

Supplementary Material

Synthesis, Chemical and Enzymatic Hydrolysis, and Aqueous Solubility of Amino Acid Ester Prodrugs of 3-Carboranyl Thymidine Analogues for Boron Neutron Capture Therapy of Brain Tumors

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²*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University.*

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*Corresponding authors:

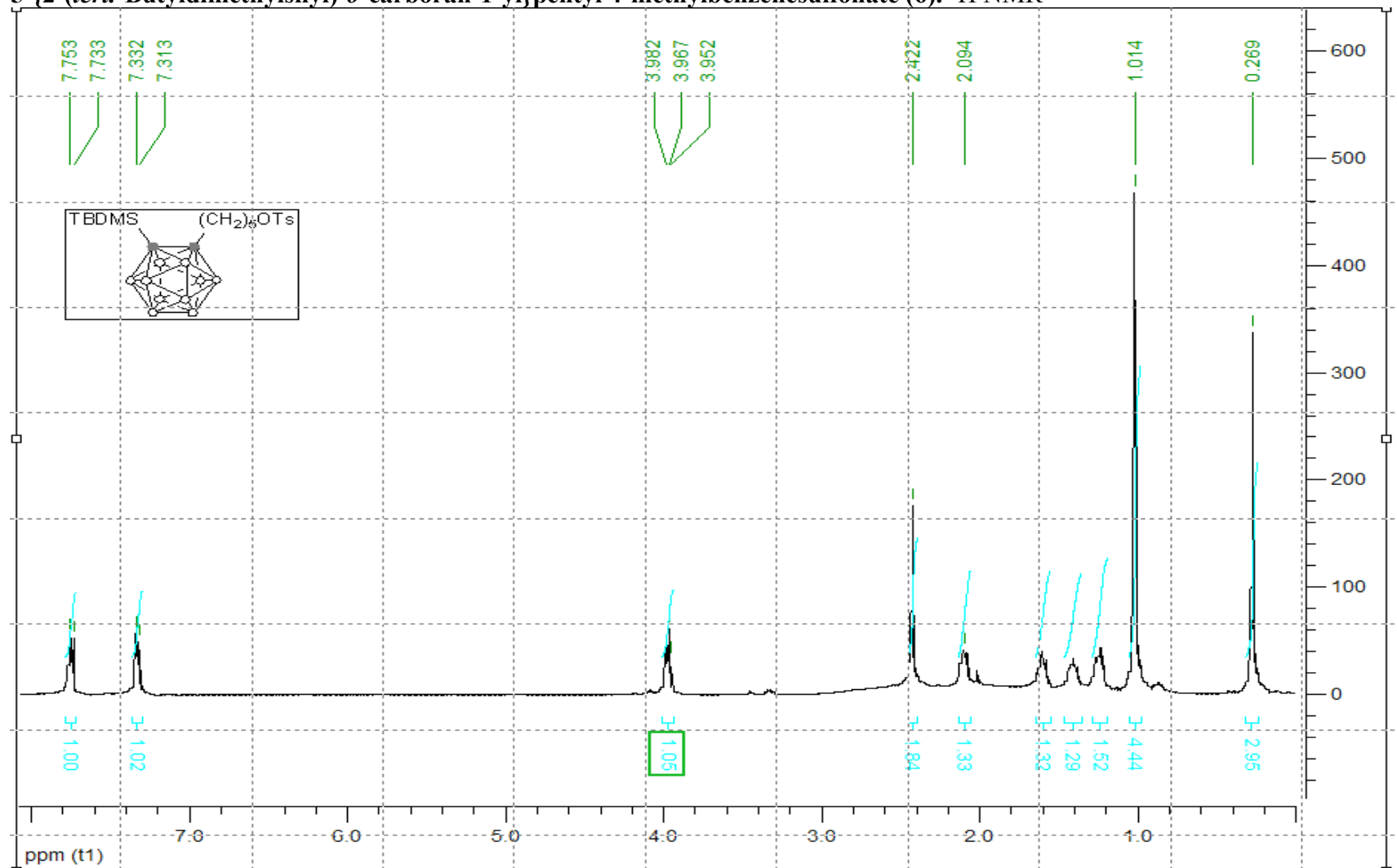
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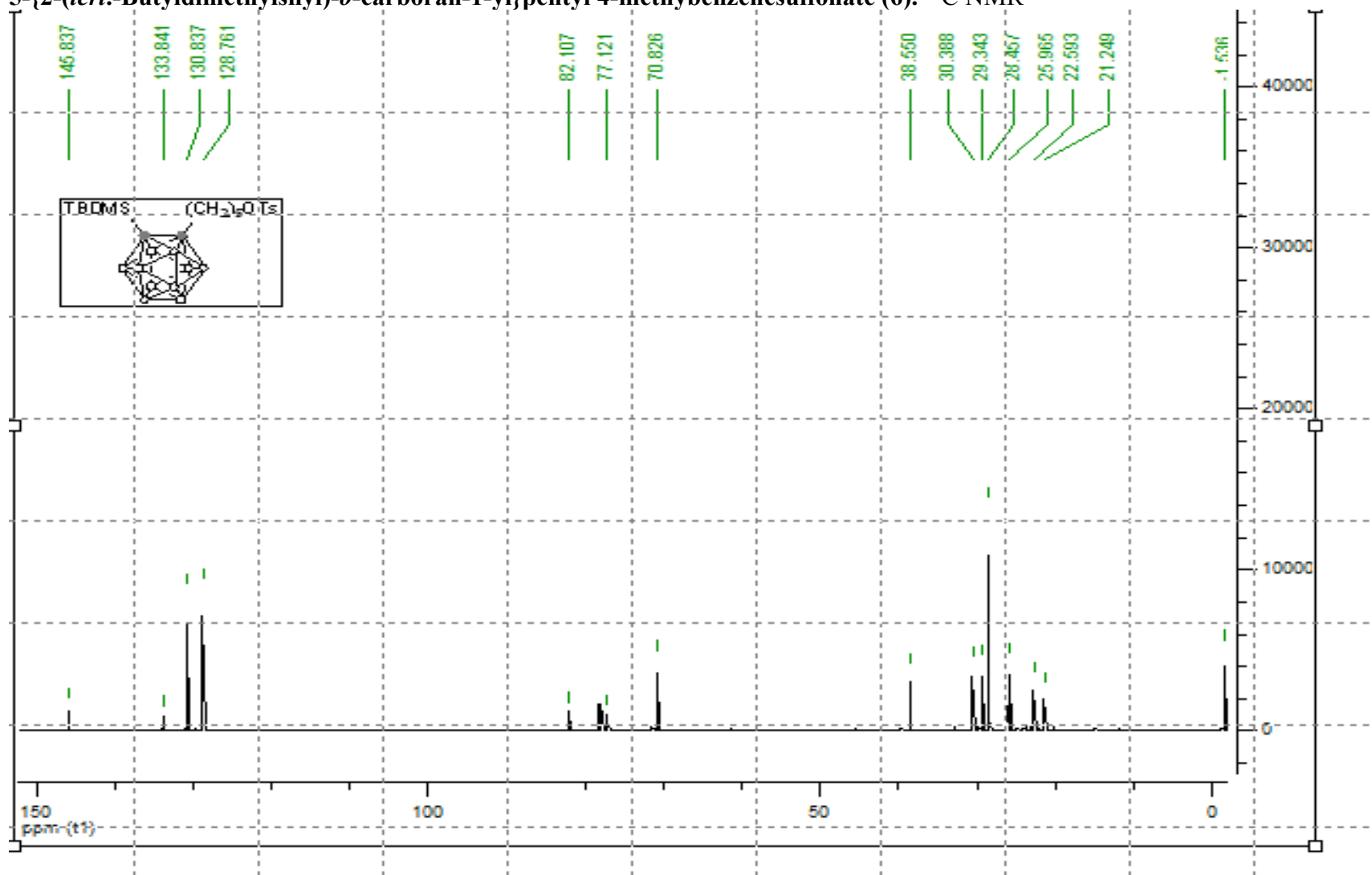
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1. HR-MS-, ¹H-NMR-, and ¹³C-NMR spectra as well as HPLC chromatograms

5-{2-(*tert.*-Butyldimethylsilyl)-*o*-carboran-1-yl}pentyl 4-methylbenzenesulfonate (6). ¹H NMR



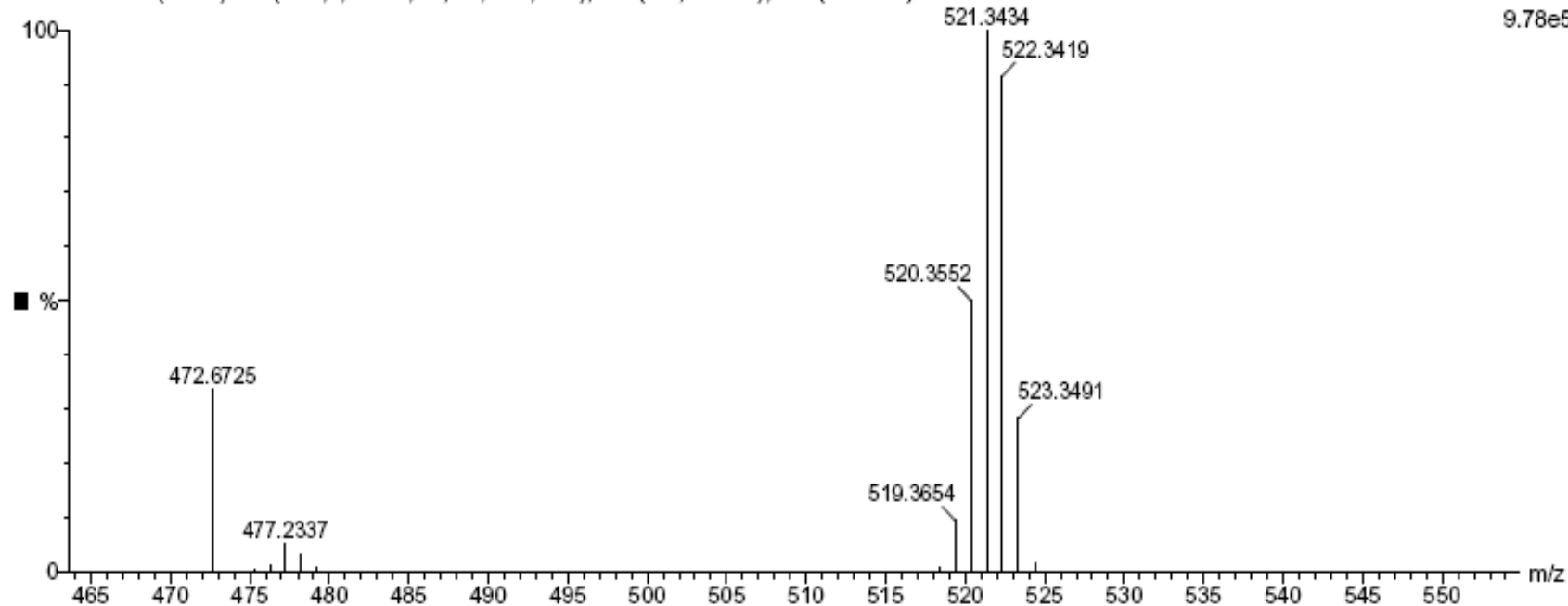
5-{2-(*tert.*-Butyldimethylsilyl)-*o*-carboran-1-yl}pentyl 4-methylbenzenesulfonate (6). ^{13}C NMR



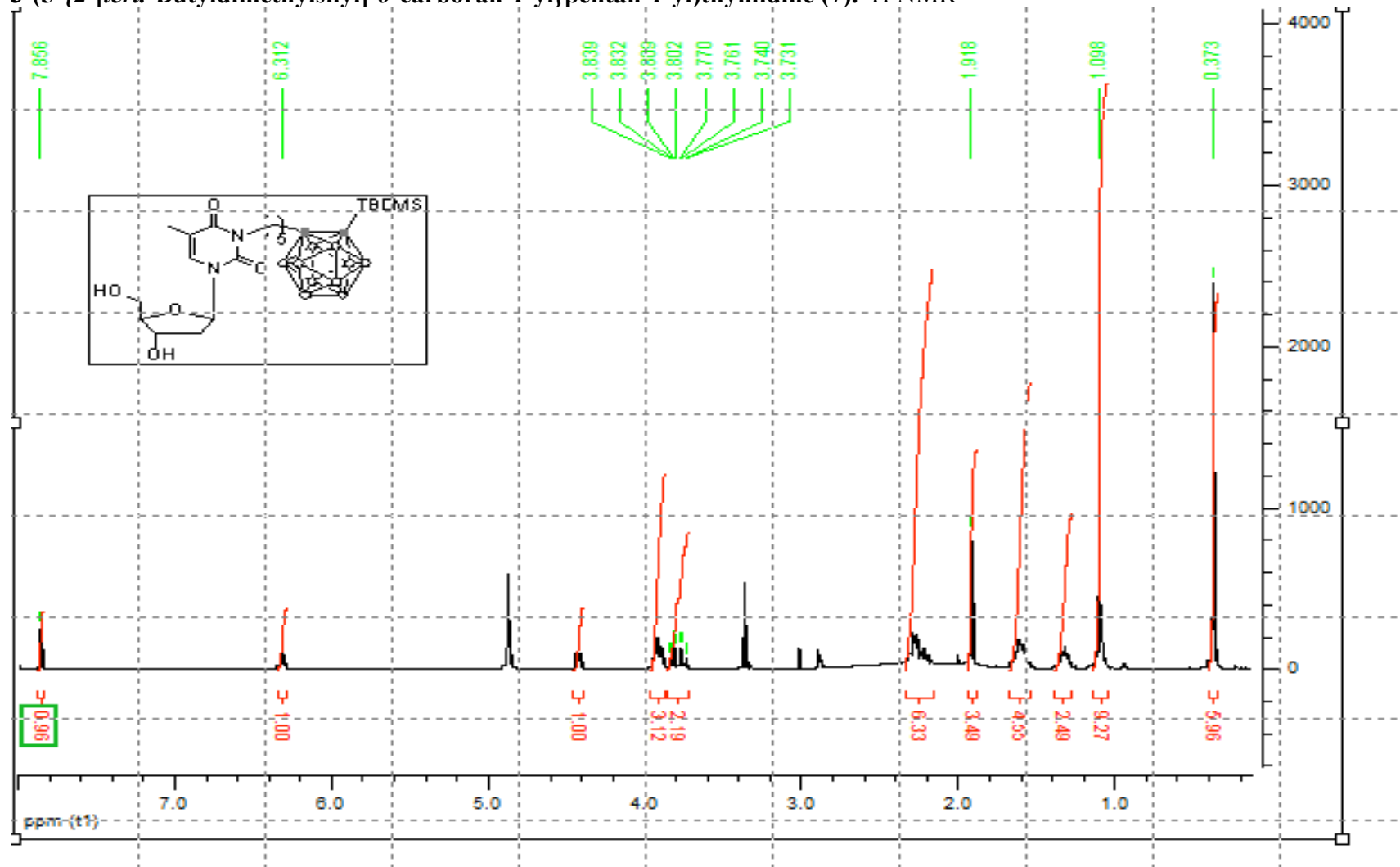
5-{2-(*tert.*-Butyldimethylsilyl)-*o*-carboran-1-yl}pentyl 4-methylbenzenesulfonate (6). HR-ESI-MS: found: m/z 521.3434

L0810081 281 (5.154) AM (Cen,4, 80.00, Ar,0.0,0.00,1.00); Sm (SG, 2x3.00); Cm (169:309)

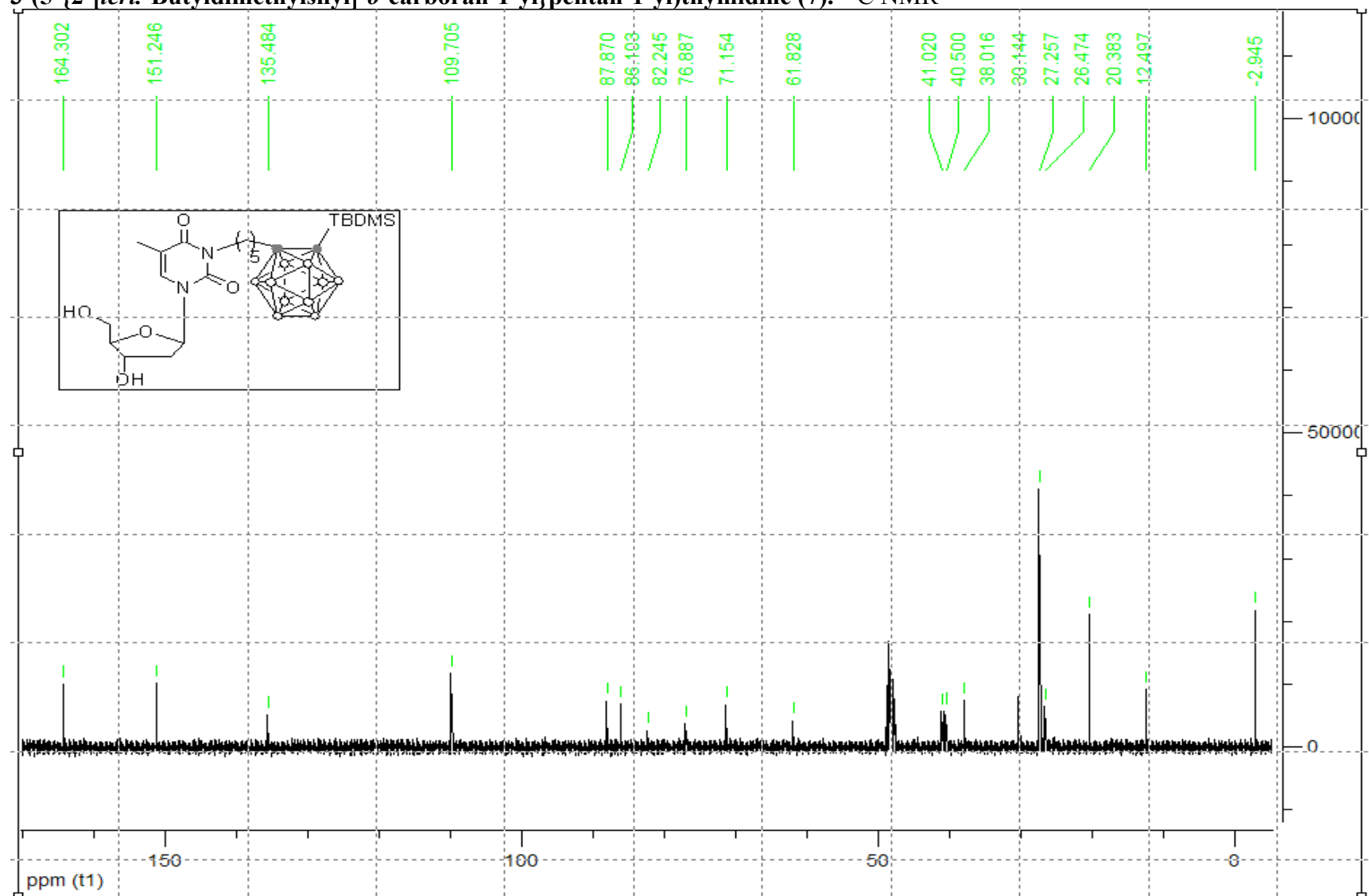
TOF MS ES+
9.78e5



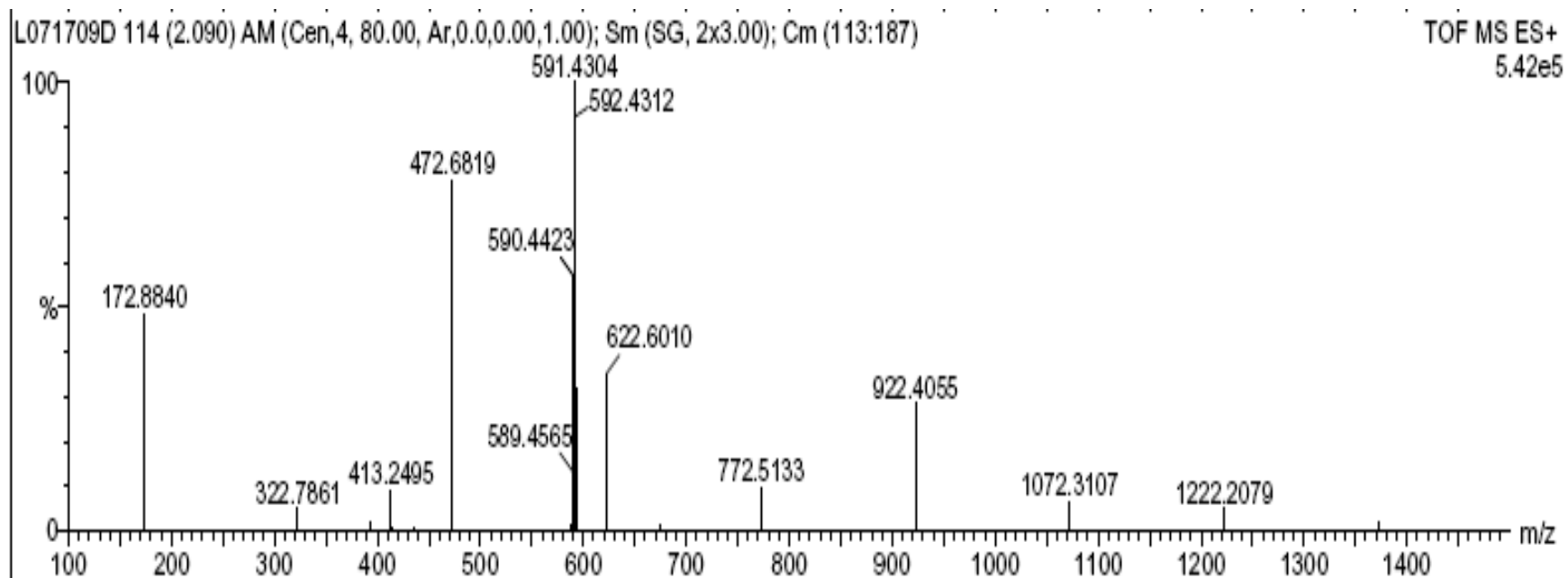
3-(5-{2-[*tert*-Butyldimethylsilyl]-*o*-carboran-1-yl}pentan-1-yl)thymidine (7). ¹H NMR



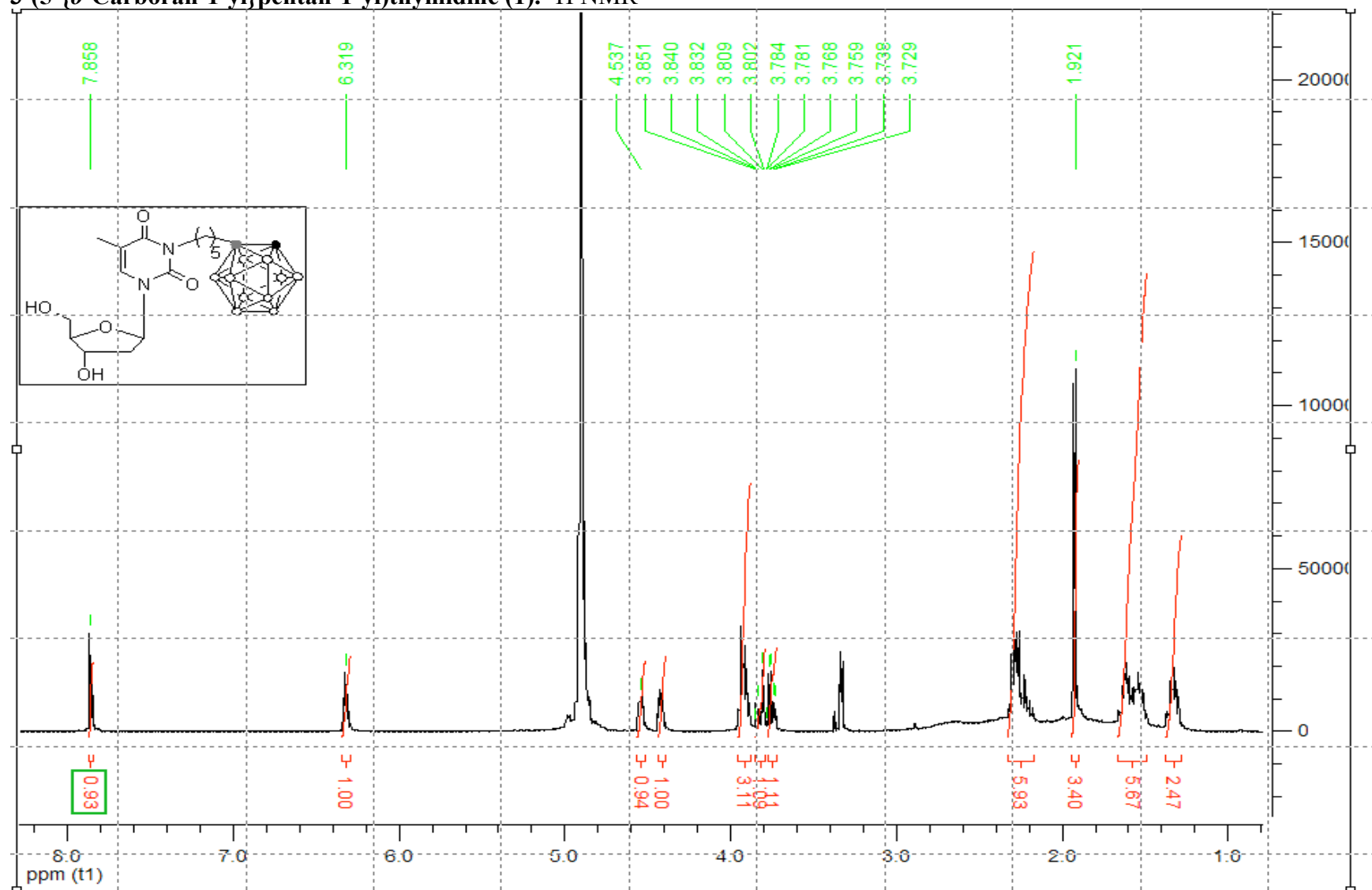
3-(5-{2-[*tert*-Butyldimethylsilyl]-*o*-carboran-1-yl}pentan-1-yl)thymidine (7). ¹³C NMR



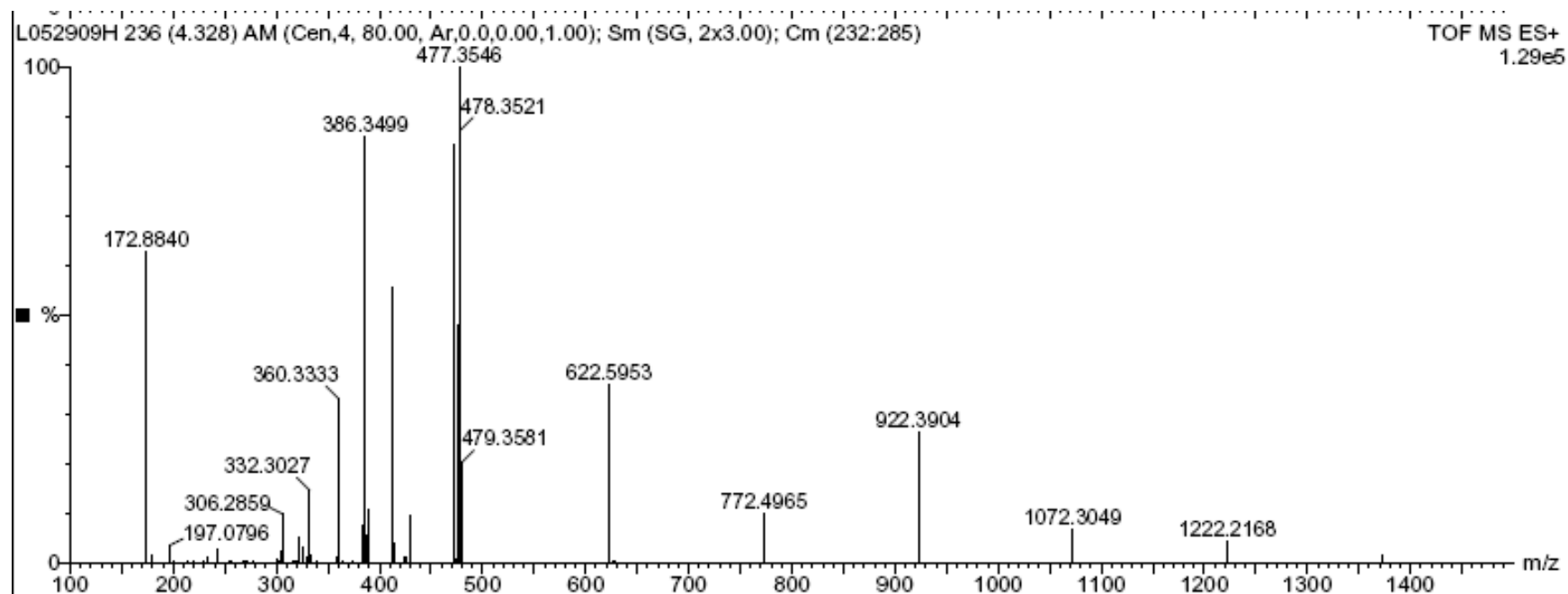
3-(5-{2-[*tert*-Butyldimethylsilyl]-*o*-carboran-1-yl}pentan-1-yl)thymidine (7). HR-ESI-MS: found: m/z 591.4304.



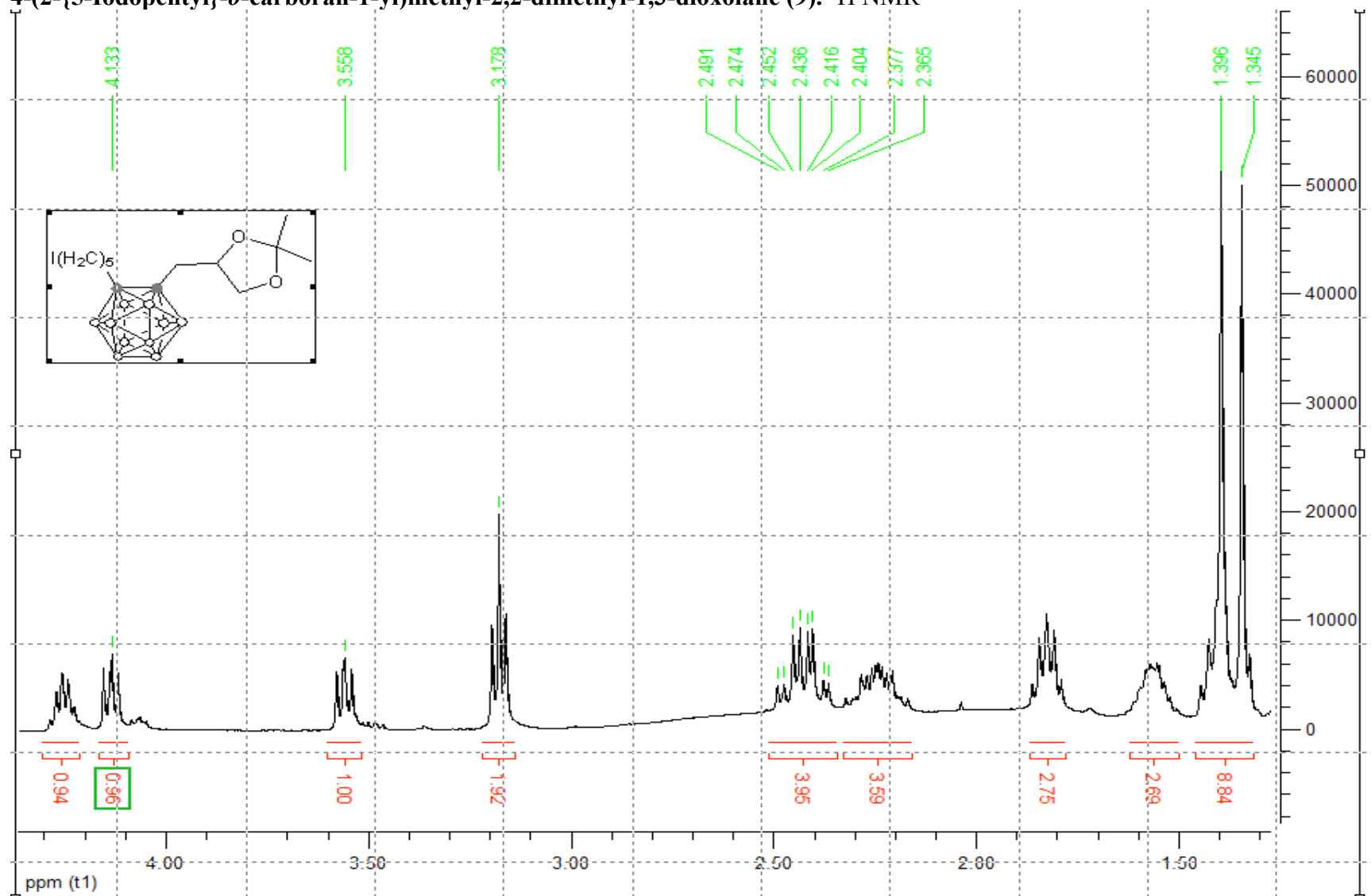
3-(5-{*o*-Carboran-1-yl}pentan-1-yl)thymidine (1). ¹H NMR



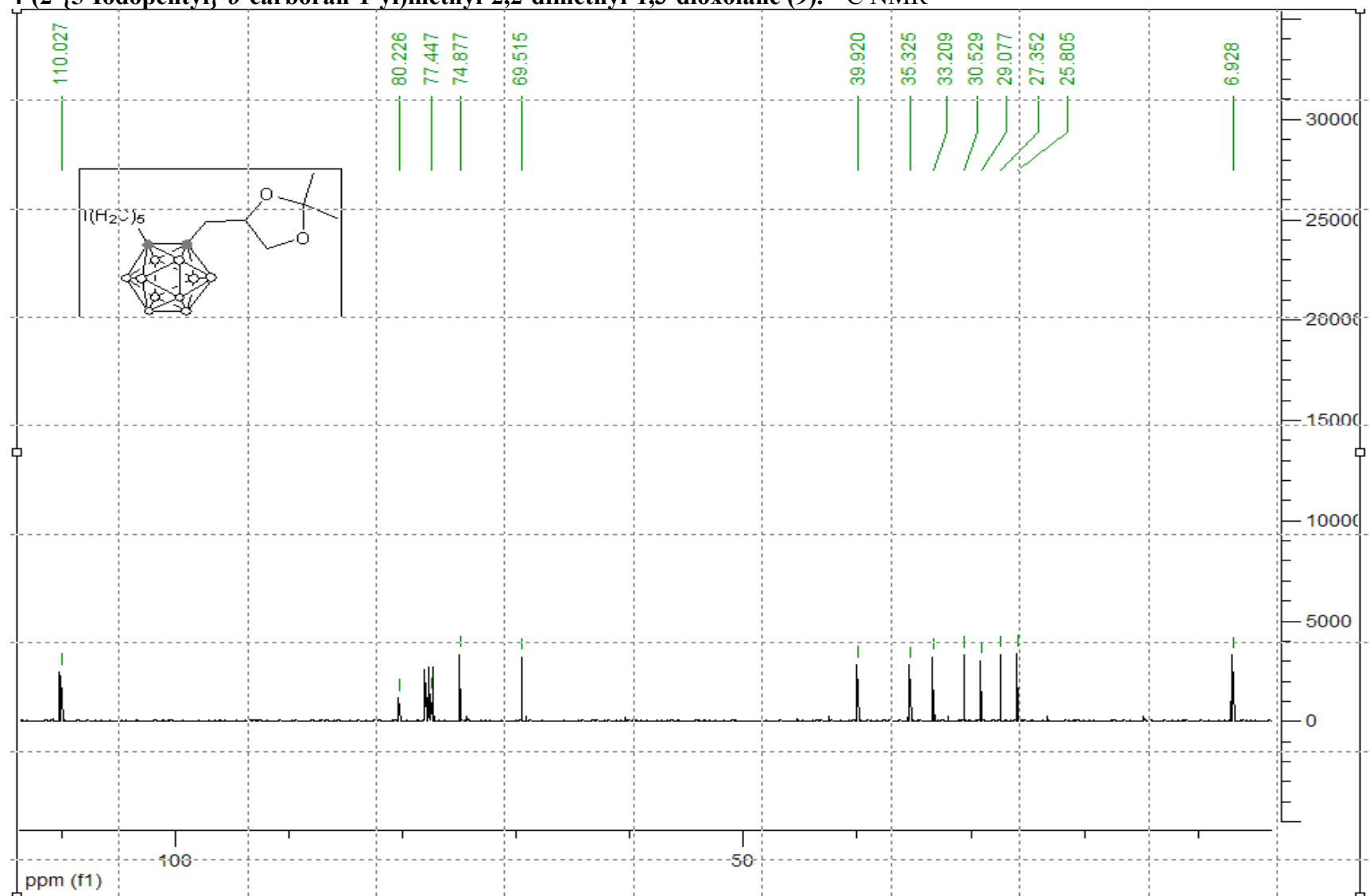
3-(5-*o*-Carboran-1-yl)pentan-1-ylthymidine (1). HR-ESI-MS: found: m/z 477.3546.



