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Synthesis, Ribosomal Selectivity, and Antibacterial Activity of Netilmicin 4'-Derivatives

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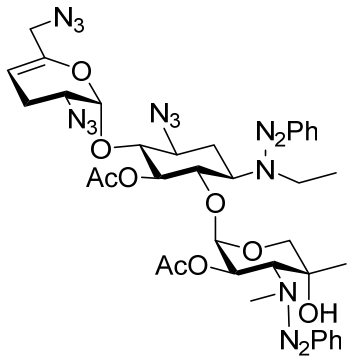
General Information

All reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise specified. All organic extracts were dried over sodium sulfate and concentrated under vacuum. Chromatographic purifications were carried out over silica gel. Analytical thin-layer chromatography was performed with pre-coated glass backed plates (w/UV 254) and visualized by UV irradiation (254 nm) or by staining with 25% H_2SO_4 in EtOH or ceric ammonium molybdate solution. **S**pecific rotations were obtained using a digital polarimeter in the solvent specified. High resolution mass spectra were recorded with an electrospray source coupled to a time-of-flight mass analyzer (Waters). ^{1}H, ^{13}C and 2D NMR spectra were recorded on 600 MHz and 500 MHz instruments.

General deprotection procedure A: Deprotection by deacetylation, Staudinger and acid cleavage of phenyl triazenes: A stirred solution of substrate (0.04 mmol, 1 equiv) in dioxane (1.5 mL) was treated with 1N NaOH (0.5 mL) and heated with stirring at 60 °C for 1.5 h. The reaction mixture was cooled to rt before 1M $P(CH_3)_3$ in THF (4.5 equiv) was added and the reaction mixture stirred at rt for 6h. The reaction mixture was then concentrated and purified by column chromatography (eluent: 5% to 12% ammonical MeOH in DCM). The product-containing fractions were concentrated, dissolved in ethanol (0.9 mL) and treated with sodium hypophosphite (2 equiv) and trifluoroacetic acid (12 equiv), and stirred at rt for 8 h. The reaction mixture was neutralized using Amberlite® IRA400 hydroxide form, filtered and dried. The crude product was dissolved in D.I. water (1 mL), acidified by glacial acetic acid till pH = 3-4 and loaded to a Sephadex column (CM Sephadex C-25) from which it was flushed with D.I. water (20 mL), then by gradient elution of 0.1% - 1.0% NH_4OH in D.I. water. The fractions containing the product were combined, acidified with glacial acetic acid and lyophilized to give a white solid.

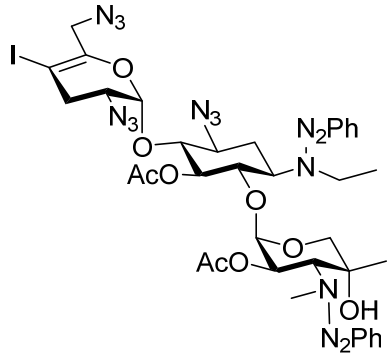
5,2''-Di-*O*-acetyl-3,2',6'-triazido-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (8).



4-Dimethylaminopyridine (7.95 g, 65.1 mmol) and **7** (2.48 g, 3.2 mmol) were dissolved in dry DCM and the resulting solution was stirred and ice cooled before acetic anhydride (1.2 mL, 13.0 mmol) was added dropwise. The reaction mixture was stirred overnight at rt under argon, then it was diluted with DCM and the organic layer was washed with aqueous $NaHCO_3$ followed by brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified via silica gel chromatography eluting with 15% to 40 % EtOAc in hexanes to give **8** (2.10 g, 75%) as a white foam; $[\alpha]_D^{25}$= -19.7 (*c* 1.0, DCM); ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.39 – 7.28 (m, 8H, Ar*H*), 7.19 – 7.13 (m, 2H, Ar*H*), 5.43 (d, *J* = 10.4 Hz, 1H, H-2''), 5.34 (t, *J* = 9.7 Hz, 1H, H-5), 5.32 (s, 1H, H-1'), 5.08 (d, *J* = 2.8 Hz, 1H, H-1''), 5.03 (dd, *J* = 5.5, 1.8 Hz, 1H, H-4'), 4.10 (s, 3H, H-6, H-3'', NCH_2), 3.88 – 3.80 (m, 2H, H-1, H-5''), 3.79 (d, *J* = 14.0 Hz, 2H, H-6', H-1), 3.73 (d, *J* = 14.0 Hz, 1H, H-6'), 3.68 – 3.60 (m, 1H, NCH_2), 3.60 – 3.53 (m, 1H, H-3), 3.42 (ddd, *J* = 11.3, 6.1, 2.4 Hz, 1H, H-2'), 3.35 (d, *J* = 12.3 Hz, 1H, H-5''), 3.15 (s, 3H, NCH_3), 2.54 – 2.46 (m, 1H, H-3'), 2.33 (dt, *J* = 15.4, 5.5 Hz, 1H, H-3'), 2.31 – 2.25 (m, 1H, H-2), 2.20 (s, 3H, COCH_3), 2.08 – 1.95 (m, 1H, H-2), 1.69 (s, 3H, COCH_3), 1.27 (s, 3H, NCH_2CH_3), 1.14 (s, 3H, 4''CH_3); ^{13}C NMR (151 MHz, CD_2Cl_2): δ 170.1 (C=O), 169.8 (C=O), 150.5 (Ar*C*), 150.4 (Ar*C*), 145.3 (C-5'), 128.8 (Ar*C*), 128.8 (Ar*C*), 125.9 (Ar*C*), 125.8 (Ar*C*), 120.6 (Ar*C*), 120.5 (Ar*C*), 98.6 (C-1''), 98.3 (C-4'), 97.1 (C-1'), 81.4 (C-6), 77.8 (C-4), 74.9 (C-5), 73.6 (C-4''), 68.9 (C-2'', C-5''), 65.9

(C-3’’), 61.6 (C-1), 60.7 (C-3), 54.4 (C-2’), 52.2 (C-6’), 43.9 (N*C*H$_2$), 38.2 (N*C*H$_3$), 34.2 (C-2), 22.4 (4’’*C*H$_3$), 21.5 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 20.1 (C-3’); ESI-HRMS: *m/z* calcd. for $C_{37}H_{48}N_{15}O_9$ $[M+H]^+$ 846.3759; found, 846.3747.

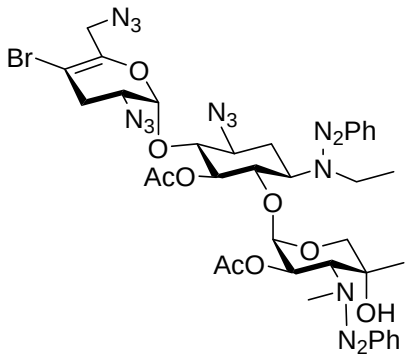
5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-iodo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (9).



To a stirred solution of compound **8** (100 mg, 0.11 mmol) in dry acetonitrile (1 mL), *N*-iodosuccinimide (37 mg, 0.16 mmol) and silver nitrate (500 mg, 0.59 mmol) were added. The reaction mixture was stirred at 80 °C for 2.5 h then cooled to rt and filtered through Celite®. The filtrate was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$ and brine, dried and concentrated. The residue was purified by silica gel column chromatography eluting with 12% acetone/hexanes to give **9** (52 mg, 45%) as white solid; $[\alpha]_D^{25}$= +33.5 (*c* 0.4, DCM); ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.38 – 7.28 (m, 8H, Ar*H*), 7.20 – 7.12 (m, 2H, Ar*H*), 5.48 – 5.39 (m, 2H, H-1’, H-2’’), 5.35 (t, *J* = 9.6 Hz, 1H, H-5), 5.12 – 5.05 (s, 1H, H-1’’), 4.24 (d, *J* = 13.8 Hz, 1H, H-6’), 4.17 – 4.06 (m, 2H, H-6, NC*H*$_2$), 4.04 (d, *J* = 13.8 Hz, 1H, H-6’), 3.90 – 3.74 (m, 3H, H-4, H-3’’, H-5’’), 3.69 – 3.58 (m, 2H, H-3, NC*H*$_2$), 3.55 (ddd, *J* = 11.1, 6.2, 2.5 Hz, 1H, H-2’), 3.35 (d, *J* = 12.3 Hz, 1H, H-5’’), 3.15 (s, 3H, NC*H*$_3$), 2.95 (dd, *J* = 16.1, 11.5 Hz, 1H, H-3’), 2.80 (dd, *J* = 16.3, 6.2 Hz, 1H, H-3’), 2.33 – 2.25 (m, 1H, H-2), 2.19 (s, 3H, COC*H*$_3$), 2.09 – 2.00 (m, 1H, H-2), 1.69 (s, 3H, COC*H*$_3$), 1.27 (s, 3H, NCH$_2$C*H*$_3$), 1.14 (s, 3H, 4’’CH$_3$); ^{13}C NMR (151 MHz,

CD_2Cl_2): δ 170.0 (C=O), 169.8 (C=O), 150.5 (Ar*C*), 150.4 (Ar*C*), 145.3 (C-5'), 128.8 (Ar*C*), 128.8 (Ar*C*), 125.9 (Ar*C*), 125.8 (Ar*C*), 120.6 (Ar*C*), 120.5 (Ar*C*), 98.6 (C-1''), 97.1 (C-1'), 81.4 (C-6), 78.3 (C-4), 74.8 (C-5), 73.6 (C-4''), 68.9 (C-2'', 5''), 66.1 (C-4'), 65.9 (C-3''), 61.5 (C-1), 60.7 (C-3), 55.0 (C-2'), 54.5 (C-6'), 43.9 (NCH_2), 34.0 (C-3'), 22.4 (4''*C*H_3), 21.4 ($COCH_3$), 20.6 ($COCH_3$), 11.9 (NCH_2CH_3); ESI-HRMS: *m/z* calcd. for $C_{37}H_{47}IN_{15}O_9$ $[M+H]^+$ 972.2726; found, 972.2701.

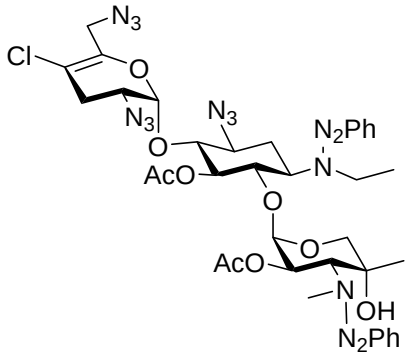
5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-bromo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (10).



In a round bottom flask, protected netilmicin **8** (500 mg, 0.59 mmol), K_2CO_3 (408 mg, 2.95 mmol), tetrabutylammonium nitrate (5 mol%) and BHT (5 mol%) were dissolved with stirring in dry acetonitrile (5 mL) and the flask was wrapped with aluminum foil before *N*-bromosuccinimide (126 mg, 0.71 mmol) was added. The reaction mixture was stirred for 1.5 h for completion, then was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$ and brine, dried and concentrated. The resulting crude product was purified using silica gel chromatography (eluent: 25% to 50% EtOAc/hexanes) to yield **69** (270 mg, 50%) as an orange solid; $[\alpha]_D^{25}$= +14.03 (*c* 0.5, DCM); ^{1}H NMR (499 MHz, CD_2Cl_2): δ 7.36 (p, *J* = 10.7, 9.4 Hz, 8H, Ar*H*), 7.21 – 7.15 (m, 2H, Ar*H*), 5.46 (dd, *J* = 11.0, 3.0 Hz, 1H, H-2''), 5.41 (d, *J* = 2.5 Hz, 1H, H-1'), 5.38 (t, *J* = 11.9 Hz, 1H, H-5), 5.10 (d, *J* = 3.1 Hz, 1H, H-1''), 4.24 (d, *J* = 13.8 Hz, 1H, H-6'), 4.19 –

4.03 (m, 2H, H-6, NCH_2), 4.01 – 3.93 (m, 2H, H-6', H-3''), 3.85 (t, J = 9.9 Hz, 1H, H-4), 3.89 – 3.83 (m, 1H, H-1), 3.81 (d, J = 13.6 Hz, 1H, H-5''), 3.71 – 3.62 (m, 2H, H-3, NCH_2), 3.59 (ddd, J = 11.2, 6.3, 2.6 Hz, 1H, H-2'), 3.37 (d, J = 12.4 Hz, 1H, H-5''), 3.17 (s, 3H, NCH_3), 2.95 (dd, J = 16.6, 11.1 Hz, 1H, H-3'), 2.75 (dd, J = 16.2, 6.4 Hz, 1H, H-3'), 2.36 – 2.26 (m, 1H, H-2), 2.22 (s, 3H, COCH_3), 2.11 – 2.01 (m, 1H, H-2), 1.72 (s, 3H, COCH_3), 1.29 (t, J = 5.7 Hz, 3H, NCH_2CH_3), 1.16 (s, 3H, 4''CH_3); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 170.1 (C=O), 169.8 (C=O), 150.5 (ArC), 143.3 (C-5'), 128.9 (ArC), 128.8 (ArC), 126.0 (ArC), 125.8 (ArC), 120.6 (ArC), 120.5 (ArC), 98.7 (C-1''), 97.0 (C-4'), 96.2 (C-1'), 81.5 (C-6), 78.5 (C-4), 74.8 (C-5), 73.6 (C-4''), 68.9 (C-2''), 66.0 (C-3''), 61.6 (C-1), 60.6 (C-3), 54.7 (C-2'), 50.9 (C-6'), 41.9 (NCH_2), 33.9 (C-2), 30.4 (C-3'), 22.4 (4''CH_3), 21.5 (COCH_3), 20.6 (COCH_3); ESI-HRMS: *m/z* calcd. for $C_{37}H_{47}BrN_{15}O_9[M+H]^+$ 924.2865; found, 924.2836.

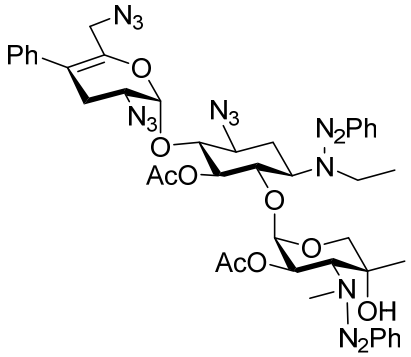
5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



A mixture of K_2CO_3 (123 mg, 0.89 mmol) and compound **8** (150 mg, 0.18 mmol) in dry acetonitrile (2 mL) was dried over 3Å molecular sieves for 1 h, then cooled to 0 °C and the flask wrapped with aluminium foil before iodobenzene dichloride[1] (58.5 mg, 0.21 mmol) was added. The reaction mixture was stirred for 45 min for complete consumption of the starting material, then was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$ and brine, dried and

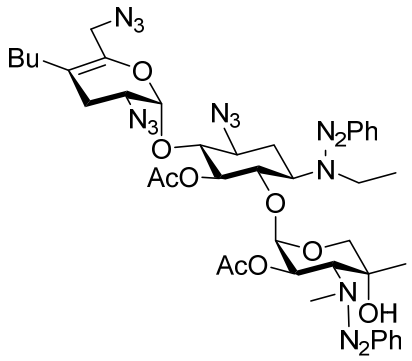
concentrated. The crude product was purified by gradient chromatography over silica gel (eluent: 15% to 30% EtOAc/hexanes) to yield **11** (45 mg, 30%) as a foam; $[\alpha]_D^{25}$= +17.25 (*c* 0.1, DCM); ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.41 – 7.27 (m, 8H, Ar*H*), 7.19 – 7.13 (m, 2H, Ar*H*), 5.43 (d, *J* = 11.7 Hz, 1H, H-2'') 5.39 – 5.31 (m, 2H, H-1', H-5), 5.08 (d, *J* = 2.9 Hz, 1H, H-1''), 4.19 (d, *J* = 13.9 Hz, 1H, H-6'), 4.16 – 3.97 (m, 2H, H-6, NC*H*$_2$), 3.92 (d, *J* = 13.9 Hz, 1H, H-6'), 3.89 – 3.75 (m, 3H, H-4, H-3'', H-5''), 3.64 – 3.59 (m, 2H, H-3, NC*H*$_2$), 3.56 (ddd, *J* = 11.3, 6.3, 2.5 Hz, 1H, H-2'), 3.34 (d, *J* = 12.4 Hz, 1H, H-5''), 3.15 (s, 3H, NC*H*$_3$), 2.84 (dd, *J* = 16.0, 11.4 Hz, 1H, H-3'), 2.61 (dd, *J* = 16.1, 6.3 Hz, 1H, H-3'), 2.33 – 2.24 (m, 1H, H-2), 2.19 (s, 3H, COC*H*$_3$), 2.08 – 1.99 (m, 1H, H-2), 1.69 (s, 3H, COC*H*$_3$), 1.31 – 1.23 (m, 3H, NCH$_2$C*H*$_3$), 1.14 (s, 3H, 4''C*H*$_3$); ^{13}C NMR (151 MHz, CD_2Cl_2): δ 170.1 (C=O), 169.8 (C=O), 150.5 (Ar*C*), 150.4 (Ar*C*), 142.3 (C-5'), 128.8 (Ar*C*), 128.8 (Ar*C*), 126.0 (Ar*C*), 125.8 (Ar*C*), 120.5 (Ar*C*), 120.5 (Ar*C*), 107.9 (C-4'), 98.7 (C-1''), 96.9 (C-1'), 81.6 (C-6), 78.5 (C-4), 74.8 (C-5), 73.6 (C-4''), 69.3 (C-2''), 68.9 (C-5''), 65.9 (C-3''), 61.5 (C-1), 60.6 (C-3), 54.3 (C-2'), 48.8 (C-6'), 44.0 (N*C*H$_2$), 34.0 (C-2), 28.5 (C-3'), 22.4 (4''*C*H$_3$), 21.5 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 11.8 (NCH$_2$*C*H$_3$); ESI-HRMS: *m/z* calcd. for $C_{37}H_{46}ClN_{15}NaO_9$ $[M+Na]^+$ 902.3189; found, 902.3177.

5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



A round bottom flask was charged with compound **10** (146 mg, 0.16 mmol), K_2CO_3 (66 mg, 0.47 mmol), phenylboronic acid (29 mg, 0.24 mmol) and Pd(dppf)Cl_2 (10 mol%) then evacuated and and flushed with argon three times. Dry dioxane (3 mL), dried over 5 Å MS, was added and the reaction mixture was heated at 90 °C with stirring for 36 h. The reaction mixture was concentrated and purified by gradient chromatography over silica gel (eluent: 3% to 5% IPA in hexanes) to give **12** in 23% yield; $[\alpha]_D^{25}$= +54.6 (*c* 0.3, DCM); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.45 – 7.23 (m, 13H, Ar*H*), 7.22 – 7.13 (m, 2H, Ar*H*), 5.47 (dd, *J* = 11.7, 2.3 Hz, 1H, H-2''), 5.44 (d, *J* = 2.5 Hz, 1H, H-1'), 5.40 (t, *J* = 9.3 Hz, 1H, H-5), 5.12 (d, *J* = 3.0 Hz, 1H, H-1''), 4.21 – 3.99 (m, 3H, H-6, H-3'', NC*H*$_2$), 3.96 (t, *J* = 9.9 Hz, 1H, H-4), 3.88 (d, *J* = 13.5 Hz, 1H, H-6'), 3.84 (d, *J* = 12.1 Hz, 1H, H-5''), 3.78 (d, *J* = 13.4 Hz, 1H, H-6'), 3.72 – 3.64 (m, 2H, H-3, NC*H*$_2$), 3.63 (ddd, *J* = 11.4, 6.0, 2.6 Hz, 1H, H-2'), 3.38 (d, *J* = 12.4 Hz, 1H, H-5''), 3.18 (s, 3H, NC*H*$_3$), 2.90 (dd, *J* = 15.9, 11.7 Hz, 1H, H-3'), 2.60 (dd, *J* = 16.1, 6.0 Hz, 1H, H-3'), 2.40 – 2.29 (m, 1H, H-2), 2.25 (s, 3H, COC*H*$_3$), 2.18 – 2.08 (m, 1H, H-2), 1.73 (s, 3H, COC*H*$_3$), 1.37 – 1.25 (m, 3H, NCH$_2$C*H*$_3$), 1.17 (s, 3H, 4''CH_3); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 170.1 (C=O), 169.9 (C=O), 150.5 (Ar*C*), 142.4 (C-5'), 138.4 (Ar*C*), 128.9 (Ar*C*), 128.8 (Ar*C*), 128.6 (Ar*C*), 128.4 (Ar*C*), 127.4 (Ar*C*), 126.0 (Ar*C*), 125.8 (Ar*C*), 120.6 (Ar*C*), 113.0 (C-4'), 98.6 (C-1''), 96.9 (C-1'), 81.6 (C-6), 78.2 (C-4), 75.0 (C-5), 73.6 (C-4''), 68.9 (C-5''), 66.0 (C-3''), 61.7 (C-1), 60.6 (C-3), 54.6 (C-2'), 49.9 (C-6'), 33.9 (N*C*H$_2$), 26.3 (C-3'), 22.4 (4''*C*H$_3$), 21.5 (CO*C*H$_3$), 20.7 (CO*C*H$_3$), 11.9 (NCH$_2$*C*H$_3$); ESI-HRMS: *m/z* calcd. for $C_{43}H_{52}N_{15}O_9$ $[M+H]^+$ 922.4072; found, 922.4070.

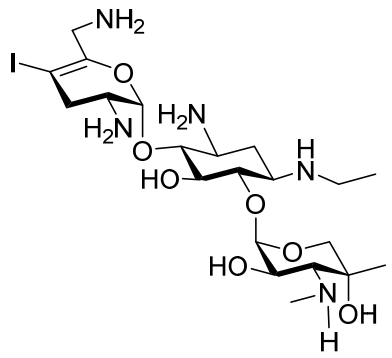
5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-butyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (13).



A round bottom flask was charged with compound **10** (300 mg, 0.32 mmol), cesium carbonate (527 mg, 1.62 mmol), potassium butyltrifluoroborate (106 mg, 0.64 mmol) and Pd(dppf)Cl_2 (10 mol%) then evacuated and flushed with argon three times. Degassed toluene (2 mL) and degassed water (1 mL) were added and the reaction mixture was heated at 90 °C for 12 h under argon. On completion, the reaction mixture was cooled and directly loaded in a silica gel column and eluted with 15% acetone in hexanes to give **13** in 8% yield as white solid, and the precursor **8** in 32% yield. $[\alpha]_D^{25}$= +23.14 (*c* 0.5, DCM); ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.41 – 7.24 (m, 8H, Ar*H*), 7.21 – 7.11 (m, 2H, Ar*H*), 5.43 (d, *J* = 11.6 Hz, 1H, H-2''), 5.32 – 5.29 (m, 1H, H-5), 5.27 (d, *J* = 2.4 Hz, 1H, H-1'), 5.07 (d, *J* = 2.8 Hz, 1H, H-1''), 4.23 – 4.00 (m, 3H, H-6, H-3'', NCH_2), 3.96 (d, *J* = 13.7 Hz, 1H, H-6'), 3.87 – 3.79 (m, 2H, H-4, H-5''), 3.77 (d, *J* = 13.6 Hz, 1H, H-6'), 3.68 – 3.60 (m, 1H, NCH_2), 3.60 – 3.54 (m, 1H, H-3), 3.40 (dq, *J* = 8.7, 2.8, 2.3 Hz, 1H, H-2'), 3.34 (d, *J* = 12.3 Hz, 1H, H-5''), 3.14 (s, 3H, NCH_3), 2.45 (dd, *J* = 16.0, 11.8 Hz, 1H, H-3'), 2.27 (m, 2H, H-2, H-3'), 2.19 (s, 3H, COCH_3), 2.11 (m, 1H, CH_2CH$_2$CH$_2$CH$_3$), 2.07 – 1.99 (m, 1H, H-2), 1.95 (M, 1H, CH_2CH$_2$CH$_2$CH$_3$), 1.69 (s, 3H, COCH_3), 1.46 – 1.23 (m, 7H, CH$_2$CH_2CH$_2$CH$_3$, CH$_2$CH$_2$CH_2CH$_3$, NCH$_2$CH_3), 1.13 (s, 3H, 4''CH_3), 0.91 (t, *J* = 5.7 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (151 MHz, CD_2Cl_2): δ 169.9 (C=O), 150.4 (Ar*C*), 139.5 (C-5), 128.8 (Ar*C*), 128.8 (Ar*C*), 125.9 (Ar*C*), 125.8 (Ar*C*), 120.5 (Ar*C*), 111.3 (C-4'), 98.5 (C-1''), 96.6 (C-1'), 81.53 (C-

6), 77.9 (C-4), 74.9 (C-5), 73.6 (C-4''), 68.9 (C-5''), 65.9 (C-3''), 61.6 (C-1), 60.6 (C-3), 54.7 (C-2'), 48.6 (C-6'), 43.9 (N*C*H_2), 34.1 (C-2), 31.3 (*C*$H_2CH_2CH_2CH_3$), 30.9 (CH_2*C*$H_2CH_2CH_3$), 23.9 (C-3'), 22.5 (CH_2CH_2*C*H_2CH_3), 22.4 (4''*C*H_3), 21.5 (CO*C*H_3), 20.6 (CO*C*H_3), 13.7 ($CH_2CH_2CH_2$*C*H_3), 11.8 (NCH$_2$*C*H_3); ESI-HRMS: *m/z* calcd. for $C_{41}H_{56}N_{15}O_9$ $[M+H]^+$ 902.4385; found, 902.4344.

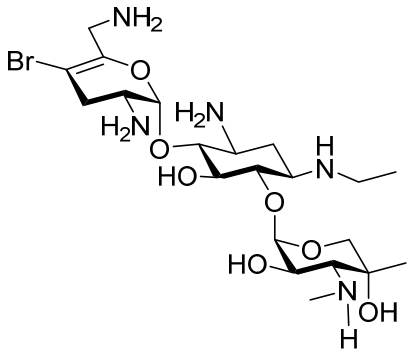
4'-Iodonetilmicin pentaacetate salt (19).



Substrate **9** (30 mg, 0.03 mmol) was deprotected using the general deprotection procedure A to yield **19** (13 mg, 57%) as a white solid; $[\alpha]_D^{25}$= +87.3 (*c* 0.3, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.63 (s, 1H, H-1'), 4.91 (s, 1H, H-1''), 4.09 (d, *J* = 10.8 Hz, 1H, H-2''), 3.95 (d, *J* = 14.6 Hz, 1H, H-6'), 3.81 (d, *J* = 13.4 Hz, 1H, H-5''), 3.79 – 3.68 (m, 3H, H-4, H-2', H-6'), 3.64 – 3.55 (m, 2H, H-5, H-6), 3.37 – 3.28 (m, 3H, H-1, H-3'', H-5''), 3.23 (t, *J* = 10.0 Hz, 1H, H-3), 3.12 (dq, *J* = 13.1, 7.2 Hz, 1H, NC*H*$_2$), 2.97 (dd, *J* = 18.3, 5.3 Hz, 1H, H-3'), 2.92 (dt, *J* = 13.4, 7.3 Hz, 1H, NC*H*$_2$), 2.76 (s, 3H, NC*H*$_3$), 2.67 (dd, *J* = 18.2, 4.1 Hz, 1H, H-3'), 2.44 – 2.35 (m, 1H, H-2), 1.66 (q, *J* = 13.0 Hz, 1H, H-2), 1.18 (s, 3H, 4''C*H*$_3$), 1.14 (t, *J* = 6.6 Hz, 3H, NCH$_2$C*H*$_3$); ^{13}C NMR (151 MHz, D_2O): δ 180.9 (C=O), 142.6 (C-5'), 101.6 (C-1''), 96.7 (C-1'), 83.2 (C-6), 79.6 (C-4), 73.6 (C-5), 69.8 (C-4''), 68.3 (C-4'), 67.6 (C-5''), 66.4 (C-2''), 63.6 (C-3''), 56.1 (C-1), 48.0 (C-

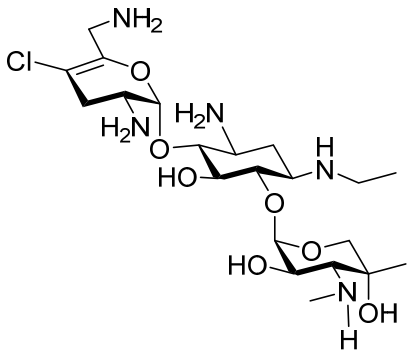
3), 47.9 (C-2'), 43.1 (NCH_2), 40.8 (C-6'), 36.2 (C-3'), 34.6 (NCH_3), 26.2 (C-2), 23.0 ($COCH_3$), 20.7 (4''CH3), 10.9 (NCH_2CH_3); ESI-HRMS: *m/z* calcd. for $C_{21}H_{41}IN_5O_7$ $[M+H]^+$ 602.2051; found, 602.2043.

4'-Bromonetilmicin pentaacetate salt (20).



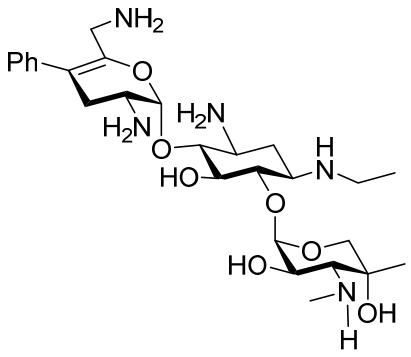
Substrate **10** (40 mg, 0.04 mmol) was deprotected using the general deprotection procedure A to yield **20** (16.2 mg, 58%) as a white solid; $[\alpha]_D^{25}$= +50.0 (*c* 1.1, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.56 (s, 1H, H-1'), 4.89 (s, 1H, H-1''), 4.07 (dt, *J* = 10.8, 3.0 Hz, 1H, H-2''), 3.91 (d, *J* = 14.5 Hz, 1H, H-6'), 3.82 (d, *J* = 12.9 Hz, 1H, H-5''), 3.70 – 3.64 (m, 2H, H-6', H-2'), 3.64 – 3.59 (m, 1H, H-4), 3.59 – 3.51 (m, 2H, H-5, H-6), 3.36 – 3.23 (m, 3H, H-1, H-3'', H-5''), 3.12 – 3.01 (m, 2H, H-3, NCH_2), 2.92 – 2.81 (m, 2H, H-3', NCH_2), 2.75 (s, 3H, NCH_3), 2.63 – 2.54 (m, 1H, H-3'), 2.33 – 2.25 (m, 1H, H-2), 1.49 (q, *J* = 12.7, 12.3 Hz, 1H, H-2), 1.17 (s, 3H, 4''CH_3), 1.11 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3); ^{13}C NMR (151 MHz, D_2O): δ 181.2 (C=O), 140.3 (C-5'), 101.5 (C-1''), 98.1 (C-4'), 96.8 (C-1'), 83.8 (C-6), 80.8 (C-4), 73.9 (C-5), 69.8 (C-4''), 67.6 (C-5''), 66.5 (C-2''), 63.6 (C-3''), 56.4 (C-1), 48.1 (C-3), 47.3 (C-2'), 40.7 (NCH_2), 39.5 (C-6'), 34.6 (NCH_3), 32.6 (C-3'), 27.4 (C-2), 23.1 ($COCH_3$), 20.8 (4''CH_3), 11.1 (NCH_2CH_3); ESI-HRMS: *m/z* calcd. for $C_{21}H_{41}BrN_5O_7$ $[M+H]^+$ 554.2189; found, 554.2200.

