Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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Synthesis and Anti-HIV Activity of Conformationally Restricted Bicyclic Hexahydroisobenzofuran Nucleoside Analogs

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General Spectroscopic and Experimental Data

General techniques. All reagents were bought from Aldrich and Acros at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. THF and CH_2Cl_2 were purified by passage through a bed of activated alumina. Pyridine (Py) was distilled from CaH_2 prior to use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. LC-ESI-MS analyses were carried out in a chromatograph with UV detector at 280 nm using a VYDAC C-18 column, Cat. Number: 218TP54, (4.6mm x 250 nm); flow 1 mL/min; r.t.; gradient MeOH/H_2O as eluent. NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz or Bruker AV-400 or 600 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain

the multiplicities: s= singlet; d= doublet, t= triplet, q= quartet, m= multiplet, br= broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]^{T}_{\lambda}$ (c: g/100mL, solvent). High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under electron spray ionization (ESI) conditions. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

The bicyclic motif of the synthetic hexahydroisobenzofuran nucleosides is abbreviated below as HIBF. The assignment of the NMR data is based on the nucleoside numbering (1'- 5') and the second ring as 6'- 9' positions (Figure 2 of the article).

Synthesis of Lactone 12. It was obtained following a previously described procedure [a) T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis, *Angew. Chem. Int. Ed.* **2004**, *43*, 739-742. b) T. P. Brady, S. H. Kim, K. Wen, C. Kim, E. A. Theodorakis, *Chemistry Eur. J.* **2005**, *11*, 7175-7190]. R_f (33% hexane/EtOAc): 0.41; $[\alpha]_D^{20}$= 19.4 (c 3.40, CH_2Cl_2); IR (film): υ 3070, 3043, 2932, 2857, 1775, 1112, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (s, 9H, ^{t}Bu), 1.90-2.25 (m, 4H, $H_{6'}$+$H_{9'}$), 2.61 (m, 1H, $H_{3'}$), 3.01 (m, 1H, $H_{2'}$), 3.80 (m, 2H, $H_{5'}$), 4.16 (m, 1H, $H_{4'}$), 5.82 (m, 2H, $H_{7'}$+$H_{8'}$), 7.43 (m, 6H, H_o+H_p), 7.69 (m, 4H, H_m); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.5 (C-^{t}Bu), 22.8, 25.8 ($C_{6'}$+$C_{9'}$), 27.1 (Me-^{t}Bu), 34.3 ($C_{3'}$), 37.7 ($C_{2'}$), 64.5 ($C_{5'}$), 85.2 ($C_{4'}$), 125.9-135.9 ($C_{7'}$+$C_{8'}$+C_m+C_o+C_p), 179.8 (C=O); MS (ESI^+, *m/z*): 407 [$(M+H)^+$, 100%]; Exact mass found for $C_{25}H_{30}O_3Si$: 406.1964.

Synthesis of Lactol 13. A solution of **12** (12.8 g, 31.5 mmol) in dry CH_2Cl_2 (150 mL) was cooled to –78 ºC under argon and treated with DIBAL-H (35 mL, 35 mmol, 1M in CH_2Cl_2) for 1 h. The reaction was quenched with MeOH (10 mL) and the solution was brought to r.t. over a 20 min period. Saturated Rochelle salt was added (stirred for 15 min) and the crude was extracted with EtOAc (4 x 100mL). Lactol **13** was isolated in 92% yield as yellow oil. R_f (33% hexane/EtOAc): 0.29; $[\alpha]_D^{20}$= -16.9 (c 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, ^{t}Bu), 1.72-1.85 (m, 2H, $H_{6'}$+$H_{9'}$), 2.18-2.25 (m, 3H, $H_{6'}$+$H_{9'}$+$H_{3'}$), 2.78 (m, 1H, $H_{2'}$), 3.08 (m, 1H, OH), 3.62 (m, 1H, $H_{5'}$), 3.83 (m, 2H, $H_{4'}$+$H_{5'}$), 5.10 (m, 1H, $H_{1'}$), 5.65 (m, 2H, $H_{7'}$+$H_{8'}$), 7.42 (m, 6H, H_o+H_p), 7.70 (m, 4H, H_m); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.8 (C-^{t}Bu), 23.1, 23.5 ($C_{6'}$+$C_{9'}$), 27.1 (Me-^{t}Bu), 32.4 ($C_{2'}$), 41.9 ($C_{3'}$), 64.8 ($C_{5'}$), 83.6 ($C_{4'}$), 103.0 ($C_{1'}$), 124.3, 125.2 ($C_{7'}$+$C_{8'}$), 128.0, 130.0, 130.1, 135.9 (C_o+C_m+C_p); MS (ESI^+, *m/z*): 409 [$(M+H)^+$, 100%]; Exact mass found for $C_{25}H_{32}O_3Si$: 408.2120.

Synthesis of Acetate 14. Lactol **13** (6.65 mmol) was dissolved in Py (40 mL) and Ac_2O (1.8 mL, 19.95 mmol) was added dropwise. The reaction was stirred overnight and then quenched with saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were dried (Na_2SO_4). The residue was purified by flash chromatography (10% hexane/EtOAc) to obtain **14** (90%). R_f (25% hexane/EtOAc): 0.65; $[\alpha]_D^{20}$= 22.8 (c 0.6, $CHCl_3$); IR (film): υ 3069, 3025, 2925, 2849, 1744, 1421, 1226, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (s, 9H, ^{t}Bu), 1.92 (m, 2H, $H_{6'}$, $H_{9'}$), 1.97 (m, 3H, CH_3), 2.26 (m, 3H, $H_{3'}$, $H_{6'}$, $H_{9'}$), 2.66 (m, 1H, $H_{2'}$), 3.73 (dd, 1H, $H_{5'}$, ^{2}J 11.5 Hz, ^{3}J 4.5 Hz), 3.84 (dd, 1H, $H_{5'}$, ^{2}J 11.5 Hz, ^{3}J 4.0 Hz), 3.90 (dt, 1H, $H_{4'}$, ^{3}J 10.0, 4.0 Hz), 5.71 (m, 2H, $H_{7'}$+$H_{8'}$), 5.97 (s, 1H, $H_{1'}$), 7.41 (m, 6H, H_o+H_p), 7.71 (m, 4H, H_m); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 19.5 (C-^{t}Bu), 21.7 (Me), 22.6, 23.0 ($C_{6'}$+$C_{9'}$), 26.9 ($3CH_3$- ^{t}Bu), 33.5 ($C_{3'}$), 40.2 ($C_{2'}$), 65.3 ($C_{5'}$), 84.5 ($C_{4'}$), 102.5 ($C_{1'}$), 124.5, 124.7 ($C_{7'}$+$C_{8'}$), 127.9, 130.0, 133.7, 135.2, 135.9 (C_{arom}), 171.2 (C=O); MS (ESI^+, *m/z*): 468 [$(M+NH_4)^+$, 100%] , 473 [$(M+Na)^+$, 45], and 489 [$(M+K)^+$, 15].

Synthesis of Acetate 15. Compound **14** (3.34 mmol) was dissolved in 60 mL of dry THF and then treated with TBAF (4.3 mL, 4.3 mmol, 1M in THF). The reaction was kept under argon at r.t. for 30 min. The solution was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried using Na_2SO_4 and then filtered. The residue was purified by flash

chromatography (30% hexane/EtOAc) to give **15** (89%). R_f (EtOAc): 0.74; $[\alpha]_D^{20}$= 47.4 (c 0.9, $CHCl_3$); IR (film): υ 3019, 2922, 2845, 1728, 1427, 1369, 1233, 932 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.85-1.92 (m, 2H, $H_{6'}$, $H_{9'}$), 2.04 (m, 3H, CH_3), 2.24 (m, 1H, $H_{3'}$), 2.33 (m, 2H, $H_{6'}$, $H_{9'}$), 2.62 (m, 1H, $H_{2'}$), 3.56 (dd, 1H, $H_{5'}$, ^2J 12.0 Hz, ^3J 3.2 Hz), 3.83 (dd, 1H, $H_{5'}$, ^2J 12.0 Hz, ^3J 2.0 Hz), 3.90 (ddd, 1H, $H_{4'}$, ^3J 10.0, 3.2, 2.0 Hz), 5.70 (m, 2H, $H_{7'}$+$H_{8'}$), 5.95 (s, 1H, $H_{1'}$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.7 (Me), 22.4, 22.9 ($C_{6'}$+$C_{9'}$), 32.2 ($C_{3'}$), 40.4 ($C_{2'}$), 63.1 ($C_{5'}$), 84.9 ($C_{4'}$), 102.7 ($C_{1'}$), 124.2, 124.7 ($C_{7'}$+$C_{8'}$), 170.5 (C=O); MS (ESI^+, m/z): 230 [$(M+NH_4)^+$, 50%], 235 [$(M+Na)^+$, 75] and 251 [$(M+K)^+$, 20].

Synthesis of Diacetate 16. A solution of **17** (31 mmol) in Py (100 mL) was treated with Ac_2O (12 mL, 124 mmol). The reaction was stirred overnight and quenched with saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic extracts were dried using Na_2SO_4 and then filtered. The residue was purified by flash chromatography (15% hexane/EtOAc) to afford **16** (93%). R_f (50% EtOAc/hexane): 0.53; $[\alpha]_D^{20}$= -21.8 (c 1.9, $CHCl_3$); IR (film): υ 3030, 2918, 2838, 1737, 1641, 1440, 1239, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.87 (m, 2H, $H_{6'}$, $H_{9'}$), 2.04 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.12-2.46 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{6'}$, $H_{9'}$), 4.01 (m, 1H, $H_{5'}$), 4.08 (m, 1H, $H_{4'}$), 4.30 (dd, 1H, $H_{5'}$, ^2J=11.5 Hz, ^3J=2.5 Hz), 5.68 (m, 2H, $H_{7'}$+$H_{8'}$), 5.96 (s, 1H, $H_{1'}$); ^{13}C NMR (**(**$CDCl_3$, 100.6 MHz): δ 21.1 (Me), 21.6 (Me), 22.4, 22,8 ($C_{6'}$+$C_{9'}$), 34.2 ($C_{3'}$), 40.0 ($C_{2'}$), 66.4 ($C_{5'}$), 81.7 ($C_{4'}$), 102.7 ($C_{1'}$), 124.0, 124.7 ($C_{7'}$+$C_{8'}$), 170.1, 170.2 (C=O); MS (ESI^+, *m/z*): 272 [$(M+NH_4)^+$, 20%] and 277 [$(M+Na)^+$, 100].

Synthesis of Diol 17. Lactol **13** (31.5 mmol) was dissolved in THF (100 mL) under argon and then treated with TBAF (37.8 mL, 37.8 mmol, 1M in THF) at r.t. for 25 min. The solution was quenched with Brine and extracted with EtOAc (3 x 100mL). The residue was chromatographied using a gradient 30-70% EtOAc/hexane to give **17** (96%). R_f (EtOAc): 0.44; $[\alpha]_D^{20}$= -16.9 (c 1.9, CH_2Cl_2); ^1H NMR ($CDCl_3$, 100.6 MHz): δ 1.80 (m, 2H, $H_{6'}$+ $H_{9'}$), 2.08-2.35 (m, 3H, $H_{6'}$+ $H_{9'}$+ $H_{3'}$), 2.65 (m, 1H, $H_{2'}$), 3.51 (m, 2H, $H_{4'}$+OH), 3.83 (d, 1H, $H_{5'}$, ^2J 13.2 Hz), 3.87 (d, 1H, $H_{5'}$, ^2J 13.2 Hz), 4.83 (br s, 1H, OH), 5.12 (s, 1H, $H_{1'}$), 5.65 (m, 2H, $H_{7'}$+$H_{8'}$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.9, 23.5 ($C_{6'}$+$C_{9'}$), 31.9 ($C_{3'}$), 41.5 ($C_{2'}$), 62.6 ($C_{5'}$), 84.0 ($C_{4'}$), 103.0 ($C_{1'}$), 124.3, 125.2 ($C_{7'}$+$C_{8'}$); MS (ESI^+, *m/z*): 193 [$(M+Na)^+$, 55%].

Synthesis of Diacetate 19. A solution of **13** (31.5 mmol) in THF (100mL) was treated with TBAOH (47.3 mmol, 33% in H_2O) at r.t. for 6 h. Then, solvents were removed in vacuo. The orange residue was treated in Py (100 mL) with Ac_2O (12 mL, 124 mmol). The reaction was stirred overnight and then quenched with saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2 (4 x 200 mL). The combined organic extracts were dried using Na_2SO_4, and then filtered. The residue was purified by flash chromatography (20% hexane/EtOAc) to give **19** (70%). R_f (50% EtOAc/hexane): 0.55; IR (film): υ 3026, 2931, 2839, 1734, 1633, 1233, 936 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.60-2.11 (m, 12H, $2CH_3$, $2H_{6'}$, $2H_{9'}$, $H_{2'}$, $H_{3'}$), 3.68 (d, 1H, $H_{5'}$, ^2J 13.0 Hz), 3.97 (dd, 1H, $H_{5'}$, ^2J 13.0 Hz, ^3J 1.2 Hz), 4.68 (s, 1H, $H_{4'}$), 5.28 (d, 1H, $H_{1'}$, ^3J 8.8 Hz), 5.54 (m, 2H, $H_{7'}$+$H_{8'}$); ^{13}C NMR (**(**$CDCl_3$, 100.6 MHz): δ 20.8 (Me), 20.9 (Me), 25.8, 26,0 ($C_{6'}$+$C_{9'}$), 34.9 ($C_{3'}$), 37.0 ($C_{2'}$), 68.1 ($C_{5'}$), 68.3 ($C_{4'}$), 97.0 ($C_{1'}$), 124.5, 125.6 ($C_{7'}$+$C_{8'}$), 169.5, 170.6 (C=O); MS (ESI^+, *m/z*): 272 [$(M+NH_4)^+$, 80%] and 277 [$(M+Na)^+$, 100].

General procedure for condensation of diacetate 16 with heterocyclic bases. To a stirred solution of the different bases (1.81 mmol) in dry MeCN (5.0 mL), BSA was added (1.5 mL, 6.338 mmol). The reaction mixture was heated at 70 ºC for 1.5 h. To the resulting clear mixture was added at r.t. a solution of diacetate **16** (0.9 mmol) in dry MeCN (3 mL), followed by DBU (0.434 mL, 2.899 mmol). This solution was cooled to 0 ºC and then TMSOTf was added dropwise (1.05 mL, 5.798 mmol). The resulting mixtures were stirred for 2-3 h. Each mixture was poured into an ice-cool saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 25 mL). Residues were purified by silica gel column chromatography to give **20** and **21** using a gradient 33-100% EtOAc/hexane.

HIBF-α/β-Uracil (20a+21a). Rf (EtOAc): 0.55; $[\alpha]_D^{20}$= -23.4 (c 0.7, $CHCl_3$); IR (KBr): υ 3200, 3032, 2922, 2844, 1743, 1686, 1461, 1271, 1237, 1042, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.00 (m, 2H), 2.12 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.20-2.58 (m, 8H), 2.83 (m, 1H, $H_{2'}$), 4.05-4.45 (m, 6H, $H_{4'}$+ $H_{5'}$), 5.68 (d, 1H, $H_{1'}$, ^3J 2.0 Hz), 5.70-5.76 (m, 6H, $2H_5$ $2H_{7'}$+$2H_{8'}$), 5.89 (d, 1H, $H_{1'}$, ^3J 4.0 Hz), 7.82 (d, 1H, H_6, ^3J 8.3 Hz), 7.64 (d, 1H, H_6, ^3J 8.3 Hz), 8.45 (br s, 1H, NH), 8.55 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 19.7 ($C_{6'}$ or $C_{9'}$), 21.08 (Me), 21.12 (Me), 22.7, 22.9, 23.6 ($C_{6'}$+$C_{9'}$), 33.6 ($C_{3'}$), 36.3 ($C_{3'}$), 37.3 ($C_{2'}$), 41.6 ($C_{2'}$), 63.6 ($C_{5'}$), 64.8 ($C_{5'}$), 80.2 ($C_{4'}$), 82.4 ($C_{4'}$), 90.0 ($C_{1'}$), 91.6 ($C_{1'}$), 101.1 (C_5), 101.4 (C_5), 123.8, 124.4, 124.7, 125.0 ($2C_{7'}$+$2C_{8'}$), 140.0 (C_6), 140.4 (C_6), 150.6 (C_2), 150.9 (C_2), 164.2 (C_4), 164.5 (C_4), 170.7 (C=O), 171.1 (C=O); MS (ESI^+, *m/z*): 307 [$(M+H)^+$, 70%], 324 [$(M+NH_4)^+$, 80], and 329 [$(M+Na)^+$, 100]; LC-ESI-MS (UV 280 nm): Coupling Ratio β/α 1.1:1 t_R(min)= 17.46, 17.91; Exact mass found for $C_{15}H_{18}N_2O_5$: 306.1206.

HIBF-α/β-Thymine (20b+21b). Rf (50% Hexane/EtOAc): 0.22; $[\alpha]_D^{20}$= -41.26 (c 1.0, $CHCl_3$); IR (KBr): υ 3197, 3032, 2926, 1744, 1684, 1662, 1473, 1271, 1237, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.67 (m,2H), 2.00 (m, 6H, CH_3), 2.14-2.60 (m, 15H, $2CH_3$, $H_{2'}$, $2H_{3'}$, 6($H_{6'}$+$H_{9'}$)), 2.85 (m, 1H, $H_{2'}$), 4.11 (m, 3H, $H_{4'}$+$2H_{5'}$), 4.31 (m, 1H, $H_{5'}$), 4.39 (m, 1H, $H_{5'}$), 4.39 (ddd, 1H, $H_{4'}$, ^2J 11.5 Hz, ^3J 3.0, 2.5 Hz), 5.68 (m, 5H, $H_{1'}$+$2H_{7'}$+$2H_{8'}$), 5.89 (m, 1H, $H_{1'}$), 7.46 (q, 1H, ^4J 1.6 Hz), 7.56 (q, 1H, ^4J 0.8 Hz), 9.08 (brs, 1H, NH), 9.20 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 12.9, 13.0 (Me), 19.8 (CH_2), 21.1, 21.2 (Me), 22.9 (CH_2), 23.1 (CH_2), 23.6 (CH_2), 34.2 ($C_{3'}$), 36.3 ($C_{3'}$), 37.3 ($C_{2'}$), 41.6 ($C_{2'}$), 64.0 ($C_{5'}$), 64.8 ($C_{5'}$), 80.1 ($C_{4'}$), 82.4 ($C_{4'}$), 89.9 ($C_{1'}$), 91.1 ($C_{1'}$), 109.5 (C_5), 110.0 (C_5), 123.9, 124.4, 124.6, 125.0 ($2C_{7'}$+$2C_{8'}$), 135.7 (C_6), 136.1 (C_6), 150.6 (C_2), 150.9 (C_2), 164.4 (C_4), 164.5 (C_4), 170.8 (C=O), 171.1 (C=O); MS (ESI^+, *m/z*): 321 [$(M+H)^+$, 100%], 338 [$(M+NH_4)^+$, 90], and 343 [$(M+Na)^+$, 95]; LC-ESI-MS (UV 280 nm): Coupling Ratio β/α 1.2:1 t_R(min)= 19.11, 19.29; Exact mass found for $C_{16}H_{20}N_2O_5$: 320.1371.

HIBF-β-5-Fluorouracil (20c). Rf (50% Hexane/EtOAc): 0.29; $[\alpha]_D^{20}$= +10.0 (c 1.3, $CHCl_3$); IR (KBr): υ 3189, 3075, 3044, 2950, 2857, 1718, 1661, 1469, 1262, 1230, 1093, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.97-2.54 (m, 9H, $H_{2'}$+$H_{3'}$+ $2H_{6'}$+$2H_{9'}$+CH_3), 4.10 (m, 1H, $H_{4'}$), 4.36 (dd, 1H, $H_{5'}$, ^2J 13.3 Hz, ^3J 2.0 Hz), 4.48 (dd, 1H, $H_{5'}$, ^2J 13.3 Hz, ^3J 3.5 Hz), 5.61 (s, 1H, $H_{1'}$), 5.72 (m, 2H, $H_{7'}$+$H_{8'}$), 8.14 (d, 1H, H_6, ^3J 6.5 Hz), 8.52 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 20.9 (Me), 22.3, 23.6 ($C_{6'}$+$C_{9'}$), 32.7 ($C_{3'}$), 41.8 ($C_{2'}$), 62.6 ($C_{5'}$), 82.2 ($C_{4'}$), 91.5 ($C_{1'}$), 124.3, 124.5, 124.8 ($C_{7'}$+$C_{8'}$+C_6), 140.2 (d, C_5, $^1J_{C,F}$ 234 Hz), 149.3 (C_2), 157.5 (d, C_4, $^2J_{C,F}$ 26 Hz), 170.7 (C=O); ^{19}F NMR ($CDCl_3$, 282 MHz): δ 167.1; MS (ESI^+, *m/z*): 325 [$(M+H)^+$, 30%], 342 [$(M+NH_4)^+$, 60], and 347 [$(M+Na)^+$, 100]; LC-ESI-MS (UV 280 nm): t_R(min)= 19.31; Exact mass found for $C_{15}H_{17}FN_2O_5$: 324.1122.

HIBF-β-5-Bromovinyluracil (20d). Rf (50% Hexane/EtOAc): 0.41; $[\alpha]_D^{20}$= -22.3 (c 0.6, $CHCl_3$); IR (KBr): υ 3424, 2926, 2874, 1793, 1747, 1700, 1472, 1368, 1280, 1166, 1109, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.05 (m, 2H, $H_{6'}$+$H_{9'}$), 2.16 (s, 3H, CH_3), 2.18-2.58 (m, 4H, $H_{6'}$, $H_{9'}$, $H_{3'}$, $H_{2'}$), 4.14 (m, 1H, $H_{4'}$), 4.29 (dd, 1H, $H_{5'}$, ^2J 12.8 Hz, ^3J 2.0 Hz), 4.58 (dd, 1H, $H_{5'}$, ^2J 12.8 Hz, ^3J 4.8 Hz), 5.64 (s, 1H, $H_{1'}$), 5.73 (m, 2H, $H_{7'}$+$H_{8'}$), 6.73 (d, 1H, H_7, ^3J 13.6 Hz), 7.40 (d, 1H, H_8, ^3J 13.6 Hz), 7.85 (s, 1H, H_6), 9.49 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.0 (CH_3), 22.3 (CH_2), 23.4 (CH_2), 33.1 ($C_{3'}$), 41.4 ($C_{2'}$), 63.2 ($C_{5'}$), 82.5 ($C_{4'}$), 91.7 ($C_{1'}$), 109.7 (C_5), 110.2 (C_8), 124.1, 124.4, ($C_{7'}$+$C_{8'}$), 128.5 (C_7), 137.7 (C_6), 149.3 (C_2), 161.8 (C_4), 170.6 (C=O); MS (ESI^+, *m/z*): 433 [$(M^{79}Br+Na)^+$, 100%], 435 [$(M^{81}Br+Na)^+$, 97]; Exact mass found for $C_{17}H_{19}BrN_2O_5$: 410.0872.

HIBF-α/β-Cytosine (20e+21e). Rf (EtOAc): 0.24; $[\alpha]_D^{20}$= -25.8 (c 0.4, MeOH); ^1H NMR (MeOH-d_4, 400 MHz): δ 1.90-2.80 (m, 23H, $2H_{3'}$+$H_{2'}$+ $4H_{6'}$+ $4H_{9'}$+ $4CH_3$), 3.00 (m, 1H, $H_{2'}$), 4.10-4.50 (m, 6H, $2H_{4'}$+$4H_{5'}$), 5.60 (m, 4H, $2H_{7'}$+$2H_{8'}$), 5.69 (s, 1H, $H_{1'}$), 5.99 (d, 1H, $H_{1'}$, ^3J 4.4 Hz), 7.48 (d, 1H, H_5, ^3J 7.4 Hz), 7.54 (d, 1H, H_5, ^3J 7.4 Hz), 8.04 (d, 1H, H_6, ^3J 7.4 Hz),

8.30 (d, 1H, H_6, ^{3}J 7.4 Hz), 9.78 (brs, 1H, NH), 9.86 (brs, 1H, NH); ^{13}C NMR (MeOH-d_4, 100.6 MHz): δ 19.6 ($C_{6'}$ or $C_{9'}$), 21.0 (Me), 21.1 (Me), 22.0, 22.8, 24.0 ($C_{6'}$+$C_{9'}$), 24.96 (Me), 24.97 (Me), 32.5 ($C_{3'}$), 36.2 ($C_{3'}$), 36.5 ($C_{2'}$), 41.2 ($C_{2'}$), 63.0 ($C_{5'}$), 64.7 ($C_{5'}$), 80.5 ($C_{4'}$), 82.5 ($C_{4'}$), 91.0 ($C_{1'}$), 92.9 ($C_{1'}$), 96.4 (C_5), 96.7 (C_5), 123.2, 123.9, 124.6, 124.7 ($C_{7'}$+$C_{8'}$), 144.5 (C_6), 145.0 (C_6), 156.40 (C_2), 155.44 (C_2), 162.9 (C_4), 163.0 (C_4), 170.6, 171.1, 171.3, 171.5 (C=O); MS (ESI$^+$, *m/z*): 370 [(M+Na)$^+$, 100%]; LC-ESI-MS (UV 280 nm): Coupling Ratio β/α 1.2:1 t_R(min)= 19.09, 19.63; Exact mass found for $C_{17}H_{21}N_3O_5$: 347.1480.

HIBF-α/β-6-Chloropurine (20f+21f). R_f (50% hexane/EtOAc): 0.37; $[\alpha]_D^{20}$= -25.8 (c 1.0, $CHCl_3$); IR (KBr): υ 3389, 2942, 2890, 1708, 1633, 1489, 1245, 1193, 1094, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.95-2.99 (m, 18H, 2CH_3+2$H_{2'}$+2$H_{3'}$+4$H_{6'}$+4$H_{9'}$), 4.10-4.35 (m, 6H, $H_{4'}$+$H_{5'}$), 5.54 (m, 2H, $H_{7'}$+$H_{8'}$), 5.70 (m, 2H, $H_{7'}$+$H_{8'}$), 5.95 (d, 1H, $H_{1'}$, ^{3}J 2.8 Hz), 6.30 (m, 1H, $H_{1'}$), 8.35 (s, 1H, H_8), 8.48 (s, 1H, H_8), 8.62 (s, 1H, H_2), 8.64 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.8 ($C_{6'}$ or $C_{9'}$), 21.1 (2Me), 22.7, 23.3, 23.7 (3C, $C_{6'}$+$C_{9'}$), 33.7 ($C_{3'}$), 36.6 ($C_{3'}$), 38.1 ($C_{2'}$), 40.7 ($C_{2'}$), 63.5 ($C_{5'}$), 64.8 ($C_{5'}$), 80.5 ($C_{4'}$), 82.6 ($C_{4'}$), 89.5 ($C_{1'}$), 91.0 ($C_{1'}$), 123.6, 124.1, 124.3, 124.6 ($C_{7'}$+$C_{8'}$), 132.2 (C_5), 132.6 (C_5), 143.5 (C_8), 143.9 (C_8), 151.0, 151.1, 151.8 (C_2+C_4), 151.9 (C_6), 152.0 (C_6), 170.8, 171.0 (C=O); MS (ESI$^+$, *m/z*): 371 [(M^{35}Cl+Na)$^+$, 100], 373 [(M^{37}Cl+Na)$^+$, 30]; LC-ESI-MS (UV 280 nm): Coupling Ratio β/α 1.5:1 t_R(min)= 21.19, 21.43; Exact mass found for $C_{16}H_{17}ClN_4O_3$: 348.0982.

HIBF-α/β-2,6-Dichloropurine (20g+21g). The two anomers were separated. **20g:** R_f (50% hexane/EtOAc): 0.52; $[\alpha]_D^{20}$= -7.3 (c 0.3, $CHCl_3$); IR (KBr): υ 3370, 2940, 2879, 1728, 1627, 1480, 1239, 1190, 1076, cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05-2.13 (m, 5H, $H_{6'}$, $H_{9'}$, CH_3), 2.40-2.63 (m, 3H, $H_{3'}$, $H_{6'}$, $H_{9'}$), 3.00 (m, 1H, $H_{2'}$), 4.21(dt, 1H, $H_{4'}$, ^{3}J 9.3, 3.4 Hz), 4.42 (m, 2H, $H_{5'}$), 5.78 (m, 2H, $H_{7'}$+$H_{8'}$), 5.97 (d, 1H, $H_{1'}$, ^{3}J 1.7 Hz), 8.55 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 20.9 (CH_3), 22.4 ($C_{9'}$), 23.5 ($C_{6'}$), 33.5 ($C_{3'}$), 40.7 ($C_{2'}$), 63.1 ($C_{5'}$), 82.5 ($C_{4'}$), 91.0 ($C_{1'}$), 123.9, 124.3 ($C_{7'}$+$C_{8'}$), 131.6 (C_5), 144.4 (C_8), 151.7 (C_4), 152.0 (C_2), 152.8 (C_6), 170.5 (C=O); MS (ESI$^+$, *m/z*): 405 [(M^{35}Cl^{35}Cl+Na)$^+$, 100%], 407 [(M^{35}Cl^{37}Cl+Na)$^+$, 80], and 409 [(M^{37}Cl^{37}Cl+Na)$^+$, 10%]; LC-ESI-MS (UV 280 nm): Ratio β/α 2.4:1 t_R(min)= 23.62, 24.27; Exact mass found for $C_{16}H_{16}Cl_2N_4O_3$: 382.0600.

21g: R_f (50% hexane/EtOAc): 0.52; $[\alpha]_D^{20}$= -40.8 (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.53 (m, 1H, $H_{6'}$), 1.56 (m, 1H, $H_{6'}$), 2.08 (m, 1H, $H_{9'}$), 2.15 (s, 3H, CH_3), 2.46 (m, 1H, $H_{9'}$), 2.66 (m, 1H, $H_{3'}$), 3.02 (m, 1H, $H_{2'}$), 4.19 (dd, 1H, $H_{5'}$, ^{3}J 12.1, 5.3 Hz), 4.30 (m, 1H, $H_{4'}$), 4.42 (dd, 1H, $H_{5'}$, ^{3}J 12.1, 2.4 Hz), 5.65 (m, 2H, $H_{7'}$+$H_{8'}$), 6.33 (d, 1H, $H_{1'}$, ^{3}J 4.3 Hz), 8.39 (s, 1H, H_8); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.6 (CH_2), 20.9 (CH_3), 23.1 (CH_2), 36.4 ($C_{3'}$), 37.9 ($C_{2'}$), 64.4 ($C_{5'}$), 80.5 ($C_{4'}$), 89.3 ($C_{1'}$), 123.3, 124.2 ($C_{7'}$+$C_{8'}$), 131.2 (C_5), 144.0 (C_8), 151.7 (C_4), 151.9 (C_2), 152.9 (C_6), 170.8 (C=O); MS (ESI$^+$, *m/z*): 405 [(M^{35}Cl^{35}Cl+Na)$^+$, 100%], 407 [(M^{35}Cl^{37}Cl+Na)$^+$, 80], and 409 [(M^{37}Cl^{37}Cl+Na)$^+$, 10]; LC-ESI-MS (UV 280 nm): Coupling Ratio β/α 2.4:1 t_R(min)= 23.62, 24.27; Exact mass found for $C_{16}H_{16}Cl_2N_4O_3$: 382.0651.

General protocols for deprotection of HIBF nucleoside derivatives 20-21. Method A (deprotection of 5'-OAc group)**.** Nucleoside derivatives **20a-f**+**21a-f** (0.1mmol) were dissolved in a 2M NH_3/MeOH solution (1.5 mL) and stirred at r.t. overnight. Residues were purified by silica gel column chromatography using a gradient 33-100% EtOAc/hexane. **Method B.** Nucleoside derivatives **20f**+**21f, 20g** and **21g** (0.1mmol) were treated with a NH_3/MeOH saturated solution (1.5 mL) and stirred at 110 ºC in a Parr reactor for 36 h. Residues were purified by silica gel column chromatography (gradient 50-100% EtOAc/hexane) obtaining **22i**, **23i** (95-97%), **22j**-**22m**, **23j**-**23m** (quantitative combined yield). **Method C**. Nucleoside derivatives **20f** and **20g** (0.11 mmol) were treated with a 2M NH_3/MeOH solution (1.8 mL) and stirred at 90-100 ºC in a Parr reactor for 30 h. Residues were purified by silica gel column chromatography using a gradient 50-100% EtOAc/hexane.

HIBF-β-Uracil (22a). From **20a** using Method A. R_f (EtOAc): 0.40; $[\alpha]_D^{20}$= +0.7 (c 0.3,

$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99 (m, 2H, $H_{6'}$+$H_{9'}$), 2.34 (m, 1H, $H_{3'}$), 2.47 (m, 2H, $H_{6'}$+$H_{9'}$), 2.53 (m, 1H, $H_{2'}$), 3.80 (dt, 1H, $H_{5'}$, ^{2}J 12 Hz, ^{3}J 3.5 Hz), 3.96 (dt, 1H, $H_{4'}$, ^{3}J 9.0 Hz, ^{3}J= 3.5 Hz), 4.07 (ddd, 1H, $H_{5'}$, ^{2}J 12.0 Hz, ^{3}J 3.5 Hz, ^{4}J 2.5 Hz), 5.70 (m, 3H, $H_{7'}$+$H_{8'}$+$H_{1'}$), 8.05 (d, 1H, H_6, ^{3}J 8.0 Hz), 8.36 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 23.1 ($C_{6'}$), 23.7 ($C_{9'}$), 32.6 ($C_{3'}$), 41.6 ($C_{2'}$), 62.0 ($C_{5'}$), 85.0 ($C_{4'}$), 91.2 ($C_{1'}$), 101.4 (C_5), 124.7, 124.8 ($C_{7'}$+$C_{8'}$), 141.0 (C_6), 150.5 (C_2), 163.5 (C_4); MS (ESI^+, *m/z*): 287 [$(M+Na)^+$, 100%]; Exact mass found for $C_{13}H_{15}N_2O_4$: 264.1104.

HIBF-β-Thymine (22b). From **20b** using Method A. R_f (50% hexane/EtOAc): 0.16; $[\alpha]_D^{20}$= -13.6 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.91 (d, 3H, Me, ^{4}J 1.0 Hz), 2.00 (m, 2H, $H_{6'}$+$H_{9'}$), 2.00 (m, 4H, $H_{6'}$+$H_{9'}$+$H_{3'}$+$H_{2'}$), 3.81 (dt, 1H, $H_{5'}$, ^{2}J 12 Hz, ^{3}J 4.0 Hz), 3.94 (dt, 1H, $H_{4'}$, ^{3}J 9.0 Hz, ^{3}J 4.0 Hz), 4.06 (ddd, 1H, $H_{5'}$, ^{3}J 9.0 Hz, ^{3}J 4.0 Hz, ^{4}J 2.5 Hz), 5.73 (m, 3H, $H_{7'}$, $H_{8'}$, $H_{7'}$), 7.79 (d, 1H, H_6, ^{4}J 1.0 Hz), 8.50 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 12.9 (Me), 23.5, 23.7 ($C_{6'}$+$C_{9'}$), 33.2 ($C_{3'}$), 41.5 ($C_{2'}$), 62.5 ($C_{5'}$), 85.0 ($C_{4'}$), 91.0 ($C_{1'}$), 110.1 (C_5), 125.0, 125.1 ($C_{7'}$+$C_{8'}$), 136.8 (C_6), 150.6 (C_2), 163.9 (C_4); MS (ESI^+, *m/z*): 301 [$(M+Na)^+$, 100%]; Exact mass found for for $C_{14}H_{18}N_2O_4$: 278.1257.

HIBF-β-5-Fluorouracil (22c). From **20c** using Method A. R_f (50% hexane/EtOAc): 0.28; $[\alpha]_D^{20}$= +28.6 (c 0.8, $CHCl_3$); IR (KBr): υ 3508, 3448, 3156, 3040, 2925, 2851, 1682, 1652, 1266, 1093, 1066, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$ 500 MHz): δ 1.98 (m, 2H, $H_{6'}$, $H_{9'}$), 2.26-2.53 (m, 4H, $H_{6'}$, $H_{9'}$, $H_{3'}$, $H_{2'}$), 3.83 (dd, 1H, $H_{5'}$, ^{2}J 12.5 Hz, ^{3}J 2.5 Hz), 3.95 (dt, 1H, $H_{4'}$, ^{3}J 8.5 Hz, ^{3}J 2.5 Hz), 4.13 (dd, 1H, $H_{5'}$, ^{2}J 12.5 Hz, ^{3}J 2.5 Hz), 5.68 (m, 1H, $H_{1'}$), 5.78 (m, 2H, $H_{7'}$+$H_{8'}$), 8.42 (d, 1H, H_6, ^{3}J 7.0 Hz), 8.50 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.9, 23.7 ($C_{6'}$+$C_{9'}$), 32.0 ($C_{3'}$), 41.7 ($C_{2'}$), 61.5 ($C_{5'}$), 85.0 ($C_{4'}$), 91.2 ($C_{1'}$), 124.6, 124.7 ($C_{7'}$+$C_{8'}$), 125.8 (d, C_6, $^2J_{C,F}$ 139.8 Hz), 140.2 (d, C_5, $^1J_{C,F}$ 930 Hz) 149.1 (C_2), 157.2 (d, C_4, $^2J_{C,F}$ 105.9 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz): δ 167.0; MS (ESI^+, *m/z*): 305 [$(M+Na)^+$, 100%]; Exact mass found for $C_{13}H_{15}FN_2O_4$: 282.1014.

HIBF-β-5-Bromovinyluracil (22d). From **20d** using Method A. R_f (50% hexane/EtOAc): 0.32; $[\alpha]_D^{20}$= -24.8 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99 (m, 2H, $H_{6'}$, $H_{9'}$), 2.30-2.52 (m, 4H, $H_{6'}$, $H_{9'}$, $H_{2'}$, $H_{3'}$), 3.85 (d, 1H, $H_{5'}$, ^{2}J 12.9 Hz), 3.99 (m, 1H, $H_{4'}$), 4.17 (d, 1H, $H_{5'}$, ^{2}J 12.9 Hz), 5.73 (m, 3H, $H_{7'}$ +$H_{8'}$+$H_{1'}$), 6.70 (d, 1H, H_7, ^{3}J 13.6 Hz), 7.32 (d, 1H, H_8, ^{3}J 13.6 Hz), 8.33 (s, 1H, H_6), 8.52 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 22.5, 23.6 ($C_{6'}$+$C_{9'}$), 31.6 ($C_{3'}$), 41.6 ($C_{2'}$), 61.1 ($C_{5'}$), 84.7 ($C_{4'}$), 91.1 ($C_{1'}$), 108.8 (C_8), 110.1 (C_5), 124.3, 124.4 ($C_{7'}$+$C_{8'}$), 128.6 (C_7), 138.8 (C_6), 149.2 (C_2), 161.3 (C_4); MS (ESI^+, *m/z*): 369 [$(M^{79}Br+H)^+$, 100%] and 371 [$(M^{81}Br+H)^+$, 96]; Exact mass found for $C_{15}H_{17}BrN_2O_4$: 368.0395.

HIBF-β-6-Chloropurine (22f). From **20f** using Method A. R_f (EtOAc): 0.50; $[\alpha]_D^{20}$= -37.2 (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.95, 2.11 (m, 2H, $H_{6'}$+$H_{9'}$), 2.43 (m, 2H, $H_{6'}$+$H_{9'}$), 2.75 (m, 1H, $H_{3'}$), 3.26 (m, 1H, $H_{2'}$), 3.82 (dd, 1H, $H_{5'}$, ^{2}J 12.2 Hz, ^{3}J 4.8 Hz), 4.10 (m, 2H, $H_{5'}$+$H_{4'}$), 5.80 (m, 2H, $H_{7'}$+$H_{8'}$), 5.94 (d, 1H, $H_{1'}$, ^{3}J 6.0 Hz), 8.46 (s, 1H, H_8), 8.78 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 22.8, 24.7 ($C_{6'}$+$C_{9'}$), 34.0 ($C_{3'}$), 40.4 ($C_{2'}$), 63.5 ($C_{5'}$), 87.2 ($C_{4'}$), 91.5 ($C_{1'}$), 124.0, 125.0 ($C_{7'}$+$C_{8'}$), 133.1 (C_5), 144.7 (C_8), 150.7 (C_4), 151.6 (C_2), 151.7 (C_6); MS (ESI^+, *m/z*): 329 [$(M^{35}Cl+Na)^+$, 100%] and 331 [$(M^{37}Cl+Na)^+$, 20]; Exact mass found for $C_{14}H_{15}ClN_4O_2$: 306.0682.

HIBF-β-6-Aminopurine (22i). From **20f** using Method B. R_f (5% CH_2Cl_2/MeOH): 0.20; $[\alpha]_D^{20}$= -19.6 (c 0.8, DMSO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.95-2.12 (m, 2H, $H_{6'}$+$H_{9'}$), 2.37-2.49 (m, 2H, $H_{6'}$+$H_{9'}$), 2.67 (m, 1H, $H_{3'}$), 3.42 (m, 1H, $H_{2'}$), 3.76 (dd, 1H, $H_{5'}$, ^{2}J 12.4 Hz, ^{3}J 3.6 Hz), 4.06 (m, 2H, $H_{4'}$+$H_{5'}$), 5.79 (m, 3H, $H_{7'}$+$H_{8'}$, $H_{1'}$), 5.90 (m, 2H, NH_2), 7.90 (s, 1H, H_8), 8.35 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 22.8, 25.2 ($C_{6'}$+$C_{9'}$), 34.4 ($C_{3'}$), 39.8 ($C_{2'}$), 64.7 ($C_{5'}$), 88.8 ($C_{4'}$), 91.5 ($C_{1'}$), 121.1 (C_5), 124.9, 125.6 ($C_{7'}$+$C_{8'}$), 140.9 (C_8), 148.6 (C_4), 152.2 (C_2), 155.9 (C_6); MS (ESI^+, *m/z*): 288 [$(M+H)^+$, 100%] and 310 [$(M+Na)^+$, 60]; Exact

mass found for $C_{14}H_{17}N_5O_2$: 287.0713.

HIBF-β-6-Amino-2-chloropurine (22j). From **20g** using Method B. R_f (10% EtOAc/MeOH): 0.44; $[\alpha]_D^{20}$= -8.5 (c 0.3, DMSO); ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 2.05 (m, 2H, $H_{6'}$+$H_{9'}$), 2.42 (m, 2H, $H_{6'}$+$H_{9'}$), 2.72 (m, 1H, $H_{3'}$), 3.16 (m, 1H, $H_{2'}$), 3.77 (dd, 1H, $H_{5'}$, ^{2}J 13.2 Hz, ^{3}J 3.6 Hz), 3.77 (dd, 1H, $H_{5'}$, ^{2}J 13.2 Hz, ^{3}J 3.6 Hz), 4.02 (m, 2H, $H_{4'}$ +$H_{5'}$), 5.79 (m, 2H, $H_{7'}$ +$H_{8'}$), 5.83 (d , $H_{1'}$, ^{3}J 6.0 Hz), 6.54 (brs, 2H, NH_2), 8.08 (s, 1H, H_8); ^{13}C NMR (CD_2Cl_2, 100.6 MHz): δ 23.4, 25.5 ($C_{6'}$+$C_{9'}$), 35.4 ($C_{3'}$), 40.8 ($C_{2'}$), 63.8 ($C_{5'}$), 87.7 ($C_{4'}$), 91.2 ($C_{1'}$), 119.8 (C_5), 124.6, 125.5 ($C_{7'}$+$C_{8'}$), 140.9 (C_8), 150.4 (C_4), 154.9 (C_2), 156.9 (C_6); MS (ESI^+, *m/z*): 322 [($M^{35}Cl$+H)$^+$, 100%], 324 [($M^{37}Cl$+H)$^+$, 20], 344 [($M^{35}Cl$+Na)$^+$, 80], and 346 [($M^{37}Cl$+Na)$^+$, 10]; $C_{14}H_{16}ClN_5O_2$.