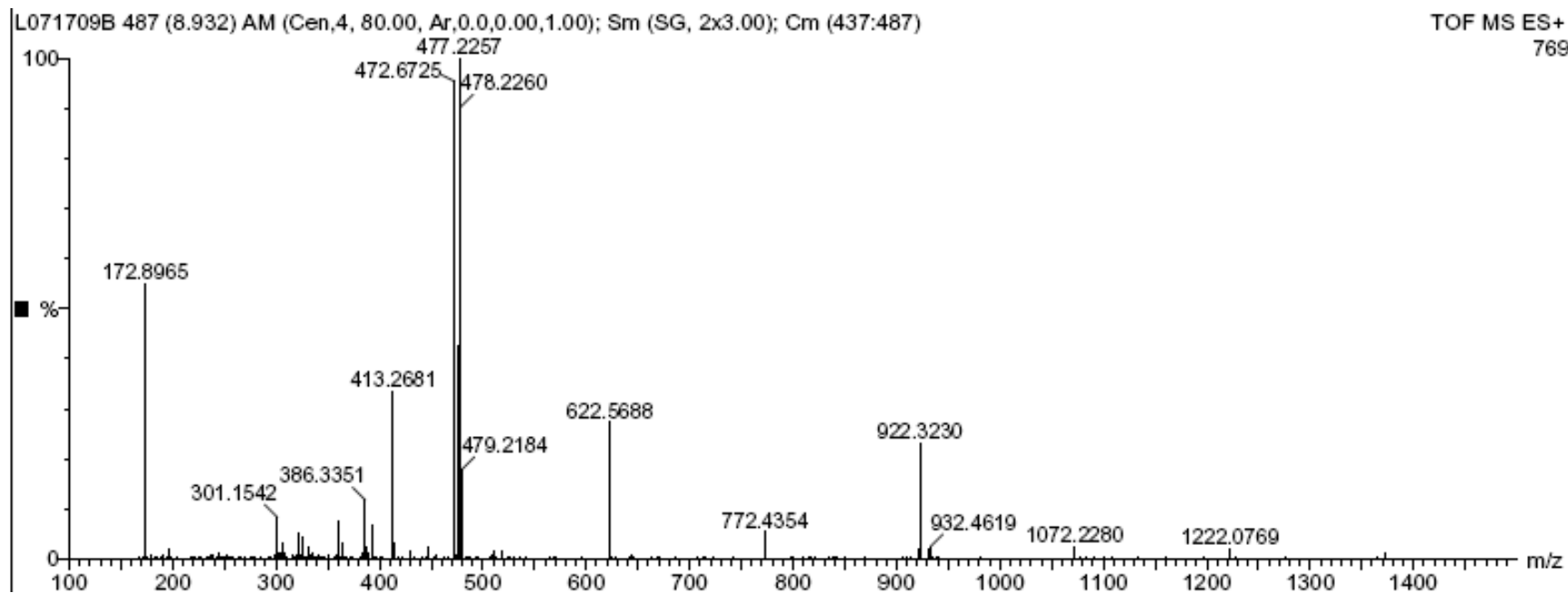
4-(2-{5-Iodopentyl}-*o*-carboran-1-yl)methyl-2,2-dimethyl-1,3-dioxolane (9). ^1H NMR



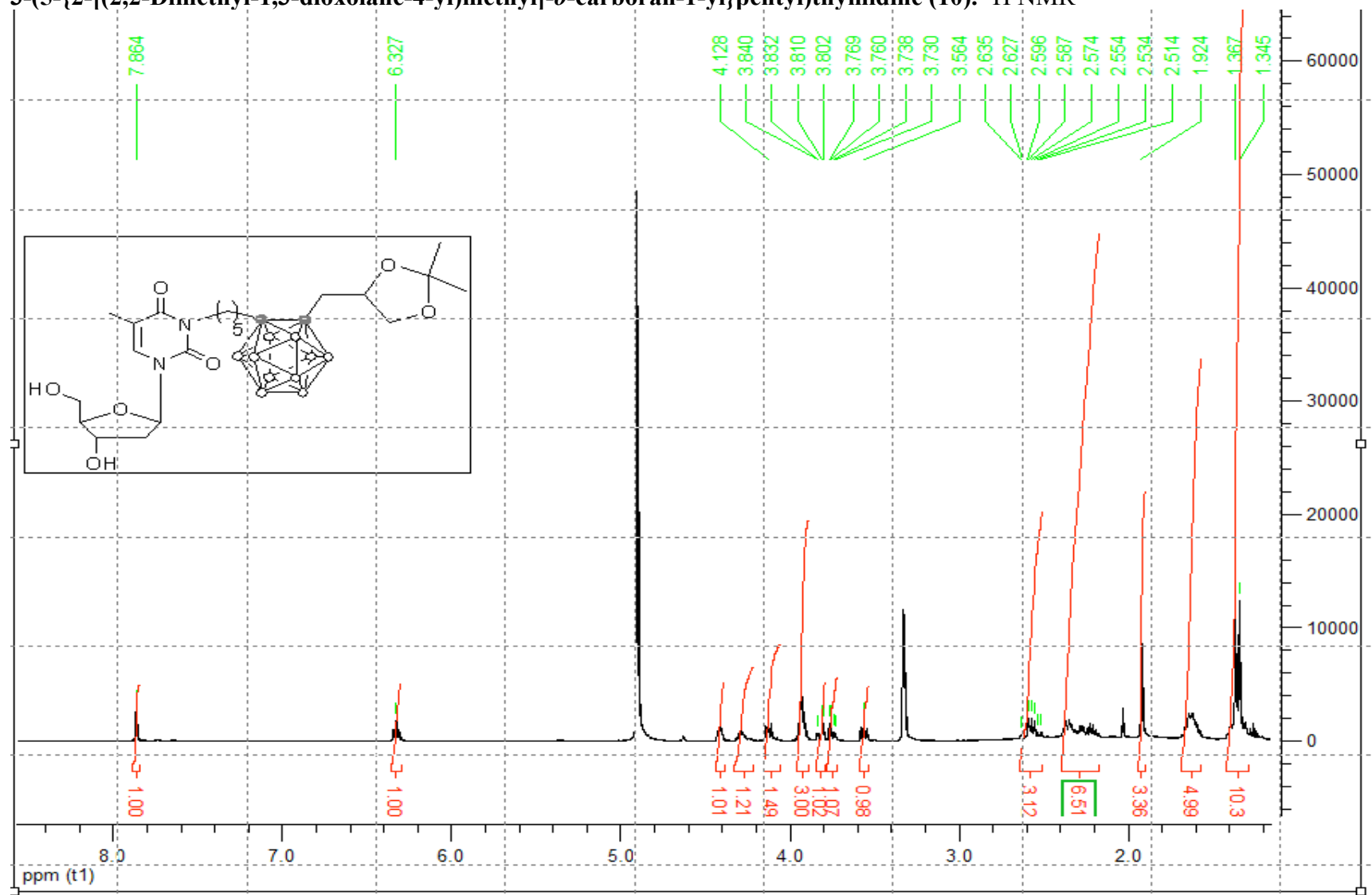
4-(2-{5-Iodopentyl}-*o*-carboran-1-yl)methyl-2,2-dimethyl-1,3-dioxolane (9). ^{13}C NMR



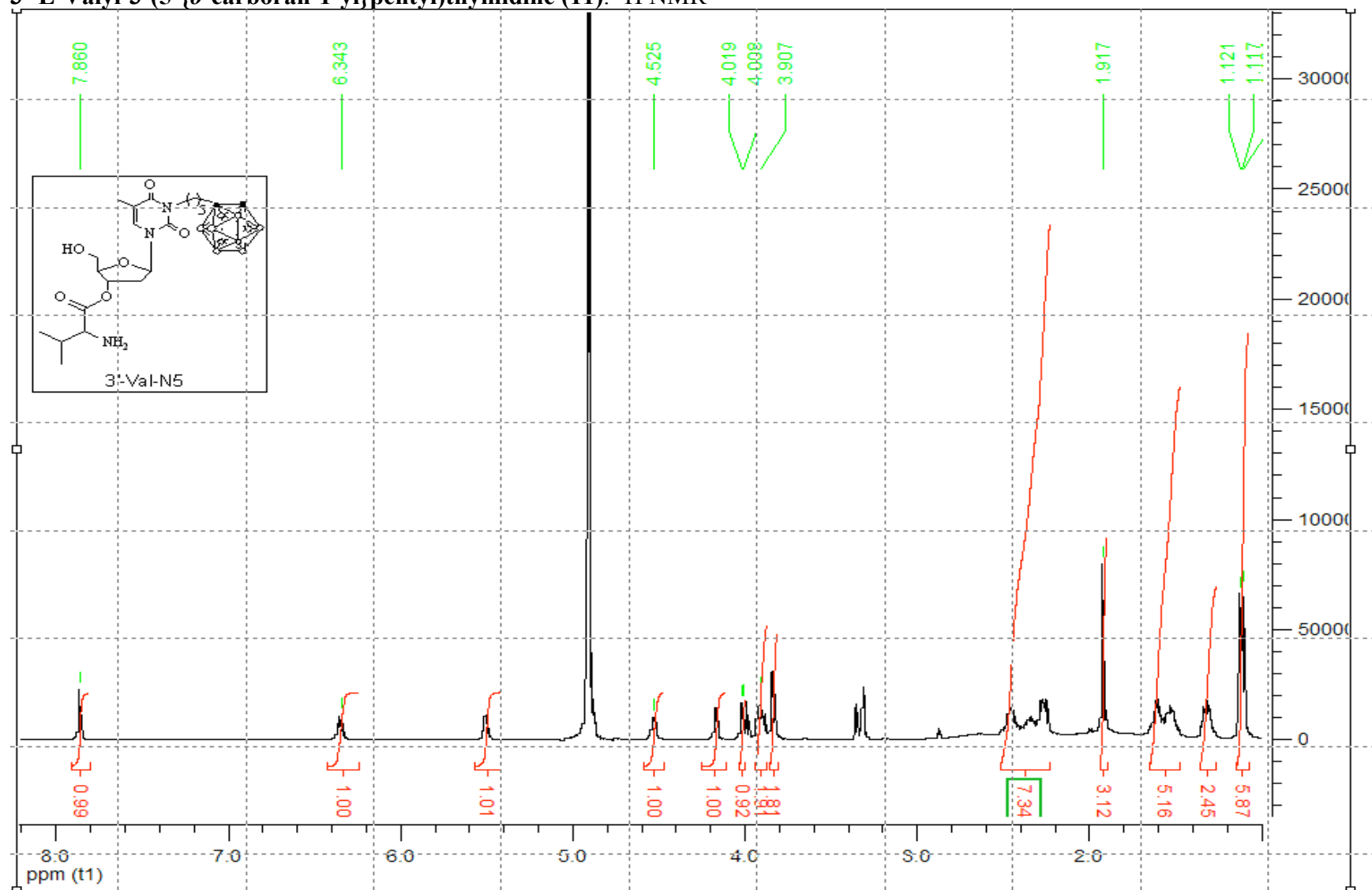
4-(2-{5-Iodopentyl}-*o*-carboran-1-yl)methyl-2,2-dimethyl-1,3-dioxolane (9). HR-ESI-MS: found: m/z 477.2257.



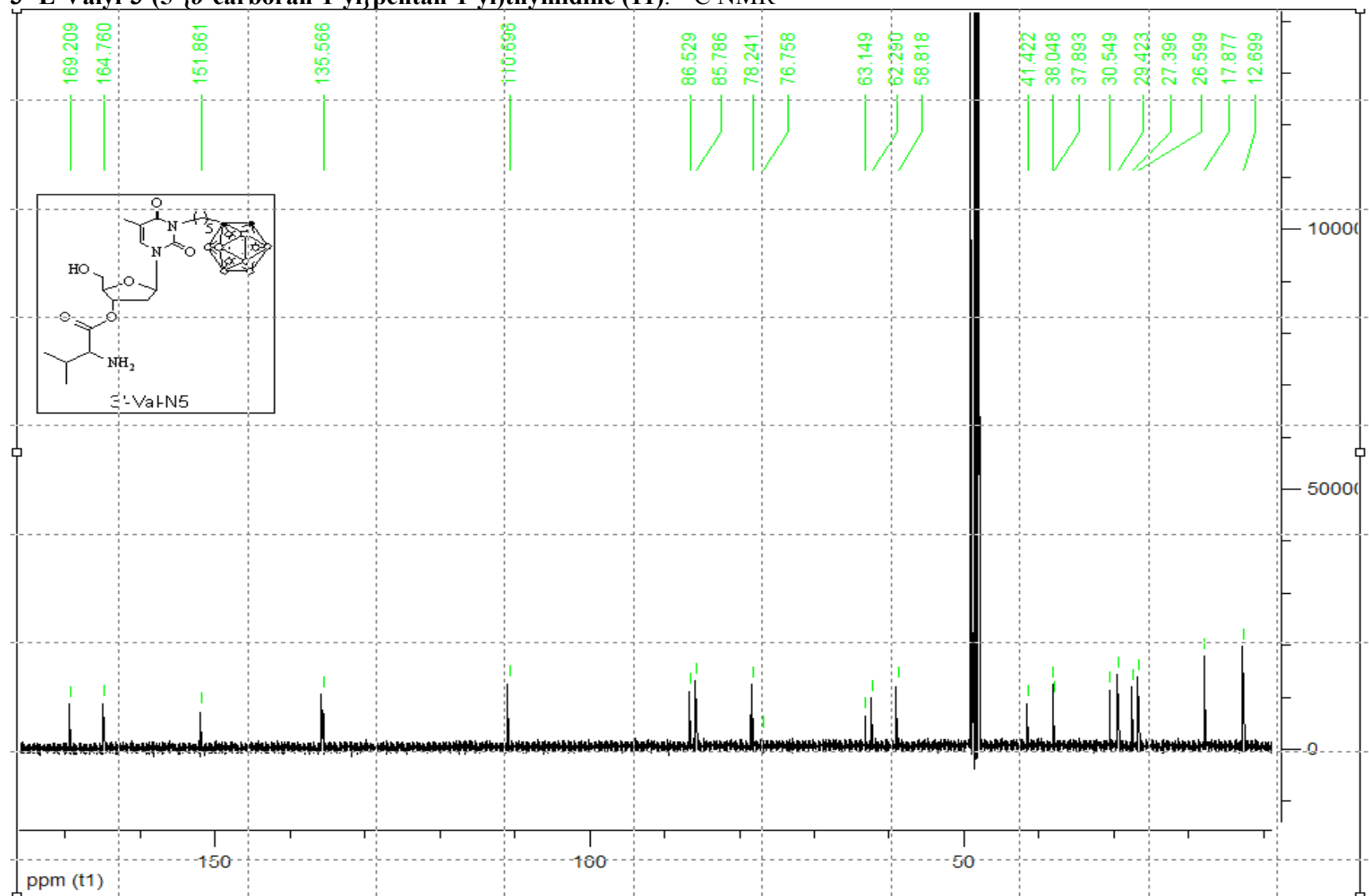
3-(5-{2-[(2,2-Dimethyl-1,3-dioxolane-4-yl)methyl]-*o*-carboran-1-yl}pentyl)thymidine (10). ¹H NMR



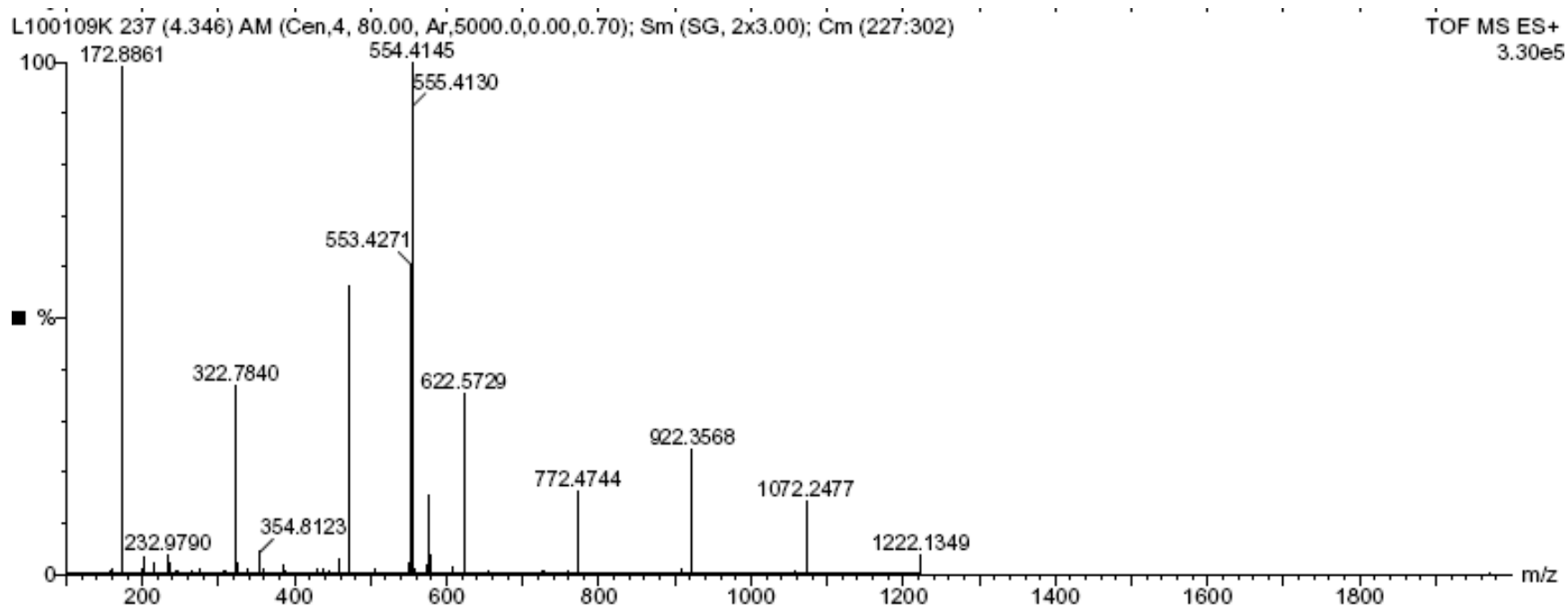
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine (11). ¹H NMR



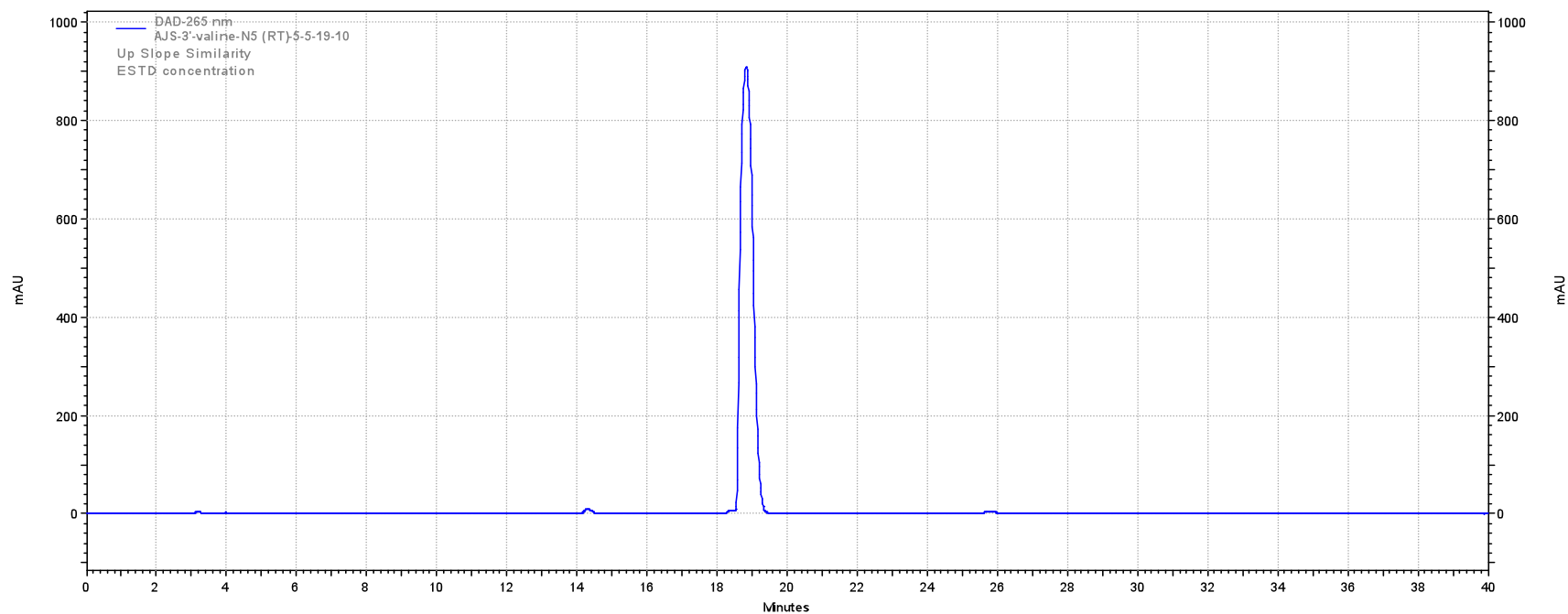
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (11). ¹³C NMR



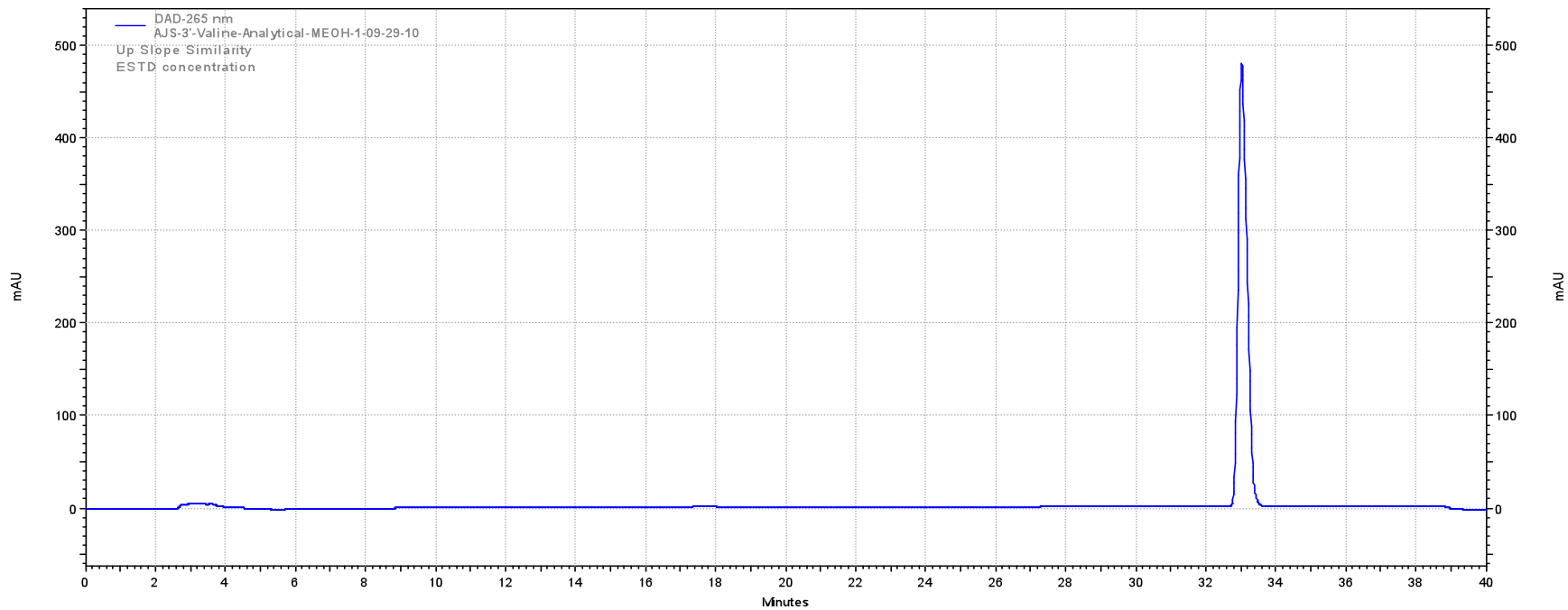
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (11). HR-ESI-MS: found: m/z 554.4145.



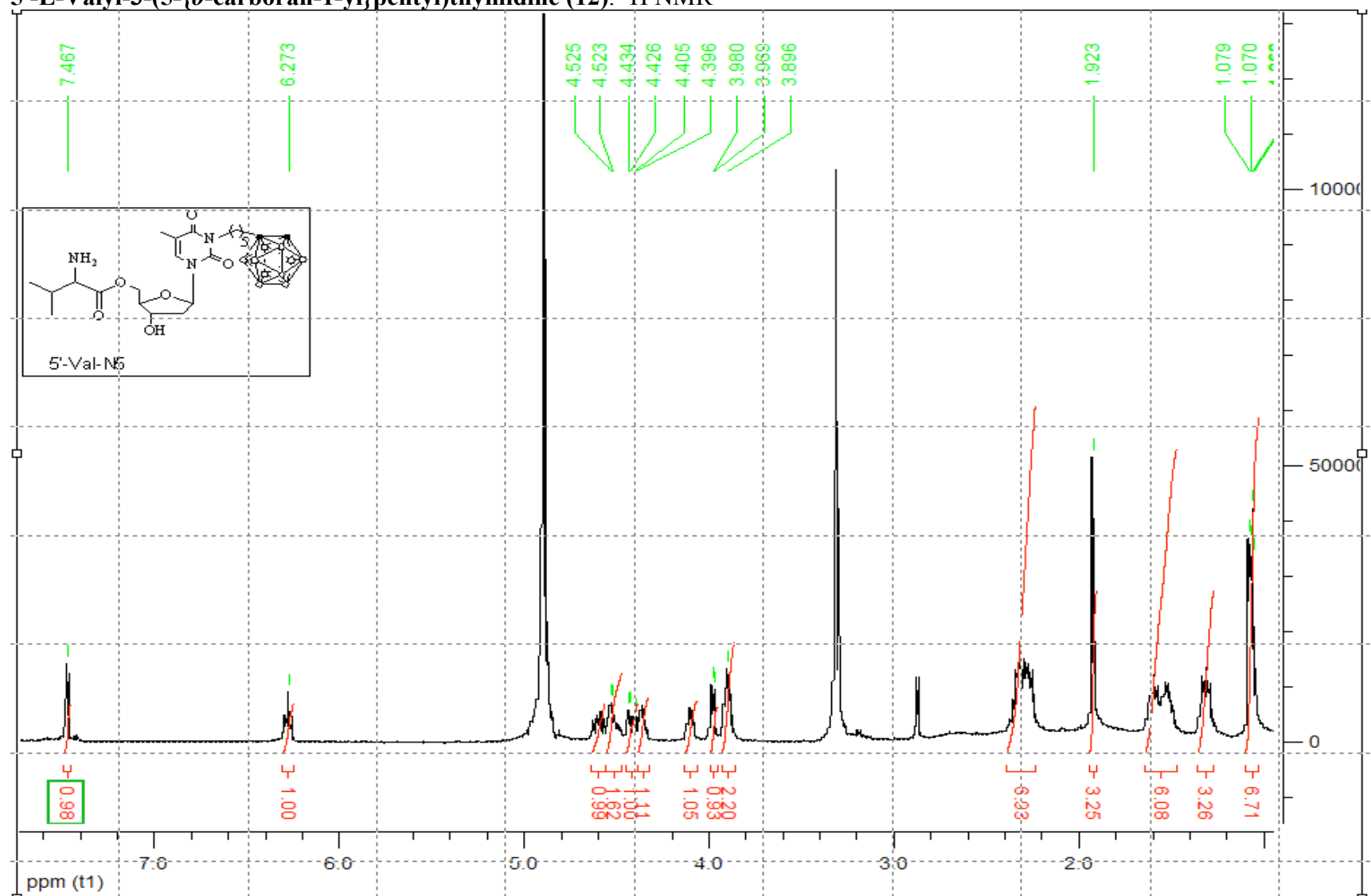
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (11). HPLC chromatogram (method A1, Table 3 in manuscript), retention time: 18.82 min.



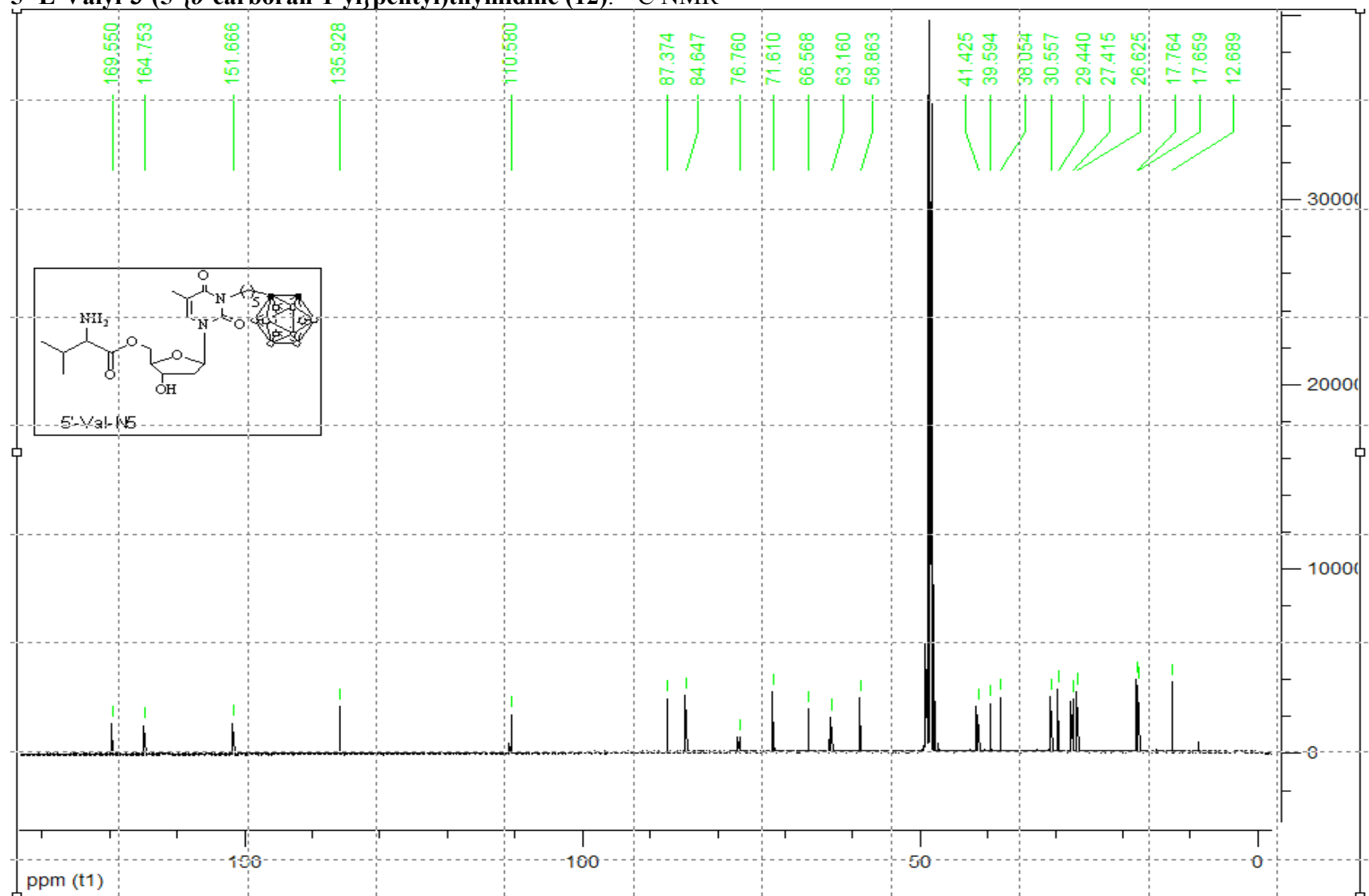
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (11). HPLC chromatogram (method B1, Table 3 in manuscript), retention time: 33.03 min.



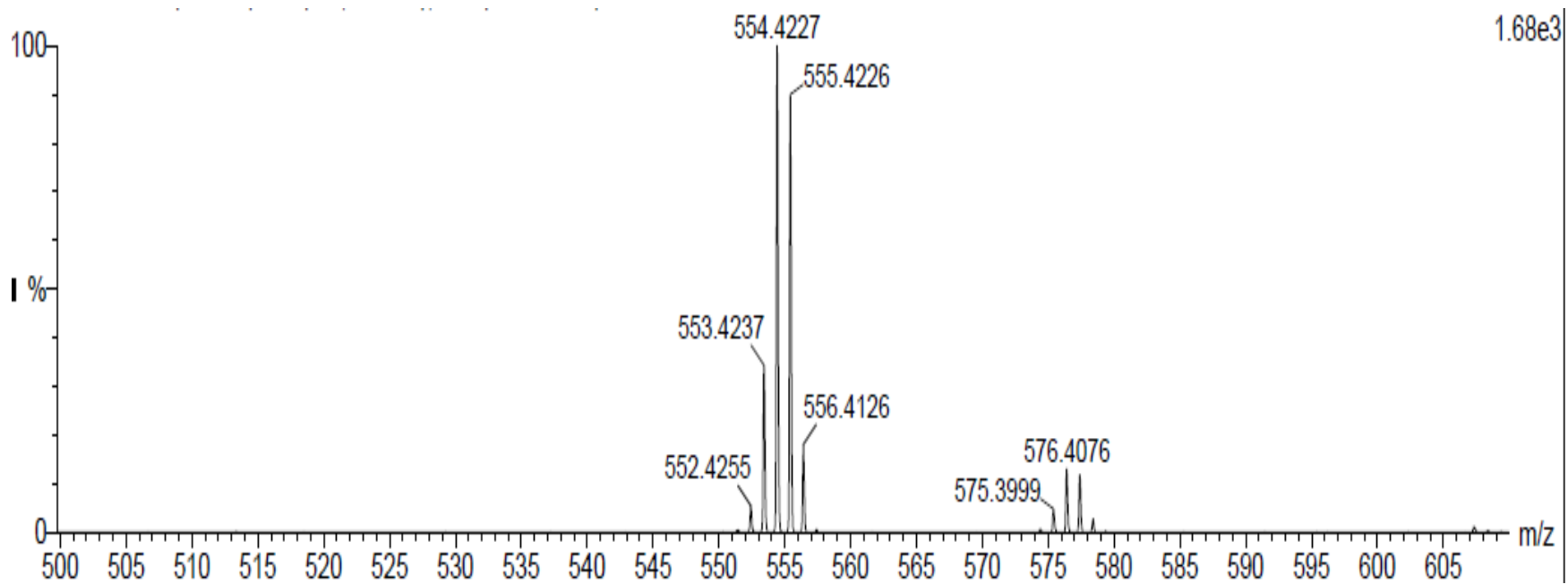
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine (12). ¹H NMR



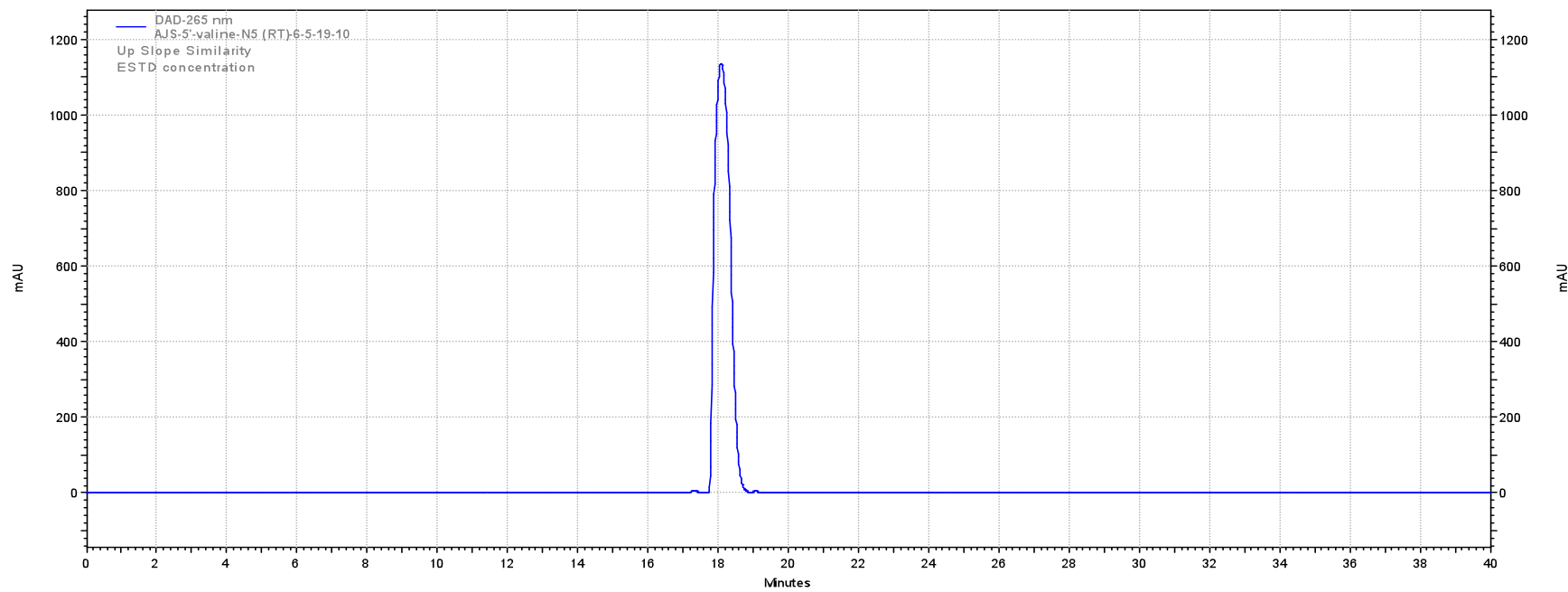
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine (12). ¹³C NMR



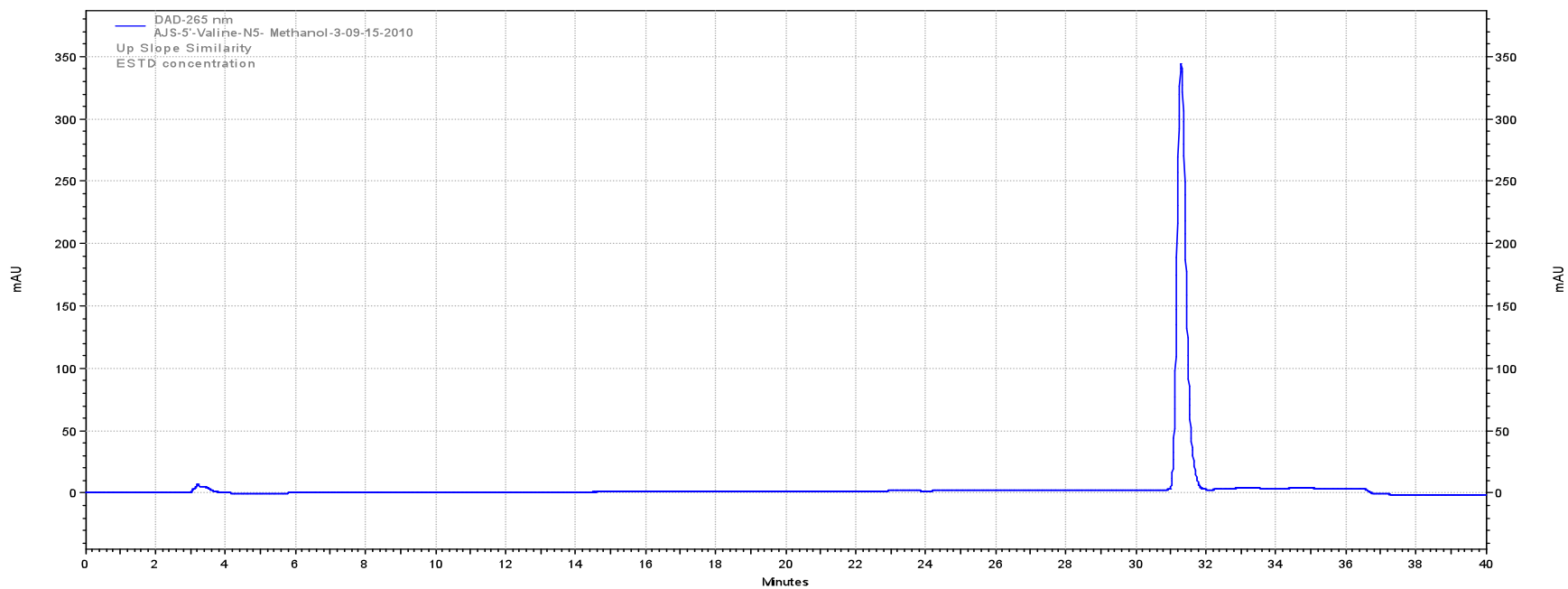
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12). HR-ESI-MS: found: m/z 554.4227, and 576.4076.



