Functionalization of 2′-Amino-LNA with additional nucleobases

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Supporting Information

General experimental

All reagents and solvents were of analytical grade and obtained from commercial suppliers and used without further purification except for dichloromethane, which was distilled prior to use. Petroleum ether of the distillation range 60-80 °C was used. Acetonitrile was dried through storage over activated 3Å molecular sieves. Anhydrous dichloromethane, 1,2-dichloroethane, and *N*,*N*'-diisopropylethylamine were dried through storage over activated 4Å molecular sieves. All reactions were conducted under an atmosphere of argon, and were monitored by thin-layer chromatography (TLC) using silica gel coated plates with fluorescence indicator (SiO_2-60, F-254) which were visualized a) under UV light, and b) by dipping in a solution of molybdato-phosphoric acid (12.5 g/L) and cerium(IV)sulfate (5 g/L) in 3% conc. sulfuric acid in water (v/v) followed by heating. Silica gel column chromatography was performed with Silica gel 60 (particle size 0.040–0.063 mm, Merck) using moderate pressure (pressure ball). Silica gel columns were generally built with an initial starting eluent containing 1% (v/v) of triethylamine or pyridine. Evaporation of solvents was carried out under reduced pressure with a temperature not exceeding 50 °C. After column chromatography, appropriate fractions were pooled, evaporated and dried at high vacuum for at least 12 h to give obtained products in high purity (>95%), unless stated otherwise. ^{1}H NMR, ^{13}C NMR and/or ^{31}P NMR ascertained sample purity. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane or deuterated solvent as the internal standard (δ_H: DMSO-d_6 2.50 ppm; δ_C: DMSO-d_6 39.51 ppm) or an external standard (δ_P: 85% H_3PO_4 0.00 ppm). Exchangeable (ex) protons were detected by disappearance of peaks on D_2O addition. Assignments of NMR spectra are based on 2D spectra (COSY, HSQC, and HMBC) and follow standard carbohydrate/nucleoside nomenclature. The carbon atom of C4′ substituents is numbered C-5″ in nucleoside derivatives. Similar conventions apply for the corresponding hydrogen atoms.

Numbering of nucleobases of N2′-functionalities is given with triple primes (e.g. H6′′′). MALDI-HRMS were recorded in positive ion mode on an IonSpec Fourier transform mass spectrometer.

Table S1. MALDI-MS of synthesized ONs.[a]

Sequence	**Found *m/z* [M-H]$^-$**	**Calc. *m/z* [M-H]$^-$**
5′-GTG AA**T**$^{\mathbf{L}}_{\mathbf{T}}$ AGC C	3251	3245
5′-GTG AA**T**$^{\mathbf{L}}_{\mathbf{A}}$ AGC C	3256	3254
5′-GTG AA**T**$^{\mathbf{L}}_{\mathbf{Ph}}$ AGC C	3199	3197
5′-GGC TA**T**$^{\mathbf{L}}_{\mathbf{T}}$ TCA C	3194	3196
5′-GGC TA**T**$^{\mathbf{L}}_{\mathbf{A}}$ TCA C	3203	3205
5′-GGC TA**T**$^{\mathbf{L}}_{\mathbf{Ph}}$ TCA C	3150	3148
5′-GGC **T**$^{\mathbf{L}}_{\mathbf{T}}$AT TCA C	3193	3196
5′-GGC **T**$^{\mathbf{L}}_{\mathbf{A}}$AT TCA C	3202	3205
5′-GGC **T**$^{\mathbf{L}}_{\mathbf{Ph}}$AT TCA C	3148	3148
5′-GTG AA**T**$^{\mathbf{L}}_{\mathbf{T}}$ **T**$^{\mathbf{L}}_{\mathbf{T}}$GC C	3426	3429
5′-GAC G**T**$^{\mathbf{L}}_{\mathbf{T}}$**T**$^{\mathbf{L}}_{\mathbf{A}}$ **T**$^{\mathbf{L}}_{\mathbf{A}}$**T**$^{\mathbf{L}}_{\mathbf{T}}$**T**$^{\mathbf{L}}_{\mathbf{A}}$ **T**$^{\mathbf{L}}_{\mathbf{T}}$**T**$^{\mathbf{L}}_{\mathbf{T}}$**T**$^{\mathbf{L}}_{\mathbf{A}}$ GCA C	6437	6434

[a] For the structure of the monomers see Fig. 1.

Full NMR assignemt

1-(2-Amino-2-deoxy-5-*O*-4,4′-dimethoxytrityl-2-*N*,4-*C*-methylene-2-*N*-(thymin-1-ylacetyl)-β-D-ribofuranosyl)thymine (3a).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (br s, 1.5H, ex, N3-H$_A$), 11.39 (br s, 1H, ex, N3-H$_B$), 11.31 (br s, 2.5H, ex, N3‴-H$_{A+B}$), 7.54 (s, 1H, H6$_B$), 7.53 (s, 1.5H, H6$_A$), 7.22-7.47 (m, 25H, H6‴$_{A+B}$, H2$_{DMT,A+B}$, H6$_{DMT,A+B}$, H2′$_{DMT,A+B}$, H6′$_{DMT,A+B}$, H2″$_{DMT,A+B}$, H3″$_{DMT,A+B}$, H4″$_{DMT,A+B}$, H5″$_{DMT,A+B}$, H6″$_{DMT,A+B}$), 6.90-6.95 (m, 10H, H3$_{DMT,A+B}$, H5$_{DMT,A+B}$, H3′$_{DMT,A+B}$, H5′$_{DMT,A+B}$), 6.09 (d, J = 4.2 Hz, 1.5H, ex, 3′-OH$_A$), 6.04 (d, J = 4.3 Hz, 1H, ex, 3′-OH$_B$), 5.63 (s, 1.5H, H1′$_A$), 5.44 (s, 1H, H1′$_B$), 4.76 (d, J = 16.7, 1.5H, COCH$_{2,A,a}$), 4.69 (s, 1H, H2′$_B$), 4.57 (d, J = 16.7, 1.5H, COCH$_{2,A,b}$), 4.51 (s, 1.5H, H2′$_A$), 4.49 (s, 2H, COCH$_{2,B}$), 4.29 (d, J = 4.2 Hz, 1.5H, H3′$_A$), 4.26 (d, J = 4.3 Hz, 1H, H3′$_B$), 3.75 (s, 15H, OCH$_3$), 3.57 (s, 2H, H5″$_B$), 3.48 (d, J = 11.1 Hz, 1H, H5′$_{B,a}$), 3.47 (d, J = 11.0 Hz, 1.5H, H5′$_{A,a}$), 3.32-3.42 (m, 5H, H5′$_{A,b}$, H5′$_{B,b}$, H5″$_A$), 1.76 (s, 7.5H, 5‴-CH$_{3,A+B}$), 1.51 (s, 4.5H, 5-CH$_{3,A}$), 1.49 (s, 3H, 5-CH$_{3,B}$).

