Electronic Supplementary Material (ESI) for ChemComm.

Electronic Supplementary Information

Divergent reactivity of an indole glucosinolate yields Lossen or Neber rearrangement products: the phytoalexin rapalexin A or a unique β-D-glucopyranose fused heterocycle

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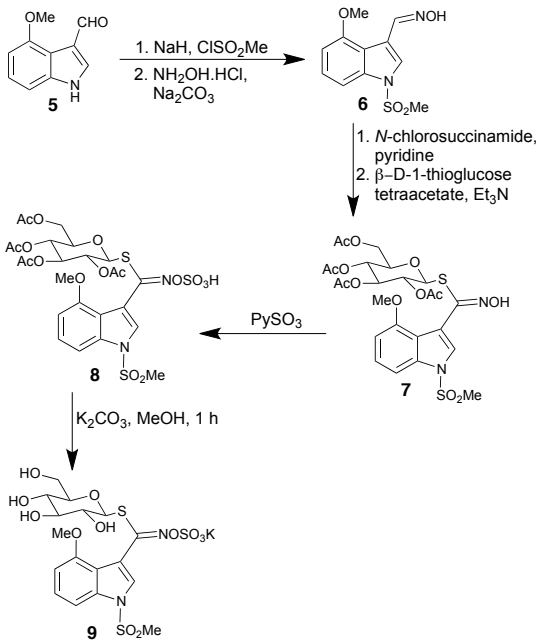
1. General experimental

Solvents were HPLC grade and used as such. Flash column chromatography (FCC) was carried out using silica gel grade 60, mesh size 230–400 Å or WP C18 prep-scale bulk packing 275 Å (J.T. Baker, NJ, USA). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker 500 MHz Avance spectrometers (for ^{1}H, 500.3 MHz and for ^{13}C, 125.8 MHz); chemical shifts (δ) are reported in parts per million (ppm) relative to TMS; spectra were calibrated using solvent peaks; spin coupling constants (J) are reported to the nearest 0.5 Hz. Fourier transform infrared (FTIR) data were recorded on a spectrometer Bio-Rad FTS-40 and spectra were measured by the diffuse reflectance method on samples dispersed in KBr. MS data [high resolution (HR), electron impact (EI)] were obtained on a VG 70 SE mass spectrometer employing a solids probe, or on a Jeol AccuToF GCv 4G mass spectrometer [field desorption (FD)] by direct insertion. HPLC-DAD analysis was carried out with Agilent 1100 and 1200 series systems equipped with quaternary pumps, autosamplers, diode array detectors (DAD, wavelength range 190–600 nm, bandwidth 4 nm), degassers and Zorbax Eclipse XDB-C18 columns (5 μL particle size silica, 150 x 4.6 mm I.D.), equipped with an in-line filter. Method A (non-polar metabolites) used the mobile phase H_2O–CH_3CN from 75:25 to 25:75, linear gradient for 35 min, and a flow rate of 1.0 mL/min; method B (polar metabolites) used the mobile phase H_2O–CH_3CN from 100:0 to 50:50 linear gradient for 25 min, followed by 50:50 to 25:75 linear gradient for 10 min and a flow rate of 1.0 mL/min. HPLC-DAD-ESI-MS analysis was carried out with an Agilent 1100 series HPLC system equipped with an autosampler, binary pump, degasser, and a diode array detector connected directly to a mass detector (Agilent G2440A MSD-Trap-XCT ion trap mass spectrometer) with an electrospray ionization (ESI) source. Chromatographic separations were carried out at room temperature using an Eclipse XDB-C-18 column (5 μL particle size silica, 150 mm x 4.6 mm I.D.). The mobile phase (method C) consisted of a linear gradient of H_2O (containing 0.2% HCO_2H) – CH_3CN (containing 0.2% HCO_2H) from 75:25 to 25:75 in 25 min and a flow rate of 1.0 mL/min. Data acquisition was carried out in positive and negative polarity modes in a single LC run, and data processing was carried out with Agilent Chemstation Software.

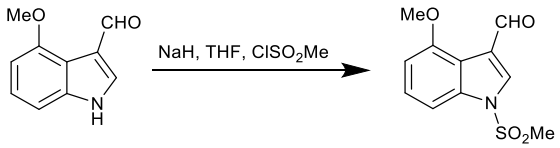
2. Compound synthesis and characterization

*2.1 Synthesis of 1-MeSO$_2$-glucorapassicin A (**9**)*



Scheme 1S Synthesis of 1-MeSO$_2$-glucorapassicin A (**9**).

1-MeSO$_2$-4-methoxyindole-3-carboxaldehyde (5a)

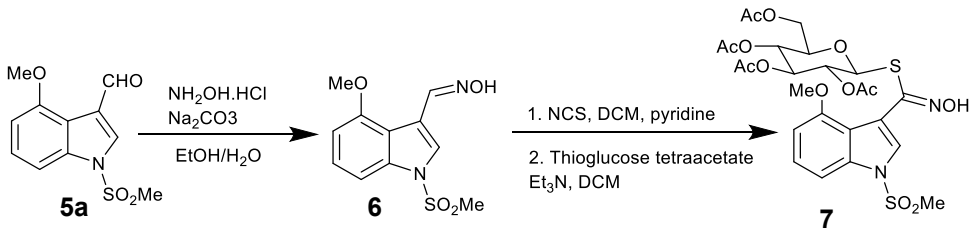


5 **5a**

A solution of 4-methoxyindole-3-carboxaldehyde (**5**) (235 mg, 1.34 mmol) in THF (3.0 mL) was added dropwise to a suspension of NaH (160 mg, 4.03 mmol) in dried THF (3.0 mL) at 0 °C. After stirring at rt for 30 min, MeSO$_2$Cl (310 μL, 4.03 mmol) was added dropwise and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with H$_2$O and extracted with EtOAc. The organic extract was dried over Na$_2$SO$_4$, concentrated and separated by FCC (EtOAc-hexane, 1:3) to give **5a** (240 mg, 0.95 mmol, 71%) as a white solid, mp 141 – 142 °C. HPLC: t_R = 13.8 min (method A). ^{1}H NMR (500 MHz, CDCl$_3$): δ 10.47 (1H, s, CHO), 8.05 (1H, s, H-2), 7.48 (1H, d, J = 8.0 Hz, H-7), 7.34

(1H, t, *J* = 8.0 Hz, H-6), 6.82 (1H, d, *J* = 8.0 Hz, H-5), 3.97 (3H, s, OMe), 3.24 (3H, s, SO_2Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.3 (CHO), 154.6 (C-4), 136.3 (C-7a), 128.5 (C-6), 127.0 (C-2), 122.1 (C-3), 117.5 (C-3a), 106.0, 105.2 (C-7, C-5), 55.7 (OMe), 41.8 (SO_2Me). HREI-MS *m/z* $[M]^+$: calc. for $C_{11}H_{11}NO_4S$: 253.0409, found 253.0400 (23%), 268.06 (100%), 189.08 (59%), 116.05 (28%), 299.08 (24%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm): 241, 312. FTIR (KBr, cm^{-1}) ν_{max}: 3000, 1677, 1534, 1502, 1374, 1269, 1181, 1175, 1101, 954, 779.

1-MeSO_2-2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosylindole-3-thiohydroximate (7)

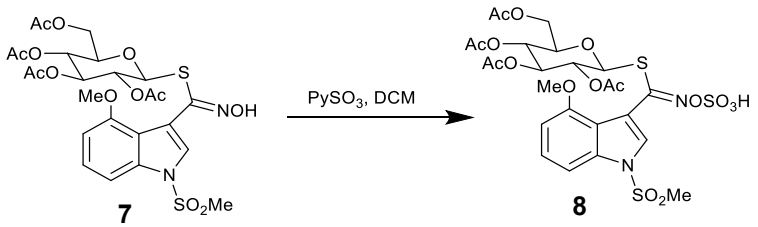


A solution of $NH_2OH.HCl$ (88 mg, 1.26 mmol) and Na_2CO_3 (67 mg, 0.63 mmol) in H_2O (1.0 mL) was added to a solution of compound **5a** (160 mg, 0.63 mmol) in ethanol (5.0 mL) at 60 °C. After stirring at 80 °C for 3 h, the reaction mixture was concentrated, diluted with H_2O and the resulting solution was extracted with EtOAc. The organic extract was dried over Na_2SO_4 and concentrated to give oxime **6** (165 mg, 0.62 mmol, 98% yield), which was used for the next step without further purification.

NCS (49 mg, 0.37 mmol) was added in portions to a solution of oxime **6** (100 mg, 0.37 mmol) in pyridine (0.3 mL) and dry CH_2Cl_2 (3.0 mL) at 0 ºC. After stirring at rt for 30 min, a solution of thio-β-D-glucose tetraacetate (122 mg, 0.34 mmol) and triethylamine (150 μL, 1.11 mmol) in CH_2Cl_2 (1.0 mL) was added. The mixture was stirred at rt for 3 h, concentrated to ca. one third, diluted with toluene and concentrated to dryness. The crude reaction mixture was separated by FCC (EtOAc-hexane, 1:1) to yield **7** (215 mg, 0.34, 90% yield) as a yellow solid, mp 111 – 112 °C. HPLC: t_R = 17.1 min (method A). ^1H NMR (500 MHz, $CDCl_3$): δ 9.10 (br, 1H, NOH), 7.56 (1H, d, *J* = 8.0 Hz, H-7), 7.54 (1H, s, H-2), 7.39 (1H, t, *J* = 8.0 Hz, H-6), 6.79 (1H, d, *J* = 8.0 Hz, H-5), 5.02 (1H, dd, *J* = 10.0, 9.0 Hz, H-2´), 4.95 (1H, t, *J* = 9.5 Hz, H-4´), 4.90 (1H, t, *J* = 9.0 Hz, H-3´), 4.41 (1H, d, *J* = 10.0 Hz, H-1), 3.98 (1H, dd, *J* = 12.5, 3.5 Hz, H-6´), 3.89 (3H, s, OMe), 3.57 (1H, dd, *J* = 12.5, 2.0 Hz, H-6´), 3.22 (3H, s, SO_2Me), 2.77-2.74 (1H, m, H-5´), 2.07 (3H, s), 2.03 (3H, s), 1.95 (3H, s), 1.92 (3H, s, 4 x OAc). ^{13}C

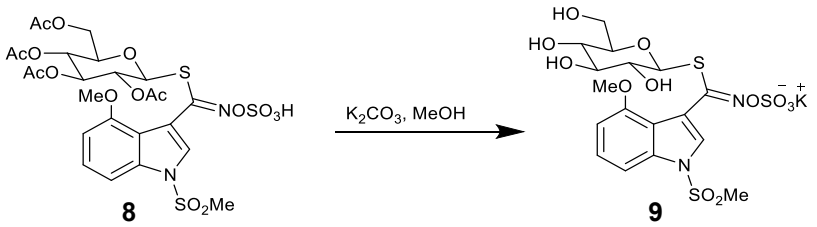
NMR (125 MHz, $CDCl_3$): δ 170.8 , 170.3, 169.4, 169.4 (4 x OAc), 154.0 (C-4), 148.8 (C=N), 135.9 (C-7a), 127.5 (C-6), 126.2 (C-2), 119.0 (C-3), 112.6 (C-3a), 106.1 (C-7), 105.1 (C-5), 81.3 (C-1´), 75.8 (C-5´), 73.9 (C-3´), 69.6 (C-2´), 67.6 (C-4´), 61.2 (C-6´), 55.9 (OMe), 41.5 (SO_2Me), 20.9, 20.8, 20.7, 20.7 (4 x OAc). HR-ESI-MS *m/z* $[M+H]^+$: calc. for $C_{25}H_{31}N_2O_{13}S_2$: 631.1262, found 631.1244 (59%), 169.05 (100%), 109.03 (95%), 331.11 (62%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm): 218, 254, 290. FTIR (KBr, cm^{-1}) ν_{max}: 1753, 1371, 1228, 1107, 1043, 963, 782.

1-MeSO_2-2',3',4',6'-tetra-*O*-acetylglucorapassicin (8)



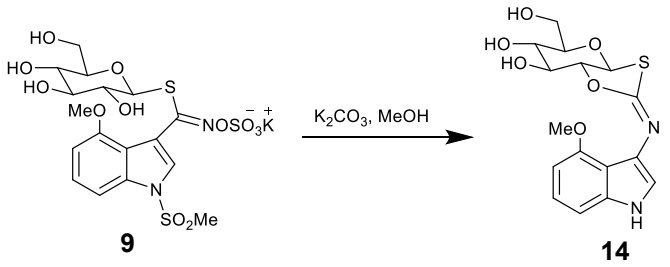
Sulfur trioxide pyridine complex (239 mg, 1.50 mmol) was added to a solution of **7** (192 mg, 0.30 mmol) in dry DCM (5.0 mL) at rt. The mixture was stirred at 40 ºC for 18 h, was concentrated, diluted with H_2O and was extracted with MeOH–$CHCl_3$ (1:4). The organic extract was dried over Na_2SO_4, concentrated and separated by FCC (MeOH-DCM, 1:9) to yield **8** (193 mg, 0.27 mmol, 91%) as a white solid, mp 120 – 121 °C. HPLC: t_R = 17.6 min (method B). ^{1}H NMR (500 MHz, MeOD): δ 7.73 (1H, s, H-2), 7.58 (1H, d, *J* = 8.0 Hz, H-7), 7.43 (1H, t, *J* = 8.0 Hz, H-6), 6.92 (1H, d, *J* = 8.0 Hz, H-5), 5.03-4.95 (2H, m, H-2´,4´), 4.92-4.87 (1H, m, H-3´), 4.65 (1H, d, *J* = 10.0 Hz, H-1´), 3.95 (1H, dd, *J* = 12.5, 3.5 Hz, H-6´), 3.94 (3H, s, OMe), 3.51 (1H, dd, *J* = 12.5, 2.5 Hz, H-6´), 3.39 (3H, s, SO_2Me), 2.88-2.84 (1H, m, H-5´), 2.08 (3H, s), 2.07 (3H, s), 1.94 (3H, s), 1.91 (3H, s, 4 x OAc). ^{13}C NMR (125 MHz, MeOD): δ 172.4, 171.6, 171.2, 171.1 (4 x OAc), 155.4, 154.9 (C-4, C=N), 137.2 (C-7a), 128.3, 128.0 (C-6, C-2), 120.3 (C-3), 113.0 (C-3a), 107.1, 106.0 (C-7, C-5), 82.7 (C-1´), 76.8 (C-5´), 75.1 (C-3´), 71.0 (C-2´), 69.1 (C-4´), 62.5 (C-6´), 56.5 (OMe), 41.6 (SO_2Me), 20.8, 20.6, 20.6 (4 x OAc). HR-ESI-MS *m/z* $[M-H]^+$: calc. for $C_{25}H_{29}N_2O_{16}S_3$: 709.0684, found 709.0694 (100%), 187.03 (32%), 212.06 (28%), 172.01 (16%), 265.01 (12%), 667.06 (4%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm): 218, 255, 290. FTIR (KBr, cm^{-1}) ν_{max}: 1753, 1372, 1231, 1107, 780.

1-MeSO$_2$-glucorapassicin (9)



K_2CO_3 (11 mg, 0.08 mmol) was added to a solution of compound **8** (30 mg, 0.04 mmol) in MeOH (1.0 mL) at rt. The mixture was stirred at rt for 30 min and filtered. The filtrate was concentrated and the crude residue was separated by FCC (MeOH-CH_2Cl_2, 1:4) to give **9** (20 mg, 0.034, 85%) as a white solid, mp 114 – 115 °C. HPLC: t_R = 9.3 min (method B). ^{1}H NMR (500 MHz, MeOD): δ 7.73 (1H, s, H-2), 7.51 (1H, d, *J* = 8.0 Hz, H-7), 7.36 (1H, t, *J* = 8.0 Hz, H-6), 6.85 (1H, d, *J* = 8.0 Hz, H-5), 4.22 (1H, d, *J* = 9.5 Hz, H-1´), 3.90 (3H, s, OMe), 3.46-3.40 (2H, m, H-6´), 3.35 (3H, s, SO_2Me), 3.26-3.19 (2H, m, H-2´, H-4´), 2.98 (1H, t, *J* = 9.0, H-3´), 2.32-2.29 (1H, m, H-5´). ^{13}C NMR (125 MHz, MeOD): δ 157.3 (C=N), 155.5 (C-4), 137.0 (C-7a), 128.3 (C-2), 127.9 (C-6), 120.3 (C-3), 113.3 (C-3a), 106.9 (C-7), 105.8 (C-5), 85.5 (C-1´), 82.0 (C-5´), 79.7 (C-3´), 73.6 (C-2´), 70.9 (C-4´), 62.2 (C-6´), 56.4 (OMe), 41.4 (SO_2Me). HR-ESI-MS *m/z* $[M-K]^+$: calc. for $C_{17}H_{21}N_2O_{12}S_3$: 541.0262, found 541.0258 (61%), 212.08 (100%), 205.16 (27%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 220, 250, 290. FTIR (KBr, cm^{-1}) ν_{max}: 3415, 1588, 1498, 1365, 1270, 1108, 780.

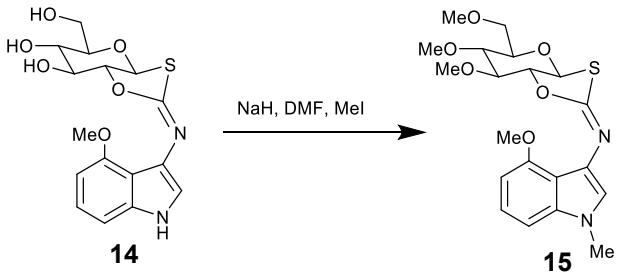
Compound X (14)



K_2CO_3 (34 mg, 0.25 mmol) was added to a solution of **9** (60 mg, 0.082 mmol) in MeOH (3.0 mL). The mixture was stirred at rt for 15 h and filtered. The filtrate was concentrated and separated by FCC (MeOH-CH_2Cl_2,1:9) to give **14** (20 mg, 0.055, 67 % yield) as a yellow solid, mp 168 – 169 °C. HPLC: t_R = 15.7 min (method B). ^{1}H NMR (500 MHz, MeOD): δ 7.03 (1H, t, *J* = 8.0 Hz, H-6), 6.93

(1H, d, *J* = 8.0 Hz, H-7), 6.81 (1H, s, H-2), 6.47 (1H, d, *J* = 8.0 Hz, H-5), 5.25 (1H, d, *J* = 9.5 Hz, H-1´), 3.93 (1H, t, *J* = 9.5 Hz, H-2´), 3.90-3.82 (2H, m, H-6´, H-3´), 3.85 (3H, s, OMe), 3.73 (1H, dd, *J* = 12.0, 5.5 Hz, H-6´), 3.59-3.55 (1H, m, H-5´), 3.51 (1H, dd, *J* = 9.5, 8.0 Hz, H-4´). ^{13}C NMR (125 MHz, MeOD): δ 164.0 (C-11), 155.4 (C-4), 138.7 (C-7a), 125.9 (C-3), 124.2 (C-6), 113.9 (C-2), 113.6 (C-3a), 106.1 (C-7), 100.7 (C-5), 88.0 (C-2´), 85.1 (C-5´), 84.3 (C-1´), 75.5 (C-3´), 72.3 (C-4´), 62.6 (C-6´), 55.8 (OMe). HR-EI-MS *m/z* [M]$^+$: calc. for $C_{16}H_{18}N_2O_6S$: 366.0886, found 366.0877 (10%), 188.06 (100%), 173.04 (53%), 204.03 (45%), 162.08 (39%), 73.03 (38%), 147.06 (34%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 226, 260, 290. FTIR (KBr, cm^{-1}) ν_{max}: 3392, 2888, 1662, 1509, 1266, 735.

Methylated compound X (15)

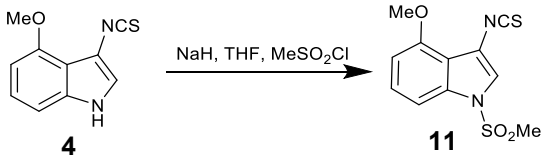


A solution of compound **14** (16 mg, 0.044 mmol) in DMF (1.0 mL) was added to a suspension of NaH (11 mg, 0.26 mmol) in DMF (0.5 mL) at 0 ºC. After stirring at rt for 15 min, CH_3I (20 μL, 0.26 mmol) was added and the mixture was stirred for an additional 15 min. The mixture was diluted with H_2O and extracted with EtOAc. The organic extract was dried over Na_2SO_4, concentrated and fractionated by FCC (EtOAc-hexane, 1:2) to give **15** (16 mg, 0.038 mmol, 86%) as a yellow solid, mp 125 – 126 °C.

HPLC: t_R = 20.0 min (method A). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (1H, t, *J* = 8.0 Hz, H-6), 6.87 (1H, d, *J* = 8.0 Hz, H-7), 6.68 (1H, s, H-2), 6.49 (1H, d, *J* = 8.0 Hz, H-5), 5.03 (1H, d, *J* = 9.5 Hz, H-1´), 3.99 (1H, t, *J* = 9.5 Hz, H-2´), 3.91 (3H, s, OMe), 3.72 (3H, s, NMe), 3.69 (3H, s, OMe), 3.67-3.60 (4H, m, H-6´,6´,3´,5´), 3.58 (3H, s, OMe), 3.41 (3H, s, OCH_3), 3.33 (1H, t, *J* = 9.0 Hz, H-4´). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9 (C-11), 154.5 (C-4), 150.3 (C-3a), 137.7 (C-7a), 124.3 (C-3), 123.2 (C-6), 116.6 (C-2), 102.7 (C-7), 99.8 (C-5), 85.9 (C-2´), 84.3 (C-3´), 83.6 (C-1´), 81.6 (C-5´), 79.2 (C-4´), 71.5 (C-6´), 61.5 (OMe), 60.1 (OMe), 59.6 (OMe), 55.8 (OCH_3), 33.3 (N-Me). HR-EI-MS *m/z* [M]$^+$: calc. for $C_{20}H_{26}N_2O_6S$: 422.1512, found 422.1500 (53%), 218.05 (100%), 202.07 (53%),

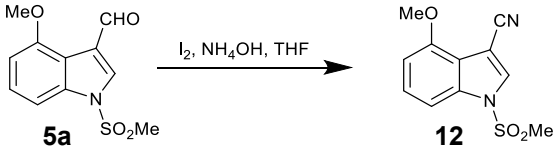
187.05 (17%), 252.01 (12%), 456.11 (6%). UV (HPLC, $CH_3CN - H_2O$) λ_{max} (nm) 228, 302. FTIR (KBr, cm^{-1}) ν_{max}:2941, 2274, 1666, 1501, 1466, 1262, 1115, 728.

1-$MeSO_2$-rapalexin A (11)



A solution of rapalexin A[1] (**4**) (20 mg, 0.10 mmol) in THF (1 mL) was added to a suspension of NaH (20 mg, 0.50 mmol) in THF (1 mL) at 0 °C. After stirring at rt for 15 min, $ClSO_2Me$ (15 μL, 0.20 mmol) was added and the mixture was stirred for an additional 15 min. The reaction mixture was diluted with H_2O, extracted with CH_2Cl_2, the organic extract was dried over Na_2SO_4, concentrated and separated by FCC (EtOAc-hexane, 1:20) to yield **11** (21 mg, 0.074 mmol, 74% yield) as a white solid, mp 145 – 146 °C. HPLC: t_R = 28.4 min (method A). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (1H, d, J = 8.5 Hz, H-7), 7.35 (1H, t, J = 8.5 Hz, H-6), 7.26 (1H, s, H-2), 6.77 (1H, d, J = 8.0 Hz, H-5), 4.00 (3H, s, OMe), 3.11 (3H, s, SO_2Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2 (C-4), 135.2 (C-7a), 127.9 (C-6), 118.8 (C-2), 116.3 (C-3), 113.8 (C-3a), 106.0, 104.8 (C-7, C-5), 55.6 (OMe), 41.1 (SO_2Me). HR-EI-MS m/z $[M]^+$: calc. for $C_{11}H_{10}N_2O_3S_2$: 282.0133, found 282.0130 (41%), 203.03 (100%), 160.00 (12%), 116.04 (8%). UV (HPLC, $CH_3CN - H_2O$) λ_{max} (nm) 252, 284. FTIR (KBr, cm^{-1}) ν_{max}: 3130, 2115, 1598, 1497, 1361, 1278, 1178, 1106, 969, 776.

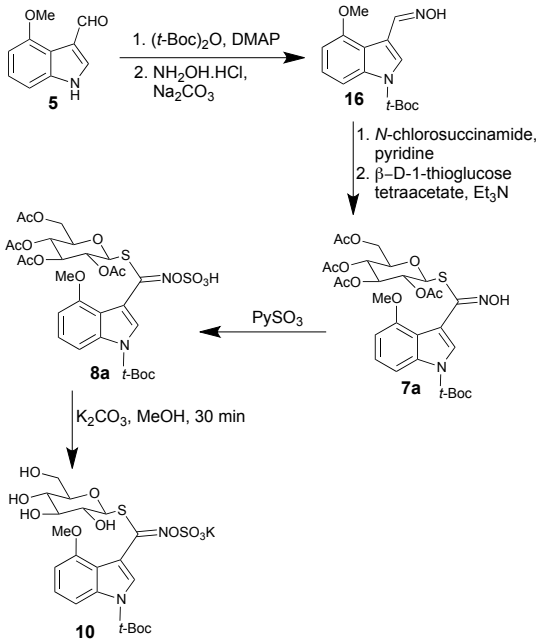
1-$MeSO_2$-4-methoxyindole-3-carbonitrile (12)



[1] M. S. C. Pedras, Q.-A. Zheng and R. S. Gadagi, *Chem. Commun.*, 2007, 368–370.

