Synthesis of novel *C*-nucleoside analogues, bearing an anomeric cyano and a 1,2,3-triazole nucleobase, as potential antiviral agents

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Synthesis and X-ray crystallographic data for carbamoyl analogue of 5b, compound 5'b.

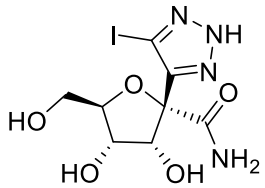
Following a two-steps procedure close to that described for compound **5b**, starting from **12b**, an hydrolysed form of **5b**, the α-carbamoyl compound **5'b** was isolated which DRX data could so confirmed the stereoselectivity of the cyanation step giving α-CN anomer.

*(2S,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)-2-(5-iodo-2H-1,2,3-triazol-4-yl)tetrahydrofuran-2-carboxamide (**5'b**)*

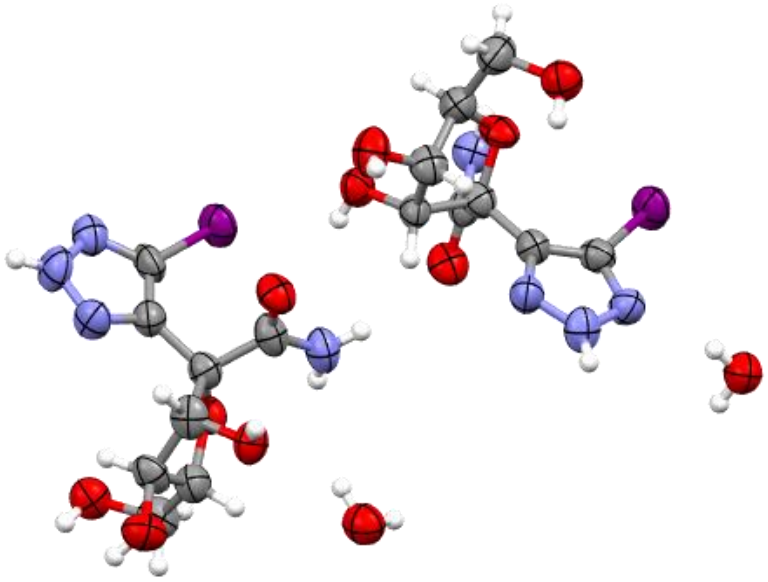
NaOH (2.7 mL of a 1 M aqueous solution, 4.40 mmol, 2 eq) was added to a stirring solution of **12b** (0.1 g, 1.36 mmol, 1 eq) in MeOH (5.5 mL, 0.25 M) at 0°C and the resulting mixture was stirred 1h at RT. It was neutralized with a 1 M HCl aqueous solution and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the expected *N*-triazole deprotected intermediate as a mixture of tautomers : HRMS (ESI^+): calcd for $[M+Na]^+$ $C_{29}H_{27}N_4O_4NaI$ = 368.9696; found 368.9695 . This latter was dissolved in dry DCM (5.4 mL, 0.1 M) and the resulting solution cooled to 0°C. BCl_3 (3.38 mL of a 1 M solution in DCM, 3.38 mmol, 5 eq) was added and the reaction mixture was stirred for 2h at this temperature. It was then quenched with cold MeOH and warmed to RT. The resulting mixture was kept stirring for 30 additional min. Volatiles were removed under reduced pressure and the obtained residue was dissolved in MeOH. It was evaporated to dryness again, and the procedure was repeated three times. Finally the obtained residue was purified by flash column chromatography on silica gel [DCM/MeOH, 8:2] to afford **5b** and **5'b** (130 mg, 0.35 mmol, 26% yield). ^{1}H NMR (300 MHz, DMSO-d_6, 298 K): δ (ppm) 14.9 (br, 1H, NH), 7.46 (d, J_{gem} = 1.9, 1H, $CONH_2$), 7.25 (d, J_{gem} = 1.9, 1H, $CONH_2$), 5.41 (d, $^3J_{OH\text{-}2'}$ = 5.4, 1H, $OH_{2'}$), 4.86 (d, $^3J_{OH\text{-}3'}$ = 8.3, 1H, $OH_{3'}$), 4.81 (dd, $^3J_{2'\text{-}OH}$ = 5.4, $^3J_{2'\text{-}3'}$ = 4.1, 1H, $H_{2'}$), 4.02 (ddd, $^3J_{4'\text{-}3'}$ = 8.5, $^3J_{4'\text{-}5'}$ = 5.3, $^3J_{4'\text{-}5'}$ = 3.2, 1H, $H_{4'}$), 3.88 (m, 1H, $H_{3'}$), 3.47 (dd, J_{gem} = 11.6, $^3J_{5'\text{-}4'}$ = 3.2, 1H, $H_{5'}$), 3.25 (dd, J_{gem} = 11.6, $^3J_{5'\text{-}4'}$ = 5.3, 1H, $H_{5'}$. ^{13}C NMR (100 MHz, CD_3OD, 303 K): δ (ppm) 174.3 (CO), 148.6 (C_4) 87.9 (C_5), 86.8 ($C_{1'}$), 85.4 ($C_{4'}$), 76.8 ($C_{2'}$), 73.2 ($C_{3'}$), 63.7 ($C_{5'}$). HRMS (ESI-): calcd for $[M+Na]^+$ $C_8H_{10}N_4O_5I$ = 368.9696; found 368.9695.

X-ray single-crystal diffraction data were collected on a Rigaku Oxford Diffraction SuperNova diffractometer equipped with Atlas CCD detector and micro-focus Cu-K_α radiation (λ = 1.54184 Å). The structures were solved by dual-space algorithm, expanded and refined on F^2 by full matrix least-squares techniques using SHELX programs (G. M. Sheldrick, SHELXT 2018/2 and SHELXL 2018/3). All non-H atoms were refined anisotropically and multiscan empirical absorption was corrected using CrysAlisPro program (CrysAlisPro, Agilent Technologies, V1.171.38.46, 2015 for **5'b**. The H atoms were placed at calculated positions and refined using a riding model.

Crystallographic data for **5'b**:



$C_{16}H_{26}I_2N_8O_{12}$, M = 776.25, T=294K, colorless needle, 0.072 x 0.035 x 0.016 mm^3, monoclinic, space group $P2_1$, a = 7.1449(9) Å, b = 15.429(3) Å, c = 11.890(2) Å, β = 99.95(1)°, V = 1291.0(4) $Å^3$, Z = 2, ρcalc = 1.997 g/cm^3, μ = 19.813 mm^{-1}, F(000) = 760, θmin = 3.774°, θmax = 73.497°, 6796 reflections collected, 4304 unique (R_{int} = 0.0652), parameters / restraints = 349 / 1, R1 = 0.0641 and wR2 = 0.1486 using 2910 reflections with I>2σ(I), R1 = 0.0904 and wR2 = 0.1763 using all data, absolute structure parameter = -0.02(2), GOF = 0.997, -1.336 < Δρ < 0.925 $e.Å^{-3}$.



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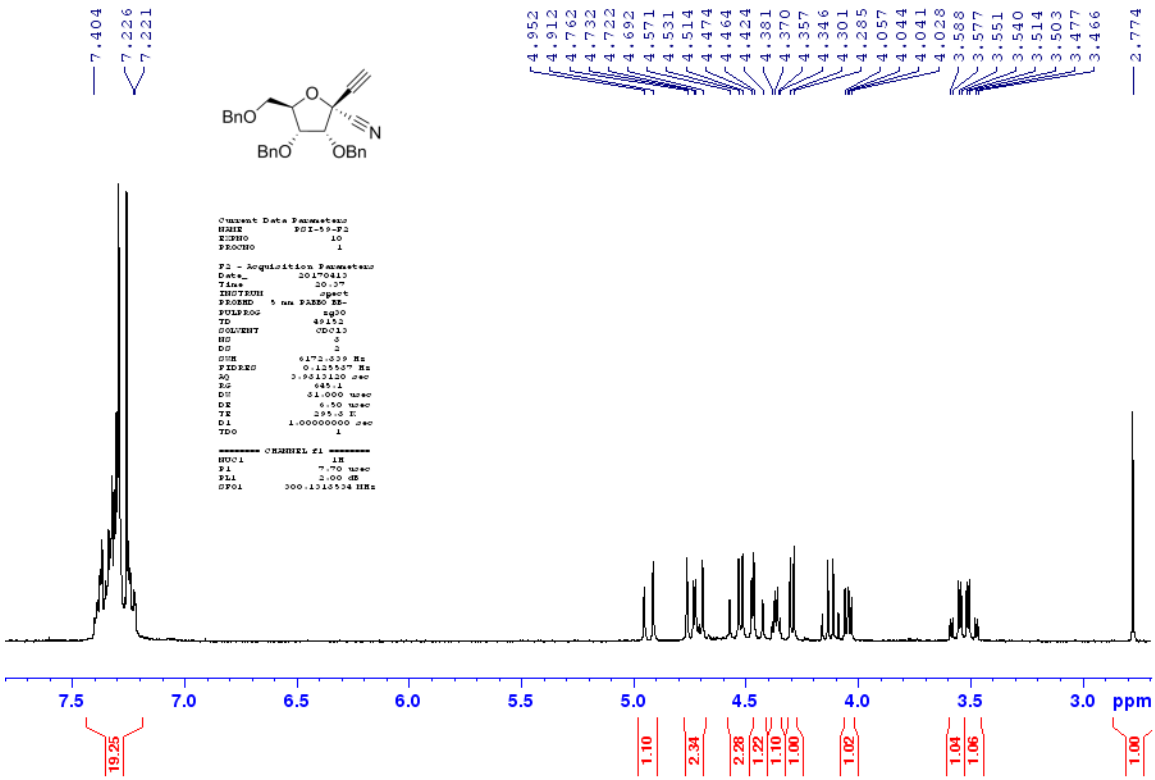

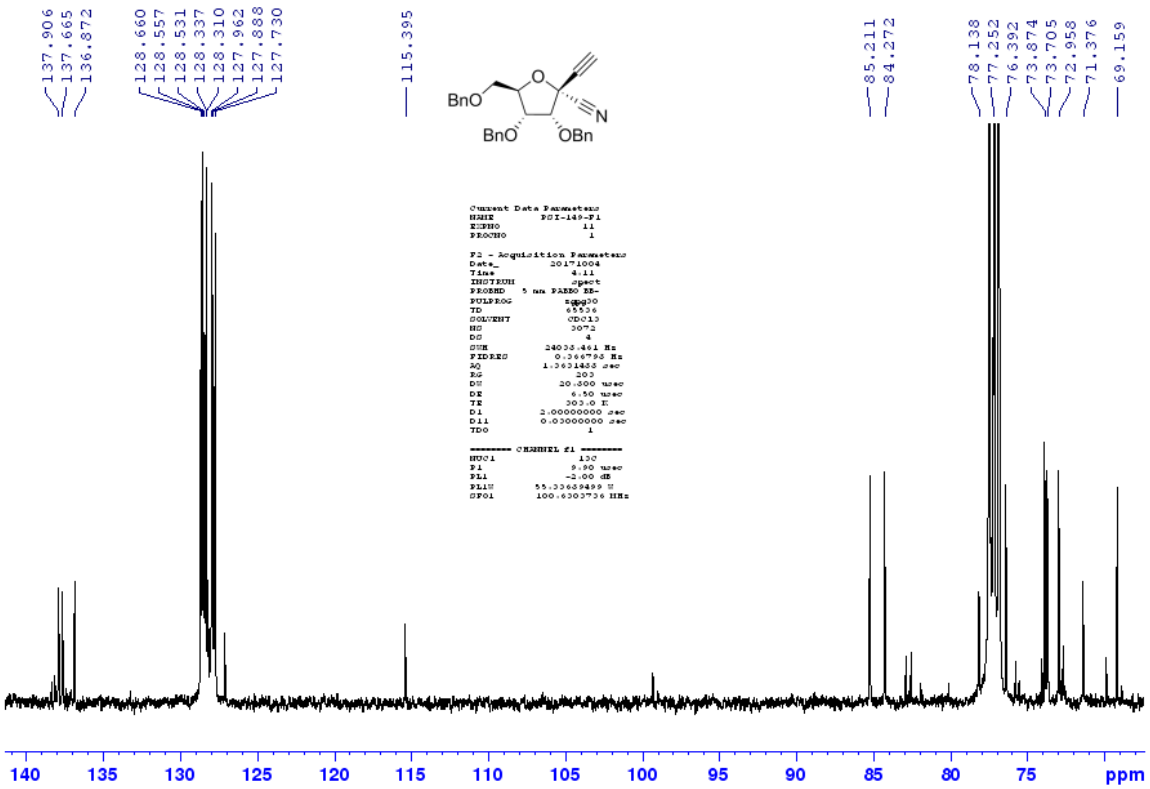

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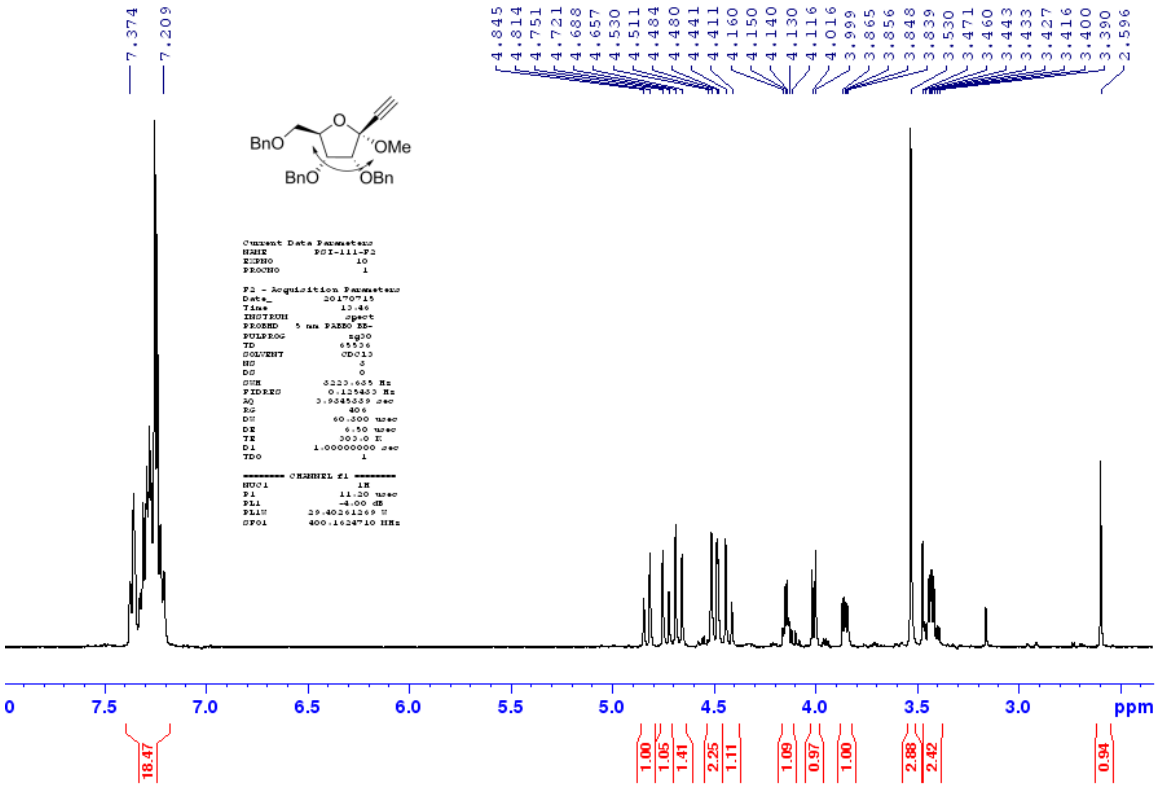