^{13}C NMR (101 MHz, DMSO-d_6): δ 165.9 (*C*OCH$_{2,A}$), 165.6 (*C*OCH$_{2,B}$), 164.3 (C4‴$_{A+B}$), 163.8 (C4$_A$), 163.7 (C4$_B$), 158.2 (C4$_{DMT,A+B}$, C4′$_{DMT,A+B}$), 158.1 (C4$_{DMT,A+B}$, C4′$_{DMT,A+B}$), 150.9 (C2‴$_{A+B}$), 149.9 (C2$_A$), 149.7 (C2$_B$), 144.53 (C1″$_{DMT,A}$), 144.47 (C1″$_{DMT,B}$), 142.1 (C6‴$_A$), 142.0 (C6‴$_B$), 135.2 (C1$_{DMT,A}$/C1′$_{DMT,A}$), 135.1 (C1$_{DMT,B}$/C1′$_{DMT,B}$), 135.0 (C1$_{DMT,A}$/C1′$_{DMT,A}$), 134.9 (C1$_{DMT,B}$/C1′$_{DMT,B}$), 134.3 (C6$_B$), 134.0 (C6$_A$), 129.74 (C2$_{DMT,A+B}$/C6$_{DMT,A+B}$/C2′$_{DMT,A+B}$/ C6′$_{DMT,A+B}$), 129.66 (C2$_{DMT,A+B}$/C6$_{DMT,A+B}$/C2′$_{DMT,A+B}$/C6′$_{DMT,A+B}$), 127.9 (C3″$_{DMT,A+B}$/ C5″$_{DMT,A+B}$), 127.6 (C2″$_{DMT,A+B}$/C6″$_{DMT,A+B}$), 126.8 (C4″$_{DMT,A+B}$), 113.22 (C3$_{DMT,A+B}$/ C5$_{DMT,A+B}$/C3′$_{DMT,A+B}$/ C5′$_{DMT,A+B}$), 113.16 (C3$_{DMT,A+B}$/C5$_{DMT,A+B}$/C3′$_{DMT,A+B}$/ C5′$_{DMT,A+B}$), 108.6 (C5$_A$), 108.5 (C5$_B$), 108.1 (C5‴$_A$), 108.0 (C5‴$_B$), 87.8 (C4′$_B$), 86.9 (C4′$_A$), 86.2 (C1′$_A$), 86.0 (C1′$_B$), 85.9 (Ar$_3$CO$_B$), 85.7 (Ar$_3$CO$_A$), 69.4 (C3′$_A$), 68.2 (C3′$_B$), 62.2 (C2′$_A$), 61.1 (C2′$_B$), 59.2 (C5′$_{A+B}$), 55.0 (OCH$_{3,A+B}$), 51.5 (C5″$_A$), 50.7 (C5″$_B$), 48.3 (CO*C*H$_{2,A}$), 47.9 (CO*C*H$_{2,B}$), 12.21 (5-CH$_{3,A}$), 12.18 (5-CH$_{3,B}$), 11.81 (5‴-CH$_{3,B}$), 11.77 (5‴-CH$_{3,A}$).

1-(2-Amino-2-*N*-(6-*N*-benzoyladenin-9-ylacetyl)-2-deoxy-5-*O*-4,4′-dimethoxytrityl-2-*N*,4-*C*-methylene-β-D-ribofuranosyl)thymine (3b).

^{1}H NMR (DMSO-d_6): δ 11.56 (br s, 1.3H, ex, NH_A/6‴-NH_A), 11.39 (br s, 1H, ex, NH_B/6‴-NH_B), 11.17 (br s, 2.3H, ex, NH_{A+B}/6‴-NH_{A+B}), 8.72 (s, 2.3H, H2‴$_{A+B}$), 8.47 (s, 1.3H, H8‴$_A$), 8.38 (s, 1H, H8‴$_B$), 8.07 (d, J = 7.5 Hz, 4.6H, $H2_{Bz,A+B}$, $H6_{Bz,A+B}$), 7.62-7.67 (m, 2.3H, $H4_{Bz,A+B}$), 7.53-7.59 (m, 6.9H, $H3_{Bz,A+B}$, $H5_{Bz,A+B}$, $H6_{A+B}$), 7.24-7.52 (m, 20.7H, $H2_{DMT,A+B}$, $H6_{DMT,A+B}$, H2′$_{DMT,A+B}$, H6′$_{DMT,A+B}$, H2″$_{DMT,A+B}$, H3″$_{DMT,A+B}$, H4″$_{DMT,A+B}$, H5″$_{DMT,A+B}$, H6″$_{DMT,A+B}$), 6.91-6.96 (m, 9.2H, $H3_{DMT,A+B}$, $H5_{DMT,A+B}$, H3′$_{DMT,A+B}$, H5′$_{DMT,A+B}$), 6.18 (d, J = 4.3 Hz, 1.3H, ex, 3′-OH_A), 6.08 (d, J = 4.3 Hz, 1H, ex, 3′-OH_B), 5.75 (s, 1.3H, H1′$_A$), 5.53 (s, 1H, H1′$_B$), 5.48 (d, J = 17.0 Hz, 1.3H, $COCH_{2,A,a}$), 5.30 (d, J = 17.0 Hz, 1.3H, $COCH_{2,A,b}$), 5.28 (d, J = 17.2 Hz, 1H, $COCH_{2,B,a}$), 5.20 (d, J = 17.2 Hz, 1H, $COCH_{2,B,b}$), 4.73 (s, 1.3H, H2′$_A$), 4.72 (s, 1H, H2′$_B$), 4.36 (d, J = 4.3 Hz, 1.3H, H3′$_A$), 4.28 (d, J = 4.3 Hz, 1H, H3′$_B$), 3.74-3.77 (m, 15.8H, $OCH_{3,A+B}$, H5″$_B$), 3.36-3.55 (m, 7.2H, H5′$_{A+B}$, H5″$_A$), 1.54 (s, 3.9H, 5-$CH_{3,A}$), 1.51 (s, 3H, 5-$CH_{3,B}$).