Iodine (12 mg, 0.047 mmol) was added to a mixture of compound **5a** (10 mg, 0.040 mmol) in THF (50 μL) and NH_4OH (0.50 mL) at rt.[2] The mixture was stirred at rt for 14 h, diluted with saturated aq. $Na_2S_2O_3$ and extracted with DCM. The organic extract was dried over Na_2SO_4, concentrated and separated by FCC ($CHCl_3$) to give **12** (5.0 mg, 0.020 mmol, 50%) as a white solid, mp 167 – 168 °C. HPLC: t_R = 16.9 min (method A). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (1H, s, H-2), 7.49 (1H, dd, *J* = 8.5, 0.5 Hz, H-7), 7.42 (1H, t, *J* = 8.0 Hz, H-6), 6.82 (1H, d, *J* = 8.0 Hz, H-5), 4.01 (3H, s, OMe), 3.25 (3H, s, SO_2Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0 (C-4), 135.3 (C-7a), 132.6 (C-2), 128.3 (C-6), 118.1 (C-3), 114.3 (C-3a), 105.8, 105.2 (C-7, C-5), 92.2 (CN), 56.1 (OMe), 41.9 (SO_2Me). HR-FD-MS *m/z* $[M]^+$: calc. for $C_{11}H_{10}N_2O_3S$: 250.0412, found: 250.0420 (100%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 227, 272, 296. FTIR (KBr, cm^{-1}) ν_{max}: 3132, 2230, 1608, 1498, 1370, 1271, 1183, 1113, 973, 782, 569.

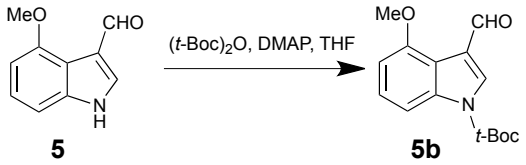
*2.2 Synthesis of 1-t-Boc-glucorapassicin A (**10**)*



Scheme 2S Synthesis of 1-*t*-Boc-glucorapassicin A (**10**).

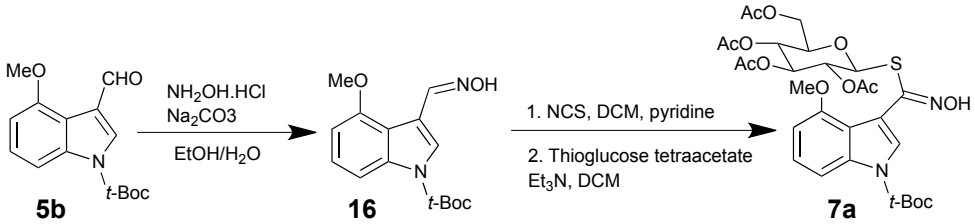
[2] S. Talukdar, J.-L. Hsu, T.-C. Chou and J.-M. Fang, *Tetrahedron Lett.*, 2001, **42**, 1103–1105.

1-*t*-Boc-4-methoxy-indole-3-carboxaldehyde (5b)



(*t*-Boc)$_2$O (450 mg, 2.06 mmol) was added to a solution of 4-methoxyindole-3-carboxaldehyde (300 mg, 1.71 mmol) in THF (6.0 mL) at rt, followed by a catalytic amount of DMAP (4 mg, 0.033 mmol). After stirring at rt for 30 min, the mixture was acidified with HCl (1M ca. 2 drops), diluted with H_2O and extracted with DCM. The organic extract was dried over Na_2SO_4, concentrated and separated by FCC (EtOAc-hexane, 1:2) to yield **5b** (434 mg, 1.58 mmol, 92%) as a white solid, mp 162 – 163 °C. HPLC: t_R = 27.8 min (method A). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.54 (1H, s, CHO), 8.22 (1H, s, H-2), 7.84 (1H, d, *J* = 8.5 Hz, H-7), 7.31 (1H, t, *J* = 8.5 Hz, H-6), 6.80 (1H, d, *J* = 8.0 Hz, H-5), 3.99 (3H, s, OMe), 1.67 (9H, s, *t*-Boc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3 (CHO), 154.3 (C-4), 149.2 (*t*-Boc), 137.3 (C-7a), 128.9 (C-6), 126.3 (C-2), 121.5 (C-3), 117.4 (C-3a), 108.8 (C-7), 104.7 (C-5), 85.6 (*t*-Boc), 55.7 (OMe), 28.2 (*t*-Boc). HR-FD-MS *m/z* $[M]^+$: calc. for $C_{15}H_{17}NO_4$: 275.1158, found: 275.1149 (100%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 220, 247, 322. FTIR (KBr, cm^{-1}) ν_{max}: 1737, 1676, 1545, 1433, 1282, 1146, 837.

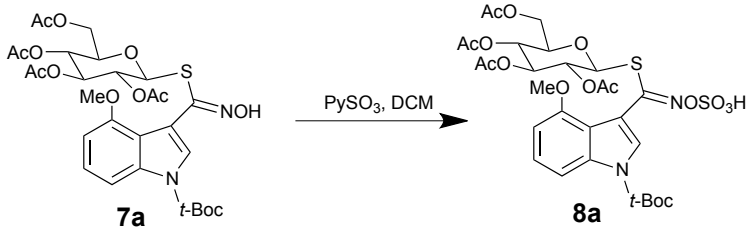
1-*t*-Boc-2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosylindole-3-thiohydroximate (7a)



A solution of $NH_2OH.HCl$ (48 mg, 0.70 mmol) and Na_2CO_3 (37 mg, 0.35 mmol) in H_2O (1.0 mL) was added to a solution of **5b** (95 mg, 0.35 mmol) in EtOH (5.0 mL) at 60 ºC. The mixture was stirred at 60 ºC for 1 h, concentrated, diluted with H_2O and extracted with EtOAc. The organic extract was dried over Na_2SO_4 and concentrated to give oxime **16** (105 mg), which was used for the next step without further purification. NCS (47 mg, 0.35 mmol) was added in portions to a solution of oxime **16**

in pyridine (0.30 mL) and CH_2Cl_2 (3.0 mL) at 0 ºC. After stirring at rt for 30 min, a solution of thio-β-D-glucose tetraacetate (121 mg, 0.33 mmol) and Et_3N (145 μL, 1.05 mmol) in CH_2Cl_2 (1.0 mL) was added and stirring was continued for 3 h. The reaction mixture was concentrated, diluted with toluene and then concentrated to dryness. The crude was separated by FCC (EtOAc-hexane, 1:1) to yield **7a** (200 mg, 0.31 mmol, 88%) as a yellow solid, mp 102 – 103 °C. HPLC: t_R = 23.0 min (method A). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (1H, d, *J* = 8.5 Hz, H-7), 7.62 (1H, s, H-2), 7.30 (1H, t, *J* = 8.5 Hz, H-6), 6.71 (1H, d, *J* = 8.0 Hz, H-5), 5.06-4.87 (2H, m, H-2´,4´), 4.90 (1H, t, *J* = 9.5 Hz, H-3´), 4.50 (1H, d, *J* = 10.5 Hz, H-1´), 3.90 (1H, dd, *J* = 12.5, 3.0 Hz, H-6´), 3.87 (3H, s, OMe), 3.48 (1H, dd, *J* = 12.5, 2.0 Hz, H-6´), 2.63-2.61 (1H, m, H-5´), 2.04 (6H, s), 1.94 (3H, s), 1.89 (3H, s, 4 x OAc), 1.67 (9H, s, *t*-Boc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 170.5, 169.3 (4 x OAc), 153.4 (C-4), 149.4, 149.2 (C=N and *t*-Boc), 136.3 (C-7a), 126.7, 126.2 (C-6, C-2), 118.5 (C-3), 111.3 (C-3a), 108.5 (C-7), 104.4 (C-5), 85.2 (*t*-Boc), 81.4 (C-1´), 75.5 (C-5´), 74.1 (C-3´), 69.7 (C-2´), 67.5 (C-4´), 60.9 (C-6´), 55.7 (OMe), 28.3 (*t*-Boc), 20.9, 20.8, 20.7, 20.6 (4 x OAc). HR-ESI-MS *m/z* $[M+H]^+$: calc. for $C_{29}H_{37}N_2O_{13}S$: 653.2011, found: 653.2000 (100%), 691.16 (64%), 331.1048 (9%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 223, 256, 296. FTIR (KBr, cm^{-1}) ν_{max}: 1751, 1434, 1372, 1227, 1154, 1044, 961, 744.

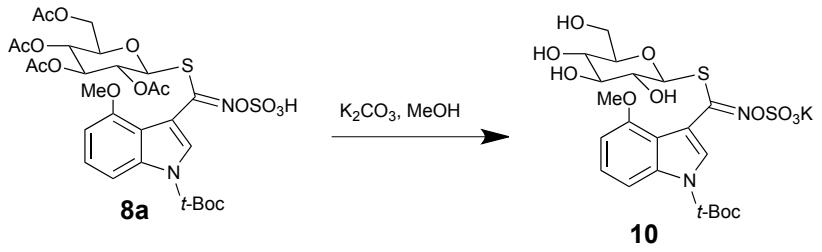
1-*t*-Boc-2',3',4',6'-tetra-*O*-acetylglucorapassicin (8a)



Sulfur trioxide pyridine complex (183 mg, 1.15 mmol) was added to a solution of **7a** (150 mg, 0.23 mmol) in dry DCM (4.0 mL). The mixture was stirred at 40 ºC for 18 h, was concentrated, diluted with H_2O and extracted with MeOH-$CHCl_3$ (1:4). The organic extract was dried over Na_2SO_4, concentrated and separated by FCC (MeOH-DCM, 1:9) to yield **8a** (140 mg, 0.19 mmol, 83%) as a white solid, mp 111 – 112 °C. HPLC: t_R = 18.2 min (method B). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (1H, d, *J* = 8.0 Hz, H-7), 7.78 (1H, s, H-2), 7.35 (1H, t, *J* = 8.0 Hz, H-6), 6.85 (1H, d, *J* = 8.0 Hz, H-5), 4.95-4.89 (3H, m, H-2´,3´,4´), 4.65-4.61 (1H, m, H-1´), 3.91 (3H, s, OMe), 3.86 (1H, dd, *J* = 12.5,

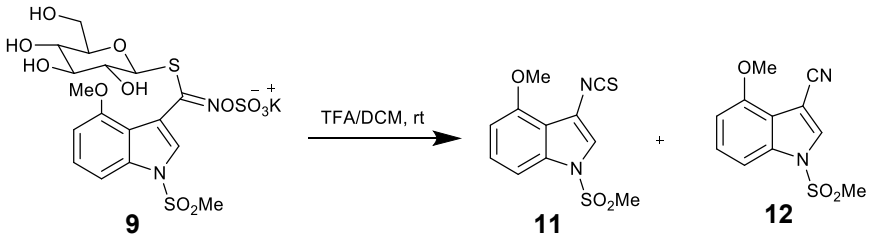
3.0 Hz, H-6´), 3.49 (1H, dd, *J* = 12.5, 2.5 Hz, H-6´), 2.70-2.67 (1H, m, H-5´), 2.07 (3H, s), 2.03 (3H, s), 1.92 (3H, s), 1.88 (3H, s, 4 x OAc), 1.69 (9H, s, *t*-Boc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 171.6, 171.1, 171.1 (4 x OAc), 156.0, 154.9 (C=N, C-4), 150.6 (*t*-Boc), 137.6 (C-7a), 127.9, 127.8 (C-6, C-2), 119.8 (C-3), 112.0 (C-3a), 109.4 (C-7), 105.6 (C-5), 86.3 (*t*-Boc), 82.6 (C-1´), 76.6 (C-5´), 75.2 (C-3´), 71.0 (C-2´), 69.1 (C-4´), 62.1 (C-6´), 56.3 (OMe), 28.4 (*t*-Boc), 20.8, 20.7, 20.6, 20.5 (4 x OAc). HR-ESI-MS *m/z* $[M-H]^+$: calc. for $C_{29}H_{35}N_2O_{16}S_2$: 731.1434, found: 731.1405 (100%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 224, 256, 297. FTIR (KBr, cm^{-1}) ν_{max}: 1750, 1372, 1227, 1059, 851, 780.

1-*t*-Boc-glucorapassicin (10)



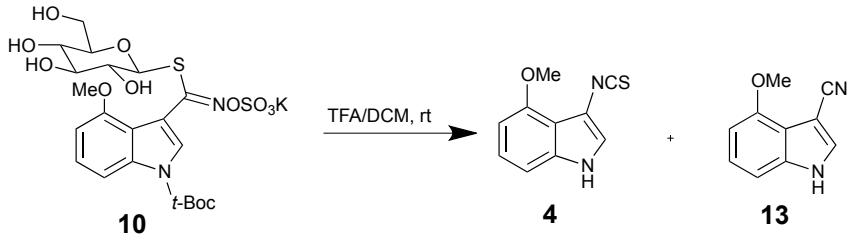
K_2CO_3 (26 mg, 0.19 mmol) was added to a solution of **8a** (70 mg, 0.095 mmol) in MeOH (2.0 mL) at rt. After stirring for 30 min, the mixture was filtered, the solvent was removed and the crude residue was separated by FCC (MeOH-DCM, 1:4) to yield **10** (40 mg, 0.066 mmol, 70%) as a white solid, mp 125 – 126 °C. HPLC: t_R = 10.9 min (method B). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (1H, d, *J* = 8.5 Hz, H-7), 7.77 (1H, s, H-2), 7.29 (1H, t, *J* = 8.5, H-6), 6.79 (1H, d, *J* = 8.0 Hz, H-5), 4.22 (1H, d, *J* = 10.0 Hz, H-1´), 3.89 (3H, s, OCH3), 3.44-3.36 (2H, m, H-6´), 3.27-3.21 (2H, m, H-2´, H-4´), 2.97 (1H, t, *J* = 9.0 Hz, H-3´), 2.21-2.20 (1H, m, H-5´), 1.68 (9H, s, *t*-Boc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1 (C=N), 155.0 (C-4), 150.7 (*t*-Boc), 137.6(C-7a), 128.0 (C-2), 127.5 (C-6), 120.0 (C-3), 112.5 (C-3a), 109.2 (C-7), 105.5 (C-5), 85.9, 85.3 (C-1´ and *t*-Boc) , 81.9 (C-5´), 79.7 (C-3´), 73.6 (C-2´), 70.6 (C-4´), 61.9 (C-6´), 56.3 (OMe), 28.4 (*t*-Boc). HR-ESI-MS *m/z* $[M-K]^+$: calc. for $C_{21}H_{27}N_2O_{12}S_2$: 563.1010, found: 563.1011 (100%). UV (HPLC, CH_3CN – H_2O) λ_{max} (nm) 225, 258, 299. FTIR (KBr, cm^{-1}) ν_{max}: 3385, 2974, 1742, 1435, 1372, 1276, 1153, 1063, 848, 780.

Transformation of 1-MeSO$_2$-glucorapassicin (9) in TFA/DCM



1-MeSO$_2$-glucorapassicin (**9**) (5 mg, 0.009 mmol) was dissolved in a mixture of TFA-DCM (1:4, 200 μL), stirred for 10 min at rt, and the solvent was removed. The mixture was dissolved in $CHCl_3$, filtered, and concentrated to yield a mixture of 1-MeSO$_2$-rapalexin (**11**) and 1-MeSO$_2$-4-methoxyindole-3-carbonitrile (**12**) (2 mg, 4:1, determined by ^{1}H NMR and HPLC).

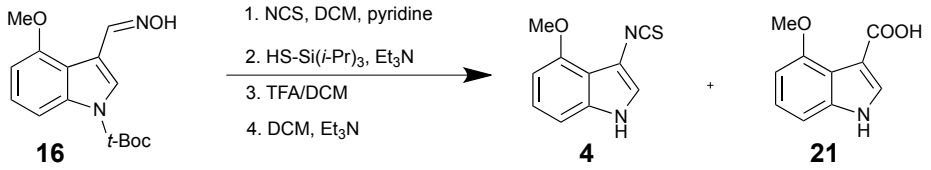
Transformation of 1-t-Boc-glucorapassicin (10) in TFA/DCM



1-*t*-Boc-glucorapassicin (**10**) (5 mg, 0.009 mmol) was dissolved in a mixture of TFA-DCM (1:4, 200 μL), stirred for 10 min at rt, and the solvent was removed. The mixture was dissolved in $CHCl_3$, filtered, and concentrated to give a mixture of rapalexin (**4**) and 4-methoxyindole-3-carbonitrile (**13**) (2 mg, 2:1, determined by ^{1}H NMR and HPLC), identical in all respects to authentic samples.[3]

[3] M.S.C. Pedras and E.E. Yaya, Org. Biomol. Chem. 2012, 10, 3613-3616.

One-pot synthesis of rapalexin A (4)



N-chlorosuccinimide (NCS) (26 mg, 0.19 mmol) was added in portions to a solution of oxime **10** (55 mg, 0.19 mmol) and pyridine (150 μL) in DCM (1.5 mL) at 0 °C. After stirring at rt for 30 min, triisopropylsilanethiol (50 μL, 0.23 mmol) was added, followed by Et_3N (80 μL, 0.57 mmol). After stirring the reaction mixture for an additional 30 min, the mixture was diluted with toluene and concentrated to dryness. The residue was dissolved in TFA/DCM (30%, 1.5 mL) and the mixture was stirred for 1 h at r. The solvent was removed, and the residue was dissolved in DCM (2 mL) and Et_3N (80 μL). After 1 h, the reaction mixture was concentrated and separated by FCC to afford rapalexin A (**4**) (12 mg, 0.059 mmol, 31%) and 4-methoxyindole-3-carboxylic acid (**21**) (10 mg, 0.052 mmol, 27%), identical in all respects to an authentic sample.[4]

[4] M. S. C. Pedras and S. Hossain, *Phytochemistry*, 2011, **72**, 2308–2316.

3. NMR spectra of new compounds

1-$MeSO_2$-4-methoxyindole-3-carboxaldehyde (5a)

1-$MeSO_2$-2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosylindole-3-thiohydroximate (7)

1-$MeSO_2$-2',3',4',6'-tetra-*O*-acetylglucorapassicin (8)

1-$MeSO_2$-glucorapassicin (9)

Compound X (14)

Methylated compound X (15)

1-$MeSO_2$-rapalexin A (11)

1-$MeSO_2$-4-methoxyindole-3-carbonitrile (12)

1-*t*-Boc-4-methoxy-indole-3-carboxaldehyde (5b)

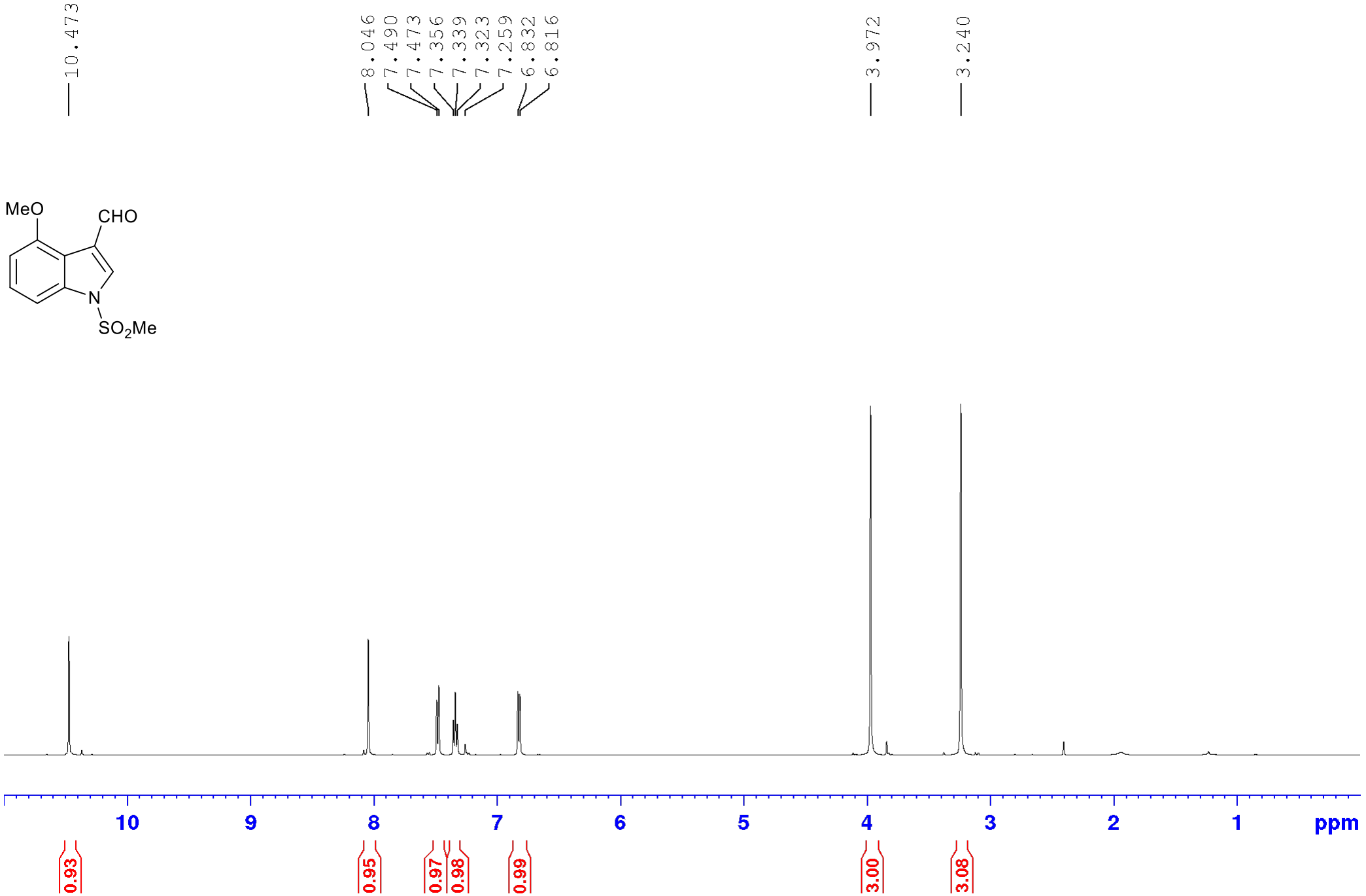
1-*t*-Boc-2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosylindole-3-thiohydroximate (7a)

1-*t*-Boc-2',3',4',6'-tetra-*O*-acetylglucorapassicin (8a)

1-*t*-Boc-glucorapassicin (10)