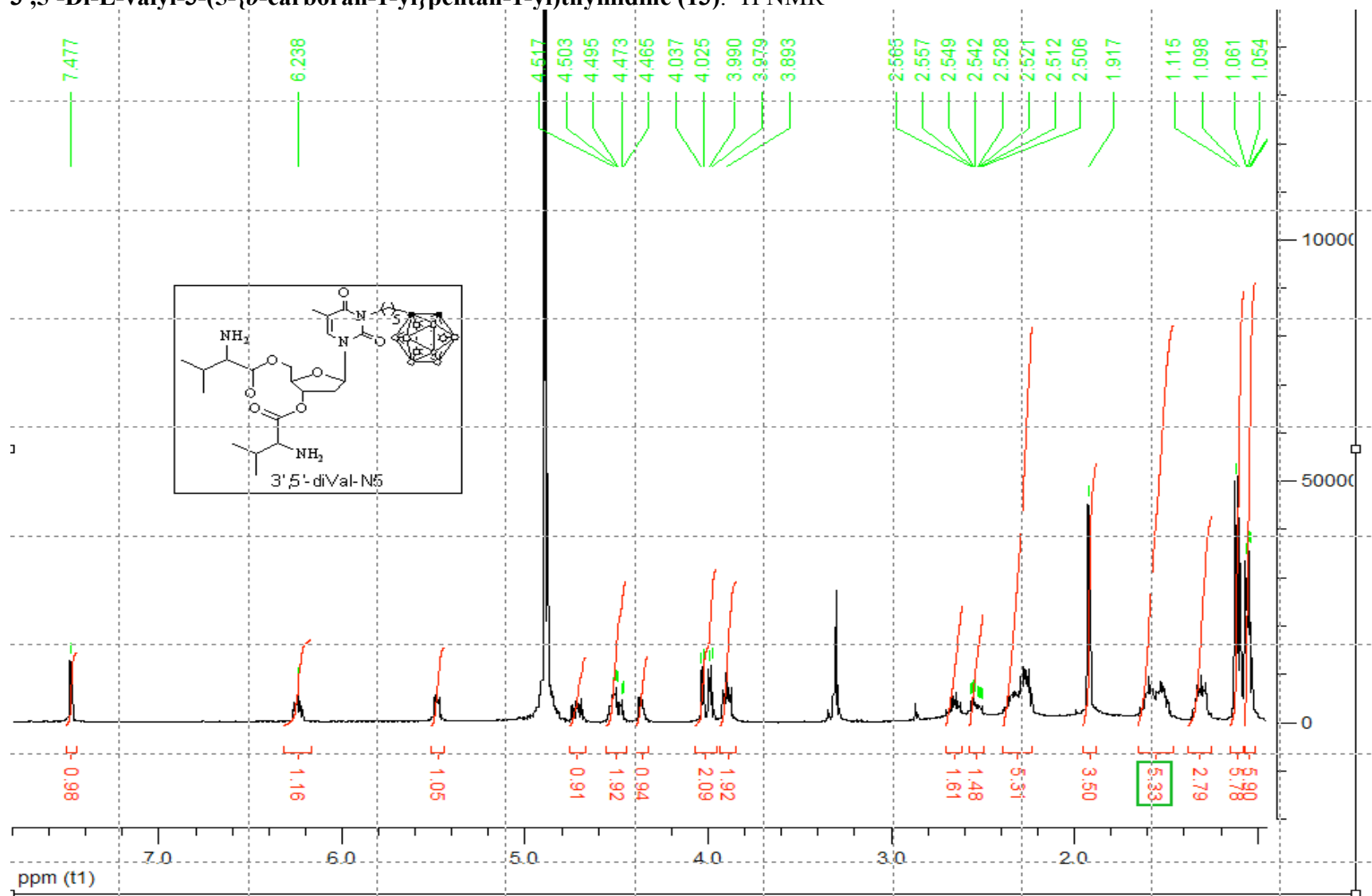
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12). HPLC chromatogram (method **A1**, Table 3 in manuscript), retention time: 18.09 min.



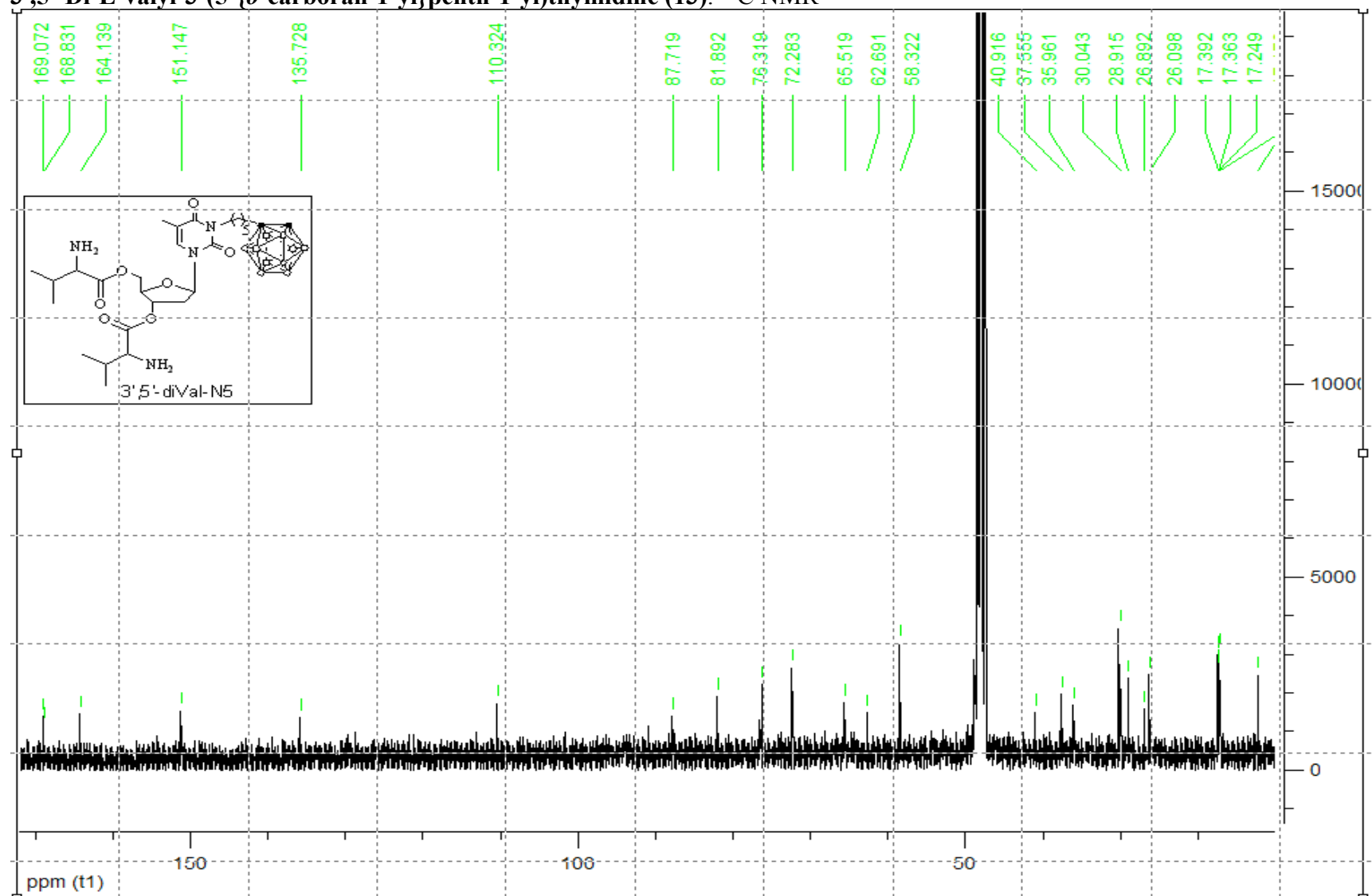
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12). HPLC chromatogram (method B1, Table 3 in manuscript), retention time: 31.29 min.



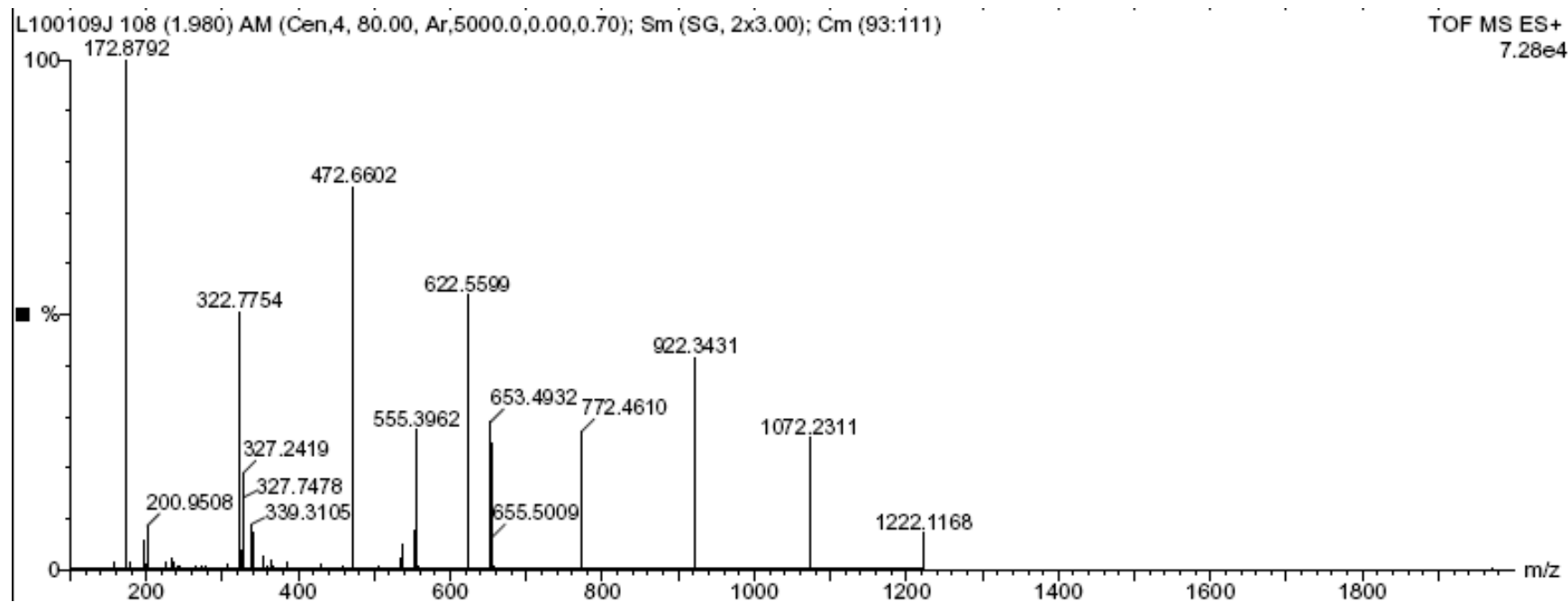
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (13). ¹H NMR



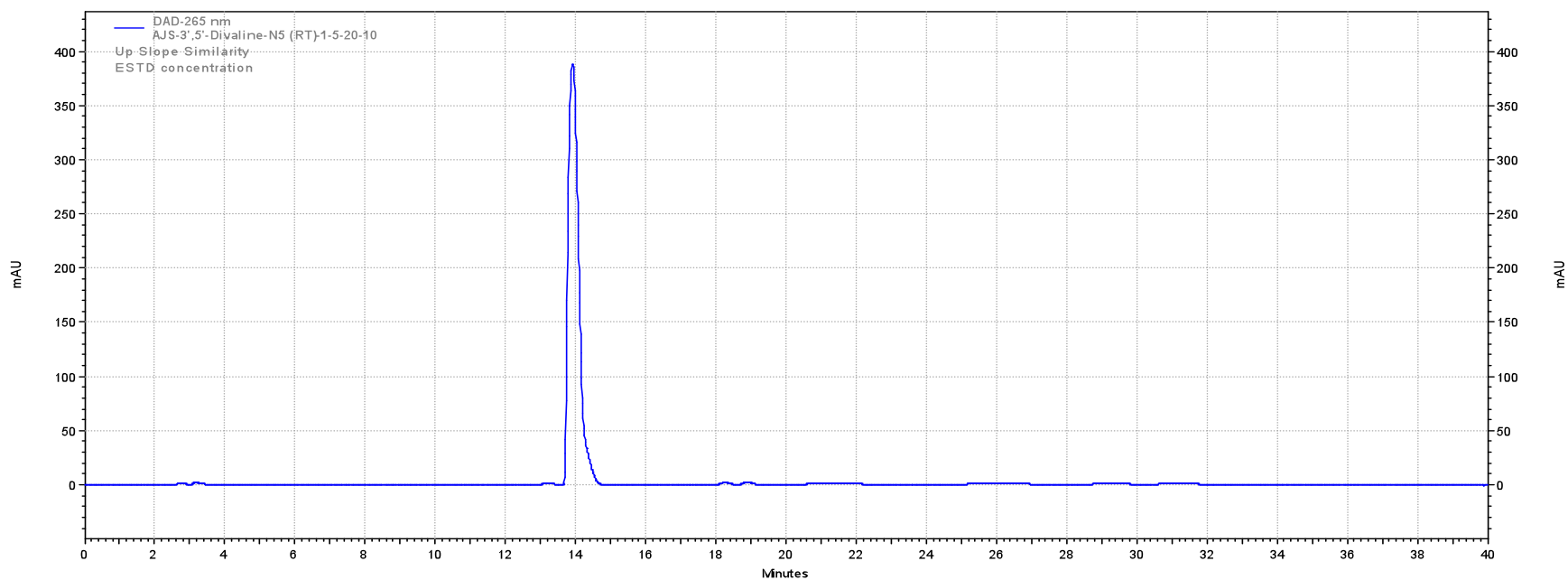
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentn-1-yl)thymidine (13). ¹³C NMR



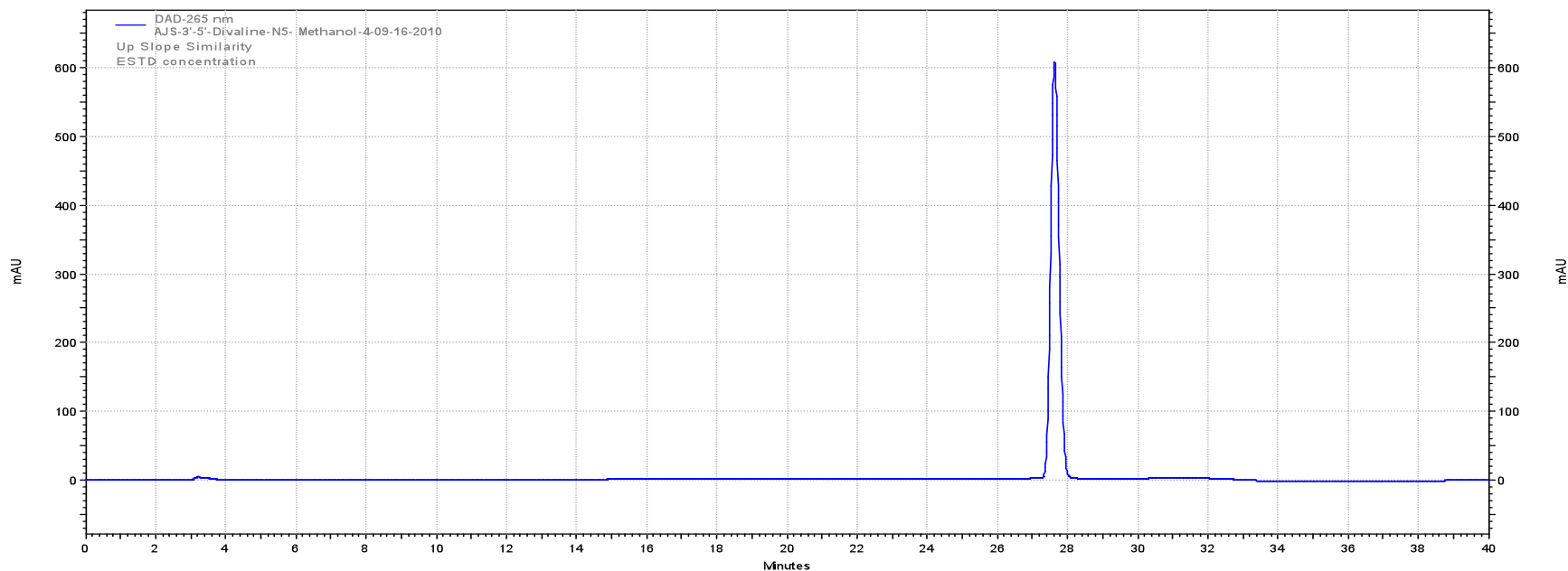
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (13). HR-ESI-MS: found: m/z 653.4932.



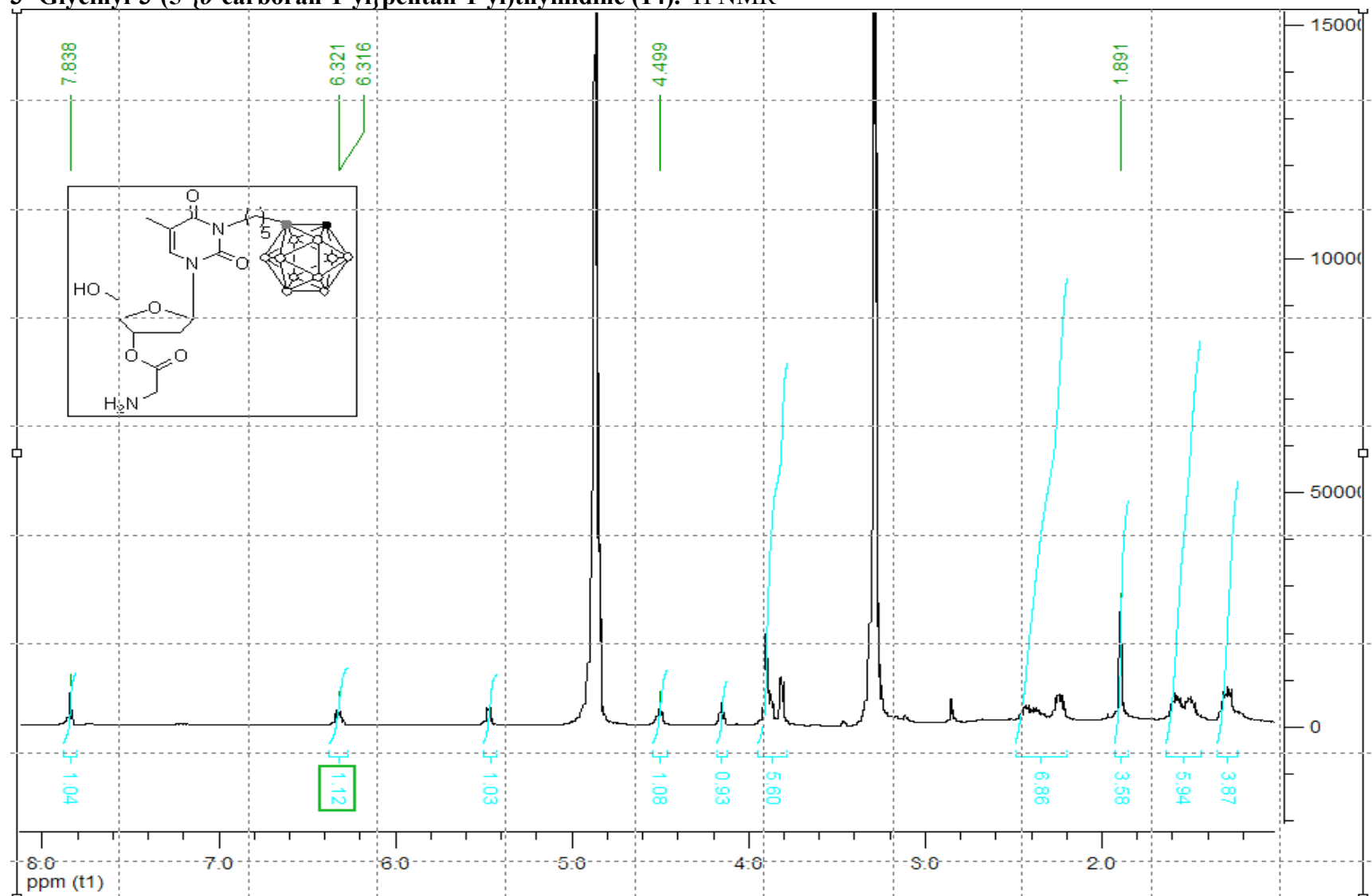
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (13). HPLC chromatogram (method A1, Table 3 in manuscript), retention time (13.91).



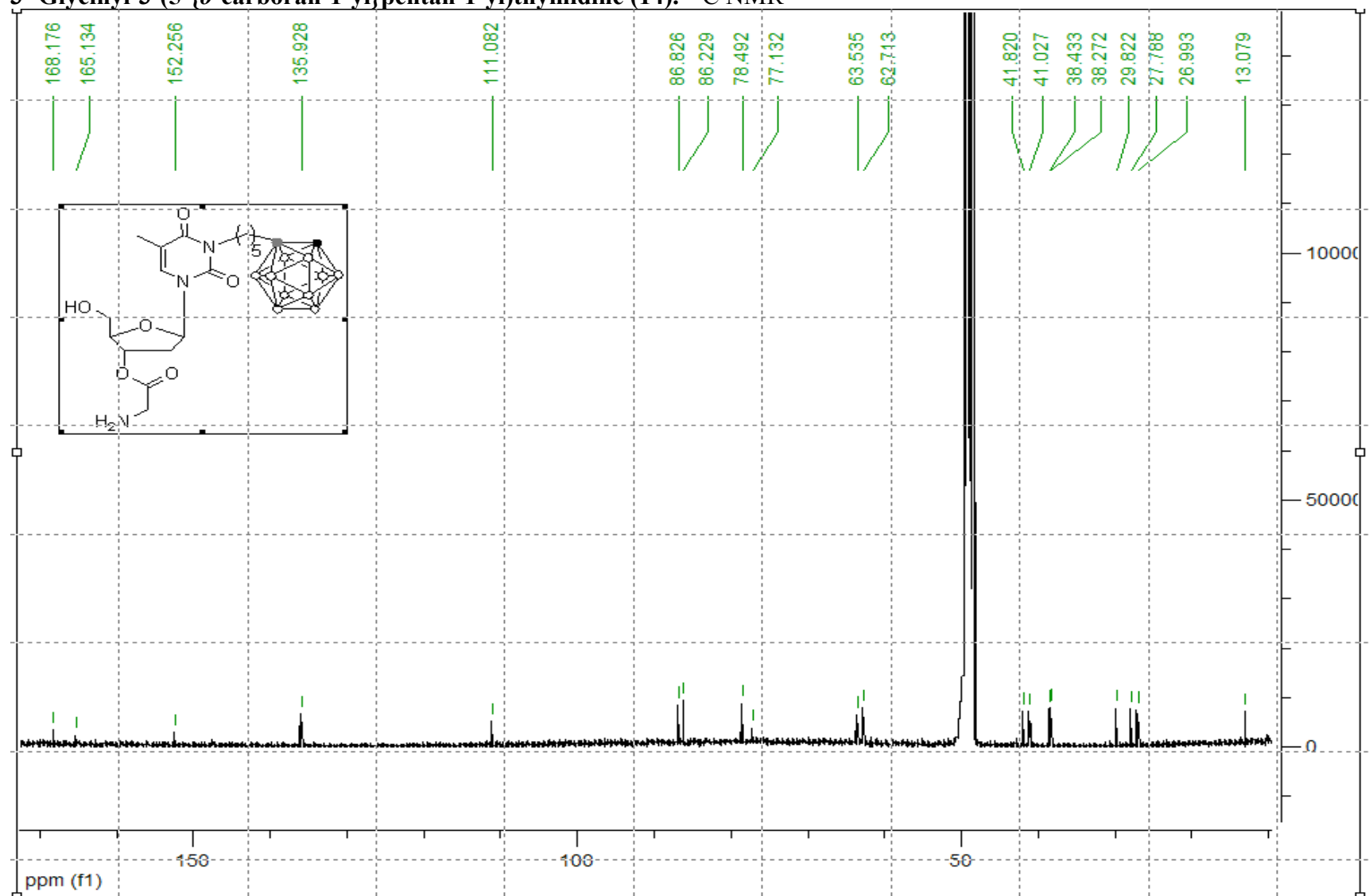
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (13). HPLC chromatogram (method B1, Table 3 in manuscript), retention time: 27.63 min.



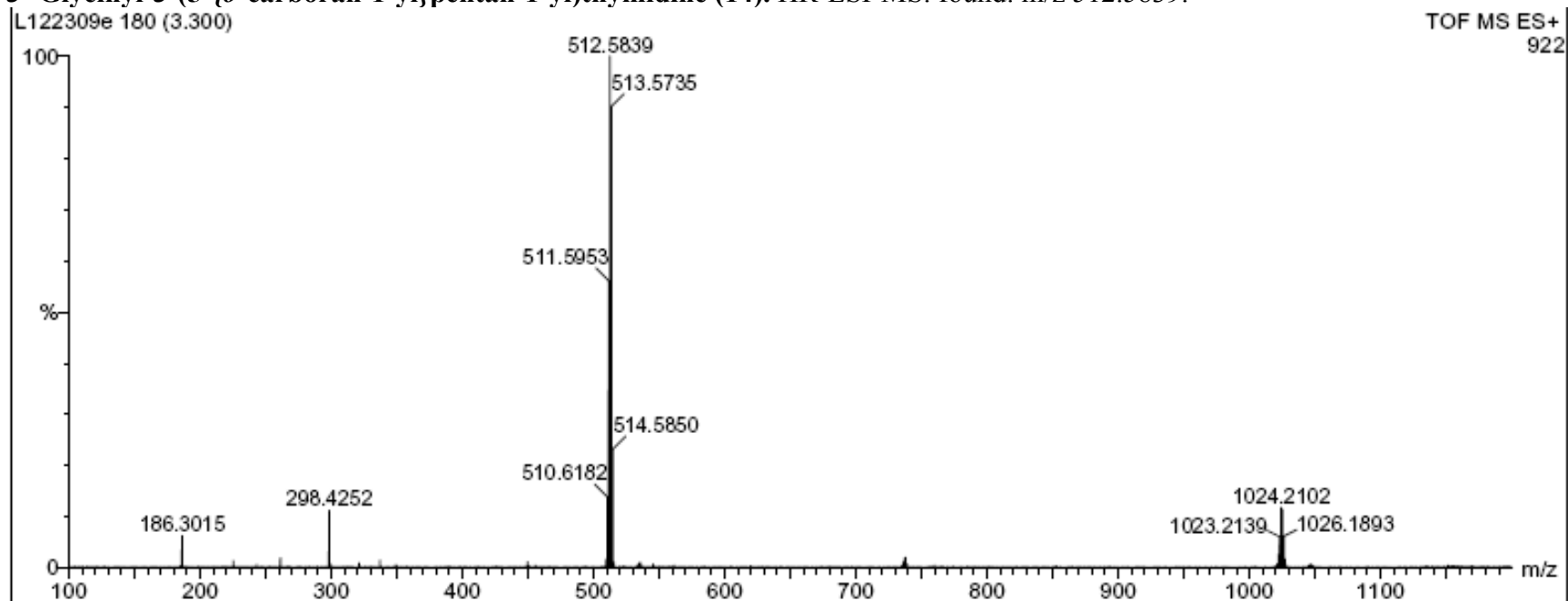
3'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14). ¹H NMR



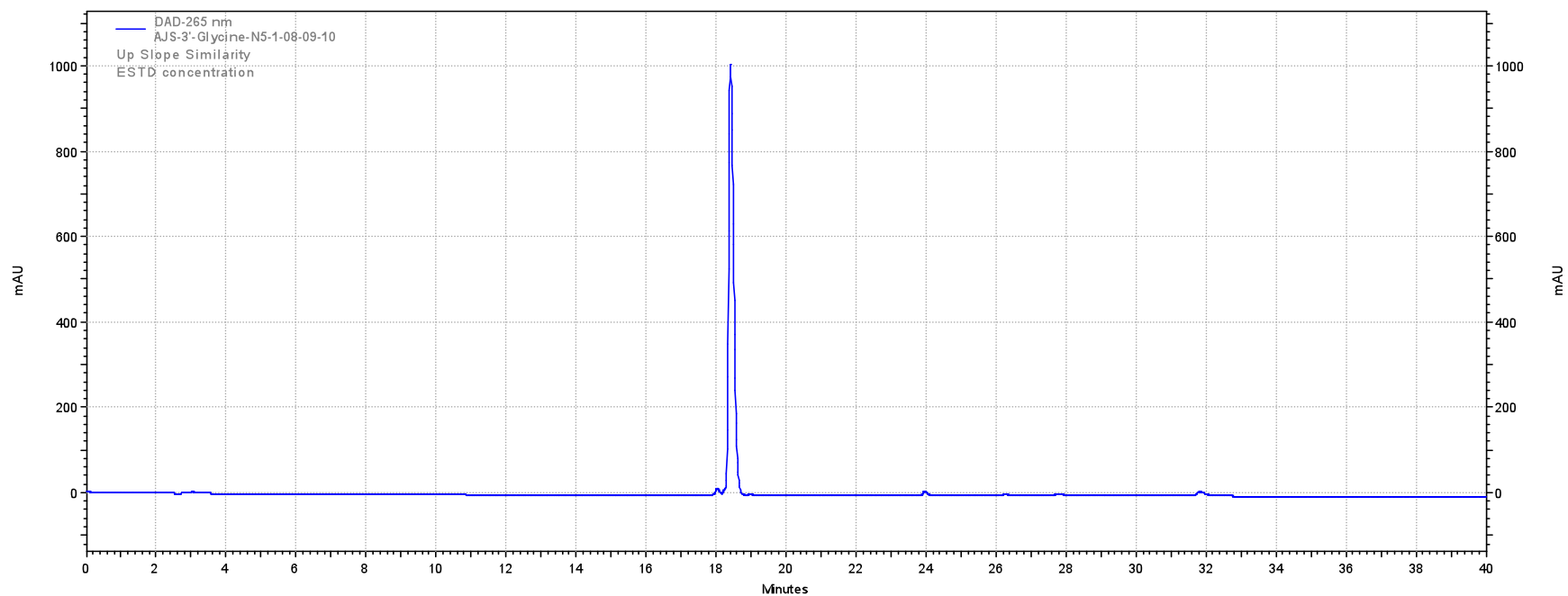
3'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14). ¹³C NMR



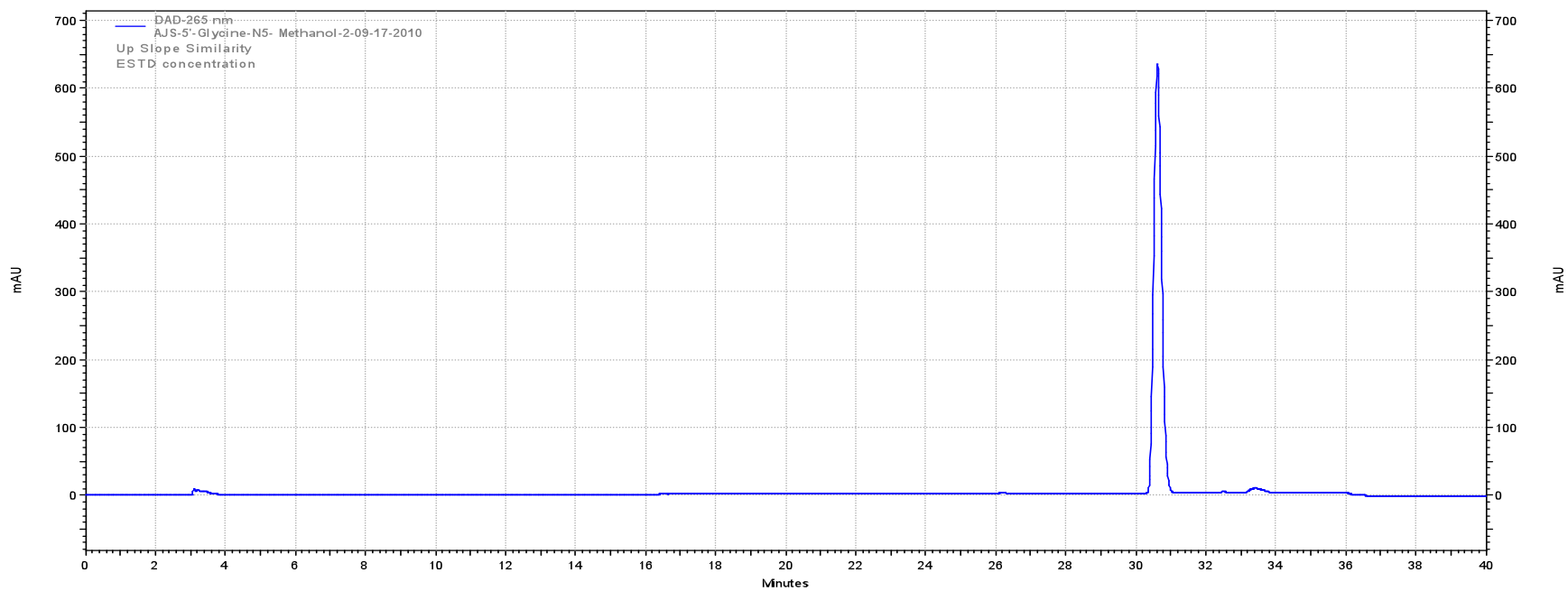
3'-Glycynyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14). HR-ESI-MS: found: m/z 512.5839.