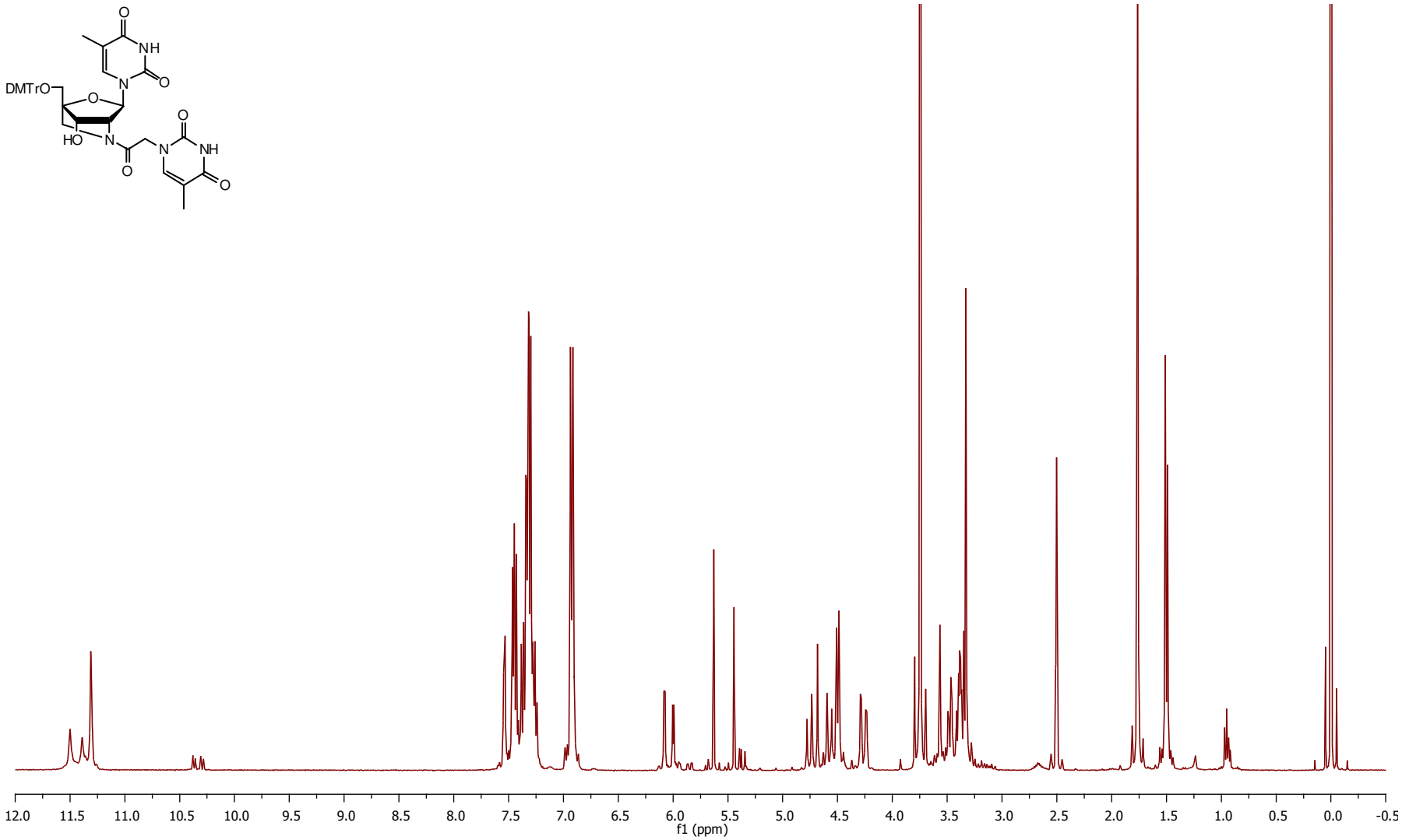
^{13}C NMR (DMSO-d_6): δ 165.5 (COPh_{A+B}), 165.2 (CO$CH_{2,A}$), 165.1 (CO$CH_{2,B}$), 163.9 ($C4_A$), 163.7 ($C4_B$), 158.24 ($C4_{DMT,A+B}$, C4′$_{DMT,A+B}$), 158.21 ($C4_{DMT,A+B}$, C4′$_{DMT,A+B}$), 158.1 ($C4_{DMT,A+B}$, C4′$_{DMT,A+B}$), 152.8 (C4‴$_{A+B}$), 151.5 (C2‴$_{A/B}$), 151.4 (C2‴$_{A/B}$), 150.1 ($C2_A$/$C2_B$/C6‴$_{A+B}$), 150.0 ($C2_A$/$C2_B$/C6‴$_{A+B}$), 149.8 ($C2_A$/$C2_B$/C6‴$_{A+B}$), 145.6 (C8‴$_A$), 145.5 (C8‴$_B$), 144.61 (C1″$_{DMT,A}$), 144.56 (C1″$_{DMT,B}$), 135.3 ($C1_{DMT,A}$/C1′$_{DMT,A}$), 135.2 ($C1_{DMT,B}$/C1′$_{DMT,B}$), 135.02 ($C1_{DMT,A}$/C1′$_{DMT,A}$), 134.99 ($C1_{DMT,B}$/C1′$_{DMT,B}$), 134.3 ($C6_B$), 134.1 ($C6_A$), 133.4 ($C1_{Bz,A+B}$), 132.3 ($C4_{Bz,A+B}$), 129.8 ($C2_{DMT,A+B}$/$C6_{DMT,A+B}$/C2′$_{DMT,A+B}$/C6′$_{DMT,A+B}$), 129.7 ($C2_{DMT,A+B}$/$C6_{DMT,A+B}$/C2′$_{DMT,A+B}$/C6′$_{DMT,A+B}$), 128.4 ($C2_{Bz,A+B}$, $C3_{Bz,A+B}$, $C5_{Bz,A+B}$, $C6_{Bz,A+B}$), 128.0 (C3″$_{DMT,A+B}$, C5″$_{DMT,A+B}$), 127.7 (C2″$_{DMT,A+B}$, C6″$_{DMT,A+B}$), 126.9 (C4″$_{DMT,A+B}$), 124.9 (C5‴$_{A+B}$), 113.3 ($C3_{DMT,A+B}$/$C5_{DMT,A+B}$/ C3′$_{DMT,A+B}$/C5′$_{DMT,A+B}$), 113.2 ($C3_{DMT,A+B}$/$C5_{DMT,A+B}$/ C3′$_{DMT,A+B}$/C5′$_{DMT,A+B}$), 108.7 ($C5_A$), 108.6 ($C5_B$), 88.0 (C4′$_B$), 87.1 (C4′$_A$), 86.4 (C1′$_A$), 86.0 (C1′$_B$), 85.9 (Ar_3CO_B), 85.8 (Ar_3CO_A), 69.5 (C3′$_A$), 68.3 (C3′$_B$), 62.5 (C2′$_A$), 61.3 (C2′$_B$), 59.4 (C5′$_A$), 59.2 (C5′$_B$), 55.1 ($OCH_{3,A+B}$), 51.6 (C5″$_A$), 51.0 (C5″$_B$), 44.6 (COCH$_{2,A}$), 44.3 (COCH$_{2,B}$), 12.29 (5-$CH_{3,A}$), 12.26 (5-$CH_{3,B}$).

1-(2-Amino-2-deoxy-5-*O*-4,4′-dimethoxytrityl-2-*N*,4-*C*-methylene-2-*N*-phenylacetyl-β-D-ribofuranosyl)thymine (3c).

