

Supporting Information

Small molecule inhibitors that discriminate between protein arginine N-methyltransferases PRMT1 and CARM1

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Chemistry: Intermediates not explicitly described within the manuscript are detailed with characterisation in the same order below. These protected compounds are numbered '**P-No.**', where No. corresponds to the number of the denuded compound in the manuscript.

General procedure for first reductive amination: method 1

5'-Amino-5'-deoxy-2',3'-O,O-(1-methylethylidene)adenosine **8**¹ (1.2 mol eq.) and aldehyde **5**,² **6**,³ **7**⁴ or **12**⁵ (1.0 mol eq.) were suspended in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (5 mL) at room temperature under Ar and the mixture gently heated with vigorous stirring to obtain a solution. $\text{NaBH}(\text{OAc})_3$ (1.4 mol eq.) was slowly added portionwise and the reaction left for 2-4 hrs at room temperature under Ar. The reaction was then quenched by addition of saturated aqueous Na_2CO_3 solution (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to yield the crude product. The product was purified by column chromatography on silica gel eluting with MeOH: CH_2Cl_2 , 5:95, unless specified otherwise.

General procedure for second reductive amination: method 2

Secondary amines **9**,³⁰ **10** or **11** (1.0 mol eq.) and aldehydes **12**,⁵ **13**, **14**, or **15** (1.1 mol eq.) with MgSO_4 (10 mol eq.) were used, then as method 1 above.

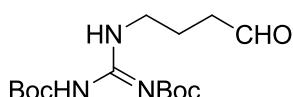
General procedure for deprotection: method 3

Intermediates from method 2 above were dissolved in TFA (4 mL) and water (0.10 mL) and stirred overnight. The mixture was concentrated *in vacuo*, dissolved in water (5 mL) and washed with EtOAc (2 x 5 mL). The aqueous layer was concentrated *in vacuo* to ~ 1mL then applied to a column of Amberlite IRA-400 (Cl^-) ion exchange resin, eluted with water, and fractions containing product freeze dried to give the hydrochloride salts **16-18**,³⁰ **19-24**.

General procedure for Swern oxidations

Oxalyl chloride (1.2 mol eq) was added into a solution of dry DMSO (2.4 mol eq.) in dry CH_2Cl_2 (15 mL) at -78 °C and stirred for 30 mins under Ar. A solution of alcohol (1 mol eq.) in dry CH_2Cl_2 (15 mL) was slowly added via cannula and the reaction stirred for 30 min. Dry Et_3N (5 mol eq.) was slowly added and the reaction stirred for 30 mins then slowly warmed to r.t. The reaction was quenched by the addition of H_2O (15 mL) and the mixture extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The product was purified by column chromatography on silica gel.

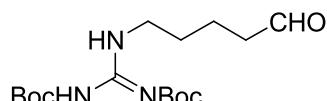
2,3-di(*tert*-Butoxycarbonyl)-1-(4-oxobutyl)guanidine (13)



Swern oxidation of 2,3-di(*tert*-butoxycarbonyl)-1-(4-hydroxybutyl)-guanidine.⁶

Elution with EtOAc: petroleum ether (40/60) 20:80 gave the product as a clear oil (1.32 g, 88%), ν_{max} / cm^{-1} 3328 (w), 3285 (w), 3007 (w), 2984 (w), 2935 (w), 1722 (s), 1636 (s), 1617 (s), 1417 (m), 1394 (w), 1369 (s), 1332 (s), 1289 (w), 1253 (w), 1240 (w), 1158 (s), 1136 (s), 1052 (w), 1027 (w); ^1H NMR δ_{H} (400 MHz, CDCl_3) 9.80 (1H, s, CHO), 8.37 (1H, br s, C(N)NH CH_2), 3.45 (2H, app. q, J = 7.1, NH CH_2), 2.54 (2H, t, J = 7.0, CH_2CHO), 1.92 (2H, quintet, J = 7.1, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.51 (18H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR δ_{C} (100 MHz, CDCl_3) 201.2 (CHO), 163.5 (C), 156.3 (C), 153.3 (C), 83.2 (C), 79.3 (C), 41.1 (CH_2), 40.0 (CH_2), 28.3 (CH_3), 28.2 (CH_3), 21.7 (CH_2); m/z (ESI) 362.2 (100%, M + MeOH + H^+), 330.2 (24%, M + H^+) Found 330.2014 $\text{C}_{15}\text{H}_{28}\text{N}_3\text{O}_5$ requires 330.2023.

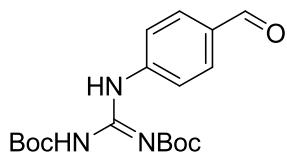
2,3-di(*tert*-Butoxycarbonyl)-1-(5-oxopentyl)-guanidine (14)



Swern oxidation of 2,3-di(*tert*-butoxycarbonyl)-1-(5-hydroxypentyl)-guanidine.⁶

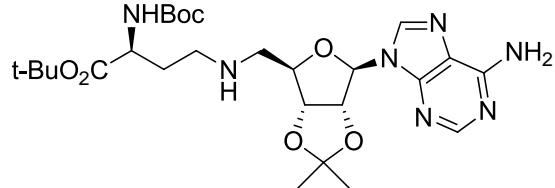
Elution with EtOAc: petroleum ether (40/60) 30:70 gave the product as a white solid (0.98 g, 81%), mp 104-106 °C; ν_{max} / cm^{-1} 3329 (w), 2986 (w), 2945 (w), 1722 (s), 1681 (m), 1635 (s), 1476 (w), 1455 (w), 1417 (s), 1394 (m), 1368 (s), 1334 (s), 1280 (m), 1254 (m), 1160 (s), 1136 (s), 1054 (w), 989 (w); ^1H NMR δ_{H} (400 MHz, CDCl_3) 9.78 (1H, d, J = 1.4, CHO), 8.34 (1H, br s, C(N)NH CH_2), 3.45 (2H, app. q, J = 7.0, NH CH_2), 2.50 (2H, td, J = 7.2, 1.4, CH_2CHO), 1.75-1.60 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.51 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.50 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR δ_{C} (100 MHz, CDCl_3) 202.0 (CHO), 163.6 (C), 156.2 (C), 153.3 (C), 83.1 (C), 79.3 (C), 43.4 (CH_2), 40.4 (CH_2), 28.5 (CH_2), 28.3 (CH_3), 28.1 (CH_3), 19.3 (CH_2); m/z (ESI) 376.2 (39%, M + MeOH + H^+), 344.2 (100%, M + H^+) Found 344.2181 $\text{C}_{16}\text{H}_{30}\text{N}_3\text{O}_5$ requires 344.2180.

1-[4-(formyl)phenyl]-2,3-bis-(*tert*-butoxycarbonyl)guanidine (15)



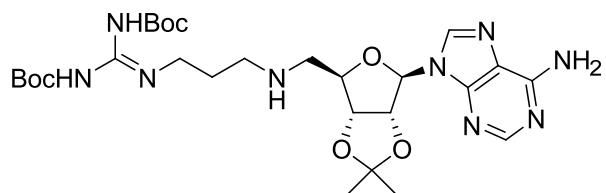
Swern oxidation of 1-[4-(hydroxymethyl)phenyl][[2,3-bis-(*tert*-butoxycarbonyl)guanidine].⁷ Elution with EtOAc: petroleum ether (40/60) 10:90 gave the product as a white solid (1.545 g, 50%), mp 133 °C (dec.) (CH_2Cl_2); ν_{max} / cm⁻¹ 3147 (w), 2986 (w), 2936 (w), 2830 (w), 2744 (w), 1722 (m), 1698 (m), 1637 (s), 1590 (s), 1558 (s), 1476 (w), 1455 (w), 1413 (s), 1370 (m), 1342 (m), 1307 (s); ¹H NMR δ_{H} (400 MHz, CDCl_3) 11.75 (1H, br s, NH), 10.67 (1H, s, NH), 9.94 (1H, s, CHO), 7.82-7.90 (4H, m, ArH), 1.55 (18H, s, $\text{C}(\text{CH}_3)_3$); ¹³C NMR δ_{C} (100 MHz, CDCl_3) 191.0 (C), 153.2 (C), 142.6 (Cx2), 132.4 (C), 130.9 (CH), 121.5 (CH), 84.3 (C), 80.2 (C), 28.1 (CH₃); *m/z* (ESI) 749.3 (100%, 2M + Na⁺), 386.2 (39%, M + Na⁺), 364.2 (38%, M + H⁺) Found 364.1867 $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_5$ requires 364.1867.

5'-[[(3*S*)-4-(*tert*-butoxy)-3-[(*tert*-butoxy)carbonyl]amino]-4-oxobutyl]amino]-5'-deoxy-2',3'-O-(1-methylethylidene)-adenosine (9)



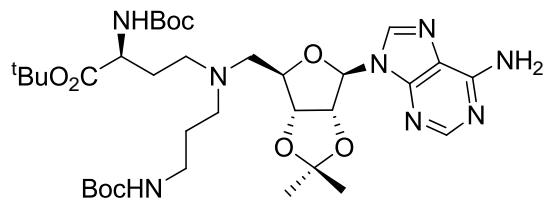
Method 1. Column chromatography on silica gel, elution with EtOAc:MeOH, 25:1, gave secondary amine **9** as a white solid (0.09 g, 73%), mp 87-89 °C; $[\alpha]^{23}_{\text{D}} -34.6$ (c 1.70 in CHCl_3); ν_{max} / cm⁻¹ 3525 (w), 3414 (w), 2980 (m), 2933 (m), 1707 (s), 1632 (s), 1589 (s), 1328 (s), 1151 (s), 1077 (m); ¹H NMR δ_{H} (400 MHz; CDCl_3) 8.33 (1H, s, ArH), 7.93 (1H, s, ArH), 6.06 (2H, s, adenosine-NH₂), 6.00 (1H, d, *J* = 8.4, NHBoc), 5.98 (1H, d, *J* = 3.6, 1'-H), 5.50 (1H, dd, *J* = 6.2, 3.6, 2'-H), 5.08 (1H, dd, *J* = 6.2, 3.2, 3'-H), 4.41-4.37 (1H, m, 4'-H), 4.34-4.25 (1H, m, CHCH_2CH_2), 2.96 (1H, dd, *J* = 12.7, 3.8, 5'-CH_aH_b), 2.80 (1H, dd, *J* = 12.7, 5.2, 5'-CH_aH_b), 2.77-2.72 (1H, m, CH_aH_bNH), 2.70-2.59 (1H, m, CH_aH_bNH), 1.90-1.77 (2H, m, CHCH_2CH_2) 1.62 (3H, s, CH₃), 1.51 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.40 (3H, s, CH₃), 1.38 (s, 9H, $\text{C}(\text{CH}_3)_3$); ¹³C NMR δ_{C} (100 MHz; CDCl_3) 171.9 (C), 155.7 (C), 155.6 (C), 153.1 (CH), 149.5 (C), 139.9 (CH), 120.4 (C), 114.6 (C), 91.1 (CH), 85.0 (CH), 83.0 (CH), 82.2 (CH), 81.7 (C), 79.4 (C), 53.0 (CH), 51.4 (CH₂), 46.3 (CH₂), 32.3 (CH₂), 28.3 (CH₃), 28.0 (CH₃), 27.4 (CH₃), 25.5 (CH₃); *m/z* (ESI) 564.3 (100%, M + H⁺) Found 564.3111 $\text{C}_{26}\text{H}_{42}\text{N}_7\text{O}_7$ requires 564.3146.

5'-[3-[2,3-di-(*tert*-butoxycarbonyl)guanidino]propyl]amino]-5'-deoxy-2',3'-O-(1-methylethylidene)-adenosine



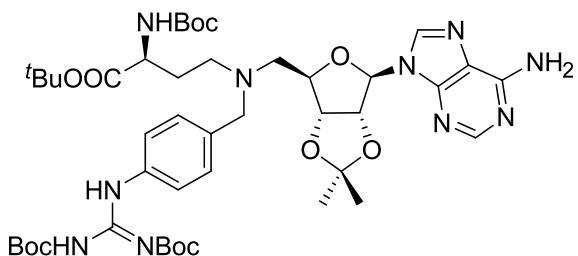
Method 1. Elution MeOH: CH₂Cl₂, from 10:90 to 15:85 gave the product as a white solid (0.516 g, 43%), mp 103-104 °C (CH₂Cl₂); [α]¹⁹_D -21.1 (c 1.00 in CHCl₃); ν_{max} / cm⁻¹ 2986 (m), 2936 (w), 1721 (m), 1632 (s), 1588 (s), 1473 (w), 1456 (w), 1417 (m), 1393 (w), 1369 (s), 1330 (s); ¹H NMR δ_H (400 MHz; CDCl₃) 8.46 (1H, br s, NH), 8.32 (1H, s, ArH), 7.95 (1H, s, ArH), 6.01 (1H, d, *J* = 3.1, 1'-H), 5.98 (2H, br s, adenosine-NH₂), 5.47 (1H, dd, *J* = 6.4, 3.1, 2'-H), 5.02 (1H, dd, *J* = 6.4, 3.3, 3'-H), 4.42-4.36 (1H, m, 4'-H), 3.51-3.44 (2H, m, C(N)NHCH₂), 2.94-2.81 (2H, m, 5'-CH₂), 2.72-2.59 (2H, m, CH₂NH), 1.70 (2H, quin, *J* = 6.8, CH₂CH₂NH), 1.60 (3H, s, CH₃), 1.48 (18H, s, C(CH₃)₃), 1.38 (3H, s, CH₃); ¹³C NMR δ_C (100 MHz; CDCl₃) 163.5 (C), 156.2 (C), 155.6 (C), 153.2 (C), 153.1 (CH), 149.4 (C), 139.9 (CH), 120.3 (C), 114.5 (C), 90.8 (CH), 58.6 (CH), 83.5 (CH), 82.9 (C), 82.4 (CH), 79.2 (C), 51.3 (CH₂), 47.1 (CH₂), 38.9 (CH₂), 29.1 (CH₂), 28.2 (CH₃), 28.0 (CH₃), 27.2 (CH₃), 25.4 (CH₃); *m/z* (ESI) 606.3 (M + H⁺, 100%) Found 606.3360 C₂₇H₄₄N₉O₇ requires 606.3358; Calc. for C₂₇H₄₃N₉O₇.

5'-deoxy-5'-[[[(3S)-4-(*tert*-butoxy)-3-[(1,1 dimethylethoxy)carbonyl]amino]-4-oxobutyl] [(3-(*tert*-butoxycarbonyl)aminopropyl]amino]-2',3'-O-(1-methylethylidene)-adenosine (P19)



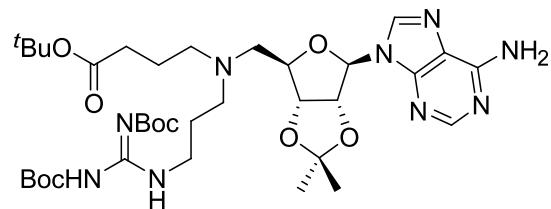
Method 2. gave a white solid (0.447 g, 71%), mp 86-87 °C (CH_2Cl_2); $[\alpha]^{23}_{\text{D}} -19.5$ (c 1.05 in CHCl_3); $\nu_{\text{max}} / \text{cm}^{-1}$ 3011 (w), 2984 (m), 2936 (w), 1712 (s), 1633 (s), 1604 (w), 1505 (m), 1369 (s), 1248 (m), 1158 (s); ^1H NMR δ_{H} (400 MHz; CDCl_3) 8.33 (1H, s, ArH), 7.93 (1H, s, ArH), 6.07 (1H, d, $J = 1.5, 1'\text{-}H$), 5.87 (2H, br s, NH_2), 5.48-5.56 (2H, m, 2'-H and NH), 5.00-5.07 (1H, br m, 3'-H), 4.32-4.36 (1H, m, 4'-H), 4.15-4.25 (1H, br m, CHCH_2), 3.05-3.21 (2H, m, NHCH_2), 2.74 (1H, dd, $J = 13.0, 7.5, 5'\text{-}CH_aH_b$), 2.54-2.63 (1H, m, $\text{CHCH}_2\text{CH}_a\text{H}_b$), 2.44-2.54 (2H, m, 5'- CH_aH_b and $\text{NHCH}_2\text{CH}_2\text{CH}_a\text{H}_b\text{N}$), 2.31-2.42 (2H, m, $\text{CHCH}_2\text{CH}_a\text{H}_b$ and $\text{NHCH}_2\text{CH}_2\text{CH}_a\text{H}_b\text{N}$), 1.89-2.00 (1H, br m, CHCH_aH_b), 1.65-1.72 (1H, m, CHCH_aH_b), 1.63 (3H, s, CH_3), 1.50-1.58 (2H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.44 (18H, s, $\text{C}(\text{CH}_3)_3$), 1.41 (3H, s, CH_3); ^{13}C NMR δ_{C} (100 MHz; CDCl_3) 171.9 (C), 156.2 (C), 155.6 (C), 153.0 (CH), 149.1 (C), 140.2 (CH), 120.3 (C), 114.4 (C), 90.9 (CH), 85.7 (CH), 84.0 (CH), 83.5 (CH), 81.7 (C), 79.6 (C), 78.8 (C), 77.2 (C), 56.1 (CH₂), 52.8 (CH), 51.6 (CH₂), 50.5 (CH₂), 38.2 (CH₂), 29.3 (CH₂), 28.5 (CH₃), 28.4 (CH₃), 28.0 (CH₃), 27.1 (CH₃), 26.9 (CH₂), 25.5 (CH₃); m/z (ESI) 721.4 (100%, M + H⁺) Found 721.4247 $\text{C}_{34}\text{H}_{57}\text{N}_8\text{O}_9$ requires 721.4243;

5'-deoxy-5'-[[[(3*S*)-4-(*tert*-butoxy)-3-[[[(1,1-dimethylethoxy)carbonyl]amino]-4-oxobutyl][[4-[2,3-bis-(*tert*-butoxycarbonyl)]guanidinophenyl]methyl]amino]-2',3'-O-(1-methylethylidene)-adenosine (P20)



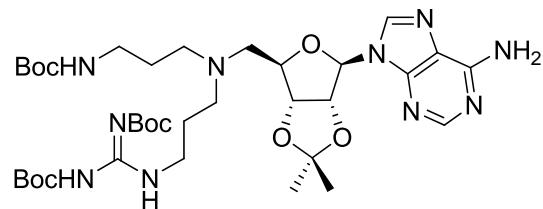
Method 2 gave the product as a white solid (0.57 g, 71%), mp 119-121 °C (CH_2Cl_2); $[\alpha]^{26}_{\text{D}} -10.3$ (c 1.00 in CHCl_3); ν_{max} / cm^{-1} 3012 (s), 2985 (m), 2937 (m), 1714 (s), 1633 (s), 1606 (s), 1564 (m), 1506 (m), 1476 (m), 1456 (m), 1416 (s), 1394 (s), 1370 (m), 1340 (s), 1303 (m), 1240 (s), 1154 (s); ^1H NMR δ_{H} (400 MHz; CDCl_3) 11.65 (1H, s, NH), 10.26 (1H, s, NH), 8.24 (1H, s, ArH), 7.80 (1H, s, ArH), 7.46 (2H, d, $J = 7.8$, ArH), 7.16 (2H, d, $J = 7.8$, ArH), 6.05 (1H, br m, 1'- H), 5.69 (2H, s, adenosine- NH_2), 5.62 (1H, br m, NH), 5.37 (1H, d, $J = 5.4$, 2'- H), 4.79-4.87 (1H, br m, 3'- H), 4.30-4.43 (1H, br m, 4'- H), 4.10-4.25 (1H, br m, CHCH_2), 3.62 (1H, d, $J = 13.4$, ArCH_aH_b), 3.43 (1H, d, $J = 13.4$, ArCH_aH_b), 2.46-2.74 (4H, m, 5'- CH_2 and CHCH_2CH_2), 1.93-2.07 (1H, m, CHCH_aH_b), 1.68-1.87 (1H, m, CHCH_aH_b), 1.61 (3H, s, CH_3), 1.55 (9H, s, $(\text{CH}_3)_3$), 1.49 (9H, s, $(\text{CH}_3)_3$), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.38 (3H, s, CH_3); ^{13}C NMR δ_{C} (100 MHz; CDCl_3) 171.7 (C), 163.6 (C), 155.4 (C), 153.5 (C x 2), 153.3 (C), 153.1 (CH), 149.2 (C), 139.9 (CH), 135.7 (C), 134.9 (C), 129.4 (CH), 122.2 (CH), 120.3 (C), 114.3 (C), 90.7 (CH), 85.3 (CH), 83.8 (CH), 83.7 (C), 83.4 (CH), 81.6 (C), 79.6 (C), 79.4 (C), 58.3 (CH₂), 55.5 (CH₂), 53.0 (CH), 50.7 (CH₂), 29.3 (CH₂), 28.4 (CH₃), 28.2 (CH₃), 28.1 (CH₃), 28.0 (CH₃), 27.1 (CH₃), 25.4 (CH₃); m/z (ESI) 911.5 (100%, $\text{M} + \text{H}^+$) Found 911.4965 $\text{C}_{44}\text{H}_{67}\text{N}_{10}\text{O}_{11}$ requires 911.4985;

5'-deoxy-5'-[[[(4-(*tert*-butoxy)-4-oxobutyl]3-[2,3-di(*tert*-butoxycarbonyl)guanidino]propyl]amino]-2',3'-O-(1-methylethylidene)-adenosine (P21)



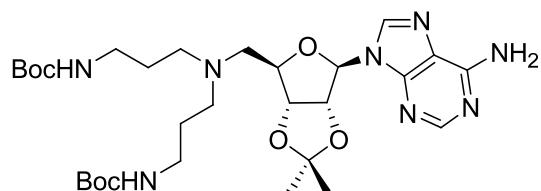
Method 2. White solid (0.468 g, 79%), mp 81-83 °C (CH_2Cl_2); $[\alpha]^{26}_{\text{D}} -13.6$ (c 1.00 in CHCl_3); ν_{max} / cm^{-1} 2984 (m), 1720 (s), 1633 (s), 1588 (s), 1475 (m), 1456 (w), 1418 (m), 1369 (s), 1331 (s), 1290 (m), 1240 (m), 1157 (s), 1135 (s); ^1H NMR δ_{H} (400 MHz; CDCl_3) 11.50 (1H, s, NH), 8.44 (1H, br m, NH), 8.36 (1H, s, ArH), 7.97 (1H, s, ArH), 6.05 (1H, d, J = 2.1, 1'-H), 5.73 (2H, s, adenosine-NH₂), 5.52 (1H, dd, J = 6.4, 2.1, 2'-H), 4.97 (1H, dd, J = 6.4, 3.2, 3'-H), 4.34 (1H, app. td, J = 6.8, 3.2, 4'-H), 3.33-3.50 (2H, m, NHCH₂), 2.74 (1H, dd, J = 13.6, 6.8, 5'-CH_aH_b), 2.58 (1H, dd, J = 13.6, 6.8, 5'-CH_aH_b), 2.39-2.55 (4H, m, COCH₂CH₂CH₂N and NHCH₂CH₂CH₂N), 2.16-2.23 (2H, m, COCH₂CH₂CH₂N), 1.61-1.73 (4H, m, COCH₂CH₂CH₂N and NHCH₂CH₂CH₂N), 1.60 (3H, s, CH₃), 1.50 (18H, s, C(CH₃)₃), 1.43 (9H, s, C(CH₃)₃), 1.39 (3H, s, CH₃); ^{13}C NMR δ_{C} (100 MHz; CDCl_3) 172.8 (C), 163.6 (C), 156.1 (C), 155.5 (C), 153.2 (C), 153.1 (CH), 149.3 (C), 140.2 (CH), 120.3 (C), 114.3 (C), 91.0 (CH), 85.6 (CH), 83.7 (CH), 83.4 (CH), 82.9 (C), 80.1 (C), 79.2 (C), 56.1 (CH₂), 53.5 (CH₂), 52.0 (CH₂), 39.3 (CH₂), 33.1 (CH₂), 28.3 (CH₃), 28.10 (CH₃), 28.08 (CH₃), 27.1 (CH₃), 26.5 (CH₂), 25.3 (CH₃), 22.0 (CH₂); m/z (ESI) 748.4 (100%, M + H⁺) Found 748.4351 C₃₅H₅₈N₉O₉ requires 748.4352; Calc. for C₃₅H₅₇N₉O₉.

5'-[3-[2,3-di-(*tert*-butoxycarbonyl)guanidino]propyl][(3-(*tert*-butoxycarbonyl)aminopropyl]amino]-5'-deoxy-2',3'-O-(1-methylethylidene)-adenosine (P22)



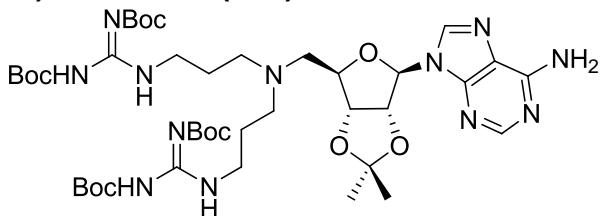
Method 2. Column chromatography on silica gel (MeOH:CH₂Cl₂ 5:95 to 10:90) gave the product as a white solid (0.187 g, 35%), mp 87-88 °C (CH₂Cl₂); [α]²³_D - 8.2 (c 1.05 in CHCl₃); ν_{max} / cm⁻¹ 3414 (w), 3328 (w), 2984 (m), 1712 (s), 1632 (s), 1506 (w), 1473 (w), 1417 (m), 1393 (w), 1368 (s), 1330 (m), 1289 (m), 1248 (m), 1158 (s), 1136 (s); ¹H NMR δ_H (400 MHz; CDCl₃) 11.49 (1H, br s, NH), 8.35 (1H, br s, NH), 8.31 (1H, s, ArH), 7.95 (1H, s, ArH), 6.09 (2H, br s, NH₂), 6.05 (1H, d, *J* = 1.9, 1'-H), 5.92 (1H, br m, 2'-H), 5.55 (1H, br m, NH), 5.05 (1H, dd, 6.4, 3.2, 3'-H), 4.82 (1H, m, 4'-H), 3.41 (2H, td, *J* = 6.9, 5.4, CONHCH₂), 2.99-3.17 (2H, m, C(N)NHCH₂), 2.65 (1H, dd, *J* = 13.3, 7.0, 5'-CH_aH_b), 2.43-2.55 (2H, m, 5'-CH_aH_b and CONHCH₂CH₂CH₂N), 2.34-2.43 (2H, m, C(N)NHCH₂CH₂CH₂N), 1.59 (3H, s, CH₃), 1.47 (18H, s, C(CH₃)₃ × 2), 1.43-1.45 (4H, m, CONHCH₂CH₂CH₂N and C(N)NHCH₂CH₂CH₂N), 1.41 (9H, s, C(CH₃)₃), 1.38 (3H, s, CH₃); ¹³C NMR δ_C (100 MHz; CDCl₃) 163.5 (C), 156.0 (C), 155.7 (C), 153.2 (C), 153.0 (CH), 149.1 (C), 140.1 (CH), 120.2 (C), 114.2 (C), 90.8 (CH), 85.7 (CH), 83.8 (CH), 83.4 (CH), 82.9 (C), 79.1 (C × 2), 78.7 (C), 56.1 (CH₂), 53.4 (CH₂), 51.5 (CH₂), 39.0 (CH₂), 38.5 (CH₂), 28.4 (CH₃), 28.2 (CH₃), 28.0 (CH₃), 27.0 (CH₃), 26.5 (CH₂), 26.2 (CH₂), 25.3 (CH₃); *m/z* (ESI) 763 (100%, M + H⁺) Found 763.4450 C₃₅H₅₉N₁₀O₉ requires 763.4461.

5'-[di(3-(*tert*-butoxycarbonyl)aminopropyl]amino]-5'-deoxy-2',3'-O-(1-methylethylidene)-adenosine (P23)



Method 2. White solid (0.421 g, 75%), mp 74-75 °C (CH_2Cl_2); $[\alpha]^{21}_{\text{D}} -11.8$ (c 1.00 in CH_2Cl_2); ν_{max} / cm^{-1} 3413 (m), 2982 (s), 2819 (w), 1706 (s), 1631 (s), 1588 (m), 1508 (s), 1473 (m), 1423 (w), 1392 (w), 1368 (s), 1330 (w), 1248 (m), 1167 (s); ^1H NMR δ_{H} (400 MHz; CDCl_3) 8.32 (1H, s, ArH), 7.94 (1H, s, ArH), 6.08 (1H, d, $J = 1.6$, 1'-H), 6.02 (2H, s, adenosine-NH₂), 5.49-5.57 (1H, m, 2'-H), 5.16-5.23 (2H, s, NH), 5.01-5.08 (1H, m, 3'-H), 4.31-4.41 (1H, m, 4'-H), 3.02-3.18 (4H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.58-2.69 (1H, m, 5'- CH_aH_b), 2.50-2.58 (1H, m, 5'- CH_aH_b), 2.34-2.50 (4H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.62 (3H, s, CH_3), 1.47-1.59 (4H, m, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.43 (18H, s, $\text{C}(\text{CH}_3)_3$), 1.41 (3H, s, CH_3); ^{13}C NMR δ_{C} (100 MHz; CDCl_3) 156.1 (C), 155.7 (C), 153.0 (CH), 149.2 (C), 140.3 (CH), 120.3 (C), 114.3 (C), 90.9 (CH), 85.9 (CH), 84.0 (CH), 83.4 (CH), 78.9 (C), 56.2 (CH₂), 51.6 (CH₂), 38.6 (CH₂), 28.7 (CH₃), 28.5 (CH₃), 27.0 (CH₃), 26.8 (CH₂), 25.4 (CH₃); m/z (ESI) 621.4 (100%, M + H⁺) Found 621.3726 $\text{C}_{29}\text{H}_{49}\text{N}_8\text{O}_7$ requires 621.3719.