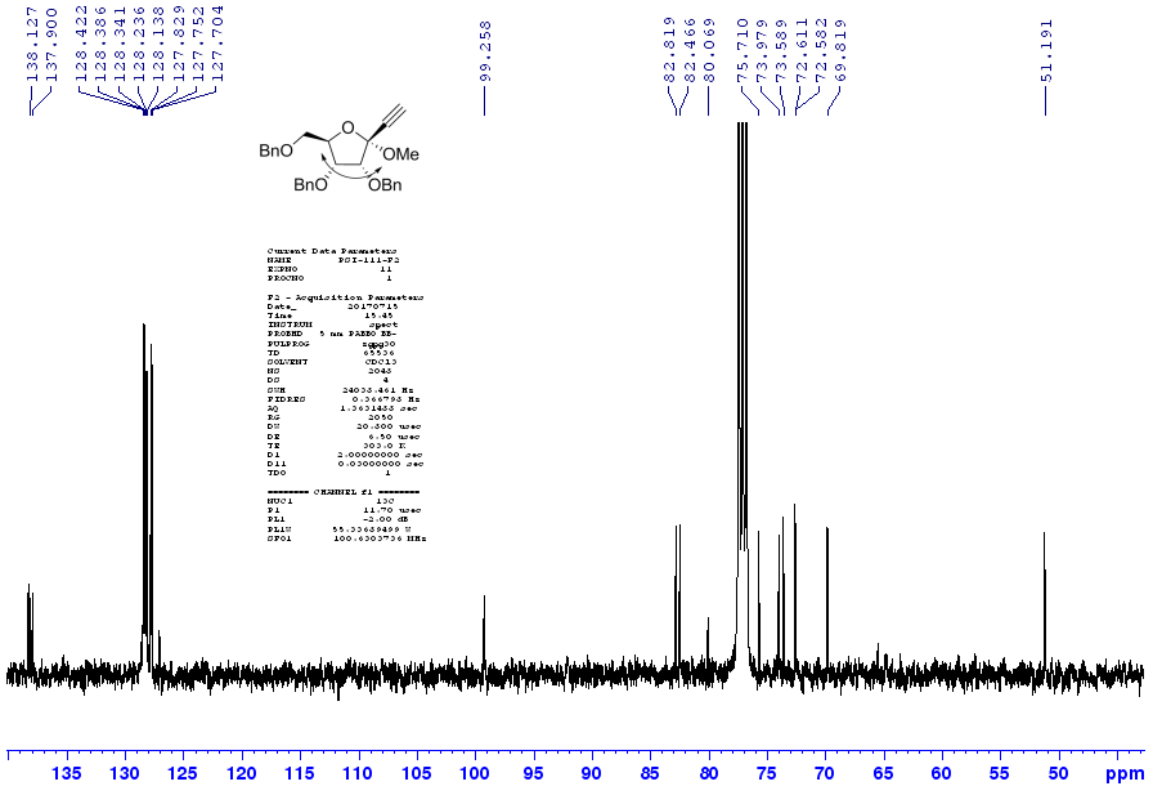

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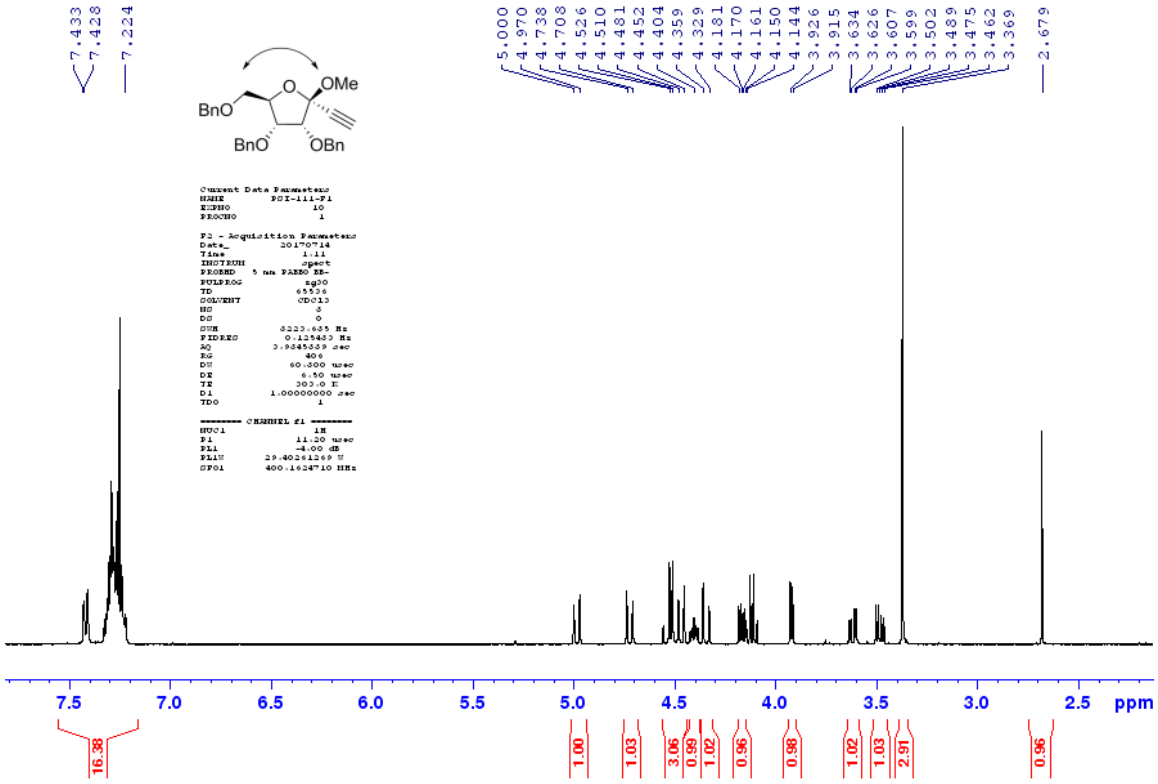

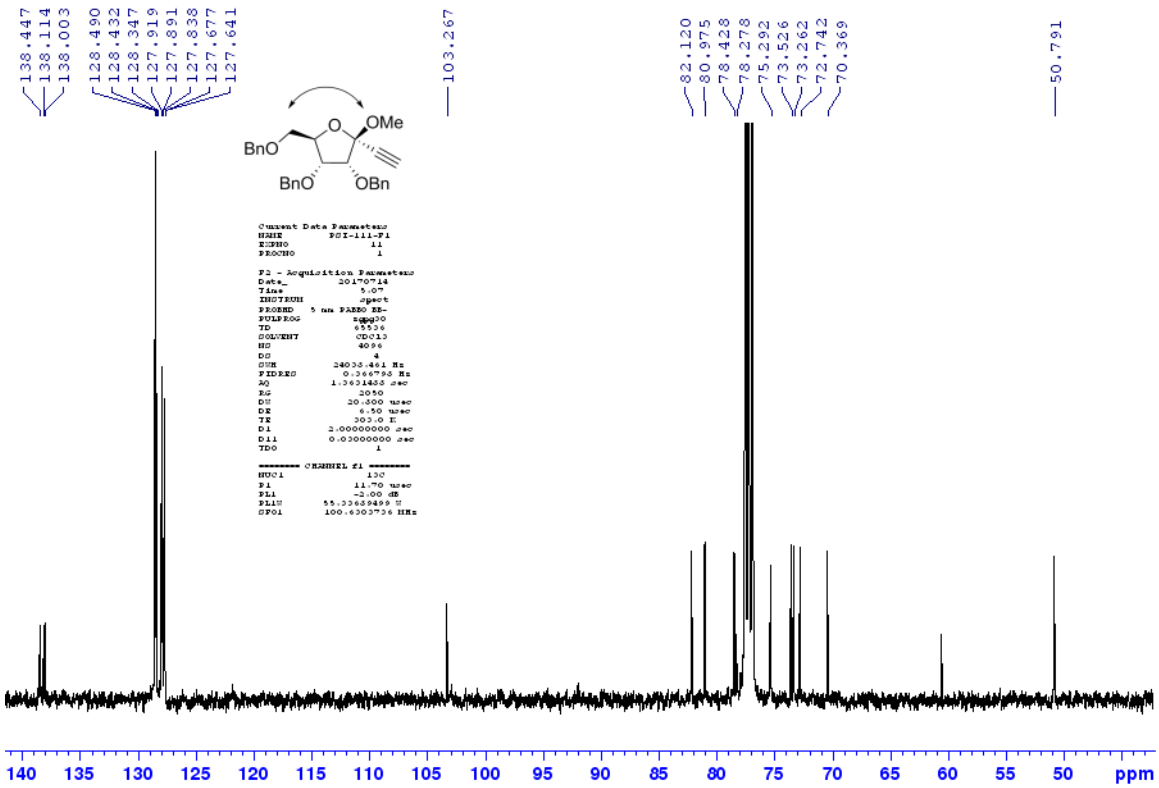

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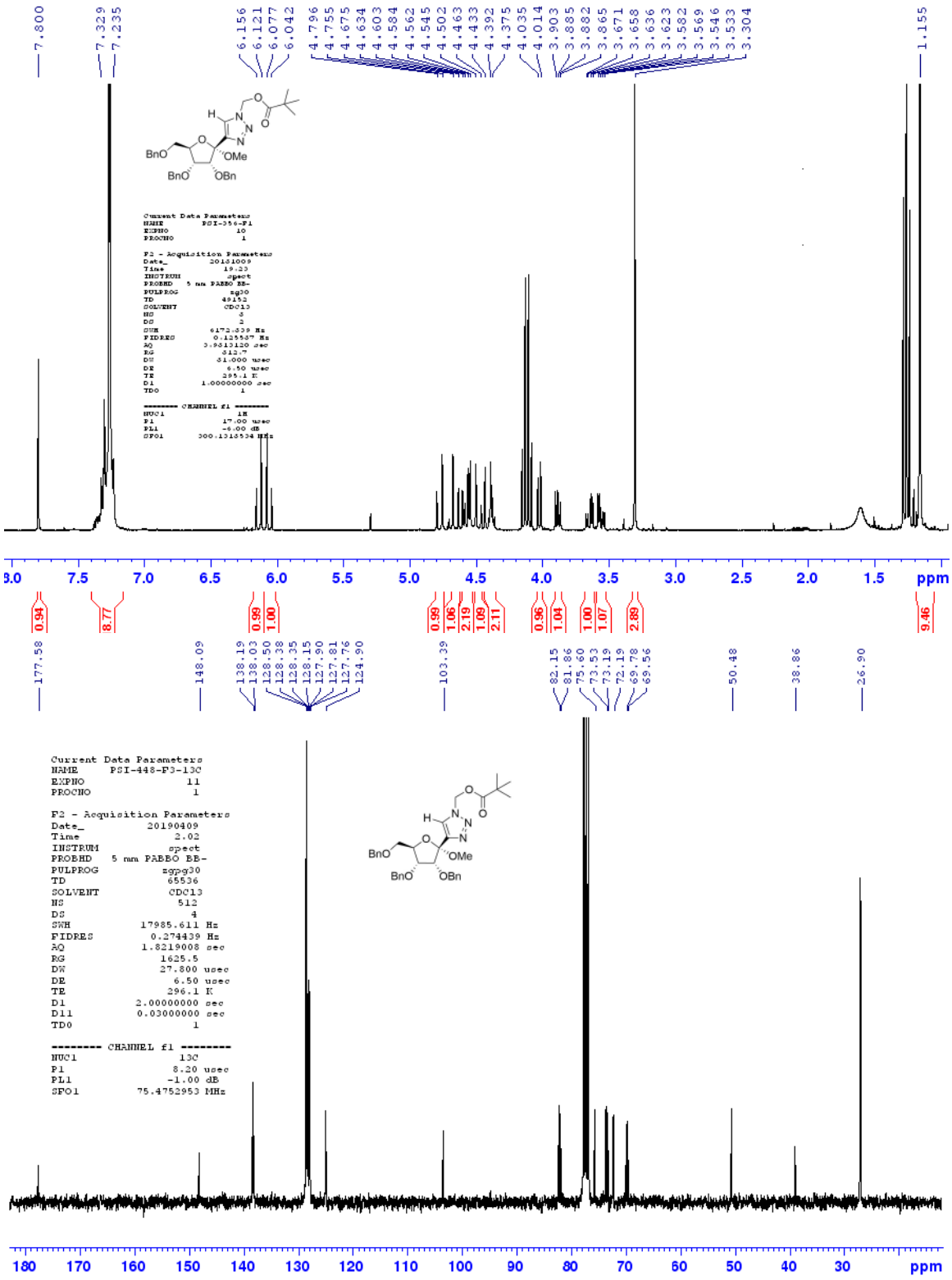

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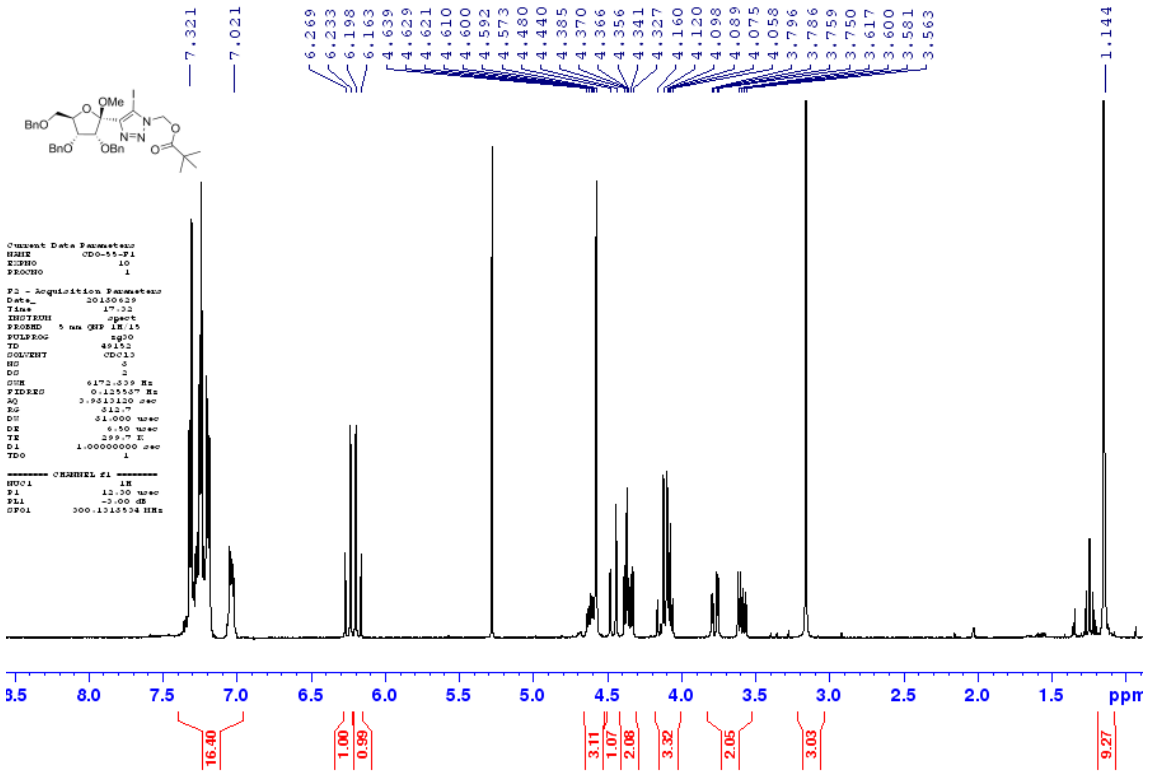

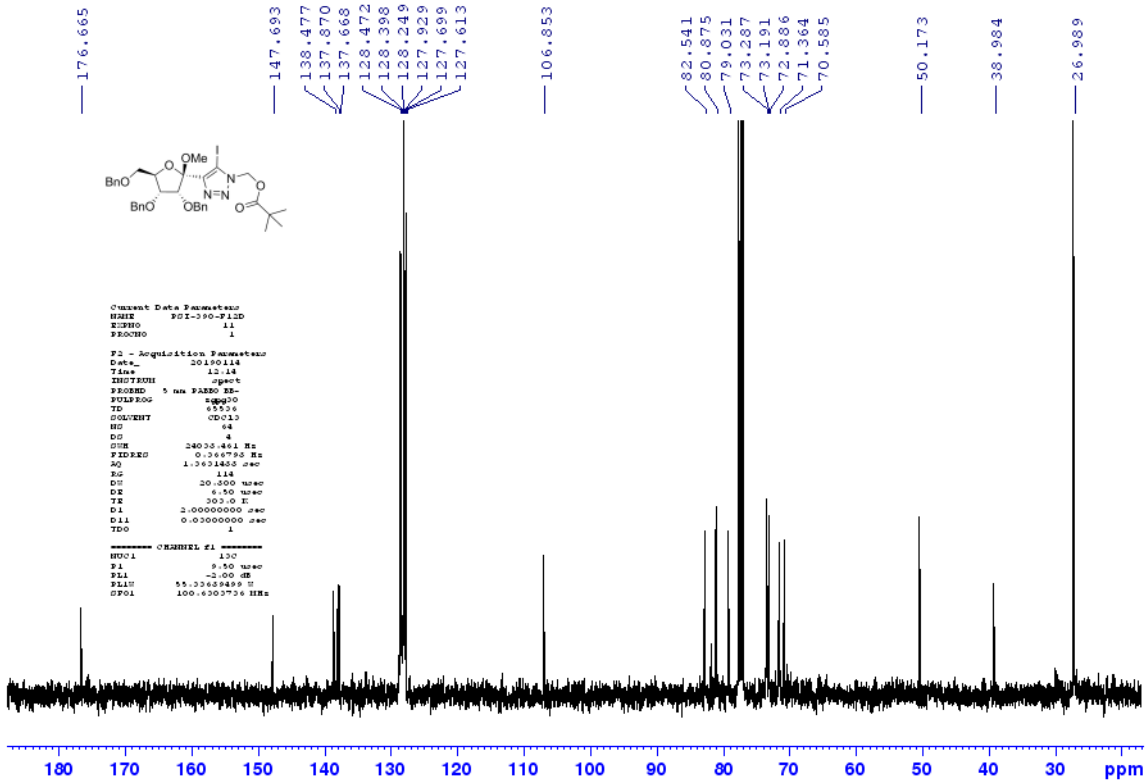

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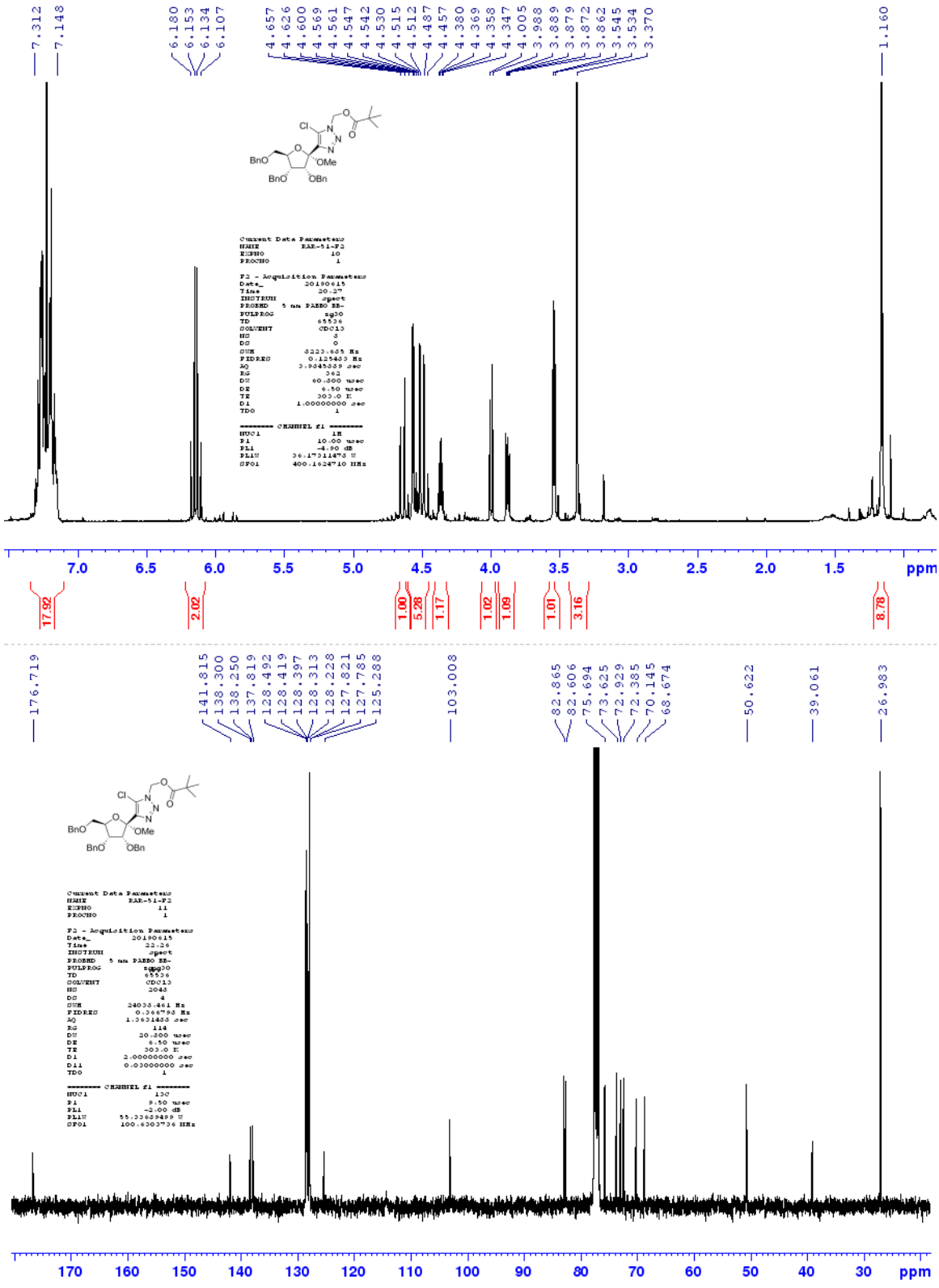