^{1}H NMR (DMSO-d_6): δ 11.50 (br s, 1.5H, ex, NH_A), 11.39 (br s, 1H, ex, NH_B), 7.57 (s, 1H, $H6_B$), 7.54 (s, 1.5H, $H6_A$), 7.39-7.46 (m, 5H, $H2''_{DMT,A+B}$, $H6''_{DMT,A+B}$), 7.20-7.37 (m, 30H, $H2_{DMT,A+B}$, $H6_{DMT,A+B}$, $H2'_{DMT,A+B}$, $H6'_{DMT,A+B}$, $H3''_{DMT,A+B}$, $H4''_{DMT,A+B}$, $H5''_{DMT,A+B}$, $H2_{Bz,A+B}$, $H3_{Bz,A+B}$, $H4_{Bz,A+B}$, $H5_{Bz,A+B}$, $H6_{Bz,A+B}$), 6.88-6.94 (m, 10H, $H3_{DMT}$, $H5_{DMT}$, $H3'_{DMT}$, $H5'_{DMT}$), 5.99 (d, J = 4.2 Hz, 1.5H, ex, 3′-OH_A), 5.96 (d, J = 4.1 Hz, 1H, ex, 3′-OH_B), 5.53 (s, 1.5H, $H1'_A$), 5.40 (s, 1H, $H1'_B$), 4.72 (s, 1H, $H2'_B$), 4.59 (s, 1.5H, $H2'_A$), 4.26 (d, J = 4.2 Hz, 1.5H, $H3'_A$), 4.24 (d, J = 4.1 Hz, 1H, $H3'_B$), 3.77 (s, 3H, $COCH_{2,A}$), 3.74 (s, 15H, $OCH_{3,A+B}$), 3.63 (d, J = 15.8 Hz, 1H, $COCH_{2,B,a}$), 3.59 (d, J = 15.8 Hz, 1H, $COCH_{2,B,b}$), 3.57 (d, J = 9.6 Hz, 1.5H, $H5''_{A,a}$), 3.51 (d, J = 9.6 Hz, 1.5H, $H5''_{A,b}$), 3.32-3.48 (m, 7H, $H5'_{A+B}$, $H5''_B$) 1.51 (s, 4.5H, 5-$CH_{3,A}$), 1.47 (s, 3H, 5-$CH_{3,B}$).

^{13}C NMR (DMSO-d_6): δ 169.3 (CO$CH_{2,A}$), 169.2 (CO$CH_{2,B}$), 163.8 ($C4_A$), 163.7 ($C4_B$), 158.2 ($C4_{DMT,A+B}$, $C4'_{DMT,A+B}$), 158.1 ($C4_{DMT,A+B}$, $C4'_{DMT,A+B}$), 150.1 ($C2_A$), 149.8 ($C2_B$), 144.62 ($C1''_{DMT,A}$), 144.55 ($C1''_{DMT,B}$), 135.4 ($C1_{DMT,A}$/$C1'_{DMT,A}$/$C1_{Ph,A}$), 135.30 ($C1_{DMT,B}$/$C1'_{DMT,B}$/$C1_{Ph,B}$), 135.27 ($C1_{DMT,A}$/$C1'_{DMT,A}$/$C1_{Ph,A}$), 135.2 ($C1_{DMT,B}$/$C1'_{DMT,B}$/$C1_{Ph,B}$), 135.02 ($C1_{DMT,A}$/$C1'_{DMT,A}$/$C1_{Ph,A}$), 134.98 ($C1_{DMT,B}$/$C1'_{DMT,B}$/$C1_{Ph,B}$), 134.4 ($C6_B$), 134.1 ($C6_A$), 129.8 ($C2_{DMT,A+B}$/$C6_{DMT,A+B}$/$C2'_{DMT,A+B}$/$C6'_{DMT,A+B}$), 129.7 ($C2_{DMT,A+B}$/$C6_{DMT,A+B}$/$C2'_{DMT,A+B}$/$C6'_{DMT,A+B}$), 129.4 ($C2_{Ph,A}$/$C3_{Ph,A}$/$C5_{Ph,A}$/$C6_{Ph,A}$), 129.3 ($C2_{Ph,B}$/$C3_{Ph,B}$/$C5_{Ph,B}$/$C6_{Ph,B}$), 128.14 ($C2_{Ph,B}$/$C3_{Ph,B}$/$C5_{Ph,B}$/$C6_{Ph,B}$), 128.11 ($C2_{Ph,A}$/$C3_{Ph,A}$/$C5_{Ph,A}$/$C6_{Ph,A}$), 127.9 ($C3''_{DMT,A+B}$, $C5''_{DMT,A+B}$), 127.7 ($C2''_{DMT,A+B}$, $C6''_{DMT,A+B}$), 126.8 ($C4_{Ph,A+B}$), 126.4 ($C4''_{DMT,A}$), 126.3 ($C4''_{DMT,B}$), 113.3 ($C3_{DMT,A+B}$/$C5_{DMT,A+B}$/$C3'_{DMT,A+B}$/$C5'_{DMT,A+B}$), 113.2 ($C3_{DMT,A+B}$/$C5_{DMT,A+B}$/$C3'_{DMT,A+B}$/$C5'_{DMT,A+B}$), 108.6 ($C5_A$), 108.5 ($C5_B$), 87.9 ($C4'_B$), 87.3 ($C4'_A$), 86.8 ($C1'_A$), 86.2 ($C1'_B$), 85.8 (Ar_3CO_B), 85.7 (Ar_3CO_A), 69.3 ($C3'_A$), 68.1 ($C3'_B$), 63.5 ($C2'_A$), 60.8 ($C2'_B$), 59.3 ($C5'_A$), 59.2 ($C5'_B$), 55.0 ($OCH_{3,A+B}$), 51.8 ($C5''_B$), 51.3 ($C5''_A$), 39.9 (COCH$_{2,A+B}$, overlap with DMSO-d_6), 12.3 (5-$CH_{3,A}$), 12.2 (5-$CH_{3,B}$).

