Supporting Information (ms. ol0526219)

General Methods

Melting points were determinated with an Electrothermal IA 9100 and are uncorrected. NMR spectra were taken with a Varian VRX 400S (400.0 MHz for ^{1}H, 100.5 MHz for ^{13}C (referenced on solvent signals)). All measurement were carried out at 300 K. Mass sectra were obtained with a Finnigan MAT95Q and a Thermo Finnigan LTQ FT spectrometer. IR spectra were recorded with a Perkin-Elmer PE 1600 FT-IR spektrometer. UV/Vis spectra were measured with a Perkin-Elmer Lambda-16 UV spectrometer. Chemicals were purchased from commercial suppliers and were used without further purification. Silica gel 60 (0.040-0.063 mm, Merck) was used for flash chromatography.

rac-(2-Amino-6,8-dioxo-7-phenyl-1-trityl-1,4,5,5a,6,7,8,8a-octahydro-imidazo[4,5-e]isoindol-5-ylmethyl)-carbamic acid *tert*-butyl ester (5) and rearranged product 6

A solution of **3** (60 mg, 0.13 mmol) and **4** (44 mg, 0.40 mmol, 2 equiv.) in $CHCl_3$ (20 ml) was stirred at room temperature for 88 h. The reaction mixture was concentrated in vacuo and purificated twice by flash-chromatography [silica gel, $CHCl_3$/MeOH (40:1); then ethyl acetate]. Racemic product **5** was obtained as pink solid (54 mg, 0.08 mmol, 66 %).

Spectral data for **5**: **mp**: 140-143 °C (decomp.). **TLC** [silica gel, $CHCl_3$/MeOH (30:1)]: R_f = 0.11. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.44-7.40 (m, 6H, phenyl-C*H*), 7.37-7.32 (m, 10H, phenyl-C*H*), 7.30-7.27 (m, 2H, phenyl-C*H*), 7.10-7.01 (m, 2H, phenyl-C*H*), 5.34 (dd, ^{3}J = 5.6, 5.9 Hz, 1H, N*H*), 3.64 (m, 2H, NHCH_2), 3.58 (s, 2H, NH_2), 3.29 (m, 1H, 5-*H*), 3.16 (dd, ^{3}J = 9.2, 7.0 Hz, 1H, 5a-*H*), 2.63 (dd, ^{2}J = 15.9, ^{3}J = 2.7 Hz, 1H, 4-H_1), 2.43 (d, ^{3}J = 9.2 Hz, 1H, 8a-*H*), 2.10 (dd, ^{2}J = 15.9, ^{3}J = 12.2 Hz, 1H, 4-H_2), 1.45 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 176.4, 174.2 (*C*-6, *C*-8 (C=O)), 156.2 (NH*C*=O), 152.9 (*C*NH_2), 141.6 (3C, phenyl-C_{quart}), 138.6 (CH$_2$*C*NC), 131.7 (phenyl-C_{quart}), 131.3 (6C, phenyl-*C*H), 129.1 (2C, phenyl-*C*H), 128.7(phenyl-*C*H), 128.2 (3C, phenyl-*p*-C*H*), 127.9 (6C, phenyl-C*H*), 126.6 (2C, phenyl-*C*H), 115.9 (CH*C*NCN$_2$), 79.4 (*C*(CH$_3$)$_3$), 76.1 (*C*Ph$_3$), 42.5 (NH*C*H$_2$), 42.1 (*C*-5a), 39.0 (*C*-8a), 38.1 (*C*-5), 28.5 (3C, C(*C*H$_3$)$_3$), 26.8 (*C*-4). **MS** (ESI): *m/z* (%) = 654 (4) [M+H$^+$], 553 (1) [(M-Boc)$^+$], 412 (4) [(M-Tr+H)$^+$], 243 (100). **HRESIMS** ($C_{40}H_{40}N_5O_4$): calcd. 654.3075, found 654.3025. **IR** (KBr): $\tilde{\nu}$ = 3436 cm^{-1}, 2976, 2929, 1711, 1624, 1532, 1497, 1446, 1382, 1249, 1169, 904, 747, 704, 568. **UV** (MeOH): λ_{max} (lg ε) = 339 nm (2.89).

Compound **5** rearranged completely to product **6** within 11 d in $CDCl_3$ and characterized without further purification.

Spectral data for **6**: **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.44-7.39 (m, 2H, phenyl-C*H*), 7.37-7.32 (m, 6H, phenyl-C*H*), 7.30-7.21 (m, 10H, phenyl-C*H*), 7.08-7.01 (m, 2H, phenyl-C*H*), 6.35-6.15 (s, br, 1H, N*H*), 5.26 (s, br, 1H, N*H*), 3.83 (s, br, 1H, 8a-*H*), 3.68-3.51 (m, 2H, NHCH_2), 3.44 (dd, ^{3}J = 7.3, 4.0 Hz, 5a-*H*), 2.47-2.32 (m, 2H, 5-*H*, 4-H_1), 2.17 (dd, ^{2}J = 16.5, ^{3}J = 10.5 Hz, 1H, 4-H_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 176.5, 174.4 (*C*-6, *C*-8 (C=O)), 156.2 (NH*C*=O), 149.5 (N*C*NH), 144.5 (3C, phenyl-C_{quart}), 133.0 (CH$_2$*C*NC), 131.5 (phenyl-C_{quart}), 128.9 (2C, phenyl-*C*H), 127.5 (phenyl-*C*H), 128.6 (9C, phenyl-C*H*), 128.4 (6C, phenyl-C*H*), 126.3 (2C, phenyl-*C*H), 112.3 (CH*C*NCN$_2$), 79.4 (*C*(CH$_3$)$_3$), 71.1 (*C*Ph$_3$), 43.2 (NH*C*H$_2$), 42.2 (*C*-5a), 40.5 (*C*-8a), 35.0 (*C*-5), 33.7 (*C*-4), 28.4 (3C, C(*C*H$_3$)$_3$). **MS** (FAB+, NBA): *m/z* (%) = 655 (2) [M+H$^+$], 243 (100). **HRFABMS** ($C_{40}H_{40}N_5O_4$): calcd. 654.3075, found 654.3033.

[3-(2-amino-1-benzyl-1*H*-imidazol-4-yl)-allyl]- carbamic acid *tert*-butyl ester (6)

Sonogashira reaction:

Prop-2-ynylcarbamic acid *tert*-butyl ester (4.35 g, 28.0 mmmol, 2 eq.) in dry THF (20 ml) was added slowly to a mixture of 1-benzyl-4-iodoimidazole (3.98 g, 14.0 mmol), copper(I)iodide (267 mg, 1.4 mmol, 10 mol-%), bis(triphenylphosphine)palladium dichloride (246 mg, 0.4 mmol, 2.5 mol-%) and diisopropylamine (2.98 g, 29.5 mmol, 2.1 eq.) in dry THF under argon atmosphere. After 24 h the reaction mixture was filtered and the solvent was removed in vacuo. Purification by flash-chromatography [silica gel, isohexane/ethyl acetate (1:1)] afforded the Sonogashira product as yellow oil (2.11 g, 6.8 mmol, 48 %).

[3-(1-benzyl-1*H*-imidazol-4-yl)-prop-2-ynyl]-carbamic acid *tert*-butyl ester :

TLC [silica gel, isohexane/ethyl acetate (1:1)]: R_f = 0.10. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.44 (s, 1H, NC*H*N), 7.37-7.31 (m, 3H, phenyl-C*H*), 7.15-7.12 (m, 2H, phenyl-C*H*), 7.02 (s, 1H, NC*H*CN), 5.05 (s, 2H, CH_2Ph), 4.82 (m, 1H, N*H*), 4.10 (d, ^3J = 5.0 Hz, 2H, NHCH_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 155.3 (NH*C*=O), 137.3 (NCHN), 135.4 (phenyl-$C_{quart.}$), 129.1/128.5/127.4 (3C, phenyl-*C*H), 124.4 (N*C*HCN), 123.2 (NCH*C*N), 85.4 (NHCH$_2$*C*C), 79.8 (NHCH$_2$C*C*), 76.3 (*C*(CH$_3$)$_3$), 51.1 (*C*H$_2$Ph), 31.2 (NH*C*H$_2$), 28.4 (3C, C(*C*H$_3$)$_3$). **MS** (EI): *m/z* (%) = 311 (5) [M$^+$], 91 (100). **HREIMS** ($C_{18}H_{21}N_3O_2$)**:** calcd. 311.1634, found 311.1632.

Azidation:

To a solution of the Sonogashira product (1.50 g, 4.8 mmol) in dry THF (50 ml) under argon atmosphere at -78 °C was added *n*-BuLi (6.6 ml, 1.6 M in hexanes, 10.6 mmol, 2.2 eq.). After 30 min at -78 °C and 10 min at room temperature to solution was cooled again to –78 °C and tosyl azide (1.42 g, 7.2 mmol, 1.5 eq.) in dry THF (5 ml) was added. After 5 min the reaction was quenched with pH 7 buffer solution (25 ml) and brine (25 ml). After extraction with dichloromethane (3 x 50 ml) the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. Purification by flash-chromatography [silica gel, isohexane/ethyl acetate (3:1)] afforded the azide as yellow solid (740 mg, 2.1 mmol, 44 %).

[3-(2-azido-1-benzyl-1*H*-imidazol-4-yl)-prop-2-ynyl]-carbamic acid *tert*-butyl ester:

mp: 118-120 °C (decomp.). **TLC** [silica gel, isohexane/ethyl acetate (3:1)]: R_f = 0.26. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.37-7.31 (m, 3H, phenyl-C*H*), 7.16-7.13 (m, 2H, phenyl-C*H*), 6.83 (s, 1H, NC*H*CN), 4.85 (s, 2H, CH_2Ph), 4.74 (m, 1H, N*H*), 4.10 (d, ^3J = 5.0 Hz, 2H, NHCH_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 155.2 (NH*C*=O), 140.6 (NCN$_3$), 135.1 (phenyl-$C_{quart.}$), 129,0/128.4/127.4 (3C, phenyl-*C*H), 122.3 (N*C*HCN), 121.5 (NCH*C*N), 86.1 (NHCH$_2$*C*C), 79.9 (NHCH$_2$C*C*), 76.9 (*C*(CH$_3$)$_3$), 49.0 (*C*H$_2$Ph), 31.2 (NH*C*H$_2$), 28.4 (3C, C(*C*H$_3$)$_3$). **MS** (EI): *m/z* (%) = 352 (4) [M$^+$], 91 (100). **HREIMS** ($C_{18}H_{20}N_6O_2$)**:** calcd. 352.1648, found 352.1622. **IR** (KBr): $\tilde{\nu}$ = 3424 cm^{-1}, 3261, 3154, 3035, 2978, 2932, 2236, 2151, 1721, 1527, 1498, 1477, 1449, 1392, 1368, 1252, 1168, 1143, 1047, 907, 857, 756, 714, 698, 650, 606. **UV** ($CHCl_3$): λ_{max} (lg ε) = 252 nm (3.11).

Reduction:

Red-Al (1.99 g, 65 % wt in toluene, 7.2 mmol, 3.5 eq.) was added to a mixture of the azide (720 mg, 2.0 mmol) in dry THF (30 ml) at 0 °C. After 5 h the reaction was quenched with saturated Na_2CO_3 (20 ml) and brine (20 ml). The mixture was extracted with dichloromethane (3 x 30 ml) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. Purification by flash-chromatography [silica gel, $CHCl_3$/MeOH/ (25:1)] afforded **6** as yellow oil (304 mg, 0.9 mmol, 46 %) and the corresponding aminoalkyne (180 mg, 0.6 mmol, 28 %).

6: TLC [silica gel, $CHCl_3$/MeOH (20:1)]: R_f = 0.05. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.36-7.30 (m, 3H, phenyl-C*H*), 7.15-7.13 (m, 2H, phenyl-C*H*), 6.45 (s, 1H, NC*H*CN), 6.25 (d, ^3J = 15.6 Hz, 1H, CH$_2$CHC*H*), 6.11 (dt, ^3J = 15.6, 6.0 Hz, 1H, CH$_2$C*H*CH), 4.87 (s, 2H, CH_2Ph),

4.66 (t, ^3J = 5.5 Hz, 1H, N*H*), 4.28 (s, 2H, NH_2), 3.82 (dd, ^3J = 6.0, 5.5 Hz, 2H, NHCH_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 155.8 (NH*C*=O), 148.2 (NCNH_2), 135.1 (phenyl-$C_{quart.}$), 134.3 (NCH*C*N), 129,1/128.2/126.9 (3C, phenyl-*C*H), 123.4 (CH_2*C*HCH), 122.9 (N*C*HCN), 114.1 (CH_2CH*C*H), 79.2 (*C*(CH_3)$_3$), 48.7 (*C*H_2Ph), 42.6 (NH*C*H_2), 28.4 (3C, C(*C*H_3)$_3$). **MS** (EI): *m/z* (%) = 328 (39) [M^+], 91 (100). **HREIMS** ($C_{18}H_{24}N_4O_2$)**:** calcd. 328.1899, found 328.1908. **IR** (KBr): $\tilde{\nu}$ = 3431 cm^{-1}, 2977, 2930, 1698, 1660, 1563, 1538, 1507, 1454, 1392, 1366, 1249, 1169, 1083, 953, 862, 700. **UV** ($CHCl_3$): λ_{max} (lg ε) = 267 nm (3.09).

