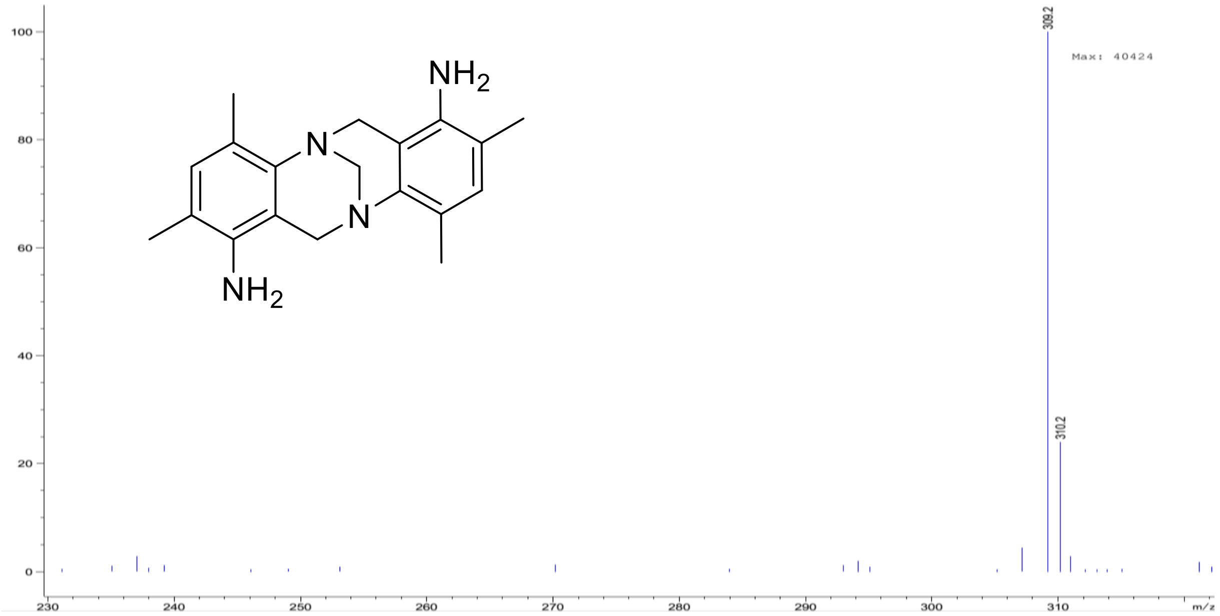
Compound 12, MS (ESI -)

13. Preparation and Purification of Compound (13)

2,4,8,10-tetramethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-1,7-diol



First, “2,4,8,10-tetramethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-1,7-diamine” was prepared according to the literature.[4] MS (ESI +; EtOAc): *m/z* $[M + H]^+$ calcd for $[C_{19}H_{25}N_4]^+$: 309.20; found 309.2.



2,4,8,10-tetramethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-1,7-diamine, MS (ESI +)

Afterwards, 2,4,8,10-tetramethyl-6H,12H-5,11-methanodibenzo [b,f][1,5] diazocine-1,7-diamine (0.60 g, 2.0 mmol, 1.0 eq.) was dissolved in H_2SO_4 (6.5%, 90 mL), and cooled down to -5°C. A sodium nitrite solution (0.30 g, 4.4 mmol, 2.2 eq.) in cold water (10 mL) was dropped into the reaction flask and stirred for 30 min at -5°C. Then, the solution's temperature was gradually raised until boil, by two hours (Attention: this step releases nitrogen gas; hence, rapid heating and sealing the container may lead to explosion). The reaction mixture was cooled down to r.t., its *p*H was adjusted to 5 (by adding 6–8 g of Na_2CO_3) and extracted with EtOAc (30ml x 5). The organic layers were combined, dried over $MgSO_4$ and evaporated until dryness to obtain the product as a white powder. Yield: 0.57 g (1.8 mmol, 92%). R_f = 0.5 (silica gel; MeOH–DCM, 8% v/v).

IR (neat): 3253, 2970, 1615, 1482, 1216, 1035, 870, 615 cm^{-1}.

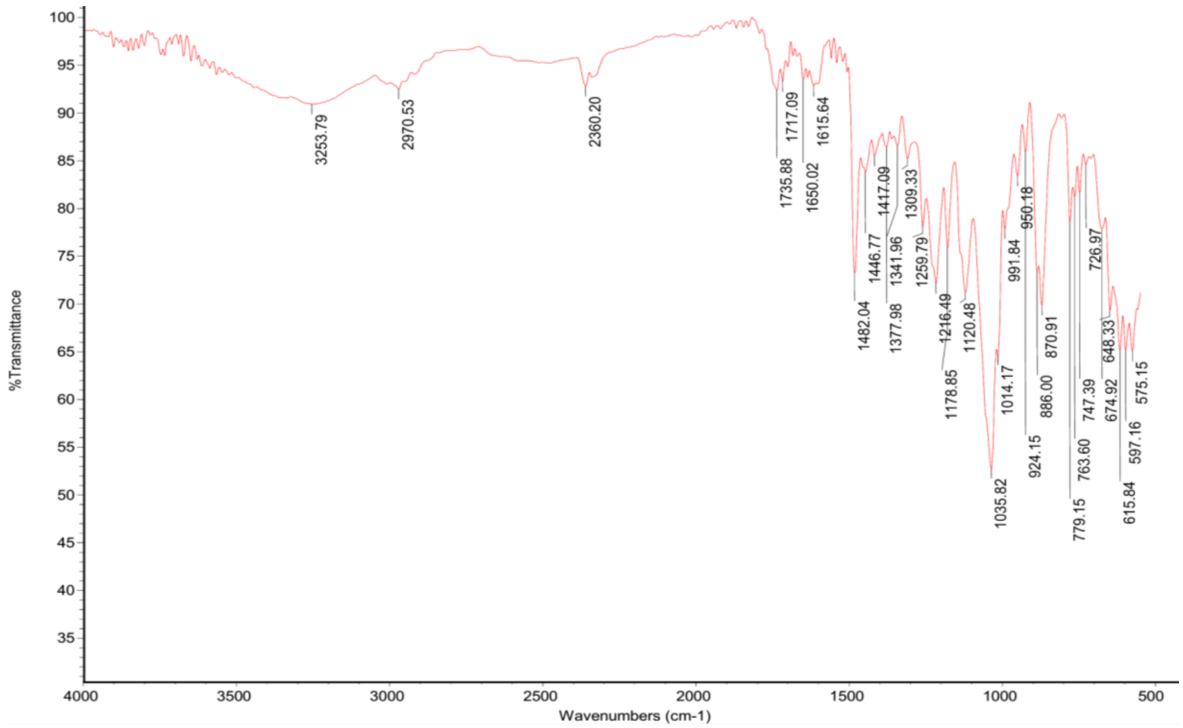
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 (s, 2H, OH), 6.89 (s, 2H, CH), 4.56 (s, 2H, NCH_2N), 4.44–4.48 (d, *J* = 17.0 Hz, 2H, CH_2), 4.08–4.04 (d, *J* = 17.2 Hz, 2H, CH_2), 2.29 (s, 6H, CH_3), 2.06 (s, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.8, 146.7, 132.3, 131.3, 131.0, 122.1, 66.4, 51.2, 15.9, 15.9.