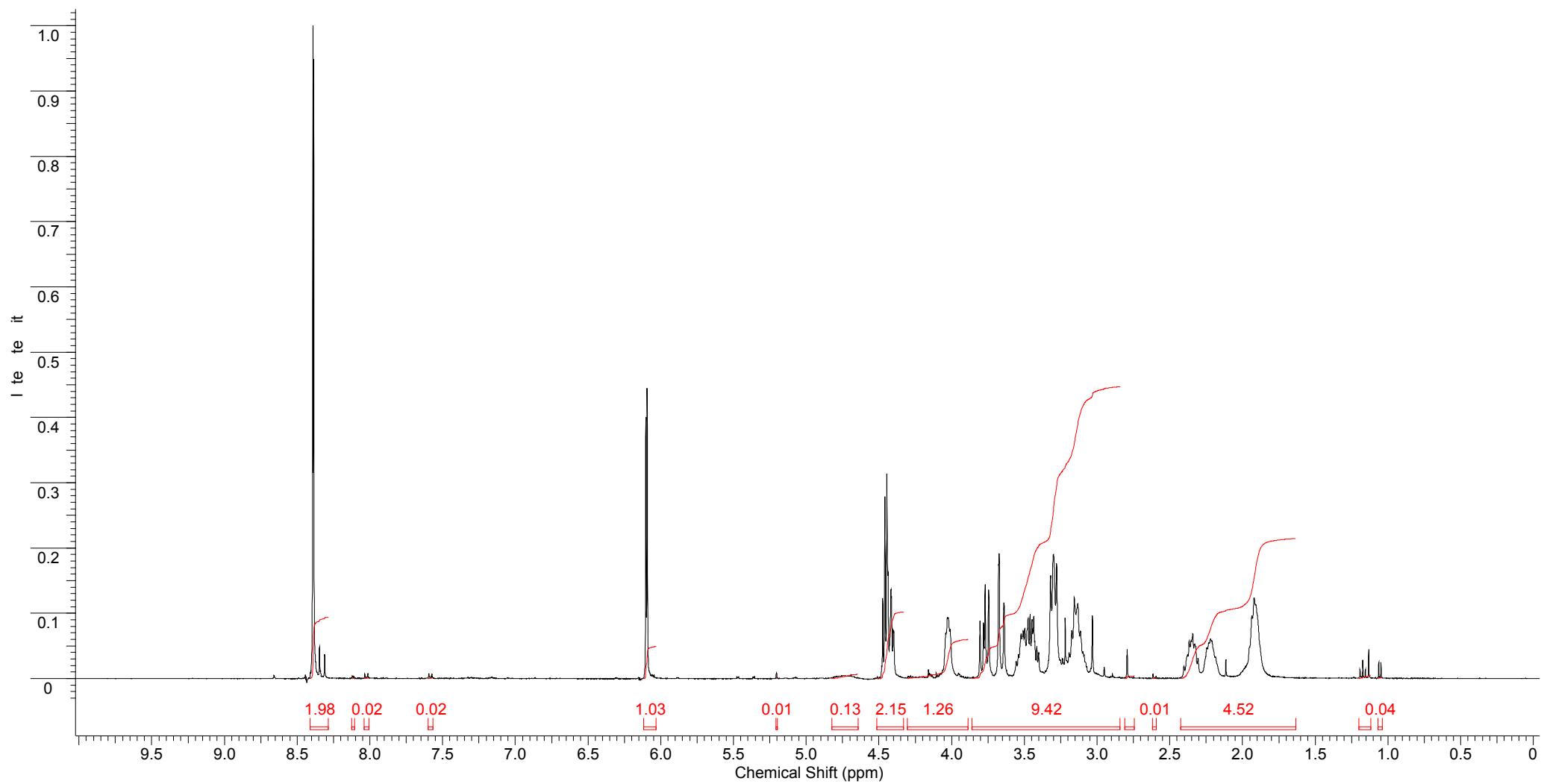
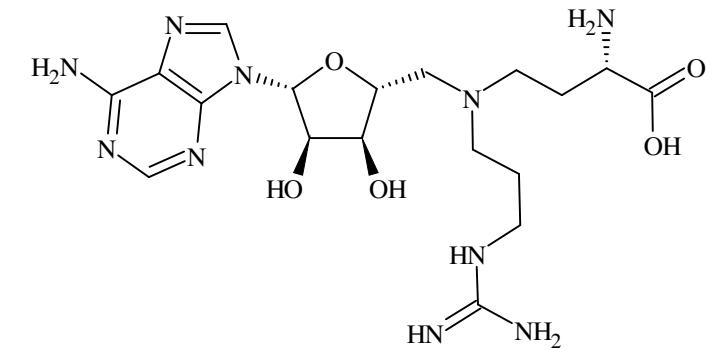
5'-5'-deoxy-[di[2,3-di-(*tert*-butoxycarbonyl)guanidino]propyl]amino]-2',3'-O-(1-methylethylidene)-adenosine (P24)

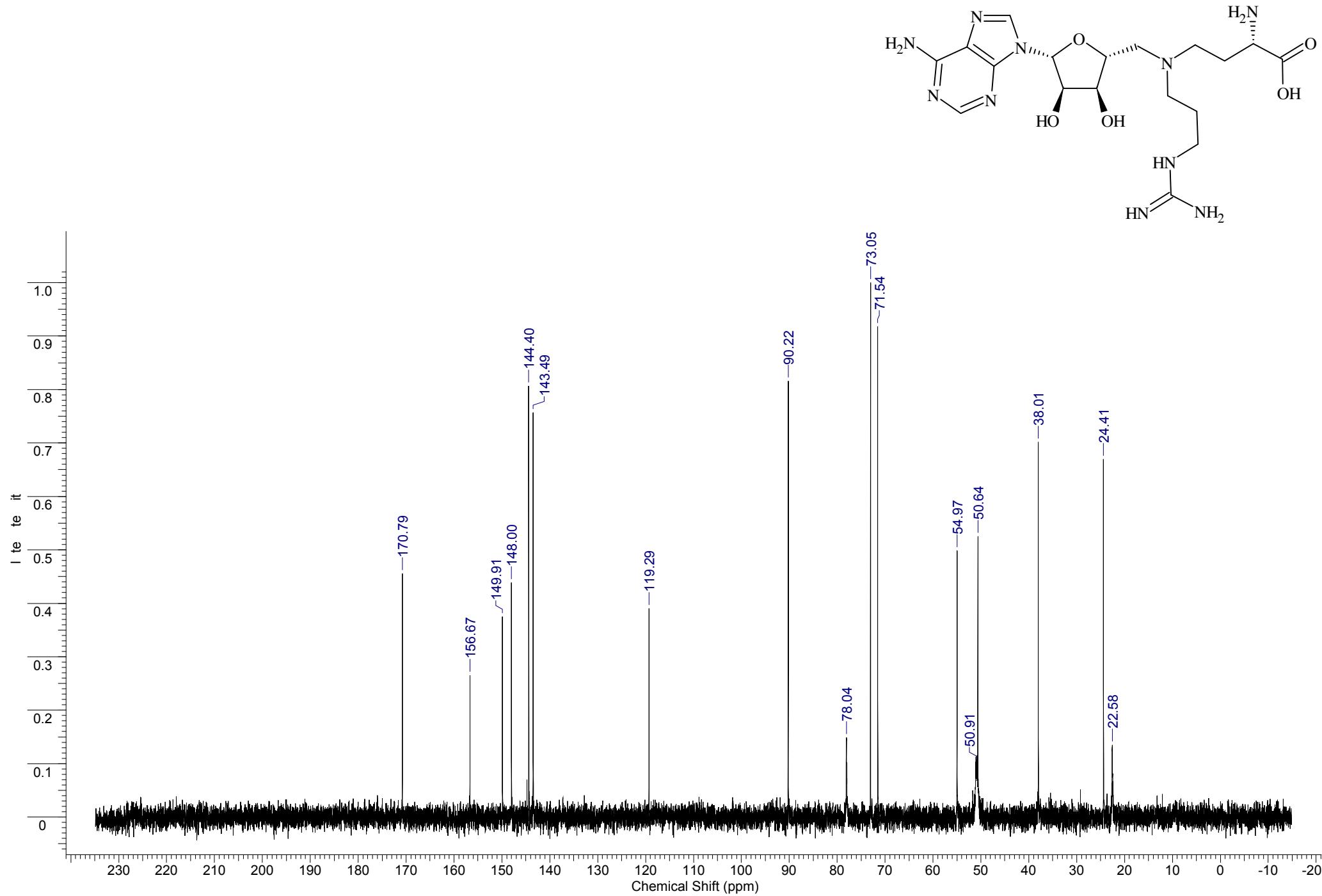


Method 2. Elution with MeOH:CH₂Cl₂ 5:95 to 10:90 gave the product as a white solid (0.181 g, 30%), mp 117-119 °C (CH₂Cl₂); [α]²¹_D -7.62 (c 1.00 in CH₂Cl₂); ν_{max} / cm⁻¹ 3414 (w), 2985 (m), 2938 (m), 1721 (s), 1632 (s), 1587 (s), 1474 (m), 1455 (m), 1417 (s), 1394 (m), 1369 (s), 1330 (s), 1157 (s), 1135 (s),; ¹H NMR δ_H (400 MHz; CDCl₃) 11.49 (2H, s, (C(N)NHCO)₂), 8.42 (2H, br m, (C(N)NHCH₂)₂), 8.34 (1H, s, ArH), 7.99 (1H, s, ArH), 6.05 (1H, d, J = 2.1, 1'-H), 5.76 (2H, br s, adenosine-NH₂), 5.54 (1H, dd, J = 6.4, 2.1, 2'-H), 4.97 (1H, dd, J = 6.4, 3.3, 3'-H), 4.34 (1H, app. td, J = 6.7, 3.3, 4'-H), 3.35-3.46 (4H, m, (NHCH₂CH₂CH₂N)₂), 2.72 (1H, dd, J = 13.6, 6.7, 5'-CH_aH_b), 2.43-2.61 (5H, m, 5'-CH_aH_b and (NHCH₂CH₂CH₂N)₂), 1.60-1.72 (4H, m, (NHCH₂CH₂CH₂N)₂), 1.59 (3H, s, CH₃), 1.49 (36H, s, C(CH₃)₃ × 4), 1.38 (3H, s, CH₃); ¹³C NMR δ_C (100 MHz; CDCl₃) 163.6 (C × 2), 156.1 (C), 155.5 (C), 153.2 (CH), 149.3 (C), 140.3 (CH), 120.3 (C), 114.3 (C), 90.9 (CH), 85.5 (CH), 83.6 (CH), 83.4 (CH), 82.9 (C), 79.1 (C), 56.0 (CH₂), 52.0 (CH₂), 39.3 (CH₂), 28.3 (CH₃), 28.0 (CH₃), 27.0 (CH₃), 26.0 (CH₂), 25.2 (CH₃); m/z (ESI) 905.5 (M + H⁺, 100%), Found 905.5196 C₄₁H₆₉N₁₂O₁₁ requires 905.5203;

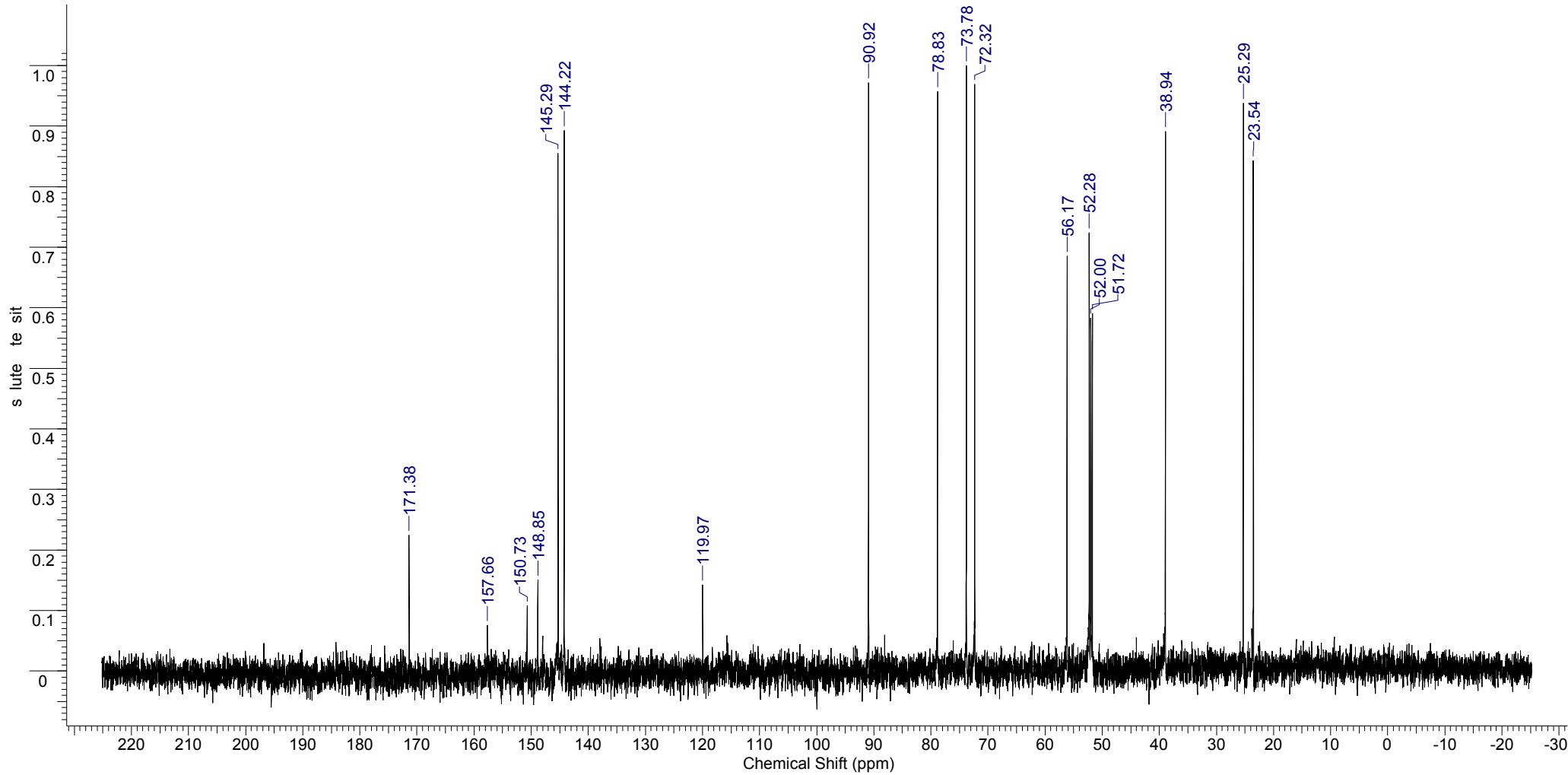
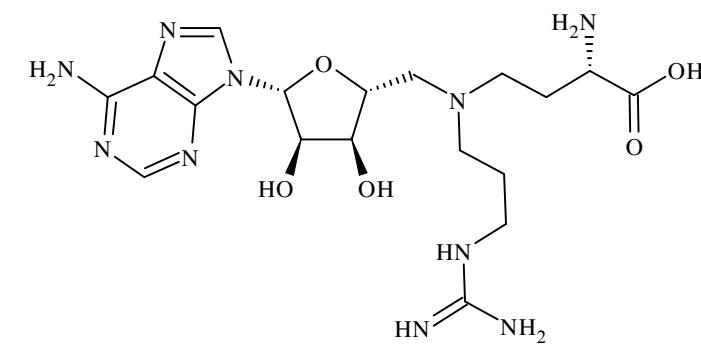
References

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2. R. M. Werner, O. Shokek and J. T. Davis, *J. Org. Chem.* 1997, **62**, 8243.
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@70 Celcius



MS Data Review All Plots - 2/25/2010 3:46 PM

Compound 16

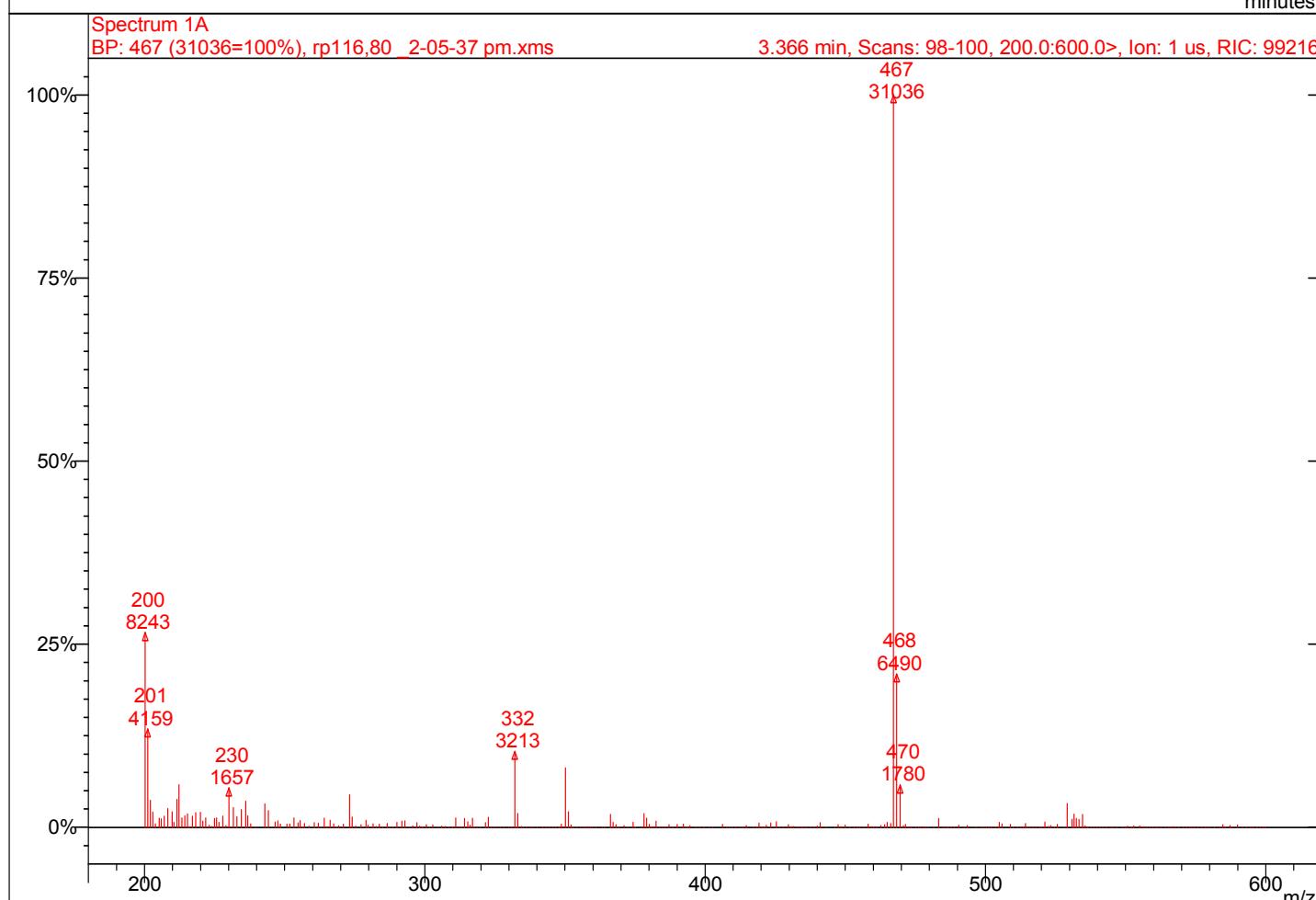
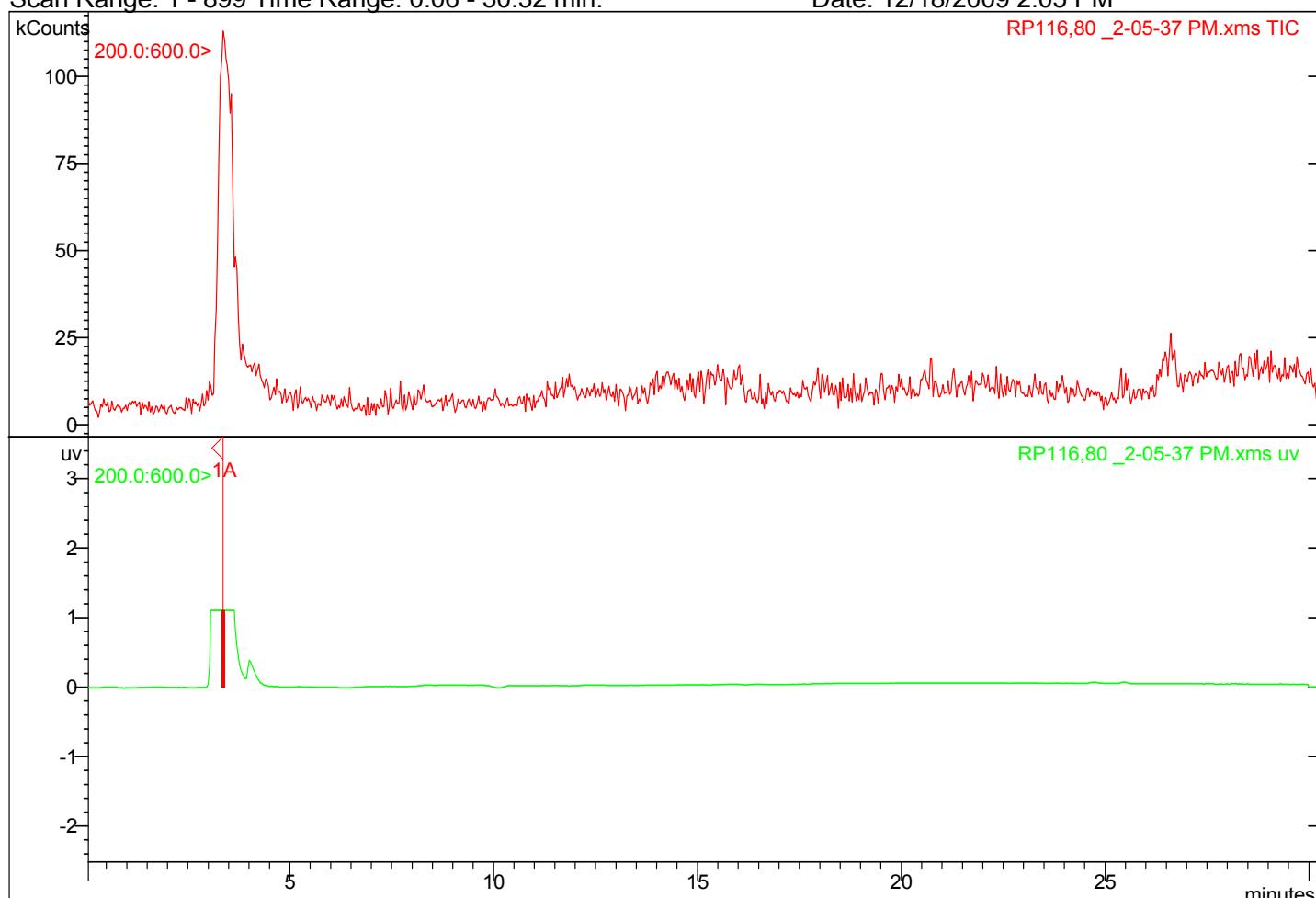
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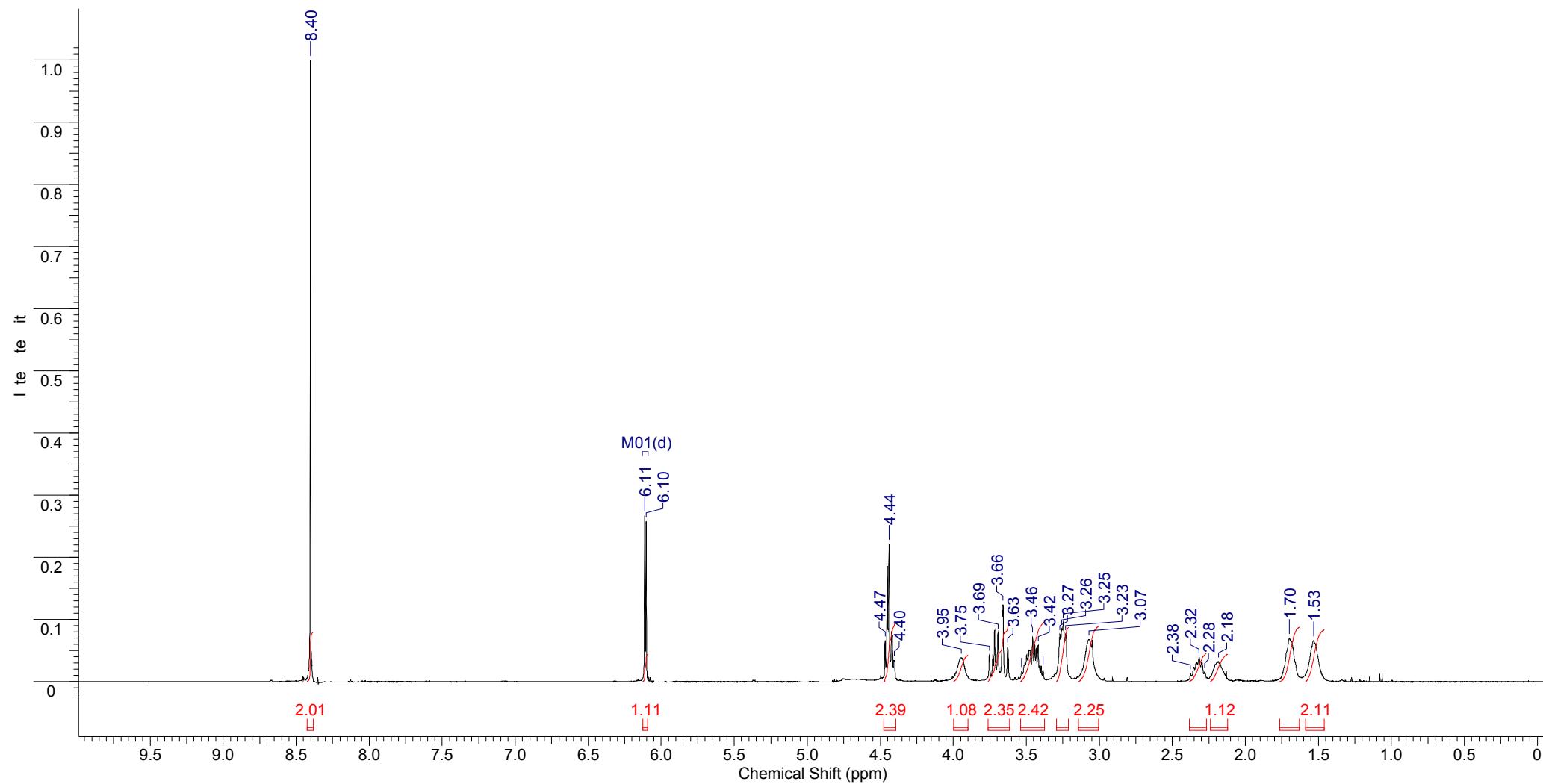
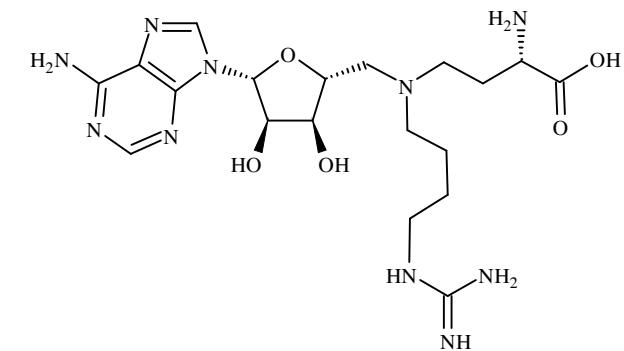
Sample: RP116,80

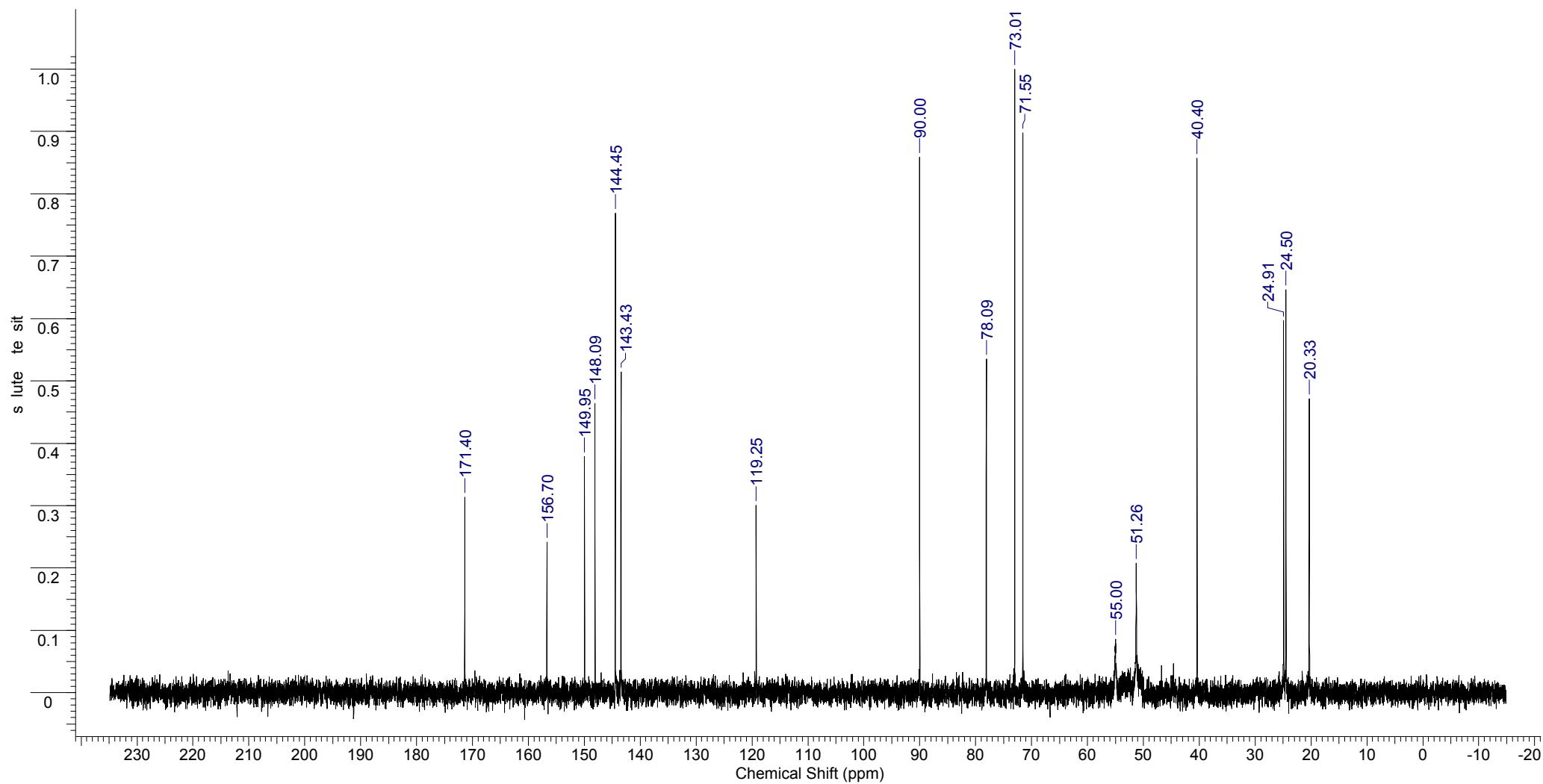
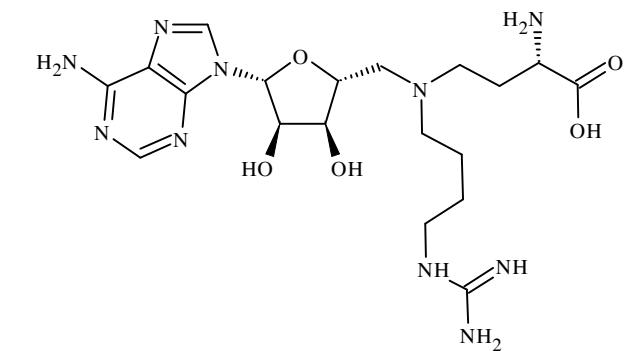
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Operator: dmt