[3-(2-amino-1-benzyl-1*H*-imidazol-4-yl)-prop-2-ynyl]- carbamic acid *tert*-butyl ester:

TLC [silica gel, $CHCl_3$/MeOH (20:1)]: R_f = 0.12. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.36-7.30 (m, 3H, phenyl-C*H*), 7.14-7.12 (m, 2H, phenyl-C*H*), 6.70 (s, 1H, NC*H*CN), 4.99 (m, 1H, N*H*), 4.87 (s, 2H, CH_2Ph), 4.07 (d, ^3J = 5.2 Hz, 2H, NHCH_2), 3.87 (s, 2H, NH_2) 1.42 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 155.3 (NH*C*=O), 147.7 (NCNH_2), 135.3 (phenyl-$C_{quart.}$), 129,2/128.3/127.0 (3C, phenyl-*C*H), 120.4 (N*C*HCN), 118.6 (NCH*C*N), 85.3 (NHCH$_2$*C*C), 79.8 (NHCH$_2$C*C*), 77.2 (*C*(CH_3)$_3$), 48.9 (*C*H_2Ph), 31.3 (NH*C*H_2), 28.4 (3C, C(*C*H_3)$_3$). **MS** (EI): *m/z* (%) = 326 (26) [M^+], 91 (100). **HREIMS** ($C_{18}H_{22}N_4O_2$)**:** calcd. 326.1743, found 326.1747. **IR** (KBr): $\tilde{\nu}$ = 3434 cm^{-1}, 2978, 2932, 2234, 1693, 1634, 1570, 1541, 1512, 1498, 1455, 1392, 1367, 1250. 1167, 1047, 1029, 941, 910, 861, 732, 702, 646. **UV** ($CHCl_3$): λ_{max} (lg ε) = 248 nm (3.02).

rac-(2-Amino-6,8-dioxo-7-phenyl-1-benzyl-1,4,5,5a,6,7,8,8a-octahydro-imidazo[4,5-e]isoindol-5-yl(methyl)- carbamic acid *tert*-butyl ester (8)

7 (73 mg, 0.22 mmol) and **4** (42 mg, 0.24 mmol, 1.1 equiv.) were stirred in $CHCl_3$ (15 ml) at room temperature. After 42 h the solvent was removed in vacuo. Purification by flash-chromatography [silica gel, $CHCl_3$/MeOH/ (20:1)] afforded racemic **8** as colorless solid (101 mg, 0.20 mmol, 91 %).

mp: 240-244 °C (decomp.). **TLC** [silica gel, $CHCl_3$/MeOH (20:1)]: R_f = 0.12. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.45-7.36 (m, 3H, *N*-phenyl-C*H*), 7.36-7.28 (m, 3H, phenyl-C*H*), 7.18 (d, ^3J = 7.3 Hz, 2H, *N*-phenyl-C*H*), 7.07 (d, ^3J = 7.3 Hz, 2H, phenyl-C*H*), 5.58 (d, ^2J = 16.9 Hz, 1H, CH_2Ph), 5.22 (t, ^3J = 6.2 Hz, 1H, N*H*), 5.00 (d, ^2J = 16.9 Hz, 1H, CH_2Ph), 4.16 (s, br, 2H, NH_2), 3.98 (d, ^3J = 8.1 Hz, 1H, 8-*H*), 3.65 (dd, ^3J = 6.2, 6.6 Hz, 2H, NHCH_2), 3.53 (dd, ^3J = 3.3, 8.1 Hz, 1H, 5a-*H*), 2.65 (d, ^2J = 11.7 Hz, 1H, 4-H_1), 2.38 (m, 1H, 5-*H*), 2.33 (d, ^2J = 11.7 Hz, 1H, 4-H_2), 1.43 (s, 9H, C(CH_3)$_3$). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 176.2, 175.0 (*C*-6, *C*-8 (C=O)), 156.2 (NH*C*=O), 149.3 (*C*NH_2), 136.1 (phenyl-$C_{quart.}$), 133.7 (CH_2*C*NC), 131.5 (*N*-phenyl-$C_{quart.}$), 129,14/129.10 (2C, phenyl-CH), 128.7 (*N*-phenyl-*C*H), 128.0 (phenyl-*C*H), 126.43/126.42 (2C, phenyl-*C*H), 114.9 (CH*C*NCN$_2$), 79.5 (*C*(CH_3)$_3$), 46.8 (*C*H_2Ph), 43.1 (NH*C*H_2), 42.3 (*C*-5a), 40.1 (*C*-8), 36.1 (*C*-5), 28.5 (3C, C(*C*H_3)$_3$), 25.1 (*C*-4). **MS** (EI): *m/z* (%) = 501 (16) [M^+], 371 (100). **HREIMS** ($C_{28}H_{31}N_5O_4$)**:** calcd. 501.2376, found 501.2356. **IR** (KBr): $\tilde{\nu}$ = 3431 cm^{-1}, 2977, 2929, 1773, 1713, 1628, 1538, 1498, 1455, 1385, 1251, 1172, 701, 627.

[3-(2-amino-1*H*-imidazol-4-yl)-allyl]- carbamic acid *tert*-butyl ester (9)

A mixture of **3** (163 mg, 0.34 mmol), MeOH (20 ml) and acetic acid (99 %, 2 ml) was stirred at 65 °C under reflux for 12 h. The solvent was removed in vacuo and purification by flash-chromatography [silica gel, $CHCl_3$/MeOH/NH_3 (70:10:1)] afforded **9** as pale yellow solid (77 mg, 0.32 mmol, 95 %).

mp: 160-162 °C (decomp.). **TLC** [silica gel, $CHCl_3$/MeOH/NH_3 (70:10:1)]: R_f = 0.16. **^{1}H NMR** (400.0 MHz, CD_3OD): δ = 6.51 (s, 1H, NC*H*C), 6.22 (dt, ^3J = 15.9 Hz, ^4J = 1.5 Hz, 1H,

CH_2CHCH), 5.87 (dt, ^3J = 15.9, 5.9 Hz, 1H, CH_2CHCH), 3.74 (d, ^3J = 5.9 Hz, 2H, $NHCH_2$), 1.44 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100.5 MHz, CD_3OD): δ = 156.9 (NHC=O), 149.8 (CNH_2), 128.7 ($NCCHN$), 122.8 (CH_2CHCH), 119.3 (CH_2CHCH), 114.4 ($NCCHN$)), 78.8 ($C(CH_3)_3$), 41.8 ($NHCH_2$), 27.4 (3C, $C(CH_3)_3$). **MS** (FAB+, NBA): *m/z* (%) = 239 (808) [$M+H^+$], 122.2 (68), 57 (100). **IR** (KBr): $\tilde{\nu}$ = 3356 cm^{-1}, 2979, 2929, 1689, 1579, 1518, 1456, 1393, 1367, 1276, 1251, 1169, 1050, 1025, 961, 862, 779, 654. **UV** (MeOH)**:** λ_{max} (lg ε) = 261 nm (2.81).

rac-(2-Amino-6,8-dioxo-7-phenyl-1,4,5,5a,6,7,8,8a-octahydro-imidazo[4,5-e]isoindol-5-yl(methyl)- carbamic acid *tert*-butyl ester (10)

9 (70 mg, 0.30 mmol) and **4** (58 mg, 0.33 mmol, 1.1 equiv.) in $CHCl_3$ (25 ml) were stirred at room temperature for 48 h. The solvent was removed in vacuo and purification by flash chromatography [silica gel, $CHCl_3$/MeOH (15:1)] afforded the racemic product **10** (75 mg, 0.09 mmol, 58 %) as pale yellow solid.

mp: 185 °C (decomp.). **TLC** [silica gel, $CHCl_3$/MeOH/NH_3 aq. (70:10:1)]: R_f = 0.22. **TLC** [silica gel, $CHCl_3$/MeOH (10:1)]: R_f = 0.17. **^{1}H NMR** (400.0 MHz, CD_3OD): δ = 7.45-7.34 (m, 3H, phenyl-C*H*), 7.15 (d, ^3J = 7.3 Hz, 2H, phenyl-C*H*), 3.69-3.60 (m, 3H, 5a-*H*, CH_2NH), 2.59 (dd, ^3J = 14.0, 3.3 Hz, 1H, 4-H_1), 2.29 (dd, ^3J = 14.0, 12.0 Hz, 1H, 4-H_2), 2.24 (m, 1H, 5-*H*), 1.44 (s, 9H, $C(CH_3)_3$). **^{1}H NMR** (400.0 MHz, DMSO-d_6): δ = 7.43 (dd, ^3J = 7.7, 7.0 Hz, 2H, phenyl- C*H*), 7.37 (d, ^3J = 7.0 Hz, 1H, phenyl-C*H*), 7.13 (d, ^3J = 7.3 Hz, 2H, phenyl-C*H*), 7.02 (t, ^3J = 5.5 Hz, 1H, CH_2NH), 5.93 (s, br, 2H, NH_2), 4.00 (d, ^3J = 7.3 Hz, 1H, 8a-*H*), 3.67 (dd, ^3J = 7.7, 3.0 Hz, 1H, 5a-*H*), 3.53 (m, 1H, CH_2NH), 3.38 (m, 1H, CH_2NH), 2.50 (m, 1H, 4-H_1), 2.17-2.07 (m, 2H, 4-H_2, 5-*H*), 1.37 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100.5 MHz, CD_3OD): δ = 177.4, 175.4 (*C*-6, *C*-8 (C=O)), 156.3 (NHC=O), 150.4 (CNH_2), 132.2 (phenyl-C_{quart}), 128.6 (2C, phenyl-*C*H), 128.0 (phenyl-*C*H), 126.5 (2C, phenyl-*C*H), 124.2 (CH_2CNC), 119.9 ($CHCNCN_2$), 78.8 ($C(CH_3)_3$), 42.8 ($NHCH_2$), 42.6 (*C*-5a), 35.9 (*C*-5), 27.4 ($C(CH_3)_3$), 22.8 (*C*-4). **^{13}C NMR** (100.5 MHz, DMSO-d_6): δ = 177.0, 175.2 (*C*-6, *C*-8 (C=O)), 156.2 (NHC=O), 149.6 (CNH_2), 132.6 (phenyl-C_{quart}), 129.3 (2C, phenyl-*C*H), 128.6 (phenyl-*C*H), 127.3 (2C, phenyl-*C*H), 124.2 (CH_2CNC), 118.7 ($CHCNCN_2$), 78.1 ($C(CH_3)_3$), 43.1 ($NHCH_2$), 43.0 (*C*-5a), 41.4 (*C*-8a), 35.8 (*C*-5), 28.8 (3C, $C(CH_3)_3$), 22.8 (*C*-4). **MS** (FAB+, NBA): *m/z* (%) = 412 (58) [$M+H^+$], 356 (98), 57 (100). **HRFABMS** ($C_{21}H_{26}N_5O_4$)**:** calcd. 412.1985, found 412.1989. **IR** (KBr): $\tilde{\nu}$ = 3402 cm^{-1}, 2978, 2931, 1711, 1624, 1599, 1500, 1444, 1368, 1252, 1170, 757, 692, 624. **UV** (MeOH)**:** λ_{max} (lg ε) = 331 nm (2.34), 234 (3.02), 203 (3.30).

1,3-Bis-[3-(2-amino-1-trityl-1*H*-imidazol-4-yl)-prop-2-ynyl]-urea (12)

To a solution of amine **11** (500 mg, 1.32 mmol, 6 equiv.) and triethylamine (0.18 ml, 1.32 mmol, 6 equiv.) in THF (50 ml) were added triphosgene (65 mg, 0.22 mmol) at 0 °C. After stirring at room temperature for 20 h the solvent was removed in vacuo and purification by flash chromatography [silica gel, $CHCl_3$/MeOH (15:1)] afforded urea **12** (467 mg, 0.59 mmol, 90 %) as pale yellow solid.

mp: 170 °C (decomp.). **TLC** [silica gel, $CHCl_3$/MeOH/NH_3 (40:10:1)]: R_f = 0.68. **^{1}H NMR** (400.0 MHz, $CDCl_3$): δ = 7.35-7.31 (m, 18H, phenyl-C*H*), 7.22-7.18 (m, 12H, phenyl-C*H*), 6.29 (s, 2H, NCC*H*N), 6.20 (d, ^3J = 15.6 Hz, 2H, CH_2CHCH), 6.10 (dt, ^3J = 15.6, 5.9 Hz, 2H, CH_2CHCH), 4.66 (t, ^3J = 5.5 Hz, 2H, C=ON*H*), 3.85 (dd, ^3J = 5.9, 5.5 Hz, 4H, NHCH_2), 3.56 (s, br, 4H, NH_2). **^{13}C NMR** (100.5 MHz, $CDCl_3$): δ = 158.0 (NH*C*=O), 149.5 (2C, *C*NH_2), 141.4 (phenyl-$C_{quart.}$), 133.1 (2C, N*C*CHN), 130.0 (12C, phenyl-*C*H), 128.2 (12C, phenyl-*C*H), 128.1 (6C, phenyl-*C*H), 123.4 (2C, CH_2CHCH), 123.1 (2C, CH_2CHCH), 115.8 (2C, NC*C*HN), 74.2 (2C, *C*Ph_3), 42.7 (2C, NCH_2). **MS** (ESI): *m/z* (%) = 787 (62) [M+H^+], 545 (88) [M-CPh_3+H^+], 243 (100). **HRFABMS** ($C_{21}H_{26}N_5O_4$)**:** calcd. 412.1985, found 412.1989.

IR (KBr): $\tilde{\nu}$ = 3435 cm^{-1}, 3059, 3032, 1968, 1617, 1533, 1492, 1446, 1325, 1241, 1187, 1157, 1110, 1086, 1034, 1002, 964, 906, 887, 747, 701, 673, 656, 638, 553. **UV** ($CHCl_3$)**:** λ_{max} (lg ε) = 270 nm (4.48).

***rac*-4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid (2-amino-6,8-dioxo-7-phenyl-3,4,5,5a,6,7,8,8a-octahydro-imidazo[4,5-e]isoindol-5-ylmethyl)-amide (13)**

Method 1: A solution of oroidin (**1**) (free base, 100 mg, 0.26 mmol) and *N*-phenylmaleimide (**4**) (89 mg, 0.51 mmol, 2 equiv.) in MeOH (10 ml) was stirred at 70 °C for 48 h. The solvent was removed in vacuo and the purification by flash chromatography [silica gel, $CHCl_3$/MeOH/NH_3 aq. (70:10:1)] afforded the racemic Diels-Alder product **13** (46 mg, 32 %) as pale red solid. **Method 2**: A solution of **1** (formate, 43 mg, 0.1 mmol), **4** (35 mg, 0.2 mmol, 2 equiv.) and $Y(OTf)_3$ (10 mg, 0.02 mmol, 20 mol %) in MeOH (4 ml) was stirred at 40 °C for 12 h. The solvent was removed in vacuo and the purification by flash chromatography [silica gel, $CHCl_3$/MeOH/NH_3 aq. (80:10:1)] afforded **13** (25 mg, 45 %) as pale red solid.