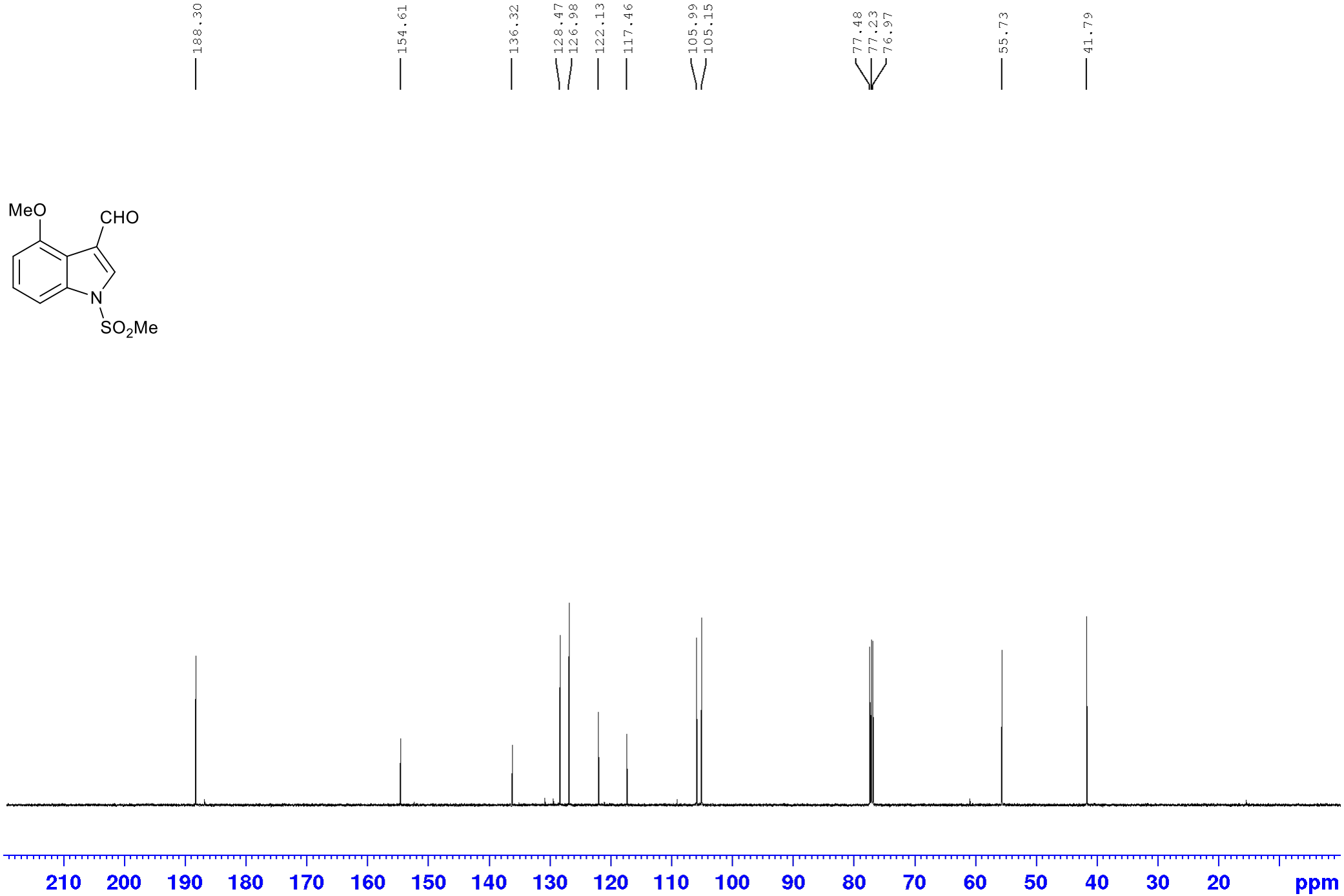
Compound **5a**

$CDCl_3$



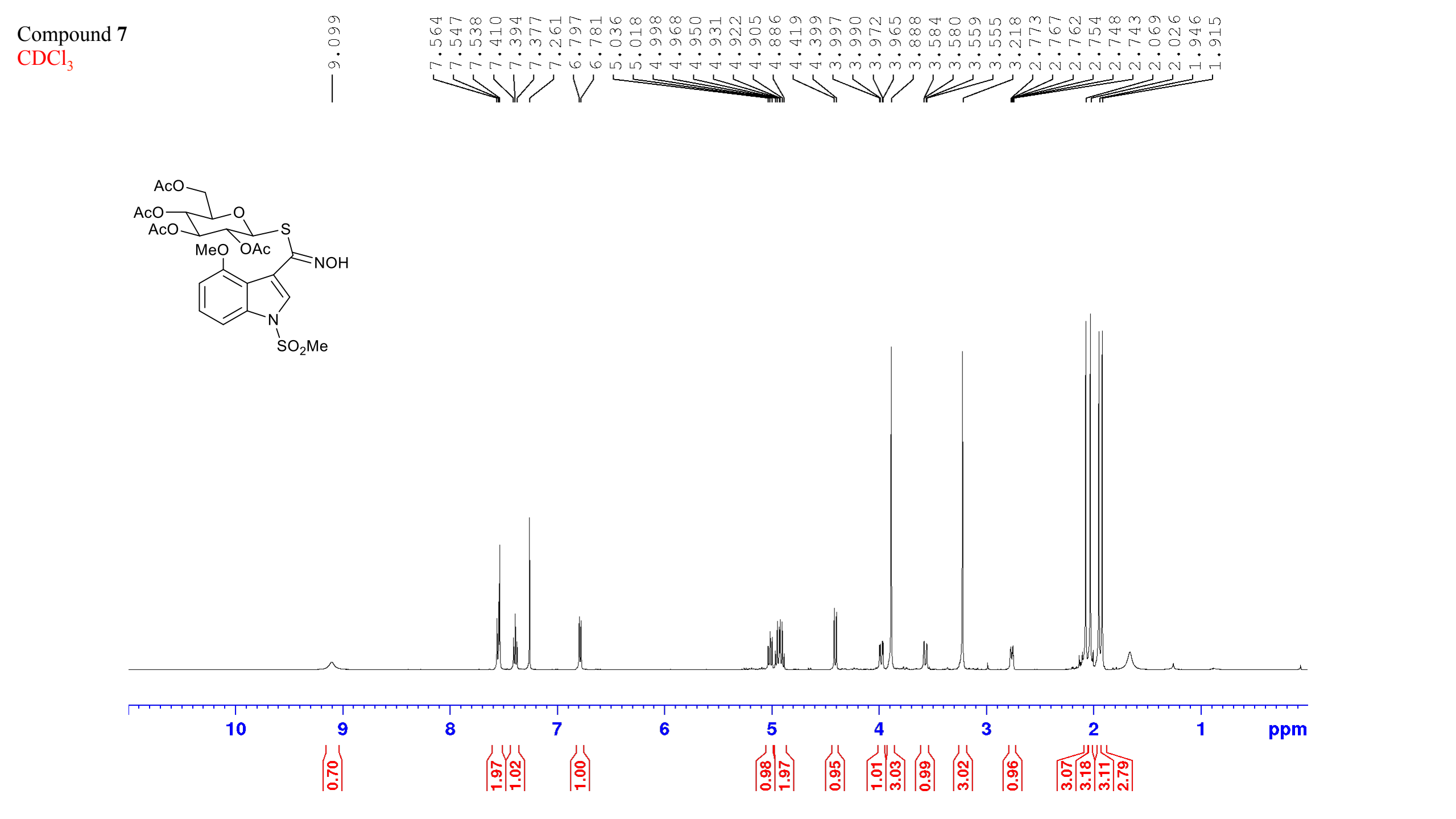
Compound **5a**

$CDCl_3$

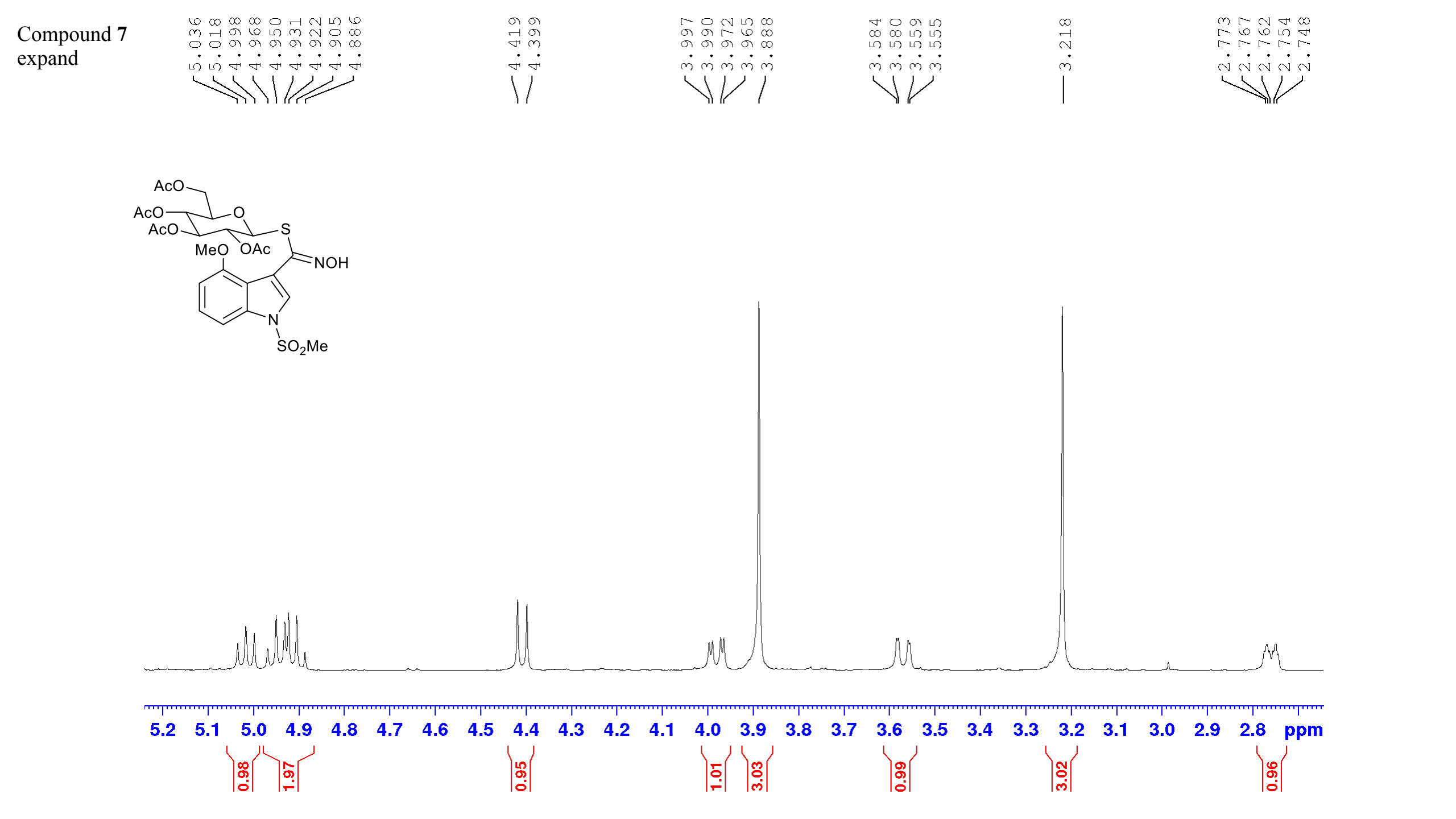


Compound **7**

$CDCl_3$

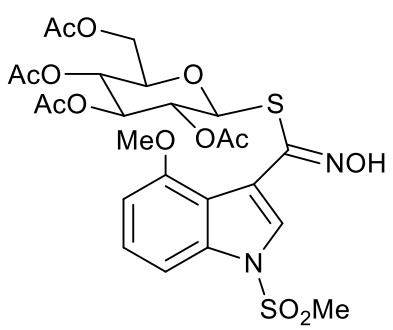


Compound **7**
expand



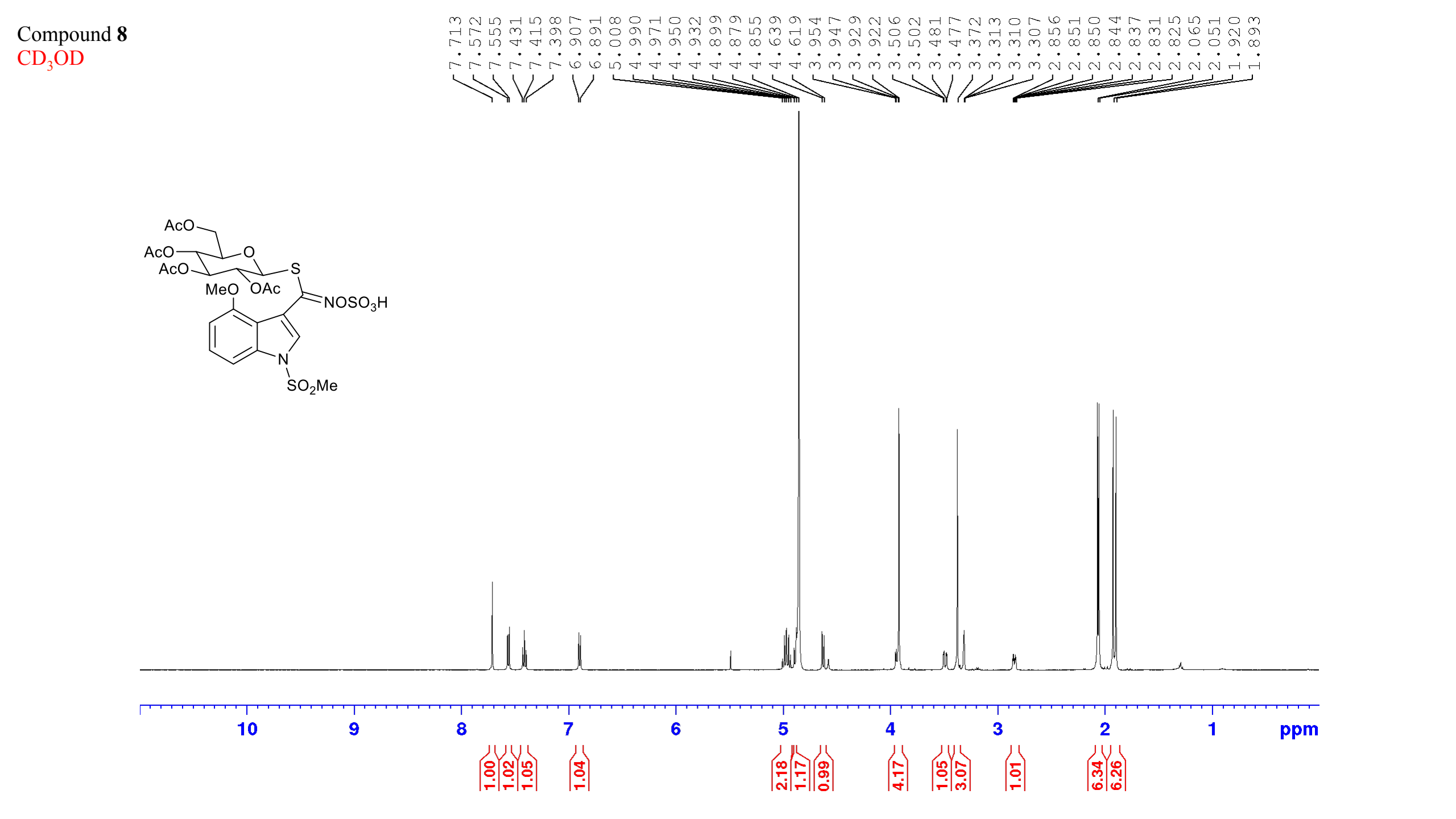
Compound **7**

$CDCl_3$

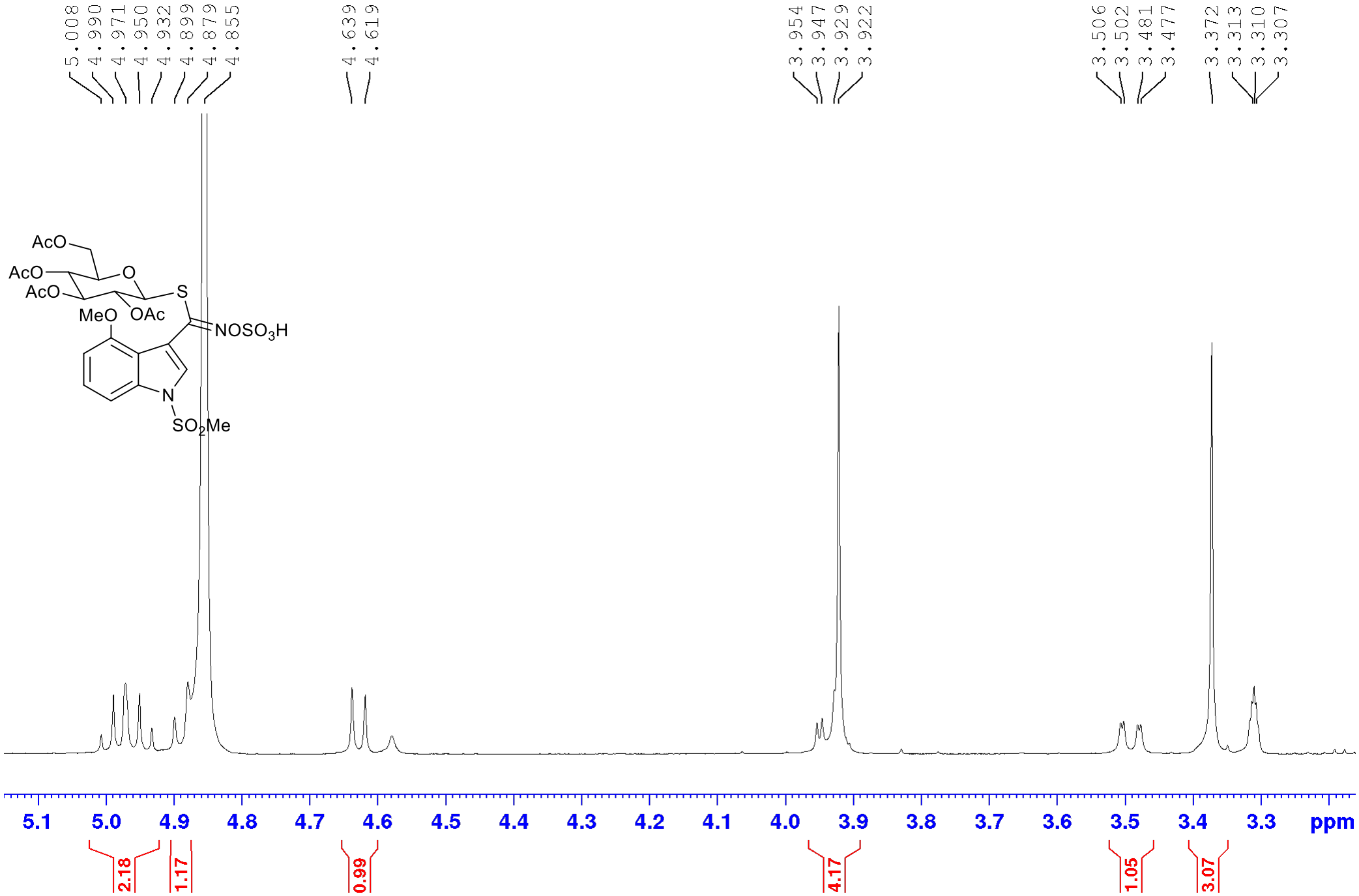


Compound **8**

CD_3OD

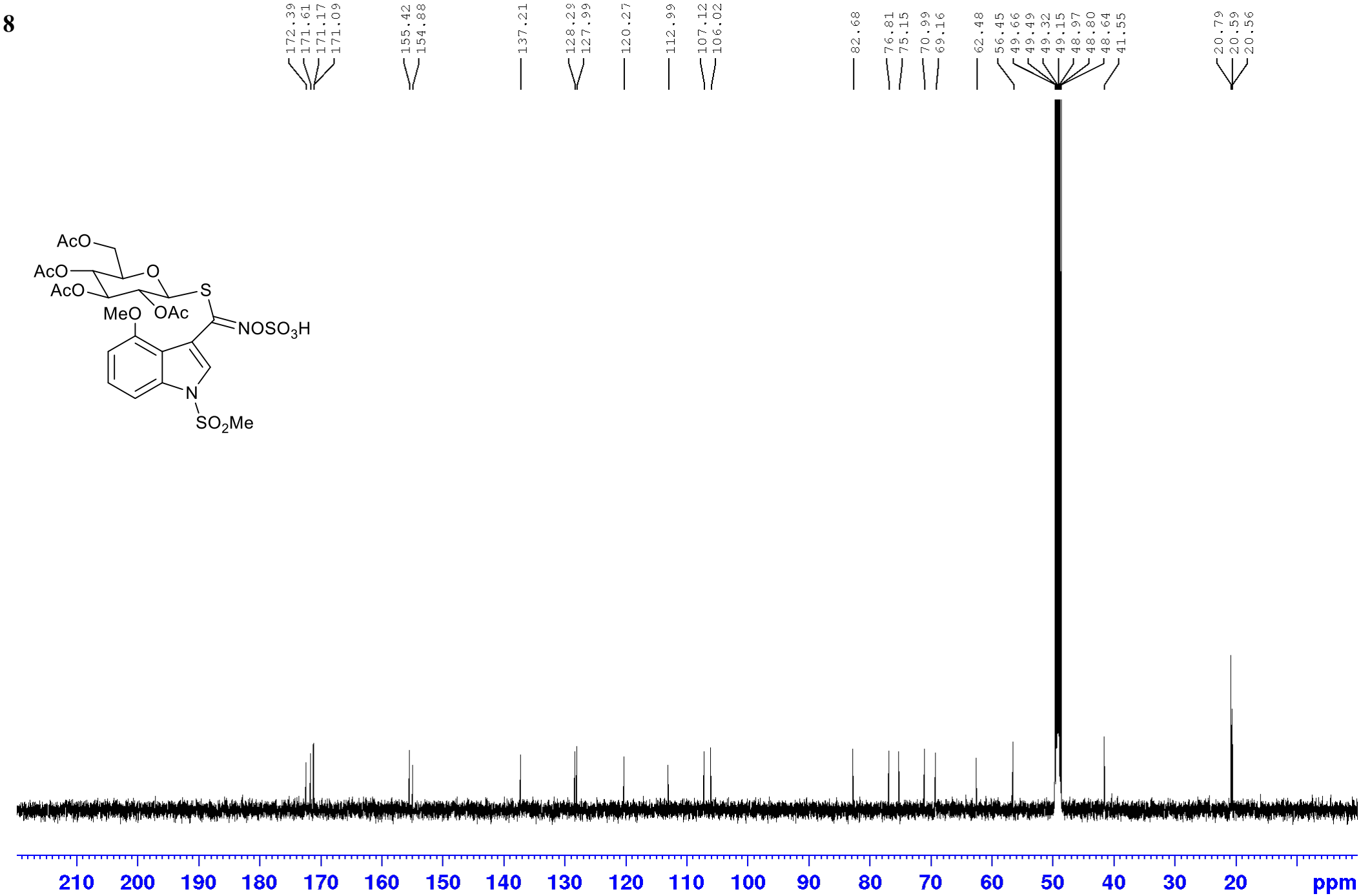


Compound 8
expansion



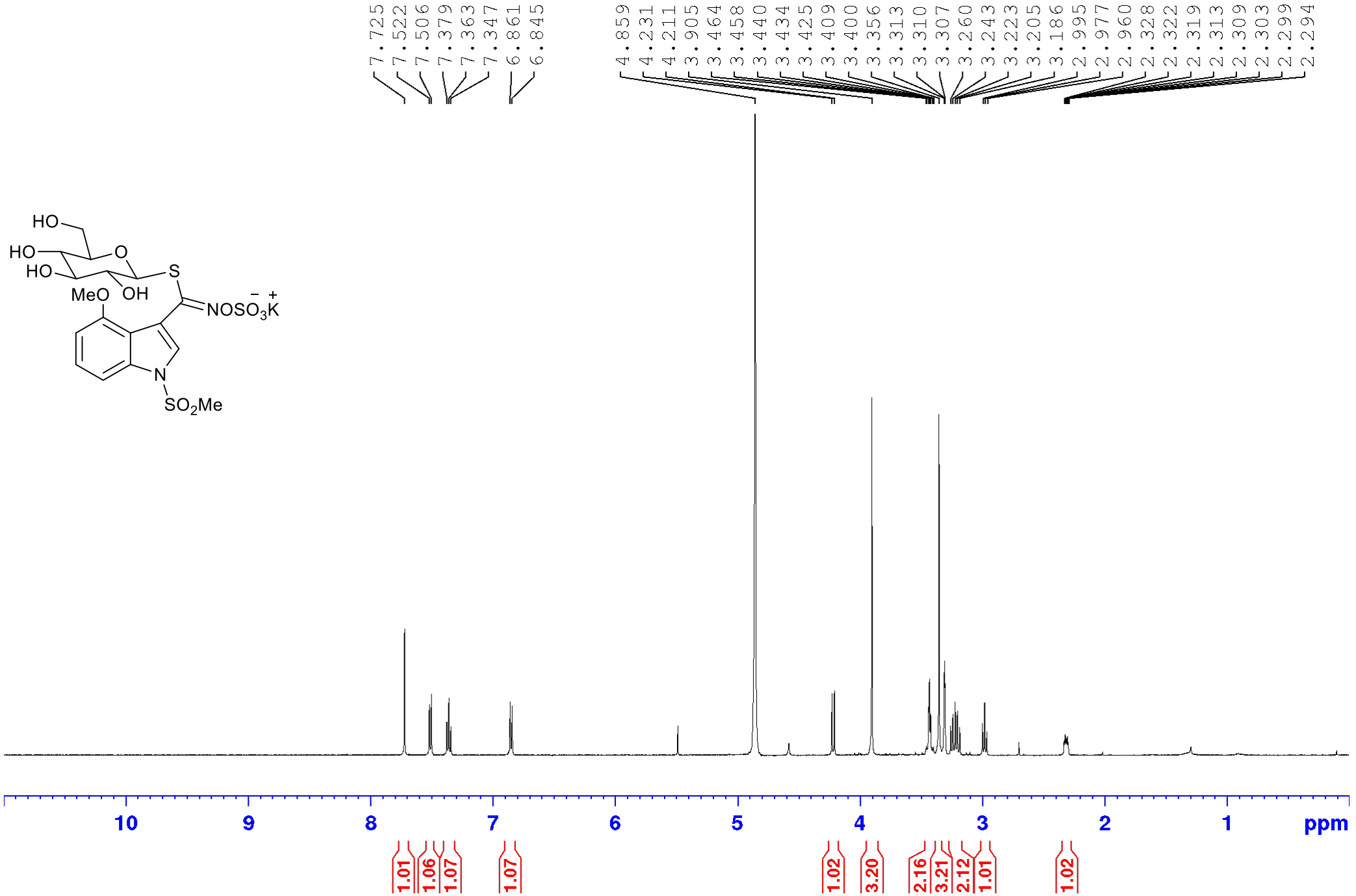
Compound **8**

CD_3OD

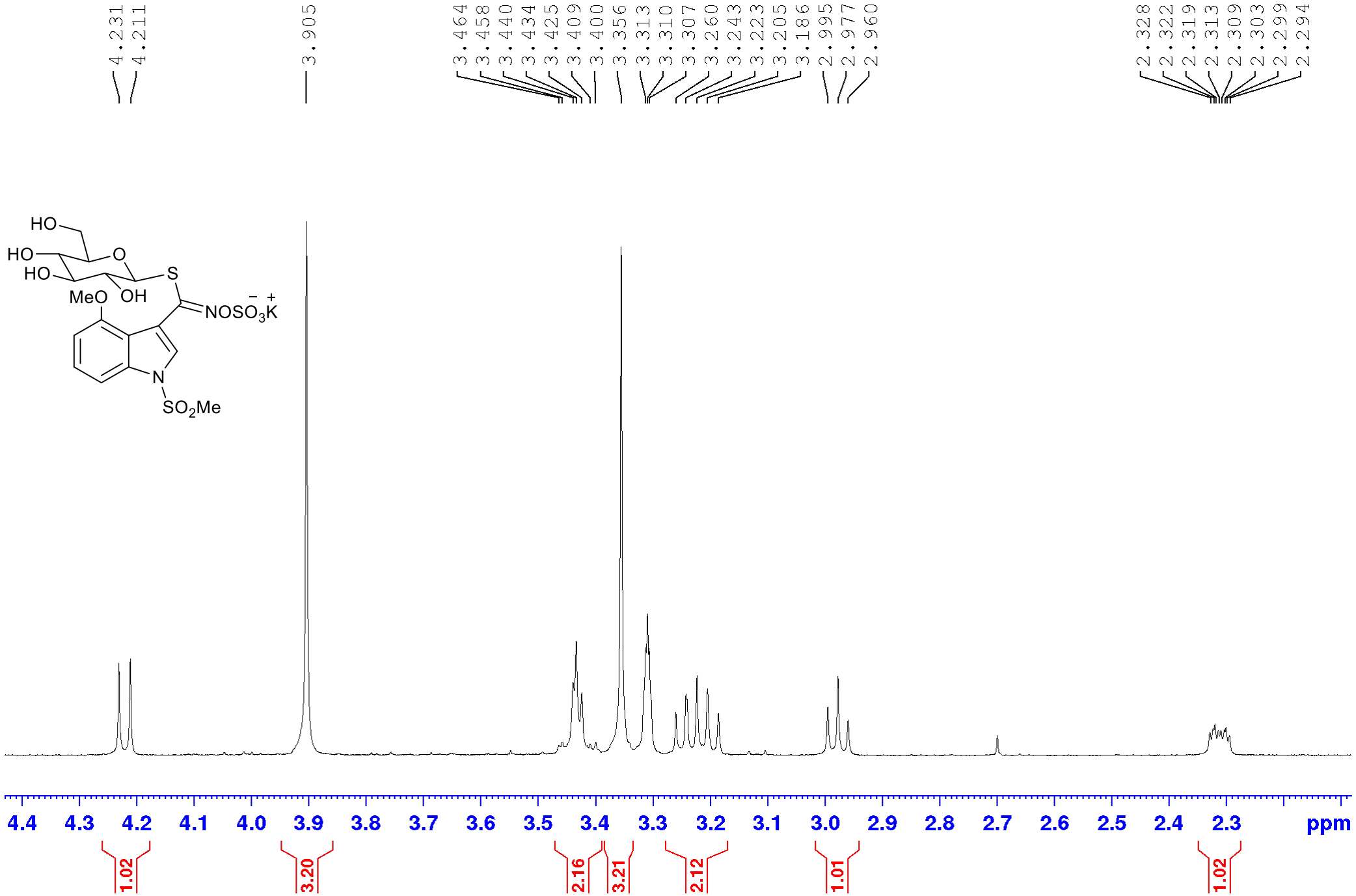


Compound **9**

CD_3OD