4'-Chloronetilmicin pentaacetate salt (21).



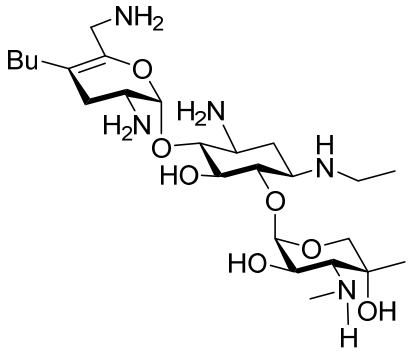
Substrate **11** (37 mg, 0.04 mmol) was deprotected using the general deprotection procedure A to yield **21** (19.6 mg, 59%) as a white solid; $[\alpha]_D^{25}$= +41.8 (*c* 1.2, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.56 (s, 1H, H-1'), 4.91 (d, *J* = 3.7 Hz, 1H, H-1''), 4.09 (dd, *J* = 10.8, 3.7 Hz, 1H, H-2''), 3.93 (d, *J* = 14.5 Hz, 1H, H-6'), 3.82 (d, *J* = 12.9 Hz, 1H, H-5''), 3.79 (t, *J* = 5.9 Hz, 1H, H-2'), 3.77 – 3.73 (m, 1H, H-4), 3.65 (d, *J* = 14.5 Hz, 1H, H-6'), 3.63 – 3.55 (m, 2H, H-5, H-6), 3.36 –3.28 (m, 3H, H-1, H-3'', H-5''), 3.20 (td, *J* = 11.4, 10.7, 3.9 Hz, 1H, H-3), 3.11 (dq, *J* = 14.2, 7.1 Hz, 1H, NC*H*$_2$), 2.91 (dq, *J* = 14.4, 7.2 Hz, 1H, NC*H*$_2$), 2.84 (dd, *J* = 18.1, 6.1 Hz, 1H, H-3'), 2.76 (s, 3H, NC*H*$_3$), 2.52 (dd, *J* = 18.0, 4.8 Hz, 1H, H-3'), 2.38 (dt, *J* = 12.4, 4.1 Hz, 1H, H-2), 1.63 (q, *J* = 12.5 Hz, 1H, H-2), 1.18 (s, 3H, 4''C*H*$_3$), 1.13 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$); ^{13}C NMR (151 MHz, D_2O): δ 181.1 (C=O), 139.7 (C-5'), 110.0 (C-4'), 101.5 (C-1''), 96.8 (C-1'), 83.3 (C-6), 80.0 (C-4), 73.6 (C-5), 69.8 (C-4''), 67.6 (C-5''), 66.4 (C-2''), 63.6 (C-3''), 56.2 (C-1), 48.0 (C-3), 46.9 (C-2), 40.8 (N*C*H$_2$), 37.4 (C-6'), 34.6 (N*C*H$_3$), 30.7 (C-3'), 26.4 (C-2), 23.0 (CO*C*H$_3$), 20.8 (4''*C*H$_3$), 10.9 (NCH$_2$*C*H$_3$); ESI-HRMS: *m/z* calcd. for $C_{21}H_{41}ClN_5O_7$ $[M+H]^+$ 510.2695; found, 510.2687.

4'-Phenylnetilmicin pentaacetate salt (22).



Substrate **12** (29 mg, 0.03 mmol) was deprotected using the general deprotection procedure A to yield **22** (14 mg, 54%) as a white solid; $[\alpha]_D^{25}$= +64.09 (*c* 0.5, H_2O); 1H NMR (600 MHz, D_2O): δ 7.36 – 7.26 (m, *J* = 26.9, 7.3 Hz, 3H, Ar*H*), 7.14 (d, *J* = 7.5 Hz, 2H, Ar*H*), 5.66 (s, 1H, H-1'), 4.95 (d, *J* = 3.7 Hz, 1H, H-1''), 4.12 (dd, *J* = 10.7, 3.7 Hz, 1H, H-2''), 3.92 – 3.83 (m, 2H, H-2', H-5''), 3.83 – 3.77 (m, 1H, H-4), 3.69 – 3.63 (m, 2H, H-5, H-6), 3.61 (d, *J* = 14.4 Hz, 1H, H-6'), 3.53 (d, *J* = 14.3 Hz, 1H, H-6'), 3.41 – 3.32 (m, 3H, H-1, H-3'', H-5''), 3.22 (td, *J* = 11.9, 4.2 Hz, 1H, H-3), 3.15 (dq, *J* = 14.5, 7.2 Hz, 1H, NCH_2), 2.95 (dq, *J* = 14.7, 7.3 Hz, 1H, NCH_2), 2.86 (dd, *J* = 18.2, 5.8 Hz, 1H, H-3'), 2.79 (s, 3H, NCH_3), 2.55 (dd, *J* = 18.3, 5.2 Hz, 1H, H-3'), 2.41 (dt, *J* = 12.3, 4.0 Hz, 1H, H-2), 1.70 – 1.61 (m, 1H, H-2), 1.21 (s, 3H, 4''CH_3), 1.17 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3); ^{13}C NMR (151 MHz, D_2O): δ 180.9 (C=O), 139.1 (C-5'), 136.5 (Ar*C*), 129.0 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 114.7 (C-4'), 101.6 (C-1''), 96.3 (C-1'), 83.5 (C-6), 80.1 (C-4), 73.9 (C-5), 69.9 (C-4''), 67.7 (C-5''), 66.5 (C-2''), 63.6 (C-3''), 56.4 (C-1), 48.2 (C-3), 46.7 (C-2'), 40.8 (NCH_2), 37.9 (C-6'), 34.6 (NCH_3), 29.2 (C-3'), 26.8 (C-2), 23.0 ($COCH_3$), 20.8 (4''CH3), 11.0 (NCH_2CH_3); ESI-HRMS: *m/z* calcd. for $C_{27}H_{46}N_5O_7$ $[M+H]^+$ 552.3397; found, 552.3391.

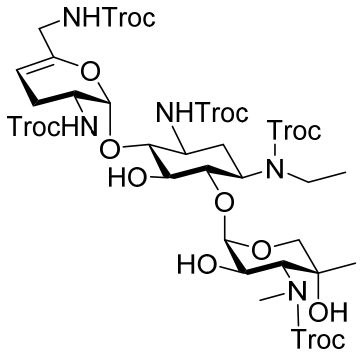
4'-Butylnetilmicin pentaacetate salt (23).



Substrate **13** (27 mg, 0.03 mmol) was deprotected using the general deprotection procedure A to yield **23** (7 mg, 27%) as a white solid;; $[\alpha]_D^{25}$= +38.02 (*c* 0.3, H_2O); 1H NMR (600 MHz, D_2O): δ 5.32 (s, 1H, H-1'), 4.86 (d, *J* = 3.7 Hz, 1H, H-1''), 3.93 (dd, *J* = 10.7, 3.6 Hz, 1H, H-2''), 3.86 (d, *J* = 12.8 Hz, 1H, H-5''), 3.69 (d, *J* = 14.2 Hz, 1H, H-6''), 3.49 (t, *J* = 9.1 Hz, 1H, H-6), 3.44 (d, *J* = 14.4 Hz, 1H, H-6''), 3.41 – 3.37 (m, 1H, H-4), 3.35 (t, *J* = 9.6 Hz, 1H, H-5), 3.30 – 3.22 (m, 2H, H-5'', H-2'), 3.01 (d, *J* = 10.9 Hz, 1H, H-3''), 2.98 – 2.90 (m, 1H, H-1), 2.89 – 2.80 (m, 1H, NCH_2), 2.80 – 2.71 (m, 1H, H-3), 2.69 – 2.57 (m, 4H, NCH_3, NCH_2), 2.19 (dd, *J* = 17.1, 5.9 Hz, 1H, H-3'), 2.11 (dt, *J* = 12.9, 3.9 Hz, 1H, H-2), 2.06 (dd, *J* = 17.6, 9.3 Hz, 1H, H-3'), 1.96 (dt, *J* = 14.4, 7.4 Hz, 1H, C$H_2$$CH_2CH_2CH_3$), 1.91 – 1.85 (m, 1H, C$H_2$$CH_2CH_2CH_3$), 1.28 – 1.15 (m, 3H, CH_2C$H_2$$CH_2CH_3$, H-2), 1.14 (s, 3H, 4''CH_3), 1.10 (dq, *J* = 14.8, 7.6 Hz, 2H, CH_2CH_2C$H_2$$CH_3$), 1.03 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 0.71 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_2$CH_3); ^{13}C NMR (151 MHz, D_2O): δ 181.4 (C=O), 135.9 (C-5'), 113.4 (C-4'), 101.3 (C-1''), 96.8 (C-1'), 84.9 (C-5), 81.4 (C-4), 74.4 (C-6), 70.5 (C-4''), 67.5 (C-5''), 67.4 (C-2''), 63.7 (C-3''), 56.9 (C-1), 48.7 (C-3), 46.5 (C-2'), 40.5 (NCH_2), 37.0 (C-6'), 35.2 (NCH_3), 30.0 (C$H_2CH_2CH_2CH_3$), 29.8 (CH_2C$H_2CH_2CH_3$), 29.7 (C-2), 27.5 (C-3'), 23.1 (COCH_3), 21.6 (CH_2CH_2CH_2CH_3), 20.9 (4''CH3), 13.0 ($CH_2CH_2CH_2$CH_3), 12.1 (NCH_2CH_3); ESI-HRMS: *m/z* calcd. for $C_{25}H_{50}N_5O_7$

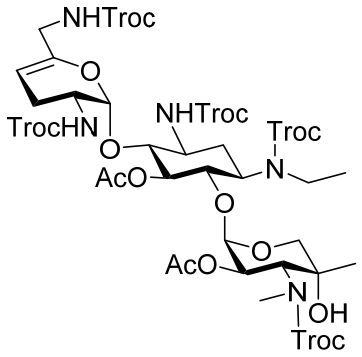
$[M+H]^+$ 532.3710; found, 532.3694. This product was contaminated with ~10% of netilmicin that we were unable to remove.

1,3,2',6',3''-Penta(trichloroethyloxycarbonyl) netilmicin (24).



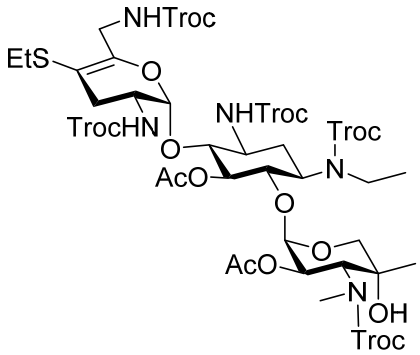
A stirred solution of netilmicin sulfate (400 mg, 0.55 mmol) in 1:1 dioxane:water (10 mL) was ice-cooled and treated with Na_2CO_3 (883 mg, 8.33 mmol) and 2,2,2-trichloroethyl chloroformate (0.46 mL, 3.33 mmol). The reaction mixture was stirred at rt for 4 h. After completion, the reaction mixture was concentrated *in vacuo* then diluted with EtOAc and washed with brine, dried and concentrated. The crude product was purified by silica gel column chromatography eluting with 4% methanol/DCM to give **24** (722 mg, 96%) as a white solid; ESI-HRMS: *m/z* calcd. for $C_{36}H_{46}Cl_{15}N_5NaO_{17}$ $[M+Na]^+$ 1367.8114; found, 1367.8109. This compound was carried forward to the next step without further characterization because of the broad nature of most signals in its NMR spectra.

5,2''-Di-*O*-acetyl-1,3,2',6',3''-penta(trichloroethyloxycarbonyl) netilmicin (25).



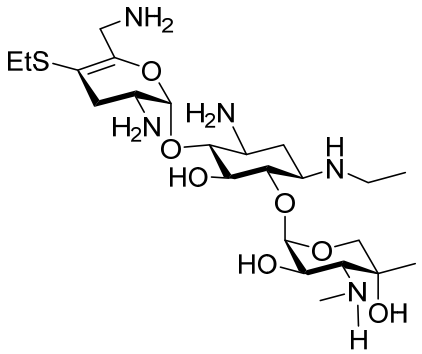
A stirred solution of compound **24** (1.06 g, 0.78 mmol) in pyridine (10 mL) was cooled to 0 °C and treated with acetic anhydride (1 mL). The resulting solution was stirred at rt for 12 h after which it was diluted with EtOAc and the organic layer was washed with aqueous $NaHCO_3$ followed by brine, dried with Na_2SO_4, and concentrated. The crude product was purified via silica gel chromatography eluting with 20% to 35 % EtOAc in hexanes to give **25** (880 mg, 78%) as a white solid; ESI-HRMS: *m/z* calcd. for $C_{40}H_{50}Cl_{15}N_5NaO_{19}$ $[M+Na]^+$ 1367.8114; found, 1367.8109. This compound was carried forward to the next step without further characterization because of the broad nature of most signals in its NMR spectra.

5,2''-Di-*O*-acetyl-1,3,2',6',3''-penta(trichloroethyloxycarbonyl)-4'-(ethylsulfanyl)-netilmicin (26).



Ethanesulfanyl chloride was freshly prepared for the reaction as described. Diethyl disulfide (1.22 mL, 10 mmol) was dissolved in dry DCM (20 mL) and cooled to -30 °C before sulfuryl chloride (0.80 mL, 10 mmol) was added dropwise. The resulting ethanesulfanyl chloride solution (0.52 mL, 0.52 mmol) was added to a stirred solution of **25** (500 mg, 0.35 mmol) previously cooled to -50 °C. The reaction mixture was stirred for 1 h before DBU (78 μL, 0.52 mmol) was added, then it was stirred for an additional 4 h. After completion, the reaction mixture was diluted with DCM and washed with aqueous $NaHCO_3$ followed by brine, dried, and concentrated. The crude product was purified via silica gel chromatography eluting with 20% to 30 % EtOAc in hexanes to give **26** (225 mg, 43%) as a white foam; ESI-HRMS: *m/z* calcd. for $C_{42}H_{54}Cl_{15}N_5NaO_{19}S$ $[M+Na]^+$ 1511.8359; found, 1511.8390. This compound was carried forward to the next step without further characterization because of the broad nature of most signals in its NMR spectra.

4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).

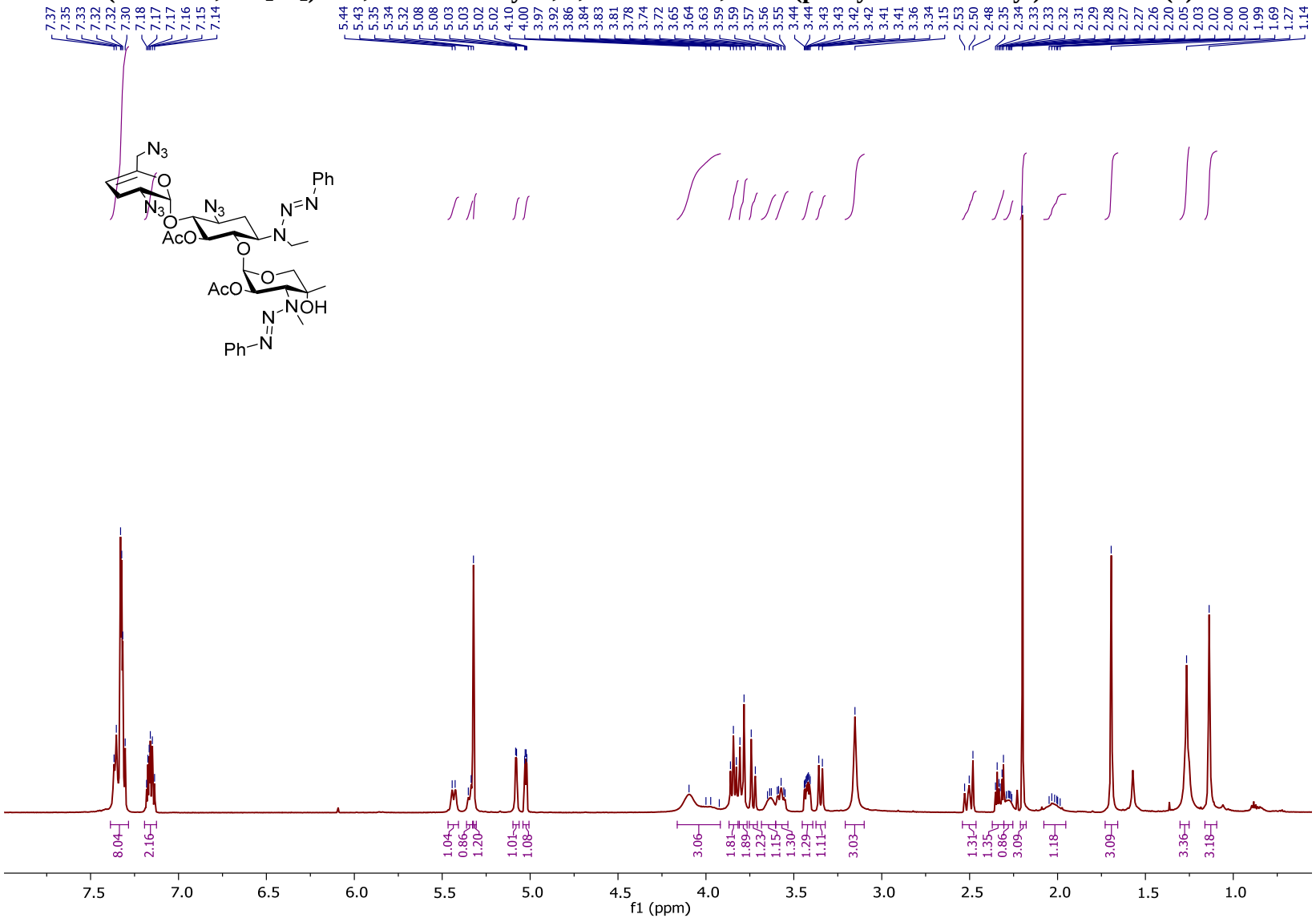


Compound **26** (100 mg, 0.066 mmol) was suspended in 6N NaOH (4 mL) in a closed vial and heated to 120 °C for 4 h during which the reaction mixture become clear. Upon completion, the reaction mixture was neutralized by 12 N H_2SO_4 till pH = 9 before it was lyophilized. The resulting solid residue was extracted with isopropyl alcohol (10 mL) and concentrated. The crude

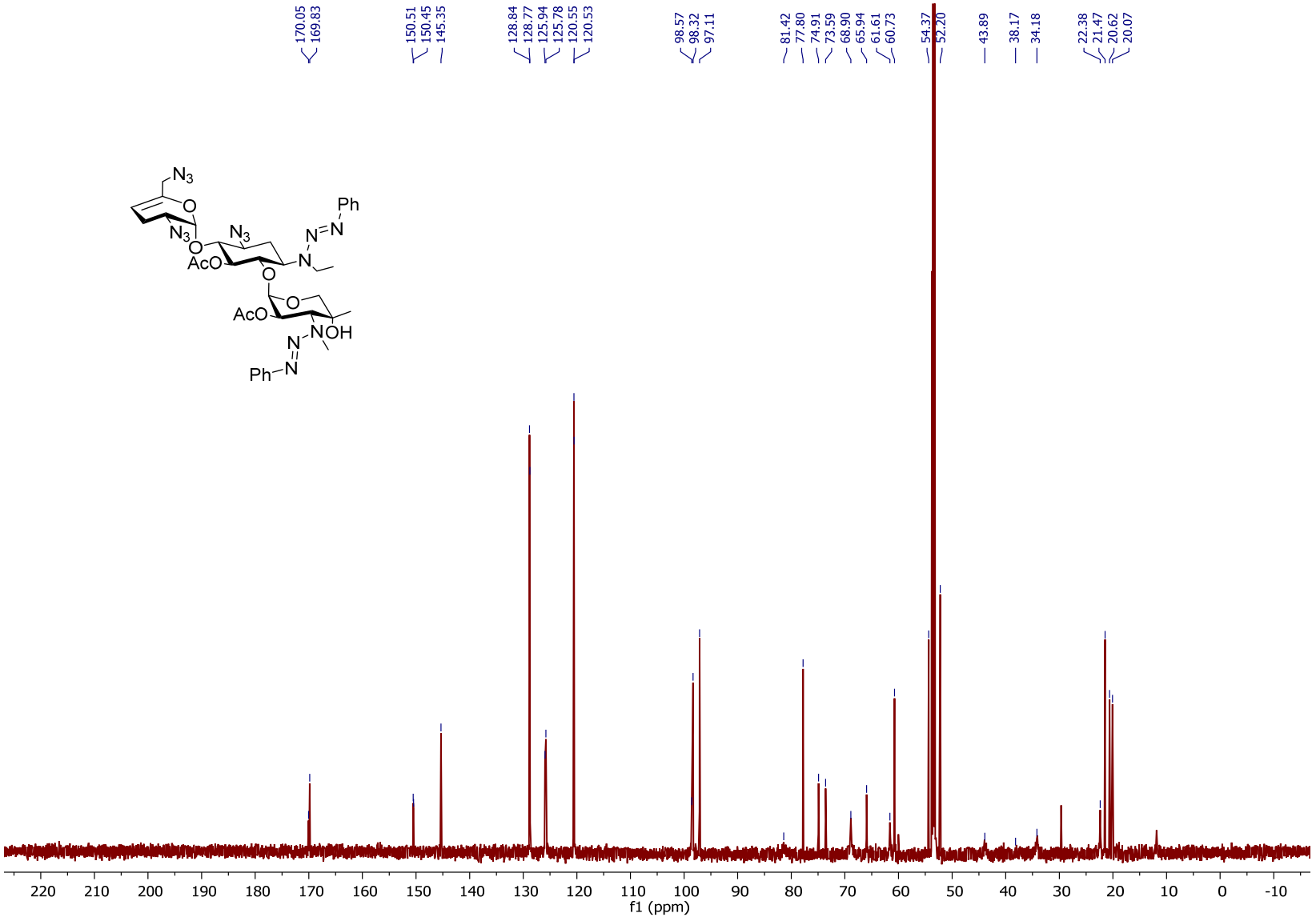
product was desalted and purified using Sephadex column (elution: D.I. water (20 mL), then gradient elution of 0.1% - 1.0% NH_4OH in D.I. water). The fractions containing the product were combined, acidified with glacial acetic acid and lyophilized to afford **27** (8 mg, 15%) as the pentaacetate salt in the form of white solid; $[\alpha]_D^{25}$= +87.4 (*c* 0.3, H_2O); ^{1}H NMR (600 MHz, D_2O): δ 5.54 (s, 1H, H-1'), 4.89 (d, *J* = 3.5 Hz, 1H, H-1''), 4.15 (d, *J* = 14.3 Hz, 1H, H-6'), 4.07 (dd, *J* = 10.8, 3.6 Hz, 1H, H-2''), 3.81 (d, *J* = 12.9 Hz, 1H, H-5''), 3.75 (t, *J* = 5.7 Hz, 1H, H-2'), 3.73 – 3.65 (m, 2H, H-6', H-4), 3.60 – 3.54 (m, 2H, H-5, H-6), 3.37 – 3.25 (m, 3H, H-1, H-3'', H-5''), 3.16 – 3.05 (m, 2H, H-3, NCH_2), 2.94 – 2.84 (m, 1H, NCH_2), 2.74 (s, 4H, H-3', NCH_3), 2.51 (hept, *J* = 6.5, 5.9 Hz, 2H, SCH_2CH$_3$), 2.42 (dd, *J* = 18.0, 5.5 Hz, 1H, H-3'), 2.34 (dt, *J* = 14.1, 4.3 Hz, 1H, H-2), 1.62 – 1.51 (m, 1H, H-2), 1.16 (s, 3H, 4''CH_3), 1.11 (t, *J* = 7.2 Hz, 3H, NCH$_2$CH_3), 1.00 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3); ^{13}C NMR (151 MHz, D_2O): δ 181.1(C=O), 145.2 (C-5''), 106.1 (C-4''), 101.5 (C-1''), 96.5 (C-1'), 83.4 (C-6), 80.2 (C-4), 73.7 (C-5), 69.8 (C-4''), 67.6 (C-5''), 66.4 (C-2''), 63.5 (C-3''), 56.3 (C-1), 48.0 (C-3), 46.8 (C-2'), 40.7 (NCH$_2$), 38.2 (C-6'), 34.5 (NCH$_3$), 28.4 (C-3'), 26.7 (C-2), 26.0 (SCH$_2$CH$_3$), 23.0 (COCH$_3$), 20.7 (4''CH3), 14.0 (SCH$_2$$CH_3$), 10.9 (NCH$_2$$CH_3$); ESI-HRMS: *m/z* calcd. for $C_{23}H_{46}N_5O_7S$ $[M+H]^+$ 536.3118; found, 536.3099.

1. Tao, J.; Tran, R.; Murphy, G. K., *J. Am. Chem. Soc.* **2013,** *135*, 16312-16315.

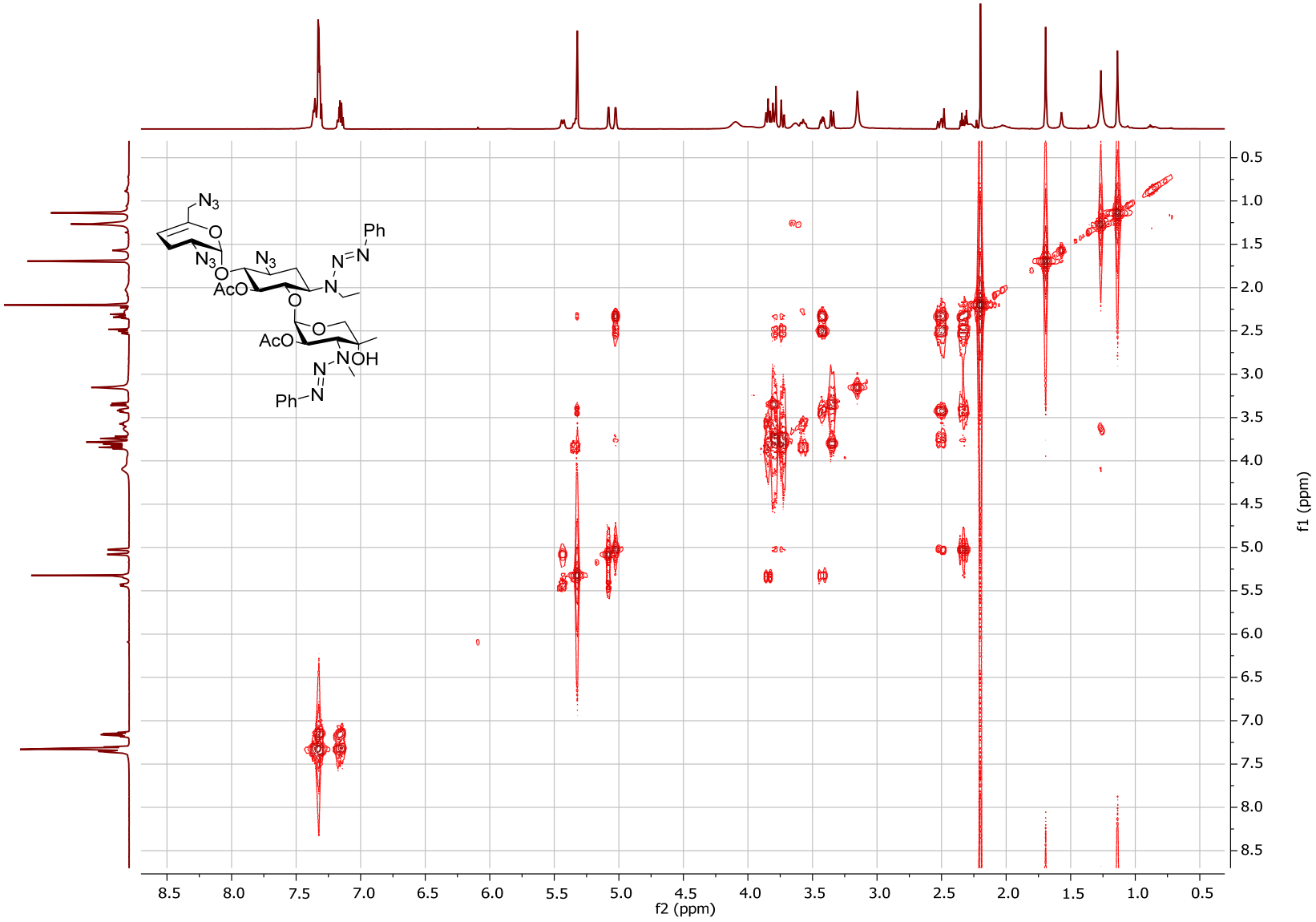
^{1}H NMR (600 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (8).



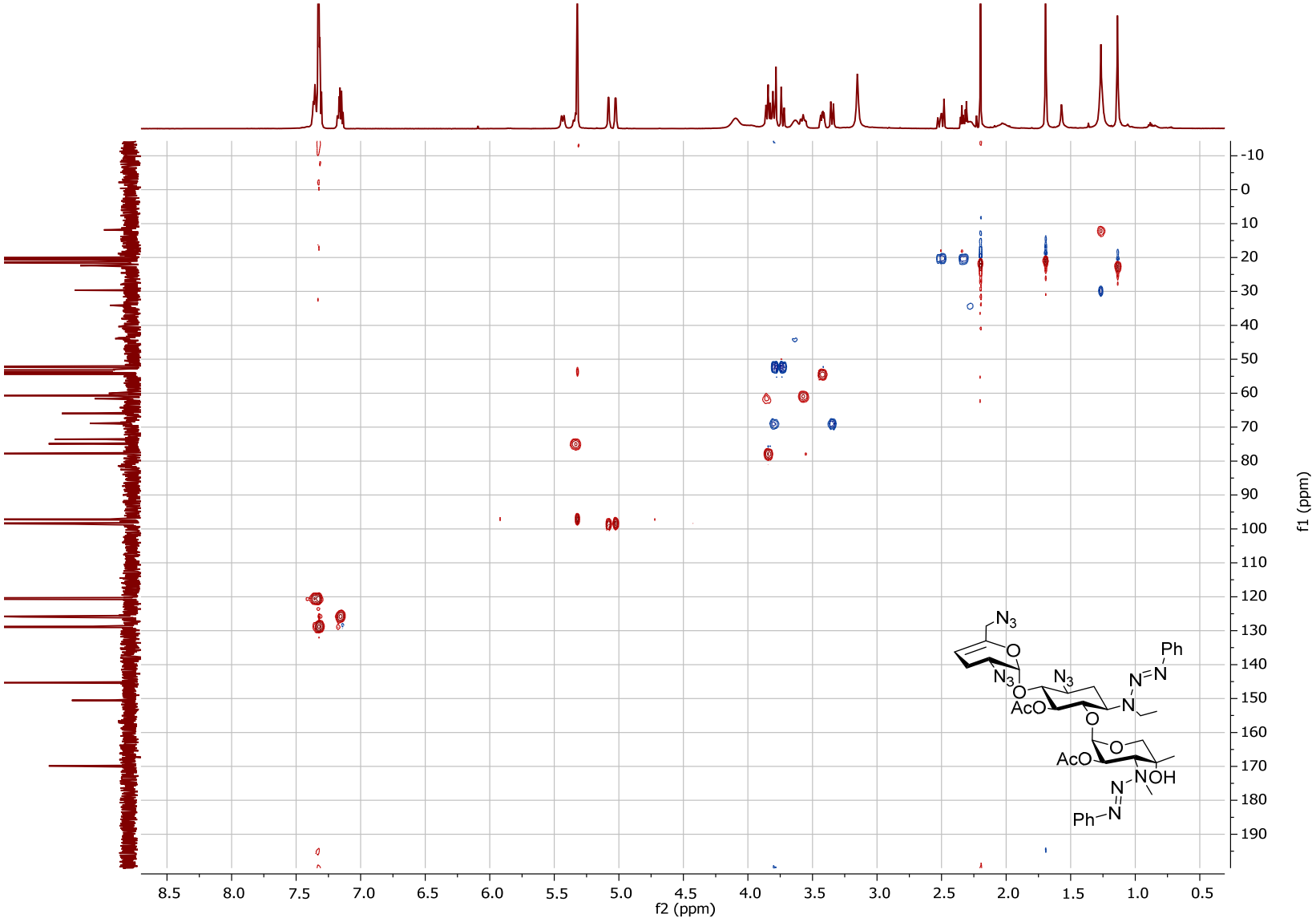
^{13}C NMR (151 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (8).



