Electronic Supplementary Information

Photoactivatable, biologically-relevant phenols with sensitivity toward 2-photon excitation

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Table of Contents

Synthesis 2

^{1}H and ^{13}C NMR Spectra 9

Determination of Molar Absorptivity Coefficient (ε) 36

Determination of Quantum Efficiency for One-Photon Photolysis (Q_u) 36

Determination of Two-Photon Uncaging Action Cross-Section (δ_u) 37

Time Courses of Photolysis 39

References 41

Synthesis

General. Compounds **1a**,[1] **8a**,[2] **8b**,[3] **9a**,[1] and **10a**[1] were prepared according to their respective literature procedures. All other reagents and solvents were purchased from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded on a Varian MercuryPlus 400 MHz, a Varian INOVA 500 MHz, or a Bruker Avance III HD 600 MHz spectrometer. UV-Vis spectra were recorded on a Cary 300 UV-Visible spectrophotometer (Varian) or a Cary 5000 UV-Vis-NIR spectrophotometer (Agilent). HPLC and uHPLC (analytical and preparative) were performed on a Varian ProStar system with ProStar 335 DAD detector, binary ProStar 210 pumps, and C18 reverse phase columns, an Agilent Infinity series system with an autosampler and diode array detector using Zorbax Eclipse C18 reverse phase columns. HRMS was performed on a Perkin Elmer Sciex API I plus Quadrupole, an Agilent 6540 HD Accurate Mass QTOF/LC/MS with electrospray ionization (ESI), or a Micromass QTOF-Ultima with ESI. Flash chromatography was performed on a Biotage Isolera 1 with SNAP cartridges packed with KP-SIL silica. KMOPS buffer consisted of 100 mM KCl and 10 mM MOPS titrated to pH 7.2 with KOH.

*2-(((3-(2-Aminoethyl)-1*H*-indol-5-yl)oxy)methyl)-7-hydroxyquinoline-8-carbonitrile (**1b**)*. Compound **10b** (0.038 g, 0.075 mmol) was dissolved in methanol. Trimethylsilyl chloride was titrated into the resulting solution until the reaction was complete by uHPLC. The solvent was removed in vacuo and the residue purified by HPLC with a 10-min gradient from 10% CH_3CN/water (0.1% TFA) to 100% CH_3CN. Fractions containing only one peak were combined and concentrated to provide **1b** was a yellow oil (0.017 g, 0.047 mmol, 63%): ^{1}H NMR (600 MHz, methanol-d_4) δ 8.53 (d, 1H), 8.15 (d, 1H), 7.85 (d, 1H), 7.39 (d, 1H), 7.34 (m, 2H), 7.18 (s, 1H), 7.03 (d, 1H), 5.54 (s, 2H), 3.25 (t, 2H), 3.12 (t, 2H); ^{13}C NMR (151 MHz, methanol-d_4) δ 160.65, 160.25, 150.07, 145.99, 137.39, 131.78, 129.99, 127.43, 123.72, 123.67, 120.69, 116.05, 111.60, 111.40, 108.02, 101.71, 97.35, 60.07, 39.69, 23.19; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{18}N_4O_2$ 359.15025; found, 359.15045.

*2-((4-(2-Amino-1-hydroxyethyl)phenoxy)methyl)-8-bromoquinolin-7-ol (**2a**)*. Compound **11a** (0.063 g, 0.052 mmol) was dissolved methanol (1 mL) and trimethylsilyl chloride (0.10 mL, 0.80 mmol) was added. The reaction was stirred in the dark and monitored by uHPLC. Upon completion, the reaction was concentrated in vacuo and purified by HPLC, 10 min gradient from 5% CH_3CN/95% H_2O (0.1% TFA) to 100% CH_3CN. Fractions containing only one peak were combined and concentrated in vacuo to provide **2a** as a yellow oil (0.014 g, 0.036 mmol, 36% yield): ^{1}H NMR (600 MHz, methanol-d_4) δ 8.74 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 7.9 Hz, 2H), 5.13 (s, 2H) 4.82 (d, J = 9.5 Hz, 1H), 4.81 (d, J = 9.6 Hz, 1H), 3.12 (t, J = 2.3 Hz, 1H), 3.03 (t, J = 2.1 Hz, 1H); ^{13}C NMR (125 MHz, methanol-d_4) δ 159.02, 155.44, 152.97, 146.13, 136.07, 134.88, 128.71, 127.80, 127.44, 119.54, 117.79, 115.93, 100.23, 74.27, 70.76, 48.77; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_3Br$ 389.04953, 391.04748; found, 389.04967, 391.04771.

*(*E*)-*N*-(4-((8-Bromo-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)-8-methylnon-6-enamide (**3a**)*. Compound **12a** (0.0446 g, 0.076 mmol) was dissolved in methylene chloride. Trifluoroacetic acid (1 mL) was added and the reaction stirred at rt for 3 h. The solvent was removed in vacuo and the residue purified by HPLC with 50% CH_3CN/50% H_2O (w/ 0.1% TFA). Fractions containing only one peak corresponding to BHQ-capsaicin were combined and concentrated to provide **3a** as a residue on the flask wall (0.0318 g, 77%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.07 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 8.4Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.85 (s, 1H), 6.71 (d, J = 8.2 Hz, 1H), 5.48 (s, 2H), 5.33 (m, 2H), 4.36 (d, 2H), 3.91 (s, 3H), 2.20 (t, J = 7.6 Hz, 2H), 1.97 (q, J = 6.9 Hz, 2H), 1.63 (t, J = 7.6 Hz, 2H), 1.39 (t, J = 7.6 Hz, 2H), 1.25 (m, broad, 1H), 0.94 (d, 6H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.20, 159.62, 154.64, 149.86, 147.52, 145.54, 138.31, 137.37, 131.99, 128.40, 126.64, 123.83, 120.27, 118.08, 117.55, 114.11, 111.99, 107.84, 72.37, 56.27, 43.62, 36.87, 32.39, 31.15, 29.47, 25.46, 22.85; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{33}BrN_2O_4$ 541.1697, 543.1676; found 541.1699, 543.1688.

*(*E*)-*N*-(4-((8-Cyano-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)-8-methylnon-6-enamide (**3b**)*. Compound **12b** (0.054 g, 0.10 mmol) was dissolved in methylene chloride. Trifluoroacetic acid was

added and the reaction stirred at rt for 1 h. The solvent was removed in vacuo and the residue purified by HPLC with 50% CH_3CN/50% H_2O (w/ 0.1% TFA) to separate isomers. Fractions containing only one peak corresponding to CyHQ-capsaicin were combined and concentrated to provide **3b** as a pale yellow oil (0.08 g, 0.2 mmol, 17% yield): ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.34 (d, 1H), 8.07 (d, 1H), 7.70 (d, 1H), 7.45 (d, 1H), 7.03 (d, 1H), 6.98 (s, 1H), 6.80 (d, 1H), 5.34 (d, 3H), 4.36 (d, 2H), 3.85 (s, 3H), 1.96 (t, 2H), 1.63 (m, 2H), 1.4 – 1.2 (m, 8 H), 0.92 (d, 3H), 0.84 (d, 3H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 162.50, 157.05, 149.60, 137.49, 133.68, 133.42, 131.59, 128.08, 123.09, 118.99, 116.28, 115.42, 114.62, 114.54, 112.46, 111.99, 111.78, 103.34, 95.10, 71.59, 56.98, 56.91, 56.85, 40.70, 38.46, 29.70, 28.44, 27.79, 25.88, 25.67; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{29}H_{33}N_3O_4$ 488.2544; found, 488.2579.

N-*(4-((8-Bromo-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)nonanamide (**4a**)*. Compound **13a** (0.055 g, 0.096 mmol) was dissolved in methylene chloride. Trifluoroacetic acid was added and the reaction stirred at rt for 2 h. The solvent was removed in vacuo and the residue purified by HPLC with 50% CH_3CN/50% H_2O (w/ 0.1% TFA). Fractions containing only one peak corresponding to BHQ-VNA were combined and concentrated to provide **4a** as a residue on the flask wall (0.029 g, 57%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.78 (broad, 1H), 5.50 (s, 2H), 4.37 (s, 2H), 3.93 (s, 3H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.64 (m, 2H), 1.4 – 1.2 (m, 10 H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.23, 159.40, 154.41, 149.63, 147.25, 145.13, 137.39, 131.73, 128.33, 123.71, 120.09, 117.86, 117.35, 114.36, 113.84, 111.72, 72.03, 56.06, 43.46, 36.84, 31.80, 29.71, 29.30, 29.14, 25.79, 22.64, 14.09; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{27}H_{33}BrN_2O_4$ 529.1702, 531.1681; found 529.1699, 531.1689.

N-*(4-((8-Cyano-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)nonanamide (**4b**)*. Compound **13b** (0.055 g, 0.096 mmol) was dissolved in methylene chloride. Trifluoroacetic acid was added and the reaction stirred at rt for 2 h. The solvent was removed in vacuo and the crude product was purified via flash chromatography eluting with EtOAc/hexane (2:1) and dried in vacuo to provide **4b** as a yellow solid. (0.029 g, 0.061 mmol, 57% yield): ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 8.25 (d, 1H), 8.00 (d, 1H), 7.65 (d, 1H), 7.25 (d, 1H), 6.96 (m, 2H), 6.77 (d, 1H), 5.36 (s, 2H), 4.28 (m, 2H), 3.88 (s, 3H), 2.19 (t, 2H), 1.60 (m, 2H), 1.4 – 1.2 (m, 10 H), 0.84 (t, 3H); ^{13}C NMR (125 MHz, methanol-*d*$_4$) δ 174.94, 161.98, 154.09, 149.01, 148.21, 144.35, 135.23, 133.30, 130.86, 129.70, 120.37, 119.76, 119.18, 116.51, 115.56, 112.77, 92.40, 69.54, 55.87, 43.73, 36.97, 31.64, 29.61, 29.42, 29.36, 28.93, 26.90, 22.80, 14.13; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{33}N_3O_4$ 476.25438; found, 476.25430.

N-*(4-((8-Bromo-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)acetamide (**5a**)*. Compound **14a** (0.073 g, 0.195 mmol) was dissolved in THF. *N*-Vanillyl acetamide (0.038 g, 0.195 mmol) and 1 M NaOH (0.3 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in CHCl3. The solution washed with water and brine, dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with a 2:3 mixture of EtOAc/Hex. The solvent was removed in vacuo to provide **5a** as a residue on the flask wall (0.0312 g, 33%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.52 (s, 2H), 5.42 (s, 2H), 4.34 (s, 2H), 3.93 (s, 3H), 3.59 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 169.94, 159.91, 155.45, 149.90, 147.60, 146.05, 137.32, 131.86, 128.10, 125.70, 124.73, 120.40, 118.23, 117.46, 114.18, 112.13, 95.69, 72.47, 56.84, 56.32, 43.82, 30.55; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{19}BrN_2O_4$ 475.0869, 477.0848; found 475.0863, 477.0852.

N-*(4-((8-Cyano-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)acetamide (**5b**)*. Compound **14b** (0.020 g, 0.047 mmol) was dissolved in methylene chloride. Trifluoroacetic acid was added and the reaction stirred at rt for 2 h. The solvent was removed in vacuo and the residue purified by HPLC with 50% CH_3CN/50% H_2O (w/ 0.1% TFA). Fractions containing only one peak were combined and concentrated to provide **5b** as a pale yellow oil (0.011 g, 0.029 mmol, 57% yield); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.36 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.42 (d,

J = 9.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.73 (s, 2H), 3.89 (q, *J* = 5.8 Hz, 2H), 3.78 (s, 2H), 1.92 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.48, 165.20, 164.60, 148.23, 147.96, 147.25, 137.70, 134.58, 125.06, 122.18, 121.32, 118.19, 117.82, 116.01, 115.72, 113.82, 94.08, 65.12, 56.13, 42.67, 21.54; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{19}N_3O_4$ 378.14483; found, 378.14475.

*8-Bromo-2-((((8*S*,9*R*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)quinolin-7-ol (**6a**)*. Compound **15a** (0.038 g, 0.069 mmol) was stirred in dichloromethane (2 mL) and trifluoroacetic acid (0.026 mL, 0.34 mmol) was added. The reaction was monitored by uHPLC. Upon completion the reaction was concentrated in vacuo and purified through reverse phase chromatography with water/CH_3CN (2:3); fractions containing product were concentrated in vacuo to provide **6a** as a pale yellow oil (0.028 g, 0.055 mmol, 80% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.13 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.72 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.88 – 6.84 (m, 1H), 6.82 (s, 1H), 5.42 (d, *J* = 1.9 Hz, 2H), 3.01 – 2.80 (m, 4H), 2.33 (d, *J* = 13.4 Hz, 2H), 2.26 – 2.07 (m, 3H), 1.96 (d, *J* = 12.7 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.72 (d, *J* = 9.9 Hz, 1H), 1.55 – 1.15 (m, 12H), 0.80 (d, *J* = 1.9 Hz, 3H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 159.86, 156.28, 154.15, 145.28, 138.19, 137.13, 133.22, 128.31, 126.45, 123.66, 117.64, 117.48, 114.86, 112.31, 81.82, 71.10, 50.04, 49.89, 49.75, 43.97, 43.25, 38.80, 36.71, 30.53, 29.80, 27.22, 26.30, 23.12, 14.70, 11.06, 8.59; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{30}N_1O_3Br$, 508.14818, 510.14613; found, 508.14873, 510.14653.

*7-Hydroxy-2-((((8*S*,9*R*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)methyl)quinoline-8-carbonitrile (**6b**)*. Compound **15b** (0.050 g, 0.10 mmol) was stirred in dichloromethane (2 mL) and trifluoroacetic acid (0.023 mL, 0.30 mmol) was added. The reaction was monitored by uHPLC. Upon completion the reaction was concentrated in vacuo to provide **6b** as a pale yellow oil. (0.037 g, 0.081 mmol, 81% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.76 (d, *J* = 7.9 Hz, 1H), 8.23 – 7.56 (m, 3H), 7.22 (t, *J* = 8.6 Hz, 1H), 6.99 – 6.54 (m, 2H), 5.63 (s, 2H), 3.84 (d, *J* = 27.3 Hz, 0H), 2.97 – 2.66 (m, 2H), 2.42 – 2.26 (m, 1H), 2.19 (ddd, *J* = 19.5, 11.9, 4.4 Hz, 1H), 2.01 – 1.83 (m, 1H), 1.83 – 1.69 (m, 1H), 1.65 – 1.17 (m, 4H), 1.00 – 0.65 (m, 3H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 169.5, 156.9, 154.5, 146.3, 138.6, 135.2, 134.4, 126.8, 122.8, 122.7, 117.7, 114.7, 112.0, 95.7, 86.7, 82.4, 66.9, 65.6, 55.0, 43.6, 43.3, 38.2, 36.5, 27.1, 26.9, 25.9, 23.1, 11.8, 11.0; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{29}H_{30}N_2O_3$ 455.23292; found, 455.23283.

*(*S*)-2-Amino-3-(4-((8-bromo-7-hydroxyquinolin-2-yl)methoxy)phenyl)propanoic acid (**7a**)*. Compound **16a** (0.045 g, 0.078 mmol) was stirred in 4.5 N HCl(aq) (2 mL) heated to an internal temperature of 65 °C. The reaction was monitored by uHPLC and upon completion was concentrated in vacuo. The crude product was purified via flash chromatography eluting with EtOAc/hexane (1:4) and dried in vacuo to yield **7a** as a light orange solid (0.015 g, 0.036 mmol, 46% yield): ^{1}H NMR (600 MHz, methanol-d_4) δ 9.10 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.25 – 7.18 (m, 2H), 5.81 (s, 2H), 4.27 (dd, *J* = 7.4, 5.7 Hz, 1H), 3.33 – 3.11 (m, 2H); ^{13}C NMR (126 MHz, methanol-d_4) δ 169.74, 161.55, 157.00, 156.13, 147.32, 138.42, 130.83, 130.77, 130.73, 130.44, 130.17, 128.17, 124.52, 121.26, 117.19, 115.48, 115.27, 96.89, 66.02, 53.76, 35.10; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{19}H_{17}N_2O_4Br$ 417.0445, 419.0424; found, 417.0446, 419.0427.

*(*S*)-2-Amino-3-(4-((8-cyano-7-hydroxyquinolin-2-yl)methoxy)phenyl)propanoic acid (**7b**)*. Compound **16b** (0.015g, 0.029 mmol) was stirred in 4.5N HCl_{aq} (2 mL) and heated to an internal temperature of 65 °C. Reaction progress was monitored b uHPLC and upon completion was concentrated in vacuo and purified by reverse phase flash chromatography on C-18 capped silica CH3CN/water (1:4) to yield a **7b** as a light orange solid (0.008 g, 0.021 mmol, 77% yield): ^{1}H NMR (600 MHz, methanol-d_4) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.1 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 9.1 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 5.46 (s, 2H), 4.23 (m, 1H), 3.14 (m, 2H); ^{13}C NMR (126 MHz, methanol-d_4) δ 172.37, 162.19, 161.18, 157.31, 148.15, 136.96, 133.68, 130.46, 130.34, 128.70, 122.75, 118.71, 115.55, 115.50, 114.93, 114.75, 99.51, 95.08, 52.17, 28.30; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{17}N_3O_4$, 364.1292; found, 364.1330.

tert-*Butyl (2-(5-((8-cyano-7-(methoxymethoxy)quinolin-2-yl)methoxy)-1*H-*indol-3-yl)ethyl)carbamate (**10b**)*. Compound **9b** (0.036 g, 0.11 mmol) was dissolved in acetone (1 mL) and *N*-Boc-serotonin (0.046 g, 0.17 mmol), and Cs_2CO_3 (0.072 g, 0.22 mmol) were added. The reaction was stirred overnight and then concentrated in vacuo and the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:2). The solvent was removed in vacuo to provide **10b** as a yellow oil (0.035 g, 0.069 mmol, 63%): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.42 (d, 1H), 8.25 (d, 1H), 7.85 (d, 1H), 7.71 (d, 1H), 7.38 (s, 1H), 7.34 (d, 1H), 6.97 (d, 1H), 5.59 (s, 2h), 5.45 (s, 2H), 3.59 (s, 3H), 3.38 (t, 2H), 2.93 (t, 3H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, acetone-d_6) δ 162.33, 161.83, 152.43, 147.98, 137.28, 134.07, 132.21, 128.16, 123.25, 122.86, 118.99, 115.82, 114.11, 112.52, 112.00, 111.95, 111.78, 102.33, 99.06, 95.15, 77.50, 71.59, 59.64, 56.06, 40.95, 40.66, 27.80, 25.82; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{30}N_4O_5$ 503.2289; found, 503.2296.

tert-*Butyl (2-(4-((8-bromo-7-(methoxymethoxy)quinolin-2-yl)methoxy)phenyl)-2-hydroxyethyl)carbamate (**11a**)*. Compound **9a** (0.035 g, 0.094 mmol) and *N*-Boc-octopamine (0.050 g, 0.20 mmol) were stirred in acetone (1 mL) and Cs_2CO_3 (0.075 g, 0.25 mmol) was added. The reaction was monitored by uHPLC and upon completion was diluted with brine, extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography eluting with EtOAc/hexane (1:1), which yielded **11a** as a yellow solid upon drying (0.021 g, 0.039 mmol, 20% yield): ^{1}H NMR (600 MHz, methanol-d_4) δ 9.05 (d, J = 8.3 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 5.27 (s, 2H), 4.82 (dd, J = 9.8, 3.4 Hz, 1H), 4.57 (s, 3H), 3.35 (s, *3*H), 3.27 – 2.70 (m, 2H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, methanol-d_4) δ 159.08, 157.02, 155.51, 155.35, 146.27, 134.91, 133.66, 128.26, 127.92, 127.48, 119.63, 115.68, 101.50, 95.78, 79.75, 72.80, 70.76, 56.35, 48.60, 28.30; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{25}H_{29}N_2O_6Br$ 533.1282, 535.1262; found, 533.1285, 535.1263.