TLC [silica gel, $CHCl_3$/MeOH/NH_3 aq. (70:10:1)]**:** R_f = 0.19. **^{1}H NMR** (CD_3OD, 200.0 MHz)**:** δ = 7.41 (m, 2H, phenyl-C*H*), 7.35 (m, 1H, phenyl-C*H*), 7.14 (m, 2H, phenyl-C*H*), 6.80 (s, 1H, BrCC*H*), 4.02 (d, ^3J = 7.3 Hz, 1H, 8a-*H*), 3.92 (d, ^3J = 6.6 Hz, 2H, NHCH_2), 3.70 (dd, ^3J = 7.3 Hz, ^3J = 3.2 Hz, 1H, 5a-*H*), 2.61 (d, ^2J = 10.8 Hz, 1H, 4-H_1), 2.40 (m, 1H, 5-*H*), 2.38 (d, ^2J = 10.8 Hz, 1H, 4-H_2). **^{1}H NMR** (DMSO-d_6, 400.0 MHz): δ = 11.71 (s, br, BrCN*H*), 8.23 (dd, ^3J = 5.9, 5.5 Hz, 1H, N*H*CH_2) 7.45 (m, 2H, phenyl-C*H*), 7.38 (m, 1H, phenyl-C*H*), 7.13 (m, 2H, phenyl-C*H*), 6.96 (s, 1H, BrCC*H*), 5.18 (s, br, 2H, NH_2), 3.97 (d, ^3J = 7.4 Hz, 1H, 8a-*H*), 3.91-3.83 (m, 1H, NHC*H*H), 3.73 (dd, ^3J = 7.4, 3.1 Hz, 1H, 5a-*H*), 3.71-3.65 (m, 1H, NHCH*H*), 2.51 (m, 1H, 4-H_1), 2.28-2.17 (m, 2H, 5-*H*, 4-H_2). **^{13}C NMR** (CD_3OD, 100.5 MHz): δ = 177.1, 175.3 (*C*-6, *C*-8 (C=O)), 160.6 (NH*C*=O), 150.4 (N*C*NH_2NH), 132.1 (phenyl-C_{quart}), 128.6 (2C, phenyl-*C*H), 128.1 (phenyl-*C*H), 127.5 (CH*C*C=O), 126.5 (2C, phenyl-*C*H), 126.3 (CH_2CHNH), 118.4 (CH*C*NCNH_2), 113.1 (*C*HCC=O), 104.8 (Br*C*NH), 98.6 (Br*C*CH), 42.7 (*C*-5a), 41.8 (NHCH_2), 35.5 (*C*-5), 22.9 (*C*-4). **^{13}C NMR** (DMSO-d_6, 100.6 MHz):δ = 176.7, 174.9 (*C*-6, *C*-8 (C=O)), 159.1 (NH*C*=O), 149.7 (N*C*NH_2NH), 132.1 (phenyl-C_{quart}), 128.7 (2C, phenyl-*C*H), 128.2 (phenyl-*C*H), 128.0 (CH*C*C=O), 126.6 (2C, phenyl-*C*H), 112.5 (*C*HCC=O), 104.5 (Br*C*NH), 97.5 (Br*C*CH), 42.5 (*C*-5a), 41.7 (NHCH_2), 41.4 (*C*-8a), 35.0 (*C*-5), 23.0 (*C*-4). **MS** (ESI)**:** *m/z* (%) = 561/563/565 (3/7/3) [M+H^+]. **HRESIMS** ($C_{21}H_{19}{}^{79}Br^{81}BrN_6O_3$)**:** calcd. 562.9866, found 562.9864. **IR** (KBr): $\tilde{\nu}$ = 3418 cm^{-1}, 2929, 1775, 1709, 1631, 1563, 1522, 1499, 1420, 1386, 1322, 1194, 1127, 978, 819, 755, 691, 627. **UV** (MeOH): λ_{max} (lg ε) = 274 nm (3.17).

rac-4,5-Dibromo-1_H_-pyrrole-2-carboxylic acid(2-amino-6,8-dioxo-3,4,5,5a,6,7,8,8a-octahydro-imidazo[4,5-e]isoindol-5-ylmethyl)-amide (15)

A solution of **1** (formate, 43 mg, 0.1 mmol), maleimide (**14**) (20 mg, 0.2 mmol, 2 equiv.) and $Y(OTf)_3$ (10 mg, 0.02 mmol, 20 mol %) in MeOH (4 ml) was stirred at 40 °C for 12 h. The solvent was removed in vacuo and the purification by flash chromatography [silica gel, $CHCl_3$/MeOH/NH_3 aq. (40:10:1)] afforded the racemic Diels-Alder product **15** (26 mg, 54 %) as pale red solid.

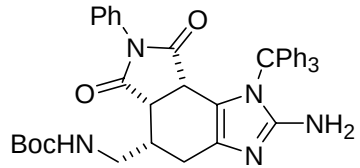
TLC [silica gel, $CHCl_3$/MeOH/NH_3 aq. (40:10:1)]: R_f = 0.17. ^{1}H NMR (DMSO-d_6, 400.0 MHz): δ = 8.22 (dd, ^3J = 5.9, 5.5 Hz, 1H, N*H*CH$_2$), 6.93 (s, 1H, BrCC*H*), 5.58 (s, br, 2H, NH$_2$), 3.86-3.79 (m, 1H, NHC*H*H), 3.73 (d, 7.2 Hz, 8a-*H*), 3.60-3.54 (m, 1H, NHCH*H*), 3.50 (dd, ^3J = 7.2, 2.9 Hz, 1H, 5a-*H*), 2.44 (d, ^3J = 10.9 Hz, 1H, 4-H_1), 2.14-2.05 (m, 2H, 5-*H*, 4-H_2). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ = 180.0, 177.9 (*C*-6, *C*-8 (C=O)), 159.9 (NH*C*=O), 150.0 (N*C*NH$_2$NH), 129.1 (CH*C*C=O), 124.9 (CH$_2$*C*HNH), 119.4 (CH*C*NCNH$_2$), 113.5 (*C*HCC=O), 105.3 (Br*C*NH), 98.6 (Br*C*CH), 44.1 (*C*-5a), 43.0 (C-8a), 42.1 (NH*C*H$_2$), 35.7 (*C*-5), 23.7 (*C*-4). **MS** (ESI): *m/z* (%) = 485/487/489 (52/100/47) [M+H$^+$]. **HRESIMS** ($C_{15}H_{13}{}^{79}Br^{81}BrO_3N_6$): calcd. 486.9552, found 486.9548. **IR** (KBr): $\tilde{\nu}$ = 3406 cm^{-1}, 1774, 1714, 1684, 1629, 1565, 1524, 1419, 1374, 1330, 1243, 1193, 1124, 1030, 977, 822, 757, 640, 616. **UV** (MeOH): λ_{max} (lg ε) = 275 nm (3.14), 218 (3.08).

rac-4-(2-Amino-3_H_-imidazol-4-ylmethyl)-6,7-dibromo-3,4-dihydro-2_H_-pyrrolo[1,2-_a_]pyrazin-1-one (_rac_-cyclooroidin) (17)

A solution of **1** (formate, 70 mg, 0.16 mmol) in water (40 ml) and ethanol (8 ml) was heated at 95 °C in a sealed tube for 45 h. The solution was filtrated, washed with diethylether (20 ml) and concentrated in vacuo. *rac*-Cyclooroidin (**17**, formate, 65 mg, 15 mmol, 93 %) was obtained as a pale yellow solid without further purification.

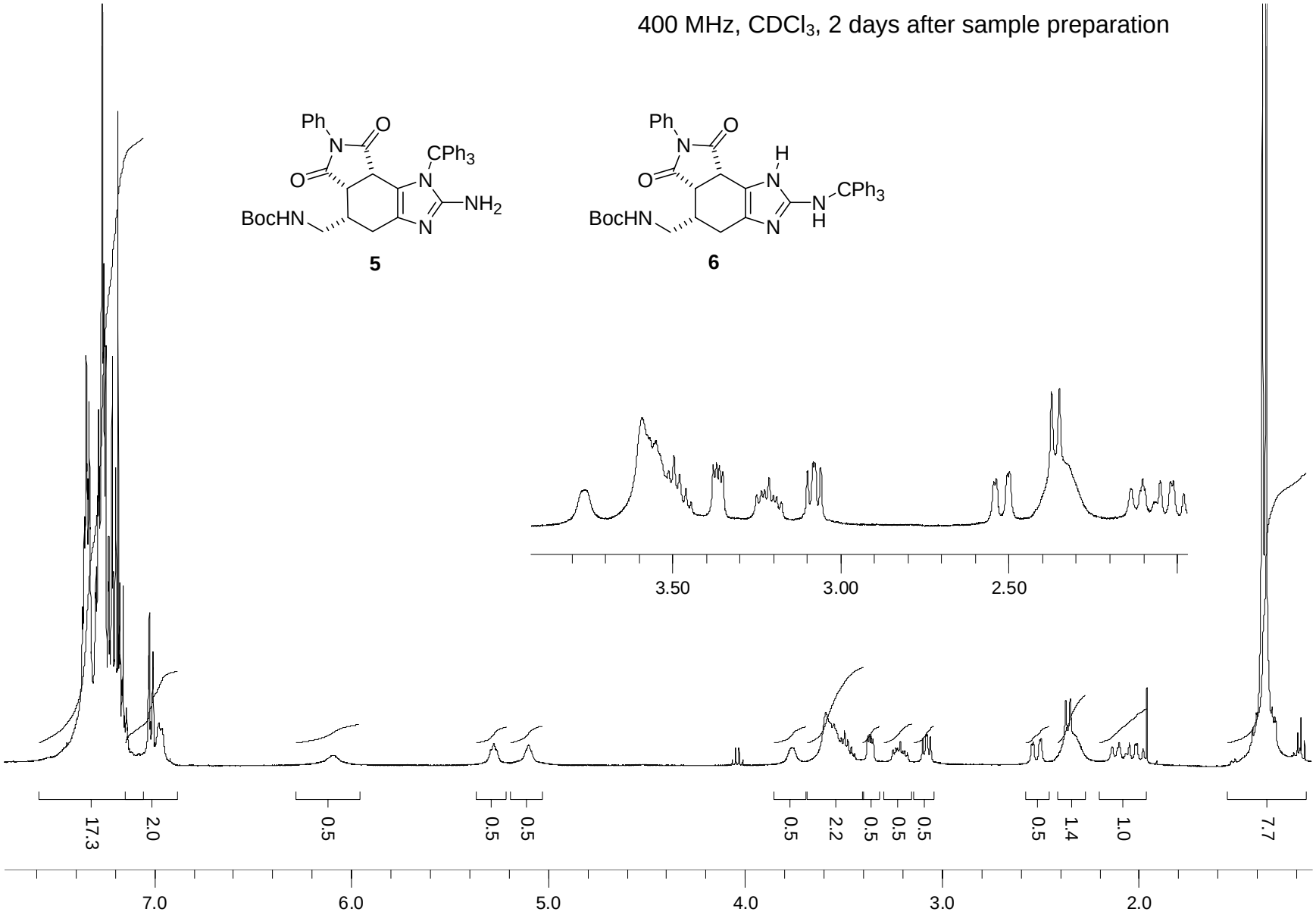
^{1}H NMR (400.0 MHz, CD_3OD): δ = 8.52 (s, 1H, *H*CO$_2$), 6.94 (s, 1H, BrCC*H*), 6.35 (s, 1H, NCC*H*N), 4.68 (m, 1H, 9-*H*), 3.87 (dd, ^2J = 13.6 Hz, ^3J = 4.2 Hz, 1H, 8a-*H*), 3.58 (dd, ^2J = 13.6 Hz, ^3J = 1.2 Hz, 1H, 8b-*H*), 2.96 (d, ^3J = 7.0 Hz, 2H, CHCH_2C). **^{13}C NMR** (100.5 MHz, CD_3OD): δ = 169.8 (H*C*O$_2$), 160.6 (*C*-6), 149.1 (*C*-14), 125.8 (*C*-11), 123.3 (*C*-5), 116.7 (*C*-4), 112.2 (*C*-12), 108.7 (*C*-2), 101.2 (*C*-3), 54.3 (*C*-9), 44.1 (*C*-8), 28.8 (*C*-10). **MS** (FAB+, NBA): *m/z* (%) = 388/390/392 (18/34/16) [M+H$^+$]. **HRFABMS** ($C_{11}H_{12}{}^{79}Br_2N_5O$)**:** calcd. 387.9409, found 387.9395. **IR** (KBr): $\tilde{\nu}$ = 3414 cm^{-1}, 2926, 1646, 1551, 1466, 1429, 1377, 1338, 1120, 1055, 965, 751, 588. **UV** (MeOH)**:** λ_{max} (lg ε) = 224 nm (3.02), 283 (2.87), 396 (1.92).

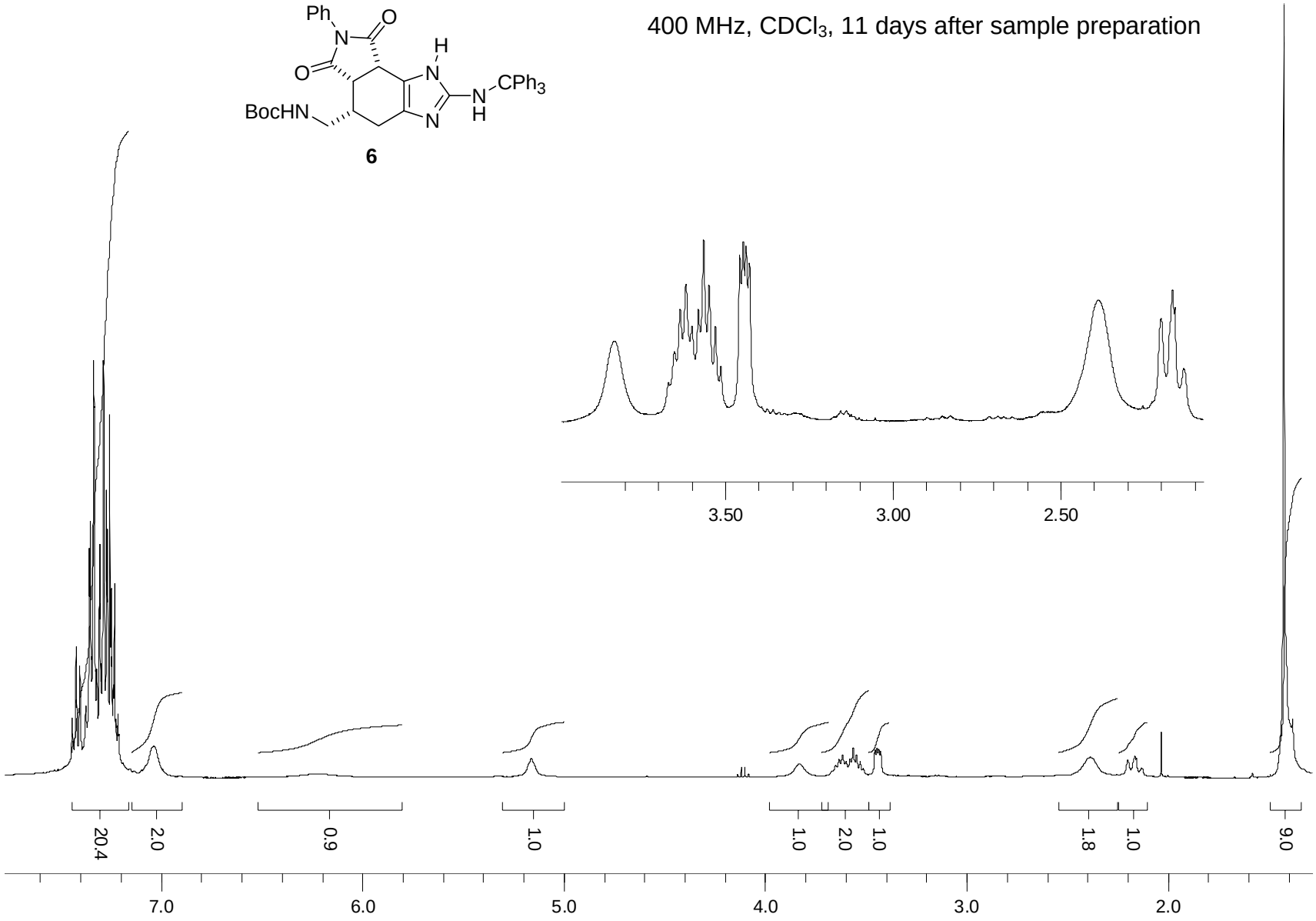
Selected NMR spectra: see following pages.