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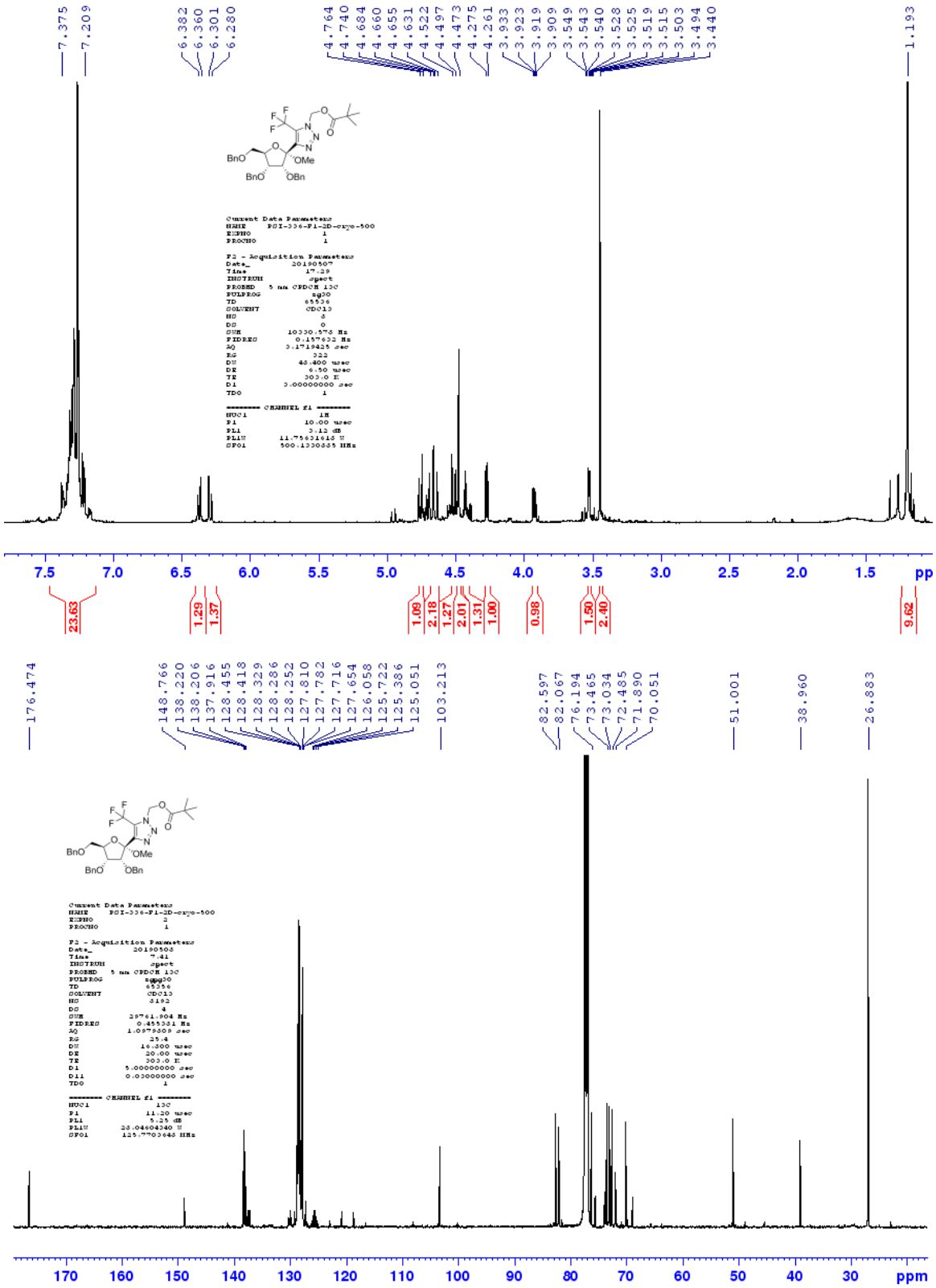

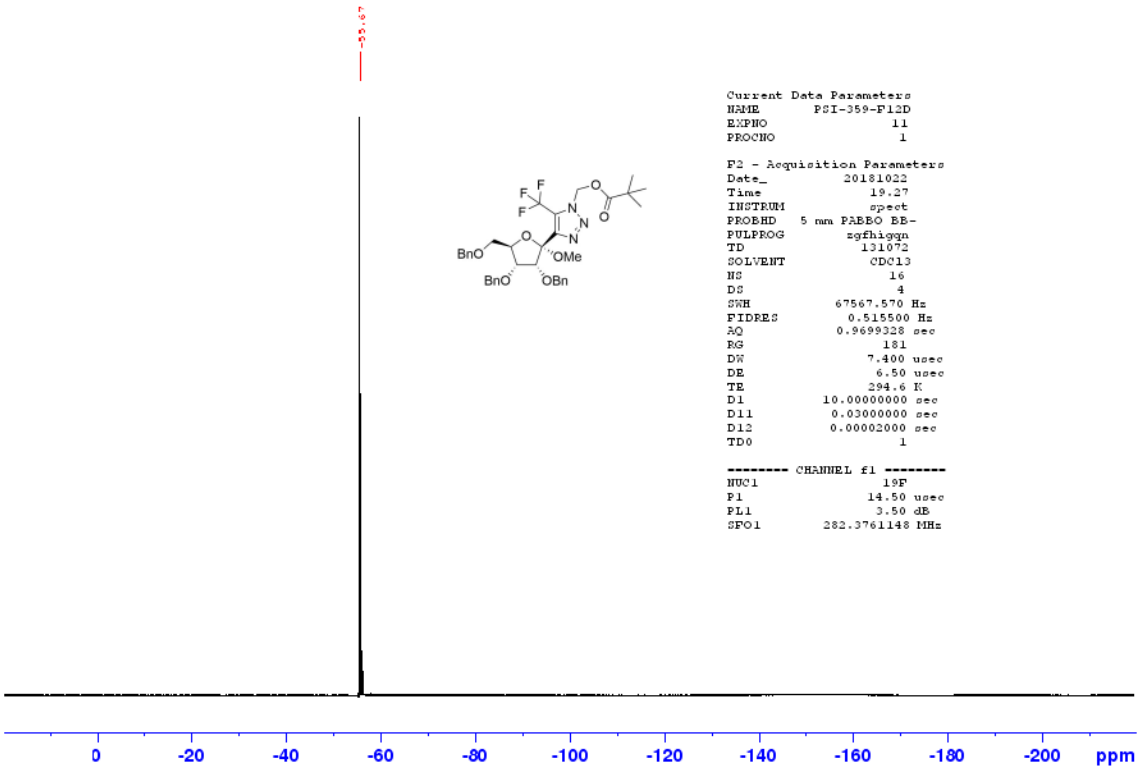


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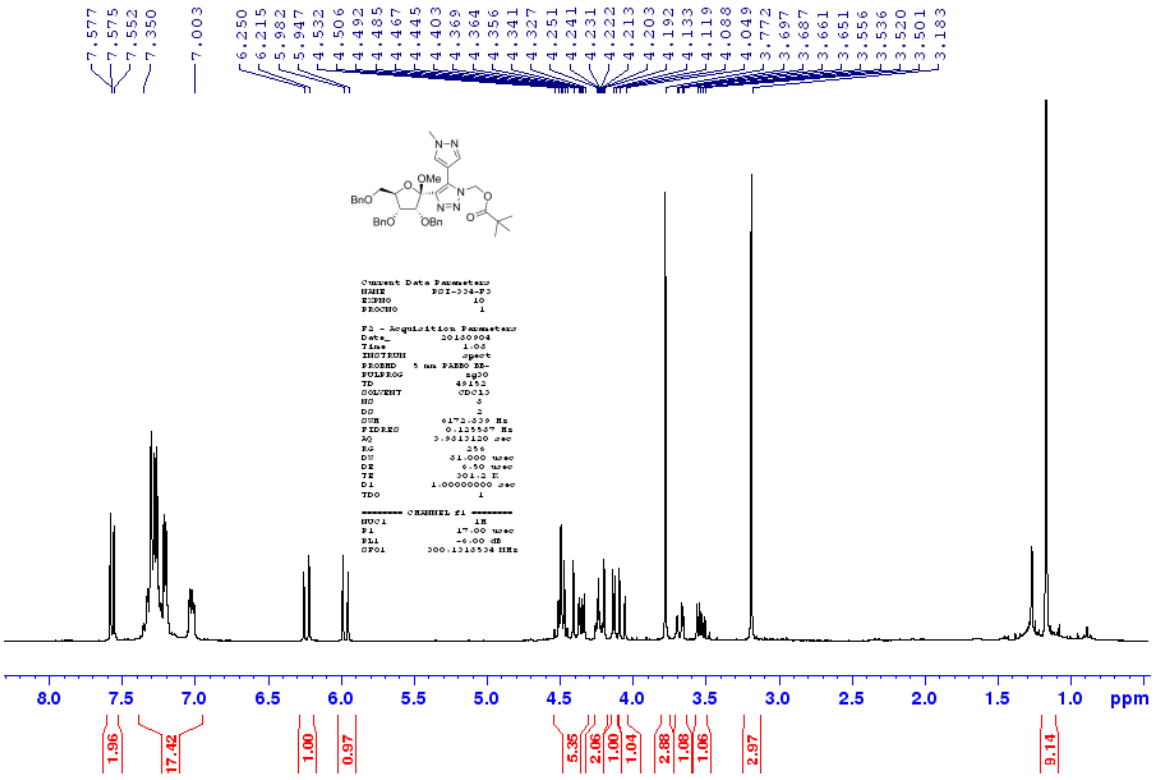
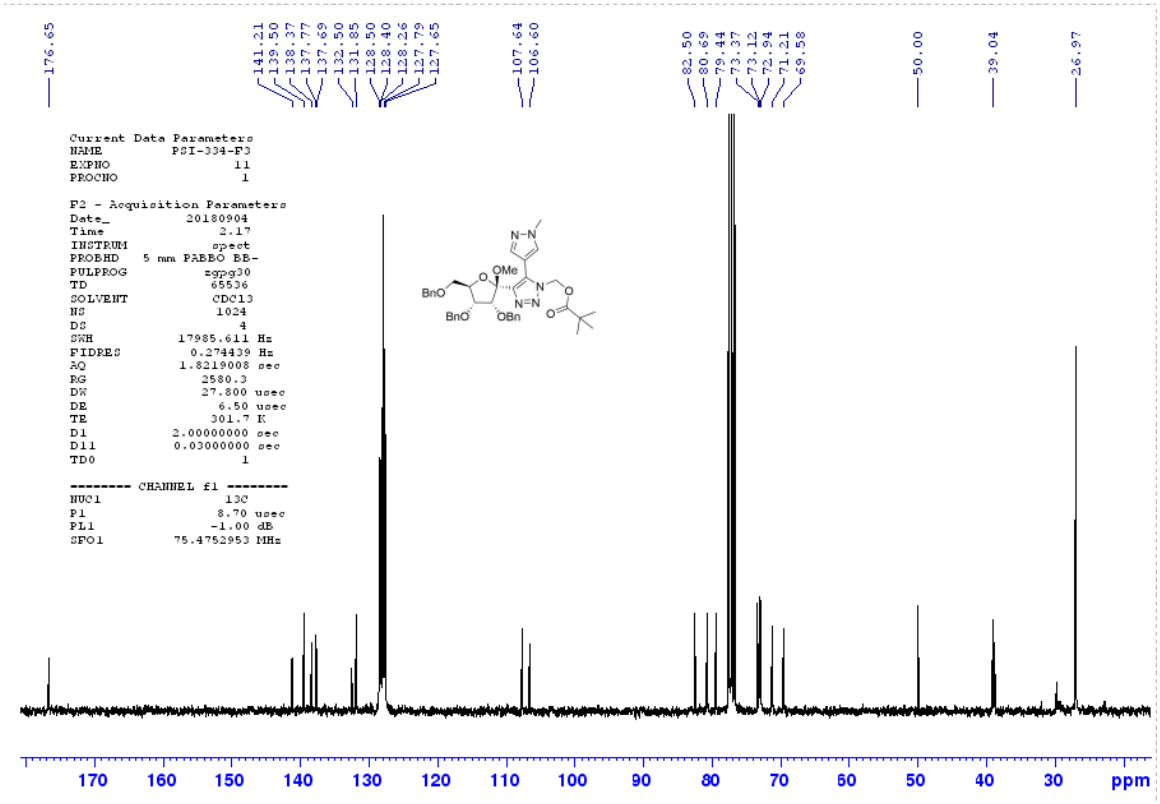
^{1}H and ^{13}C NMR spectra of compound (11h)





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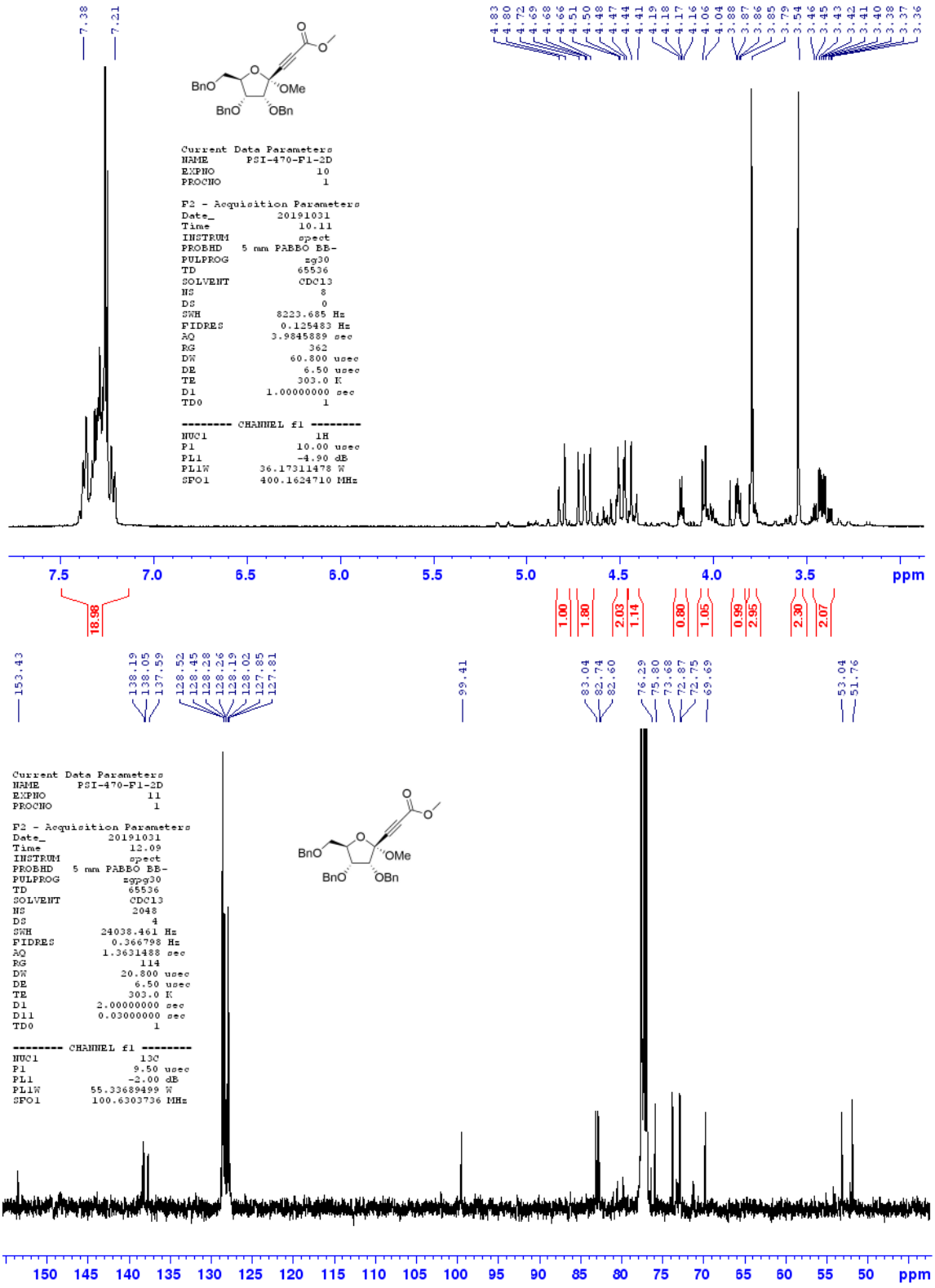