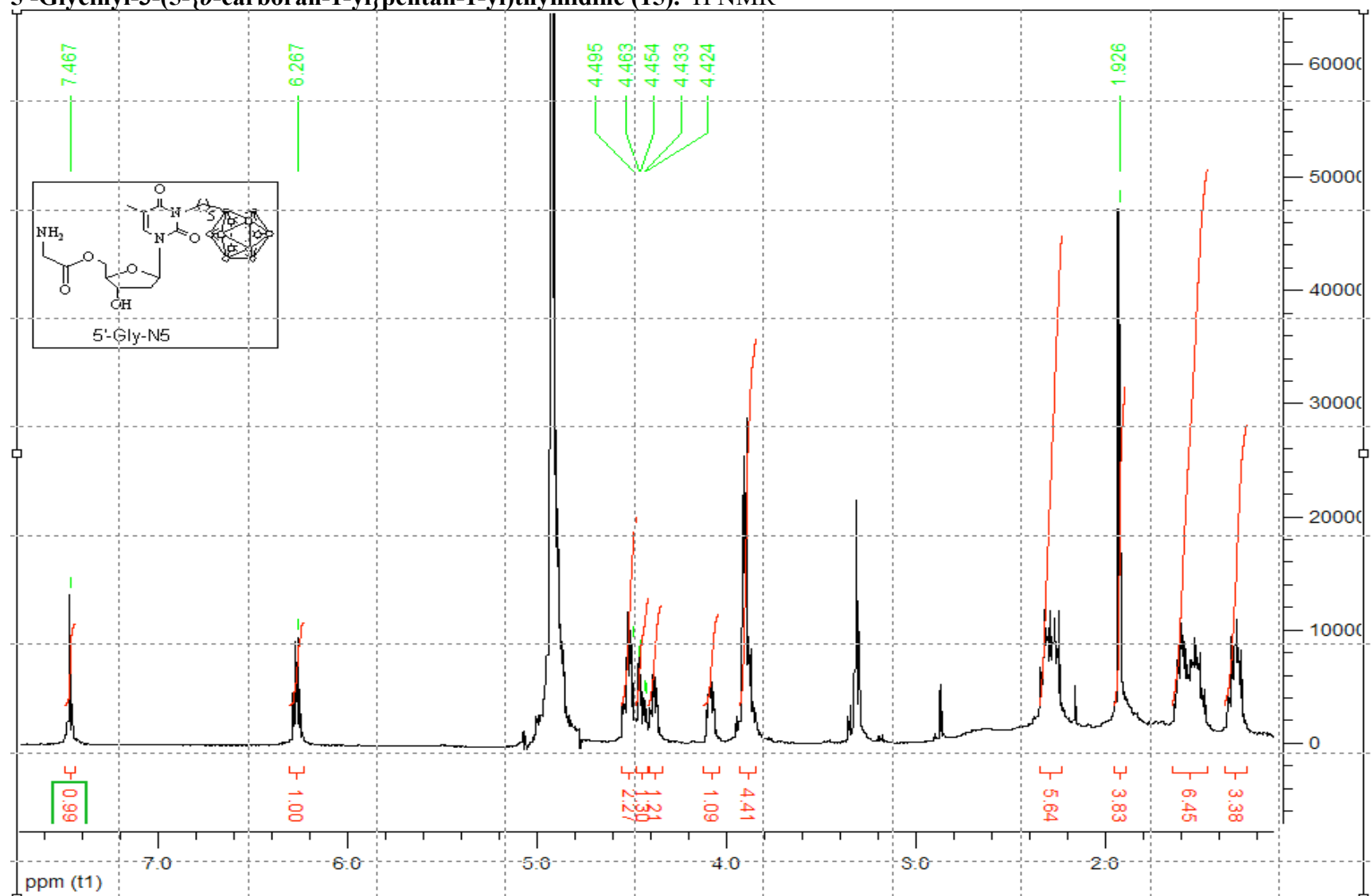
3'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14). HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 18.43 min.



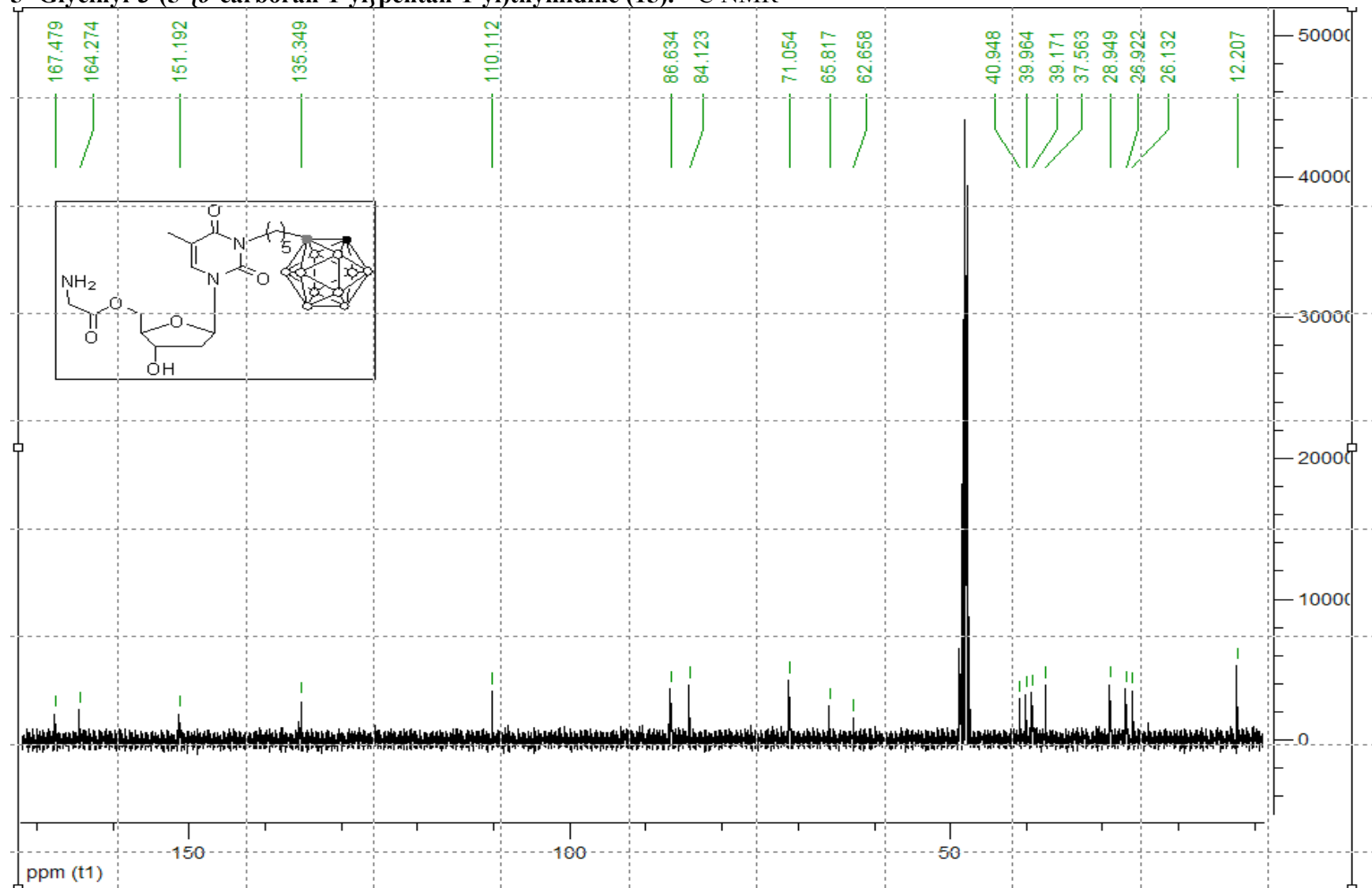
3'-Glyciny-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14). HPLC chromatogram (method B2, Table 3 in manuscript), retention time: 30.61min.



5'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (15). ¹H NMR



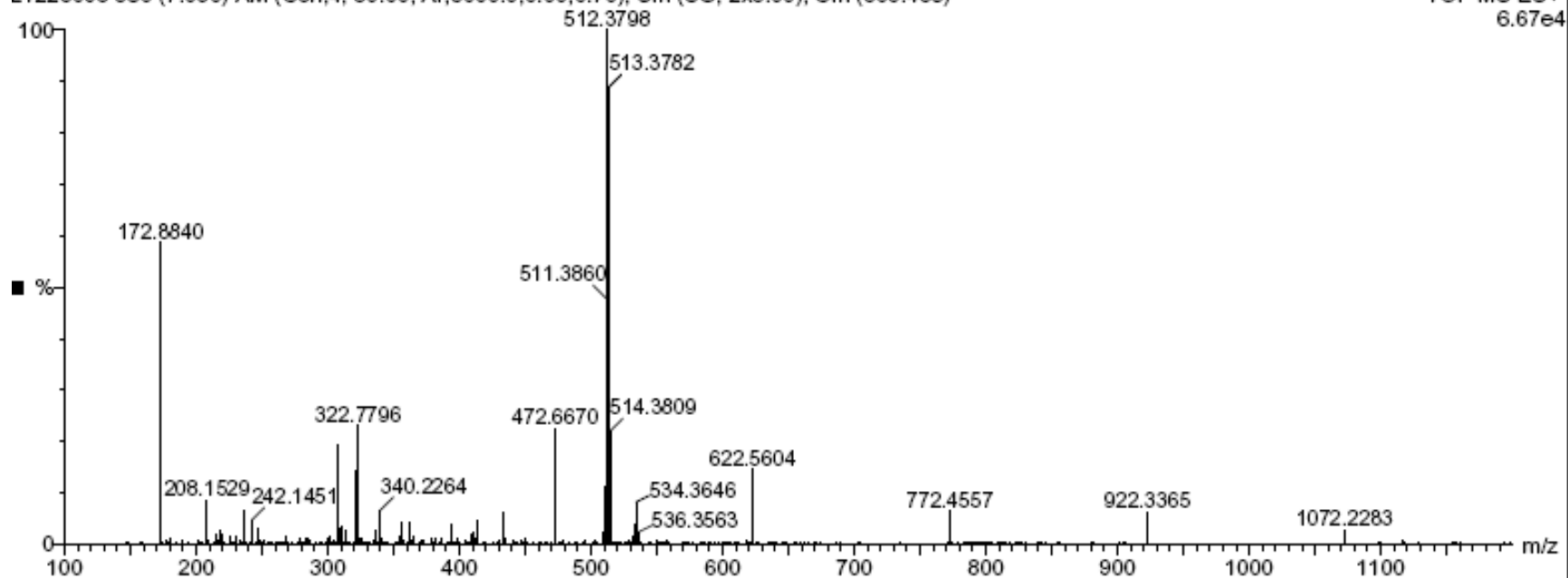
5'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (15). ¹³C NMR



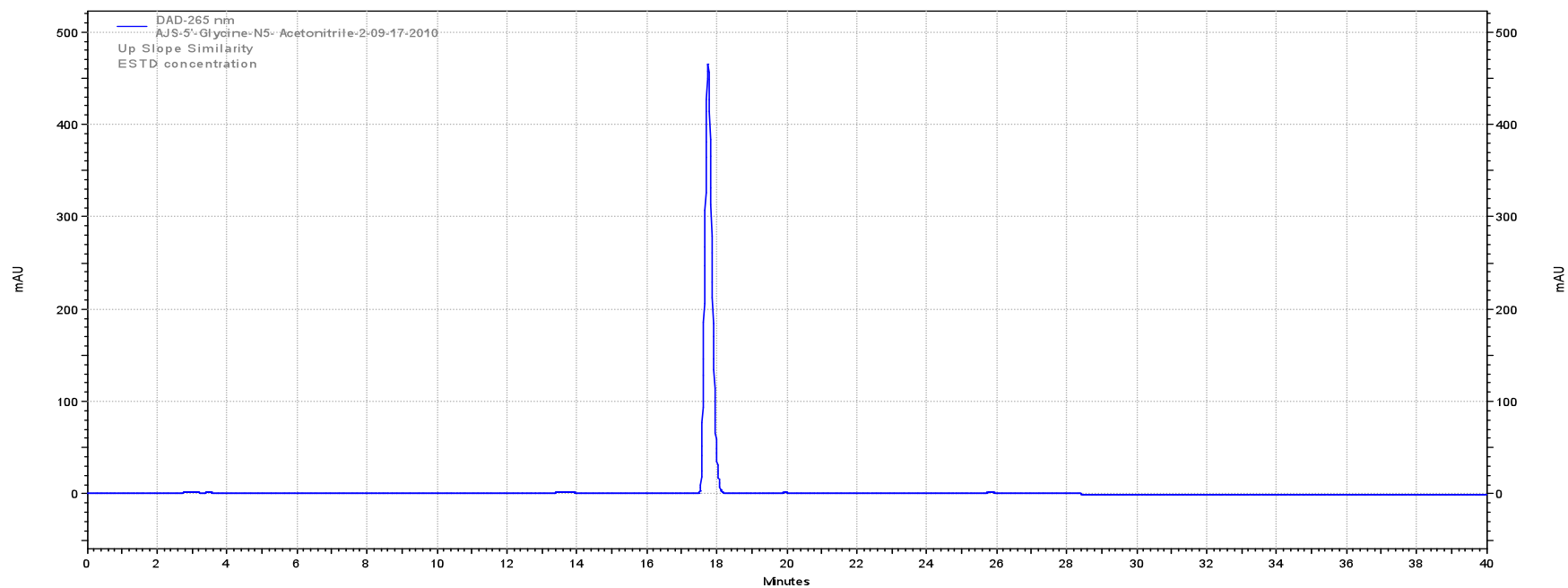
5'-Glycyl-3-(5-*o*-carboran-1-yl)pentan-1-yl)thymidine (15). HR-ESI-MS: found: m/z 512.3798.

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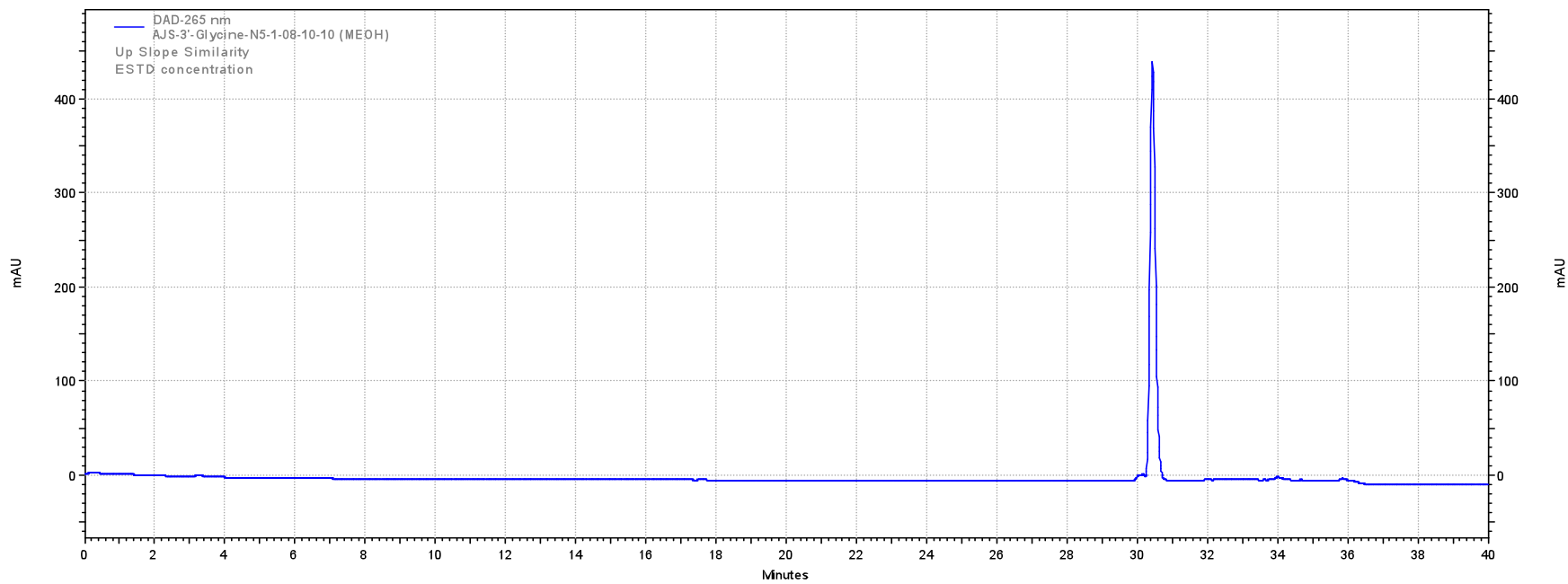
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6.67e4



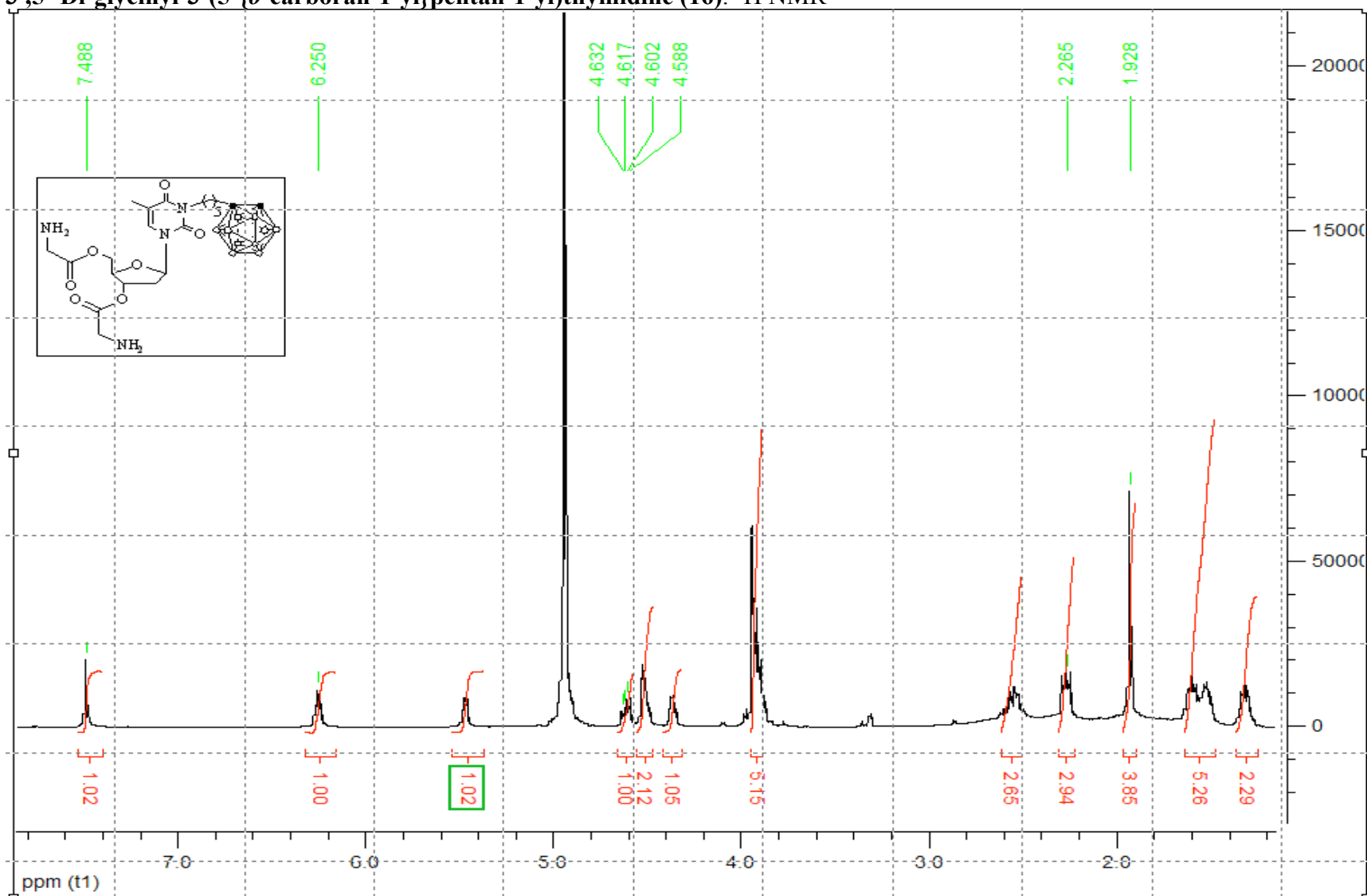
5'-Glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (15). HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 17.57 min.



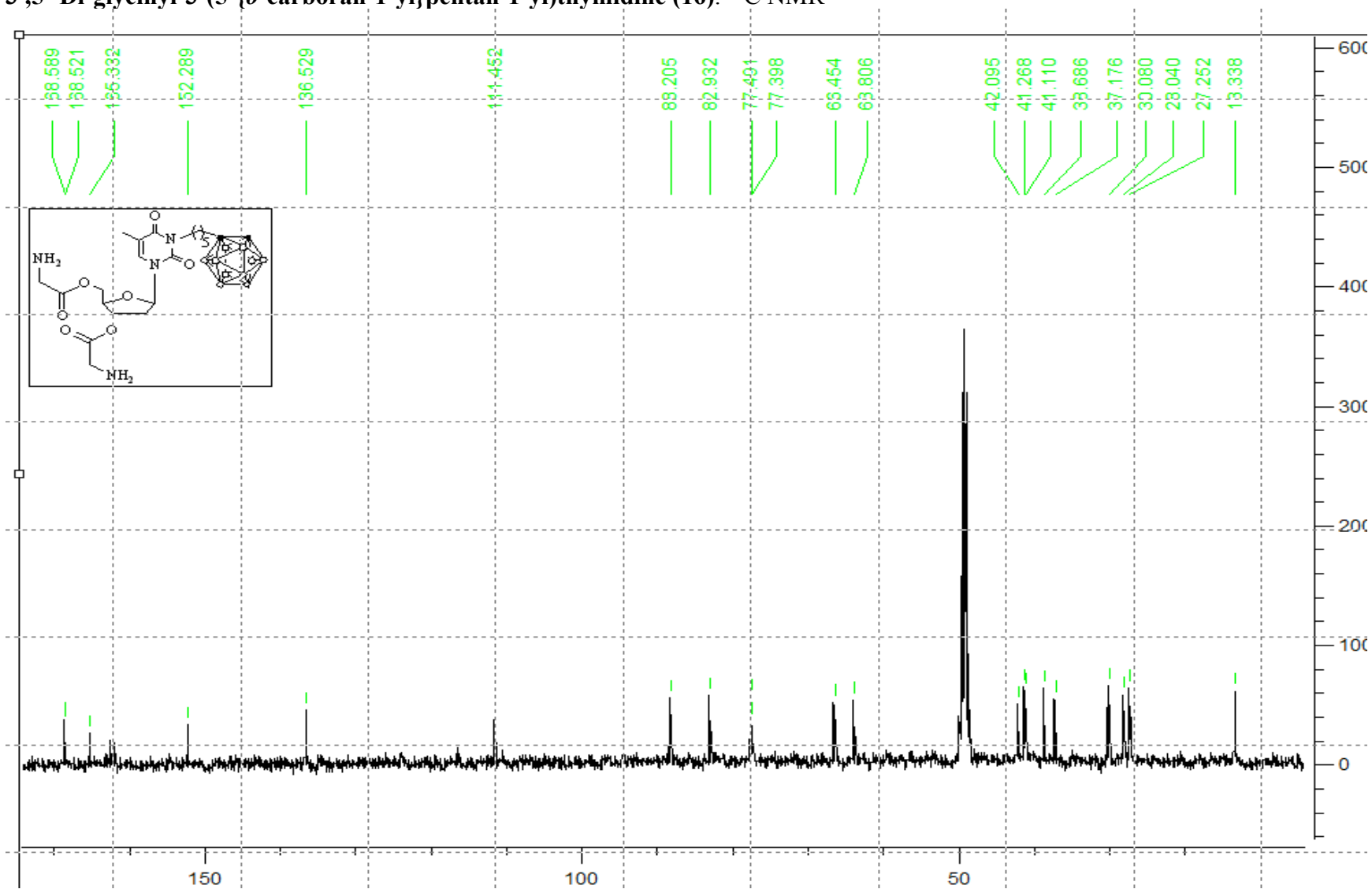
5'-Glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (15). HPLC chromatogram (method B2, Table 3 in manuscript), retention time: 30.40 min.



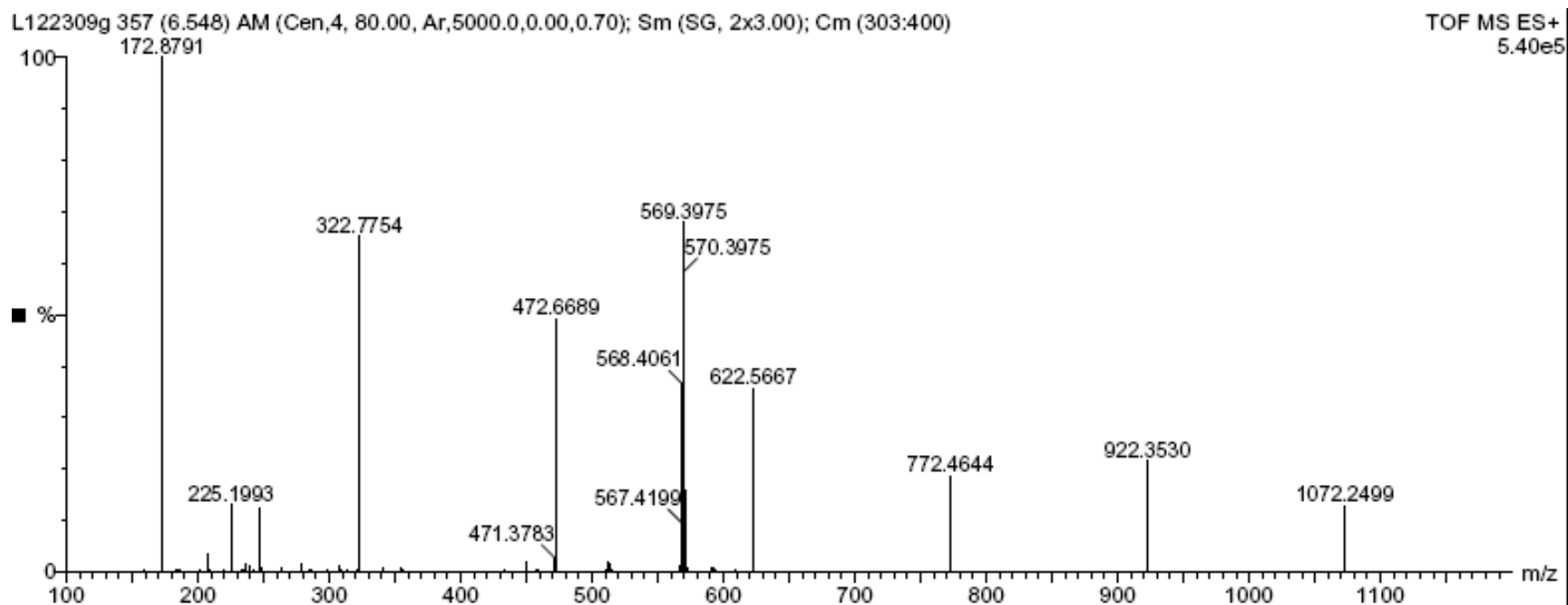
3',5'-Di-glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (16). ¹H NMR



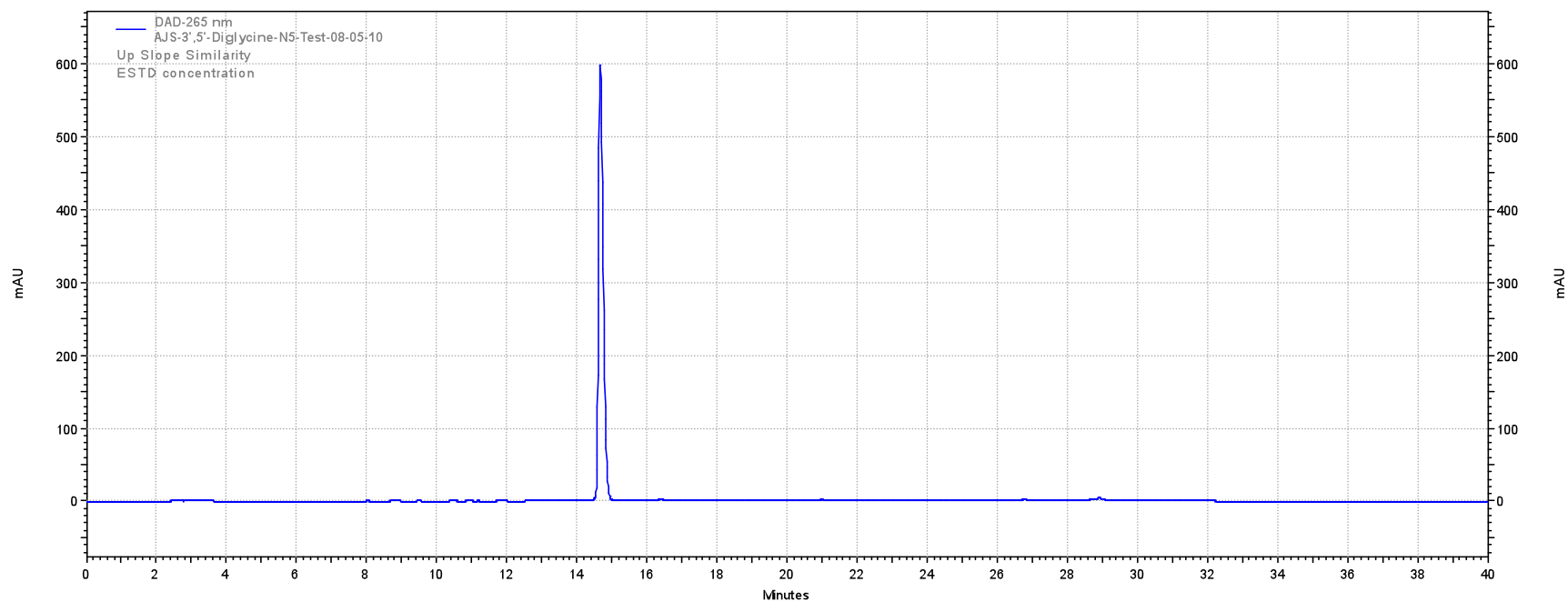
3',5'-Di-glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (16). ¹³C NMR



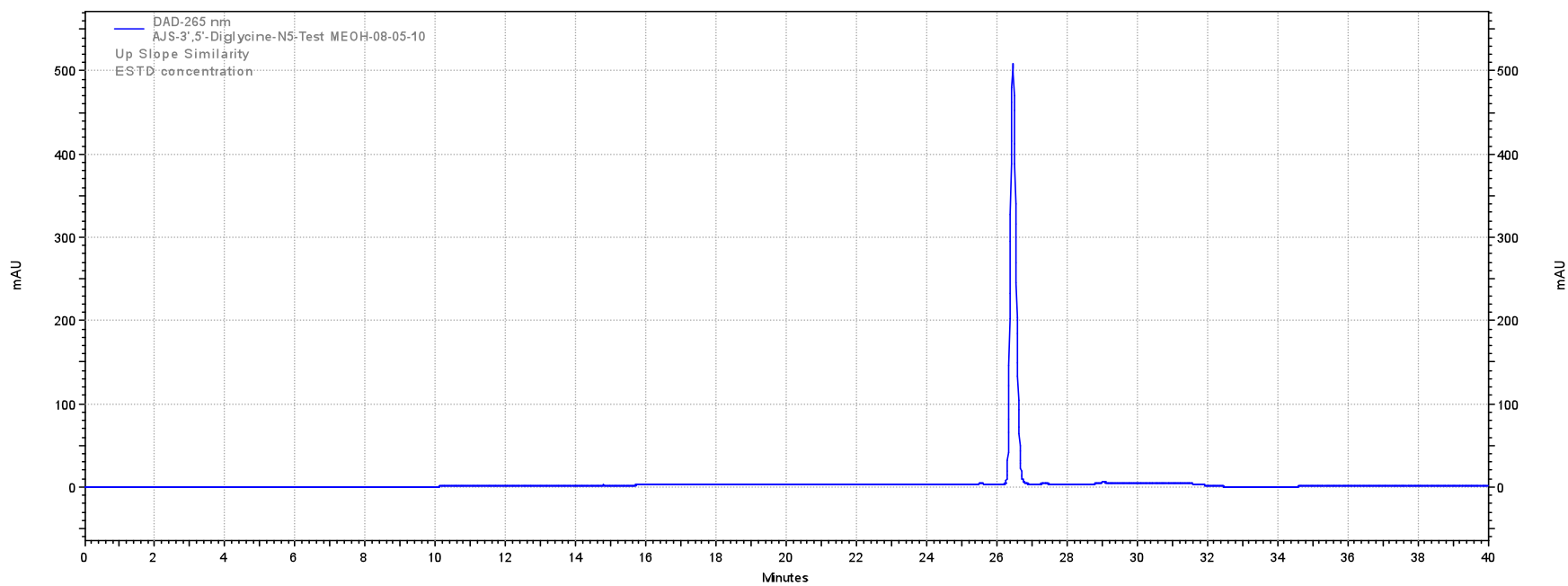
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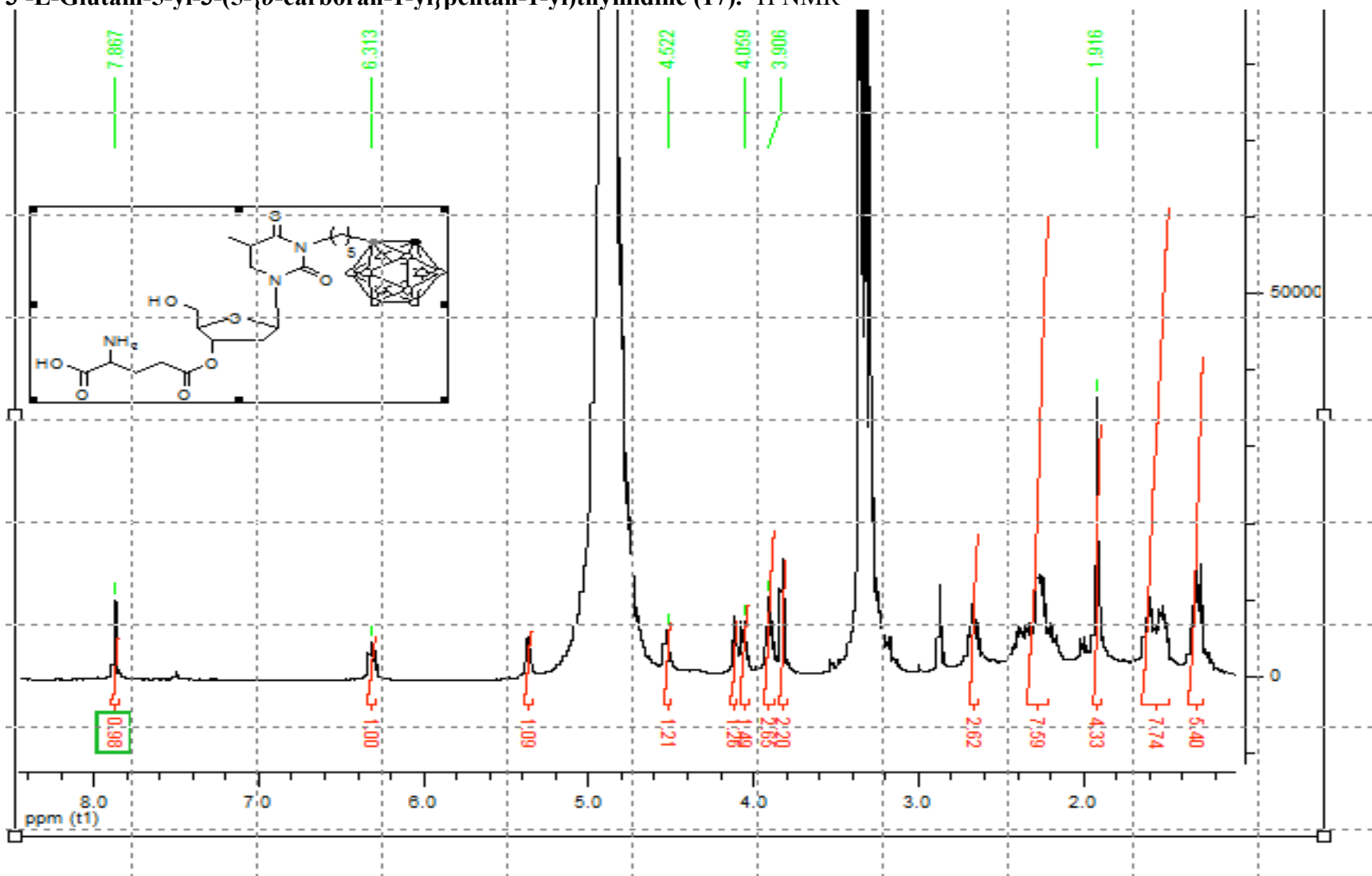
3',5'-Di-glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (16). HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 14.67 min.