3a; ^{1}H NMR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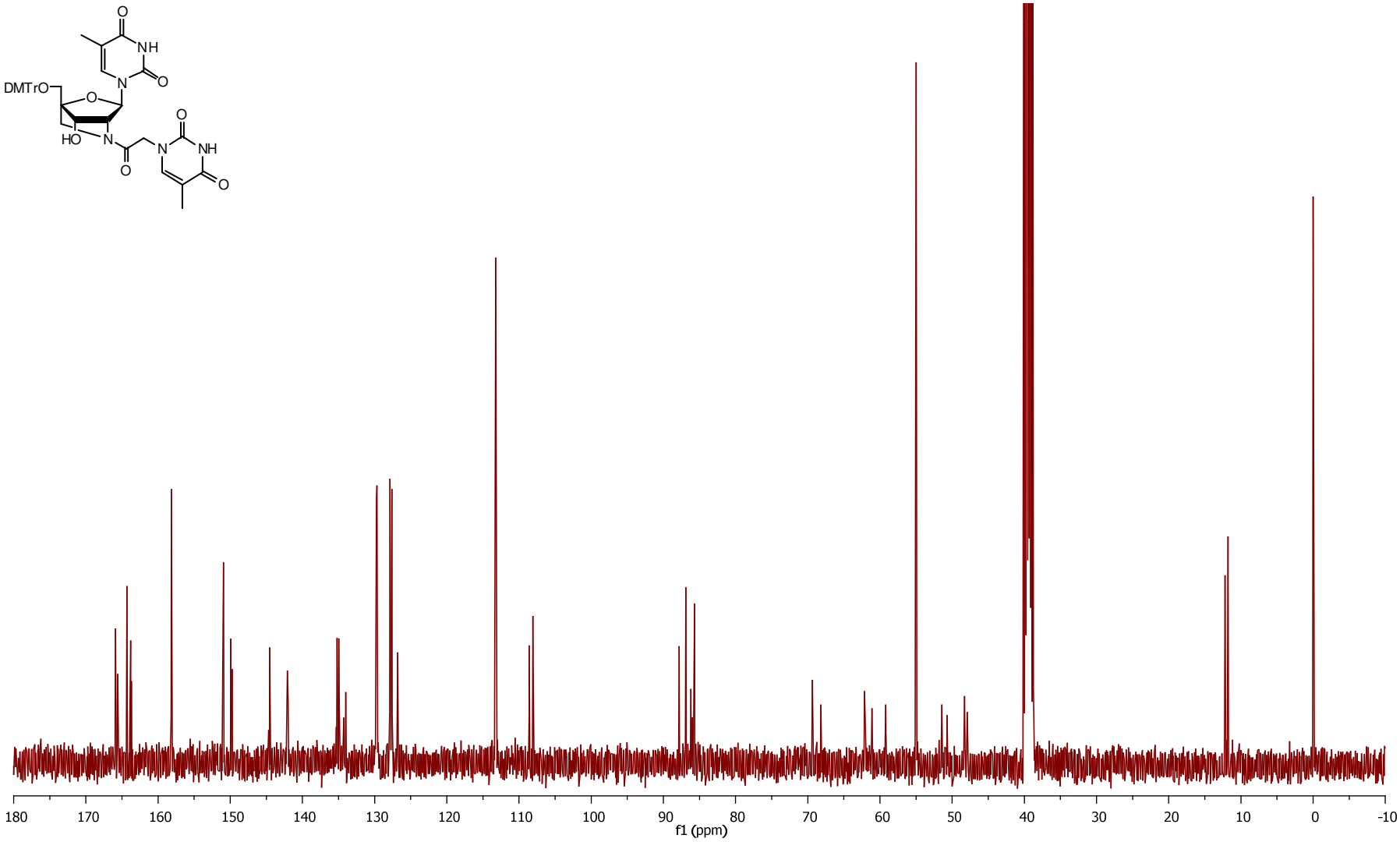
3a; ^{13}C NMR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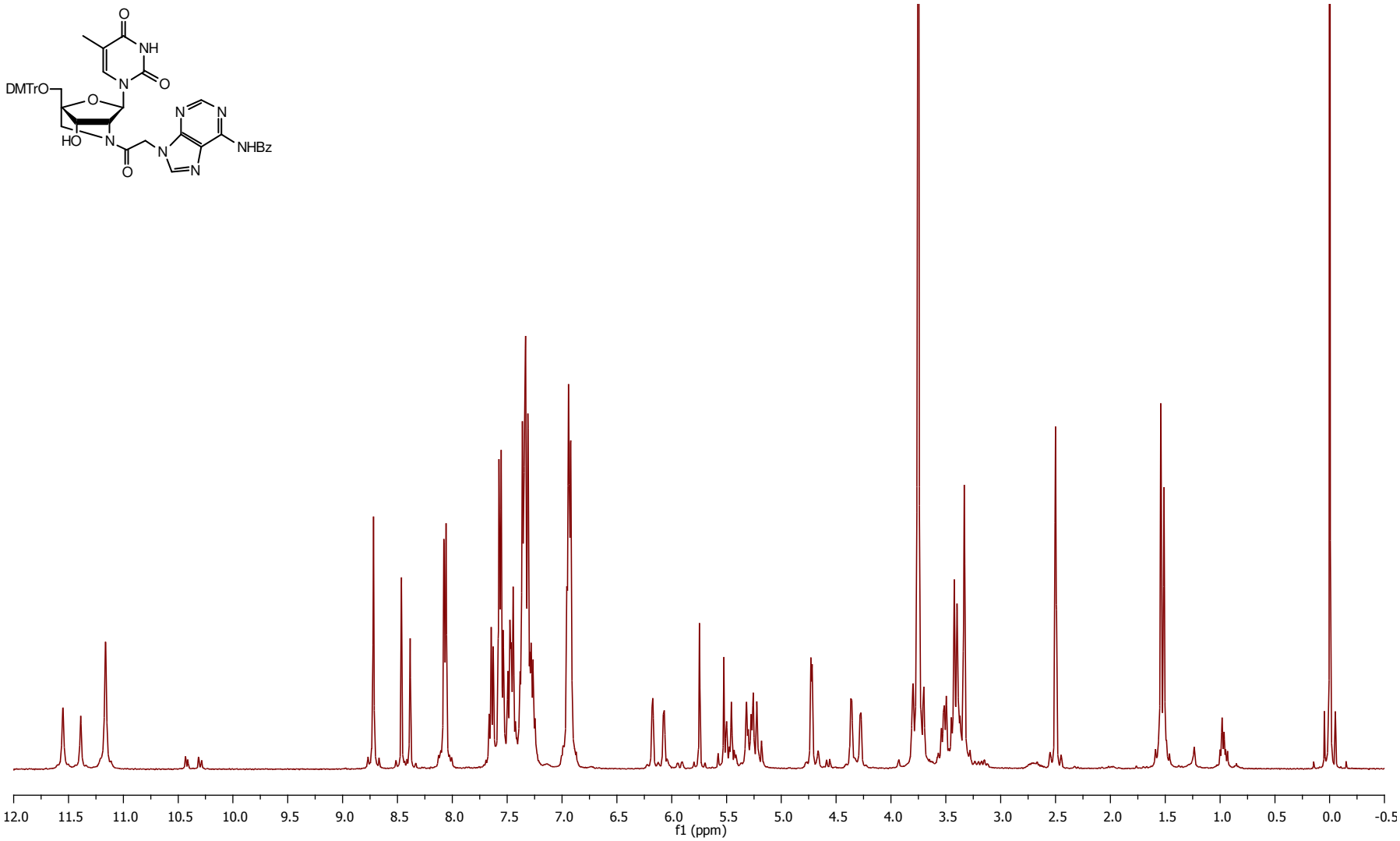
3b; ^{1}H NMR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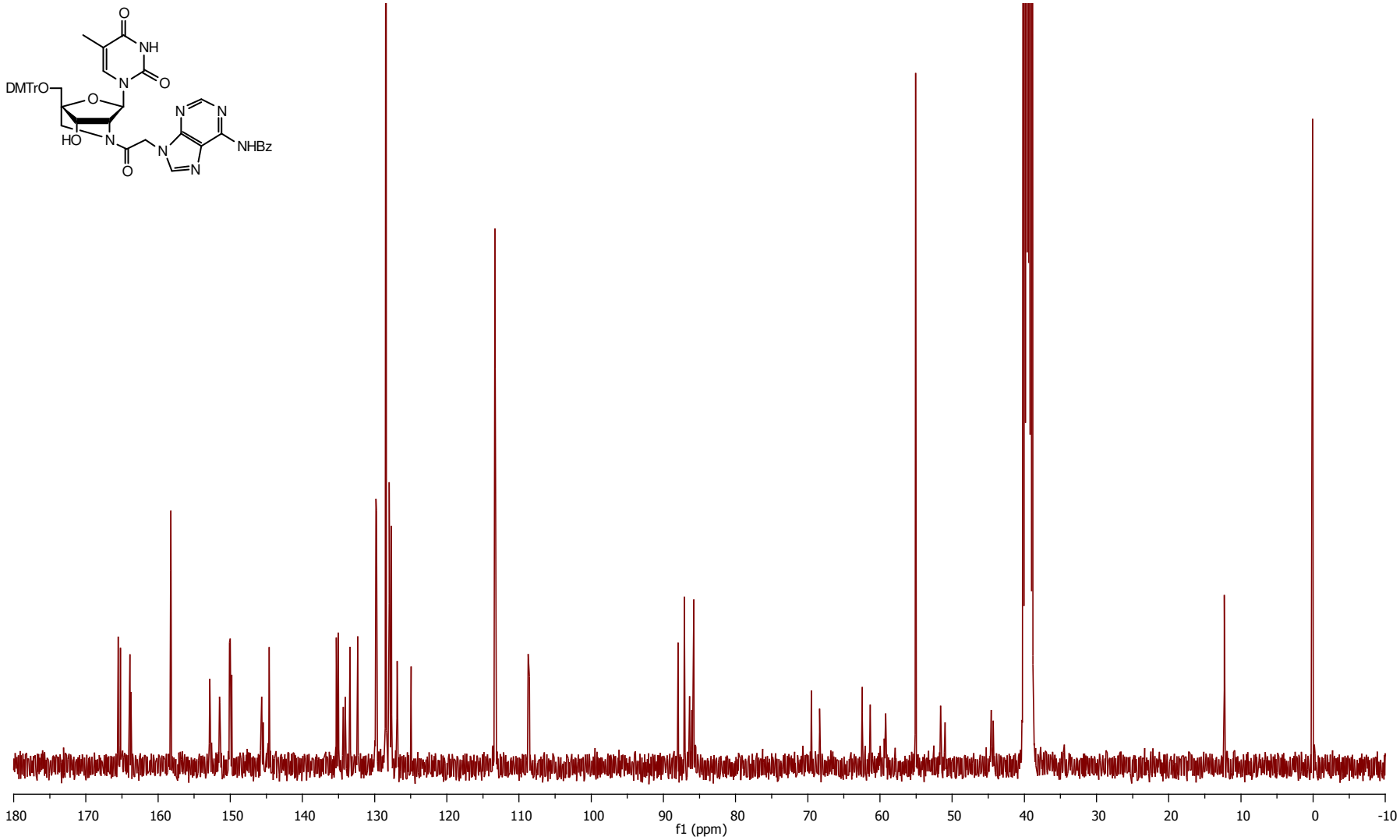
3b; ^{13}C NMR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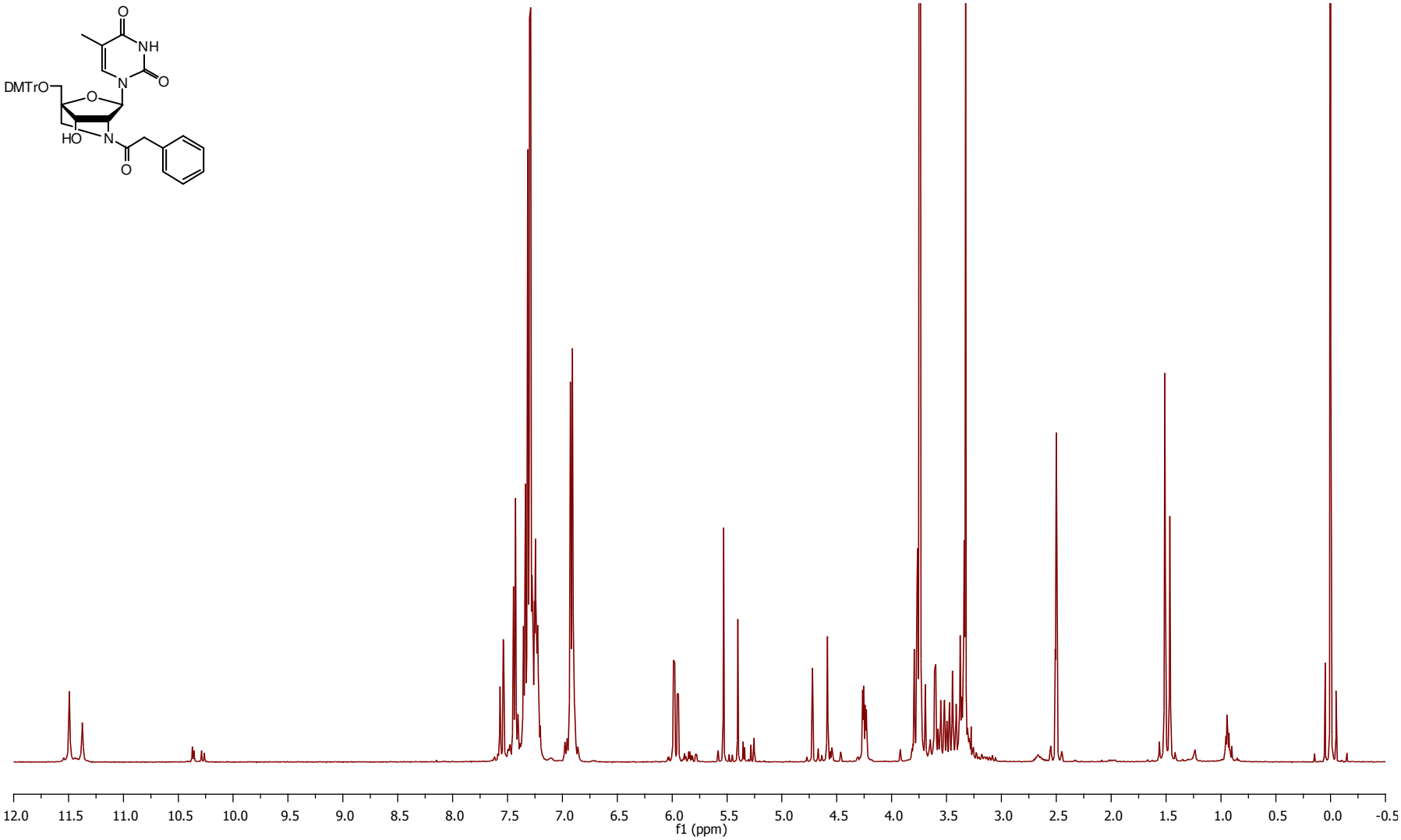
f1 (ppm)