HIBF-β-6-Methoxypurine (22k). From **20f** using Method C. R_f (EtOAc): 0.39; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.83 (m, 1H, $H_{6'}$ or $H_{9'}$), 2.08 (m, 1H, $H_{6'}$ or $H_{9'}$), 2.33, 2.42 (2m, 2H, $H_{6'}$, $H_{9'}$), 2.74 (m, 1H, $H_{3'}$), 3.45 (m, 1H, $H_{2'}$), 3.75 (m, 1H, $H_{5'}$), 4.08 (m, 2H, $H_{5'}$+ $H_{4'}$), 4.19 (s, 3H, OMe), 5.50 (m, 1H, OH), 5.76 (m, 3H, $H_{1'}$, $H_{7'}$, $H_{8'}$), 8.05 (s, 1H, H_8), 8.55 (s, 1H, H_2); MS (ESI^+, *m/z*): 325 [(M+Na)$^+$, 100%]; Exact mass found for $C_{15}H_{18}N_4O_3$: 302.0774.

HIBF-β-2-Chloro-6-methoxypurine (22l). From **20g** using Method C. R_f (EtOAc): 0.44; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.01 (m, 2H, $H_{6'}$+$H_{9'}$), 2.39 (m, 2H, $H_{6'}$+$H_{9'}$), 2.72 (m, 1H, $H_{3'}$), 3.23 (m, 1H, $H_{2'}$), 3.80 (m, 1H, $H_{5'}$), 4.04 (m, 2H, $H_{4'}$+$H_{5'}$), 5.79 (m, 3H, $H_{1'}$, $H_{7'}$, $H_{8'}$), 8.12 (s, 1H, H_8); MS (ESI^+, *m/z*): 359 [($M^{35}Cl$+Na)$^+$, 100%] and 361 [($M^{37}Cl$+Na)$^+$, 20]; Exact mass found for $C_{15}H_{17}ClN_4O_3$: 336.1102.

HIBF-β-2,6-Diaminopurine (22m). From **20g** using Method B. R_f (10% EtOAc/MeOH): 0.17; $[\alpha]_D^{20}$= -19.1 (c 2.5, DMSO); ^{1}H NMR (MeOH-*d*$_4$, 400 MHz): δ 2.27 (m, 2H, $H_{6'}$+$H_{9'}$), 2.57 (m, 2H, $H_{6'}$+$H_{9'}$), 2.78 (m, 1H, $H_{3'}$), 3.14 (m, 1H, $H_{2'}$), 3.90 (dd, 1H, $H_{5'}$, ^{2}J 13.2 Hz, ^{3}J 3.6 Hz), 4.10 (m, 2H, $H_{4'}$+$H_{5'}$), 5.92 (m, 2H, $H_{7'}$+$H_{8'}$), 5.97 (d , $H_{1'}$, ^{3}J 4.8 Hz), 8.31 (s, 1H, H_8); ^{13}C NMR (MeOH-*d*$_4$, 100.6 MHz): δ 23.0 ($C_{6'}$), 24.1 ($C_{9'}$), 34.3 ($C_{3'}$), 40.6 ($C_{2'}$), 62.7 ($C_{5'}$), 86.3 ($C_{4'}$), 90.0 ($C_{1'}$), 113.8 (C_5), 124.4, 125.0 ($C_{7'}$+$C_{8'}$), 137.4 (C_8), 151.1 (C_4), 156.6 (C_2), 160.6 (C_6); MS (ESI^+, *m/z*): 303 [(M+H)$^+$, 100%]; $C_{14}H_{18}N_6O_2$.

HIBF-α-Thymine (23b). From **21b** using Method A. R_f (50% hexane/EtOAc): 0.10; $[\alpha]_D^{20}$= -34.5 (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$ 500 MHz): δ 1.61-1.82 (m, 2H, $H_{6'}$, $H_{9'}$), 1.94 (s, 3H, Me), 2.36 (m, 2H, $H_{6'}$, $H_{9'}$), 2.62 (m, 1H, $H_{3'}$), 2.85 (m, 1H, $H_{2'}$), 3.81 (m, 1H, $H_{4'}$), 3.92 (ddd, 1H, $H_{5'}$, ^{2}J 12 Hz, ^{3}J 6.0 Hz, ^{4}J 3.0 Hz), 4.06 (m, 1H, $H_{5'}$), 5.69 (m, 2H, $H_{7'}$ +$H_{8'}$), 5.89 (d, 1H, $H_{1'}$, ^{3}J 4.0 Hz), 7.45 (d, 1H, H_6, ^{4}J 1.0 Hz), 8.19 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 12.9 (Me), 19.9, 23.0 ($C_{6'}$+$C_{9'}$), 35.1 ($C_{3'}$), 37.6 ($C_{2'}$), 63.2 ($C_{5'}$), 83.0 ($C_{4'}$), 89.9 ($C_{1'}$), 109.3 (C_5), 123.8, 124.6 ($C_{7'}$+$C_{8'}$), 136.2 (C_6), 150.1 (C_2), 163.9 (C_4); MS (ESI^+, *m/z*): 301 [(M+Na)$^+$, 100%]; Exact mass found for $C_{14}H_{18}N_2O_4$: 278.1260.

HIBF-α-5-Bromovinyluracil (23d). From **21d** using Method A. R_f (50% hexane/EtOAc): 0.14; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.66 (m, 1H, $H_{6'}$ or $H_{9'}$), 1.82 (m, 1H, $H_{9'}$ or $H_{6'}$), 2.01, 2.38 (2m, 2H, $H_{6'}$, $H_{9'}$), 2.67 (m, 1H, $H_{3'}$), 2.89 (m, 1H, $H_{2'}$), 3.69 (m, 1H, $H_{4'}$), 3.95 (d, 1H, $H_{5'}$, ^{2}J 12.0 Hz), 4.08 (d, 1H, $H_{5'}$, ^{2}J 12.0 Hz), 5.70 (m, 2H, $H_{7'}$ +$H_{8'}$), 5.92 (d, 1H, $H_{1'}$, ^{3}J 4.0 Hz), 6.73 (d, 1H, H_7, ^{3}J 13.8 Hz), 7.43 (d, 1H, H_8, ^{3}J 13.8 Hz), 7.64 (s, 1H, H_6), 8.12 (br s, 1H, NH); MS (ESI^+, *m/z*): 369 [($M^{79}Br$+H)$^+$, 100] and 371 [($M^{81}Br$+H)$^+$, 96]; Exact mass found for $C_{15}H_{17}BrN_2O_4$: 368.0874.

HIBF-α-6-Chloropurine (23f). From **21f** using Method A. R_f (EtOAc): 0.40; $[\alpha]_D^{20}$= -9.7 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.50-1.75 (m, 2H, $H_{6'}$+$H_{9'}$), 2.00, 2.48 (m, 2H, $H_{6'}$+$H_{9'}$), 2.83 (m, 1H, $H_{3'}$), 3.06 (m, 1H, $H_{2'}$), 3.75 (dd, 1H, $H_{5'}$, ^{2}J 12.6 Hz, ^{3}J 4.2 Hz), 4.02 (dd, 1H, $H_{5'}$, ^{2}J 12.6 Hz, ^{3}J 2.4 Hz), 4.23 (dt, 1H, $H_{4'}$, ^{3}J 10.2 Hz, 3 Hz), 5.67 (m, 2H, $H_{7'}$+$H_{8'}$), 6.40 (d, 1H, $H_{1'}$, ^{3}J 4.2 Hz), 8.43 (s, 1H, H_8), 8.74 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 19.7, 23.1 ($C_{6'}$+$C_{9'}$), 35.2 ($C_{3'}$), 38.2 ($C_{2'}$), 62.8 ($C_{5'}$), 83.2 ($C_{4'}$), 89.5 ($C_{1'}$), 123.5, 124.3

($C_{7'}$+$C_{8'}$), 132.1 (C_5), 143.3 (C_8), 150.7 (C_4), 152.0 (C_2), 155.5 (C_6); MS (ESI^+, *m/z*): 329 [($M^{35}Cl$+Na)$^+$, 100%] and 331 [($M^{37}Cl$+Na)$^+$, 30]; Exact mass found for $C_{14}H_{15}ClN_4O_2$: 306.0548.

HIBF-α-6-Aminopurine (23i). From **21f** using Method B. R_f (5% CH_2Cl_2/MeOH): 0.09; $[\alpha]_D^{20}$= -9.6 (c 2.5, MeOH); ^{1}H NMR (MeOH-*d*$_4$, 400 MHz): δ 1.50, 1.85 (2m, 2H, $H_{6'}$+$H_{9'}$), 2.10, 2.42 (2m, 2H, $H_{6'}$+$H_{9'}$), 2.75 (m, 1H, $H_{3'}$), 2.90 (m, 1H, $H_{2'}$), 3.75 (dd, 1H, $H_{5'}$, ^{2}J 12.2 Hz, ^{3}J 4.8 Hz), 3.95 (m, 1H, $H_{5'}$, ^{2}J 12.2 Hz, ^{3}J 2.8 Hz), 4.16 (m, 1H, $H_{4'}$), 5.74 (m, 2H, $H_{7'}$+$H_{8'}$), 6.39 (d, 1H, $H_{1'}$, ^{3}J 4.4 Hz), 8.23 (s, 1H, H_8), 8.33 (s, 1H, H_2); ^{13}C NMR (MeOH-*d*$_4$, 100.6 MHz): δ 19.4, 22.9 ($C_{6'}$+$C_{9'}$), 35.5 ($C_{3'}$), 38.3 ($C_{2'}$), 62.1 ($C_{5'}$), 83.5 ($C_{4'}$), 89.0 ($C_{1'}$), 119.0 (C_5), 123.4, 124.2 ($C_{7'}$+$C_{8'}$), 139.0 (C_8), 148.2 (C_4), 152.4 (C_2), 155.9 (C_6); MS (ESI^+, *m/z*): 288 [(M+H)$^+$, 100%] and 310 [(M+Na)$^+$, 60]; Exact mass found for $C_{14}H_{17}N_5O_2$: 287.0772.

HIBF-α-6-Amino-2-chloropurine (23j). From **21g** using Method B. R_f (6.6% EtOAc/MeOH): 0.37; $[\alpha]_D^{20}$= -25.9 (c 1.0, DMSO); ^{1}H NMR (MeOH-*d*$_4$, 400 MHz): δ 1.73 (m, 1H, $H_{6'}$), 2.02 (m, 1H, $H_{9'}$), 2.26 (m, 1H, $H_{6'}$), 2.58 (m, 1H, $H_{9'}$) 2.91 (m, 1H, $H_{3'}$), 3.07 (m, 1H, $H_{2'}$), 3.85 (dd, 1H, $H_{5'}$, ^{2}J 12.2 Hz, ^{3}J 4.6 Hz), 4.05 (dd, 1H, $H_{5'}$, ^{2}J 12.2 Hz, ^{3}J 2.8 Hz), 4.35 (ddd, 1H, $H_{4'}$, ^{3}J 9.5Hz, 4.6Hz, 2.8 Hz), 5.79 (m, 2H, $H_{7'}$ +$H_{8'}$), 6.42 (d , $H_{1'}$, ^{3}J 4.4 Hz), 8.42 (s, 1H, H_8); ^{13}C NMR (MeOH-*d*$_4$, 100.6 MHz): δ 19.8 ($C_{6'}$), 23.3 ($C_{9'}$), 35.9 ($C_{3'}$), 38.7 ($C_{2'}$), 62.5 ($C_{5'}$), 84.0 ($C_{4'}$), 89.3 ($C_{1'}$), 118.2 (C_5), 123.8, 124.6, ($C_{7'}$+$C_{8'}$), 139.7 (C_8), 150.0 (C_4), 154.3 (C_2), 157.0 (C_6); MS (ESI^+, *m/z*): 322 [($M^{35}Cl$+H)$^+$, 100%] and 324 [($M^{37}Cl$+H)$^+$, 20]; $C_{14}H_{16}ClN_5O_2$.

HIBF-α-2,6-Diaminopurine (23m). From **21g** using Method B. R_f (10% EtOAc/MeOH): 0.12; $[\alpha]_D^{20}$= -59.8 (c 0.8, MeOH); ^{1}H NMR (MeOH-*d*$_4$, 600 MHz): δ 1.72 (m, 1H, $H_{6'}$), 2.04 (m, 1H, $H_{6'}$), 2.26 (m, 1H, $H_{9'}$), 2.58 (m, 1H, $H_{9'}$), 2.89 (m, 1H, $H_{3'}$), 3.06 (m, 1H, $H_{2'}$), 3.84 (dd, 1H, $H_{5'}$, ^{2}J 12.0 Hz, ^{3}J 4.8 Hz), 4.03 (dd, 1H, $H_{5'}$, ^{2}J 12.0 Hz, ^{3}J 3.0 Hz), 4.29 (m, 1H, $H_{4'}$), 5.81 (m, 2H, $H_{7'}$+$H_{8'}$), 6.32 (d , $H_{1'}$, ^{3}J 4.8 Hz), 8.12 (s, 1H, H_8); ^{13}C NMR (MeOH-*d*$_4$, 150.9 MHz): δ 19.4 ($C_{6'}$), 22.9 ($C_{9'}$), 35.5 ($C_{3'}$), 38.1 ($C_{2'}$), 62.1 ($C_{5'}$), 83.2 ($C_{4'}$), 88.5 ($C_{1'}$), 113.0 (C_5), 123.6, 124.1 ($C_{7'}$+$C_{8'}$), 136.0 (C_8), 150.5 (C_4), 156.1 (C_2), 160.4 (C_6); MS (ESI^+, *m/z*): 303 [(M+H)$^+$, 100%]; $C_{14}H_{18}N_6O_2$.

HIBF-α/β-Uracil (24a). From **20a**+**21a** using Method A. R_f (EtOAc): 0.40β, 0.36α; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80-2.89 (m, 12H, 4$H_{6'}$, 4$H_{9'}$, 2$H_{2'}$, 2$H_{3'}$), 3.48 (d, 1H, OH, ^{3}J 3.5 Hz), 3.64 (m, 1H), 3.79 (dt, 1H, $H_{5'}$, ^{2}J 12.0 Hz, ^{3}J 3.0 Hz), 3.92 (m, 1H), 3.96 (dt, 1H, $H_{3'}$, ^{3}J 9.0 Hz, ^{3}J 3.0 Hz, 4.07 (m, 2H), 5.70 (m, 7H, 2$H_{7'}$ +2$H_{8'}$+$H_{1'}$+2H_5), 5.90 (d, 1H, $H_{1'}$, ^{3}J 4.5 Hz), 7.65 (d, 1H, H_6, ^{3}J 8.0 Hz), 8.05 (d, 1H, H_6, ^{3}J 8.5 Hz), 8.60 (br s, 1H, NH), 8.73 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.8, 23.0, 23.1, 23.7 ($C_{6'}$+$C_{9'}$), 32.7 ($C_{3'}$), 35.1 ($C_{3'}$), 37.6 ($C_{2'}$), 41.6 ($C_{2'}$), 62.0 ($C_{5'}$), 63.0 ($C_{5'}$), 83.1 ($C_{4'}$),85.0 ($C_{4'}$), 90.1 ($C_{1'}$), 91.2 ($C_{1'}$), 101.0 (C_5), 101.4 (C_5), 123.7, 124.6, 124.7, 124.8 (2$C_{7'}$+2$C_{8'}$), 140.4 (C_6), 141.0 (C_6), 150.3 (C_2), 150.7 (C_2), 163.6 (C_4), 163.7 (C_4); MS (ESI^+, *m/z*): 287 [(M+Na)$^+$, 100%].

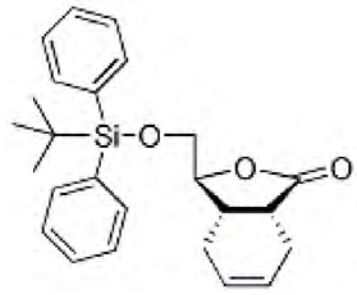
HIBF-α/β-Cytosine (24h). From **20h**+**21h** using Method A. R_f (EtOAc/MeOH 10%): 0.20; $[\alpha]_D^{20}$= -28.6 (c 0.7, MeOH); ^{1}H NMR (MeOH-*d*$_4$, 500 MHz): δ 1.90-2.84 (m, 12H, 2$H_{6'}$+2$H_{9'}$+2$H_{3'}$+2$H_{2'}$), 3.62 (m, 1H), 3.74 (m, 1H), 3.82 (m, 1H), 3.90 (m, 1H), 3.94 (m, 1H), 4.00 (m, 1H), 5.66 (m, 1H, $H_{1'}$), 5.70 (m, 3H, $H_{7'}$+$H_{8'}$+H_5), 5.86 (m, 4H, $H_{1'}$+$H_{7'}$+$H_{8'}$+H_5), 7.86 (d, 1H, H_6, ^{3}J 8.0 Hz), 8.33 (d, 1H, H_6, ^{3}J 7.0 Hz); ^{13}C NMR (MeOH-*d*$_4$, 100.6 MHz): δ 20.7, 23.6, 23.9, 24.8 ($C_{6'}$+$C_{9'}$), 33.3 ($C_{3'}$), 36.6 ($C_{3'}$), 38.8 ($C_{2'}$), 43.0 ($C_{2'}$), 61.8 ($C_{5'}$), 63.5 ($C_{5'}$), 84.3 ($C_{4'}$), 86.4 ($C_{4'}$) 91.5 ($C_{1'}$), 92.7 ($C_{1'}$), 94.6 (C_5), 94.8 (C_5), 124.8, 125.5, 125.6, 125.7 ($C_{7'}$+$C_{8'}$), 142.7 (C_6), 142.9 (C_6), 158.2 (C_2), 158.4 (C_2), 167.7 (C_4), 167.8 (C_4); MS (ESI^+, *m/z*): 264 [(M+H)$^+$, 70%] and 286 [(M+Na)$^+$, 100]; Exact mass found for $C_{13}H_{17}N_3O_3$: 263.1318.

Synthesis of HIBF-β-2,6-Diaminopurine (20m). A solution of **20n** (30 mg, 0.076 mmol) in

a mixture THF/H_2O was treated with Me_3P (15.4 μL, 0.174 mmol). Immediately, N_2 gave off and the solution became yellowish. The reaction was stirred for 26 h and then solvents were removed. The residue was purified by silica gel chromatography (2-10% MeOH/EtOAc) to give **20m** in 73% yield. R_f (20% EtOAc/MeOH): 0.49; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (m, 2H, $H_{6'}$+$H_{9'}$), 2.09 (s, 3H, CH_3), 2.34-2.47 (m, 3H, $H_{3'}$, $H_{6'}$, $H_{9'}$), 3.04 (m, 1H, $H_{2'}$), 4.13 (m, 1H, $H_{4'}$), 4.40 (m, 2H, $H_{5'}$), 4.72 (brs, 2H, NH_2), 5.40 (br s, 2H, NH_2), 5.75 (m, 2H, $H_{7'}$+$H_{8'}$), 5.78 (d, $H_{1'}$, ^{3}J 3.5 Hz), 7.82 (s, 1H, H_8); MS (ESI^+, *m/z*): 367 [$(M+Na)^+$, 100%]; $C_{16}H_{20}N_6O_3$.

Synthesis of HIBF-β-2,6-Diazidopurine (20n). A solution of **20g** (0.262 mmol, 100 mg) in DMF (1.8 mL) was treated with NaN_3 (1.048 mmol, 68 mg) at 70 ºC for 4 h. Solvent was removed and the residue obtained was purified by silica gel flash chromatography (gradient 30-50% EtOAc/hexane) to give **20n** in 76% yield. R_f (50% hexane/EtOAc): 0.47; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.10 (m, 2H, $H_{6'}$+$H_{9'}$), 2.12 (s, 3H, CH_3), 2.35-2.48 (m, 3H, $H_{3'}$, $H_{6'}$, $H_{9'}$), 2.98 (m, 1H, $H_{2'}$), 4.16 (m, 1H, $H_{4'}$), 4.49 (m, 2H, $H_{5'}$), 5.74 (m, 2H, $H_{7'}$+$H_{8'}$), 5.92 (s , 1H, $H_{1'}$), 8.29 (s, 1H, H_8); MS (ESI^+, *m/z*): 419 [$(M+Na)^+$, 100%]; $C_{16}H_{20}N_{10}O_3$.

Synthesis of HIBF-β-Hypoxanthine 22o. Nucleoside **22i** (20 mg, 0.070 mmol) was dissolved in a phosphate buffer pH=7/ 3% DMSO (400 μL) and treated with 1 mg of ADA dissolved in that buffer (100 μL). The residue was purified by flash chromatography (gradient 5%-20% MeOH/EtOAc) to give **22o** (50%). R_f (10% EtOAc/MeOH): 0.10; ^{1}H NMR (MeOH-d_4, 600 MHz): δ 2.25 (m, 2H, $H_{6'}$+$H_{9'}$), 2.65 (m, 2H, $H_{6'}$+$H_{9'}$), 2.83 (m, 1H, $H_{3'}$), 3.06 (m, 1H, $H_{2'}$), 3.94 (dd, 1H, $H_{5'}$, ^{2}J 12.3 Hz, ^{3}J 3.6 Hz), 4.12 (dd, 1H, $H_{5'}$, ^{2}J 12.3 Hz, ^{3}J 3.0 Hz), 4.17 (dt, 1H, $H_{4'}$, ^{3}J 8.4 Hz, 3.6 Hz), 5.96 (m, 2H, $H_{7'}$+$H_{8'}$), 6.17 (d, 1H, $H_{1'}$, ^{3}J 3.6 Hz), 8.23 (s, 1H, H_8), 8.73 (s, 1H, H_2); ^{13}C NMR (MeOH-d_4, 150.9 MHz): δ 22.9, 23.0 ($C_{6'}$+$C_{9'}$), 33.1 ($C_{3'}$), 41.3 ($C_{2'}$), 61.4 ($C_{5'}$), 85.7 ($C_{4'}$), 90.1 ($C_{1'}$), 123.8 ($C_{7'}$ or $C_{8'}$), 124.4 (C_5), 123.9 ($C_{8'}$ or $C_{7'}$), 139.1 (C_8), 145.2 (C_4), 148.0 (C_2), 157.5 (C_6); MS (ESI^+, m/z): 289 [$(M+H)^+$, 100%] and 311 [$(M+Na)^+$, 60].



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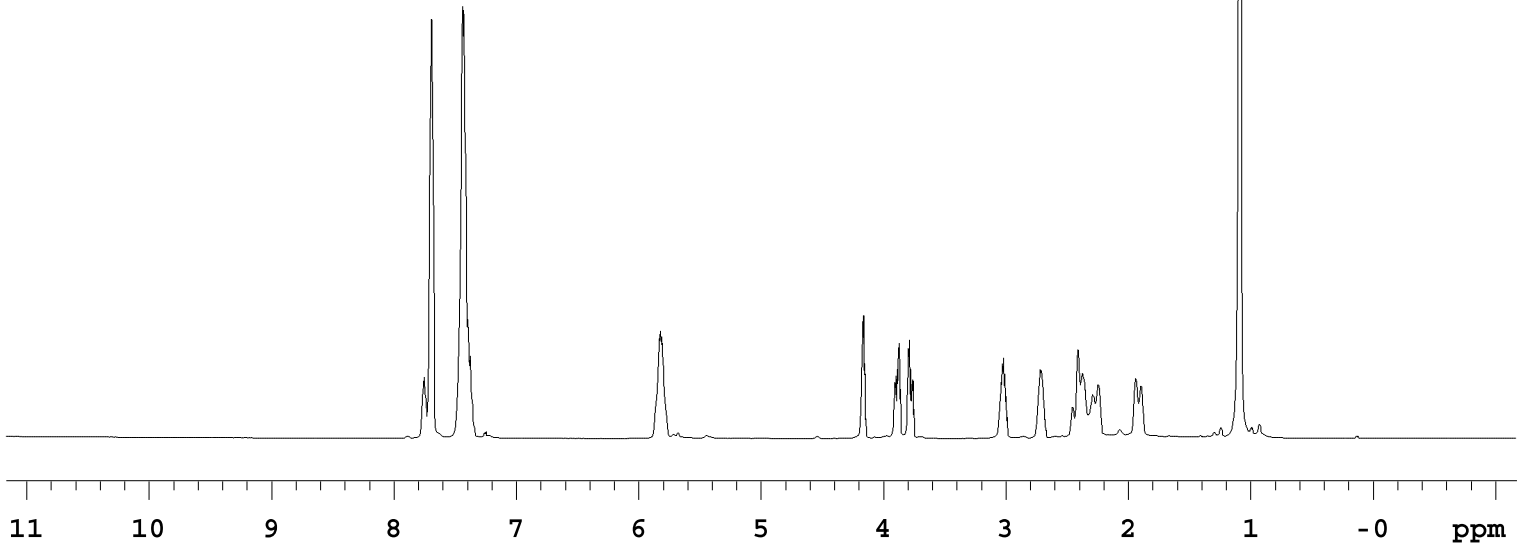

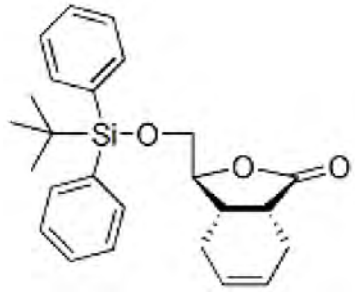

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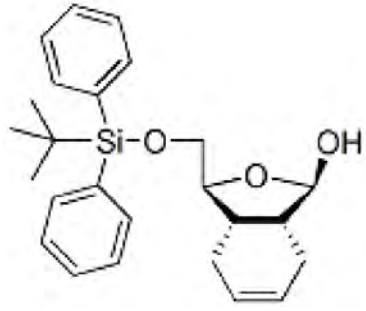

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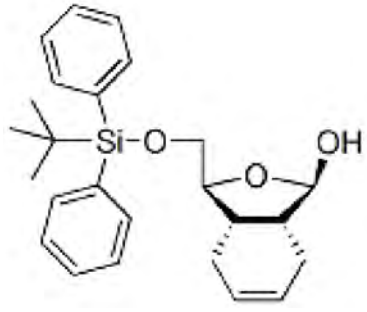

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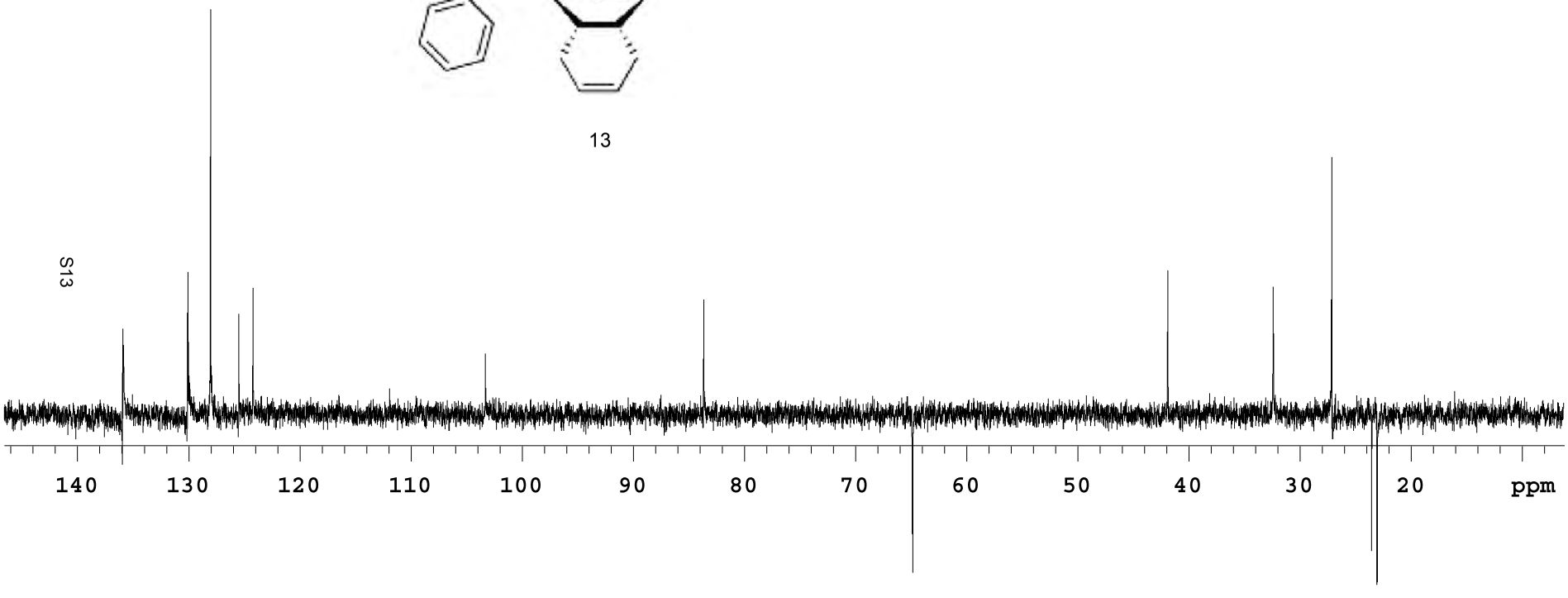

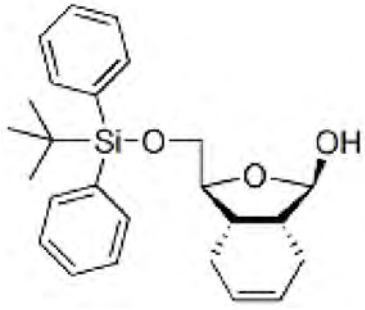

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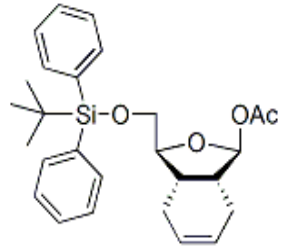

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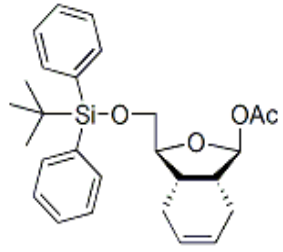

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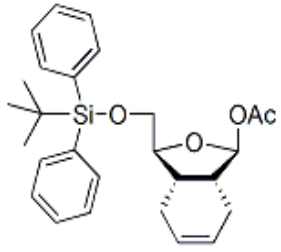

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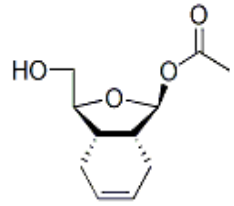

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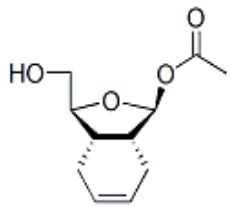

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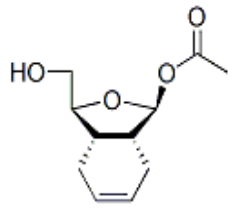

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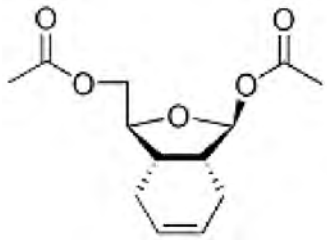

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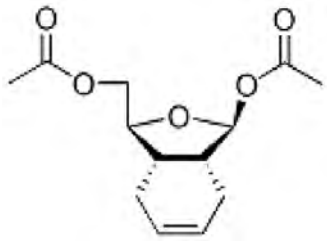

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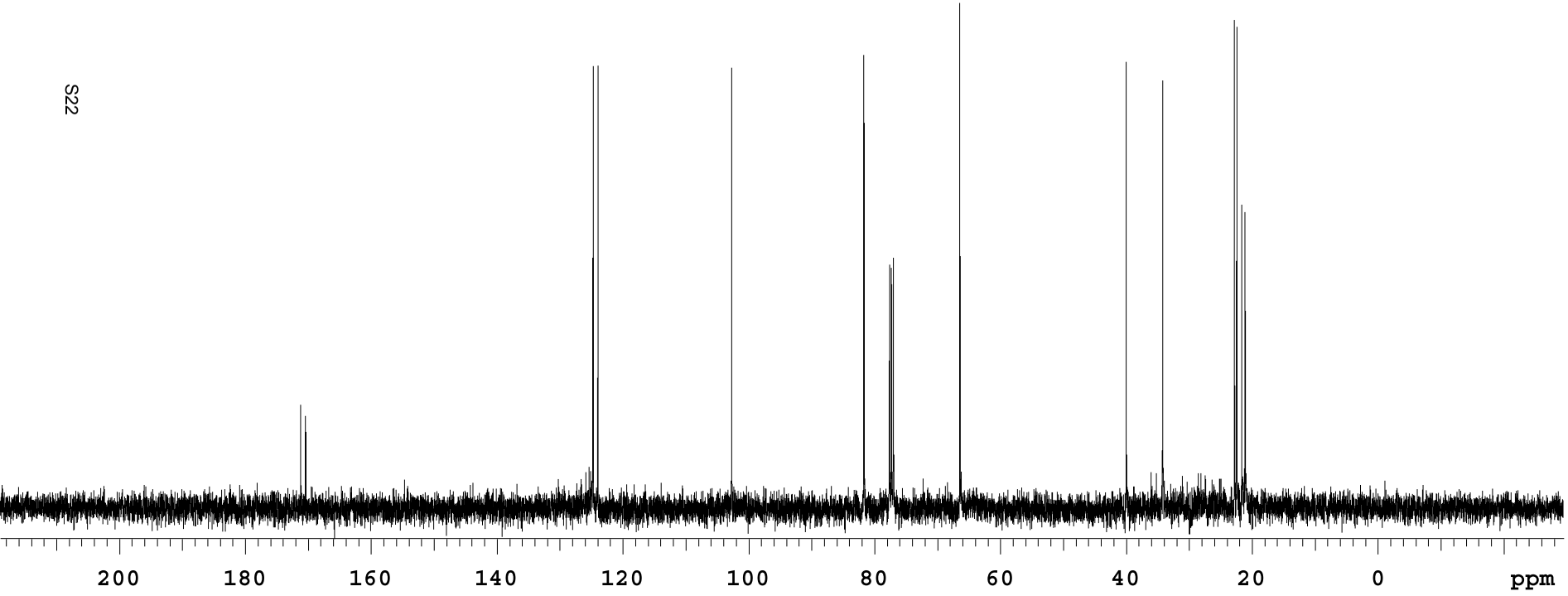

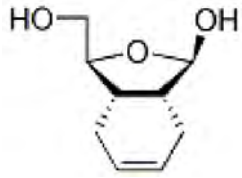

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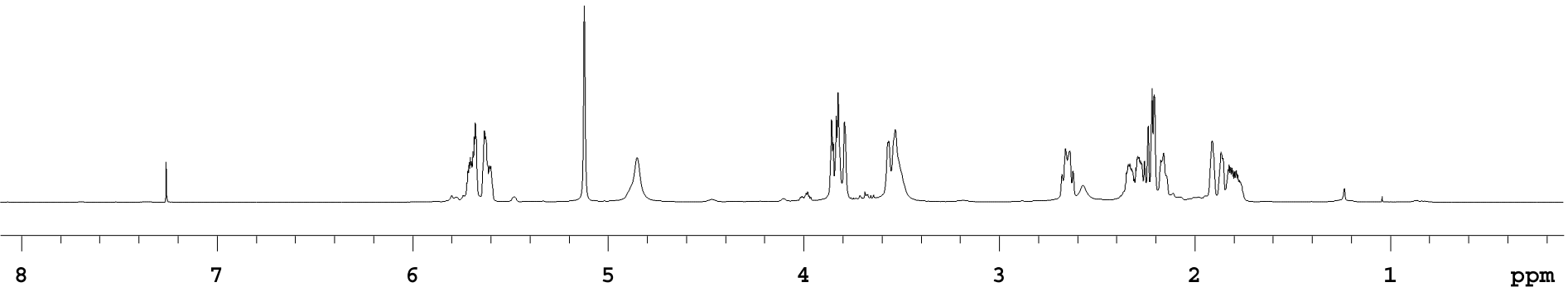

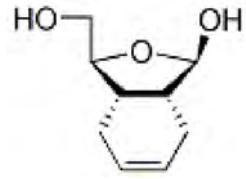

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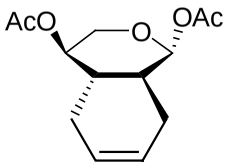

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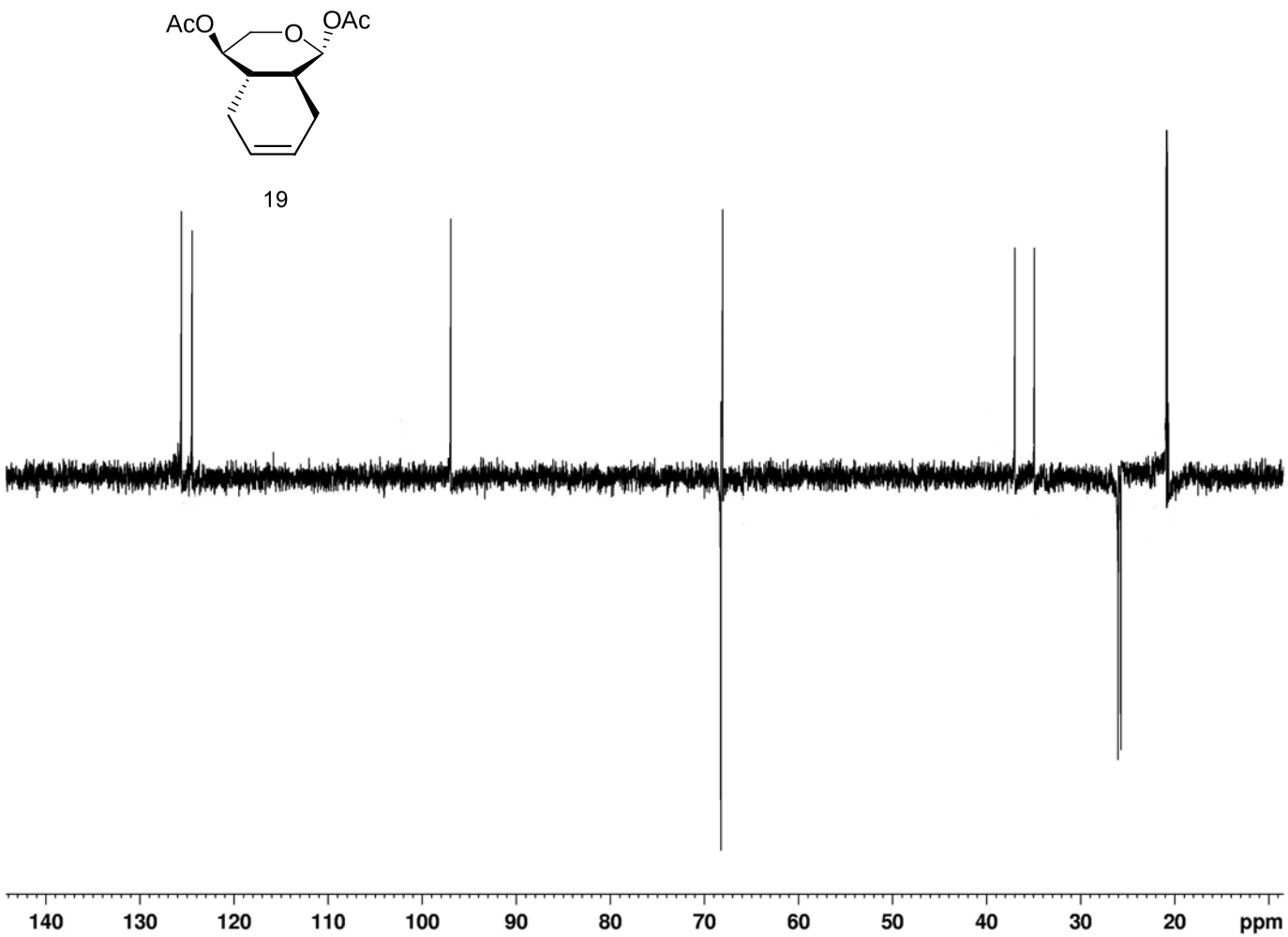
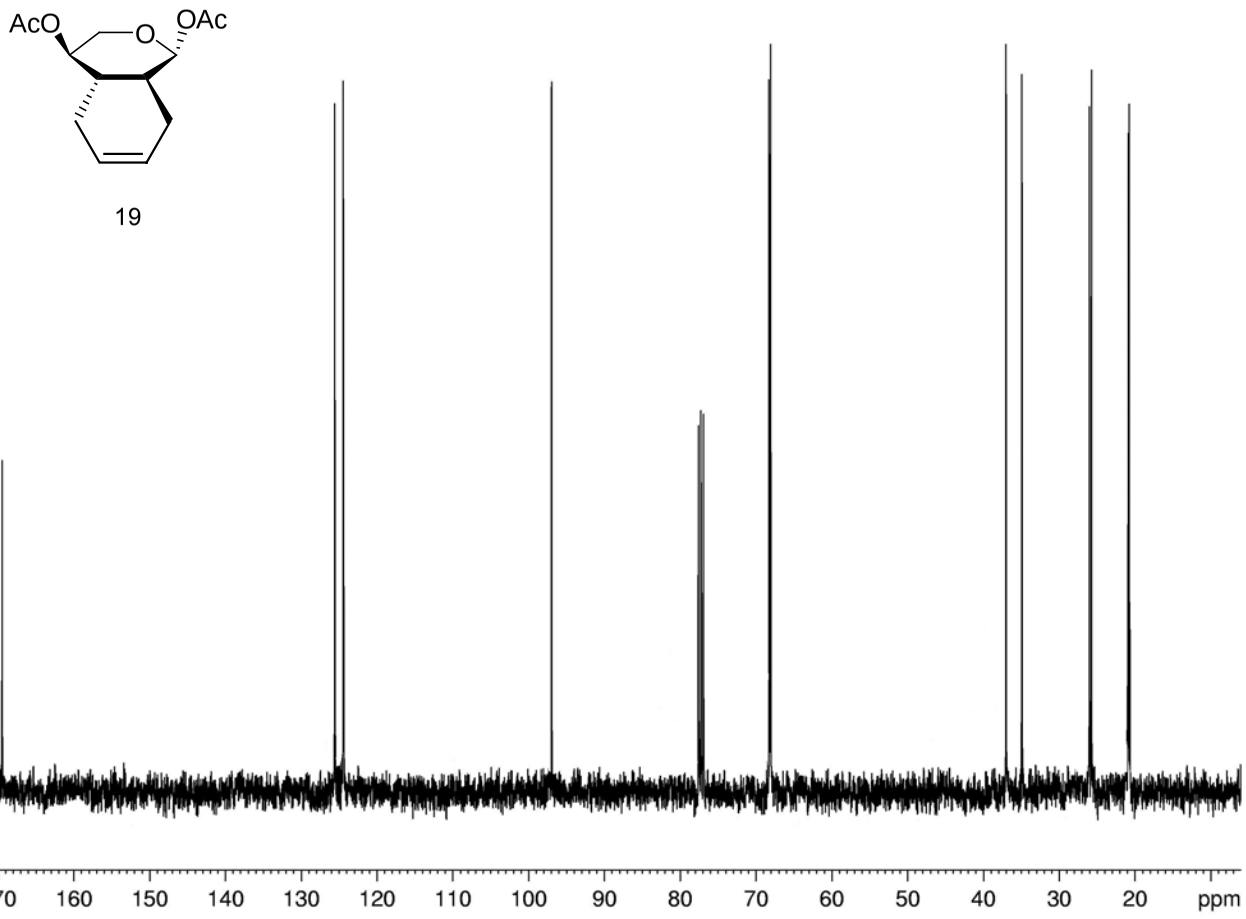