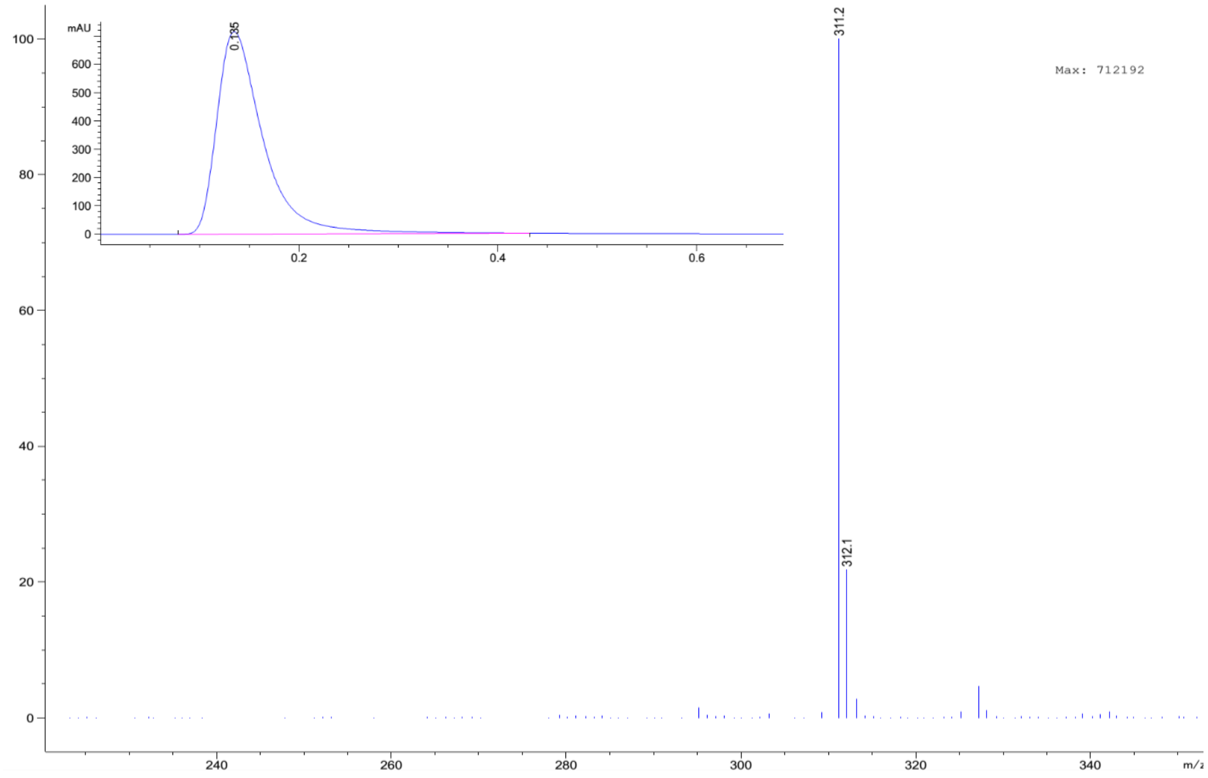
MS (ESI +; EtOAc): *m/z* $[M + H]^+$ calcd for $[C_{19}H_{23}N_2O_2]^+$: 311.17; found 311.2.

UV/Vis: (ACN): λ (lg ε) = 285 (3.563) nm.

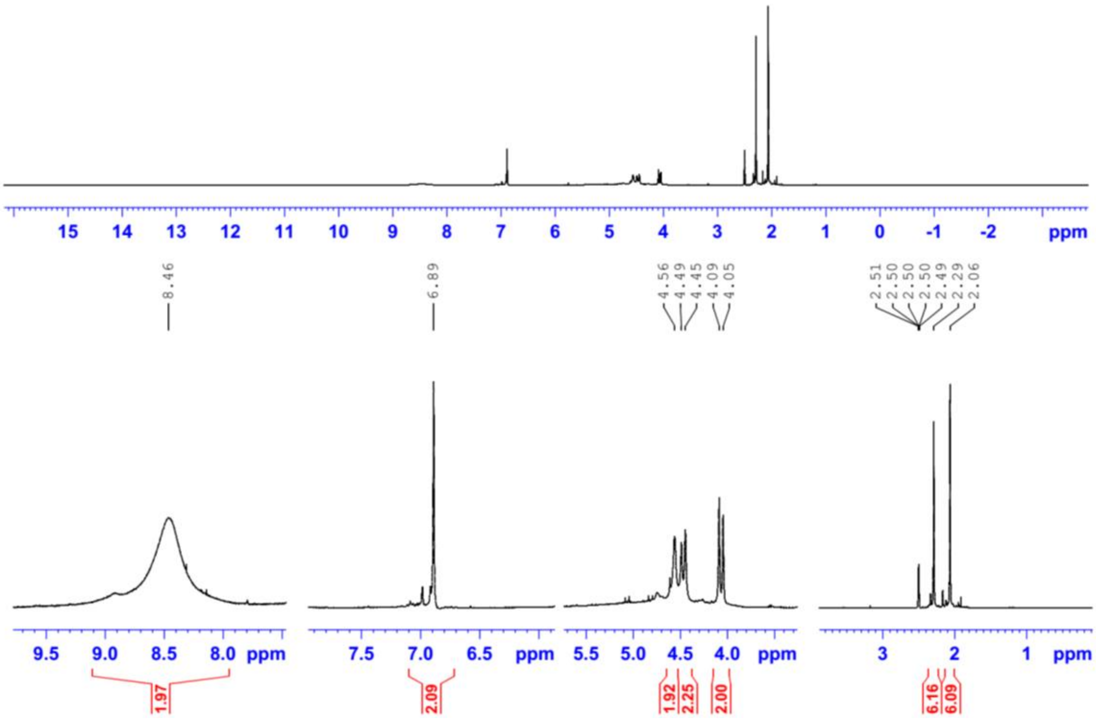
Anal. calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.44; H, 6.96; N, 8.84.