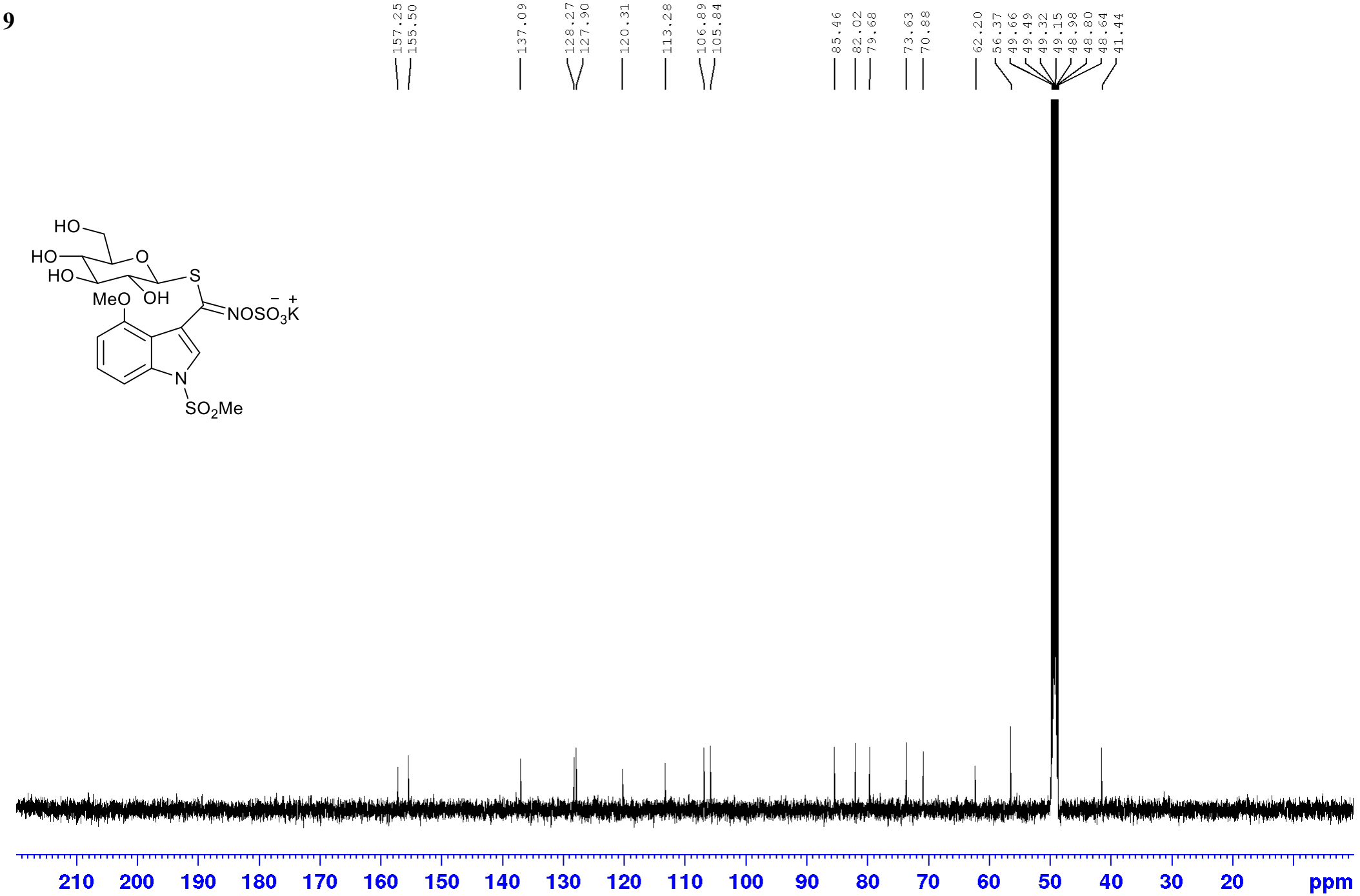


Compound **9**
expansion



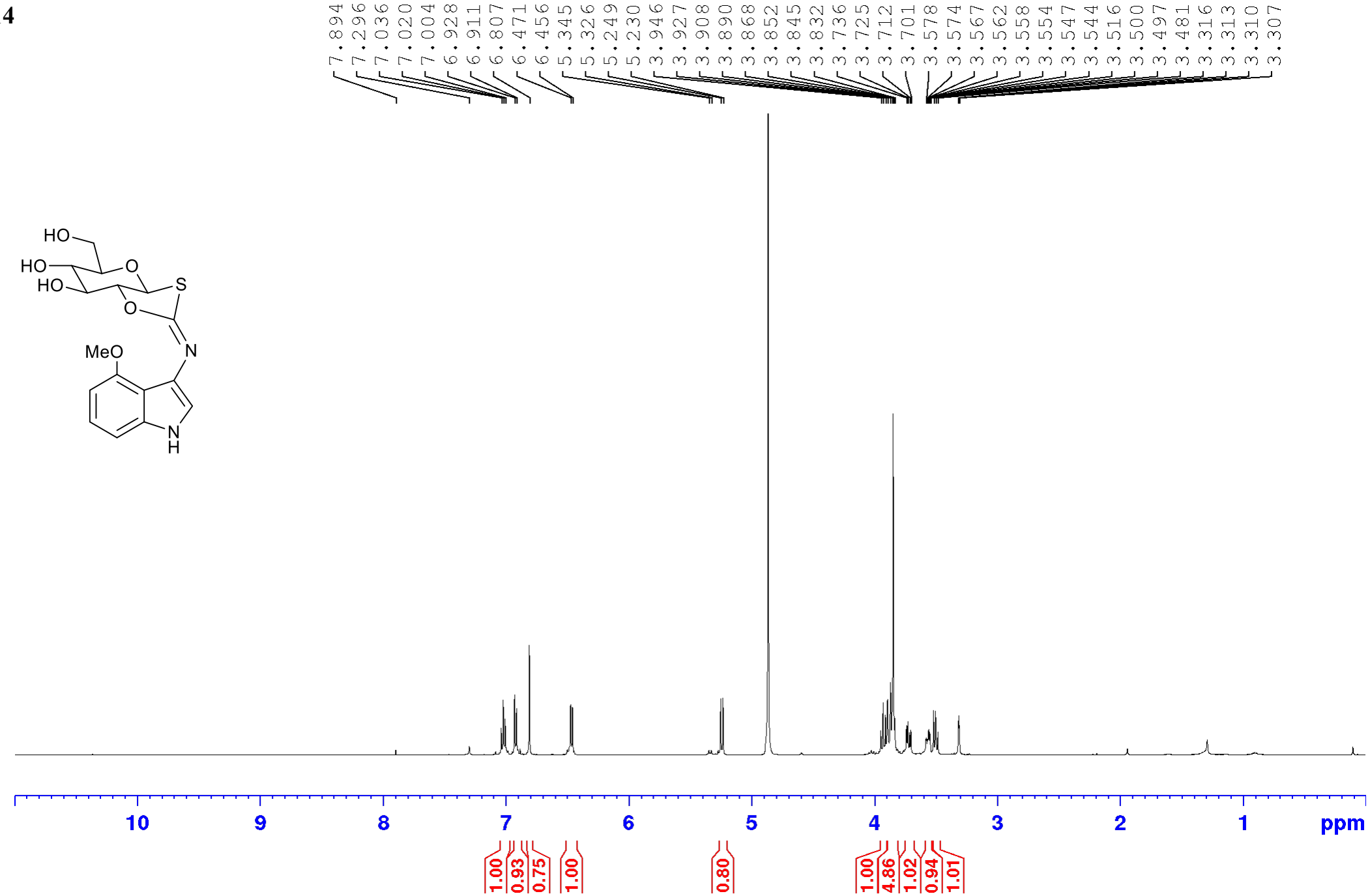
Compound **9**

CD_3OD

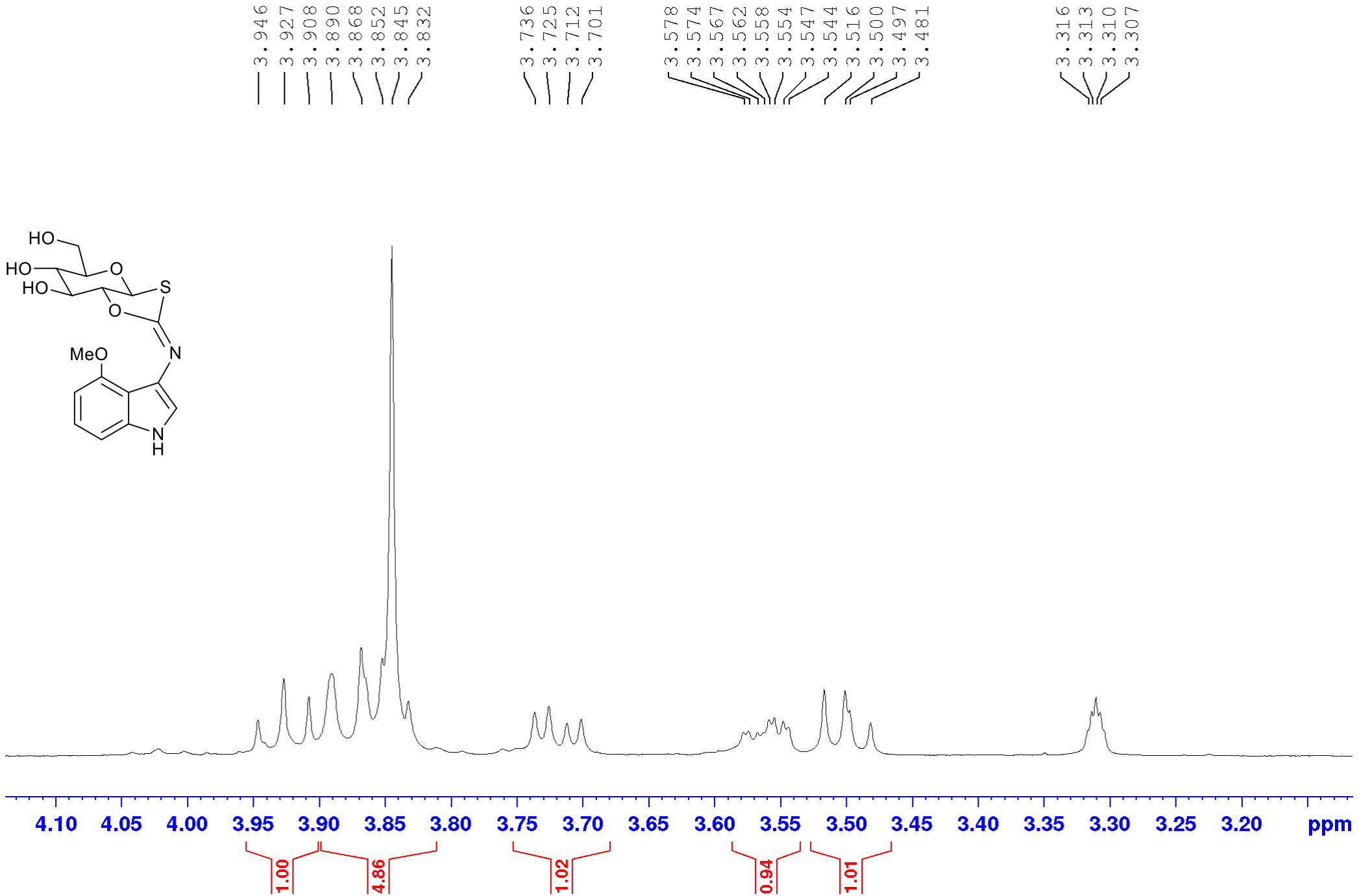


Compound **14**

CD_3OD

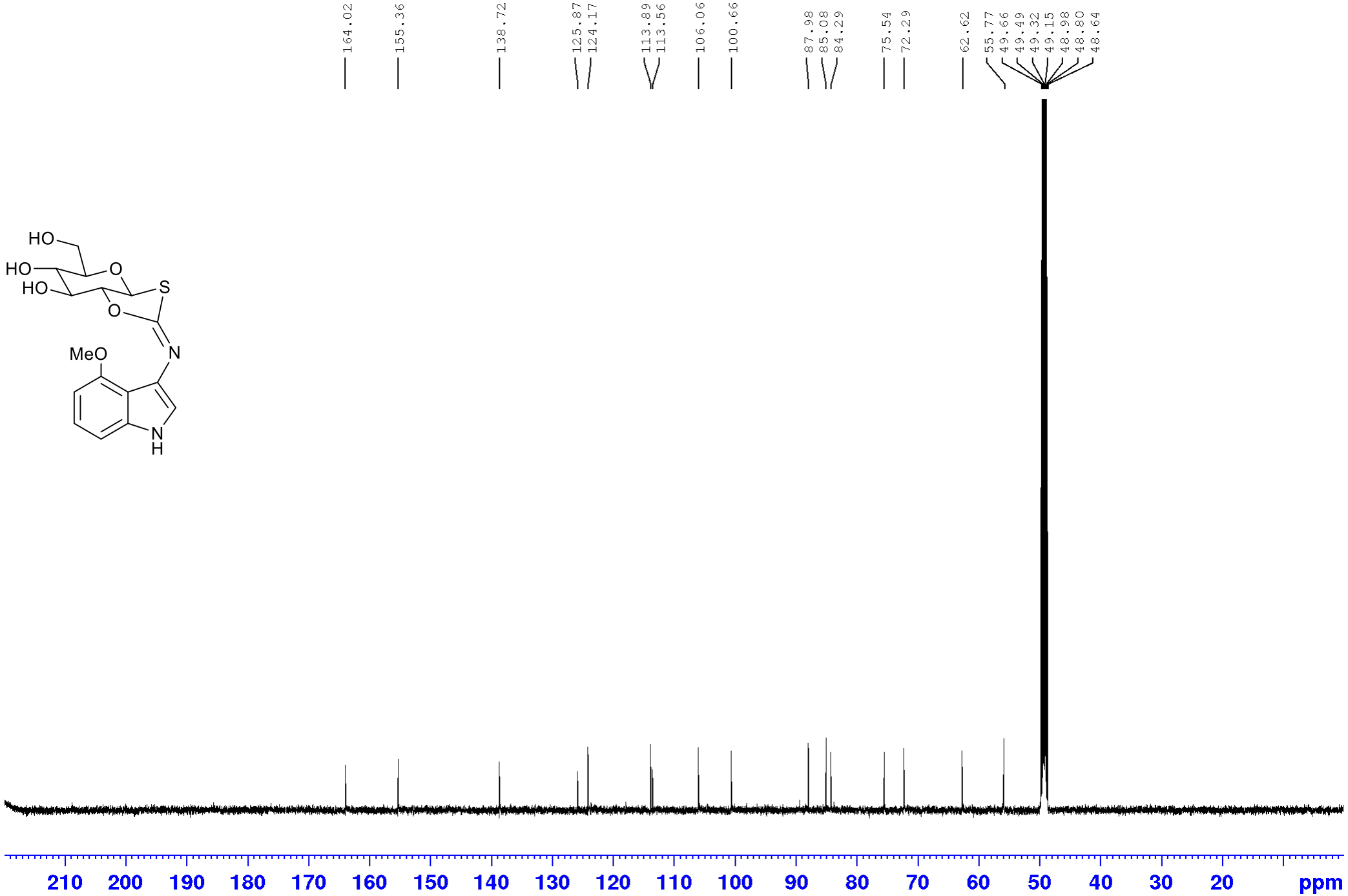


Compound **14**
expansion



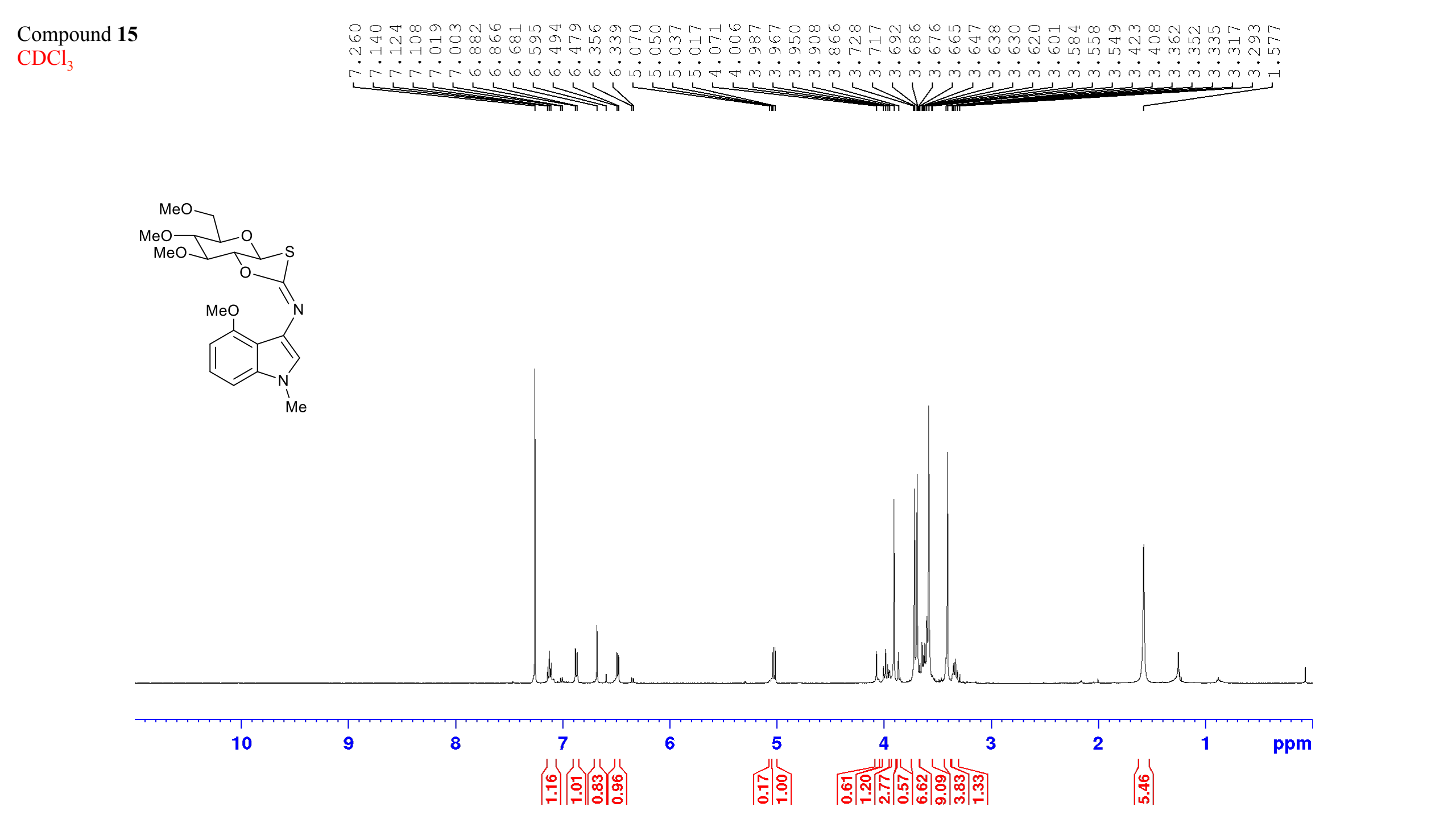
Compound **14**

CD_3OD

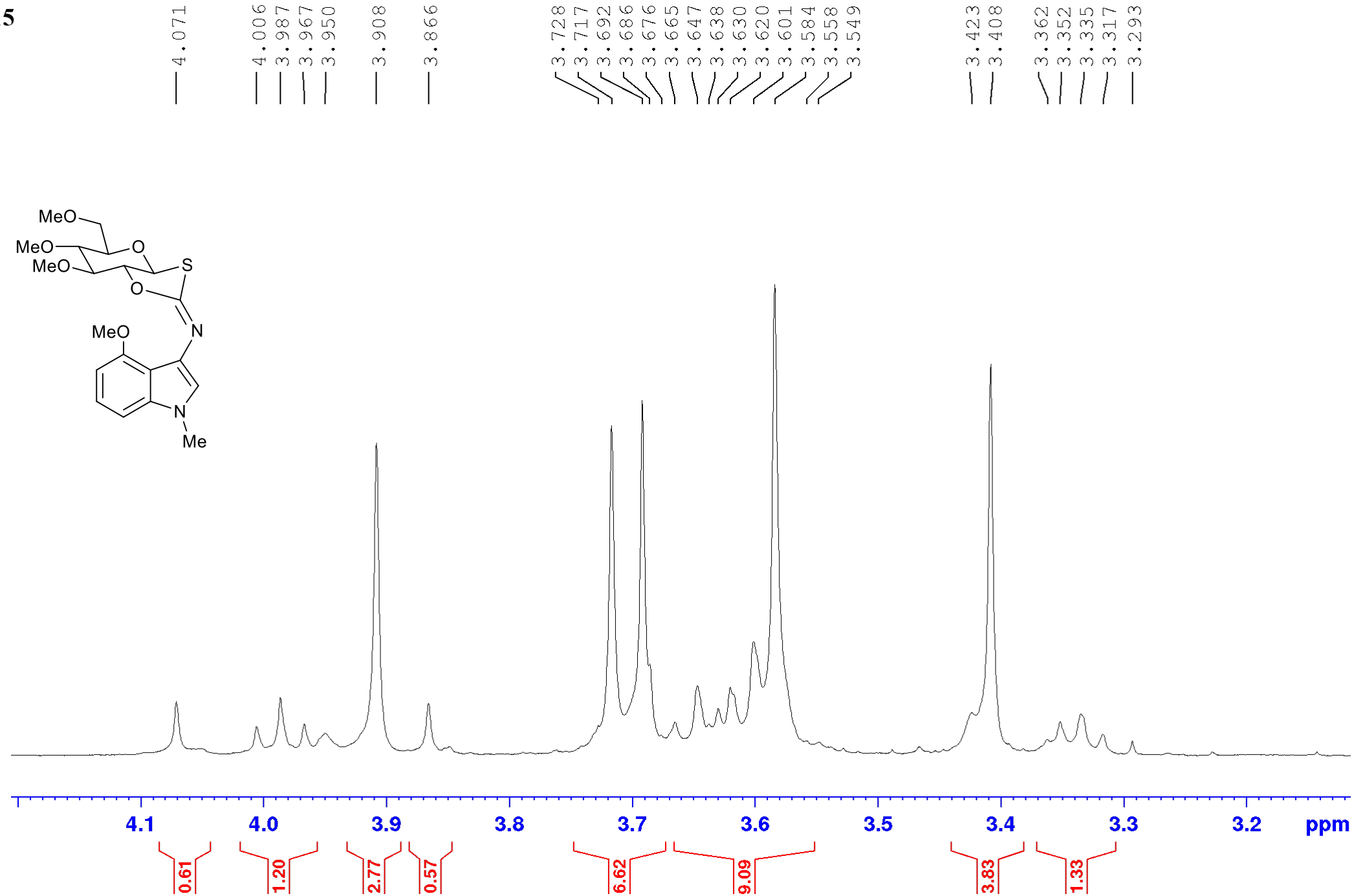


Compound **15**

$CDCl_3$

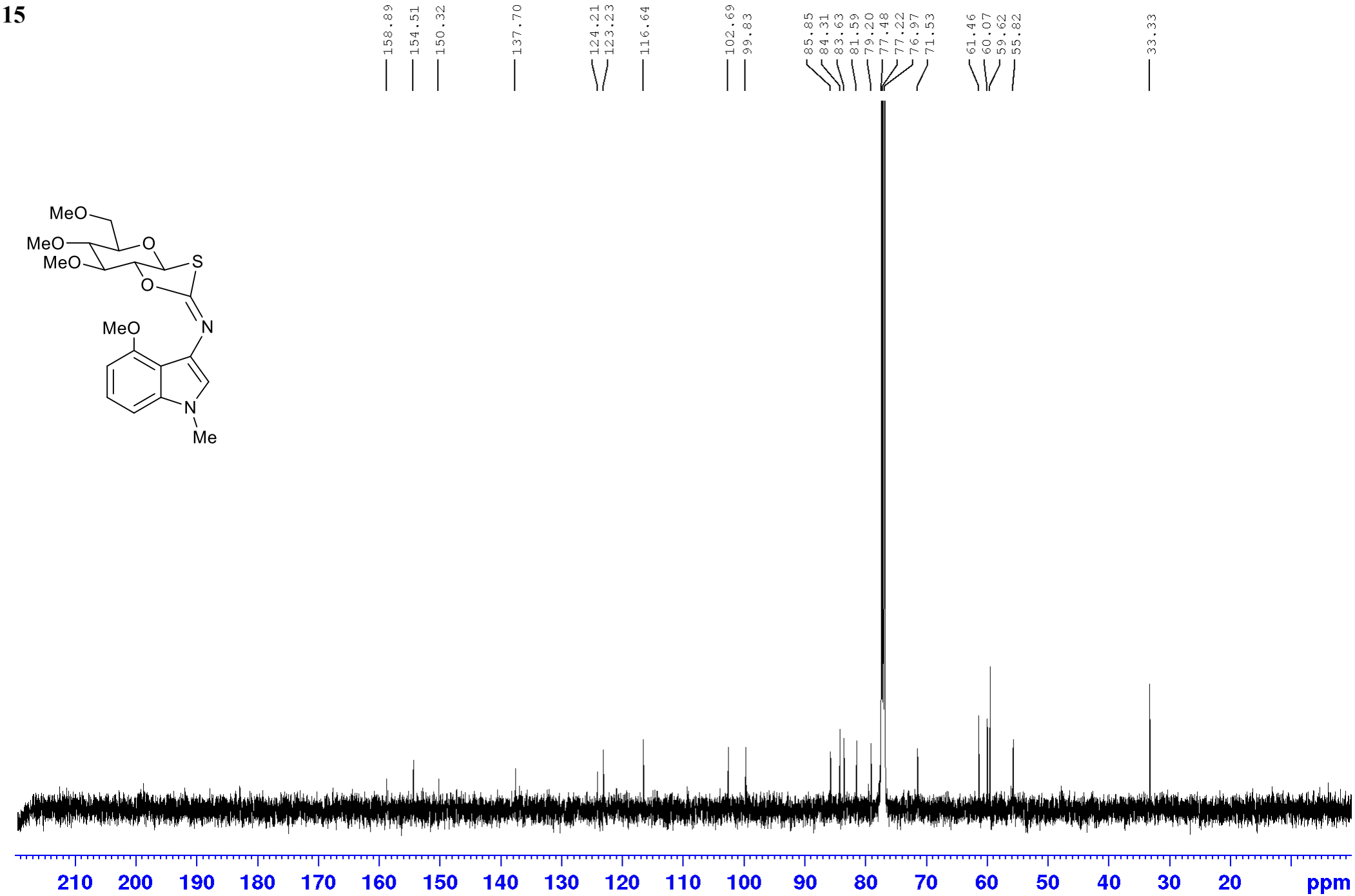


Compound **15**
expansion



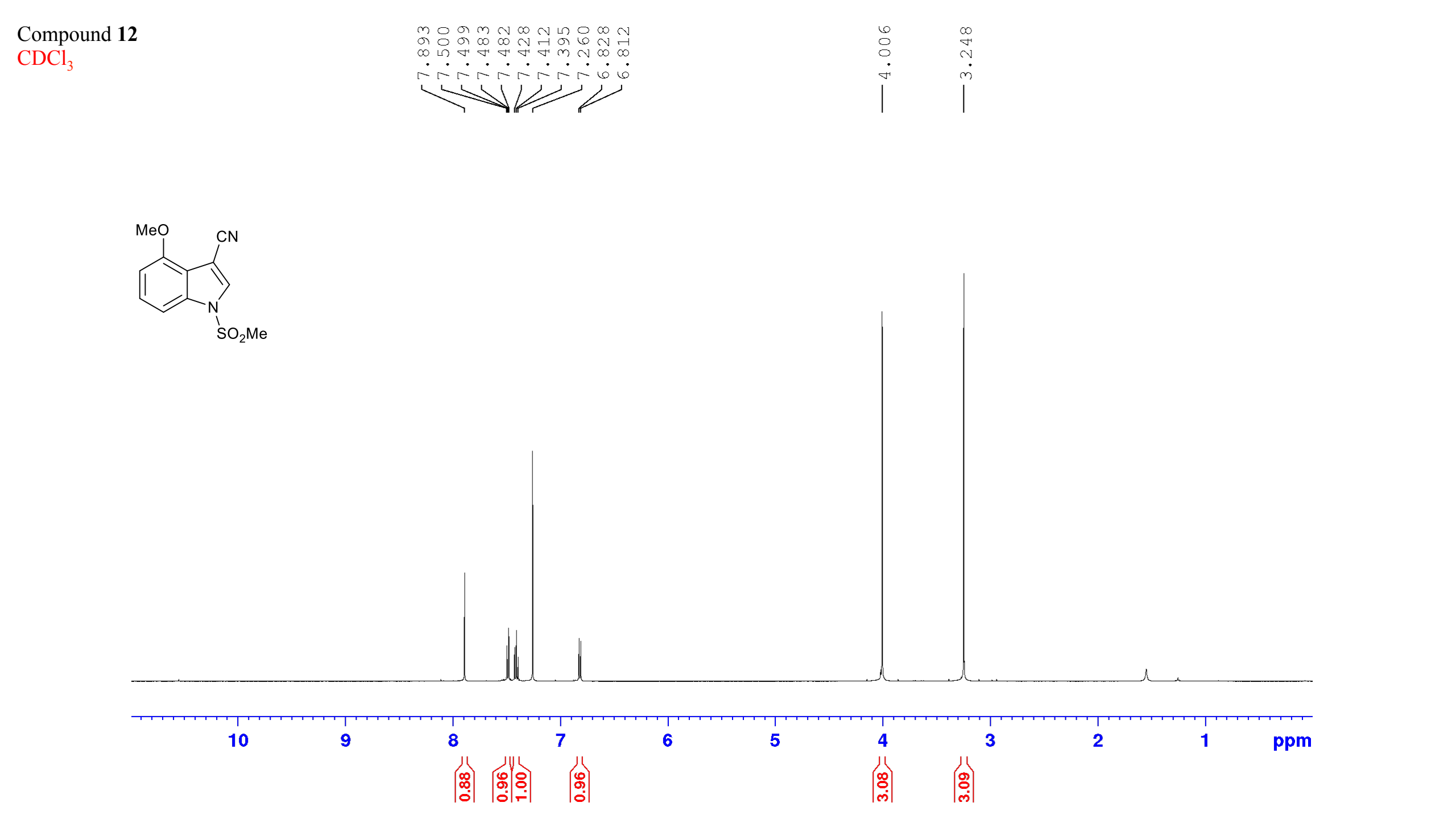
Compound **15**

$CDCl_3$



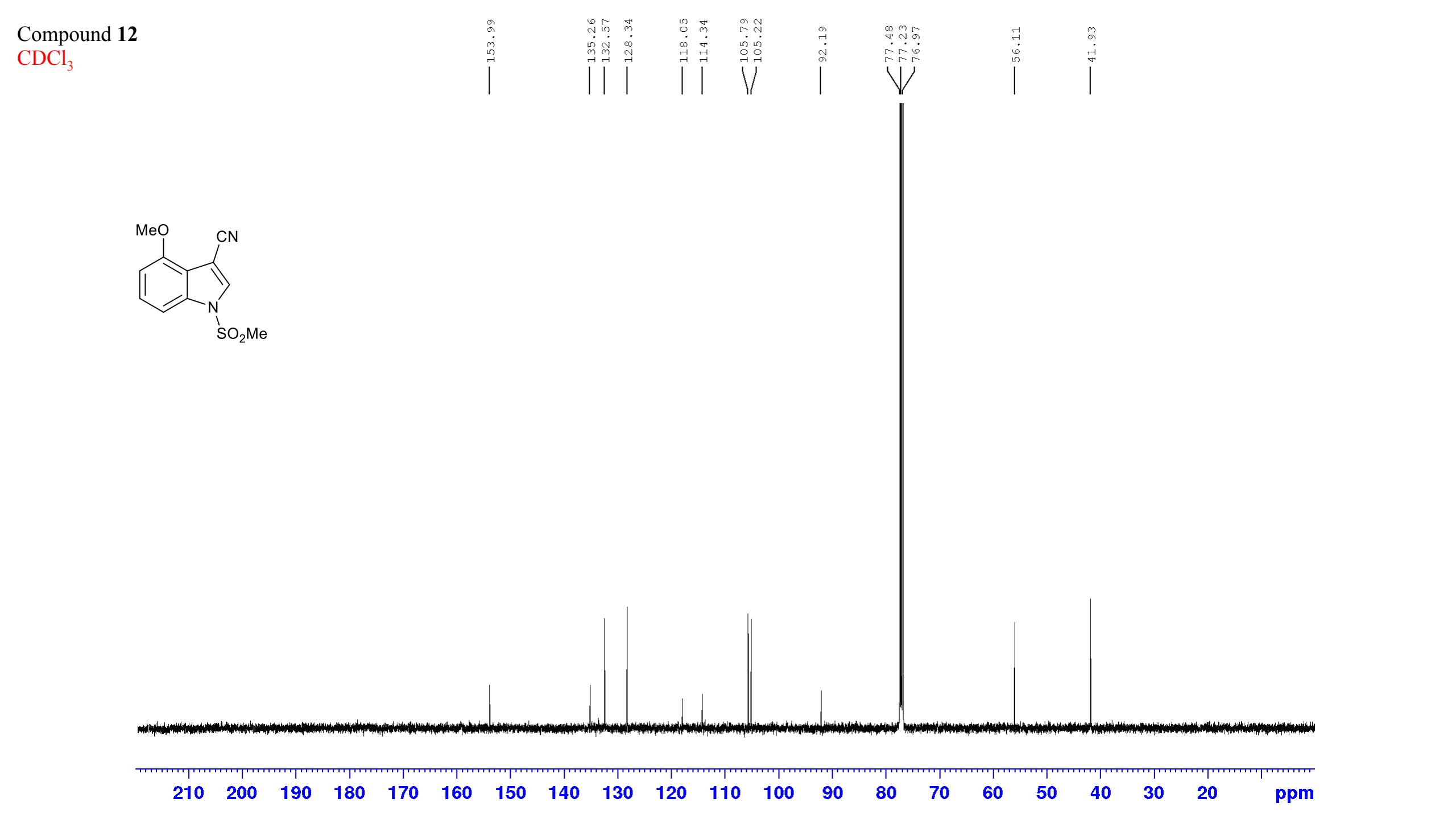
Compound **12**

$CDCl_3$