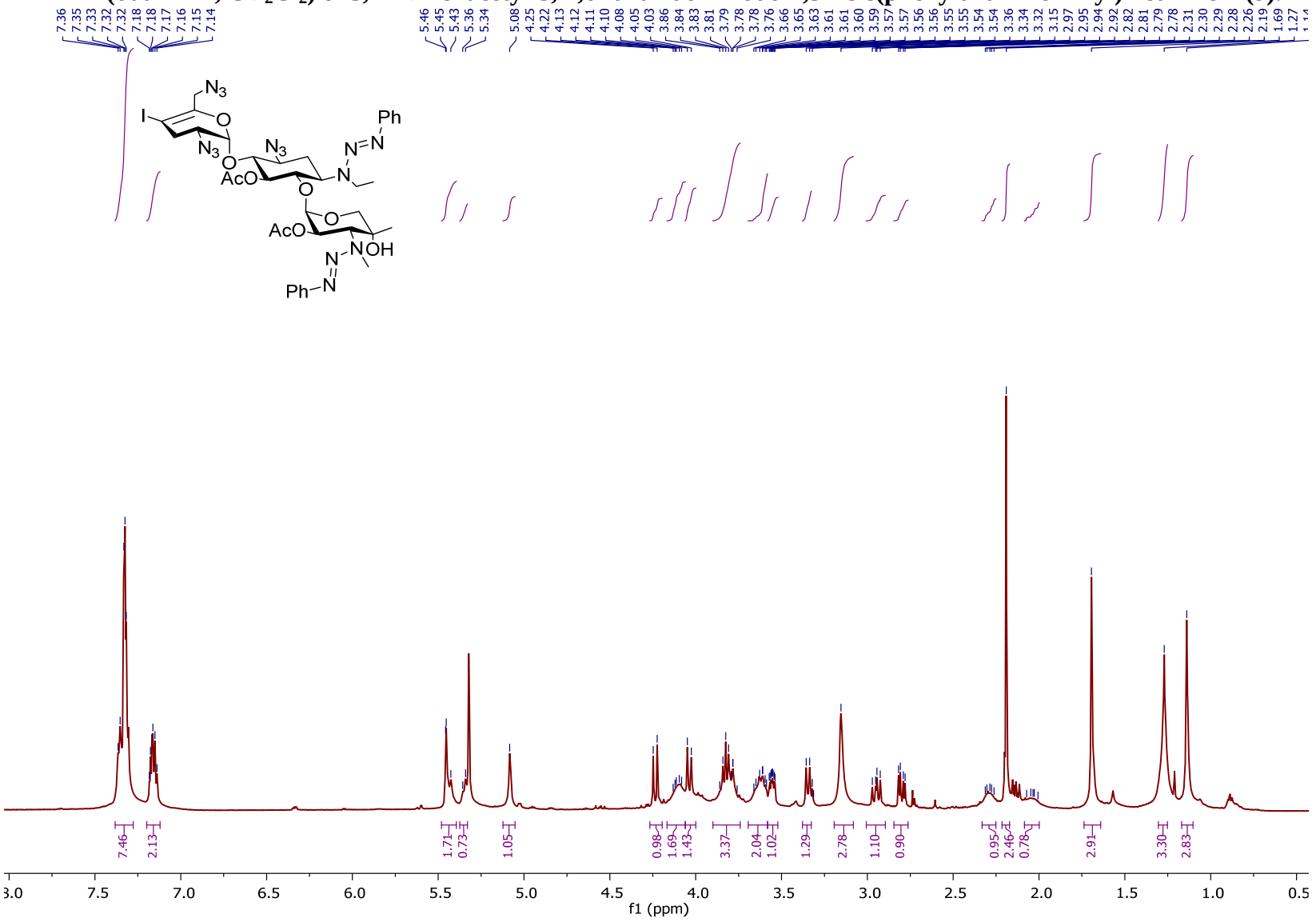
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (8).



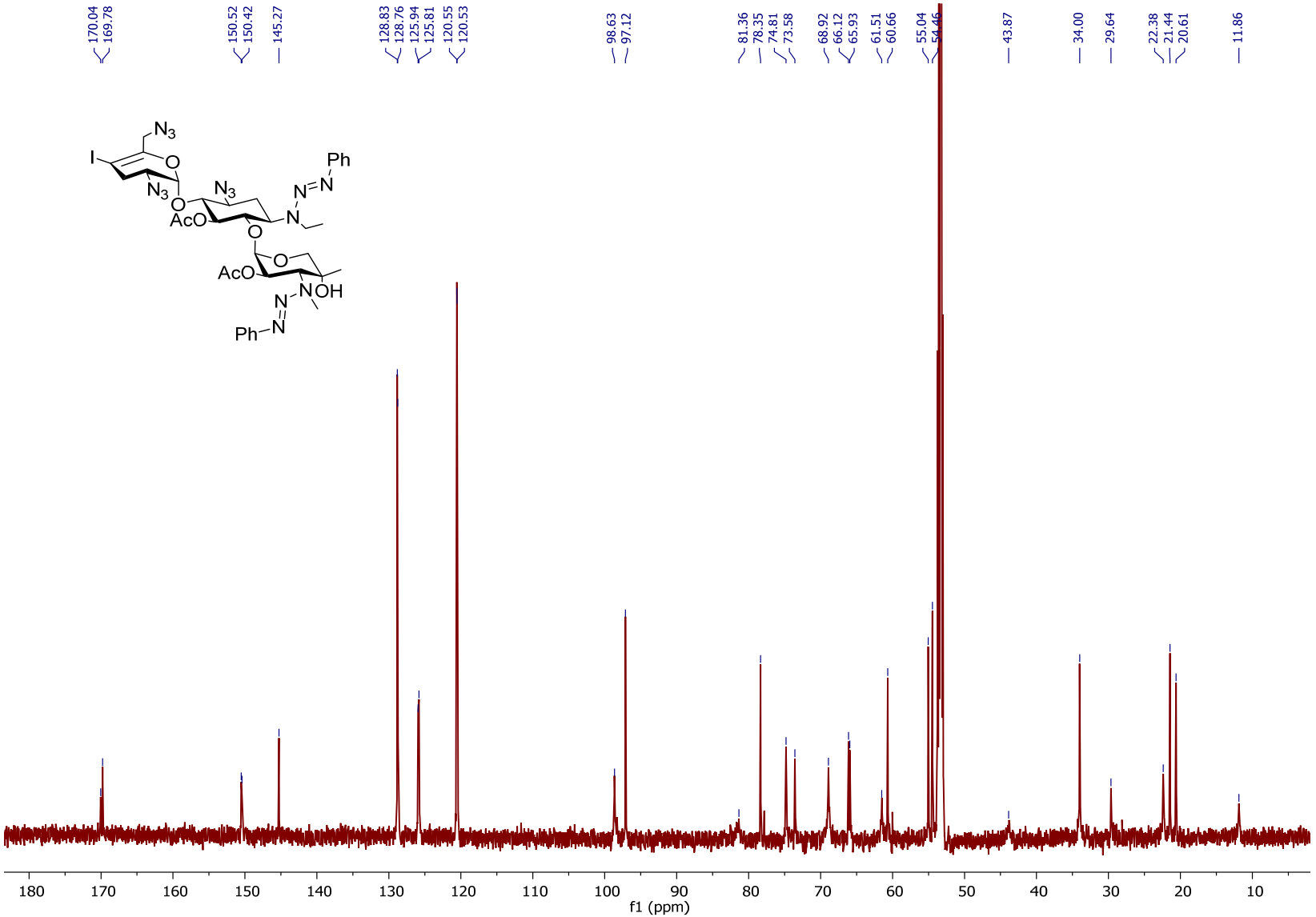
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (8).



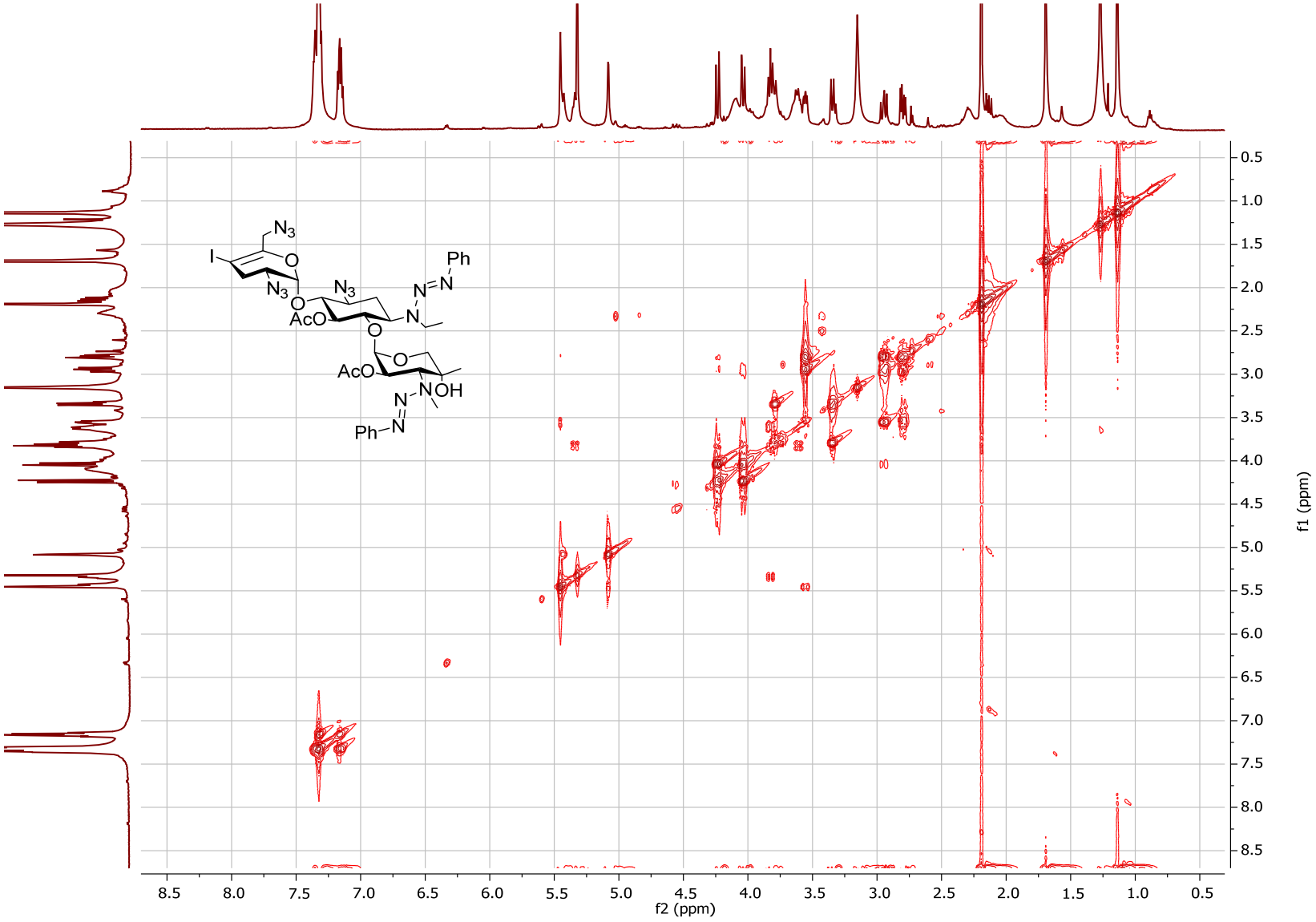
^{1}H NMR (600 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-iodo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (9).



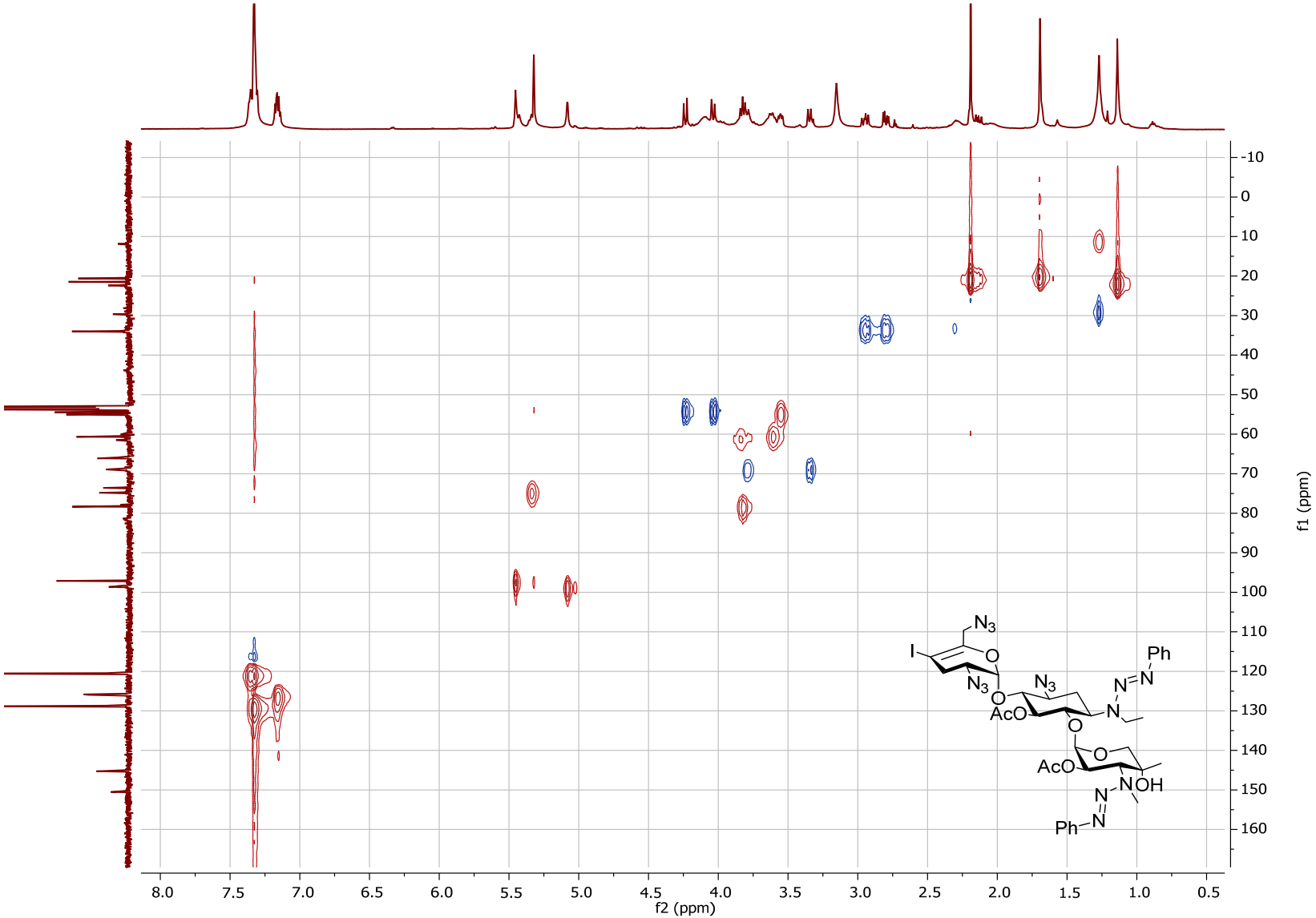
^{13}C NMR (151 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-iodo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (9).



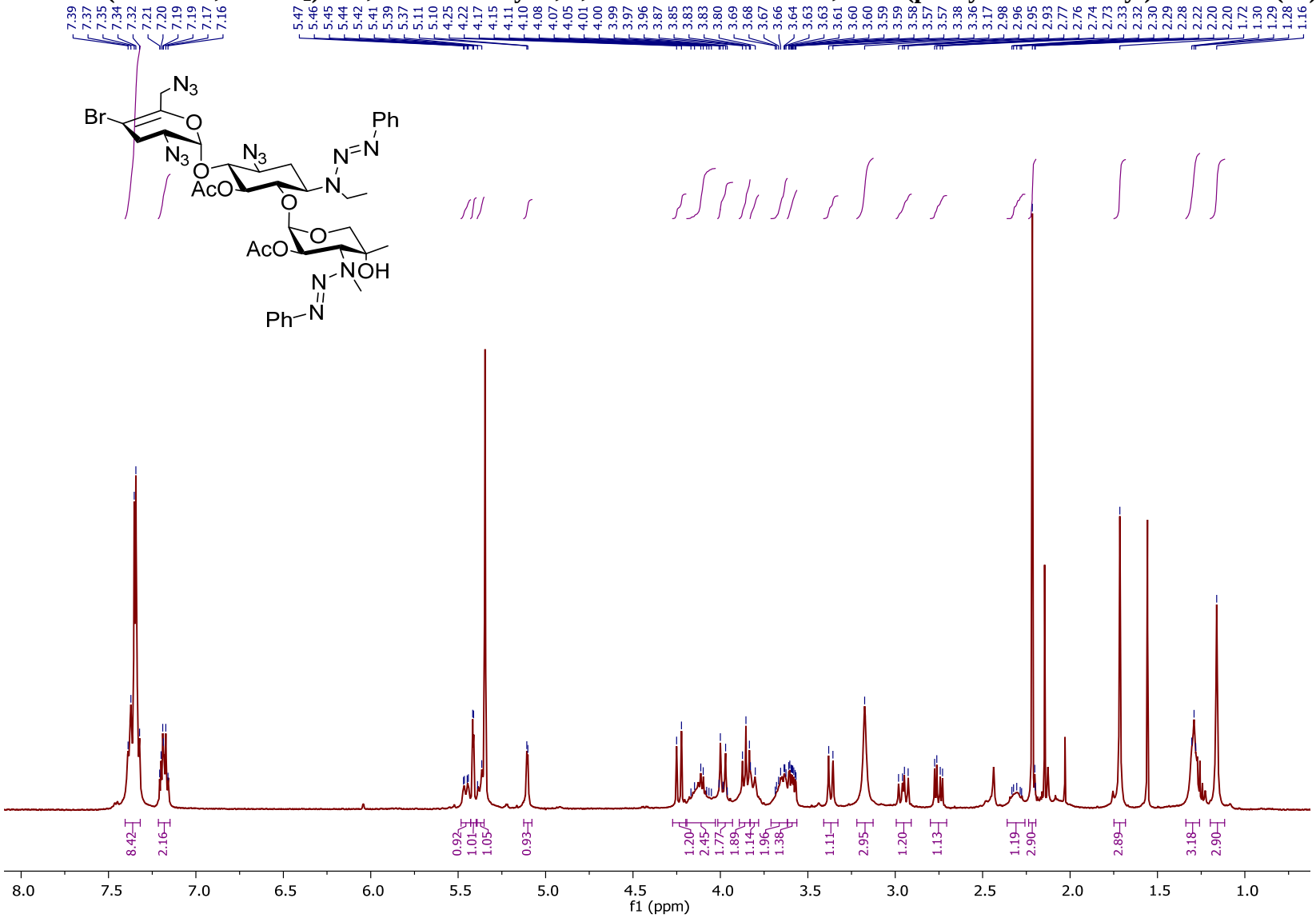
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-iodo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (9).



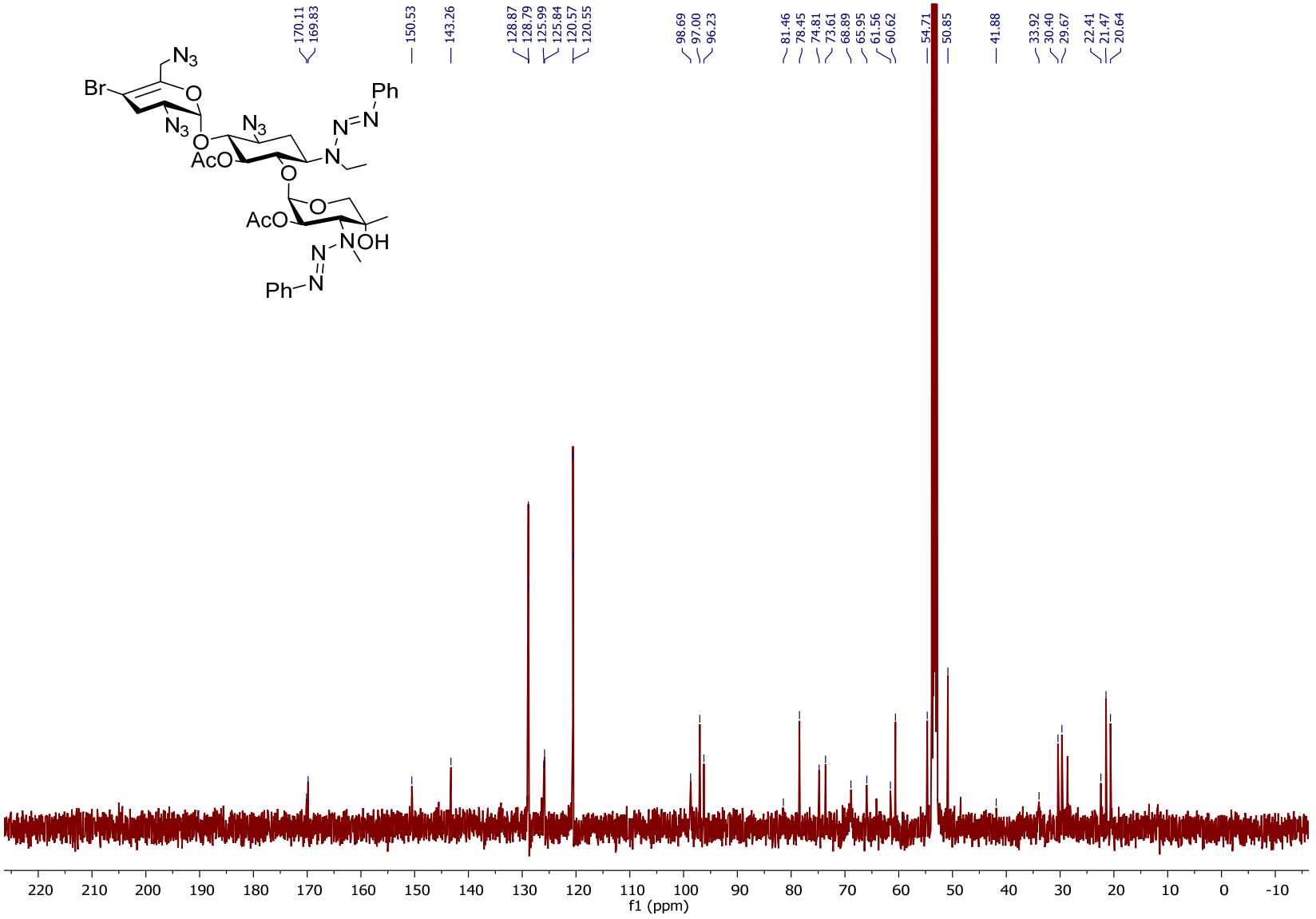
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-iodo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (9).



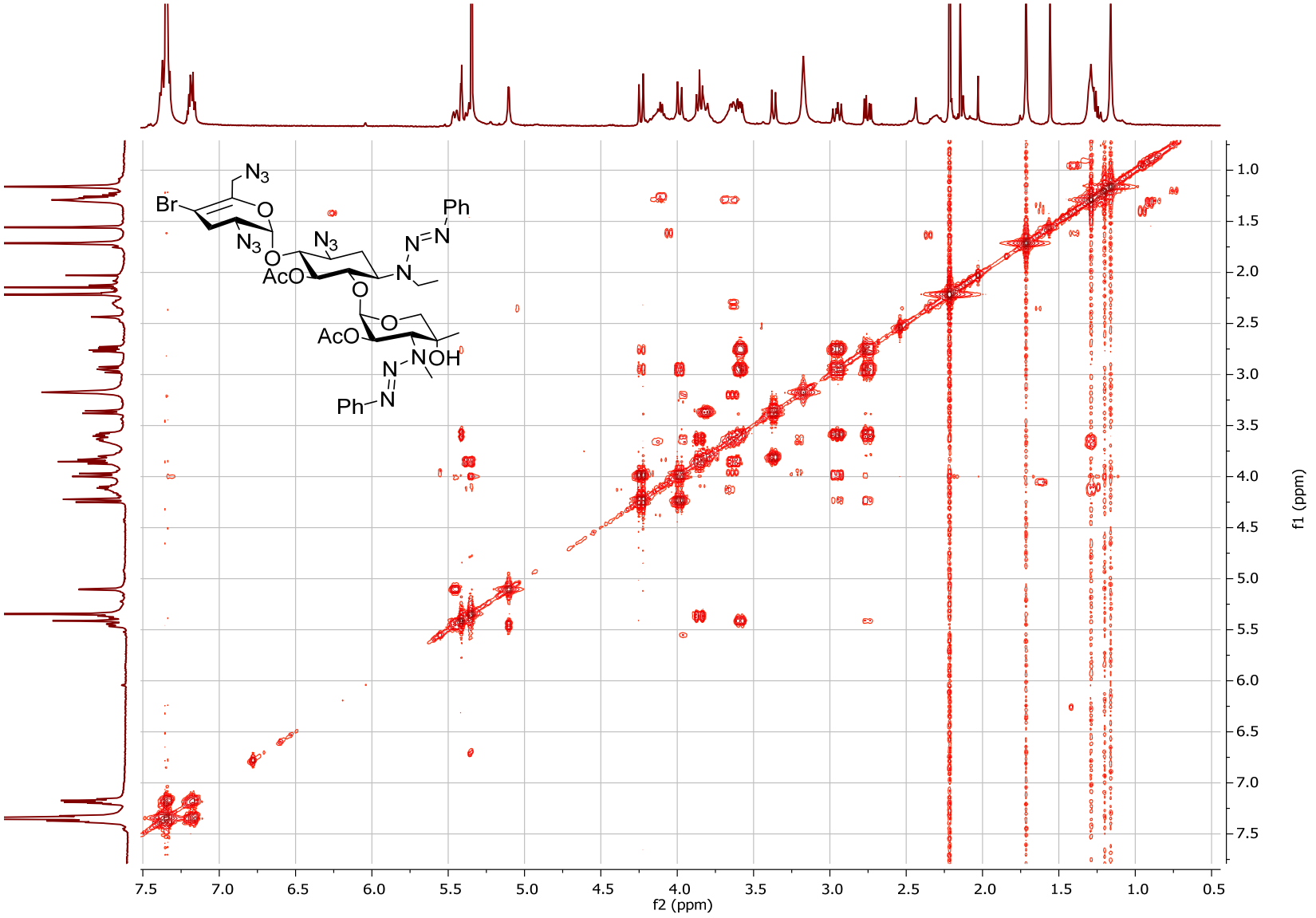
^{1}H NMR (500 MHz, $CD2Cl_2$) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-bromo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (10).



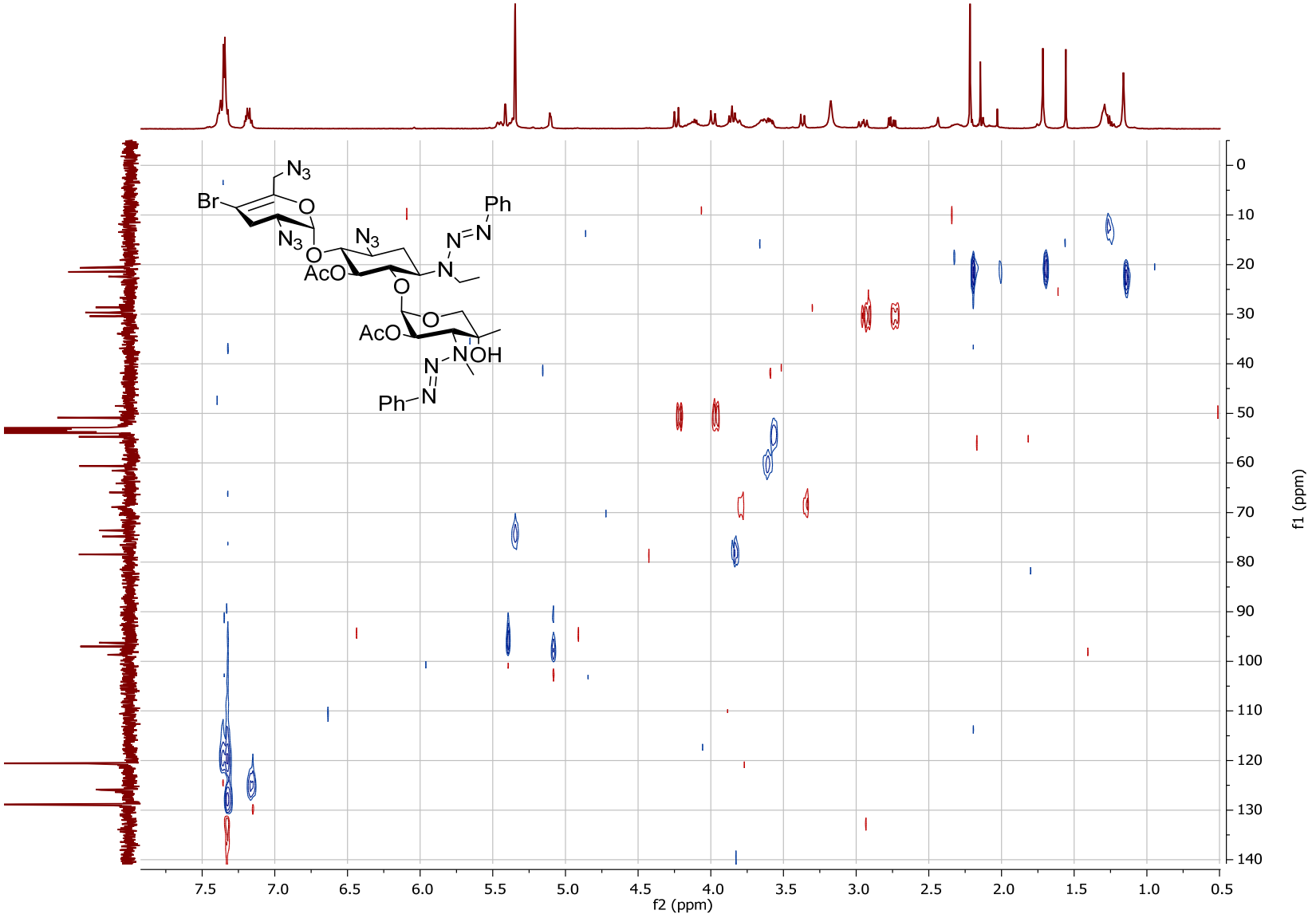
^{13}C NMR (126 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-bromo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (10).