3c; ^{1}H NMR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6.0
5.5
5.0
4.5
4.0
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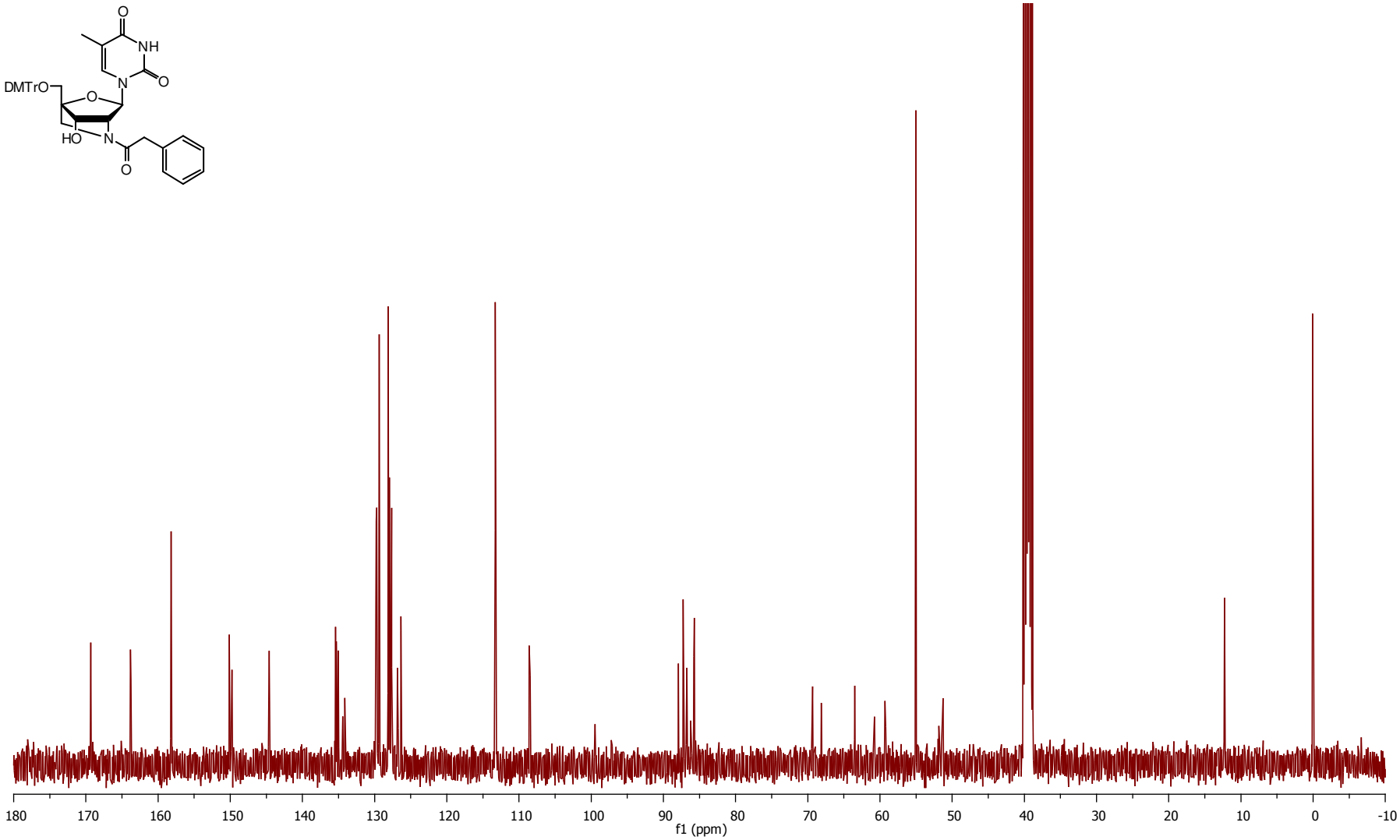
f1 (ppm)