*(*E*)-N-(4-((8-Bromo-7-hydroxyquinolin-2-yl)methoxy)-3-methoxybenzyl)-8-methylnon-6-enamide* (**12a**). Compound **9a** (0.160 g, 0.425 mmol) was dissolved in THF. Capsaicin (0.095 g, 0.31 mmol) and 1 M NaOH (0.35 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in $CHCl_3$. The solution washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with silica gel, eluting with a gradient from 10% hexanes to 1:1 EtOAc/hexanes, yielding **12a** as a solid (0.0446 g, 25%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.10 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.85 (s, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.50 (s, 2H), 5.41 (s, 2H), 5.32 (m, 2H), 4.34 (d, 2H), 3.91 (s, 3H), 3.58 (s, 3H), 2.18 (t, J = 6.8 Hz, 2H), 1.97 (q, J = 6.8 Hz, 2H), 1.87 (m, 1H), 1.64 (m, J = 7.7 Hz, 2H), 1.37 (m, J = 7.7 Hz, 2H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 172.99, 159.90, 155.42, 149.85, 147.48, 146.01, 138.27, 137.31, 132.10, 128.10, 126.67, 124.70, 120.26, 118.22, 117.42, 114.11, 111.98, 95.66, 72.43, 56.83, 56.25, 43.55, 36.86, 32.40, 31.14, 29.49, 25.46, 22.85; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{33}BrN_2O_4$ 585.1964, 587.1944; found 585.1979, 587.1950.

*(*E*)-*N*-(4-((8-Cyano-7-(methoxymethoxy)quinolin-2-yl)methoxy)-3-methoxybenzyl)-8-methylnon-6-enamide (**12b**)*. Compound **9b** (0.092 g, 0.25 mmol) was dissolved in THF. Capsaicin (0.076 g, 0.25 mmol) and 1 M KOH (0.35 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in $CHCl_3$. The solution washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:3). The solvent was removed in vacuo to provide **12b** as a pale yellow oil (0.054 g, 0.10 mmol, 37% yield): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, 1H), 7.97 (d, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 6.88 (d, 2H), 6.72 (d, 1H), 5.74 (broad, 1H), 5.49 (s, 2H), 5.46 (s, 2H), 5.33 (m, 1H), 4.36 (s, 2H), 3.92 (s, 3H), 3.59 (s, 3H), 2.20 (t, 2H), 1.65 (m, 2H), 1.4 – 1.2 (m, 8H), 0.94 (d, 3H), 0.85 (d, 3H); ^{13}C NMR (126 MHz, methanol-d_4) δ 159.60, 158.69, 147.05, 145.59, 144.47, 135.50, 134.40, 131.09, 129.47, 129.45, 123.90, 120.19, 117.48, 116.16, 112.97,

112.18, 111.27, 109.13, 92.52, 69.41, 54.35, 53.46, 40.64, 34.08, 29.65, 28.39, 26.72, 22.69, 20.08, 20.06; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{31}H_{37}N_3O_5$ 532.28060; found, 532.28058.

N-*(4-((8-Bromo-7-(methoxymethoxy)quinolin-2-yl)methoxy)-3-methoxybenzyl)nonanamide (**13a**)*. Compound **9a** (0.107 g, 0.30 mmol) was dissolved in THF. *N*-Vanillyl nonanamide (0.095 g, 0.32 mmol) and 1 M NaOH (0.40 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in CHCl3. The solution washed with water and brine, dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with a 2:3 mixture of EtOAc/hexane. The solvent was removed in vacuo to provide **13a** as a residue on the flask wall (0.055 mg, 32%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.18 (d, *J* = 8.3 Hz,1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.85 (s, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.78 (broad, 1H), 5.49 (s, 2H), 5.40 (s, 2H), 4.36 (s, 2H), 3.90 (s, 3H), 3.54 (s, 3H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.60 (m, *J* = 7.6 Hz, 2H), 1.4 – 1.2 (m, 10 H), 0.84 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 173.06, 159.93, 155.43, 149.88, 147.53, 146.04, 137.31, 132.09, 128.09, 124.72, 120.30, 118.22, 117.44, 114.14, 112.02, 95.68, 72.46, 56.84, 56.28, 43.59, 37.06, 32.00, 29.52, 29.49, 29.33, 25.98, 22.82, 14.25; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{29}H_{37}BrN_2O_5$ 573.1964, 575,1944; found 573.1972, 575.1952.

N-*(4-((8-Cyano-7-(methoxymethoxy)quinolin-2-yl)methoxy)-3-methoxybenzyl)nonanamide (**13b**)*. Compound **9b** (0.10 g, 0.30 mmol) was dissolved in THF. *N*-vanillyl nonanamide (0.095 g, 0.32 mmol) and 1 M KOH (0.40 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in $CHCl_3$. The solution washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:3). The solvent was removed in vacuo to provide **13b** as a pale yellow oil (0.055 g, 0.11 mmol, 32% yield): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, 1H), 7.97 (d, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 6.88 (m, 2H), 6.72 (m, 1H), 5.78 (broad, 1H), 5.46 (s, 2H), 5.50 (s, 2H), 4.36 (d, 2H), 3.90 (s, 3H), 3.59 (s, 3H), 2.20 (t, 2H), 1.60 (m, 2H), 1.4 – 1.2 (m, 10 H), 0.84 (t, 3H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 172.92, 162.18, 161.28, 149.63, 148.16, 147.06, 136.99, 133.67, 120.06, 118.75, 115.54, 113.87, 111.73, 95.10, 71.97, 67.97, 56.92, 56.04, 43.23, 36.81, 31.81, 29.33, 29.31, 29.15, 25.79, 25.62, 22.64, 14.08; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{30}H_{37}N_3O_5$ 520.28060; found, 520.28064.

N-*(4-((8-Bromo-7-(methoxymethoxy)quinolin-2-yl)methoxy)-3-methoxybenzyl)acetamide (**14a**)*. Compound **9a** (0.073 g, 0.195 mmol) was dissolved in THF. *N*-Vanillyl acetamide (0.038 g, 0.195 mmol) and 1 M NaOH (0.3 mL) were added and the reaction stirred overnight. The mixture was concentrated and the residue dissolved in chloroform. The solution washed with water and brine, dried over anhydrous MgSO4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography with a 2:3 mixture of EtOAc/Hex. The solvent was removed in vacuo to provide **14a** as a residue on the flask wall (0.0312 g, 33%): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.52 (s, 2H), 5.42 (s, 2H), 4.34 (s, 2H), 3.93 (s, 3H), 3.59 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 169.94, 159.91, 155.45, 149.90, 147.60, 146.05, 137.32, 131.86, 128.10, 125.70, 124.73, 120.40, 118.23, 117.46, 114.18, 112.13, 95.69, 72.47, 56.84, 56.32, 43.82, 30.55; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{23}BrN_2O_5$ 475.0869, 477.0848; found 475.0863, 477.0852.

N-*(4-((8-Cyano-7-(methoxymethoxy)quinolin-2-yl)methoxy)-3-methoxybenzyl)acetamide (**14b**)*. Compound **9b** (0.045 g, 0.14 mmol) was dissolved in acetone (1 mL) and *N*-vanillyl acetamide (0.095 g, 0.32 mmol) and Cs_2CO_3 (0.091 g, 0.28 mmol) were added. The reaction was then stirred. The mixture was concentrated and the residue dissolved in $CHCl_3$. The solution washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography eluting with EtOAc/hexane (2:3). The solvent was removed in vacuo to provide **14b** (0.014 g, 0.033 mmol, 24% yield): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.05 – 6.83 (m, 2H), 6.77 – 6.61 (m, 1H), 5.50 (s, 2H), 5.46 (s, 2H), 4.36 (d, *J* = 5.7 Hz, 2H), 3.93 (s, 3H), 3.59 (s, 2H); ^{13}C NMR

(151 MHz, methanol-d_4) δ 167.46, 162.10, 146.99, 145.35, 145.11, 144.20, 141.16, 135.44, 127.70, 122.56, 119.91, 119.61, 117.53, 115.36, 115.31, 111.99, 97.05, 89.08, 85.03, 60.92, 53.89, 40.84, 32.58, 26.18; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_5$ 422.1710; found, 422.1716.

*(8*S*,9*R*,13*S*,14*S*,17*S*)-3-((8-Bromo-7-(methoxymethoxy)quinolin-2-yl)methoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-ol (**15a**)*. Compound **9a** (0.030 g, 0.079 mmol) and estradiol (0.022 g, 0.079 mmol) were stirred in acetone (1 mL) and Cs_2CO_3 (0.051 g, 0.16 mmol) was added. The reaction was monitored by uHPLC, and upon completion was dried onto silica gel and the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:3). The purified sample was dried in vacuo to provide **15a** as a yellow solid (0.025 g, 0.45 mmol, 48% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.21 – 8.17 (m, 1H), 7.89 – 7.76 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.04 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.77 (s, 2H), 5.64 (s, 2H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.30 (s, 3H), 2.84 (dt, *J* = 11.9, 3.8 Hz, 2H), 2.19 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.02 (d, *J* = 7.2 Hz, 1H), 1.87 (q, *J* = 6.4 Hz, 1H), 1.72 (ddt, *J* = 32.6, 13.7, 6.6 Hz, 2H), 1.62 – 1.39 (m, 3H), 1.35 – 1.13 (m, 4H), 1.09 (t, *J* = 7.0 Hz, 1H), 0.63 (s, 3H); ^{13}CNMR (125 MHz, chloroform-*d*) δ 156.43, 155.51, 155.35, 146.27, 138.91, 134.91, 134.50, 128.26, 127.92, 126.48, 119.63, 115.68, 115.03, 112.58, 101.50, 95.78, 81.37, 70.62, 56.35, 49.92, 44.38, 43.98, 36.89, 36.09, 32.61, 31.07, 27.49, 26.94, 23.64, 12.50; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{30}H_{34}N_1O_4Br$ 552.17440, 554.17235; found, 552.17438, 554.17251.

*2-((((8*S*,9*R*,13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (**15b**)*. Compound **9b** (0.045 g, 0.14 mmol) and estradiol (0.038 g, 0.14 mmol) were stirred in acetone (1 mL) and Cs_2CO_3 (0.091 g, 0.28 mmol) was added. The reaction was monitored by uHPLC, and upon completion was dried onto silica gel and the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:4). The purified sample was dried in vacuo to provide **15b** as a yellow solid (0.038 g, 0.076 mmol, 57% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.76 (s, 1H), 5.45 (s, 2H), 5.36 (s, 2H) 3.69 (t, *J* = 8.4 Hz, 1H), 3.58 (s, 3H) 2.82 (d, *J* = 5.1 Hz, 2H), 2.56 (s, 1H) 2.28 (d, *J* = 10.9 Hz, 1H), 2.16 (t, *J* = 18.0 Hz, 1H), 2.08 (h, *J* = 18.7 Hz, 1H), 1.93 (d, *J* = 12.4 Hz, 1H), 1.87 (dd, *J* = 2.5 Hz, 1H), 1.68 (q, *J* = 3.8 Hz, 1H), 1.50-1.10 (m, 7H), 0.75 (s, 3H); ^{13}CNMR (600 MHz, chloroform-*d*) δ 162.2, 161.6, 156.0, 148.0, 138.2, 136.9, 133.8, 133.3, 126.4, 122.7, 118.7, 115.4, 114.7, 112.2, 99.2, 95.0, 81.5, 70.8, 56.8, 49.9, 49.3, 43.9, 43.1, 38.7, 36.6, 30.1, 29.7, 27.1; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{31}H_{34}N_2O_4$ 499.25913; found, 499.25291.

*(*S*)-Methyl 3-(4-((8-bromo-7-(methoxymethoxy)quinolin-2-yl)methoxy)phenyl)-2-((*tert-*butoxycarbonyl)amino)propanoate (**16a**)*. Compound **9a** (0.085 g, 0.23 mmol), *N*-Boc-L-tyrosine methyl ester (0.090 g, 0.31 mmol), and K_2CO_3 (0.095 g, 0.69 mmol) were stirred in acetone (2 mL) and heated to reflux. The reaction was monitored by uHPLC, and upon completion the reaction mixture was loaded onto celite, dried in vacuo. The crude product was purified via flash chromatography eluting with EtOAc/hexane (2:3) and dried in vacuo to provide **16a** as a yellow solid (0.089 g 0.16 mmol, 69% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 5.42 (d, *J* = 2.9 Hz, 4H), 5.02 (d, *J* = 8.3 Hz, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 3.12 – 2.86 (m, 2H), 1.43 (d, *J* = 3.2 Hz, 9H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 172.4, 159.6, 157.4, 155.2, 145.7, 137.1, 130.9, 128.5, 124.4, 118.0, 117.1, 115.5, 114.9, 112.0, 95.3, 79.9, 71.2, 69.5, 56.6, 54.5, 53.7, 52.2, 37.4, 31.7, 31.5, 29.2, 28.3, 22.6; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{27}H_{31}N_2O_7Br$ 575.13874 577.13669; found, 575.13934, 577.13773.

*(*S*)-methyl 2-((*tert-*butoxycarbonyl)amino)-3-(4-((8-cyano-7-(methoxymethoxy)quinolin-2-yl)methoxy)phenyl)propanoate (**16b**)*. Compound **9b** (0.025 g, 0.067 mmol), *N*-Boc-L-tyrosine methyl ester (0.025 g, 0.085 mmol), and K_2CO_3 (0.016 g, 0.12 mmol) were stirred in acetone (2 mL) and heated to reflux. The reaction was monitored by uHPLC, and upon the crude product was purified via flash chromatography eluting with EtOAc/hexane (1:2) and dried in vacuo to provide **16b** as a yellow

solid (0.031 g, 0.059 mmol, 67% yield): ^{1}H NMR (600 MHz, chloroform-*d*) δ 8.17 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 5.7 Hz, 1H), 6.97(d, J = 5.7Hz, 2H), 5.46 (s, 2H), 5.41 (s, 2H), 4.54 (m, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.03 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 172.3, 162.1, 161.1, 157.3, 155.3, 155.1, 148.1, 136.9, 133.6, 130.4, 128.7, 122.7, 118.7, 115.5, 114.9, 99.5, 95.0, 79.9, 70.9, 69.5, 56.9, 54.4, 53.7, 52.2, 37.4, 31.7, 29.2, 28.2; HRMS-ESI (*m/z*) $[M+H]^+$ calcd for $C_{28}H_{31}N_3O_7$ 522.22348; found, 522.22302.

^{1}H and ^{13}C NMR Spectra

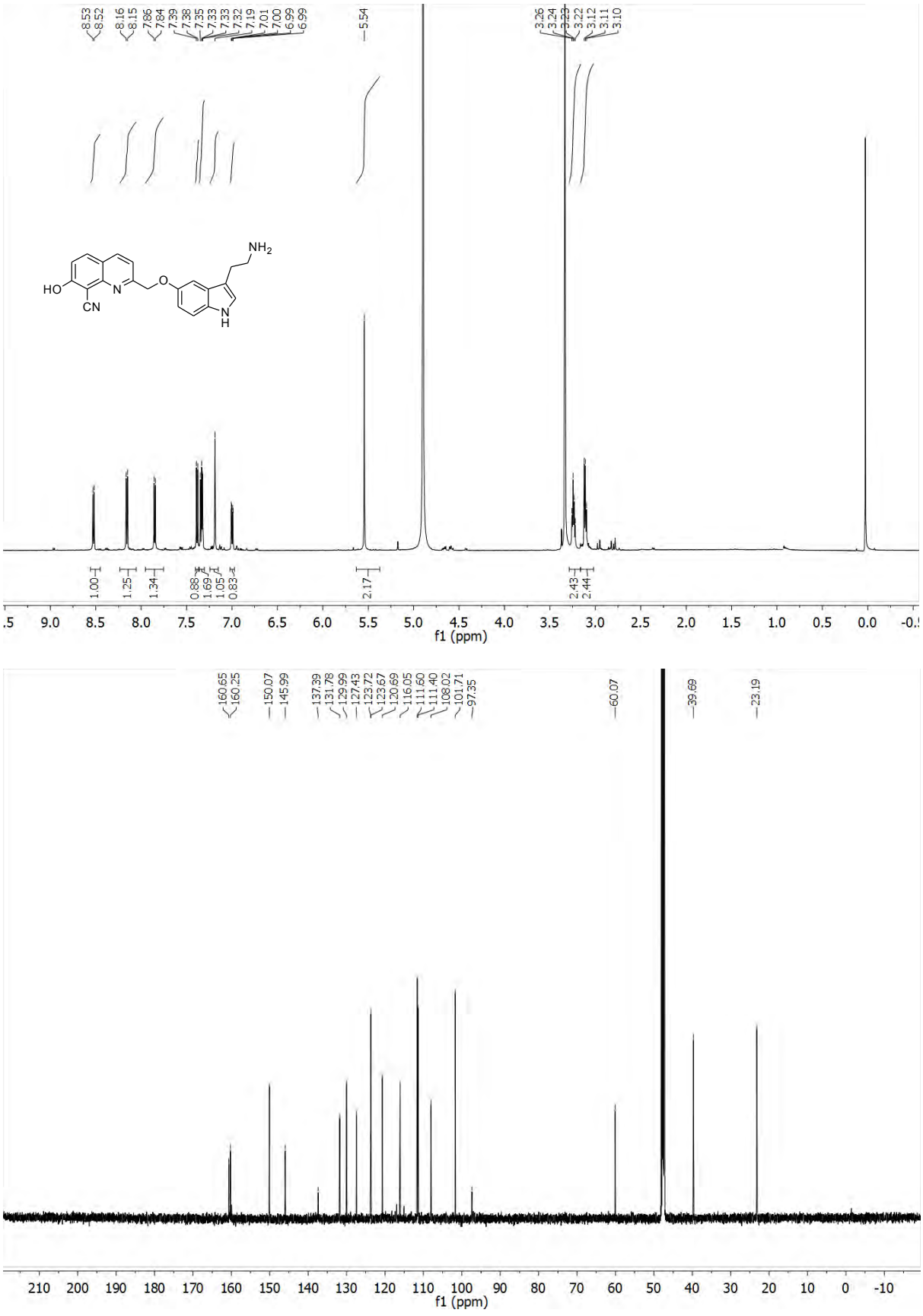

Figure S1. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **1b**.