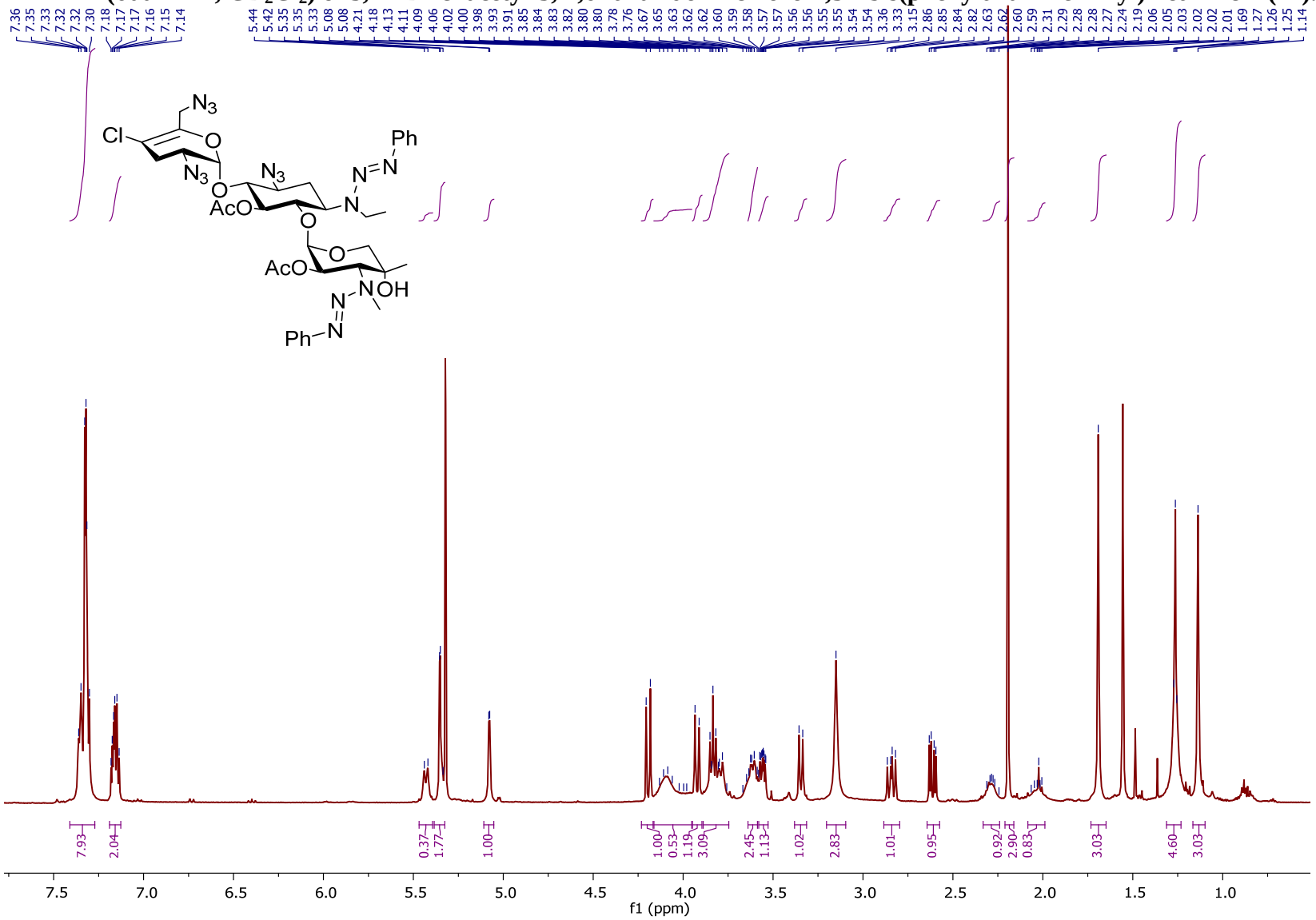
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-bromo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (10).



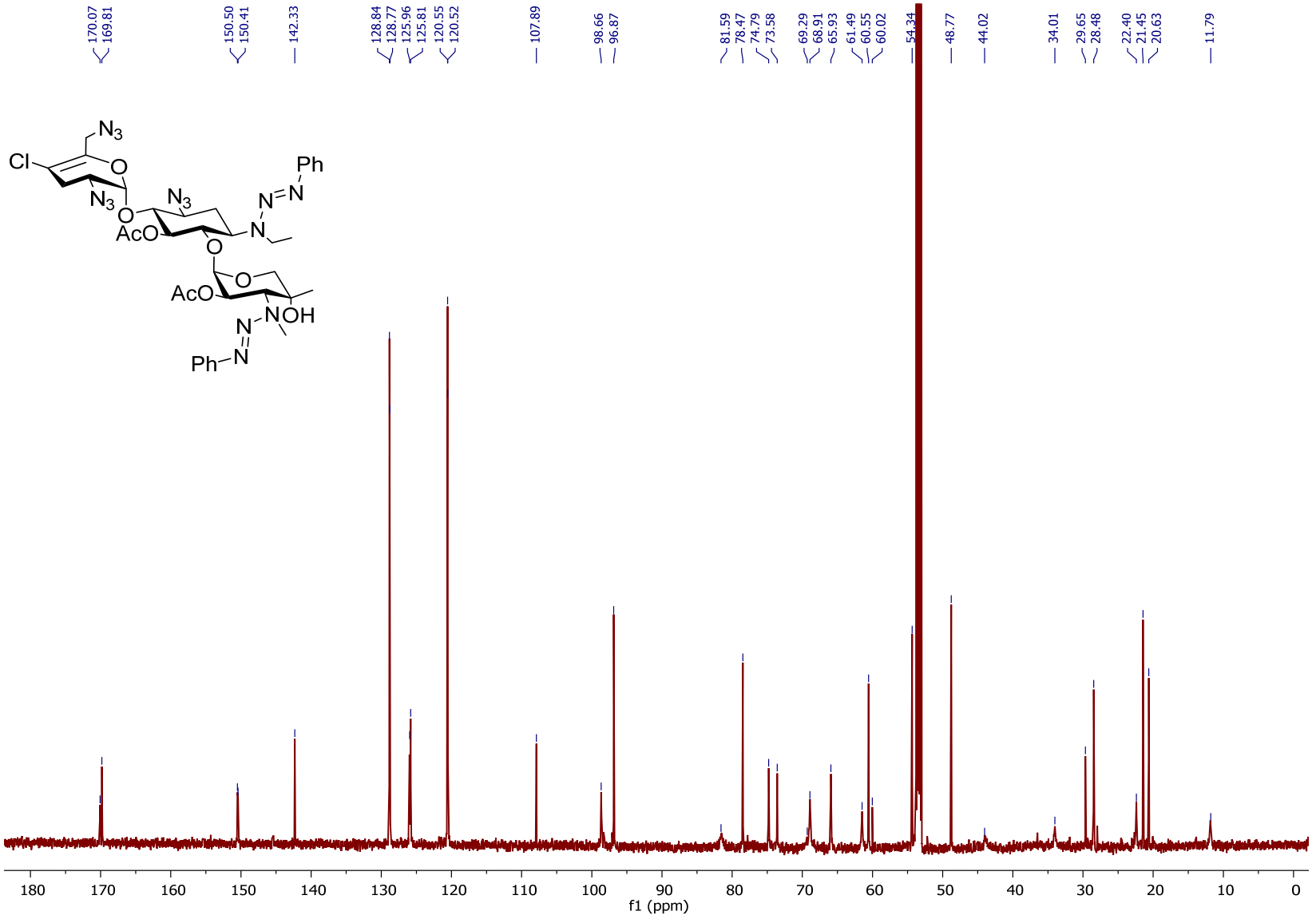
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-bromo-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (10).



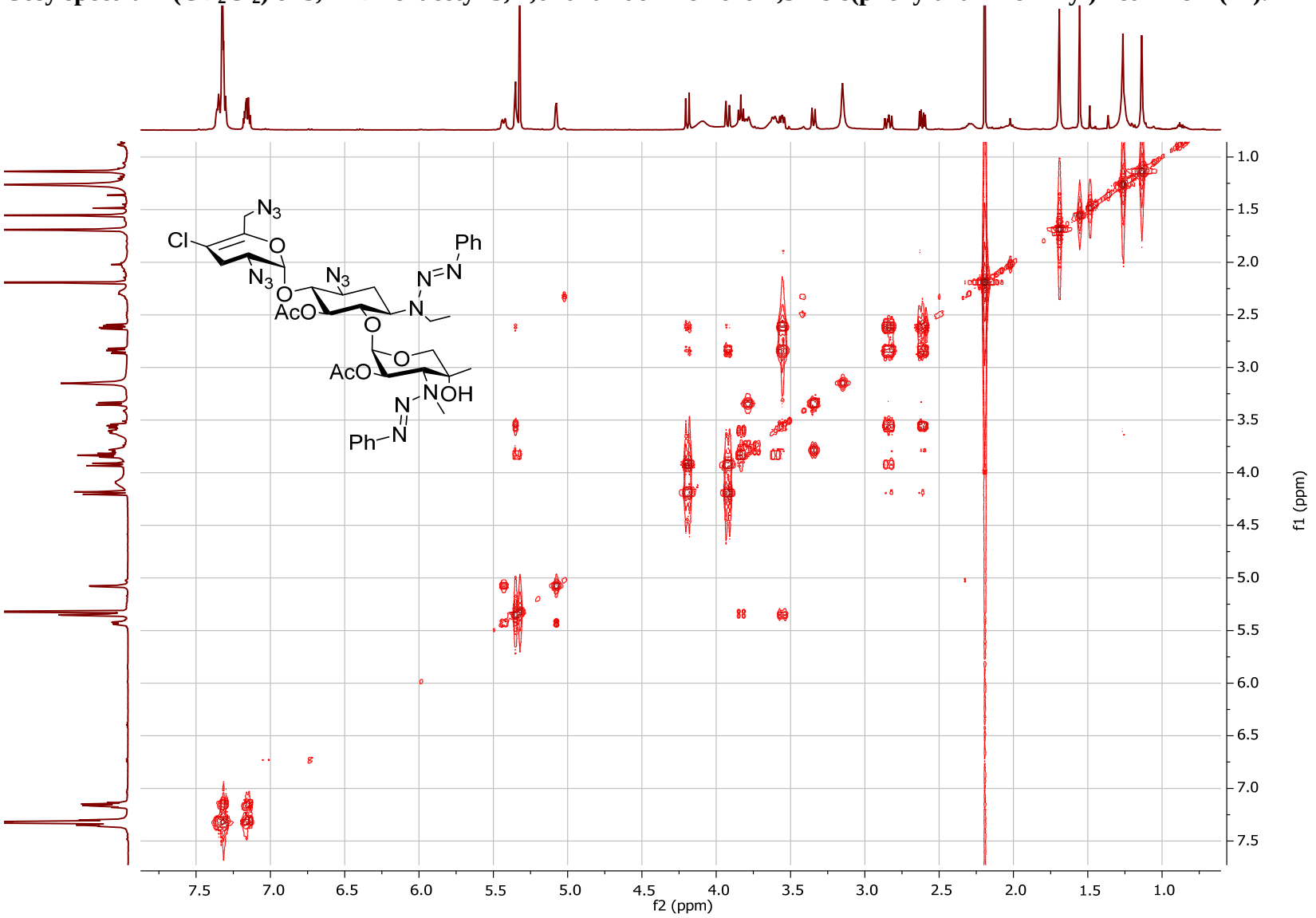
^{1}H NMR (600 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



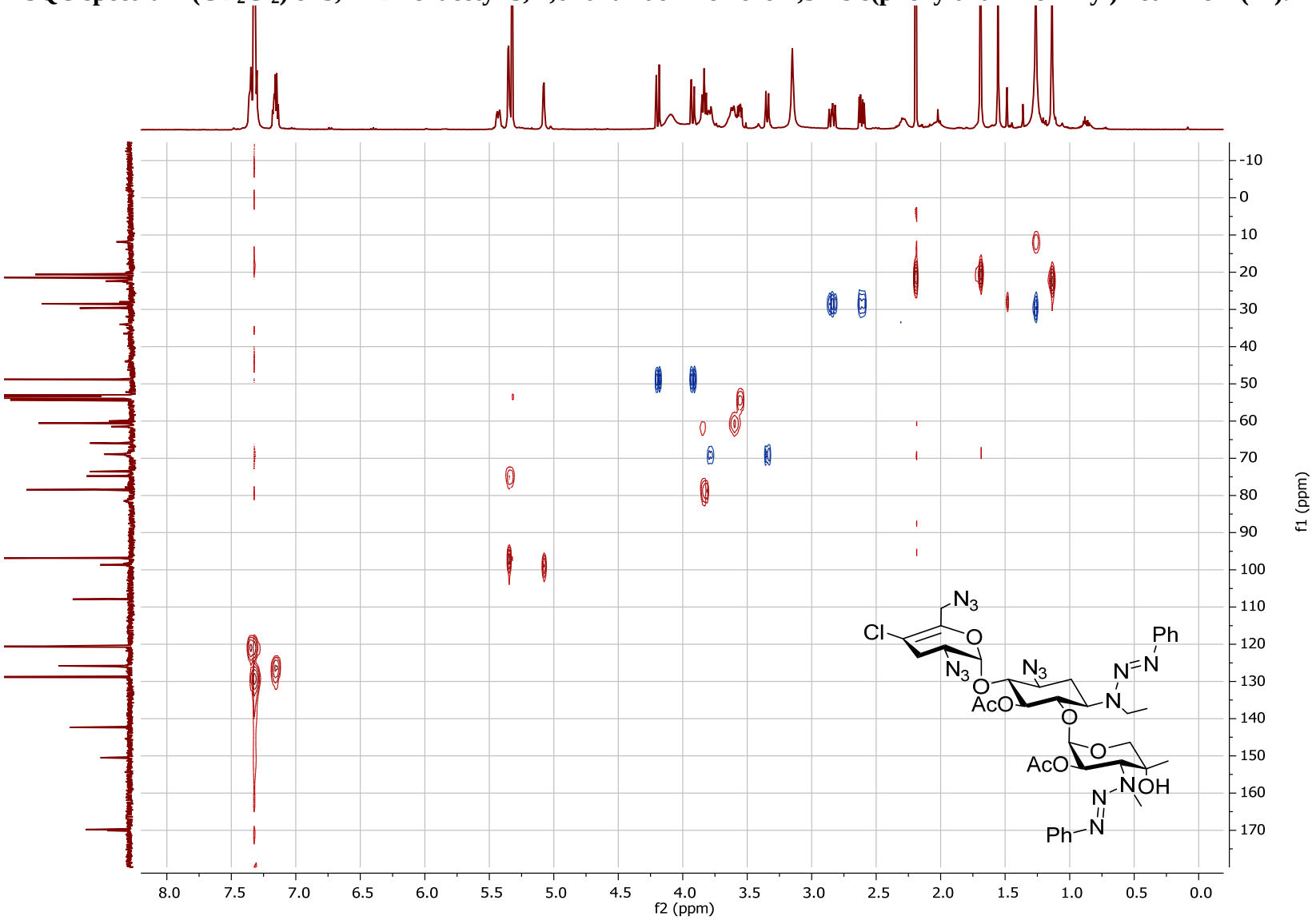
^{13}C NMR (151 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



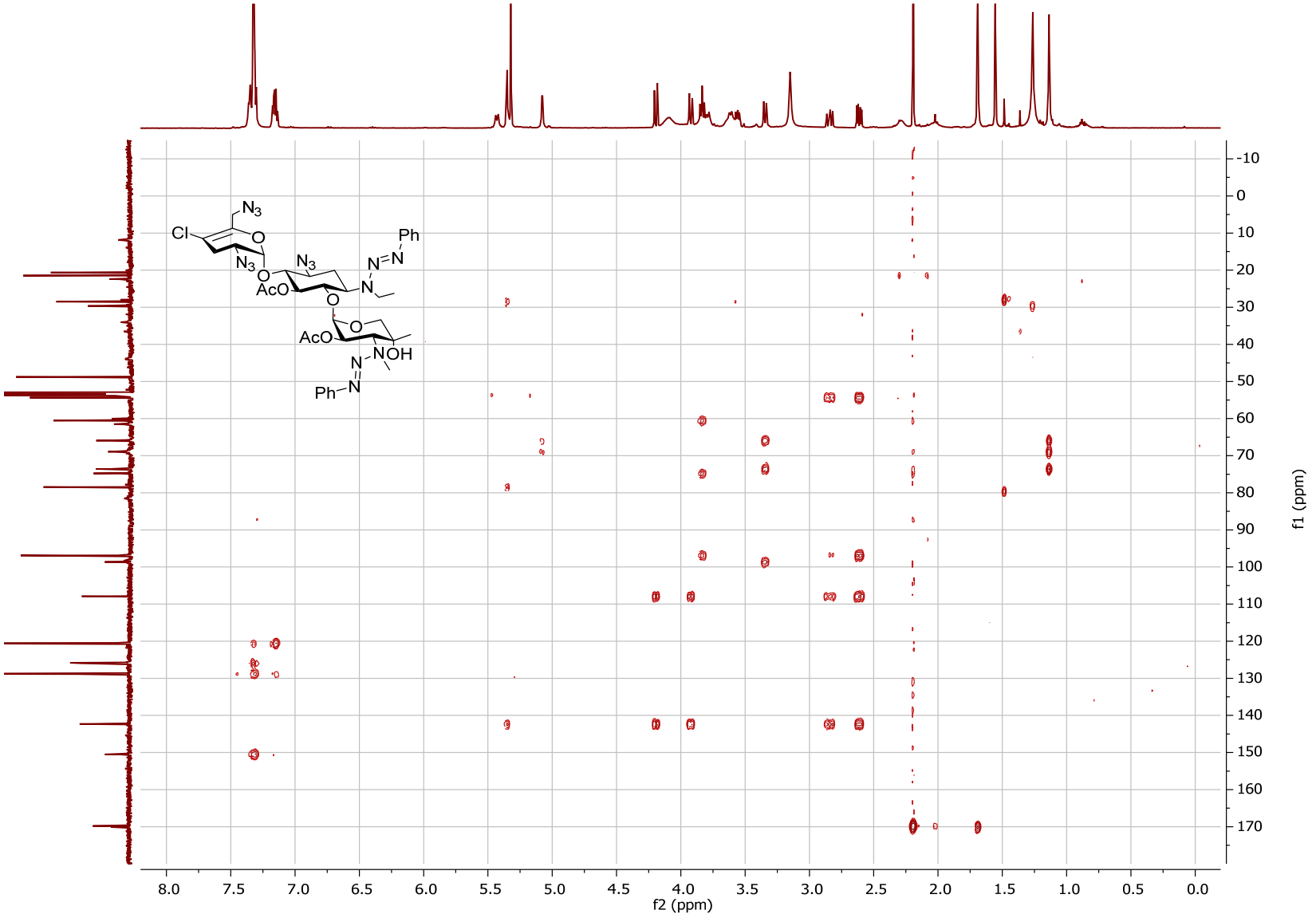
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



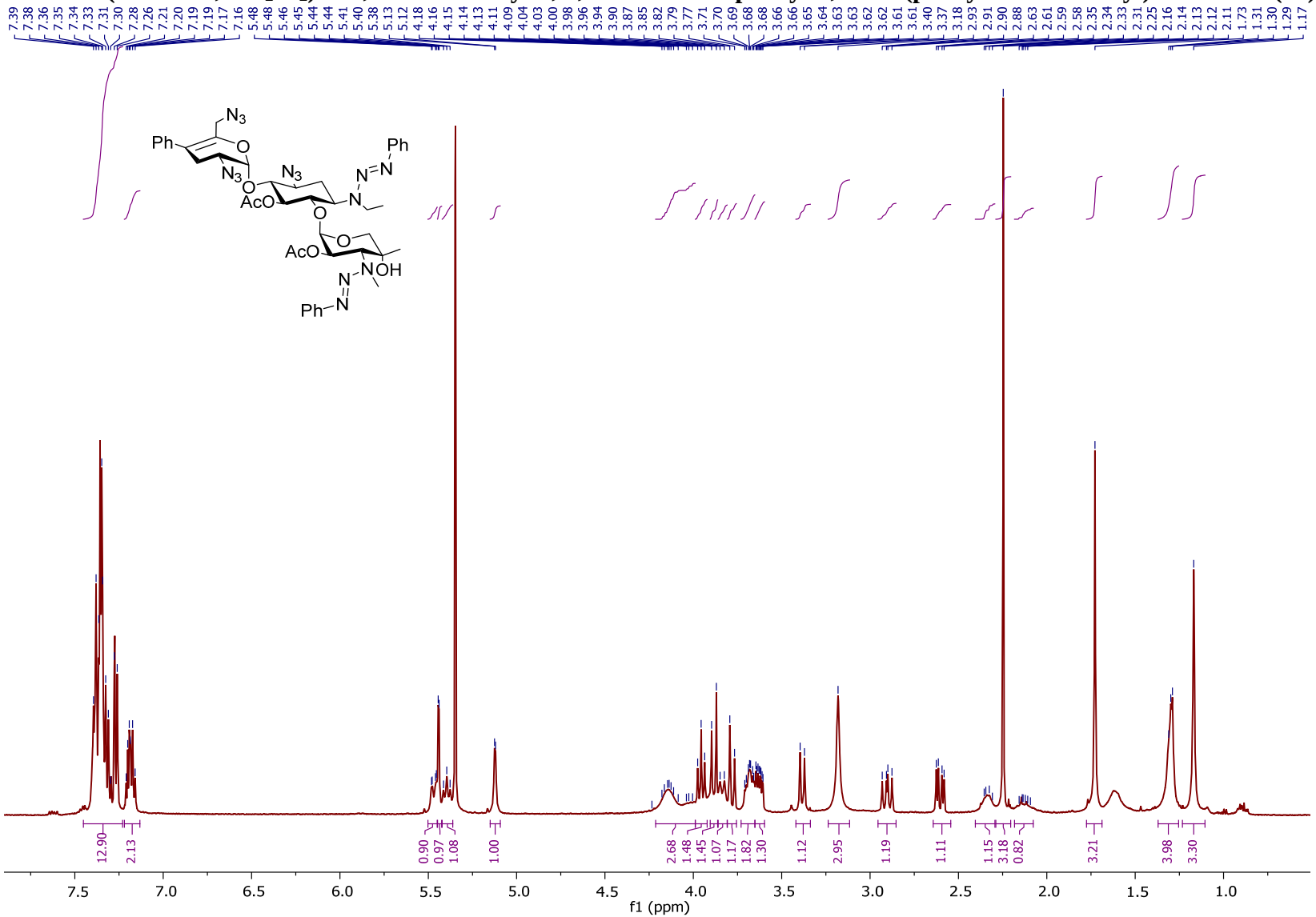
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



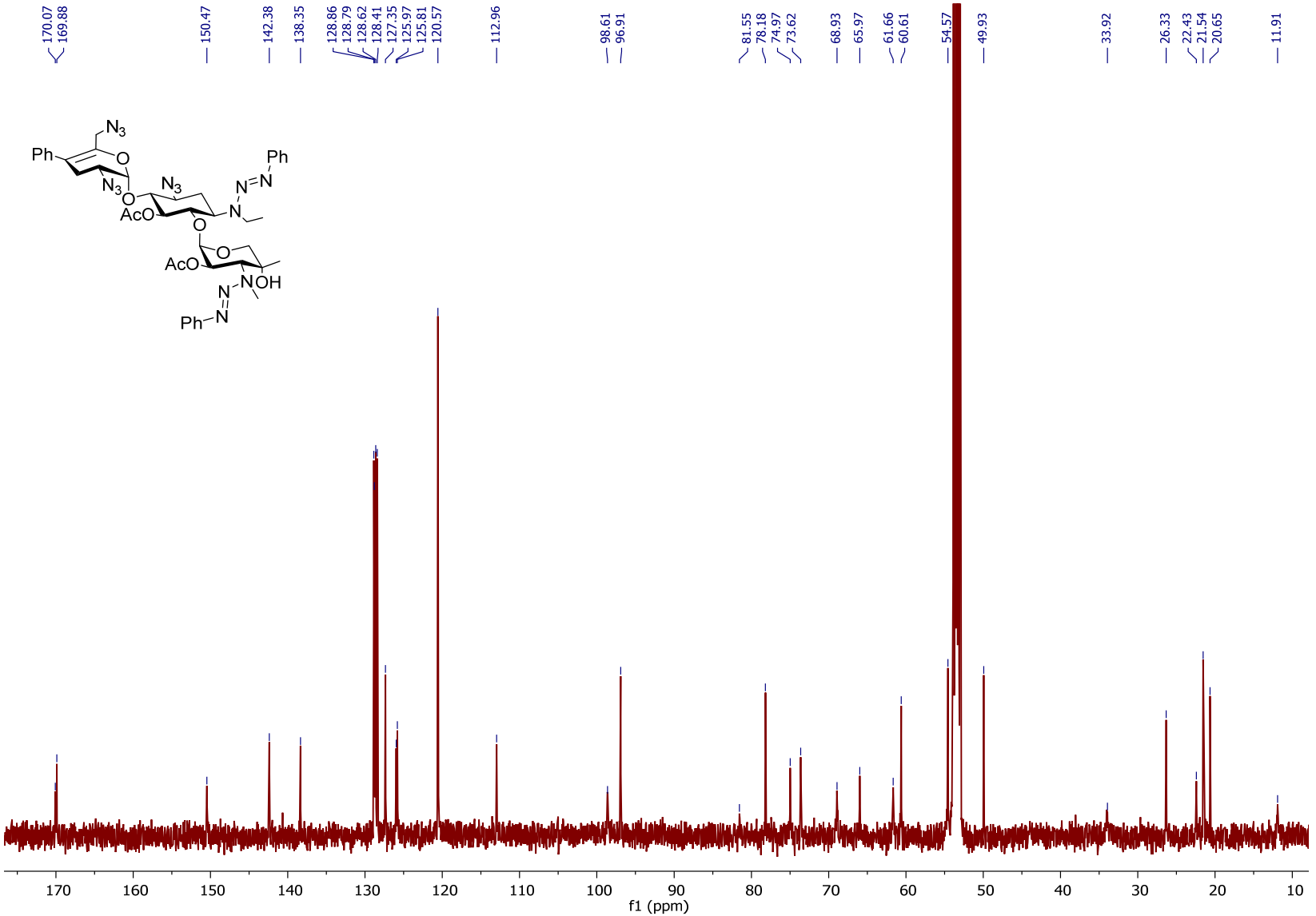
HMBC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-chloro-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (11).