AcO
O
OAc
19
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


AcO
O
OAc
19
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120
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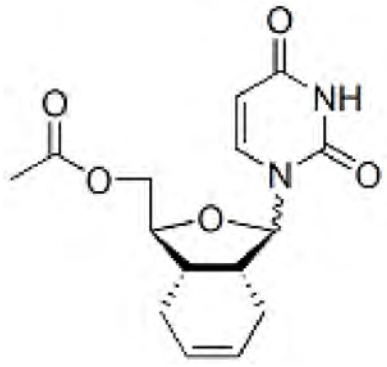
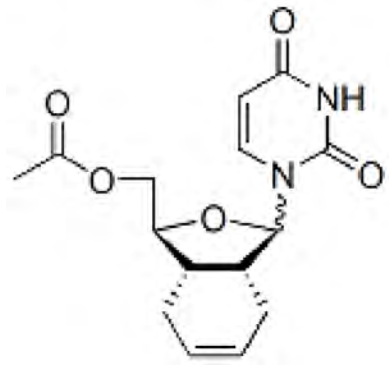
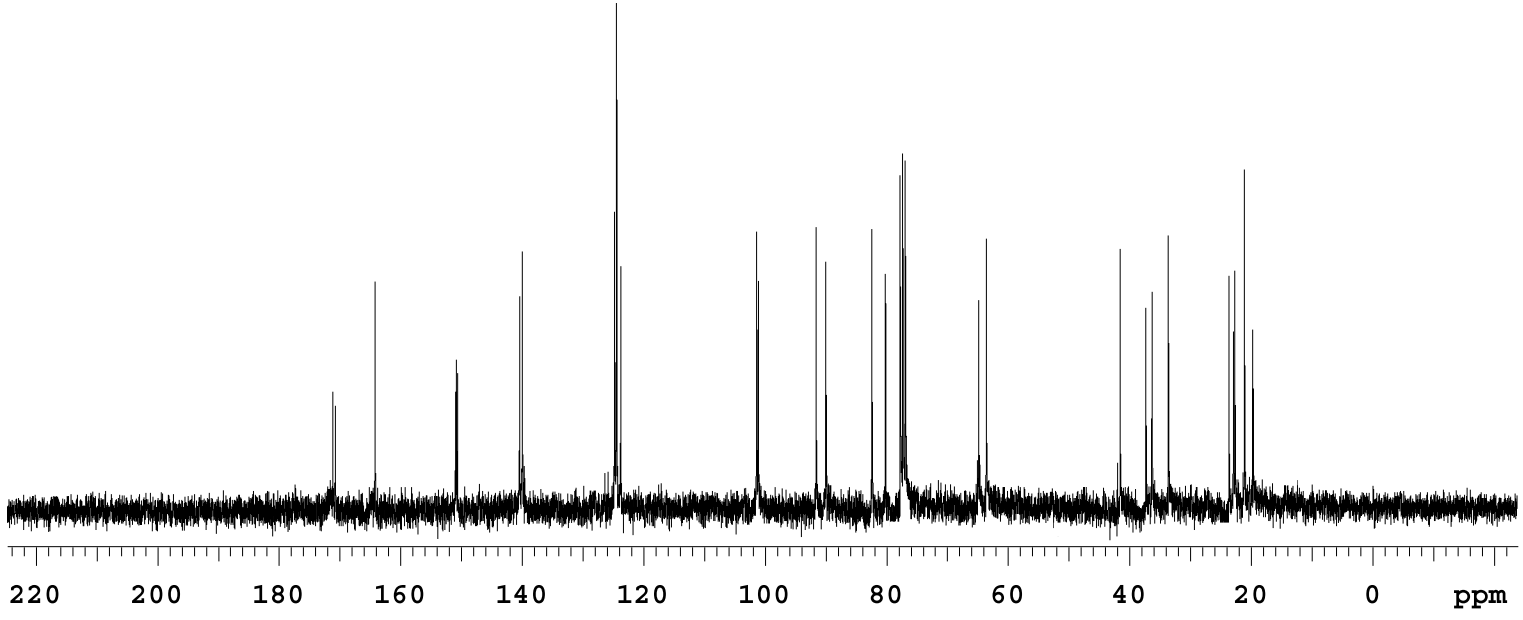
40
30
20
ppm

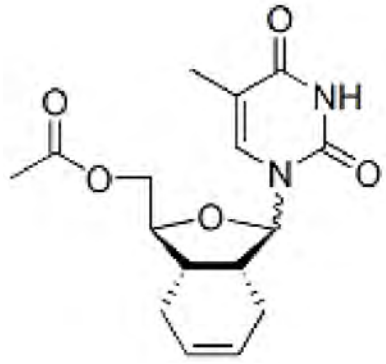


20a+21a



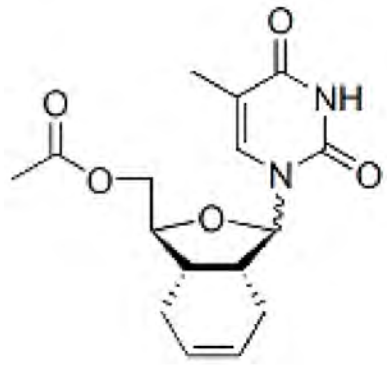
20a+21a



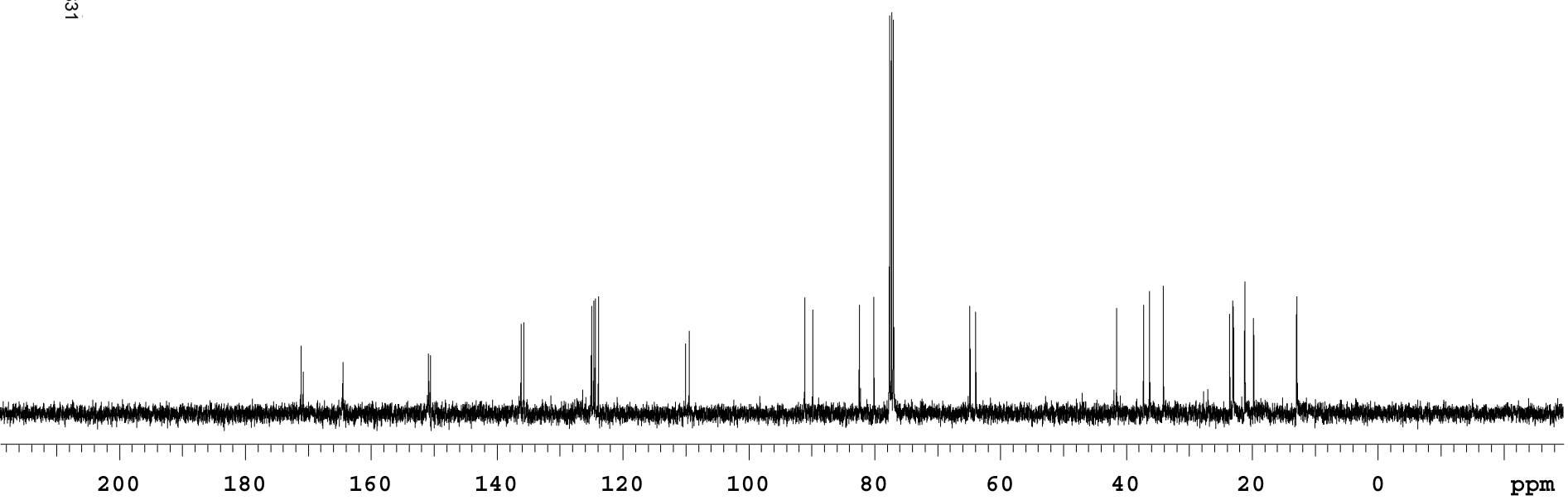


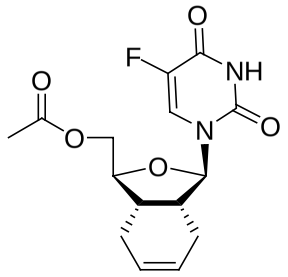
20b+21b

S30

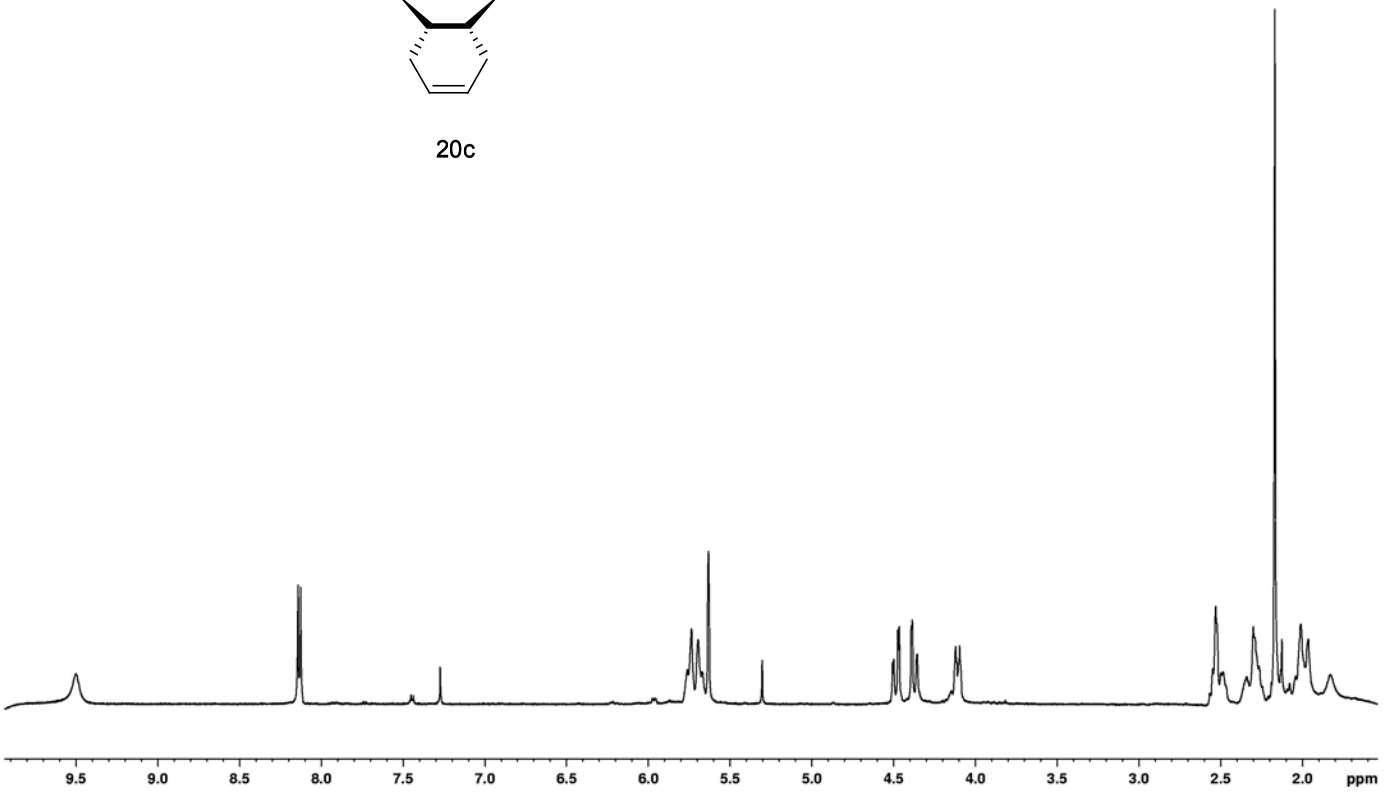


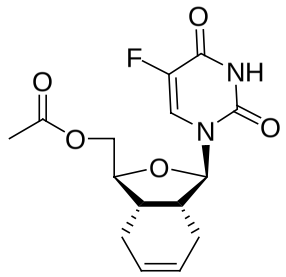
20b+21b



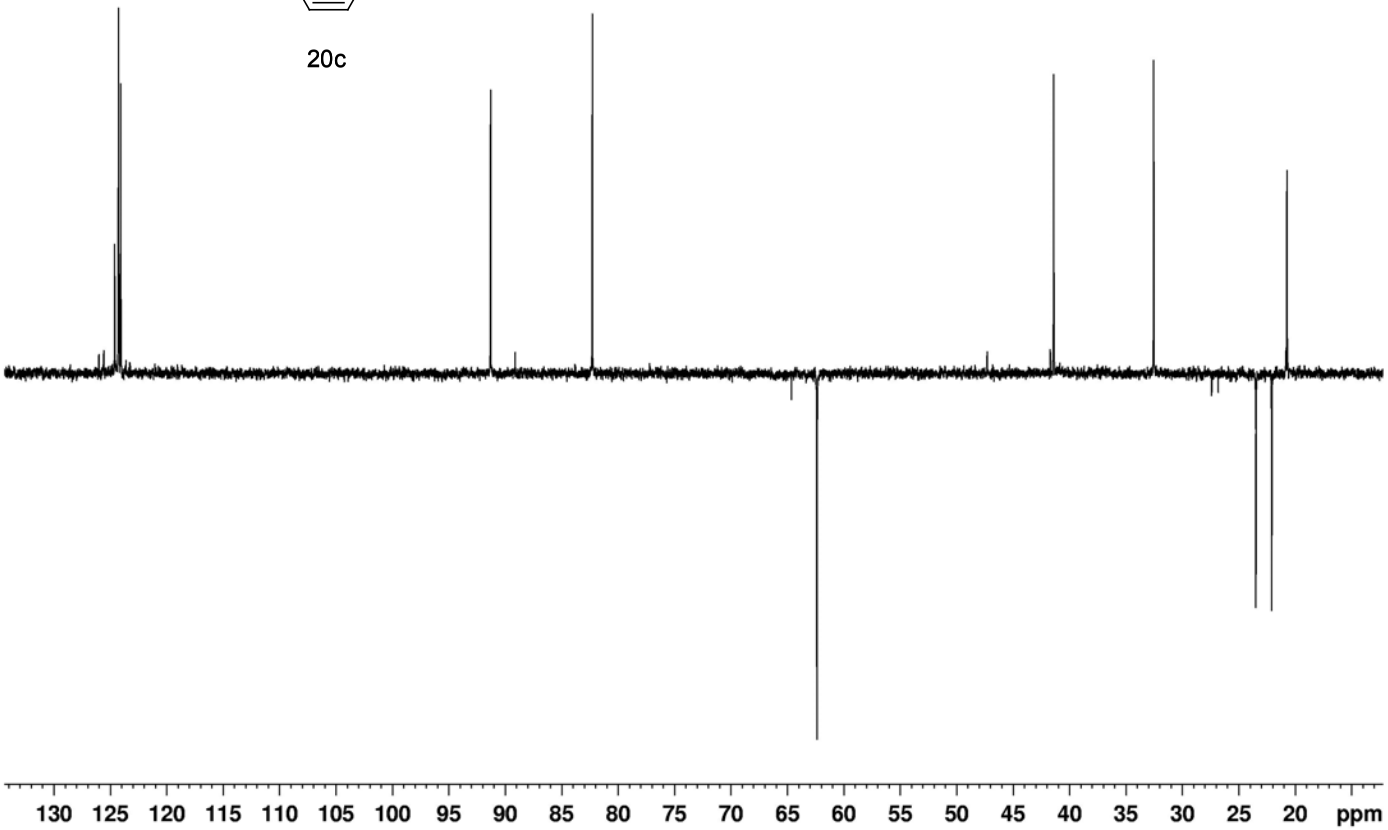


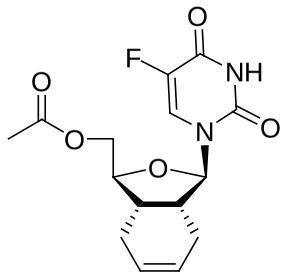
20c




O
F
NH
O
O
N
O
O

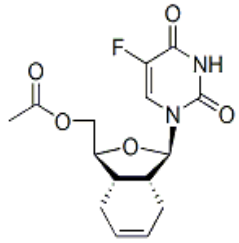
20c


130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 ppm

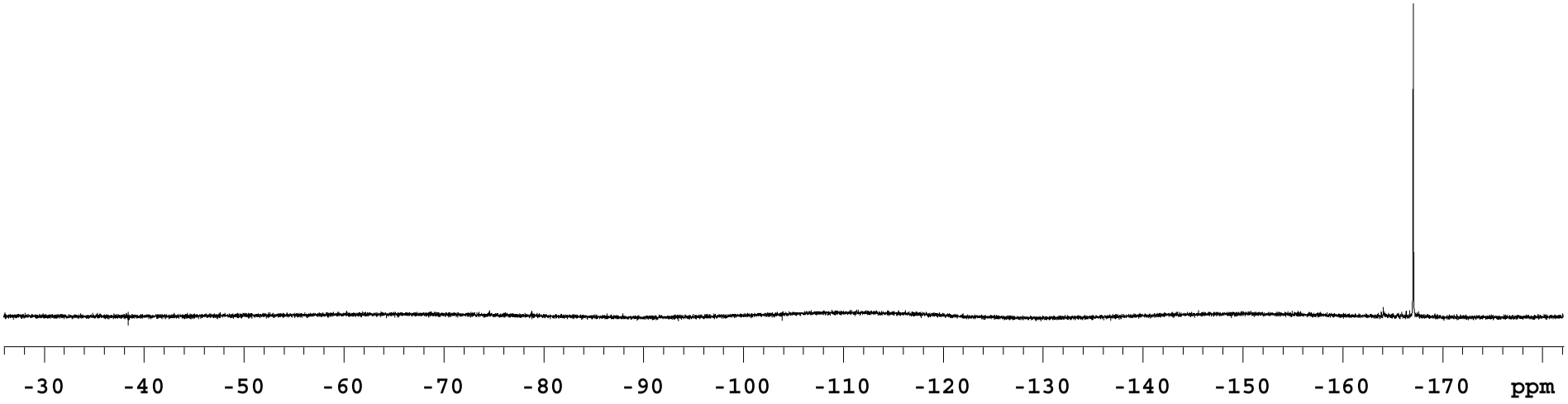

O
F
NH
O
N
O
O
O

20c

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


O
F
NH
O
O
N
O
O

20c


-30
-40
-50
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-70
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-90
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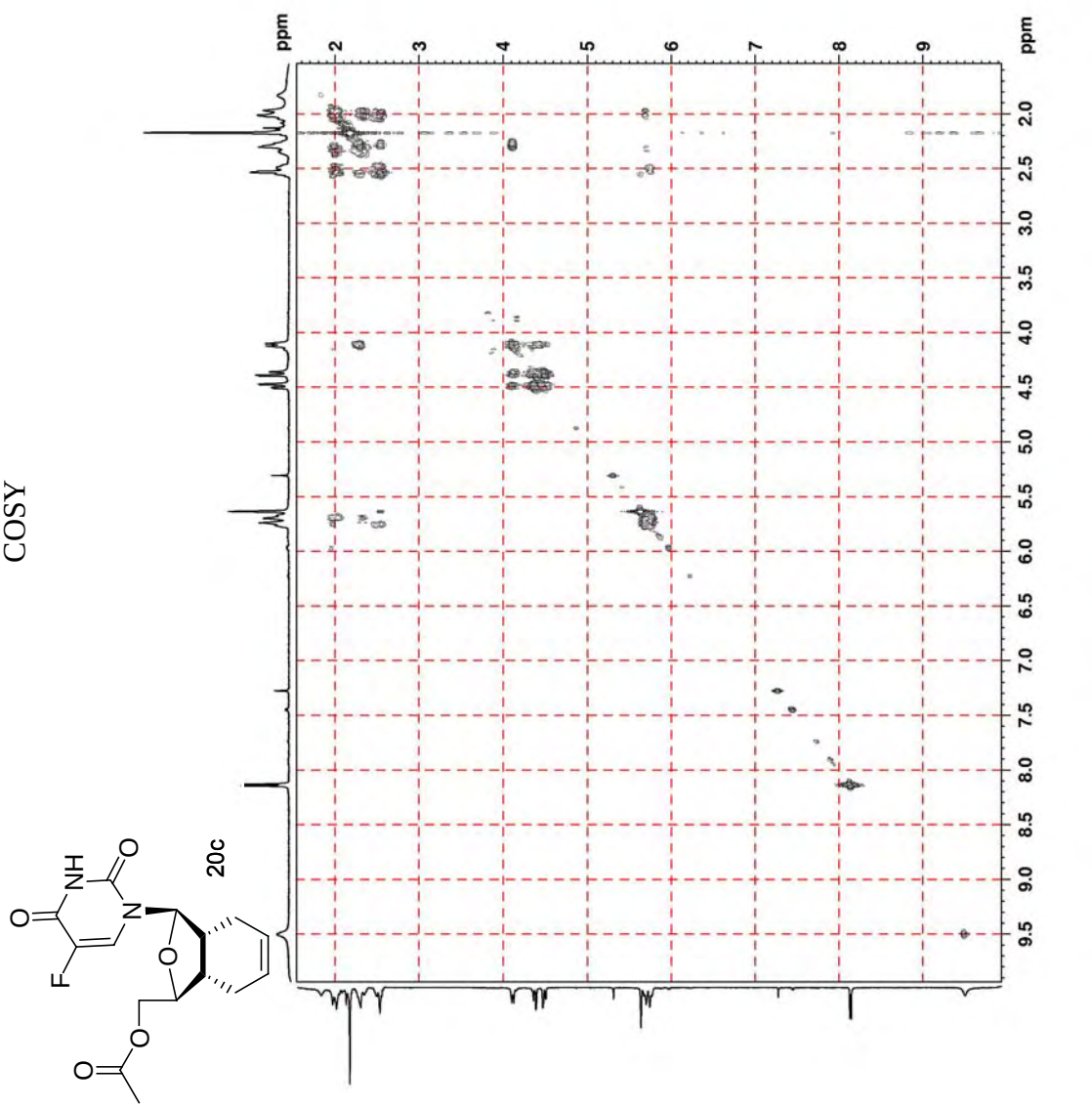
-110
-120
-130
-140
-150
-160
-170
ppm

COSY


20c
NH
O
O
N
F
O
O
O
ppm
2
3
4
5
6
7
8
9
ppm
2.0
2.5
3.0
3.5
4.0
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6.0
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7.0
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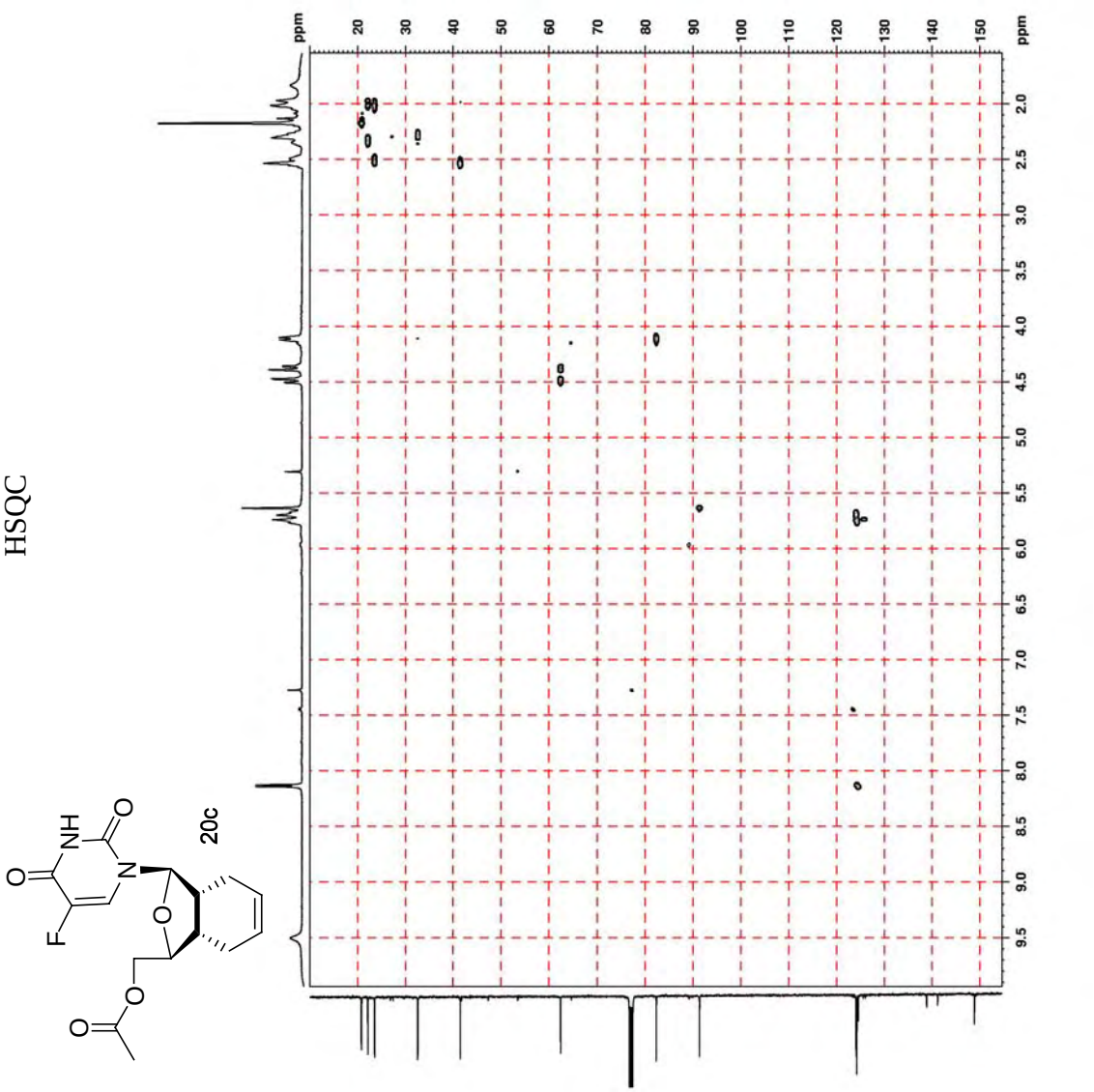
8.0
8.5
9.0
9.5

HSQC


20c
NH
O
O
N
F
O
O
O
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm
2.0
2.5
3.0
3.5
4.0
4.5
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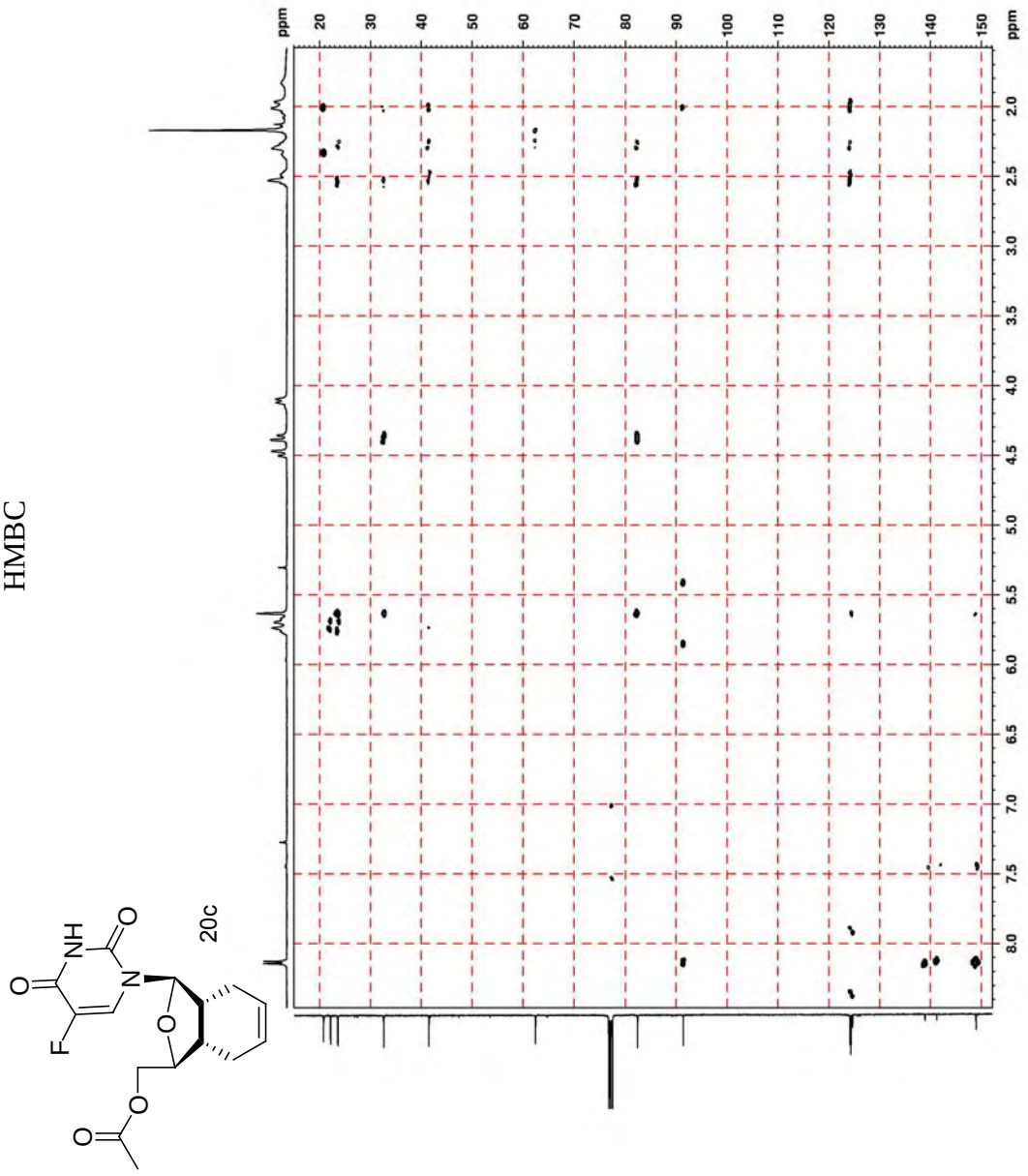
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5

HMBC


20c
NH
O
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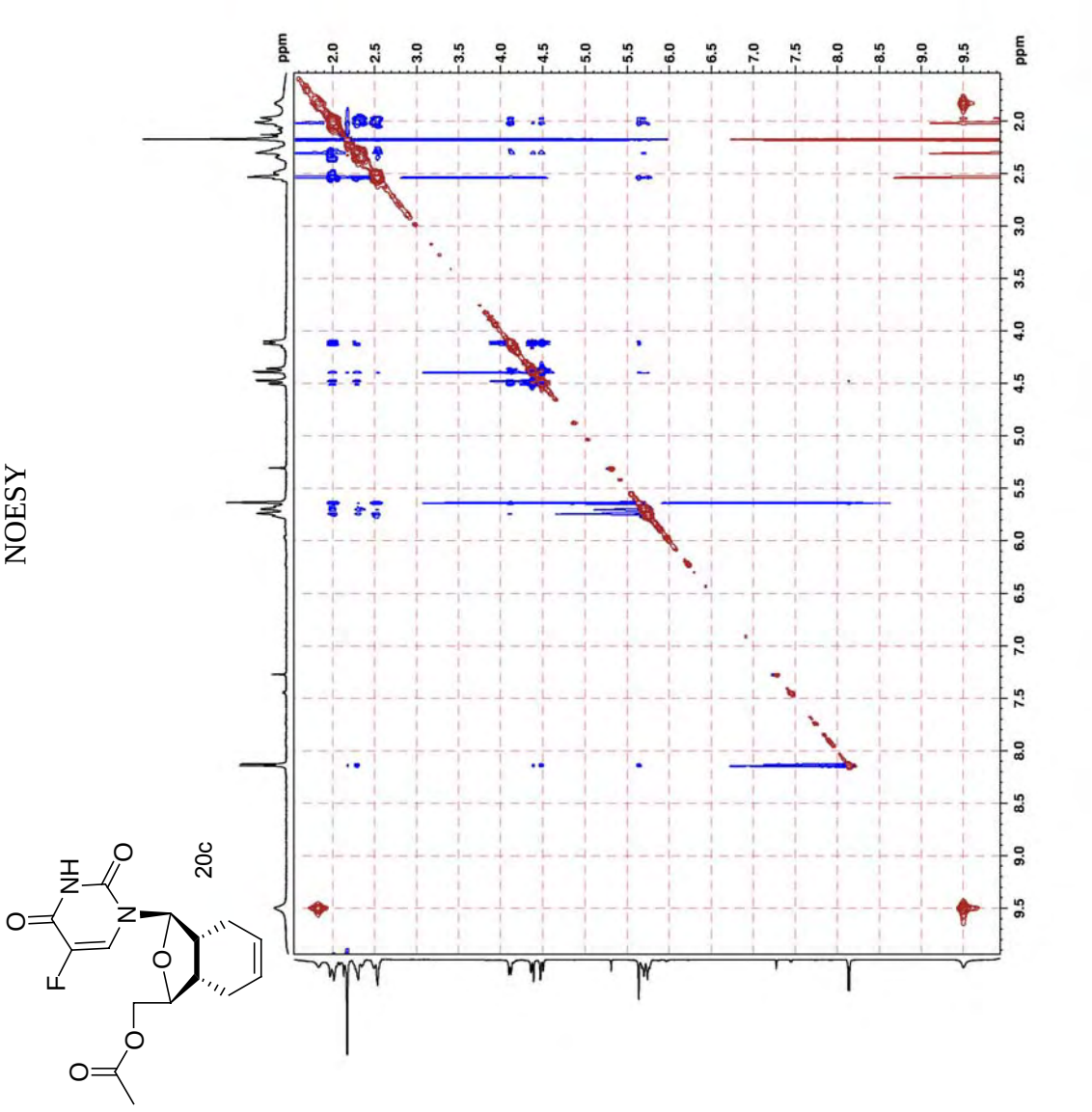
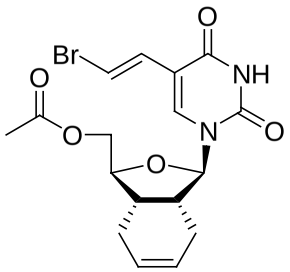
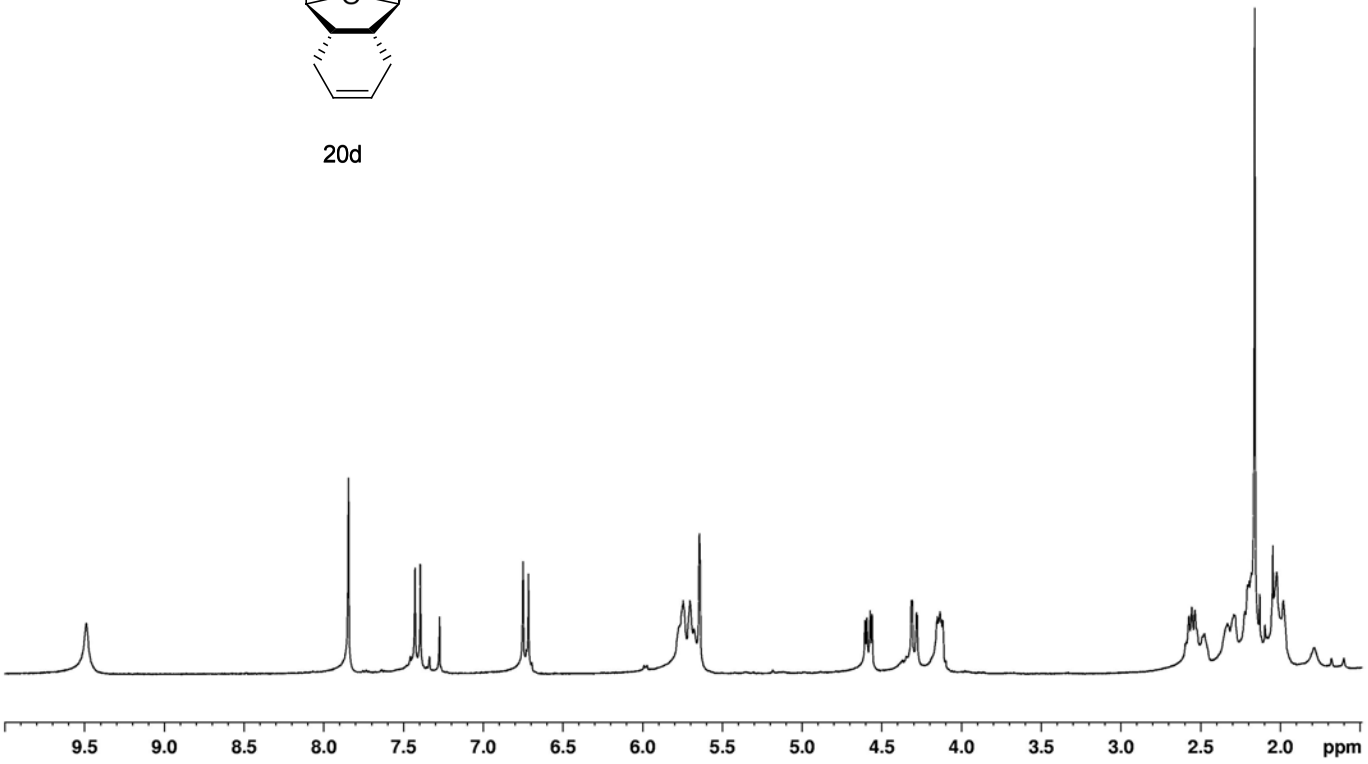
N
F
O
O
O
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

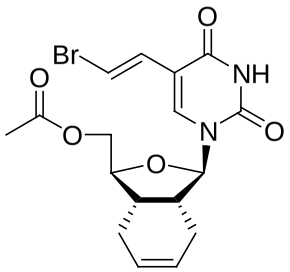
NOESY



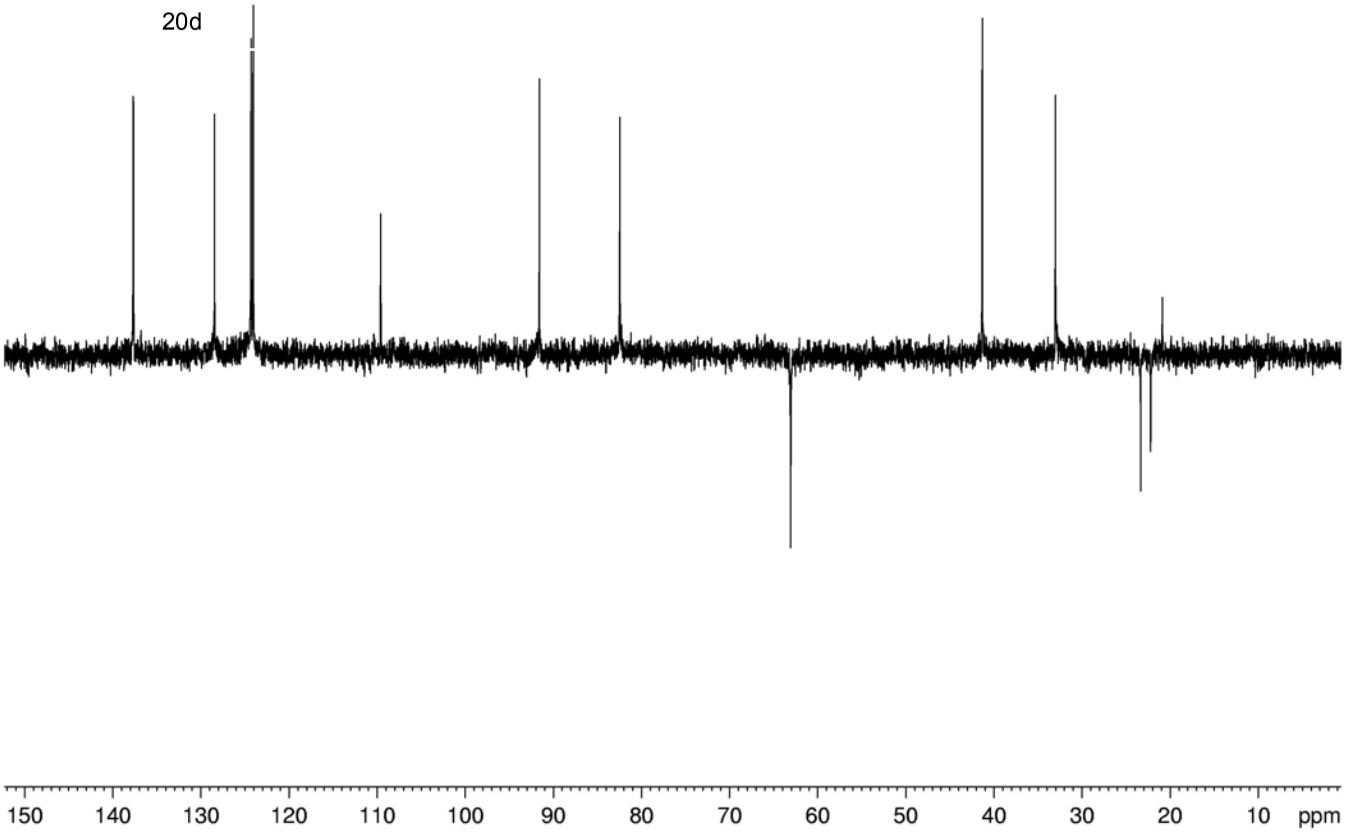


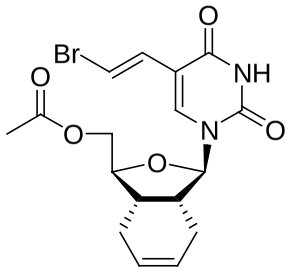
20d





20d




Br
O
NH
O
O
N
O
O

20d

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180
170
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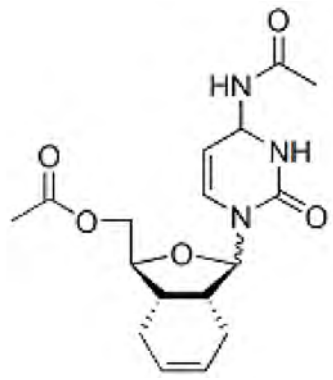
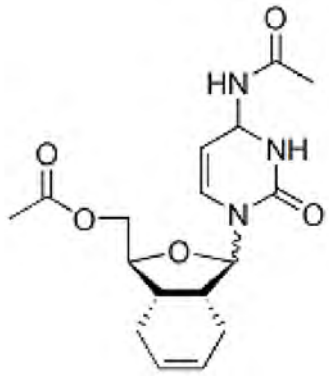
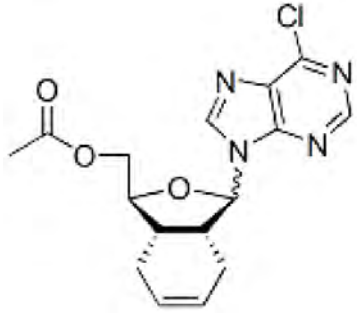
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



