Supporting Information

An unexpected reaction of trimethylsilyl fluorosulfonyldifluoroacetate with imidazoles. Formation of *N*-difluoromethylthioureas.

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General Experimental Information

^{1}H (Me_4Si) NMR spectra were determined with solutions in $CDCl_3$ at 400 MHz, ^{13}C (Me_4Si) at 100.6 MHz and ^{19}F (CCl_3F) at 376.4 MHz unless otherwise noted. UV spectra were recorded in MeOH solution. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) techniques and HRMS using FAB mode. An "acid free" trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) was prepared as reported.[4] The purity of TFDA was conveniently evaluated by ^{19}F NMR in $CDCl_3$ (dried over molecular sieves 4A) where TFDA shows peak at δ -103.20 while the signal from fluorosulfonyldifluoroacetic acid (FDA) appears at -103.91. TFDA and FDA were purchased from Aldrich Co. Sodium fluoride (NaF) was dried in the oven.

Synthetic Details and Compound Characterization Data

6-*N*-Phtaloyl-9-(2,3-*O*-isopropylidene-5-deoxy-β-*D*-*erythro*-pent-4-enofuranosyl)adenine (1). Phtaloyl dichloride (75 μL, 105 mg, 0.52 mmol) was added to a stirred solution of 9-(2,3-*O*-isopropylidene-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine[5b] (75 mg, 0.26 mmol) in pyridine (1.0 mL). After 2 h, the volatiles were evaporated and the residue was partitioned (1N $HCl/H_2O//CHCl_3$). The organic layer was washed ($NaHCO_3/H_2O$//brine), dried (Na_2SO_4), evaporated and chromatographed (0 → 5 % $MeOH/CHCl_3$) to give **1** (82 mg, 76%) as an yellow oil: UV (MeOH) λ_{max} 276 nm, λ_{min} 245 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.62 (s, 3H), 4.65 (d, J = 2.6 Hz, 1H), 4.69 (d, J = 1.9 Hz, 1H), 5.38 (d, J = 6.0 Hz, 1H), 5.61 (d, J = 6.0 Hz, 1H), 6.37 (s, 1H), 7.81-7.83 (m, 2H), 7.99-8.02 (m, 2H), 8.20 (s, 1H), 9.00 (s,

1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.9, 27.0, 79.8, 82.9, 89.6, 91.1, 114.7, 124.7, 130.2, 132.1, 135.2, 144.7, 144.9, 153.1, 153.2, 161.6, 165.7; MS (APCI) *m/z* 420 (100, MH^+); HRMS (FAB) Calcd for $C_{21}H_{18}N_5O_5$ (MH^+): 420.1308; Found: 420.1300.

9-[(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-7-difluoromethyl-6-(phthalimido)purine-8(*7H*, *9H*)-thione (2). A solution of **1** (75 mg, 0.18 mmol) in anhydrous in toluene (2.0 mL) containing NaF (1.4 mg, 0.03 mmol) was refluxed for 15 min. Acid-free TFDA (174 mg, 0.1 mL, 0.7 mmol) was added dropwise via a teflon needle at the rate of 0.15 mL/h (controlled by syringe pump). The solution was refluxed for 14 h, cooled to ambient temperature and was evaporated. The complex reaction mixture (TLC, ^{19}F NMR) was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated and column chromatographed (30 → 70% EtOAc/hexane) to give crude **2** (19 mg, 19%) in addition to other fluorine-contained products. Repurification of the crude **2** (column chromatographed; 20 → 50% EtOAc/hexane) gave **2** (11 mg, 11%): UV (MeOH) λ_{max} 319 nm, λ_{min} 272 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.57 (s, 3H), 1.70 (ddd, *J* = 5.9, 10.1, 14.8 Hz, 1H), 1.80 (ddd, *J* = 7.1, 10.3, 15.0 Hz, 1H), 5.32 (d, *J* = 5.9 Hz, 1H), 5.43 (d, *J* = 6.1 Hz, 1H), 6.87 (s, 1H), 7.77-7.82 (m, 2H), 7.83 (t, *J* = 58.2 Hz, 1H), 7.90-7.96 (m, 2H), 8.84 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (t, *J* = 10.6 Hz), 25.6, 26.5, 73.6 (t, *J* = 9.3 Hz), 79.9, 85.0, 90.9, 109.65 (t, *J* = 281.7 Hz), 109.69 (t, *J* = 255.9 Hz), 114.2, 124.4, 124.5, 131.7, 131.8, 133.7, 134.7, 135.0, 135.1, 153.1, 154.1, 165.3,165.7, 172.1; ^{19}F NMR (376.4 MHz, $CDCl_3$) δ -99.52 (dd, *J* = 57.8, 224.1 Hz, 1F), -100.84 (dd, *J* = 59.0, 223.9 Hz, 1F), -135.01 (ddd, *J* = 6.2,

15.0, 163.5 Hz, 1F), -143.92 (ddd, J = 6.4, 14.1, 164.1 Hz, 1F); MS (APCI) m/z 552 (100, MH^+); HRMS (FAB) Calcd for $C_{23}H_{18}F_4N_5O_5S$ (MH^+): 552.0959; Found: 552.0957..