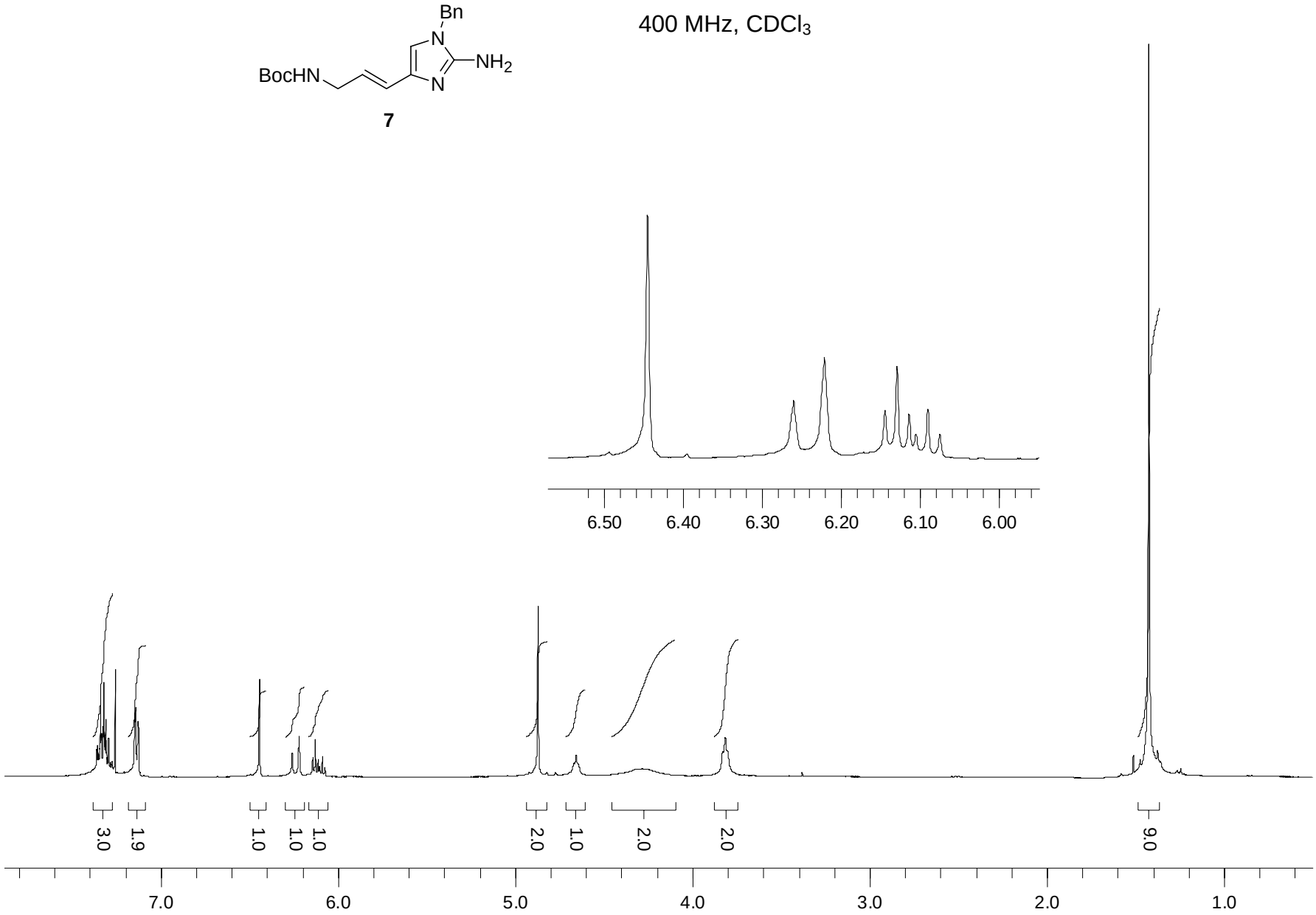


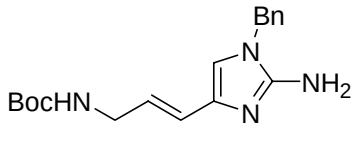
5

200 MHz, $CDCl_3$, 5 min after sample preparation


400 MHz, CDCl3, 2 days after sample preparation
Ph
N
O
O
CPh3
N
NH2
BocHN
N
5
Ph
N
O
O
H
N
N
CPh3
BocHN
N
H
6
3.50
3.00
2.50
17.3
2.0
0.5
0.5
0.5
0.5
2.2
0.5
0.5
0.5
0.5
1.4
1.0
7.7
7.0
6.0
5.0
4.0
3.0
2.0

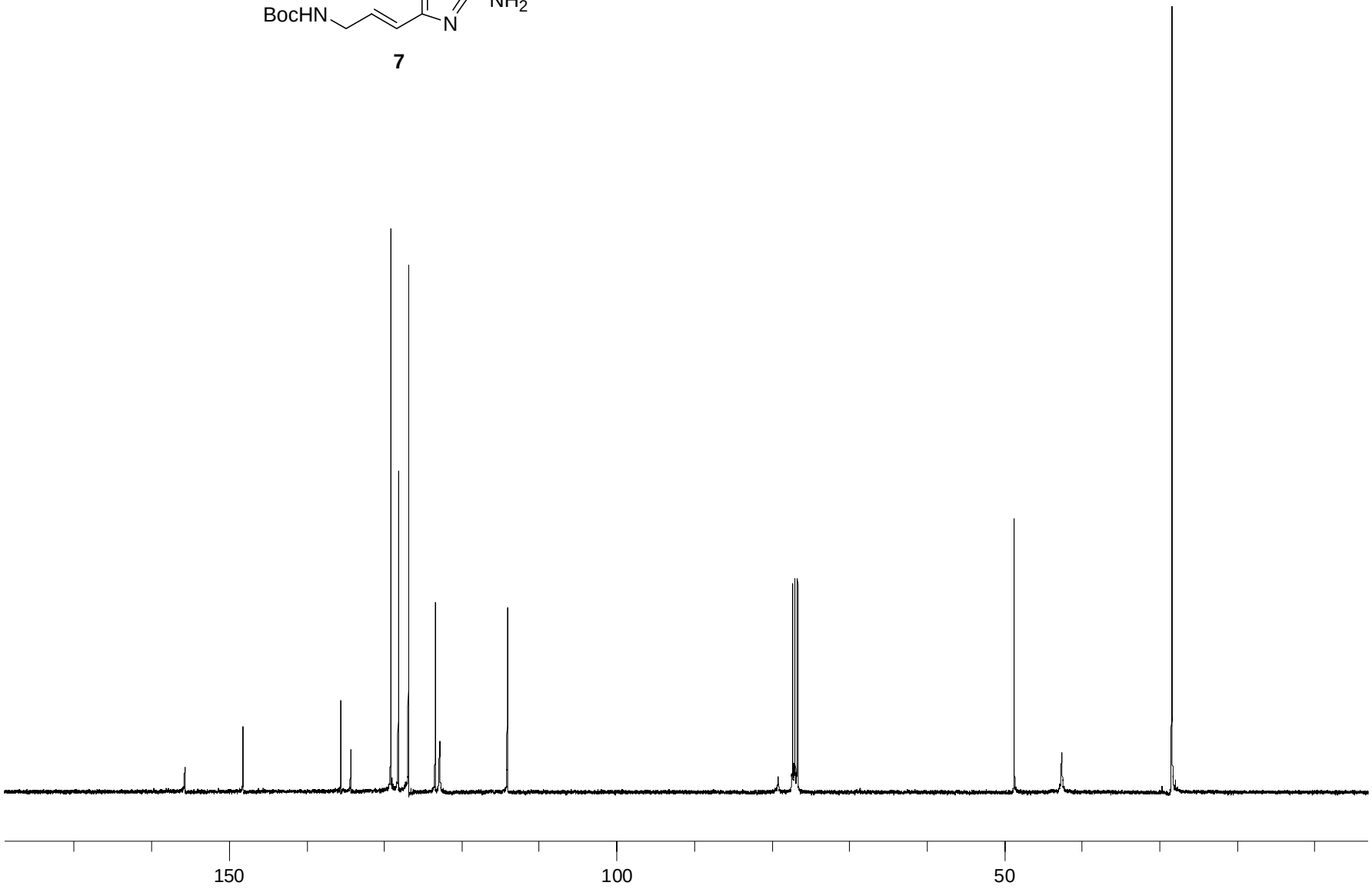

Ph
O
N
O
H
N
N
CPh3
N
H
BocHN
N
6
400 MHz, CDCl3, 11 days after sample preparation
3.50
3.00
2.50
20.4
2.0
0.9
1.0
1.0
2.0
1.0
1.8
1.0
9.0
7.0
6.0
5.0
4.0
3.0
2.0

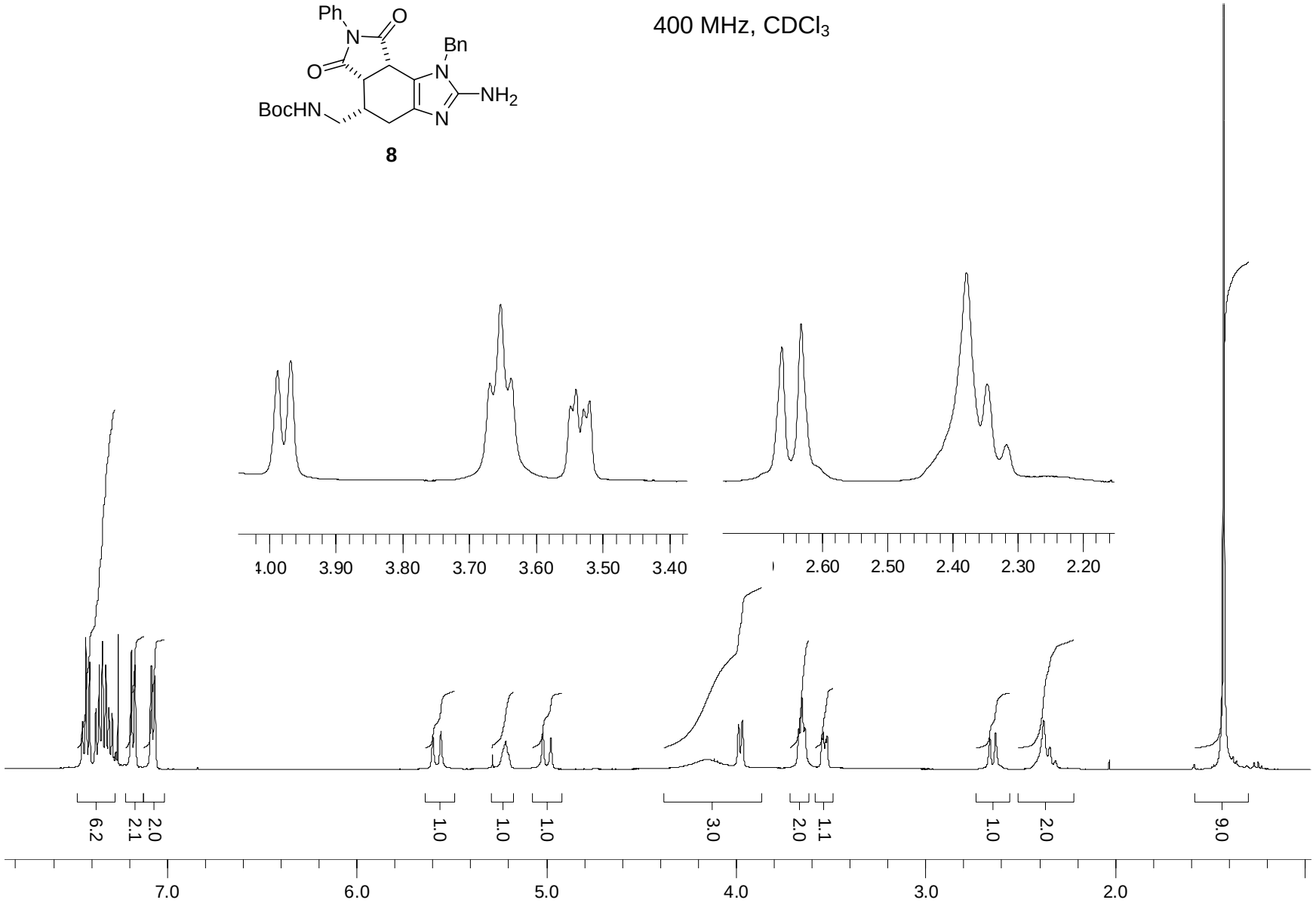

Bn
N
NH2
BocHN
N
7
400 MHz, CDCl3
6.50
6.40
6.30
6.20
6.10
6.00
3.0
1.9
1.0
1.0
1.0
2.0
1.0
2.0
2.0
9.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