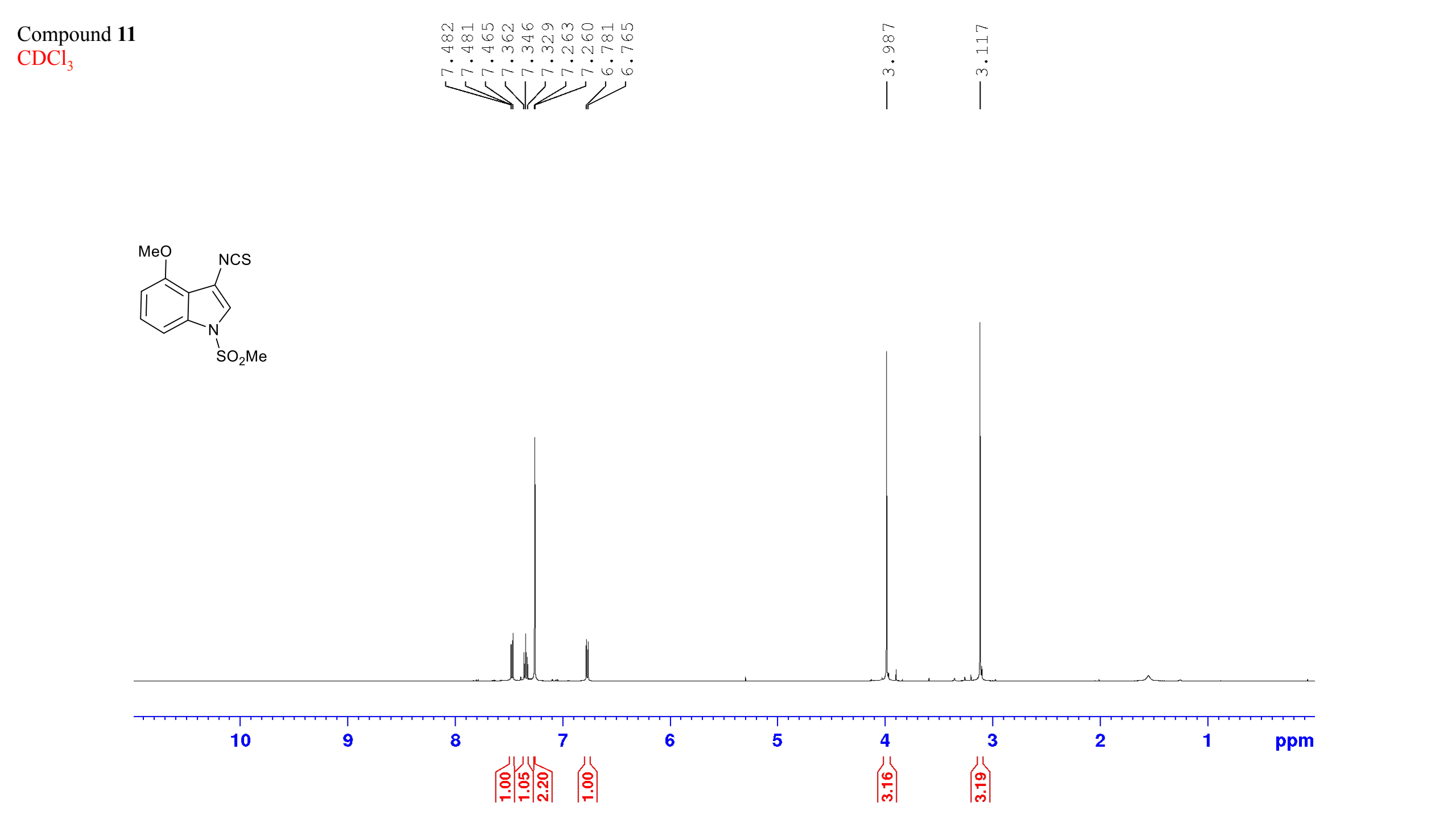
Compound **12**

$CDCl_3$



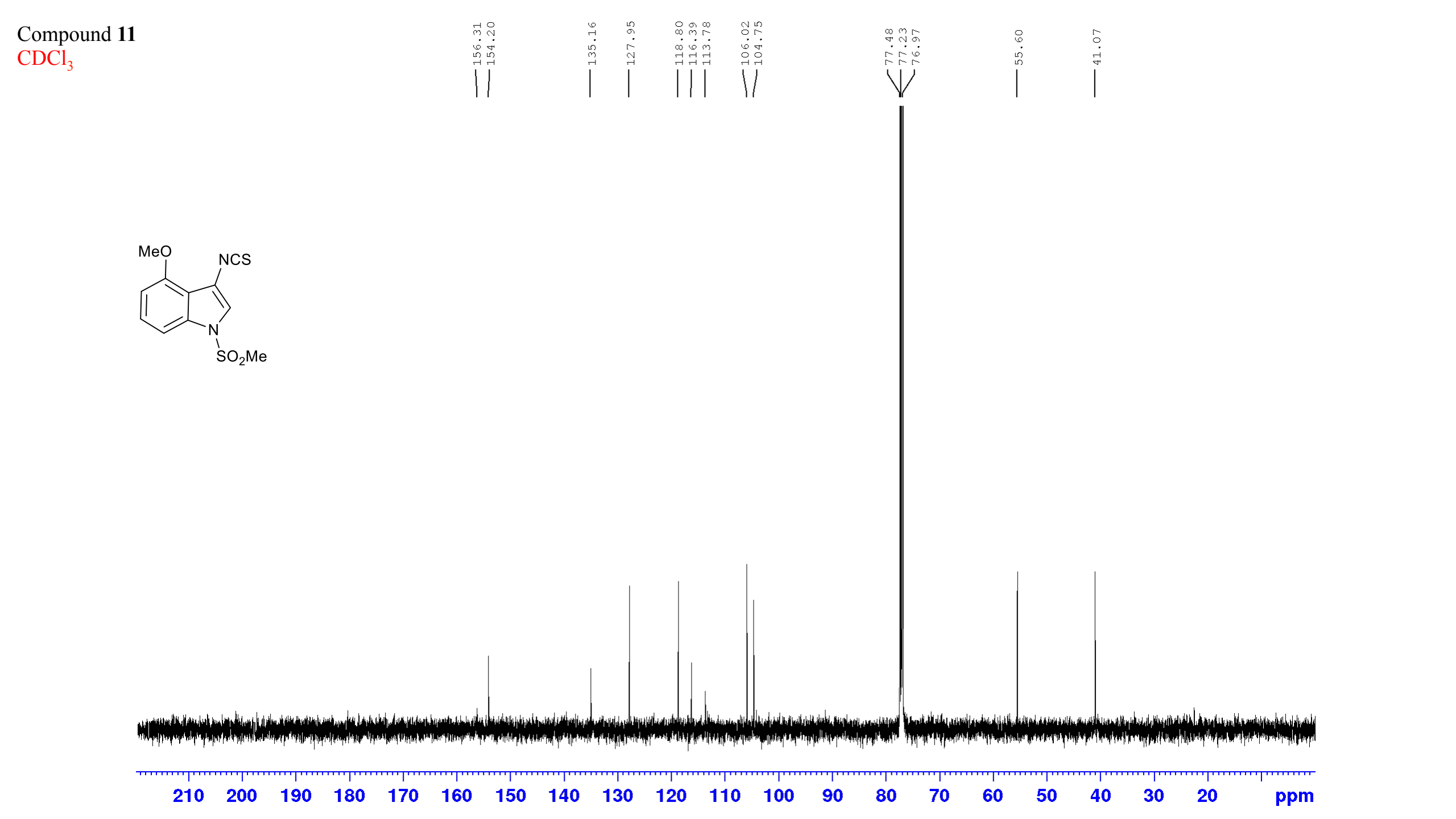
Compound **11**

$CDCl_3$



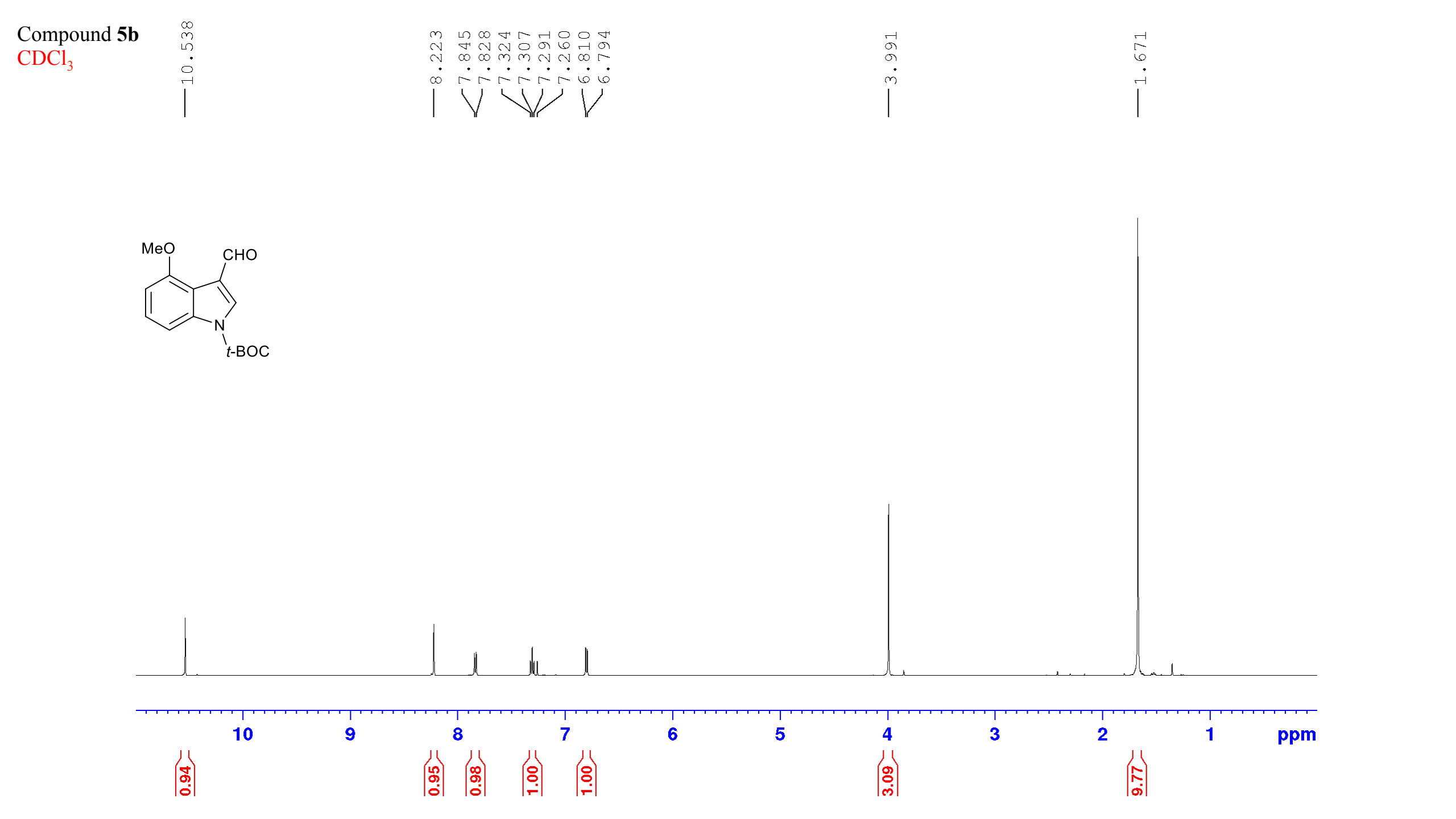
Compound **11**

$CDCl_3$



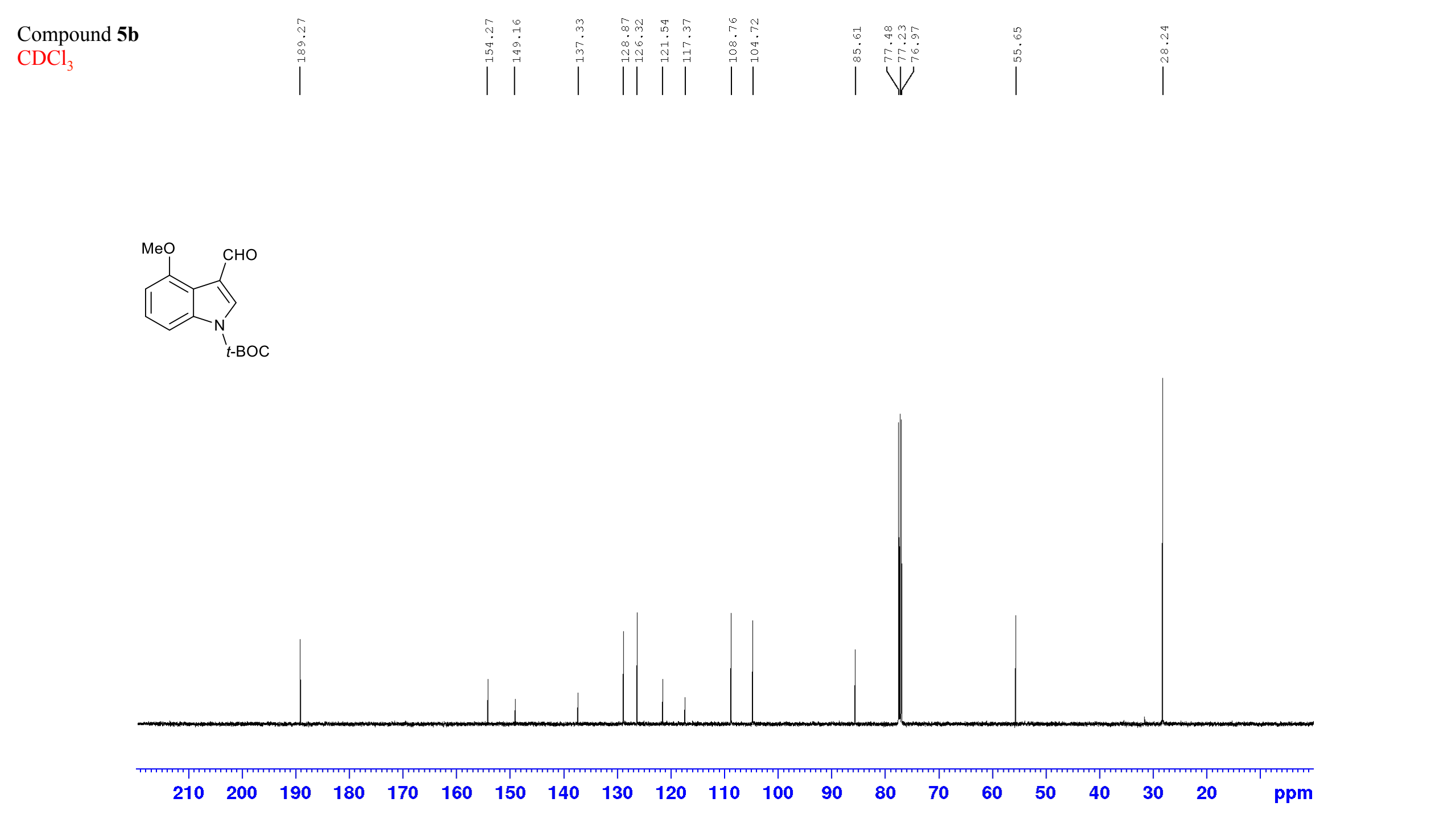
Compound **5b**

$CDCl_3$



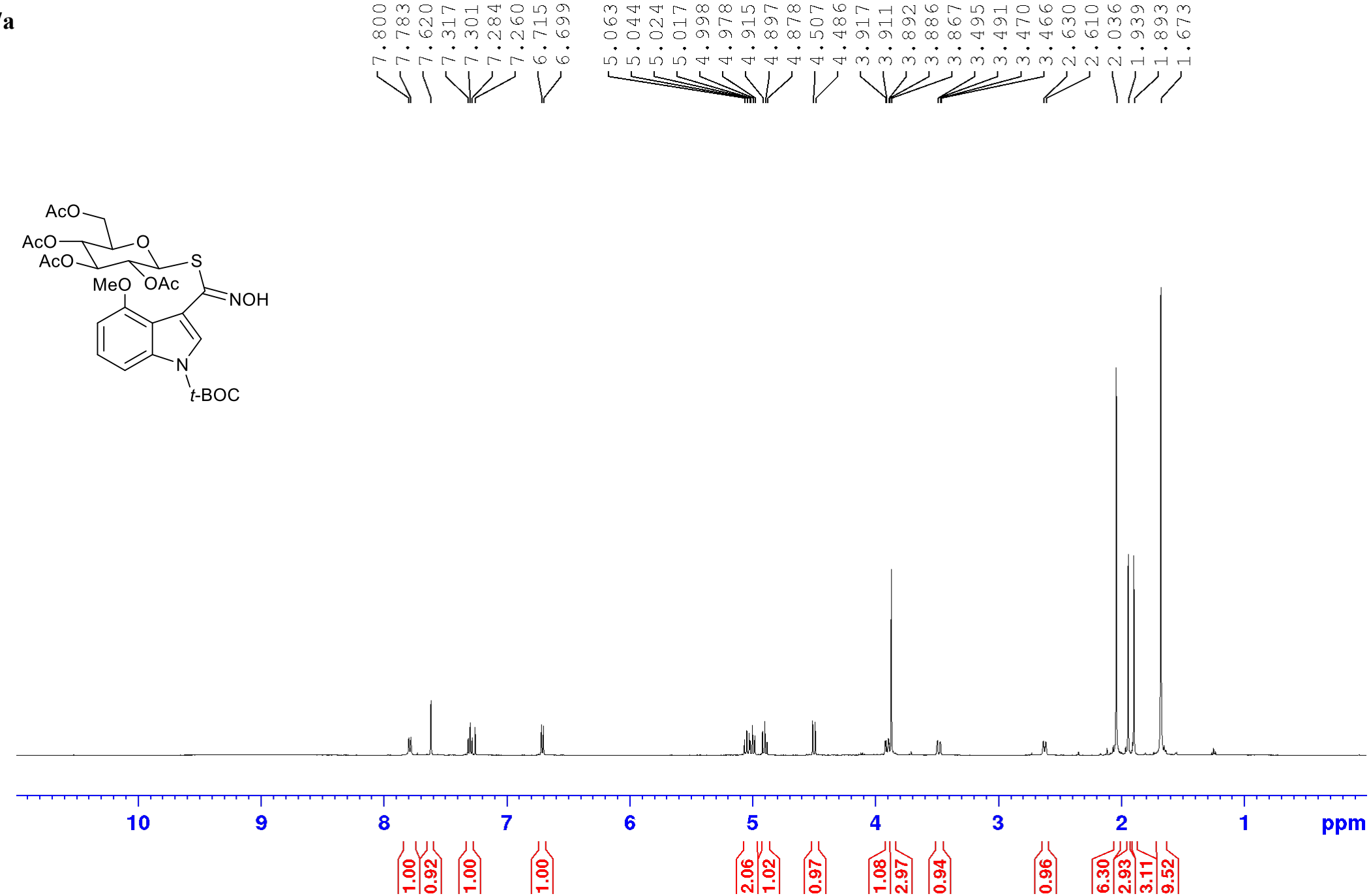
Compound **5b**

$CDCl_3$



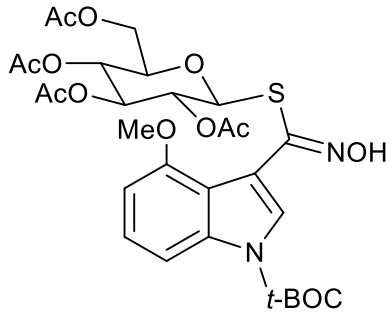
Compound **7a**

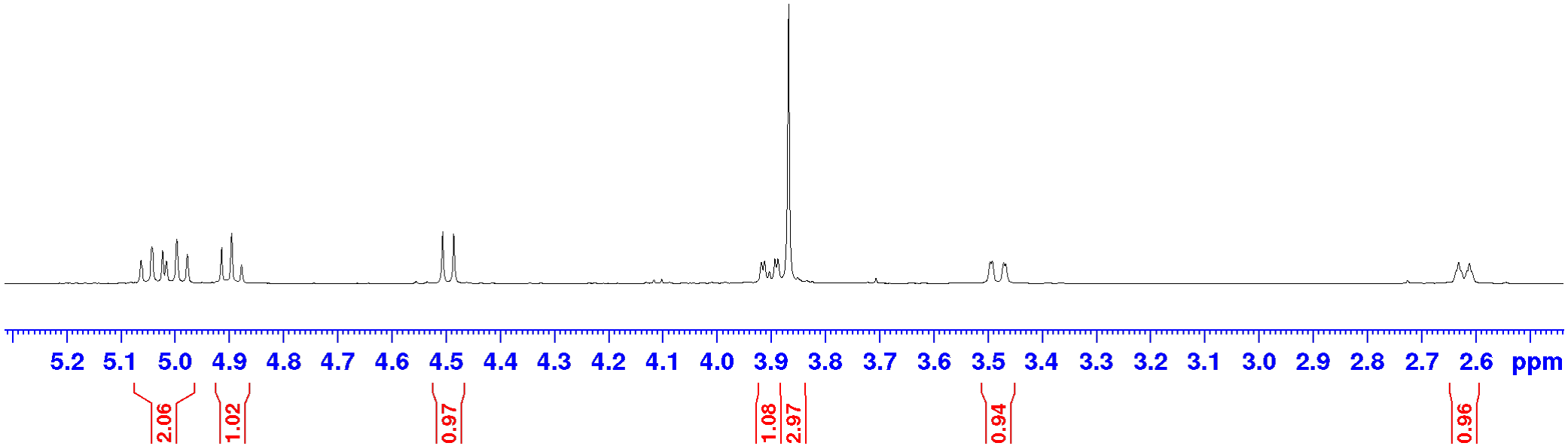
$CDCl_3$



Compound **7a**
expansion

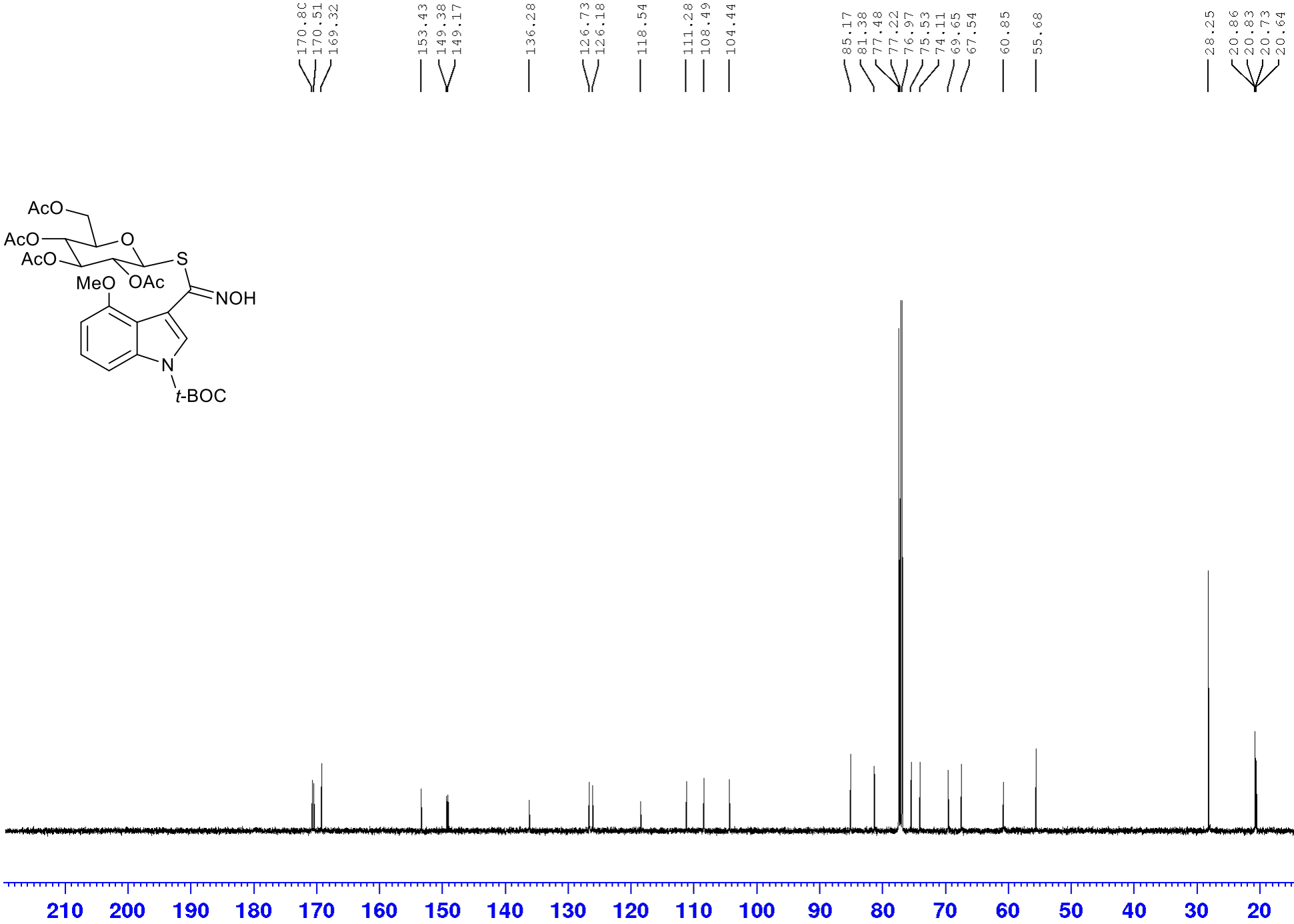
5.063
5.044
5.024
5.017
4.998
4.978
4.915
4.897
4.878
4.507
4.486
3.917
3.911
3.892
3.886
3.867
3.495
3.491
3.470