General Procedure for the reaction of TFDA with benzimidazoles and imidazoles. Under nitrogen, into a 25 ml of three-necked flask equipped with condenser was added 10 mL of anhydrous 1,2-dimethoxyethane, benzimidazole or imidazole (1 mmol) and anhydrous sodium fluoride (0.1 mmol). The system was degassed and filled with dry nitrogen with a balloon. The mixture was heated to 105 ^{o}C (bath temperature) and stirred for about 15 minutes. Then TFDA (1g, 4mmol) was added dropwise at this temperature through a syringe pump, 0.4ml/h. After addition, the mixture was stirred overnight at 105°C. Cooled to room temperature and the solvent was removed, the residue was purified by silica gel chromatography (Ethyl acetate/hexane = 1:5).

Compound 6a: solid, mp 104-105 ^{o}C, yield 63%; ^{1}H NMR, δ 5.24 (s, 2H), 6.62 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.36-7.39 (m, 3H), 7.72 (t, J = 59.8 Hz, 1H); ^{19}F NMR, δ -100.1 (d, J = 60.1 Hz, 2F); ^{13}C NMR, δ 50.8, 109.4 (t, J = 249.8 Hz), 112.1, 118.7, 128.6, 128.8, 129.3, 135.0, 164.7; MS (EI) m/z 242 (M^++2), 241(M^++1), 240 (M^+), 207, 91; Anal. Calcd for $C_{11}H_{10}F_2N_2S$: C, 54.99; H, 4.19; N, 11.66. Found: C, 55.08; H, 4.25; N, 11.32.

Compound 6b: solid, mp 74-75 ^{o}C, yield 52%; ^{1}H NMR, δ 3.62 (s, 3H), 6.75 (d, J = 2.6 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 7.66 (t, J = 60.2 Hz, 1H); ^{19}F NMR, δ -100.2 (d, J = 60.1 Hz, 2F); ^{13}C NMR, δ 34.7, 109.5,111.8, 119.9, 164.5; HRMS (CI) Calcd for

$C_5H_7F_2N_2S$[M+H]: 165.0298. Found: 165.0304; Anal. Calcd for $C_5H_6F_2N_2S$: C, 36.58; H, 3.68; N, 17.06. Found: C, 36.56; H, 3.25; N, 17.30.

Compound 6c: solid, mp 113-114 ^oC, yield 51%; ^1H NMR, δ 3.21 (s, 3H), 7.15-7.19 (m , 2H), 7.25 (t, *J* = 59.1 Hz, 1H), 7.26-7.33 (m, 8H); ^{19}F NMR, δ -96.0 (d, *J* = 60.1 Hz, 2F); ^{13}C NMR, δ 29.1, 109.3 (t, *J* = 245.3), 118.0, 124.5, 127.9, 128.2, 128.4, 128.7, 128.9, 129.0, 130.4, 131.1, 152.3; Anal. Calcd for $C_{17}H_{14}F_2N_2S$: C, 64.54; H, 4.46; N, 8.85. Found: C, 64.70; H, 4.41; N, 8.74.

Compound 8a : solid, mp 108-109 ^oC, yield 53%; ^1H NMR, δ 3.77 (s, 3H), 7.22 (d, *J* = 8.1 Hz,), 7.31 (t, *J* = 8 Hz,), 7.35 (t, *J* = 7.8 Hz,), 7.57 (d, *J* = 7.7 Hz,), 8.02 (t, *J* = 58.8 Hz, 1H); ^{19}F NMR, δ -103.2 (d, *J* = 60.1 Hz, 2F); ^{13} C NMR, δ 31.1, 109.5, 111.2 (t, *J* = 249 Hz), 111.8, 124.2, 124.8, 127.9, 132.9, 169.8; HRMS (CI) Calcd for $C_9H_9F_2N_2S$: 215.0454. Found: 215.0443.

Compound 8b: solid, mp 107-108 ^oC, yield 57%; ^1H NMR, δ 3.74 (s, 3H), 3.87(s, 3H),6.92(d, *J* = 8.9 Hz, 1H), 7.10 (bs, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 8.02 (t, *J* = 58.8 Hz, 1H); ^{19}F NMR, δ -103.6 (d, *J* = 58.1Hz, 2F); ^{13}C NMR, δ 31.4, 56.3, 97.2 (t, *J* = 3 Hz), 110.0, 111.3 (t, *J* = 248 Hz), 112.1, 127.0, 128.8, 157.6, 169.2; HRMS (CI) Calcd for $C_{10}H_{11}F_2N_2OS$[M+H]: 245.0569. Found: 245.0565; Anal. Calcd for $C_{10}H_{10}F_2N_2OS$: C, 49.17; H, 4.13; N, 11.47. Found: C, 48.88; H, 4.03; N, 11.27.

Compound 8c: solid, mp 134-135 ^oC, yield 41%; ^1H NMR, δ 3.75 (s, 3H), 7.12(d , *J* =8.1 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.56 (bs, 1H), 7.98 (t, *J* = 59.2 Hz, 1H); ^{19}F NMR, δ -103.4 (d, *J* = 58.1 Hz, 2F); ^{13}C NMR, δ 31.3, 110.1, 110.9 (t, *J* = 249 Hz), 112.0 (t, *J* = 3

Hz),125.1, 128.5, 130.3, 131.5, 170.4; HRMS (CI) Calcd for $C_9H_7ClF_2N_2S$: 247.9987. Found: 247.9989; Anal. Calcd for $C_9H_7ClF_2N_2S$: C, 43.47; H, 2.84; N, 11.26. Found: C, 43.38; H, 2.78; N, 10.74.