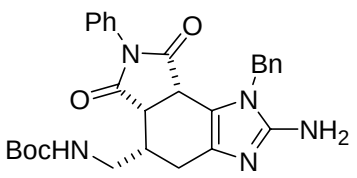


7

100.6 MHz, $CDCl_3$

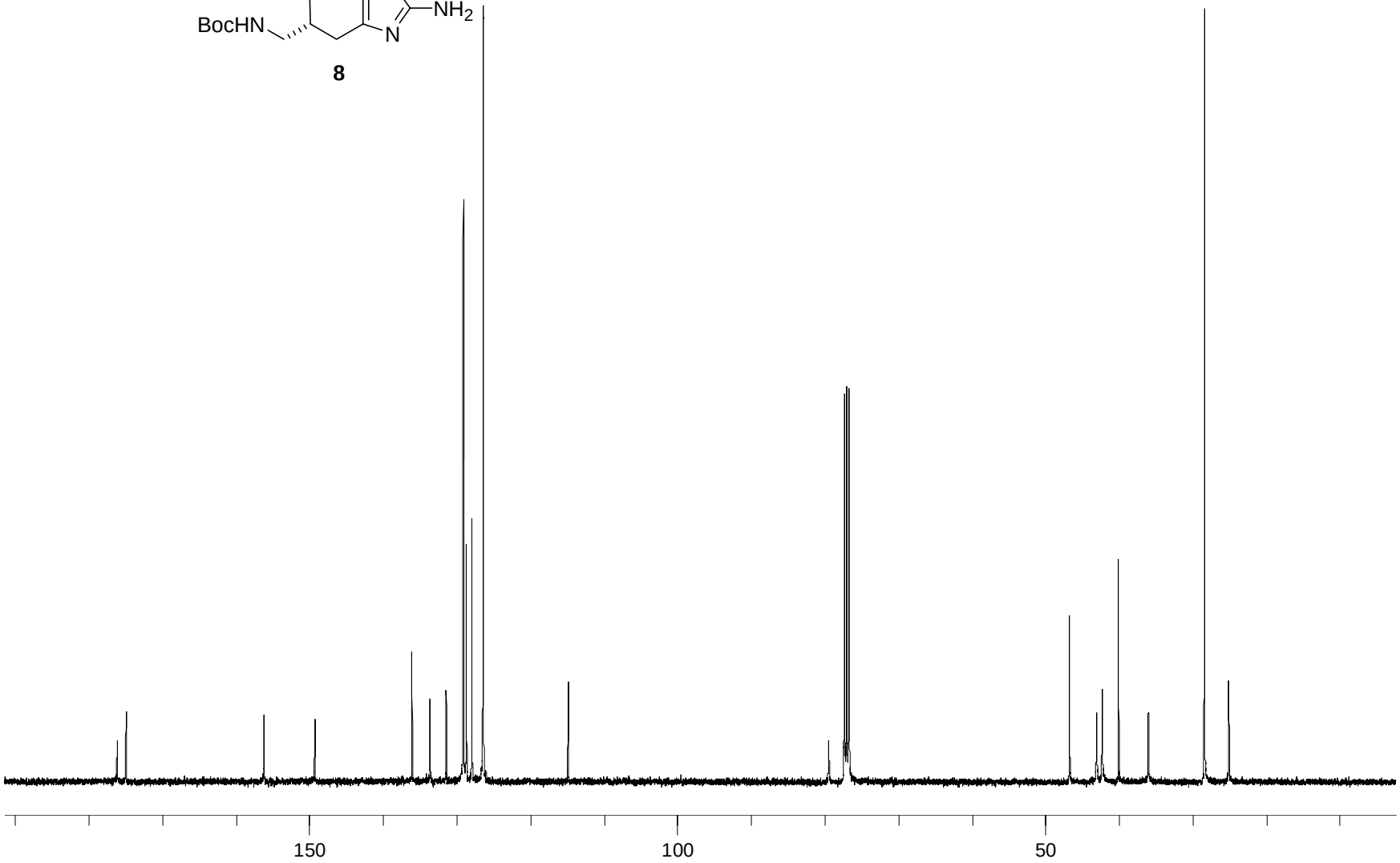


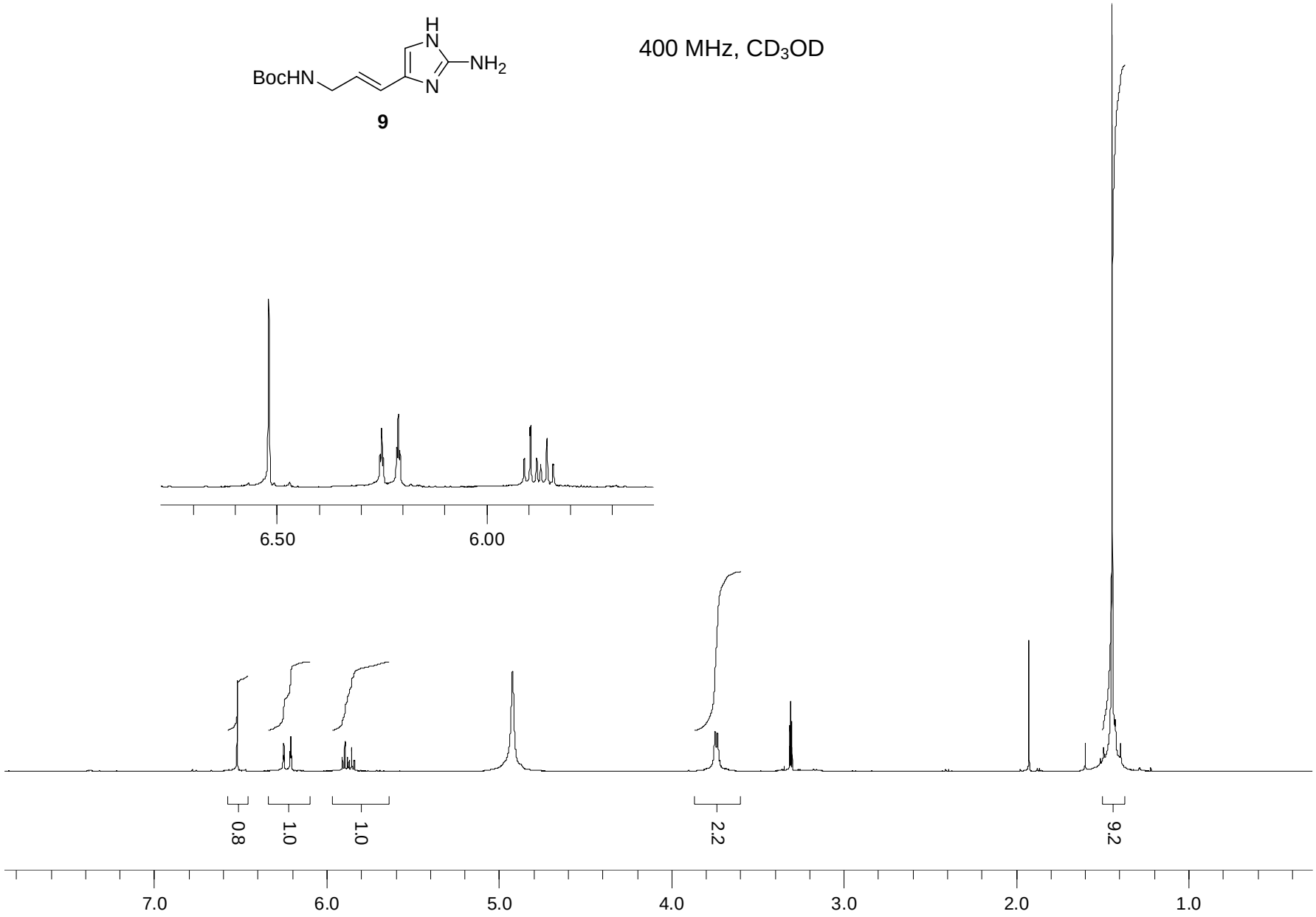

Ph
O
N
Bn
O
N
NH2
BocHN
N
8
400 MHz, CDCl3
4.00
3.90
3.80
3.70
3.60
3.50
3.40
2.60
2.50
2.40
2.30
2.20
6.2
2.1
2.0
1.0
1.0
1.0
3.0
2.0
1.1
1.0
2.0
9.0
7.0
6.0
5.0
4.0
3.0
2.0