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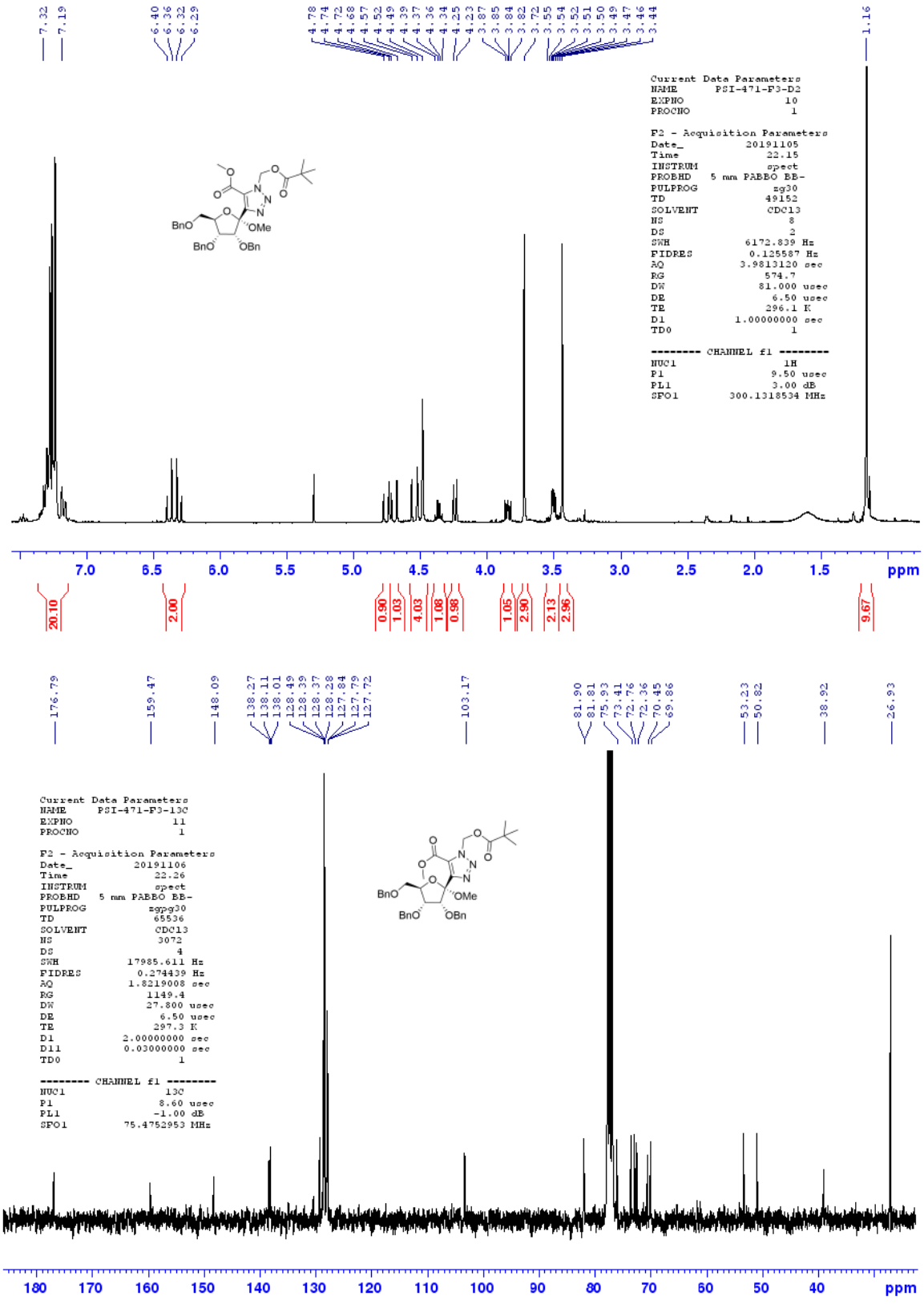

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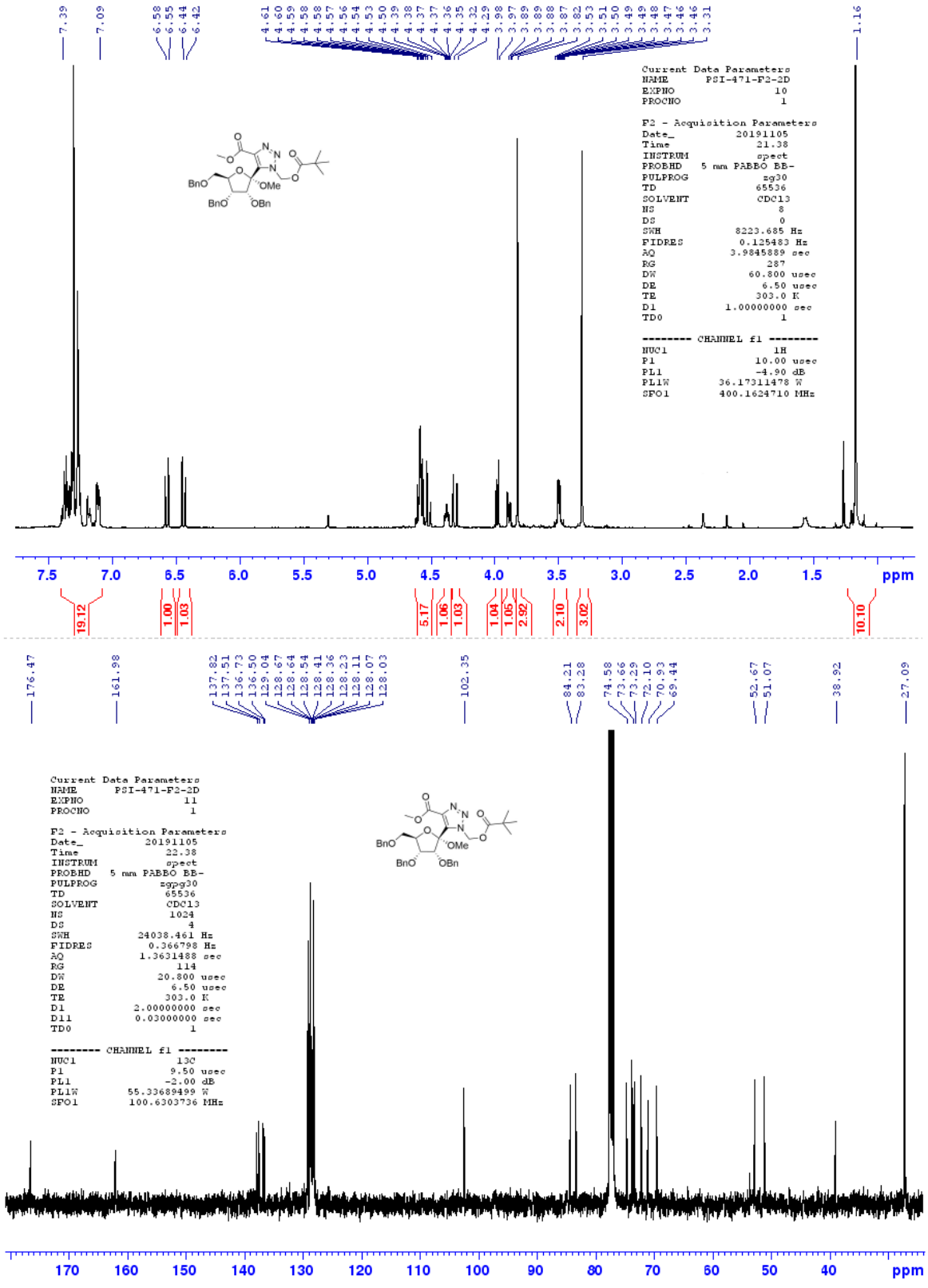

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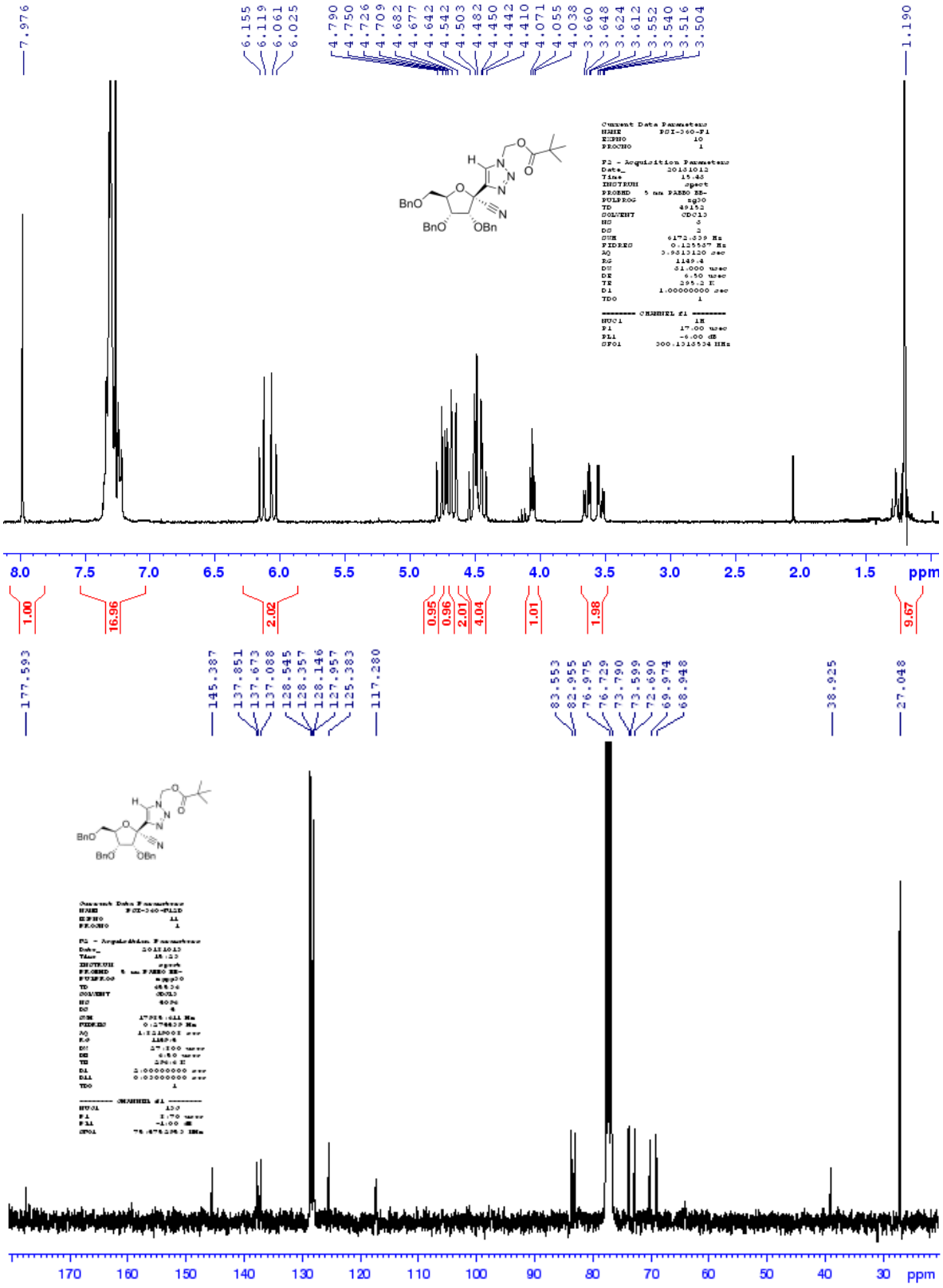

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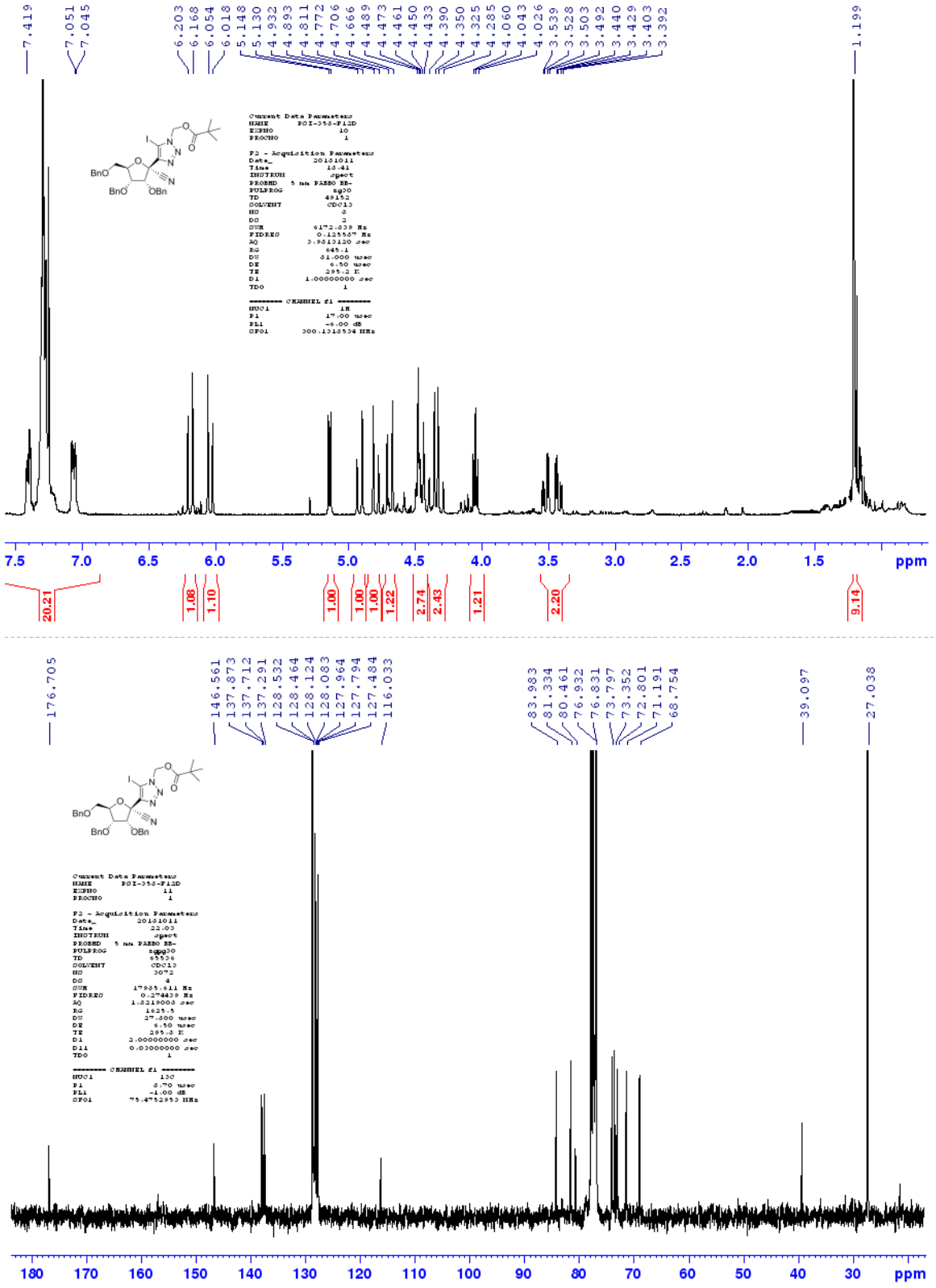

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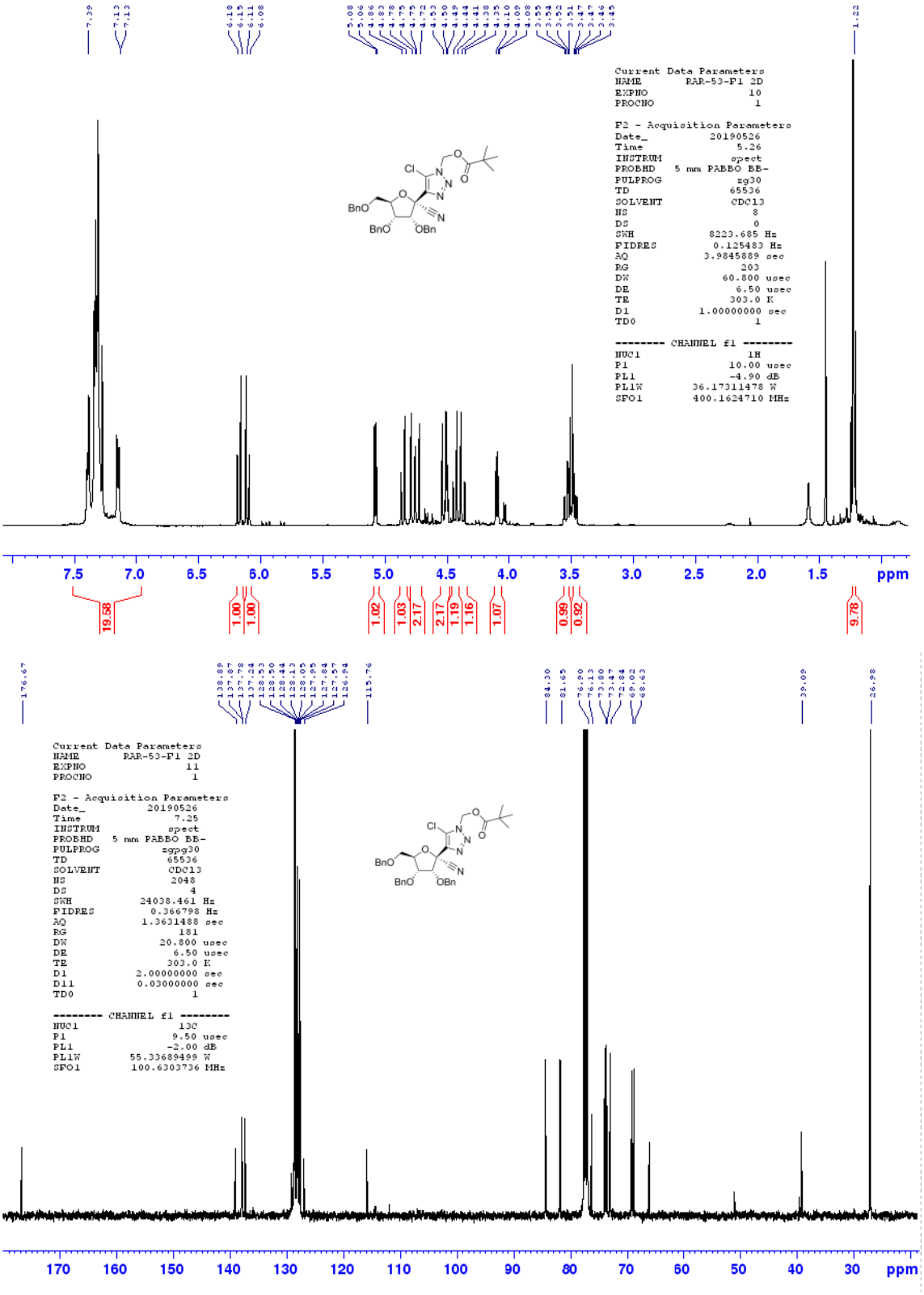