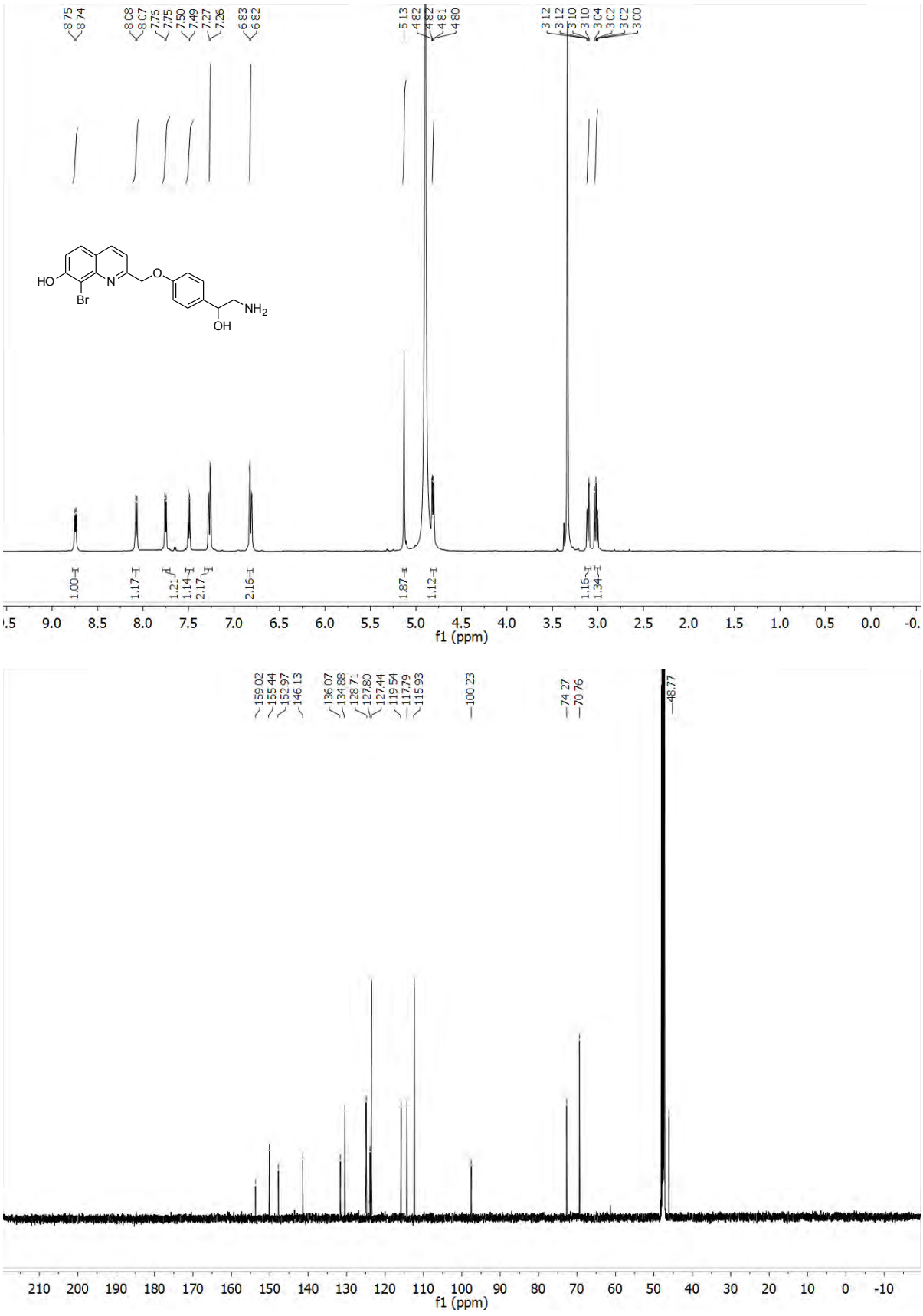

Figure S2. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **2a**.

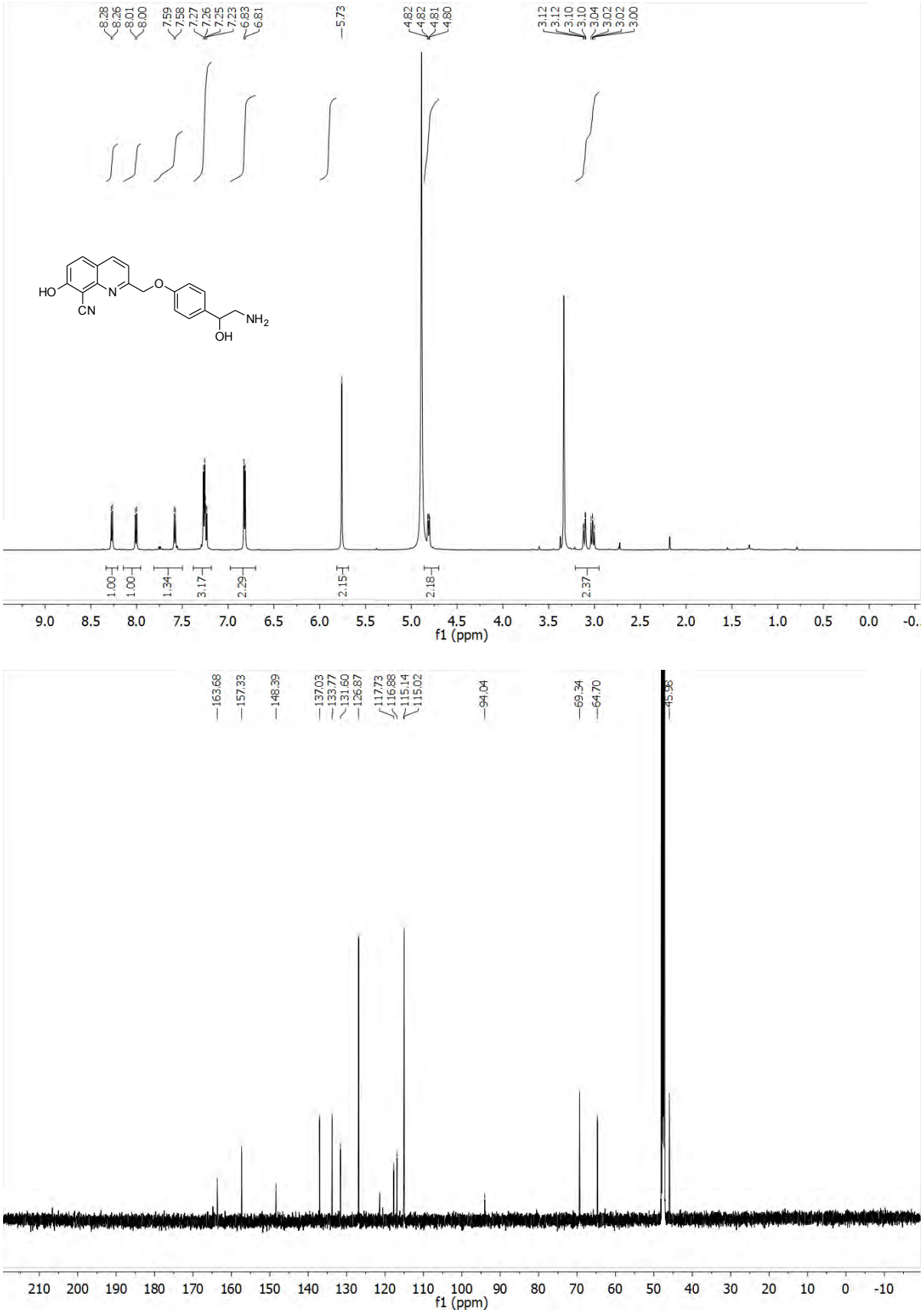

Figure S3. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **2b**.

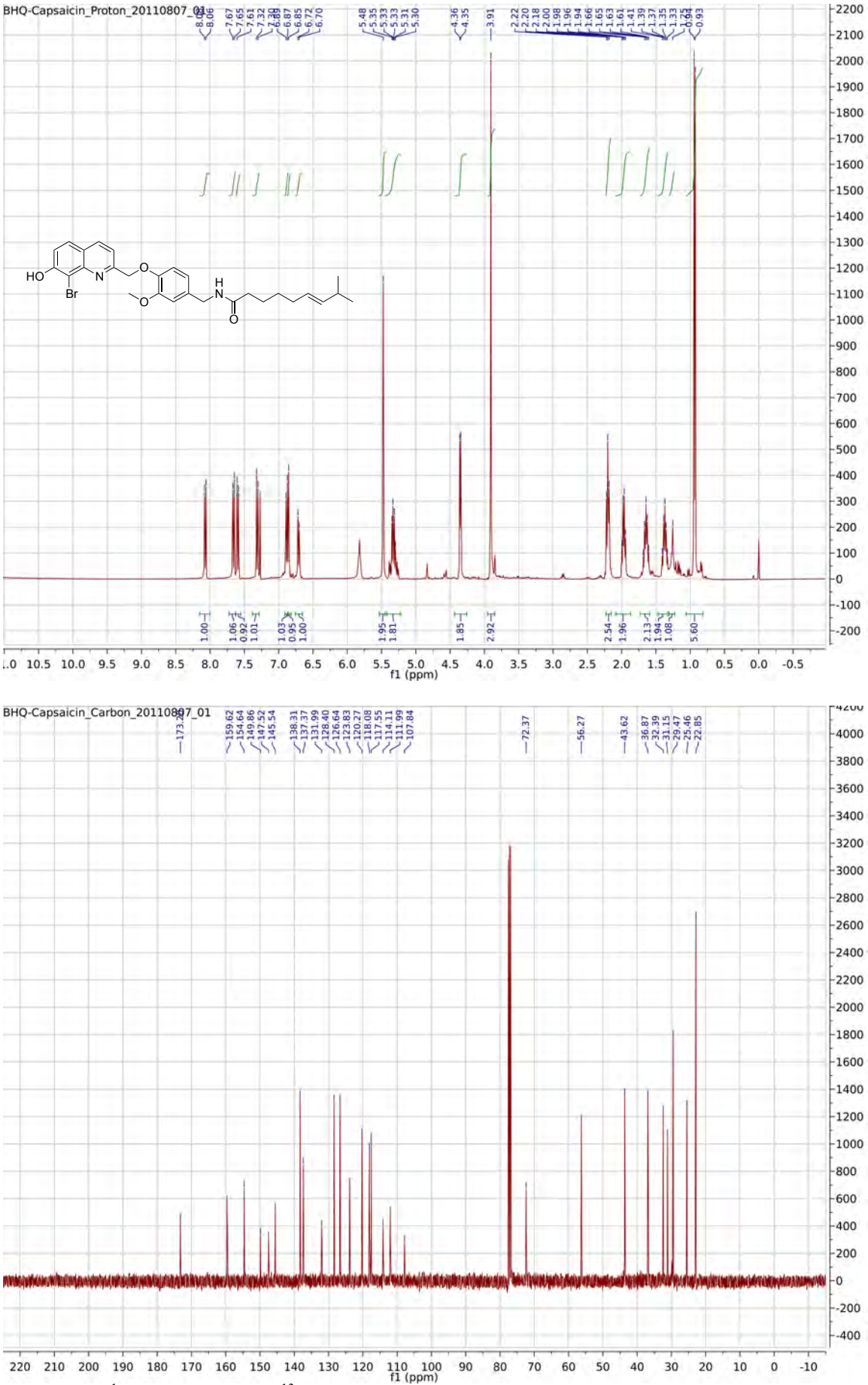

Figure S4. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **3a**.

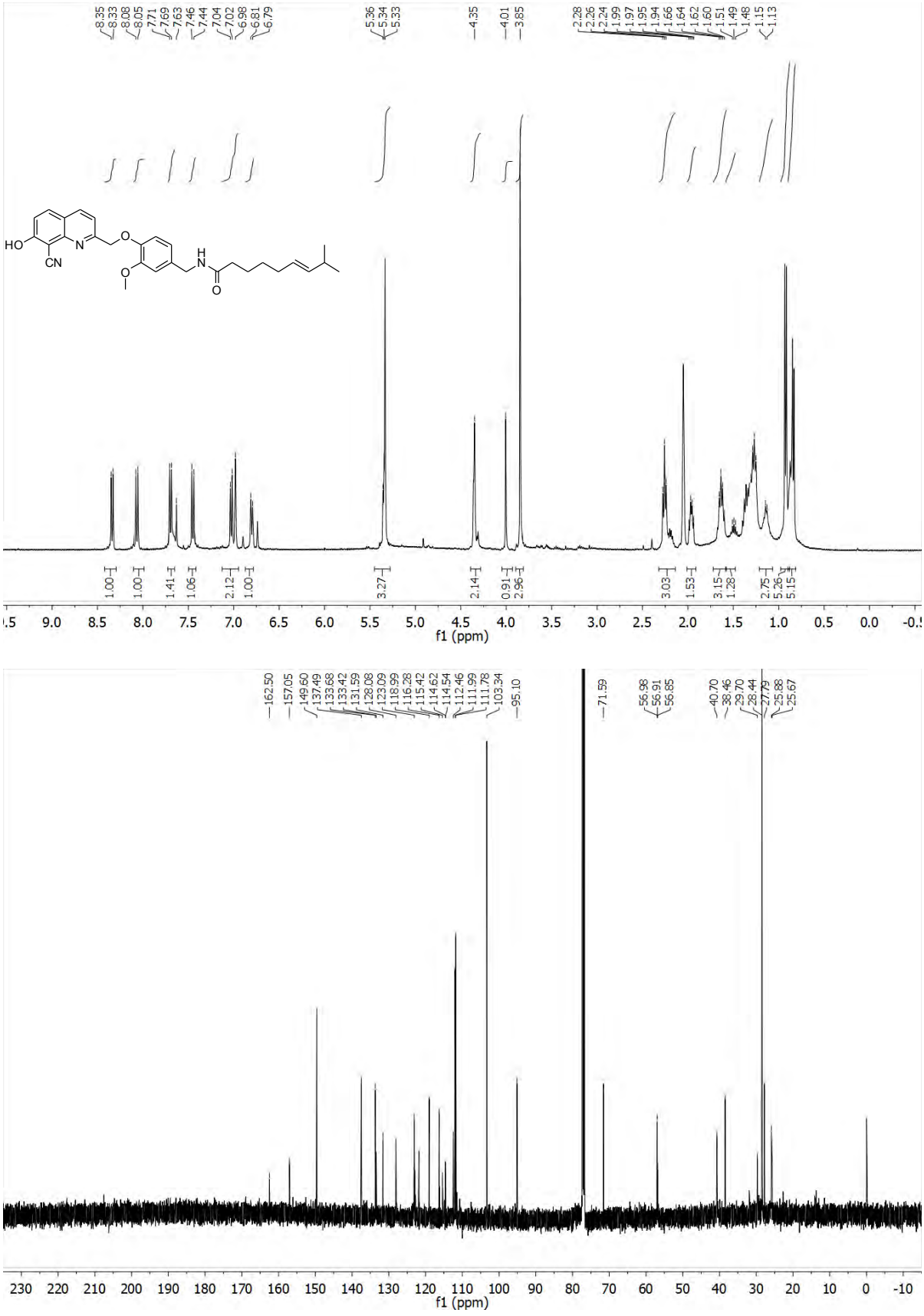

Figure S5. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **3b**.

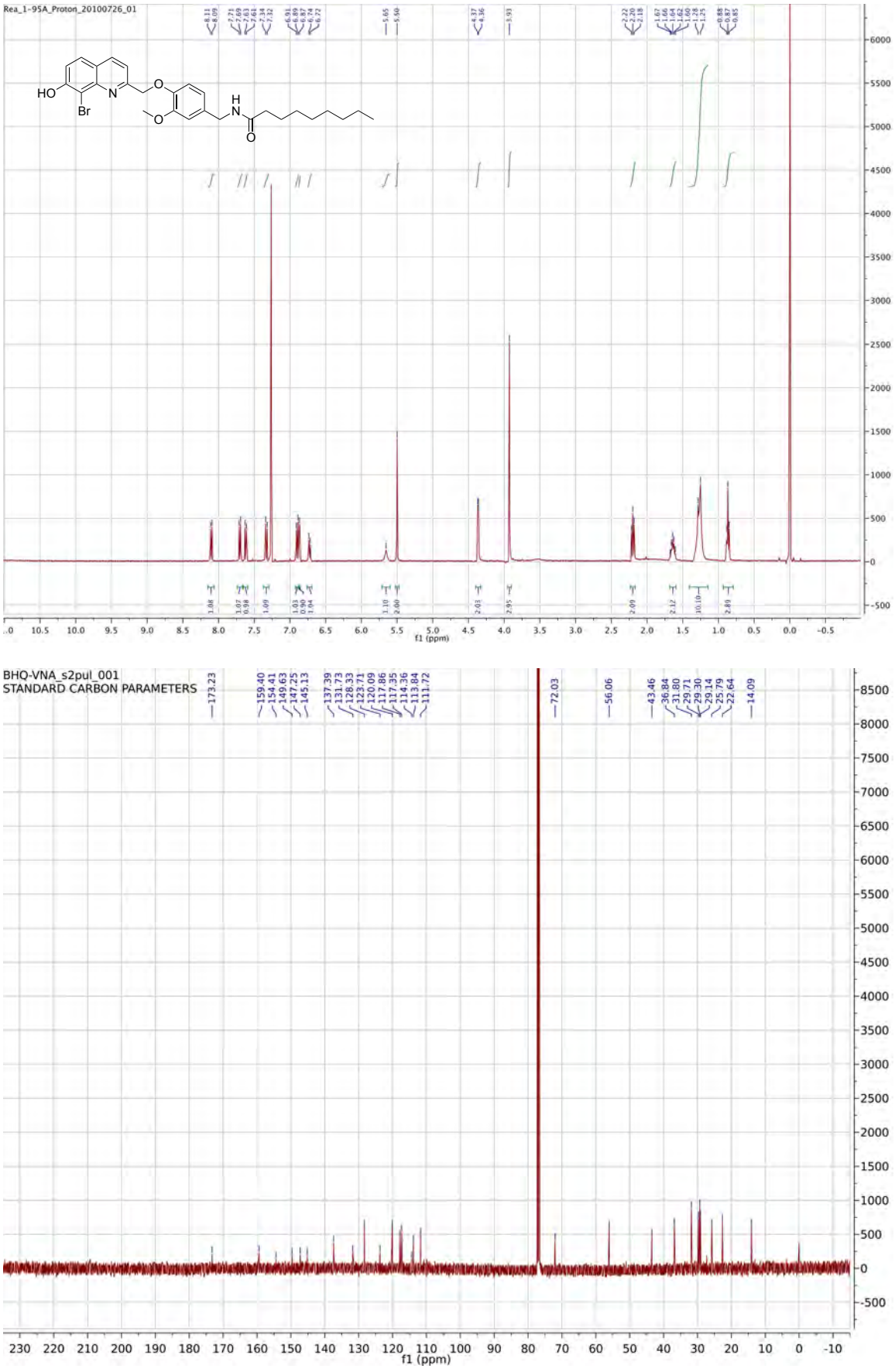

Figure S6. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **4a**.