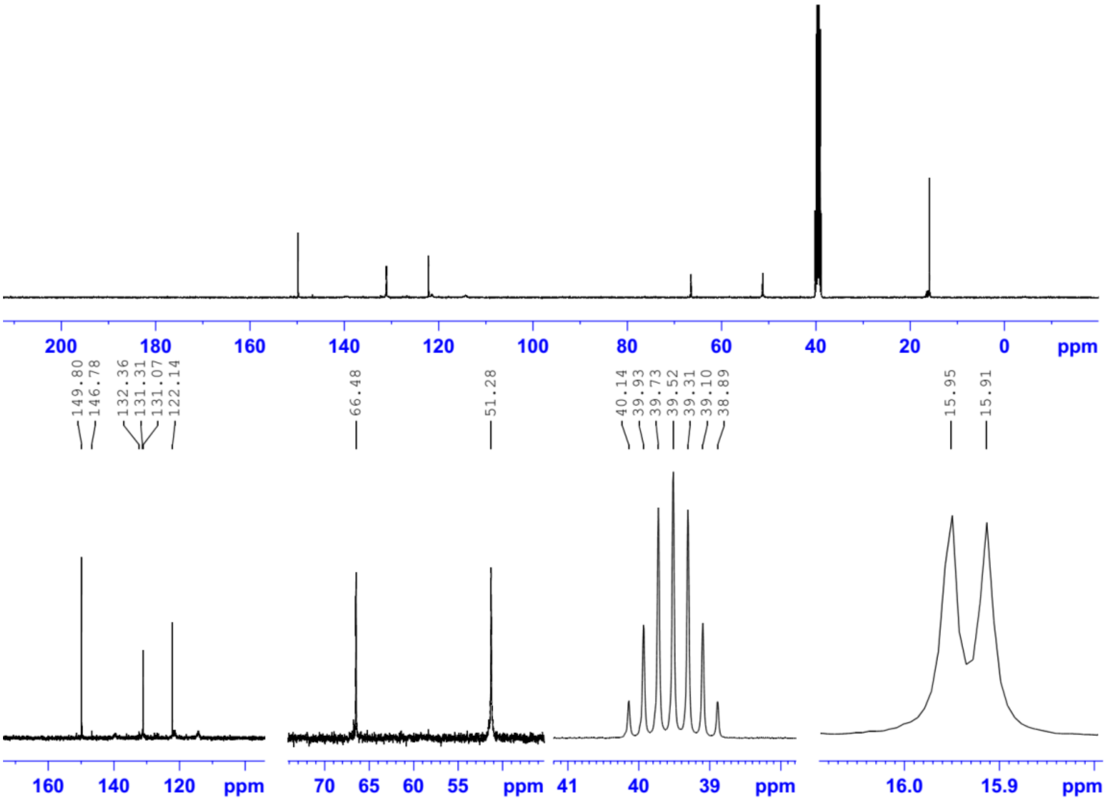
Compound 13, IR transmittance (neat)



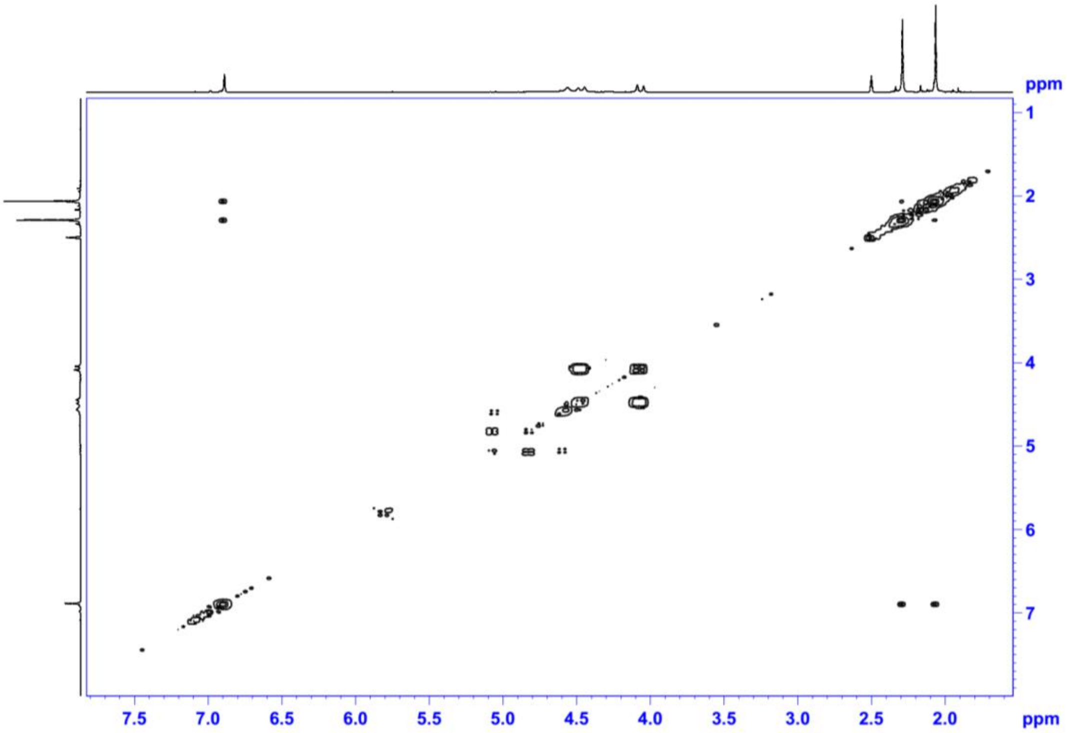
Compound 13, MS (ESI +)