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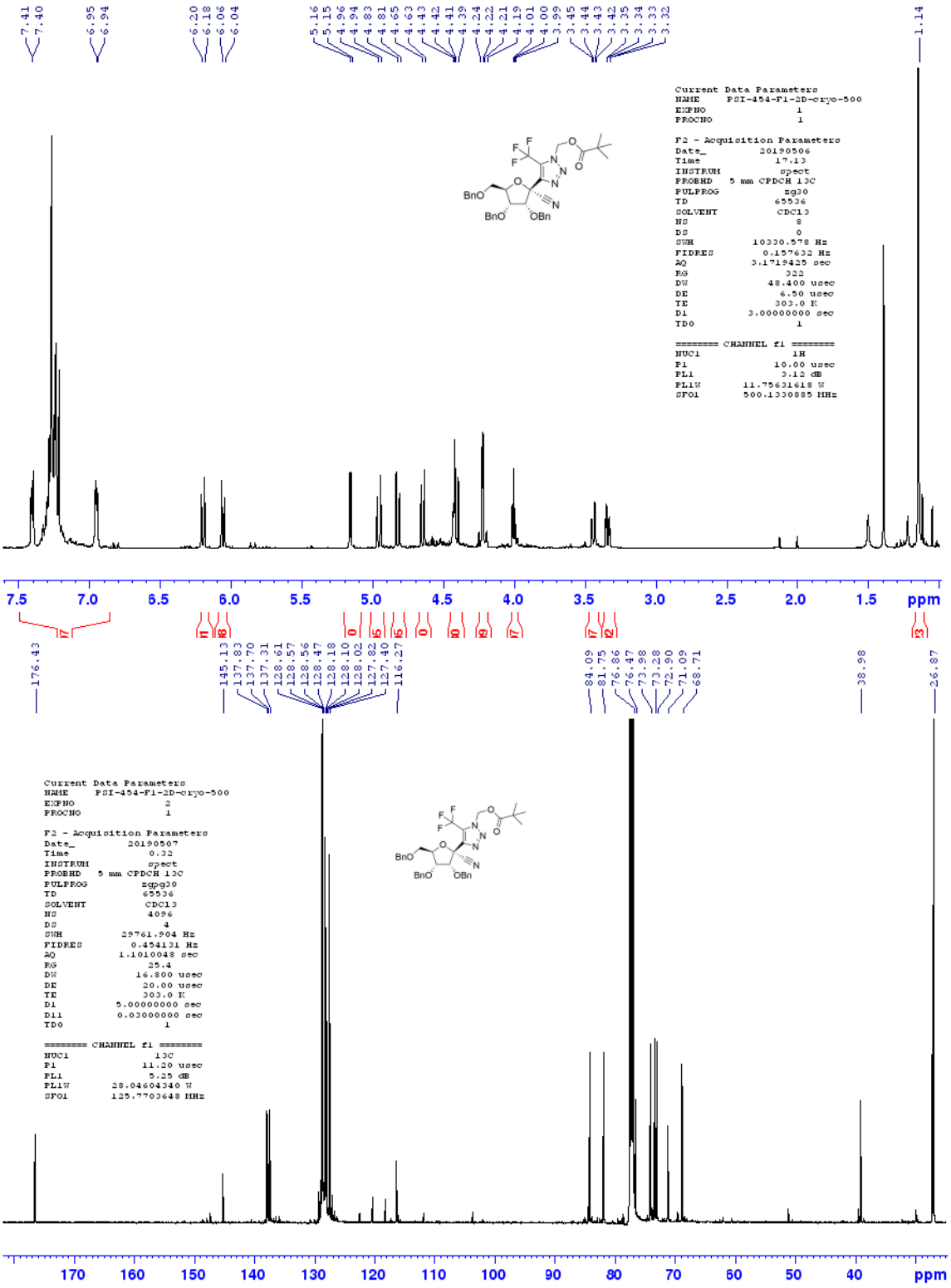

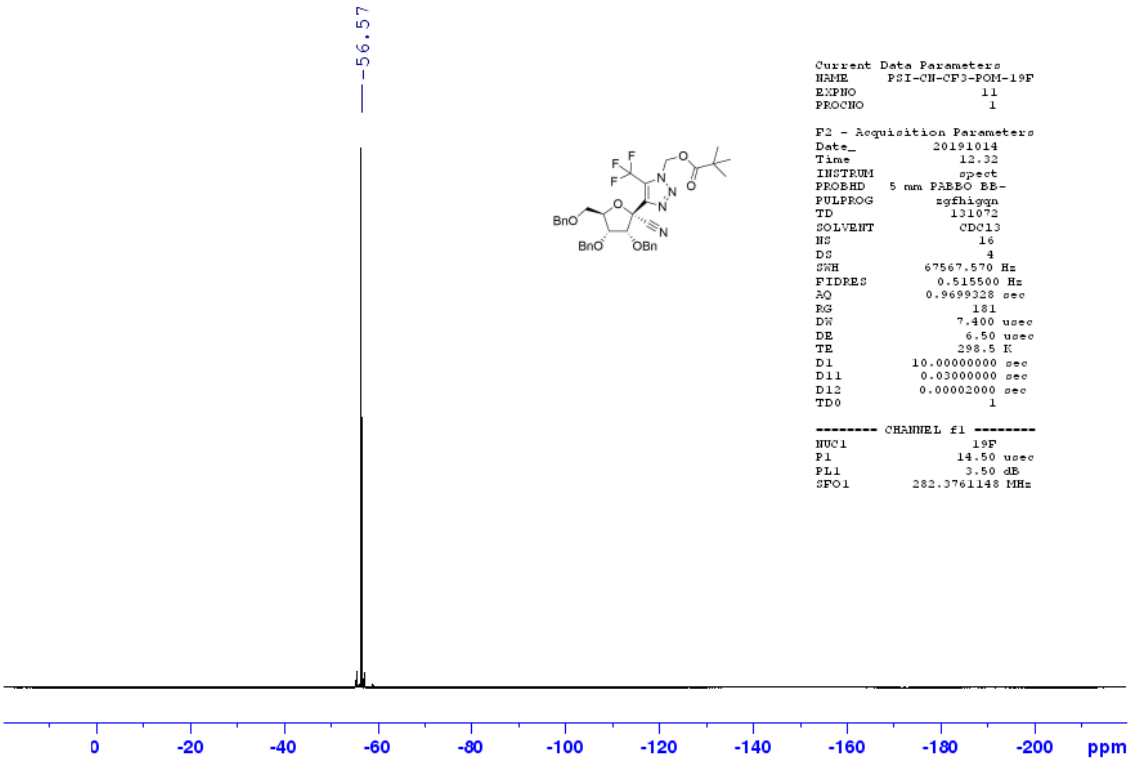
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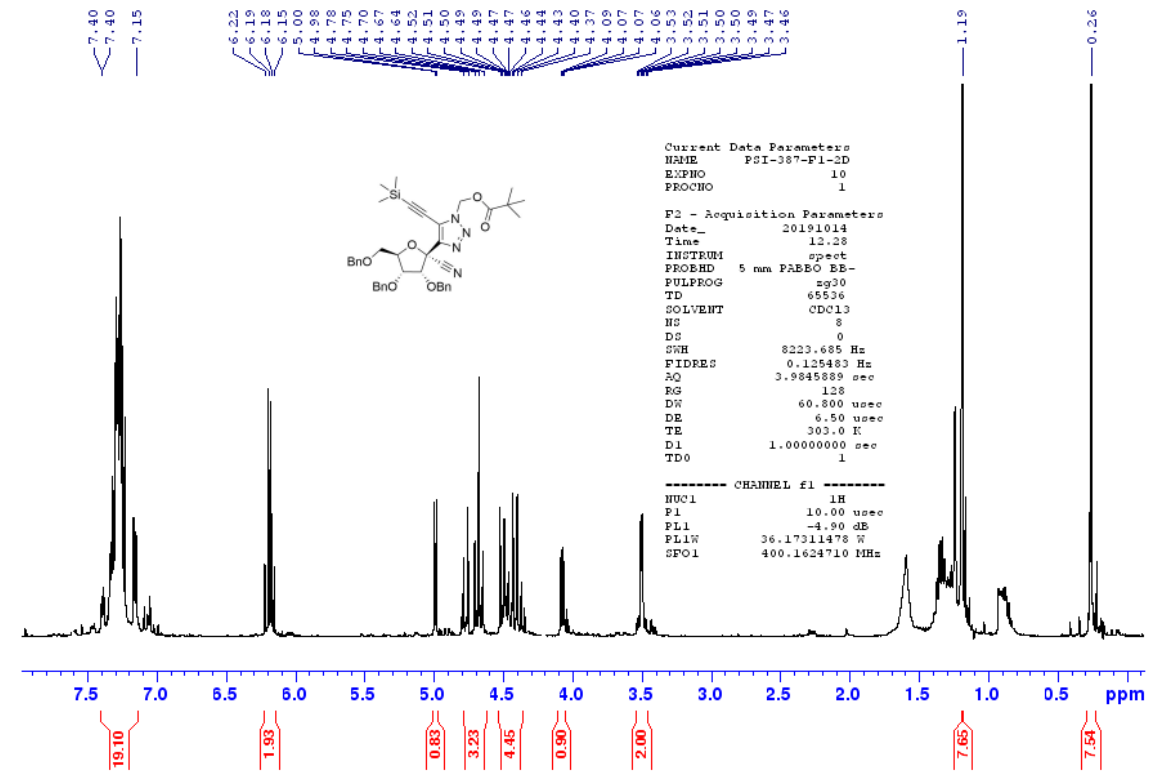

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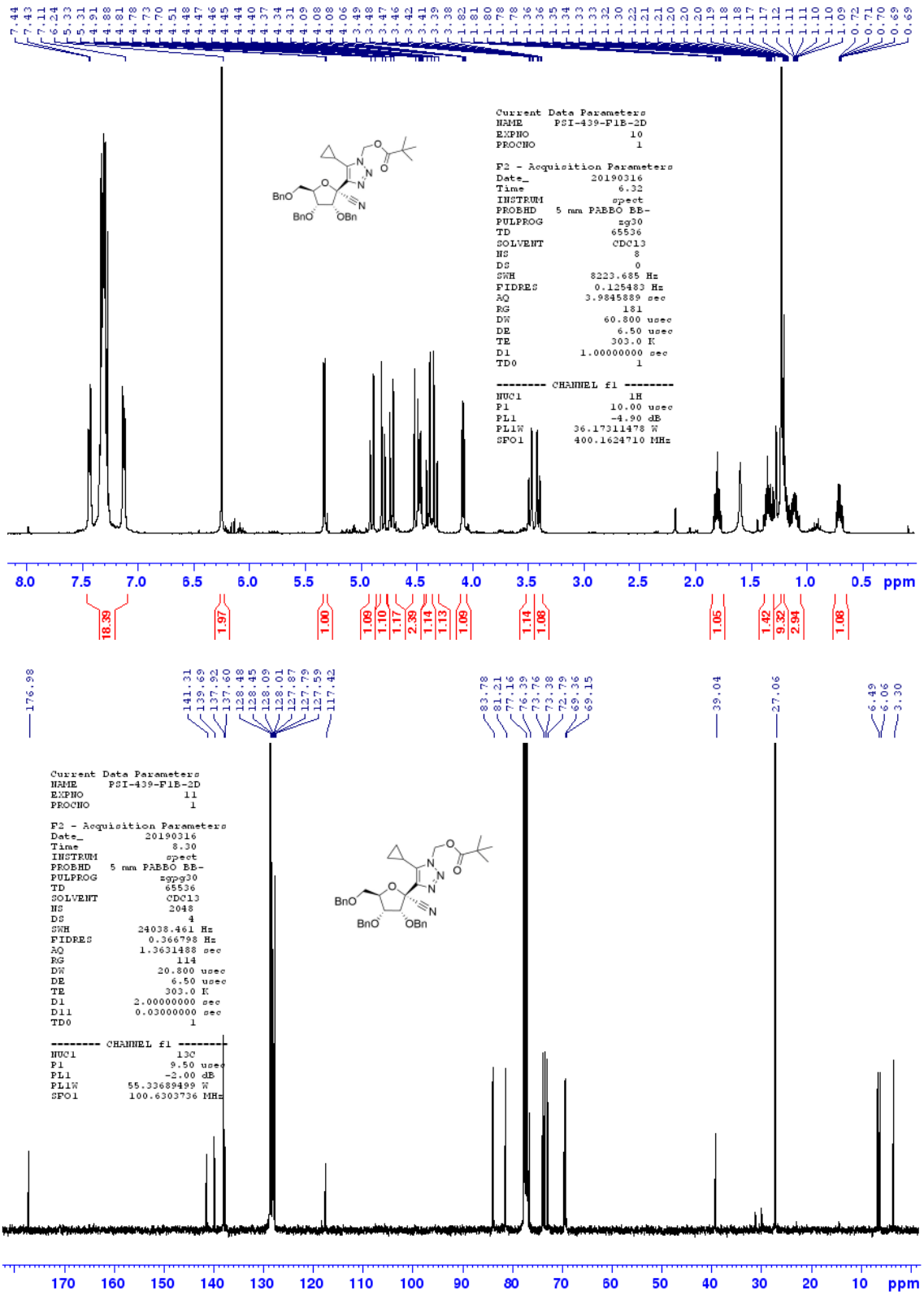

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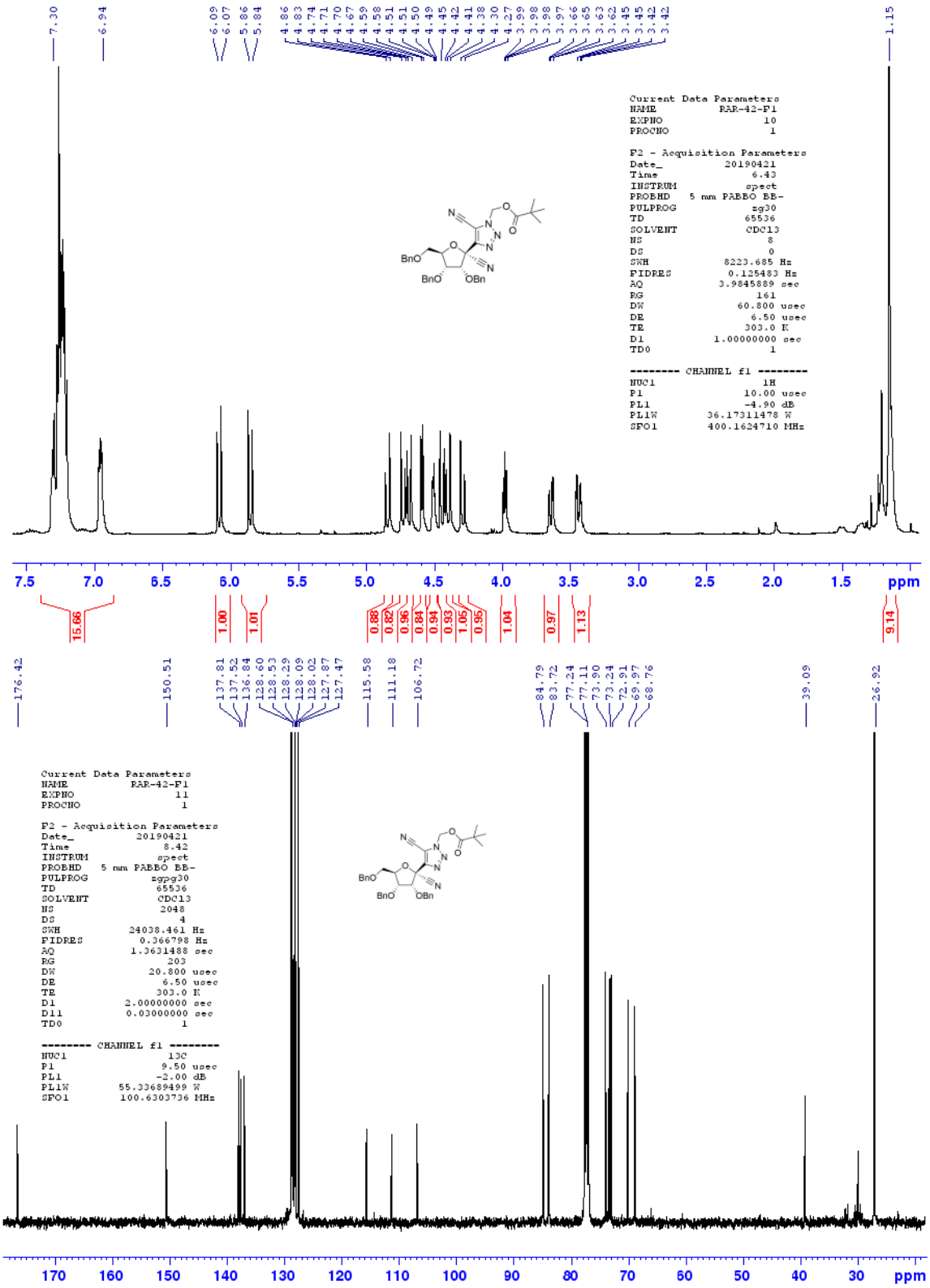

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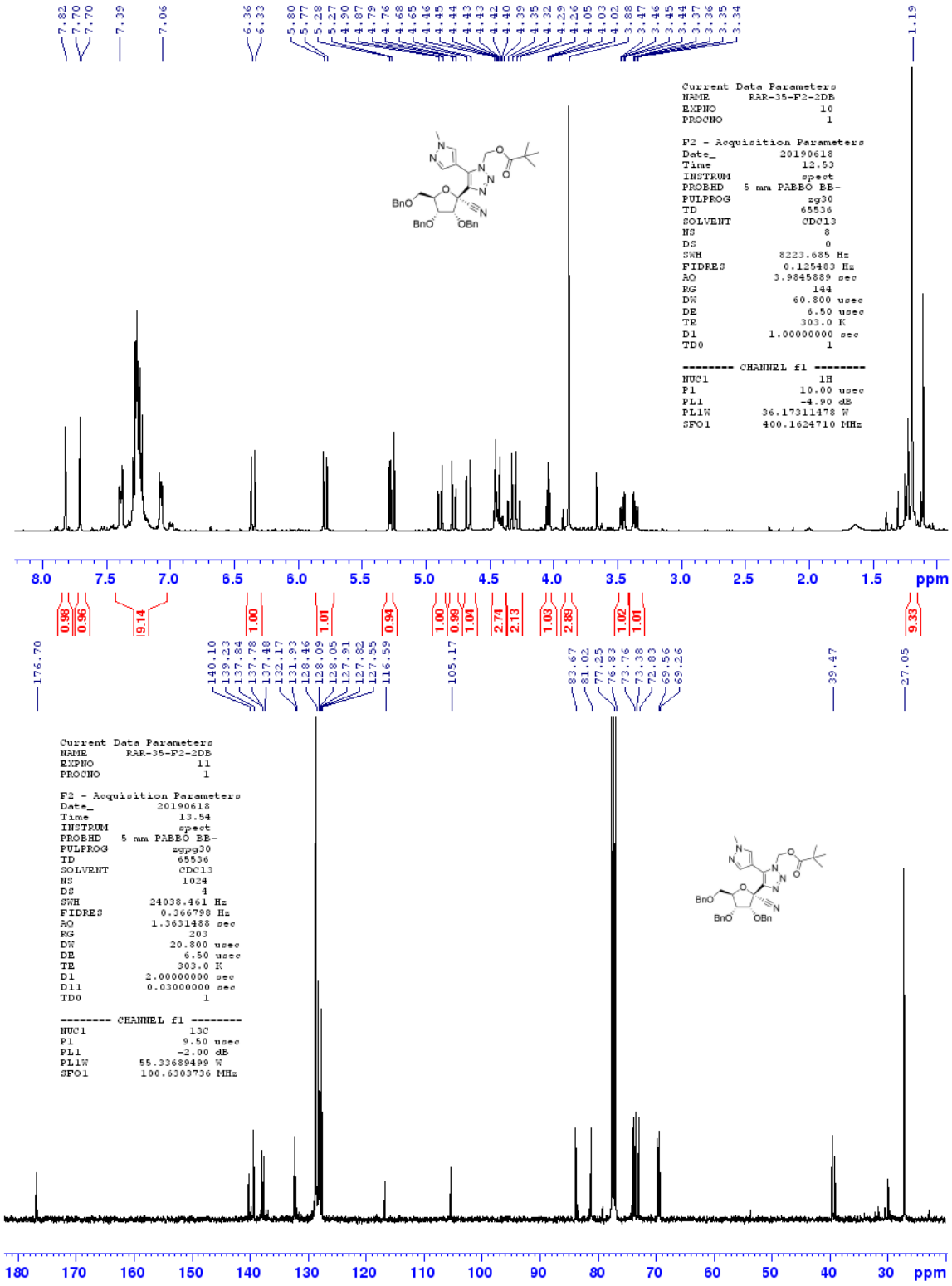