3.466
2.630
2.610





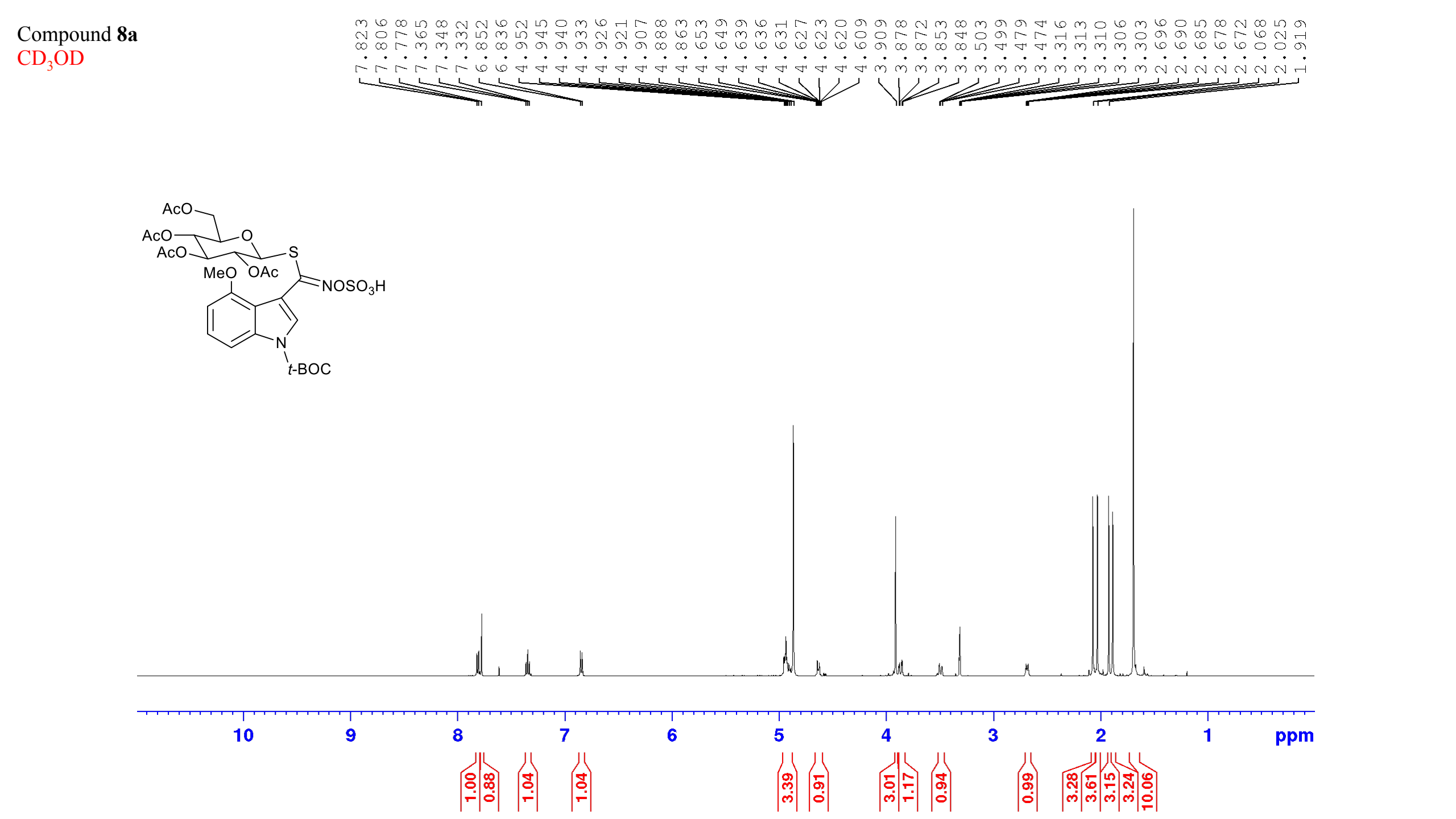
Compound **7a**

$CDCl_3$

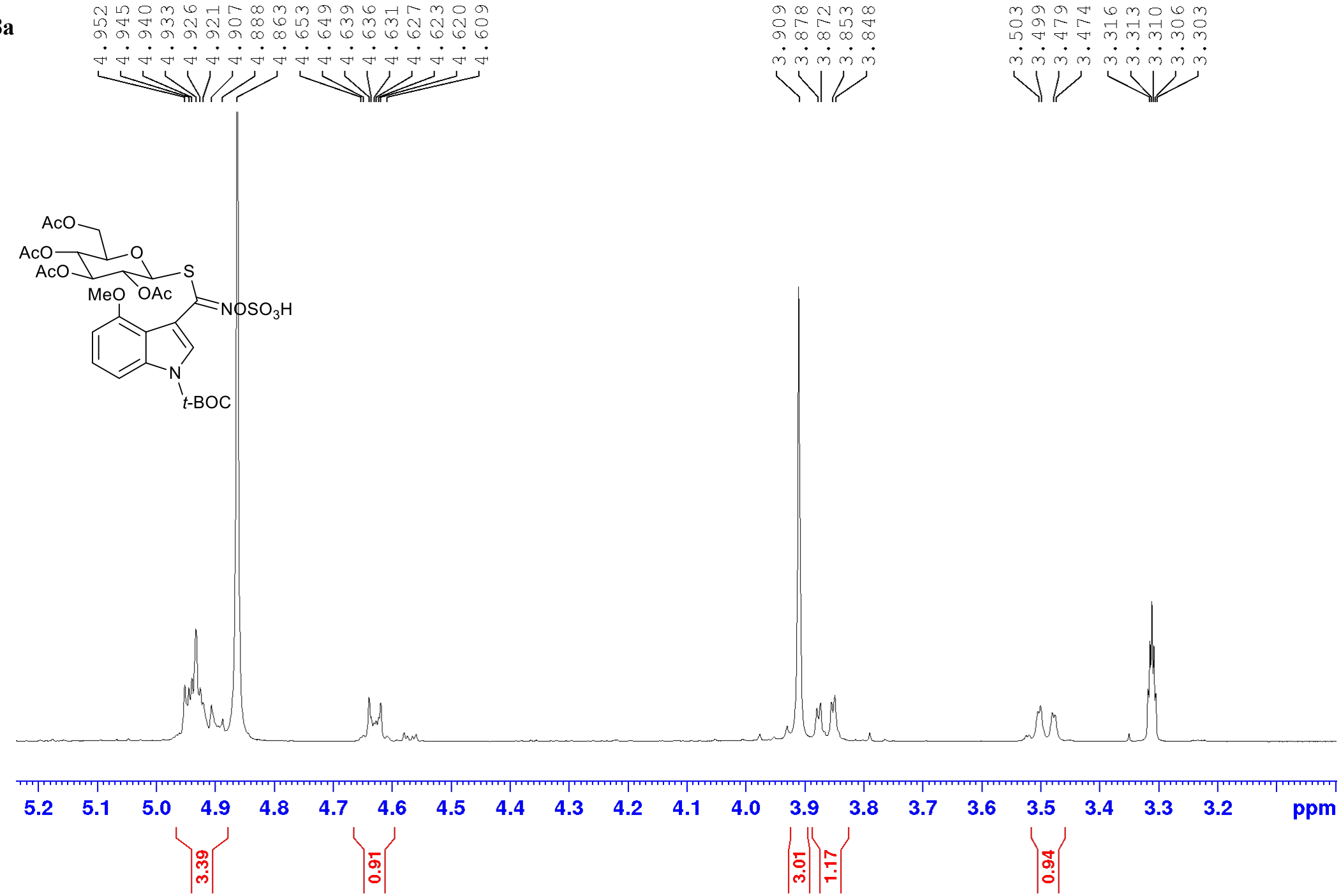


Compound **8a**

CD_3OD

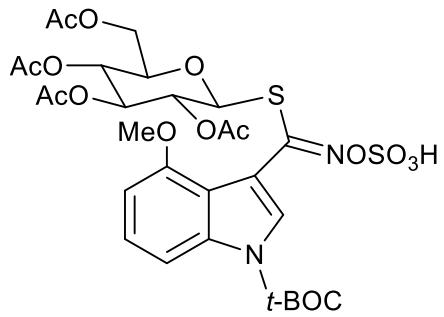


Compound **8a**
expansion



Compound **8a**

CD_3OD

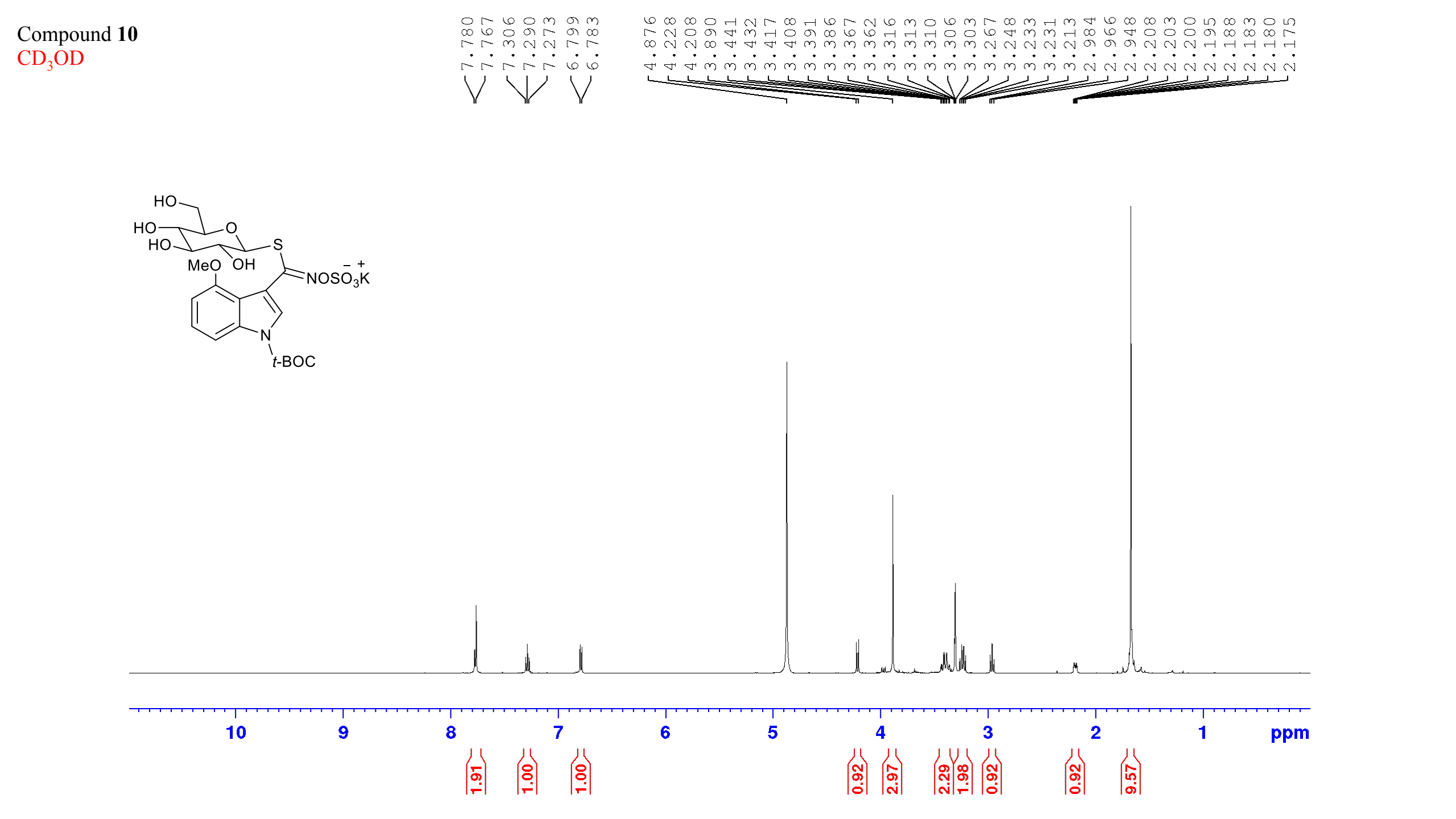


172.15
171.57
171.09
171.05
155.99
154.86
150.57
137.62
127.90
127.81
119.79
111.97
109.39
105.56
86.27
82.55
76.63
75.23
70.99
69.05
62.09
56.26
49.66
49.49
49.32
49.15
48.98
48.81
48.64
28.42
20.79
20.73
20.60
20.55

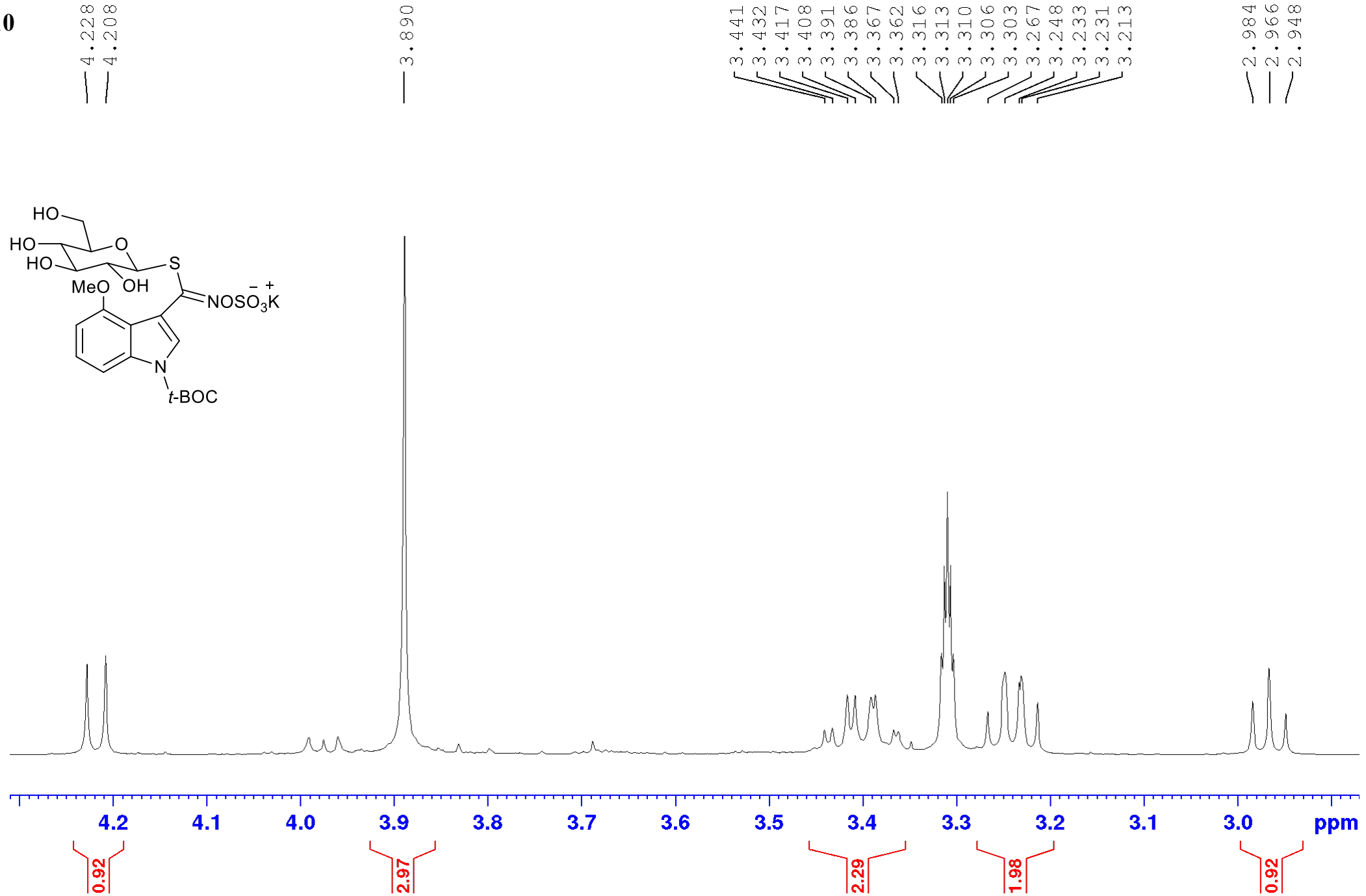
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Compound **10**