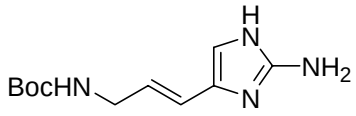


8

100.6 MHz, $CDCl_3$

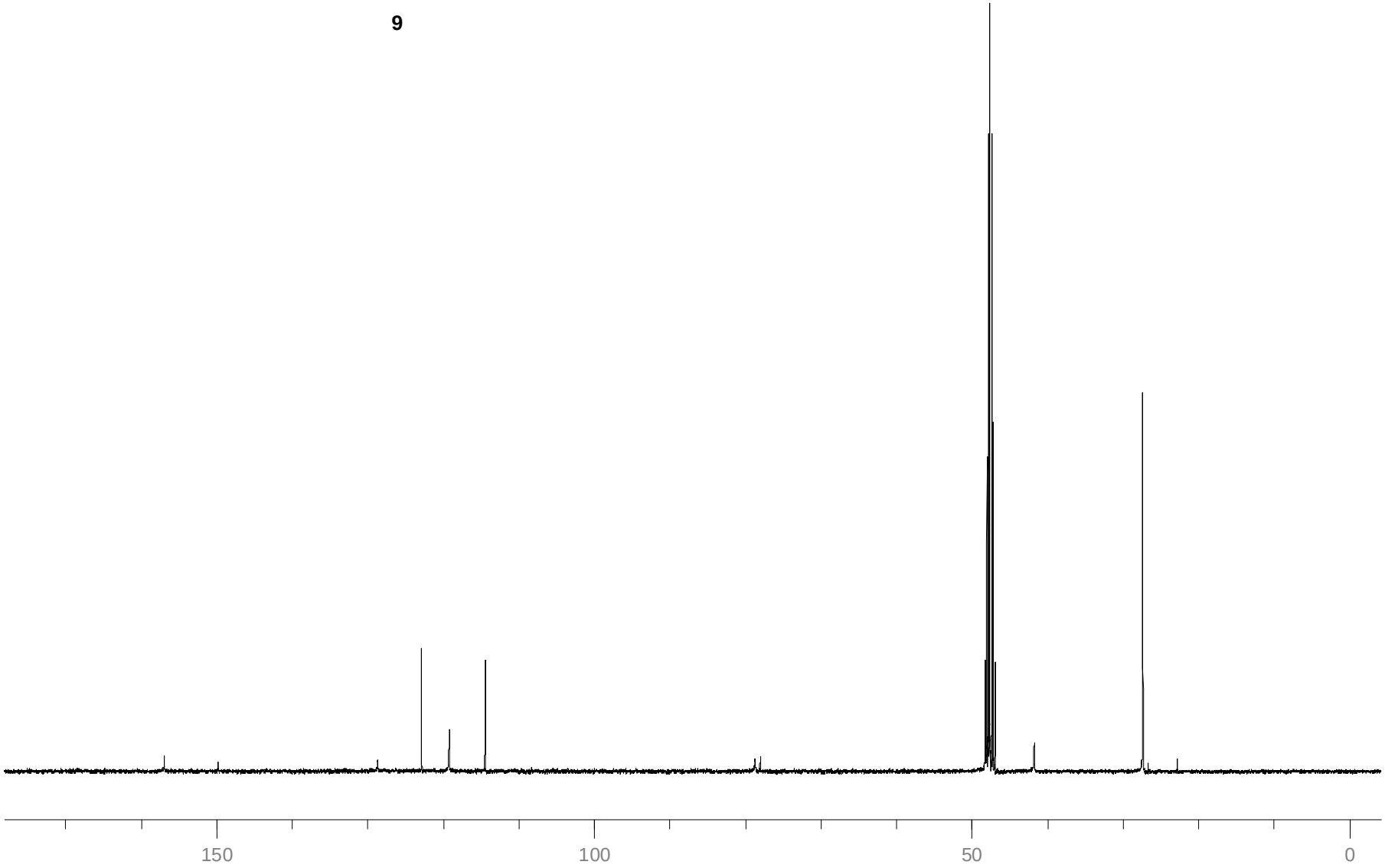


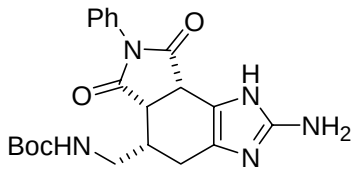

H
N
NH2
BocHN
N
9
400 MHz, CD3OD
6.50
6.00
0.8
1.0
1.0
2.2
9.2
7.0
6.0
5.0
4.0
3.0
2.0
1.0



9

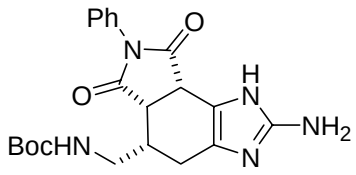
100.6 MHz, CD_3OD





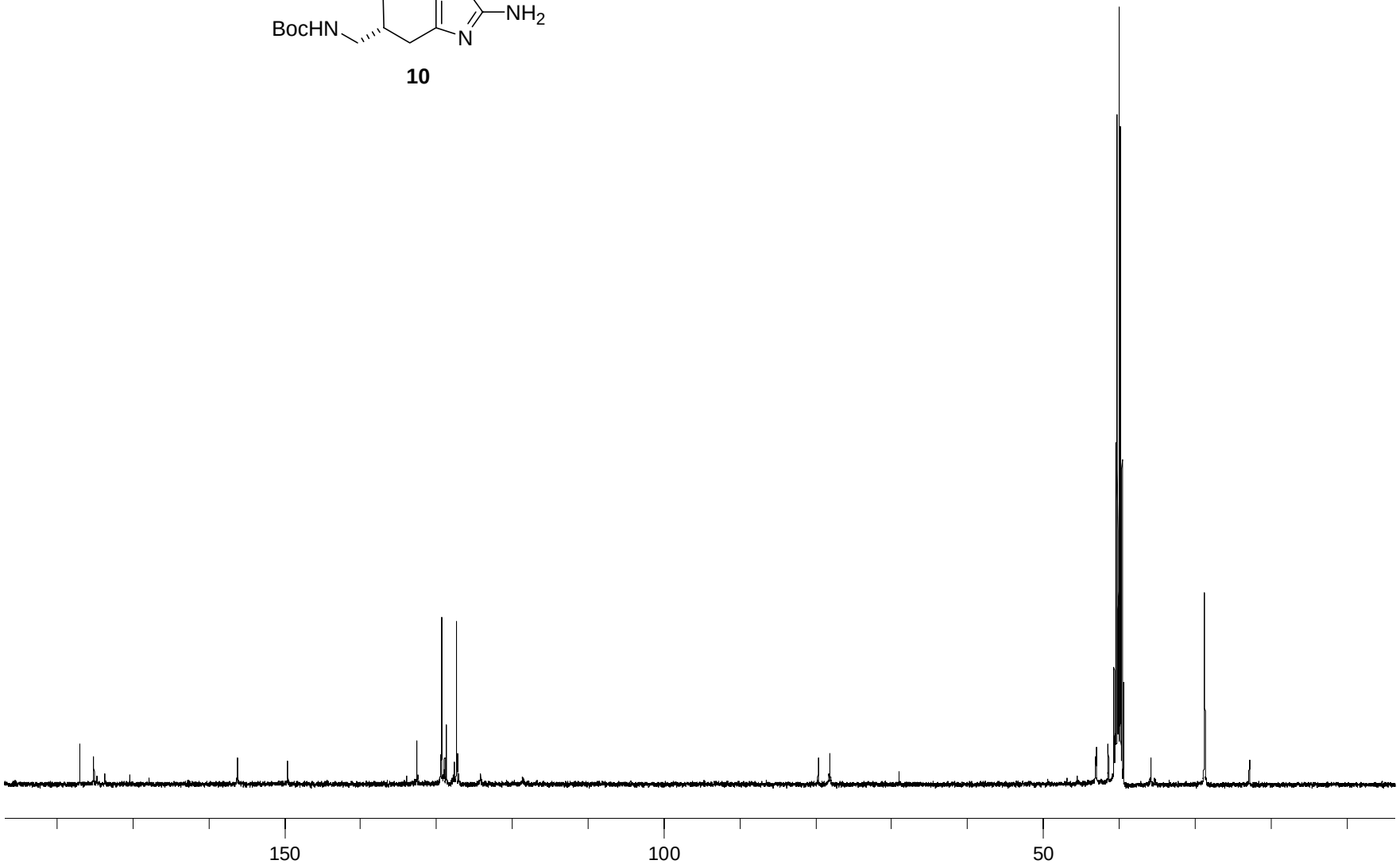
10

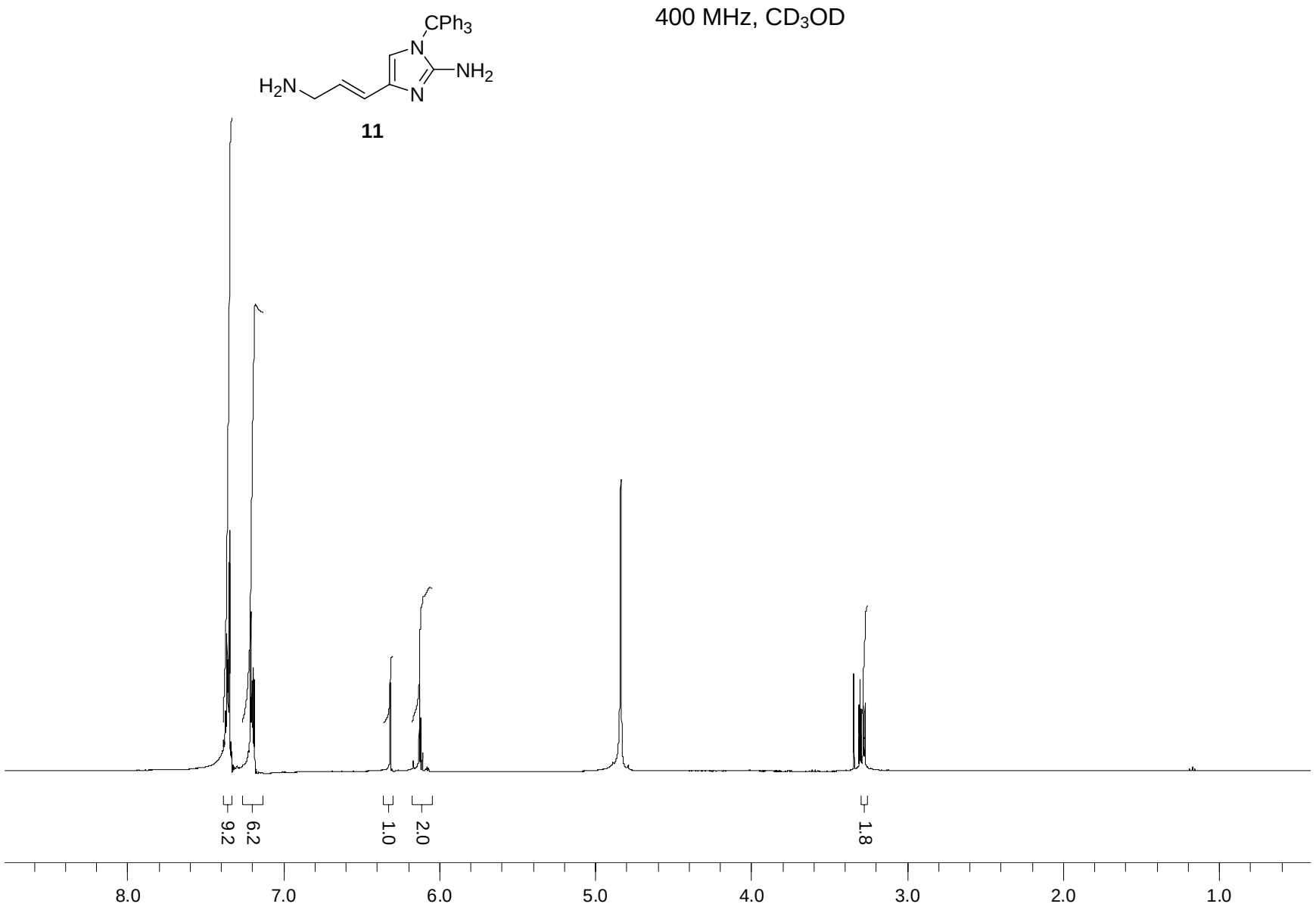
400 MHz, DMSO-d_6

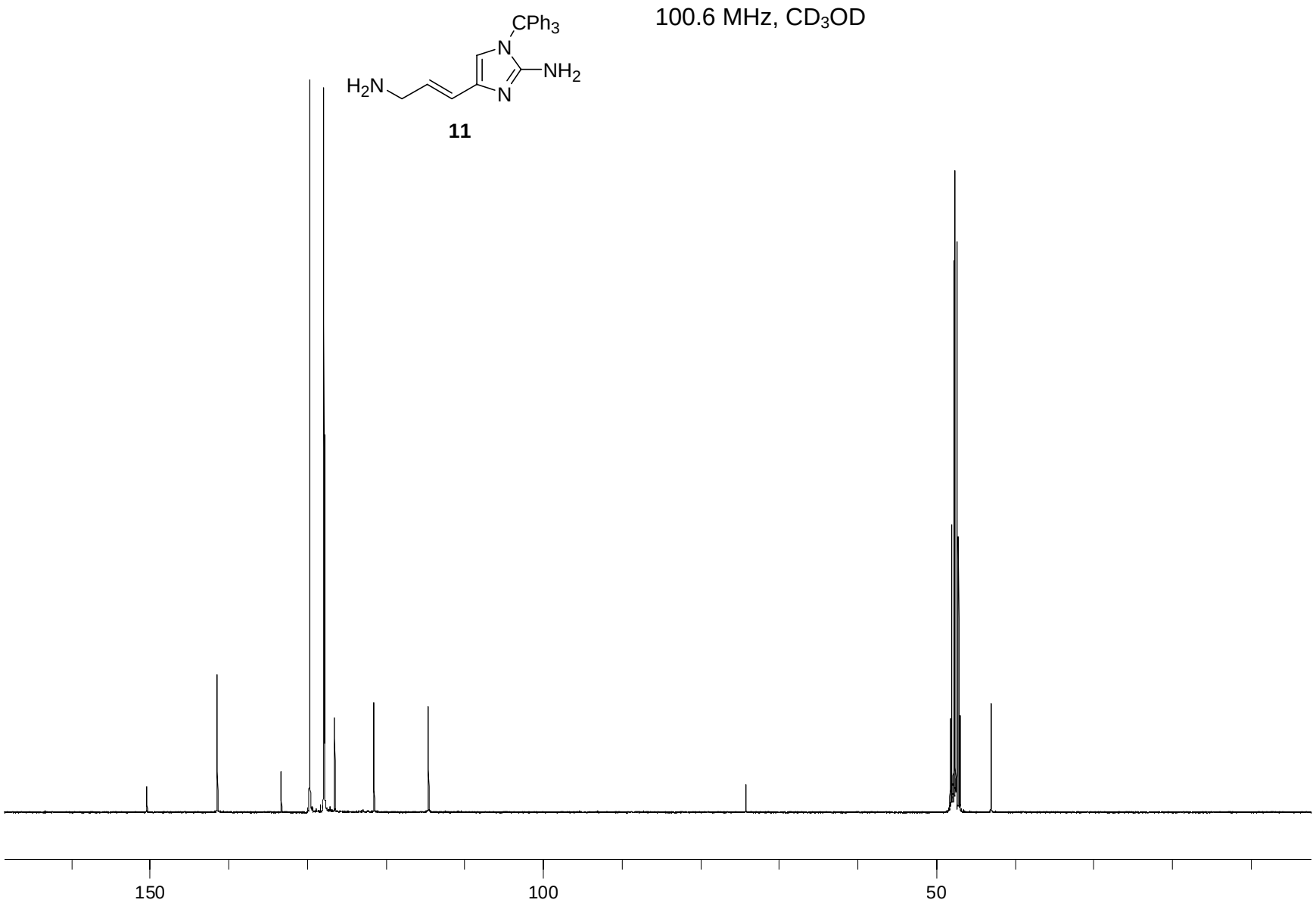


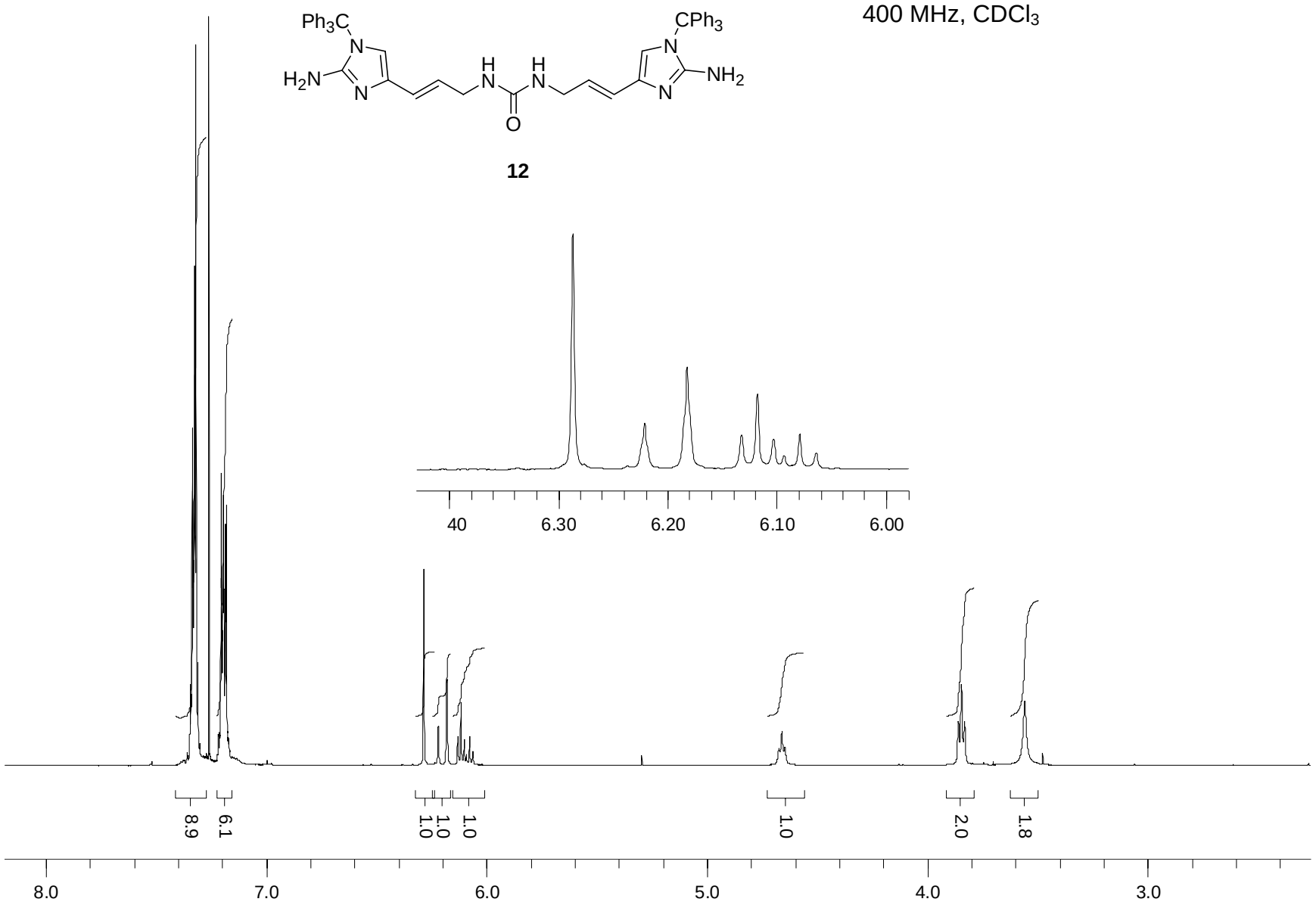
10

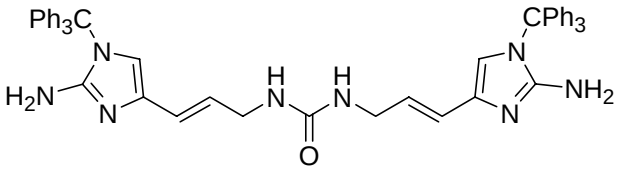
100.6 MHz, DMSO-d_6




400 MHz, CD3OD
CPh3
N
NH2
H2N
N
11
9.2
6.2