3c; ^{13}C NMR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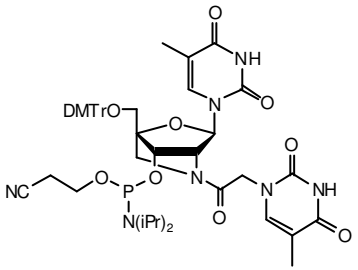
0
-10
f1 (ppm)

4a; ^{31}P NMR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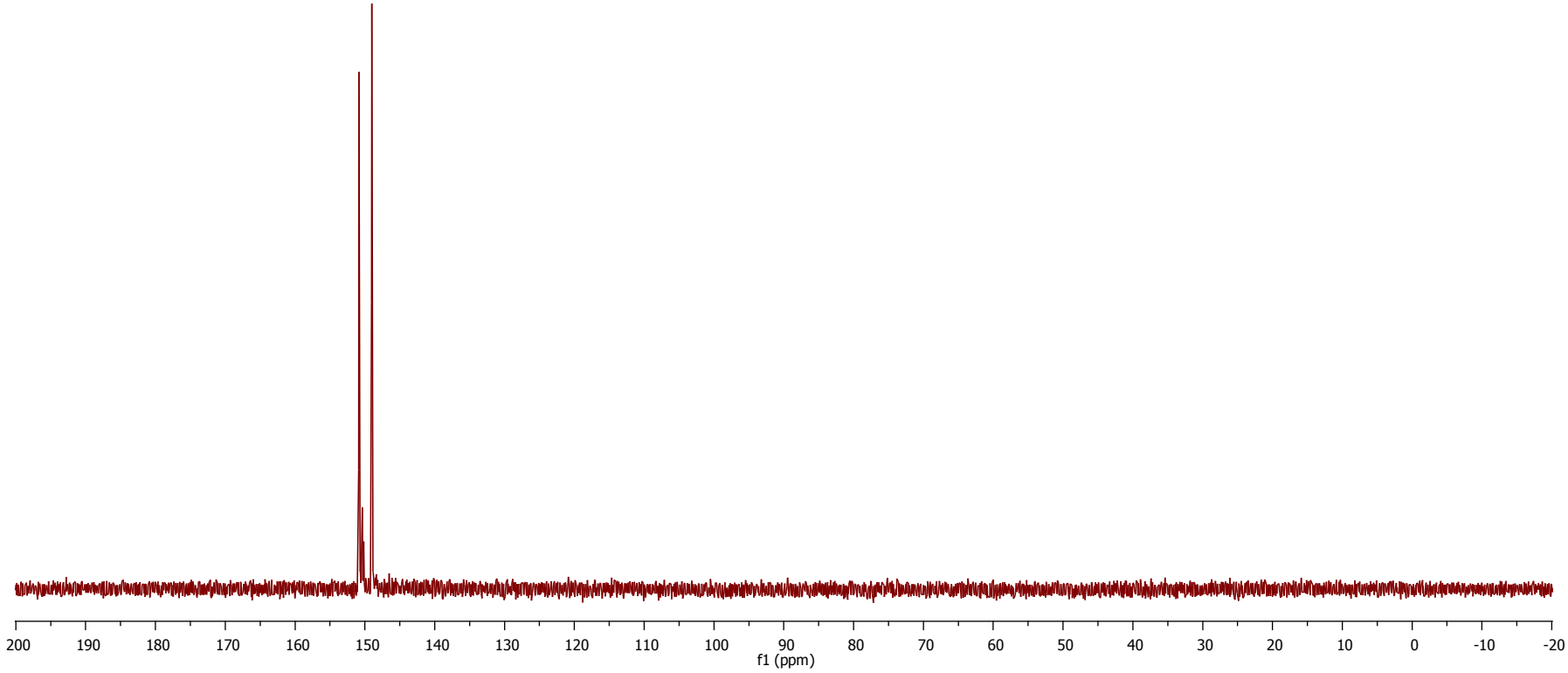
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160
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140
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120
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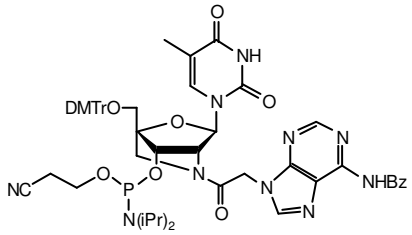
-10
-20
f1 (ppm)