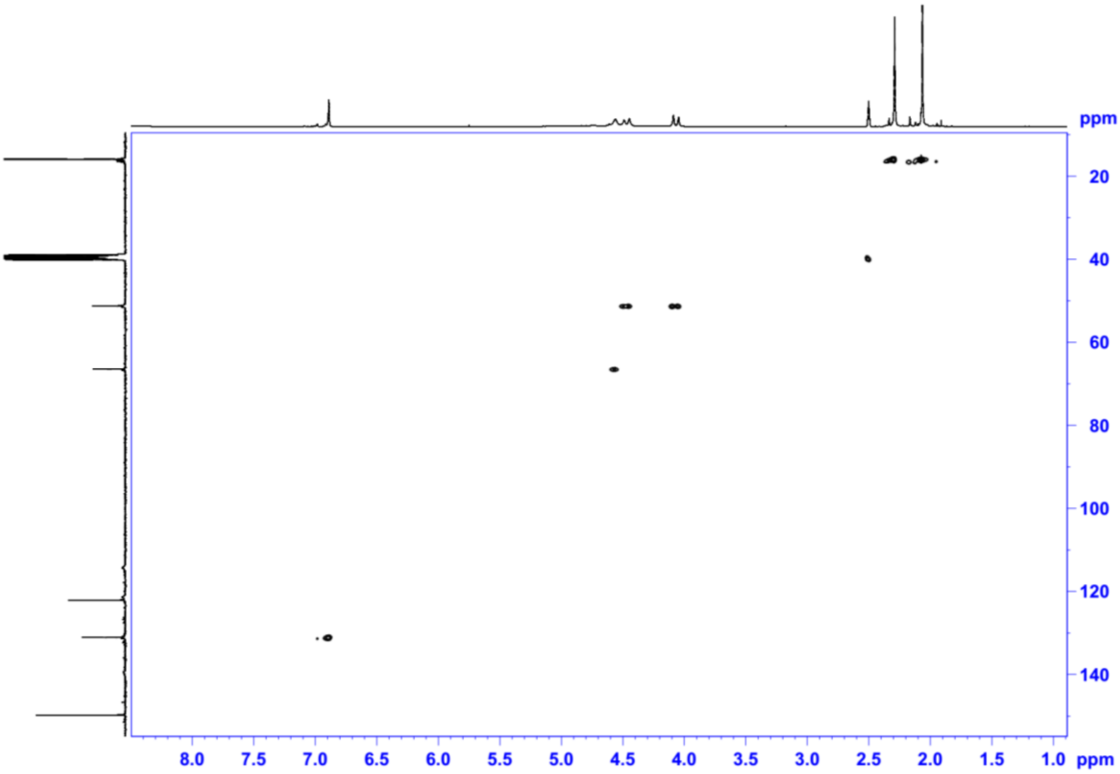
Compound 13, ^{1}H NMR (400 MHz, DMSO-d_6)



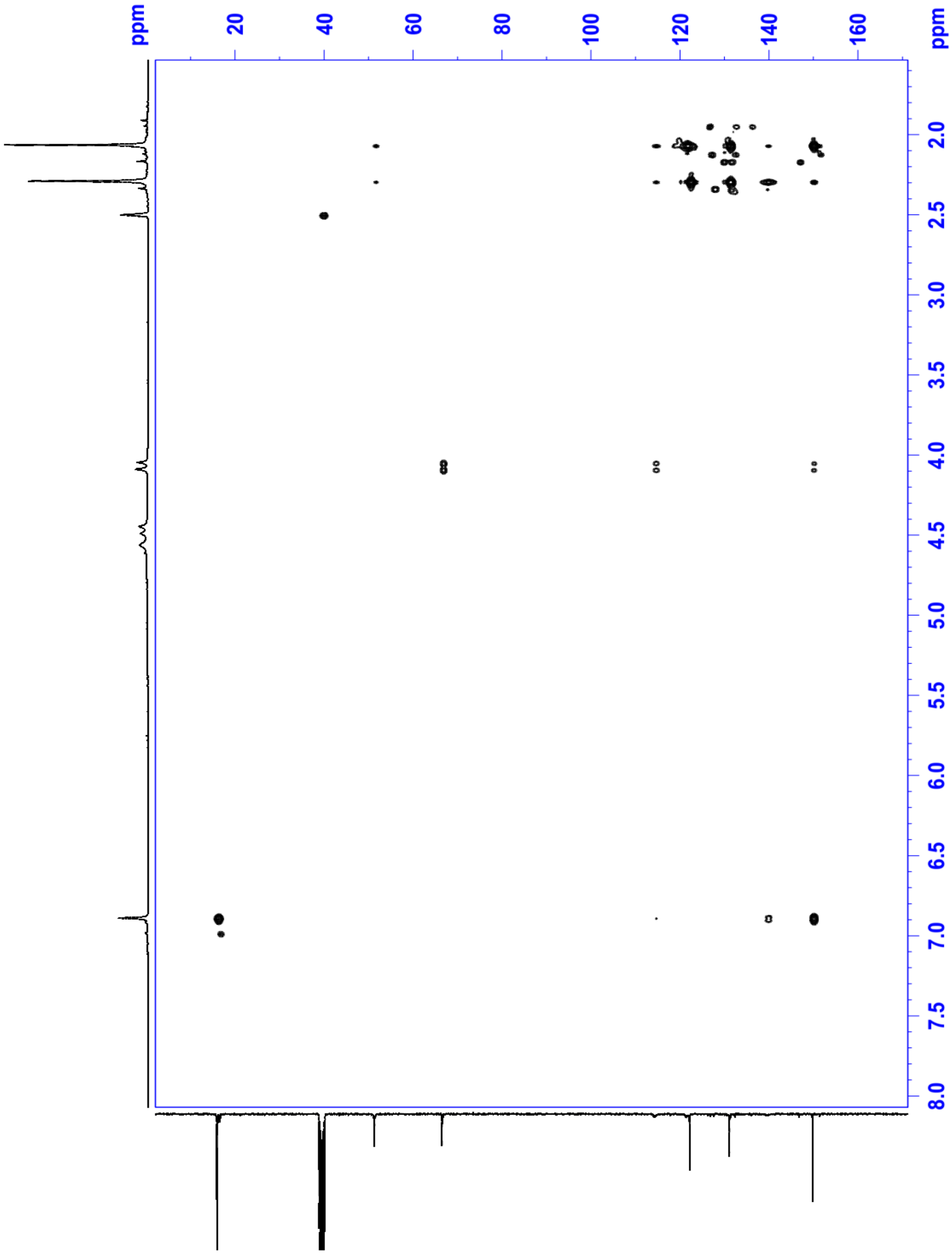
Compound 13, ^{13}C NMR (100 MHz, DMSO-d_6)