CD_3OD

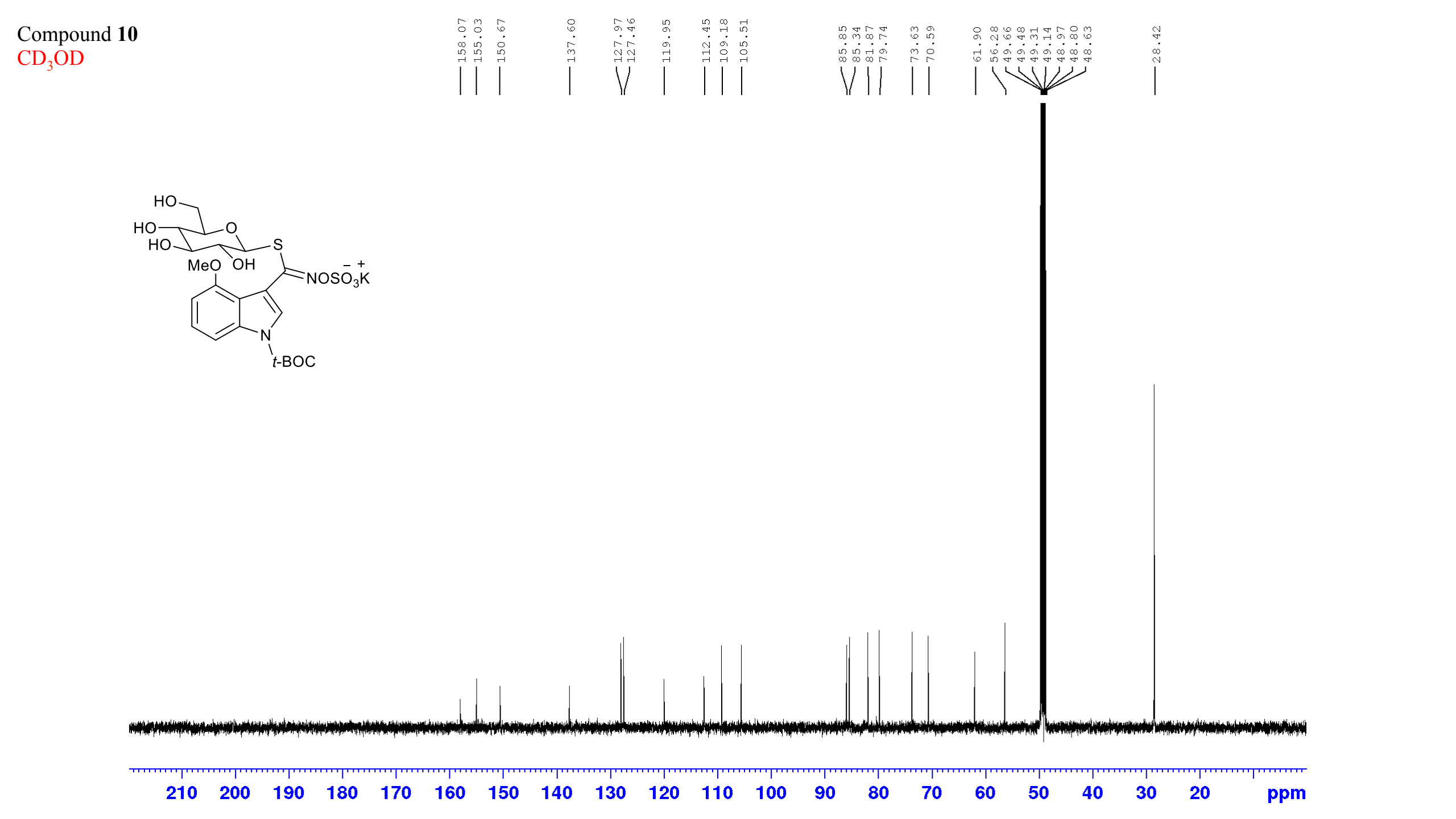


Compound **10**
expansion



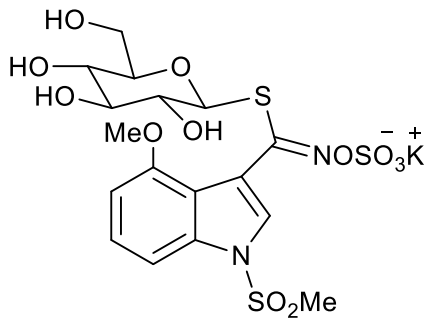
Compound **10**

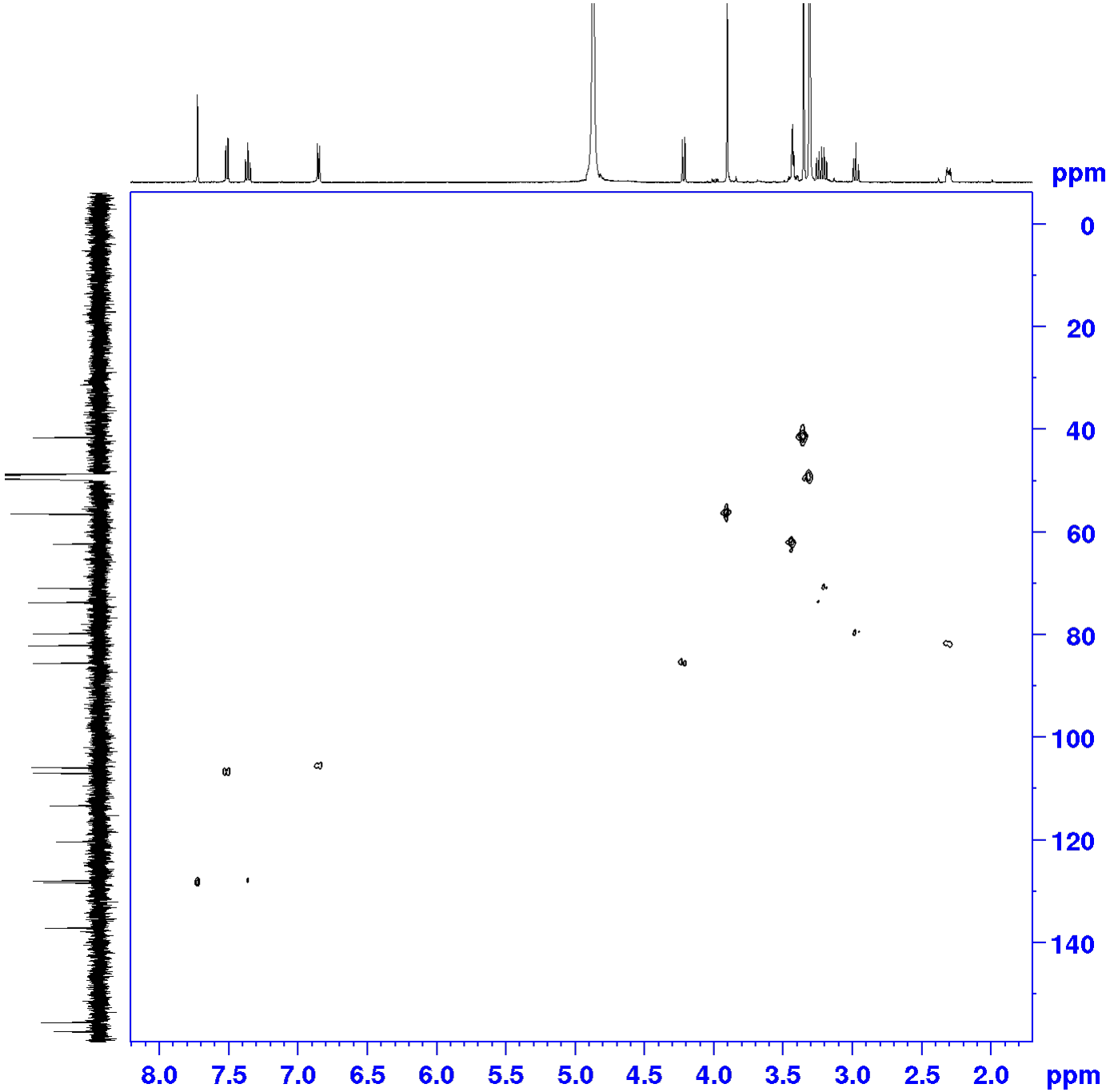
CD_3OD



Compound **9**

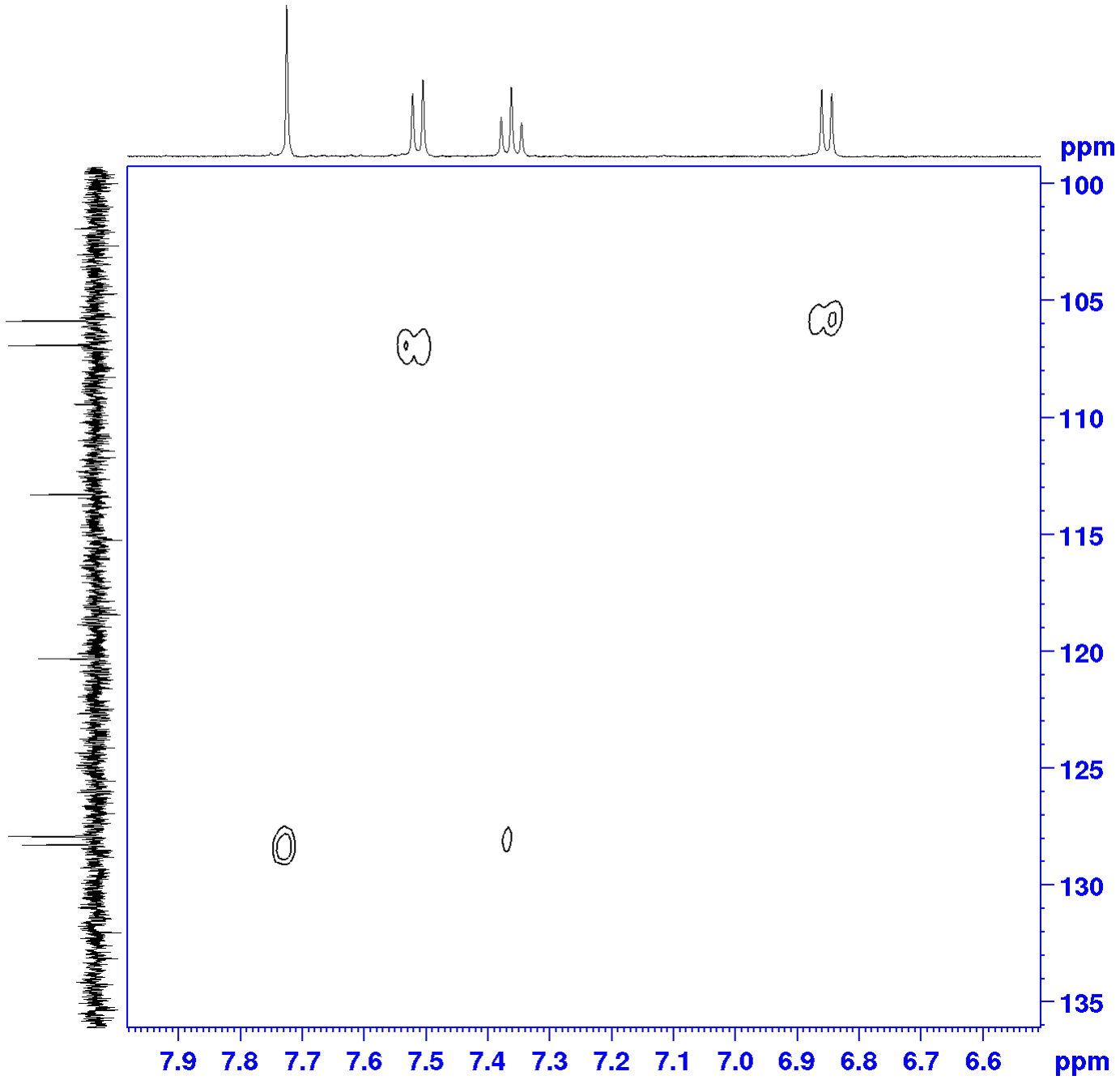
HMQC





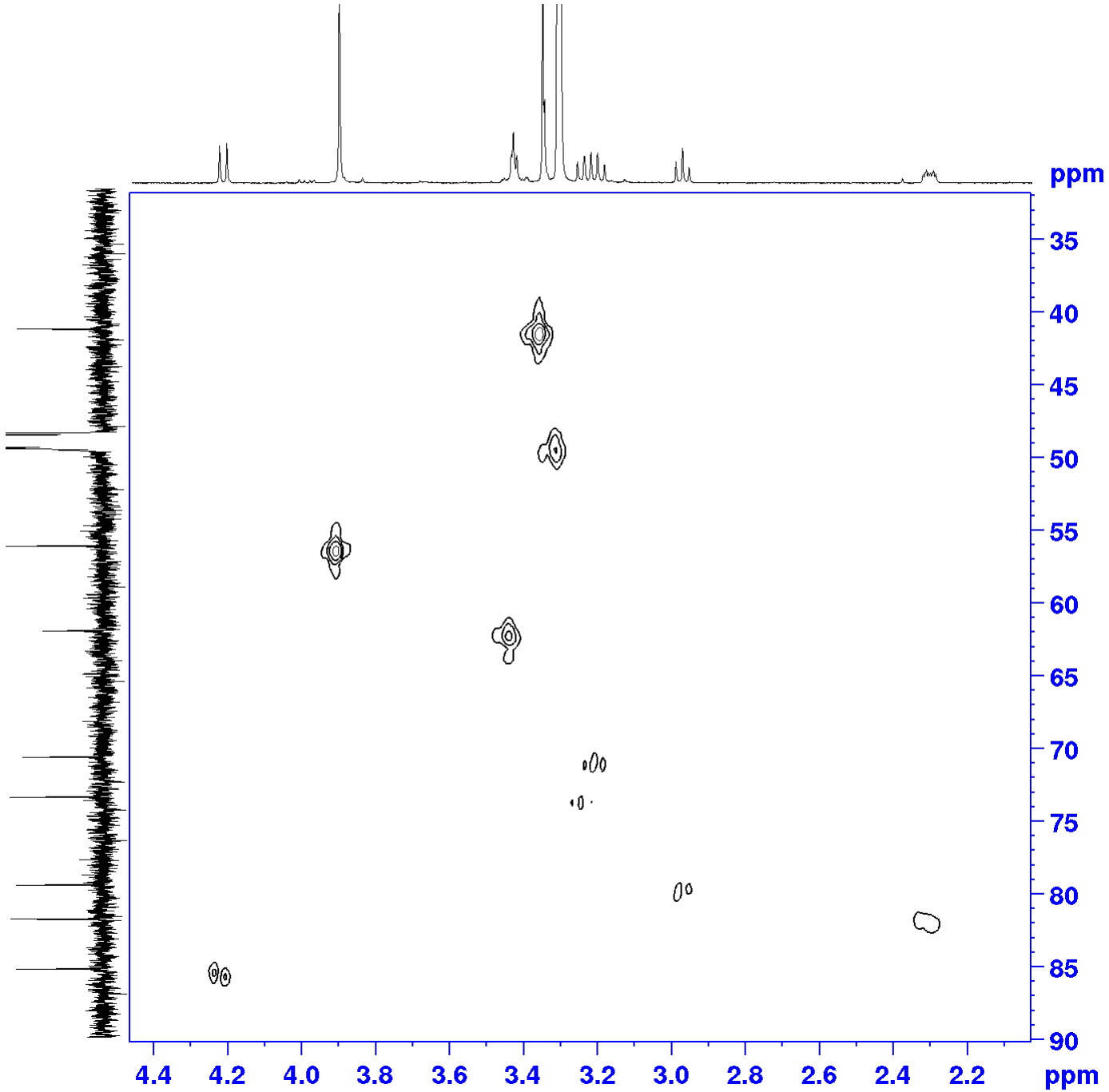
Compound **9**

HMQC expand

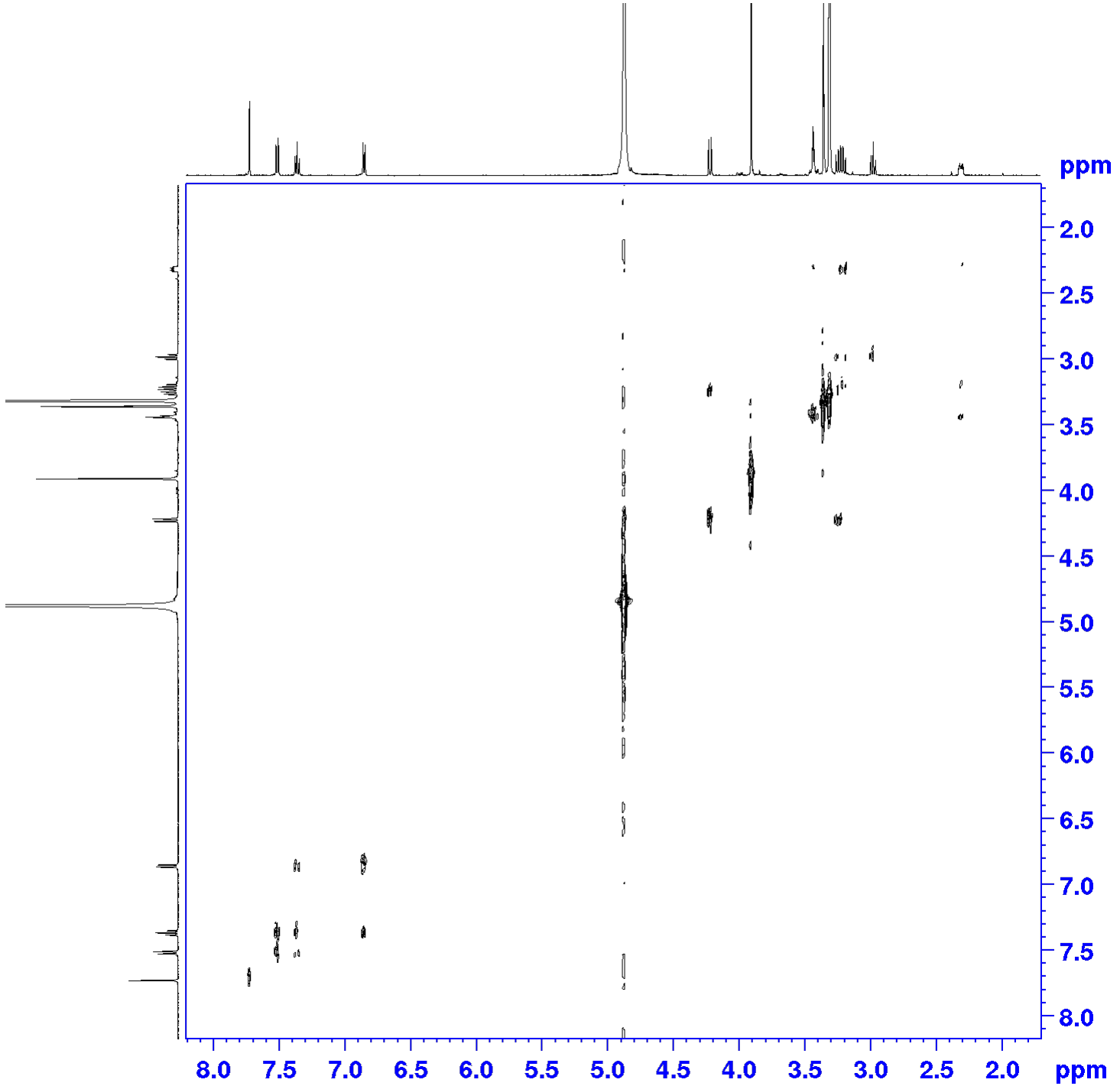


Compound **9**

HMQC expansion

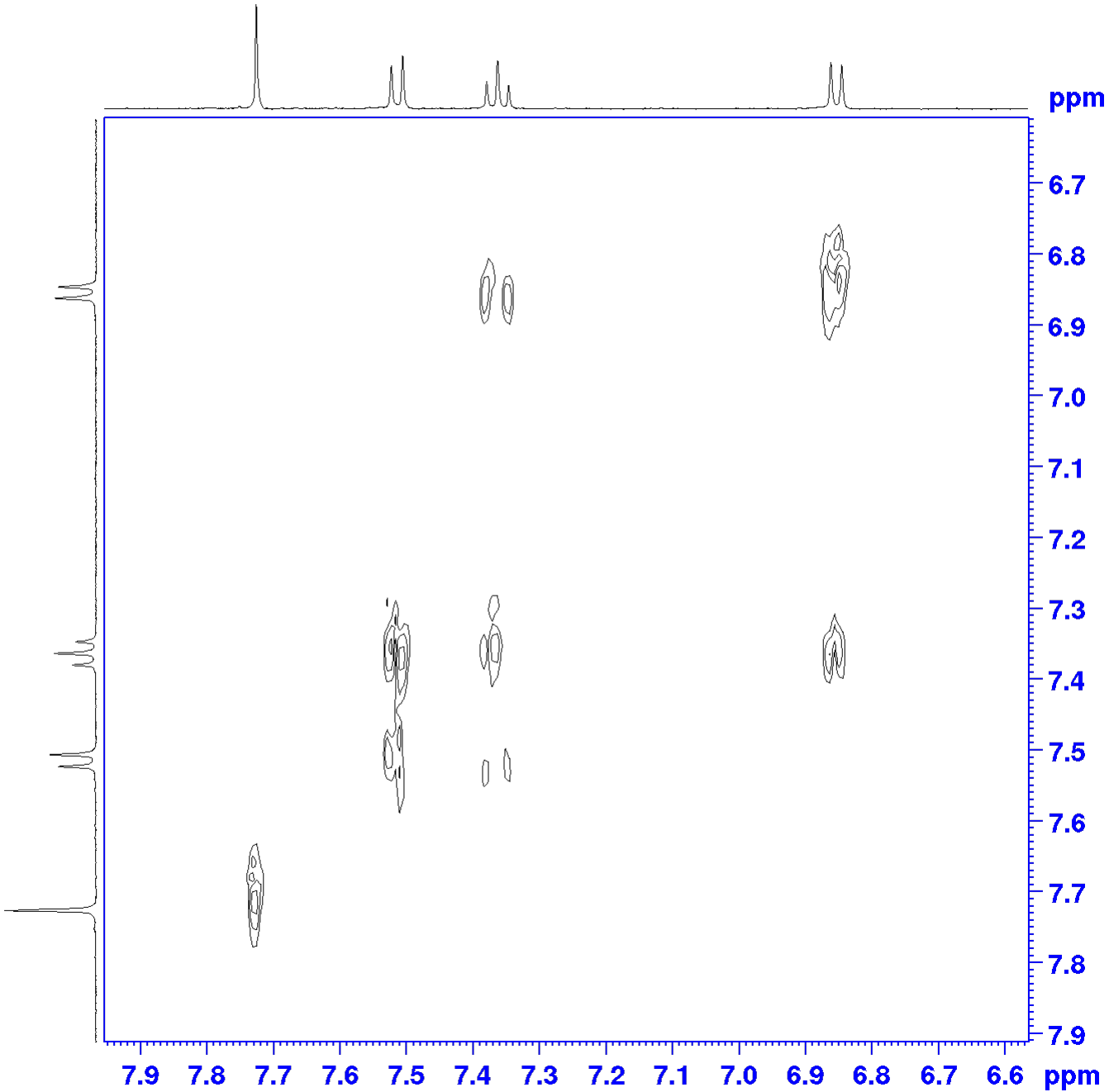


Compound **9**
COSY

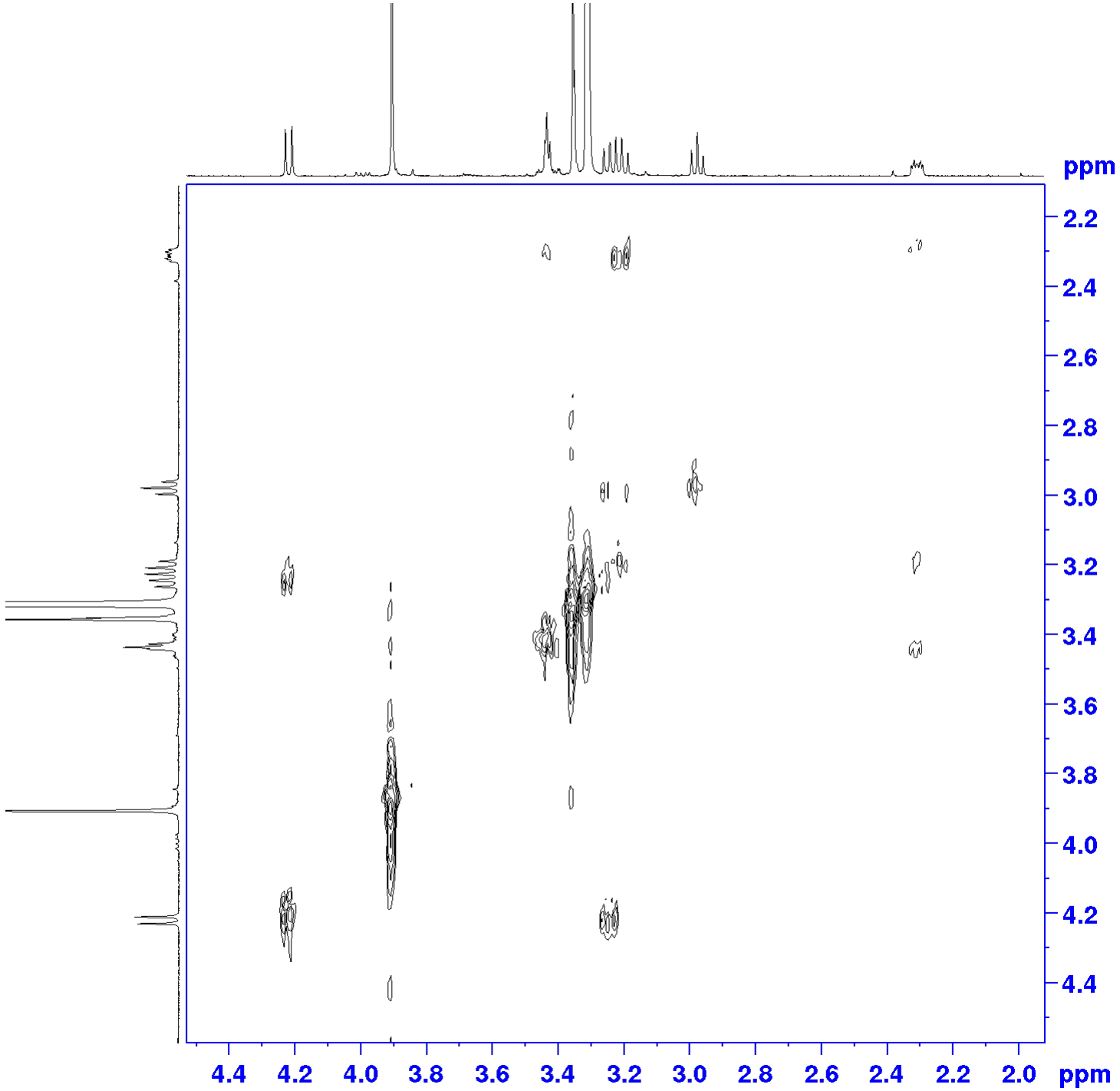


Compound **9**

COSY expand

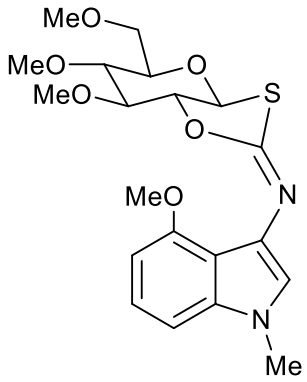