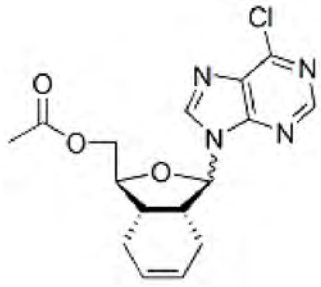
20e+21e



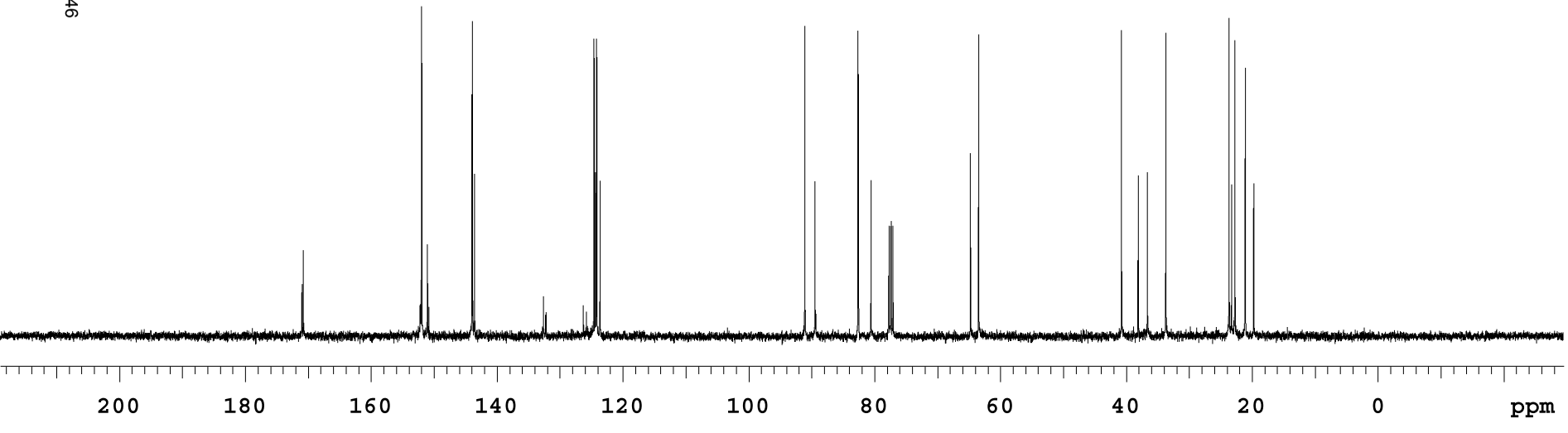
20e+21e

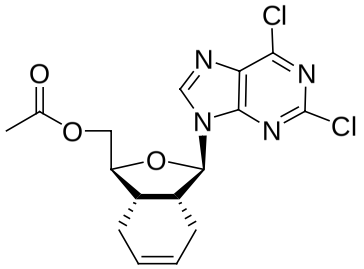


20f+21f

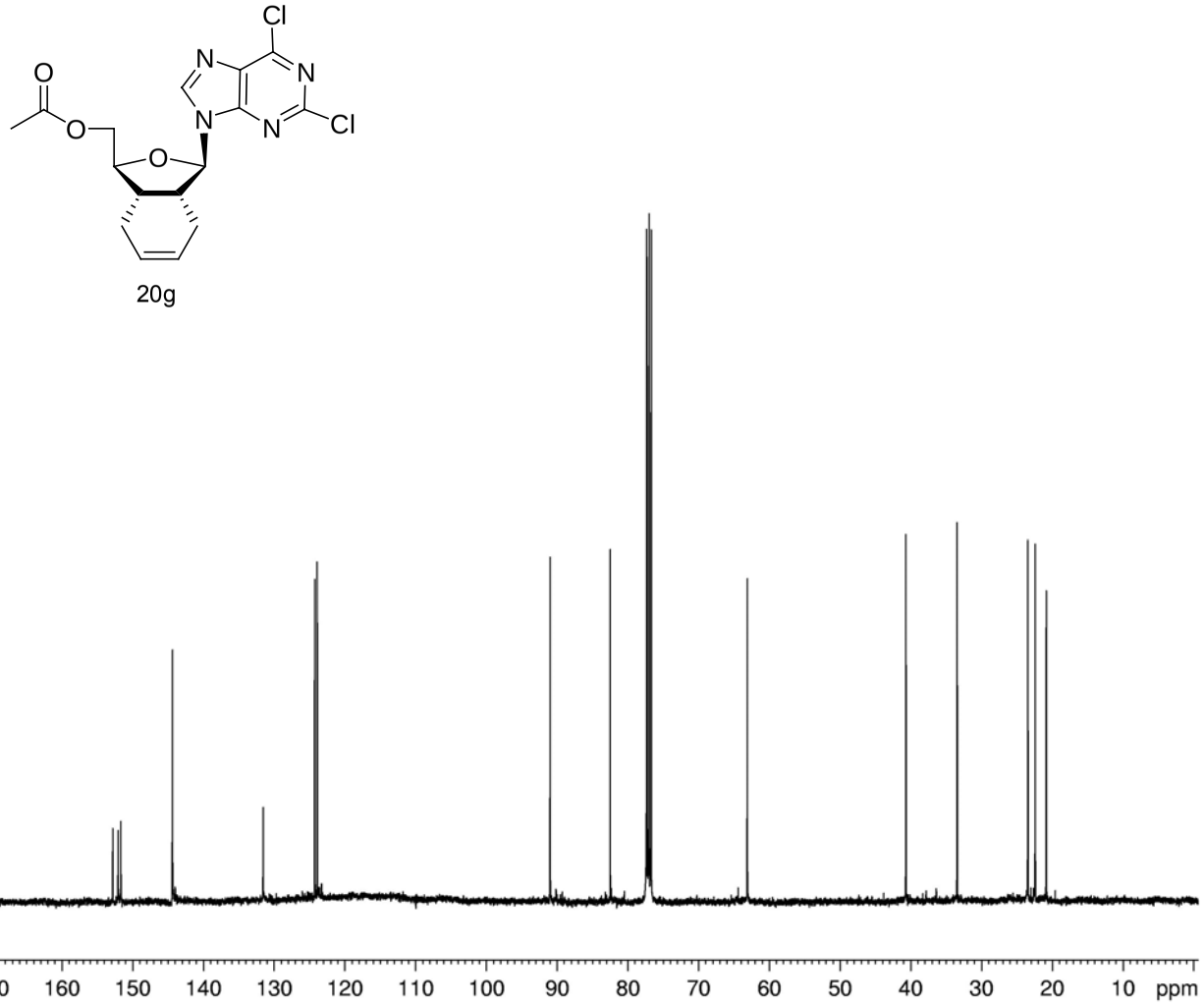


20f+21f





20g


Cl
N
N
O
O
N
N
Cl
20g
180
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90
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70
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30
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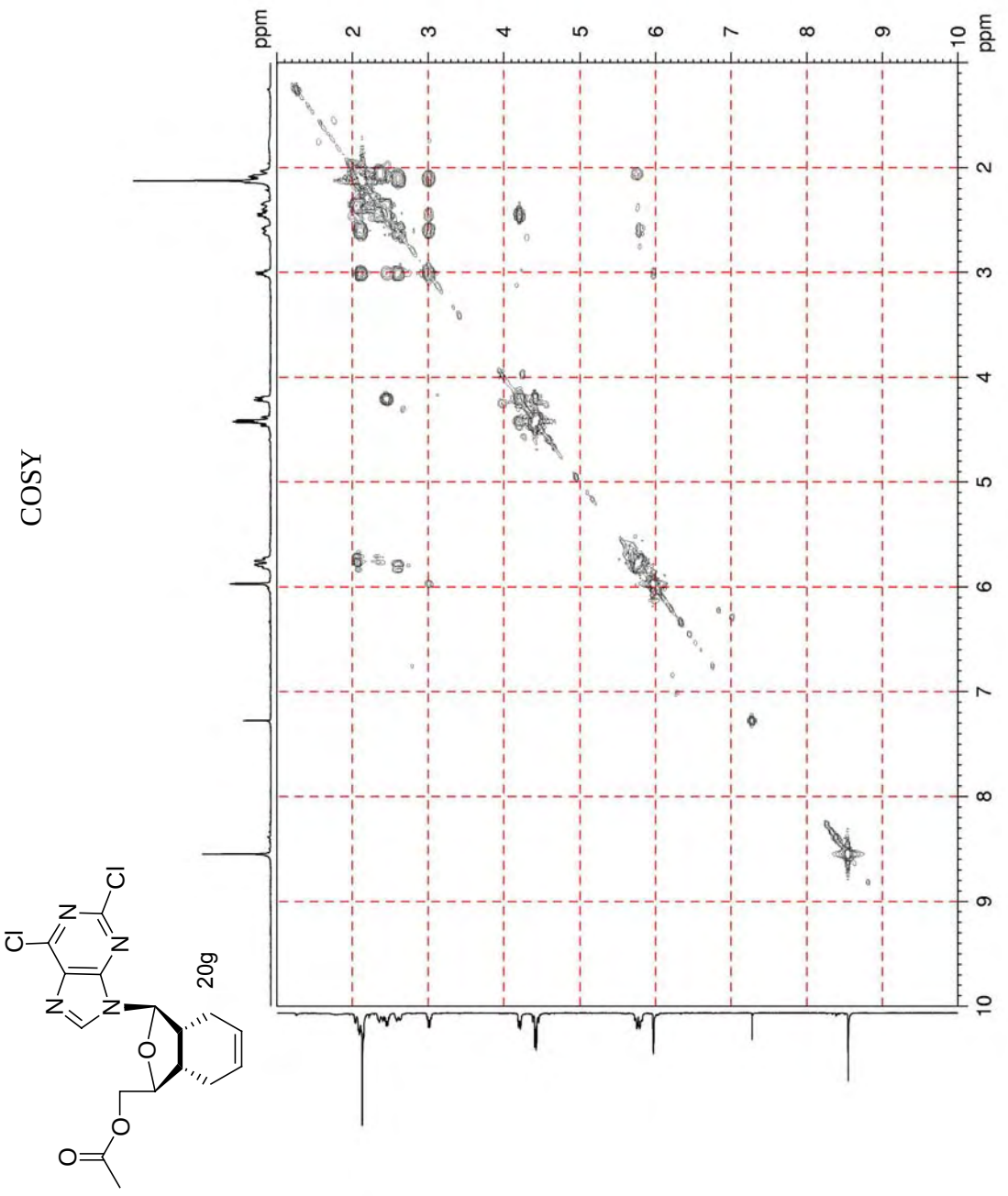
10
ppm


COSY
20g
Cl
Cl
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N
N
N
O
O
O
ppm
2
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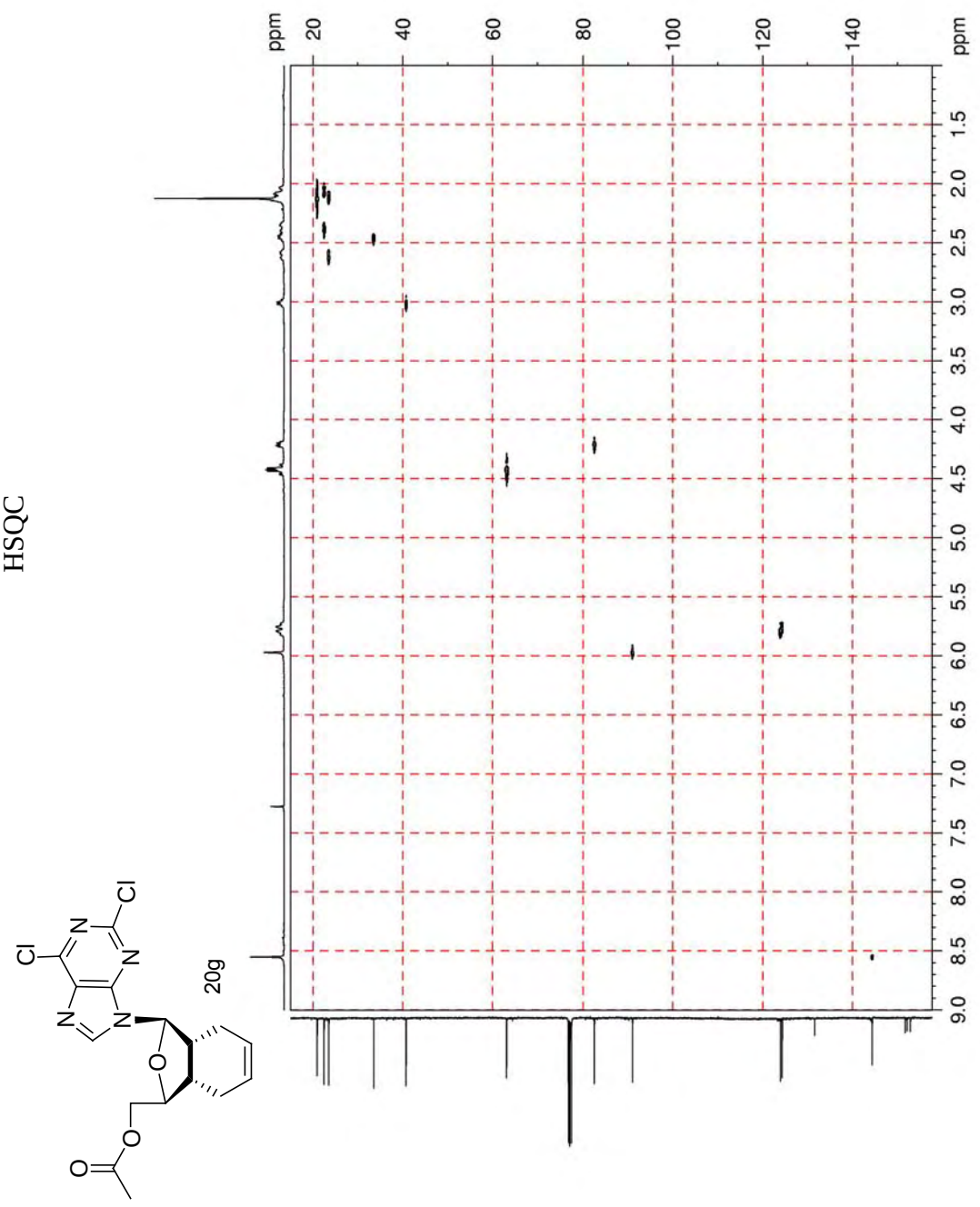
4
5
6
7
8
9
10

HSQC


ppm
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80
100
120
140
ppm
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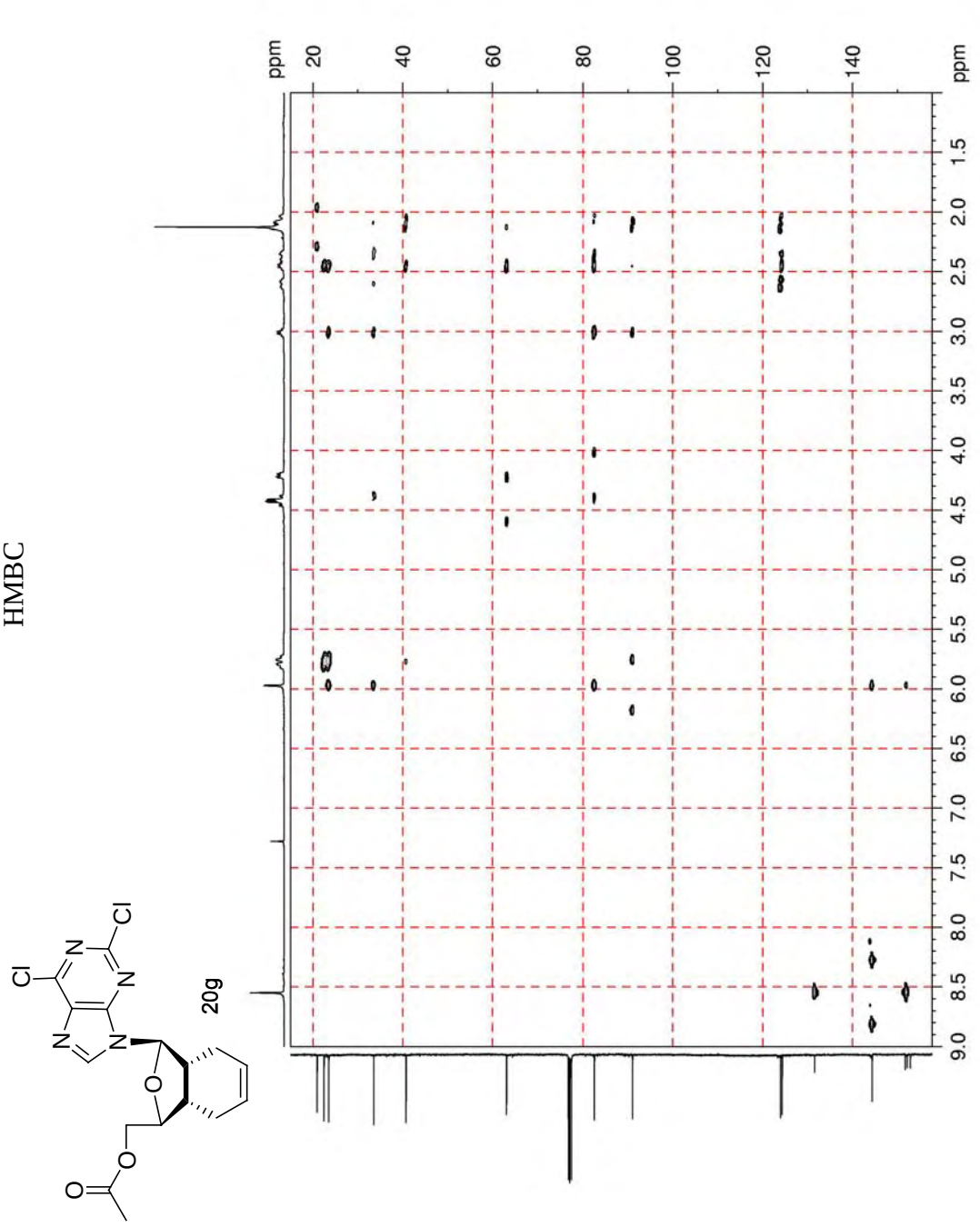
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
Cl
Cl
N
N
N
N
O
O
O
20g

HMBC


ppm
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80
100
120
140
ppm
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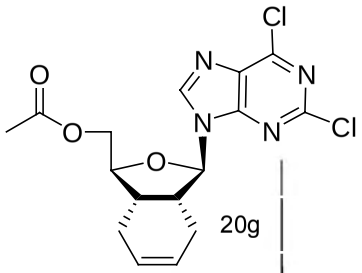
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
Cl
Cl
N
N
N
N
O
O
O
20g


Cl
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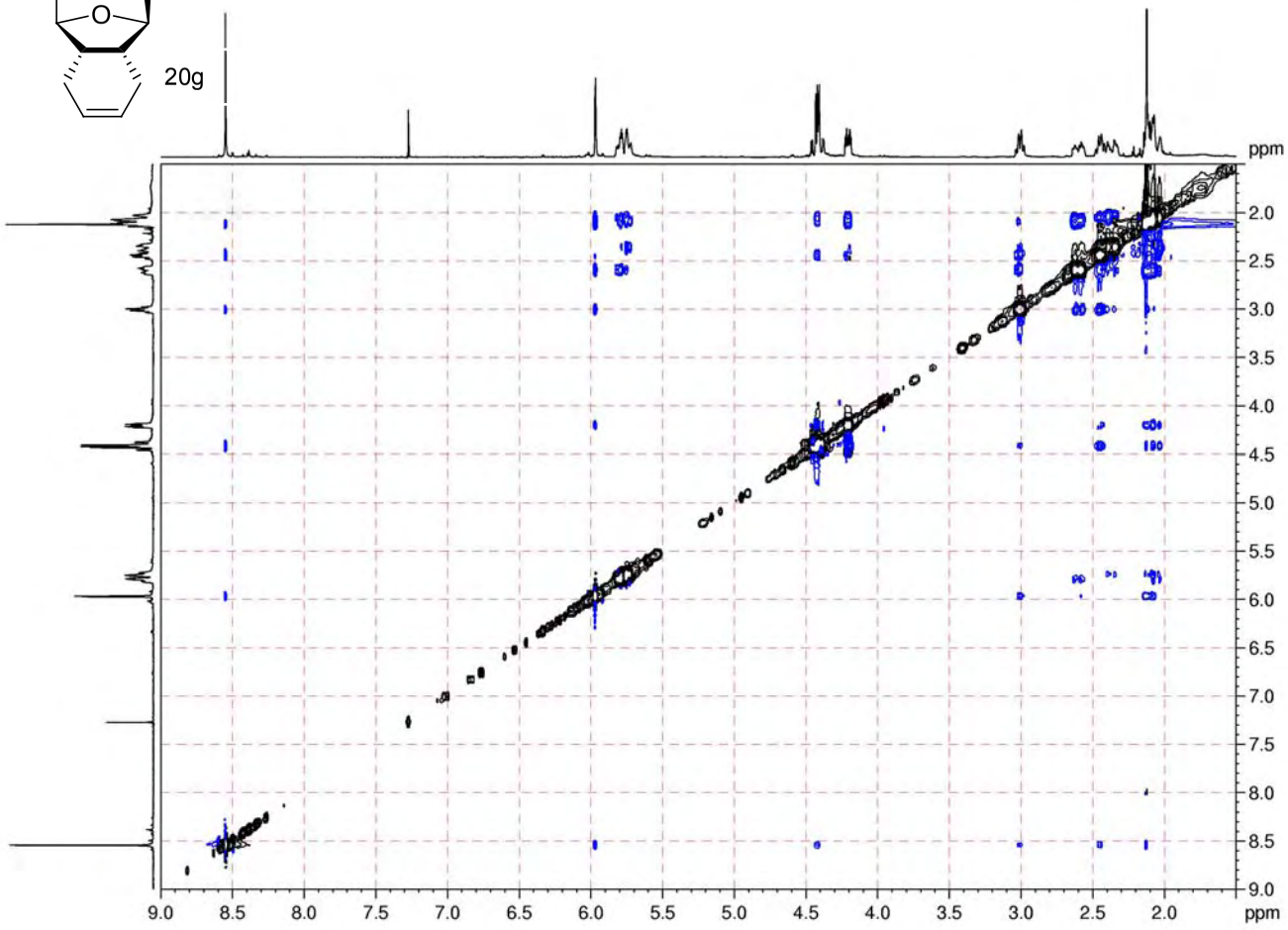
N
N
N
Cl
O
O
O
20g

NOESY


ppm
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3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
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9.0
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8.0
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6.0
5.5
5.0
4.5
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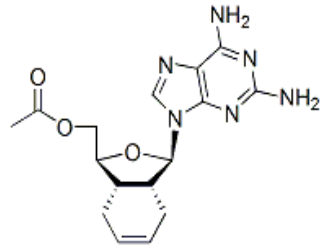
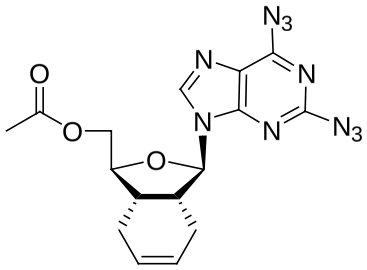
3.5
3.0
2.5
2.0
ppm



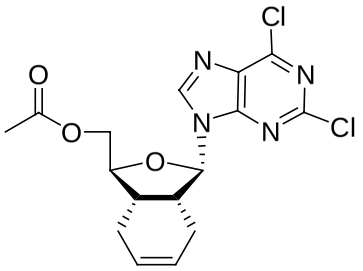
20m

S53

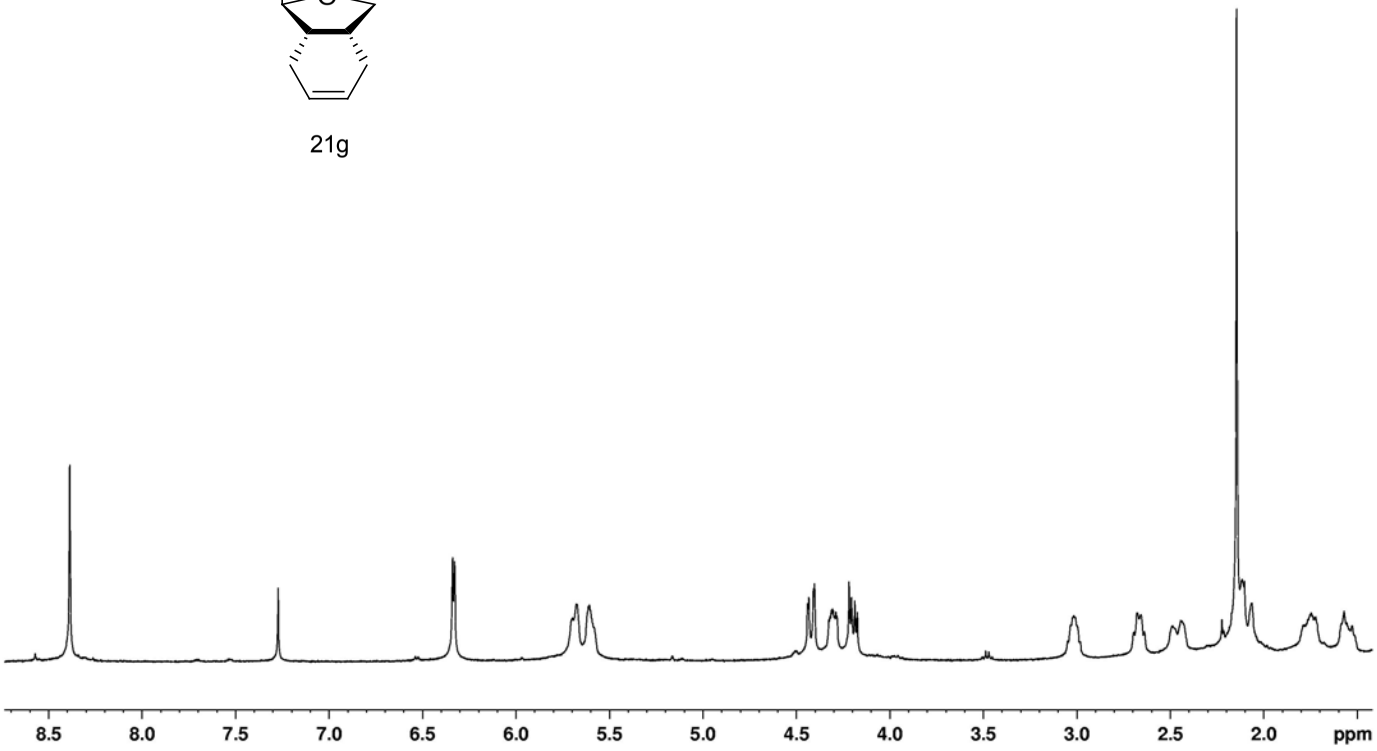
9 8 7 6 5 4 3 2 ppm

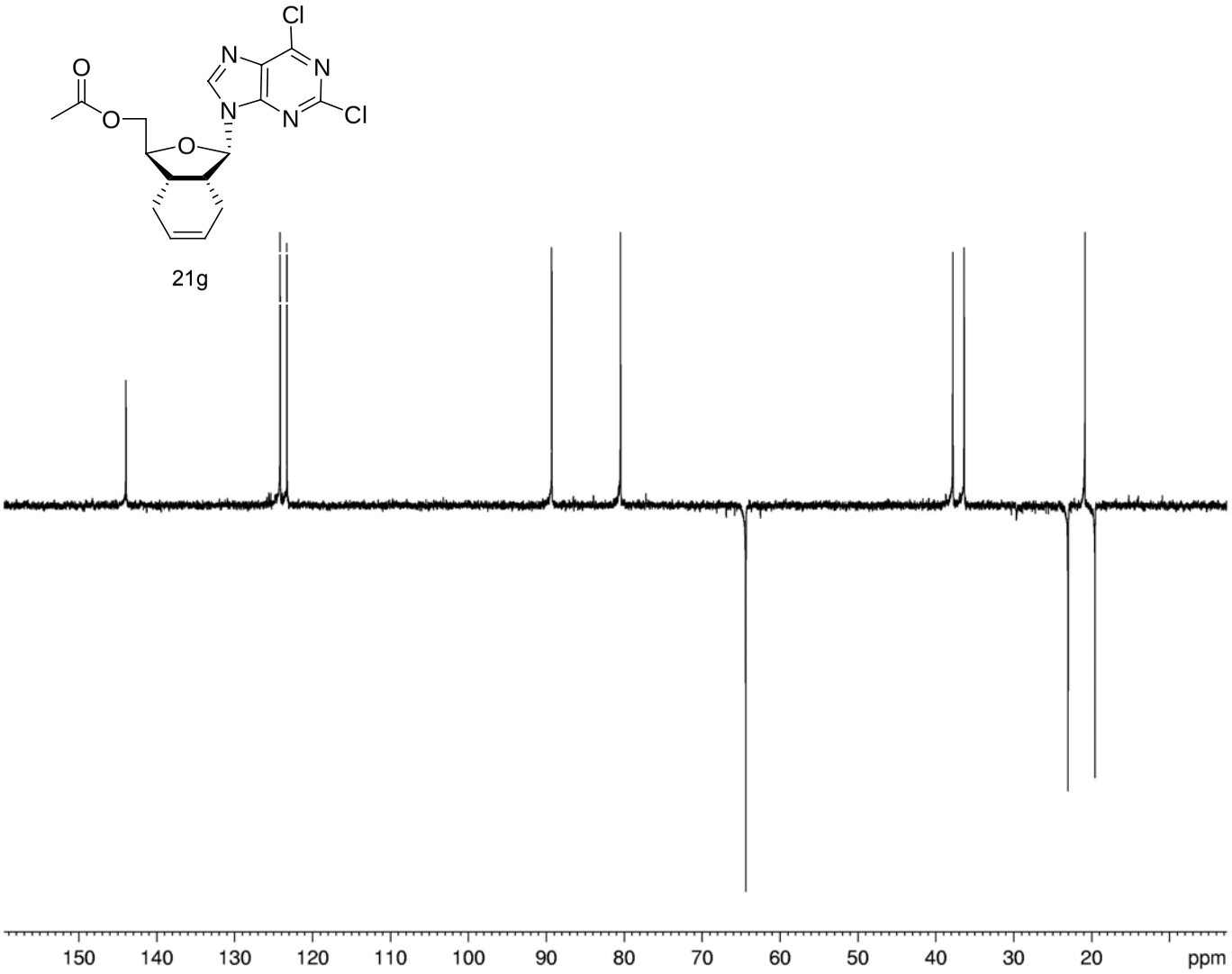


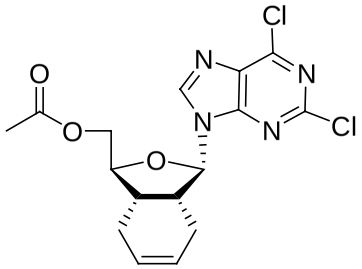
20n



21g




Cl
N
N
N
N
Cl
O
O
O
21g
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Cl
N
N
O
N
N
Cl
O
O

21g

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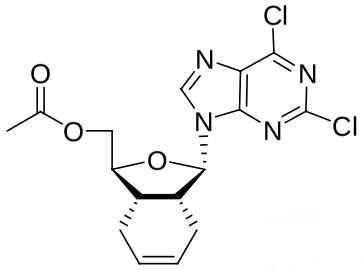
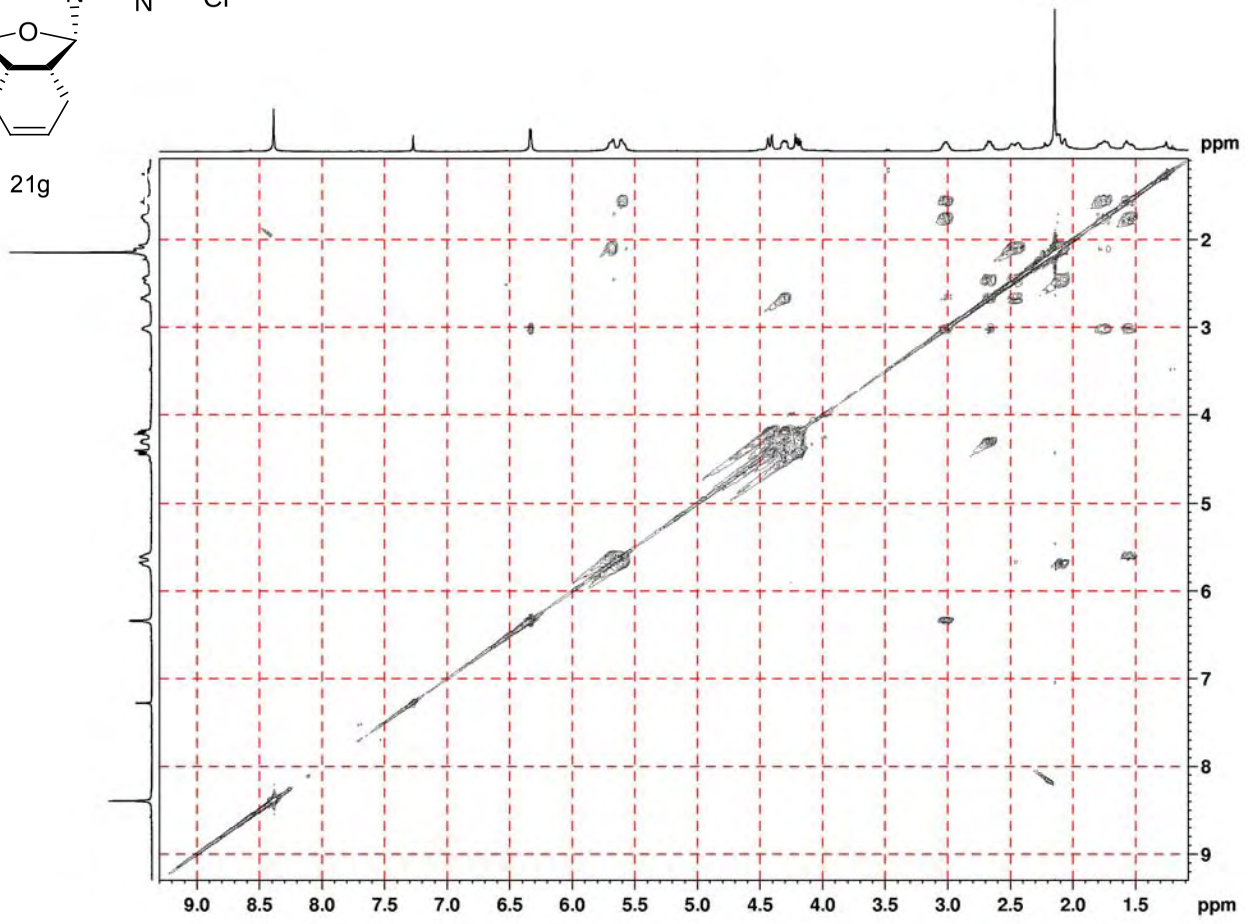
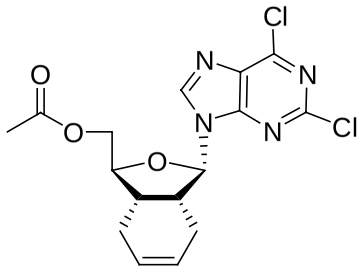
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

COSY


Cl
N
N
N
N
Cl
O
O
O

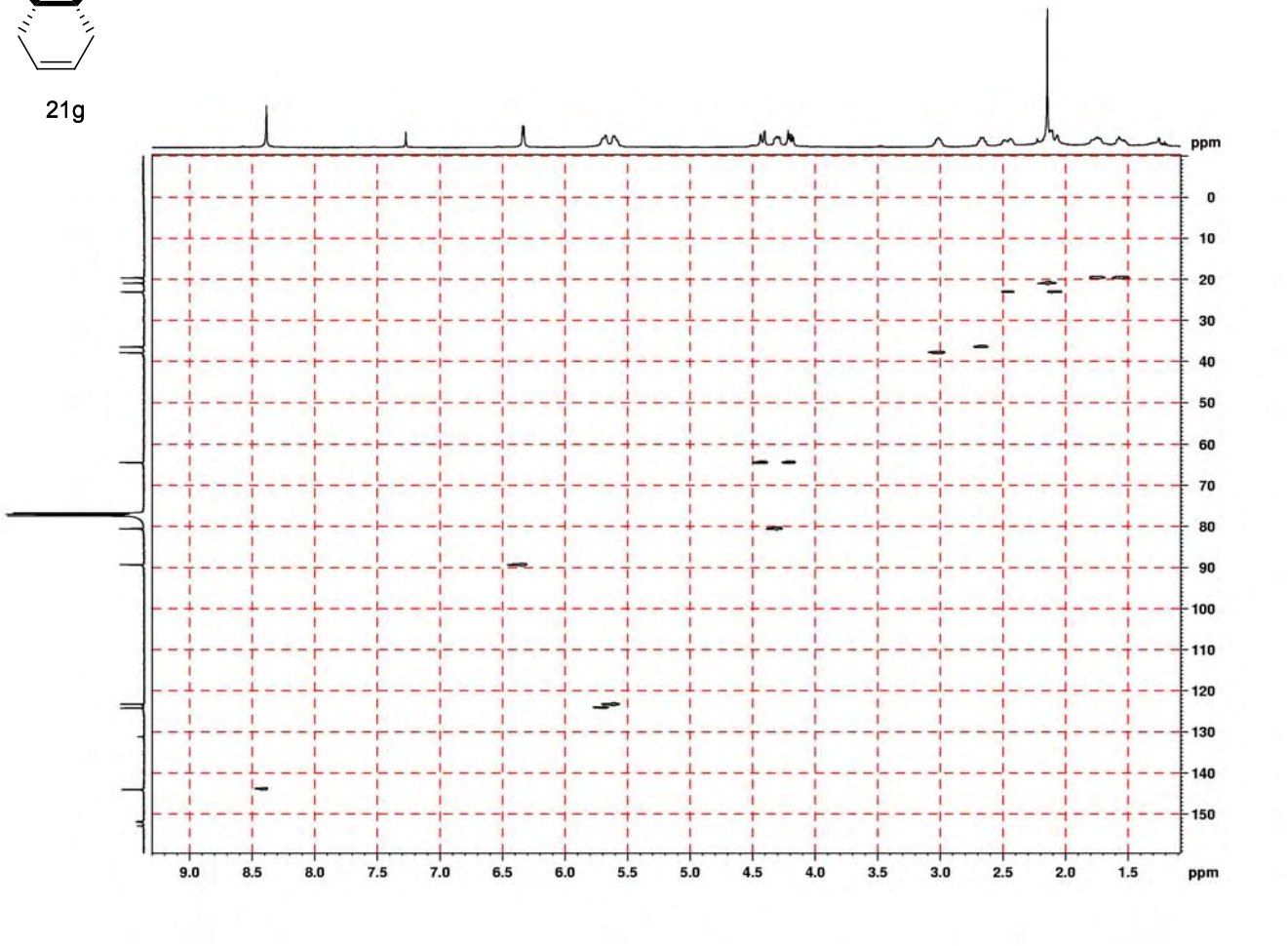
21g


ppm
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Cl
N
N
N
N
Cl
O
O
O

21g

HSQC


ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.0
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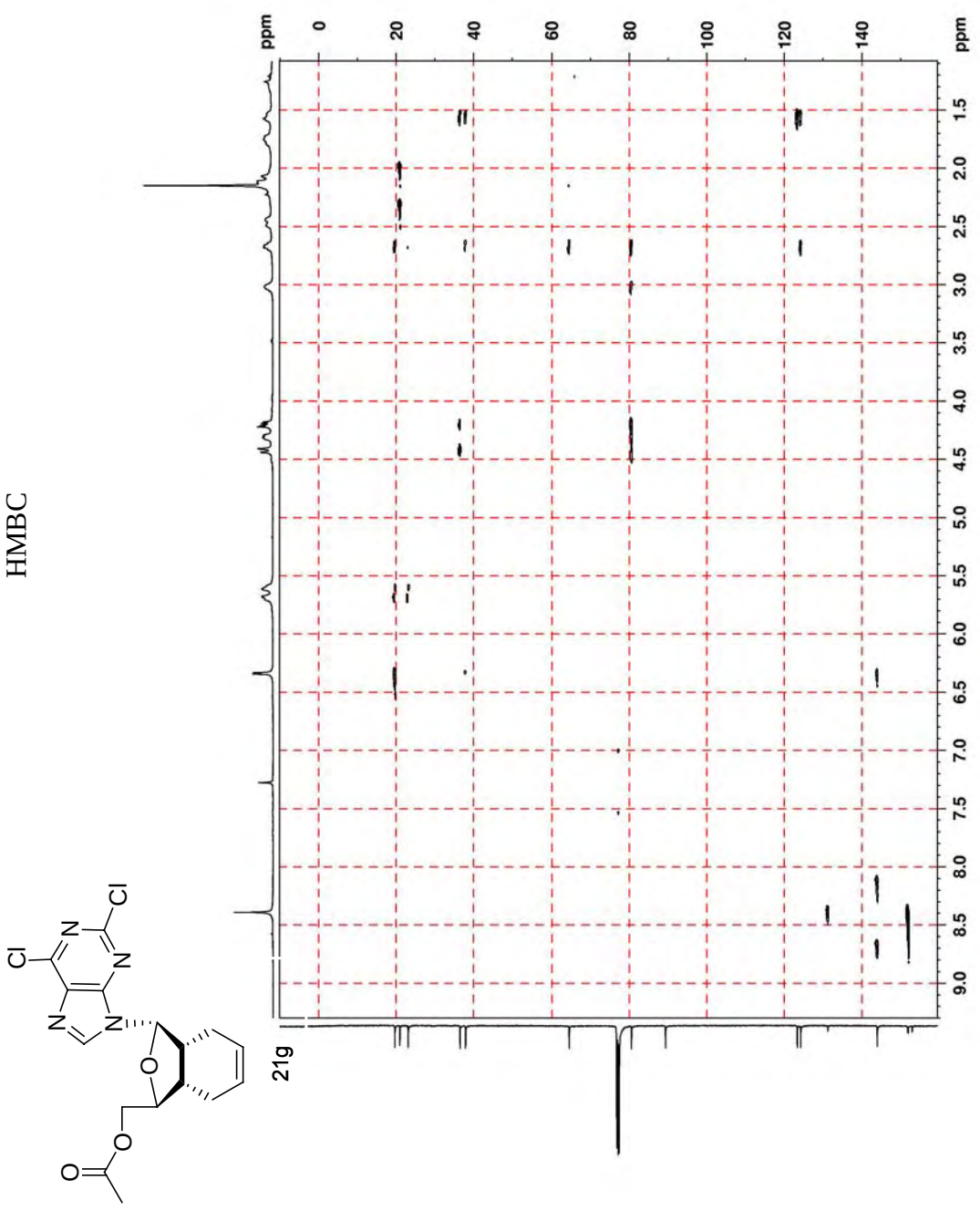
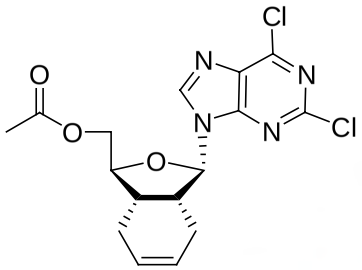
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