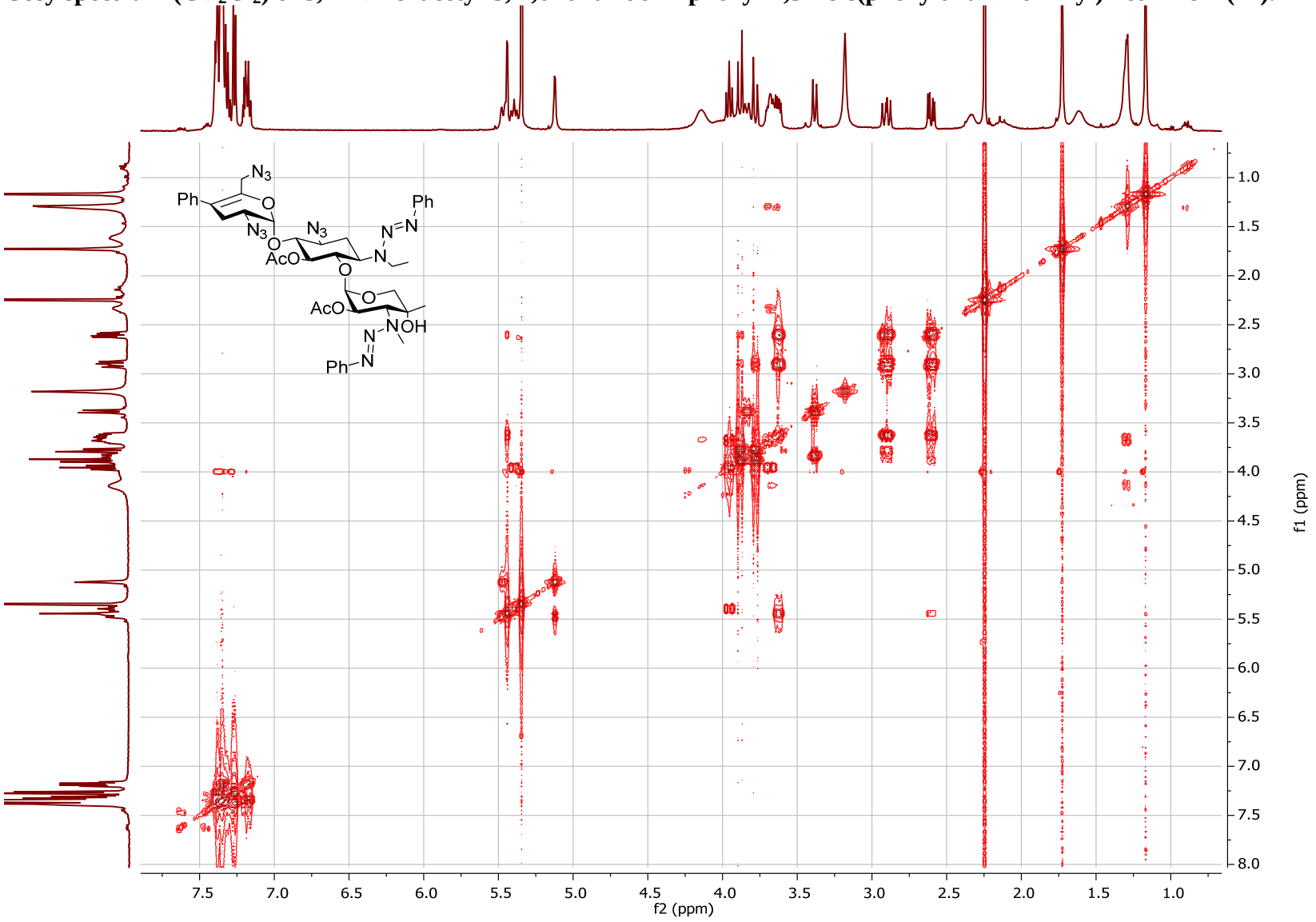
^{1}H NMR (500 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



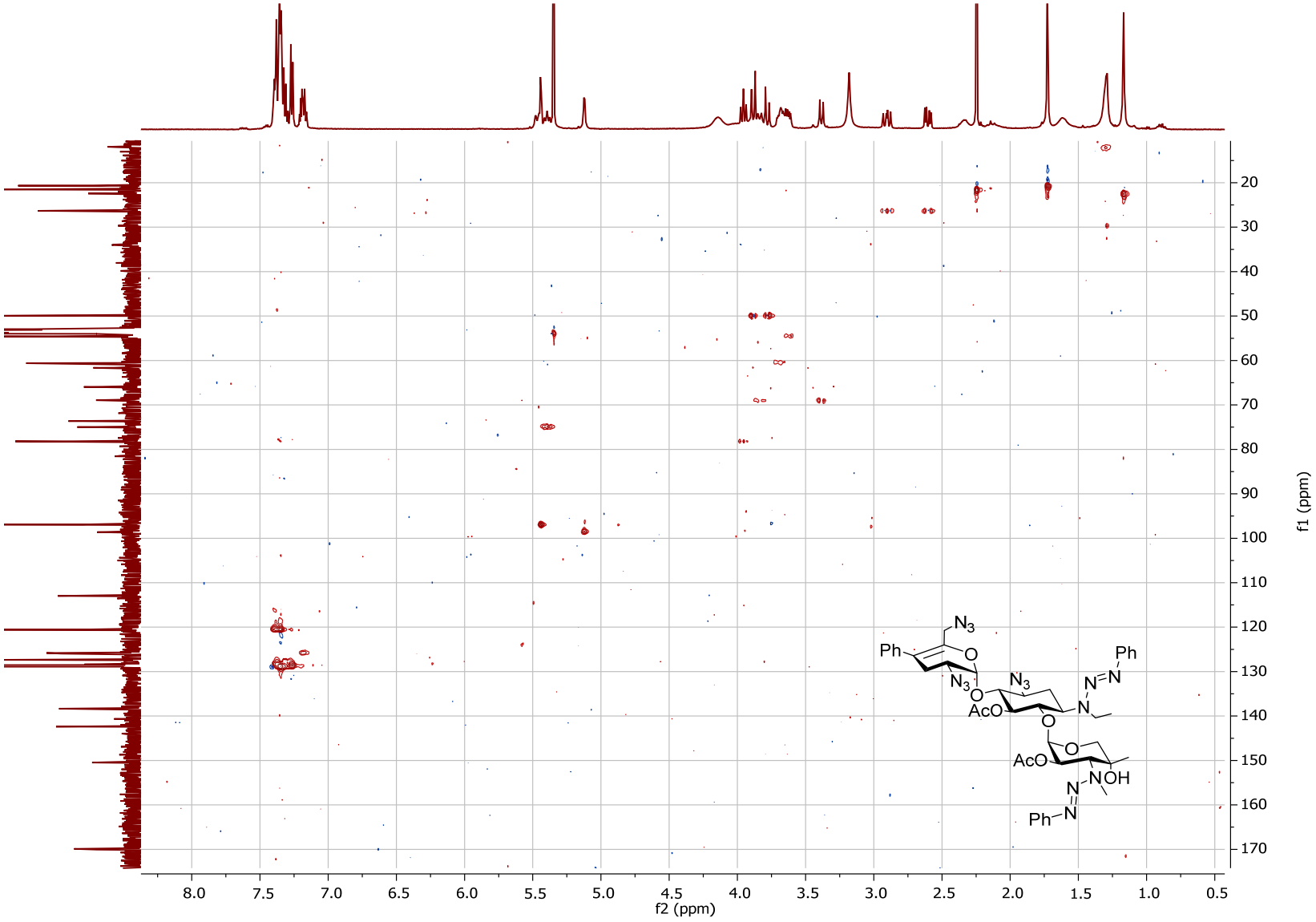
^{13}C NMR (126 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



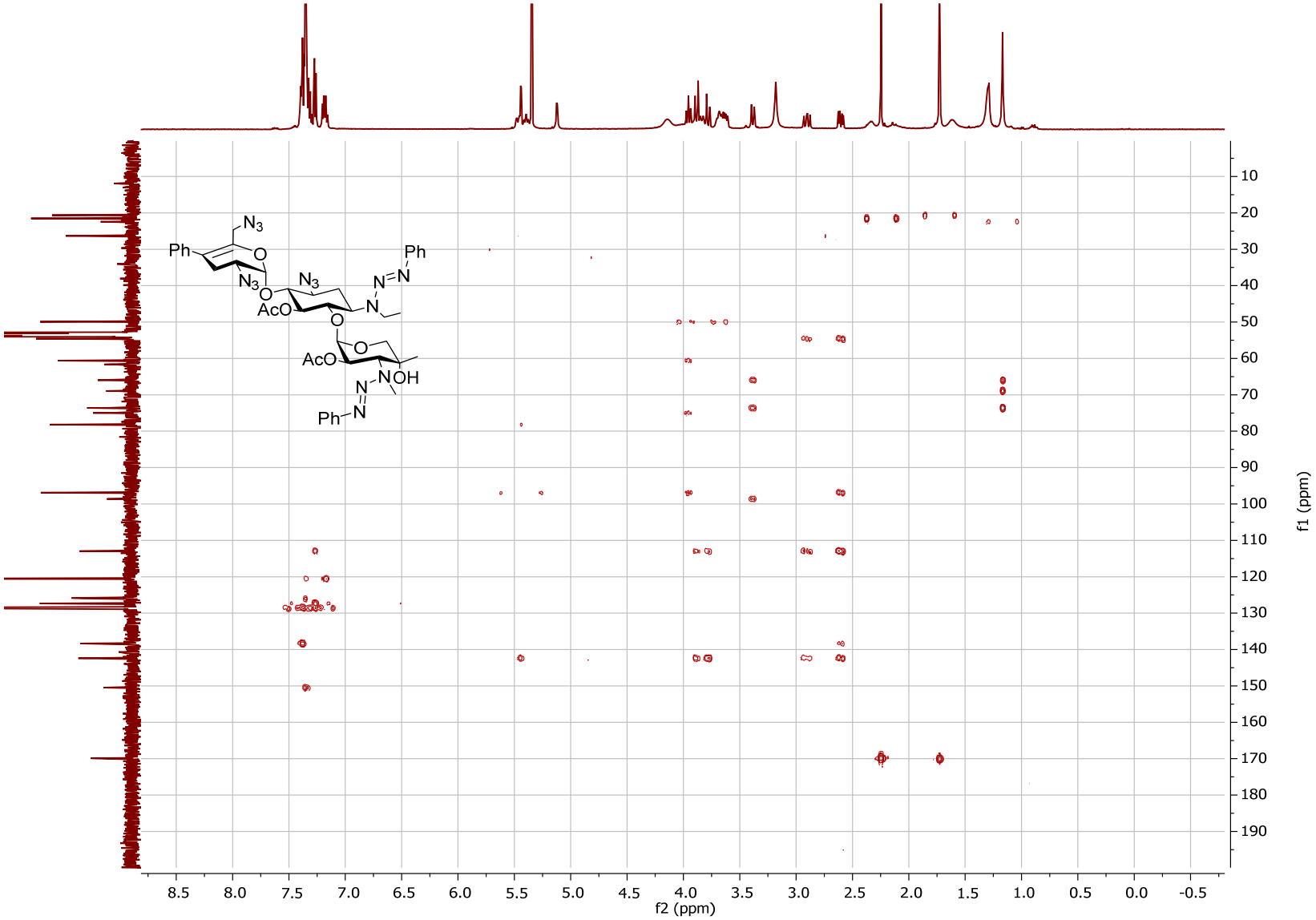
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



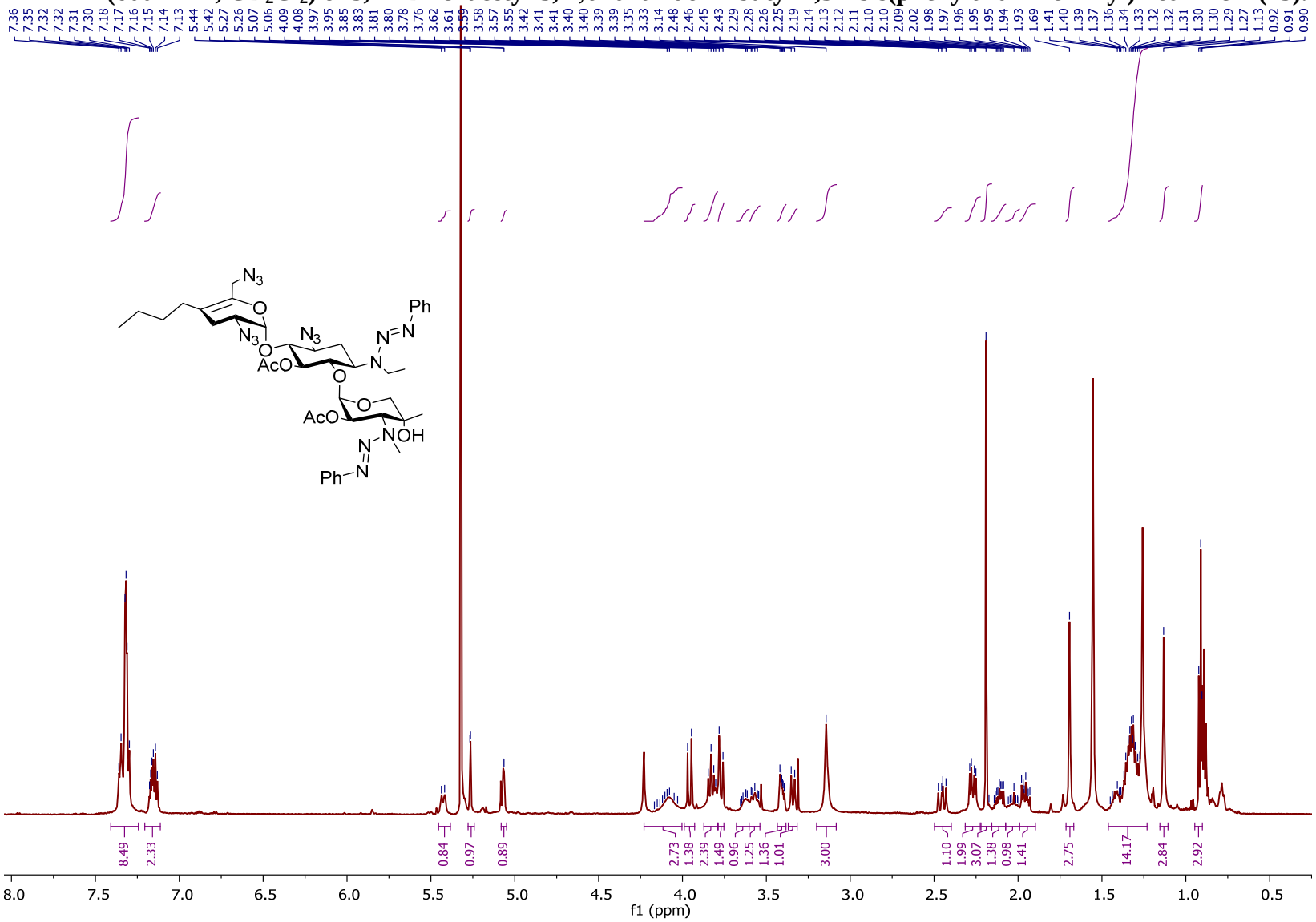
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



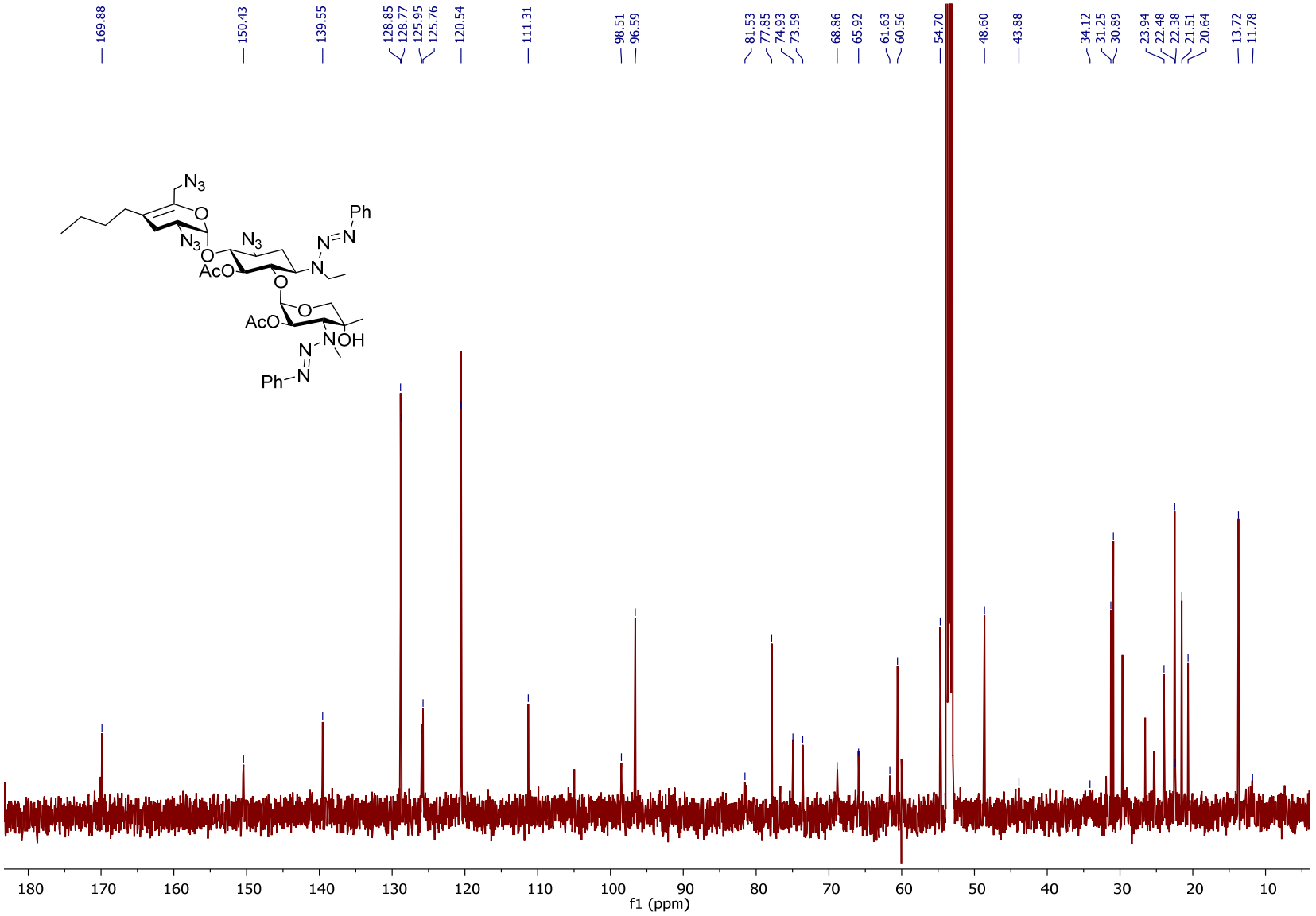
HMBC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-phenyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (12).



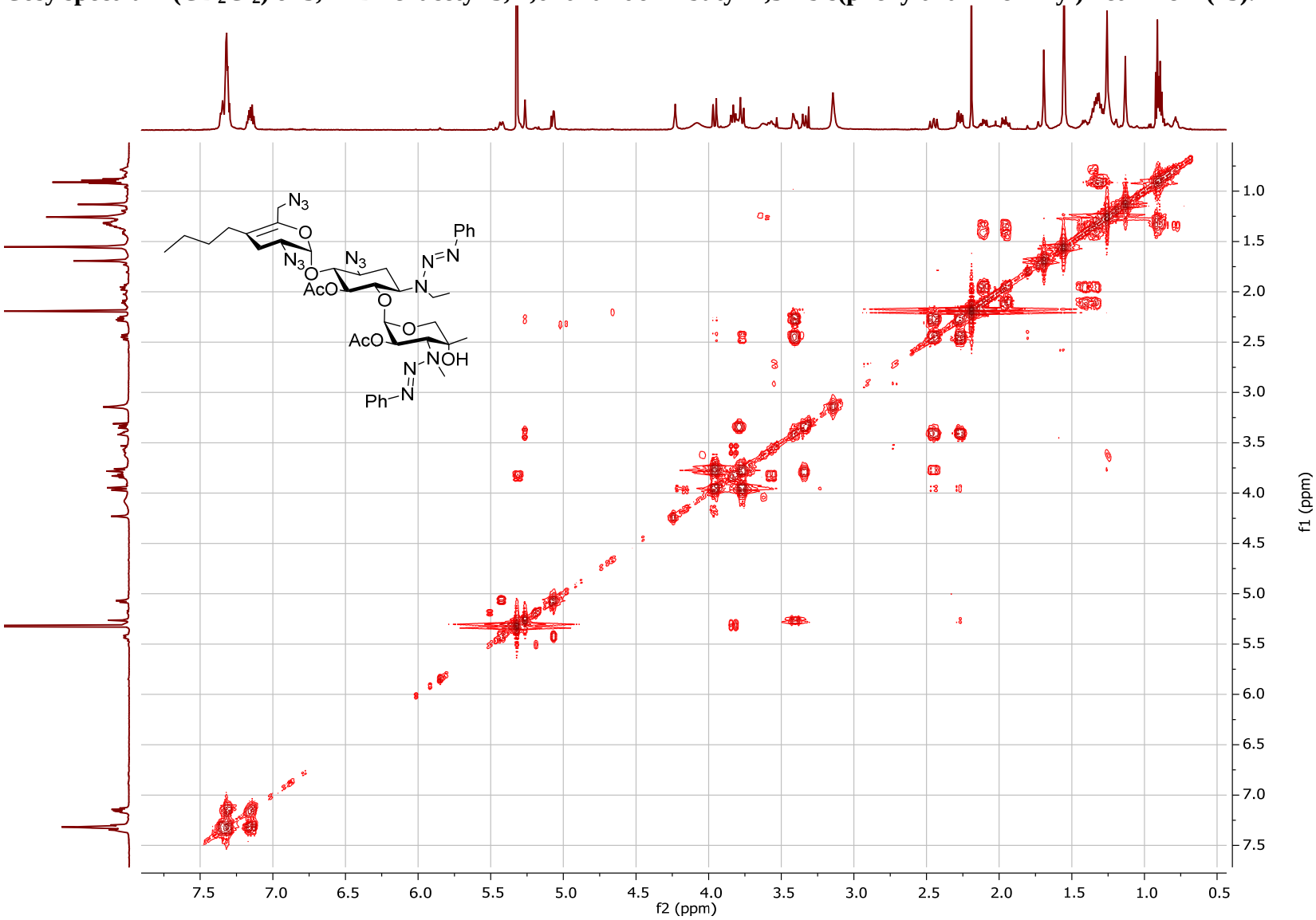
^{1}H NMR (600 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-butyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (13).



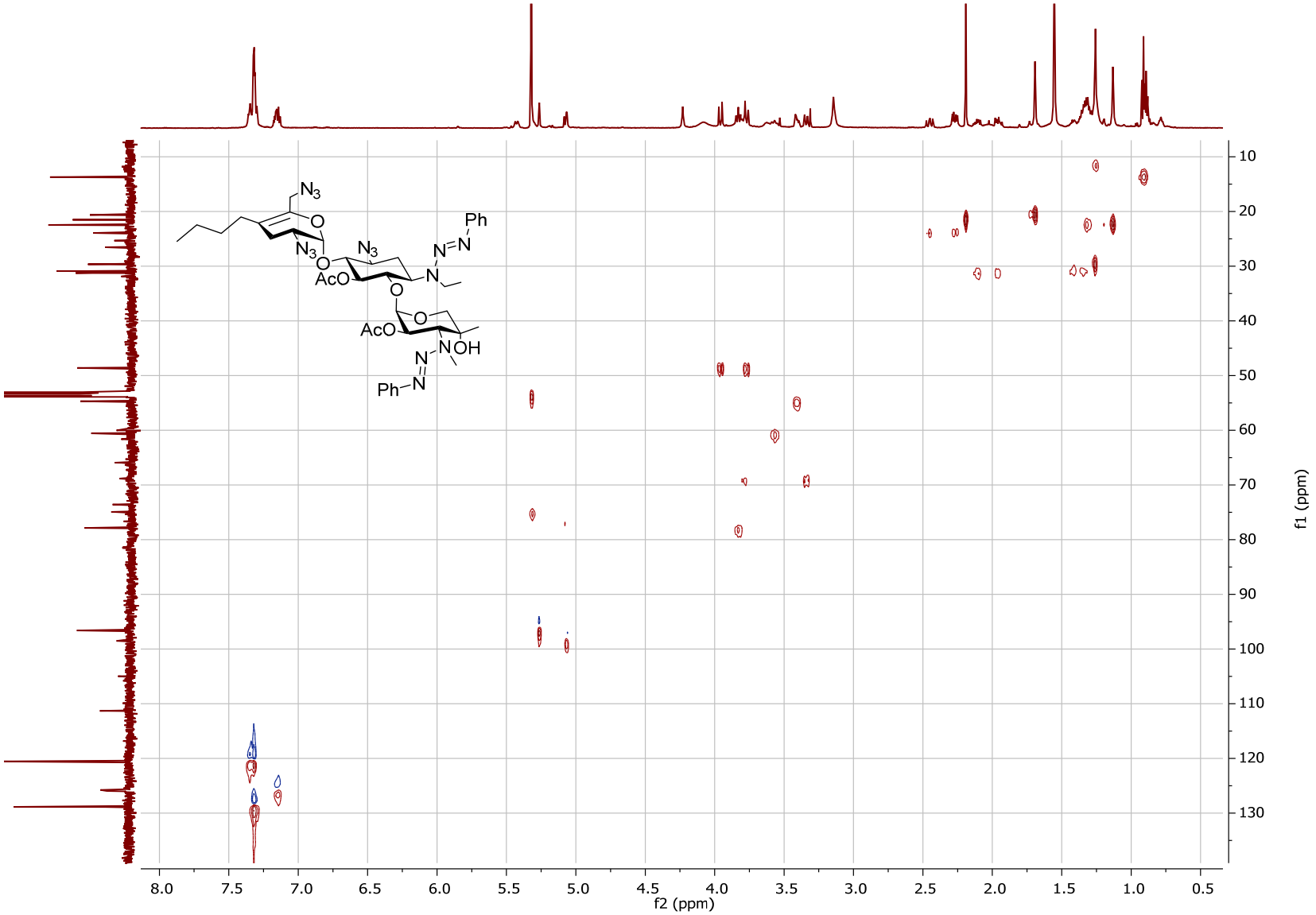
^{13}C NMR (151 MHz, CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-butyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (13).



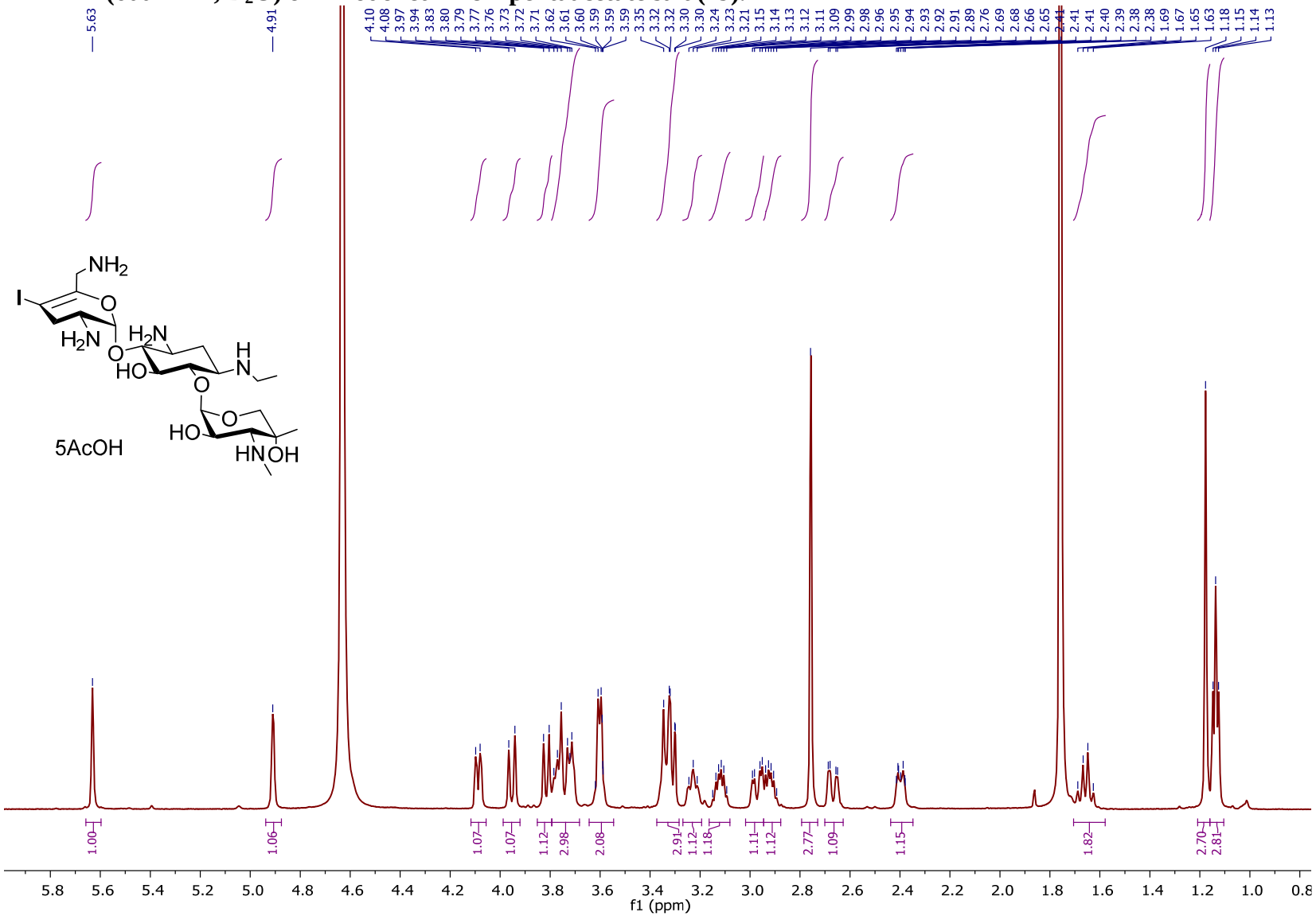
Cosy spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-butyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (13).



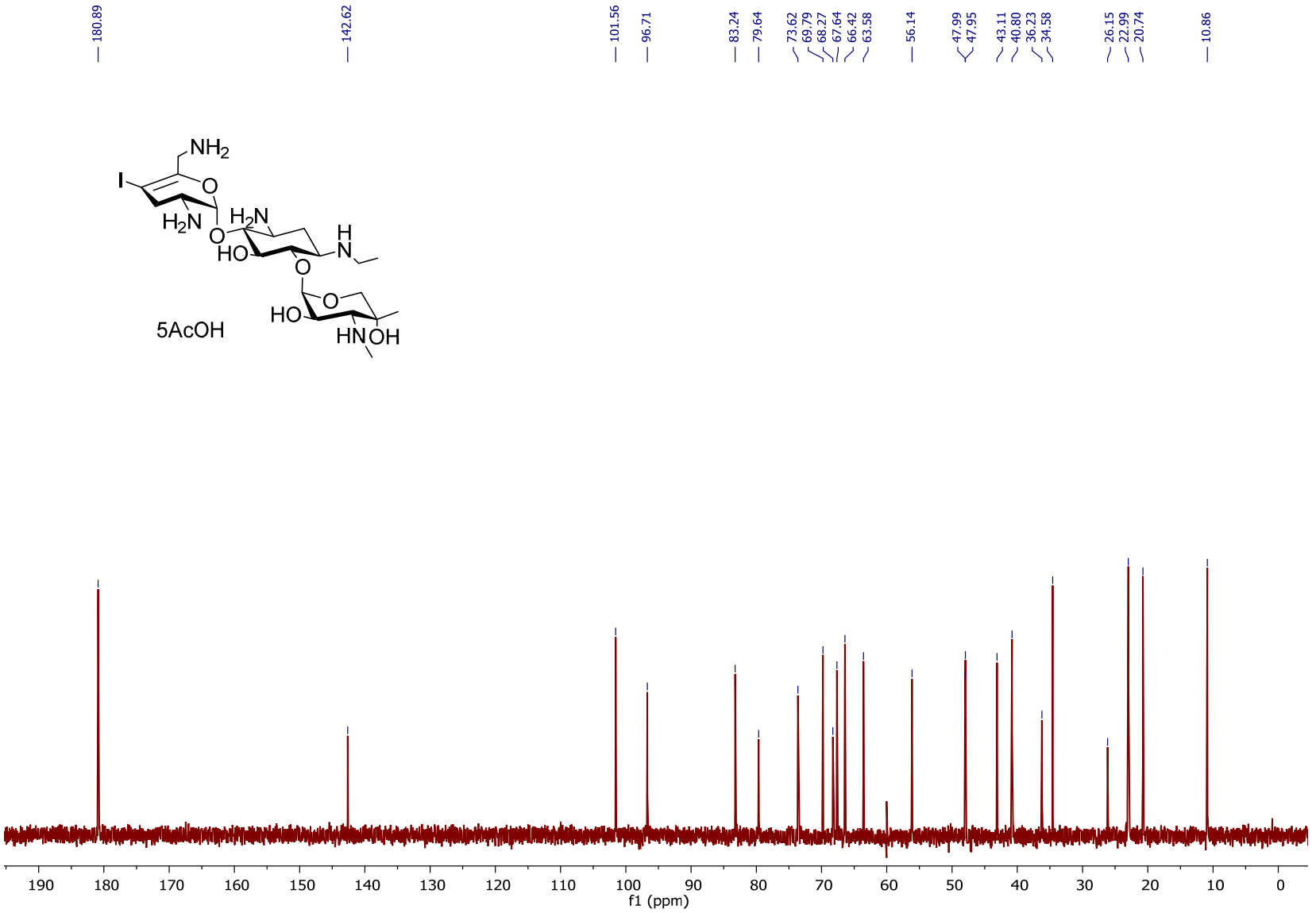
HSQC spectrum (CD_2Cl_2) of 5,2''-Di-*O*-acetyl-3,2',6'-triazido-4'-butyl-1,3''-bis(phenyltriaz-2-en-1-yl) netilmicin (13).