X-ray experimental: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces.

The structure was solved by the Direct Methods in *SHELXTL6*,[23] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The H atoms on C2 and C3 were located from a Difference Fourier map and refined freely. Coupled with the geometry around them and the fact that their displacement parameters were equivalent, Atoms C2 and C3 were assigned as Carbon atoms. The displacement parameters of the ring N atoms are also equivalent. Attempts at placing the N atoms in other locations of the ring produced a Difference Fourier maps with relatively high electron density peaks around ring atoms wrongly assigned as Carbon atoms. The current model provided the lowest R values with the cleanest Difference Fourier map. A total of 153 parameters were refined in the final cycle of refinement using 2125 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 3.65% and 10.55%, respectively. Refinement was done using F^2.

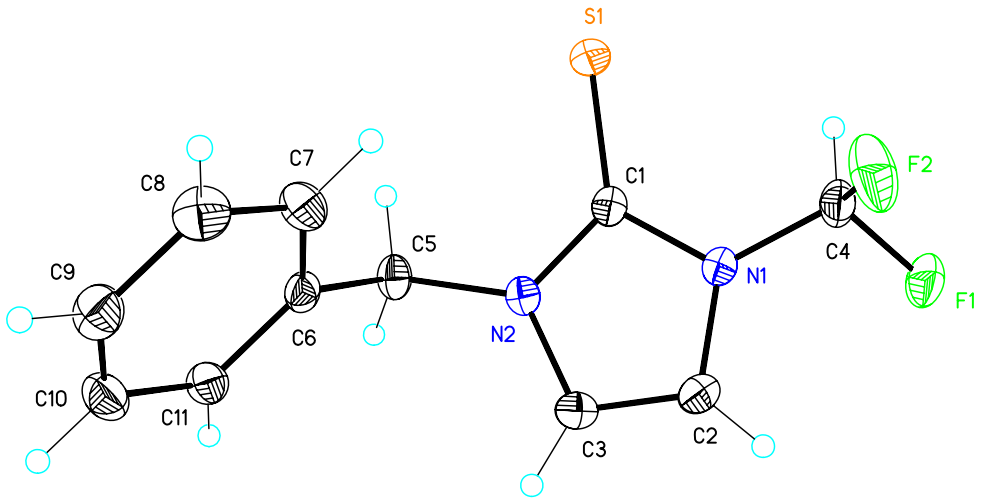


Figure 1. ORTEP drawing of 1-benzyl-3-(difluoromethyl)-1*H*-imidazole-2(3*H*)-thione (**6a**)

References

(4) Dolbier, W. R., Jr.; Tian, F.; Duan, J.-X.; Li, A.-R.; Ait-Mohand, S.; Bautista, O.; Buathong, S.; Baker, J. M.; Crawford, J.; Anselme, P.; Cai, X.-H.; Modzelewska, A.; Koroniak, H.; Battiste, M. A.; Chen, Q.-Y. *J. Fluorine Chem.* **2004**, *125*, 459-469.

(5b) McCarthy, J. R., Jr.; Robins, R. K.; Robins, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4993-4999.

(23) SHELXTL6 (2000). Bruker-AXS, Madison, Wisconsin, USA.