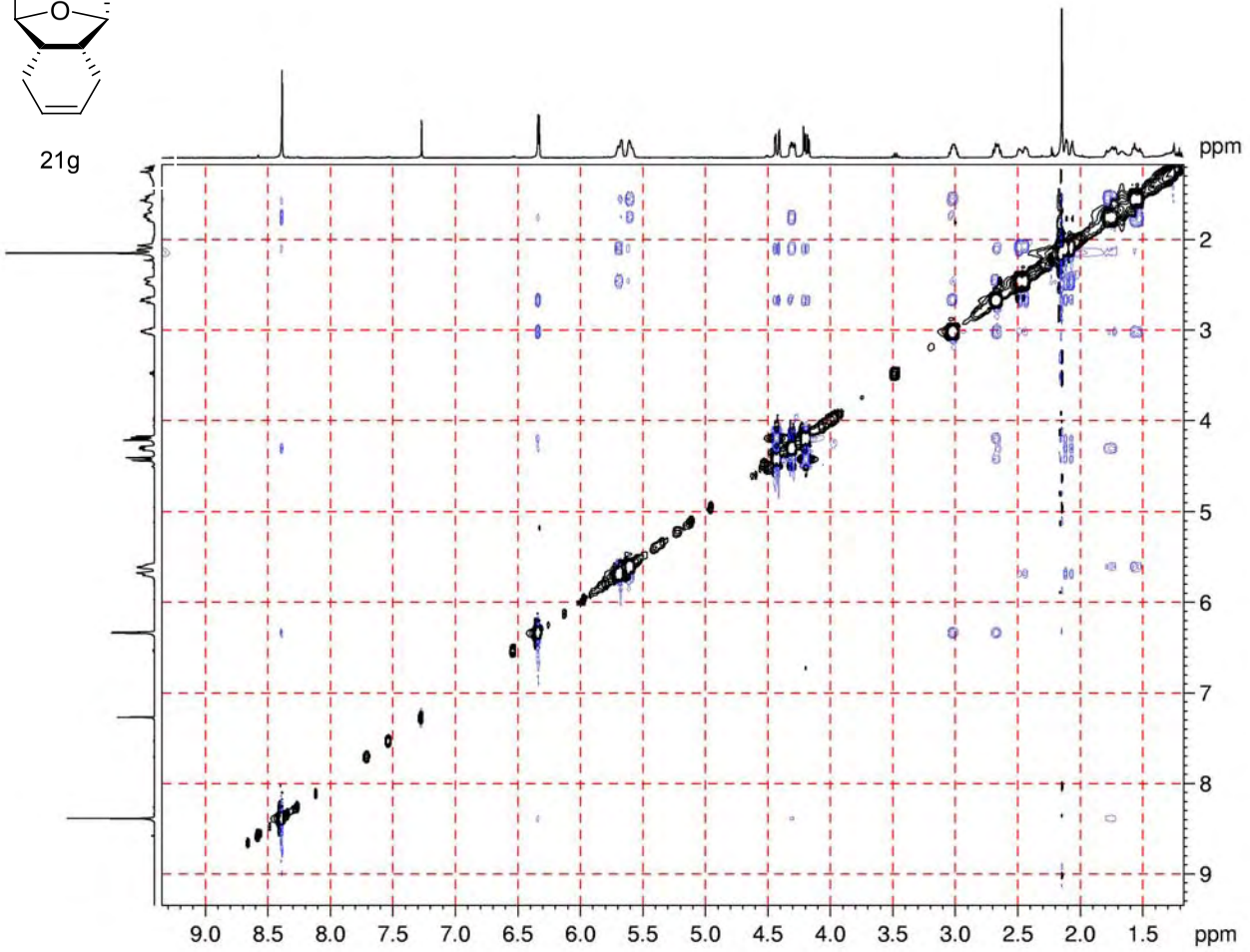
HMBC

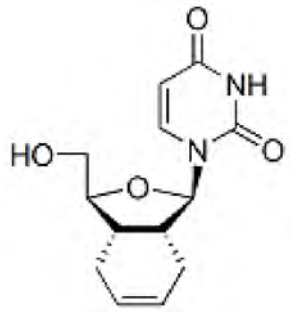

Cl
Cl
N
N
N
N
O
O
O
21g
ppm
0
20
40
60
80
100
120
140
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0


Cl
N
N
N
N
Cl
O
O
O

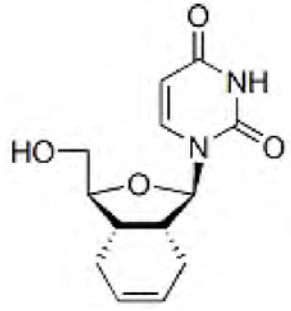
21g

NOESY

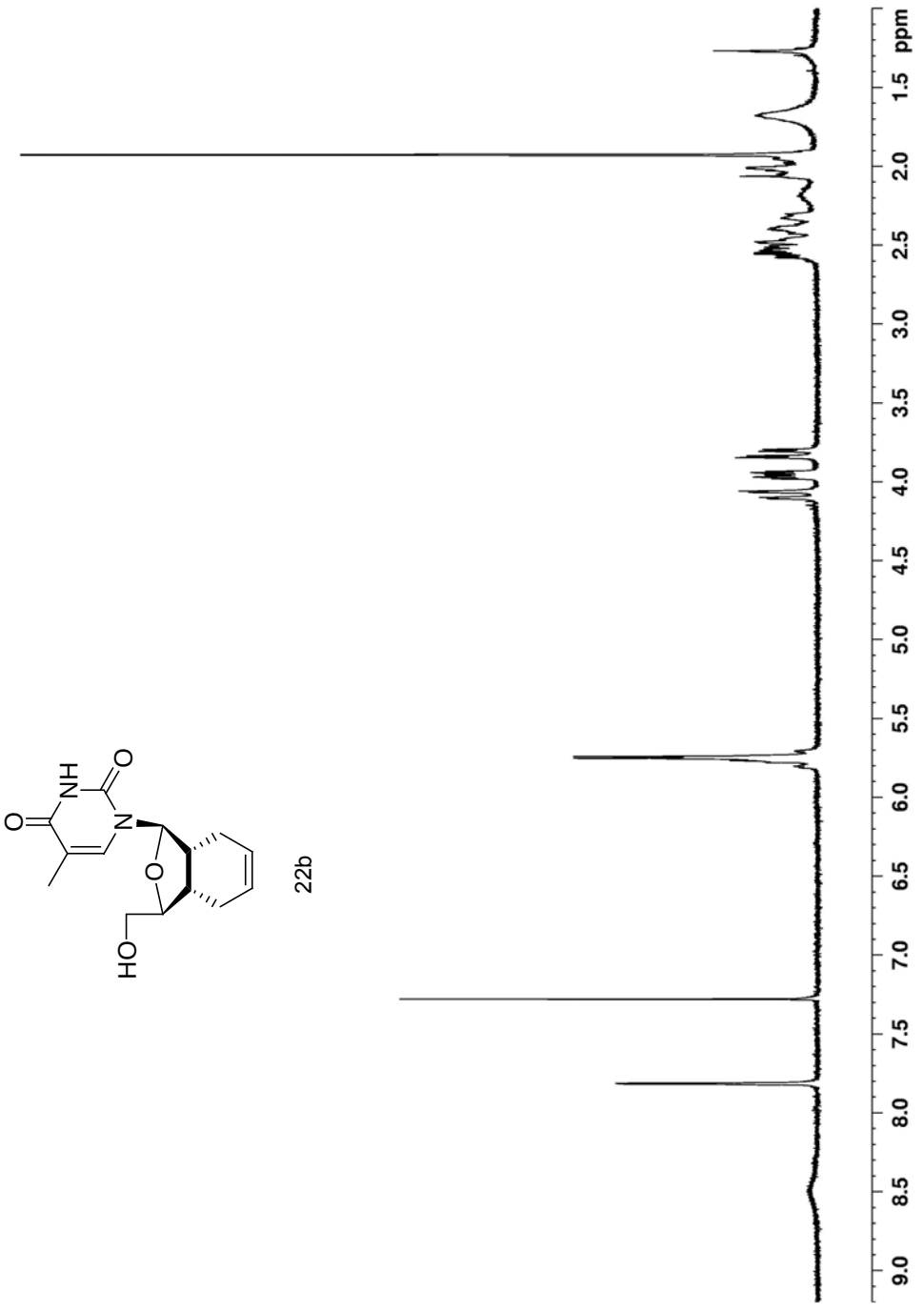

ppm
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

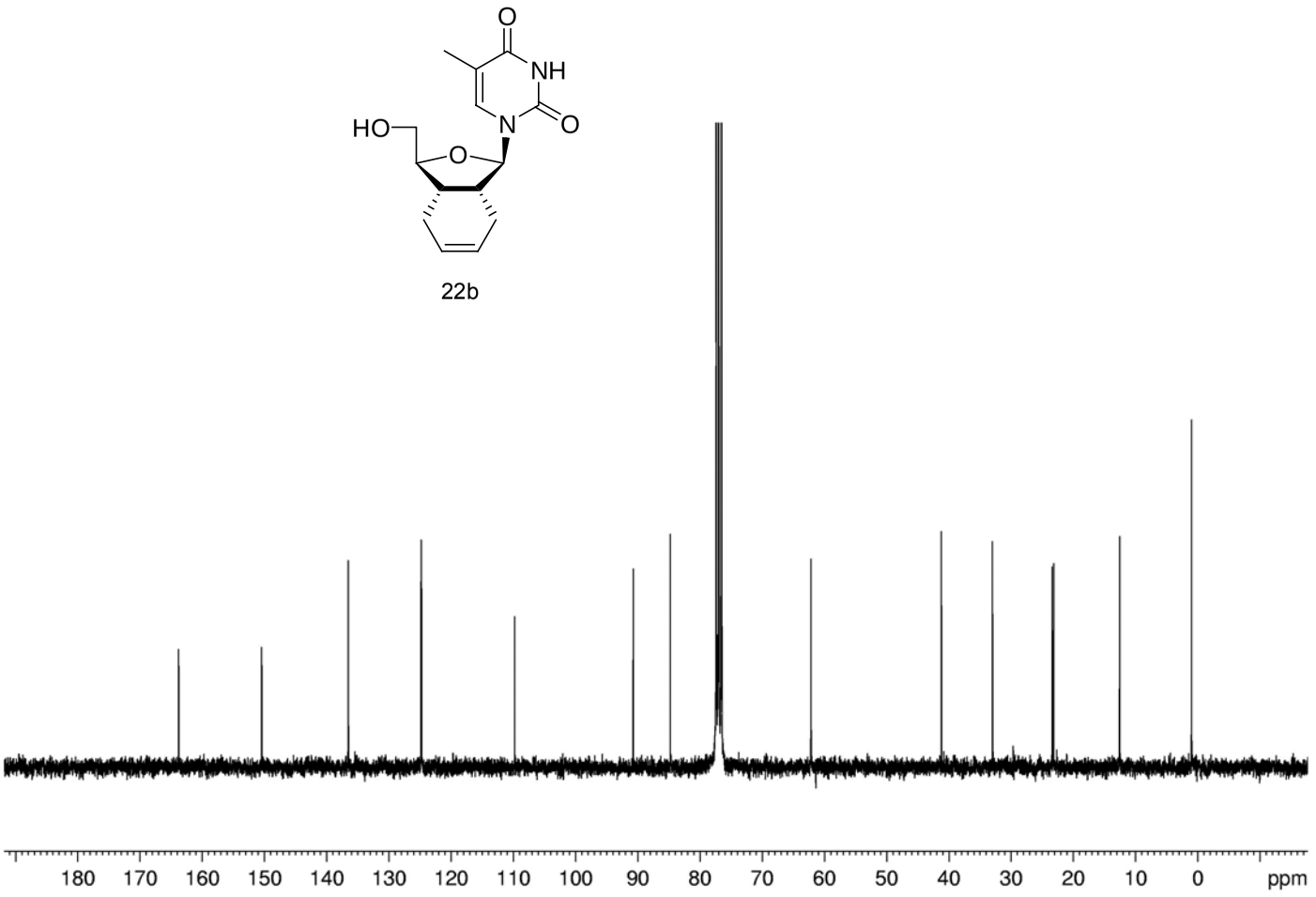


22a

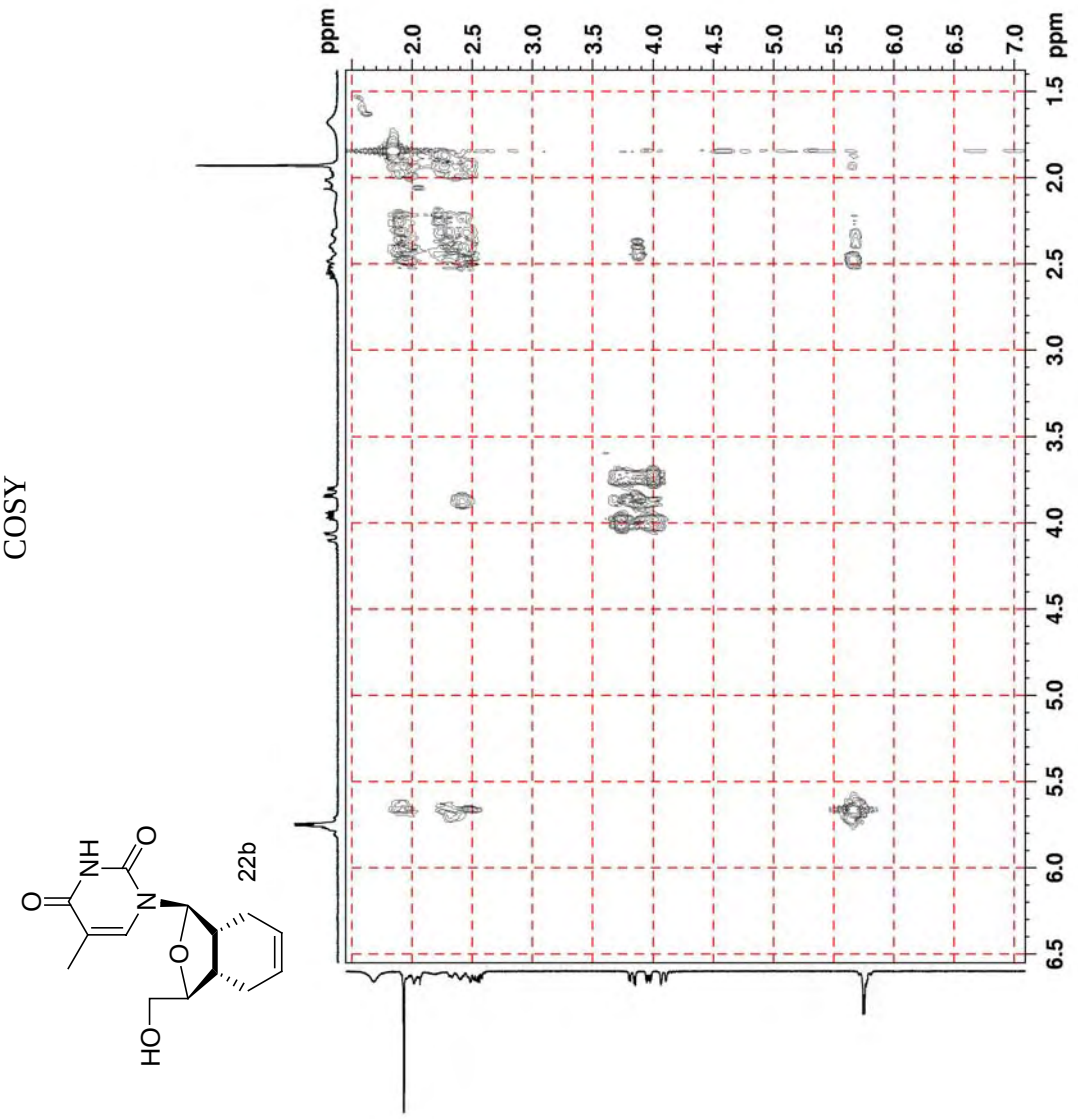


22a

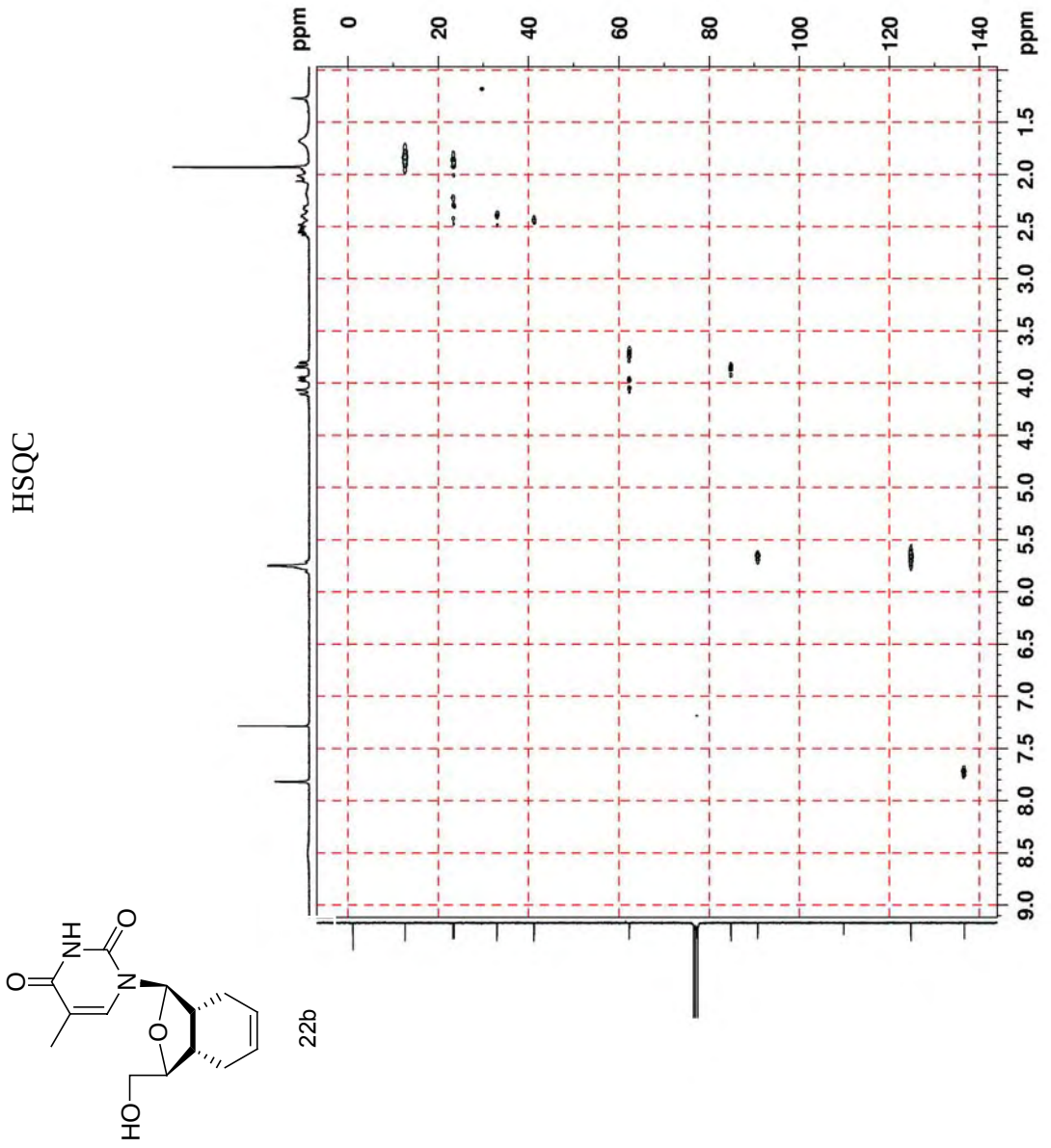

NH
O
O
N
O
HO
22b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


O
NH
HO
N
O
O
22b
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

COSY

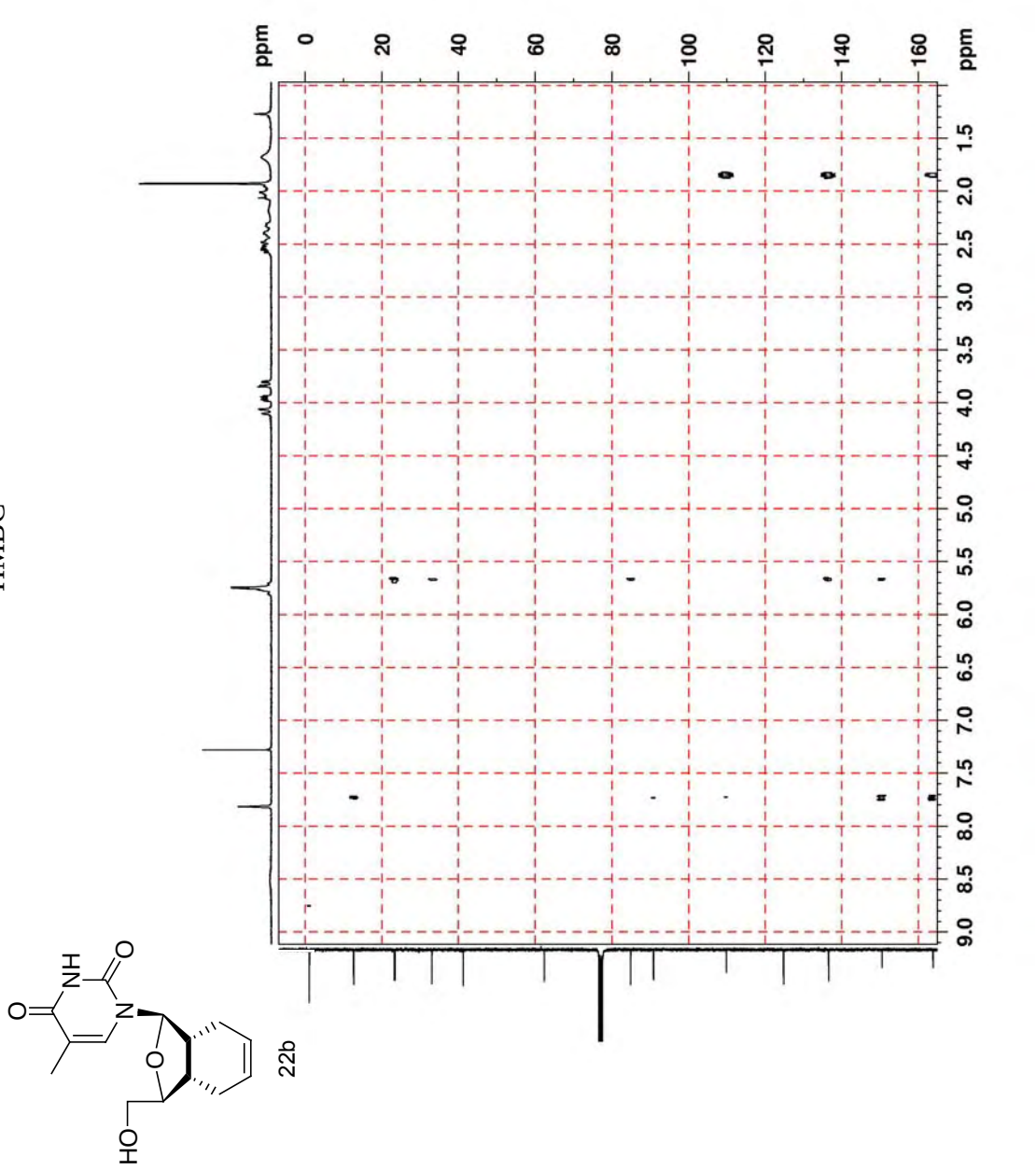

22b
NH
O
O
N
O
HO
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5

HSQC

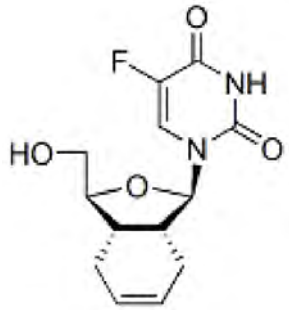

ppm
0
20
40
60
80
100
120
140
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
NH
O
O
N
O
HO

22b

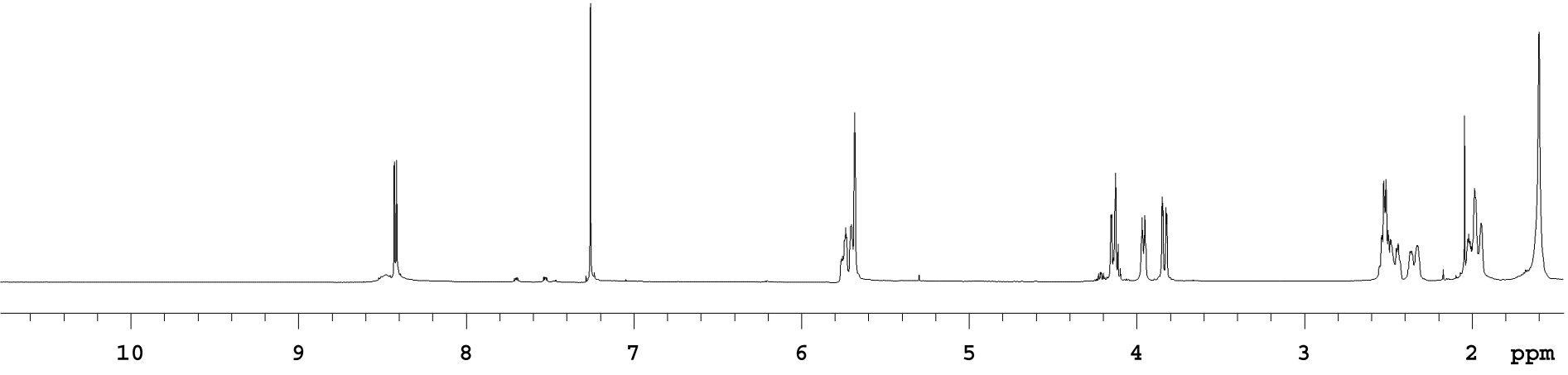
HMBC

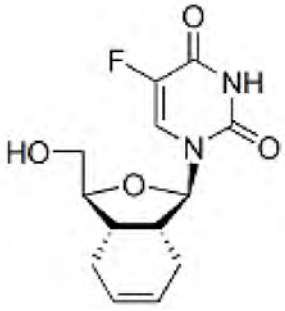

ppm
0
20
40
60
80
100
120
140
160
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
NH
O
O
N
O
HO