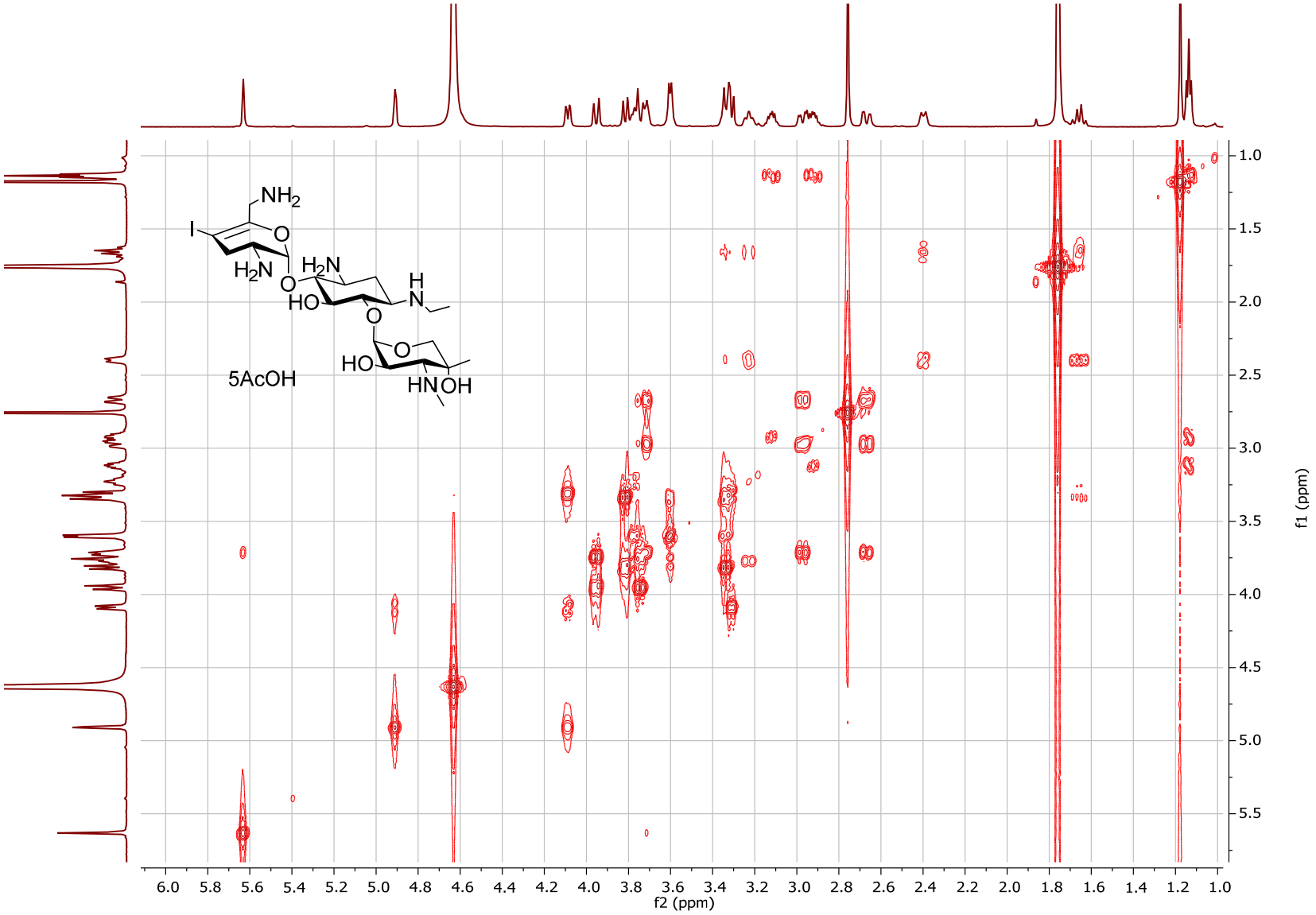
^{1}H NMR (600 MHz, D_2O) of 4'-Iodonetilmicin pentaacetate salt (19).



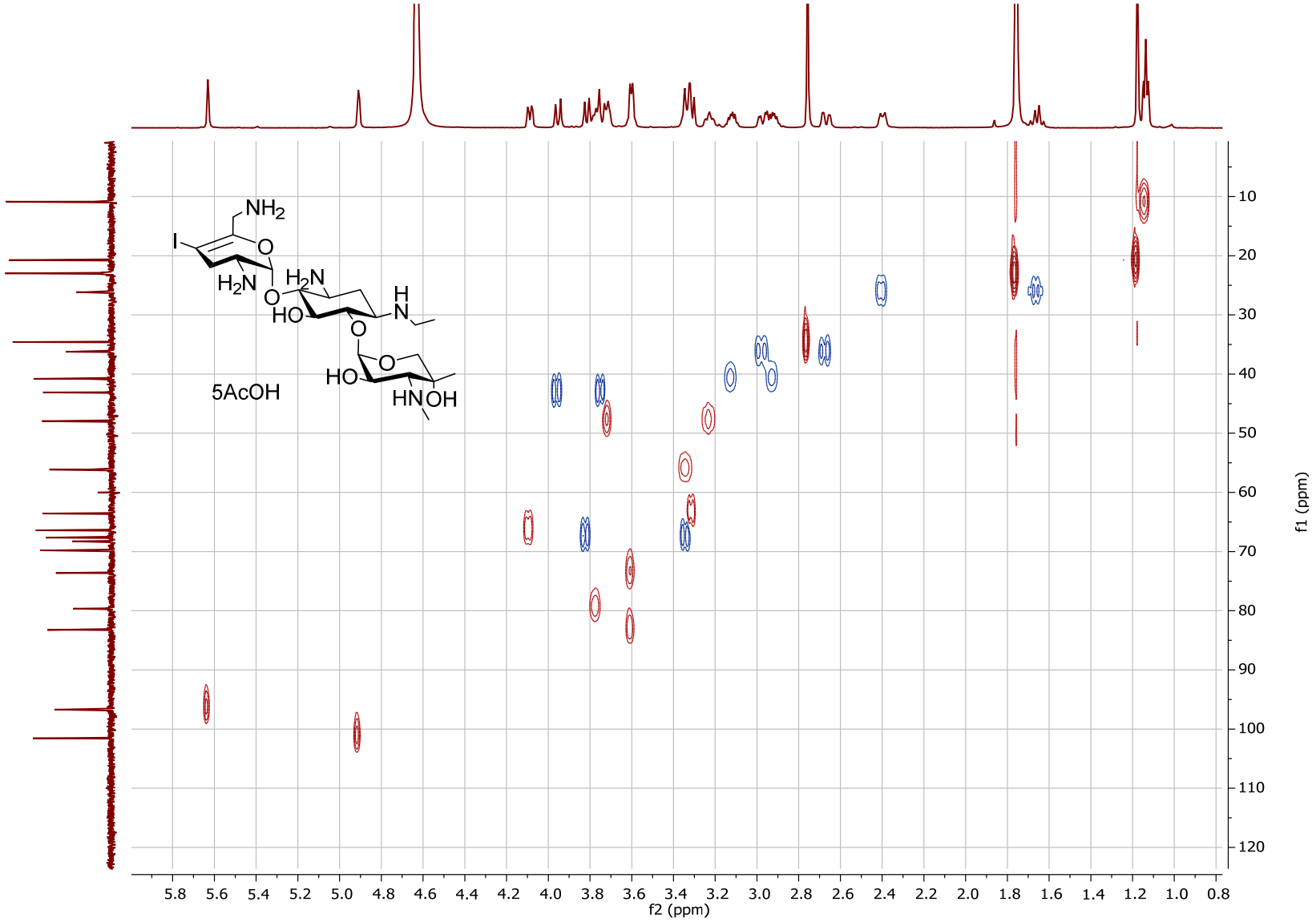
^{13}C NMR (151 MHz, D_2O) of 4'-Iodonetilmicin pentaacetate salt (19).



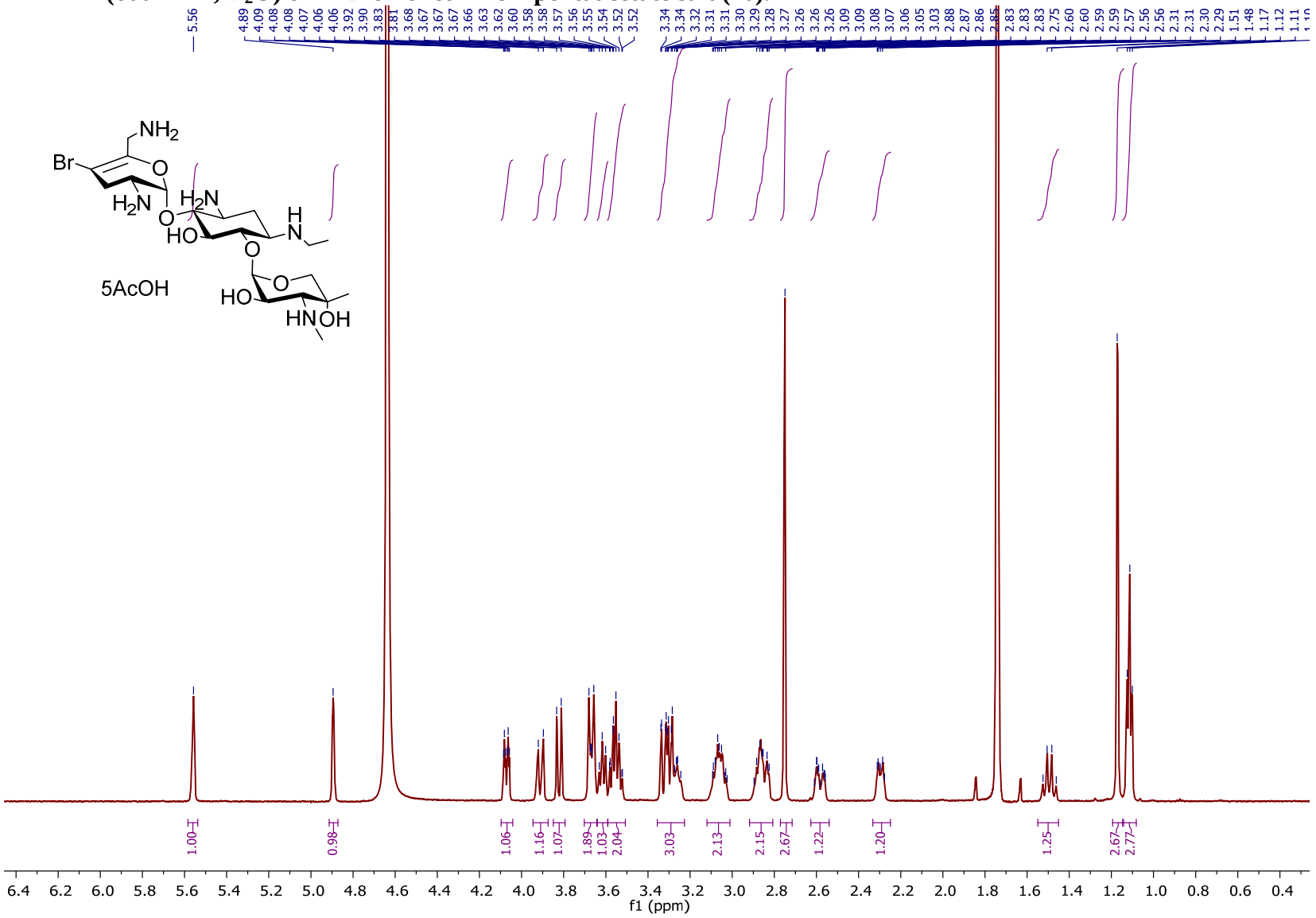
Cosy spectrum (D_2O) of 4'-Iodonetilmicin pentaacetate salt (19).



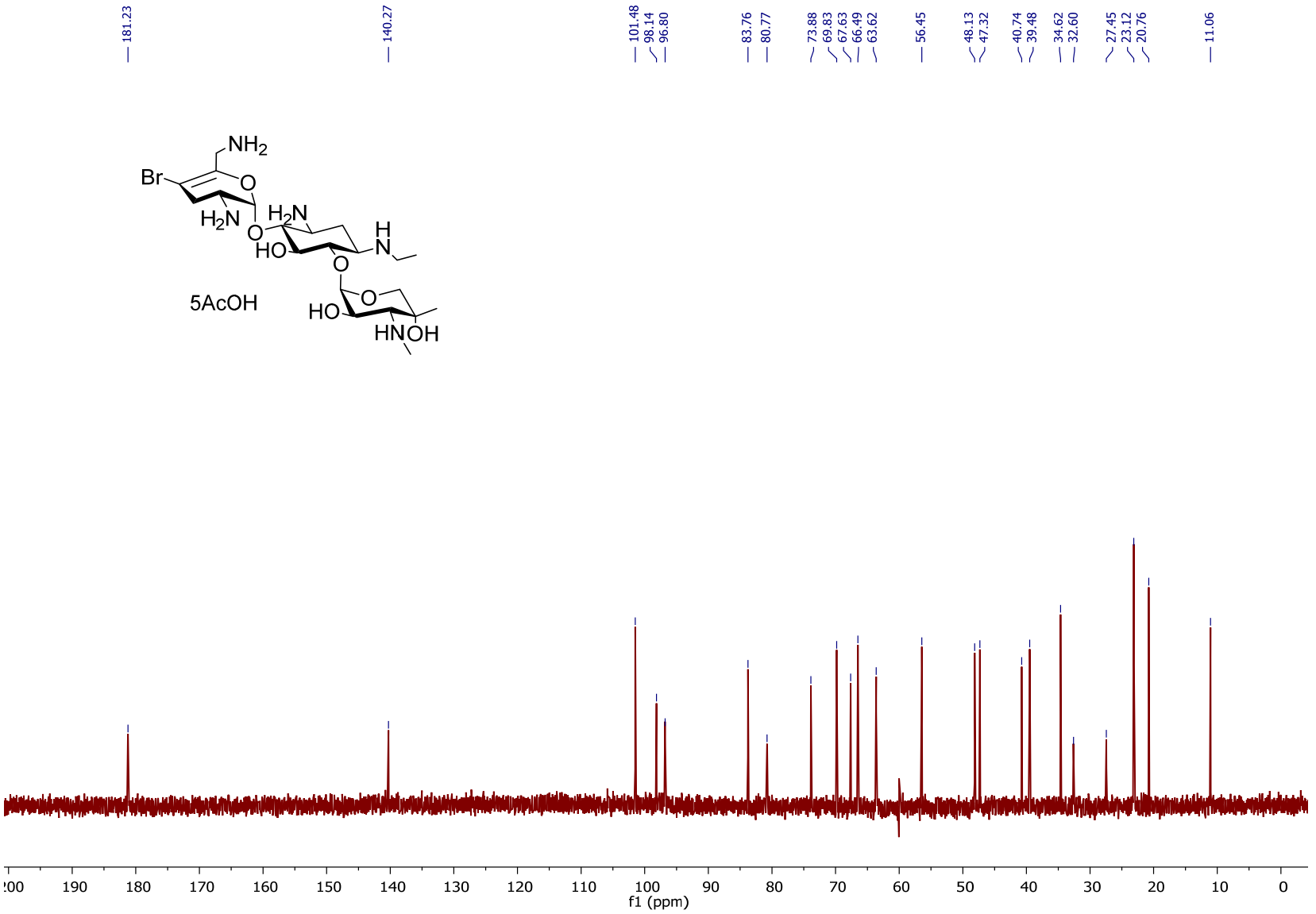
HSQC spectrum (D_2O) of 4'-Iodonetilmicin pentaacetate salt (19).



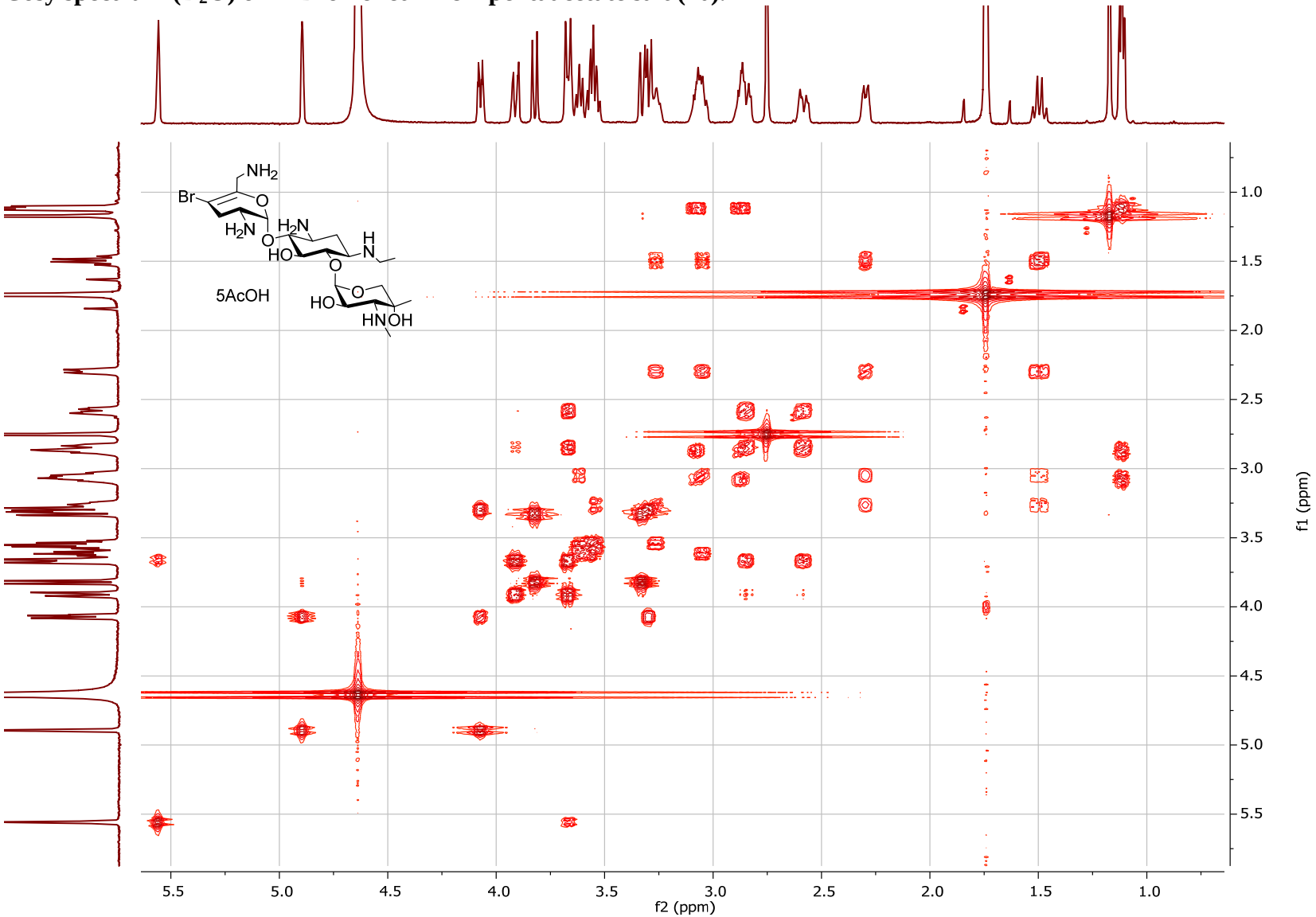
^{1}H NMR (600 MHz, D_2O) of 4'-Bromonetilmicin pentaacetate salt (20).



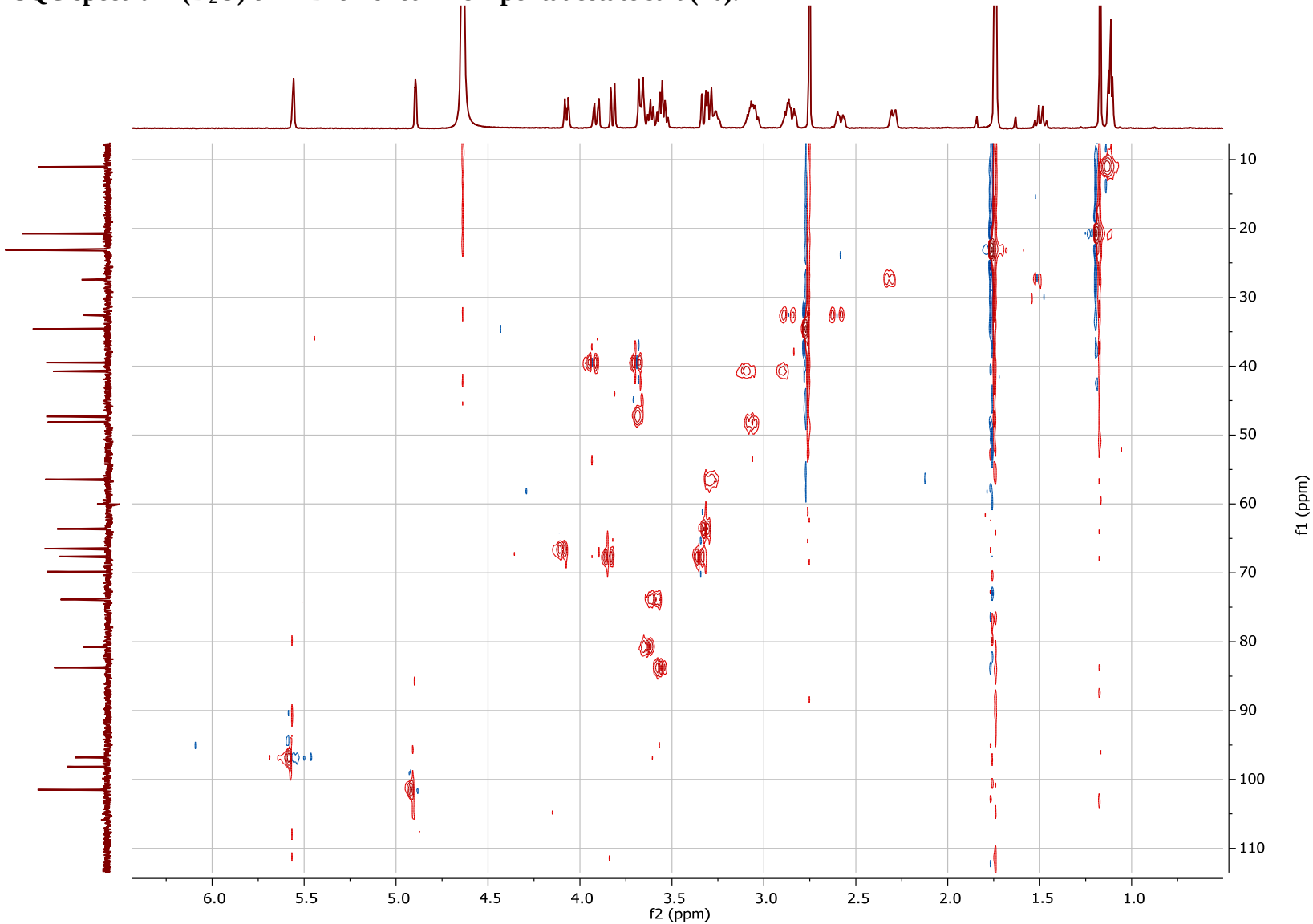
^{13}C NMR (151 MHz, D_2O) of 4'-Bromonetilmicin pentaacetate salt (20).



Cosy spectrum (D_2O) of 4'-Bromonetilmicin pentaacetate salt (20).

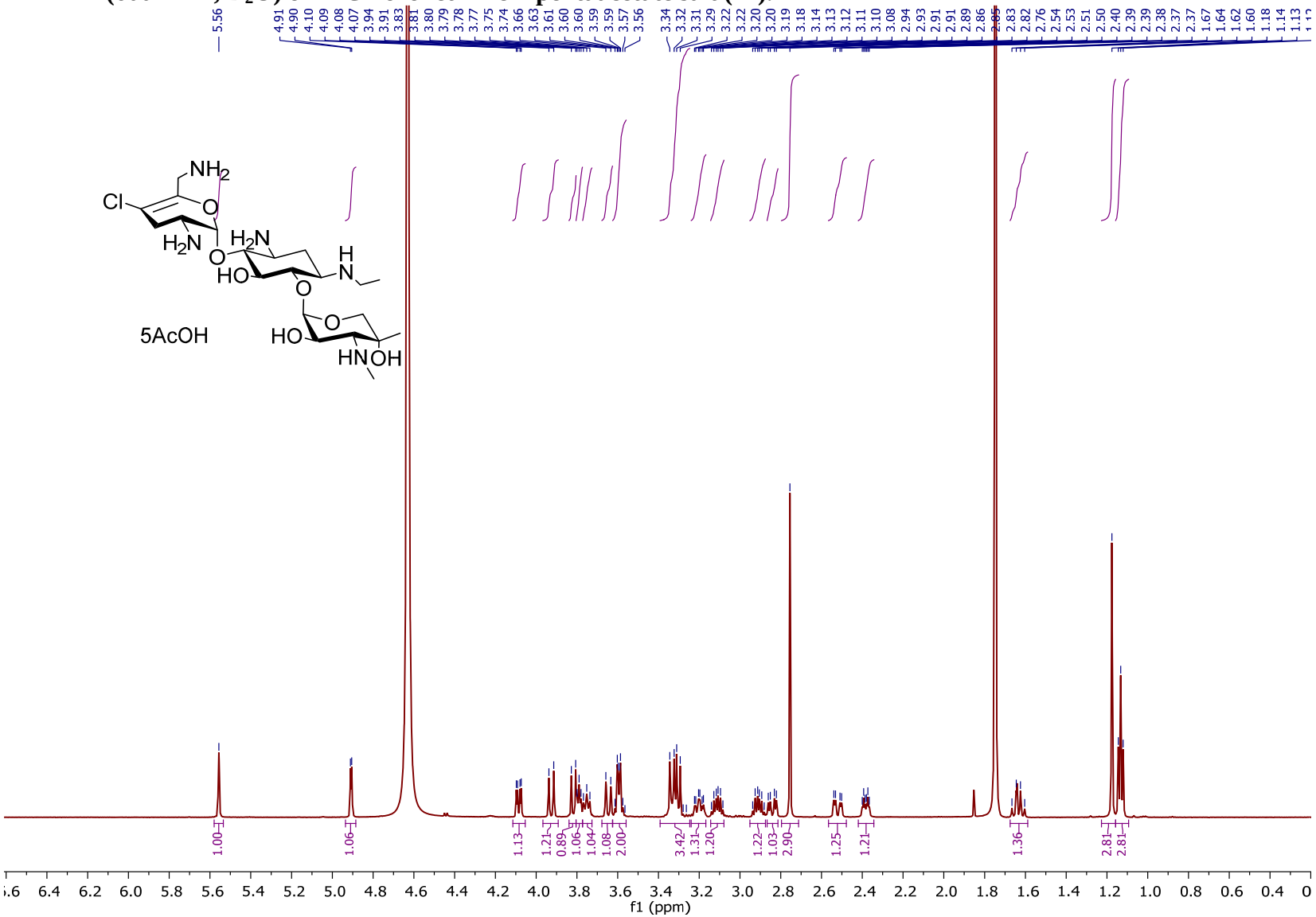


HSQC spectrum (D_2O) of 4'-Bromonetilmicin pentaacetate salt (20).

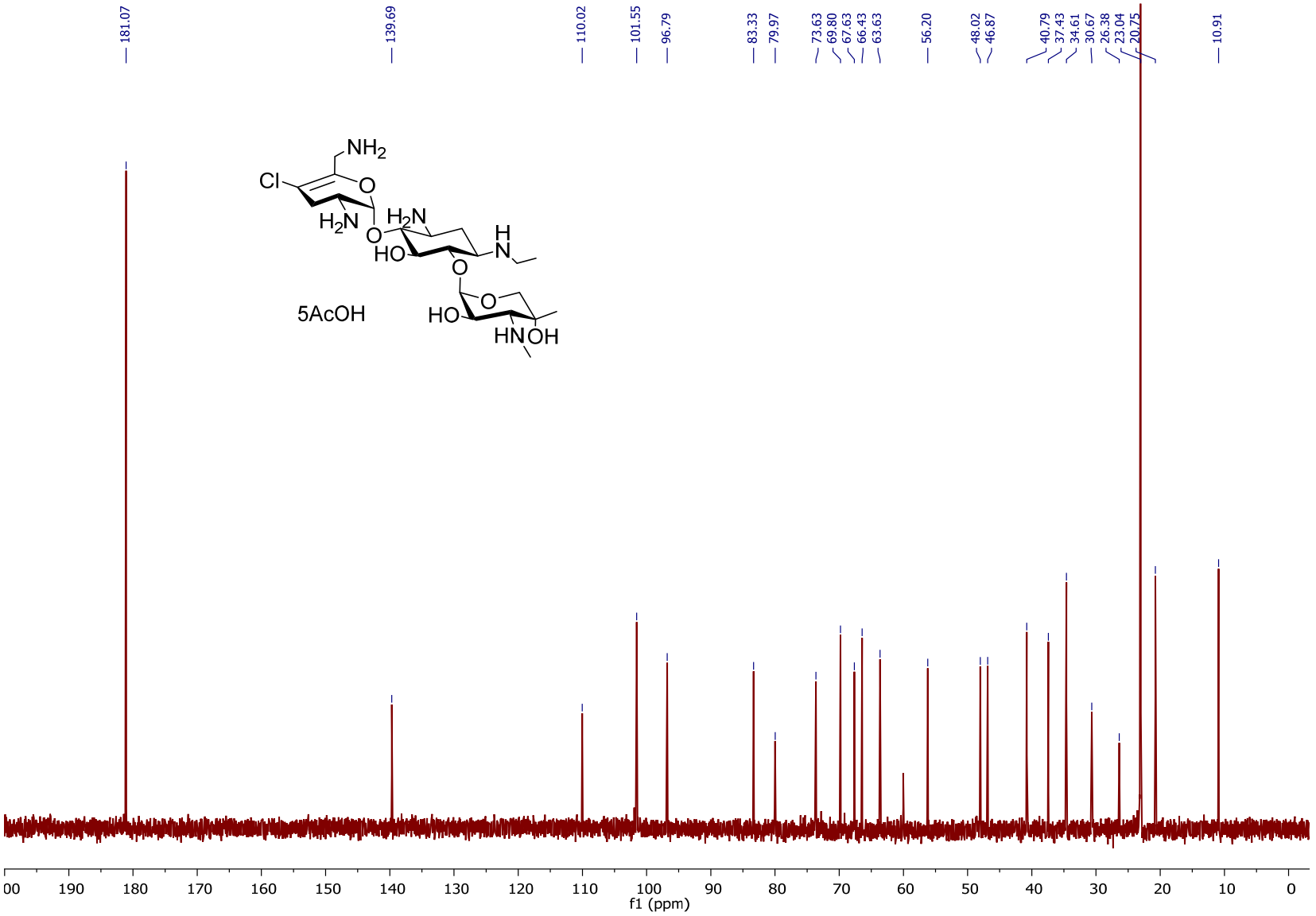


HMBC spectrum (D_2O) of 4'-Bromonetilmicin pentaacetate salt (20).