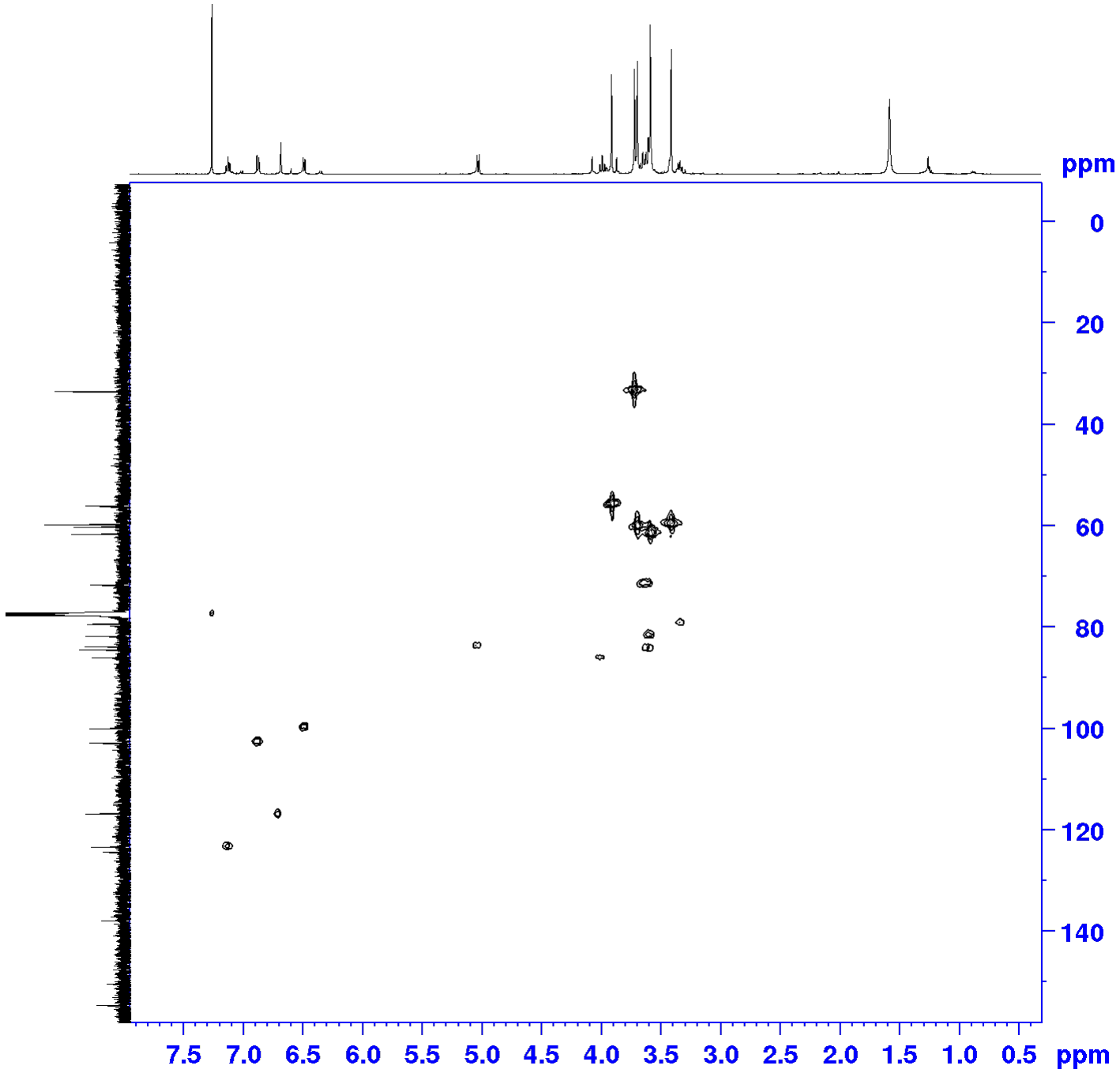
Compound **9**
COSY expand



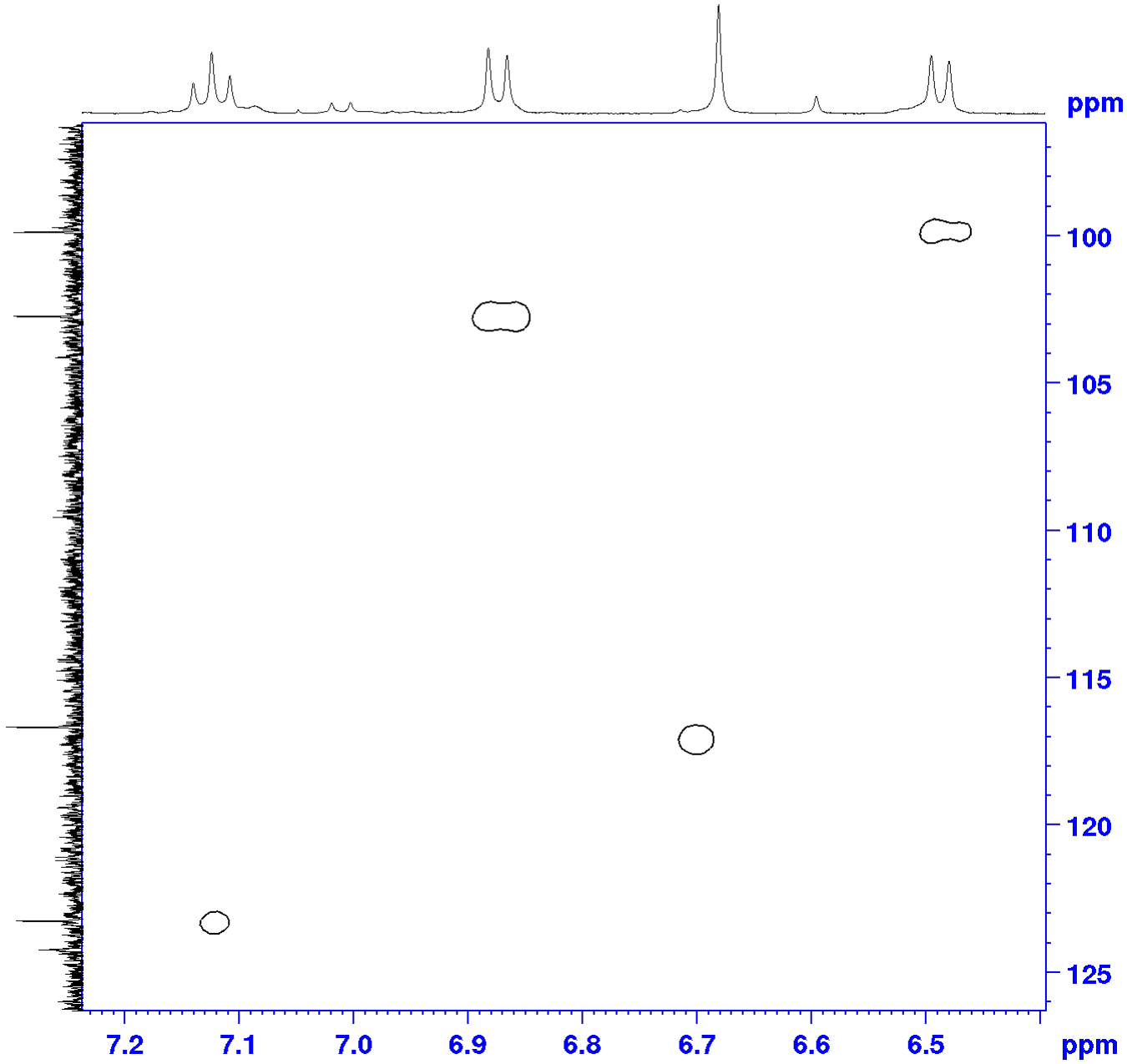
Compound **15**

HMQC

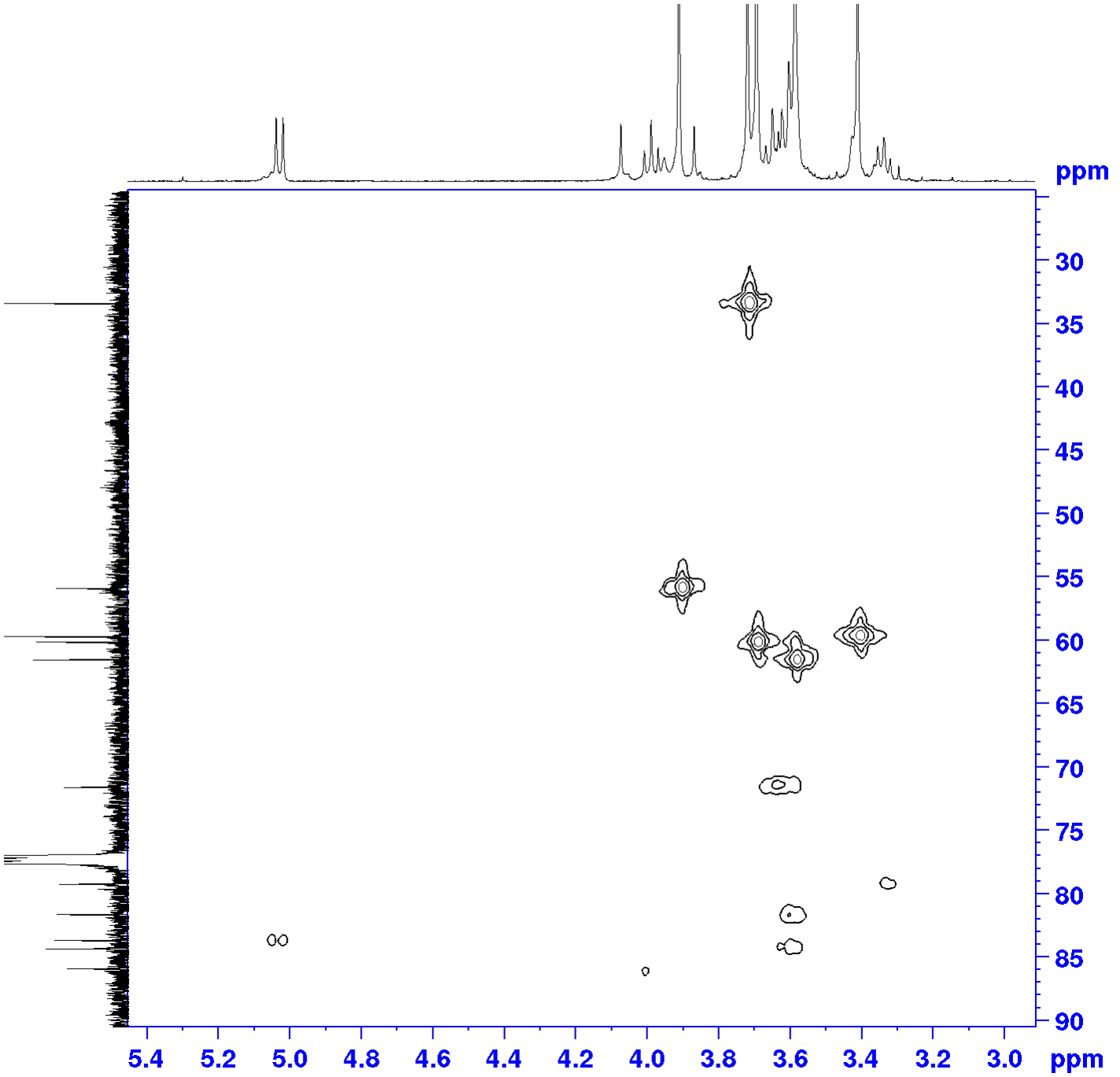




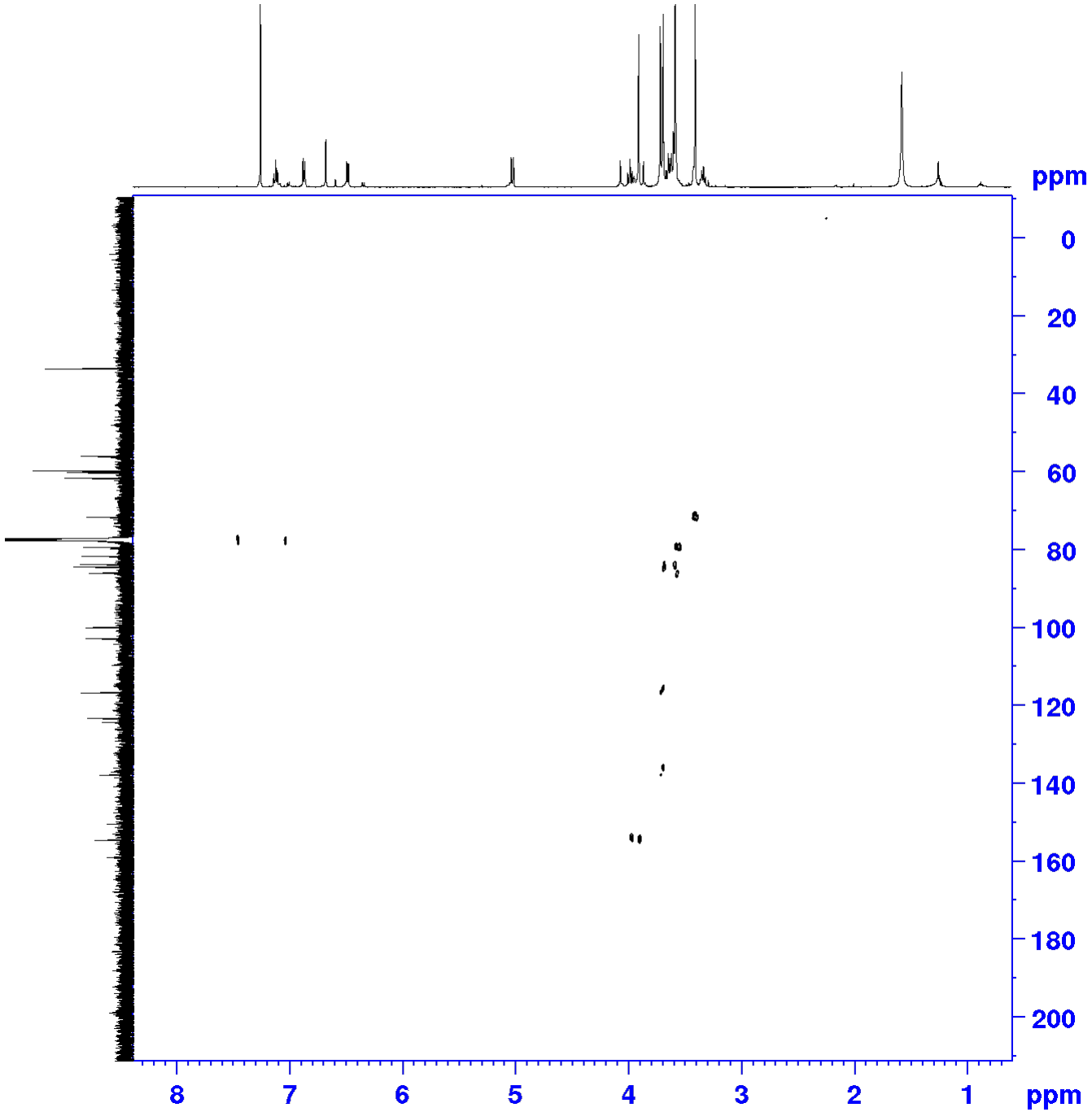
Compound **15**
HMQC expand



Compound **15**
HMQC expand

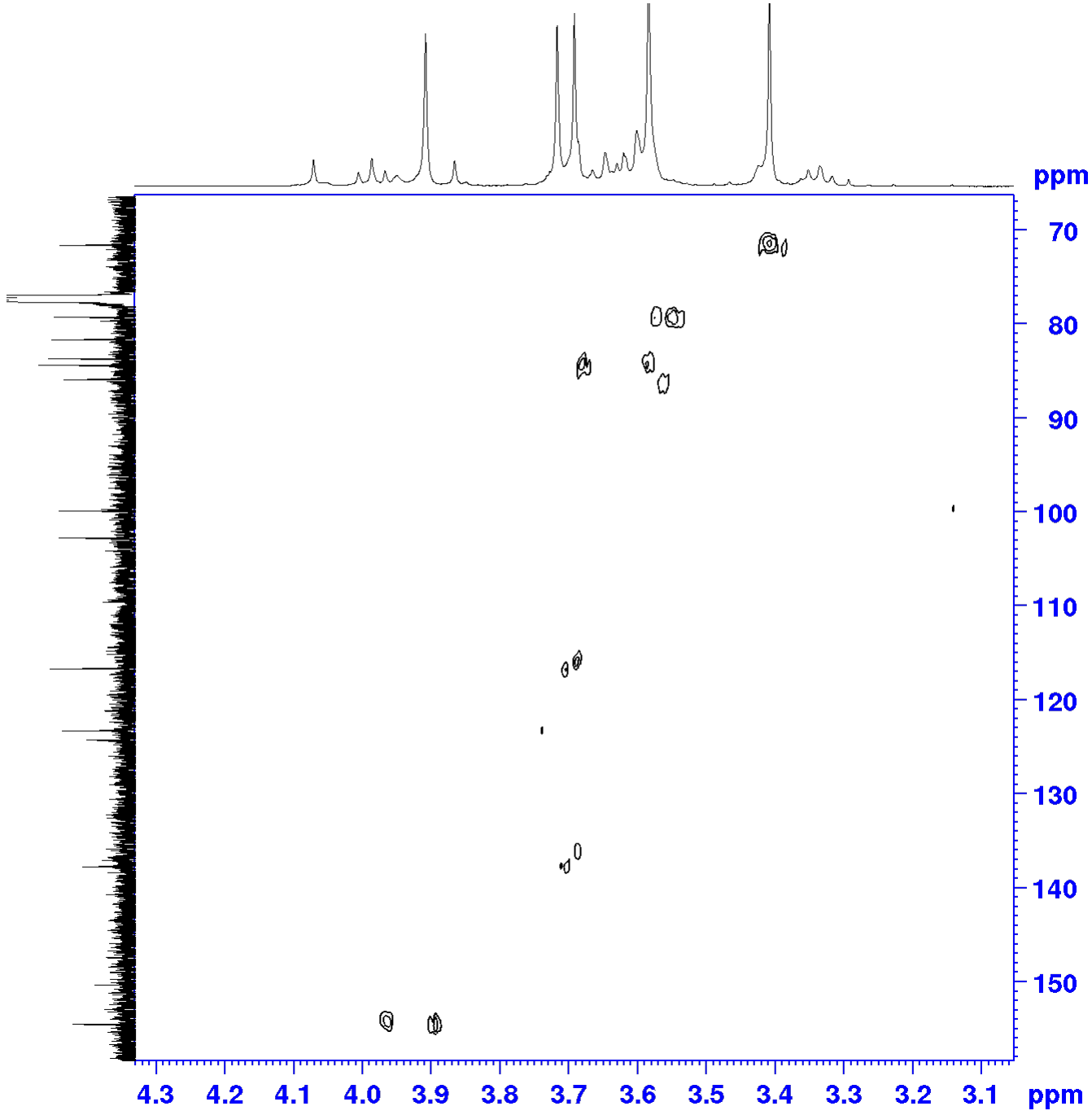


Compound **15**
HMBC

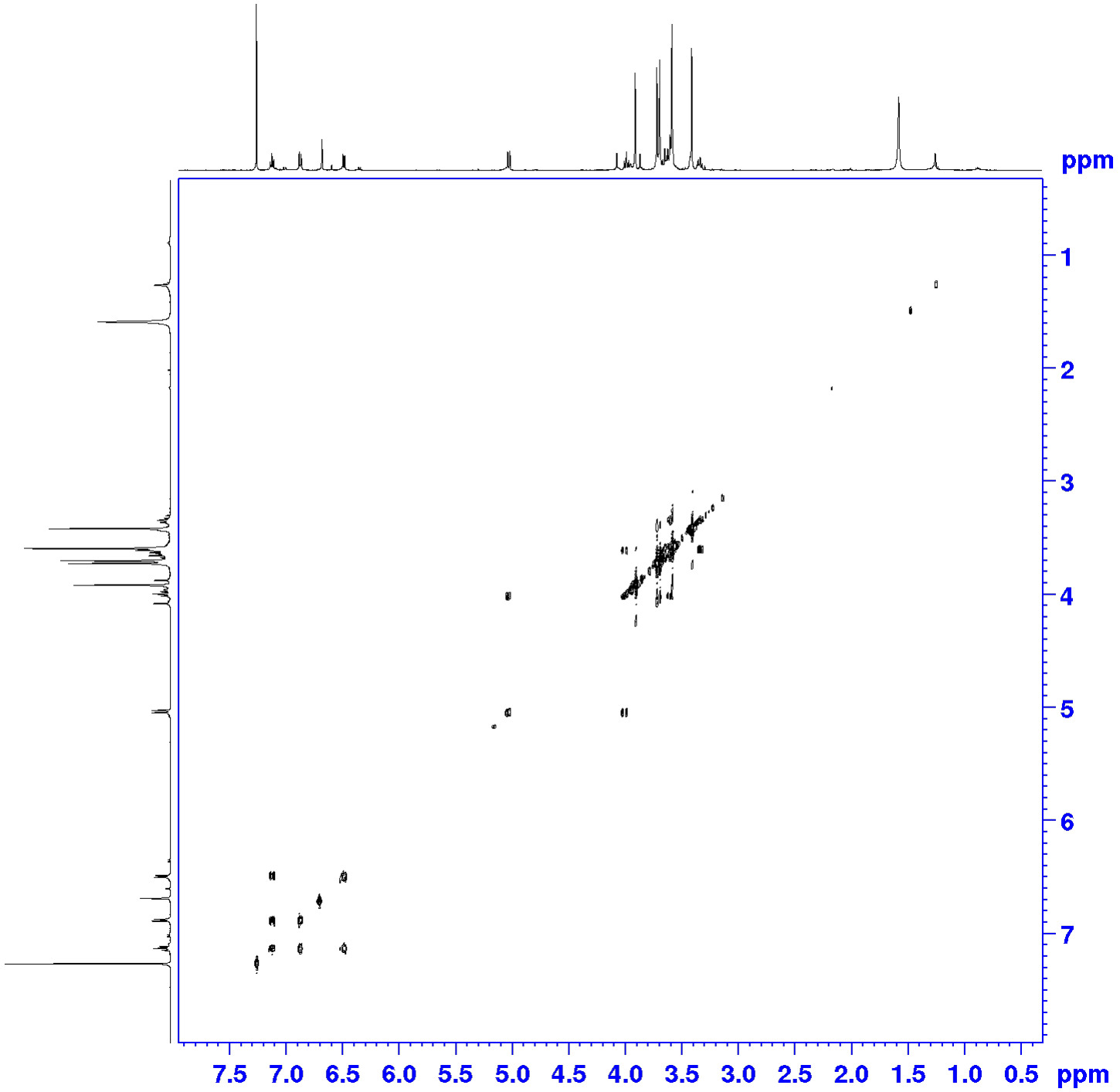


Compound **15**

HMBC expansion

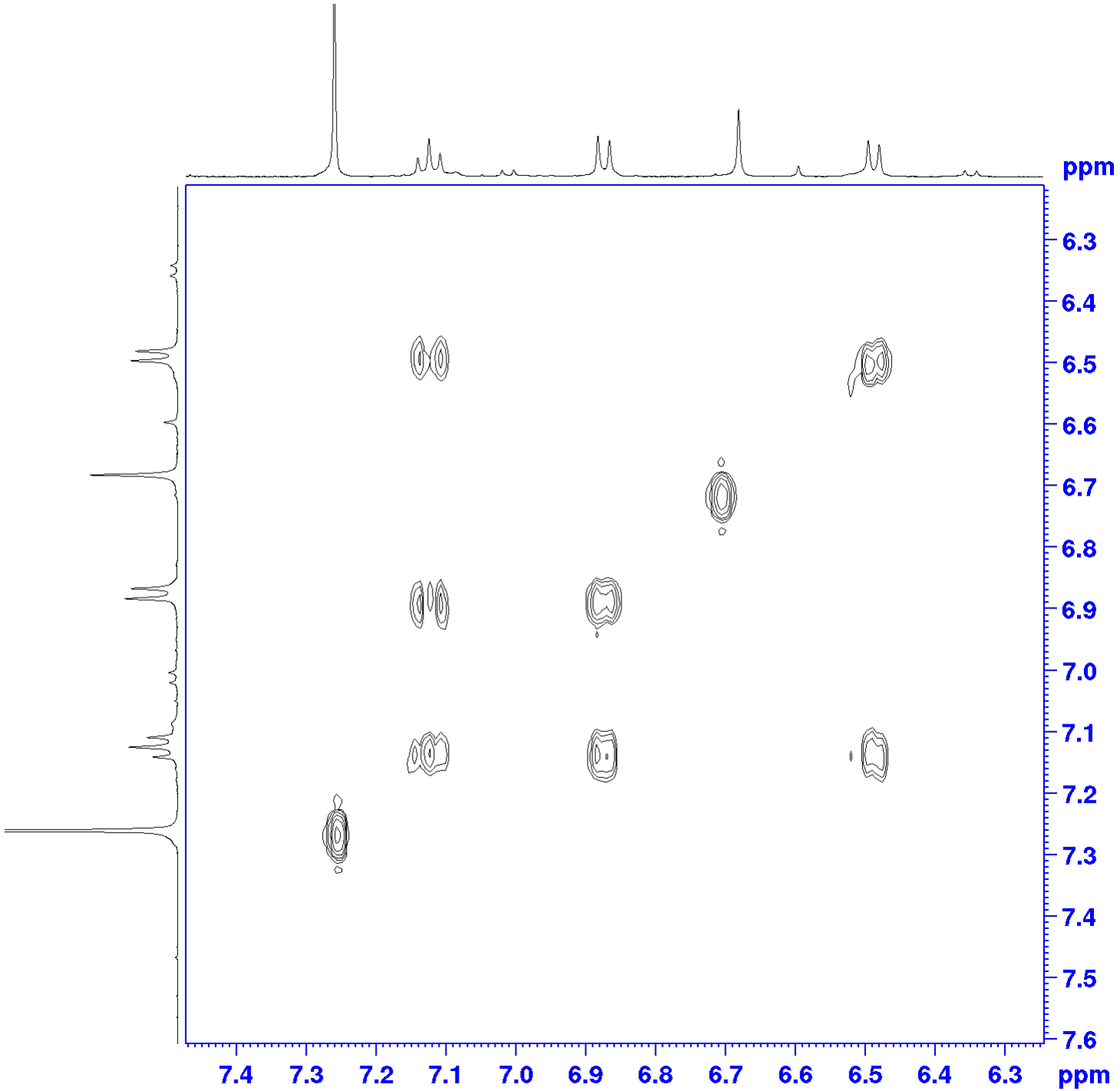


Compound **15**
COSY



Compound **15**

COSY expansion



Compound **15**

COSY expansion