Fig. 2. Proton spectrum of compound **8a**

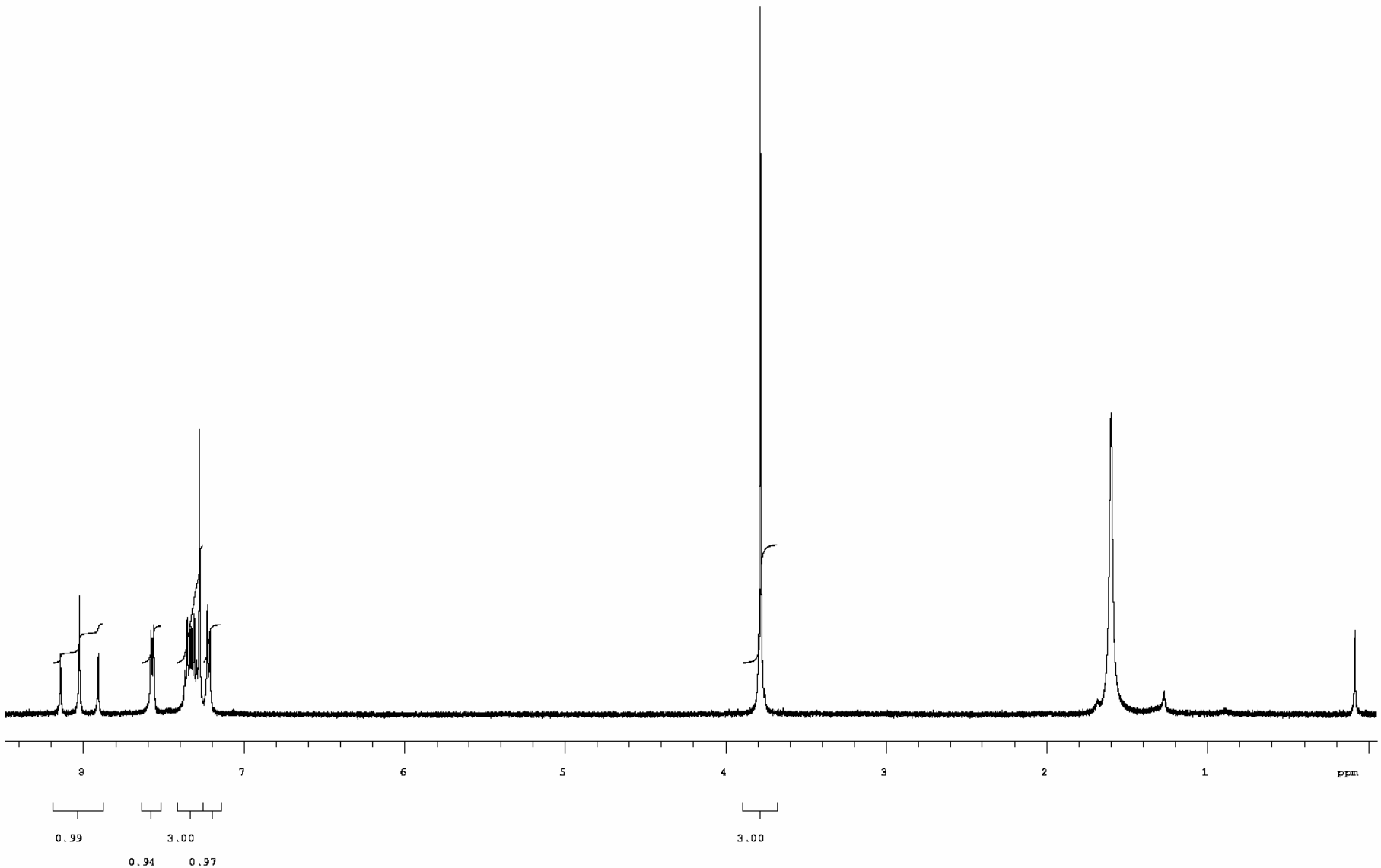


Fig. 3. gHMBC spectrum of compound **8a**.