1.0
2.0
1.8
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

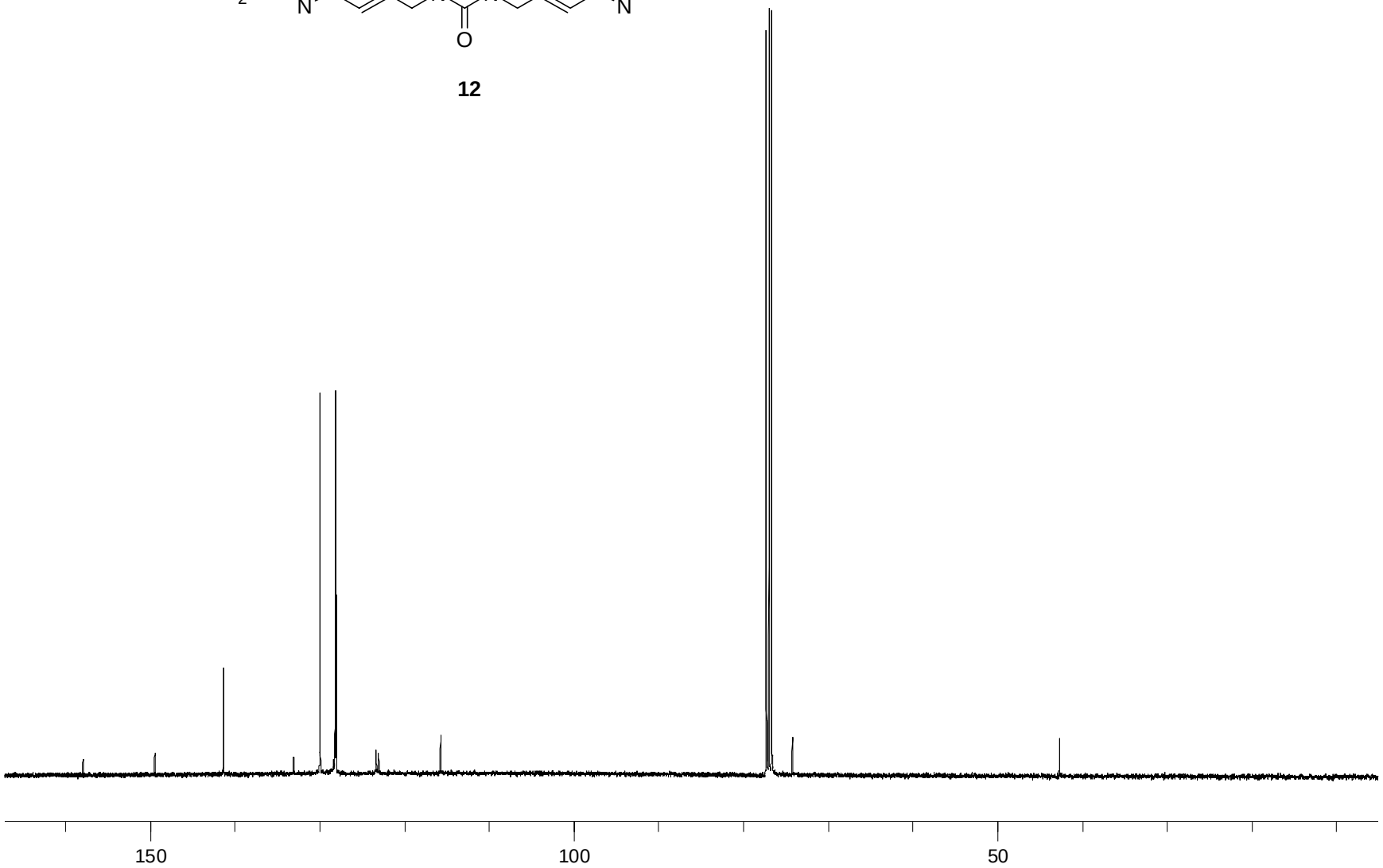

100.6 MHz, CD3OD
CPh3
N
NH2
H2N
N
11
150
100
50

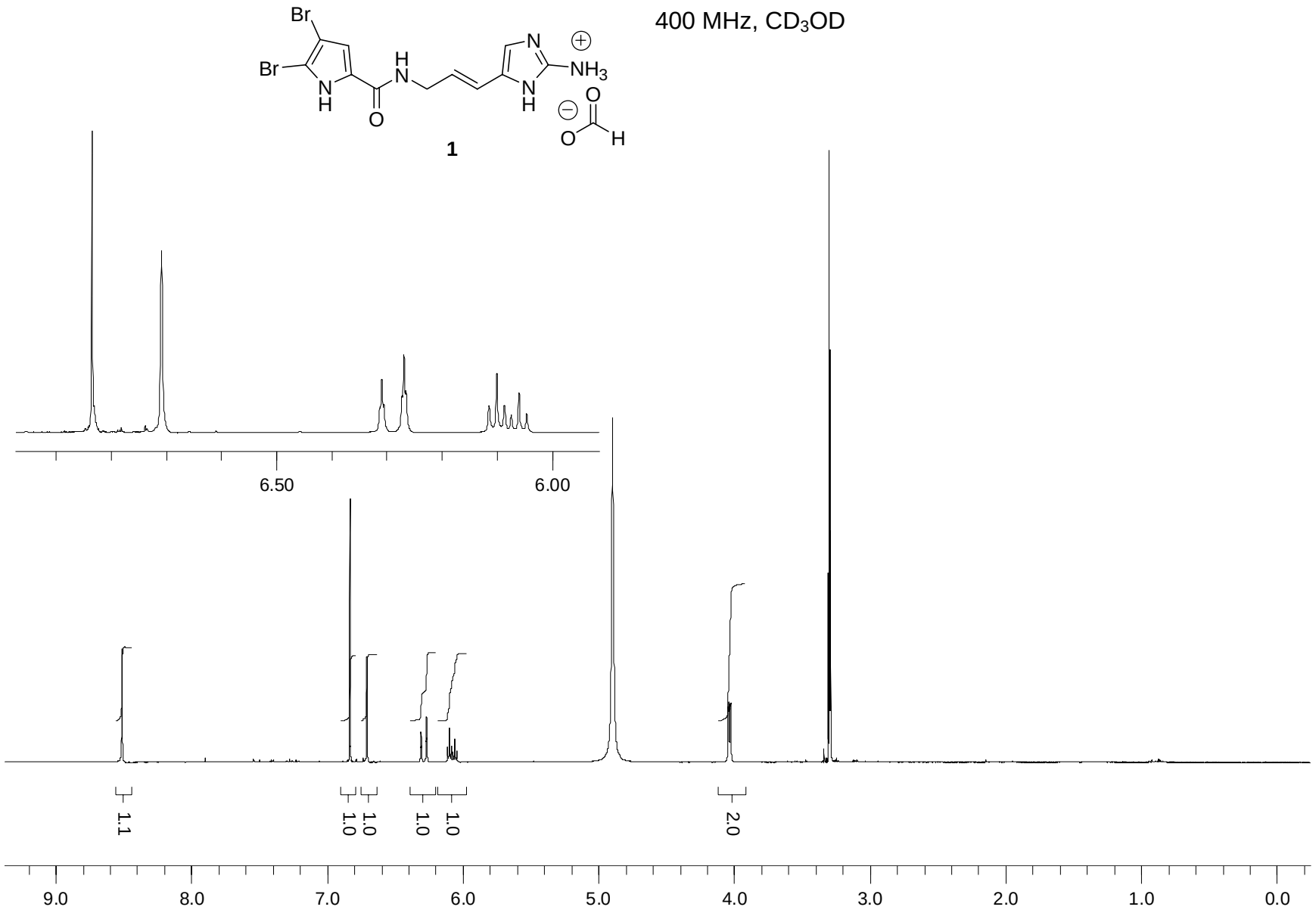

400 MHz, CDCl3
Ph3C
CPh3
H2N
NH2
H
N
O
12
40
6.30
6.20
6.10
6.00
8.9
6.1
1.0
1.0
1.0
1.0
2.0
1.8
8.0
7.0
6.0
5.0
4.0
3.0

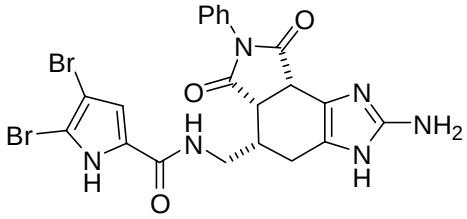


12

100.6 MHz, $CDCl_3$

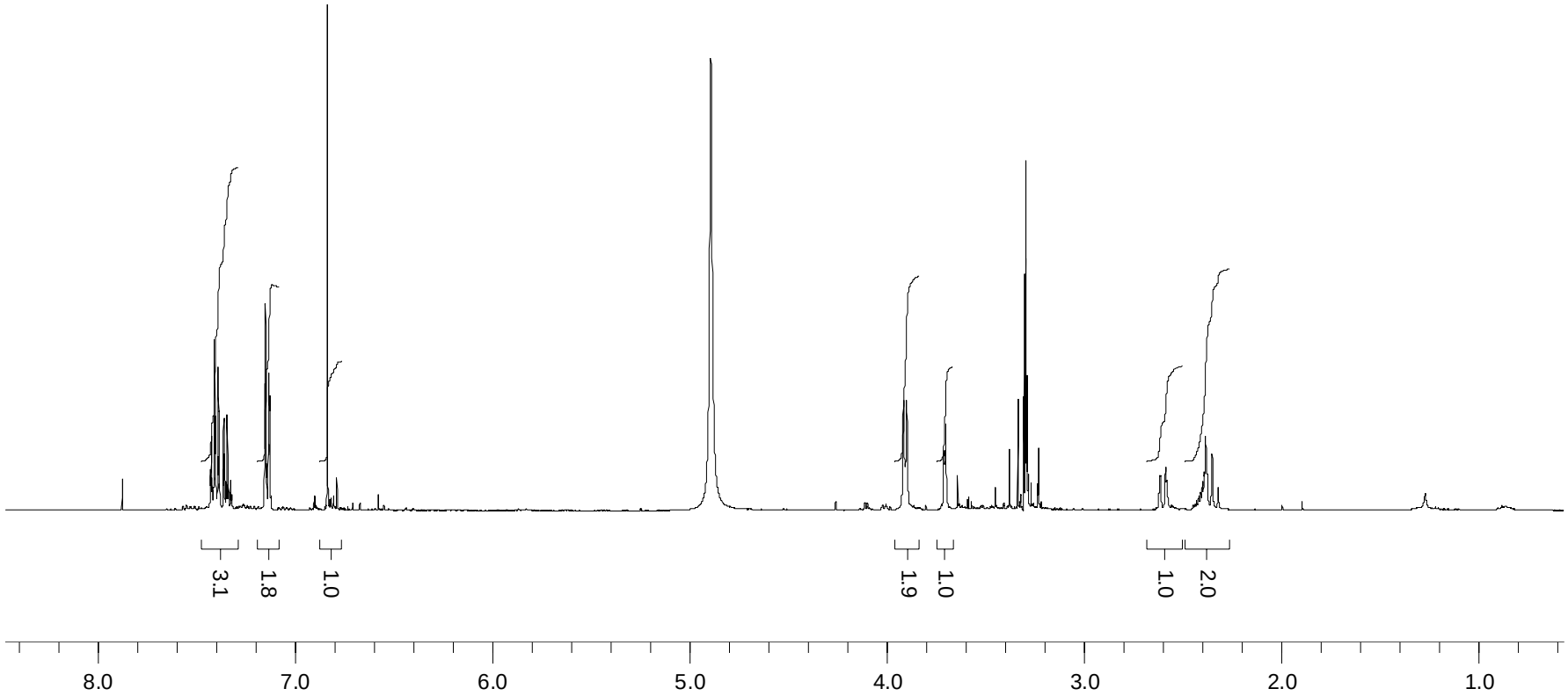


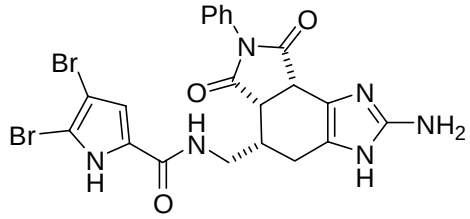

400 MHz, CD3OD
Br
Br
N
H
H
N
O
N
NH3
N
H
O
O
O
H
1
6.50
6.00
1.1
1.0
1.0
1.0
1.0
2.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