22b



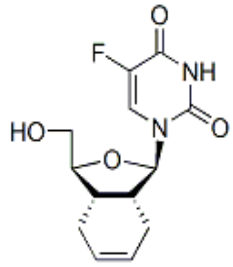
22c



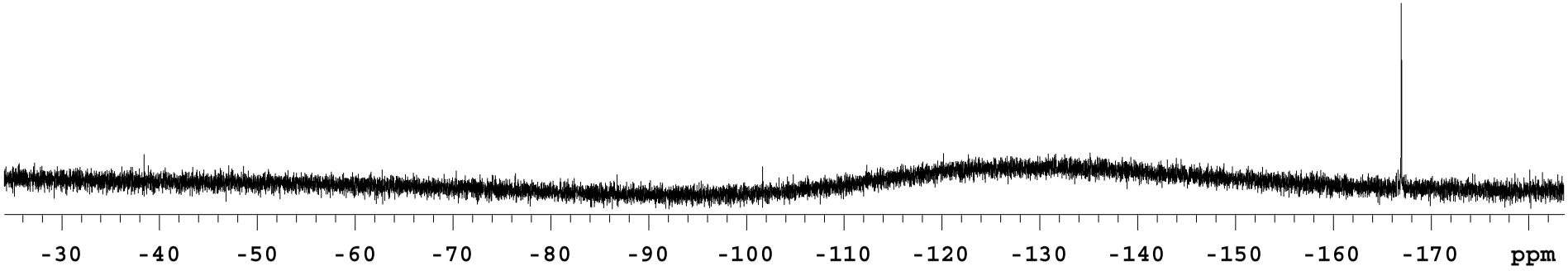


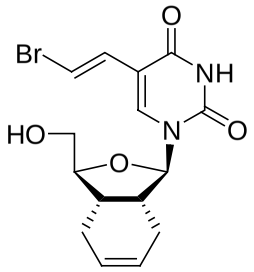
22c

160 140 120 100 80 60 40 20 ppm

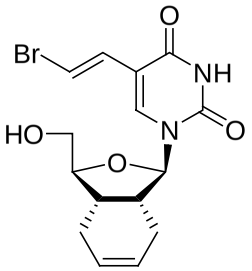

O
F
NH
HO
N
O
O

22c

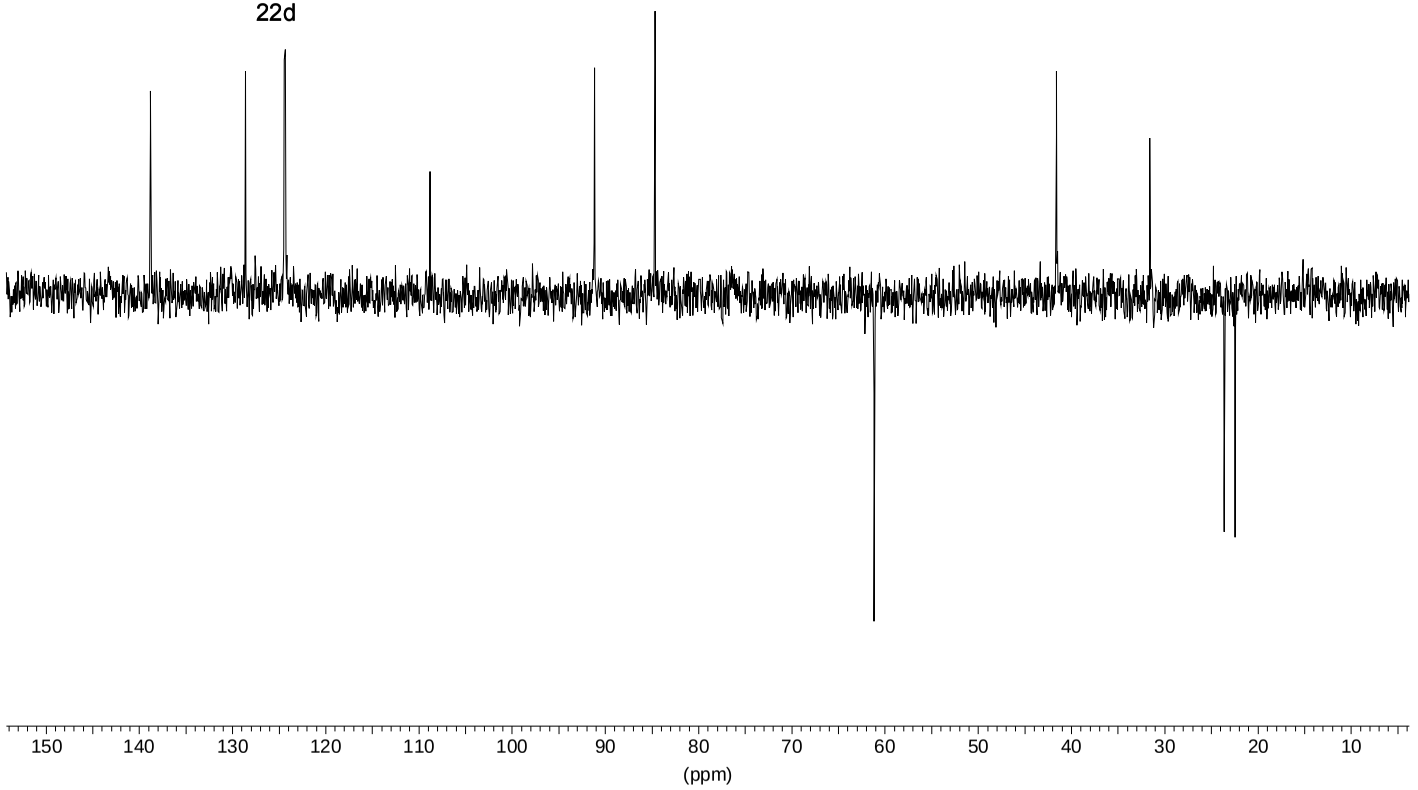

-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
ppm

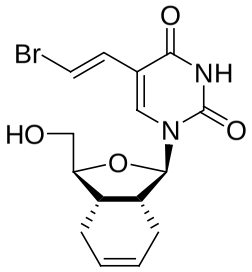


22d

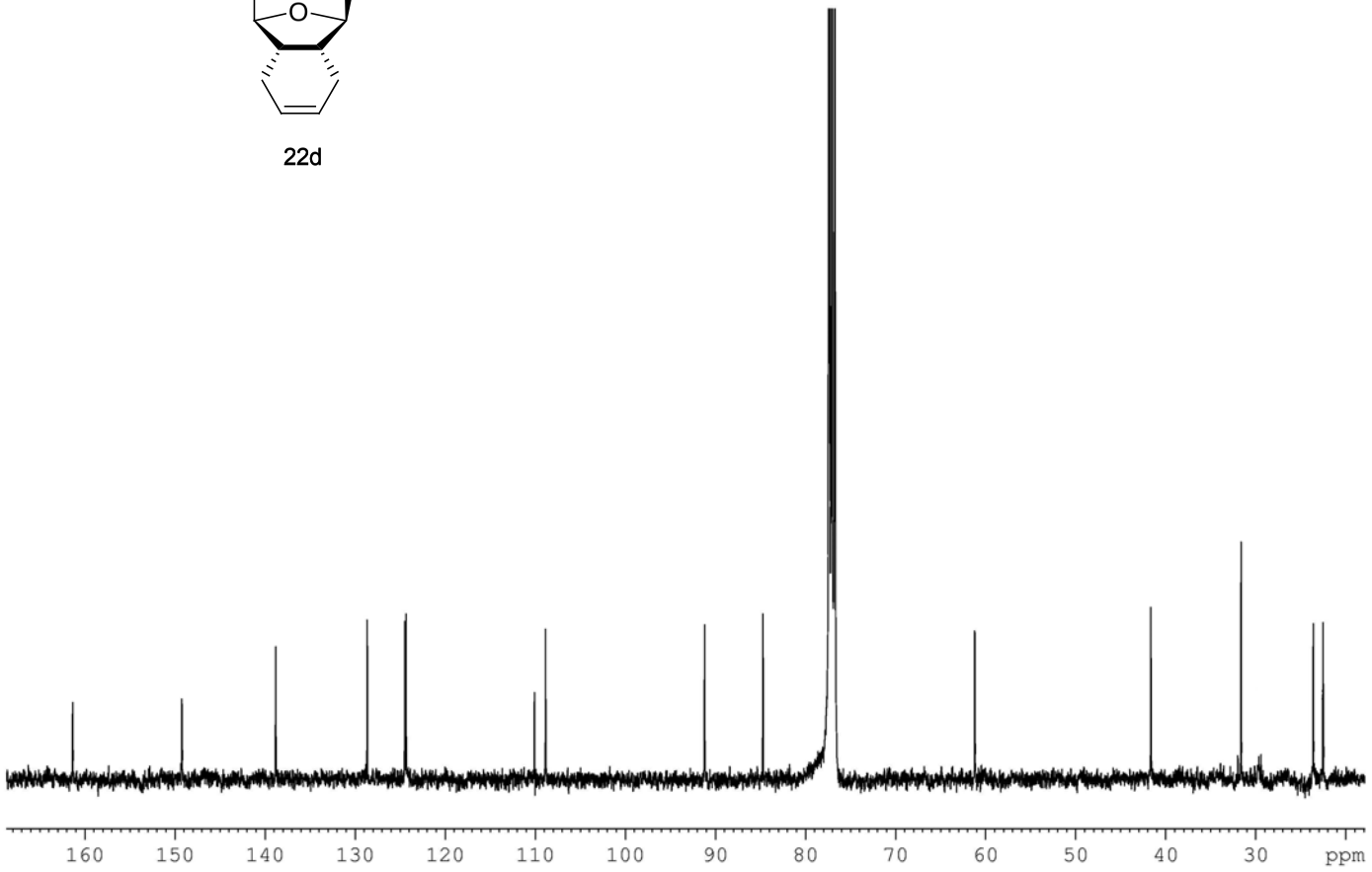


22d

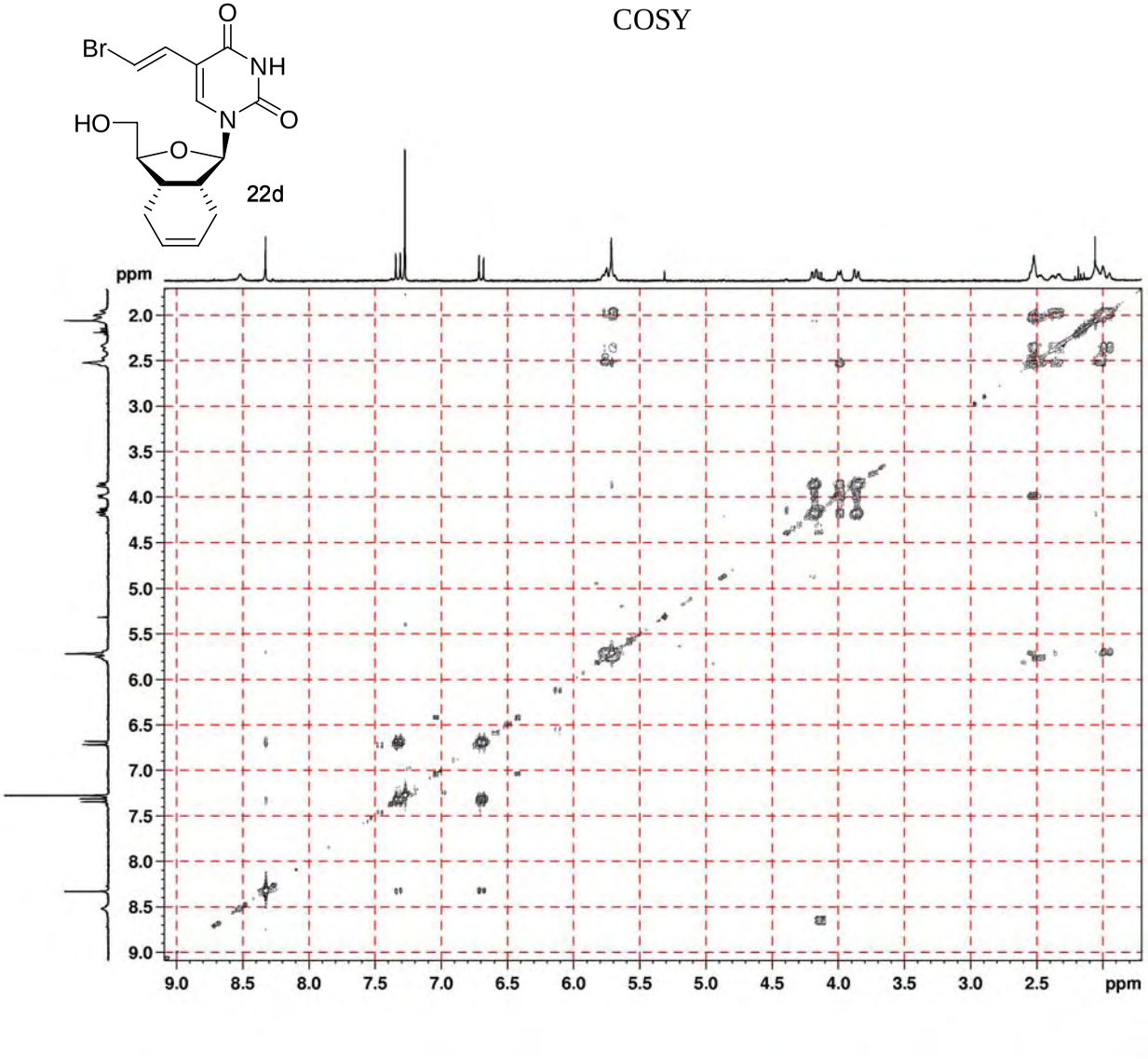




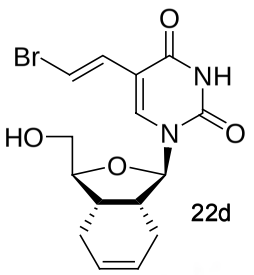
22d



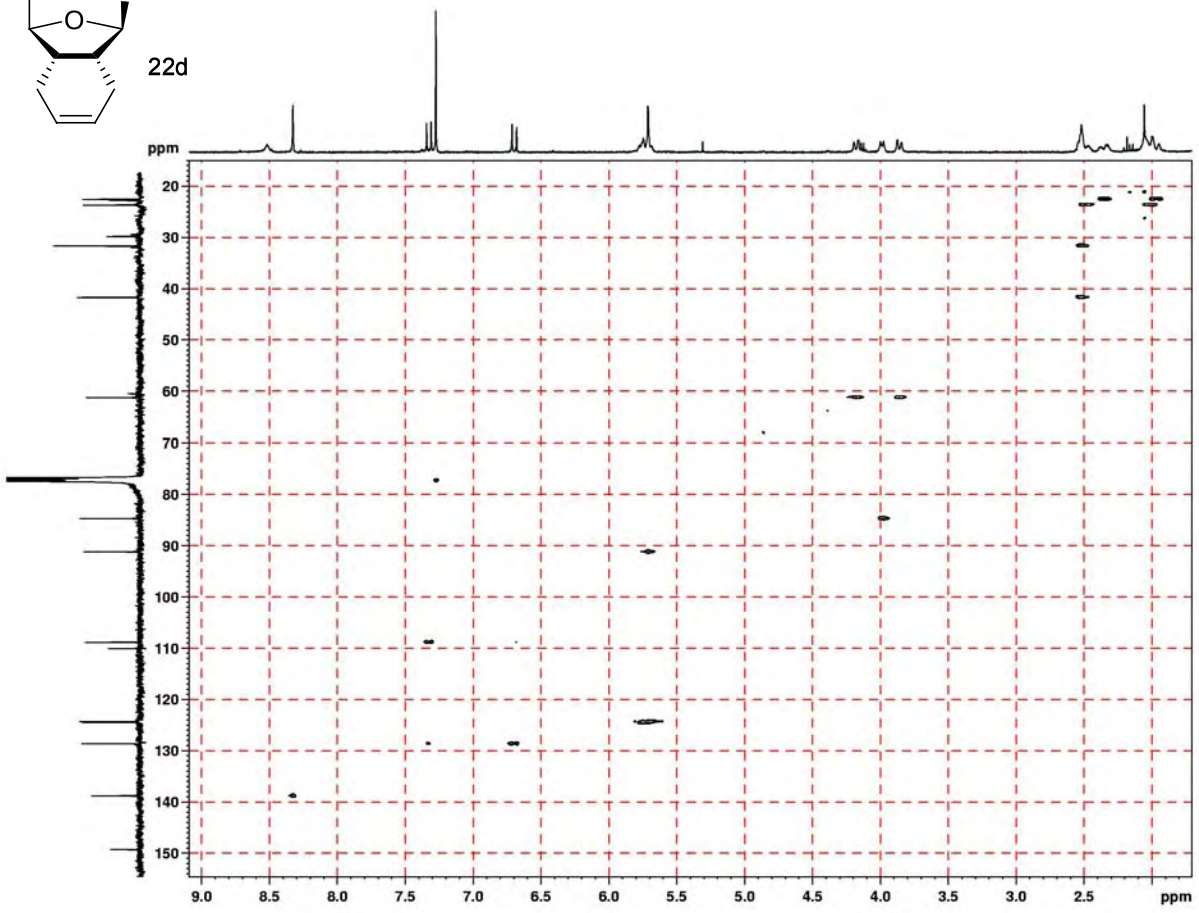
COSY


Br
O
NH
N
O
HO
O
22d
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

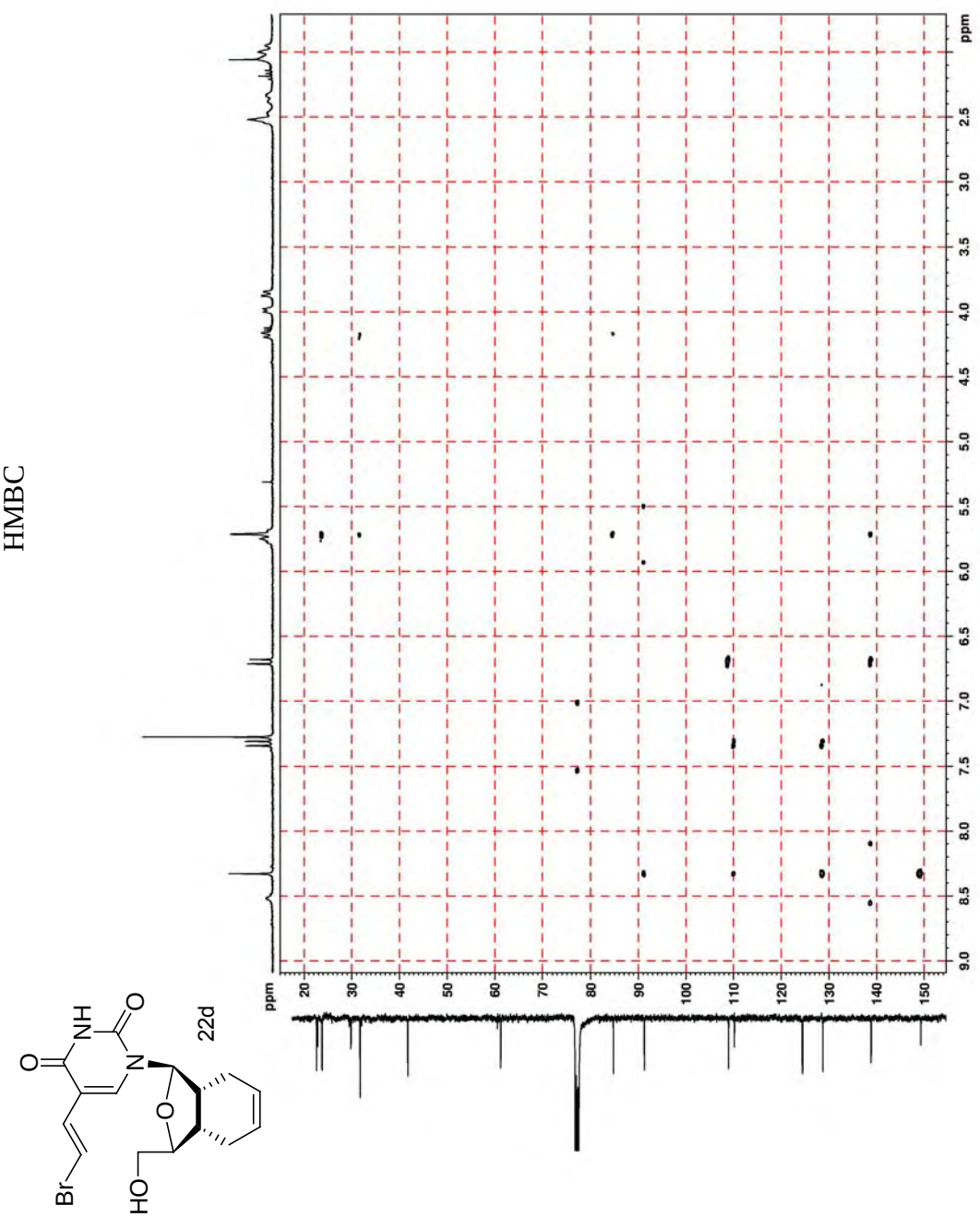
HSQC

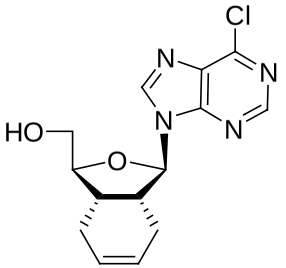

Br
O
NH
N
O
HO
O

22d

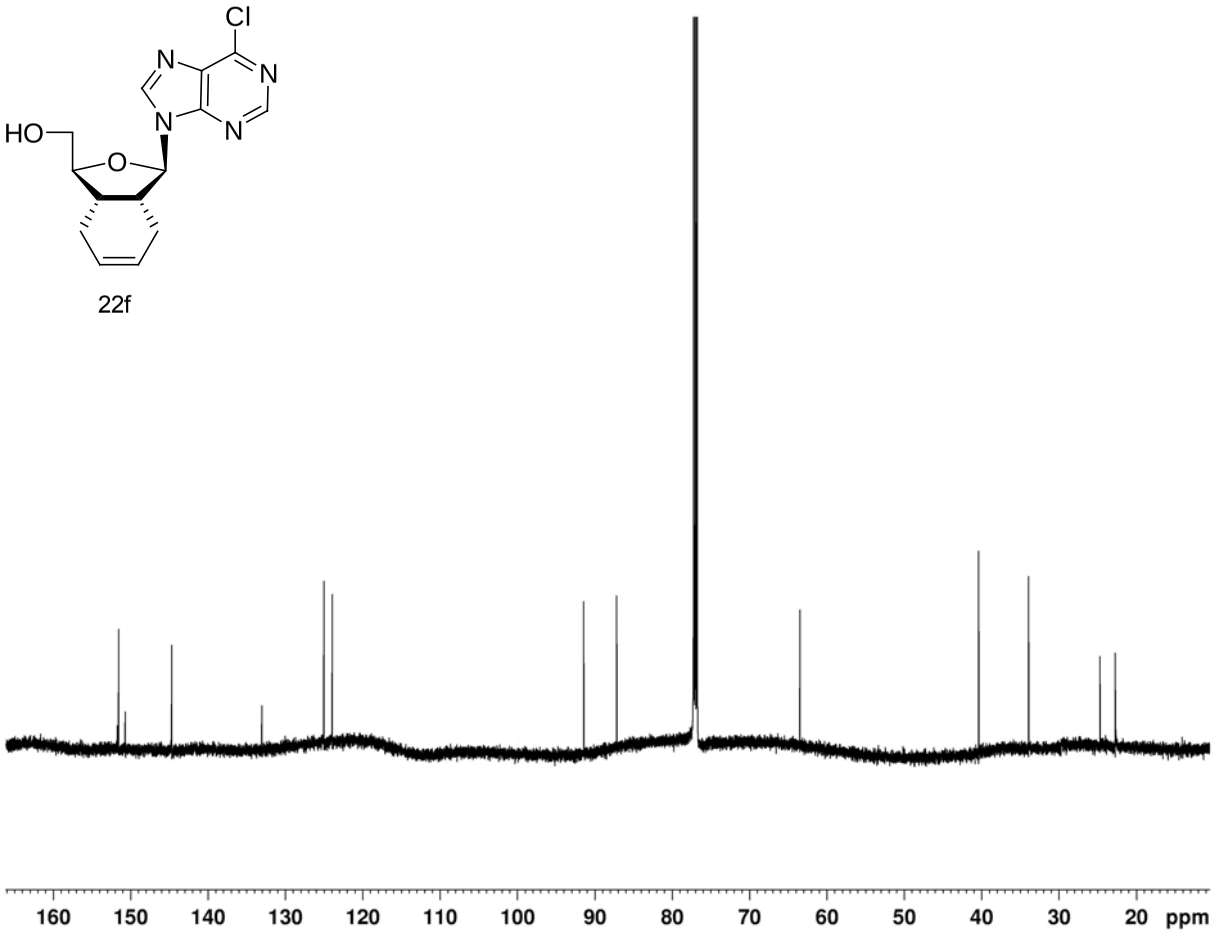

ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

HMBC

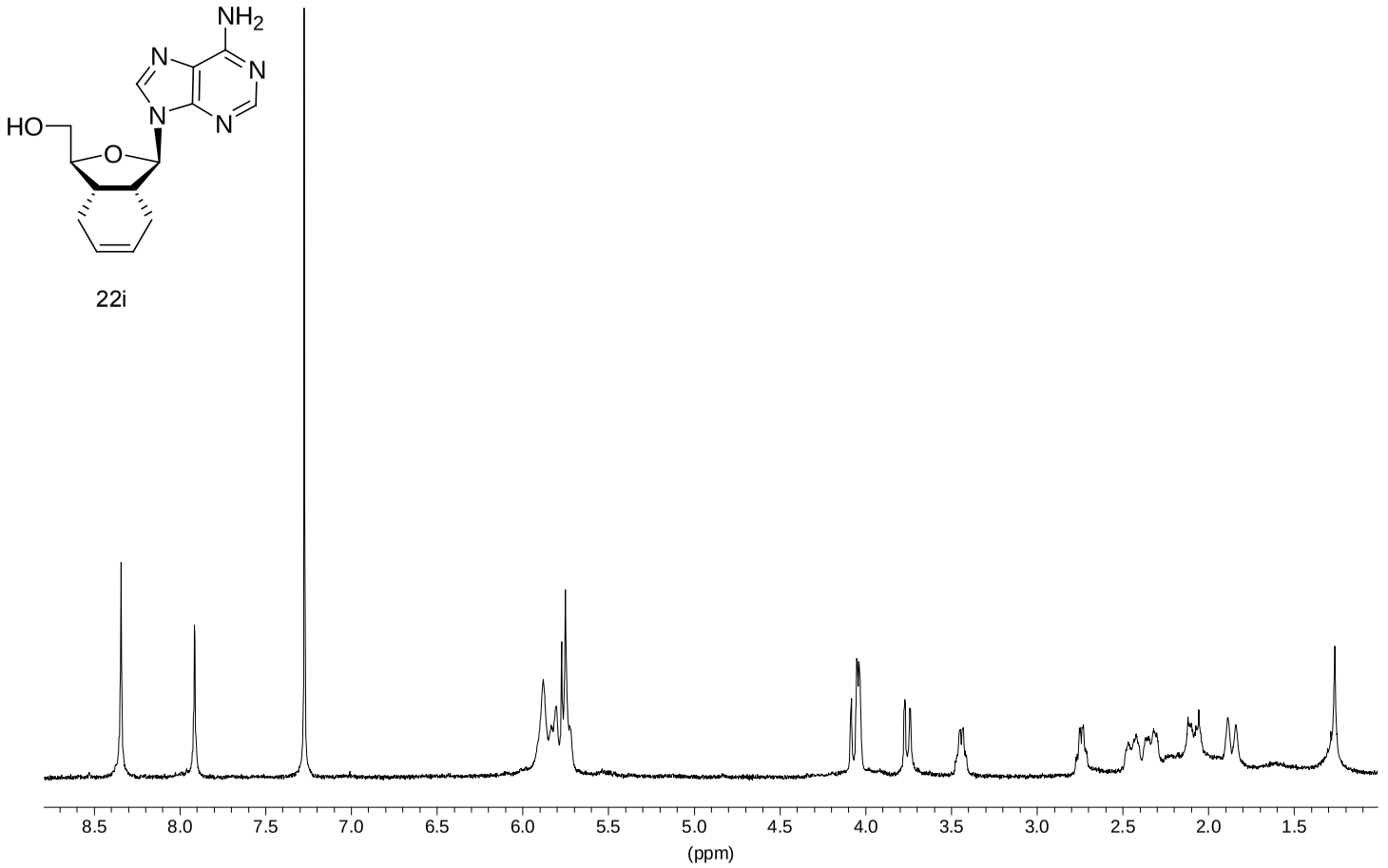


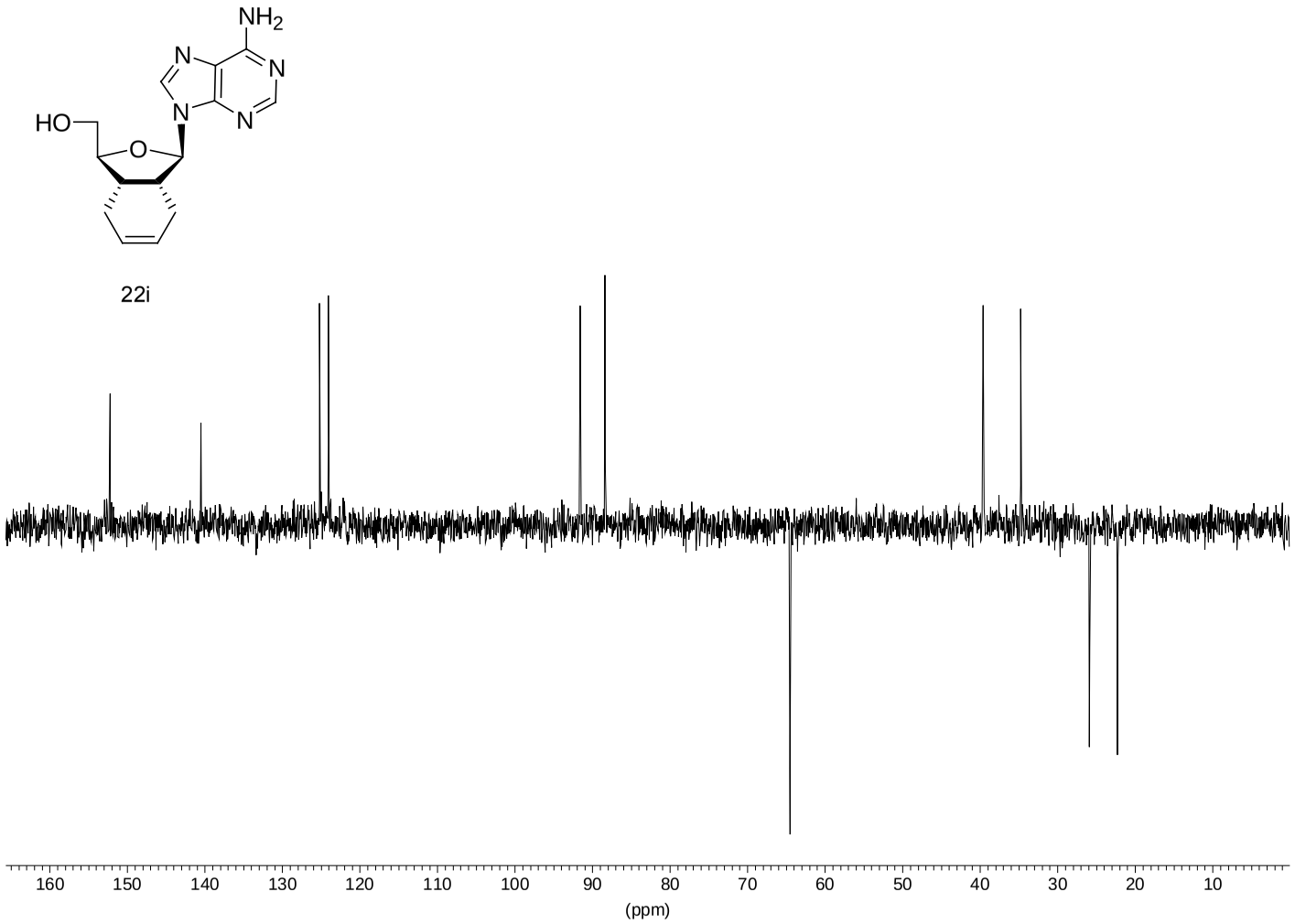


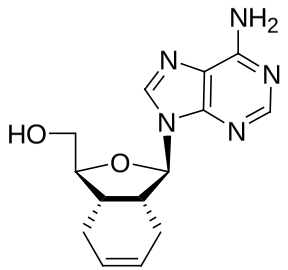
22f



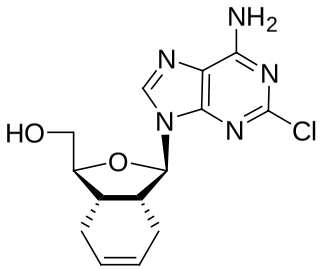
22f


NH2
N
N
N
N
HO
O
22i
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

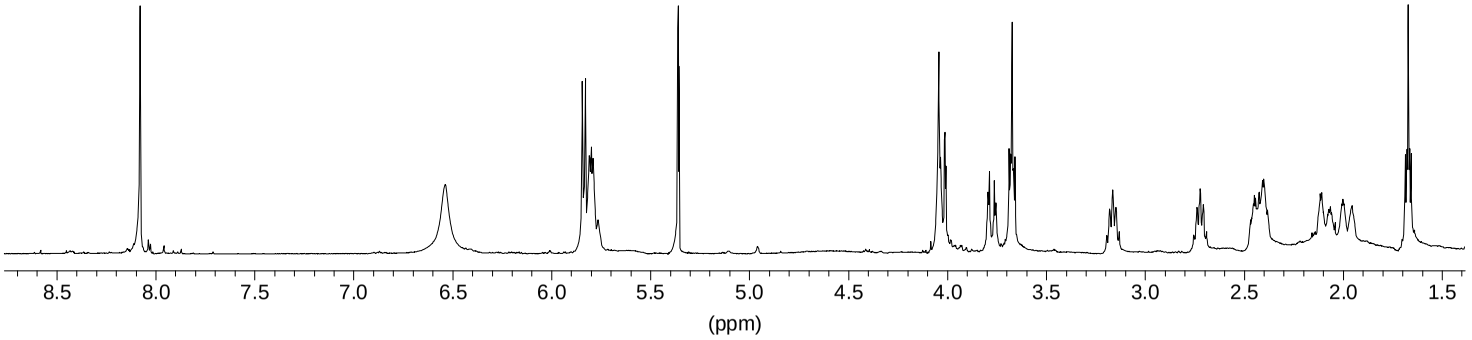

NH2
N
N
N
N
HO
O
22i
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

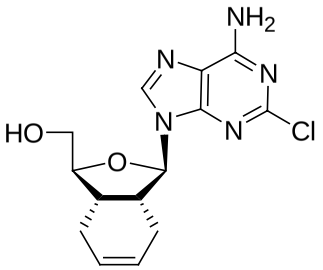


22i

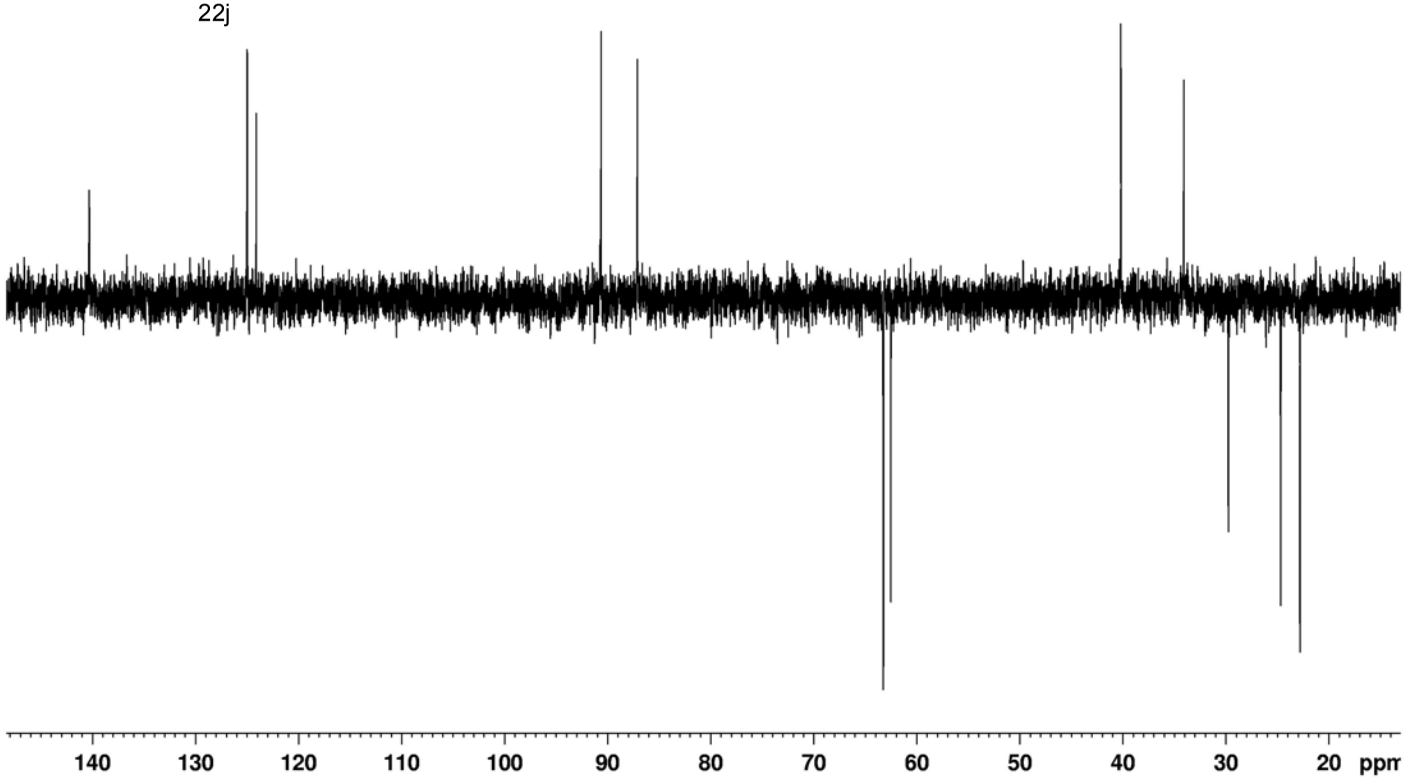


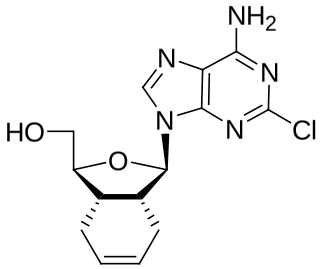
22j





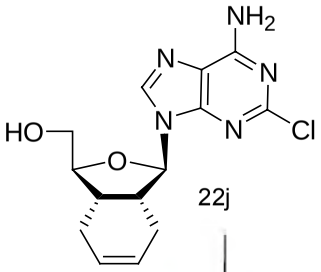
22j




NH2
N
N
N
N
Cl
HO
O

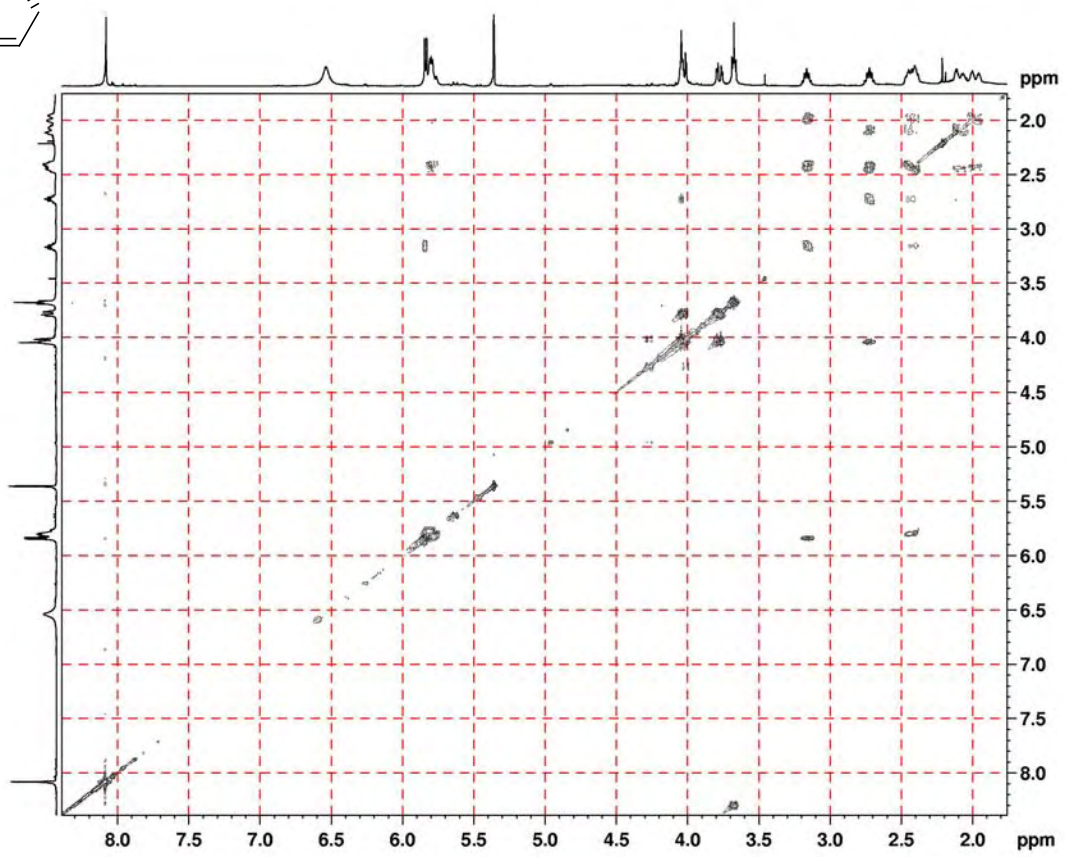
22j

160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

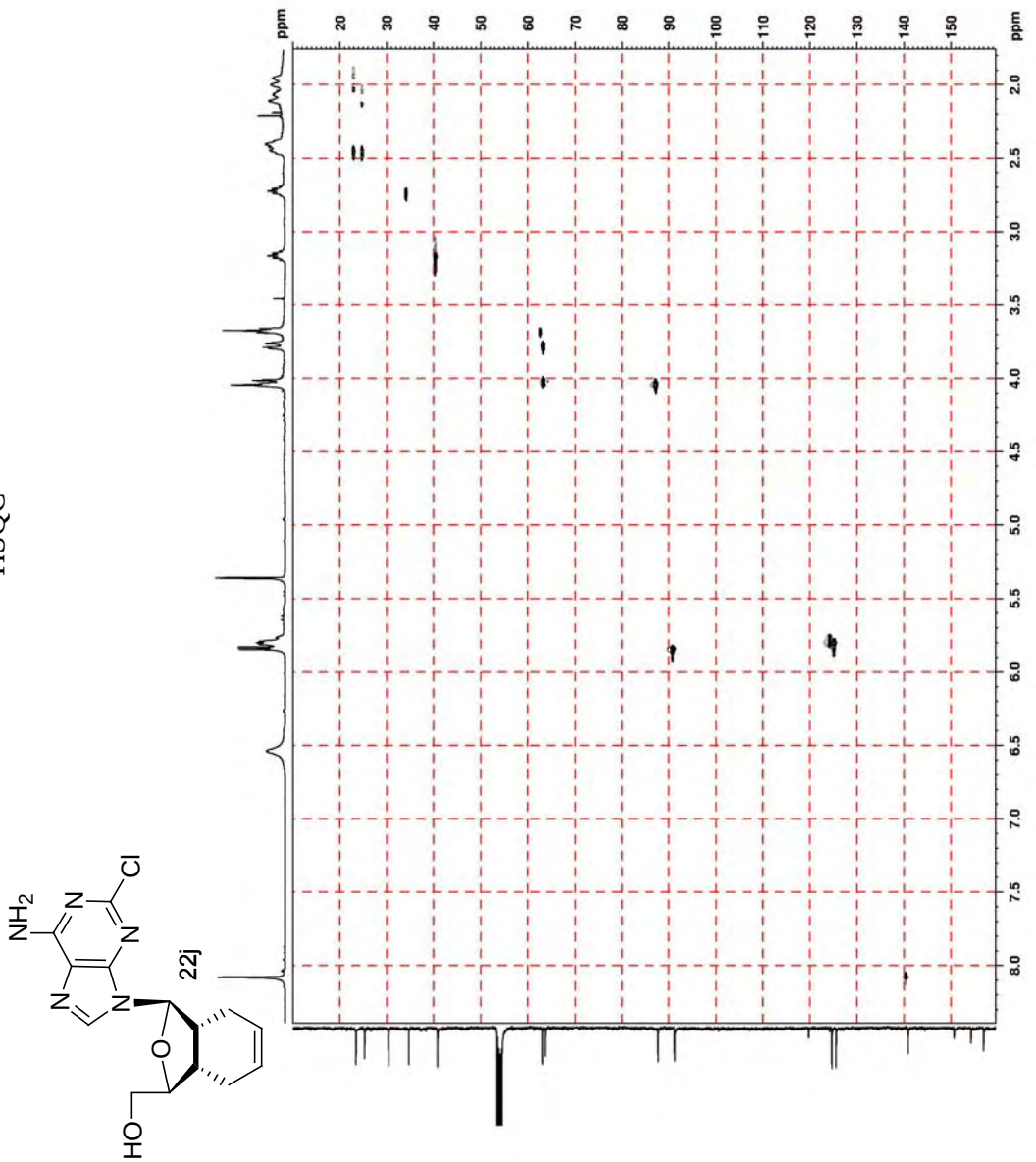

NH2
N
N
N
N
Cl
HO
O

22j

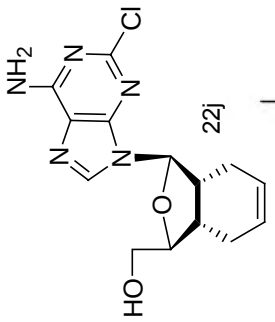
COSY


ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

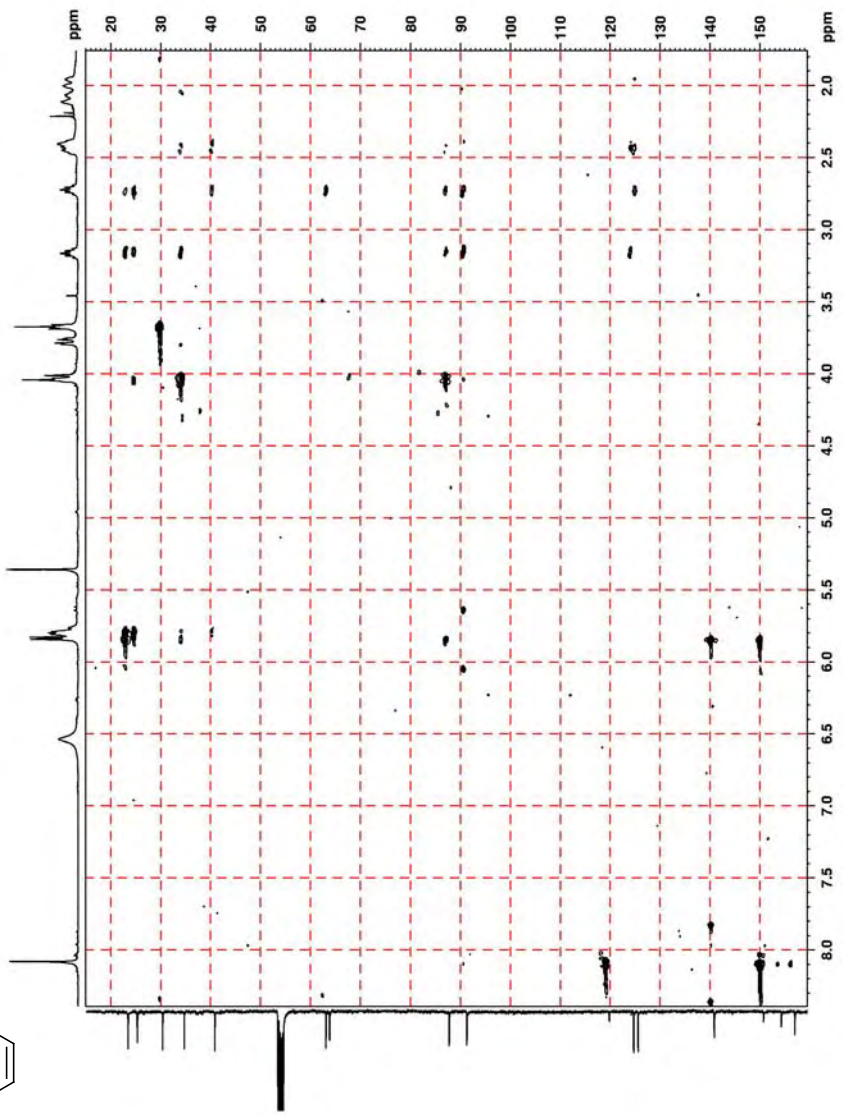
HSQC


NH2
N
Cl
N
N
N
O
HO
22j
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0

HMBC


NH2
N
Cl
N
N
N
O
HO

22j


ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm
2.0
2.5
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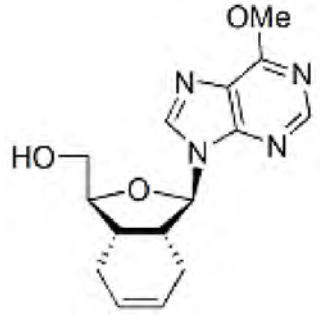
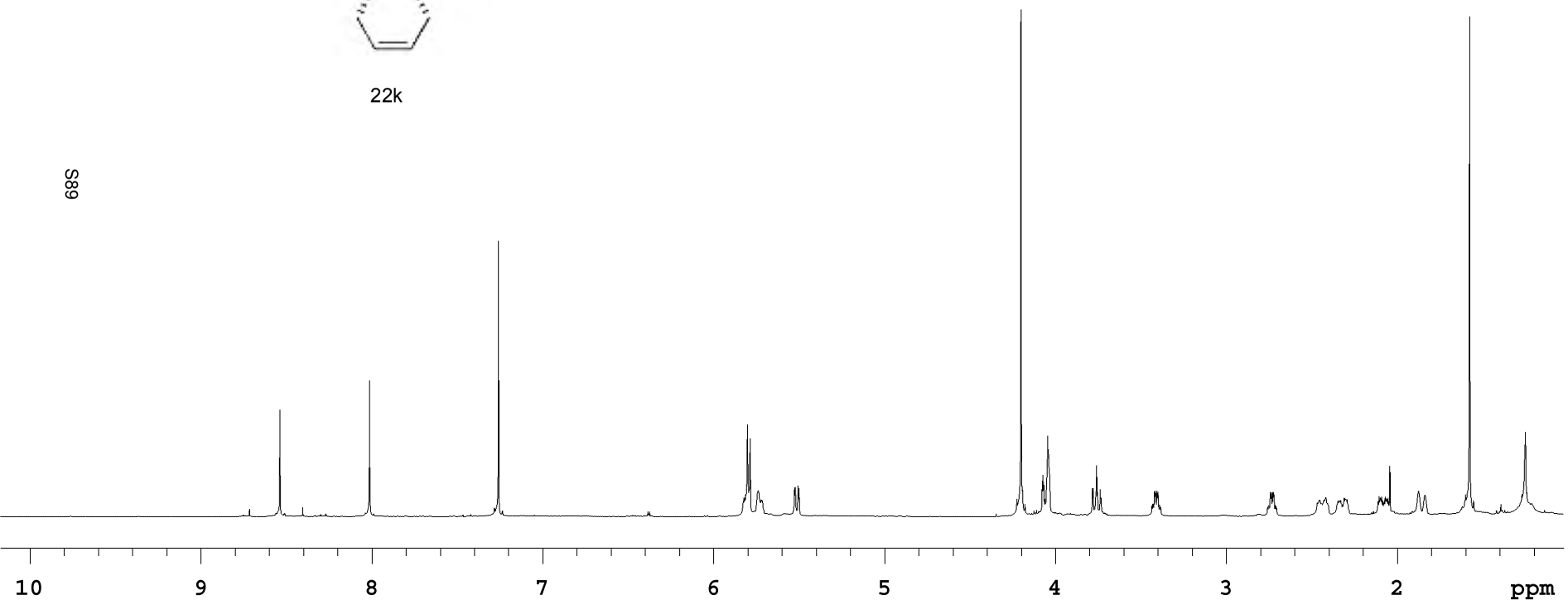
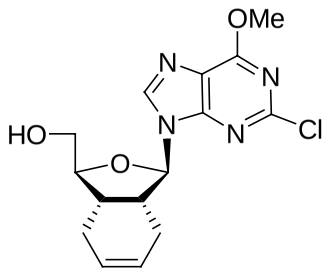
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0