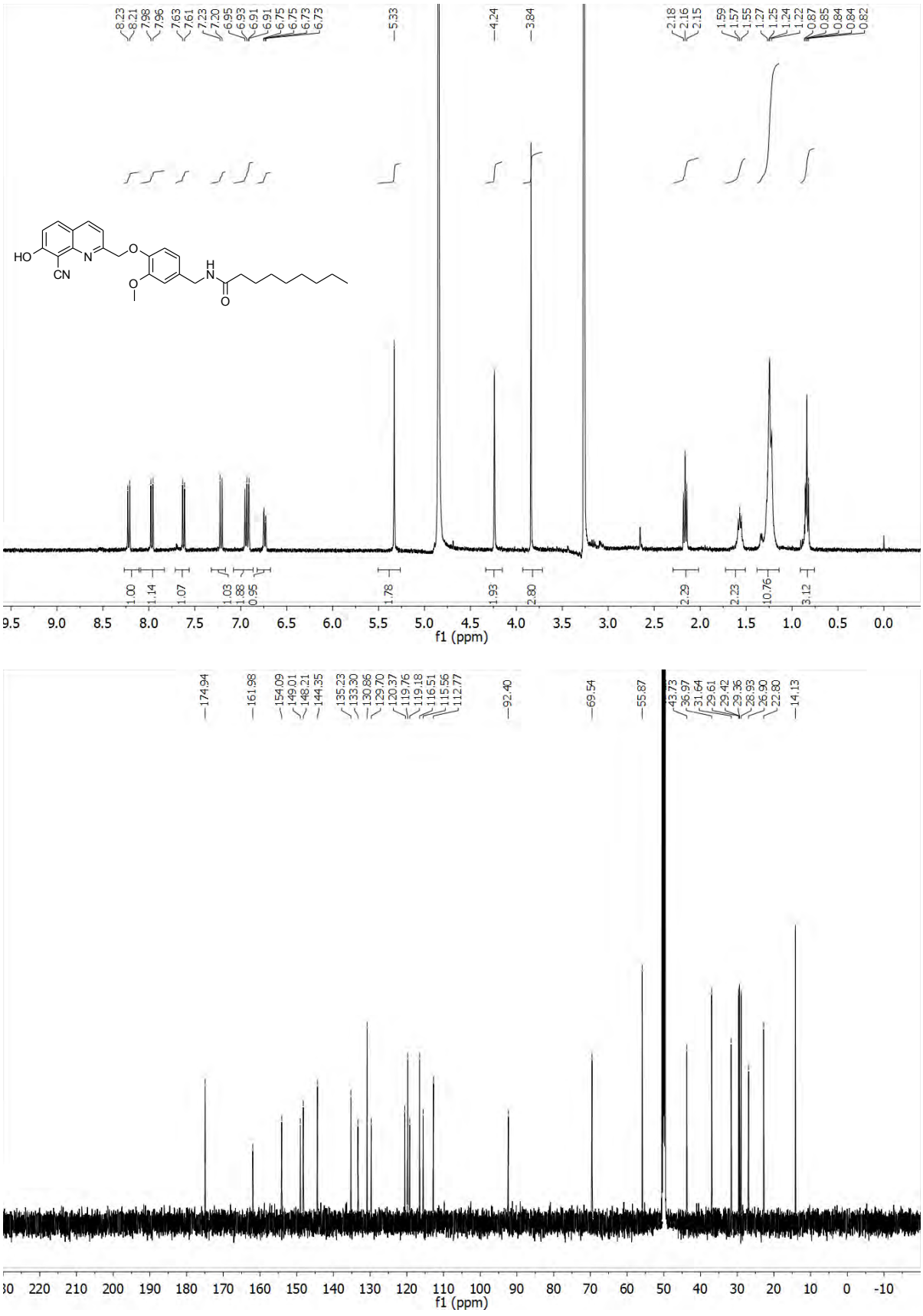

Figure S7. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **4b**.

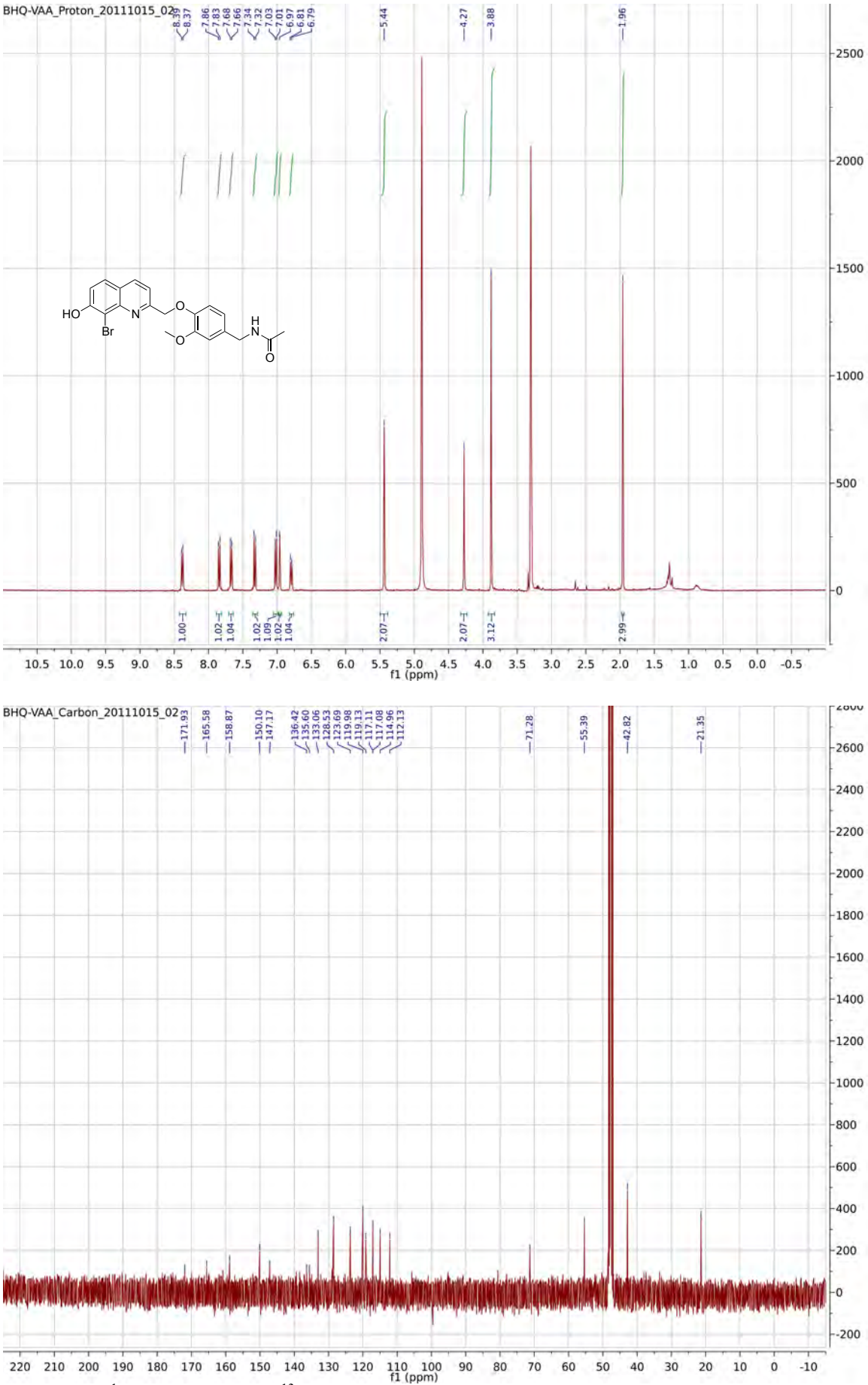

Figure S8. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **5a**.

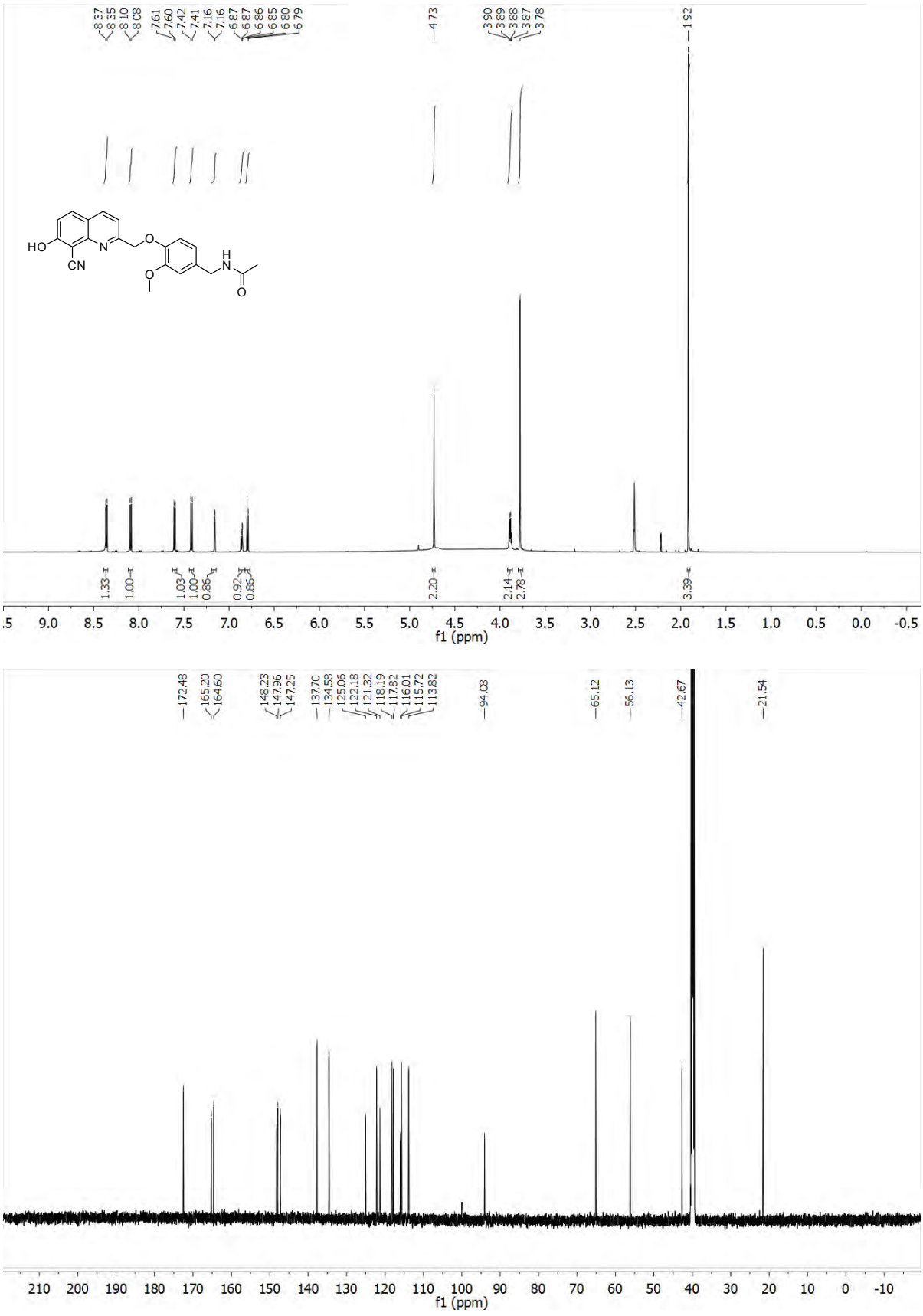

Figure S9. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **5b**.

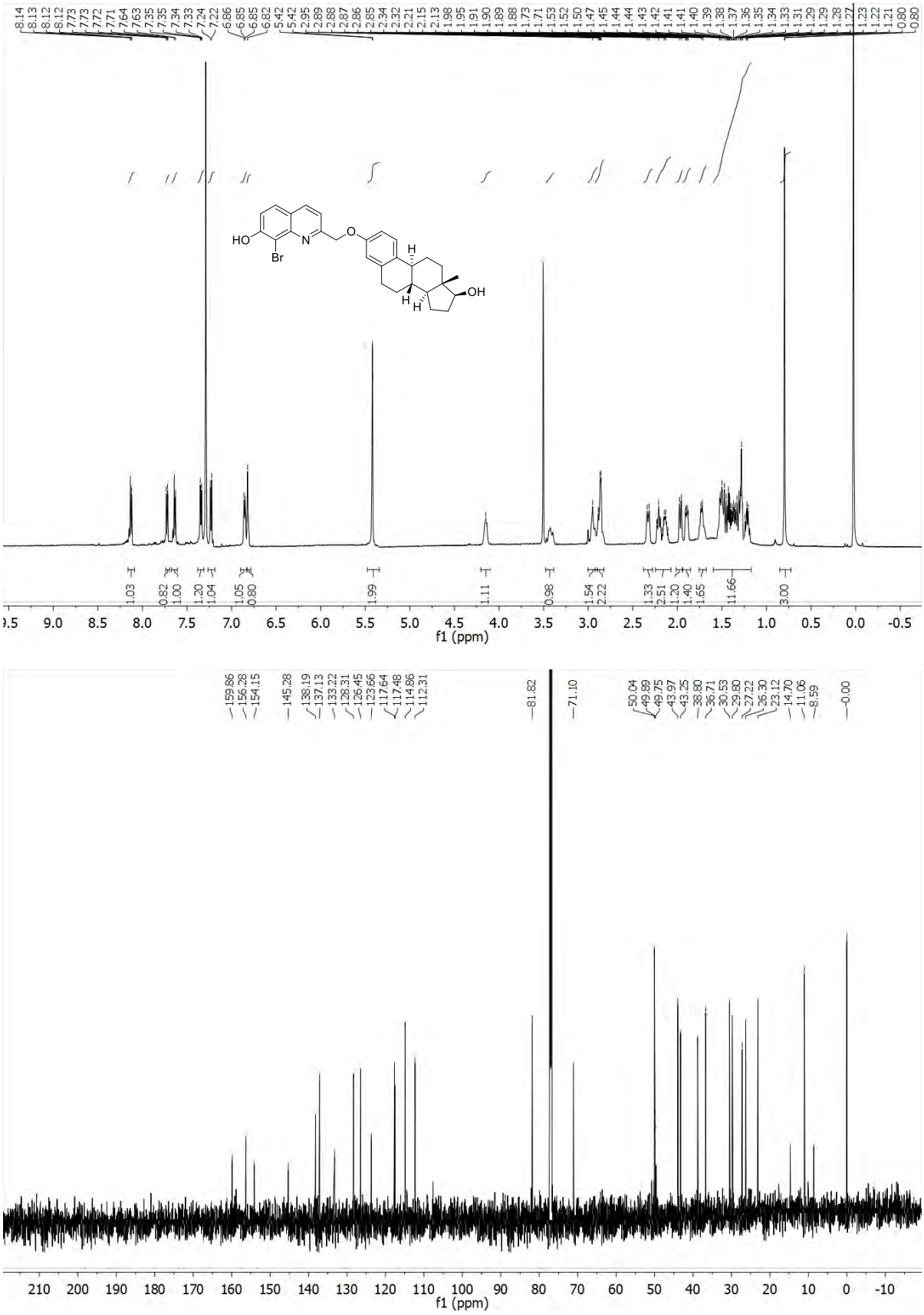

Figure S10. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **6a**.

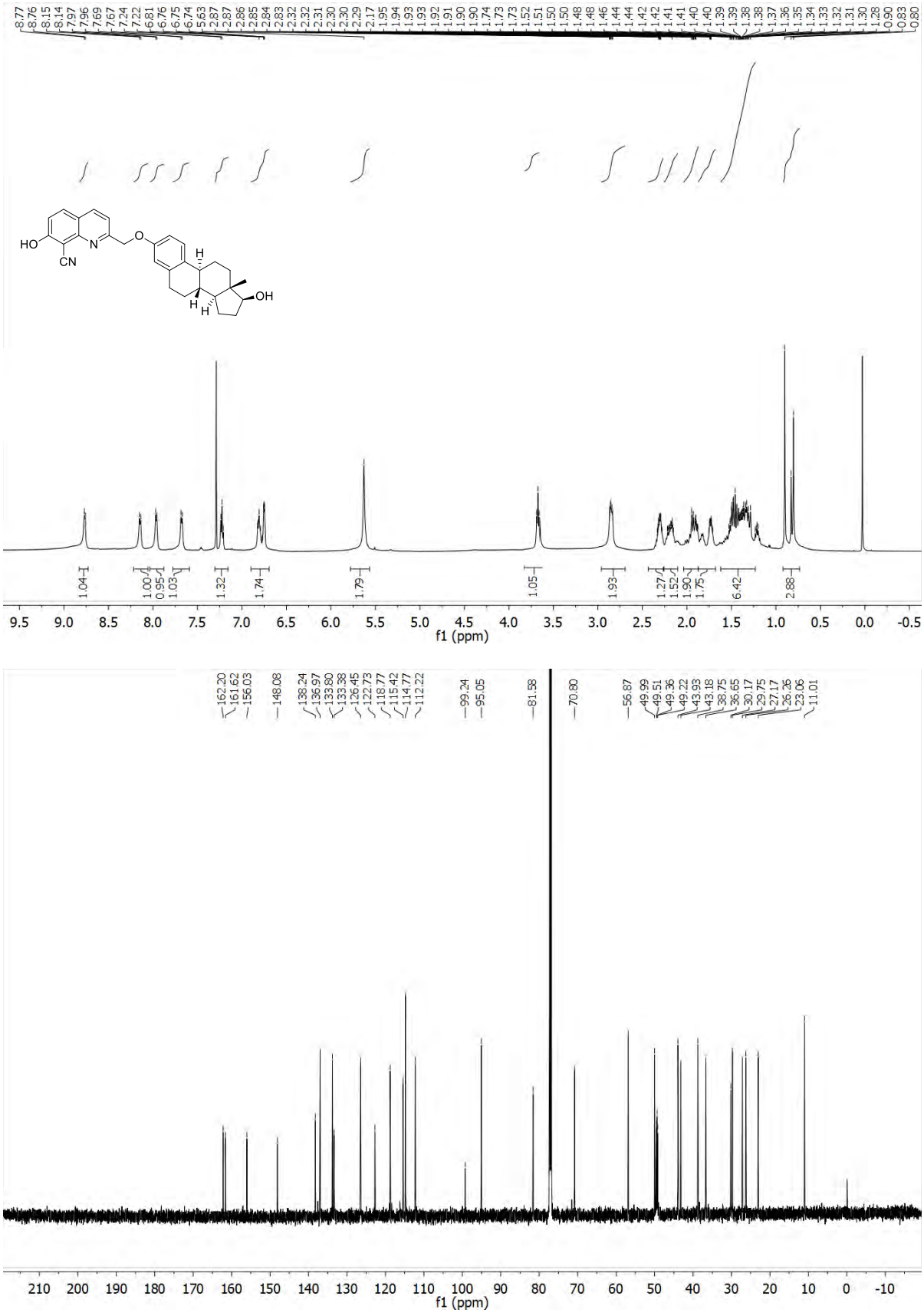

Figure S11. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **6b**.