Compound 13, COSY (DMSO-d_6)



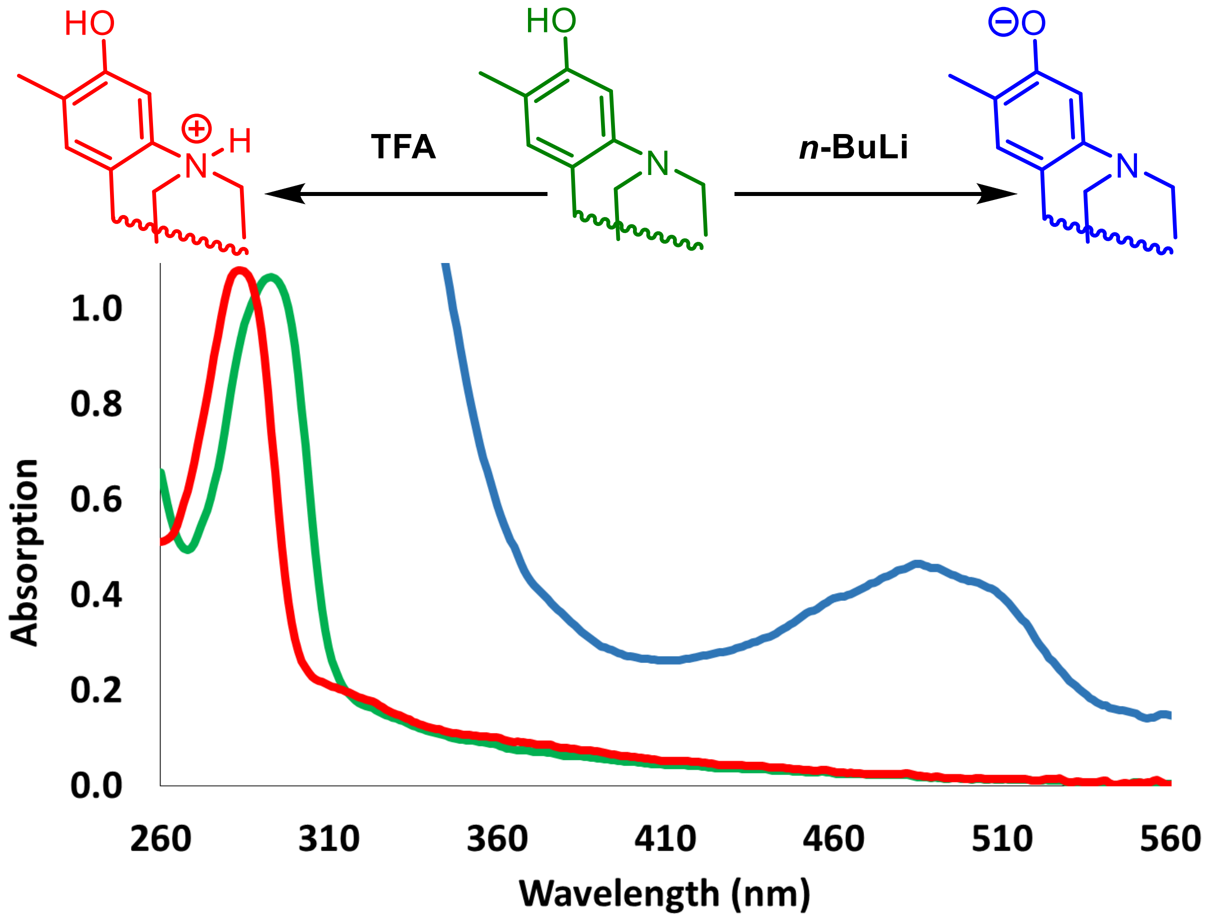
Compound 13, HSQC (DMSO-d_6)



Compound 13, HMBC(DMSO-d_6)

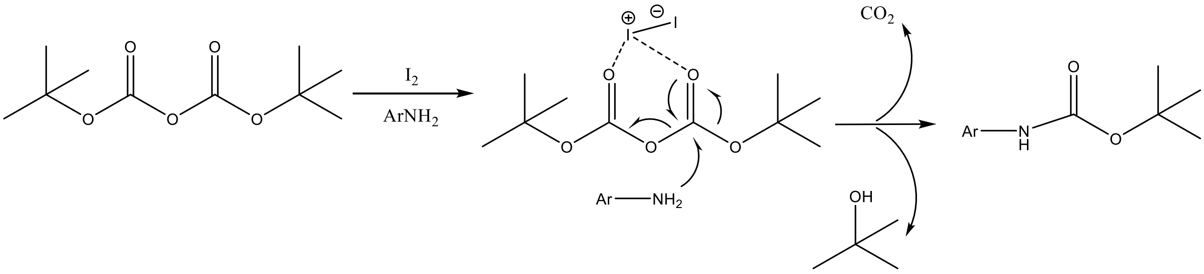
14. UV/Vis Studies of Compound (3)