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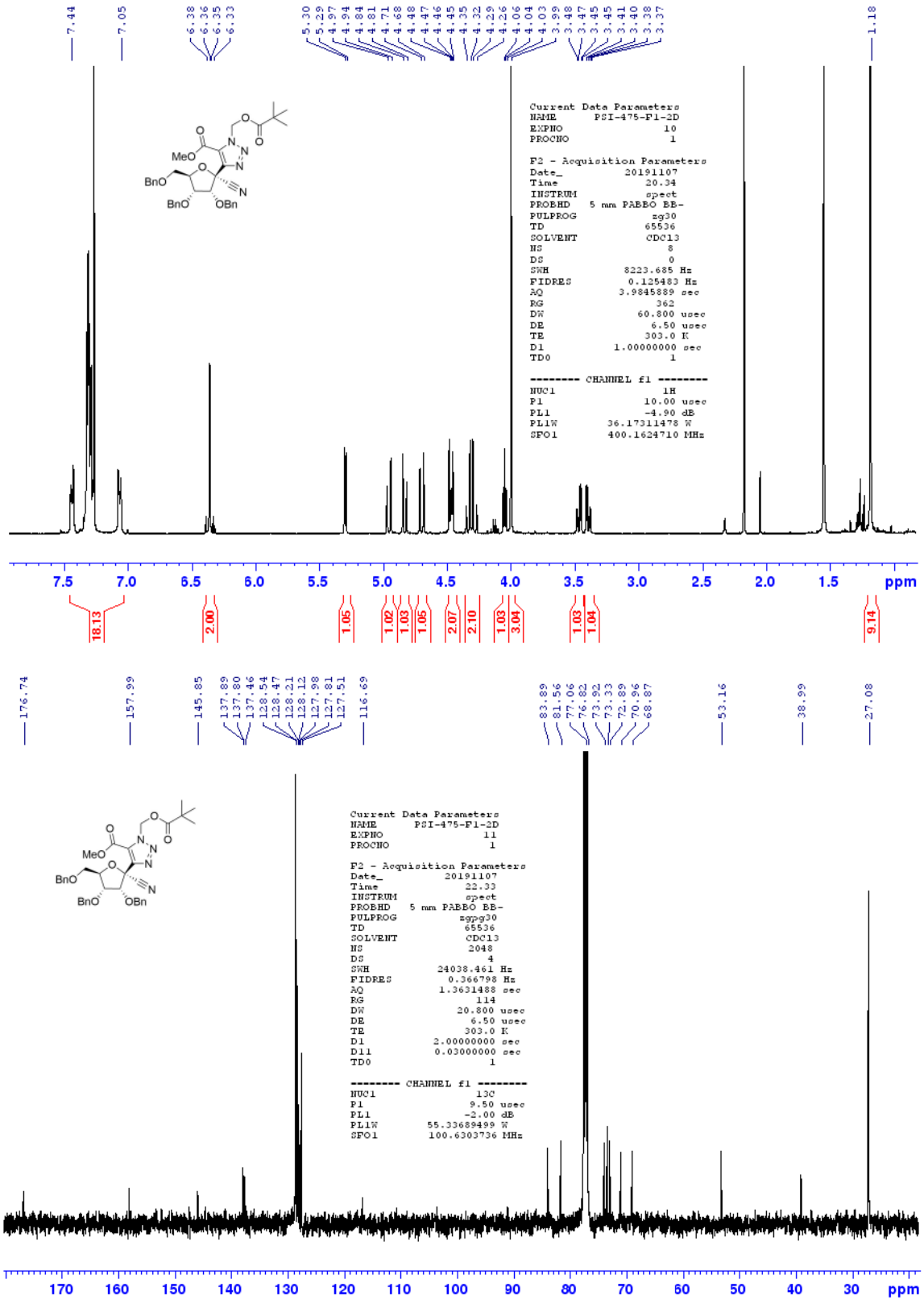

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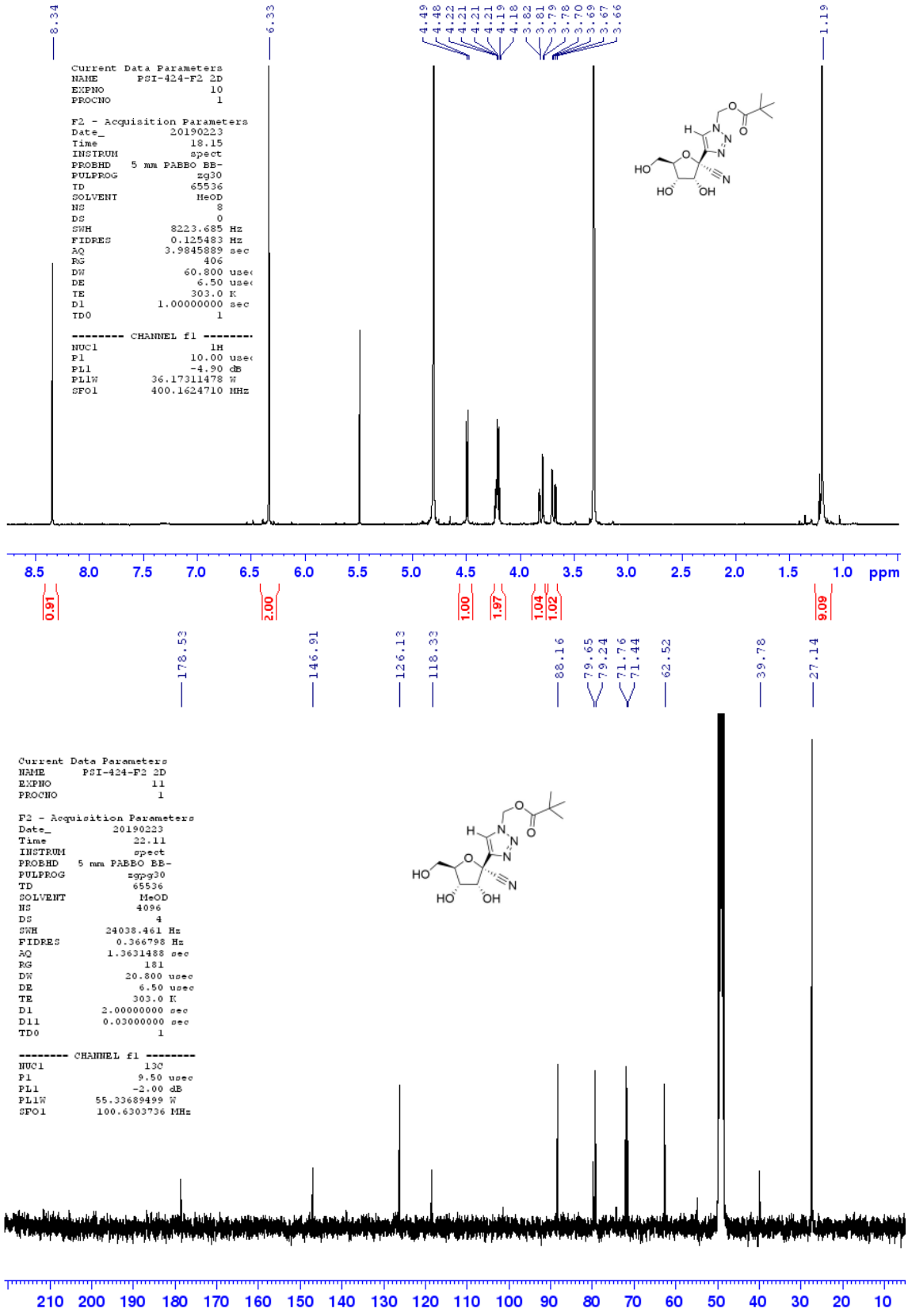

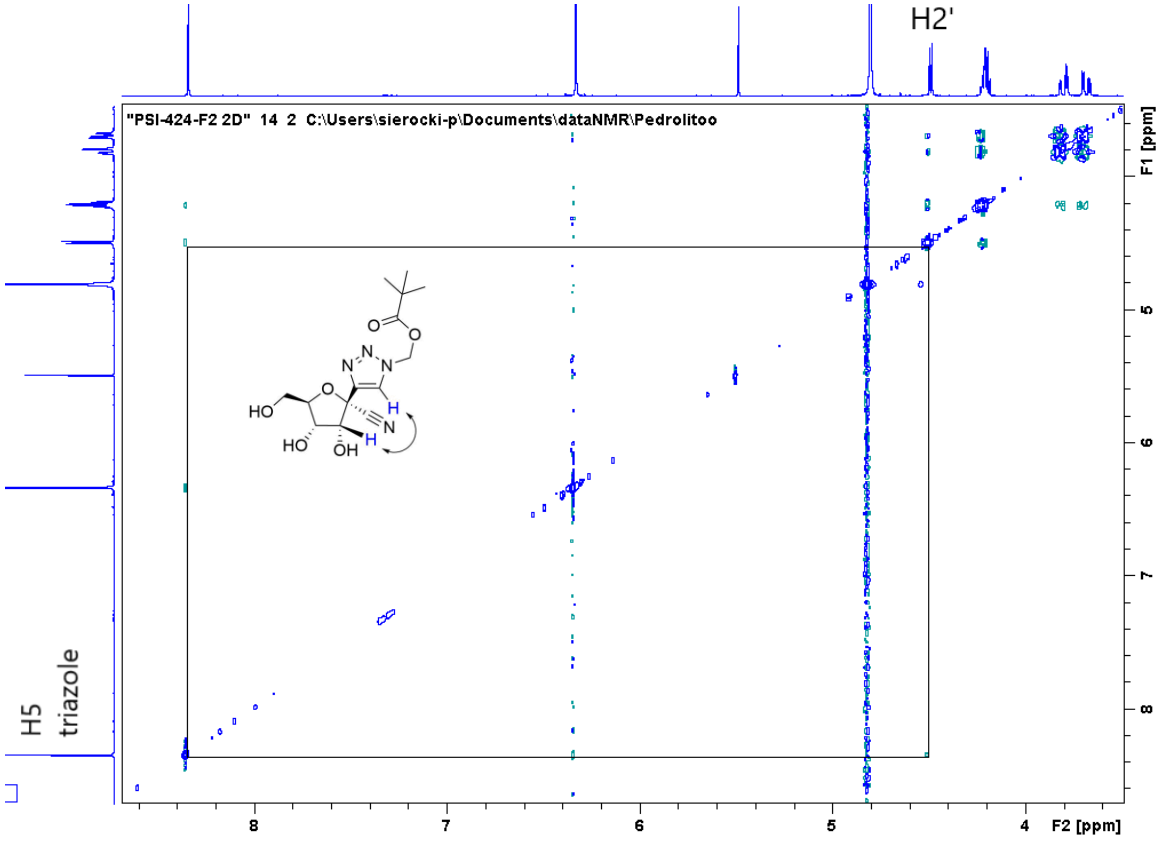
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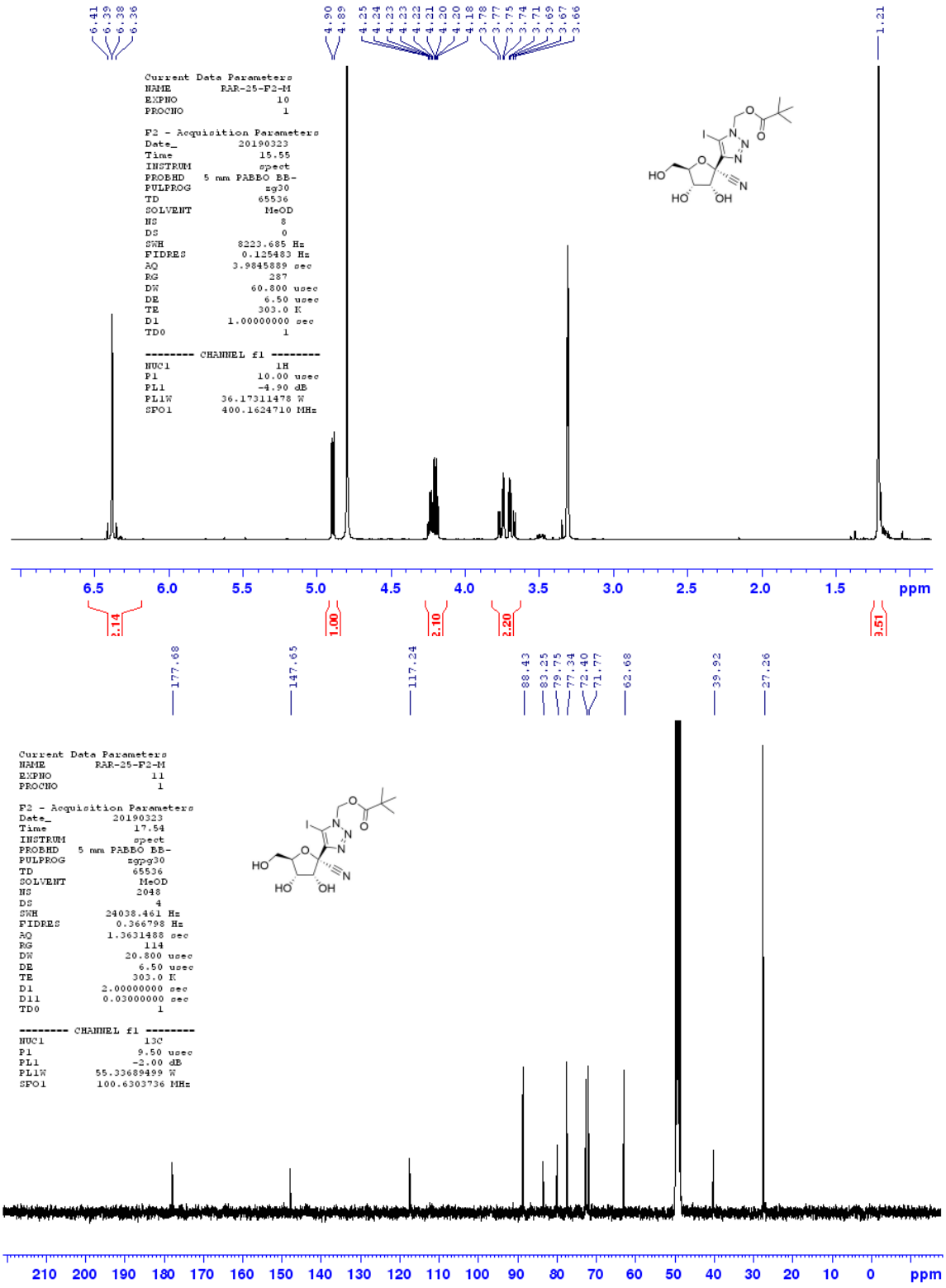
^{1}H and ^{13}C NMR spectra of compound (13b)



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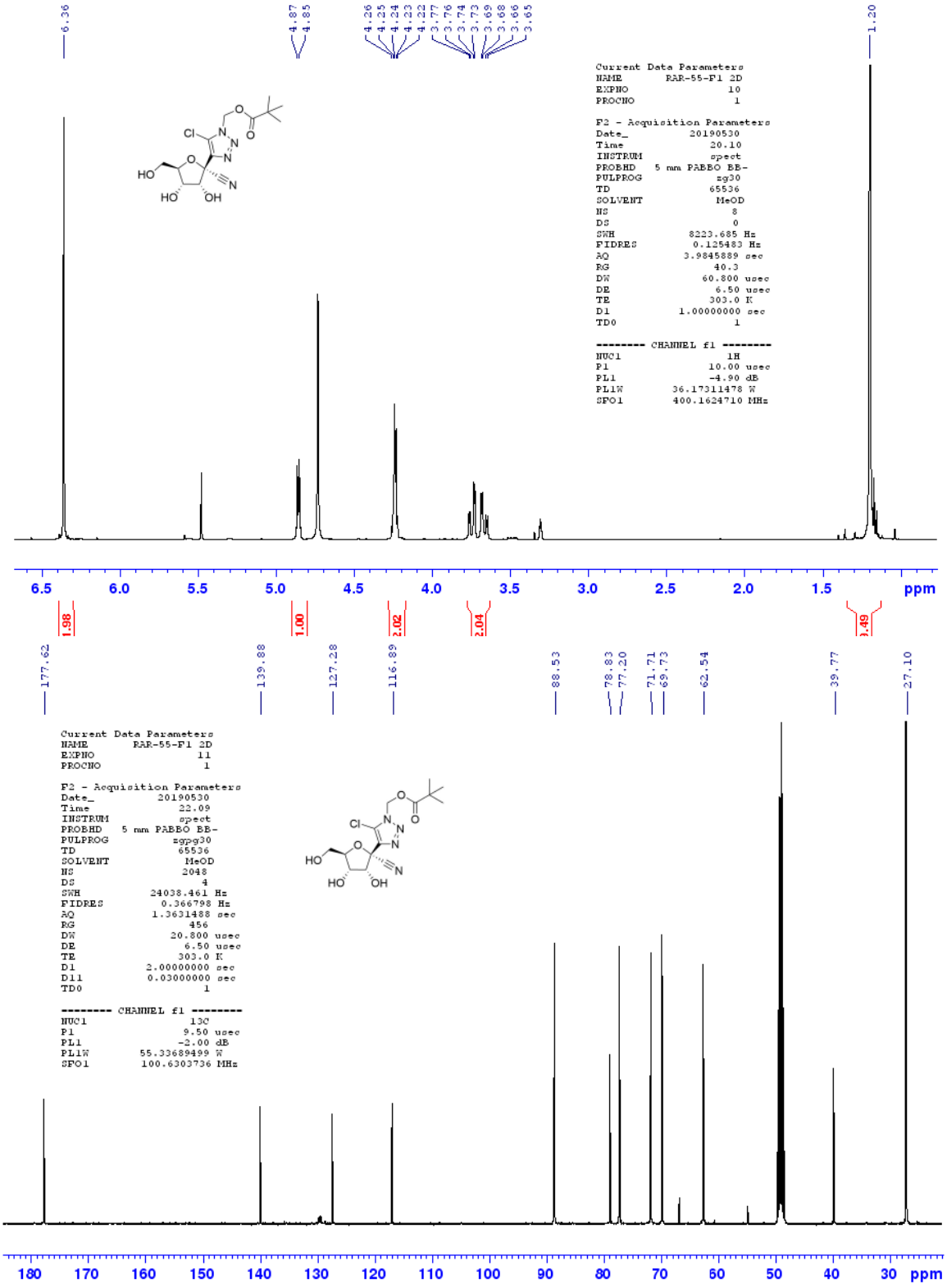