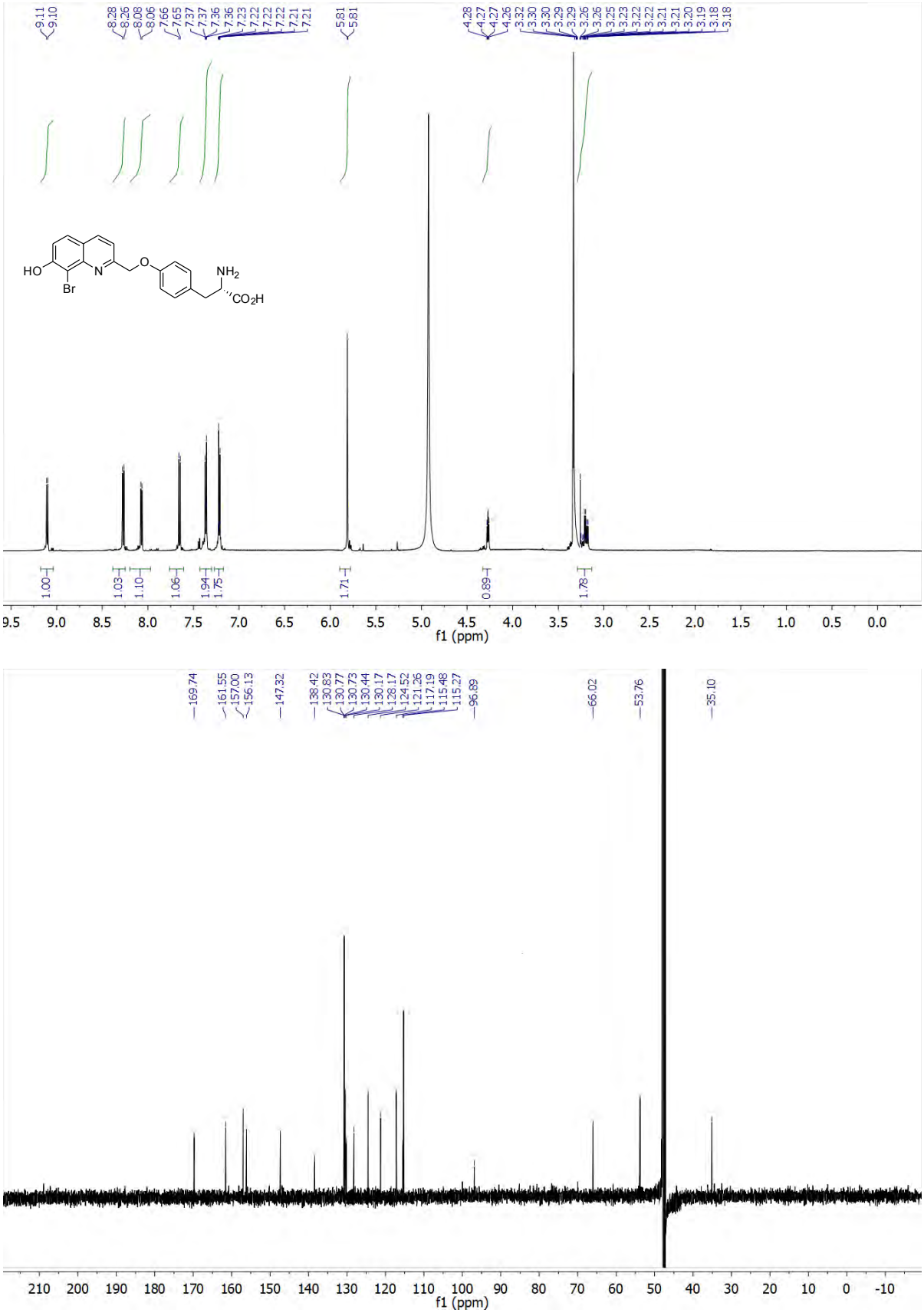

Figure S12. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **7a**.

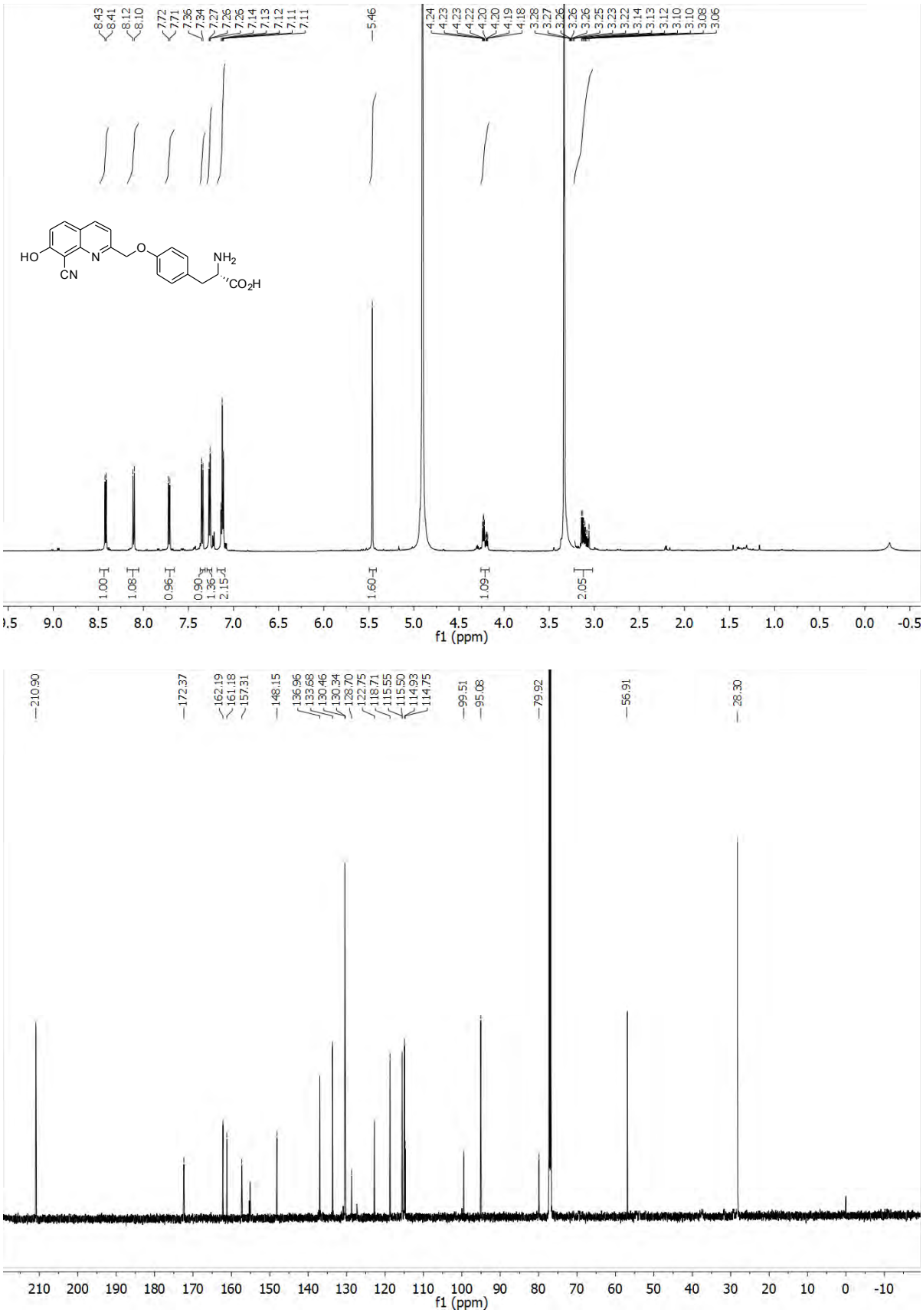

Figure S13. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **7b**.

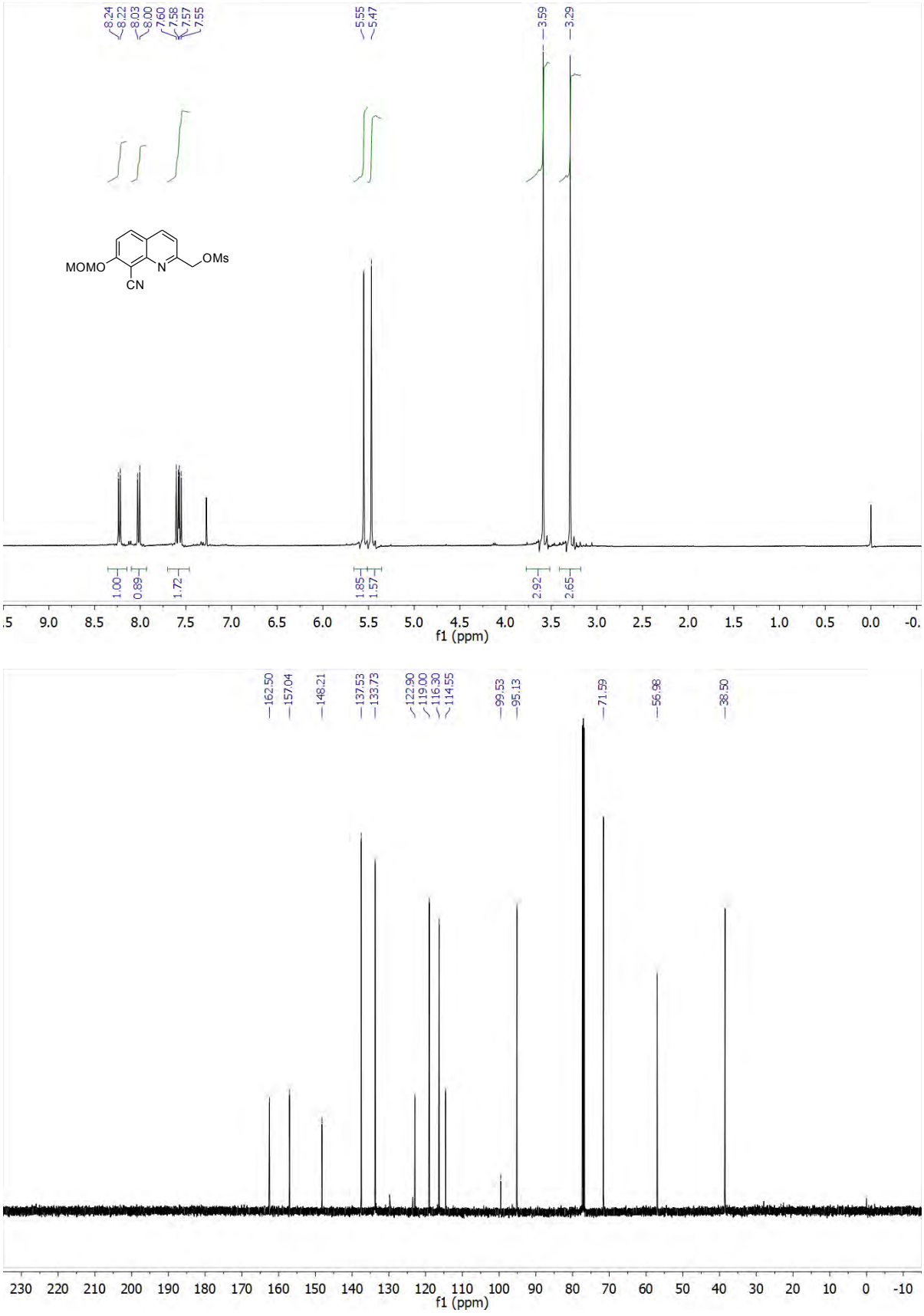

Figure S14. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **9b**.

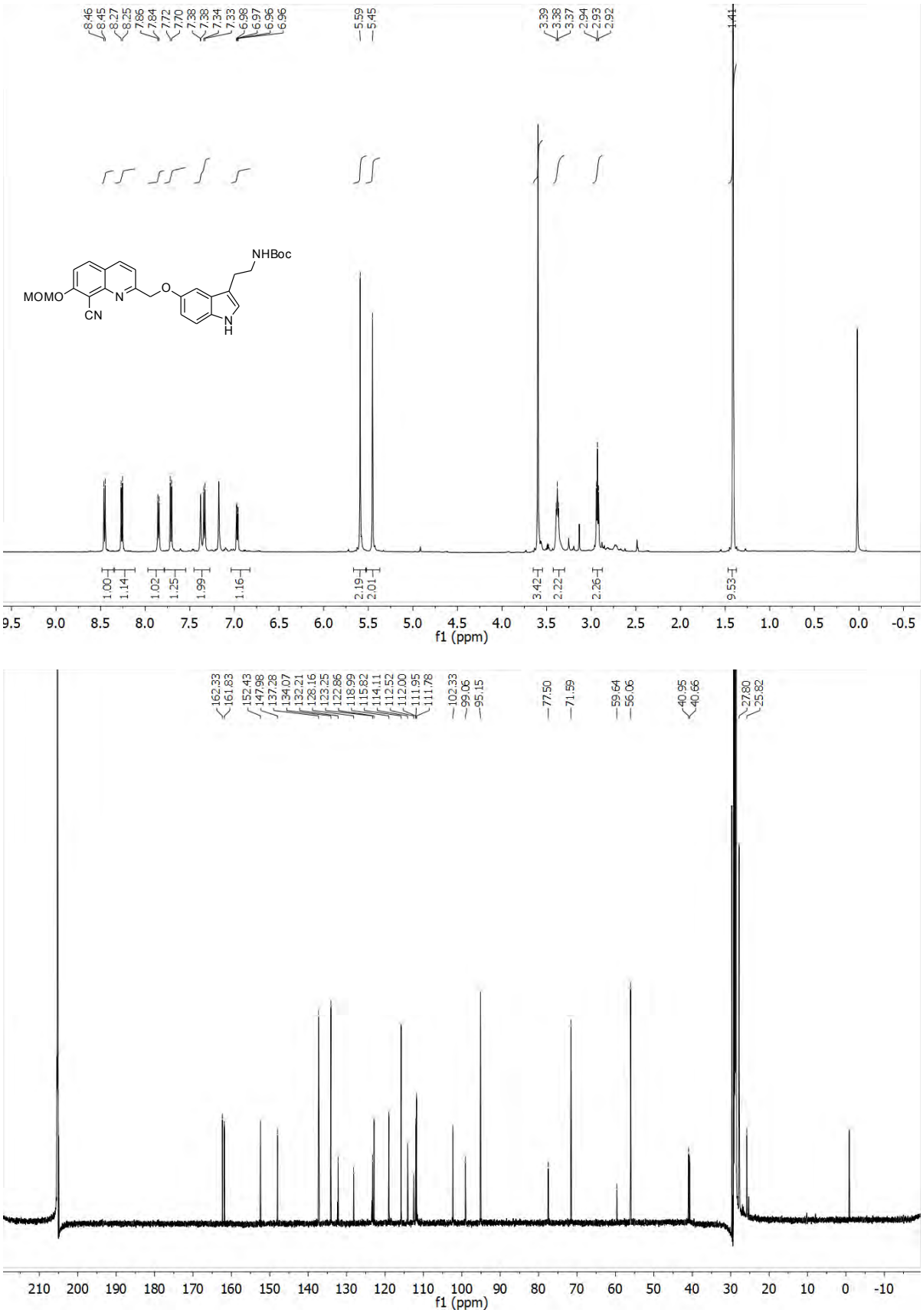

Figure S15. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **10b**.

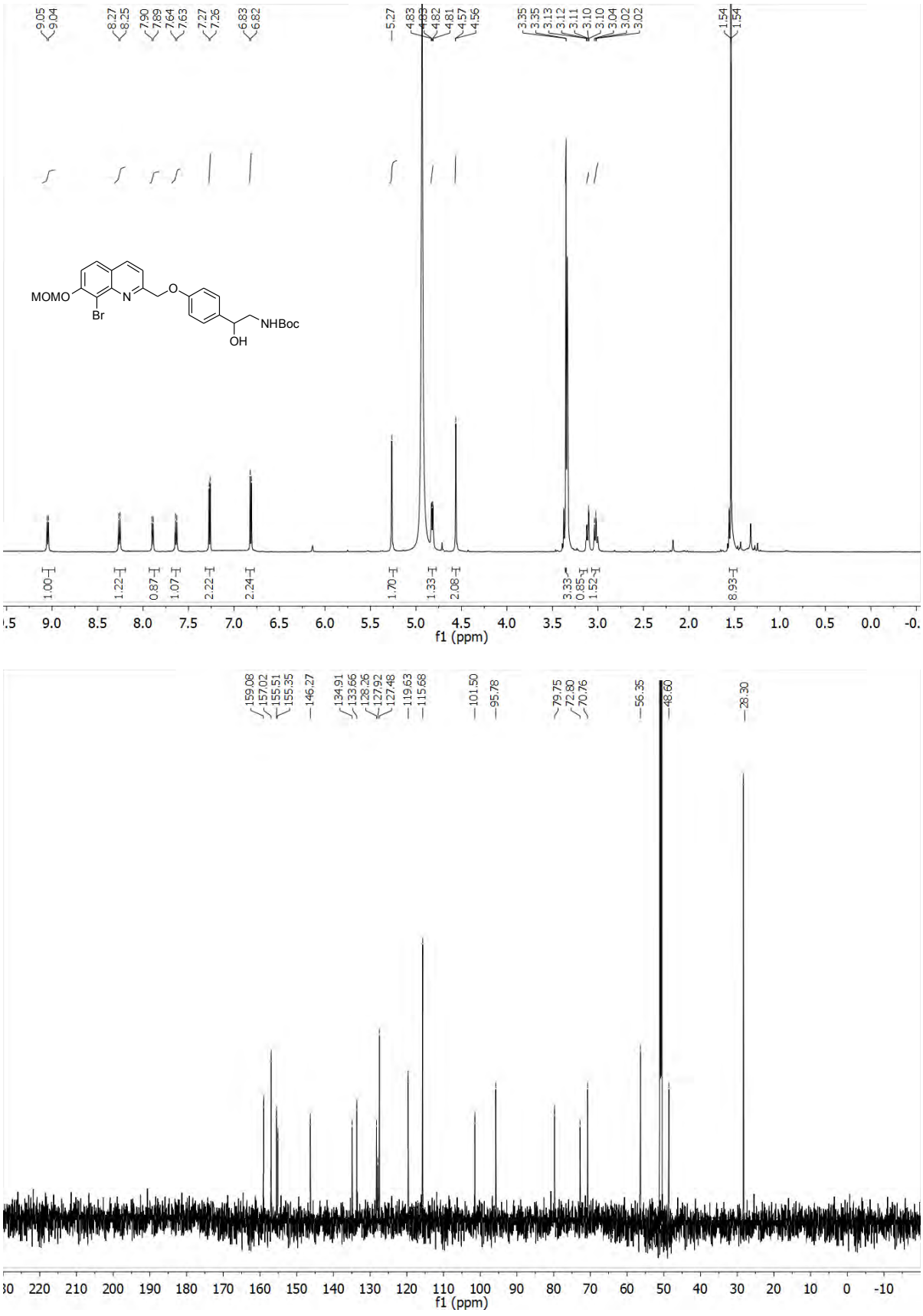

Figure S16. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **11a**.