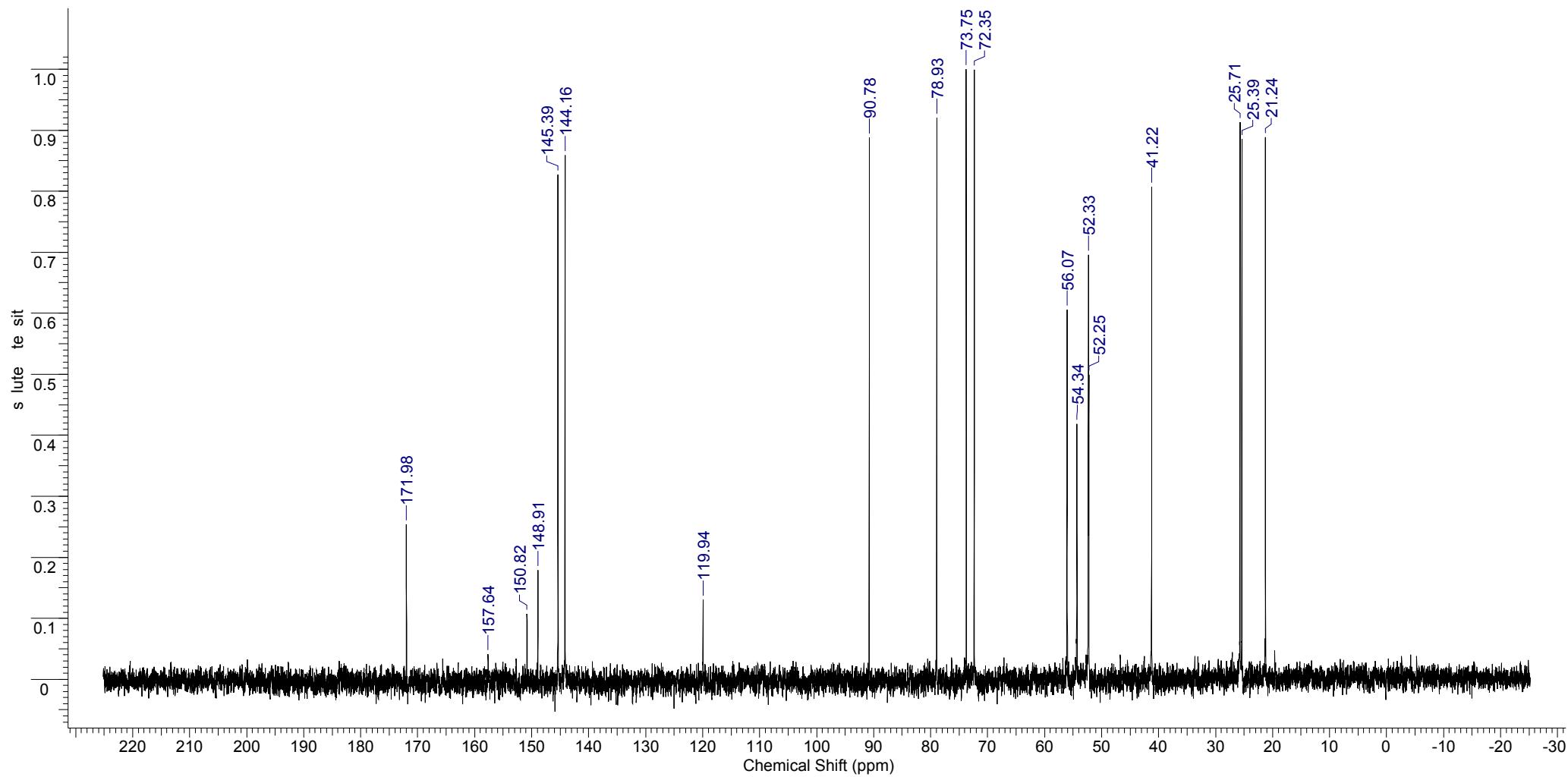
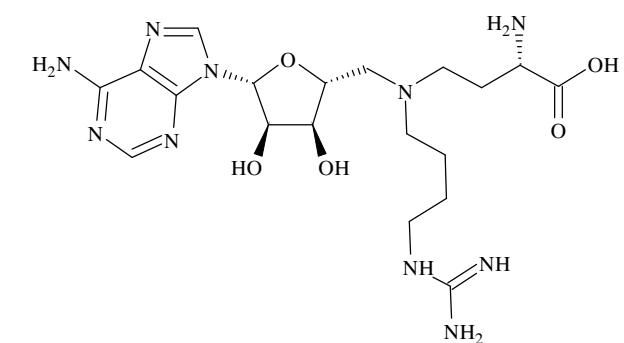
Date: 12/18/2009 2:05 PM







@70 Celcius



MS Data Review All Plots - 2/25/2010 4:45 PM

Compound 17

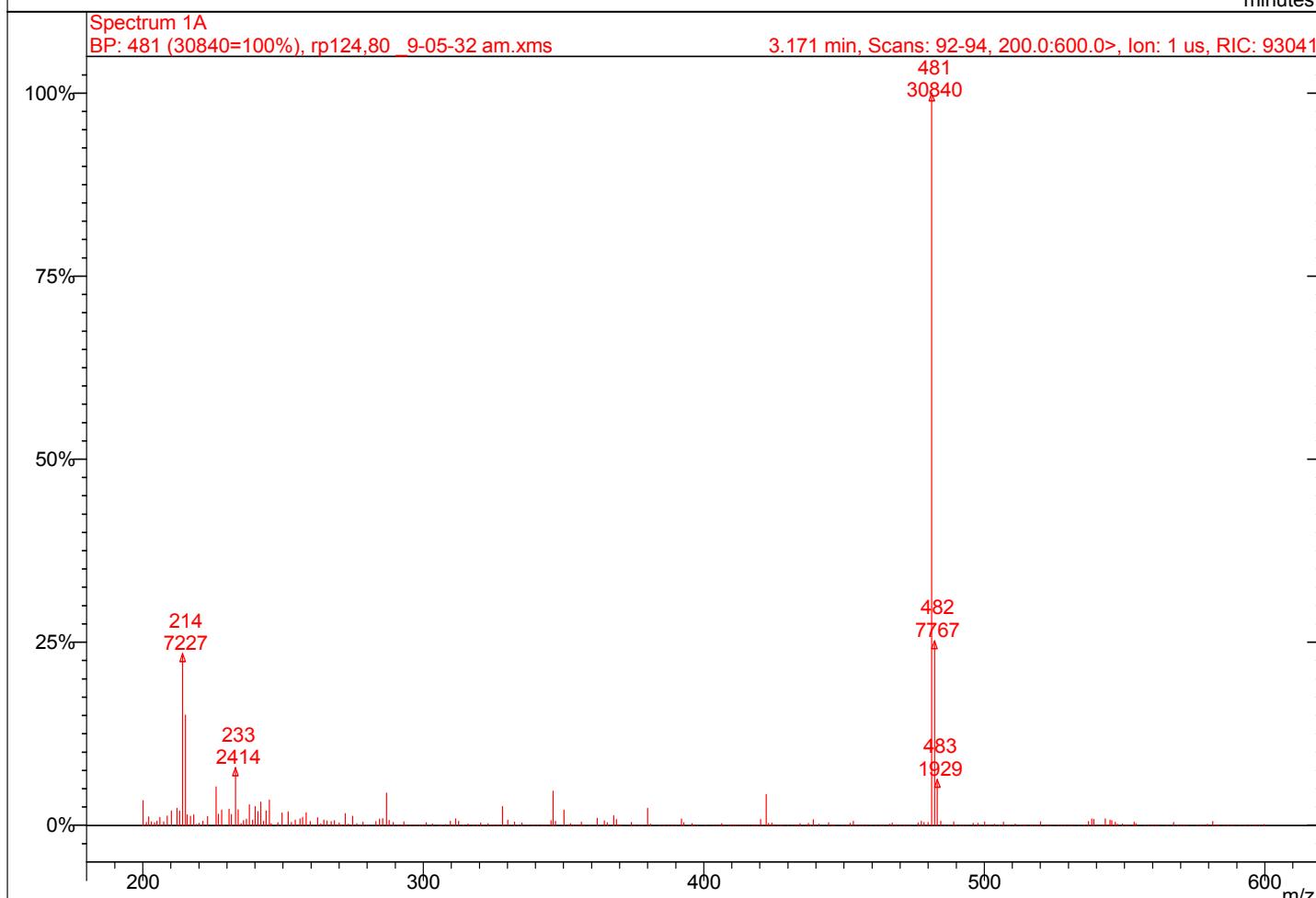
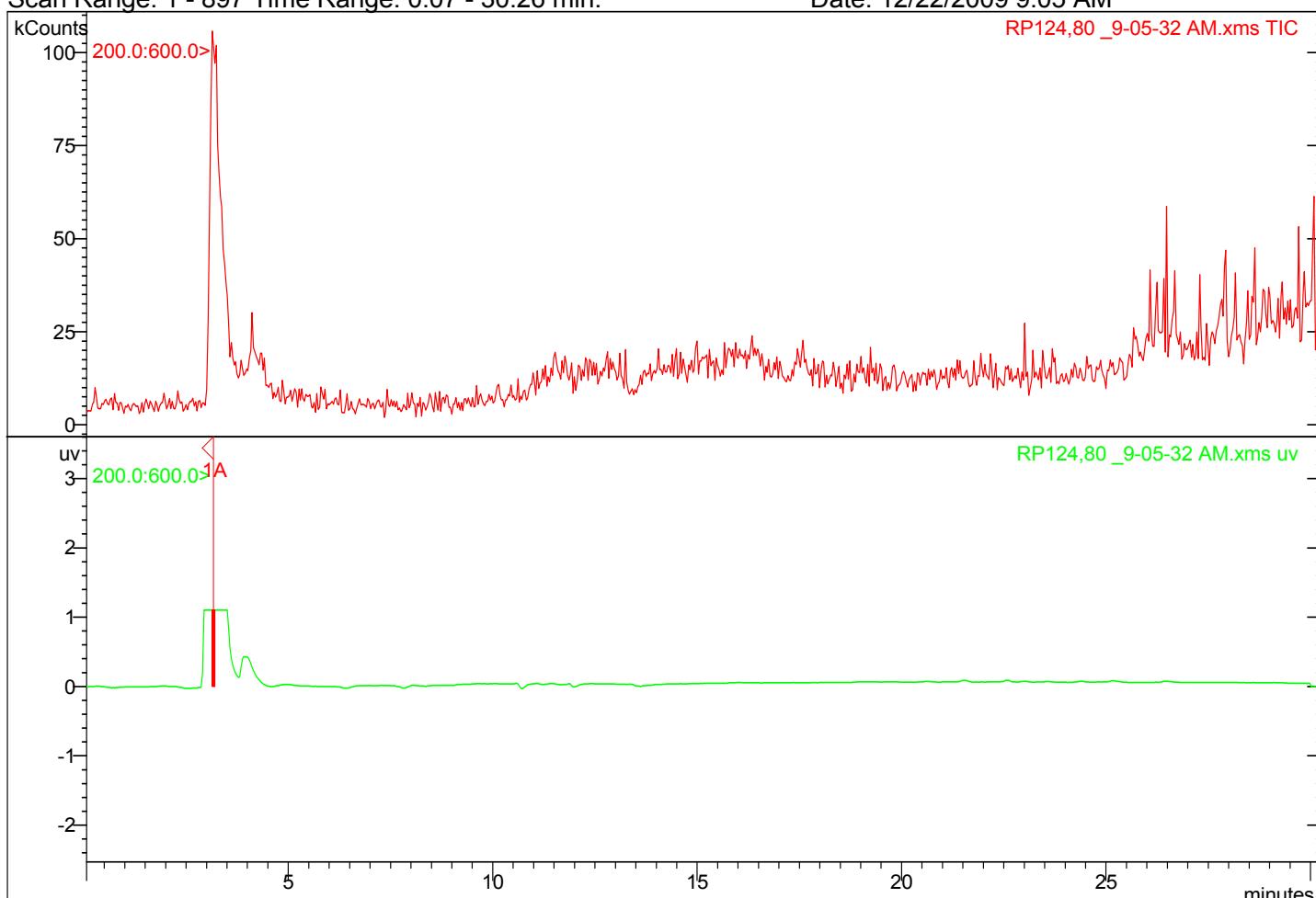
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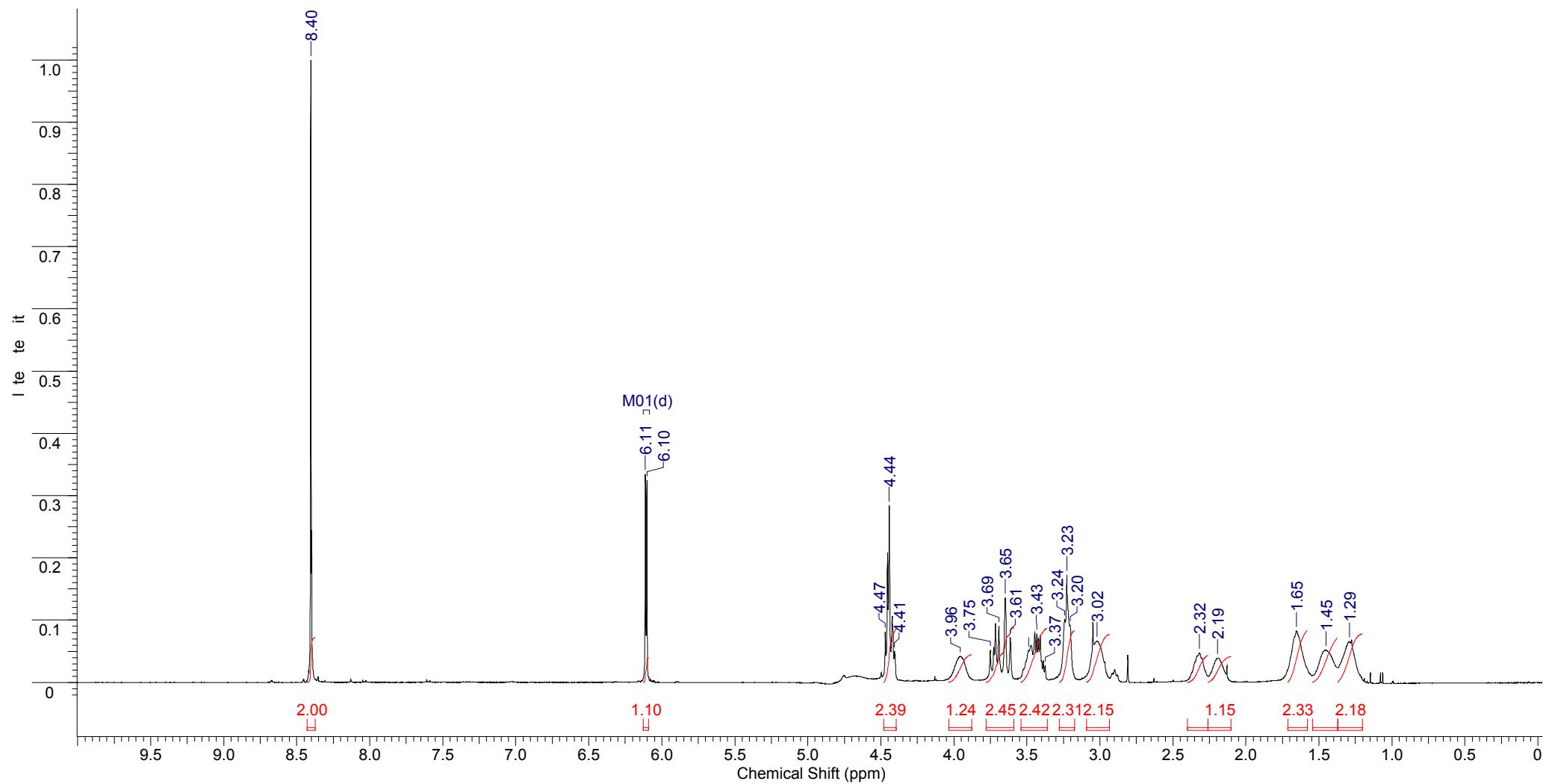
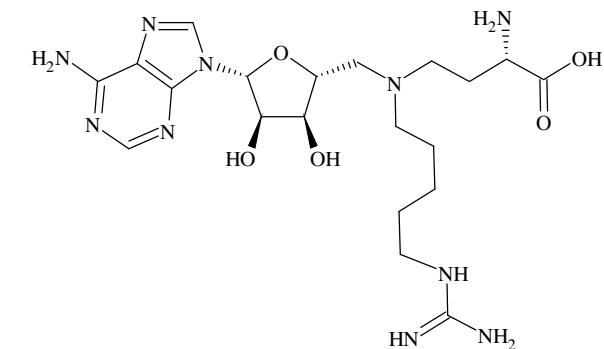
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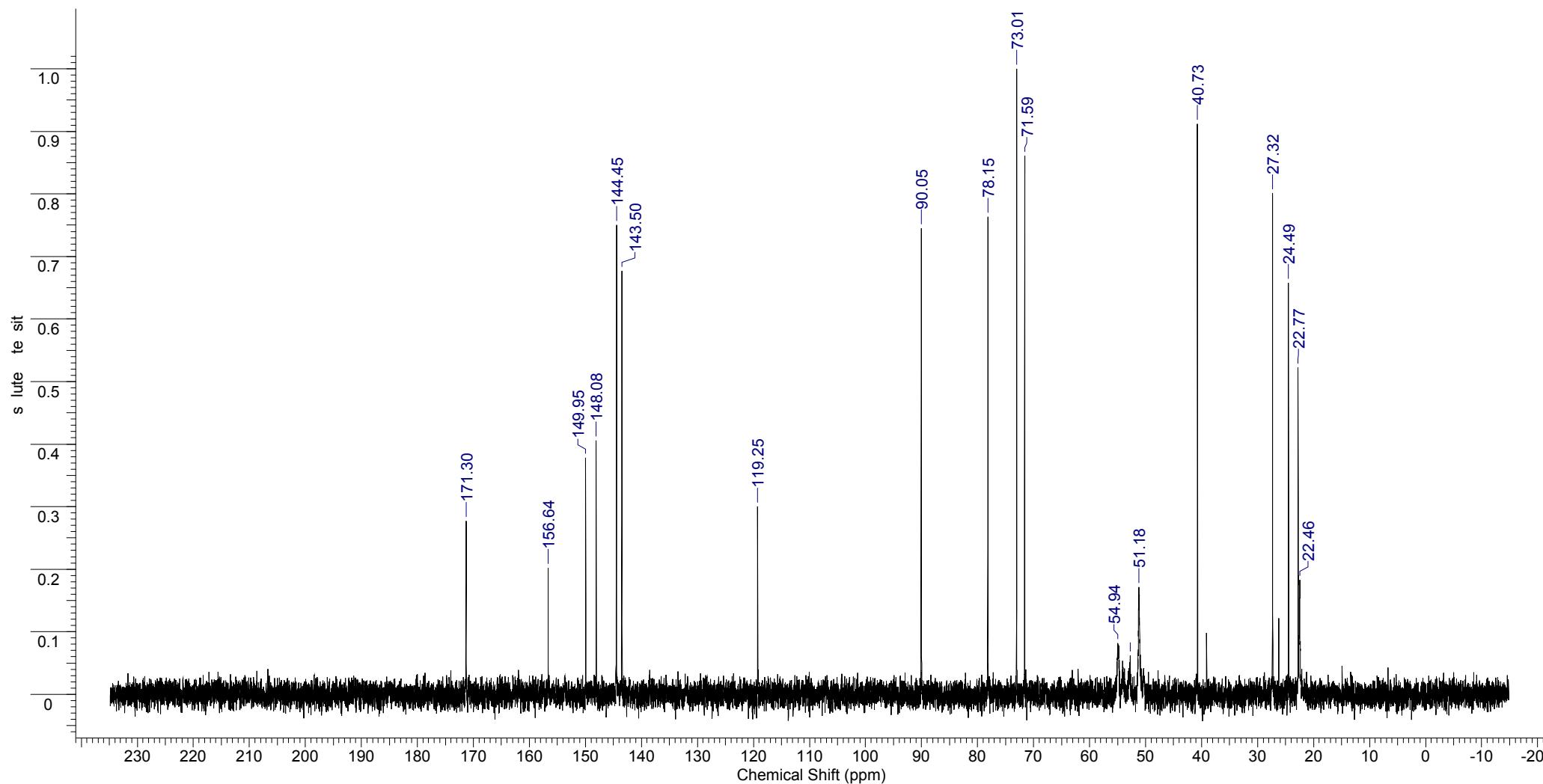
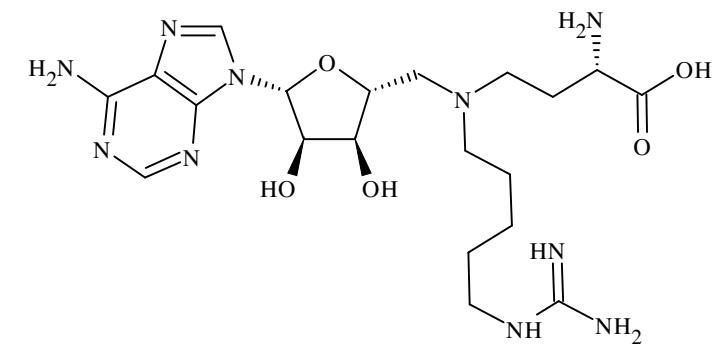
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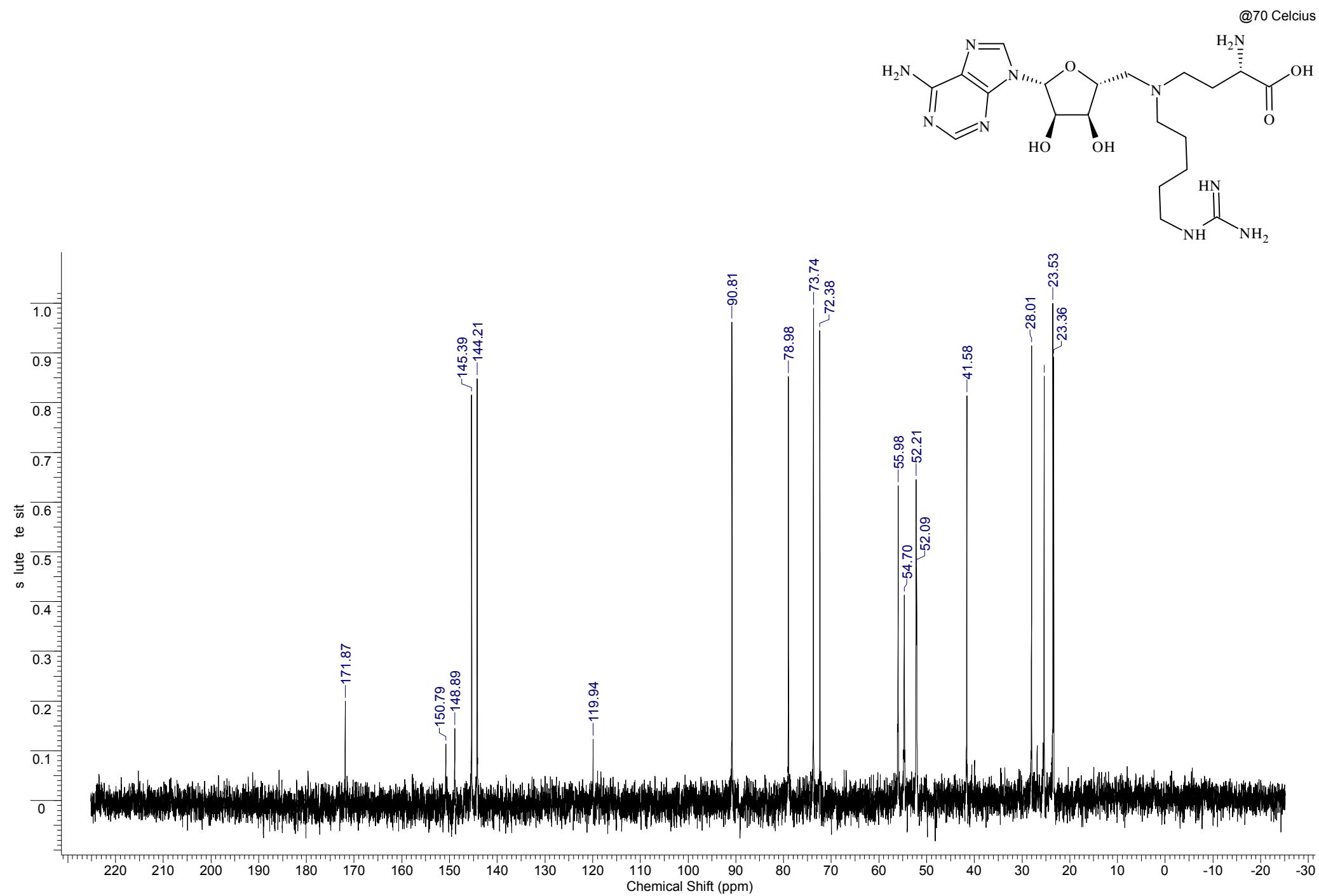
Operator: dmt