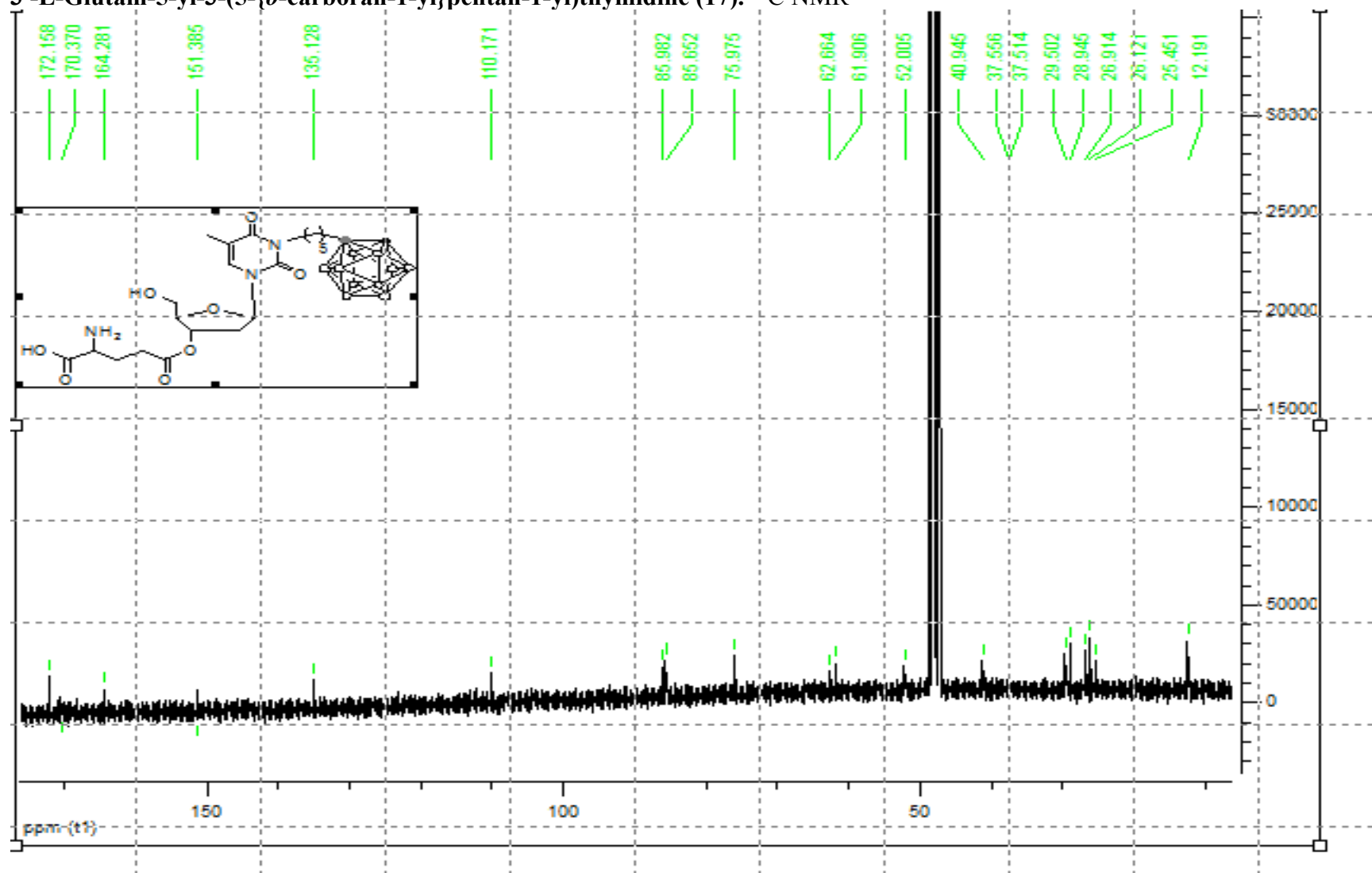
3',5'-Di-glycinyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (16). HPLC chromatogram (method B2, Table 3 in manuscript), retention time: 26.45 min.



3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17). ¹H NMR

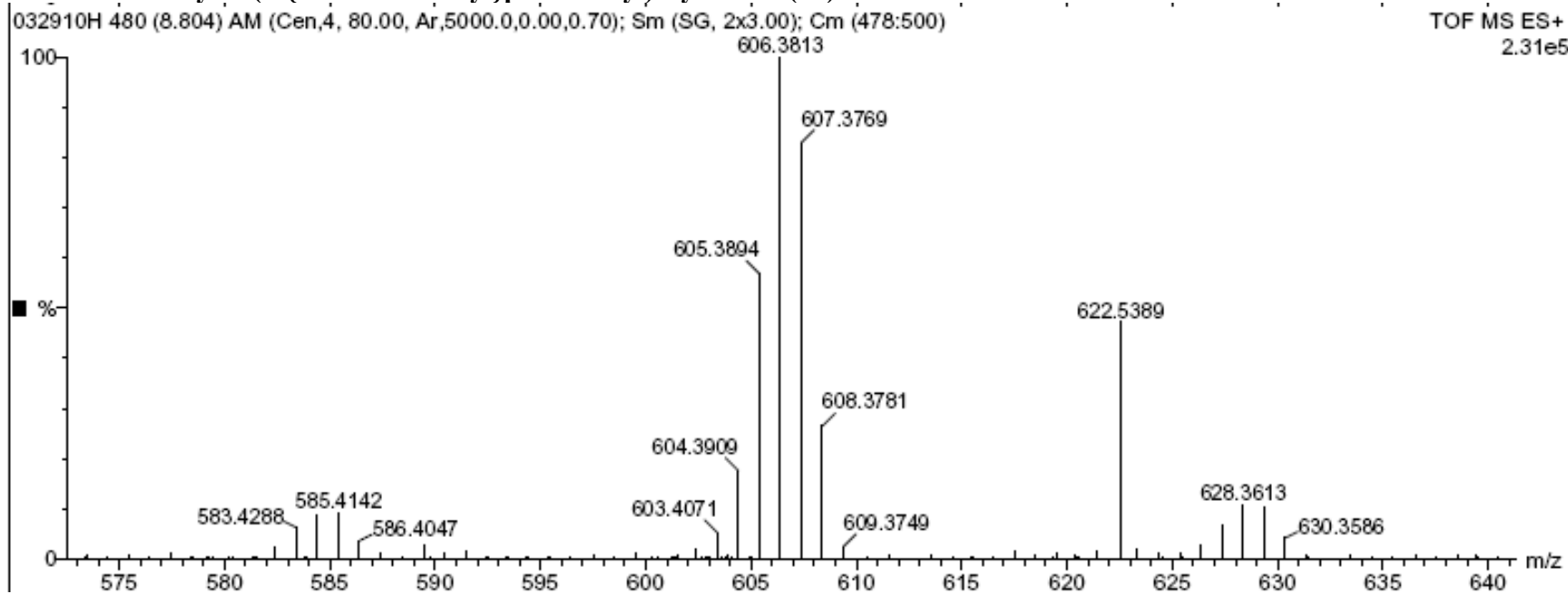


3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17). ¹³C NMR

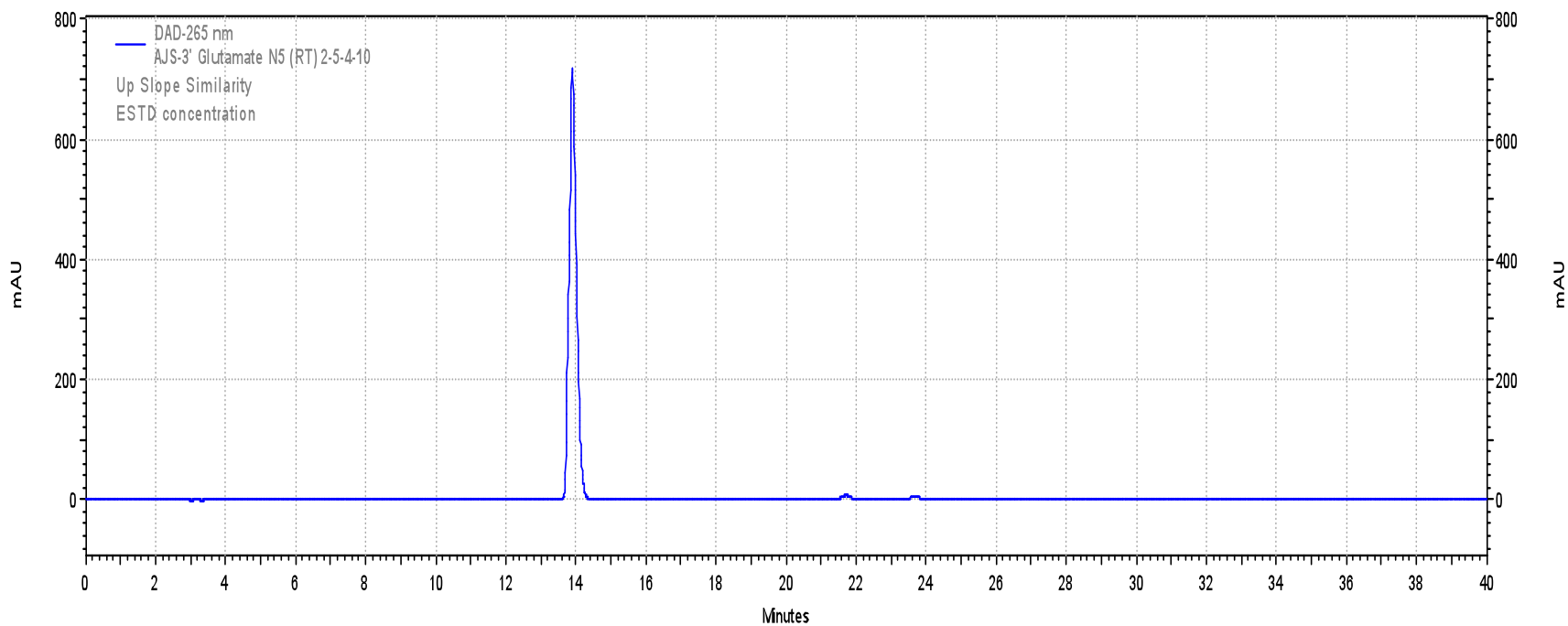


3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17). HR-ESI-MS: found: m/z 606.3813.

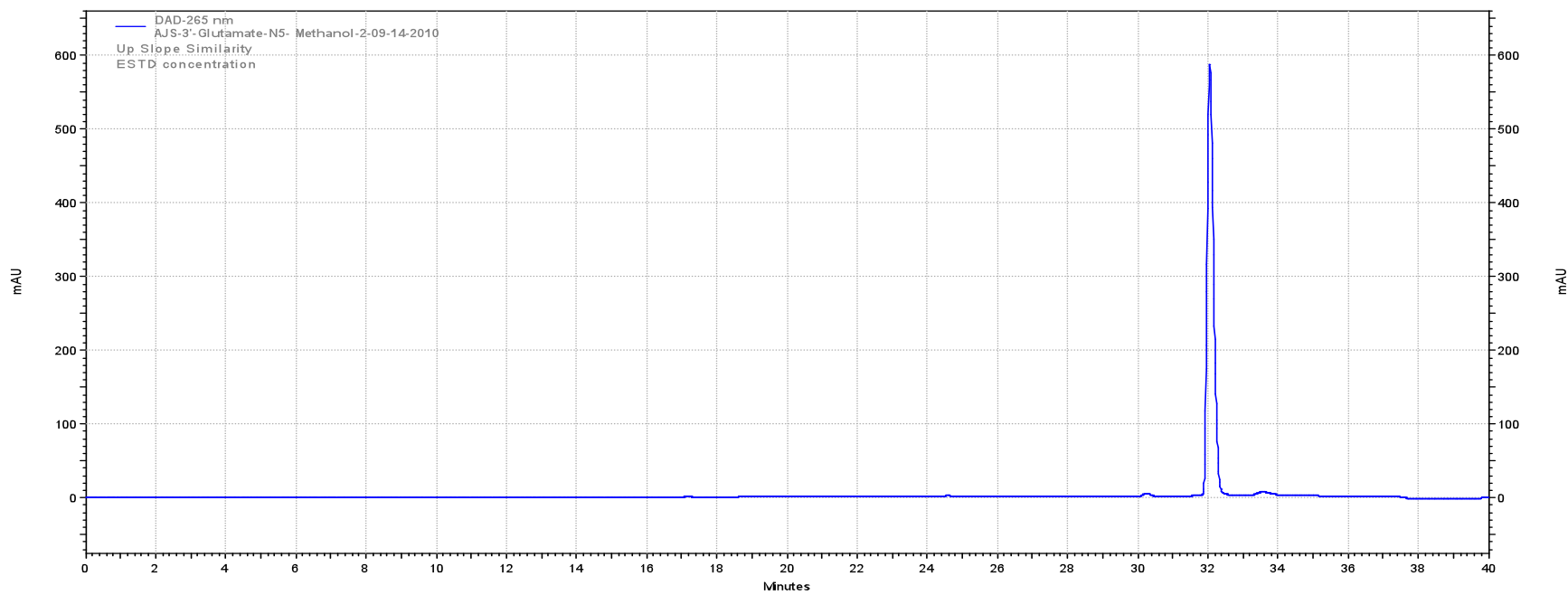
TOF MS ES+
2.31e5



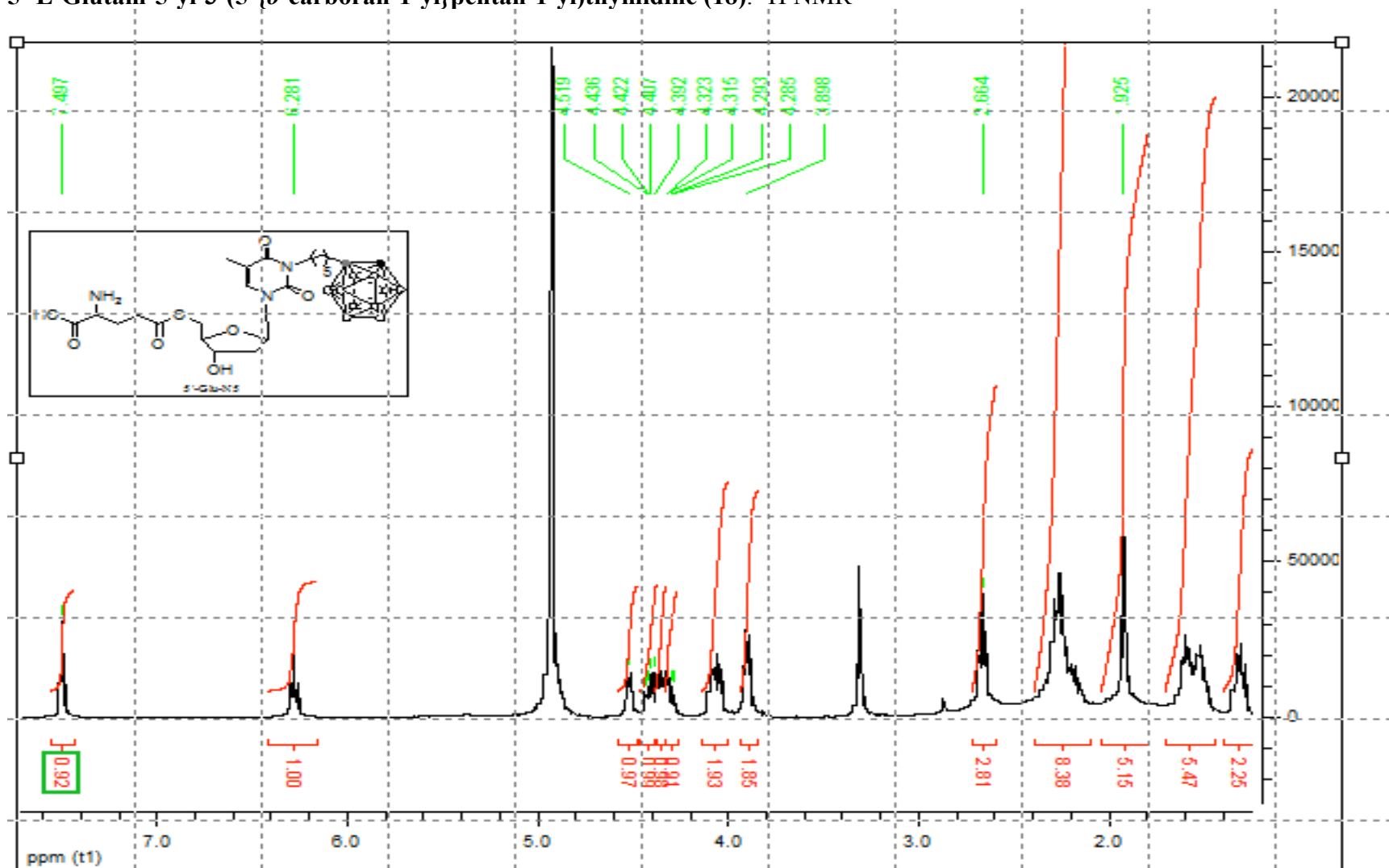
3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17). HPLC chromatogram (method A3, Table 3 in manuscript), retention time: 13.99 min.



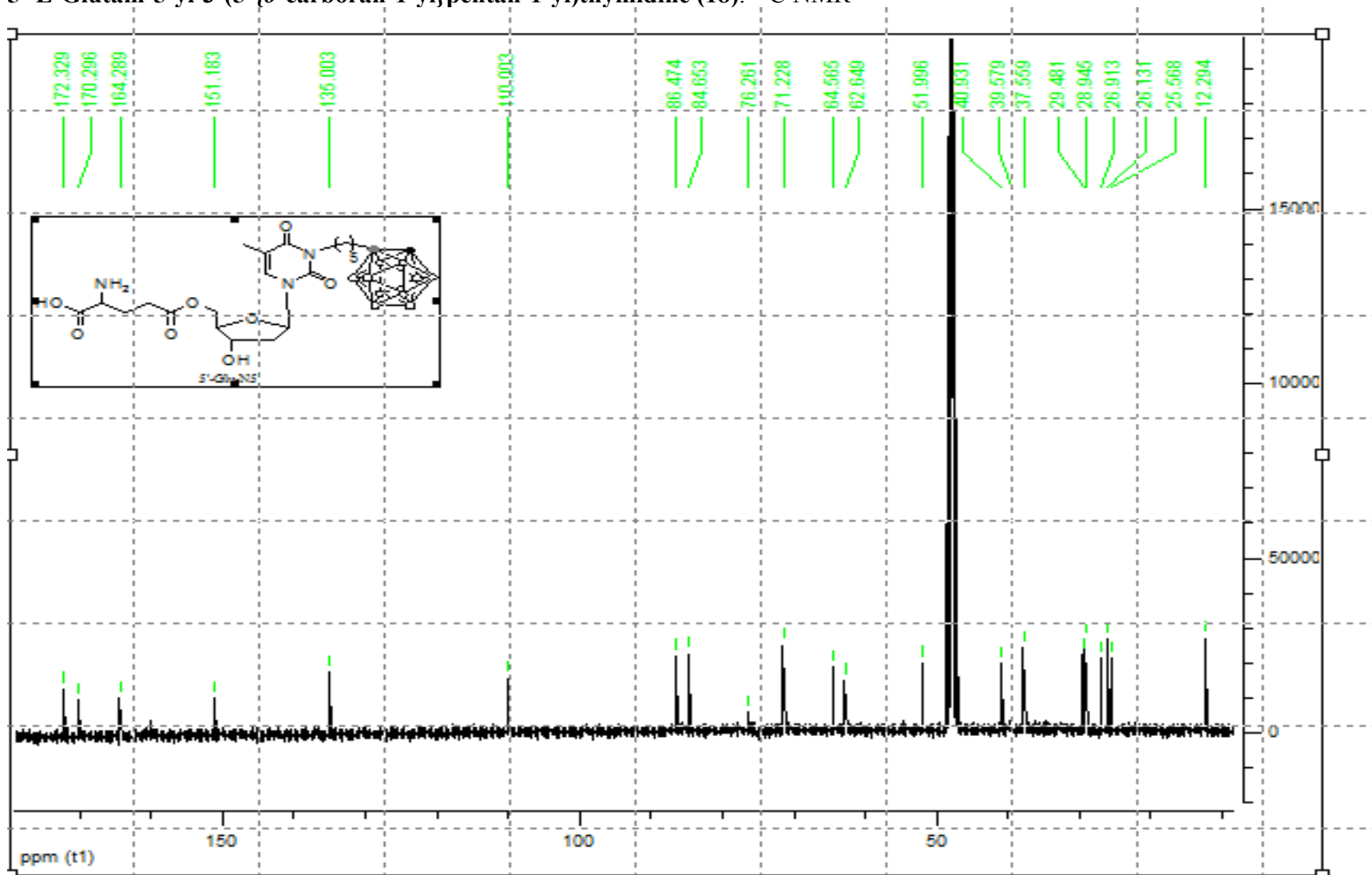
3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17) . HPLC chromatogram (method B3, Table 3 in manuscript), retention time: 32.05 min.



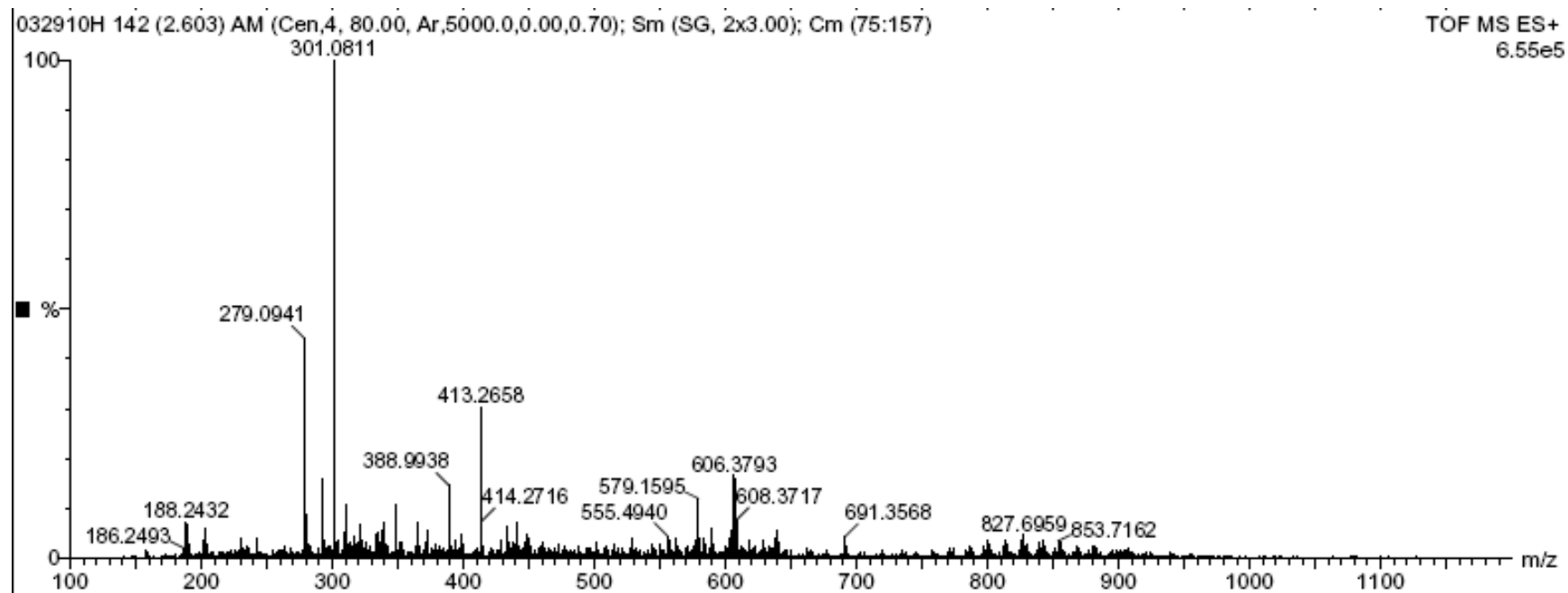
5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18). ¹H NMR



5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18). ¹³C NMR

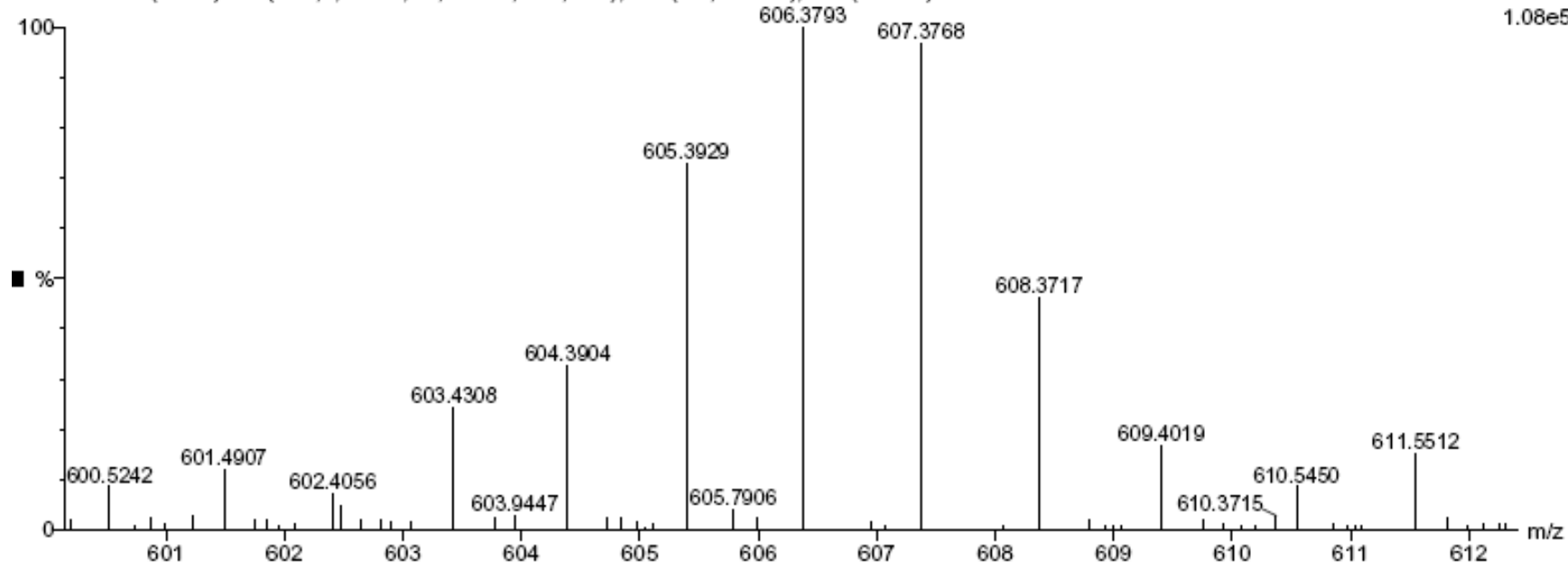


5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18). HR-ESI-MS: found: m/z 606.3793.

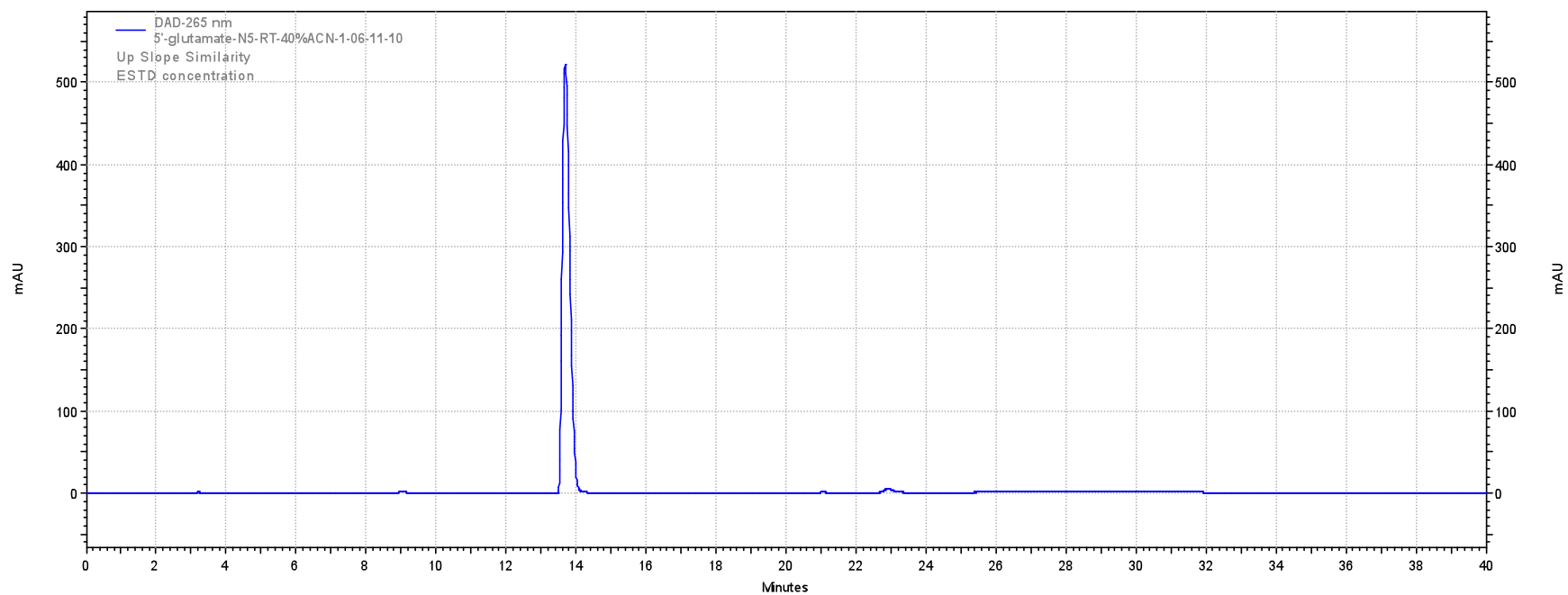


032910H 142 (2.603) AM (Cen,4, 80.00, Ar,5000.0,0.00,0.70); Sm (SG, 2x3.00); Cm (75:157)

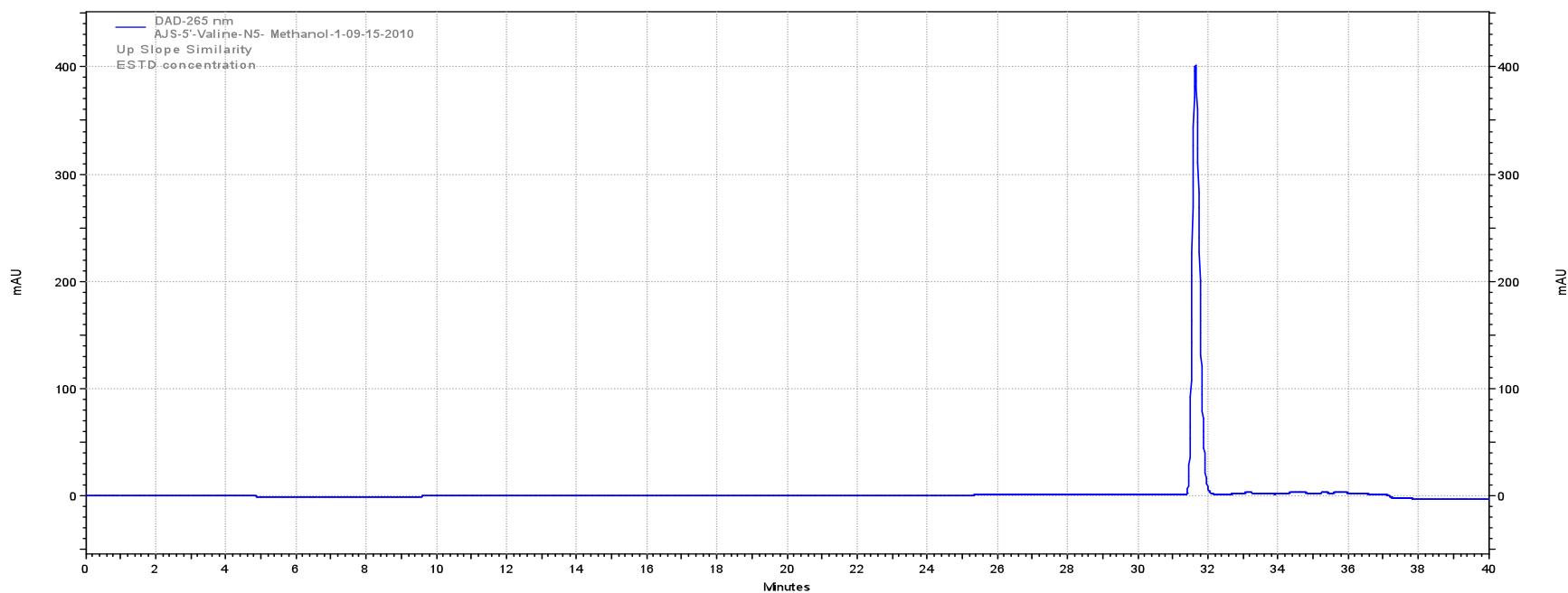
TOF MS ES+
1.08e5



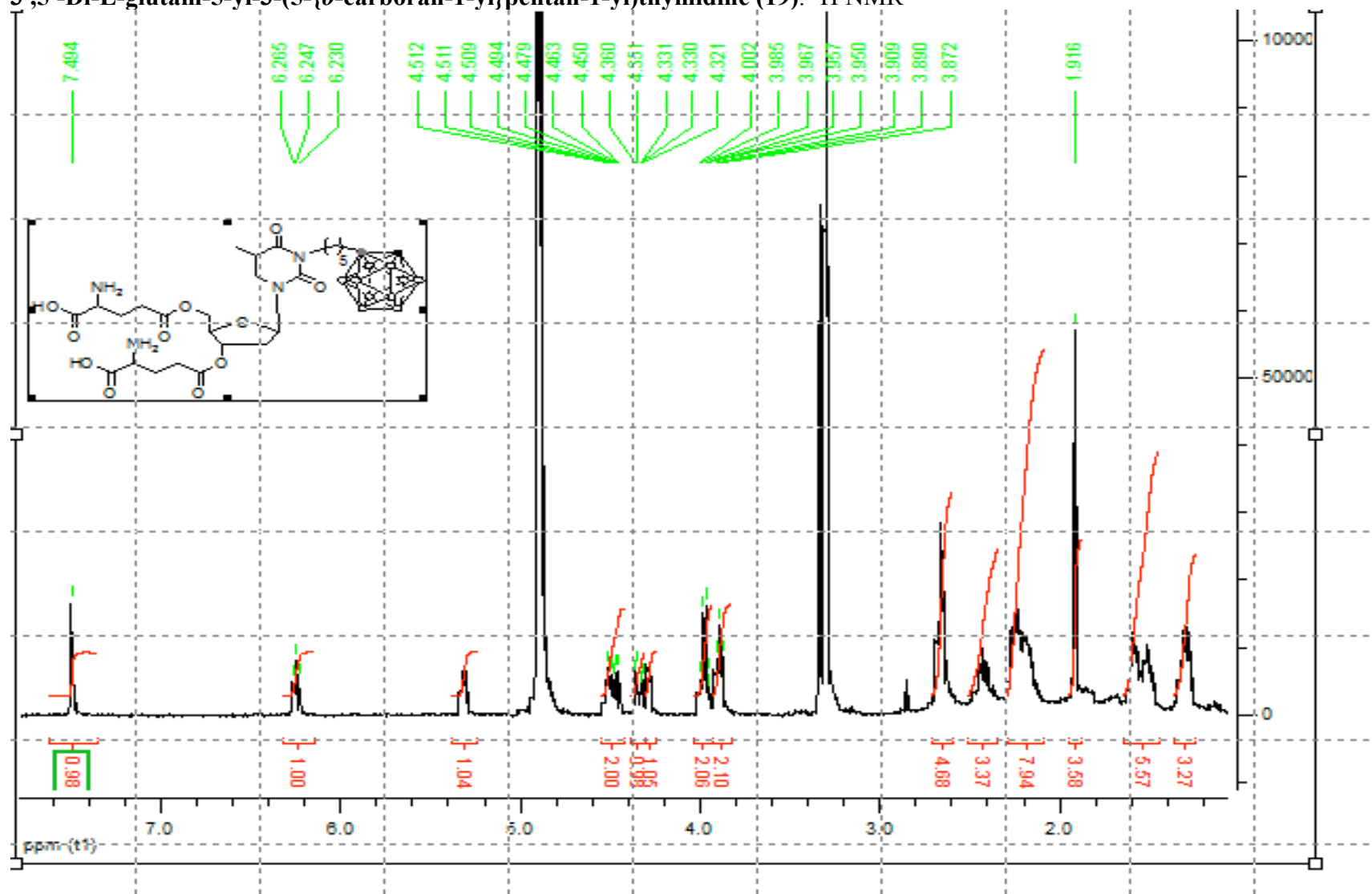
5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18). HPLC chromatogram (method A3, Table 3 in manuscript), retention time: 13.69 min.



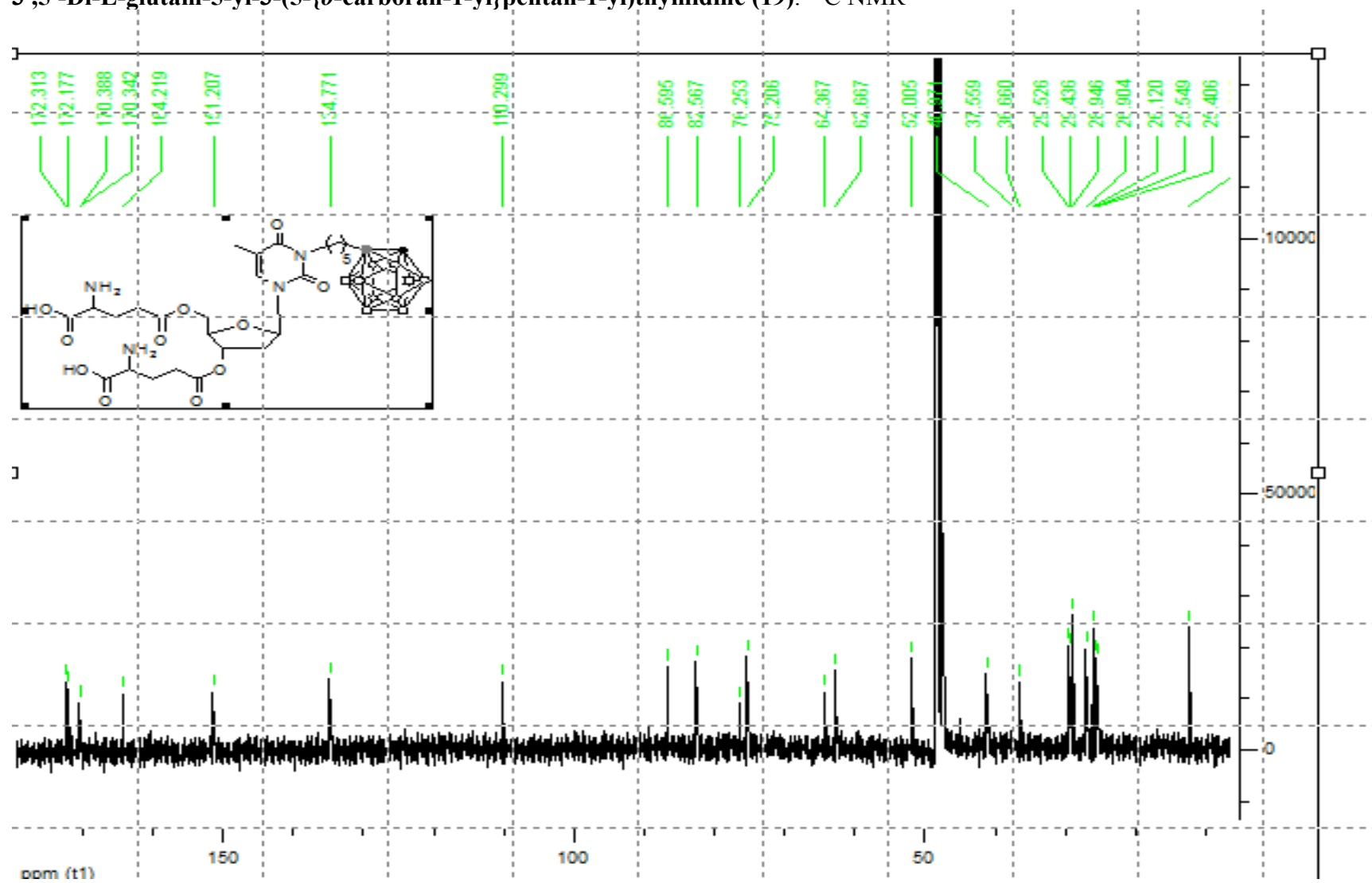
5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18) . HPLC chromatogram (method B3, Table 3 in manuscript), retention time: 31.64 min.