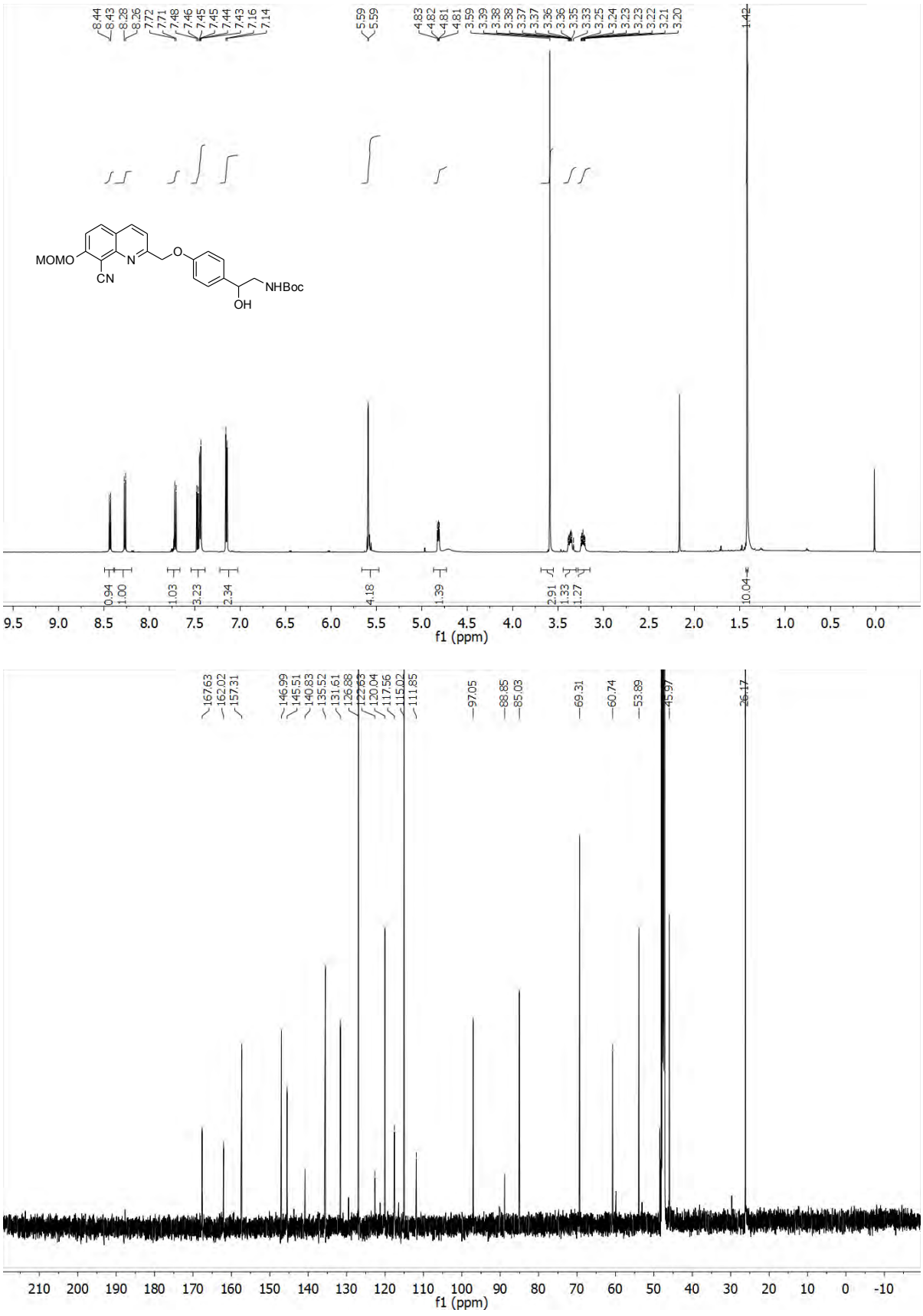

Figure S17. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **11b**.

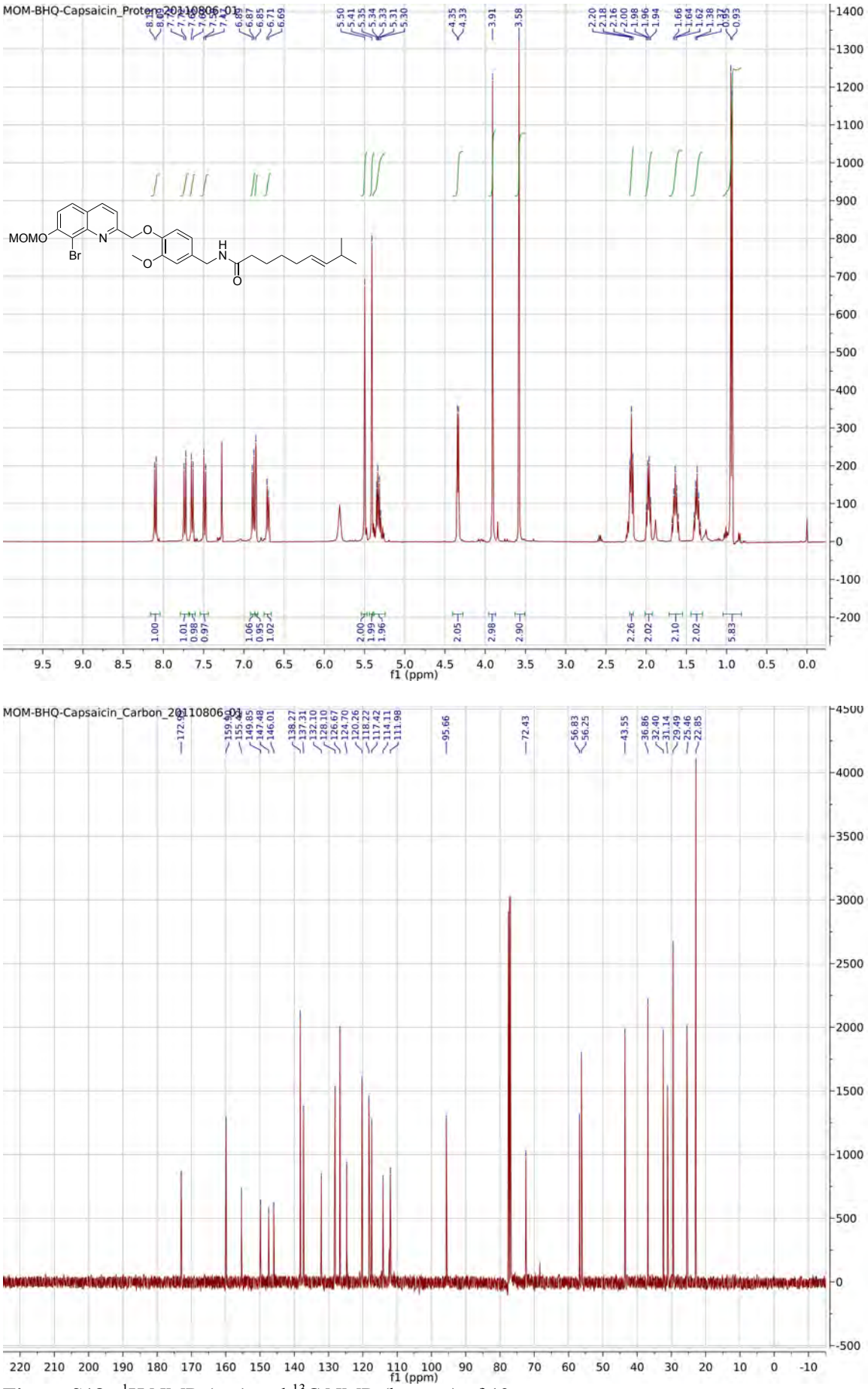

Figure S18. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **12a**.

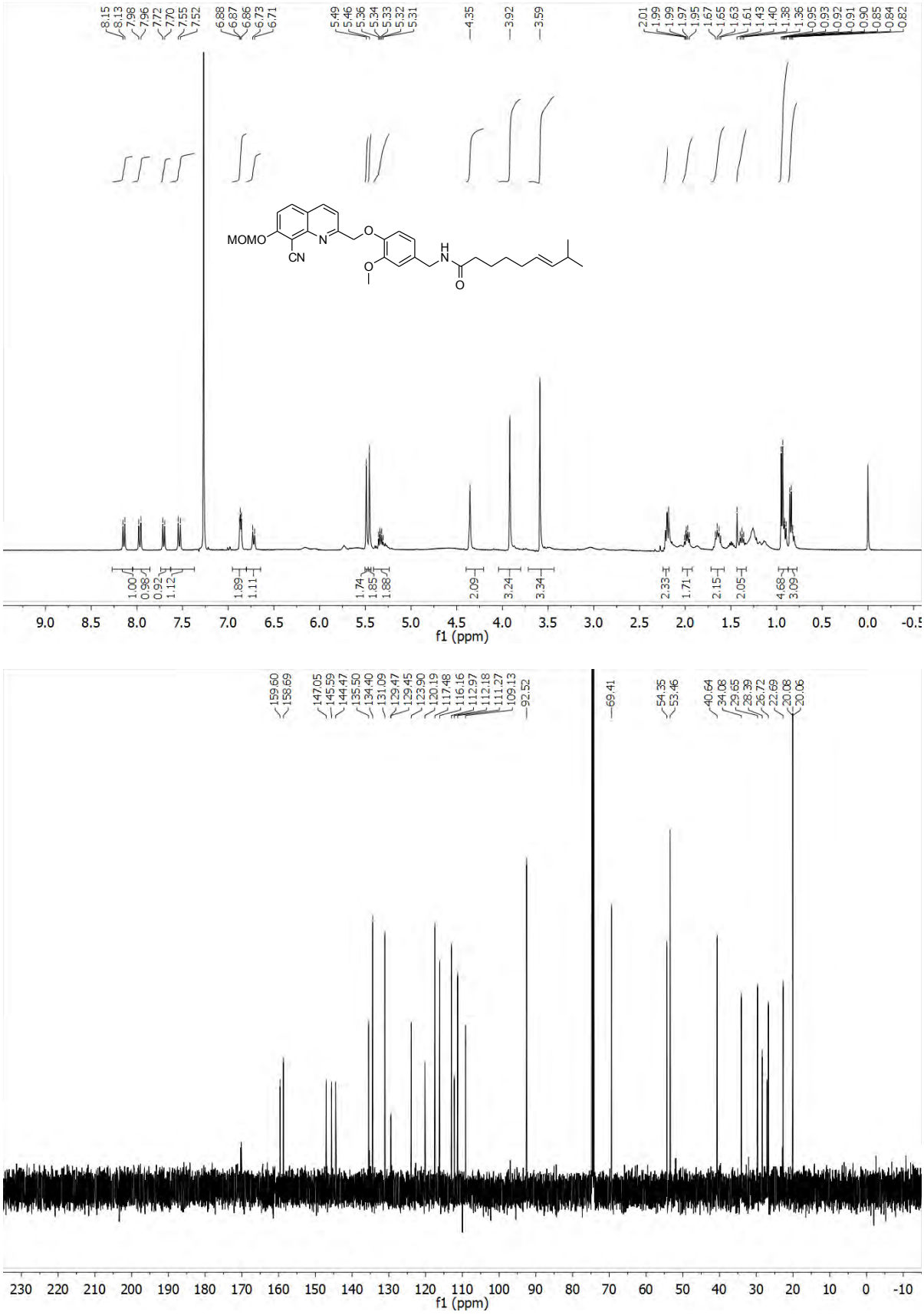

Figure S19. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **12b**.

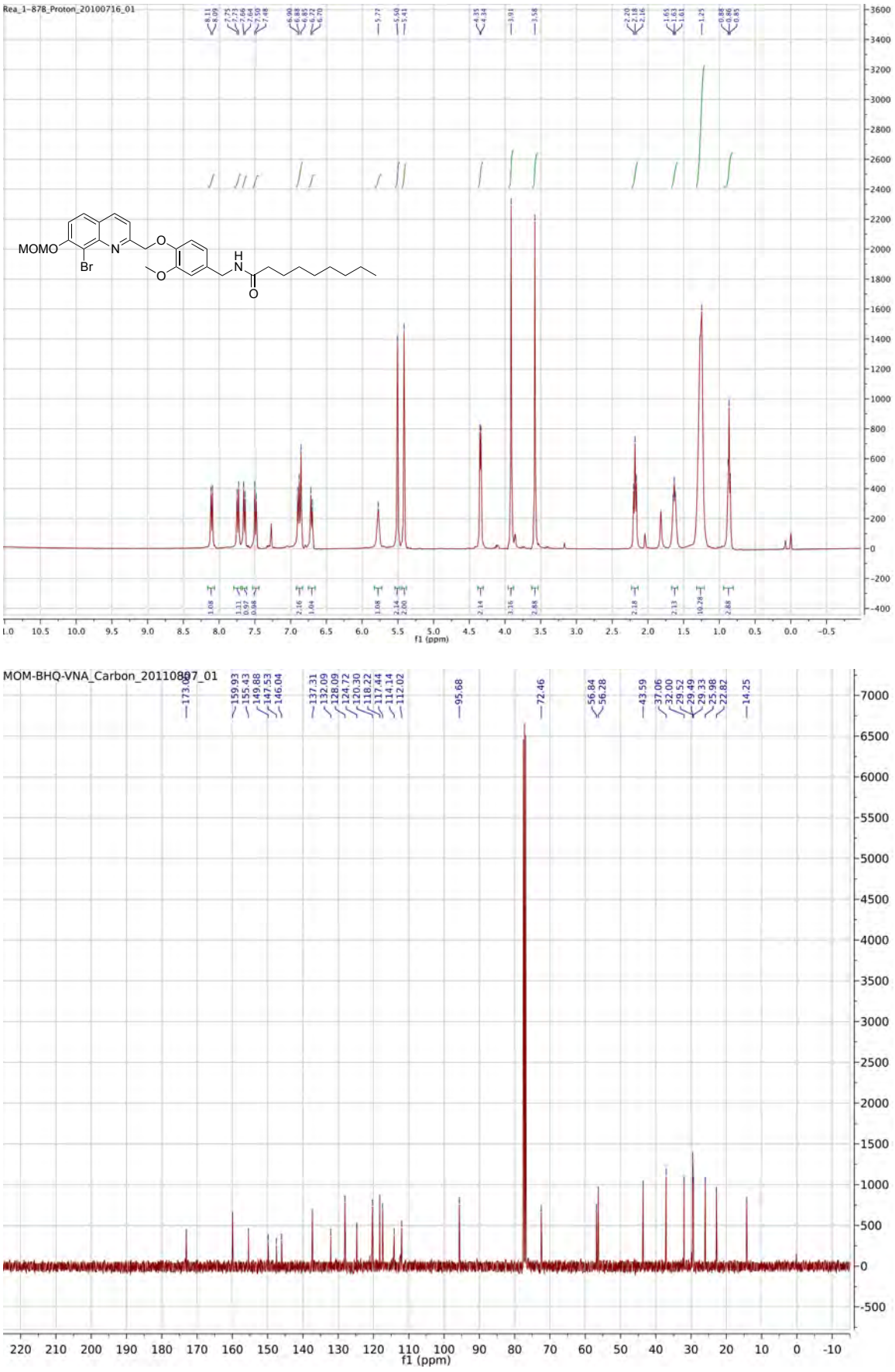

Figure S20. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **13a**.

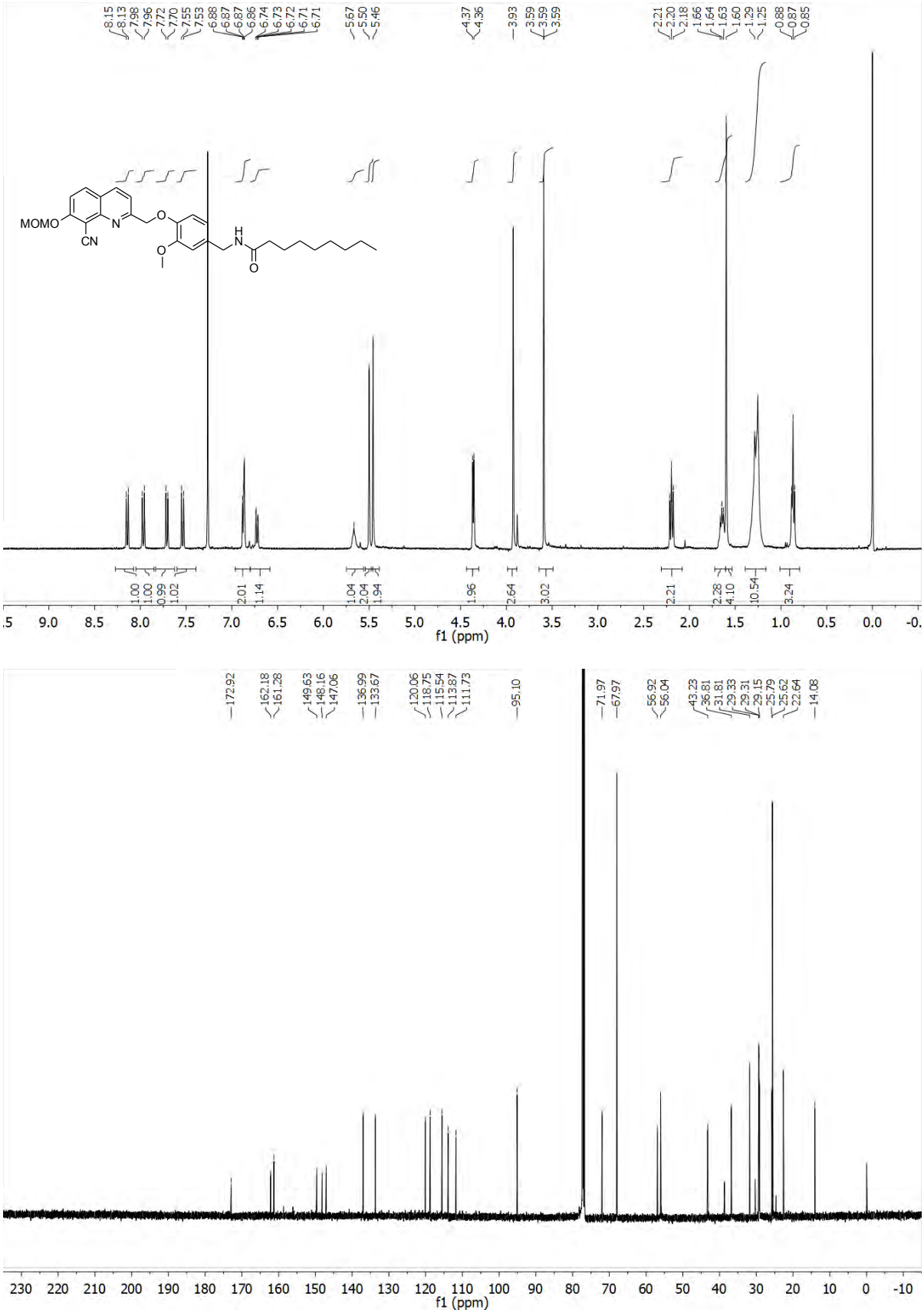

Figure S21. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **13b**.