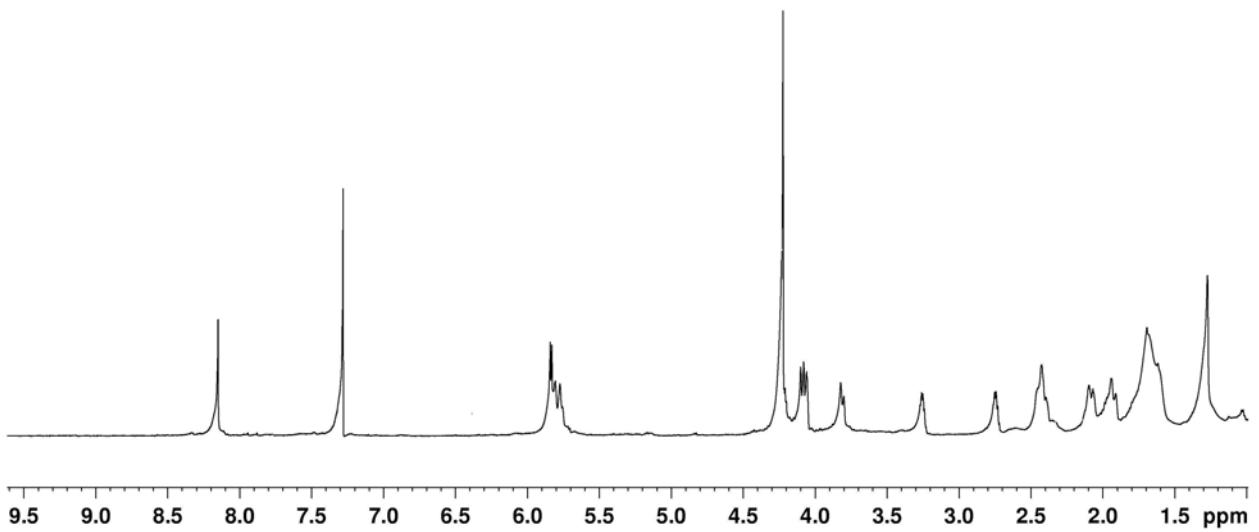
22k

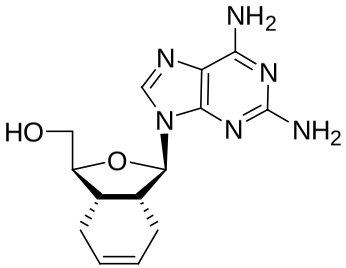
S89



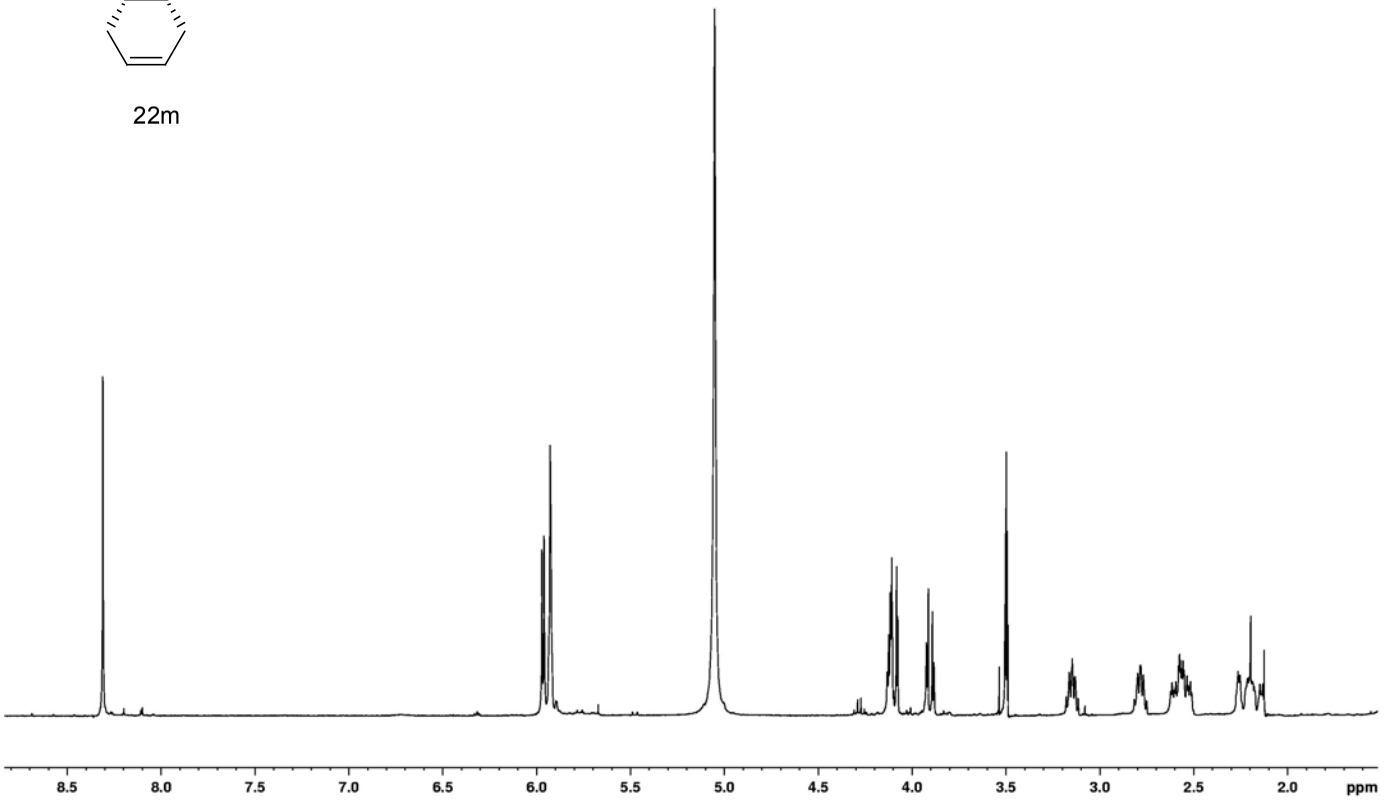


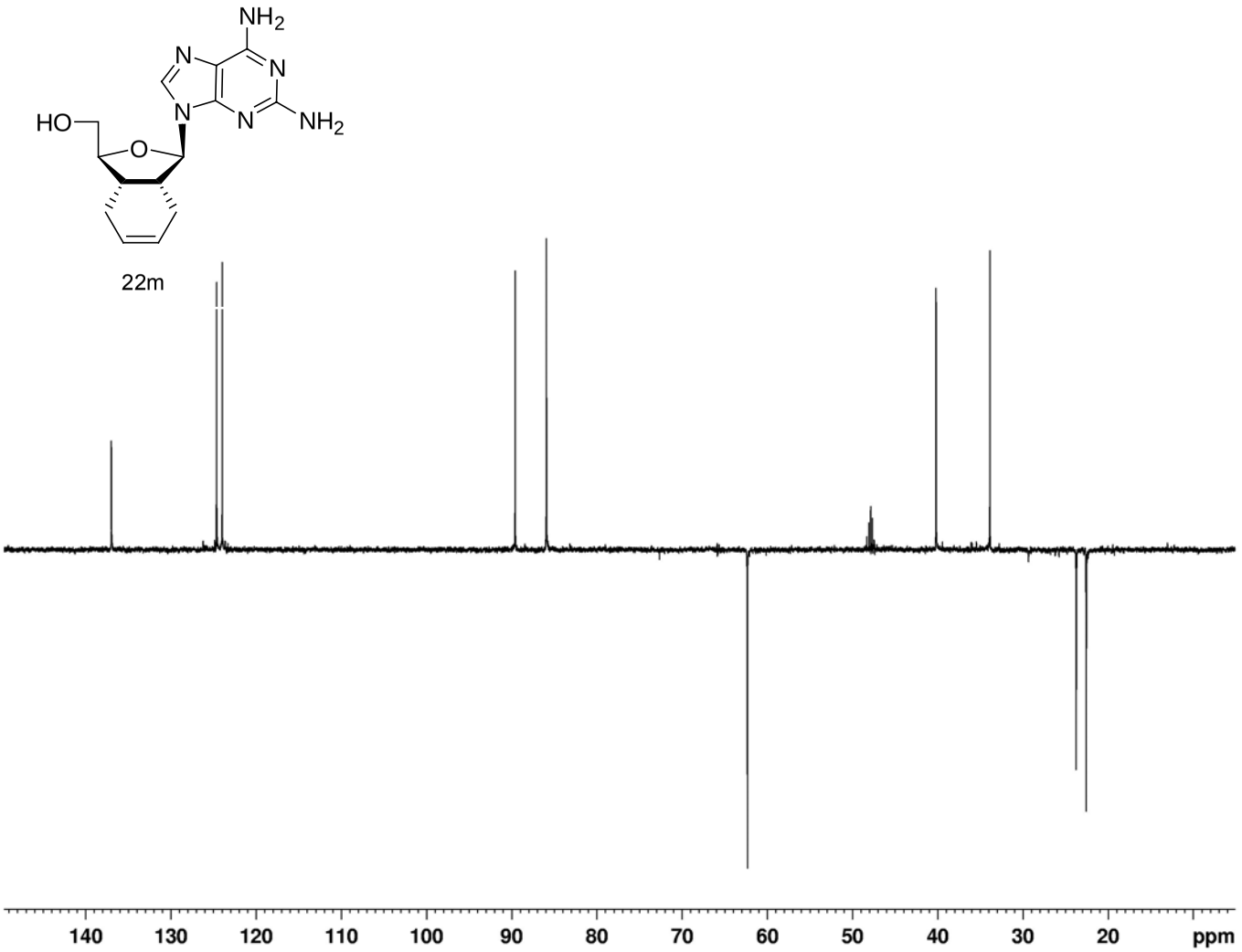
22l

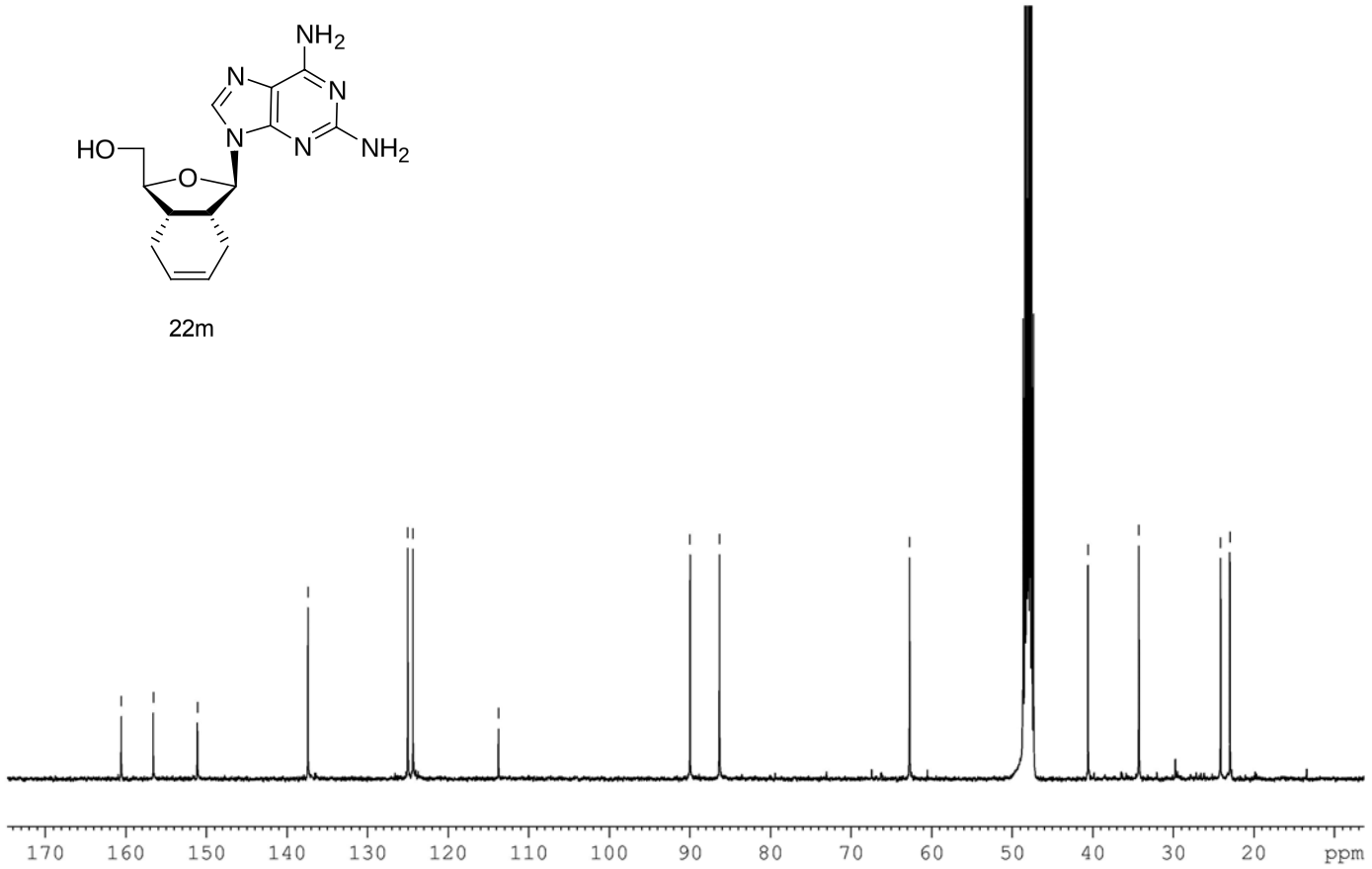


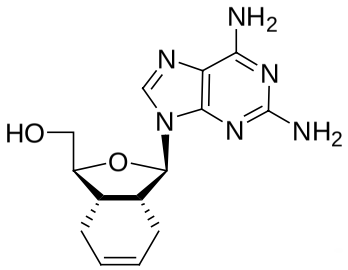


22m



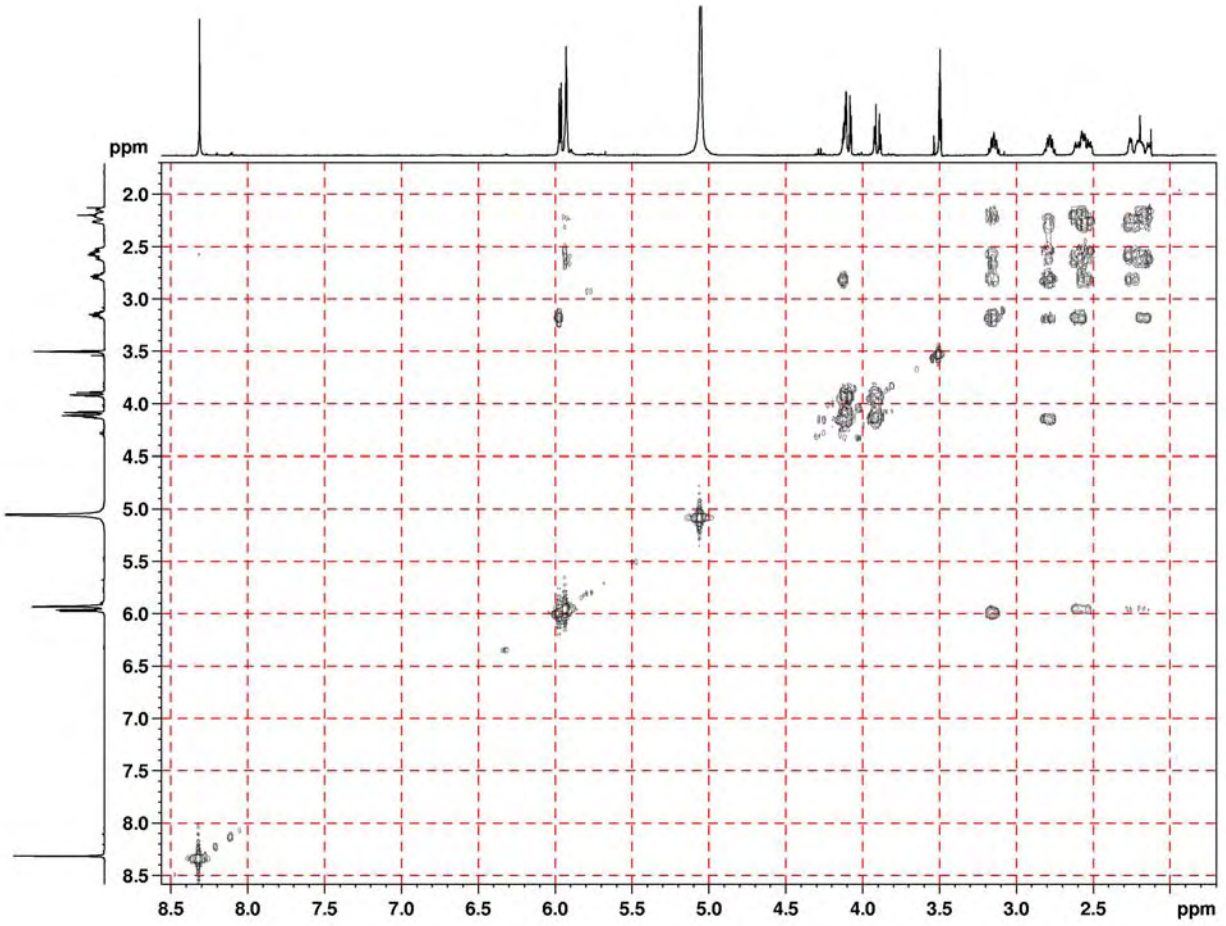

NH2
N
N
N
N
NH2
HO
O
22m
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

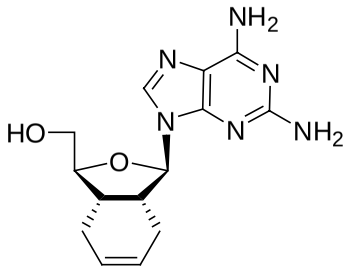

NH2
N
N
N
N
NH2
HO
O
22m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


NH2
N
N
N
N
NH2
HO
O

22m

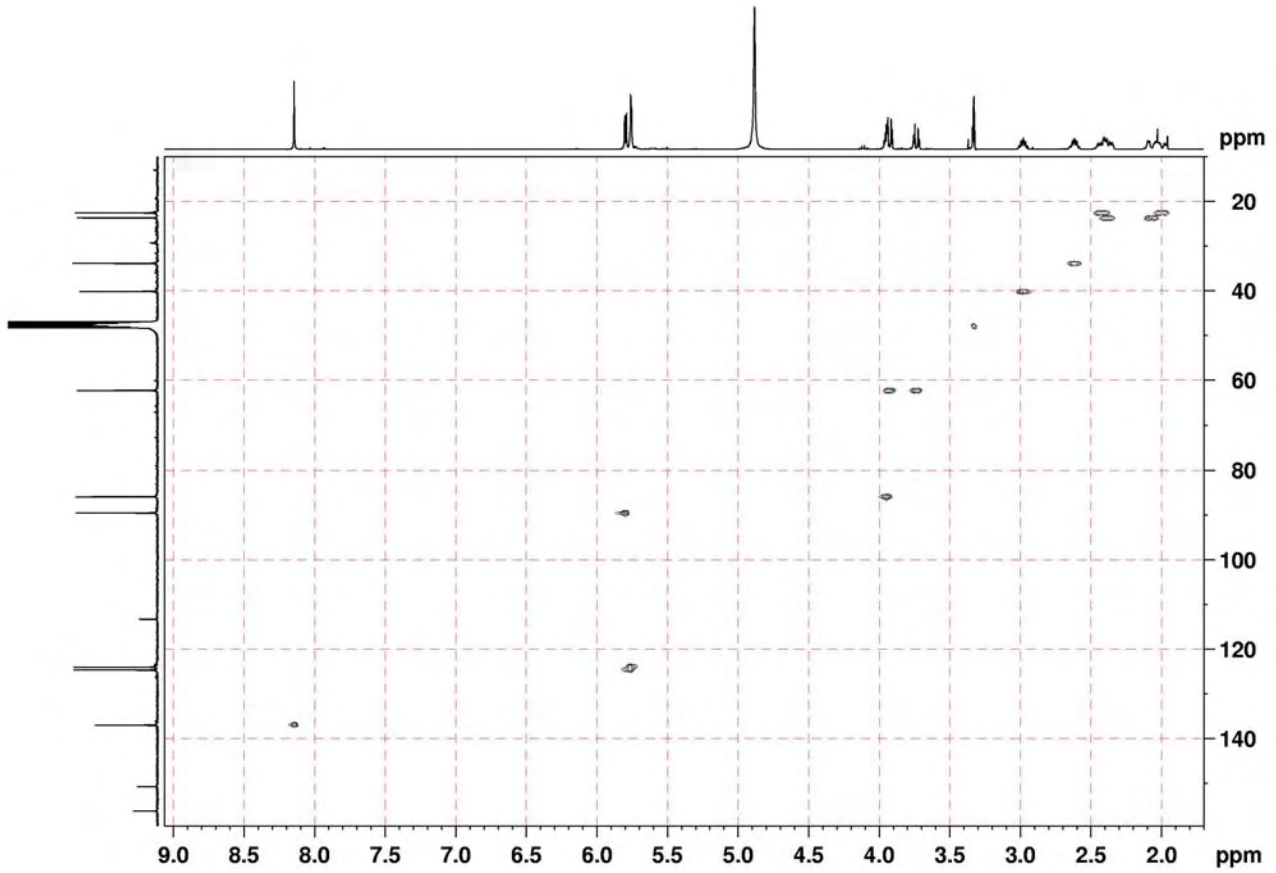
COSY


ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

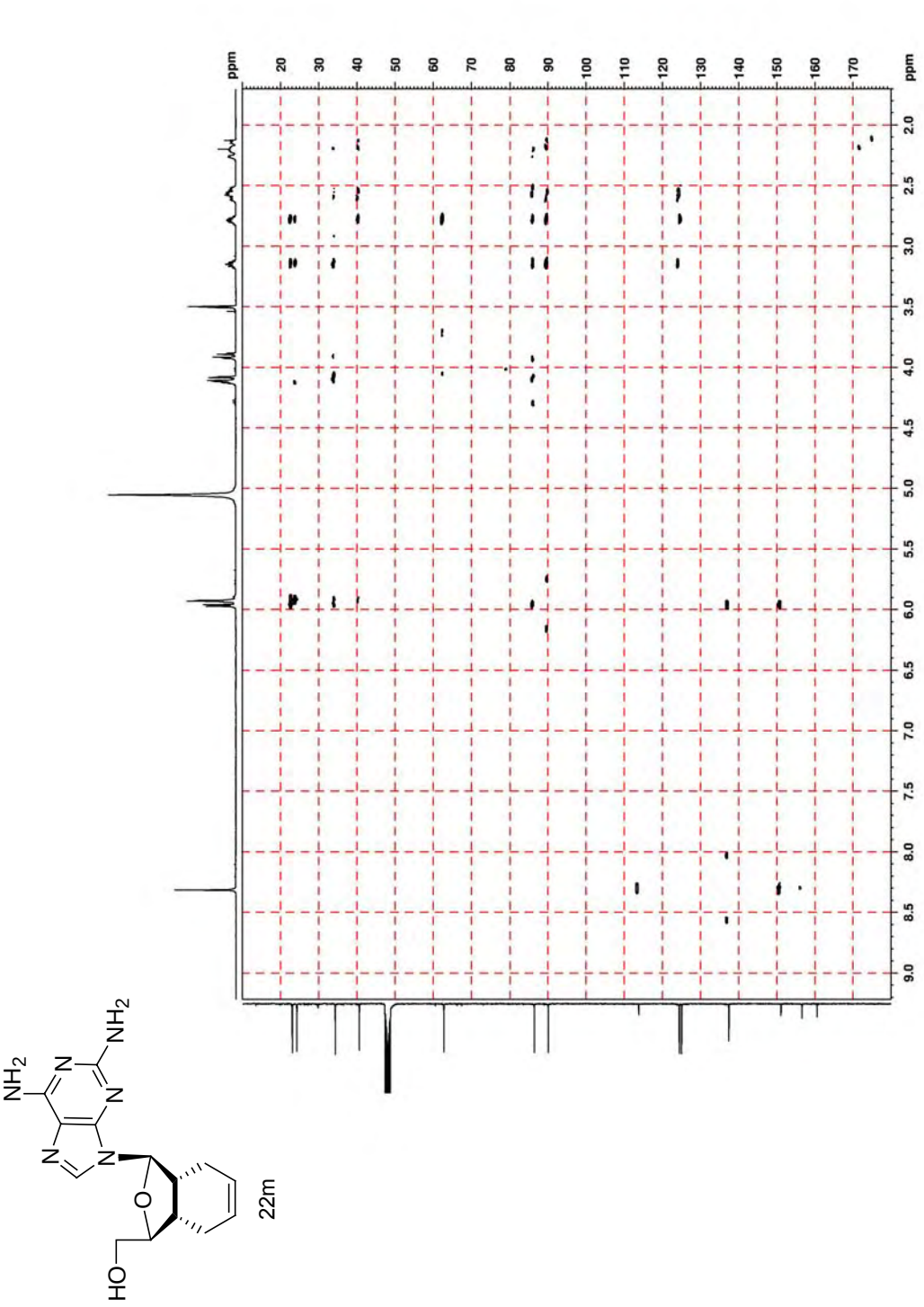

NH2
N
N
N
N
NH2
HO
O

22m

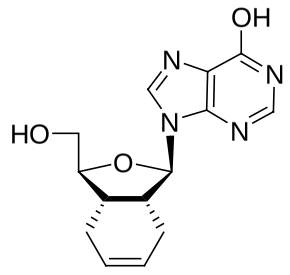
HSQC


ppm
20
40
60
80
100
120
140
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

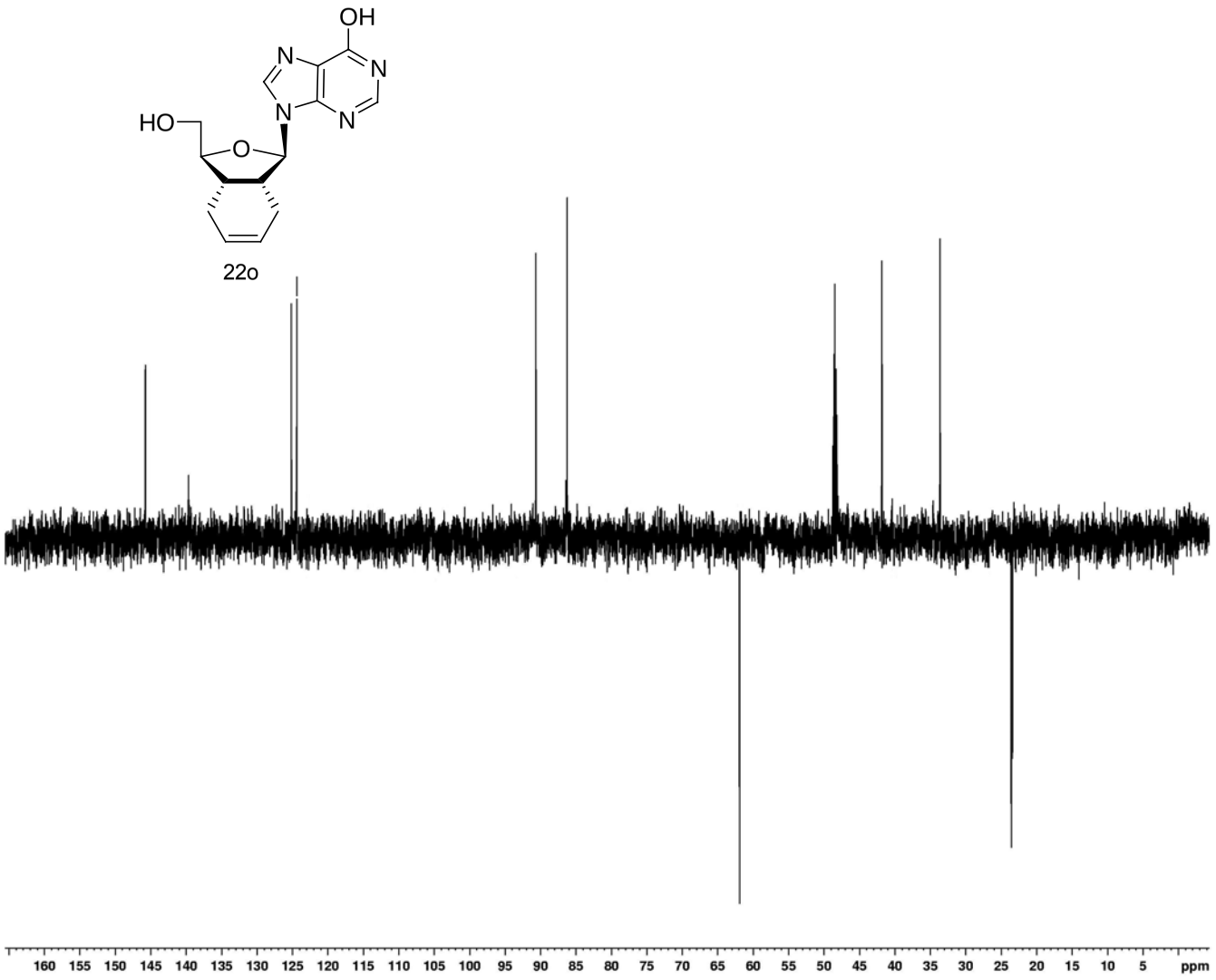
HMBC

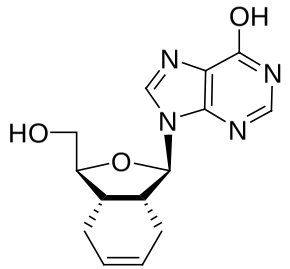

ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
NH2
NH2
N
N
N
N
O
HO

22m



22o

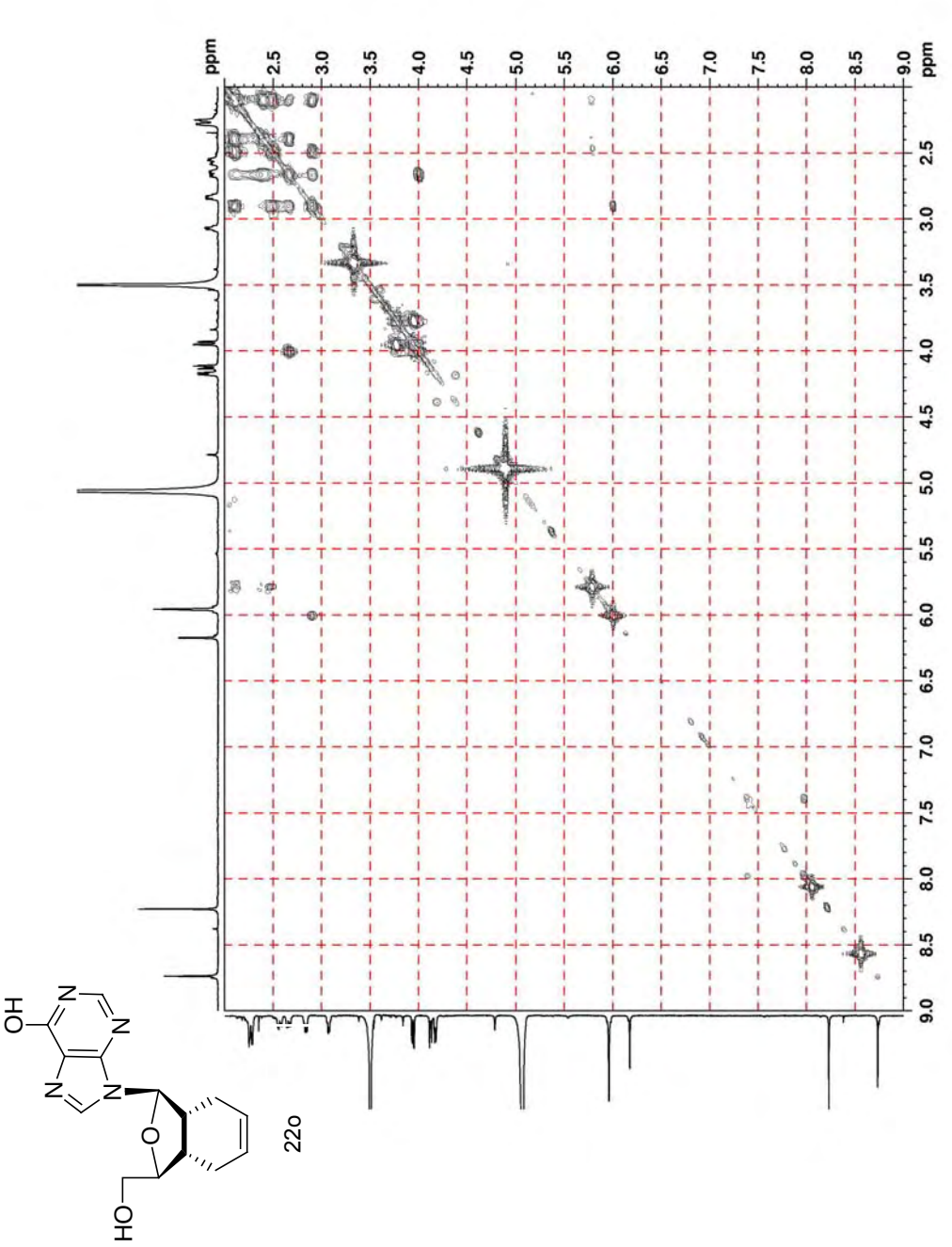

OH
N
N
N
N
HO
O
22o
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm


OH
N
N
N
N
HO
O

22o

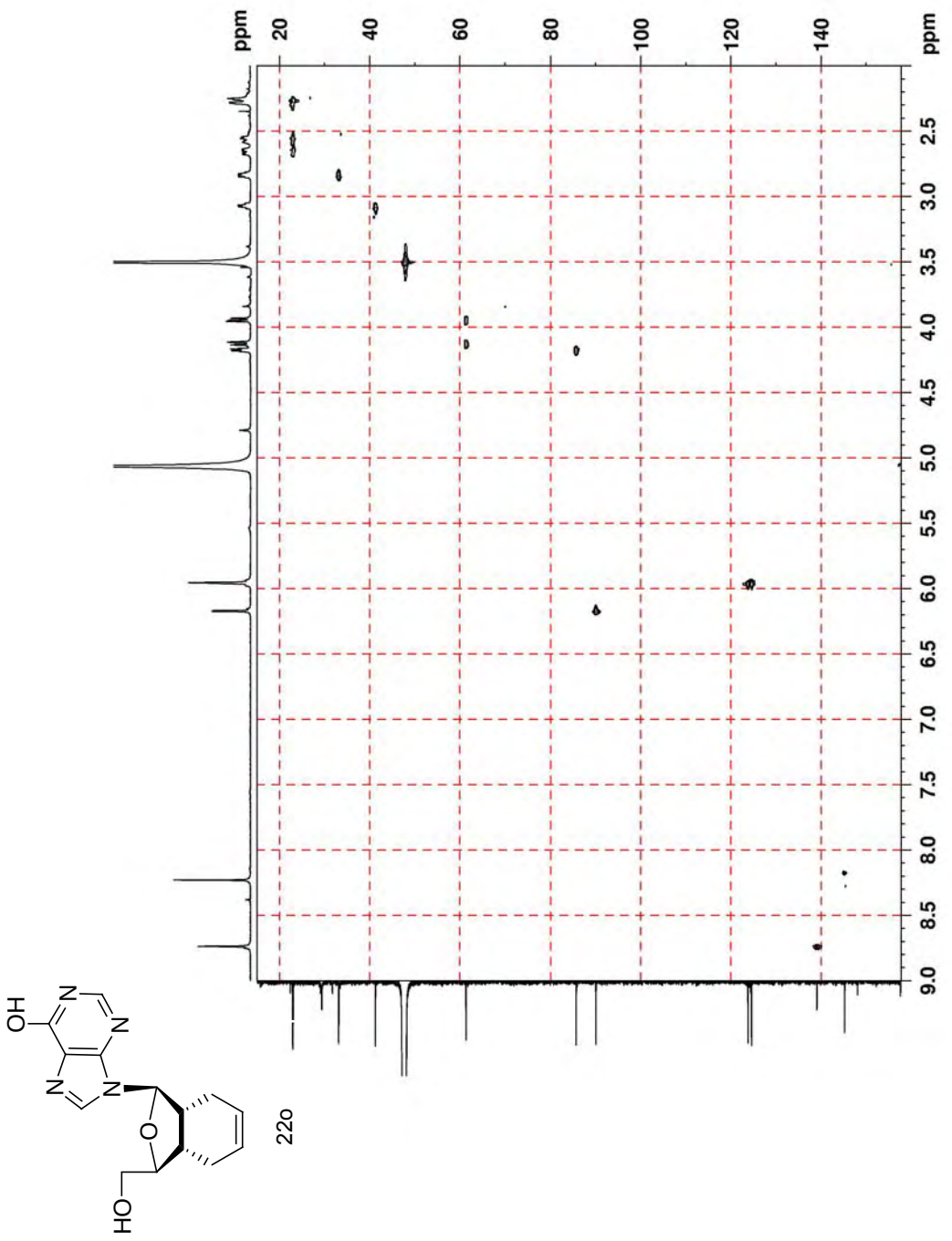
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 ppm

COSY



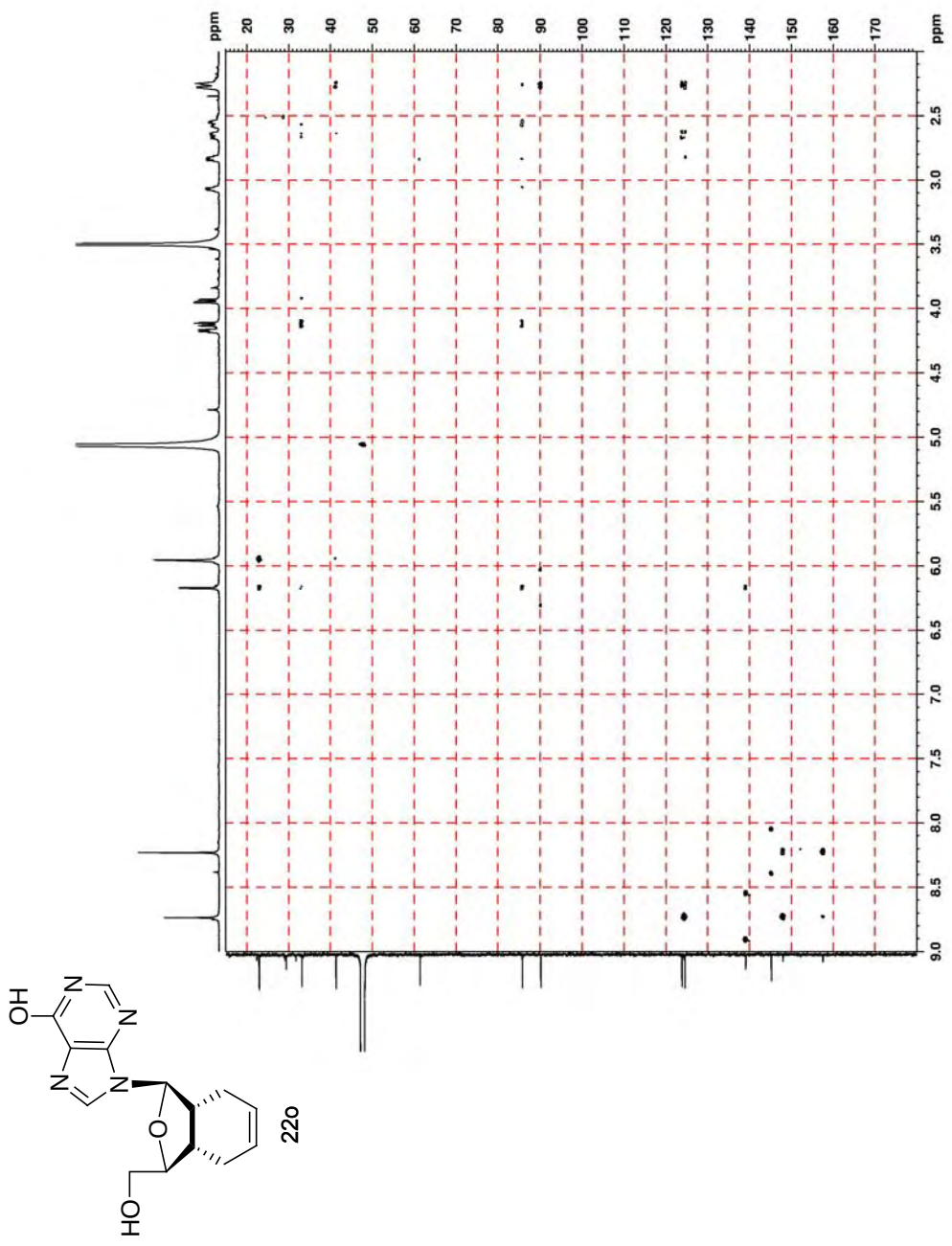
22o

HSQC


ppm
20
40
60
80
100
120
140
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
OH
N
N
N
N
O
HO

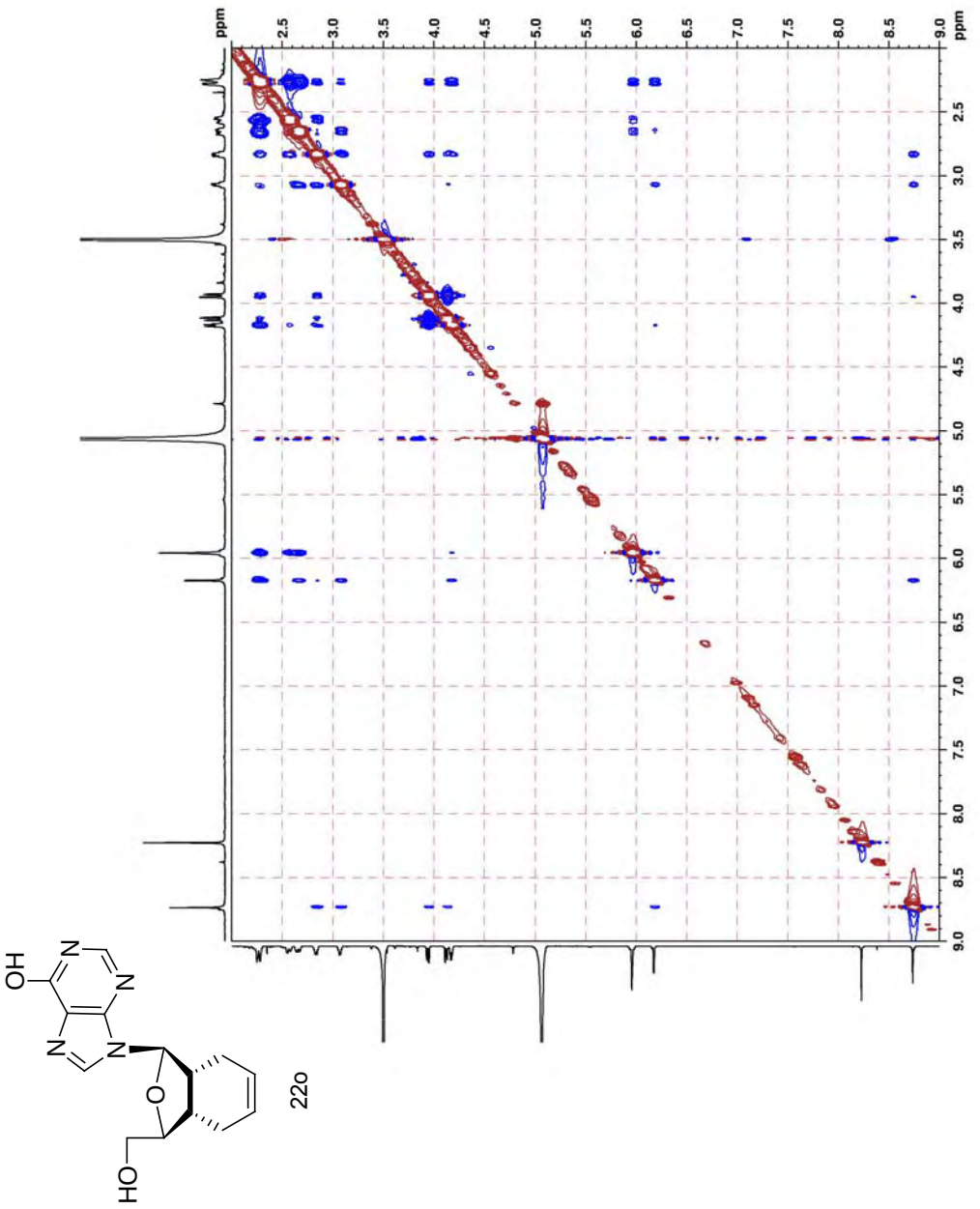
22o

HMBC

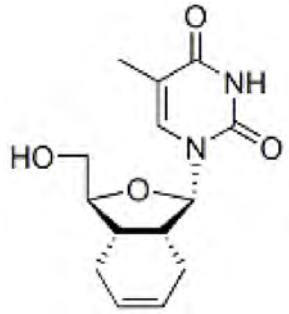

ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
ppm
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
OH
N
N
N
N
O
HO