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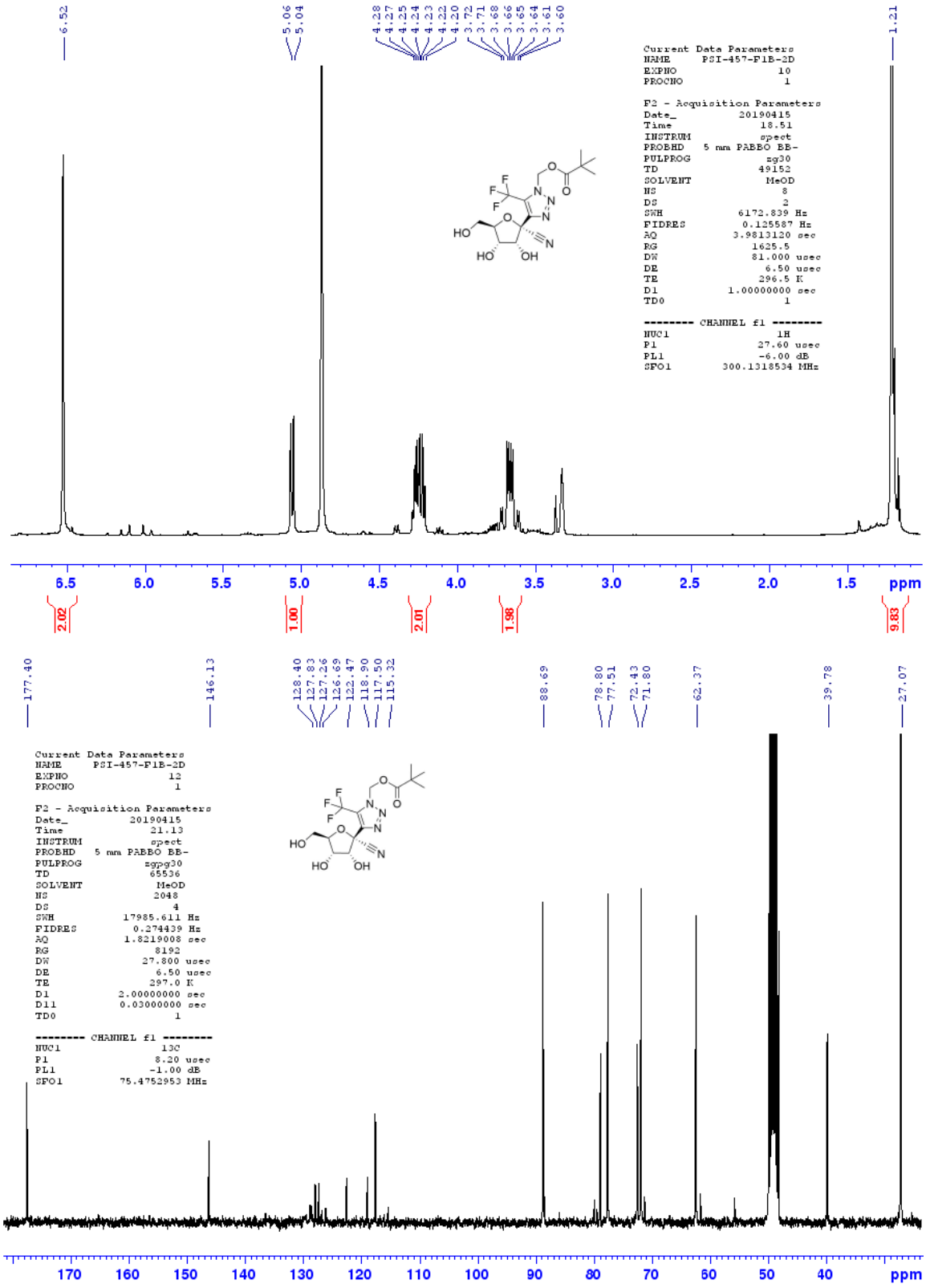

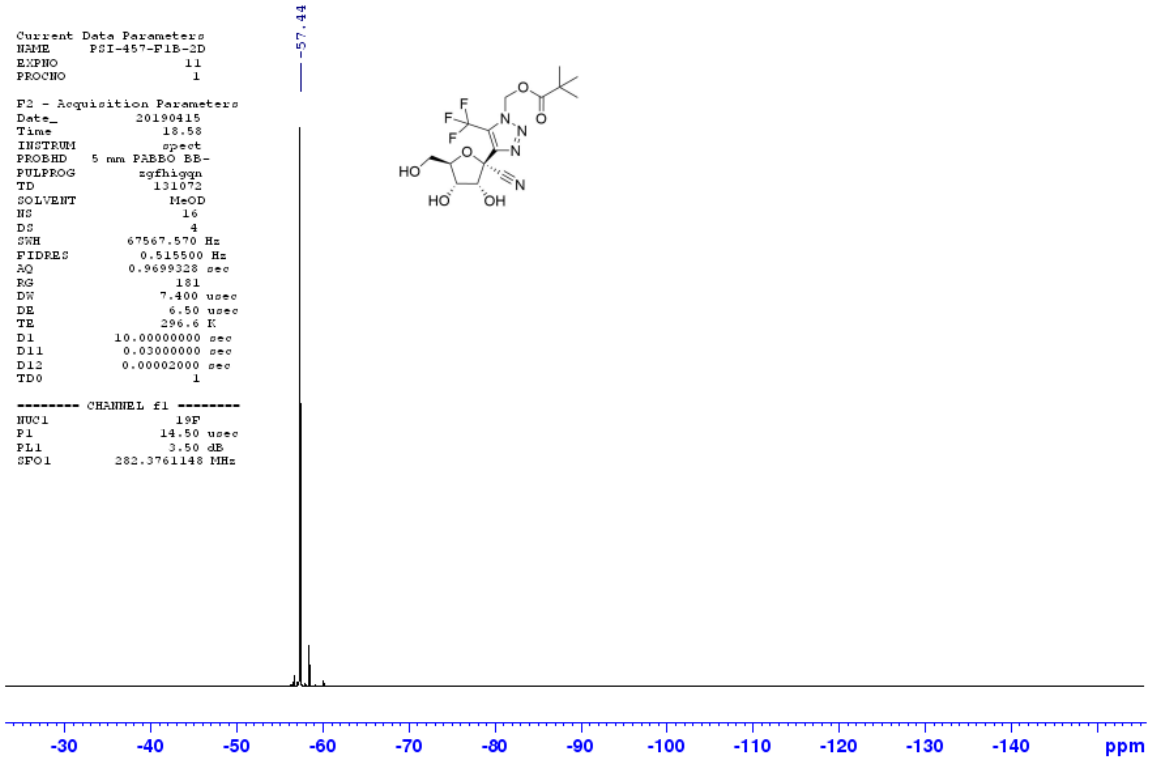
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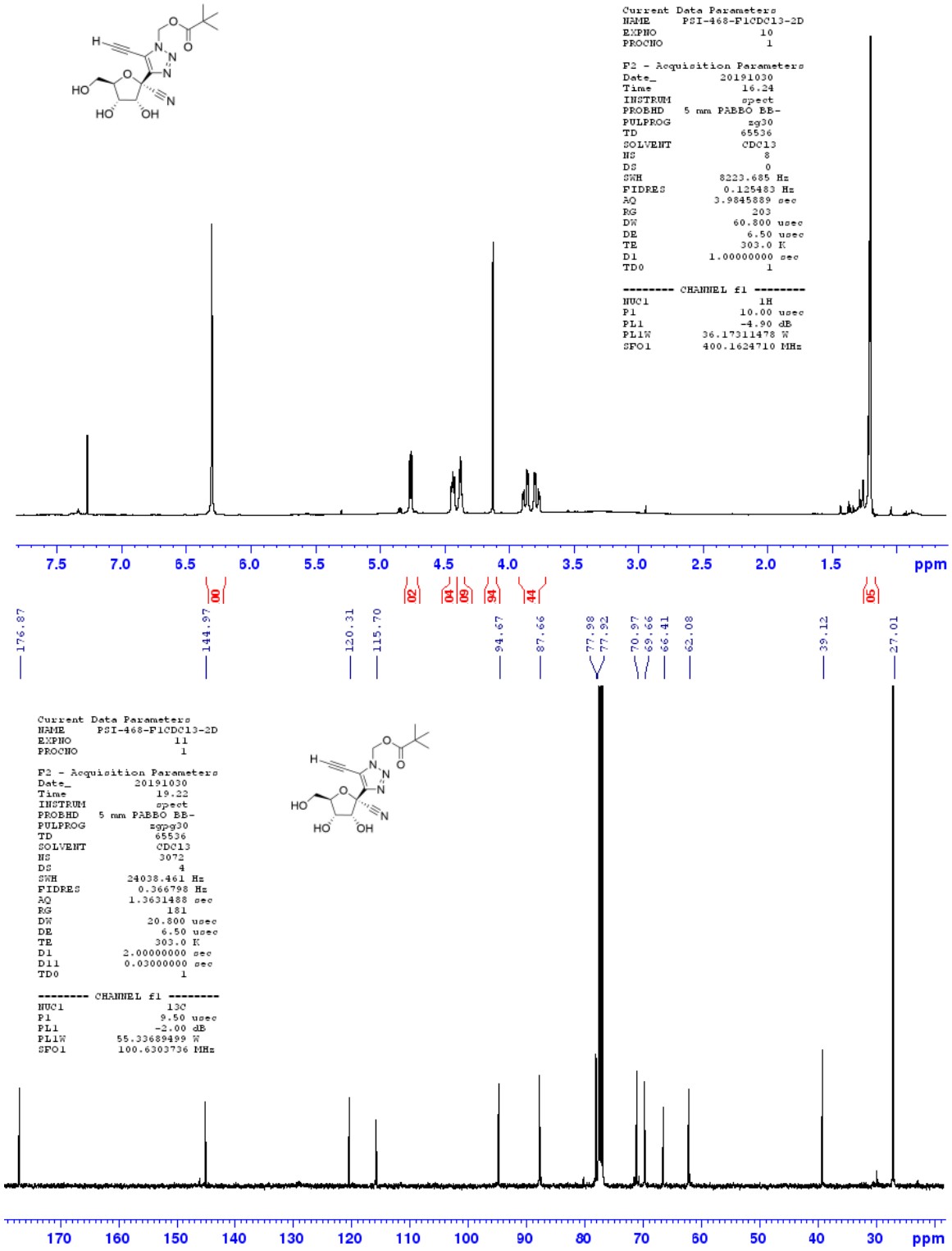

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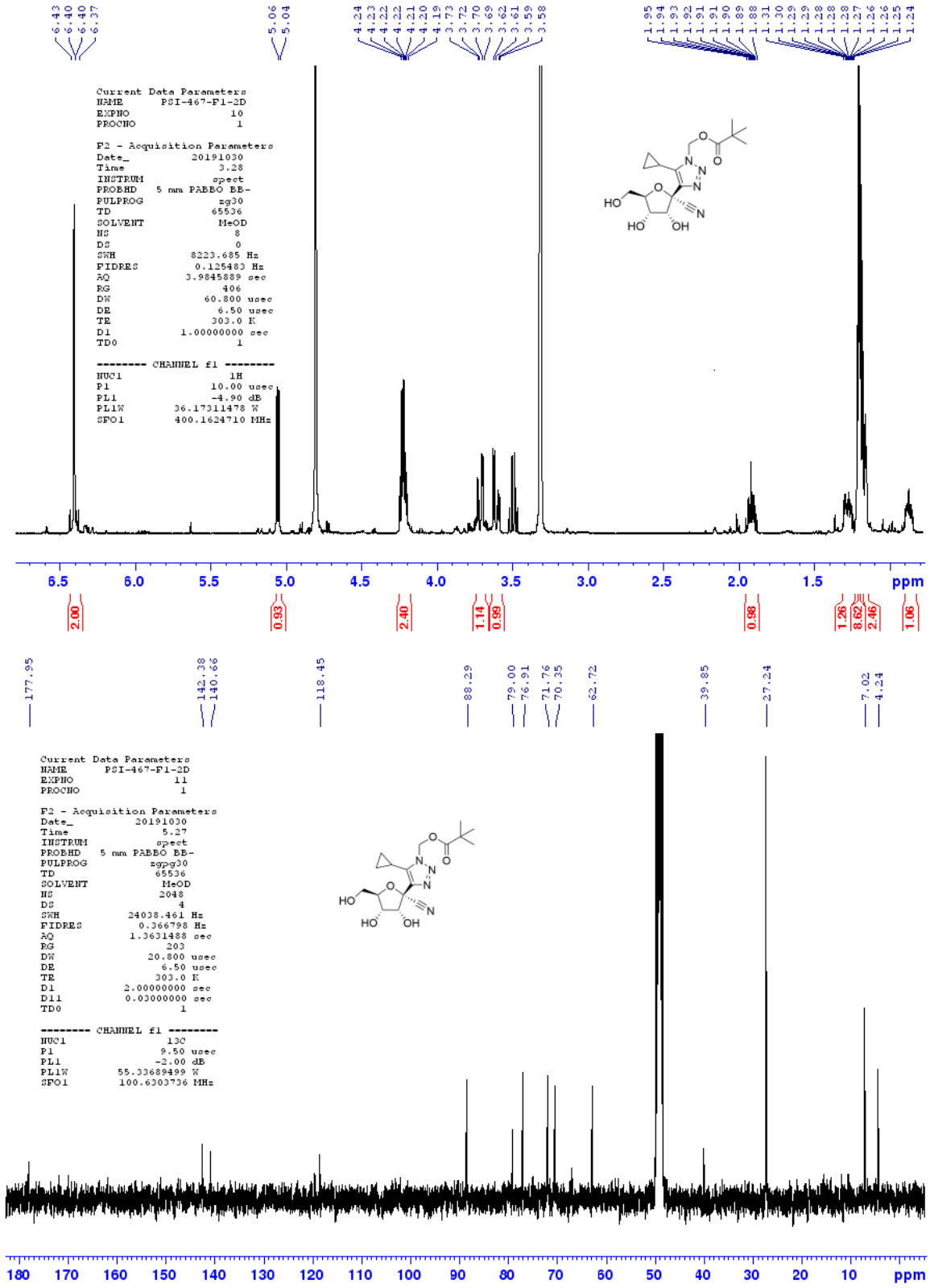