3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19). ¹H NMR

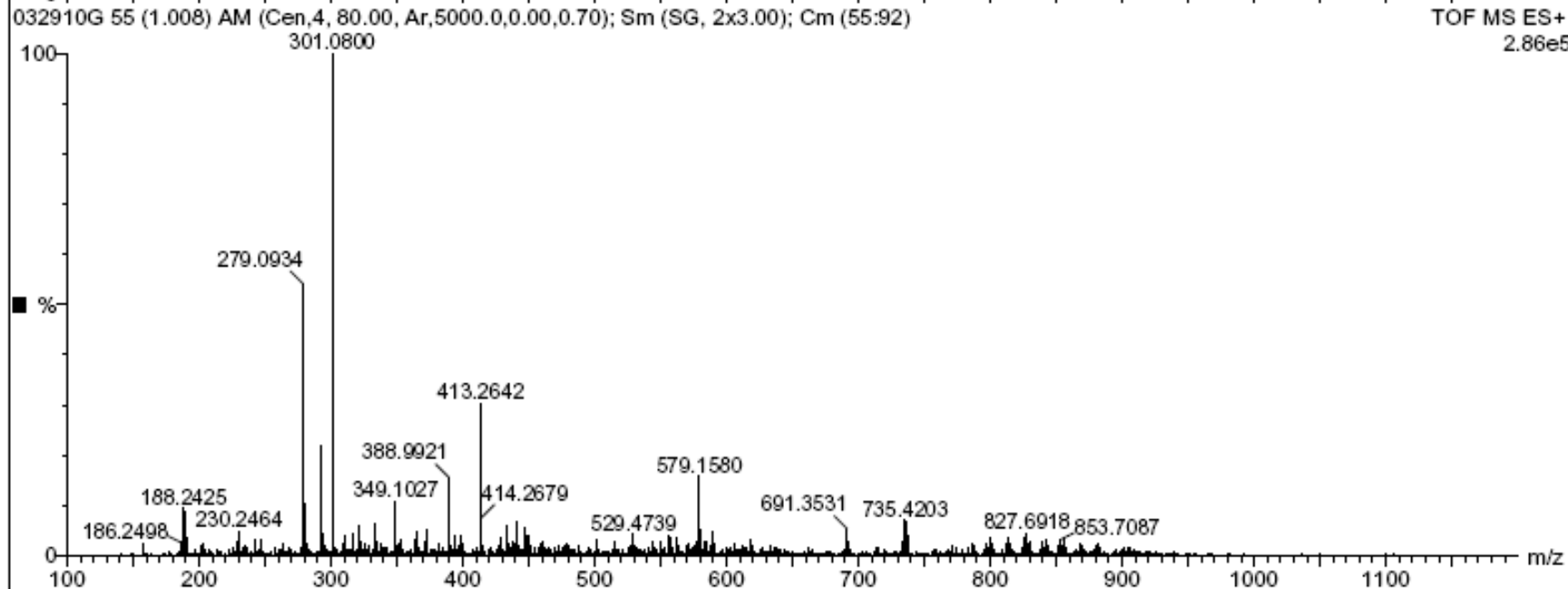


3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19). ¹³C NMR



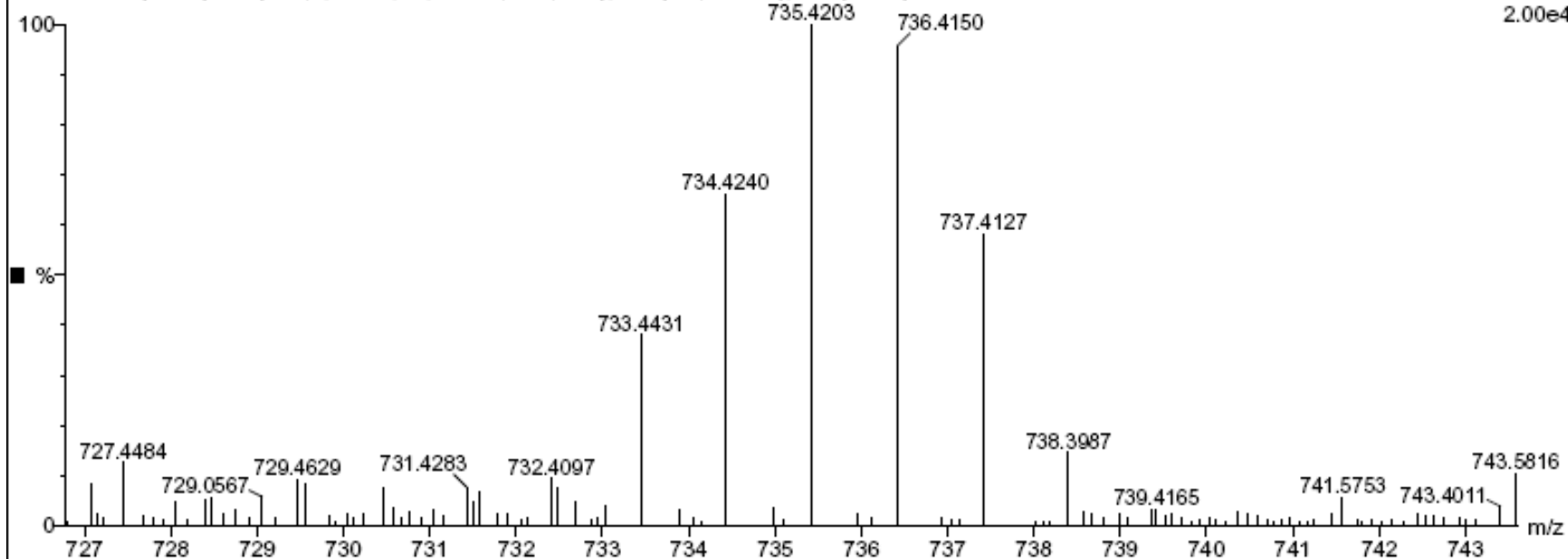
3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19). HR-ESI-MS: found: m/z 735.4203.

TOF MS ES+
2.86e5

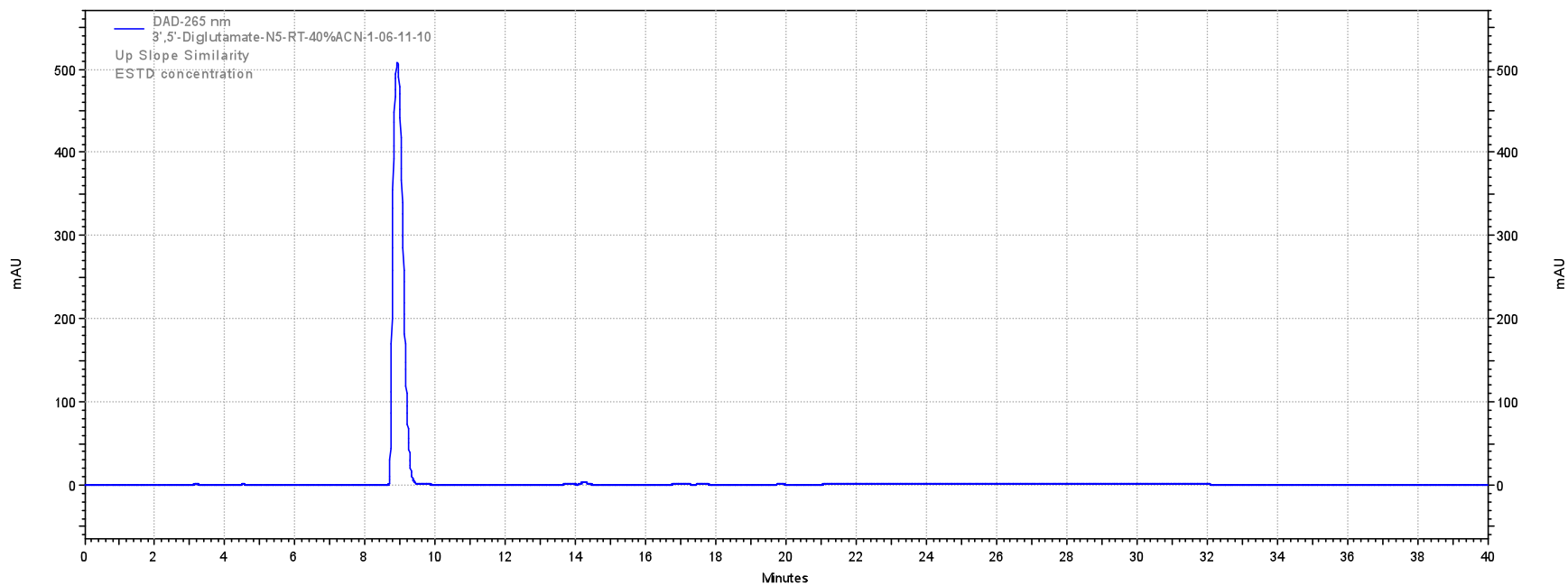


032910G 55 (1.008) AM (Cen,4, 80.00, Ar,5000.0,0.00,0.70); Sm (SG, 2x3.00); Cm (55:92)

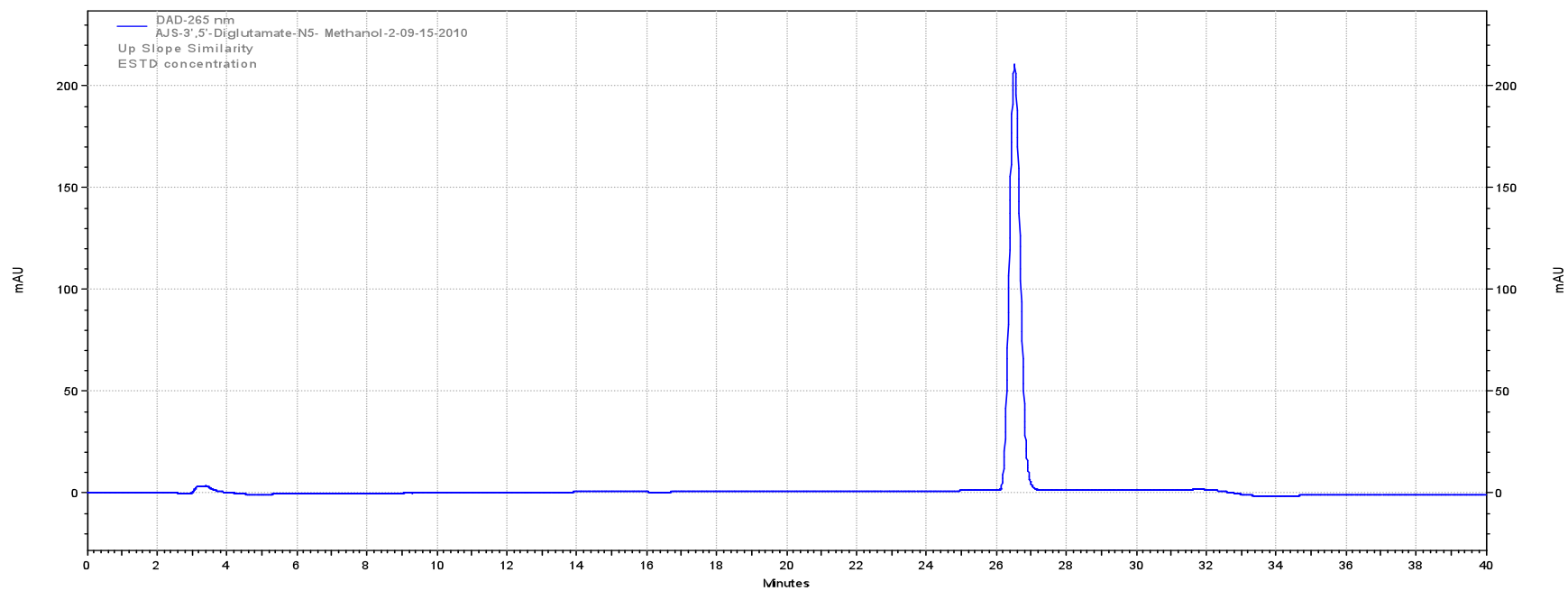
TOF MS ES+
2.00e4



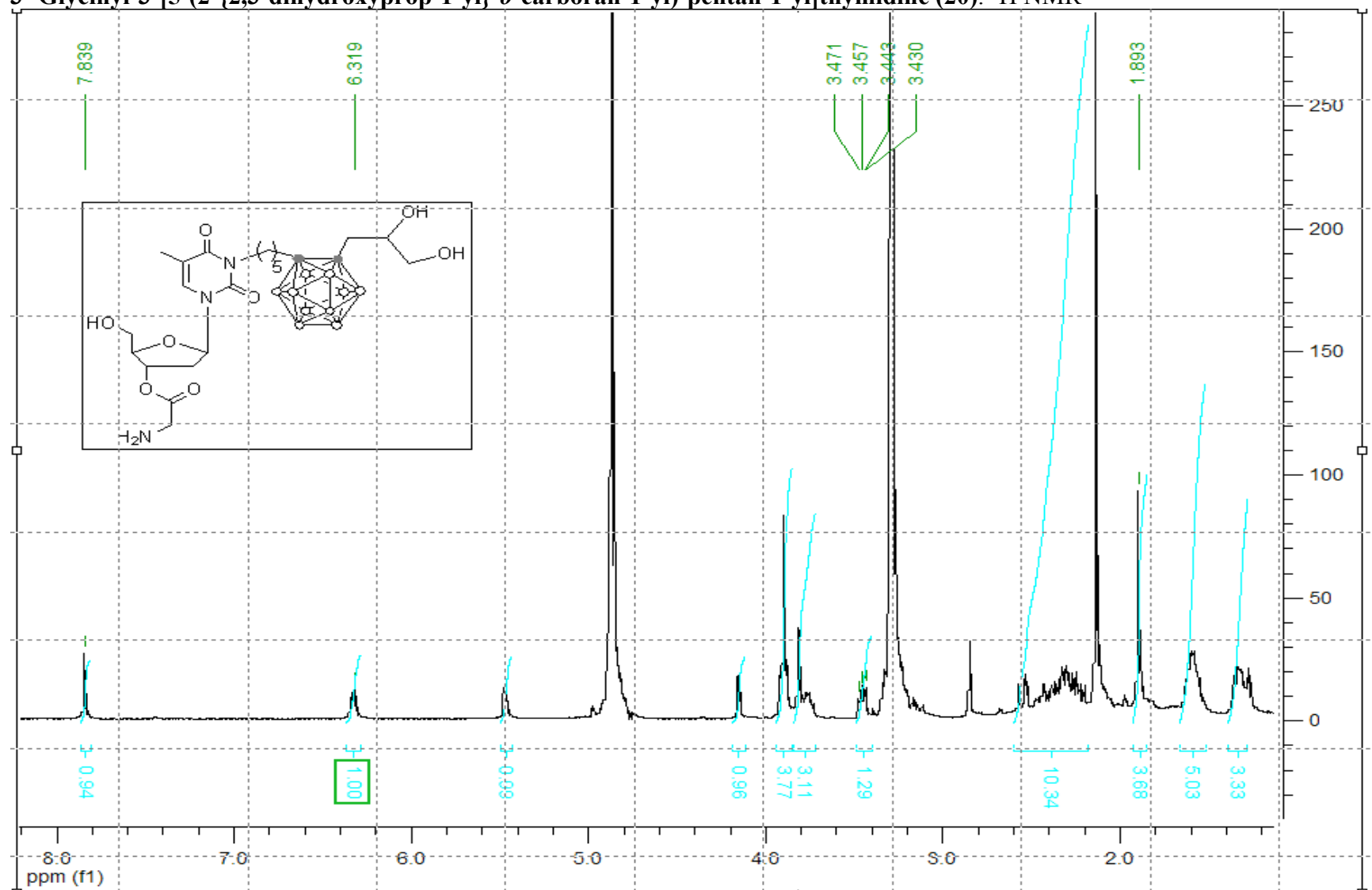
3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19). HPLC chromatogram (method A3, Table 3 in manuscript), retention time: 8.92 min.



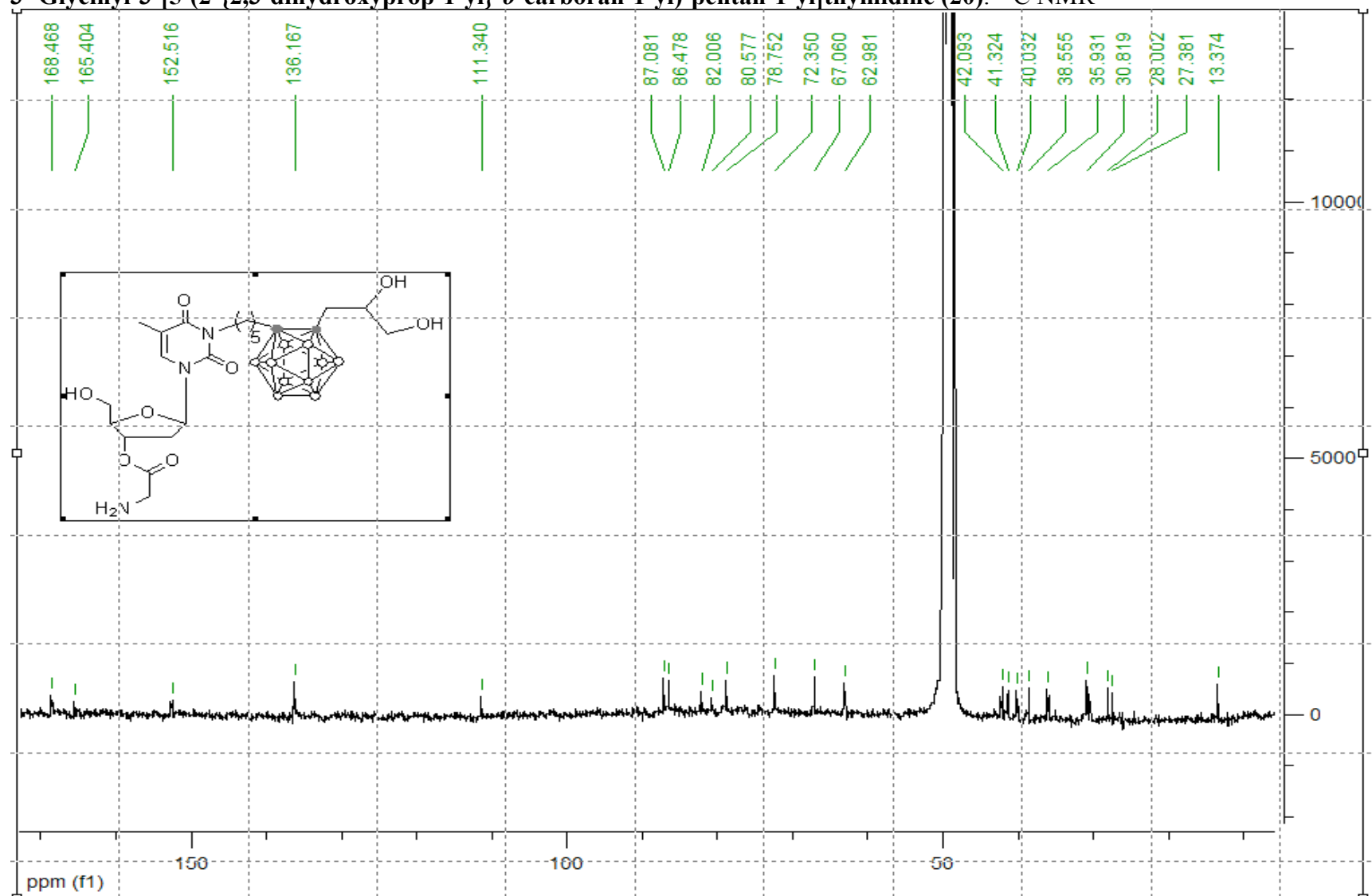
3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19). HPLC chromatogram (method B3, Table 3 in manuscript), retention time: 26.50 min.



3'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (20). ¹H NMR



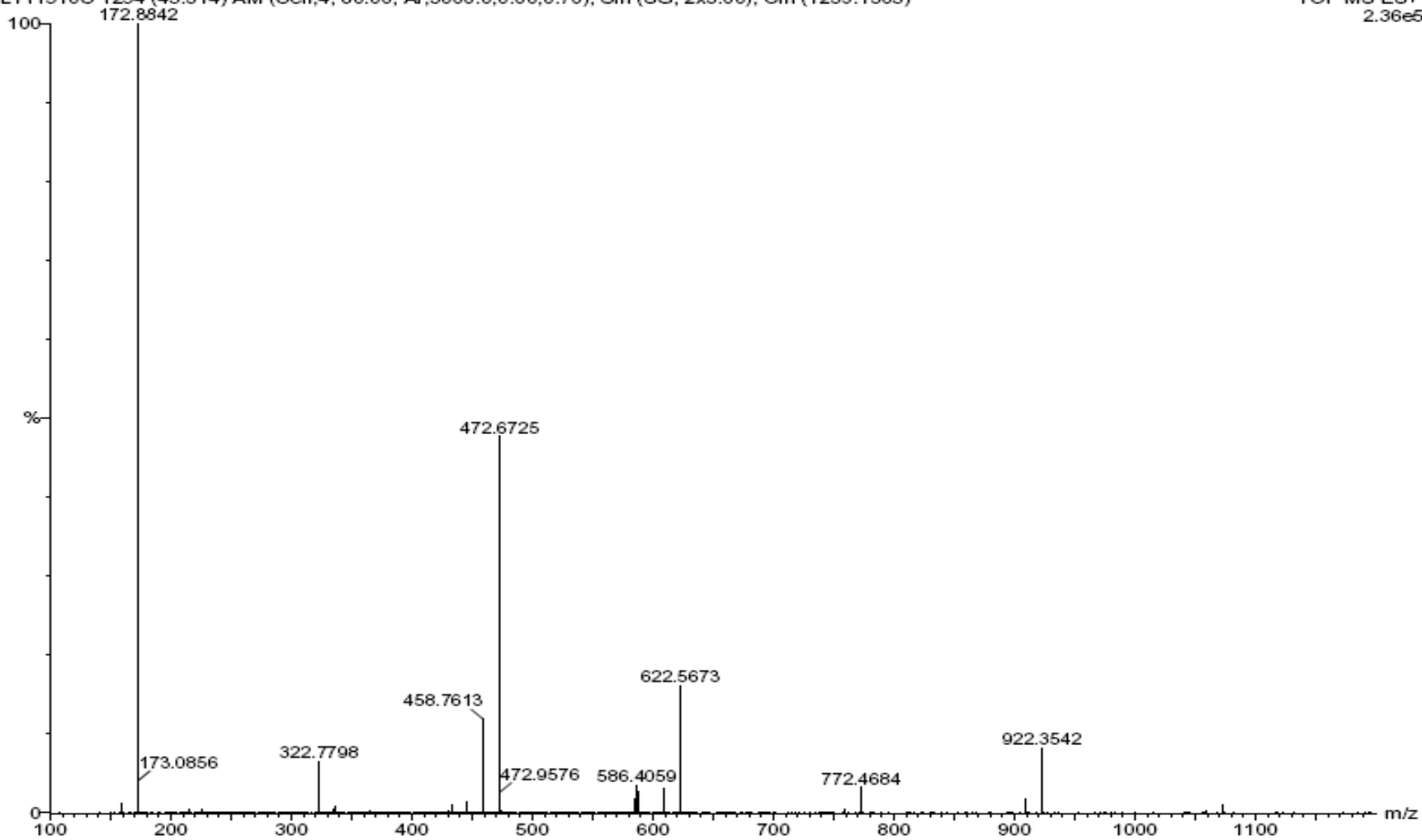
3'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (20). ^{13}C NMR



3'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl] thymidine (20). HR-ESI-MS: found: m/z 586.4059.

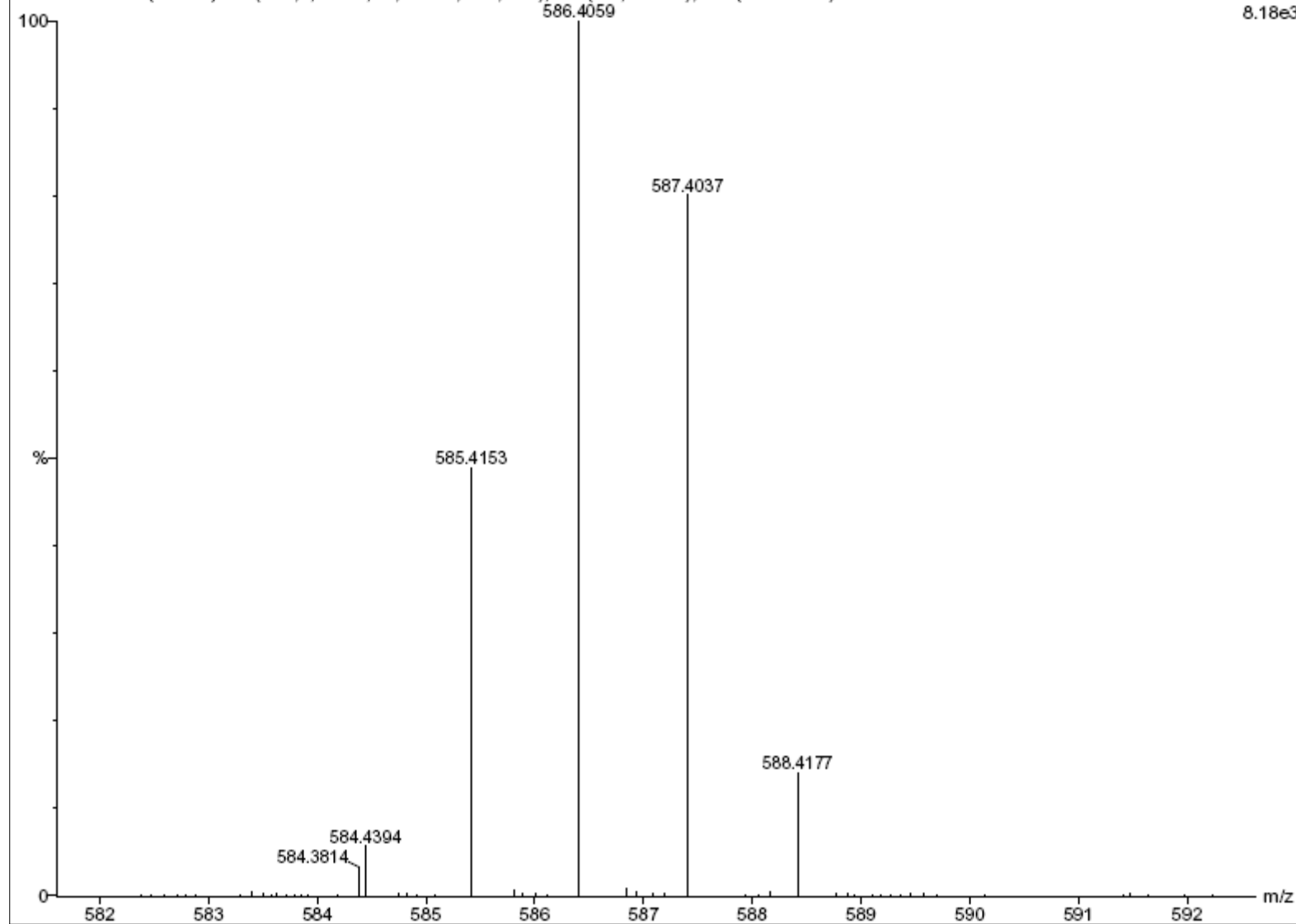
L111910C 1294 (45.314) AM (Cen,4, 80.00, Ar,5000.0,0.00,0.70); Sm (SG, 2x3.00); Cm (1239:1305)

TOF MS ES+
2.36e5

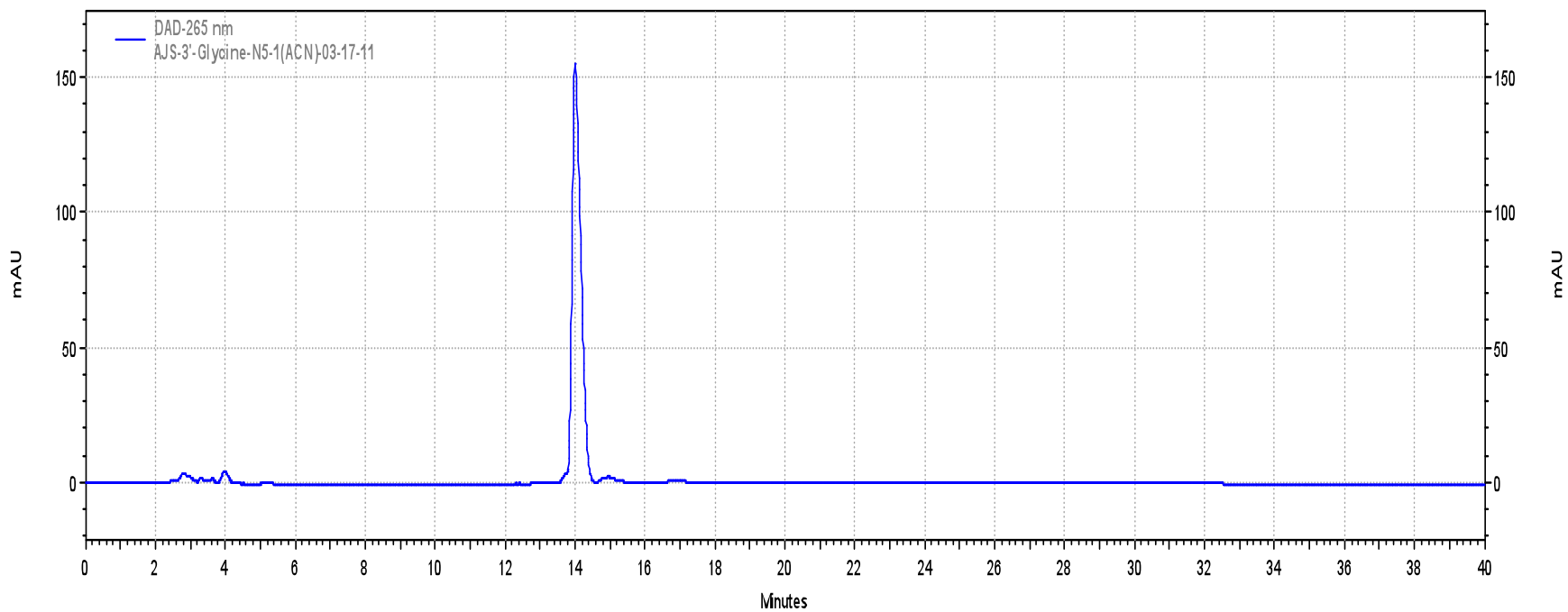


L111910C 1294 (45.314) AM (Cen,4, 80.00, Ar,5000.0,0.00,0.70); Sm (SG, 2x3.00); Cm (1239:1305)

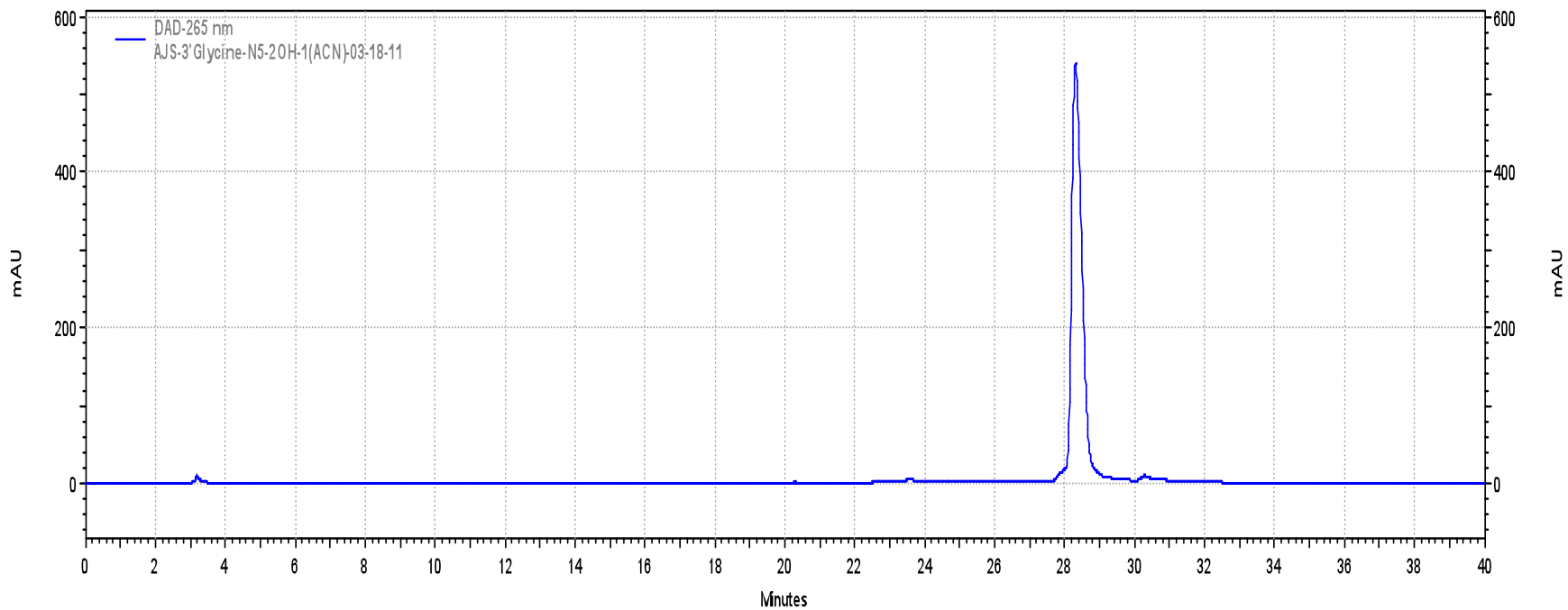
TOF MS ES+
8.18e3



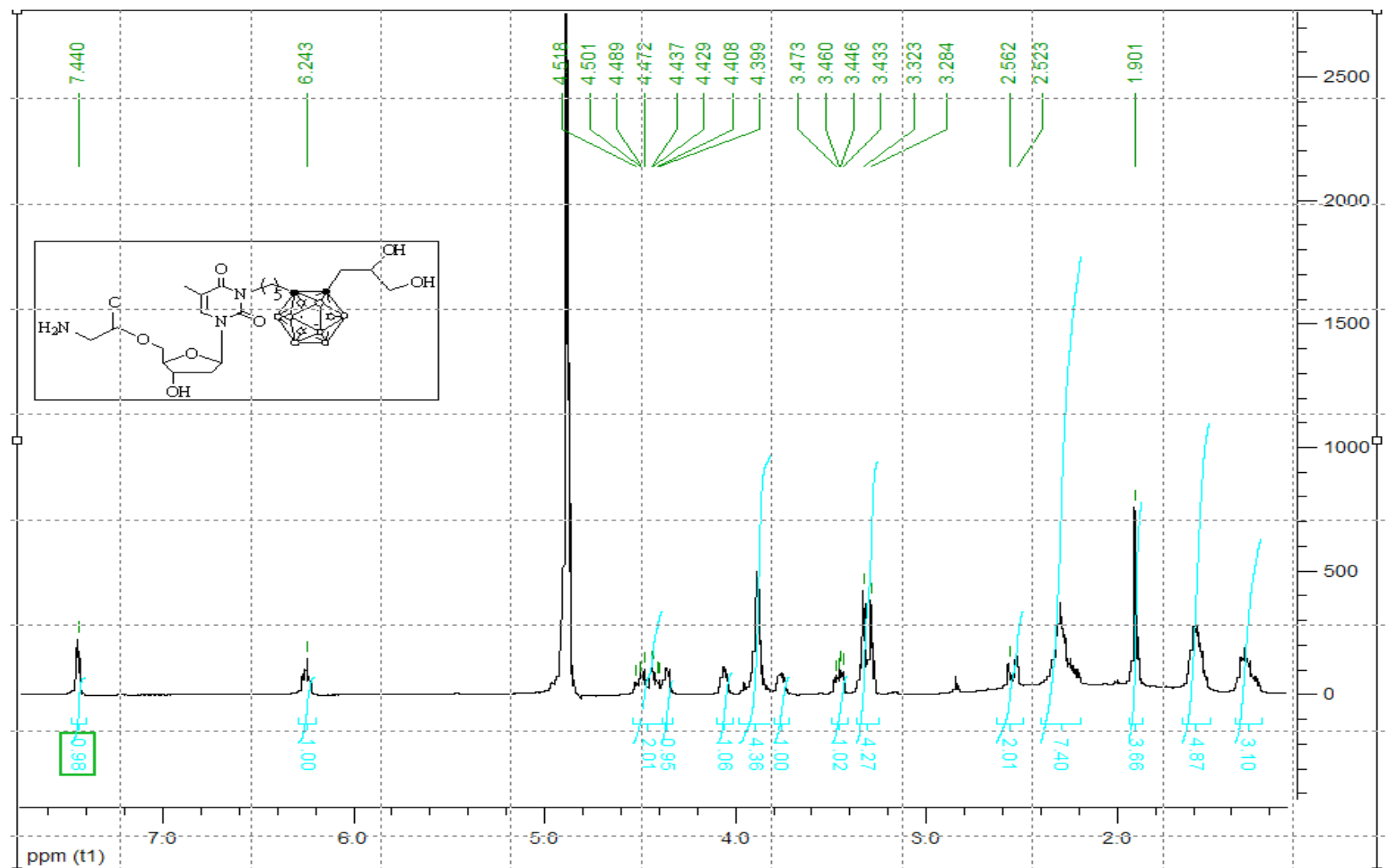
3'-GlycinyI-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (20). HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 14.00 min.