22o

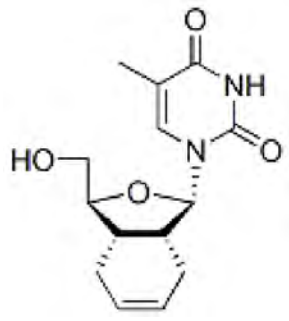
NOESY



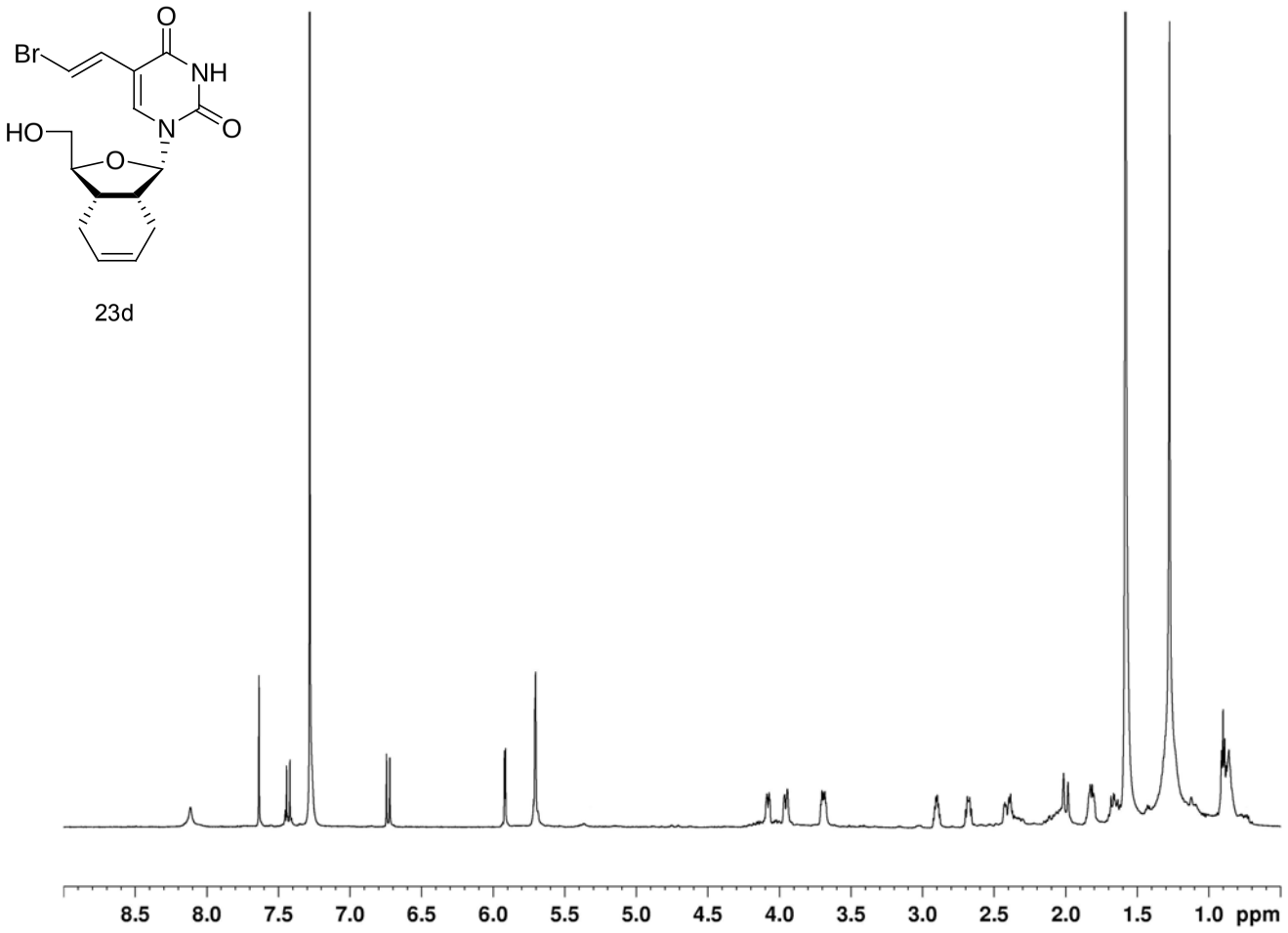
22o



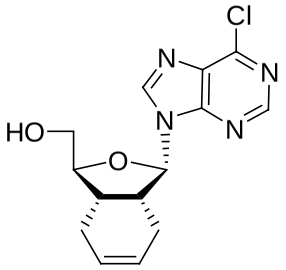
23b



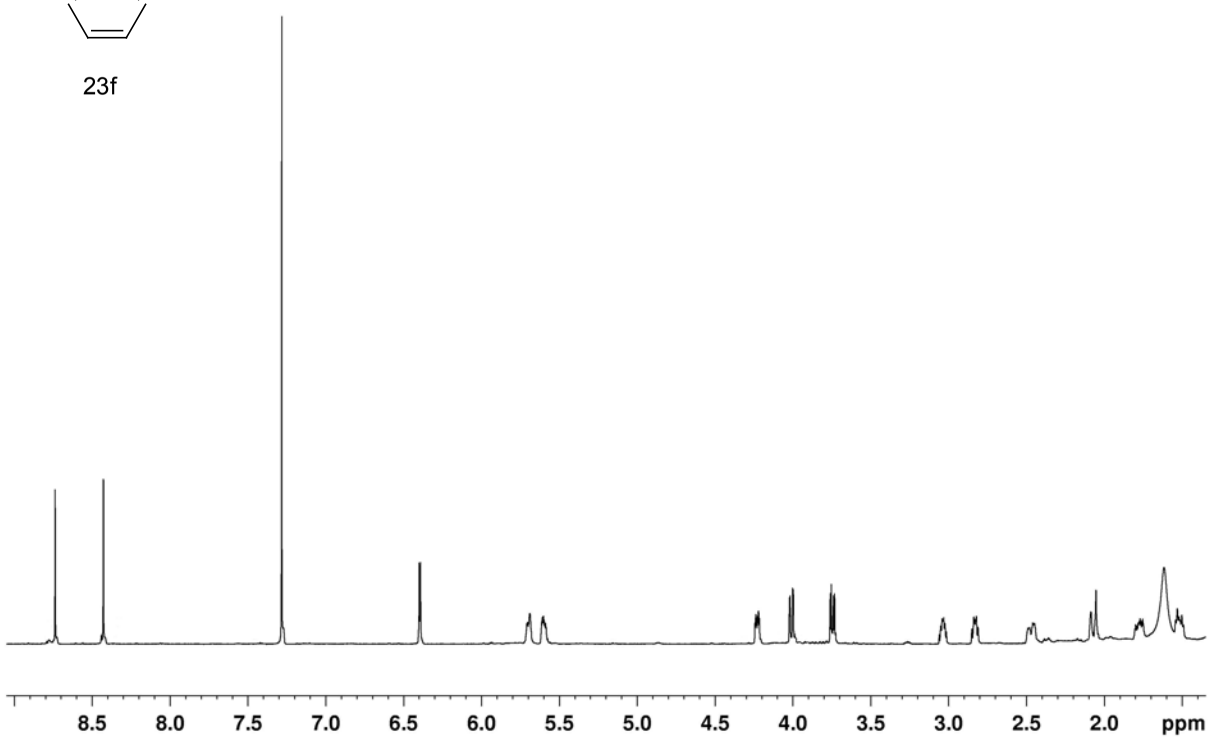
23b

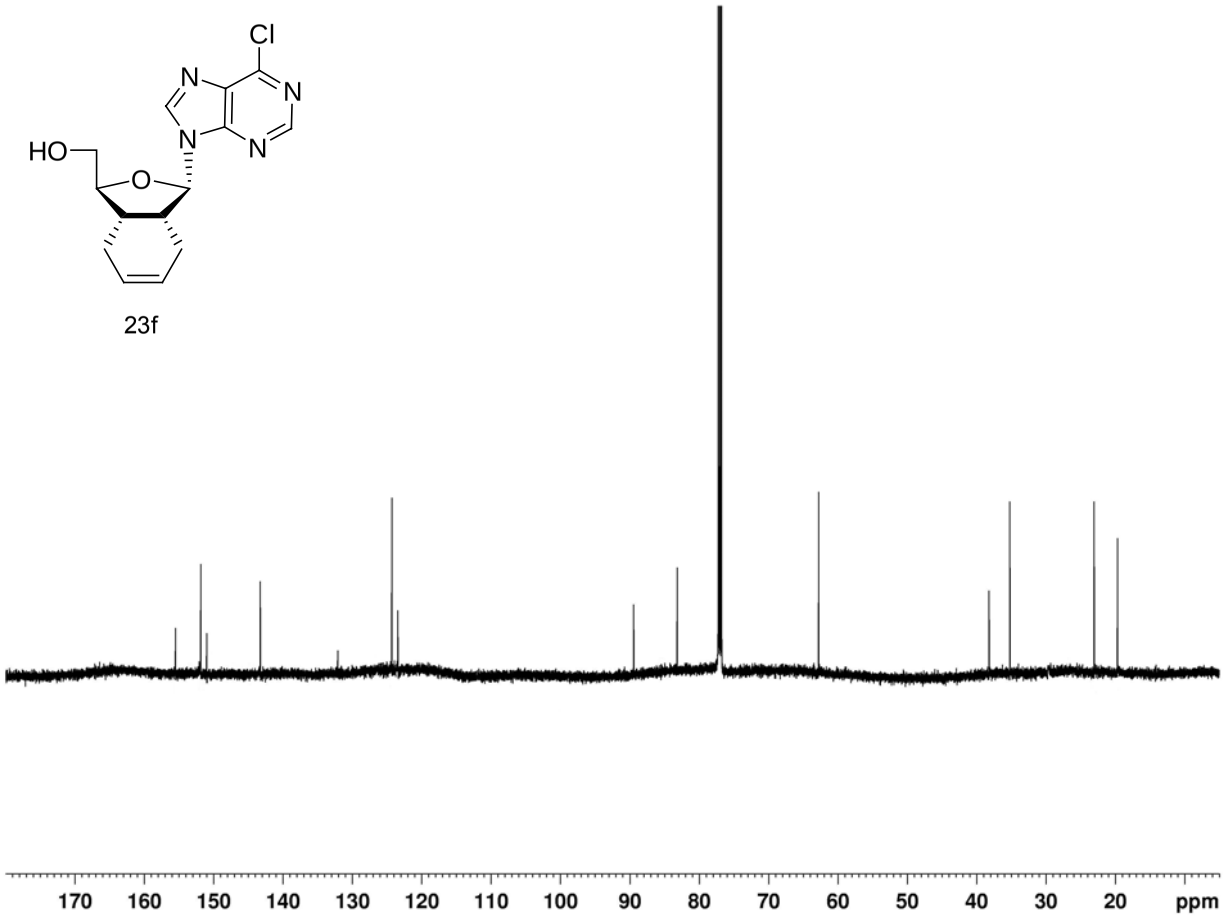


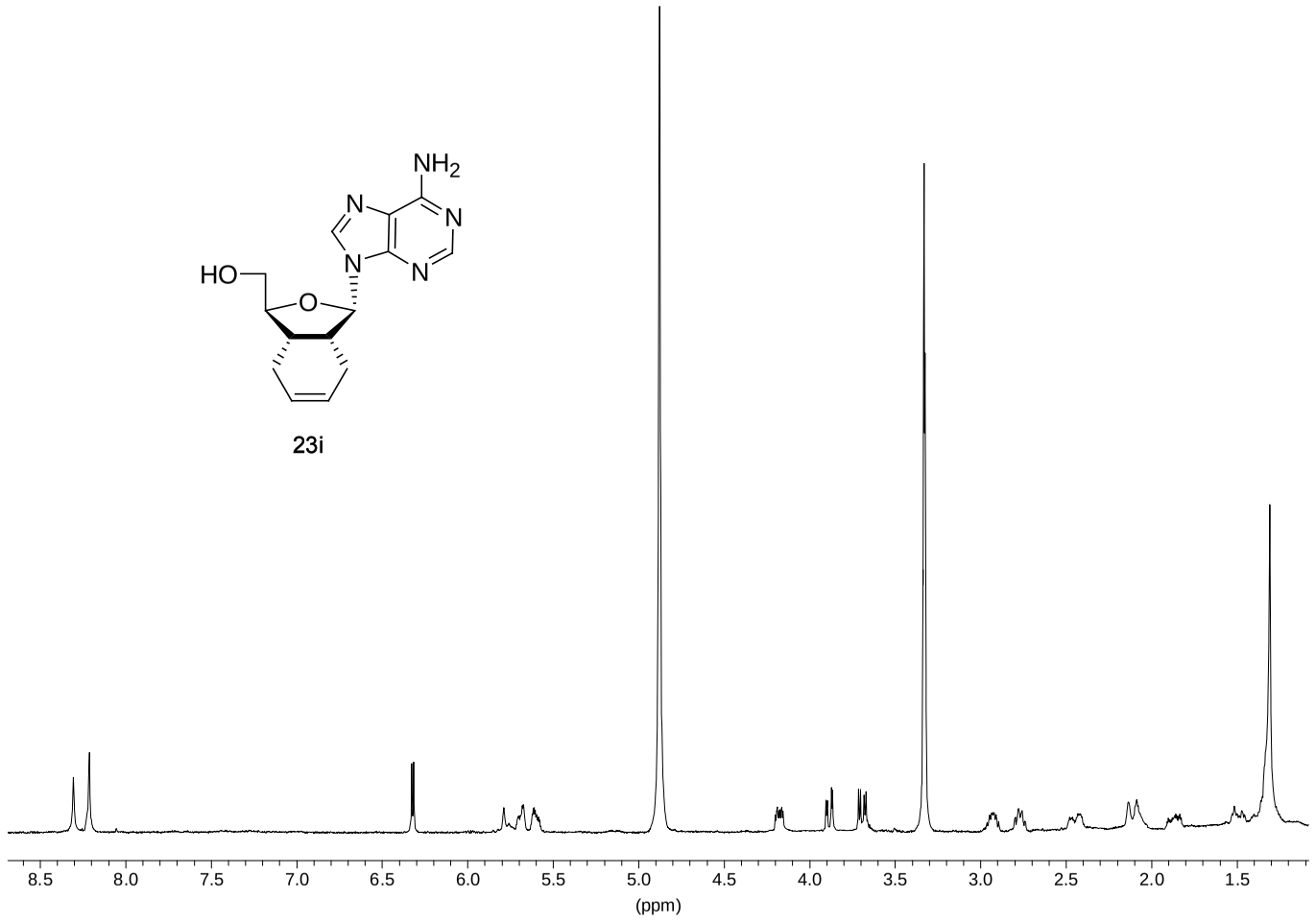
23d



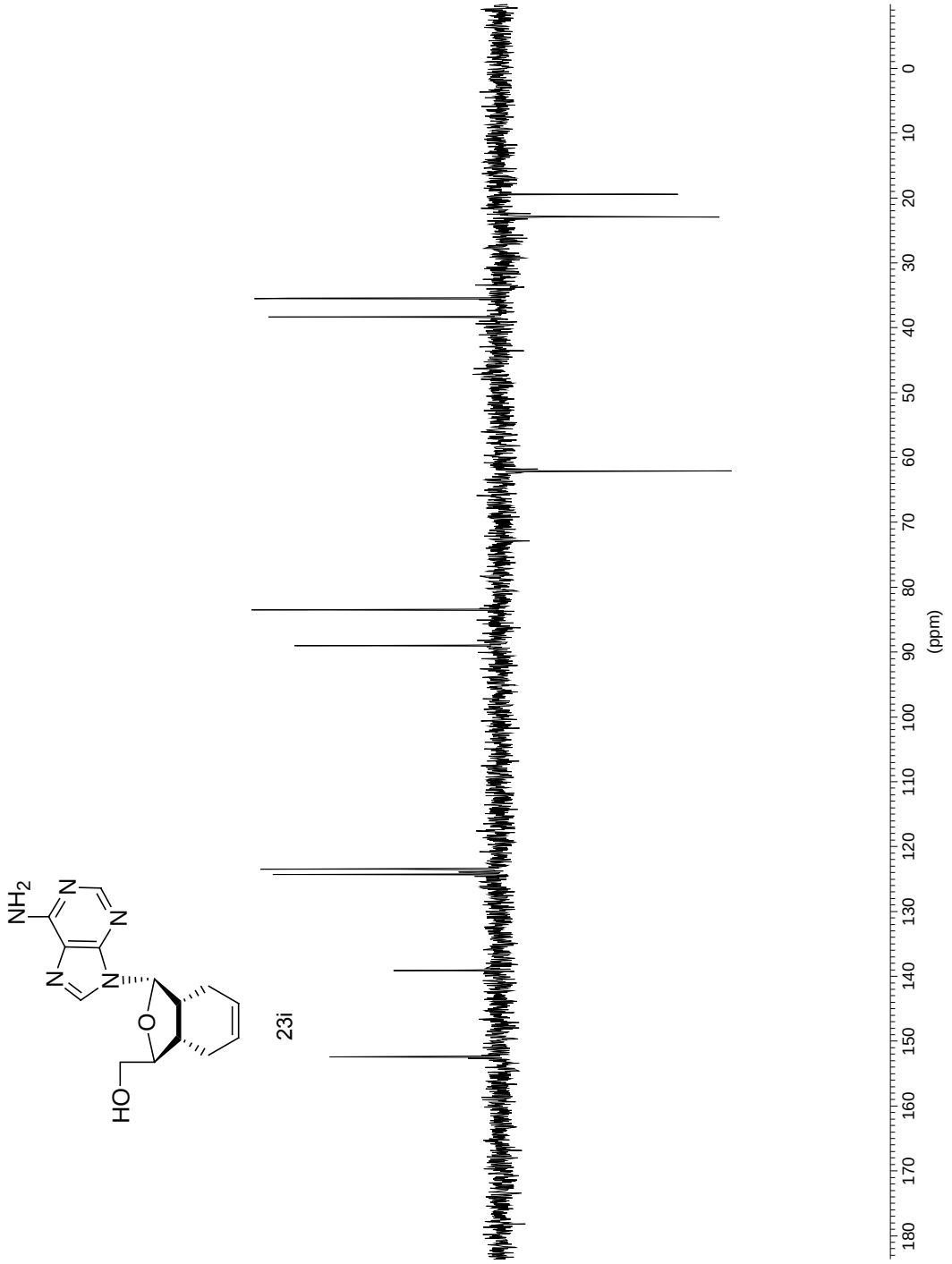
23f




Cl
N
N
N
N
HO
O
23f
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



23i


NH2
N
N
N
N
O
HO
23i
0
10
20
30
40
50
60
70
80
90
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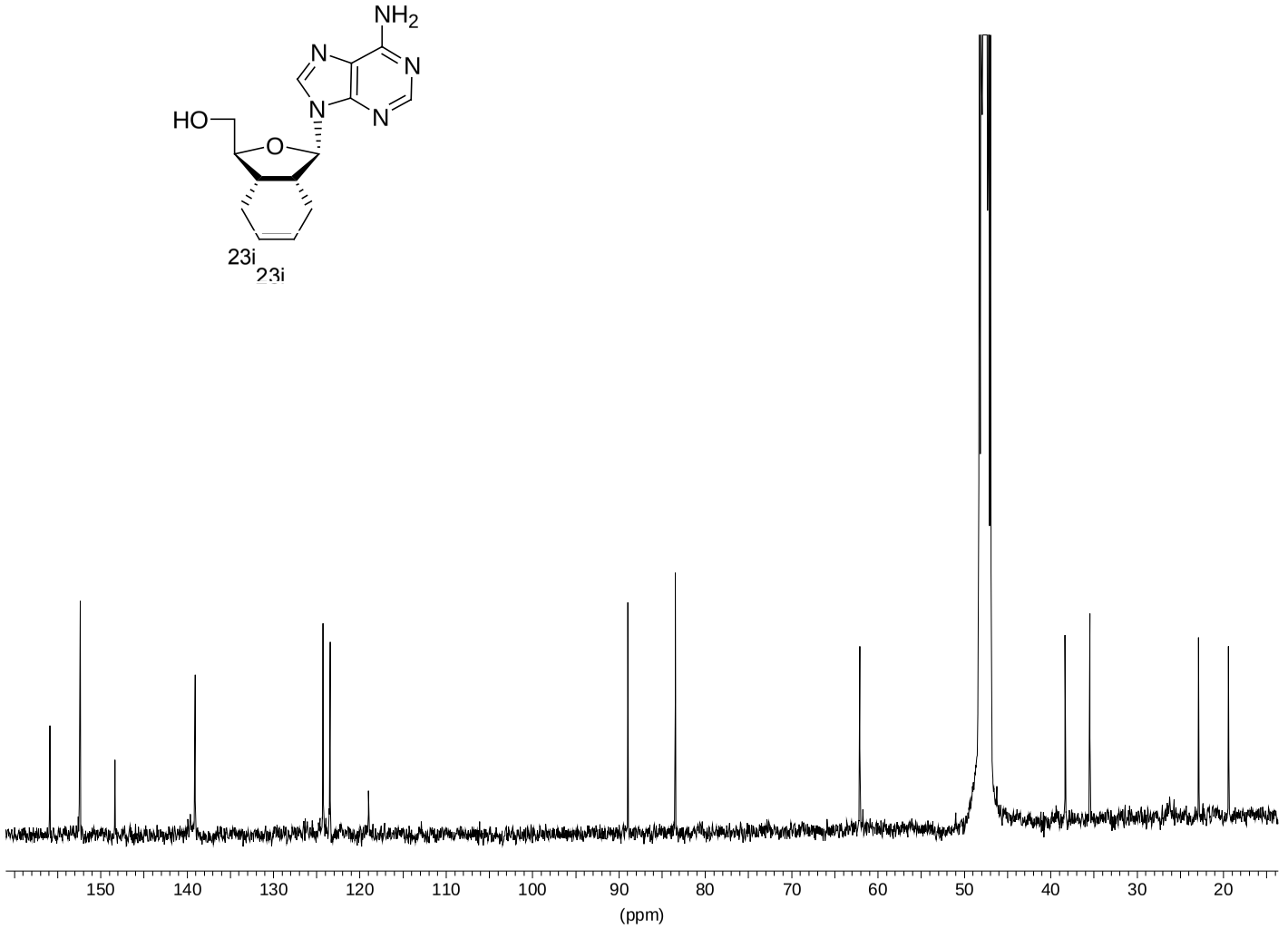
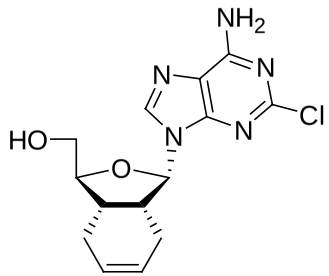
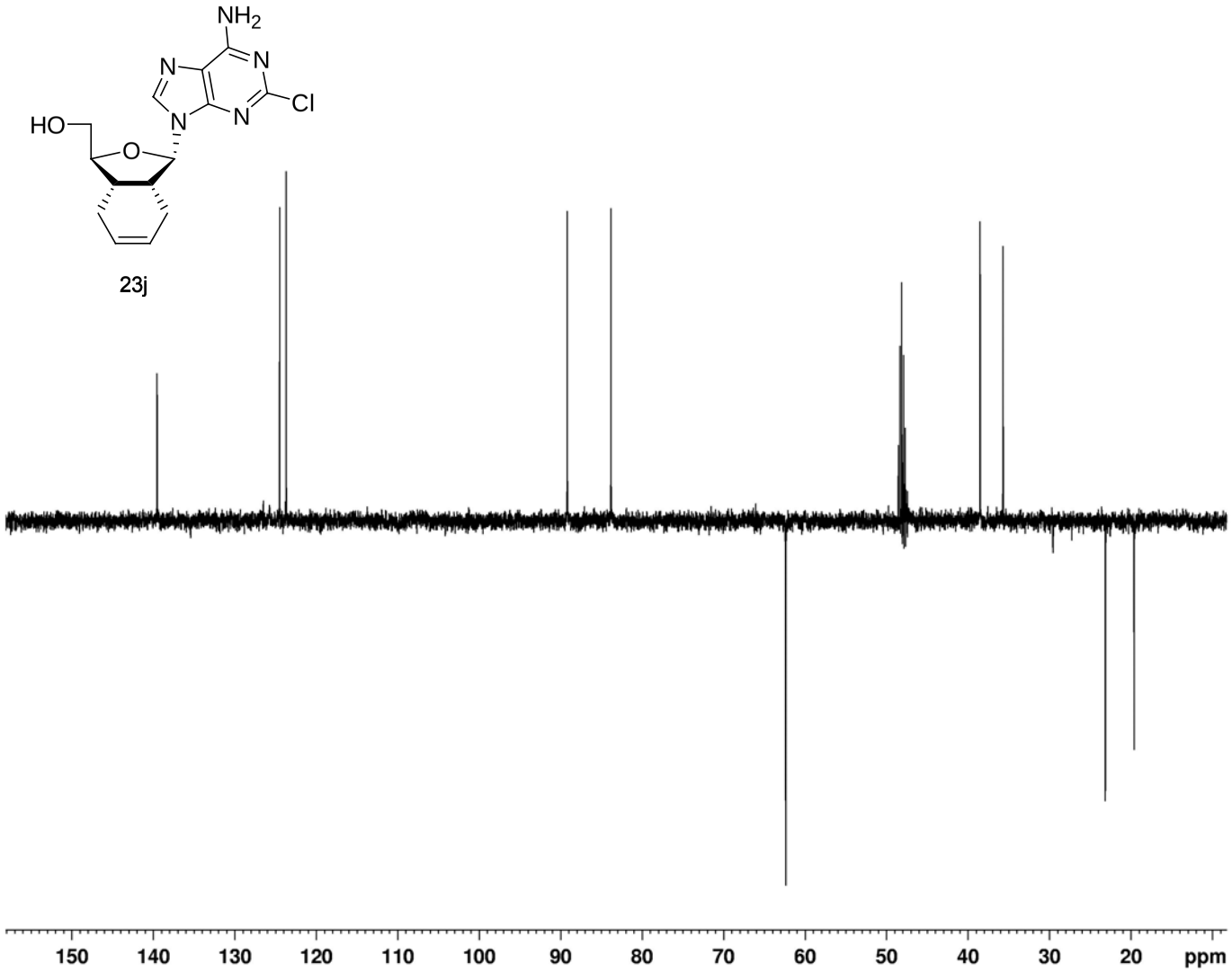
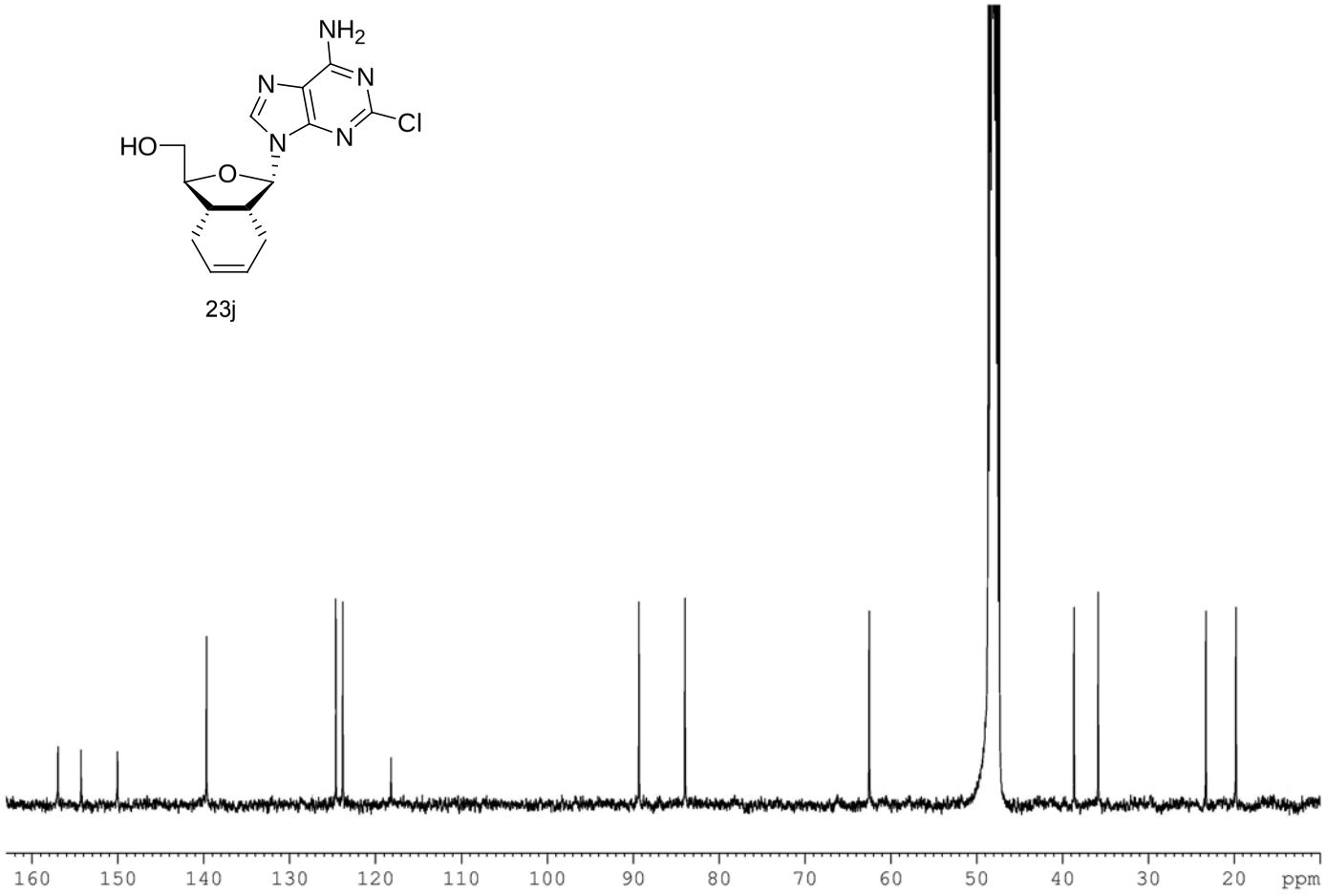
110
120
130
140
150
160
170
180
(ppm)


NH2
N
N
N
N
HO
O
23i
23i
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)

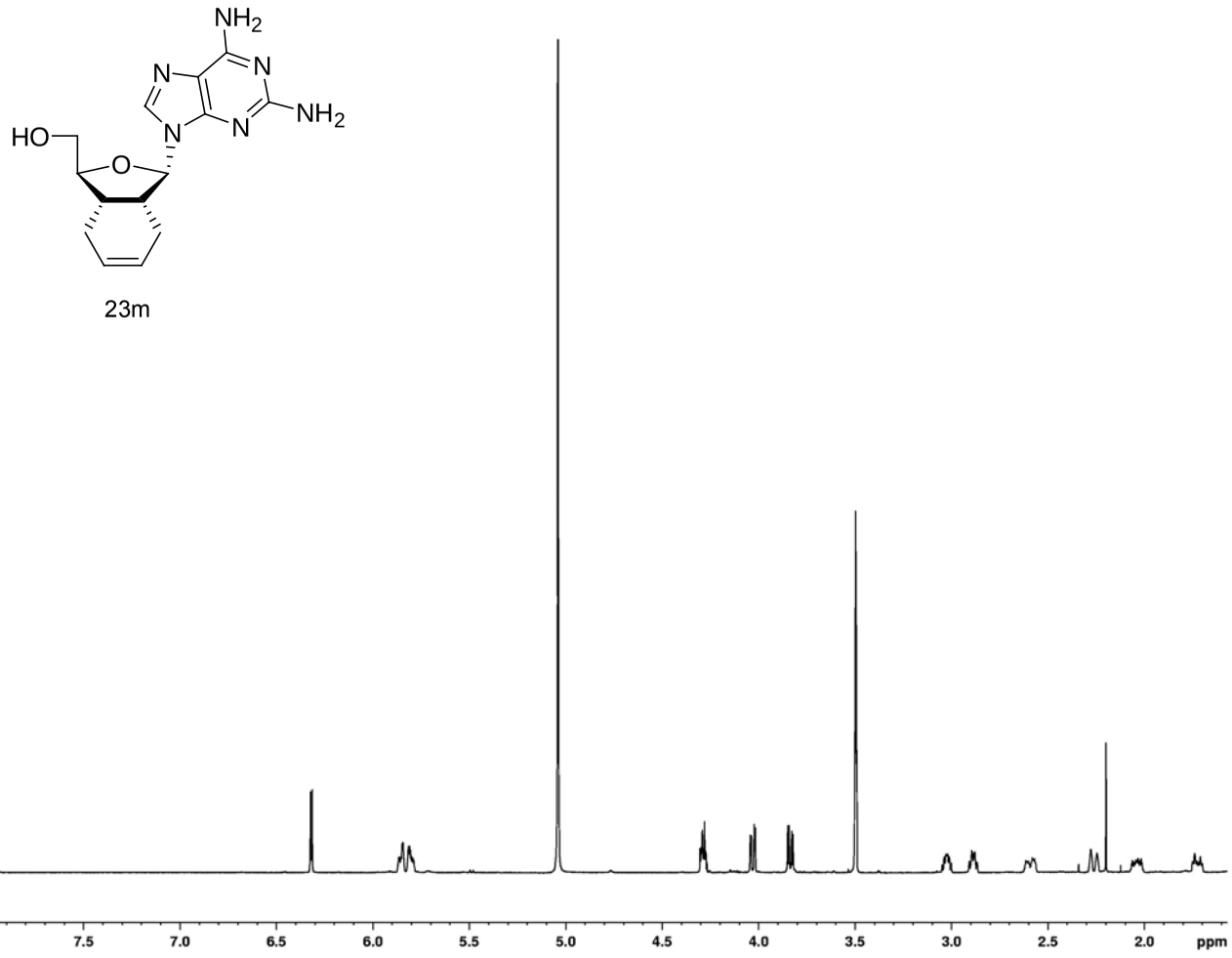


23j

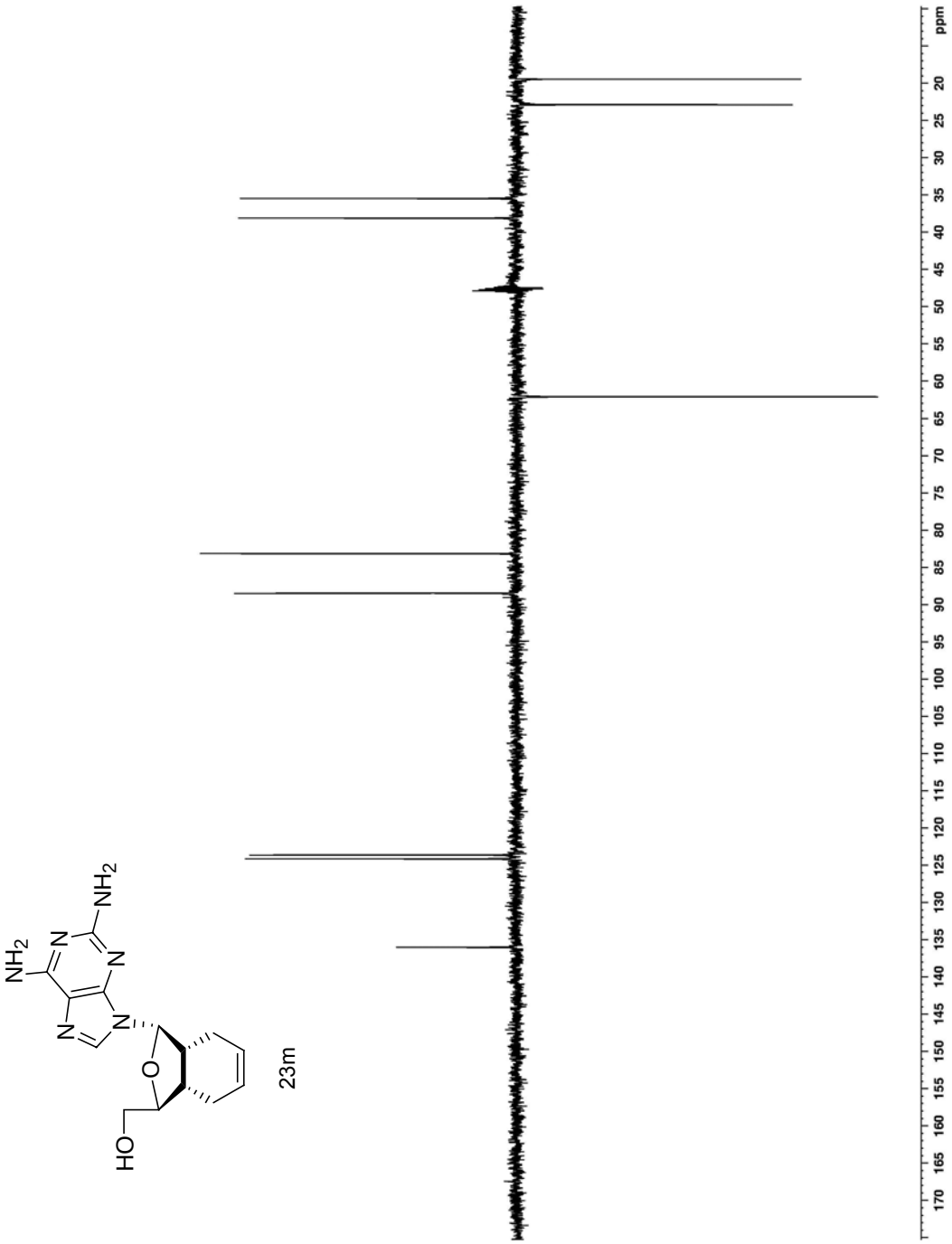

NH2
N
N
N
N
Cl
HO
O
23j
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

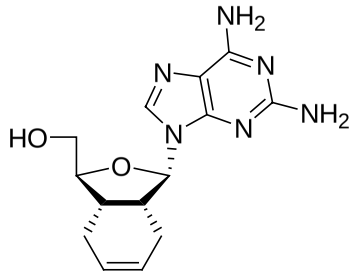

NH2
N
N
N
N
Cl
HO
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

23j



23m

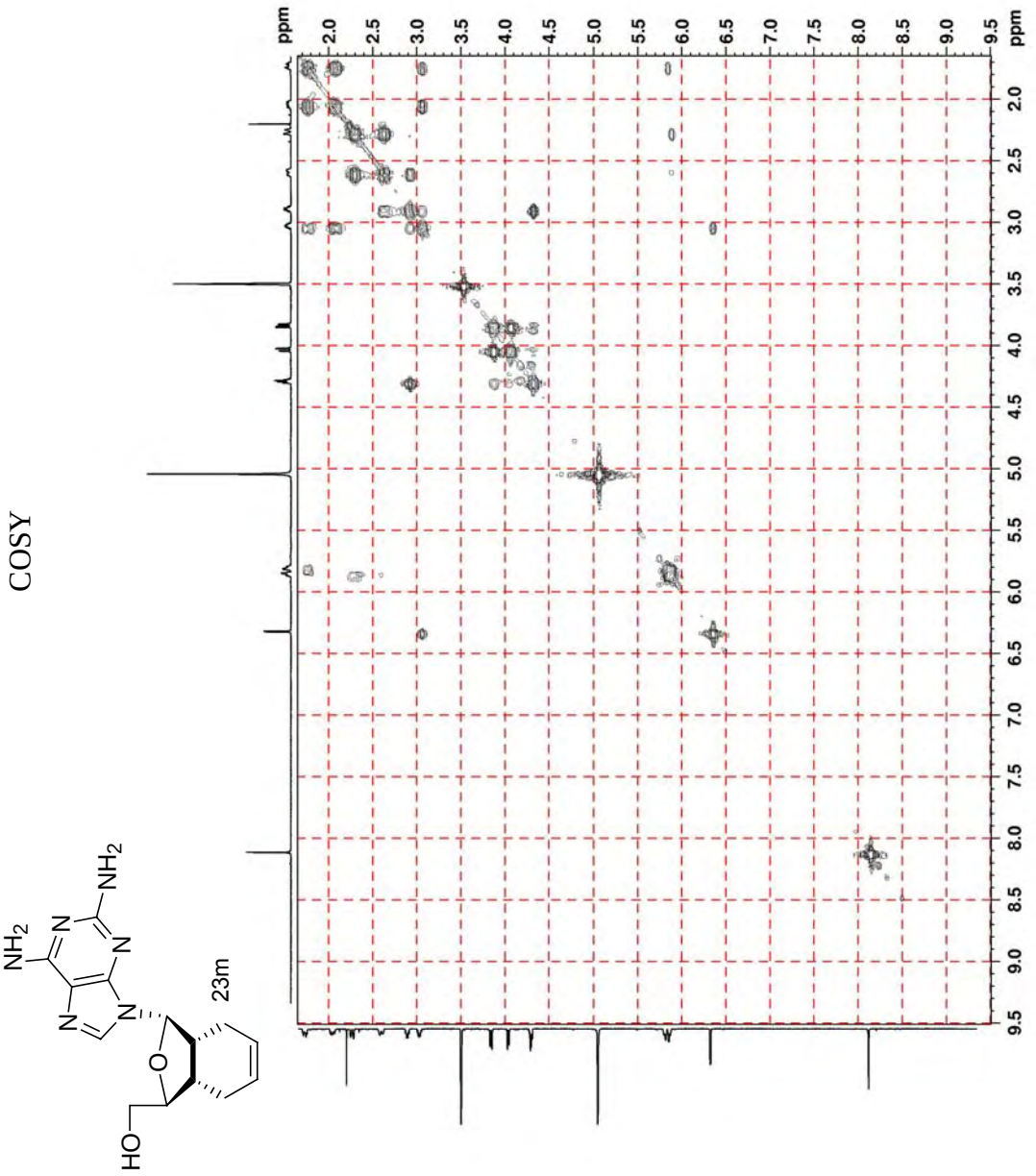

NH2
NH2
N
N
N
N
O
HO
23m
ppm
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20


NH2
N
N
N
N
NH2
HO
O

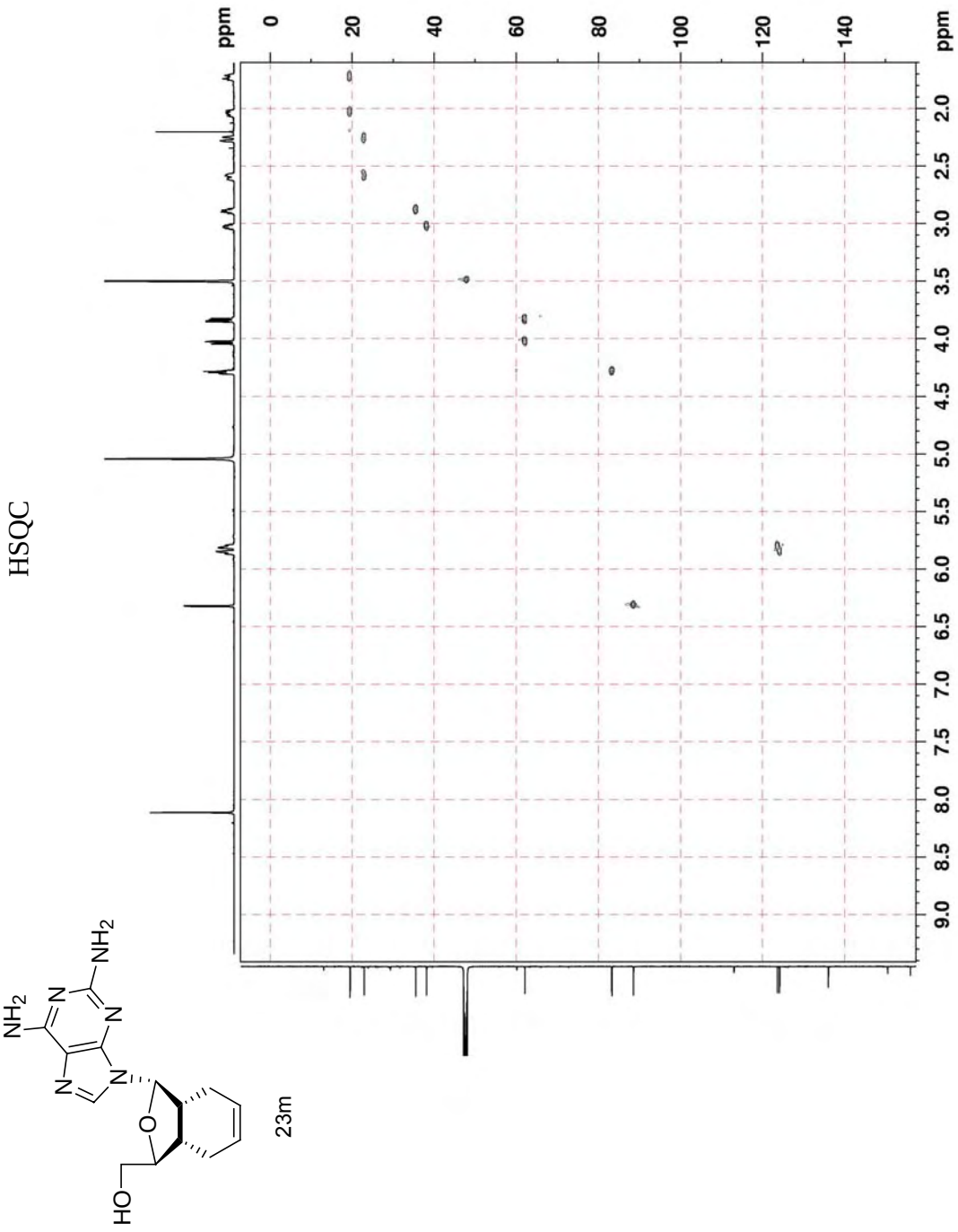
23m

165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 ppm

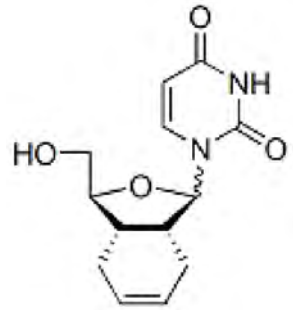
COSY


NH2
NH2
N
N
N
N
O
HO
23m
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5

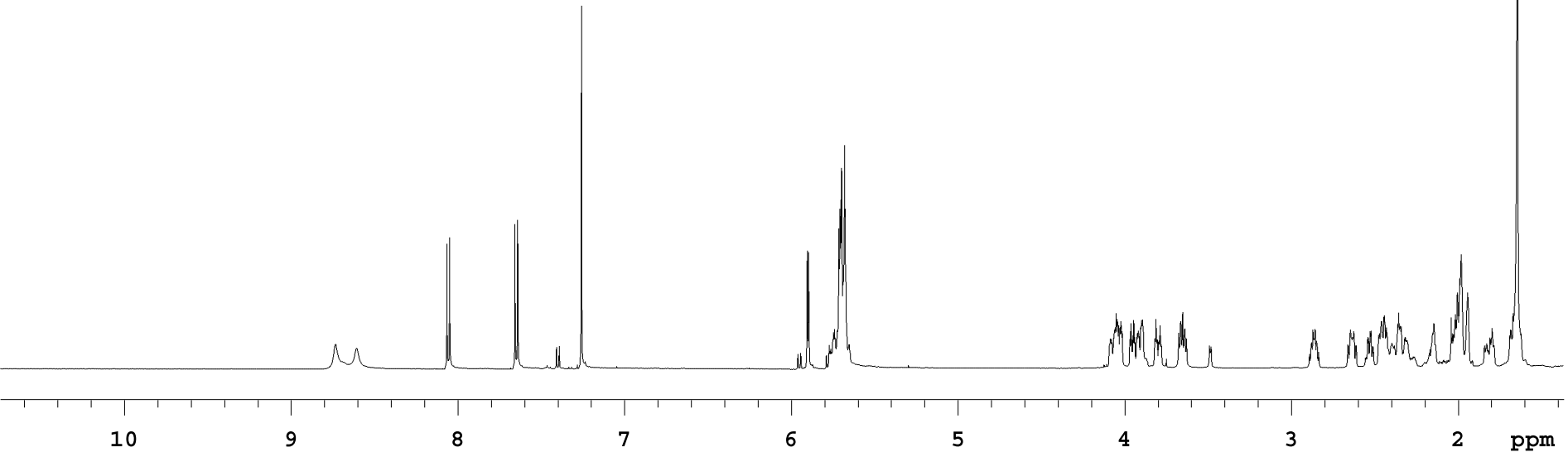
HSQC

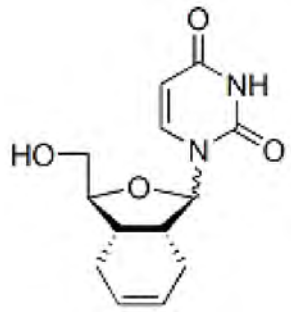

ppm
0
20
40
60
80
100
120
140
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
NH2
NH2
N
N
N
N
O
HO

23m

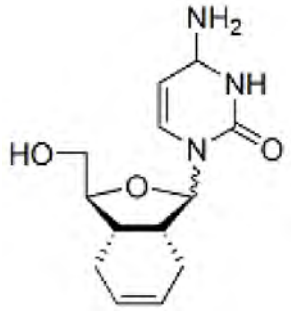


24a

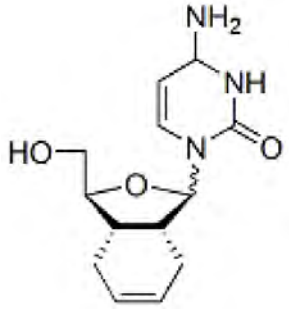




24a



24h



24h