Date: 12/22/2009 9:05 AM









MS Data Review All Plots - 2/25/2010 4:52 PM

Compound 18

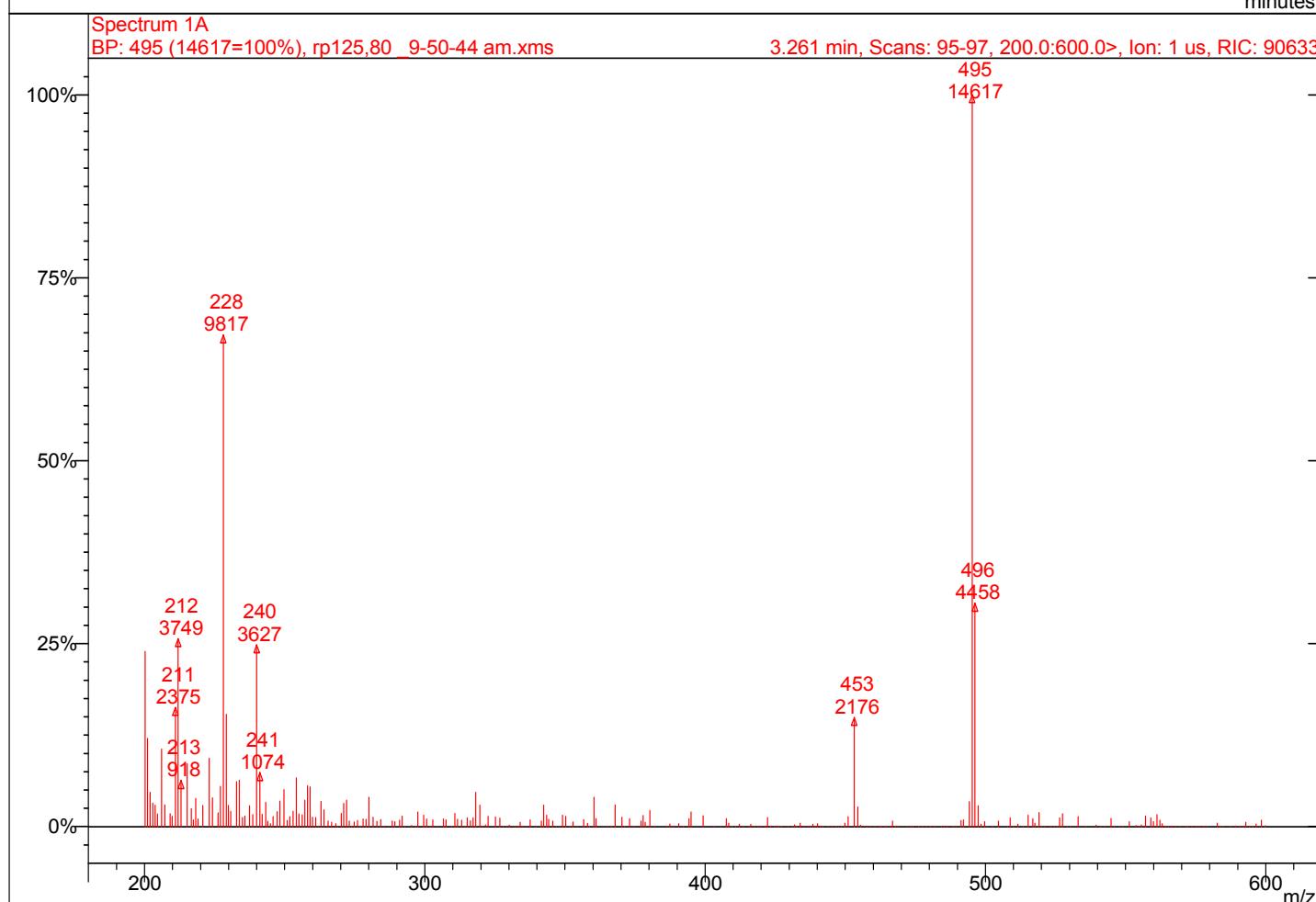
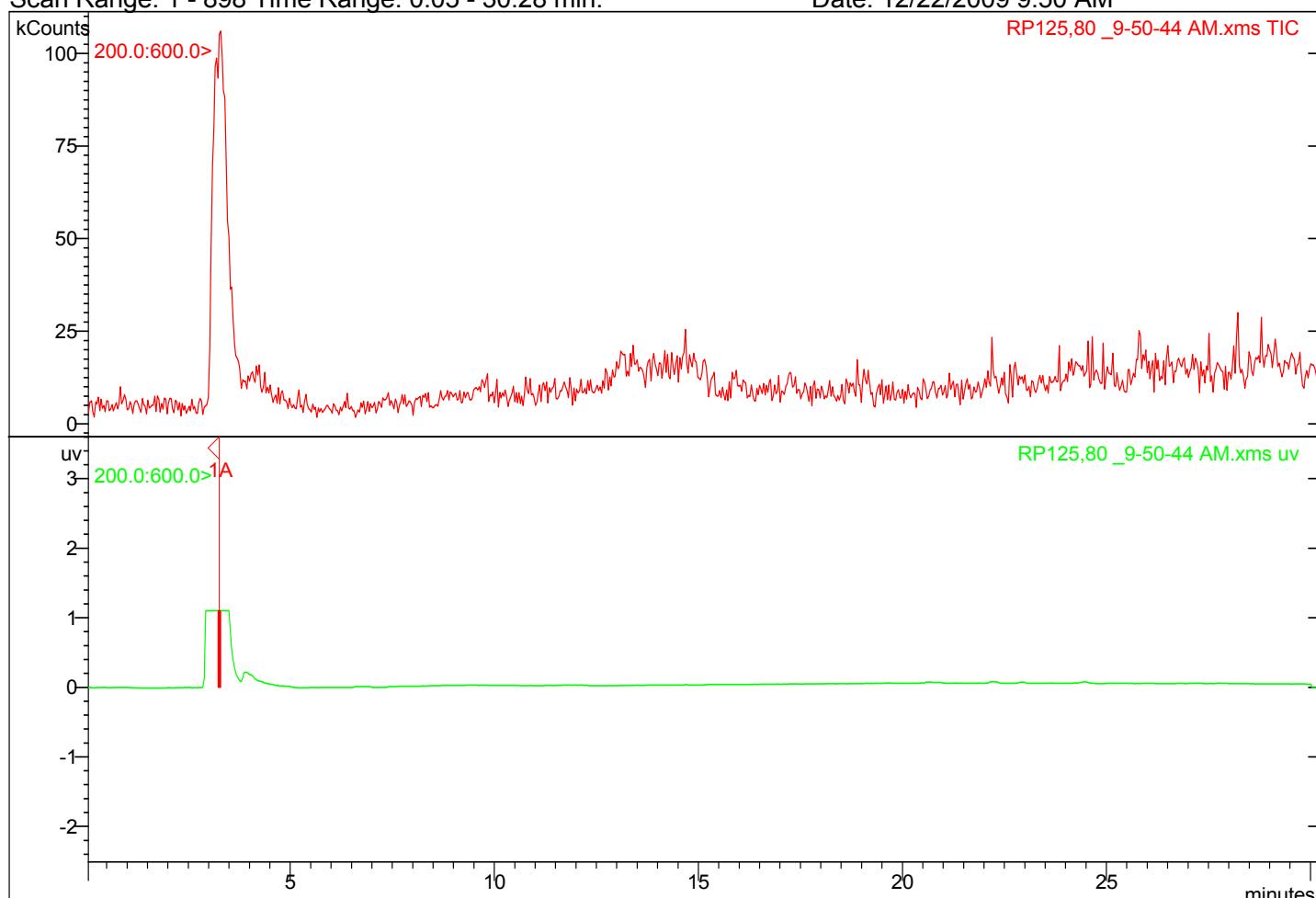
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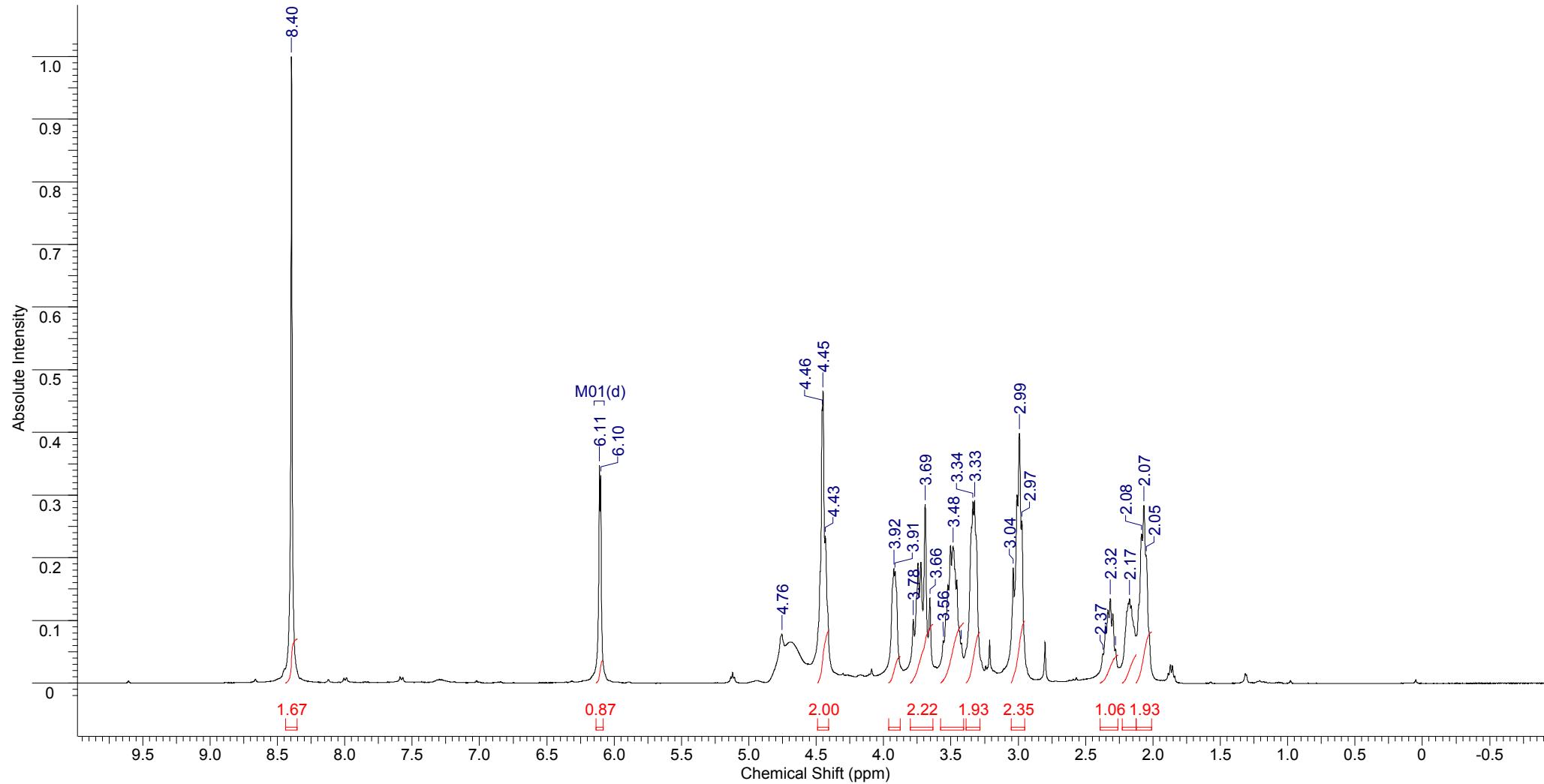
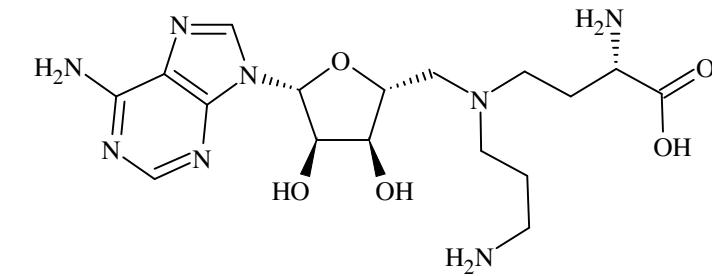
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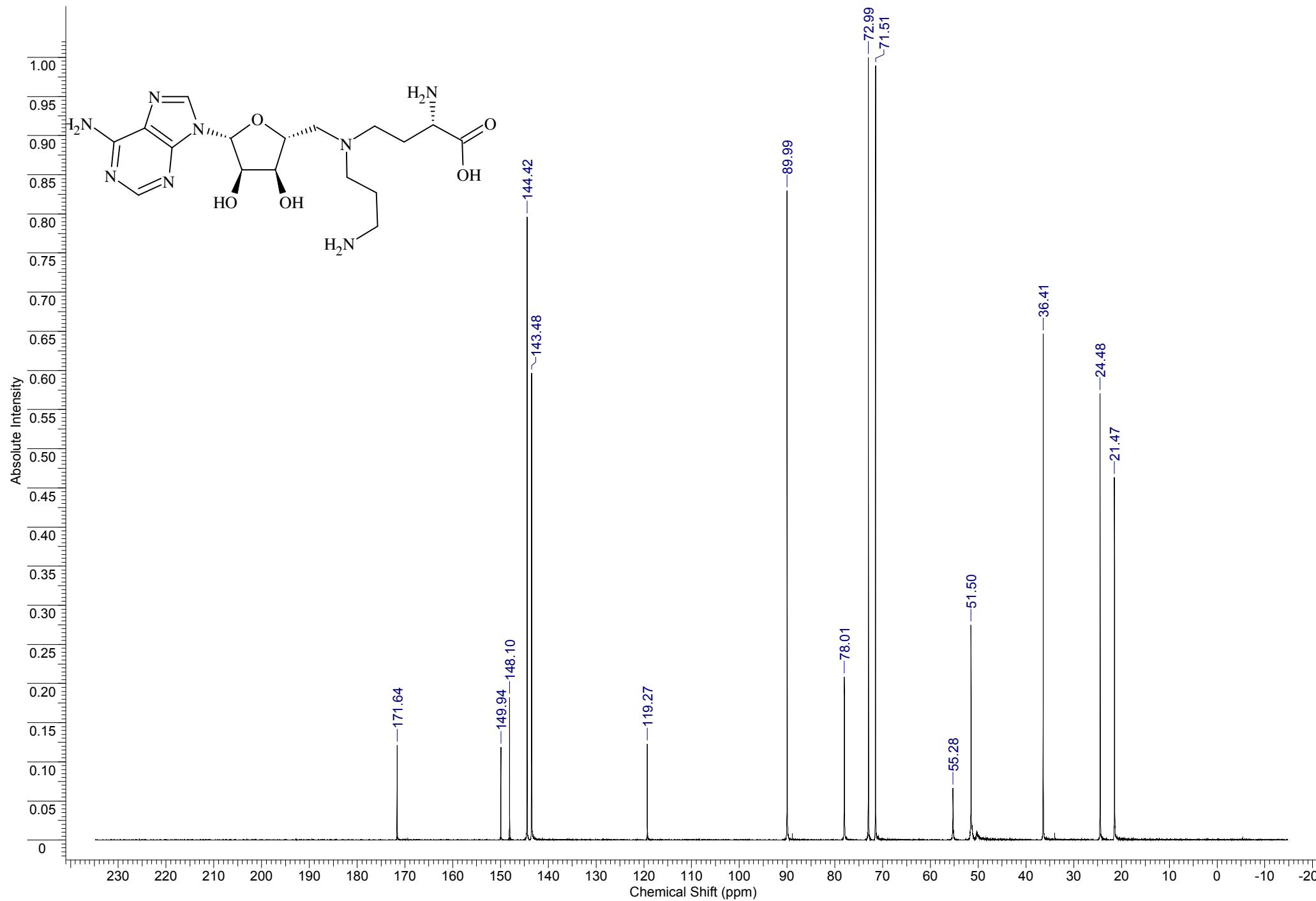
Scan Range: 1 - 898 Time Range: 0.05 - 30.28 min.

Operator: dmt

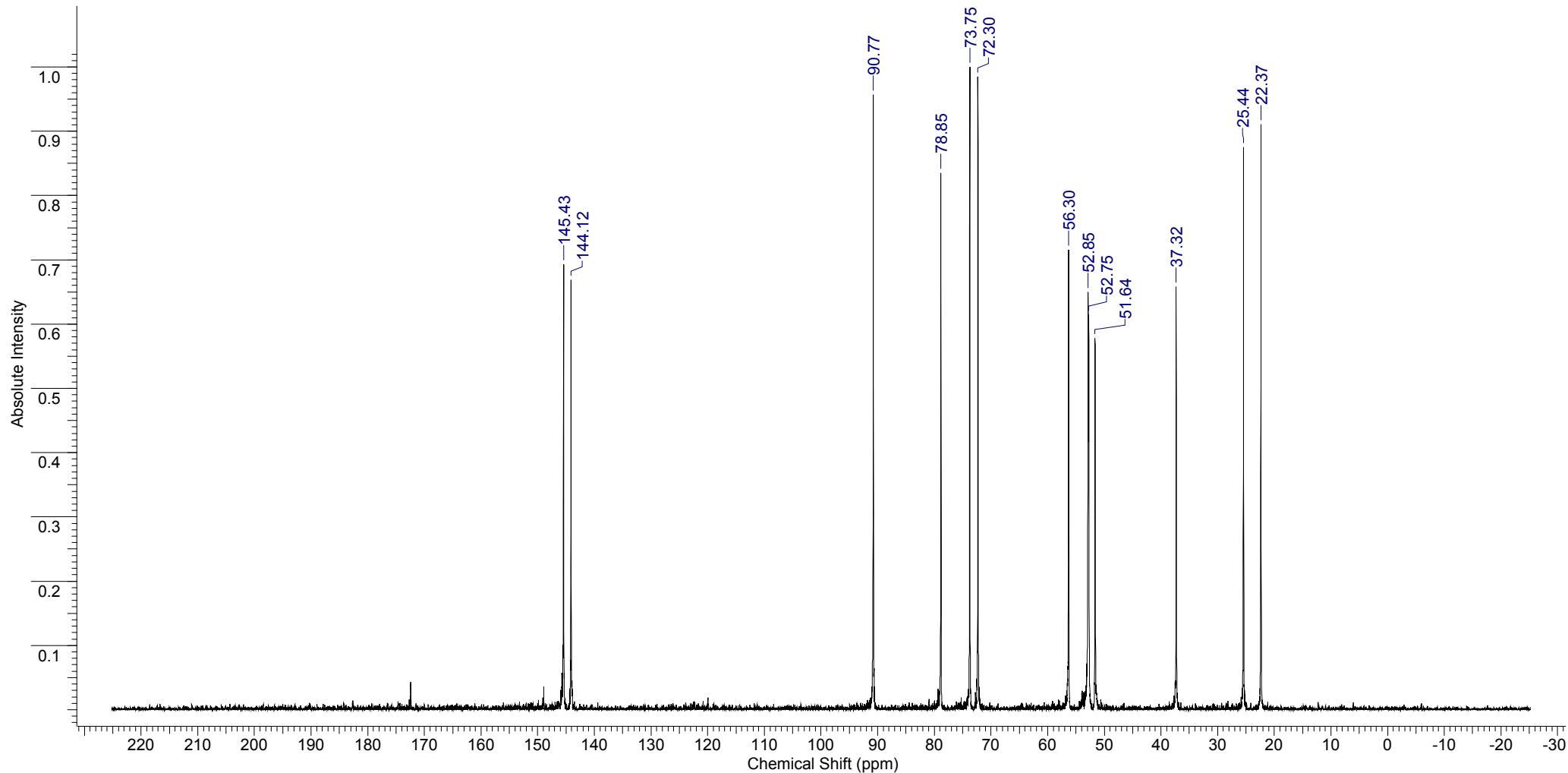
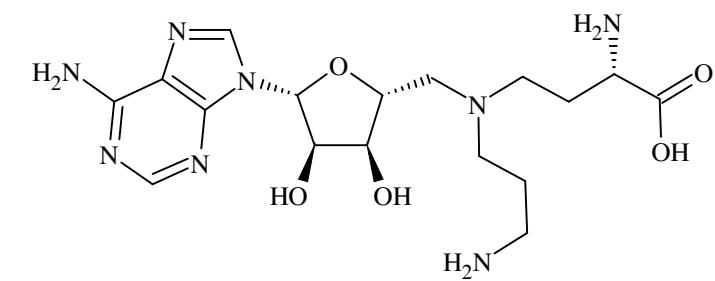
Date: 12/22/2009 9:50 AM







@70 Celcius

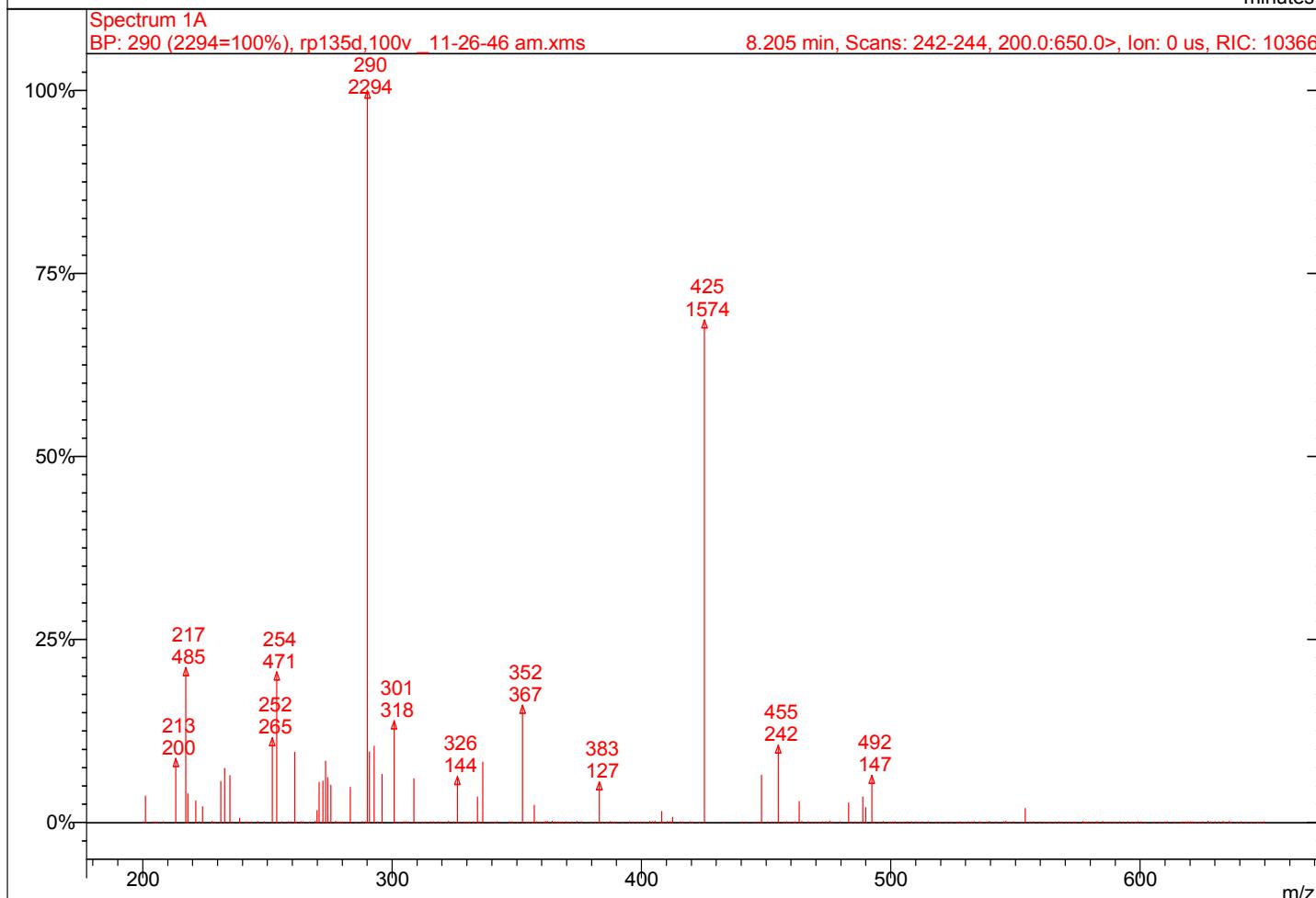
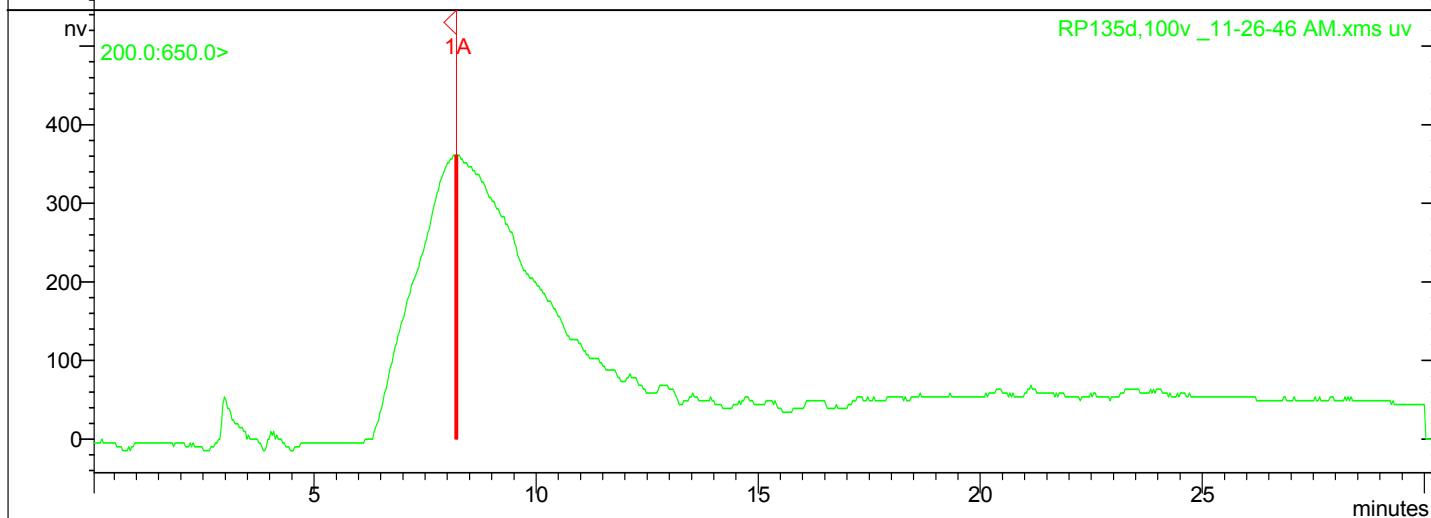
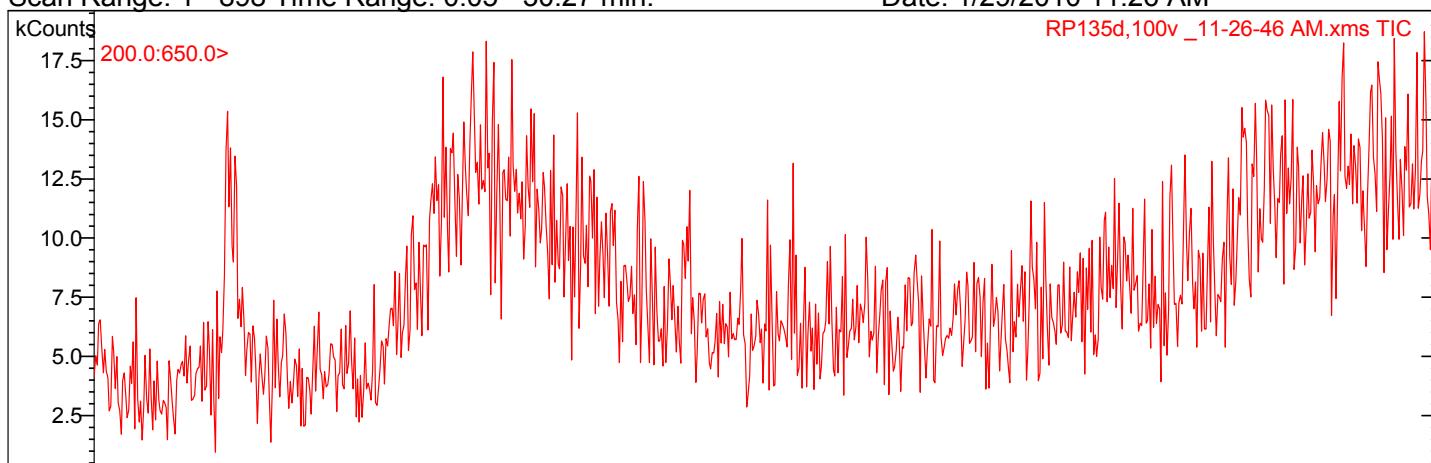


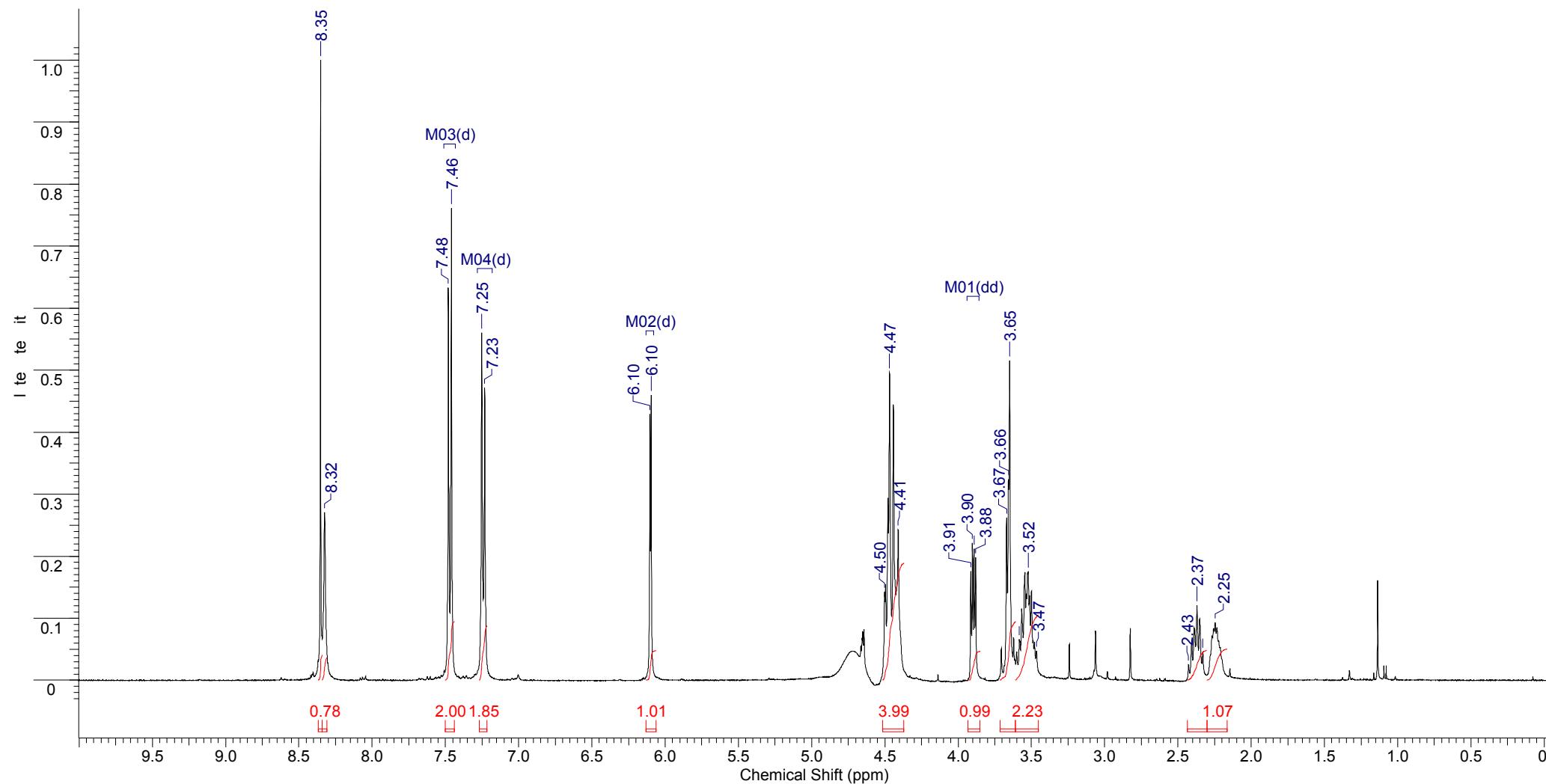
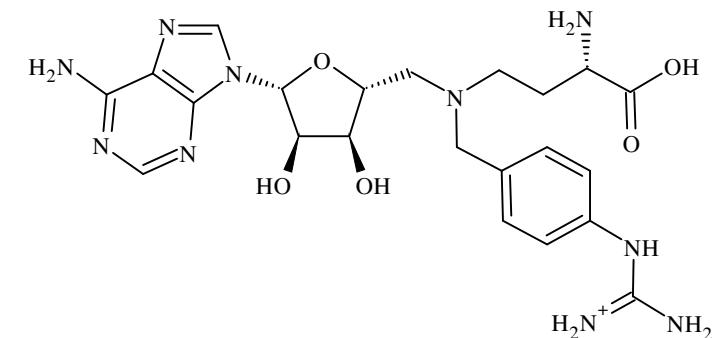
MS Data Review All Plots - 2/25/2010 4:55 PM

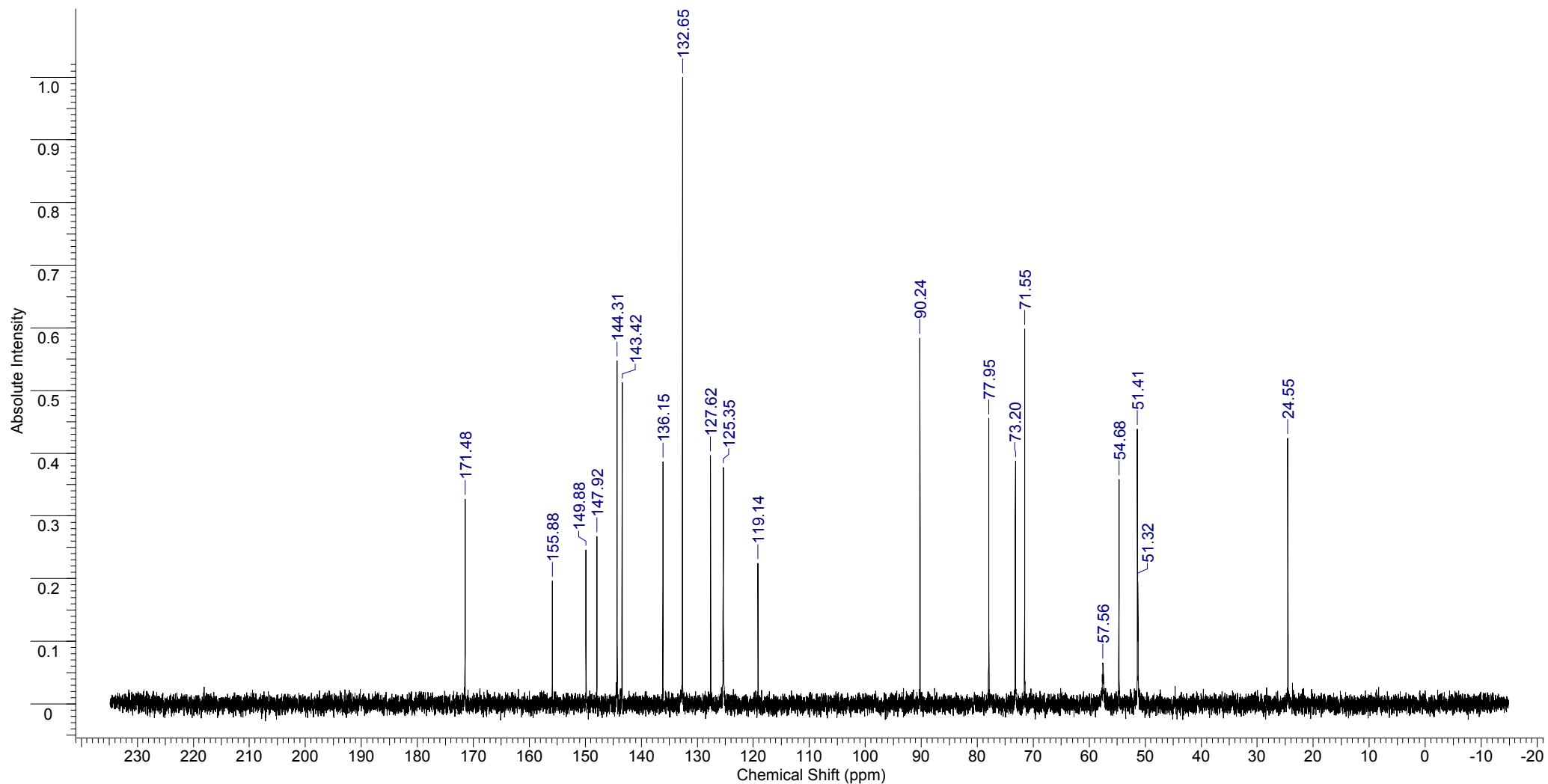
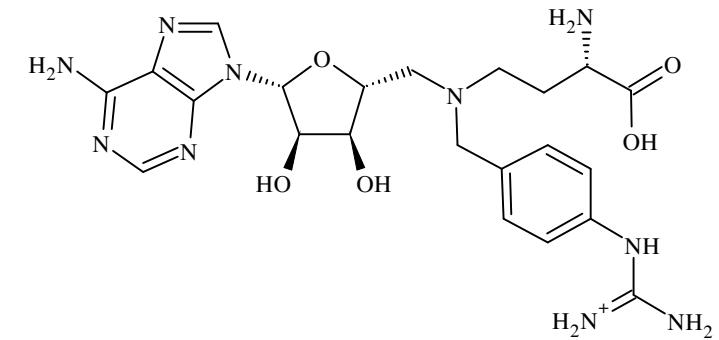
Compound 19

File: c:\varianws\data\dmf\290110\rp135d,100v_11-26-46 am.xms
Sample: RP135d,100v
Scan Range: 1 - 898 Time Range: 0.05 - 30.27 min.