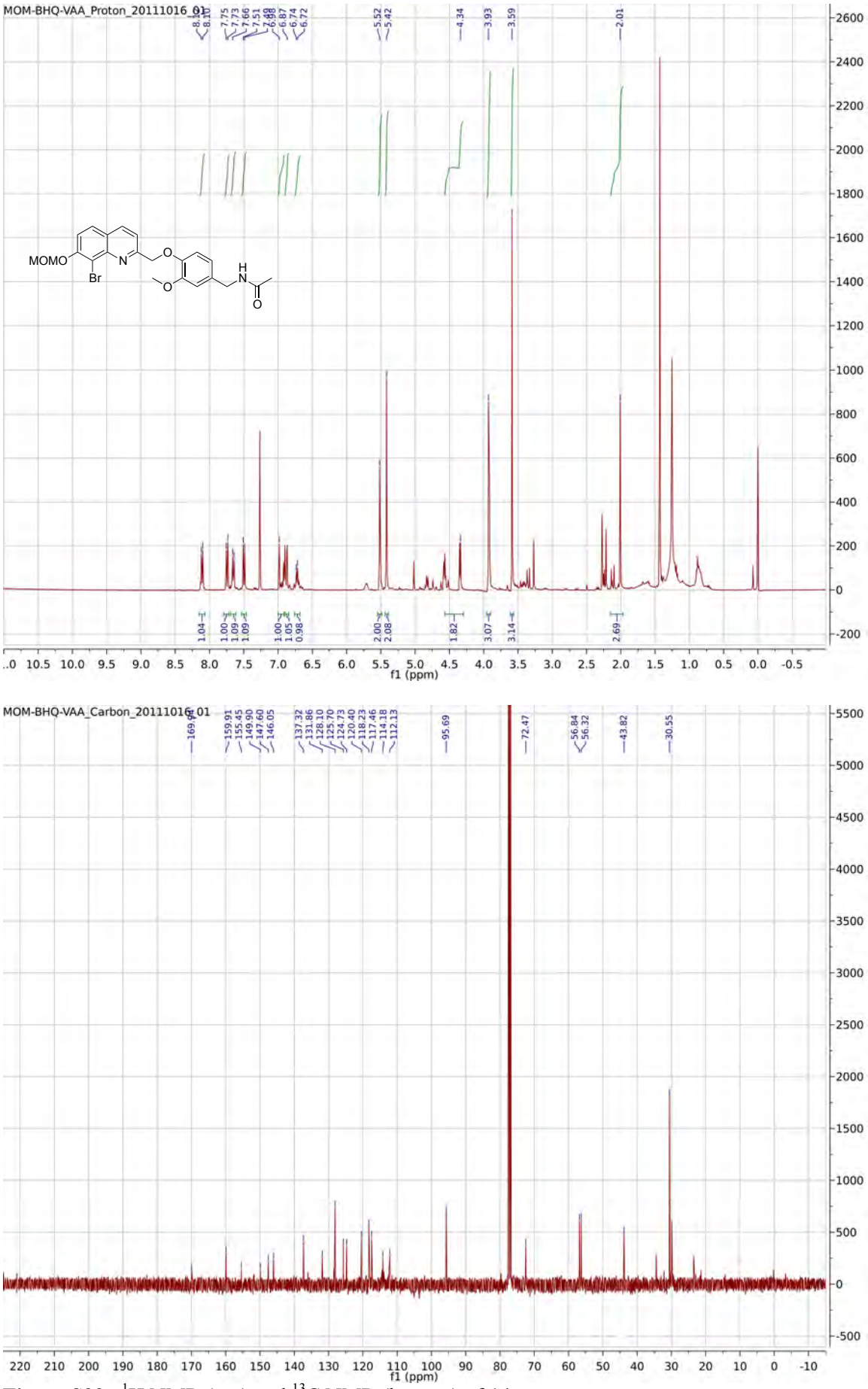

Figure S22. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **14a**.

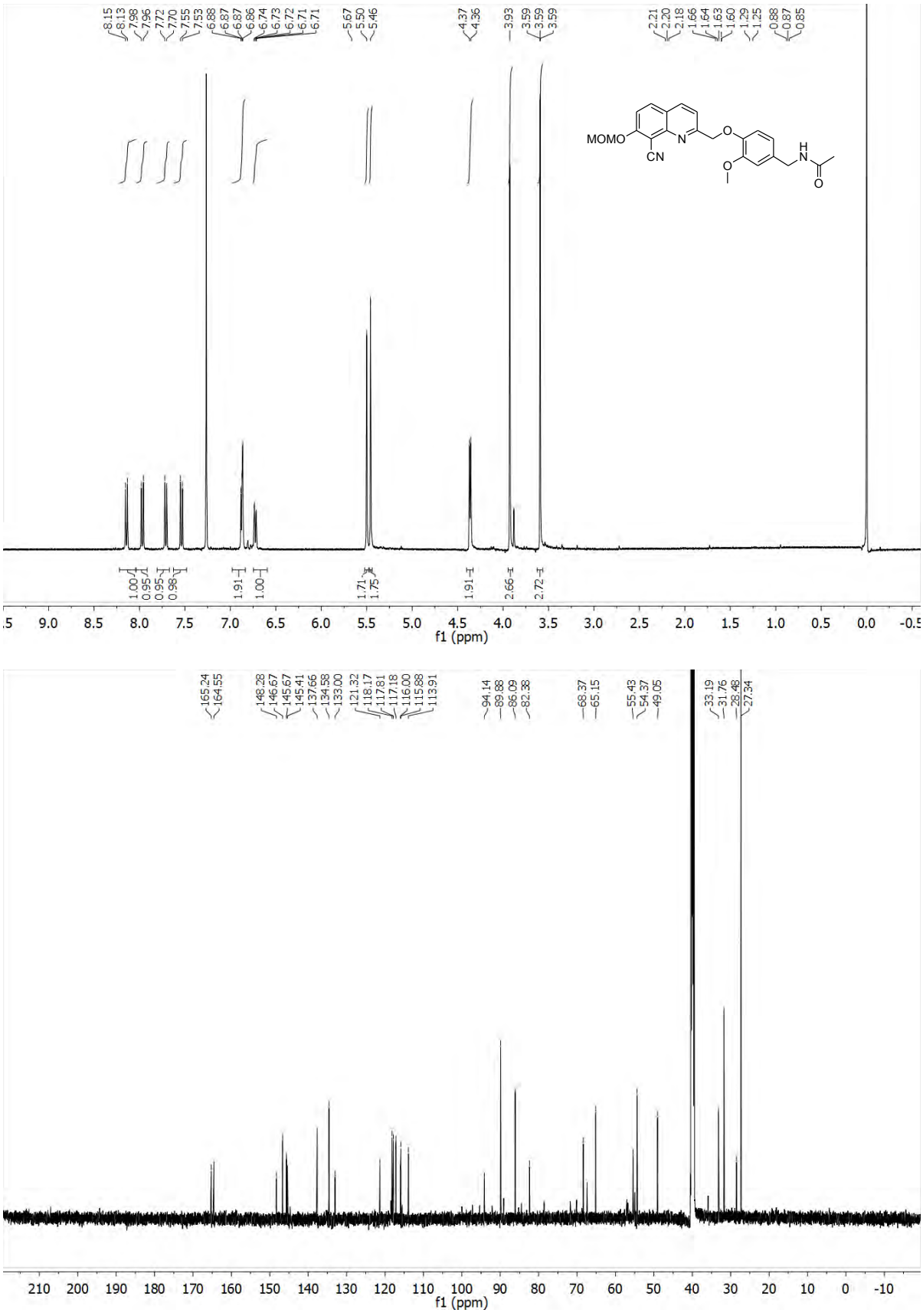

Figure S23. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **14b**.

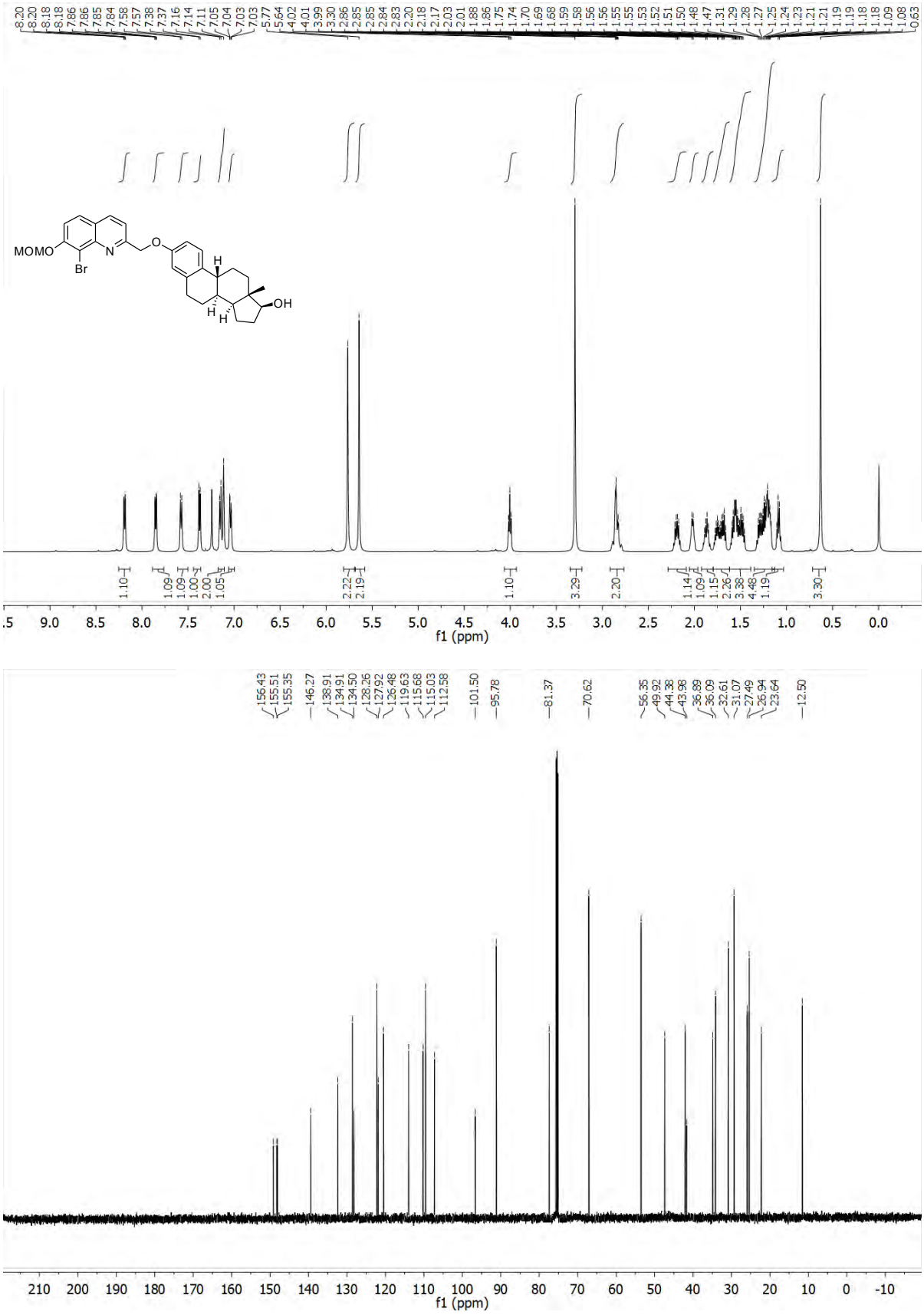

Figure S24. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **15a**.

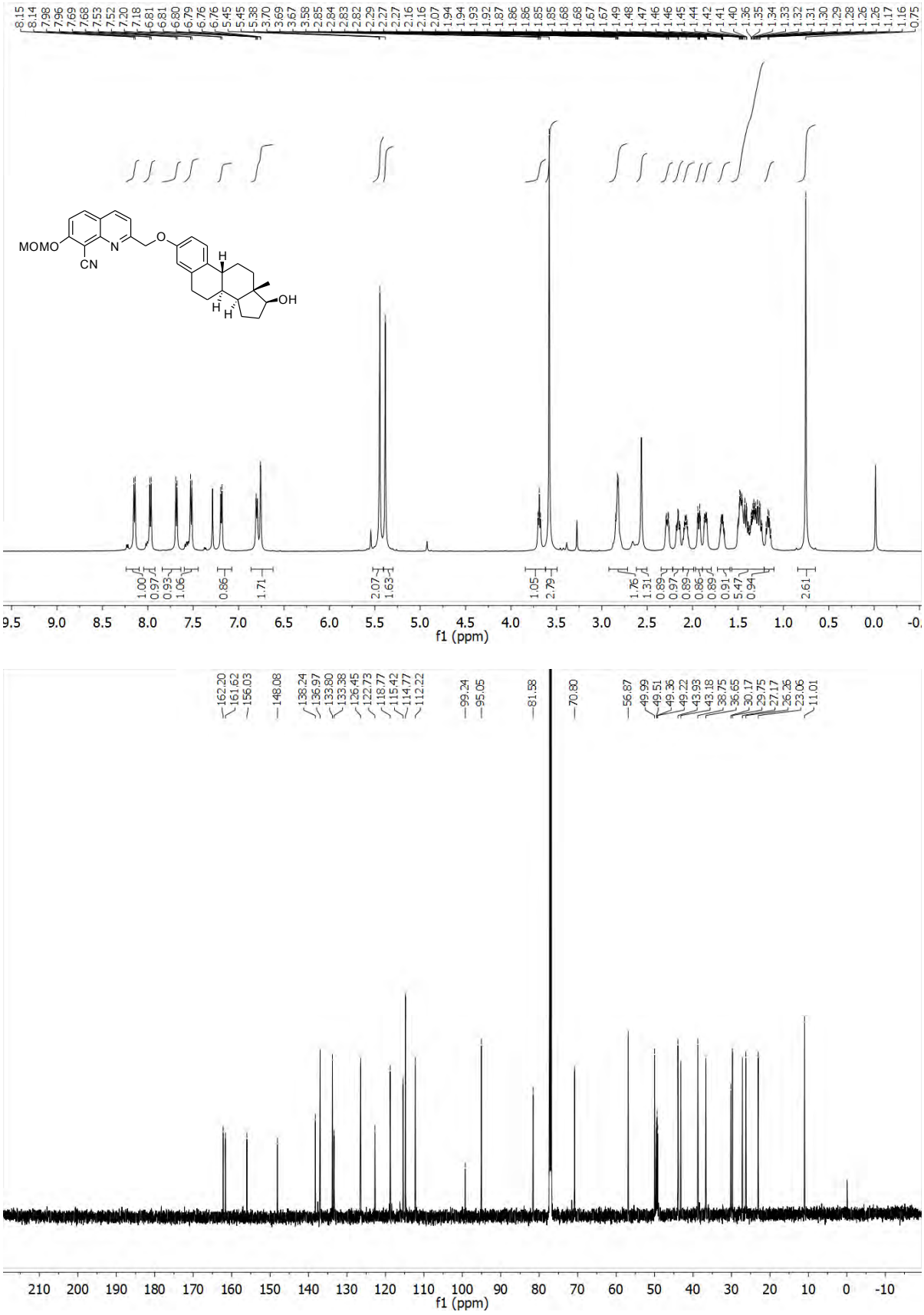

Figure S25. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **15b**.

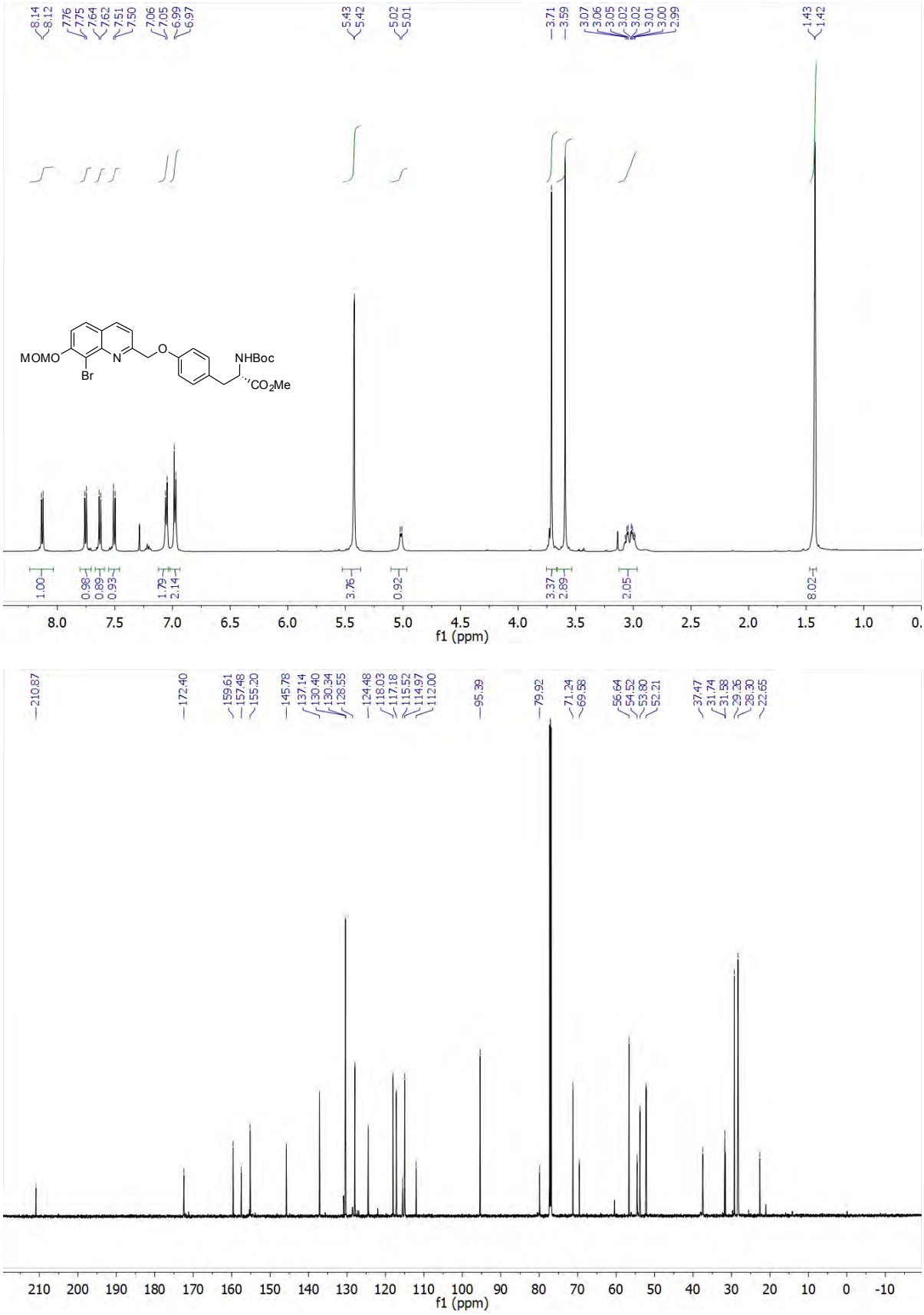

Figure S26. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **16a**.