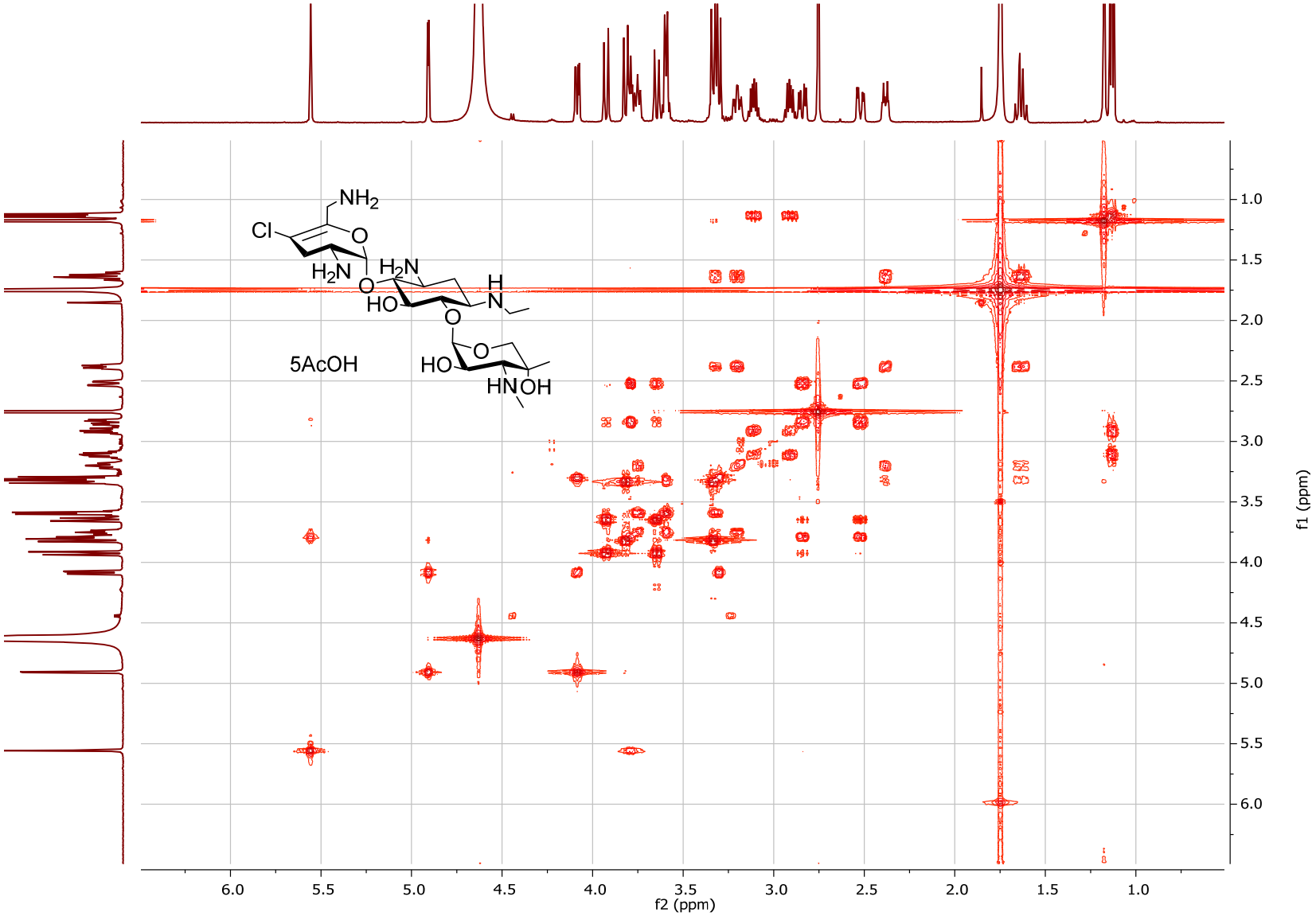
^{1}H NMR (600 MHz, D_2O) of 4'-Chloronetilmicin pentaacetate salt (21).



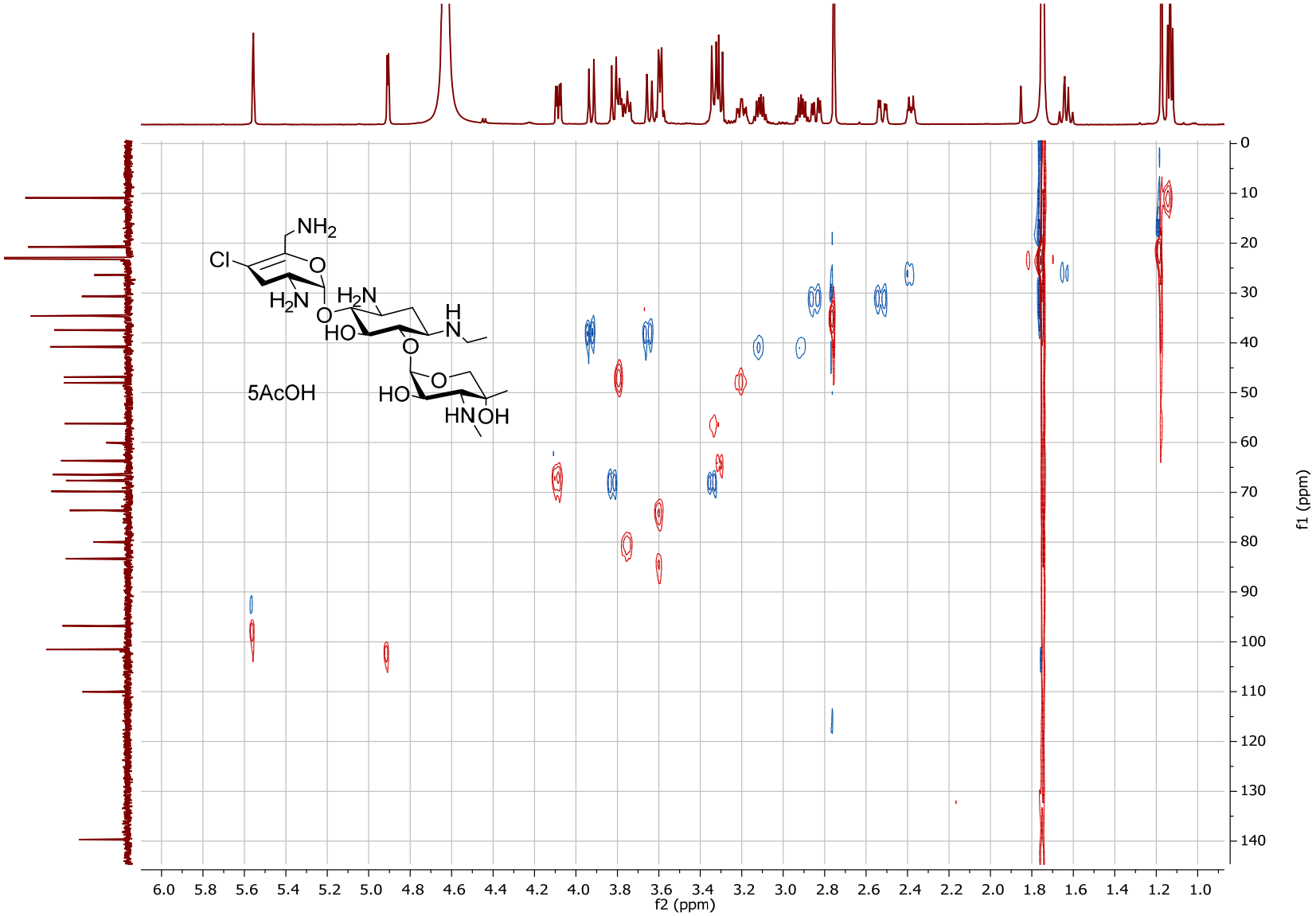
^{13}C NMR (151 MHz, D_2O) of 4'-Chloronetilmicin pentaacetate salt (21).



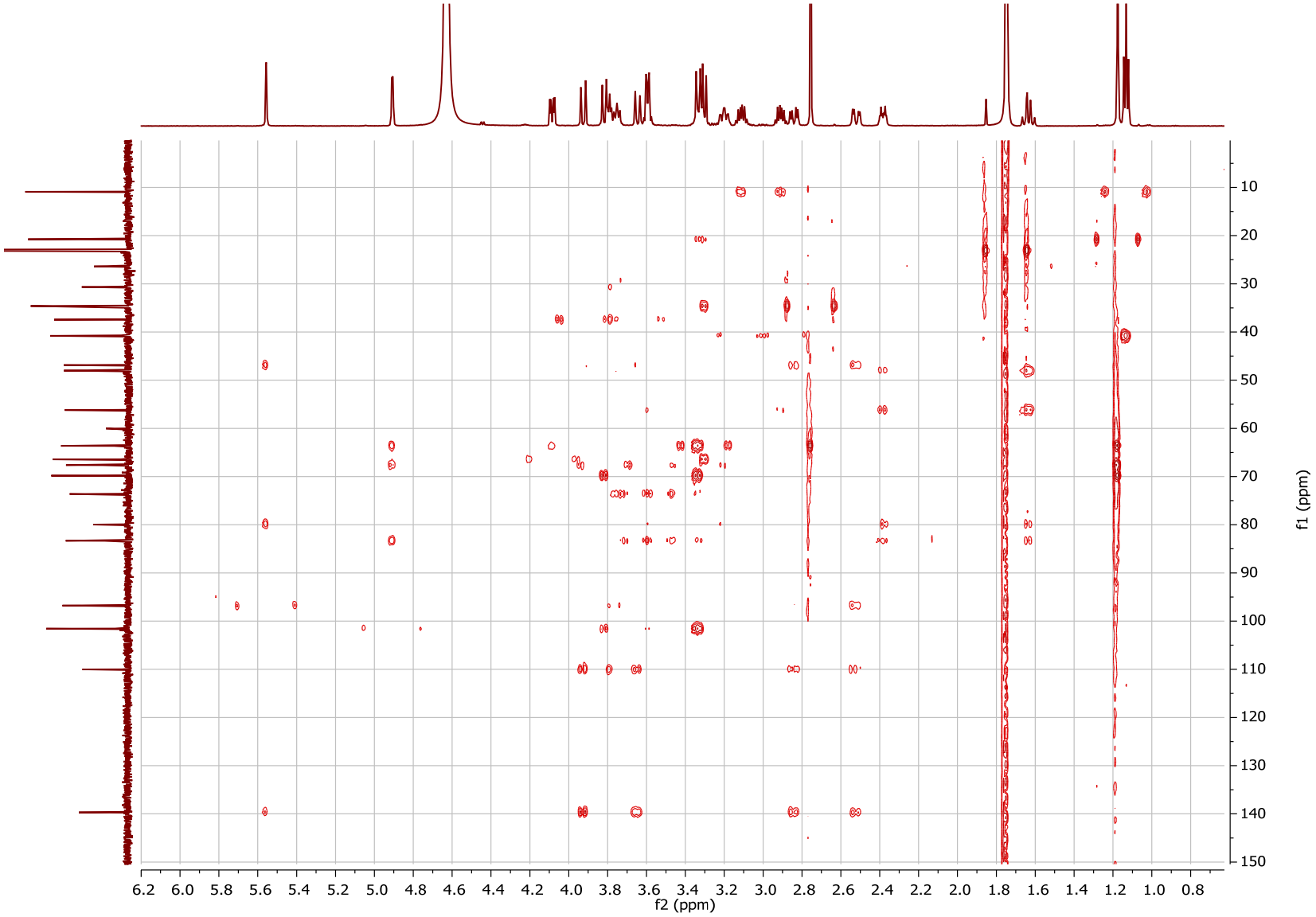
Cosy spectrum (D_2O) of 4'-Chloronetilmicin pentaacetate salt (21).



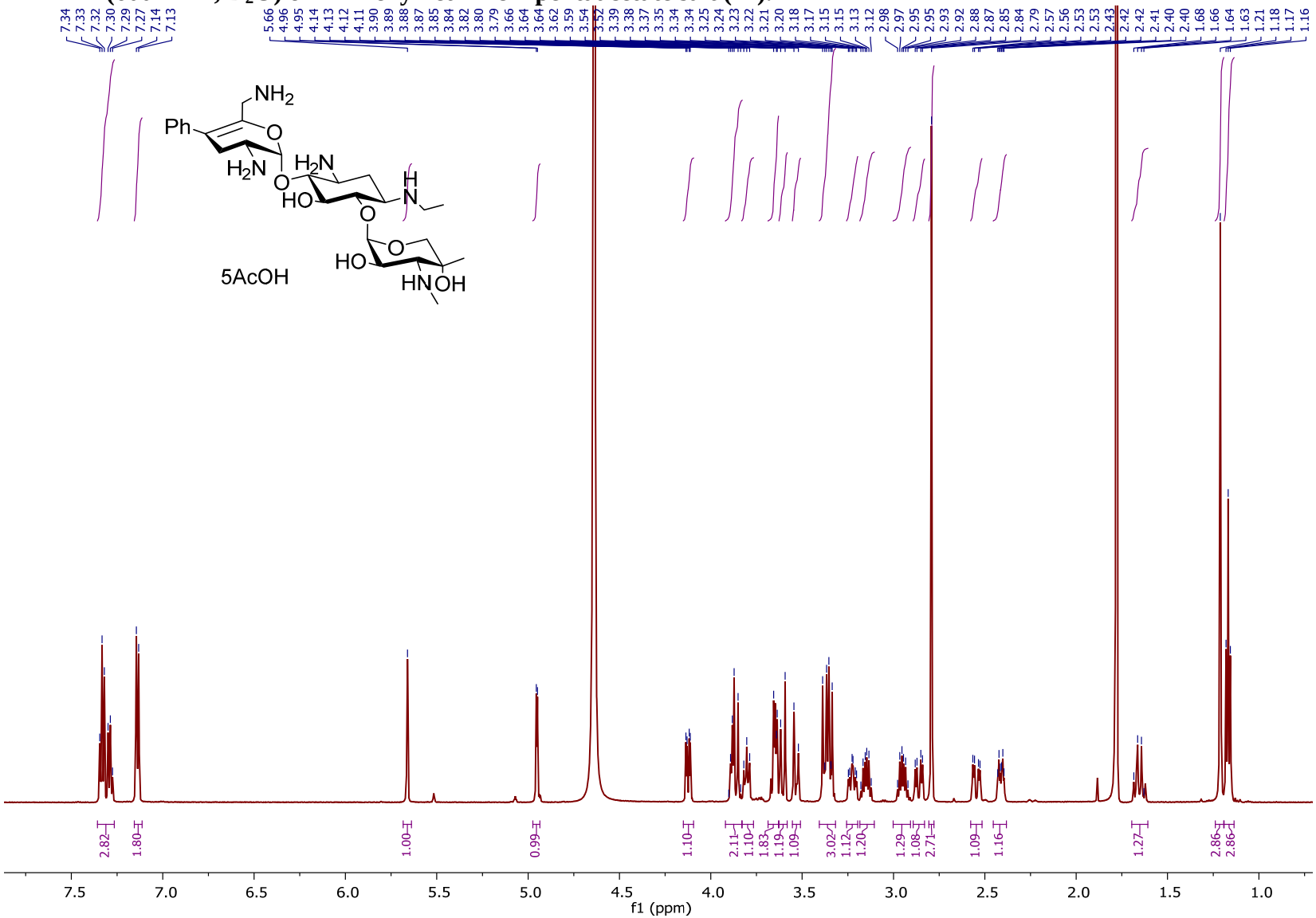
HSQC spectrum (D_2O) of 4'-Chloronetilmicin pentaacetate salt (21).



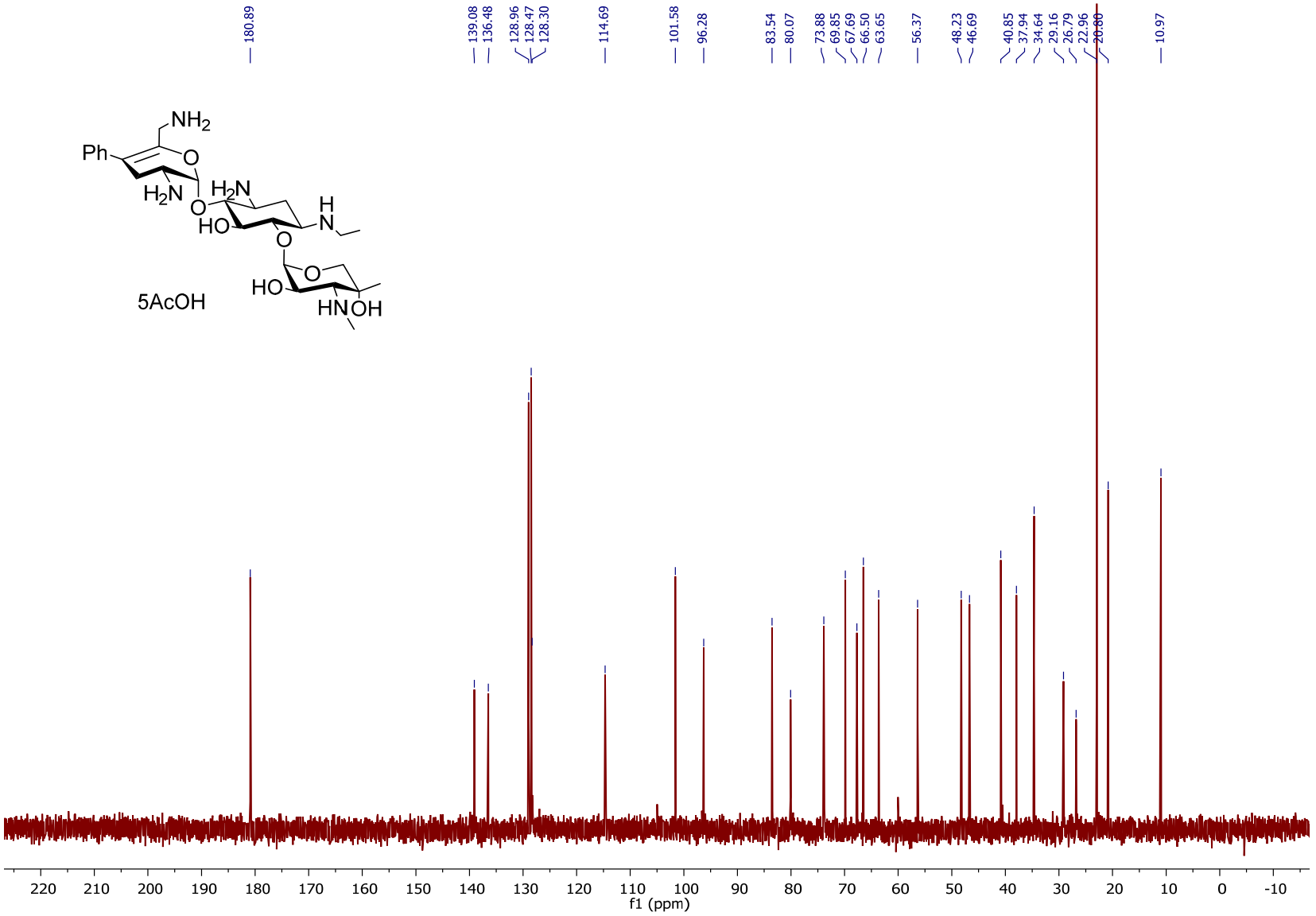
HMBC spectrum (D_2O) of 4'-Chloronetilmicin pentaacetate salt (21).



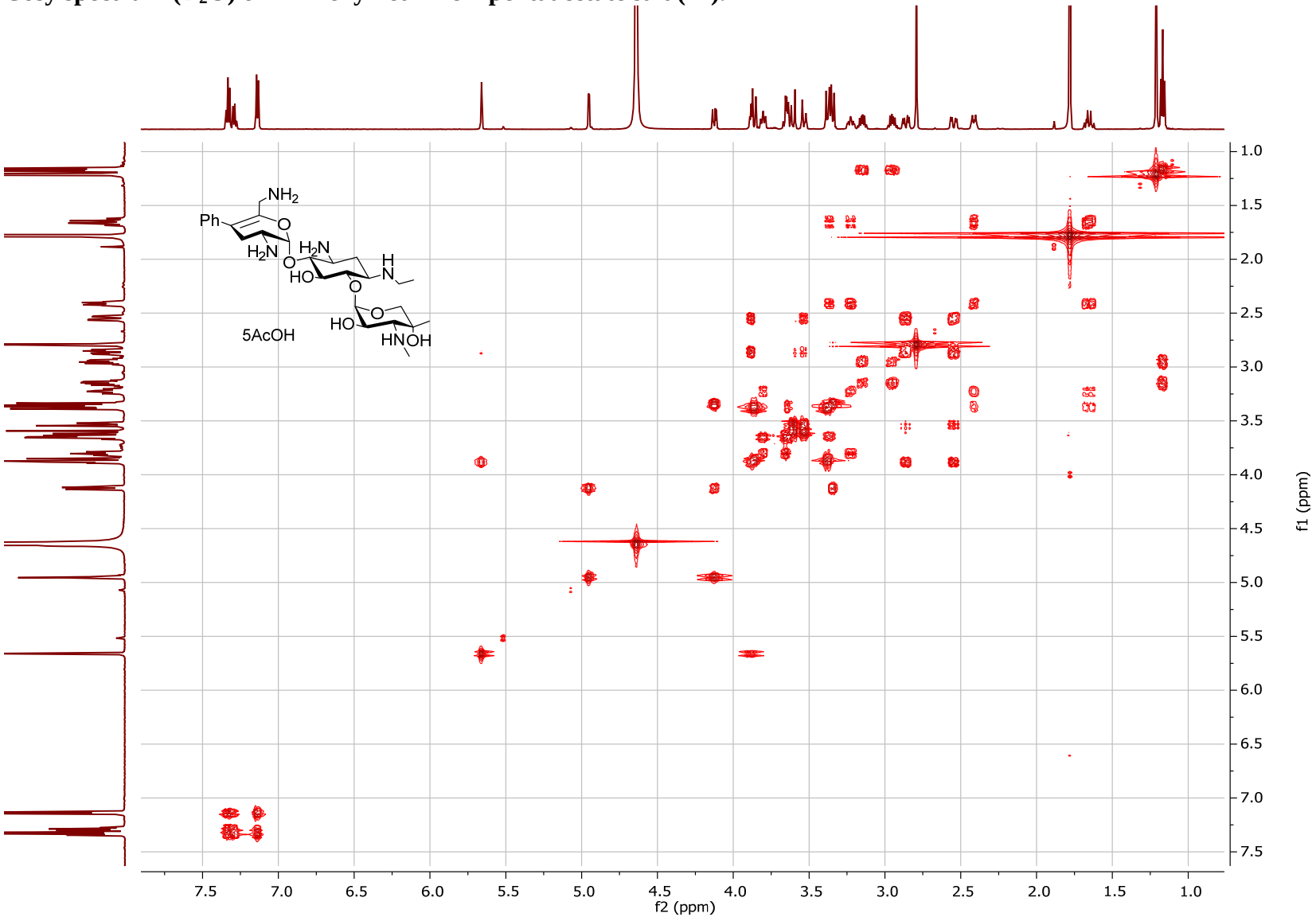
^{1}H NMR (600 MHz, D_2O) of 4'-Phenylnetilmicin pentaacetate salt (22).



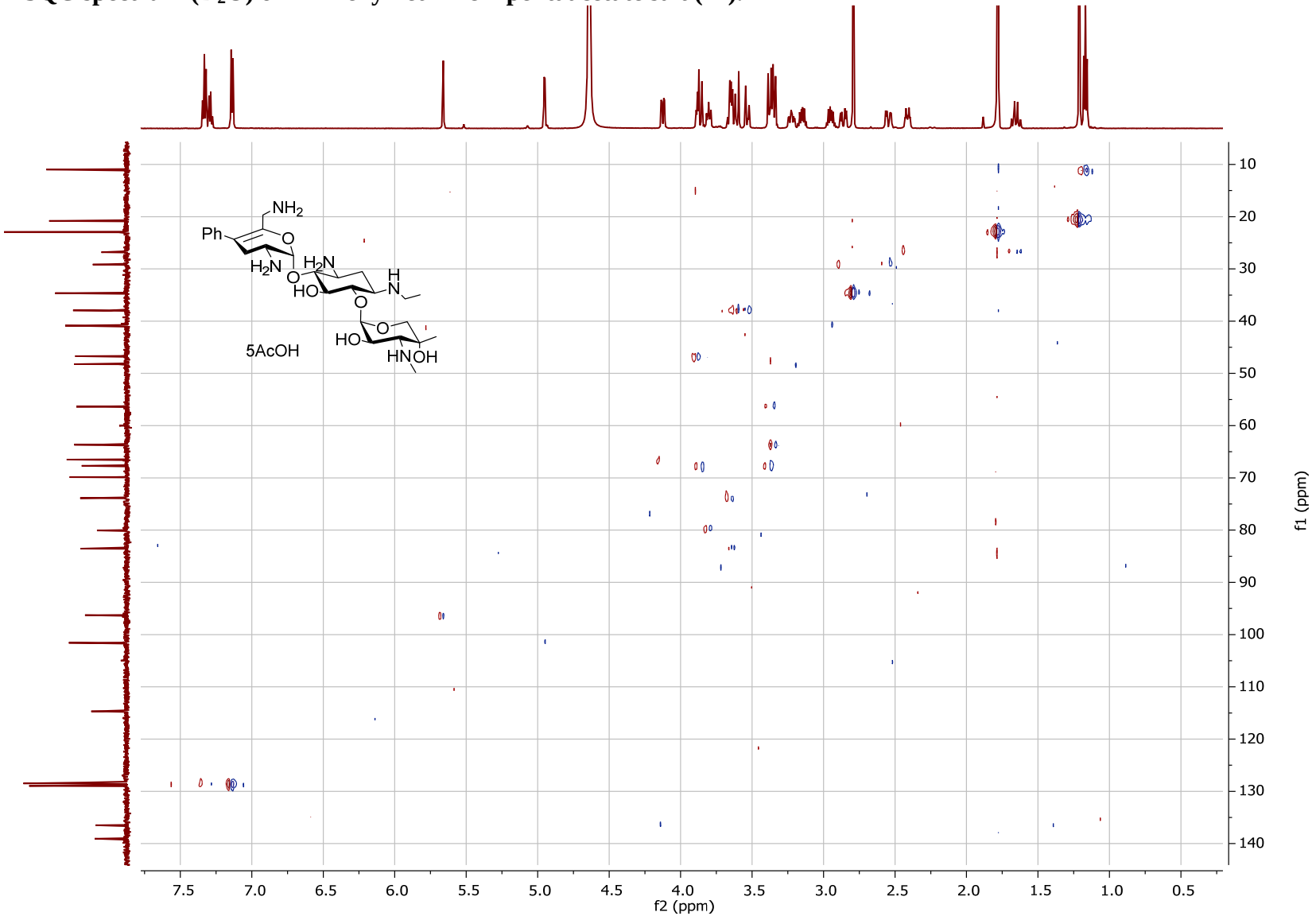
^{13}C NMR (151 MHz, D_2O) of 4'-Phenylnetilmicin pentaacetate salt (22).



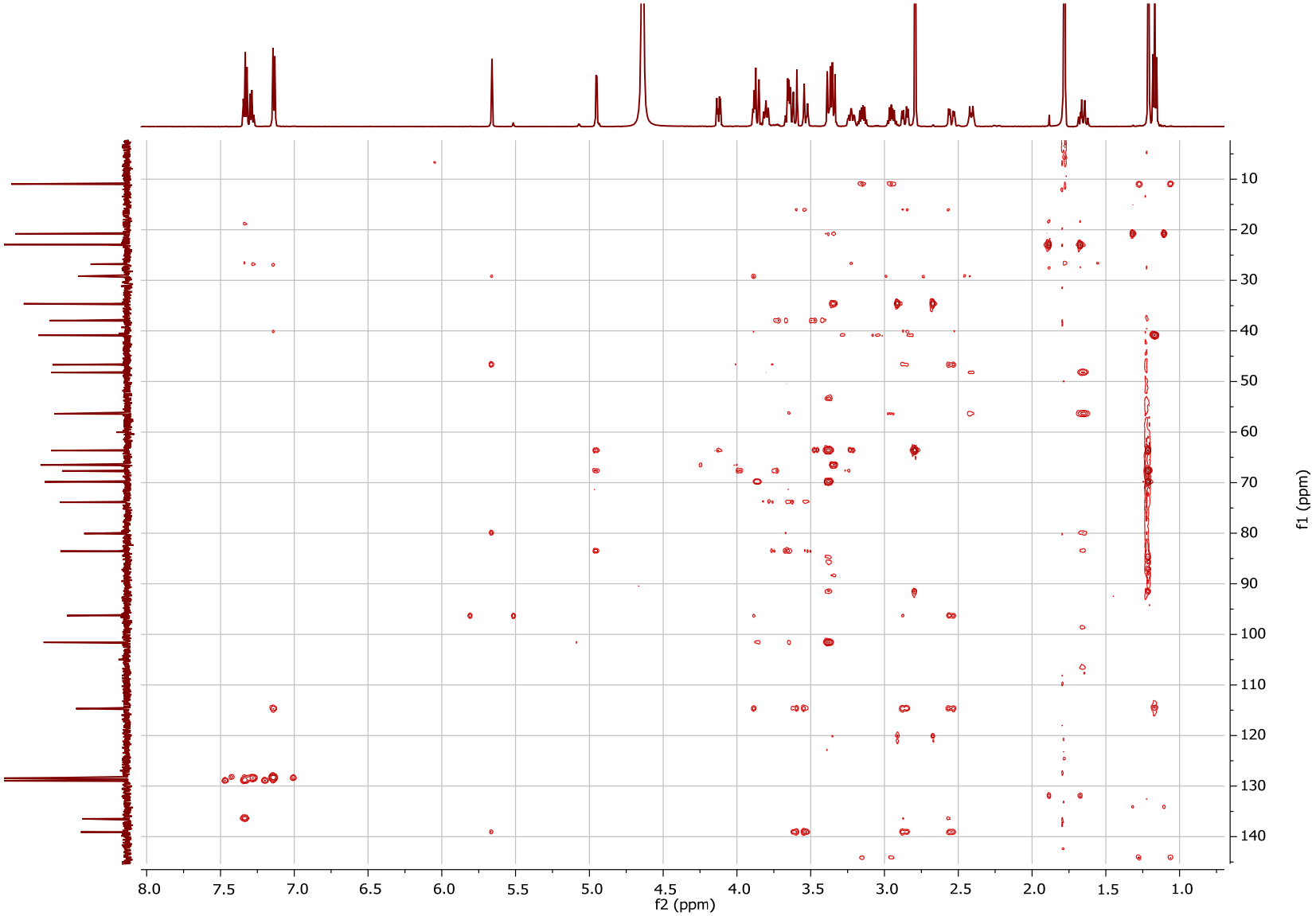
Cosy spectrum (D_2O) of 4'-Phenylnetilmicin pentaacetate salt (22).