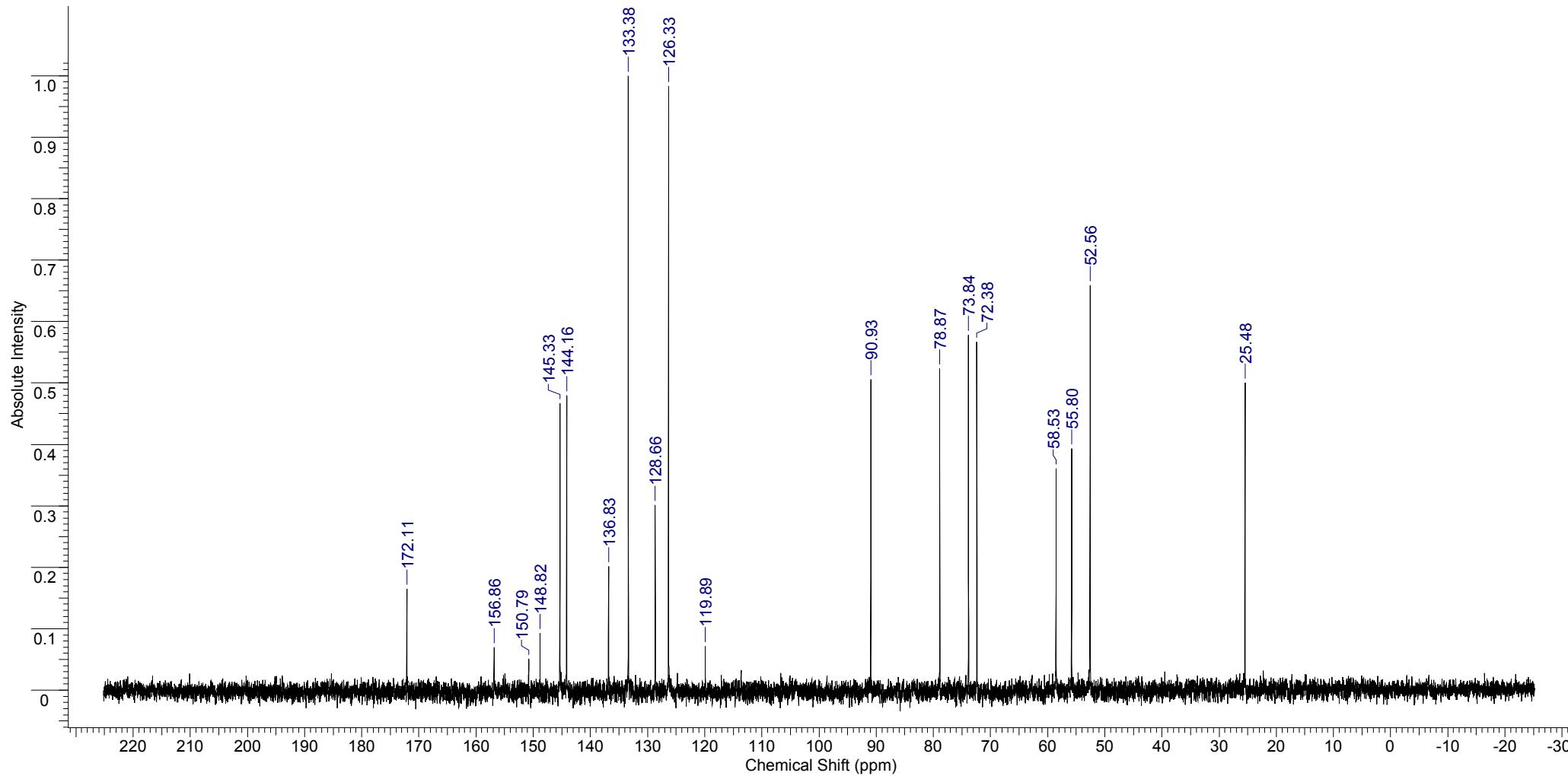
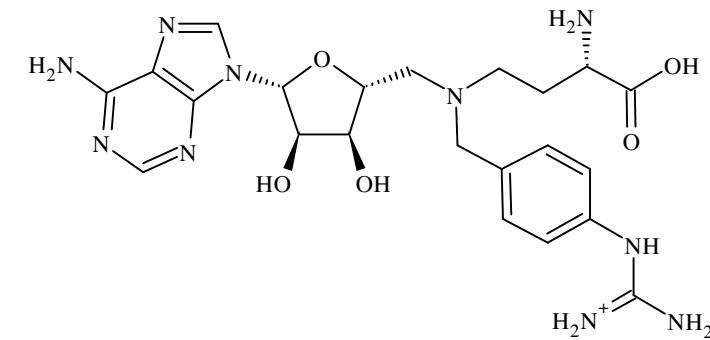
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Date: 1/29/2010 11:26 AM







@ 70 Celcius



MS Data Review All Plots - 2/25/2010 5:25 PM

Compound 20

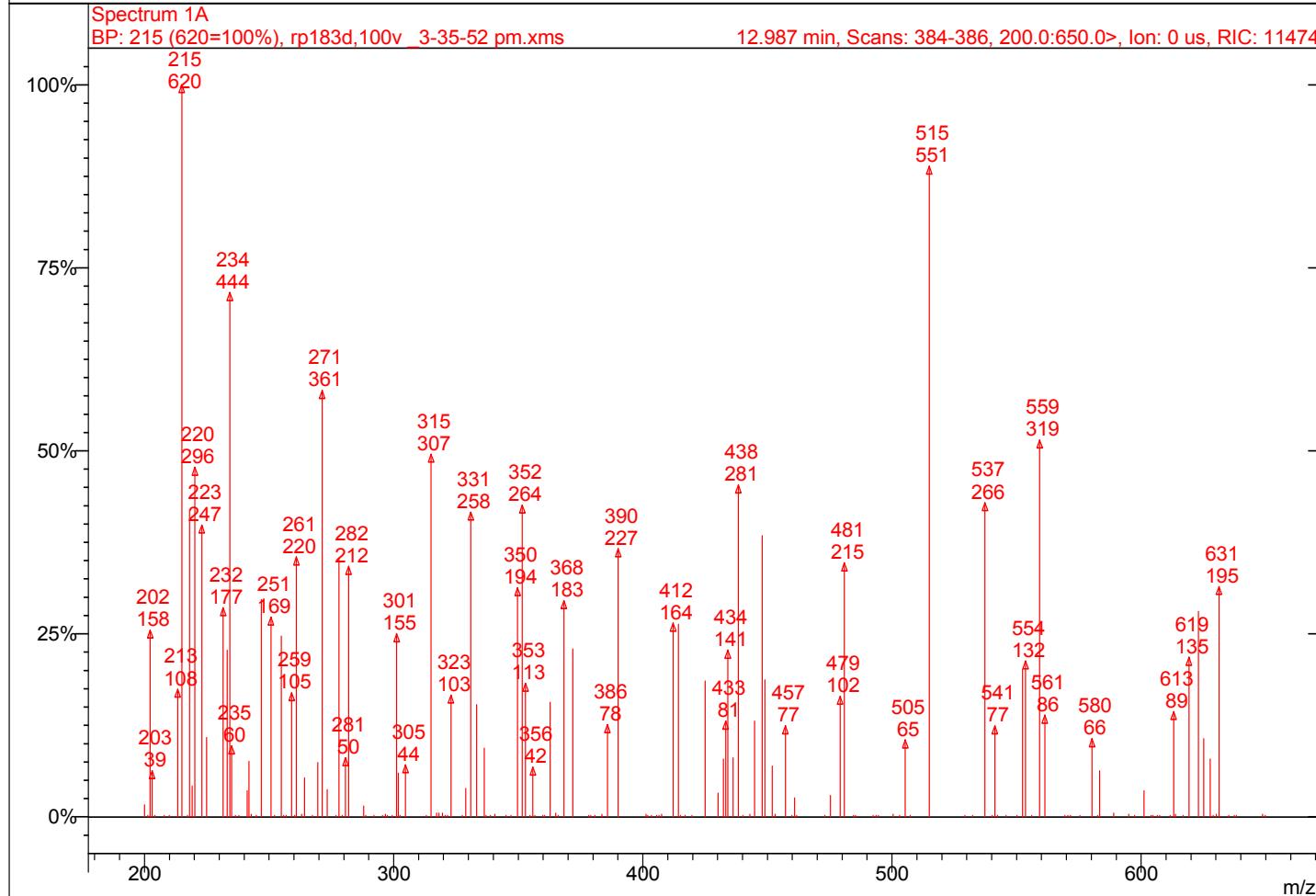
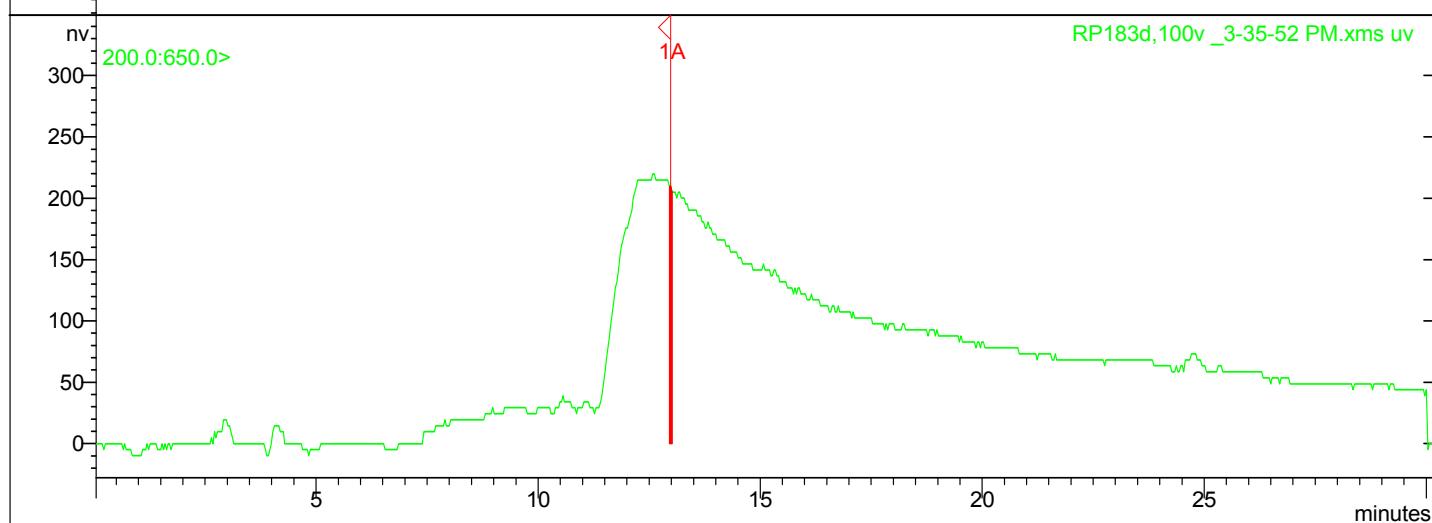
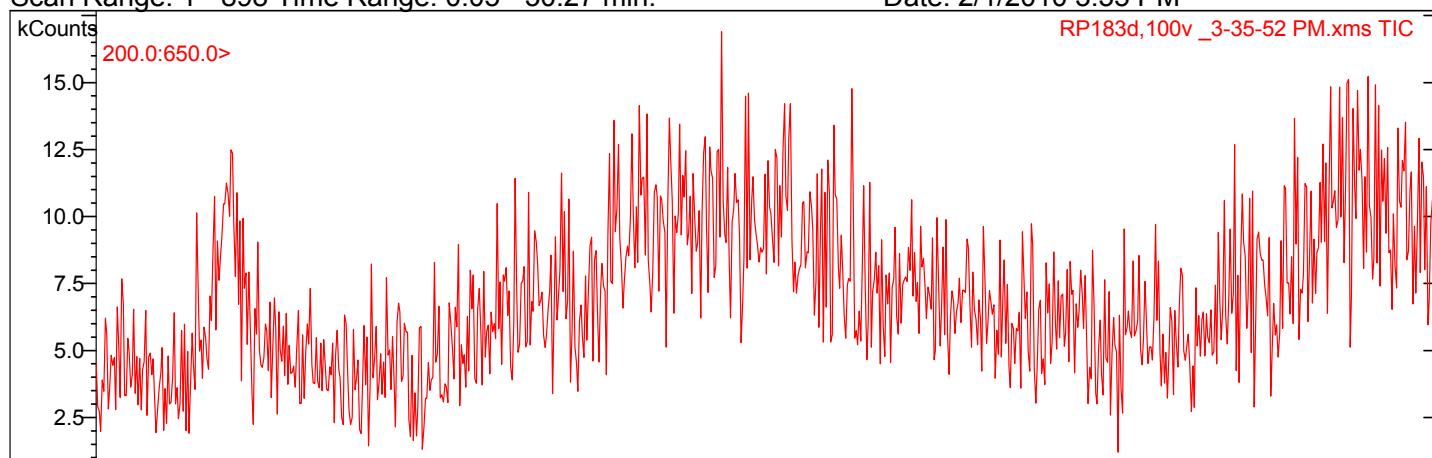
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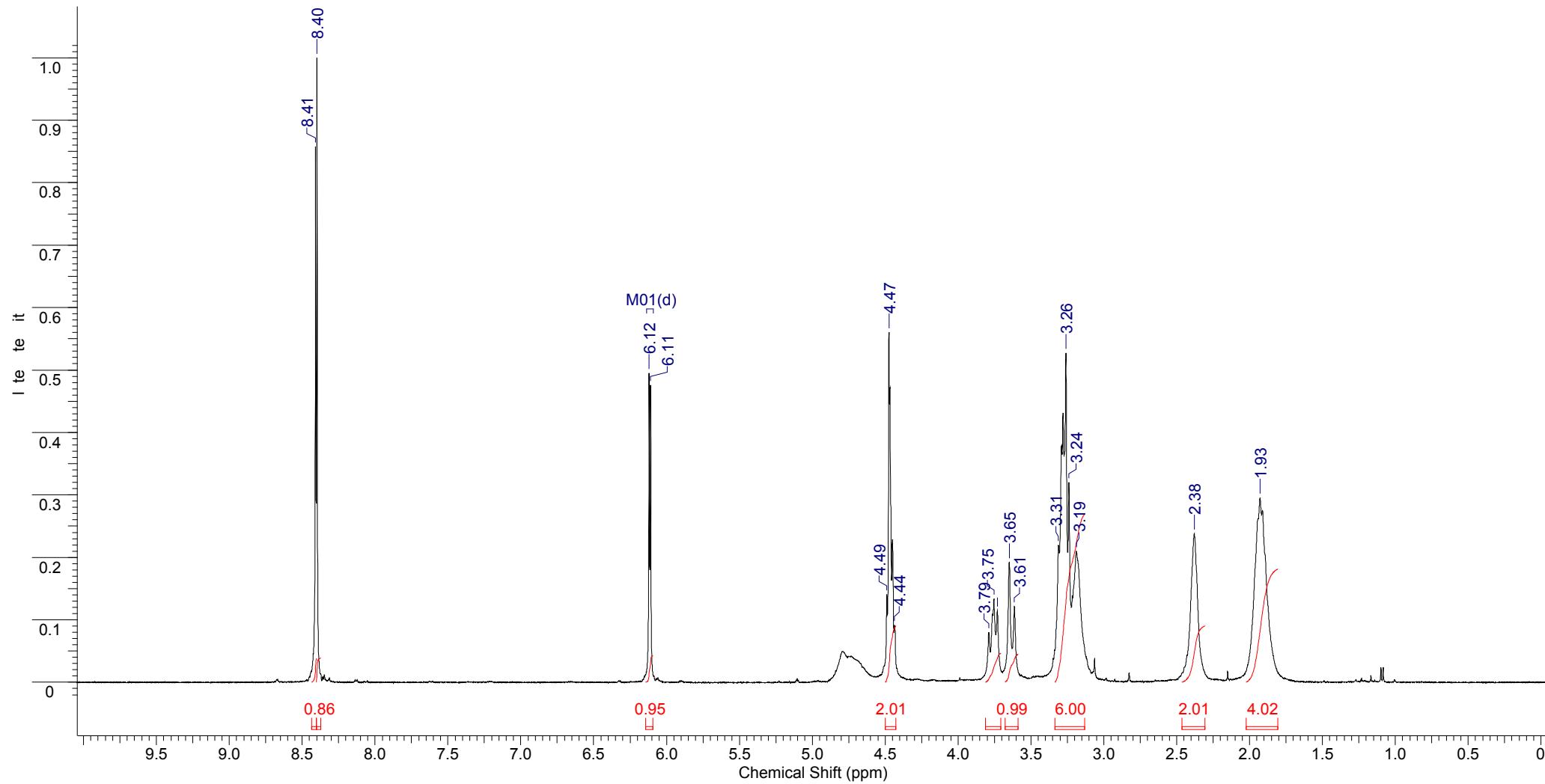
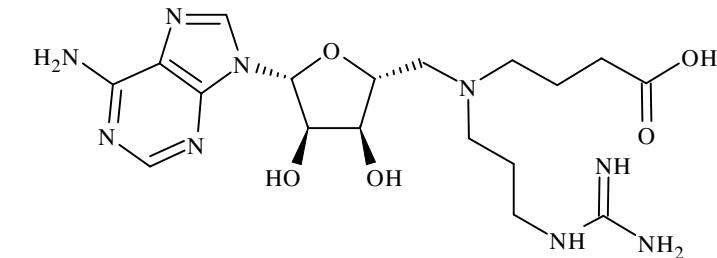
Sample: RP183d, 100v

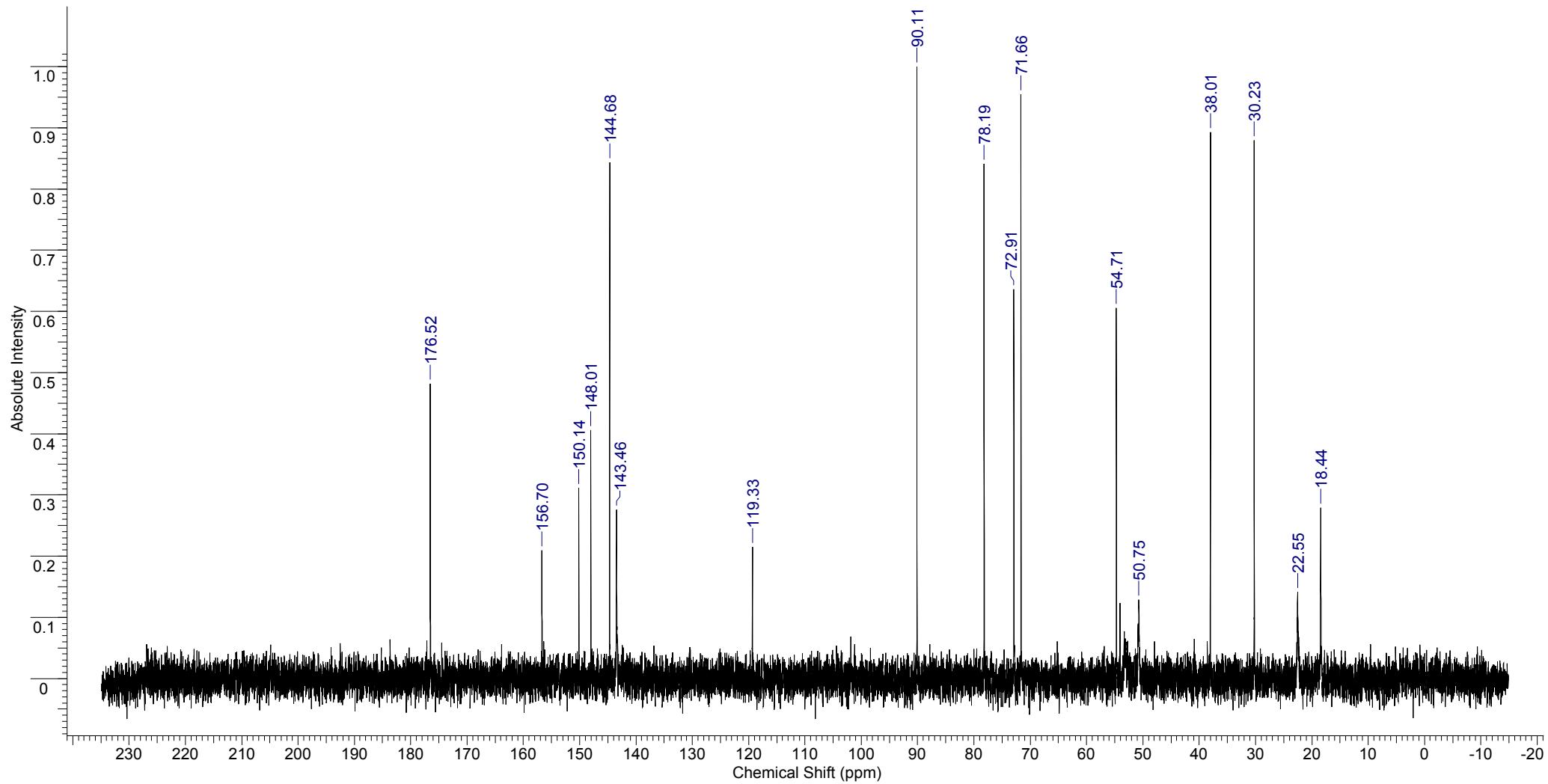
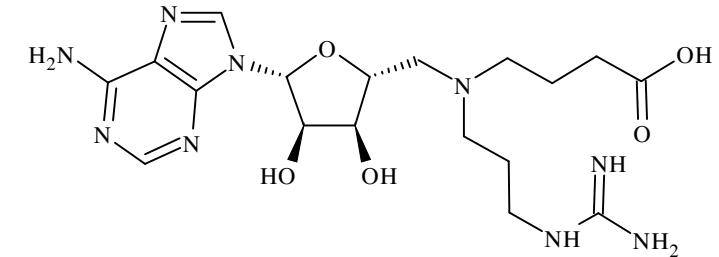
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Operator: dmt

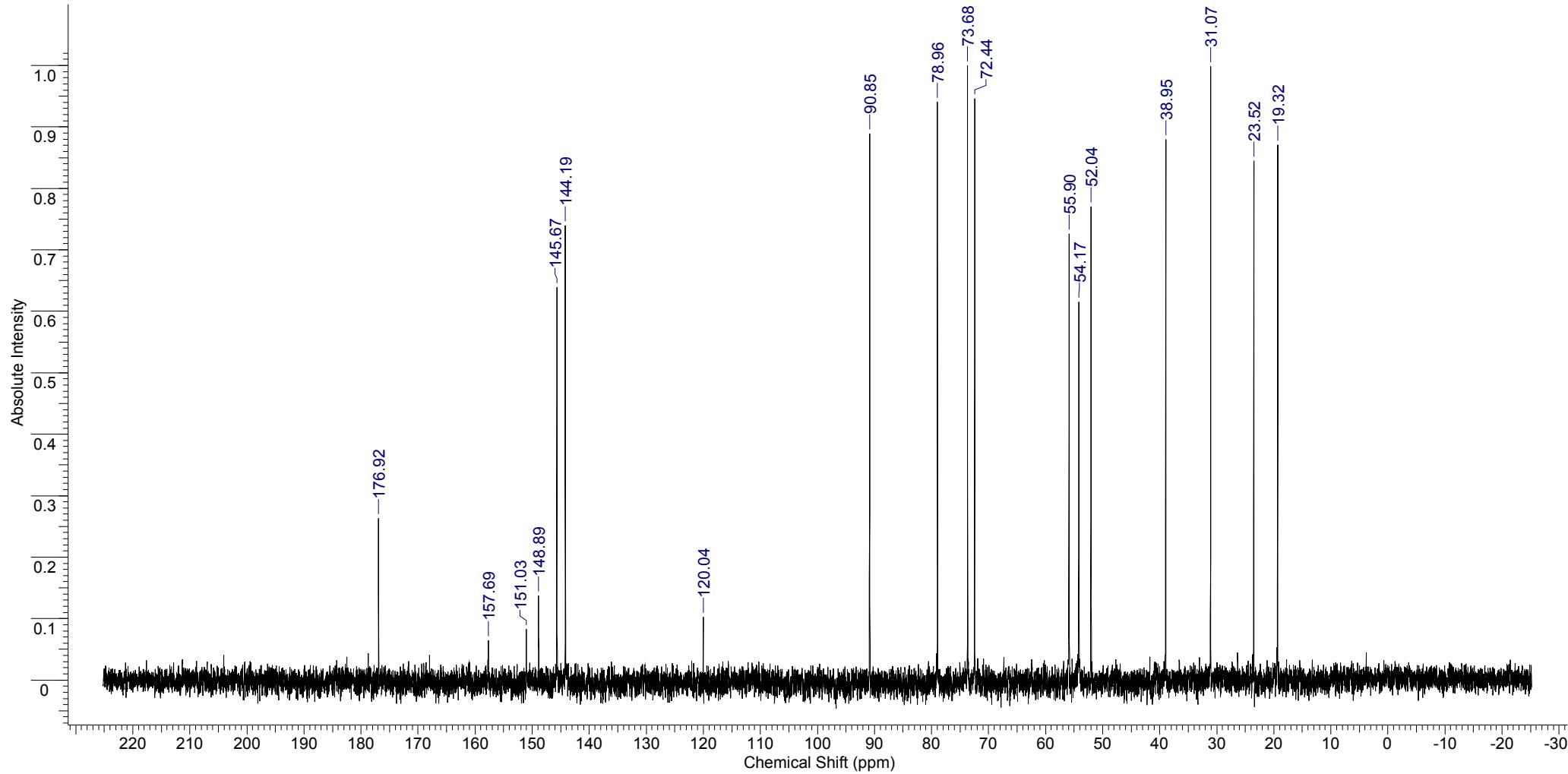
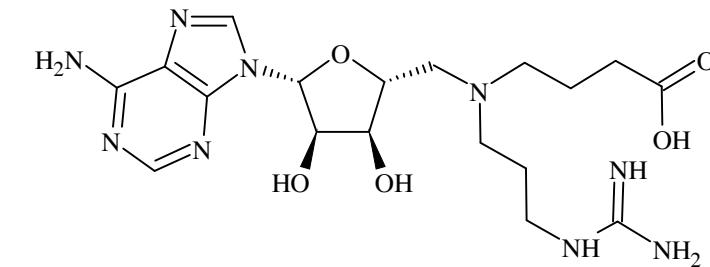
Date: 2/1/2010 3:35 PM