2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine-3,9-diol

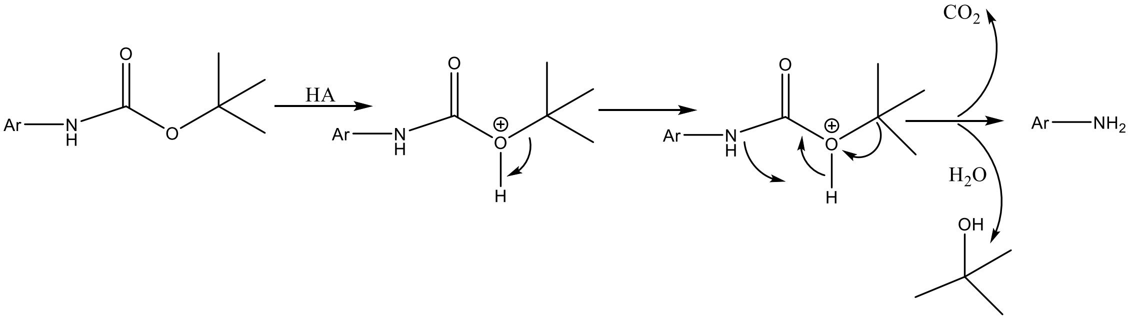


Compound 3, UV/Vis spectra in acetonitrile (in green), in the presence of TFA (in red), and in the presence of *n*-BuLi (in Blue).

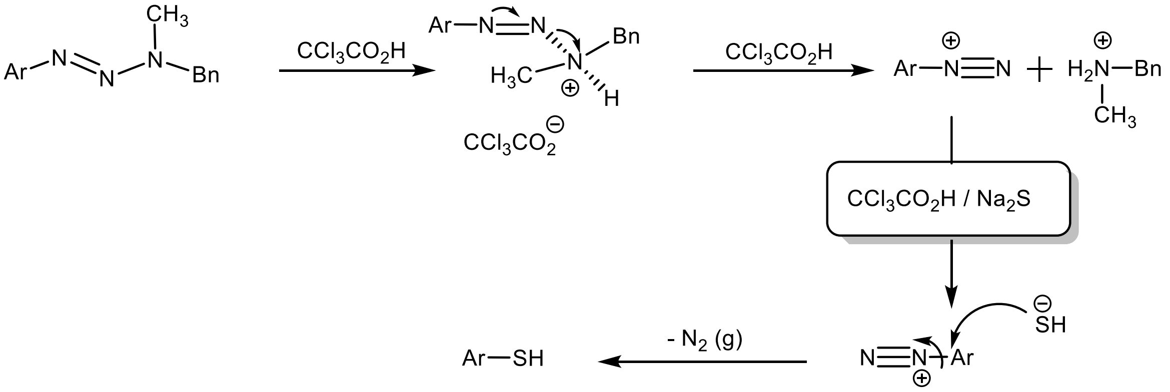
Relevant mechanisms



Iodine-catalyzed *N*-Boc protection [1]



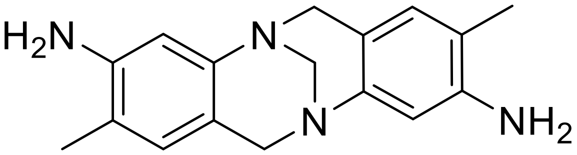
Acid-catalyzed *N*-Boc deprotection in aqueous solution [5]



Acid-catalyzed cleavage of triazene and its transformation to thiophenol [6]