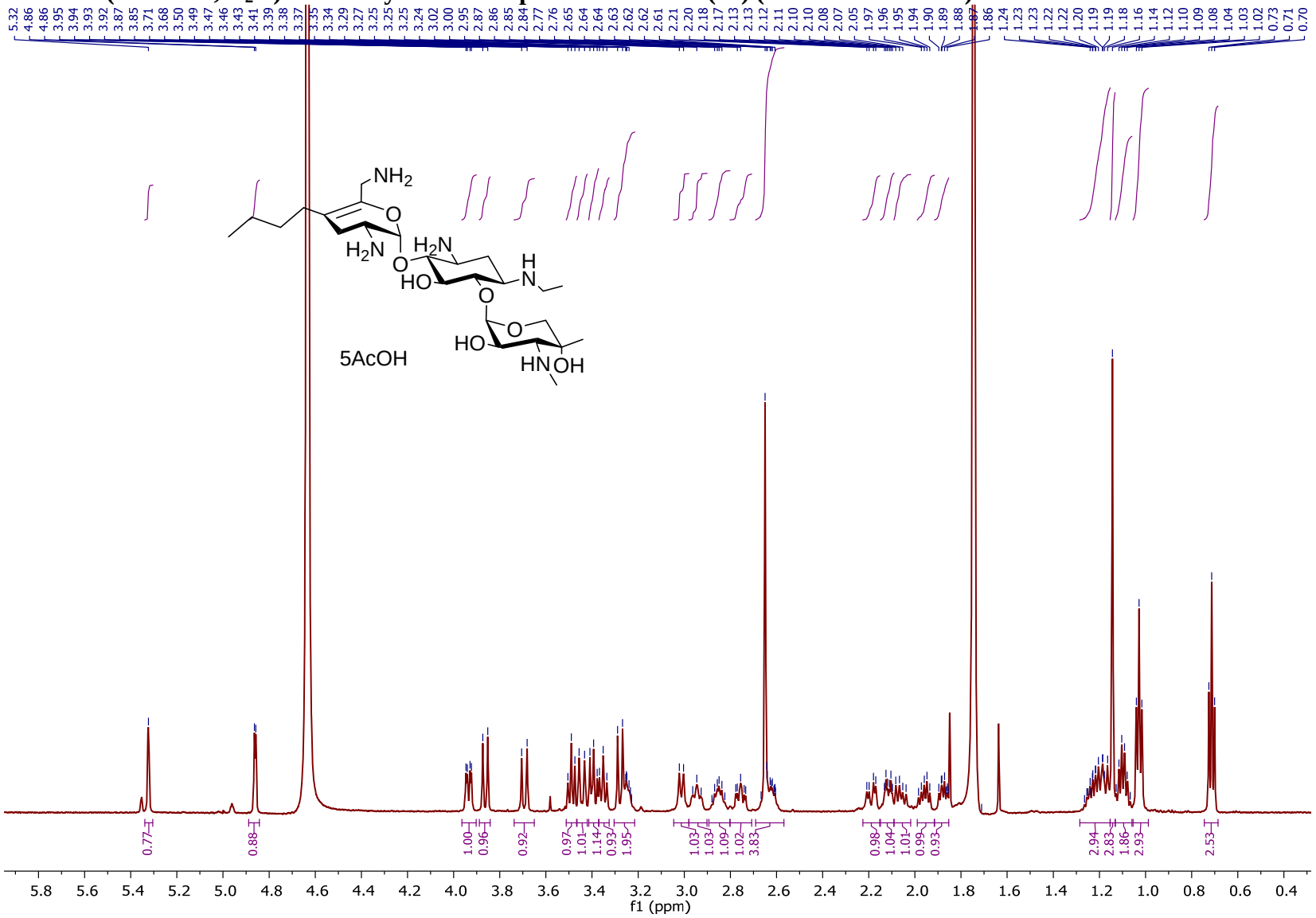
HSQC spectrum (D_2O) of 4'-Phenylnetilmicin pentaacetate salt (22).



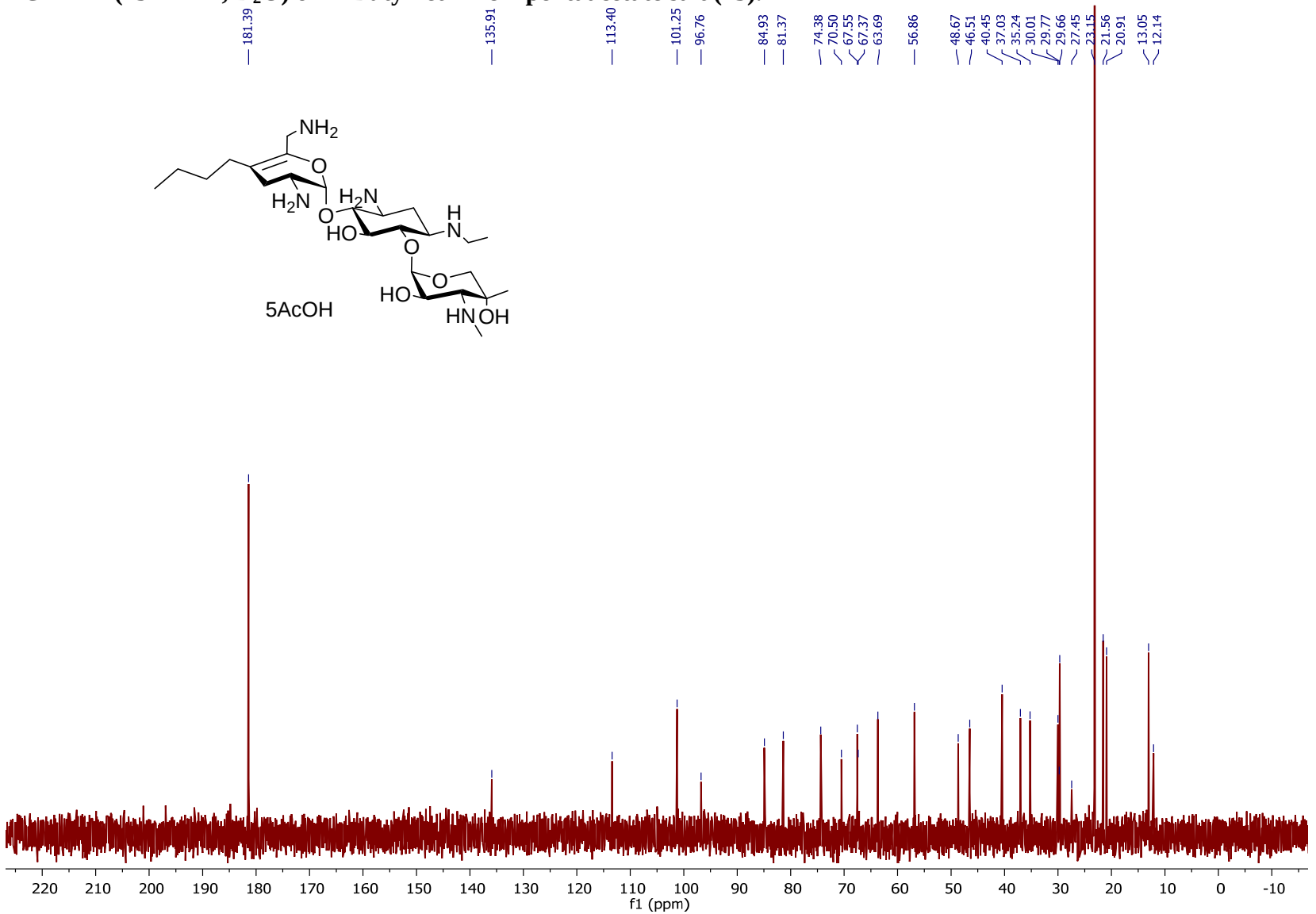
HMBC spectrum (D_2O) of 4'-Phenylnetilmicin pentaacetate salt (22).



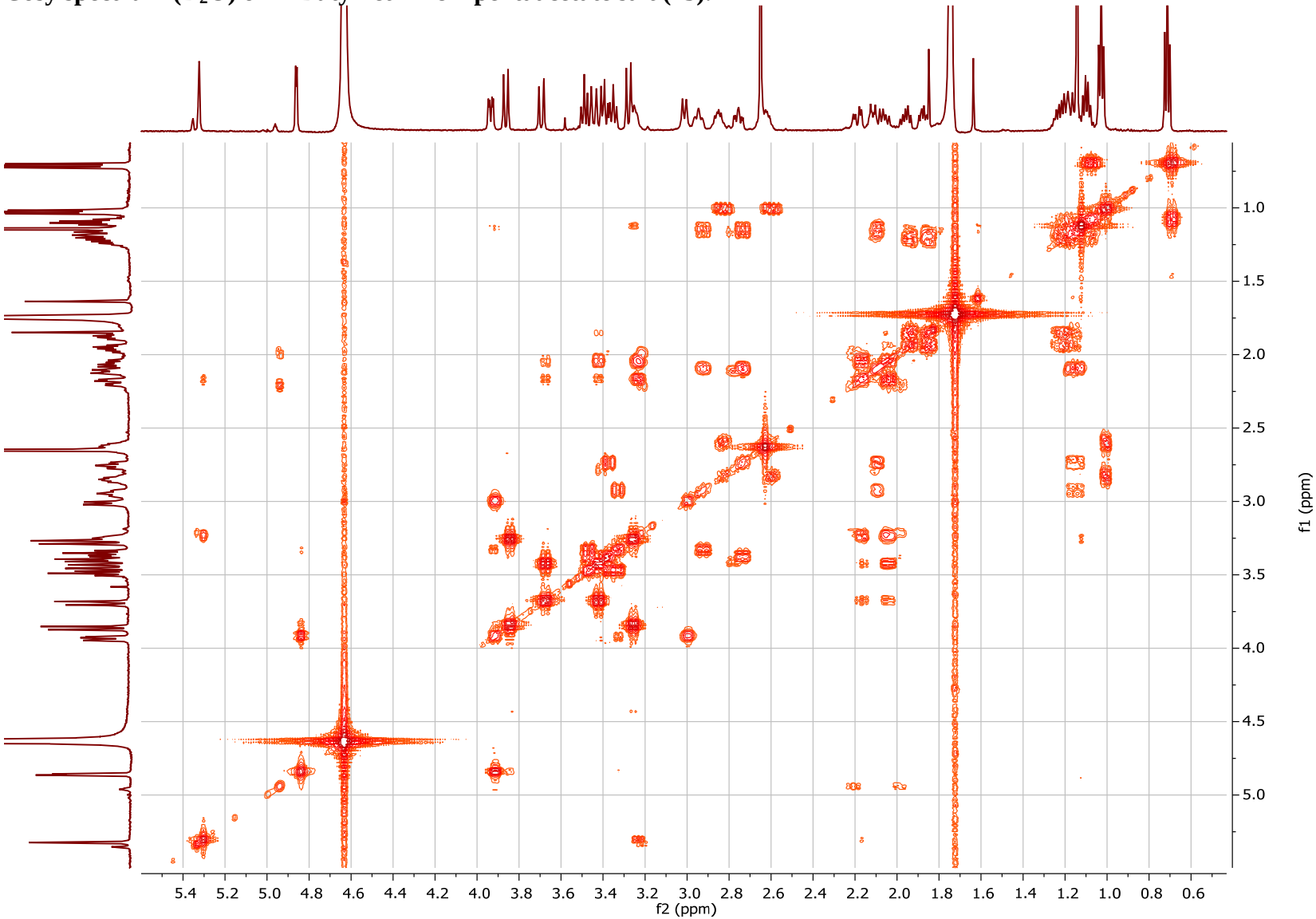
^{1}H NMR (600 MHz, D_2O) of 4'-Butylnetilmicin pentaacetate salt (23) (+ ~10% netilmicin).



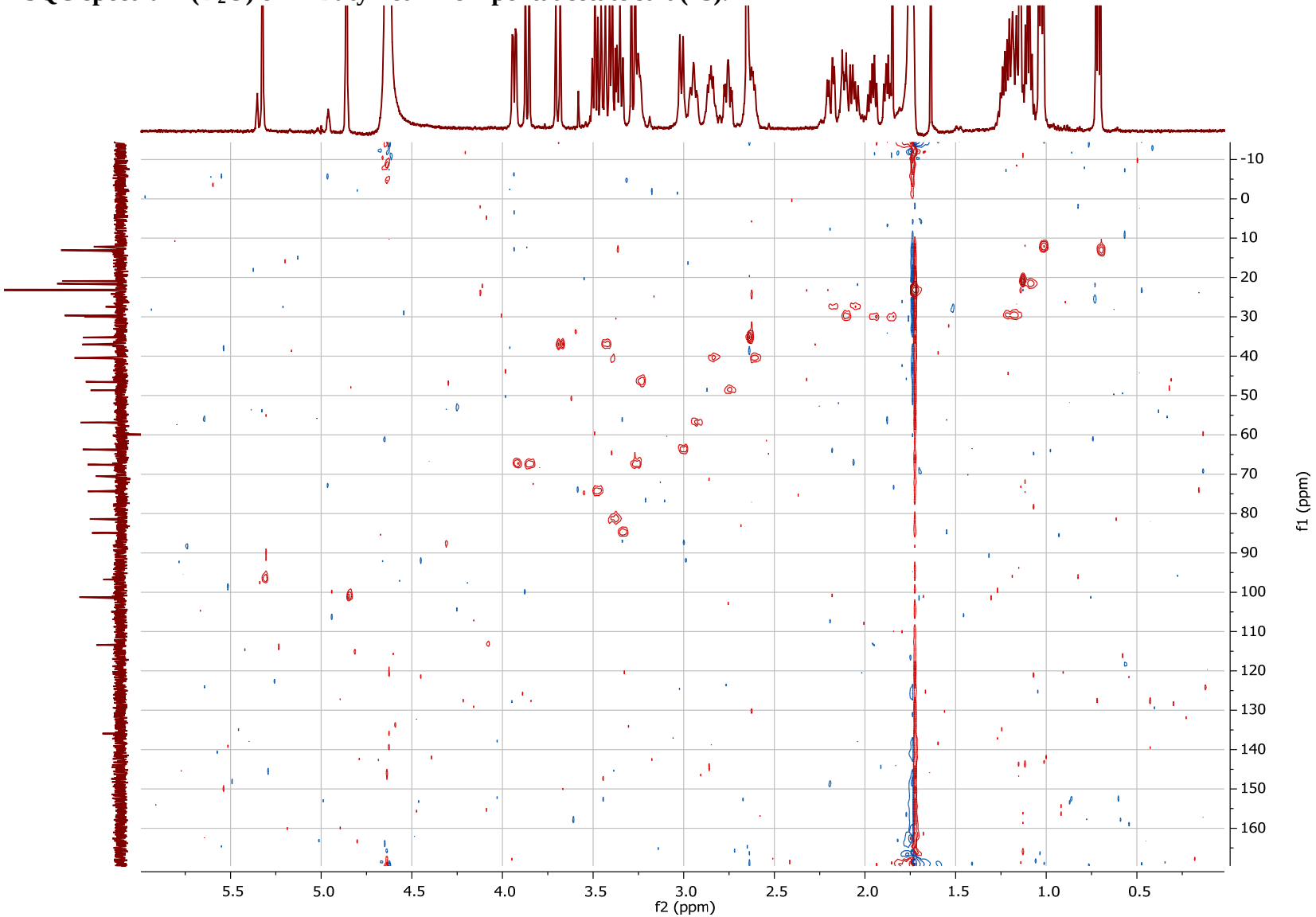
^{13}C NMR (151 MHz, D_2O) of 4'-Butylnetilmicin pentaacetate salt (23).



Cosy spectrum (D_2O) of 4'-Butylnetilmicin pentaacetate salt (23).

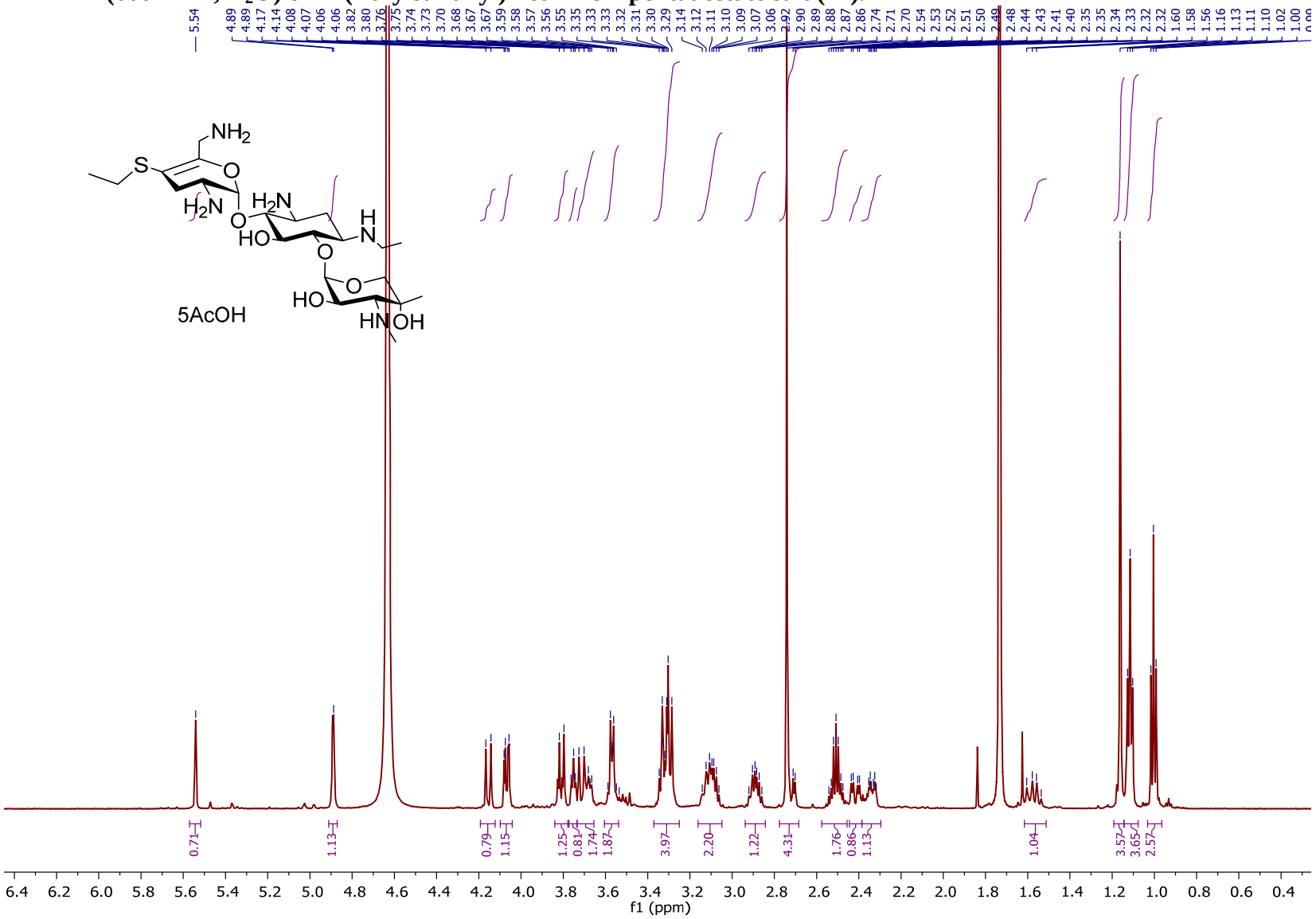


HSQC spectrum (D_2O) of 4'-Butylnetilmicin pentaacetate salt (23).

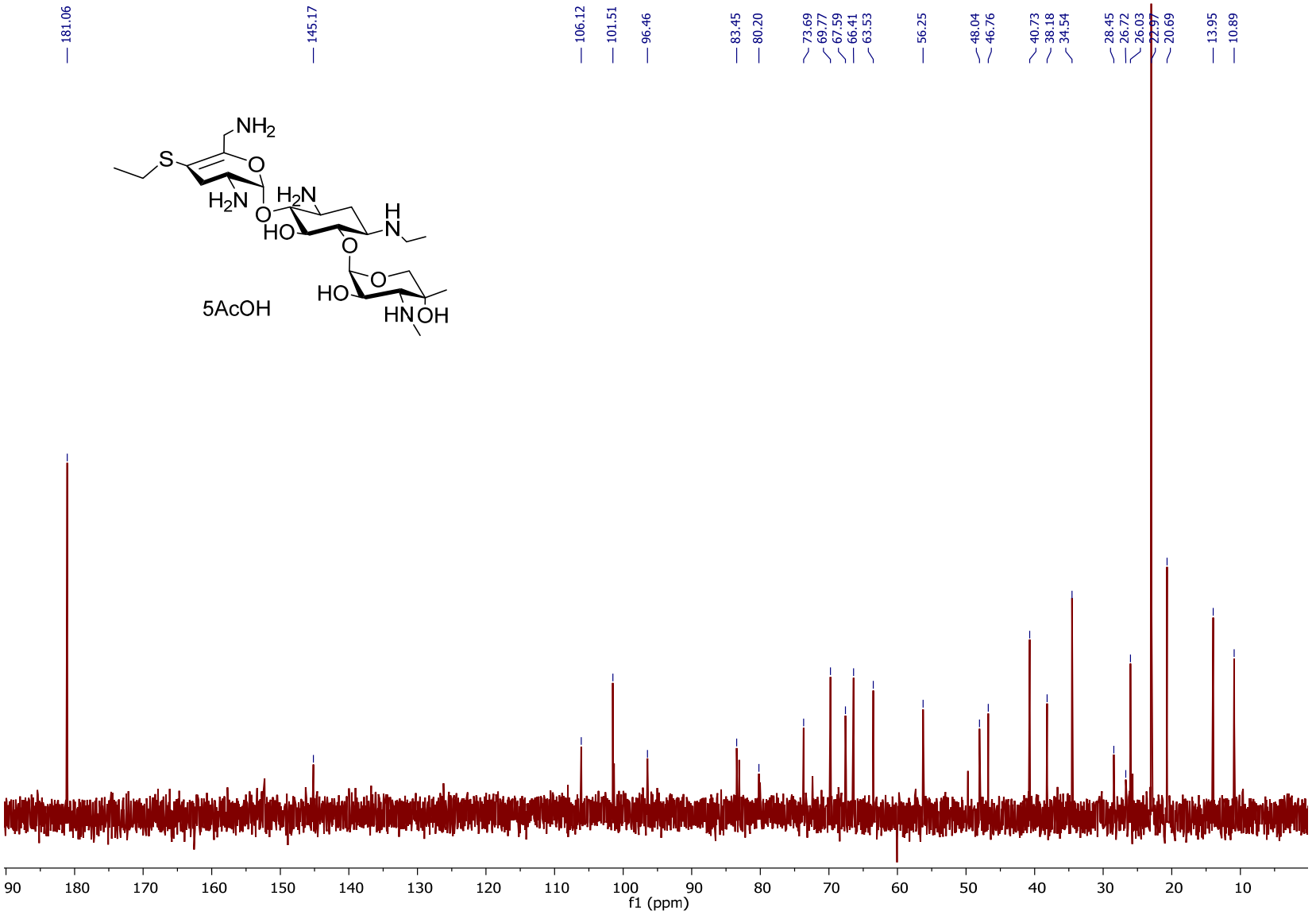


HMBC spectrum (D_2O) of 4'-Butylnetilmicin pentaacetate salt (23).

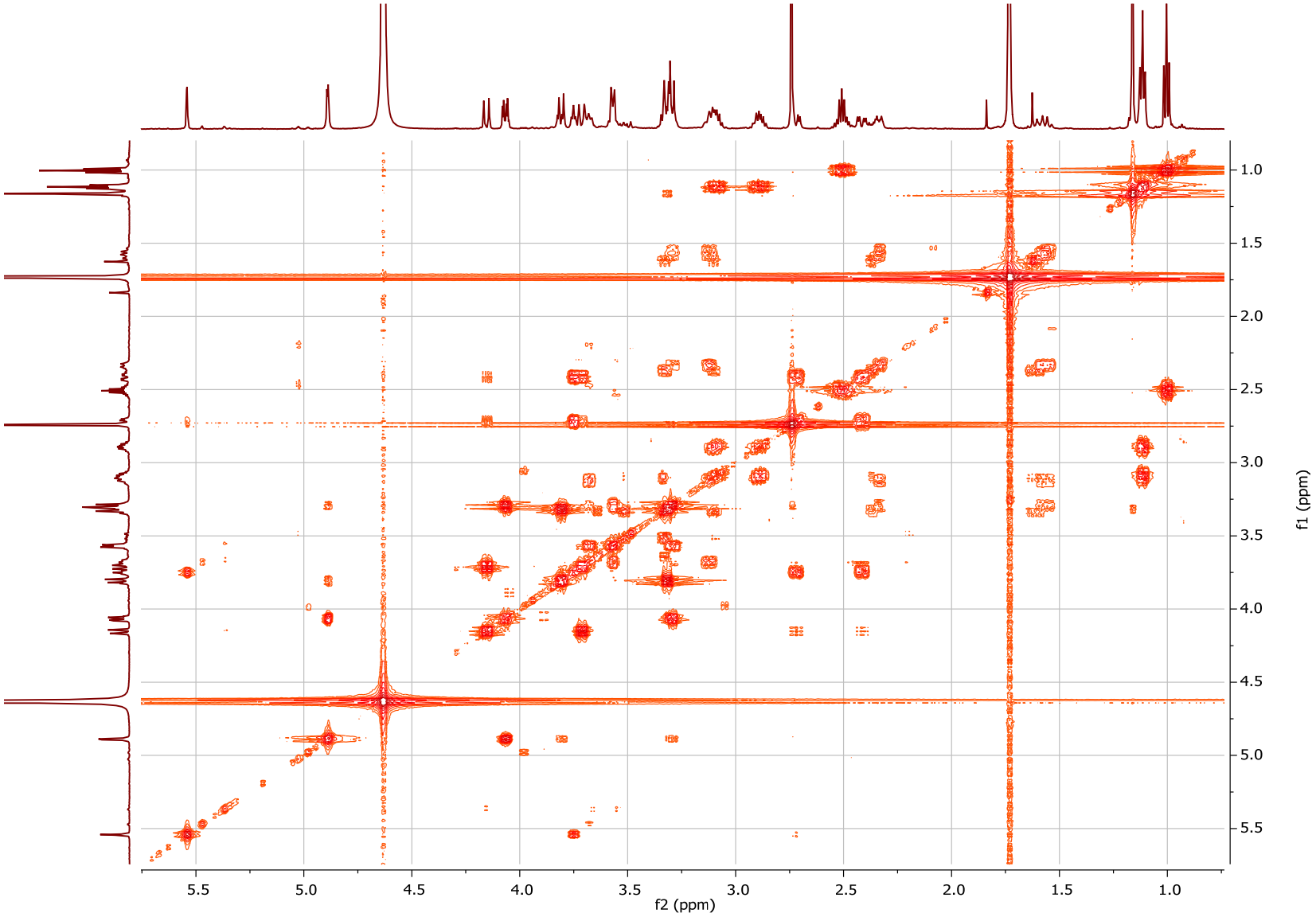
^{1}H NMR (600 MHz, D_2O) of 4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).



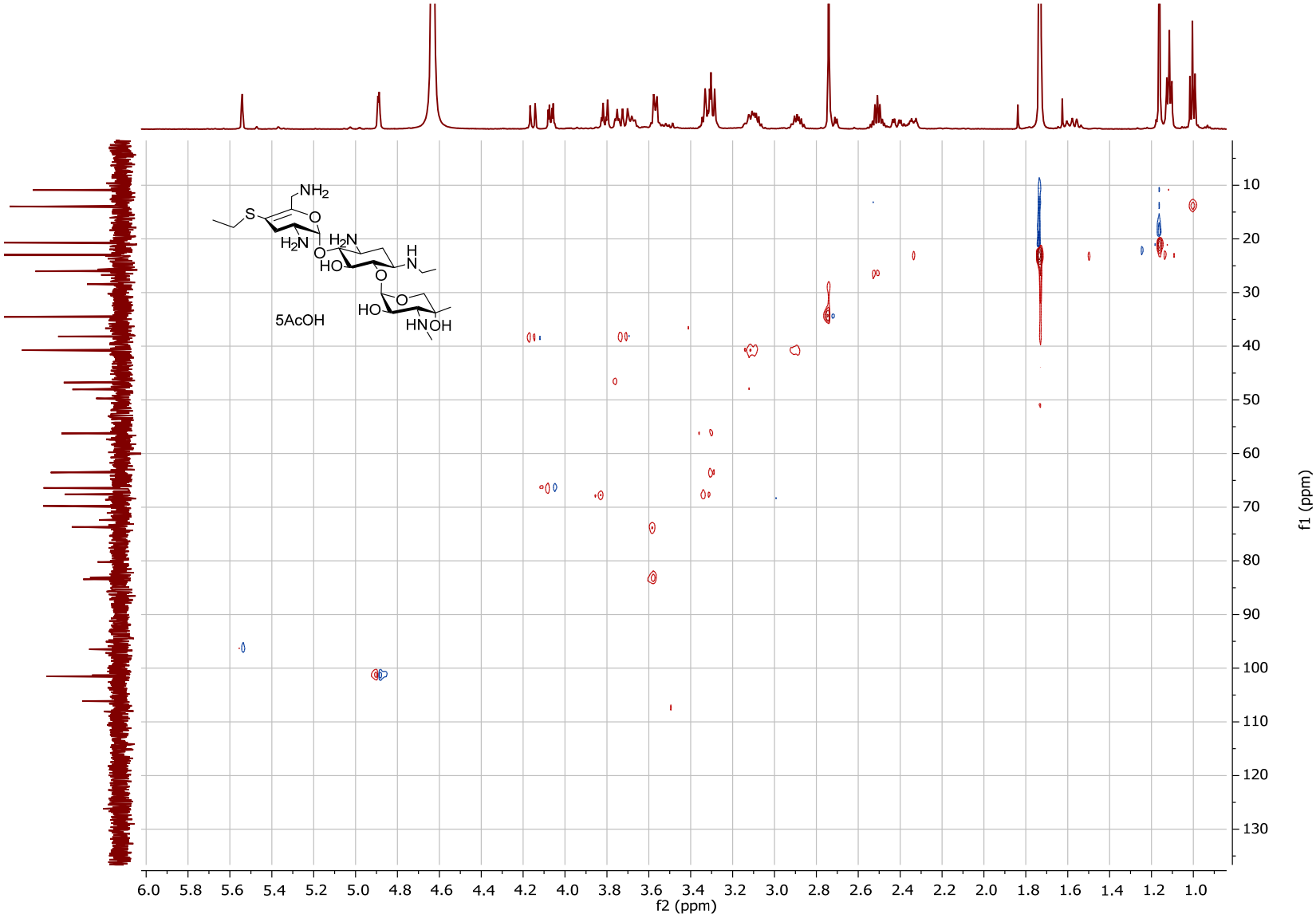
^{13}C NMR (151 MHz, D_2O) of 4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).



Cosy spectrum (D_2O) of 4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).



HSQC spectrum (D_2O) of 4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).



HMBC spectrum (D_2O) of 4'-(Ethylsulfanyl) netilmicin pentaacetate salt (27).