@70 Celcius

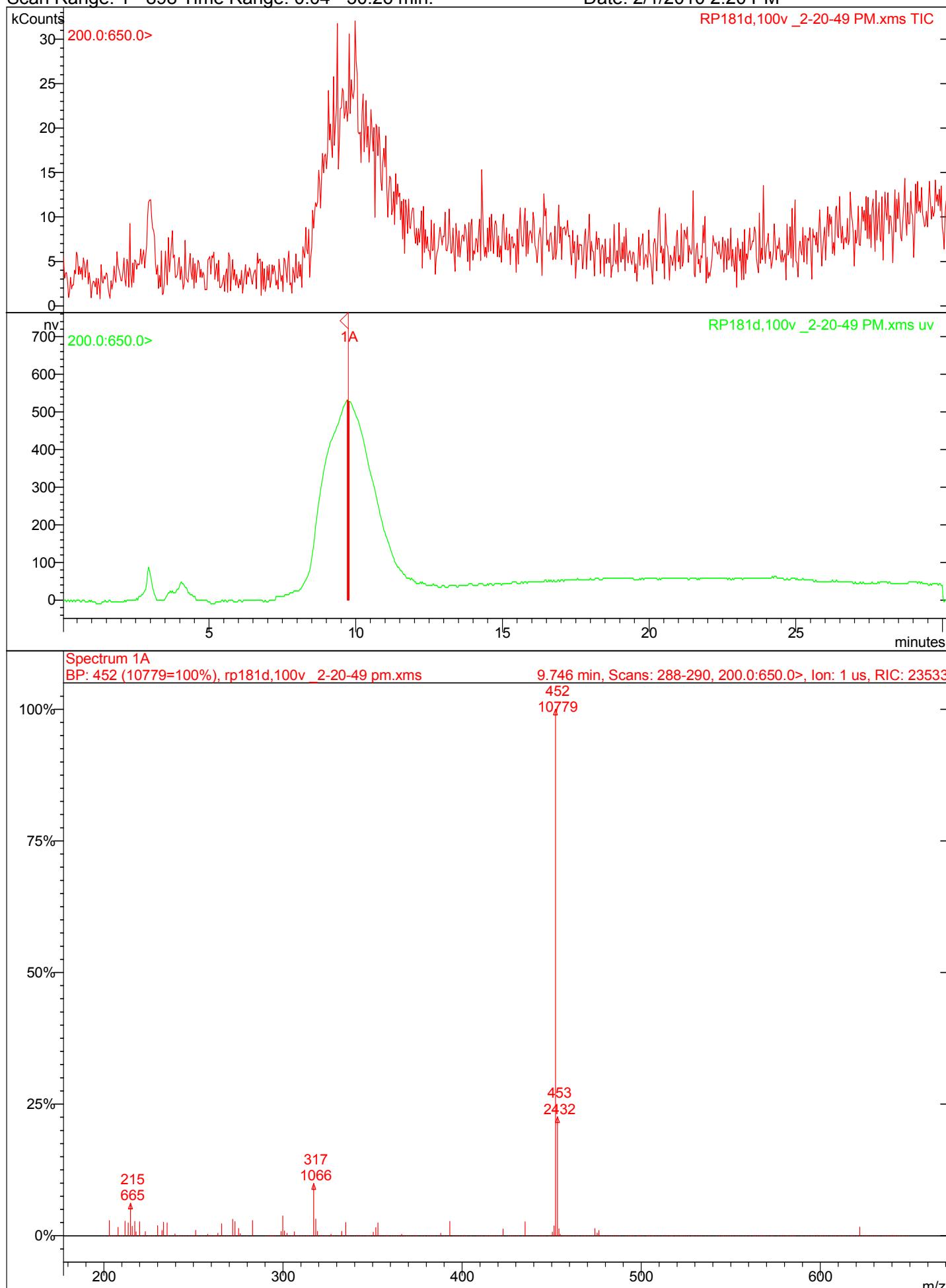


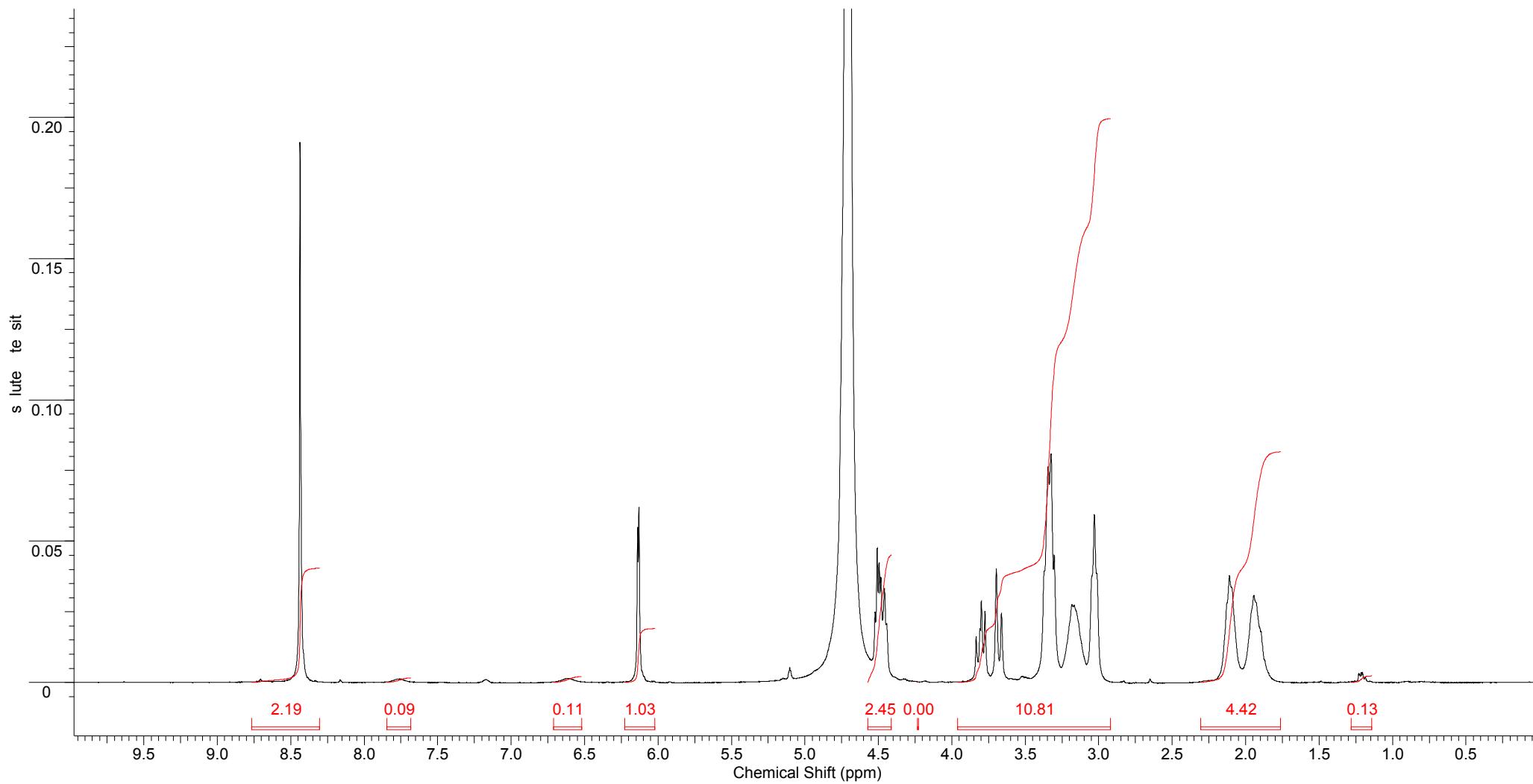
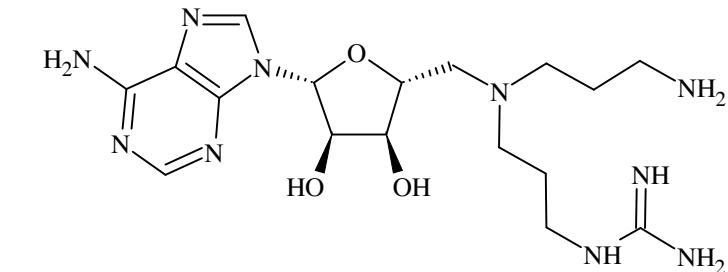
MS Data Review All Plots - 2/25/2010 4:57 PM

Compound 21

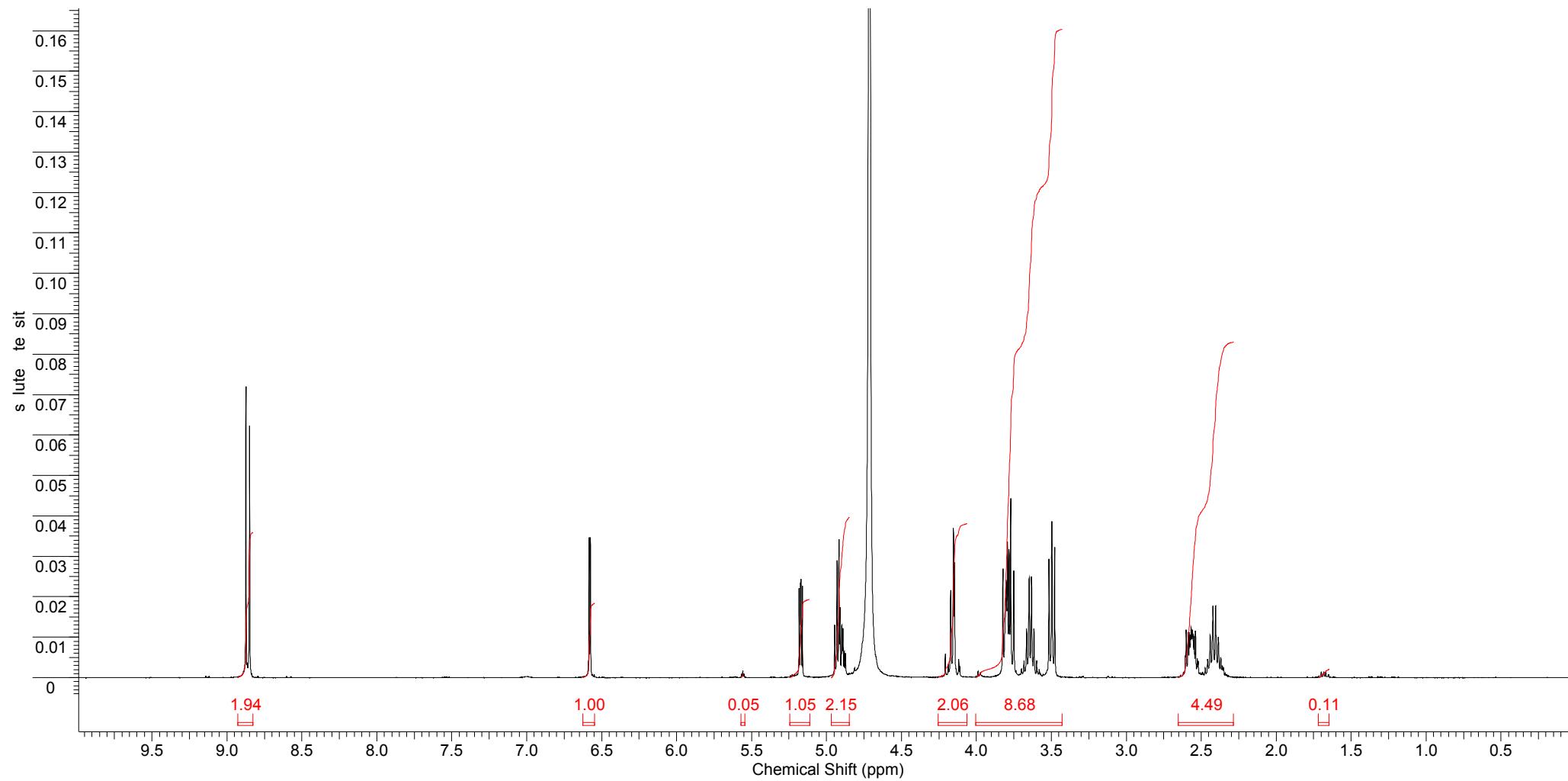
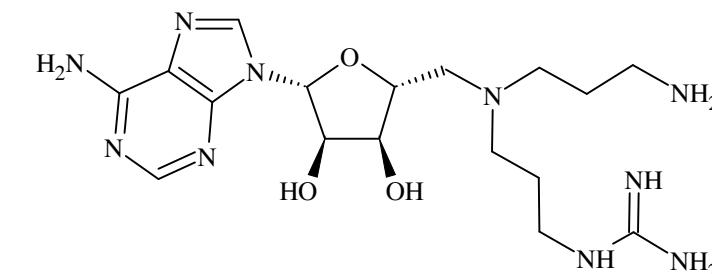
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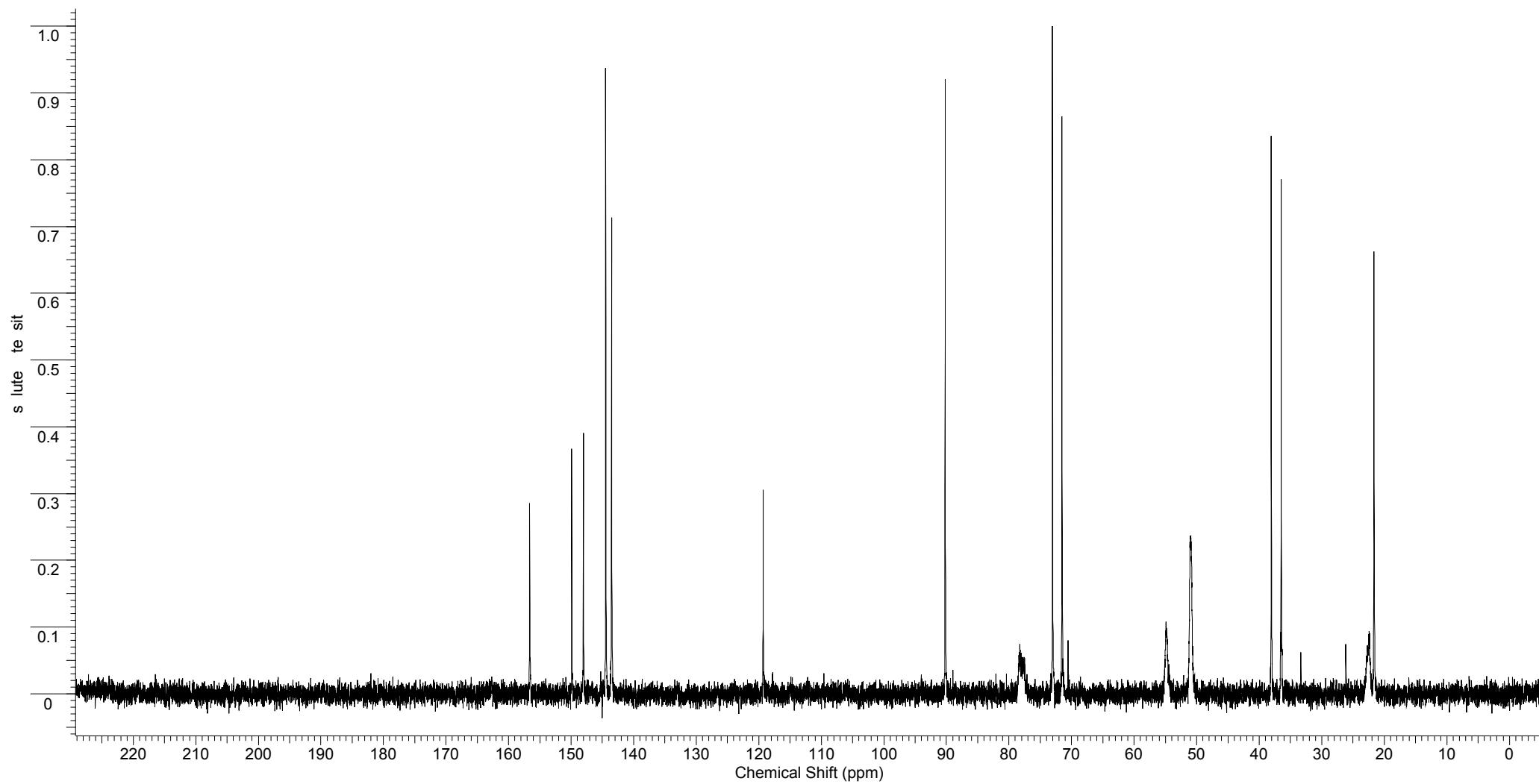
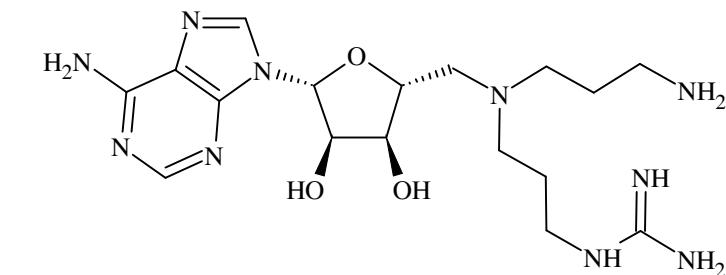
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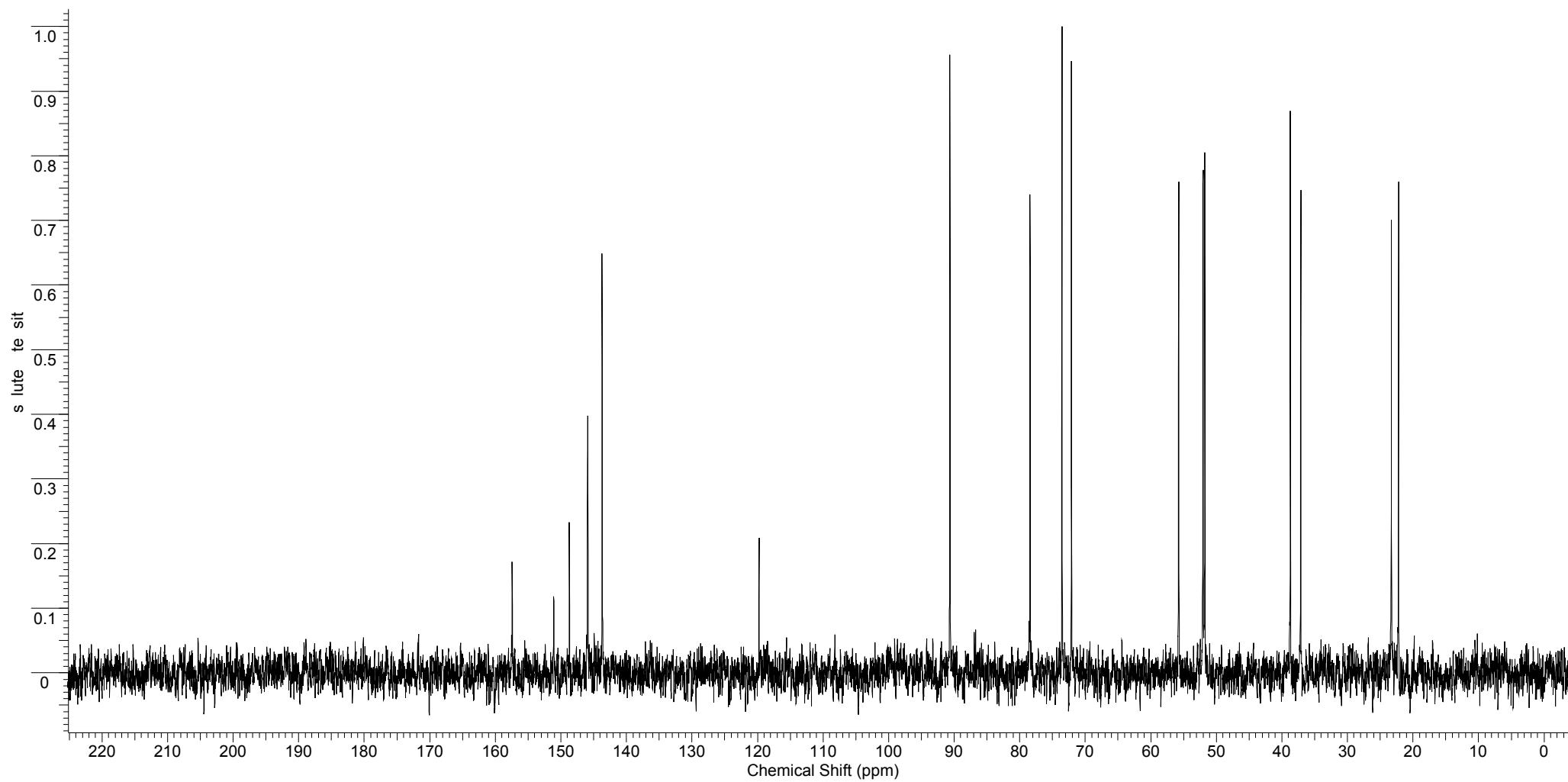
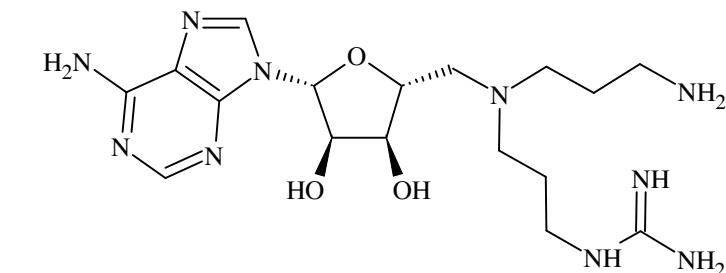




@70 Celcius







MS Data Review All Plots - 2/25/2010 5:05 PM

Compound 22

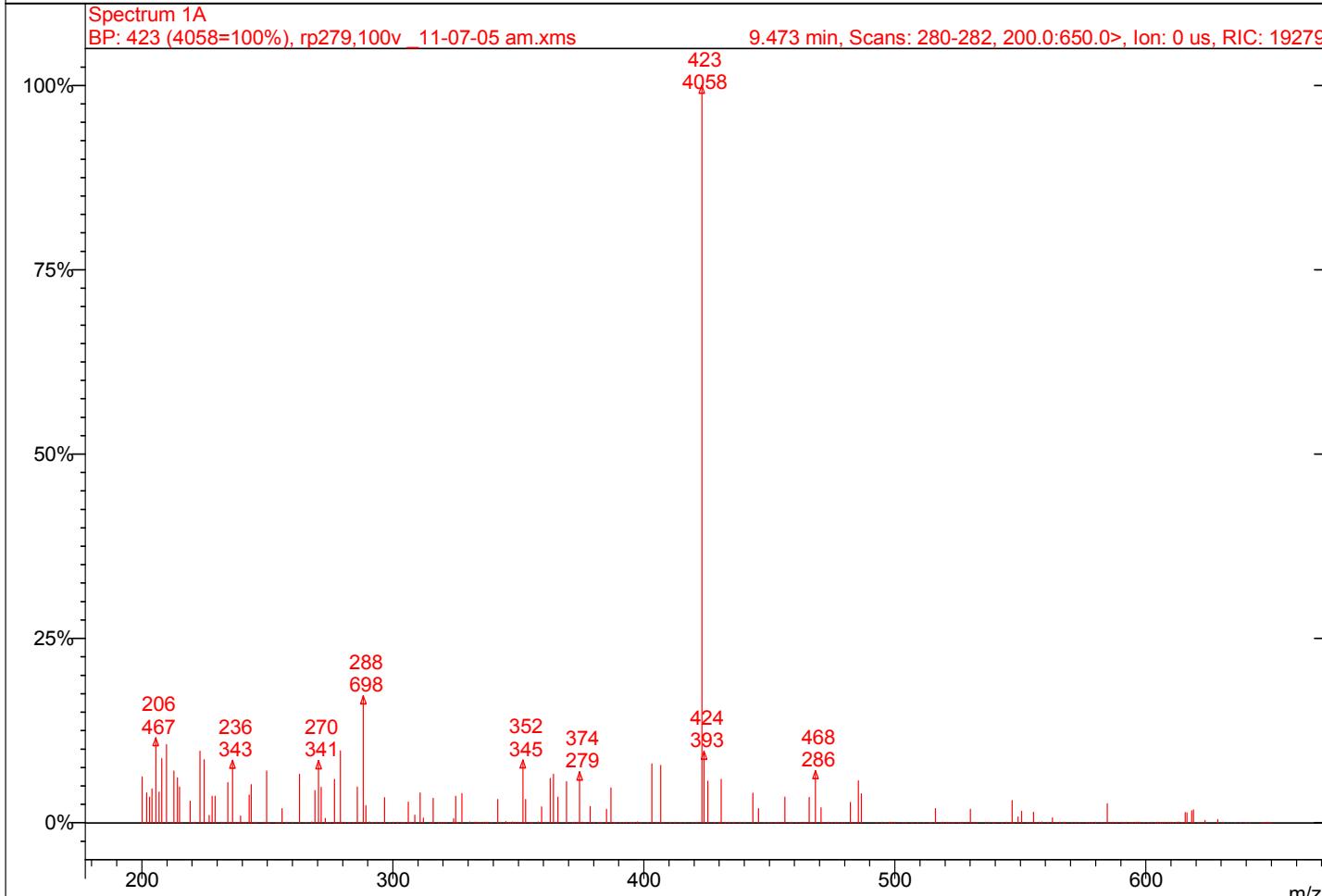
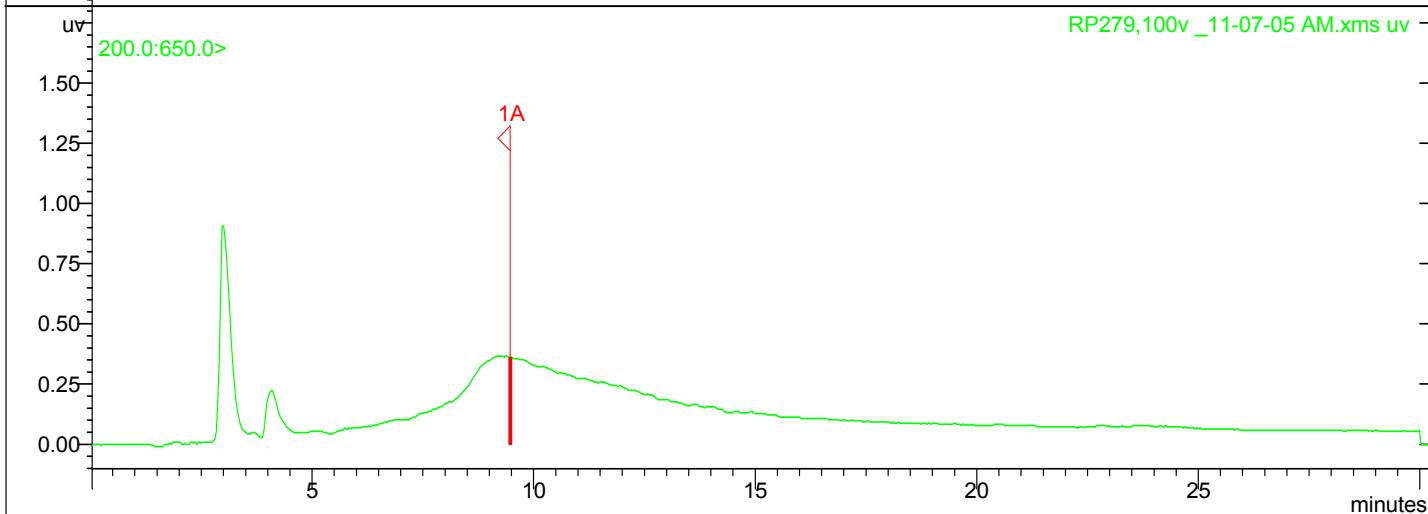
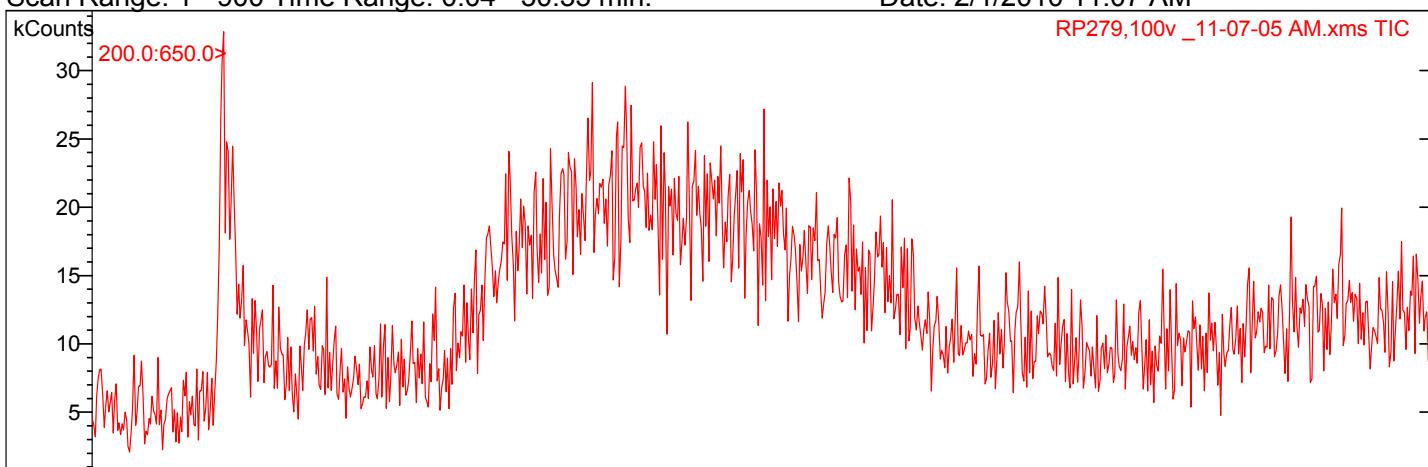
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Sample: RP279,100v

Scan Range: 1 - 900 Time Range: 0.04 - 30.33 min.