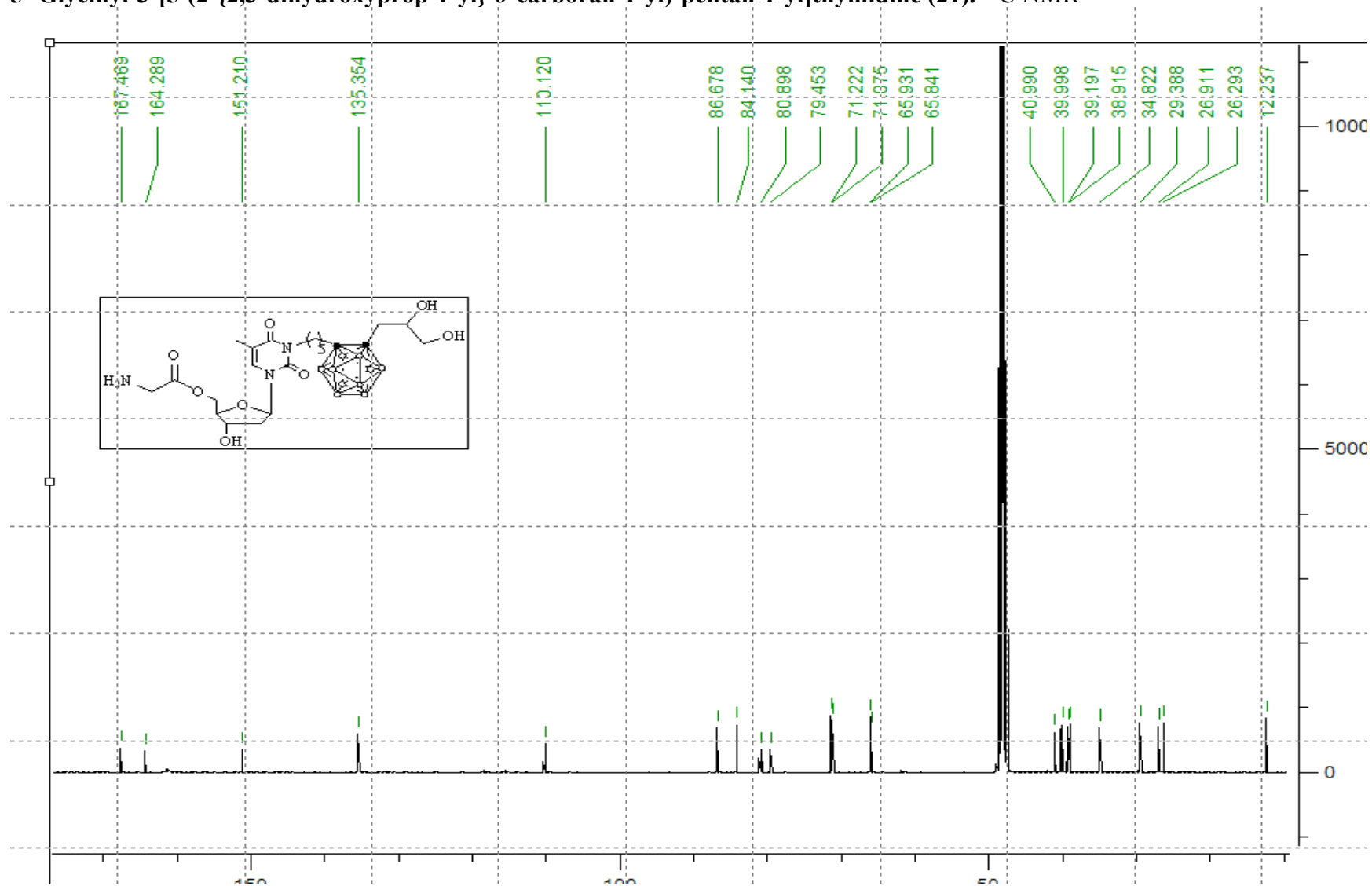
3'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (20). HPLC chromatogram (method B2, Table 3 in manuscript), retention time: 28.30 min.



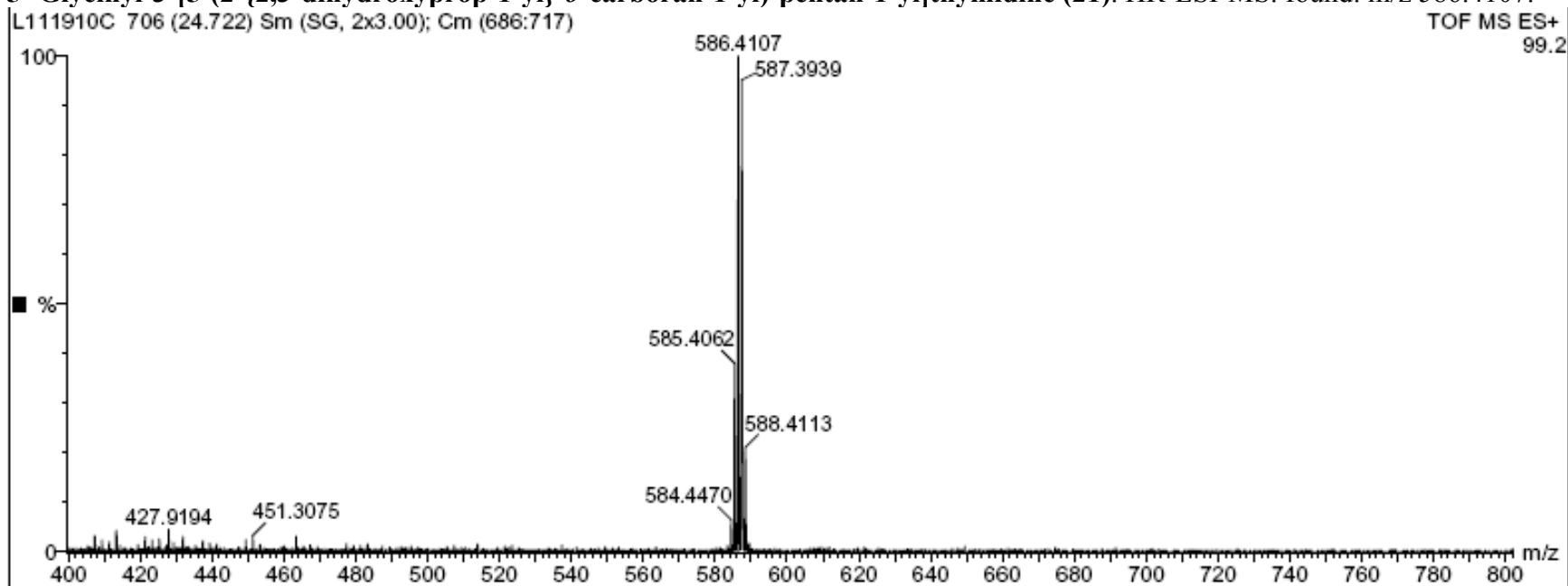
5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (21). ¹H NMR



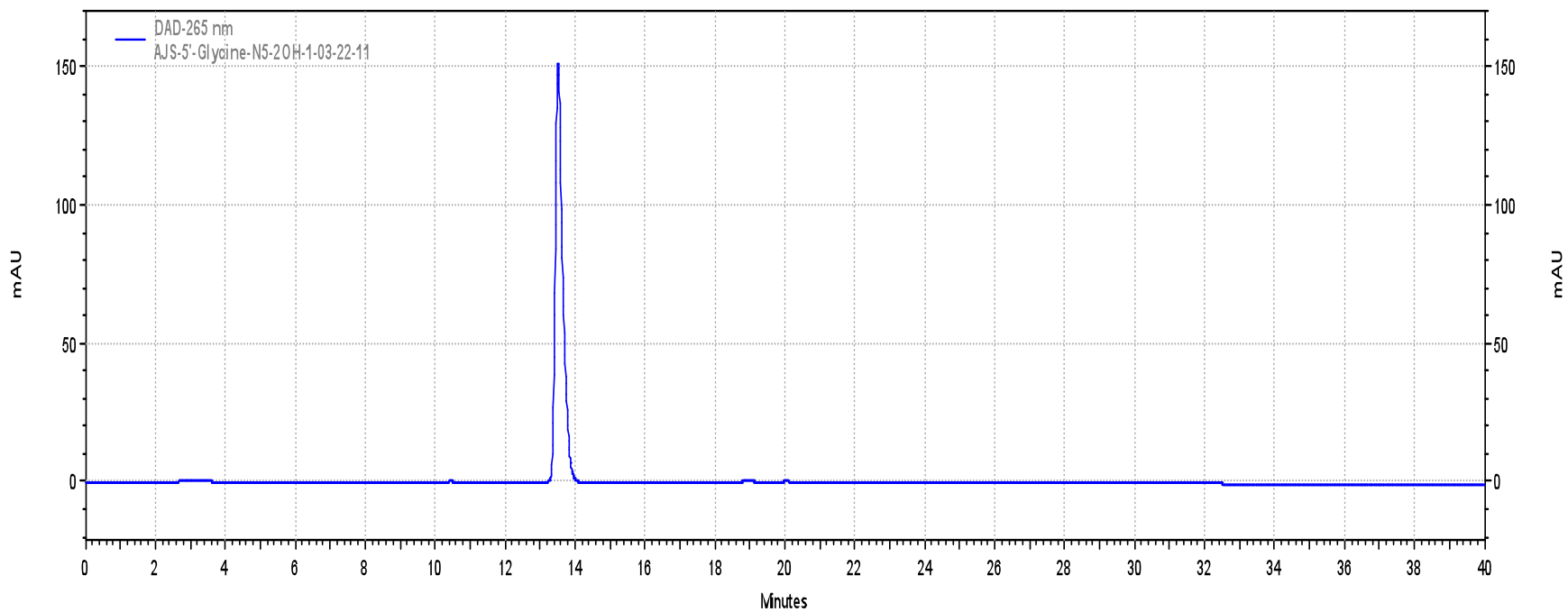
5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (21). ^{13}C NMR



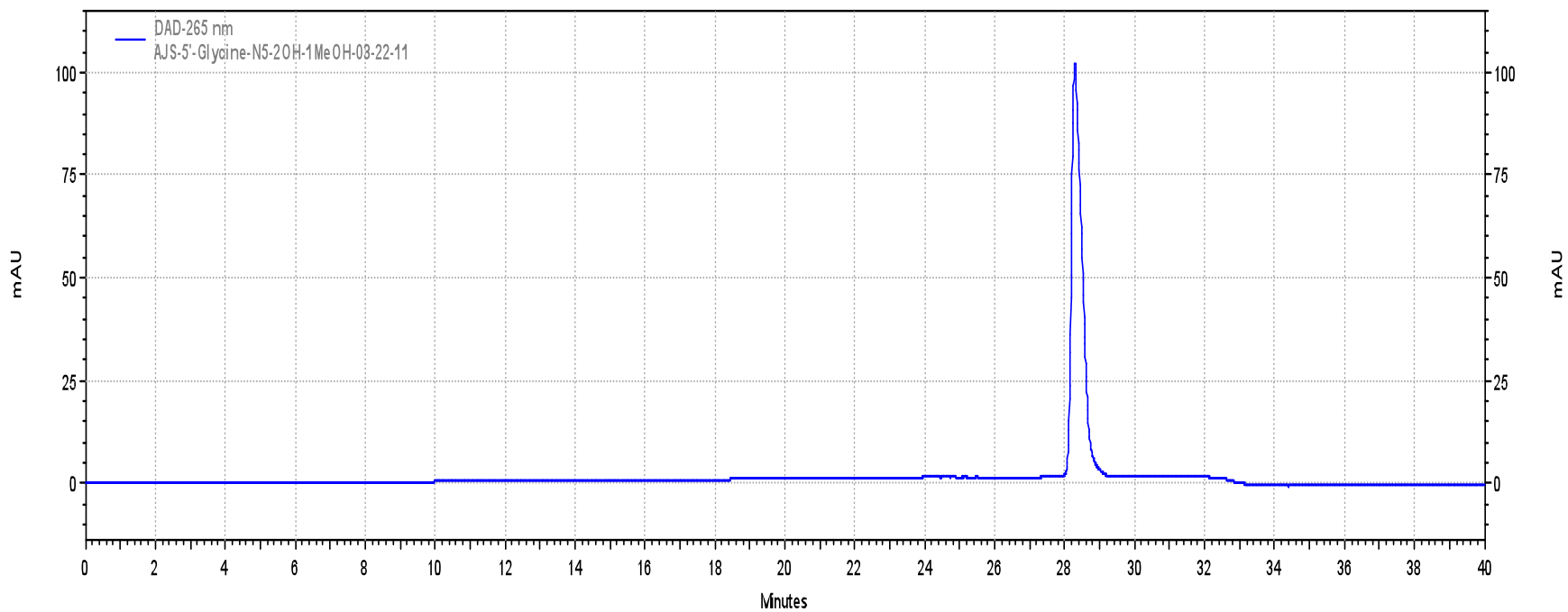
5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (21). HR-ESI-MS: found: m/z 586.4107.



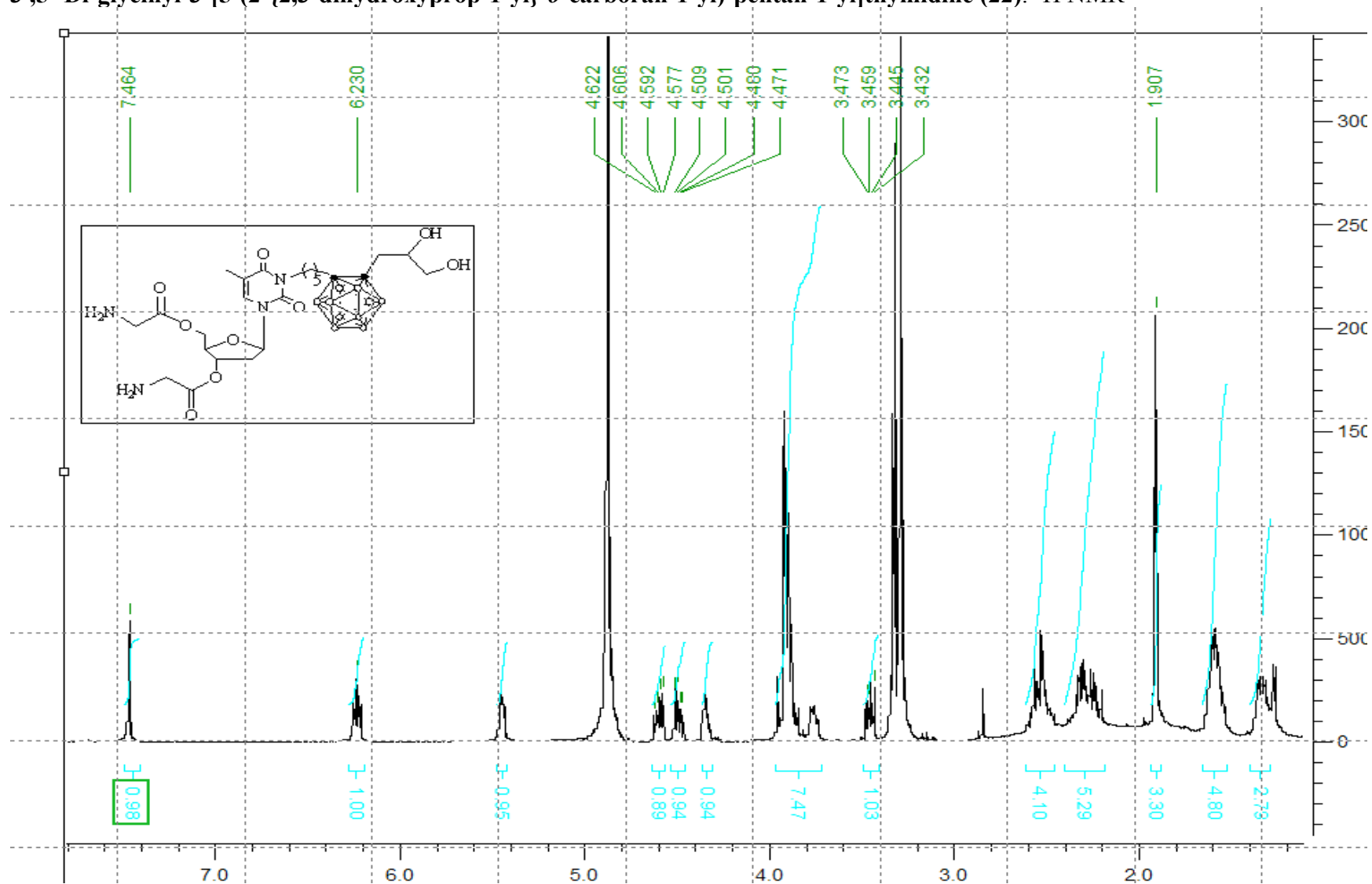
5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (21). HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 13.51 min.



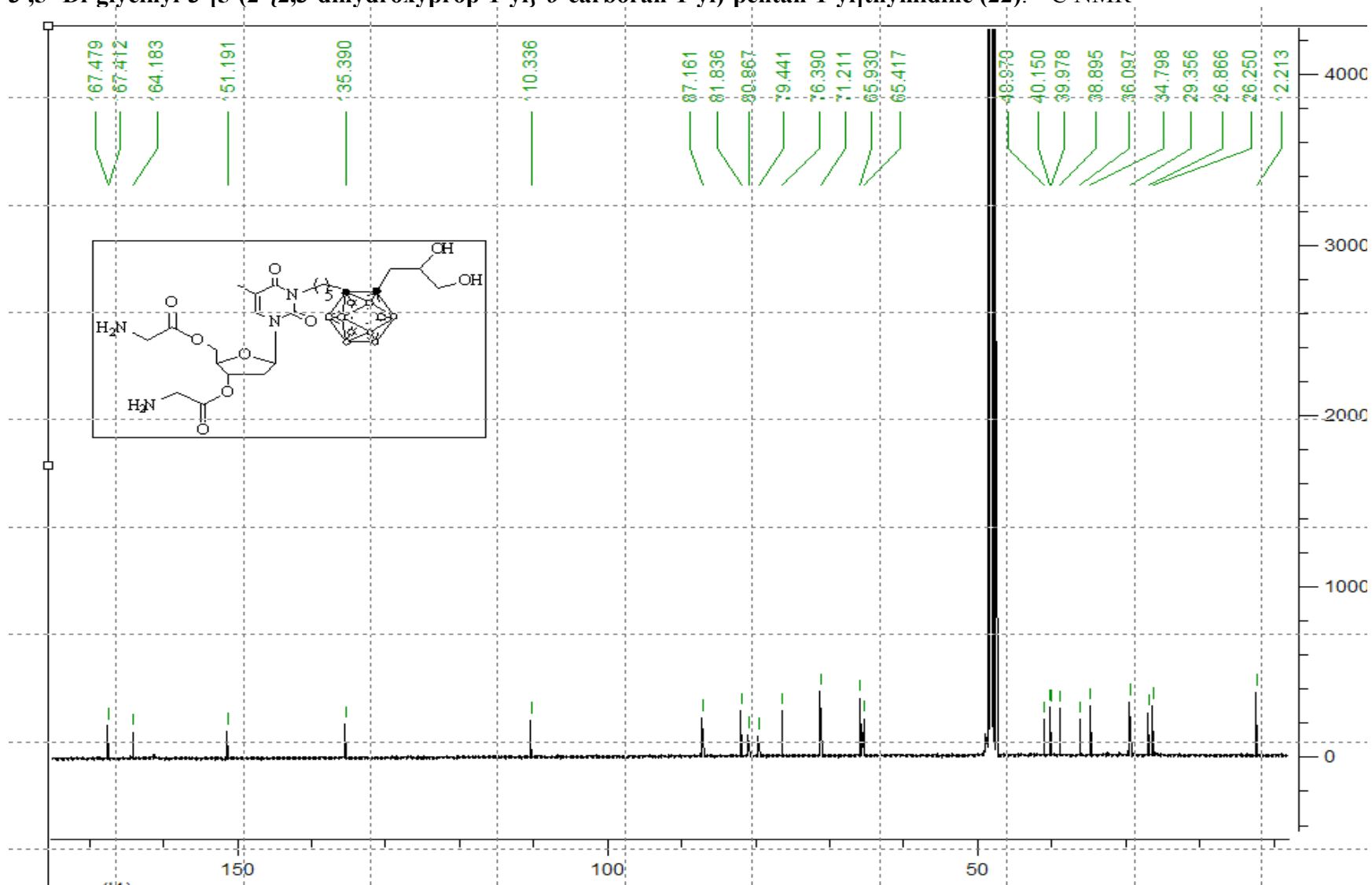
5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (21). HPLC chromatogram(method B2, Table 3 in manuscript), retention time: 28.28 min.



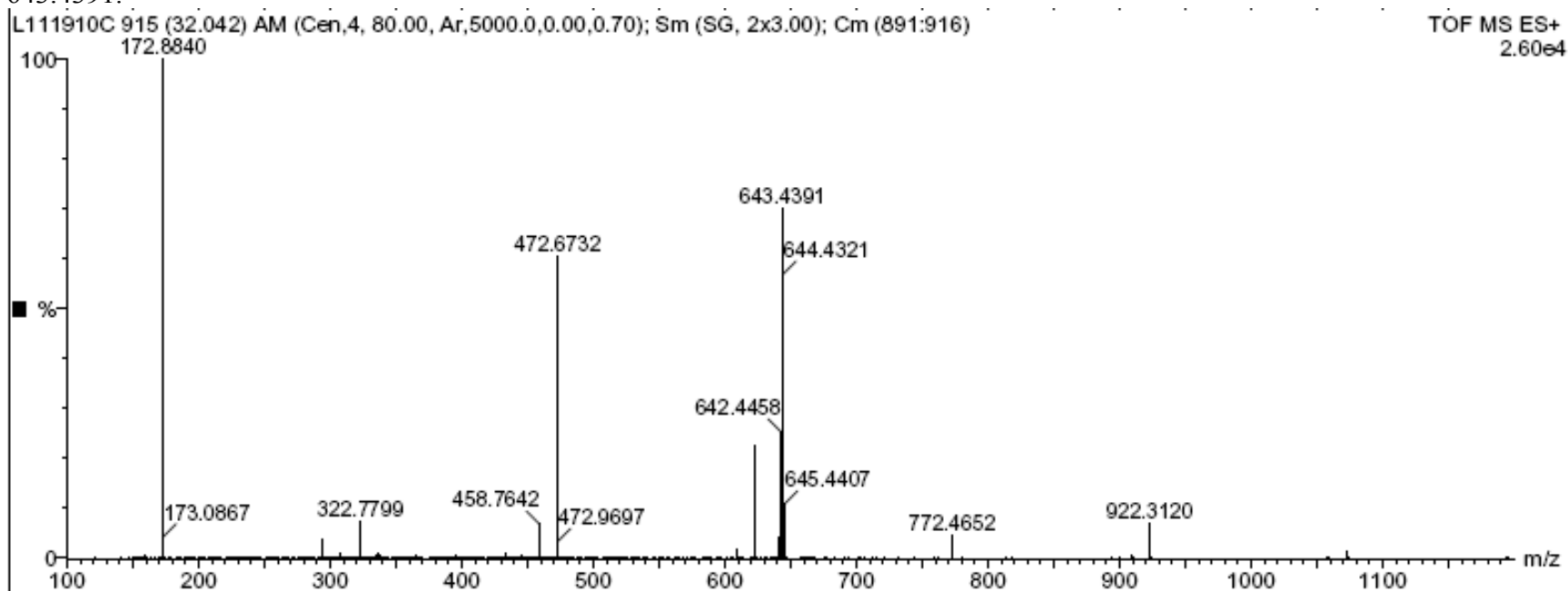
3',5'-Di-glycinyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (22). ¹H NMR



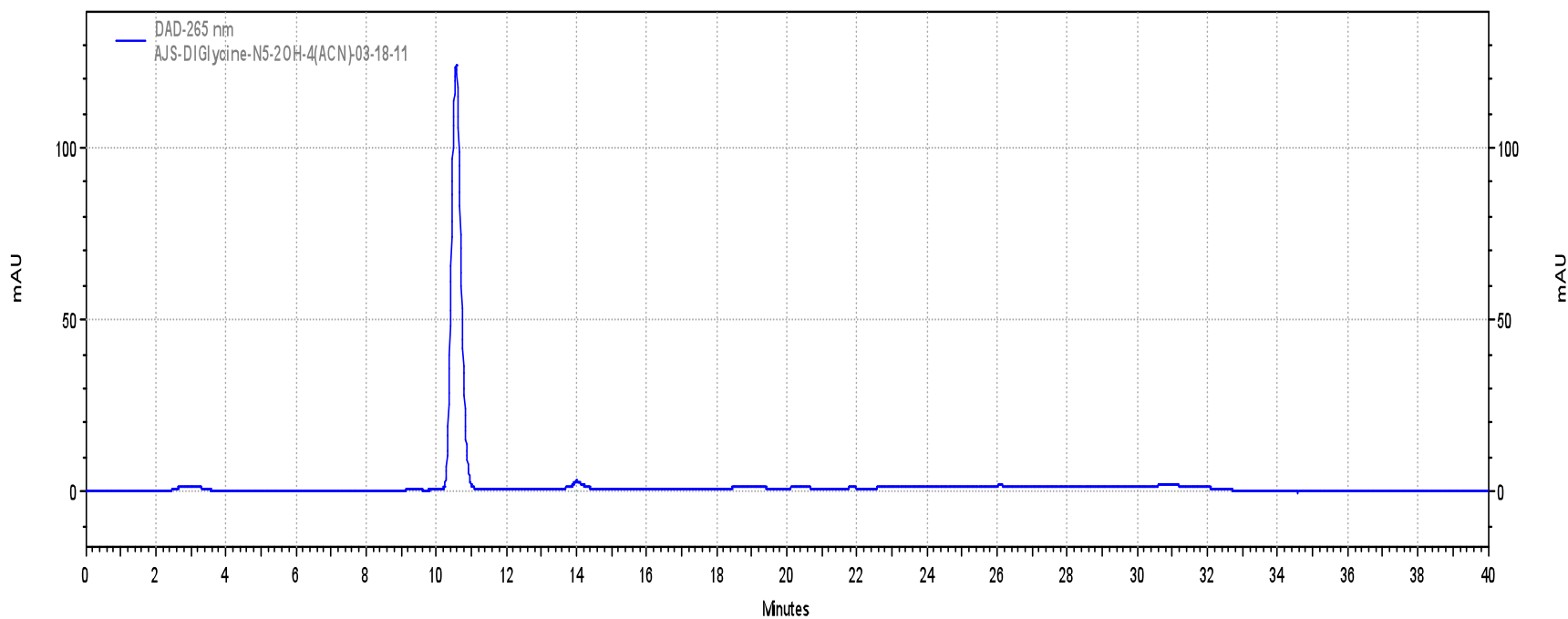
3',5'-Di-glycinyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (22). ¹³C NMR



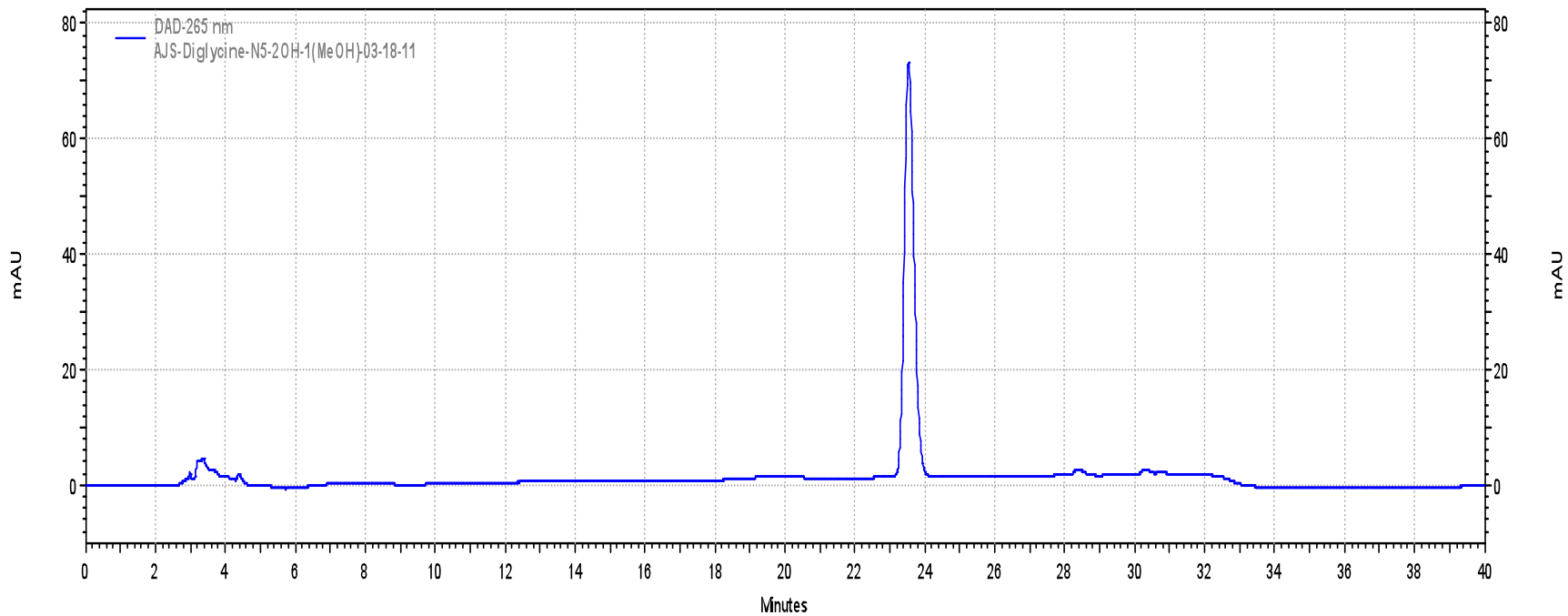
3',5'-Di-glycinyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (22). HR-ESI-MS: found: m/z 643.4391.



3',5'-Di-glycinyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (22) HPLC chromatogram (method A2, Table 3 in manuscript), retention time: 10.55 min.



3',5'-Di-glycinyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)-pentan-1-yl]thymidine (22) HPLC chromatogram (method B2, Table 3 in manuscript), retention time: 23.52 min.



2. ¹H-NMR data and R_f values for Boc-protected forms of the amino acid ester prodrugs 11-22

The progress of the formation of the Boc-protected forms of the amino acid ester prodrugs **11-22** was monitored by TLC (ethyl acetate:hexanes, 8:5).

3'-Boc-L-valyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. *R_f* 0.5; ¹H-NMR (CD₃OD): δ 0.95-1.01 (m, 6H, CH(CH₃)₂), 1.34-1.40 (m, 2H, NC₂H₄CH₂), 1.42 (s, 9H, C(CH₃)₃), 1.48-1.61 (m, 4H, NCH₂CH₂, and CH₂CH₂-C_{carborane}), 1.93 (s, 3H, CH₃), 2.04-2.35 (m, 5H, CH₂-C_{carborane}, H-2", H-2', and CH(CH₃)₂), 3.82-3.90 (m, 2H, H-5", and H-5'), 3.90 (t, *J* = 6.8 Hz, 2H, CH₂N), 3.98 (d, *J* = 4.4 Hz, 1H, OCCHNH), 4.14-4.20 (m, 1H, H-4'), 4.51 (s, 1H, carboranyl-CH), 5.31-5.38 (m, 1H, H-3'), 6.30 (t, *J* = 6.8 Hz, 1H, H-1'), 7.86 (s, 1H, H-6).

5'-Boc-L-valyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. *R_f* 0.3; ¹H-NMR (CD₃OD): δ 0.93-0.97 (m, 6H, CH(CH₃)₂), 1.28-1.35 (m, 2H, NC₂H₄CH₂), 1.42 (s, 9H, C(CH₃)₃), 1.48-1.65 (m, 4H, NCH₂CH₂, and CH₂CH₂-C_{carborane}), 1.93 (s, 3H, CH₃), 2.04-2.35 (m, 5H, CH₂-C_{carborane}, H-2", H-2', and CH(CH₃)₂), 3.89 (t, *J* = 6.8 Hz, 2H, CH₂N), 4.03 (d, *J* = 4.4 Hz, 1H, OCCHNH), 4.09-4.15 (m, 1H, H-3'), 4.31-4.41 (m, 3H, H-5", H-5', and H-4'), 4.52 (s, 1H, carboranyl-CH), 6.26 (t, *J* = 6.8 Hz, 1H, H-1'), 7.49 (s, 1H, H-6).

3',5'-Di(Boc-L-valyl)-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. *R_f* 0.8; ¹H-NMR (CD₃OD): δ 0.95-1.05 (m, 12H, 2CH(CH₃)₂), 1.34-1.42 (m, 2H, NC₂H₄CH₂), 1.47 (s, 18H, 2C(CH₃)₃), 1.57-1.62 (m, 4H, NCH₂CH₂, and CH₂CH₂-C_{carborane}), 1.90 (s, 3H, CH₃), 2.08-2.17 (m, 4H, CH₂-C_{carborane}, H-2", and H-2'), 2.23-2.30 (m, 1H, CH(CH₃)₂), 2.61-2.70 (m, 1H, CH(CH₃)₂), 3.92 (t, *J* = 6.8 Hz, 2H, CH₂N), 3.98 (d, *J* = 4.4 Hz, 2H, 2OCCHNH), 4.14-4.20 (m, 1H, H-4'), 4.52-4.63 (m, 3H, H-5", H-5', and carboranyl-CH), 5.29-5.35 (m, 1H, H-3'), 6.31 (t, *J* = 6.8 Hz, 1H, H-1'), 7.49 (s, 1H, H-6).

3'-Boc-glyciny-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.2; $^1\text{H-NMR}$ (CD_3OD): δ 1.27-1.34 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.43 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.55-1.65 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.93 (s, 3H, CH_3), 2.23-2.29 (m, 4H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2" and H-2'), 3.80-3.85 (s, 4H, OCCH_2NH , H-5", H-5'), 3.89 (t, $J = 6.4$ Hz, 2H, CH_2N), 4.25-4.33 (m, 1H, H-4'), 4.52 (s, 1H, carboranyl- CH), 5.32-5.41 (m, 1H, H-3'), 6.28 (t, $J = 6.7$ Hz, 1H, H-1'), 7.51 (s, 1H, H-6).

5'-Boc-glyciny-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.16; $^1\text{H-NMR}$ (CD_3OD): δ 1.27-1.34 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.42 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.46-1.64 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.92 (s, 3H, CH_3), 2.20-2.30 (m, 4H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2" and H-2'), 3.81-3.84 (s, 2H, OCCH_2NH), 3.89 (t, $J = 6.4$ Hz, 2H, CH_2N), 4.06-4.12 (m, 1H, H-3'), 4.30-4.42 (m, 3H, H-5", H-5', and H-4'), 4.51 (s, 1H, carboranyl- CH), 6.26 (t, $J = 6.7$ Hz, 1H, H-1'), 7.50 (s, 1H, H-6).

3',5'-Di-Boc-glyciny-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.42; $^1\text{H-NMR}$ (CD_3OD): δ 1.27-1.34 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.43 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.45 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.50-1.65 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.93 (s, 3H, CH_3), 2.26 (t, $J = 6.6$ Hz, 2H, $\text{CH}_2\text{-C}_{\text{carborane}}$), 2.40-2.47 (m, 2H, H-2" and H-2'), 3.89-3.95 (m, 6H, CH_2N , and $2\text{OCCH}_2\text{NH}$), 4.27-4.31 (m, 1H, H-4'), 4.40 (dd, $J = 11.9$, and 3.4 Hz, 1H, H-5"), 4.45 (dd, $J = 11.9$, and 3.4 Hz, 1H, H-5'), 4.51 (s, 1H, carboranyl- CH), 5.32-5.39 (m, 1H, H-3'), 6.26 (t, $J = 6.7$ Hz, 1H, H-1'), 7.50 (s, 1H, H-6).

3'-Boc-L-glutam-5-yl-1-tert.-butyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.2; $^1\text{H-NMR}$ (CD_3OD): δ 1.20-1.27 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.41 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.44 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.48-1.64 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.92 (s, 3H, CH_3), 2.20-2.41 (m, 6H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2", H-2', and CH_2CHNH), 2.45 (t, $J = 6.2$ Hz, 2H, CH_2COO), 3.77-3.81 (m, 2H, H-5", and H-5'), 3.87 (t, $J = 6.2$ Hz, 2H, CH_2N), 4.06-4.10 (m, 1H, OCCHNH), 4.41 (m, 1H, H-4'), 4.53 (s, 1H, carboranyl- CH), 5.29-5.33 (m, 1H, H-3'), 6.28 (t, $J = 6.1$ Hz, 1H, H-1'), 7.51 (s, 1H, H-6).