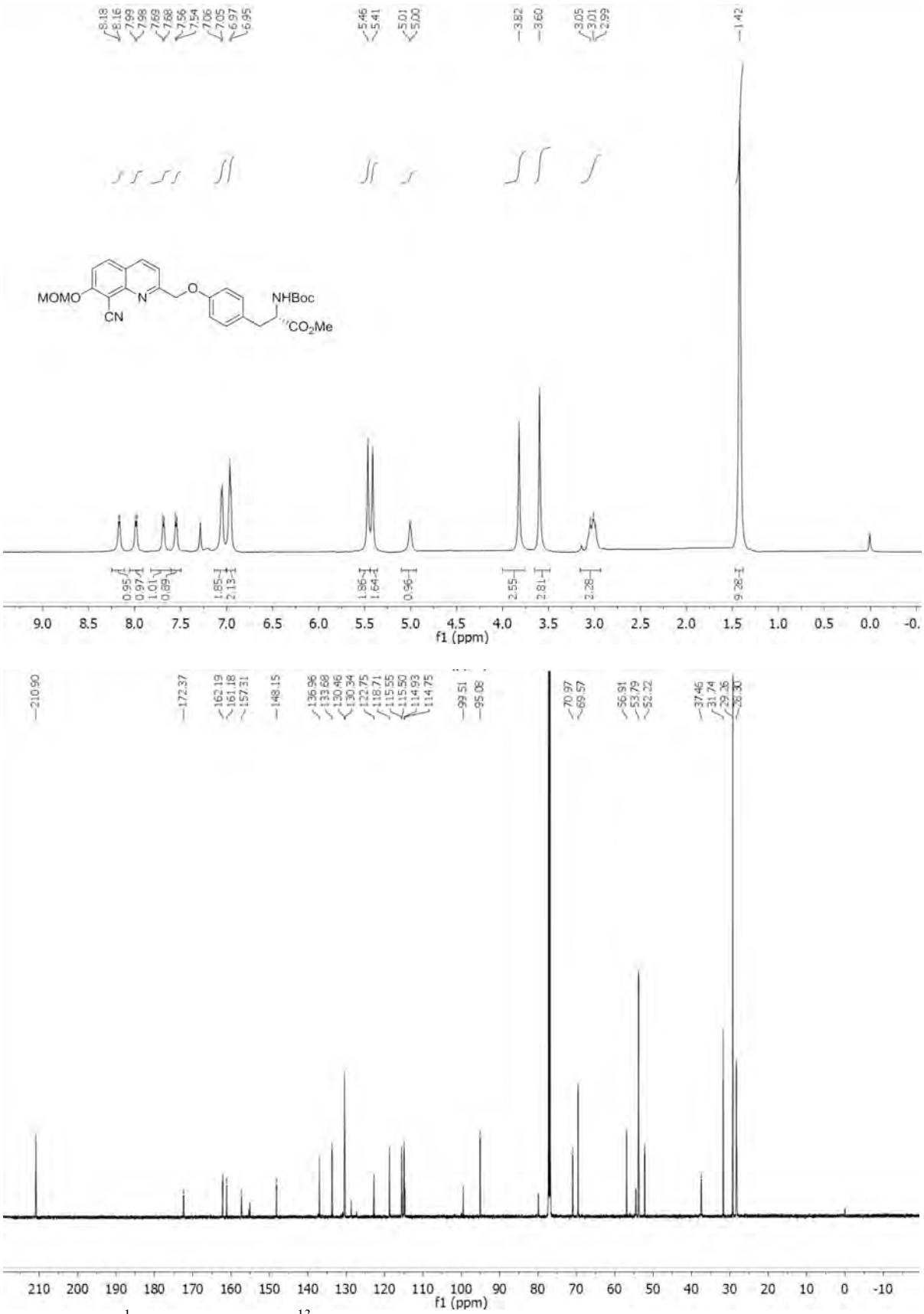

Figure S27. ^{1}H NMR (top) and ^{13}C NMR (bottom) of **16b**.

Determination of Molar Absorptivity Coefficient (ε)

UV-Vis spectra were acquired by analyzing solutions (100 μM) of the relevant substrate prepared as described for one-photon photolysis with a spectral window measuring from 240 to 400 nm. A blank sample of KMOPS was used as a baseline. This method was repeated three times and the three absorbencies measured were averaged and the molar absorptivity (ε) at λ = 370 nm was calculated according to the Beer-Lambert Law.

Determination of the Quantum Efficiency for One-Photon Photolysis

Solutions (100 μM) of the relevant substrate in KMOPS were irradiated in quartz cuvettes (21-Q-10, Starna, Atascadero, CA) with light from a mercury lamp (Spectroline SB-100P, Specronics) filtered through two glass filters (CS0-52 and CS7-60, Ace Glass) to restrict the wavelength to 365 ± 15 nm or a 365 ± 10 nm LED (OptoLED Lite, Cairn Research, UK). Aliquots (25 μL) were removed at various time points and analyzed by HPLC (Microsorb-MV 100-5 C18 250 × 4.6 mm column, Agilent) or uHPLC (Zorbax RRHD Eclipse XDB-C18, 2.1 × 150 mm column, Agilent) using an external standard to determine concentrations. Reaction progress was plotted and the data fit to a single exponential curve. The quantum efficiency (Q_u) of the photolysis was calculated using

$$Q_u = \left(I\sigma t_{90\%}\right)^{-1}$$

where I is the intensity (einstein·cm^{-2}·s^{-1}), σ is the decadic extinction coefficient (cm^2·mol^{-1}), and $t_{90\%}$ is the time at which 90% of the starting material has been consumed (s).[4]

Compound	Light Source	Method	Mobile Phase	Retention time (t_R)
BHQ-*O*-5HT (**1a**)	mercury lamp	HPLC	A	5.5 min
CyHQ-*O*-5HT (**1b**)	LED	uHPLC	B	2.4 min
BHQ-octopamine (**2a**)	LED	uHPLC	B	3.0 min
CyHQ-octopamine (**2b**)	LED	uHPLC	B	2.9 min
BHQ-VAA (**5a**)	mercury lamp	HPLC	C	8.9 min
CyHQ-VAA (**5b**)	LED	uHPLC	B	2.5 min
BHQ-estradiol (**6a**)	LED	uHPLC	B	5.9 min
CyHQ-estradiol (**6b**)	LED	uHPLC	B	5.7 min
BHQ-tyrosine (**7a**)	LED	uHPLC	B	2.8 min
CyHQ-tyrosine (**7b**)	LED	uHPLC	B	2.7 min

Mobile phase A: Isocratic, 40% CH_3CN/60% H_2O (0.1% TFA), 1 mL/min flow rate
Mobile phase B: Gradient of 5% CH_3CN/95% H_2O (0.1% TFA) to 100% CH_3CN over 6 min, 100% CH_3CN for 2 min, 0.3 mL/min flow rate, 35 °C column temperature
Mobile phase C: Isocratic, 30% CH_3CN/70% H_2O (0.1% TFA), 1 mL/min flow rate

The intensity (I) of the LED was measured by potassium ferrioxalate actinometry.[5] A 6 mM solution of potassium ferrioxalate (3 mL) was irradiated with the light source for 30 or 60 s. A portion of this solution (2 mL) was combined with aqueous buffer (3 mL), 0.1% phenanthroline solution (3 mL), and 2 M KF solution (1 mL) in a 25-mL volumetric flask. Deionized water was added to generate a 25-mL solution. A blank solution was also prepared using the same method, but the potassium ferrioxalate used in the blank was not irradiated. Both solutions rested for 1 h, and the blank was then used as a baseline against which the absorbance of the irradiated solution was measured at 510 nm. The following equation was used to calculate lamp intensity:

$$I = \frac{V_3 \Delta D_{510}}{1000 \varepsilon_{510} V_2 \Phi_{Fe} t}$$

where V_3 is the volume of the diluted sample (25 mL), ΔD_{510} is the change in absorption at 510 nm, ε_{510} is the extinction coefficient of the actinometry solution (1.11 × 10^4 M^{-1} cm^{-1}), V_2 is the volume of the potassium ferrioxalate solution taken for analysis (2 mL), Φ_{Fe} is the quantum yield for the production of ferrous ions from potassium ferrioxalate at 365 nm (1.26), and t is the irradiation time.

Determination of the Two-Photon Uncaging Action Cross-Section

Solutions (100 μM) of the substrates in KMOPS were prepared and stored in the dark. Aliquots (25 μL) of this solution were placed in a microcuvette (10 × 1 × 1 mm illuminated dimensions, 25 μL effective filling volume) and irradiated with a fs-pulsed and mode-locked Ti:Sapphire laser (Chameleon Ultra II, Coherent or a Mai Tai HP DeepSee, Spectra-Physics) with 740-nm light at an average power of 220-300 mW. Three samples of each substrate were irradiated for various time periods and analyzed by HPLC or uHPLC as described for one-photon experiments.

A solution of fluorescein at pH 9.0 was prepared to act as a standard because of its well-characterized 2PE cross-section (δ_{aF} = 30 GM at 740 nm)[6] and quantum yield (Φ_{F2} = 0.9).[7, 8] UV-Vis absorption spectroscopy was used to verify concentration. Aliquots (25 μL) of fluorescein solution were placed in the microcuvette and irradiated by the laser under the same conditions used for the caged compounds. The fluorescence output of the solution was measured at a right angle to the incident laser beam with a radiometer (IL-1700 with SED033 detector, International Light) before and after the caged compound samples were irradiated and the two values were averaged to determine the time-averaged fluorescent photon flux ($<F(t)>$, photons/s). The following equation was used to calculate the two-photon action cross-section (δ_u)for each compound:

$$\delta_u = \frac{N_P \phi Q_{F2} \delta_{aF} C_F}{<F(t)> C_S}$$

N_P: number of product molecules formed per unit time (molecules/s) determined by uHPLC
ϕ: collection efficiency of the detector
Q_{F2}: quantum yield of fluorescein at pH 9.0 – 11.0 (0.9)
δ_{aF}: 2-Photon fluorescence cross-section of fluorescein at 740 nm (30 GM)
C_F: concentration of fluorescein (μM)
$<F(t)>$: time averaged fluorescent photon flux (photon/s)
C_s: concentration of substrate (μM)

The collection efficiency of the detector (ϕ) is calculated with the following equation

$$\phi = \frac{Ay}{4\pi R^2 n^2}$$

A: area of detector (0.33 cm^2)
y: fraction of integrated emission spectrum transmitted to the detector by the interference filter (0.465)
R: distance from the center of the cuvette to the detector
n: refractive index of water (1.33)

The number of product molecules formed per unit time N_p was calculated with the following equation:

$$N_P = \frac{C_S V_S A' - H C_S V_S A'}{t}$$

C_s: concentration of substrate (μM)
V_s: volume of substrate (25 μL)
A': 6.022×10^{23} molecules/mol
H: fraction of substrate remaining
t: time (s)

The time averaged photon flux $<F(t)>$ was calculated with the following equation:

$$<F(t)> = \frac{FA\lambda}{rhc}$$

F: fluorescence reading on radiometer (A)
A: area of detector (0.33 cm^2)
λ: wavelength (535×10^{-9} m)

r: spectral response of the detector (0.09385 or 0.0276 $A \cdot cm^{-2} \cdot W^{-1}$ at 535 nm for the Coherent or Spectra-Physics set-ups, respectively)

h: Plank's constant (6.63×10^{-34} J·s)

c: speed of light (3.00×10^{8} m/s)

Time Courses of Photolysis

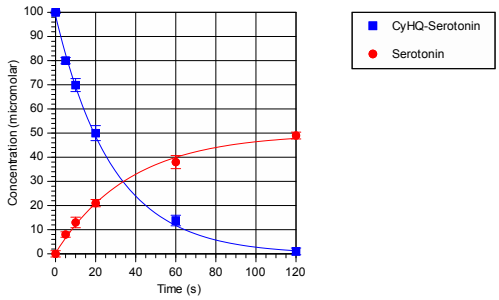

Figure S28 1PE Photolysis of CyHQ-*O*-5HT

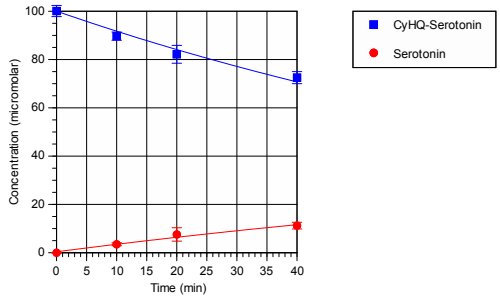

Figure S29 2PE Photolysis of CyHQ-*O*-5HT

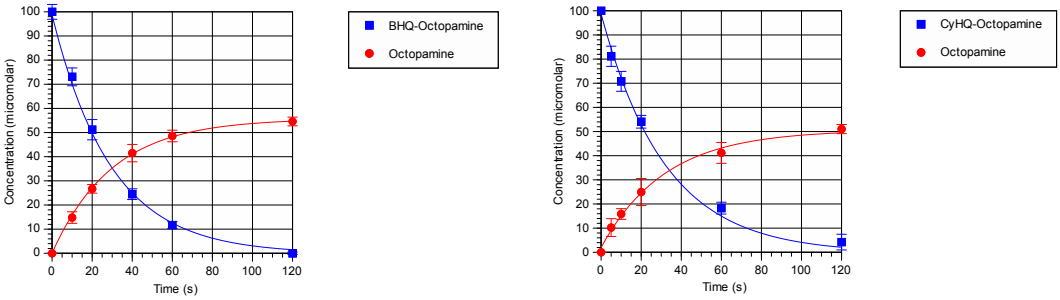

Figure S30 1PE Photolysis of BHQ-octopamine (left) and CyHQ-octopamine (right)

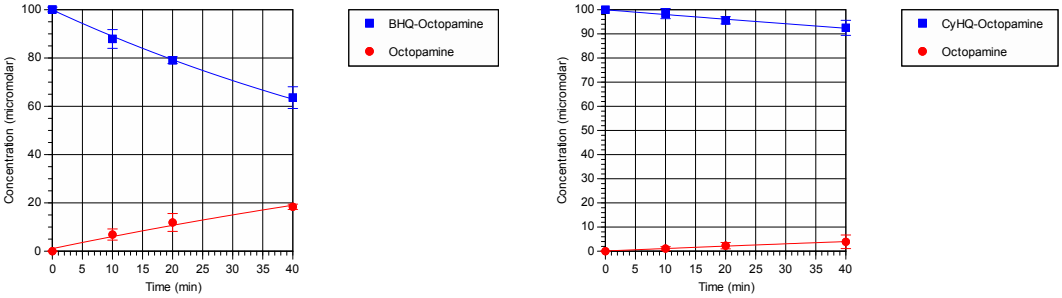

Figure S31 2PE Photolysis of BHQ-octopamine (left) or CyHQ-octopamine (right)

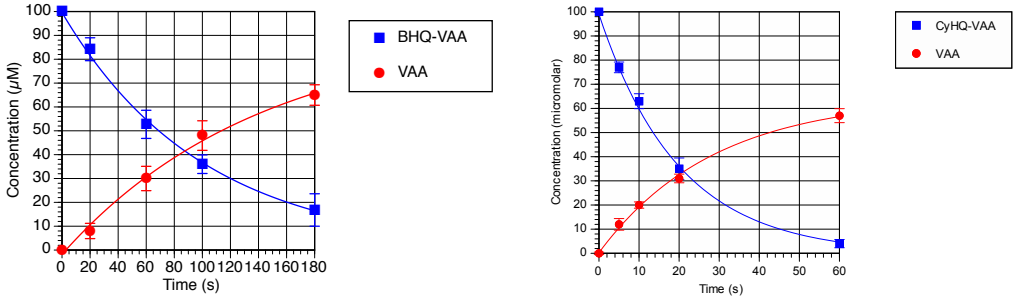

Figure S32 1PE Photolysis of BHQ-VAA (left) and CyHQ-VAA (right)

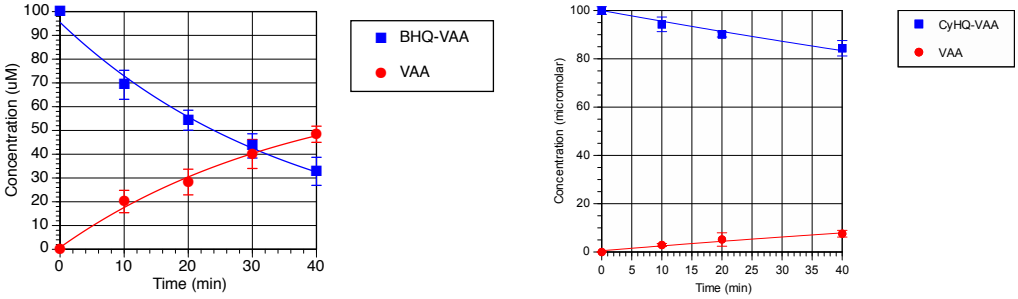

Figure S33 2PE Photolysis of BHQ-VAA (left) and CyHQ-VAA (right)

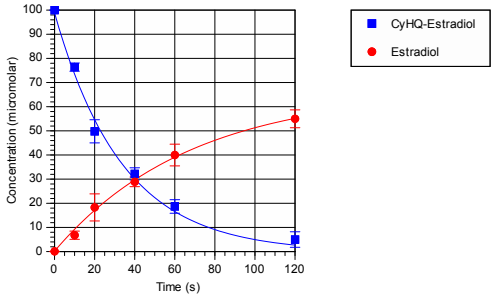

Figure S34 1PE Photolysis of CyHQ-estradiol

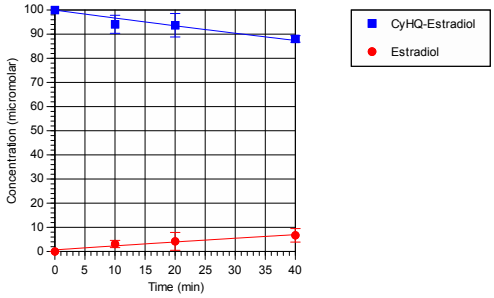

Figure S35 2PE Photolysis of CyHQ-estradiol

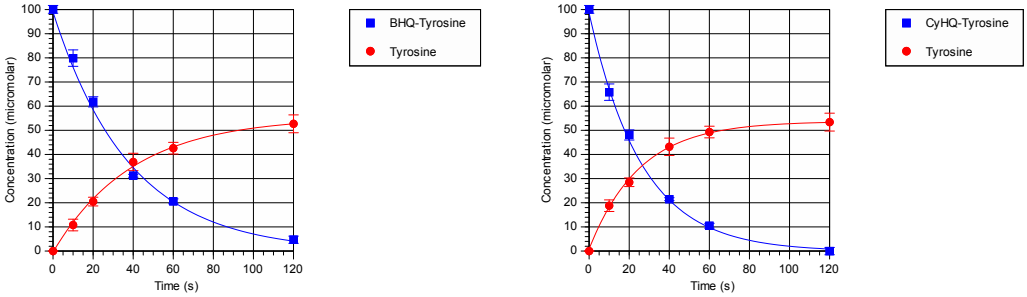

Figure S36 1PE Photolysis of BHQ-tyrosine (left) and CyHQ-tyrosine (right)

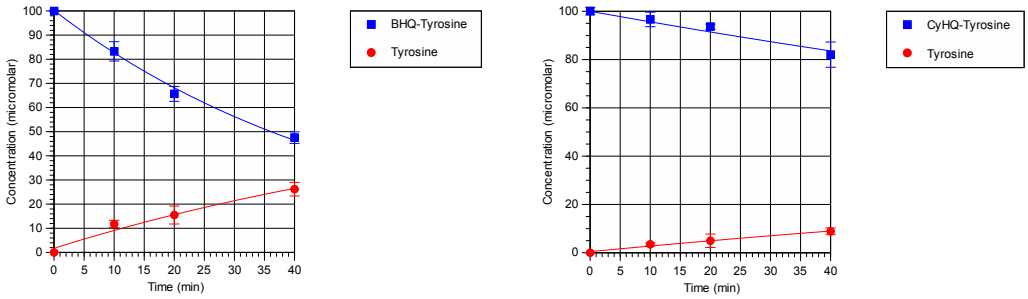

Figure S37 2PE Photolysis of BHQ-tyrosine (left) and CyHQ-tyrosine (right)

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