Operator: dmt

Date: 2/1/2010 11:07 AM



MS Data Review All Plots - 2/25/2010 5:06 PM

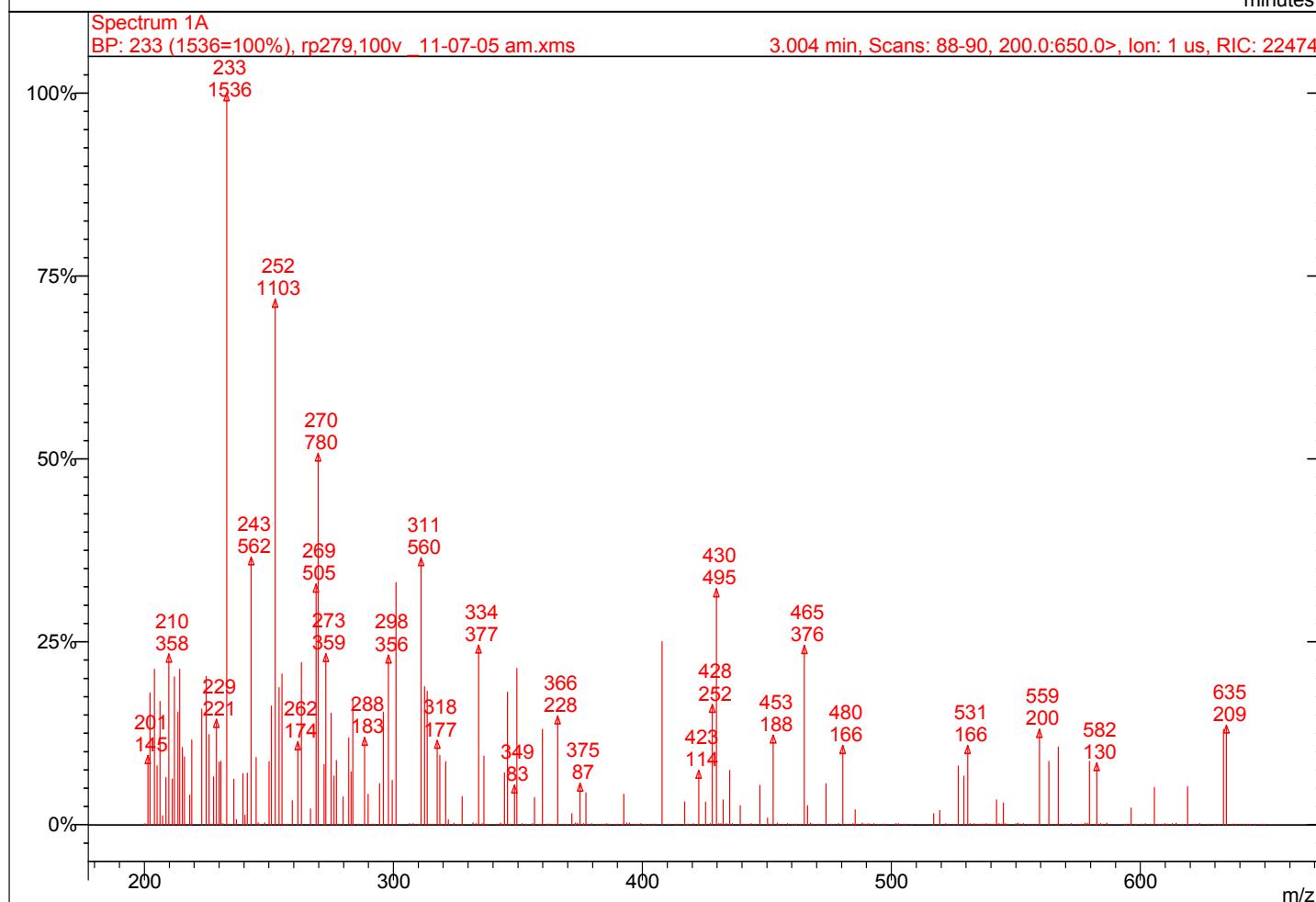
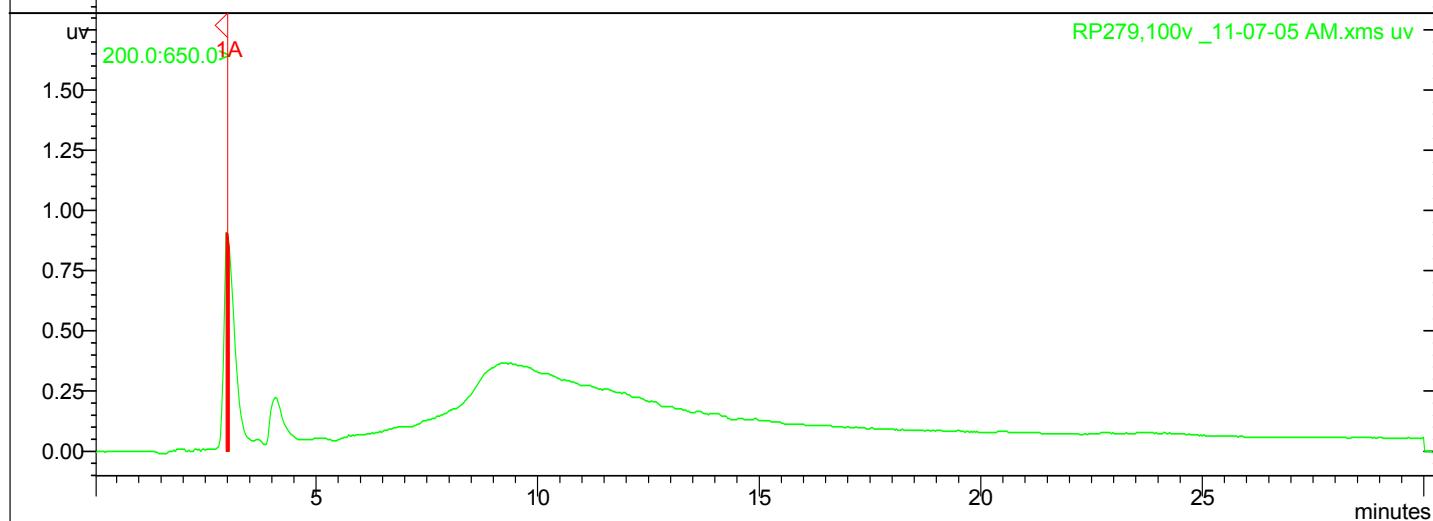
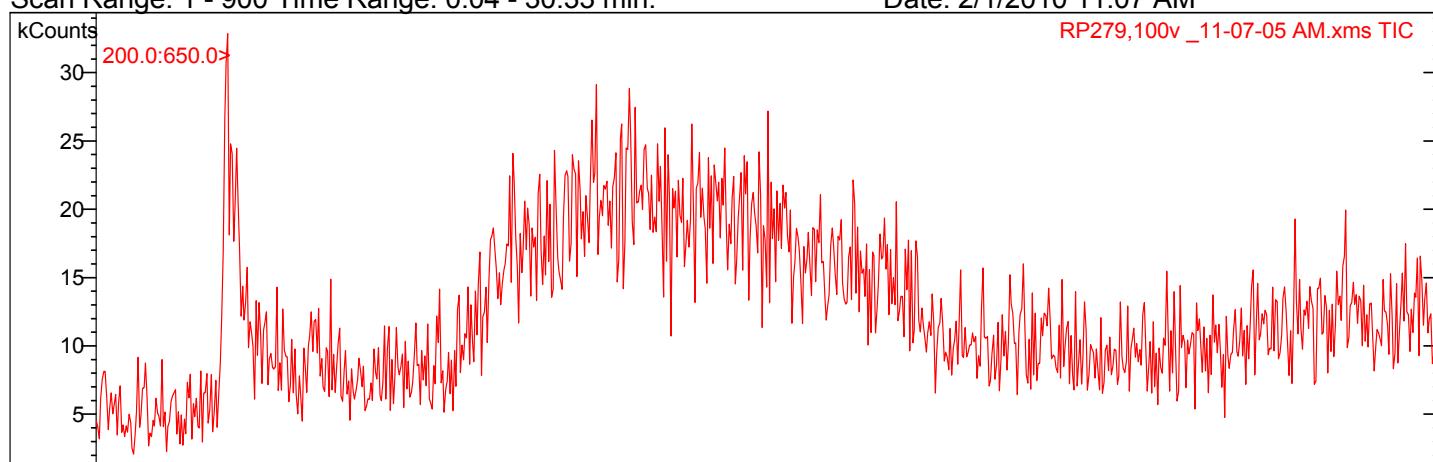
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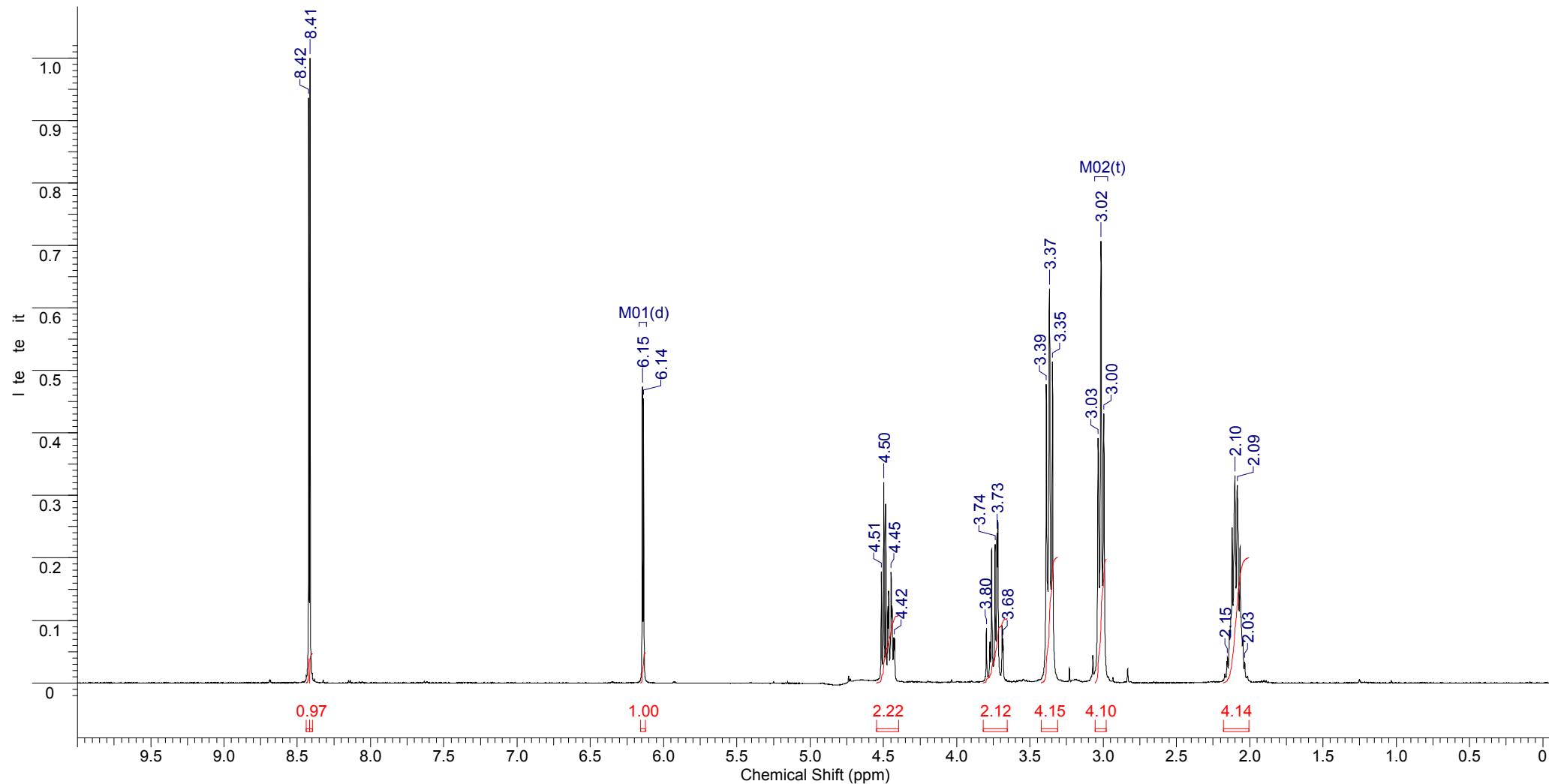
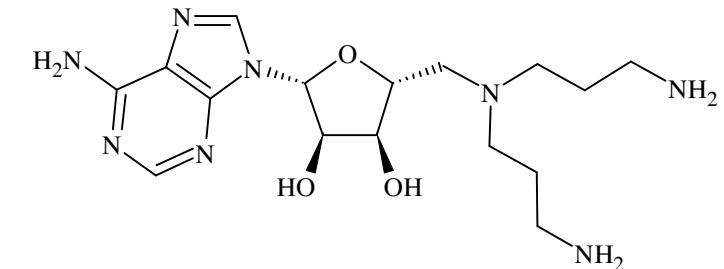
Sample: RP279,100v

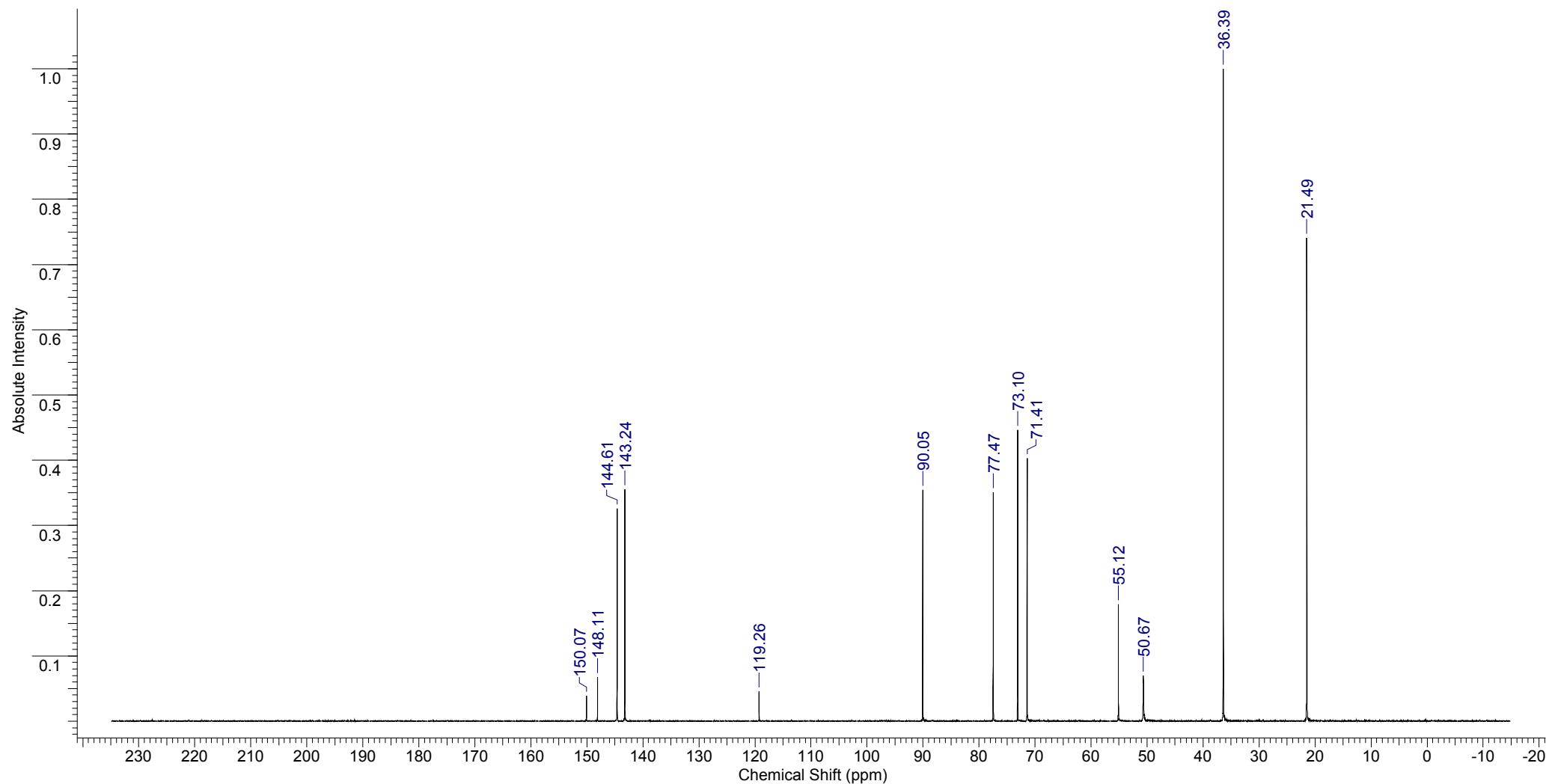
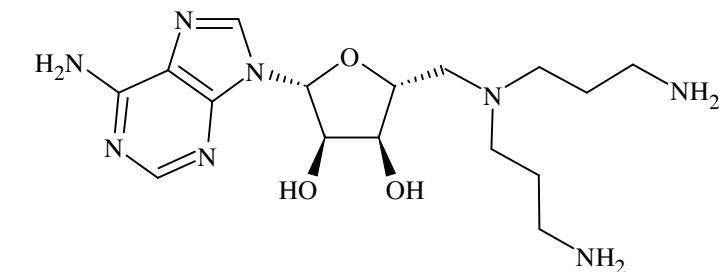
Scan Range: 1 - 900 Time Range: 0.04 - 30.33 min.

Operator: dmft

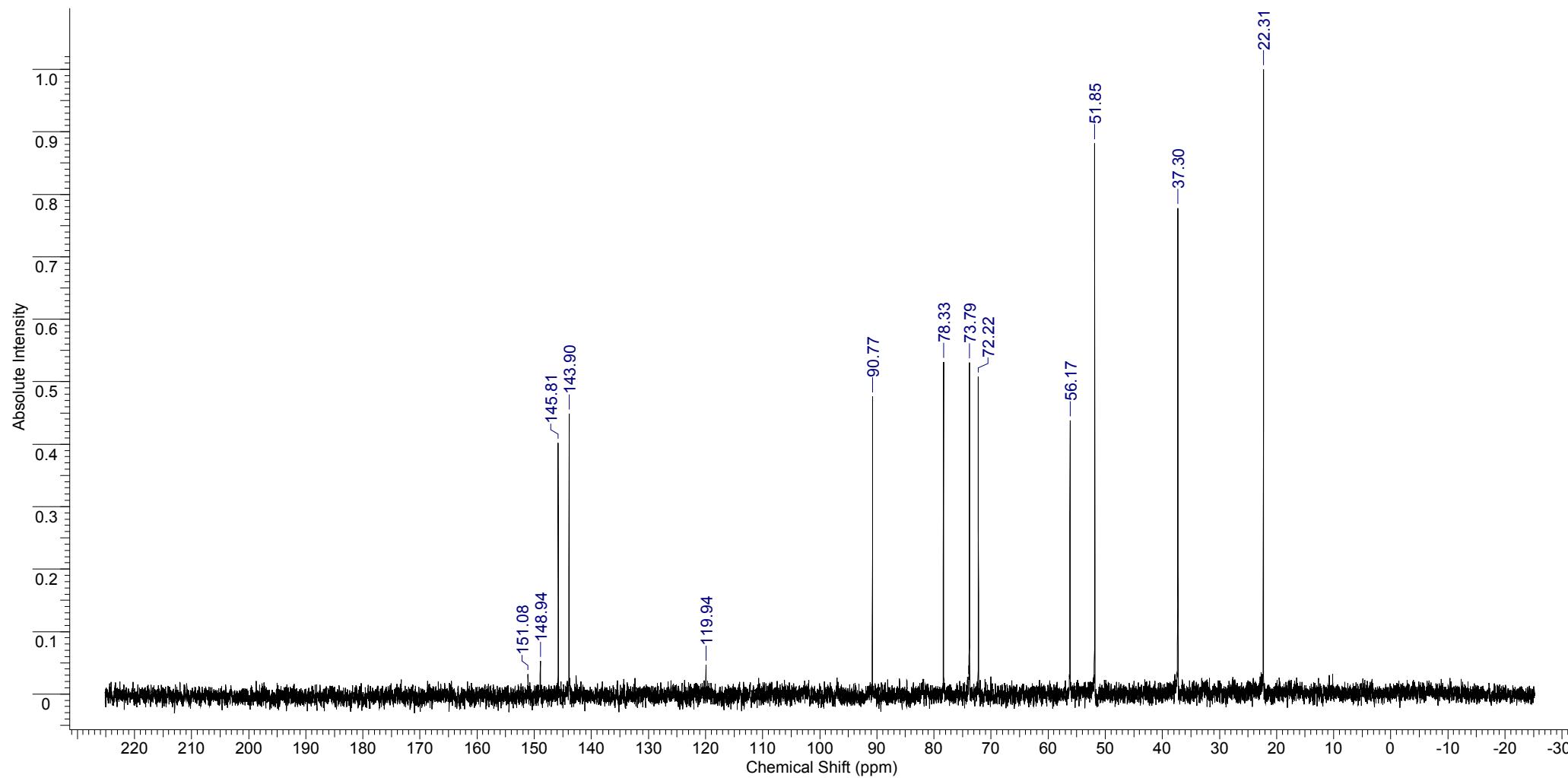
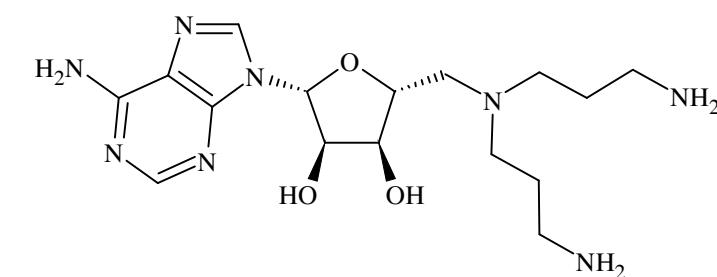
Date: 2/1/2010 11:07 AM







@70 Celcius



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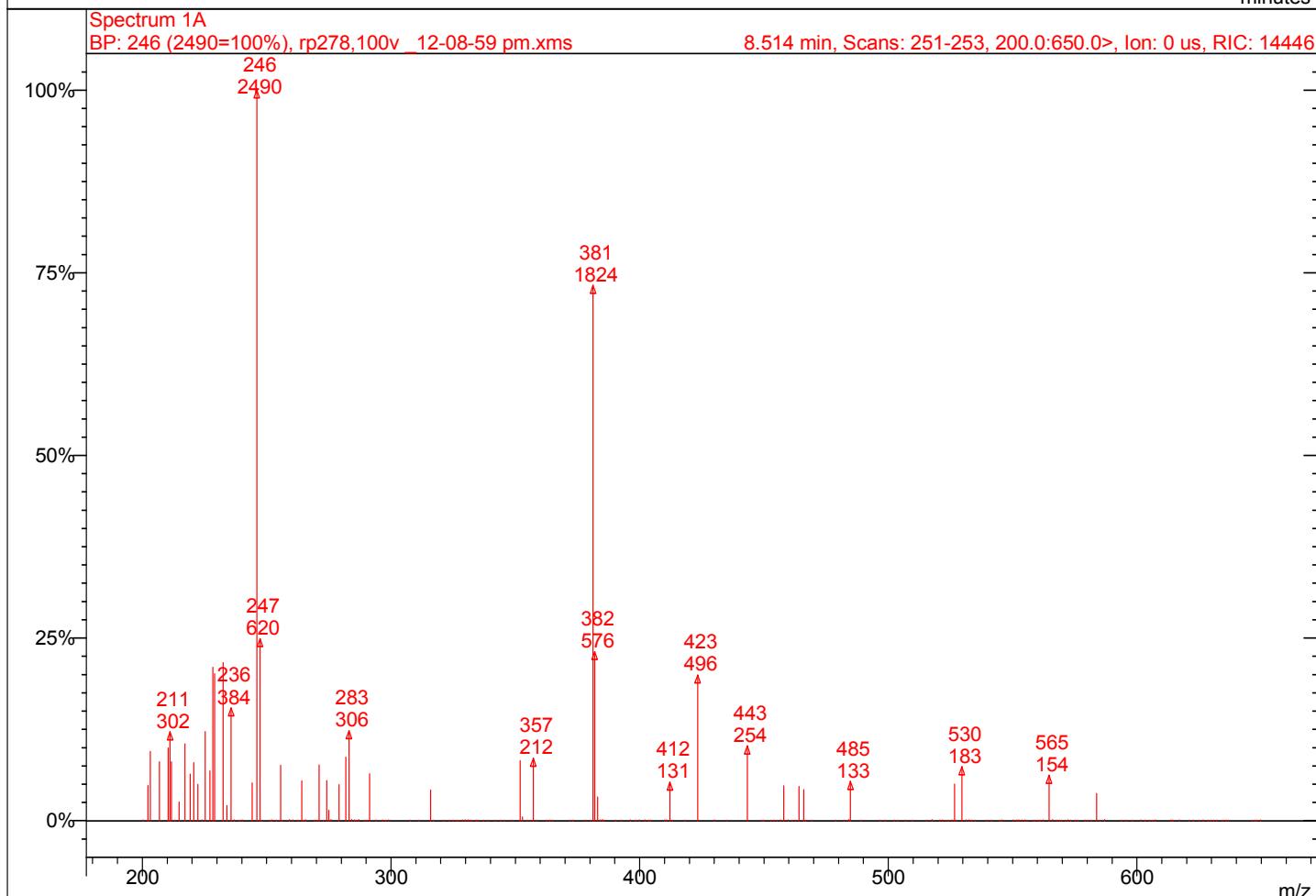
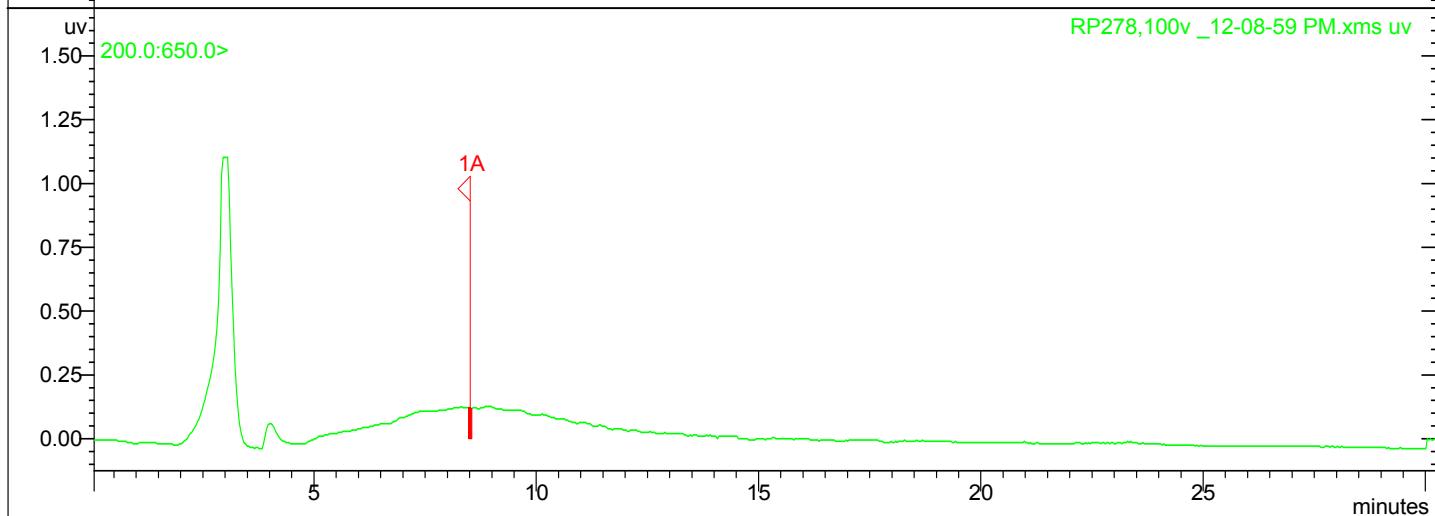
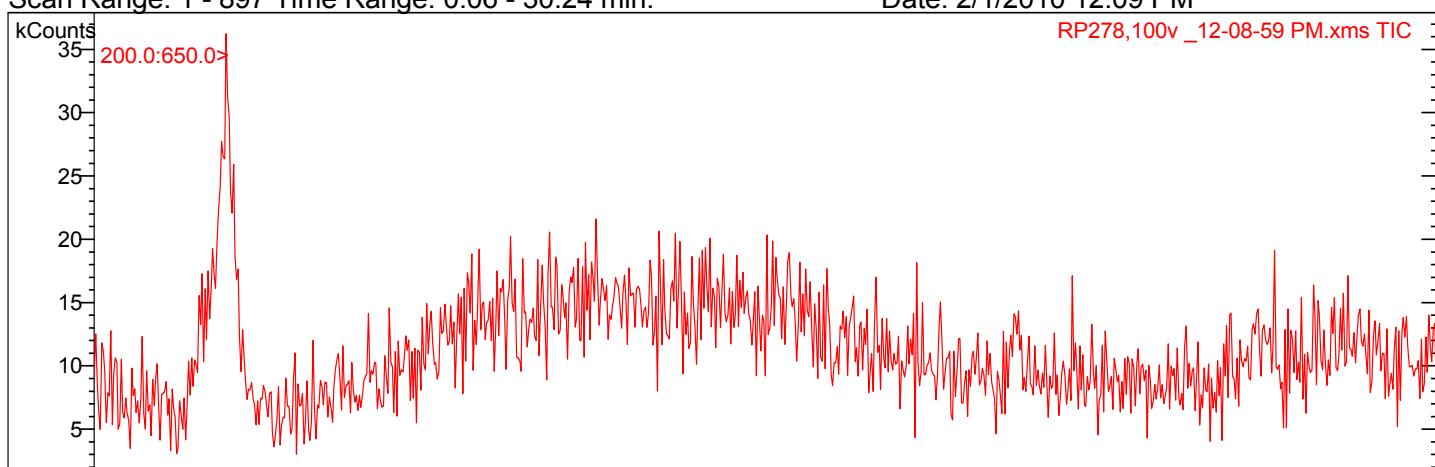
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Sample: RP278,100v

Scan Range: 1 - 897 Time Range: 0.06 - 30.24 min.