5'-Boc-L-glutam-5-yl-1-tert.-butyl-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.4; $^1\text{H-NMR}$ (CD_3OD): δ 1.20-1.26 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.43 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.44 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.48-1.64 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.92 (s, 3H, CH_3), 2.15-2.35 (m, 6H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2'', H-2', and CH_2CHNH), 2.47 (t, $J = 6.2$ Hz, 2H, CH_2COO), 3.85-3.92 (m, 3H, CH_2N , and H-3'), 4.23-4.32 (m, 2H, OCCHNH , and H-5''), 4.33-4.41 (m, 2H, H-4', and H-5'), 4.53 (s, 1H, carboranyl- CH), 6.27 (t, $J = 6.1$ Hz, 1H, H-1'), 7.51 (s, 1H, H-6).

3',5'-Di-Boc-L-glutam-5-yl-1-tert.-butyl ester-3-(5-{*o*-carboran-1-yl}pentyl)thymidine. R_f 0.7; $^1\text{H-NMR}$ (CD_3OD): δ 1.27-1.38 (m, 2H, $\text{NC}_2\text{H}_4\text{CH}_2$), 1.44 (s, 18H, $2(\text{CH}_3)_3\text{C}$), 1.47 (s, 18H, $2(\text{CH}_3)_3\text{C}$), 1.55-1.70 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.92 (s, 3H, CH_3), 2.05-2.18 (m, 4H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2'', and H-2'), 2.23-2.29 (m, 4H, $2\text{CH}_2\text{CHNH}$), 2.40-2.52 (m, 4H, $2\text{CH}_2\text{COO}$), 3.89 (t, $J = 7.2$ Hz, 2H, CH_2N), 3.93-4.99 (m, 2H, 2OCCHNH), 4.25-4.31 (m, 1H, H-4'), 4.35 (dd, $J = 11.9$, and 3.4 Hz, 1H, H-5''), 4.44 (dd, $J = 11.9$, and 3.4 Hz, 1H, H-5'), 4.52 (s, 1H, carboranyl- CH), 5.26-5.31 (m, 1H, H-3'), 6.25 (t, $J = 6.1$ Hz, 1H, H-1'), 7.52 (s, 1H, H-6).

3'-Boc-glycynyl-3-(5-{2-[(2,2-dimethyl-1,3-dioxolane-4-yl)methyl]-*o*-carboran-1-yl}pentyl)thymidine. R_f 0.5; $^1\text{H-NMR}$ (CD_3OD): δ 1.28-1.41 (m, 8H, $(\text{CH}_3)_2\text{C}$ and $\text{NC}_2\text{H}_4\text{CH}_2$), 1.43 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.53-1.64 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.91 (s, 3H, CH_3), 2.19-2.40 (m, 4H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2'' and H-2'), 2.45-2.61 (m, 2H, $\text{CHCH}_2\text{-C}_{\text{carborane}}$), 3.45-3.77 (m, 2H, CH_2O), 3.79-3.88 (m, 2H, H-5'' and H-5'), 3.89-3.97 (m, 4H, CH_2N , and OCCH_2NH), 4.01-4.09 (m, 1H, CH_2CHO), 4.31-4.36 (m, 1H, H-4'), 5.40-5.46 (m, 1H, H-3'), 6.23 (t, $J = 6.7$ Hz, 1H, H-1'), 7.46 (s, 1H, H-6).

5'-Boc-glycynyl-3-(5-{2-[(2,2-dimethyl-1,3-dioxolane-4-yl)methyl]-*o*-carboran-1-yl}pentyl)thymidine. R_f 0.4, $^1\text{H-NMR}$ (CD_3OD): δ 1.24-1.40 (m, 8H, $(\text{CH}_3)_2\text{C}$ and $\text{NC}_2\text{H}_4\text{CH}_2$), 1.44 (s, 9H, $(\text{CH}_3)_3\text{C}$), 1.51-1.62 (m, 4H, NCH_2CH_2 , and $\text{CH}_2\text{CH}_2\text{-C}_{\text{carborane}}$), 1.91 (s, 3H, CH_3), 2.18-2.38 (m, 4H, $\text{CH}_2\text{-C}_{\text{carborane}}$, H-2'' and H-2'), 2.51 (d, $J = 4.4$ Hz, 2H, $\text{CH}_2\text{-C}_{\text{carborane}}$), 3.27-3.36 (m, 2H, CH_2O), 3.72-

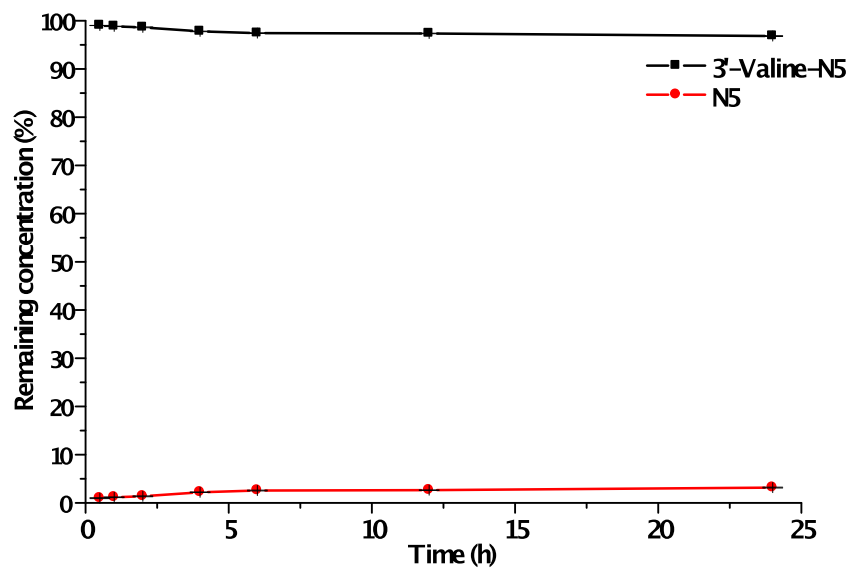
3.80 (m, 1H, H-3'), 3.82-3.94 (m, 4H, OCCH₂NH, and CH₂N), 4.02-4.08 (m, 1H, CH₂CHO), 4.31-4.38 (m, 1H, H-4'), 4.43 (dd, $J = 11.7$, and 3.6 Hz, 1H, H-5''), 4.49 (dd, $J = 11.7$, and 3.6 Hz, 1H, H-5'), 6.24 (t, $J = 6.7$ Hz, 1H, H-1'), 7.44 (s, 1H, H-6).

3',5'-Di-Boc-glycinyl-3-(5-{2-[(2,2-dimethyl-1,3-dioxolane-4-yl)methyl]-*o*-carboran-1-yl}pentyl)thymidine. $R_f = 0.7$, ¹H-NMR (CD₃OD): δ 1.25-1.42 (m, 8H, (CH₃)₂C and NC₂H₄CH₂), 1.43 (s, 9H, (CH₃)₃C), 1.45 (s, 9H, (CH₃)₃C), 1.53-1.64 (m, 4H, NCH₂CH₂, and CH₂CH₂-C_{carborane}), 1.91 (s, 3H, CH₃), 2.22-2.40 (m, 4H, CH₂-C_{carborane}, H-2'' and H-2'), 2.46-2.60 (m, 2H, CH₂-C_{carborane}), 3.45-3.71 (m, 2H, CH₂O), 3.82-3.98 (m, 6H, CH₂N and 2OCCH₂NH), 4.01-4.06 (m, 1H, CH₂CHO), 4.32-4.37 (m, 1H, H-4'), 4.49 (dd, $J = 11.7$, and 3.6 Hz, 1H, H-5''), 4.59 (dd, $J = 11.7$, and 3.6 Hz, 1H, H-5'), 5.42-5.48 (m, 1H, H-3'), 6.23 (t, $J = 6.7$ Hz, 1H, H-1'), 7.46 (s, 1H, H-6).

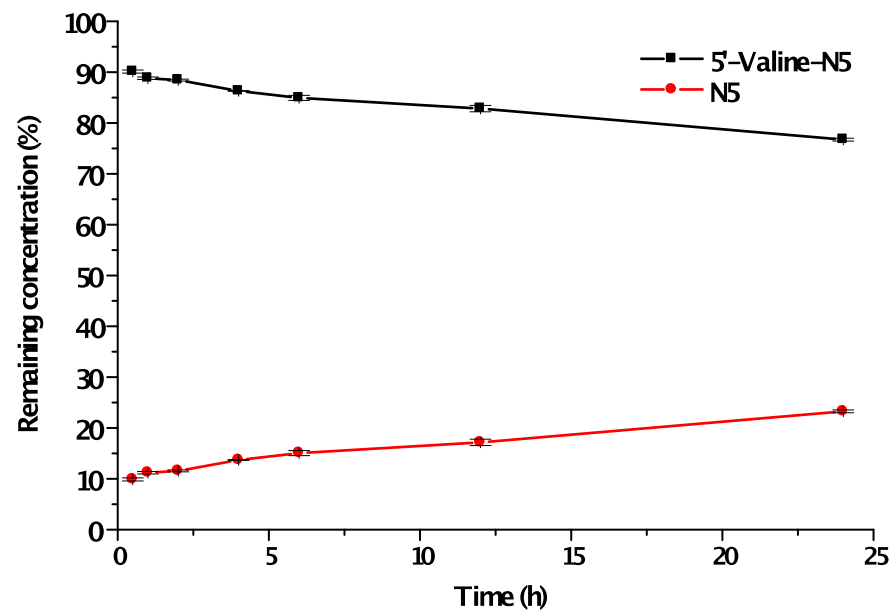
3. The percentage of the remaining concentrations of the amino acid ester prodrugs following incubation in phosphate buffer saline (PBS), Bovine serum, and Bovine cerebrospinal fluid (CSF) at 37 °C at various time intervals

a. The percentage of the remaining concentrations of the amino acid ester prodrugs **11-19**, and **21** following incubation in PBS at 37 °C at various time intervals.

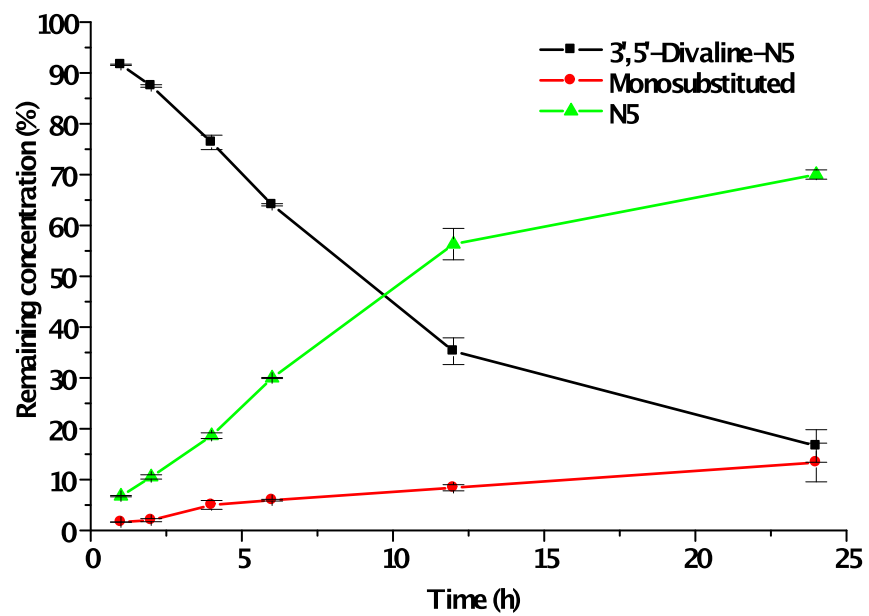
3'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (11).



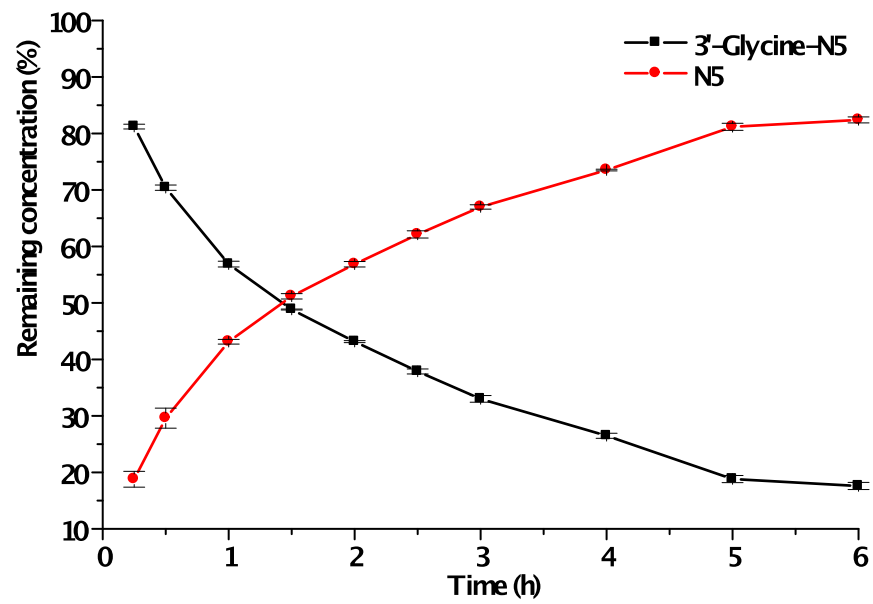
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12).



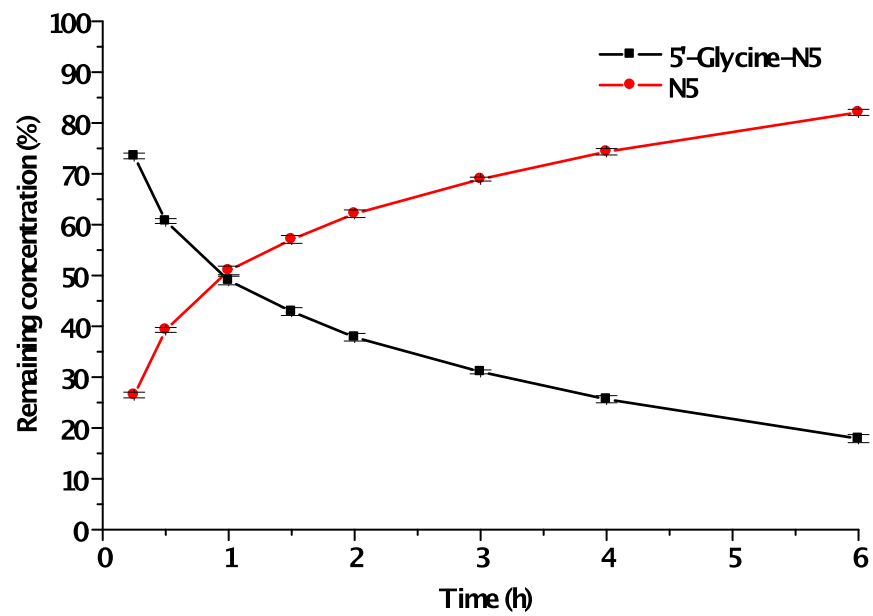
3',5'-Di-L-valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (13).



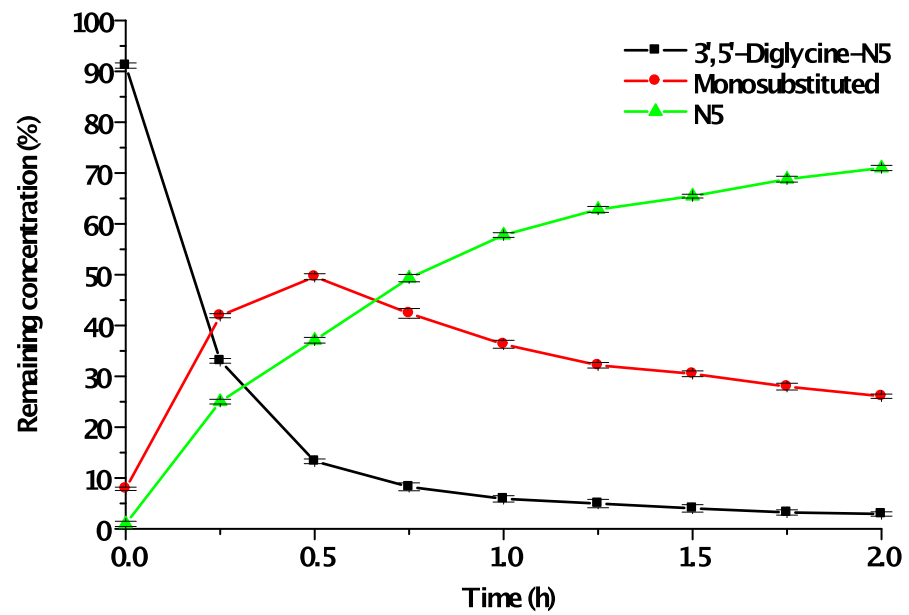
3'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (14).



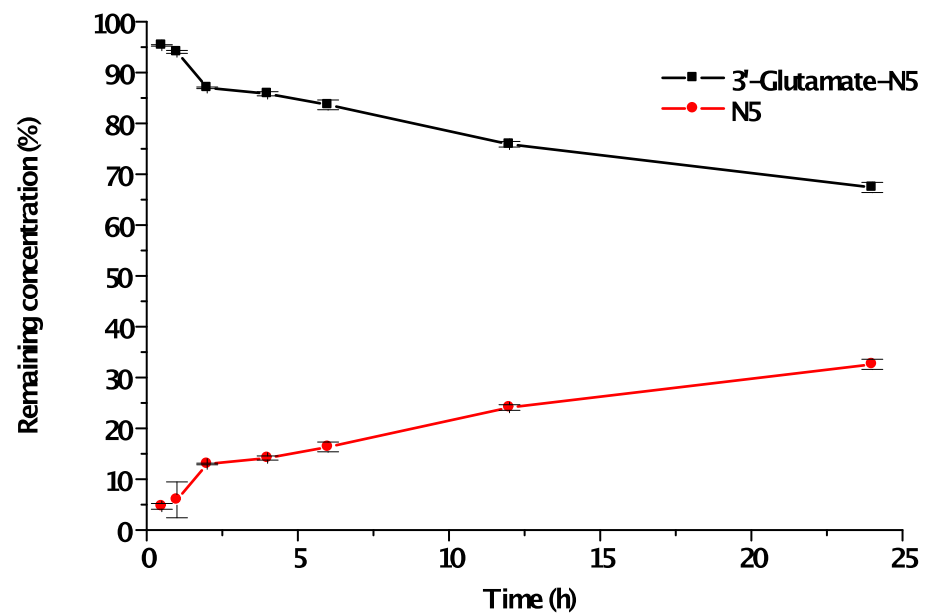
5'-Glycyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (15).



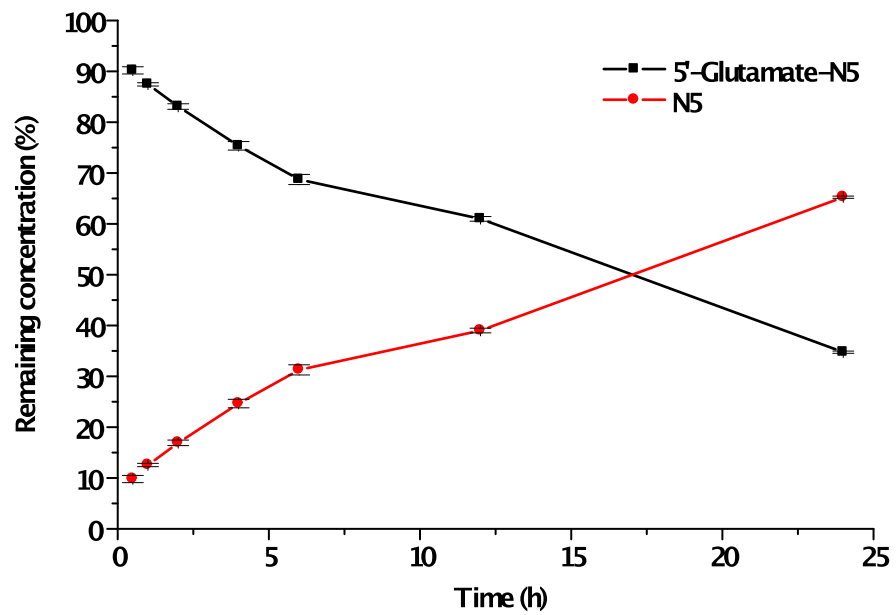
3',5'-Di-glyciny-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (16).



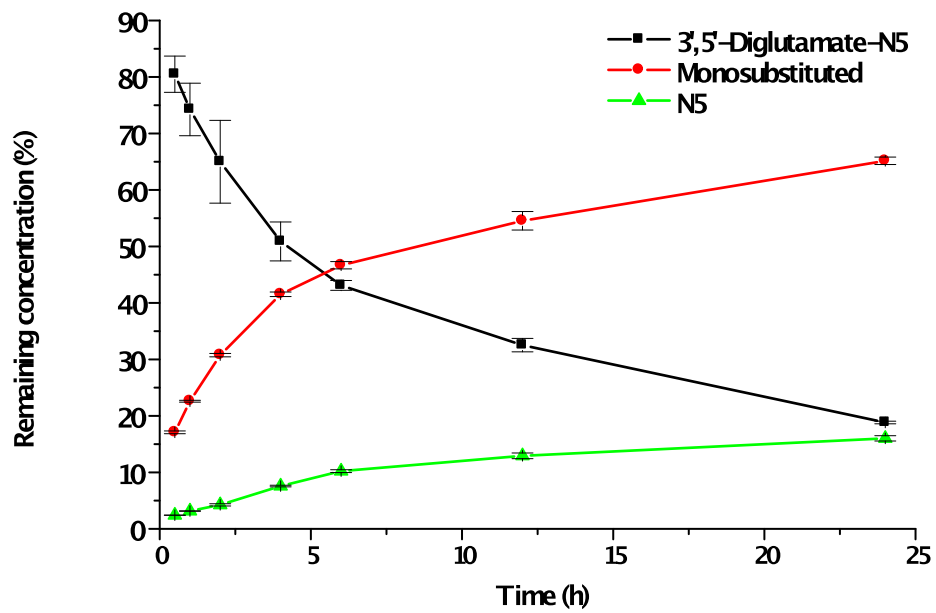
3'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (17).



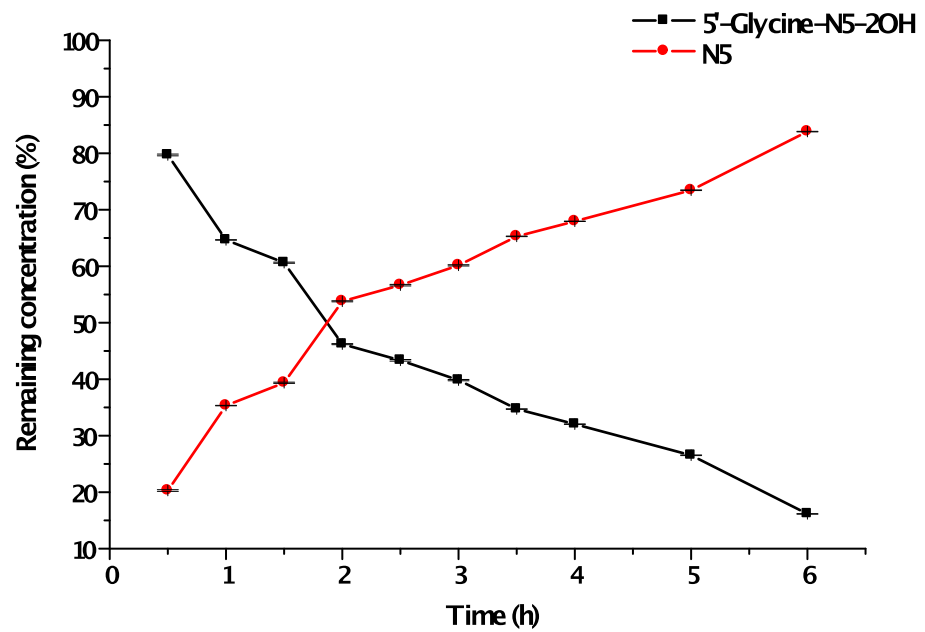
5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18).



3',5'-Di-L-glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (19).

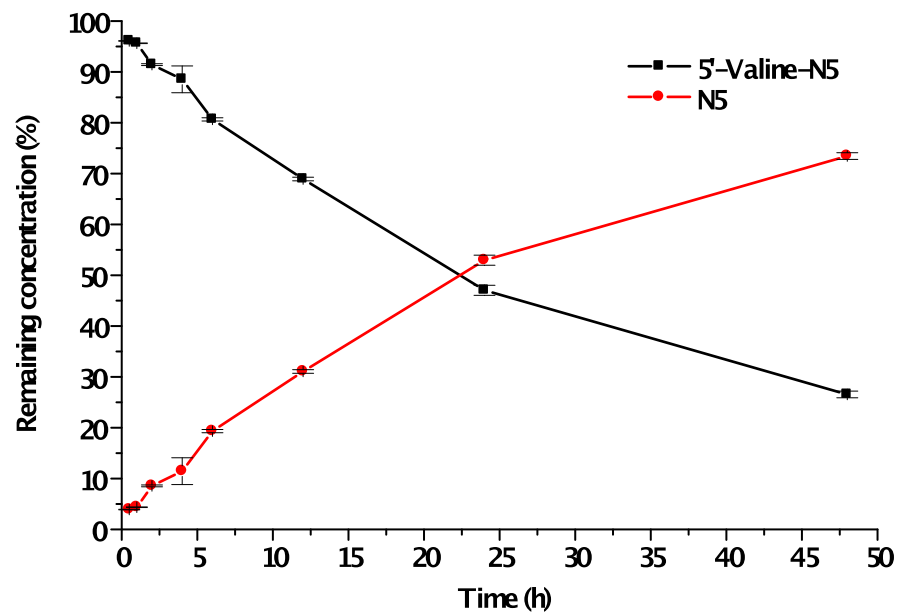


5'-Glycyl-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)pentan-1-yl]thymidine (21).

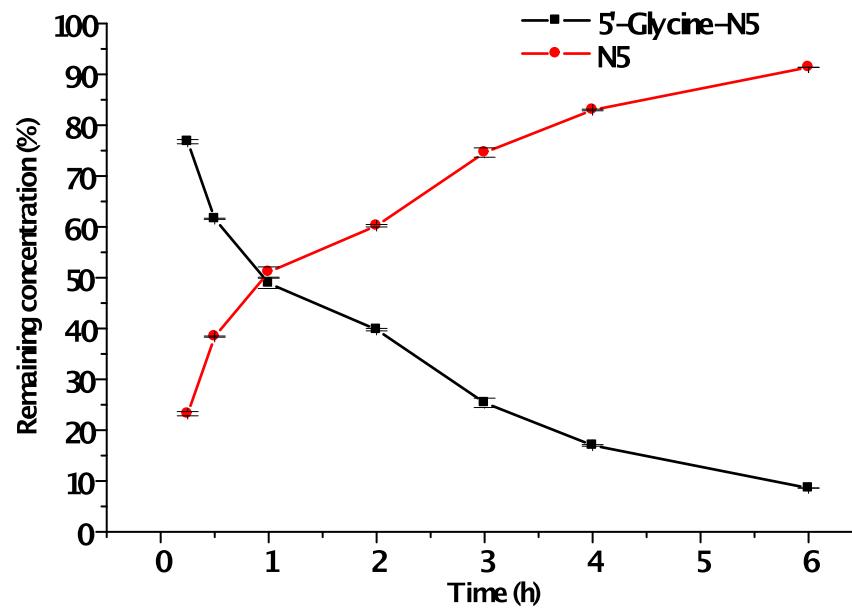


b. The percentage of the remaining concentrations of the amino acid ester prodrugs **12**, **15**, **18**, and **21** following incubation in Bovine serum at 37 °C at various time intervals.

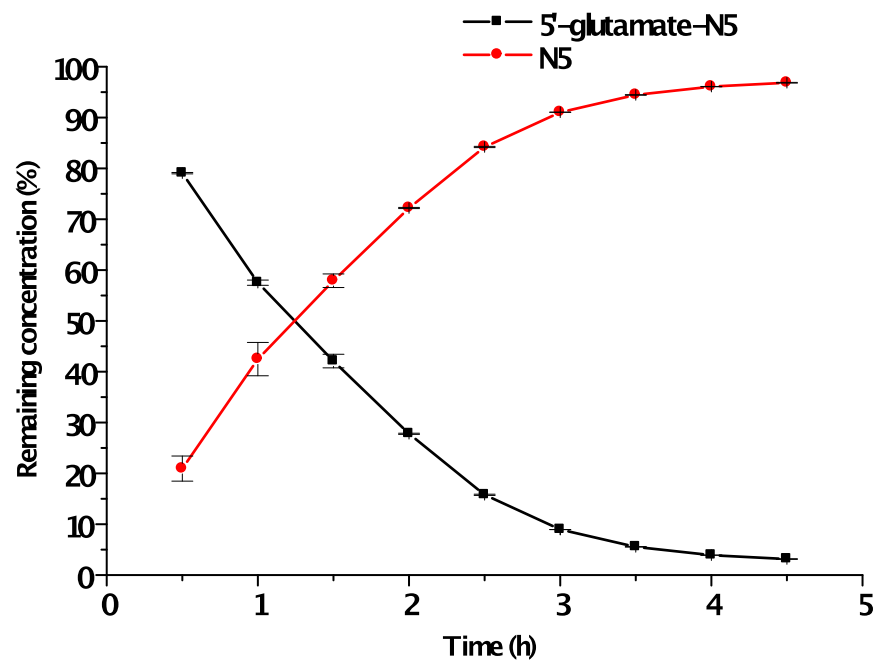
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12).



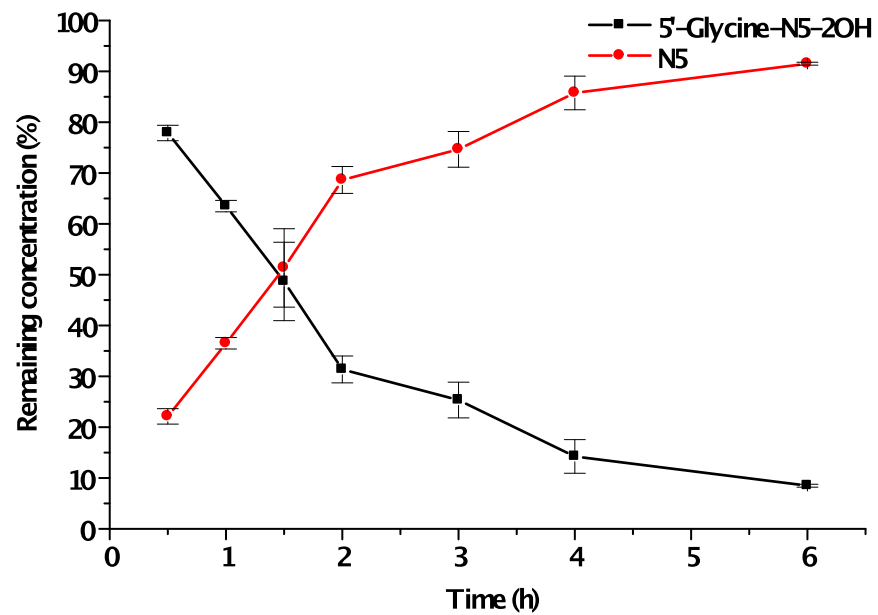
5'-Glycyl-3-(5-*o*-carboran-1-yl)pentan-1-yl)thymidine (15).



5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18).

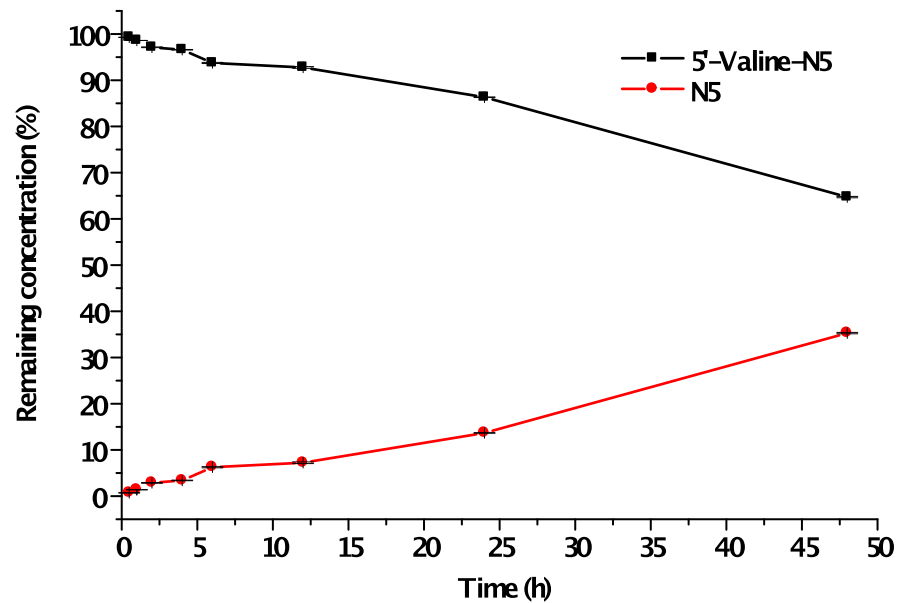


5'-Glyciny-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)pentan-1-yl]thymidine (21).

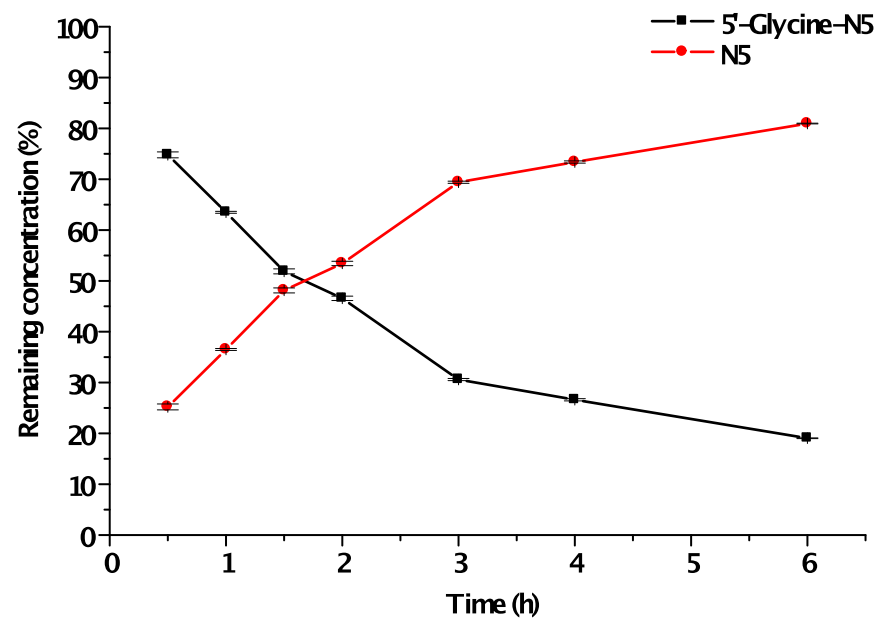


- c. The percentage of the remaining concentrations of the amino acid ester prodrugs **12**, **15**, **18**, and **21** following incubation in CSF at 37 °C at different time intervals.

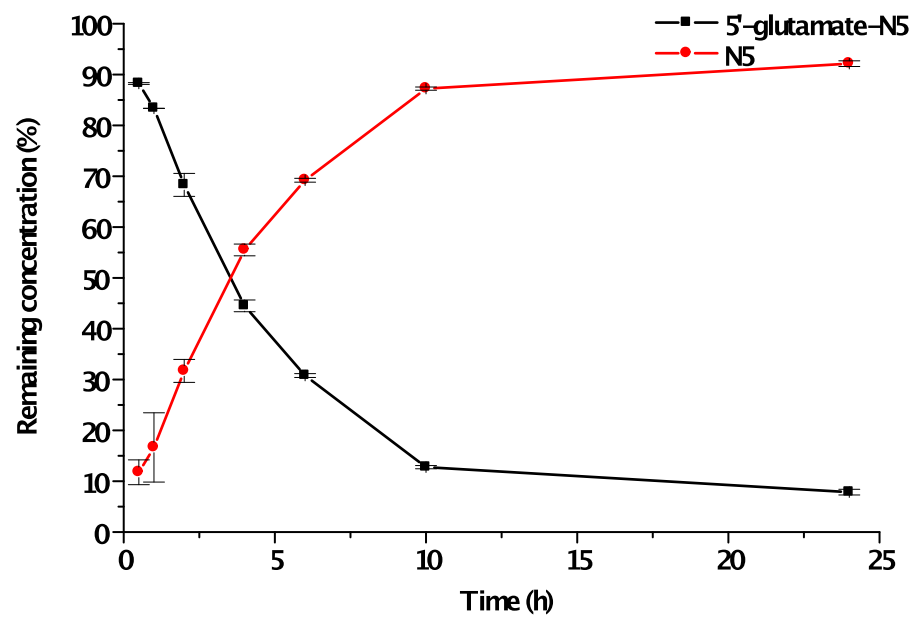
5'-L-Valyl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (12).



5'-Glyciny-3-(5-*o*-carboran-1-yl)pentan-1-yl)thymidine (15).



5'-L-Glutam-5-yl-3-(5-{*o*-carboran-1-yl}pentan-1-yl)thymidine (18).



5'-Glyciny-3-[5-(2-{2,3-dihydroxyprop-1-yl}-*o*-carboran-1-yl)pentan-1-yl]thymidine (21).