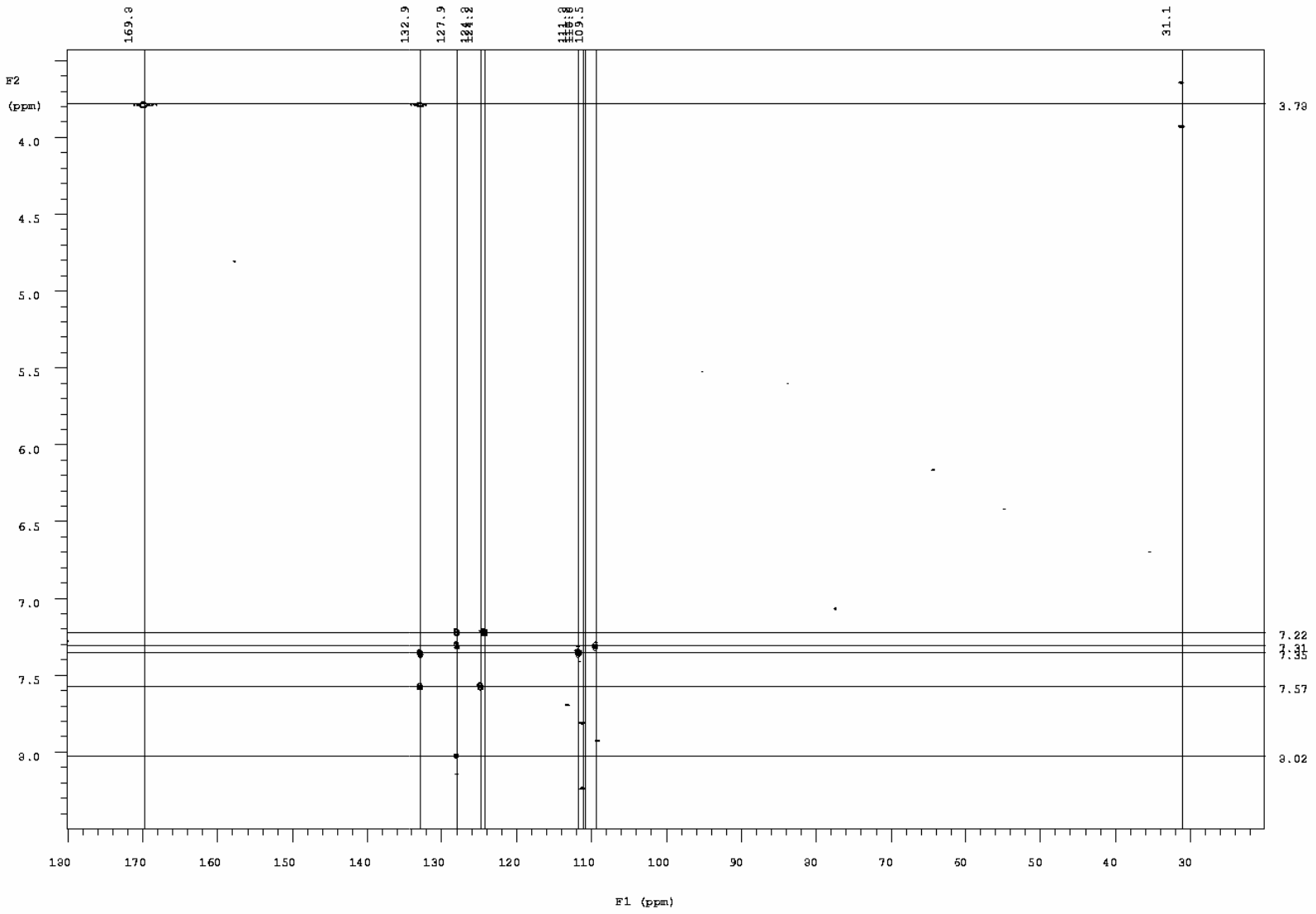
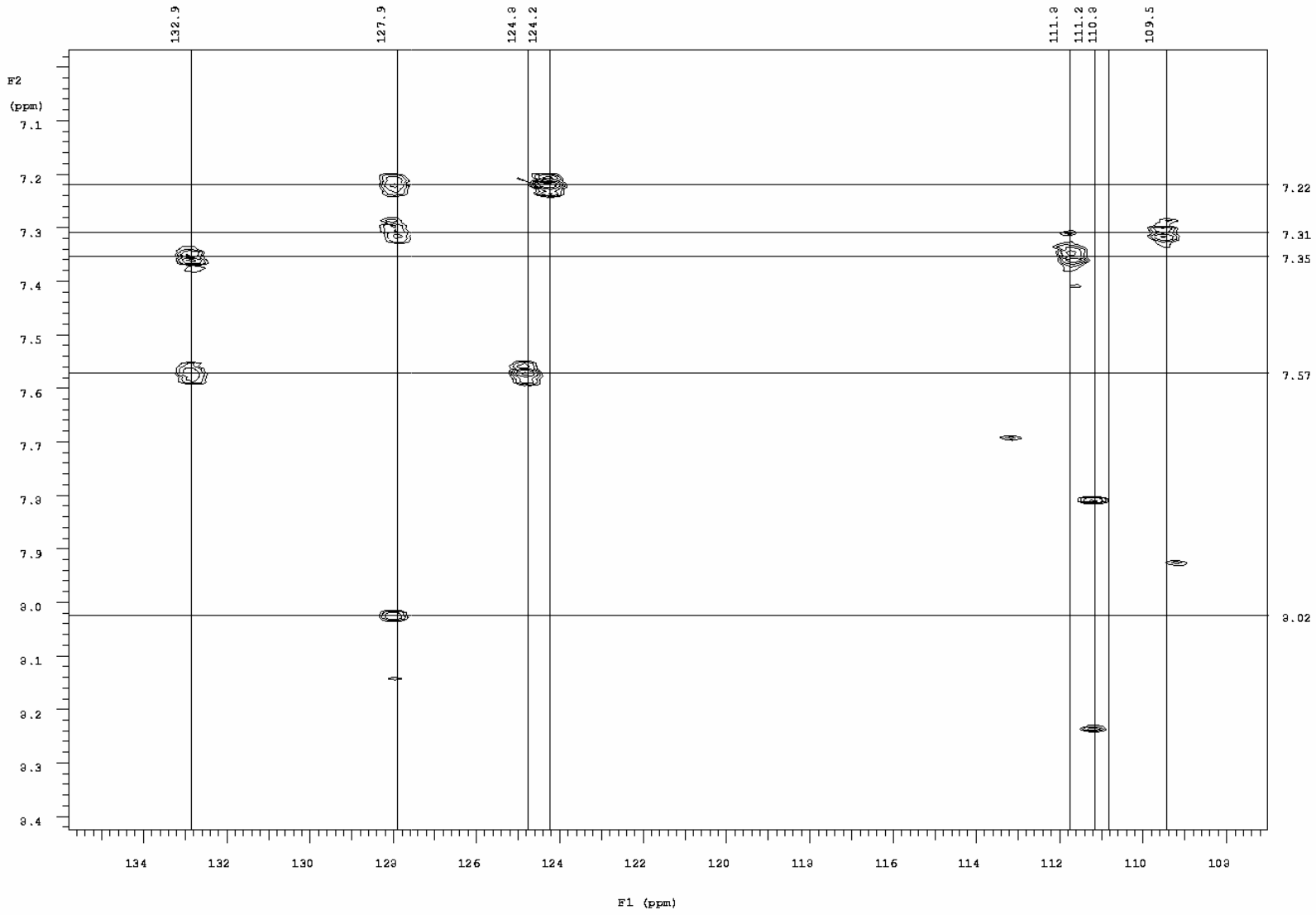