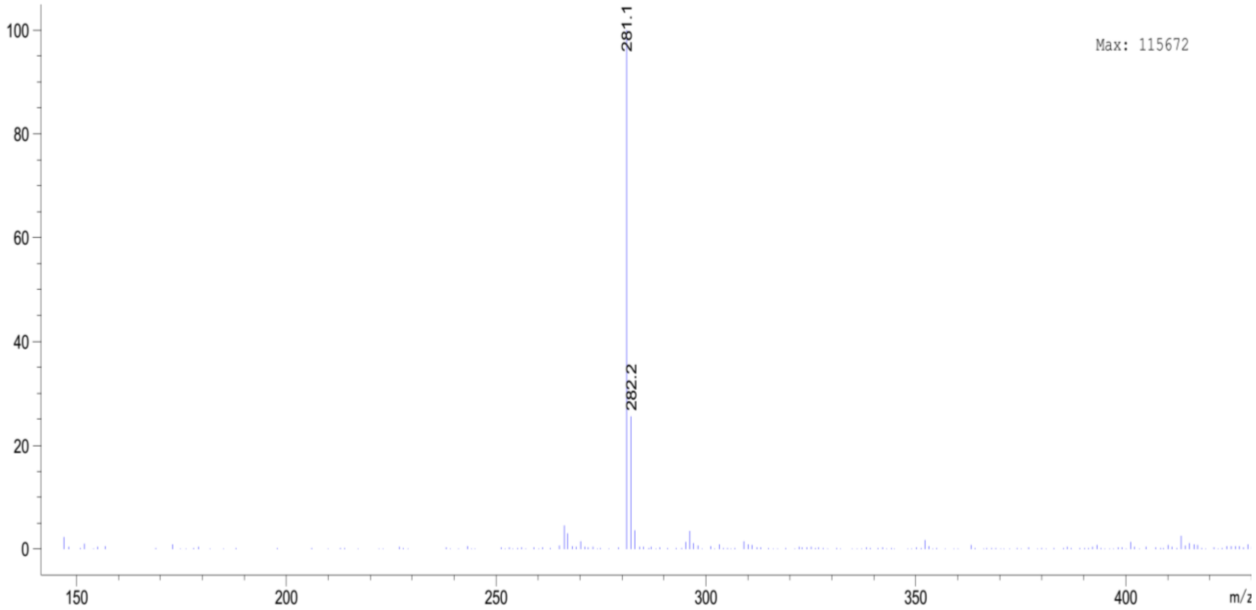
Starting materials

15. Hünlich's base preparation

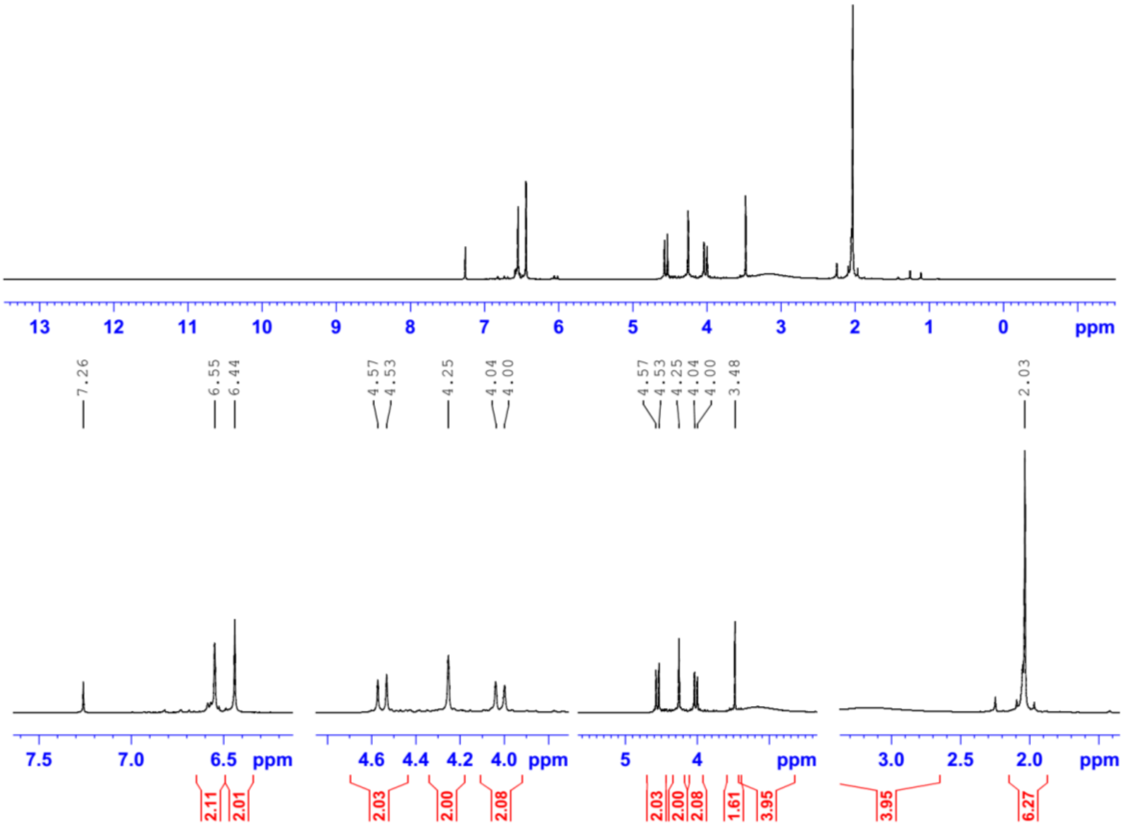


Hünlich's base was prepared according to a previous report. [7]

^{1}H NMR (400 MHz, $CDCl_3$ – CD_3OD, 2:1): δ = 6.55 (s, 2 H, CH), 6.44 (s, 2 H, CH), 4.53–4.57 (d, *J* = 16.2 Hz, 2 H, CH_2), 4.25 (s, 2 H, NCH_2N), 4.00–4.04 (d, *J* = 16.3 Hz, 2 H, CH_2), 2.35–3.45 (br, 4 H, NH_2), 2.03 (s, 6 H, CH_3). MS (ESI +; MeOH): *m/z* $[M + H]^+$ calcd for $[C_{17}H_{21}N_4]^+$: 281.17; found: 281.1 and 282.2.

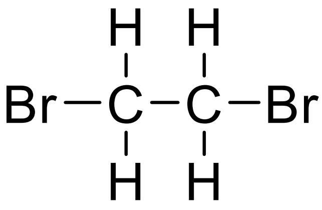


Hünlich's base, MS (ESI +)



Hünlich's base, ^{1}H NMR (400 MHz, $CDCl_3$ – CD_3OD, 2:1 v/v)

16. 1,2-dibromoethane



$$\mathrm{Br-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-Br}$$

Bromine (200.0 g, 1.25 mol) was cooled down to -5°C into a reactor equipped with a stirring magnet bar, condenser, and thermometer. A constant stream of ethylene gas was gently injected, by immersing a gas distribution tube, into the bromine. This process continued for 40-60 min until achieving a total discolouration of the bromine and seeing the crude starts freezing. The obtained yellowish liquid was then rinsed by NaOH (1M, 100 ml X 3), saturated sodium thiosulfate solution (20 ml), and then dried over $MgSO_4$ and filtered. The obtained colourless liquid was then distilled twice and passed through a column filled with anhydrous $NaHCO_3$ before bottling it in an amber glass bottle and tightly sealing its cap.

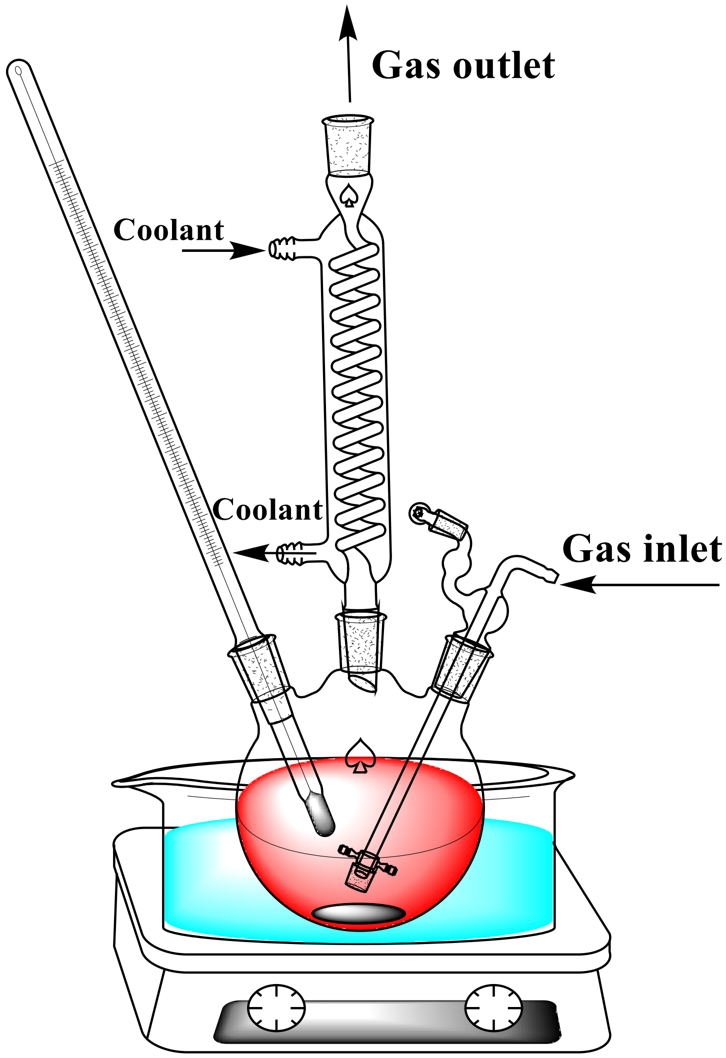
Notification: This reaction is extremely exothermic and the flow of the gas should be very slow to avoid bumping and boiling the bromine over. Using appropriate gas-mask and adequate ventilation are crucial.