13

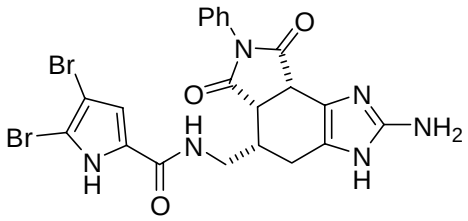
400 MHz, CD_3OD





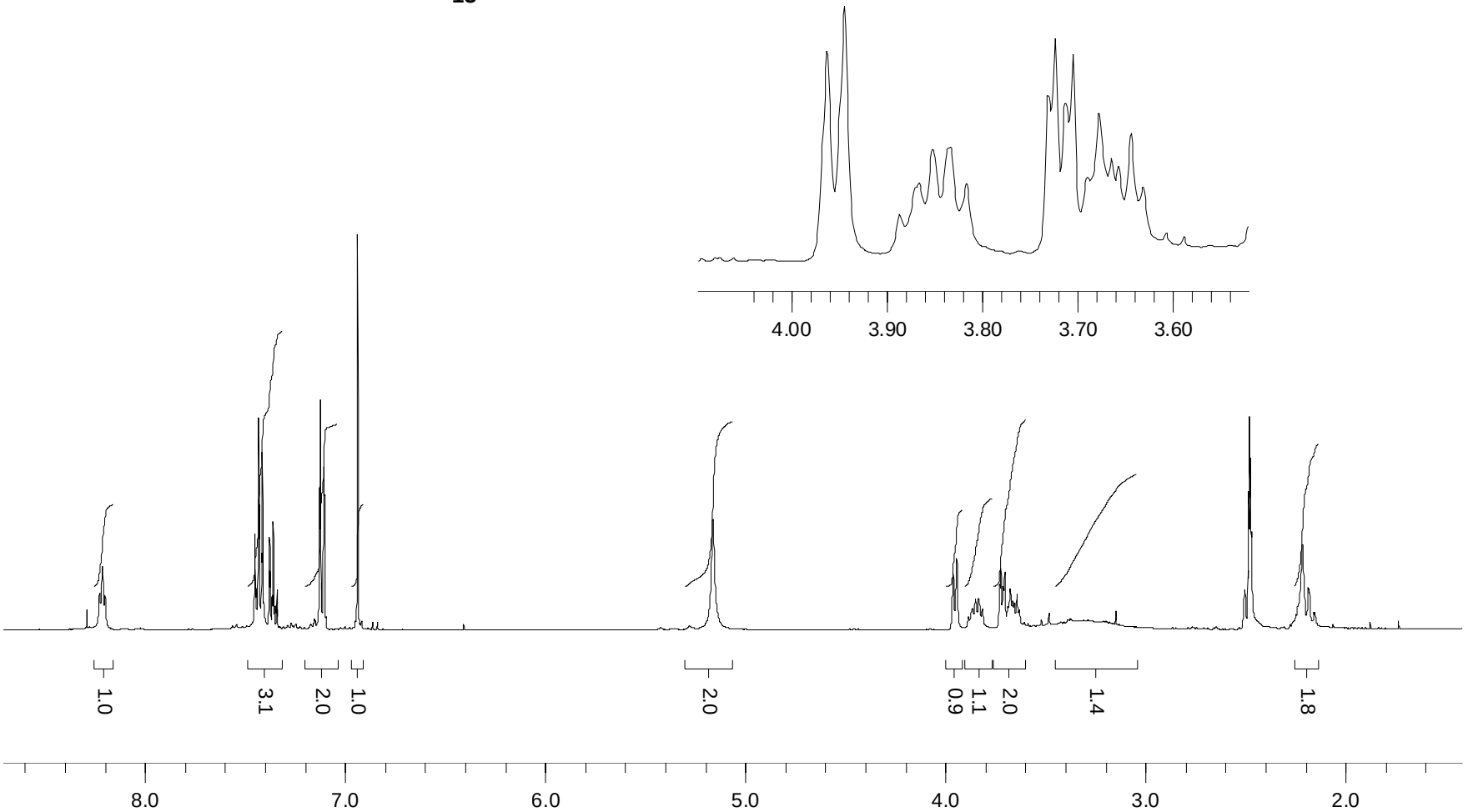
13

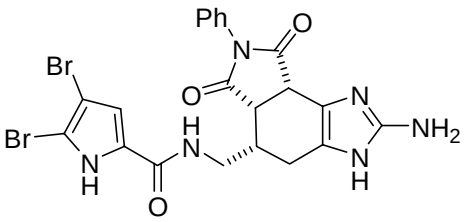
100.6 MHz, CD_3OD



13

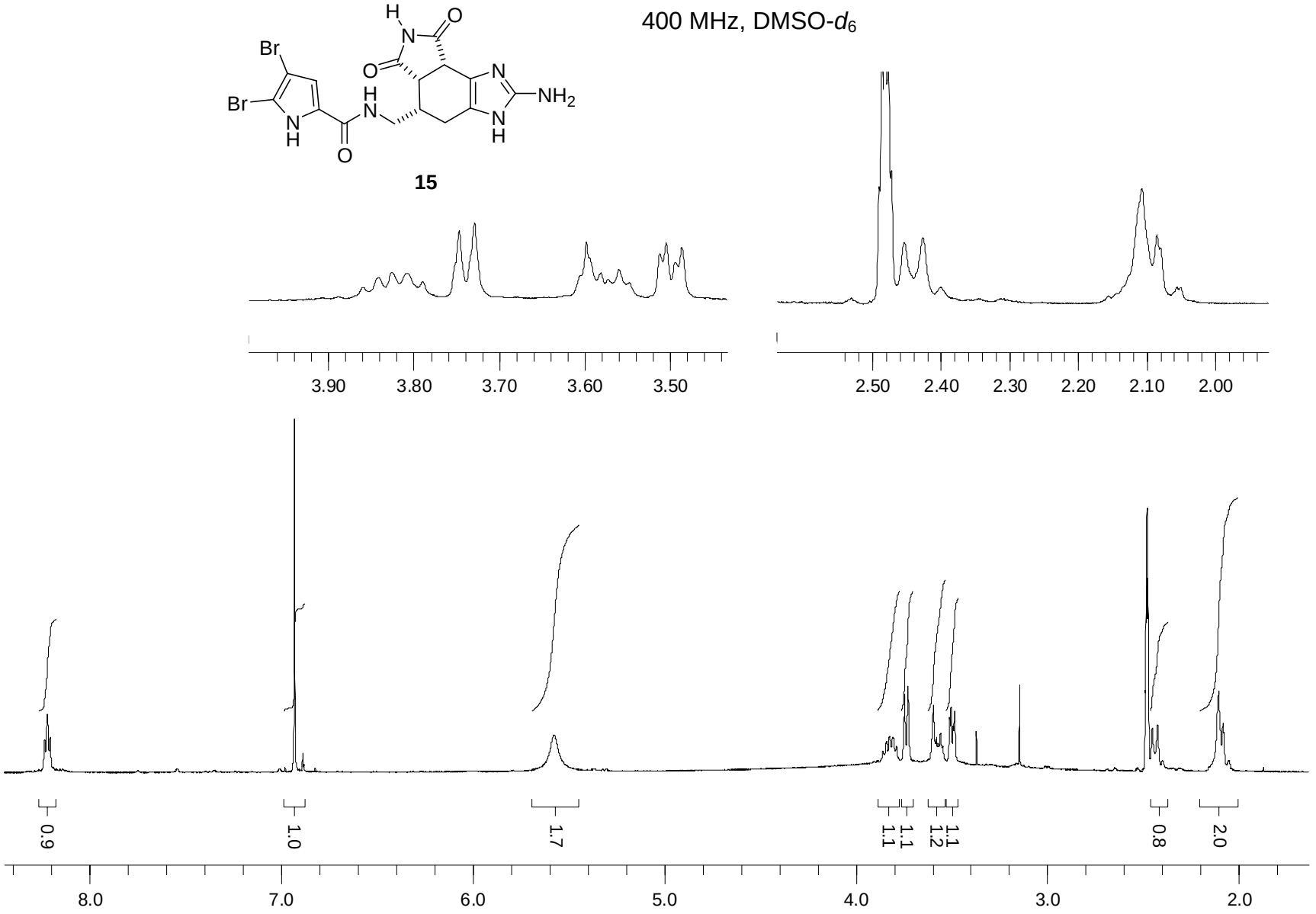
400 MHz, DMSO-d_6

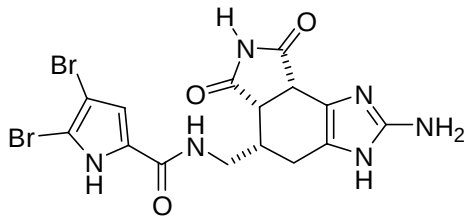




13

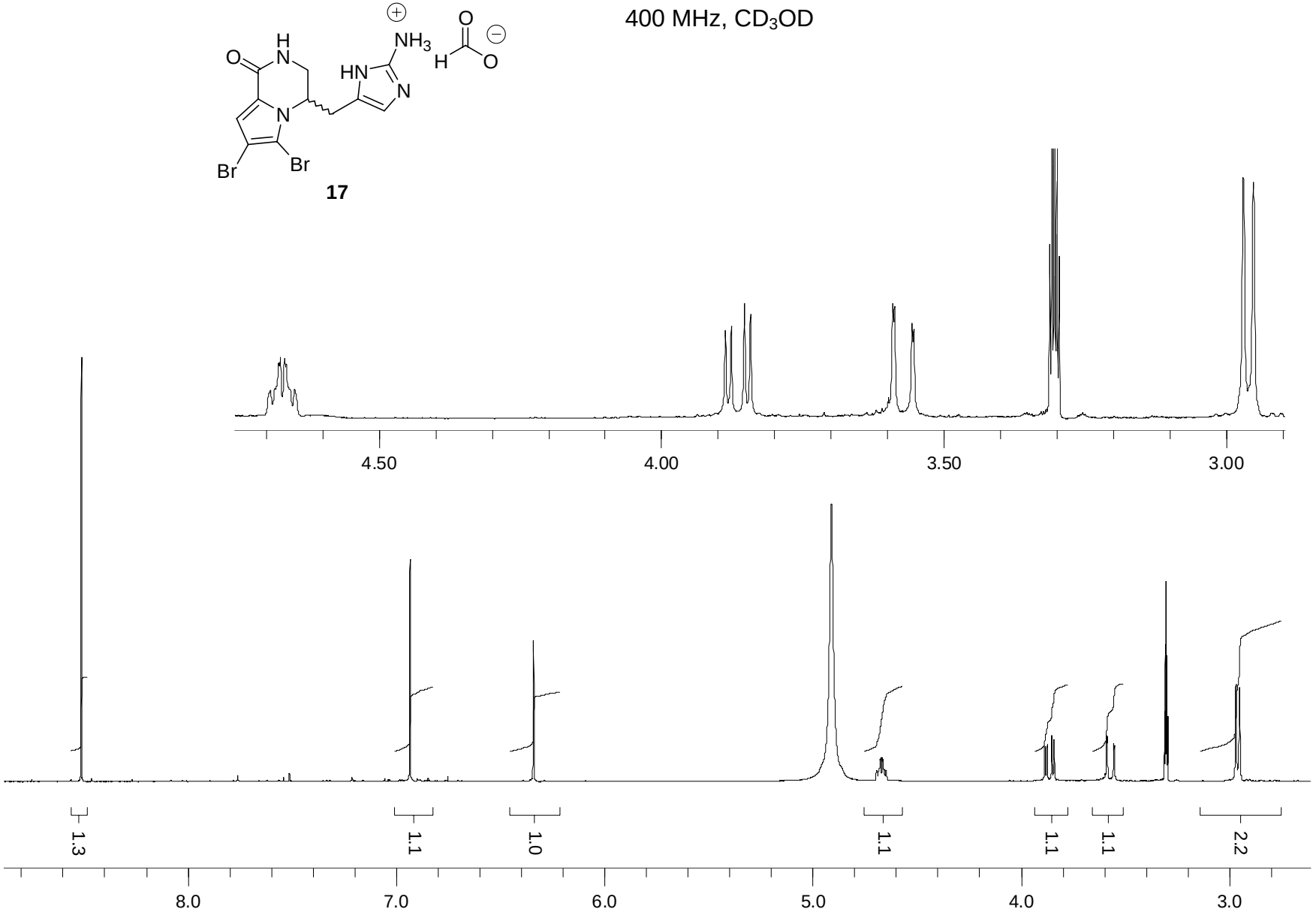
100.6 MHz, DMSO-d_6


400 MHz, DMSO-d_6
15
3.90
3.80
3.70
3.60
3.50
2.50
2.40
2.30
2.20
2.10
2.00
0.9
1.0
1.7
1.1
1.1
1.2
1.1
0.8
2.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0

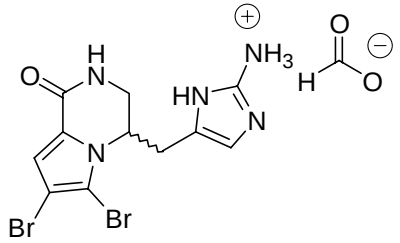


15

100.6 MHz, DMSO-d_6


400 MHz, CD3OD
NH3
HN
N
H
O
Br
Br
4.50
4.00
3.50
3.00
1.3
1.1
1.0
1.1
1.1
1.1
2.2
8.0
7.0
6.0
5.0
4.0
3.0

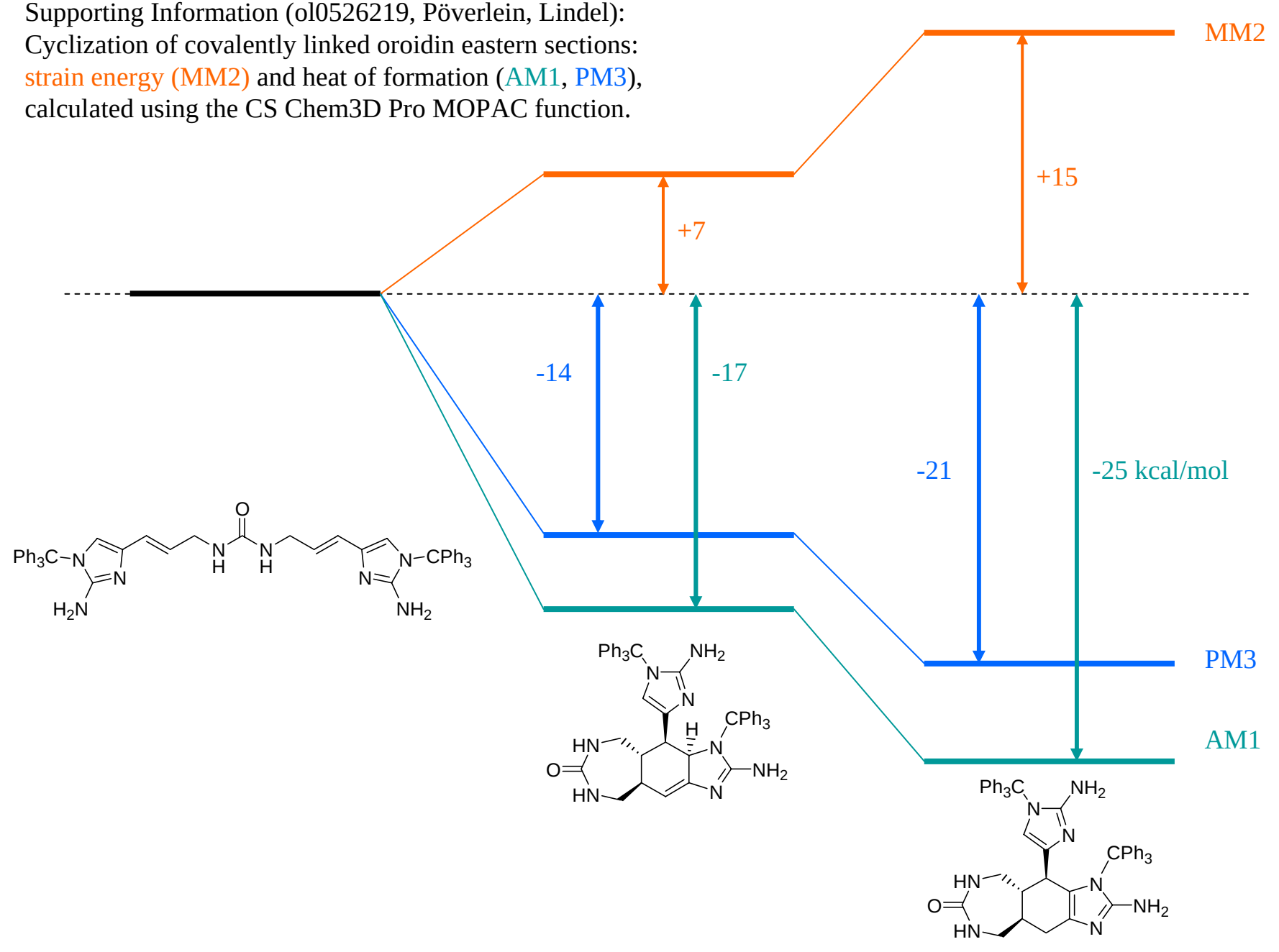
17



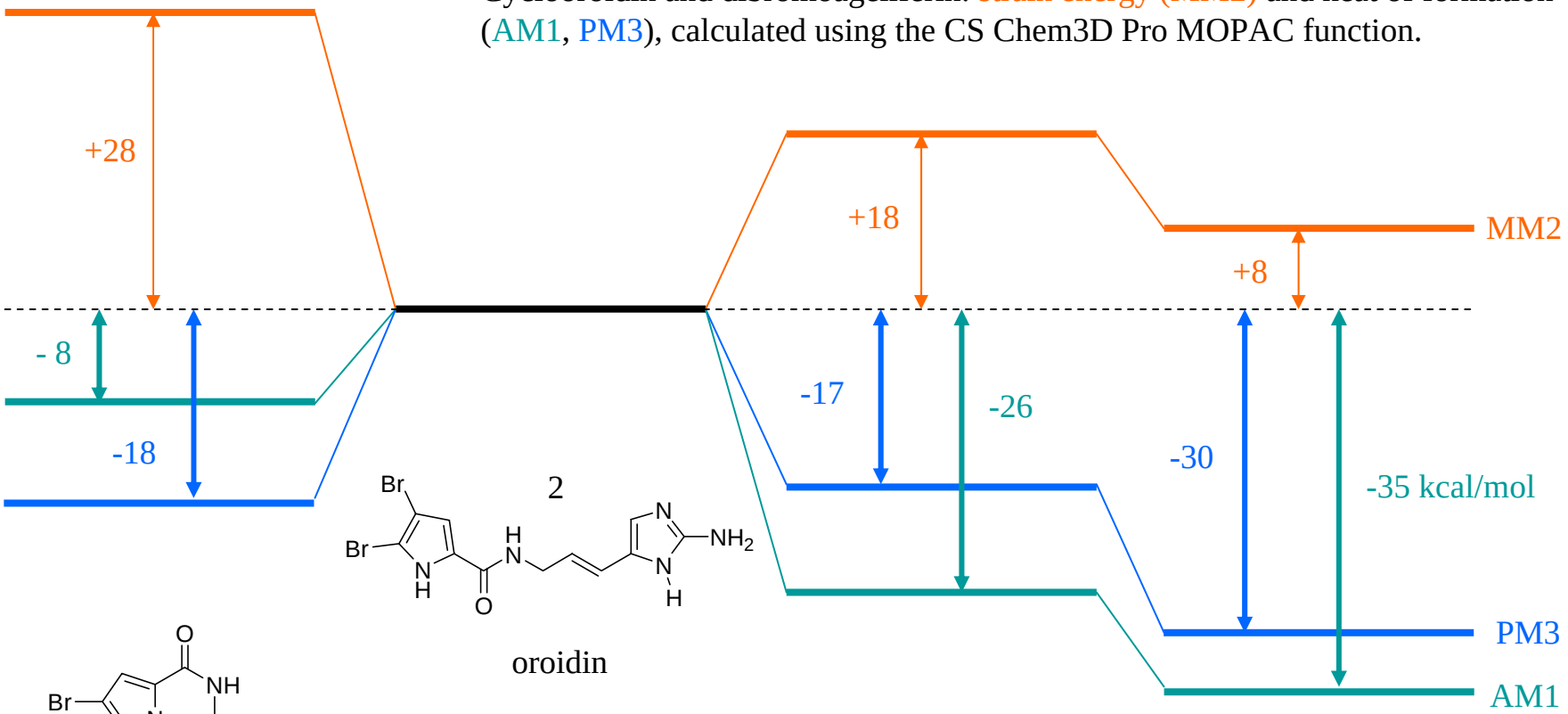
17

100.6 MHz, CD_3OD

Supporting Information (ol0526219, Pöverlein, Lindel):
Cyclization of covalently linked oroidin eastern sections:
strain energy (MM2) and heat of formation (AM1, PM3),
calculated using the CS Chem3D Pro MOPAC function.



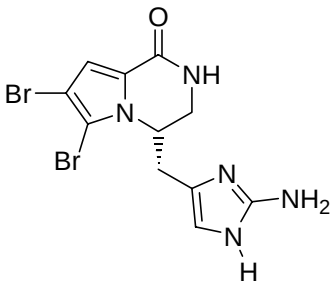
Supporting Information (ol0526219, Pöverlein, Lindel):
Cyclooroidin and dibromoageliferin: strain energy (MM2) and heat of formation (AM1, PM3), calculated using the CS Chem3D Pro MOPAC function.



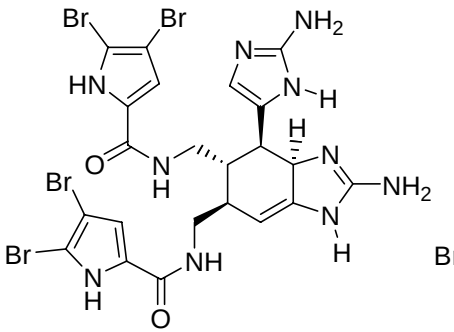
2

oroidin

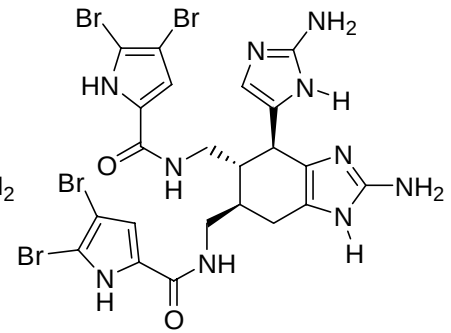
2



cyclooroidin



oroidin [4+2] dimer



dibromoageliferin

favored by reaction entropy