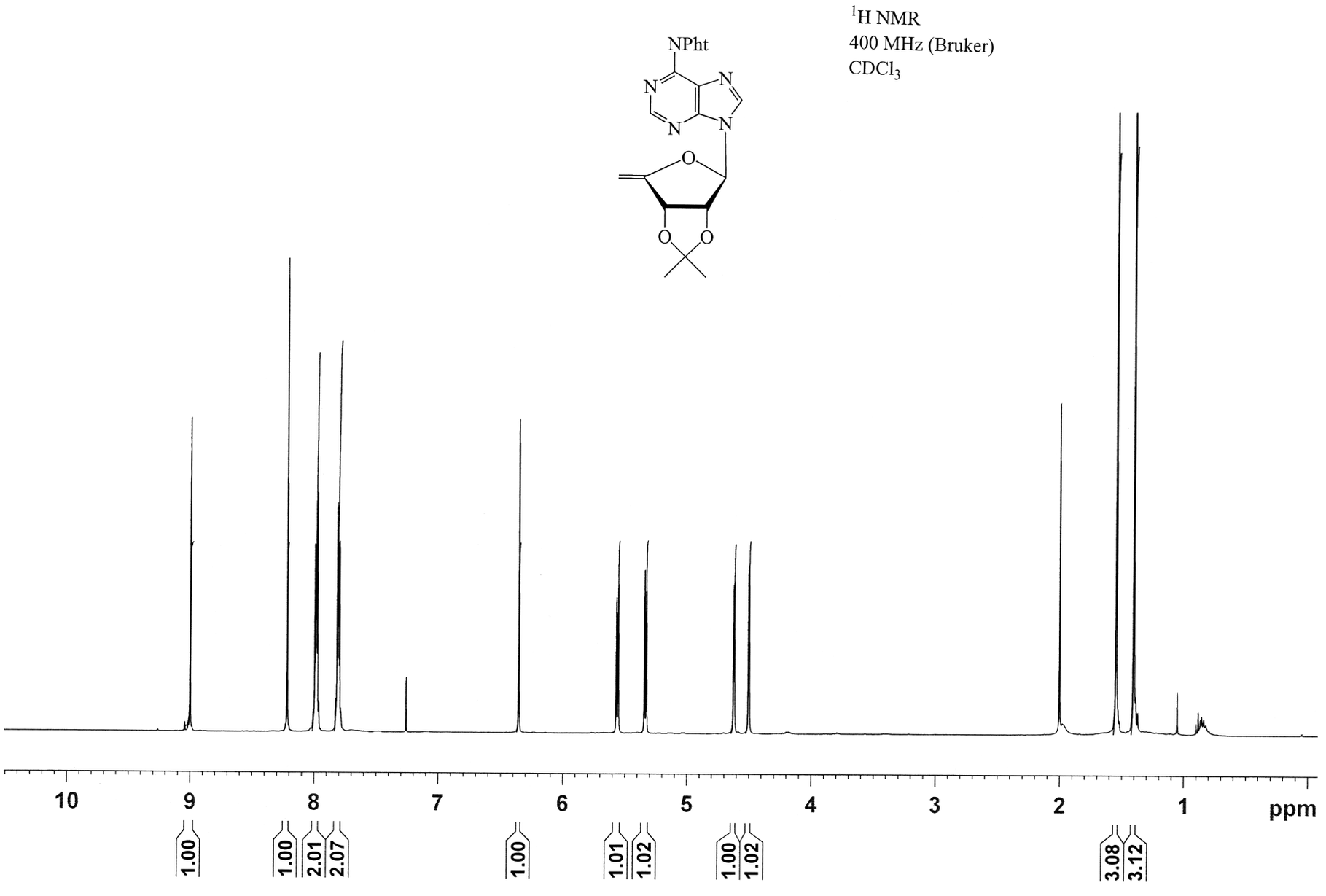