Operator: dmt

Date: 2/1/2010 12:09 PM



MS Data Review All Plots - 2/25/2010 5:17 PM

Compound 23

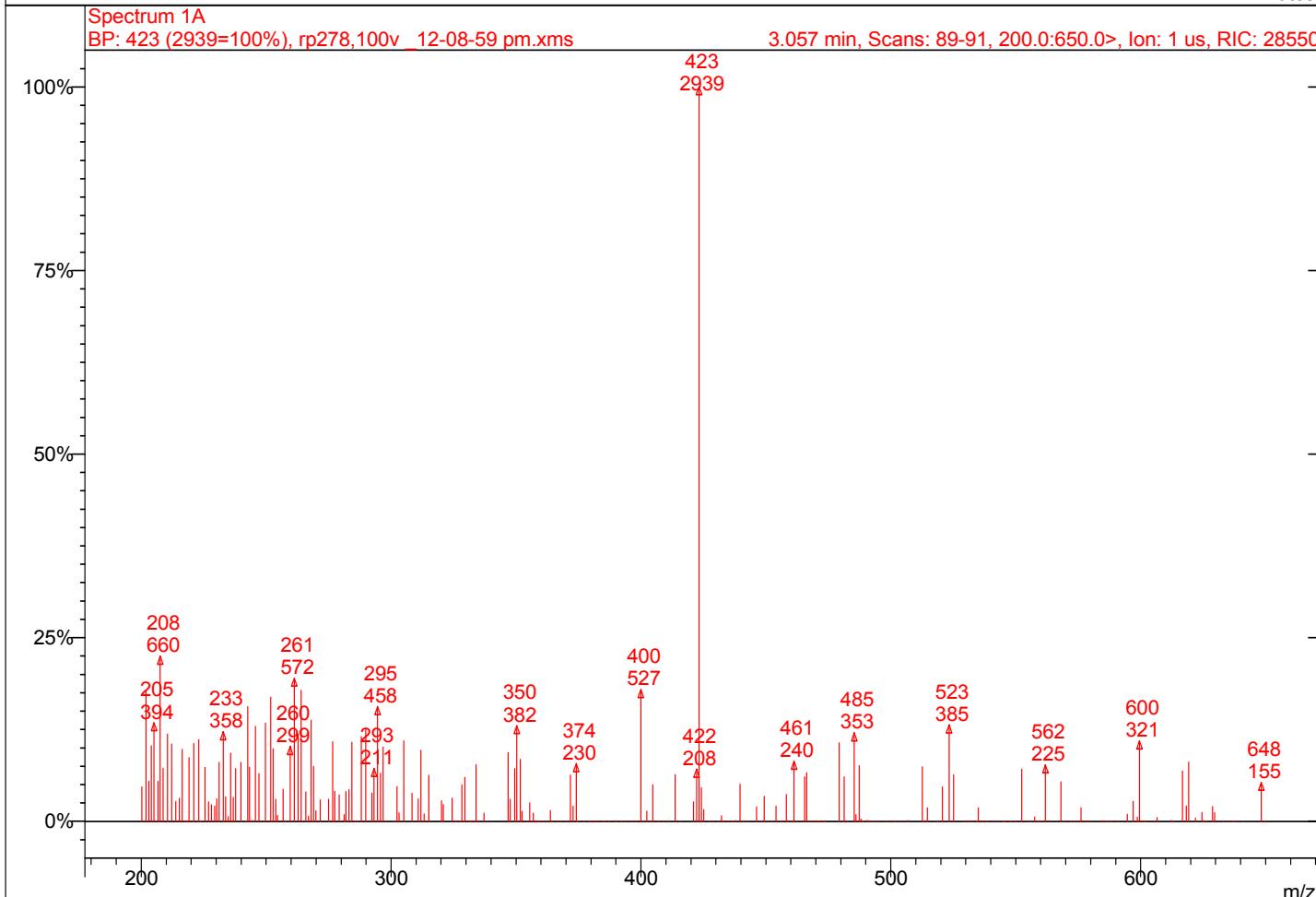
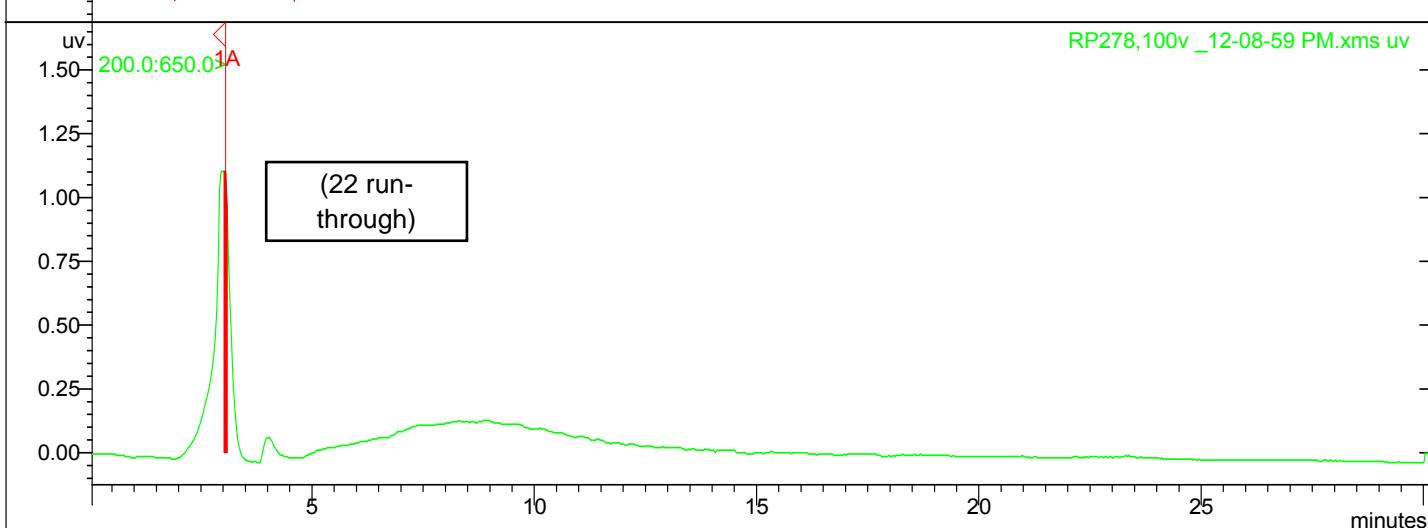
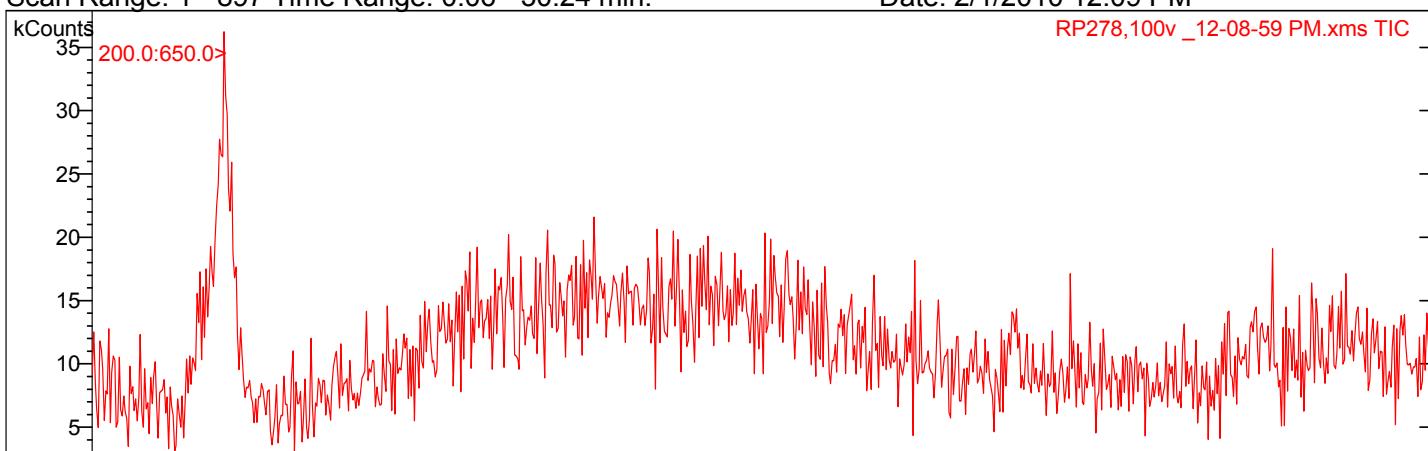
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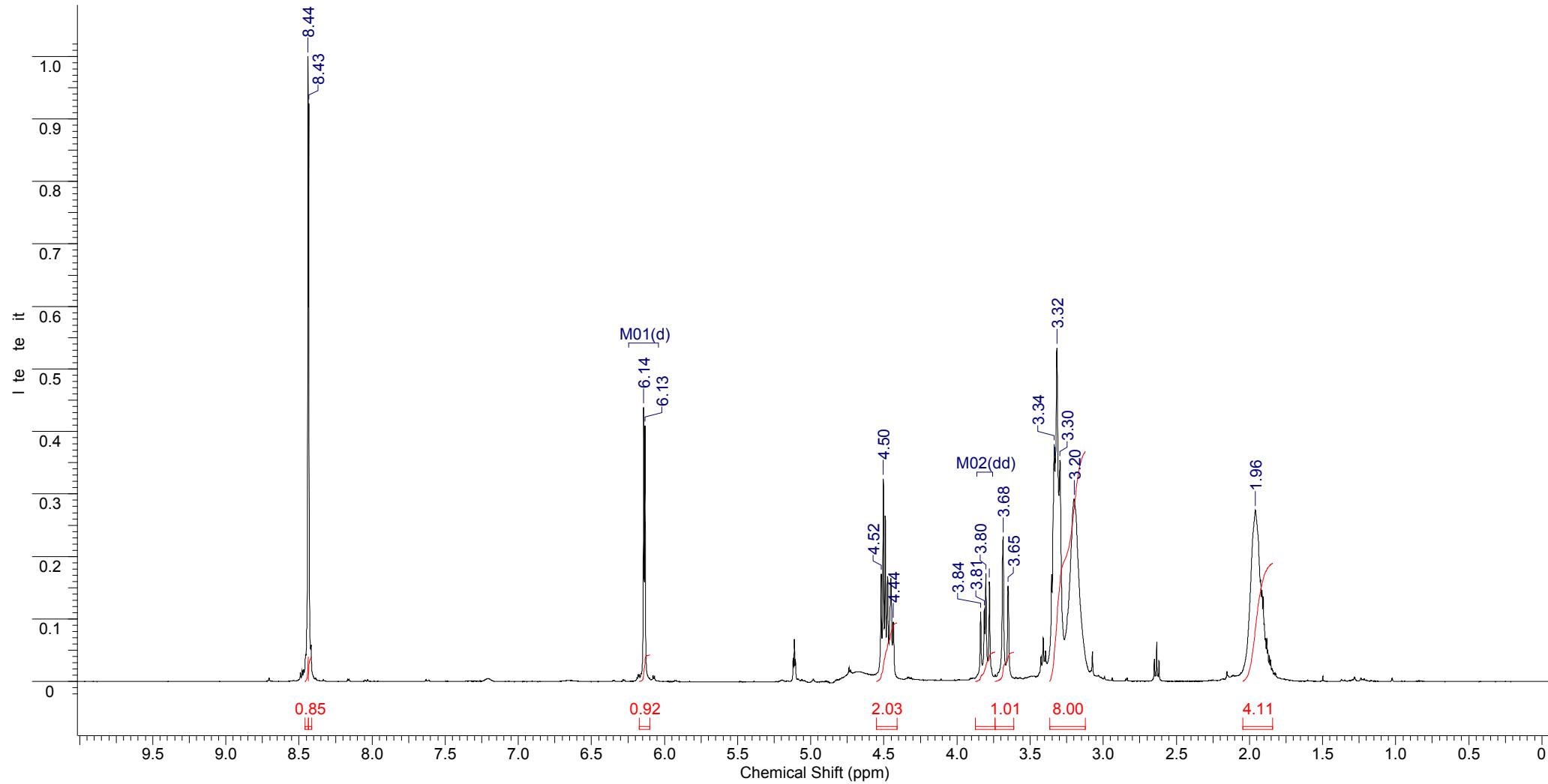
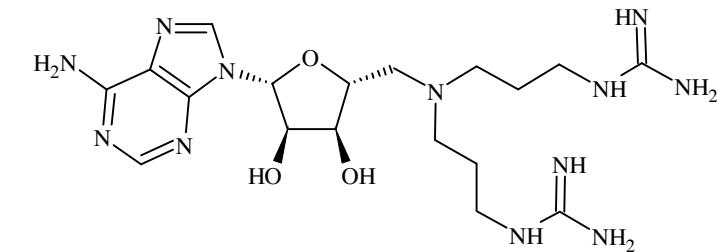
Sample: RP278,100v

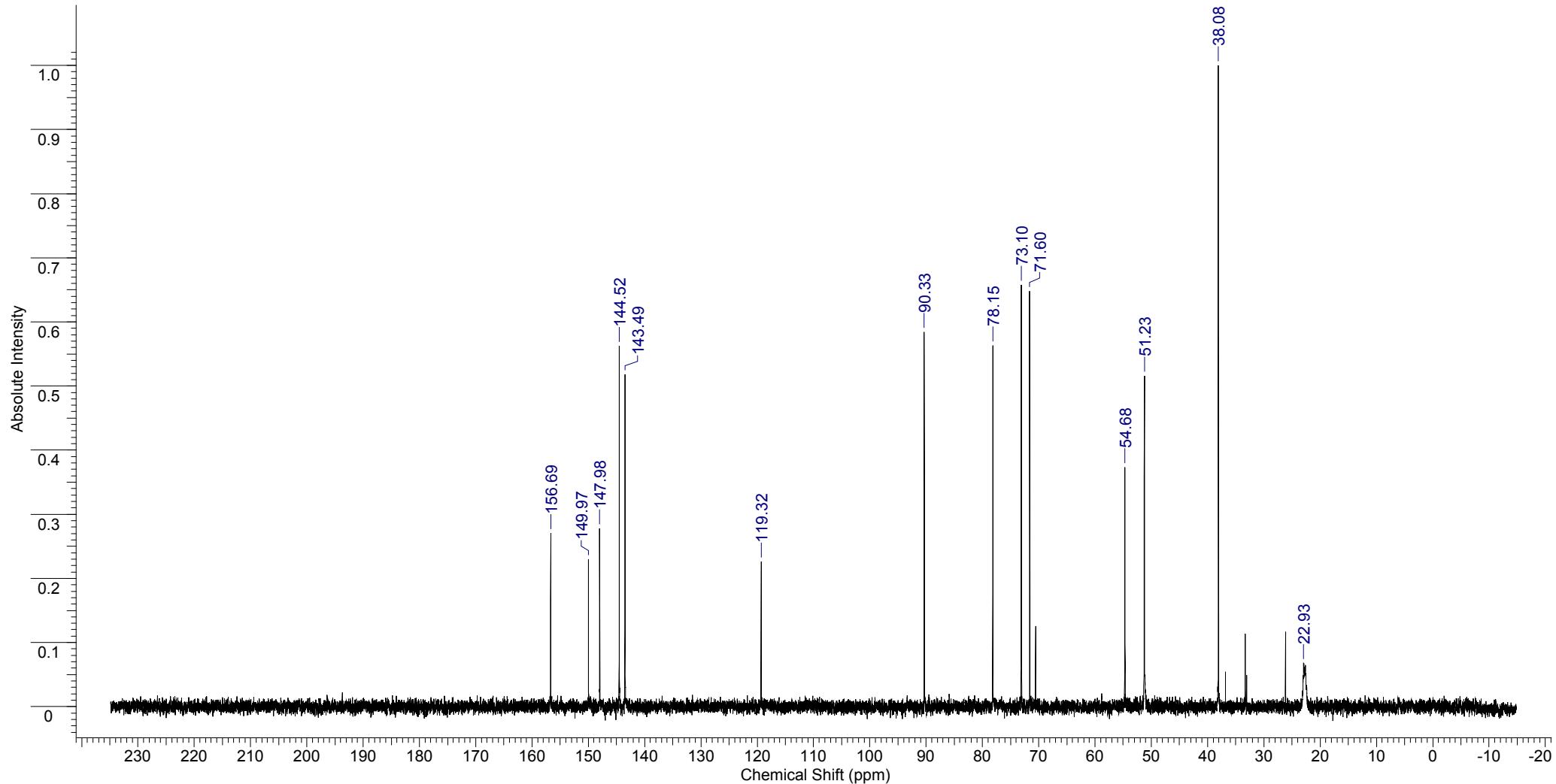
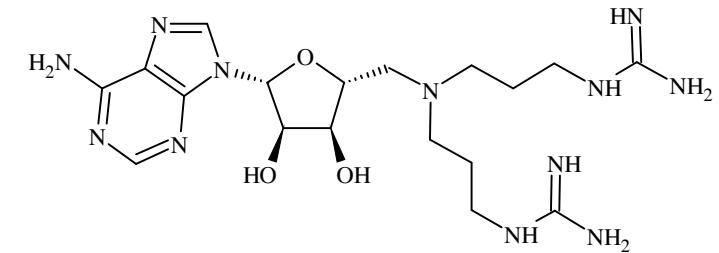
Scan Range: 1 - 897 Time Range: 0.06 - 30.24 min.

Operator: dm

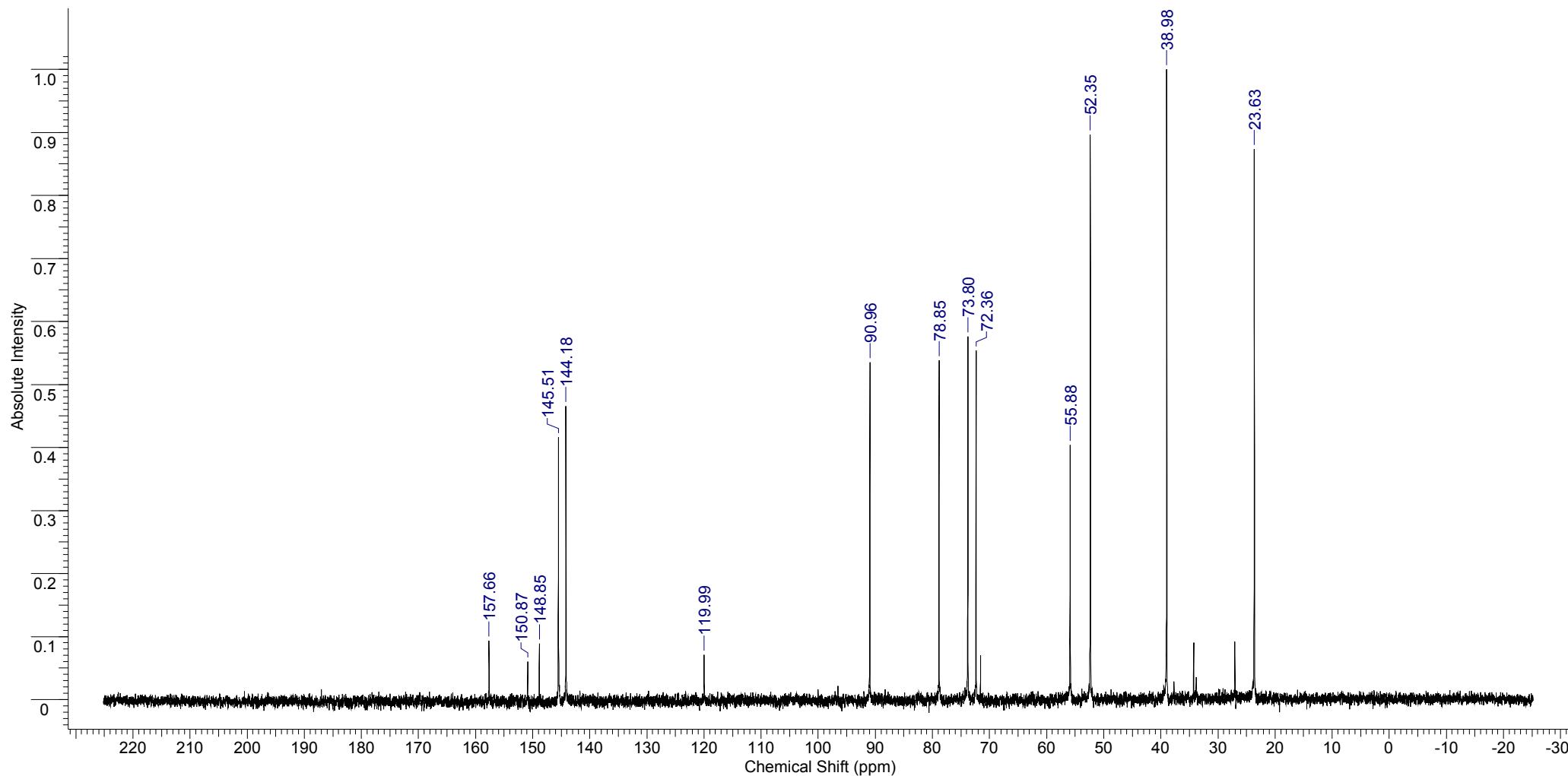
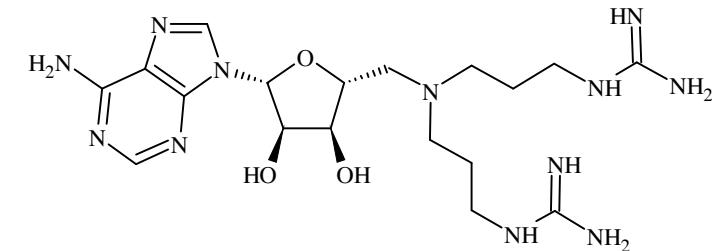
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@70 Celcius



MS Data Review All Plots - 2/25/2010 5:09 PM

Compound 24

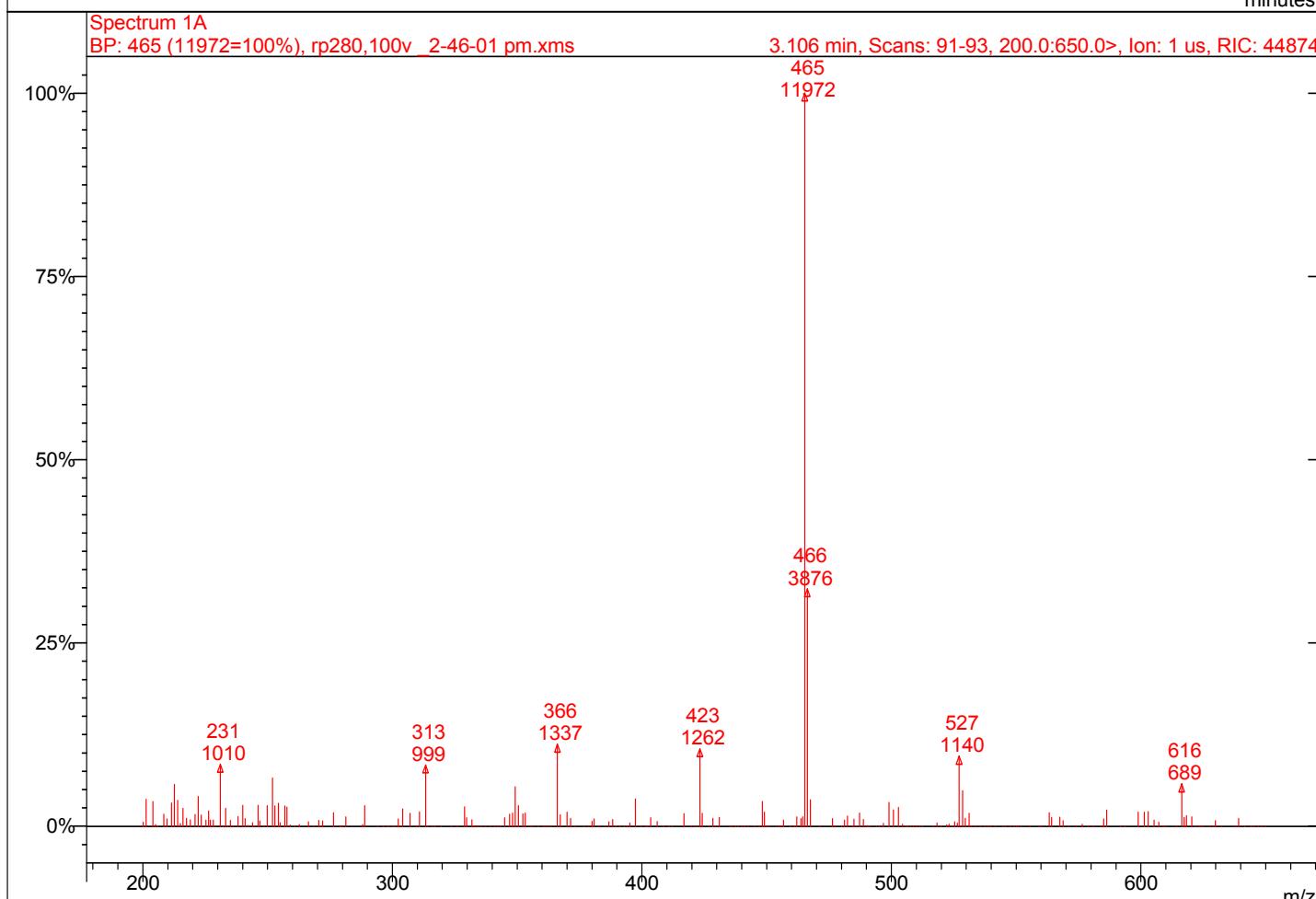
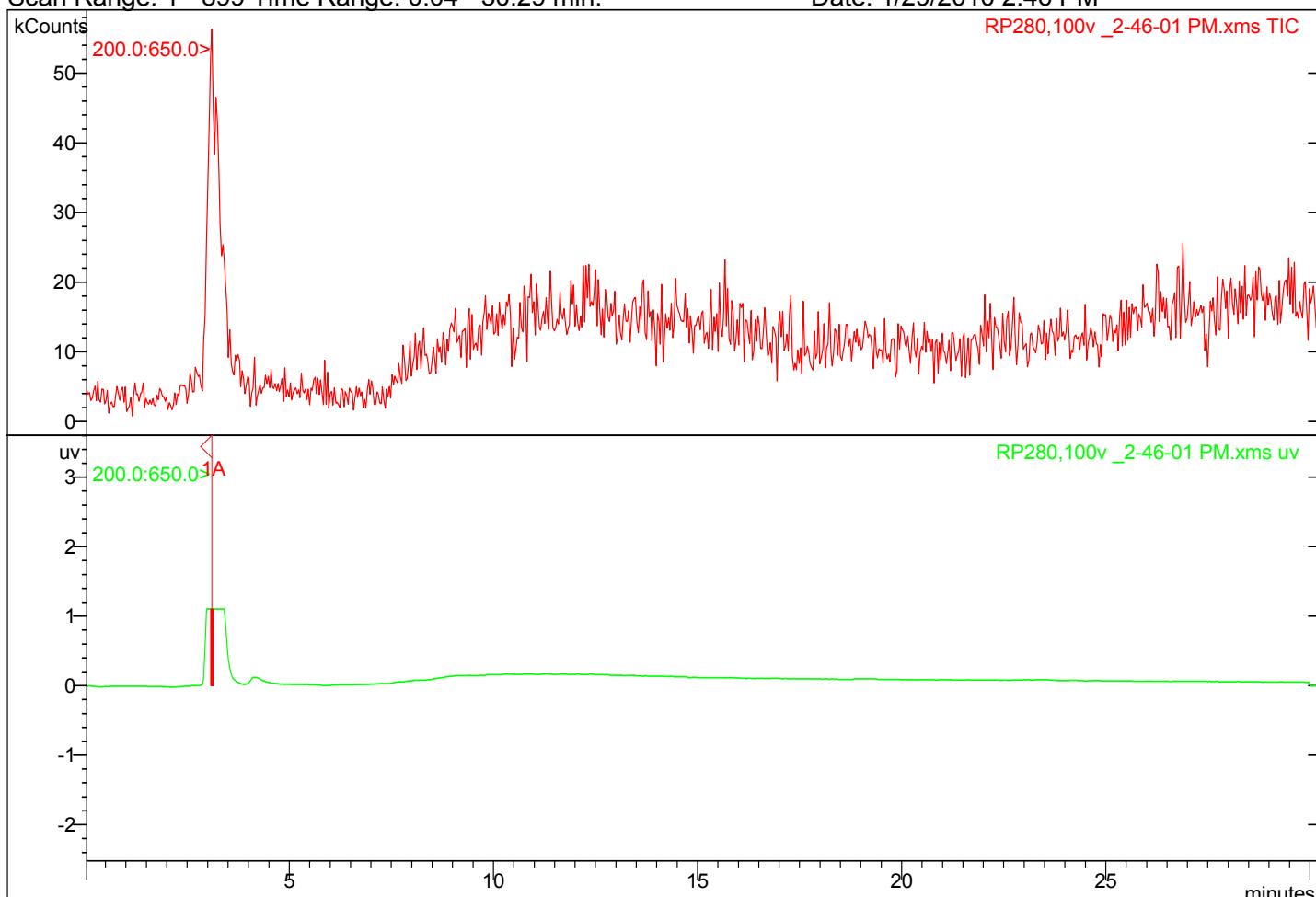
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Sample: RP280,100v

Scan Range: 1 - 899 Time Range: 0.04 - 30.29 min.

Operator: dm

Date: 1/29/2010 2:46 PM



Information added after peer-review:

Table 1: Distances (\AA) measured between nearest oxygen of binding site residue and nearest nitrogen of guanidinium for flexibly docked ligand and rigid CARM1 receptor, or overlaid PRMT1 (bold).

Residue	16			17			18			20		
	N1	N2	N3	N1	N2	N3	N1	N2	N3	N1	N2	N3
E258		3.19			5.94			6.85		6.05	8.56	
E267	3.41		3.16	2.98		3.30	2.86		3.69	3.65		3.15
Asn162		9.53			8.79			7.71			8.25	
Glu47		6.04			4.40			3.15			4.50	
	19											
Residue	NH_3^+											
E258	5.20											
E267	2.73											
Asn162	12.11											
Glu47	7.71											

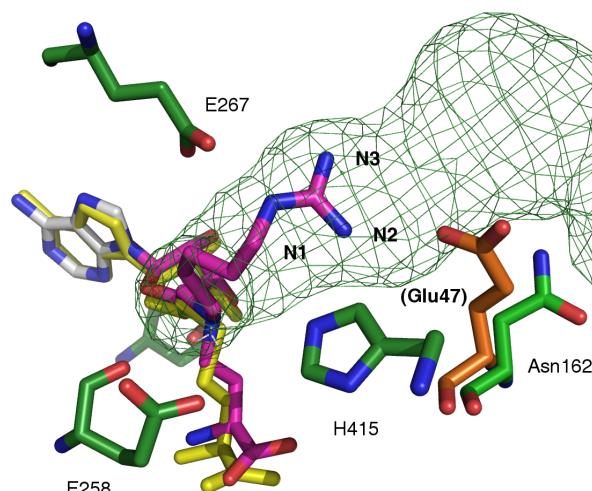


Figure 1: Docked structure of **18** showing numbering of nitrogens in Table 1 above

Further images relevant to the Docking discussion:

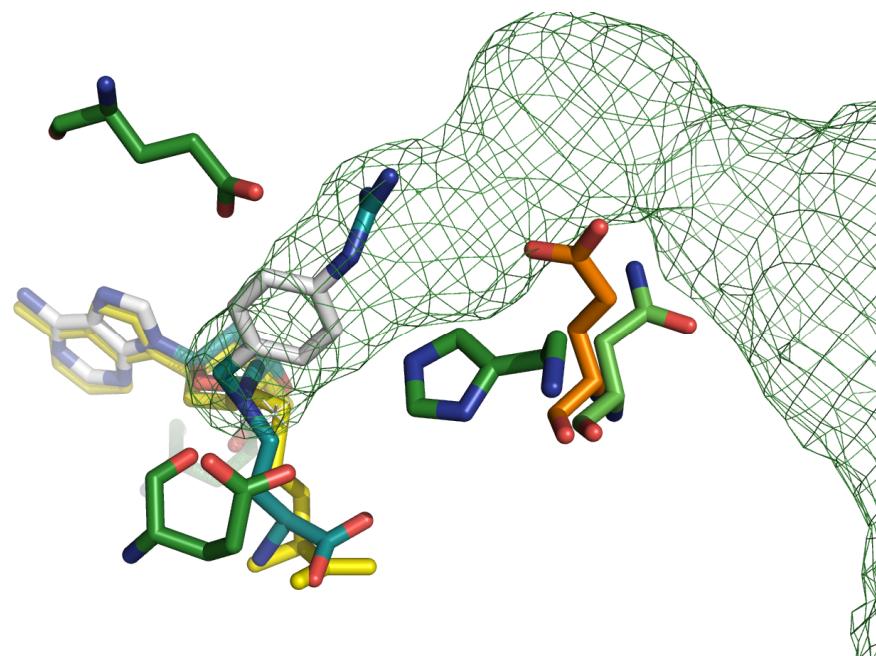


Figure 2: Result of docking inhibitor **20** (white backbone) with CARM1 binding site (2Y1X.pdb, selected residues green backbone), also AdoHcy **2** (yellow), substrate arginine channel (green mesh). PRMT1 residue superimposed, Glu47 (orange, bold in parentheses).

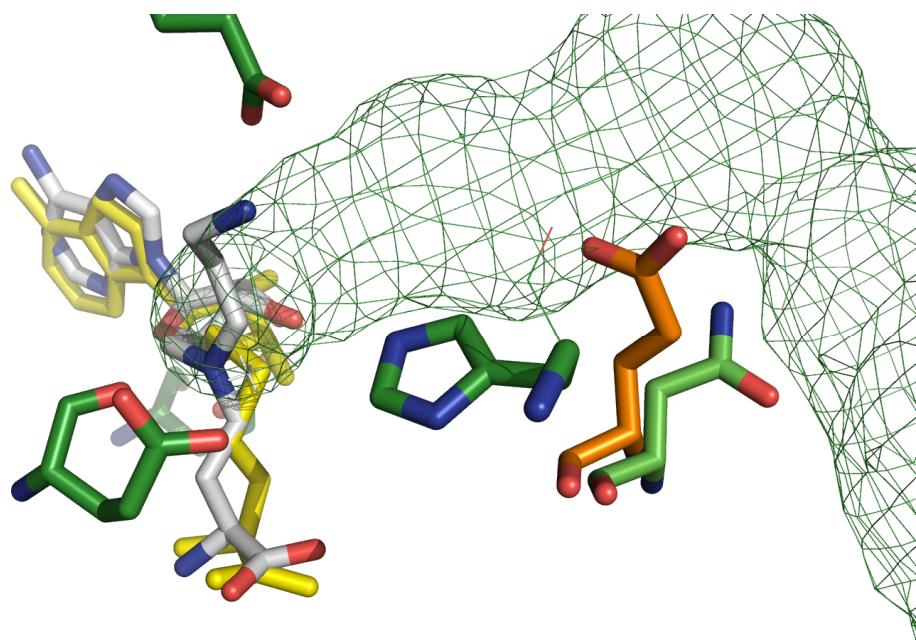


Figure 3: Result of docking inhibitor **19** (white backbone) with CARM1 binding site (2Y1X.pdb, selected residues green backbone), also AdoHcy **2** (yellow), substrate arginine channel (green mesh). PRMT1 residue superimposed, Glu47 (orange, bold in parentheses).