4b; ^{31}P NMR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N
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O
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NC
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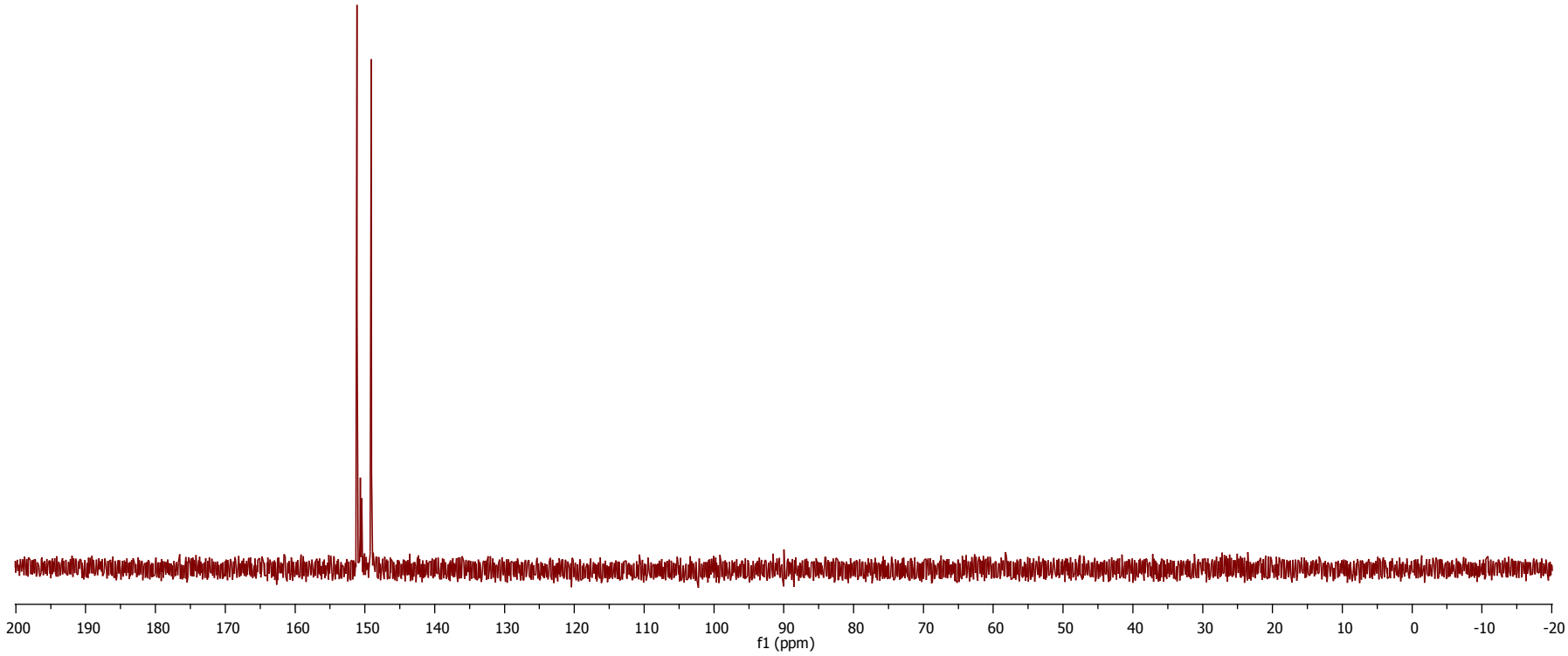
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-10
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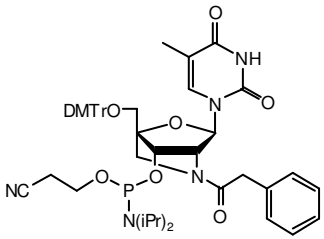
f1 (ppm)

4c; ^{31}P NMR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O
DMTrO
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NC
O
P
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N
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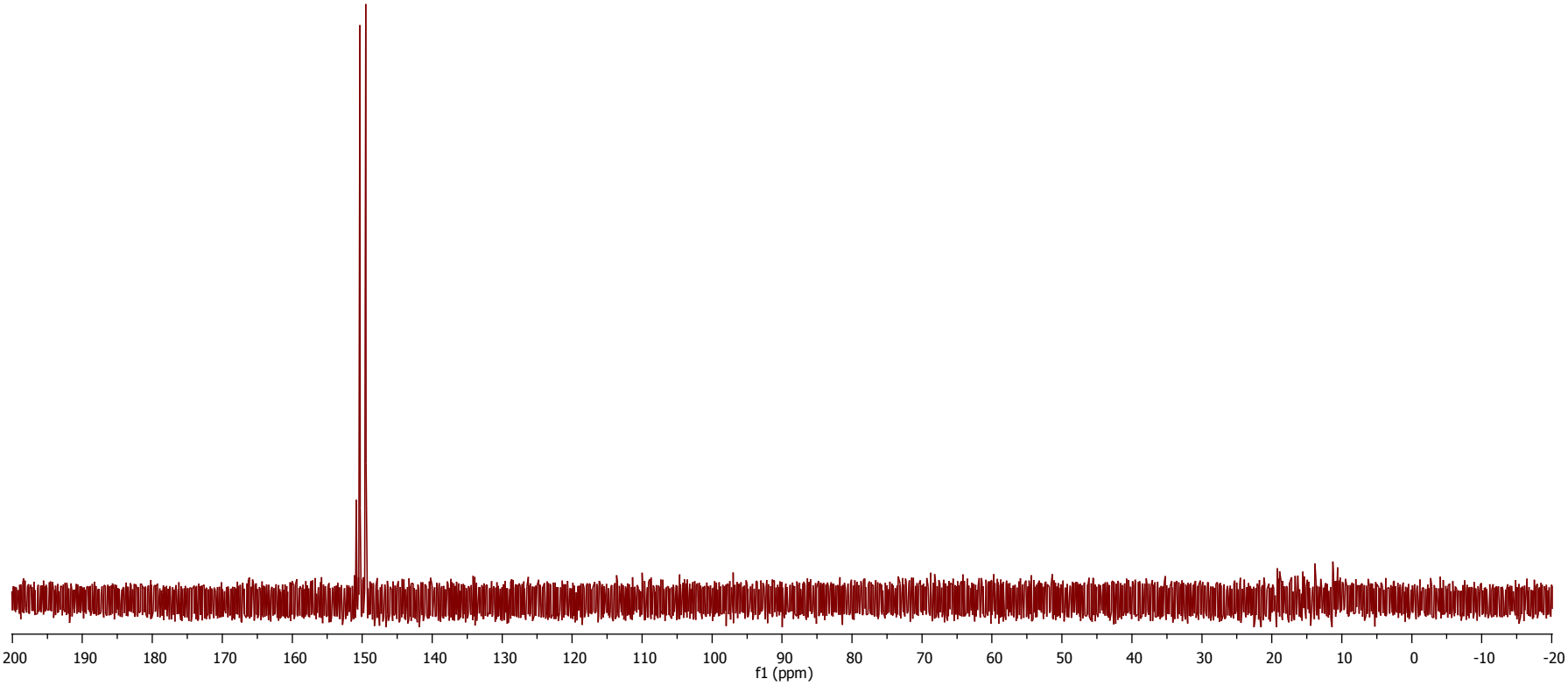
N(iPr)2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f1 (ppm)