Fig. 4. Expansion of the gHMBC spectrum of compound **8a**.

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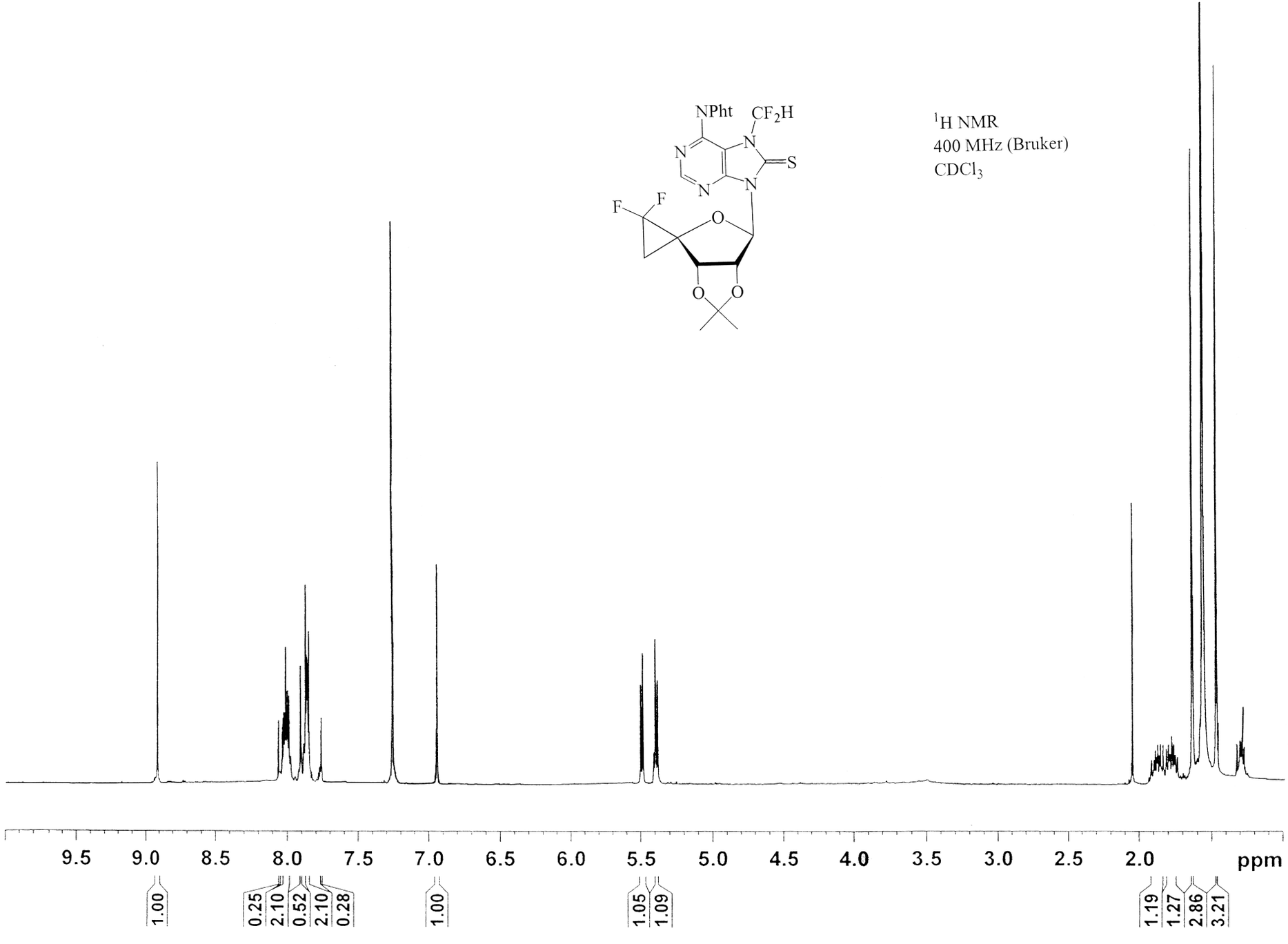
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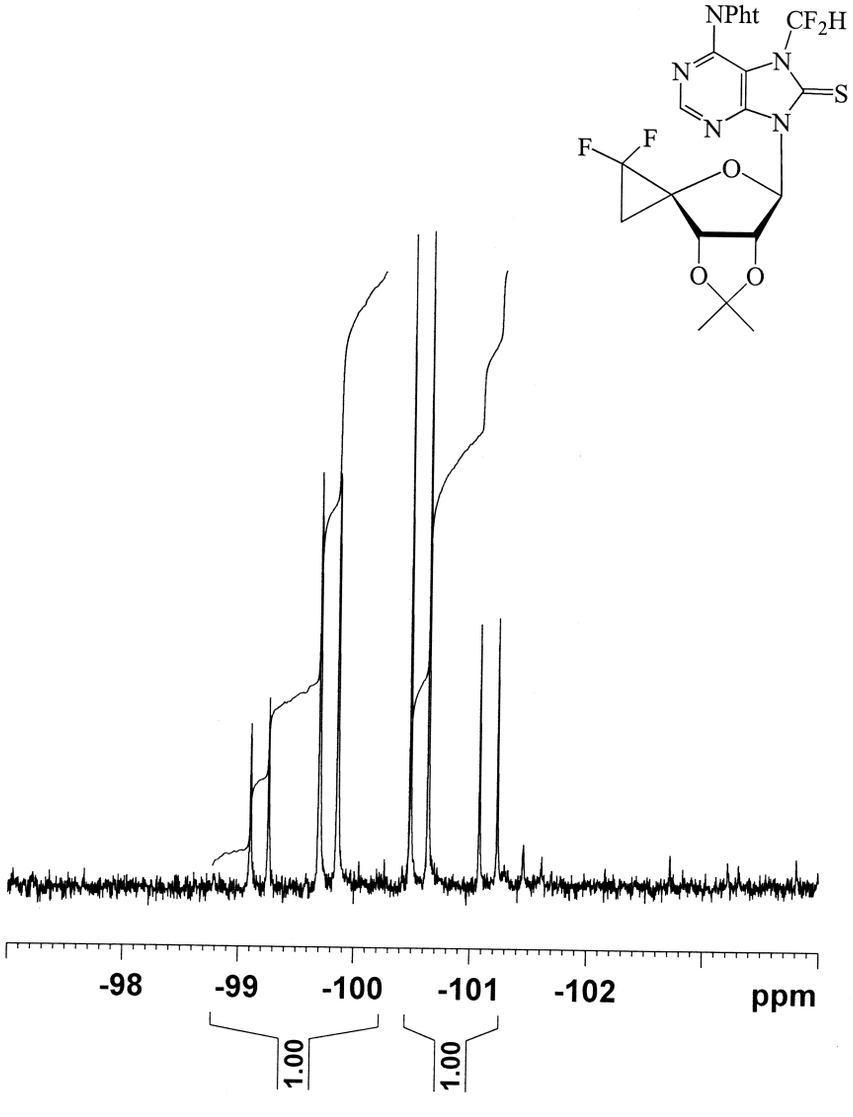