Yield: 214.16 g (1.14 mol, 91%); *R_f*: N/A.

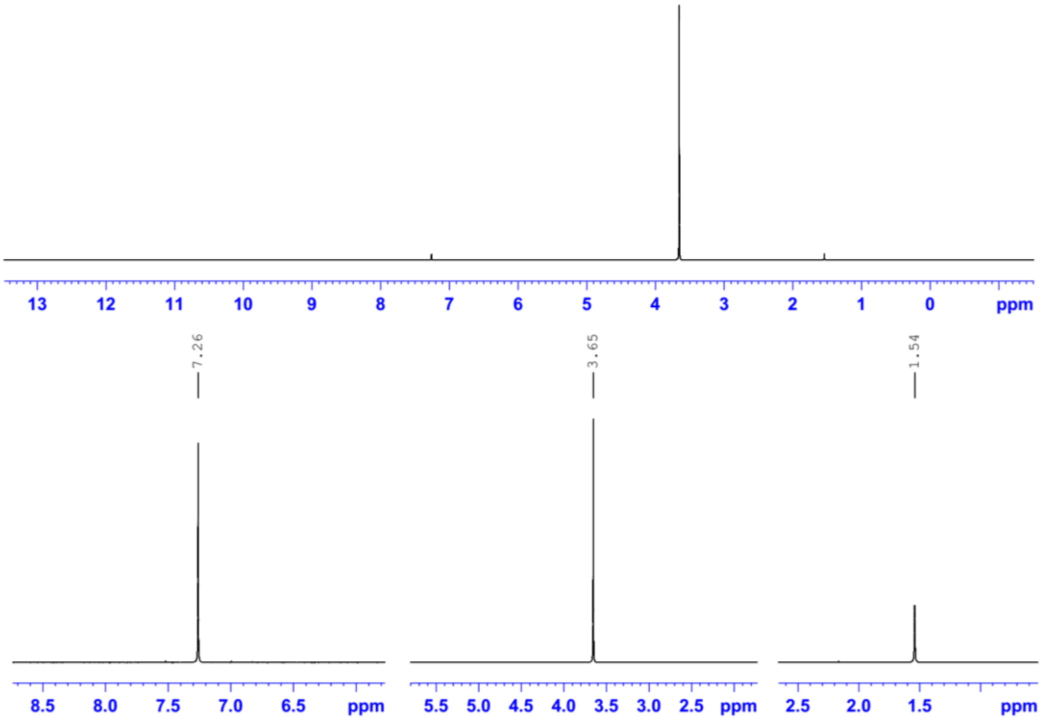
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, CH_2).

MS: m/z $[M - Br]^+$ calcd for $[C_2H_4Br]^+$: 106.96, found 106.95.

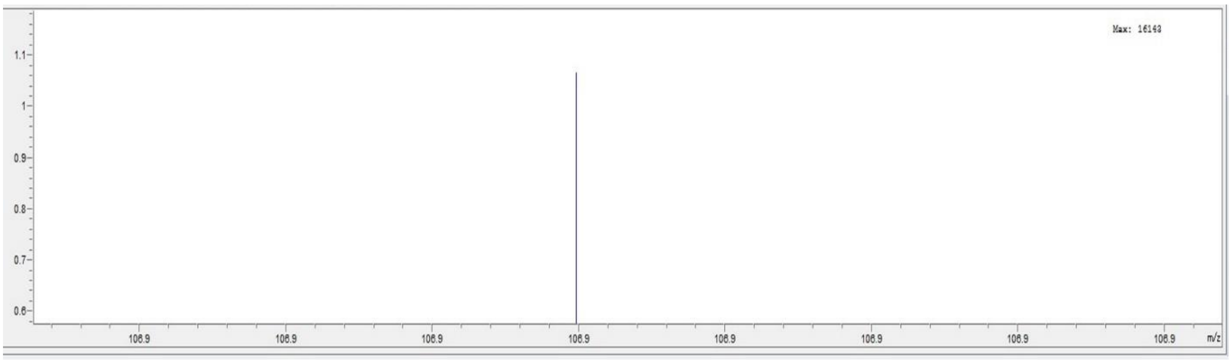
Boiling point: 131 ± 1°C, Melting point: 9.5 ± 0.2°C.



Bromination reactor



1, 2-Dibromoethane, ^{1}H NMR (400 MHz, $CDCl_3$)



1, 2-Dibromoethane, MS

References

(1) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006,** 71, 8283.
(2) Kazem-Rostami, M. *Synthesis* **2017,** 49, 1214.
(3) Mahon, A. B.; Craig, D. C.; Try, A. C. *Arkivoc* **2008,** 12, 148.
(4) Bhuiyan, M. D. H.; Mahon, A. B.; Jensen, P.; Clegg, J. K.; Try, A. C. *Eur. J. Org. Chem.* **2009,** 2009, 687.
(5) Zinelaabidine, C.; Souad, O.; Zoubir, J.; Malika, B.; Nour-Eddine, A. *Int. J. Chem.* **2012,** 4, 73.
(6) Khazaei, A.; Kazem-Rostami, M.; Moosavi-Zare, A. R.; Bayat, M.; Saednia, S. *Synlett* **2012,** 23, 1893.
(7) Rigol, S.; Beyer, L.; Hennig, L.; Sieler, J.; Giannis, A. *Org. Lett.* **2013,** 15, 1418.