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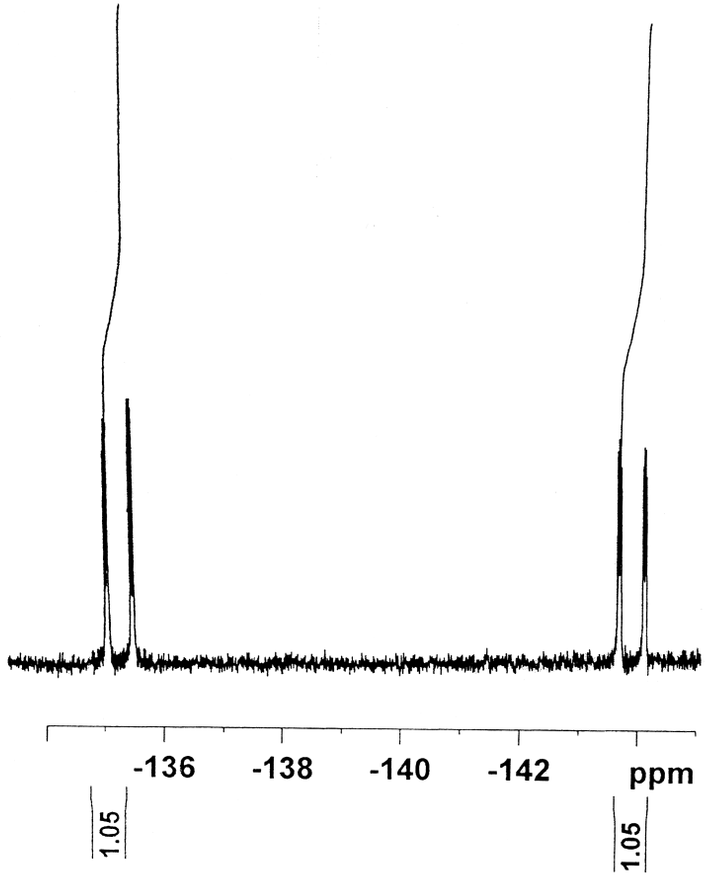

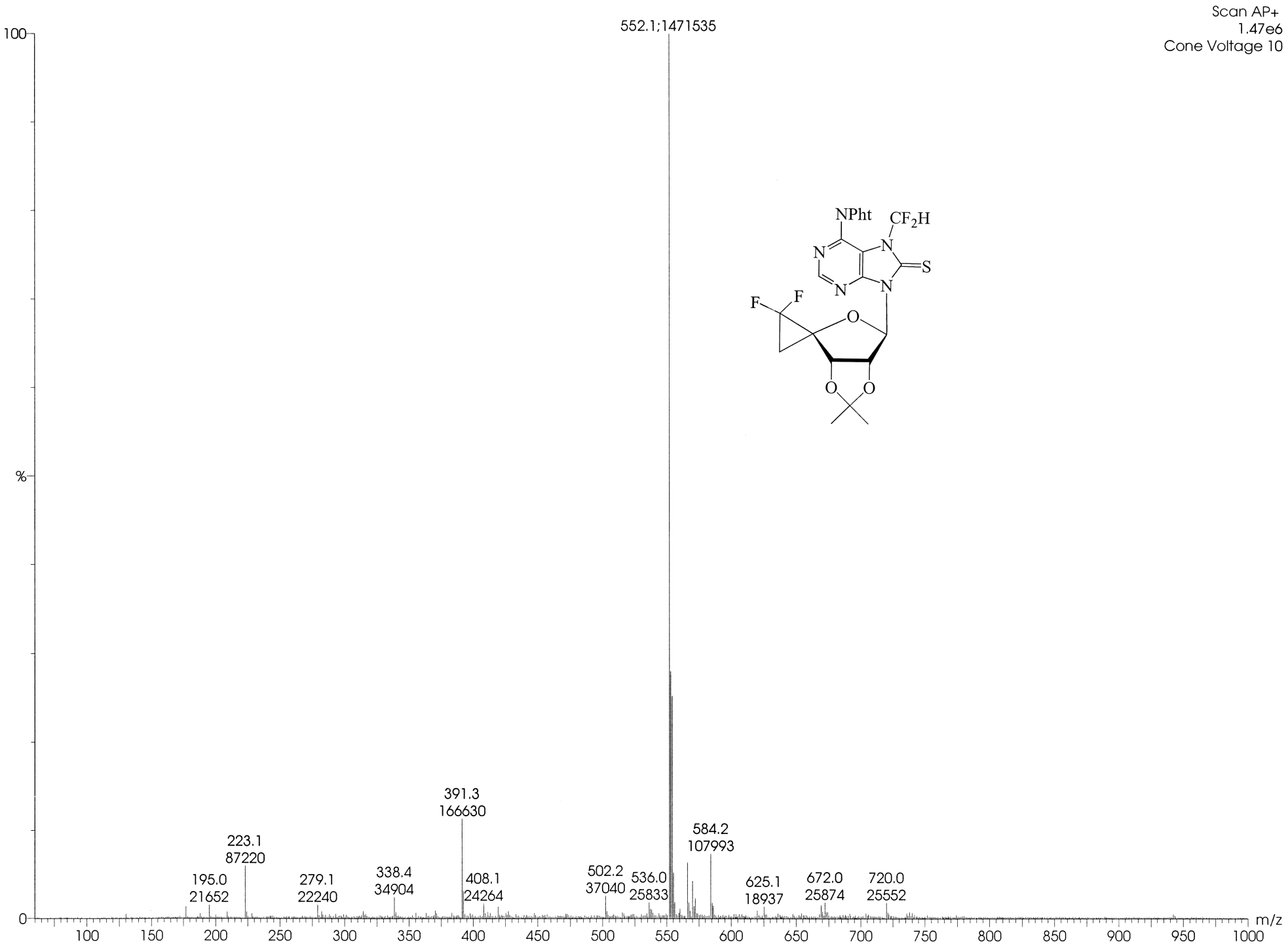
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