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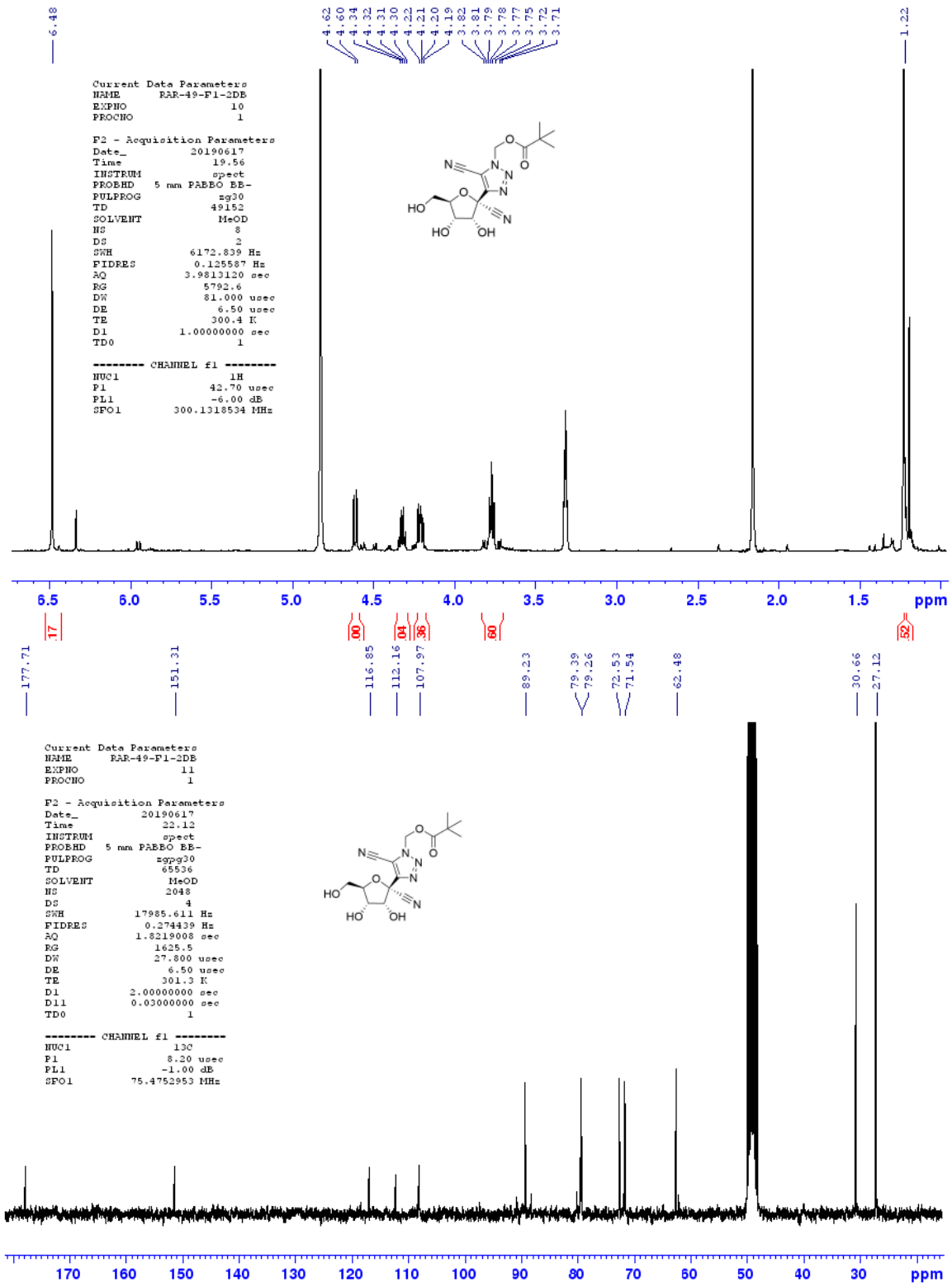
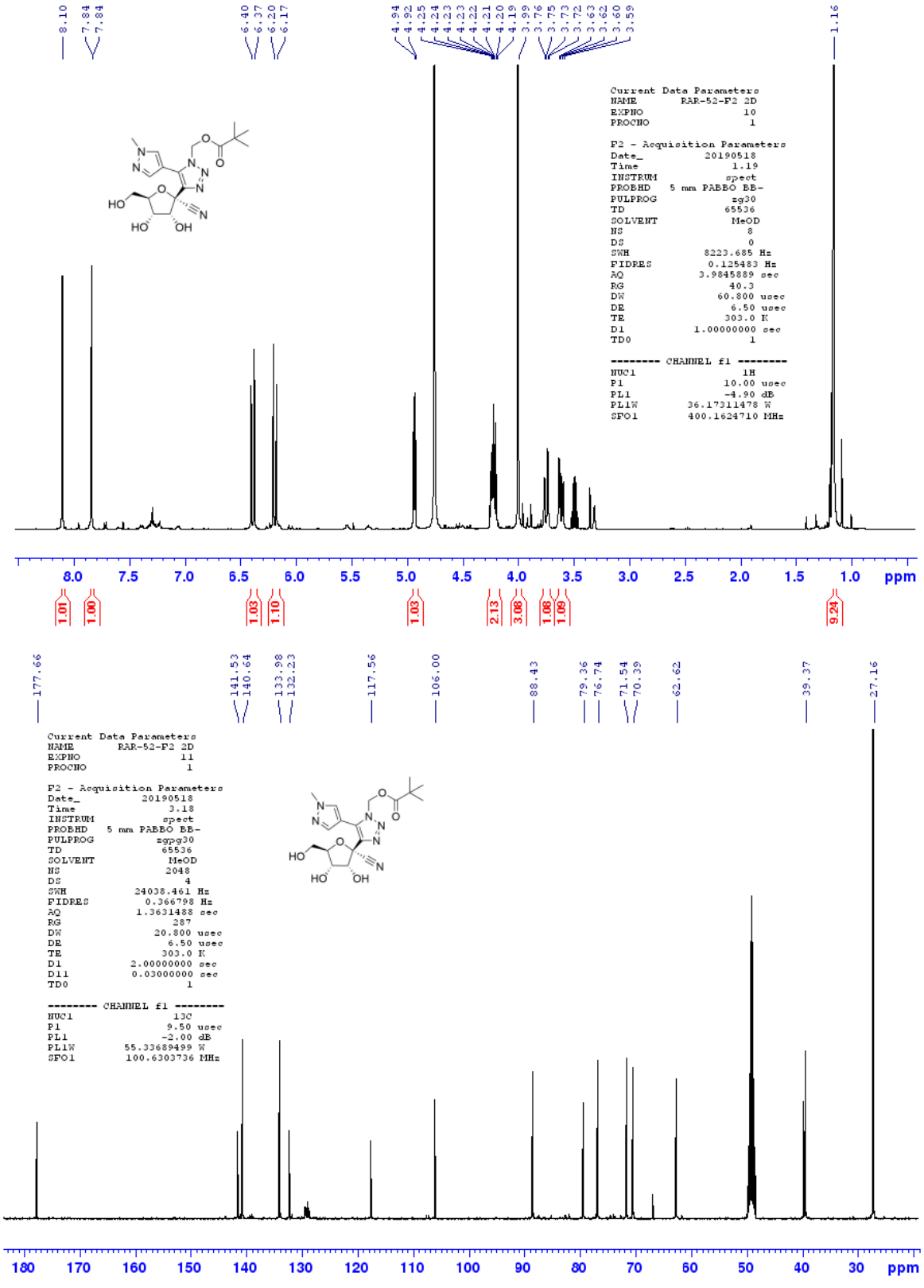
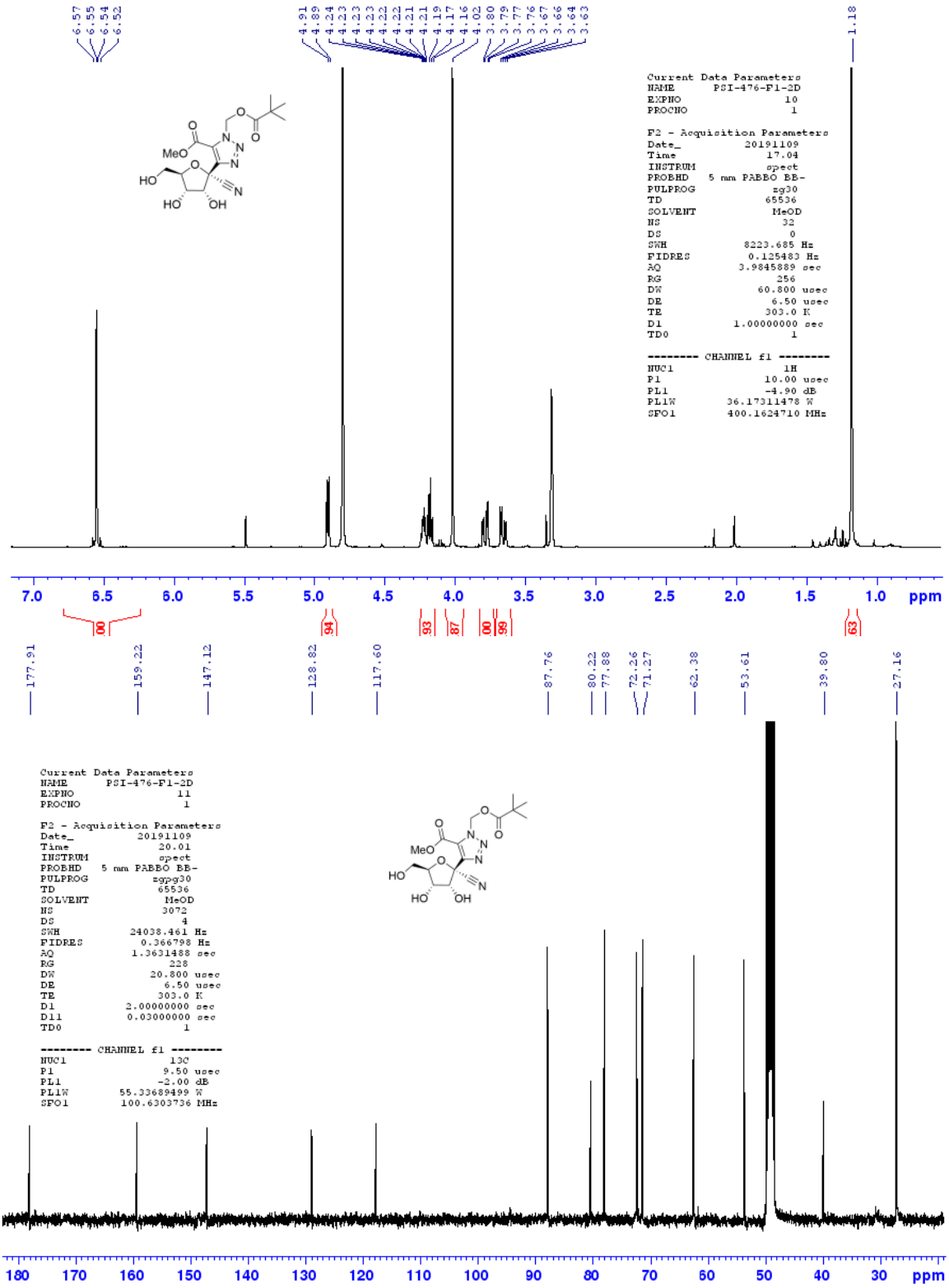


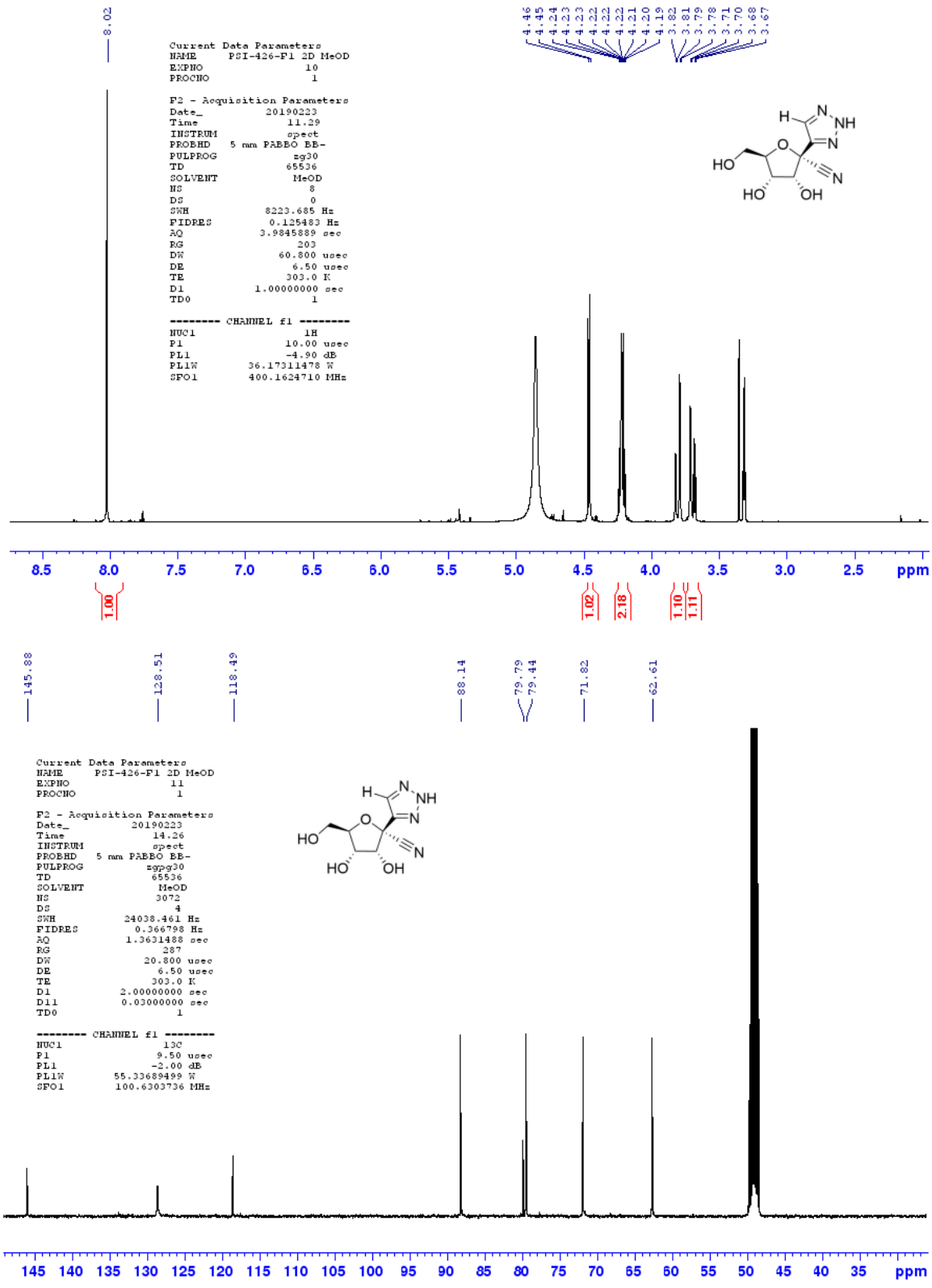
^{1}H and ^{13}C NMR spectra of compound (13h)



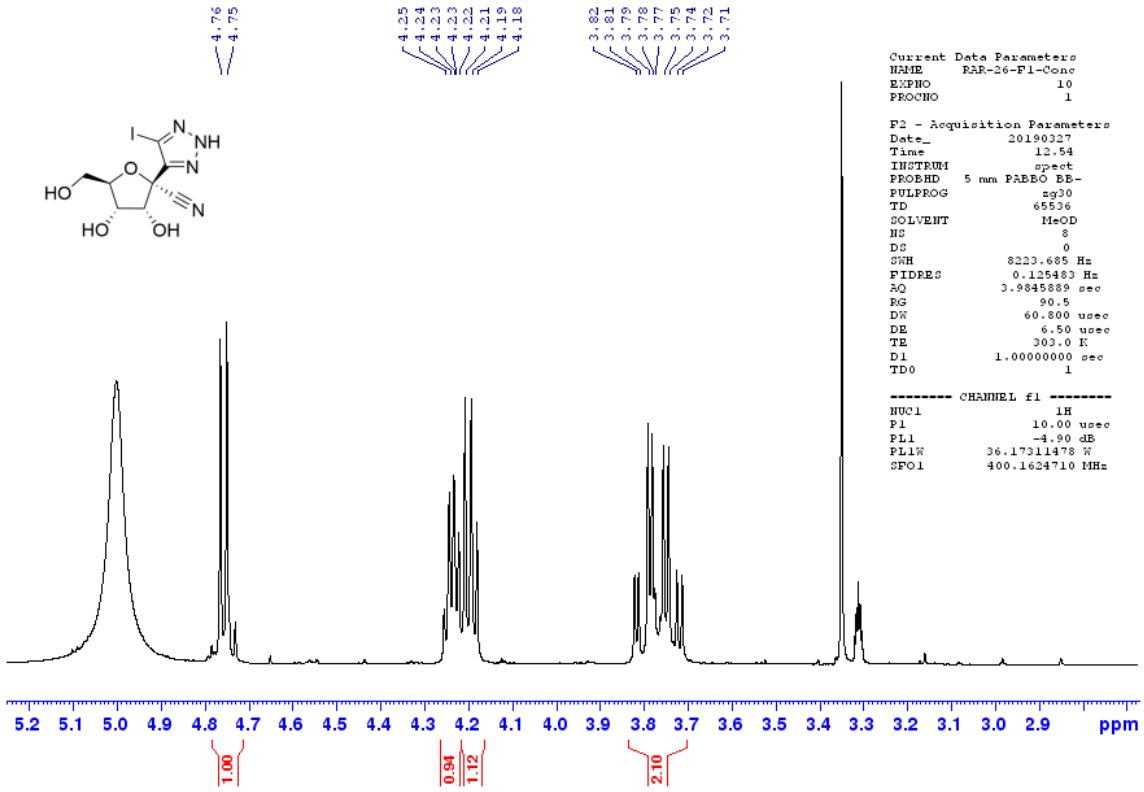
^{1}H and ^{13}C NMR spectra of compound (13i)

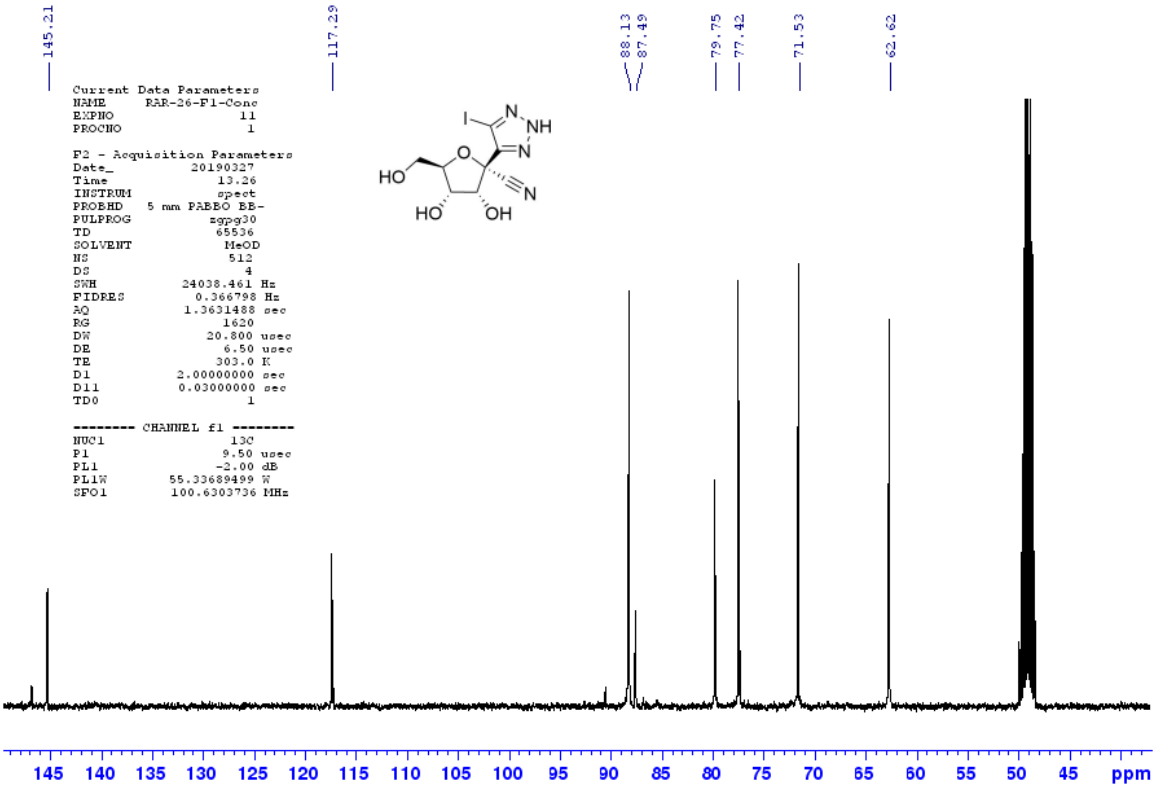


^{1}H and ^{13}C NMR spectra of compound (5a)

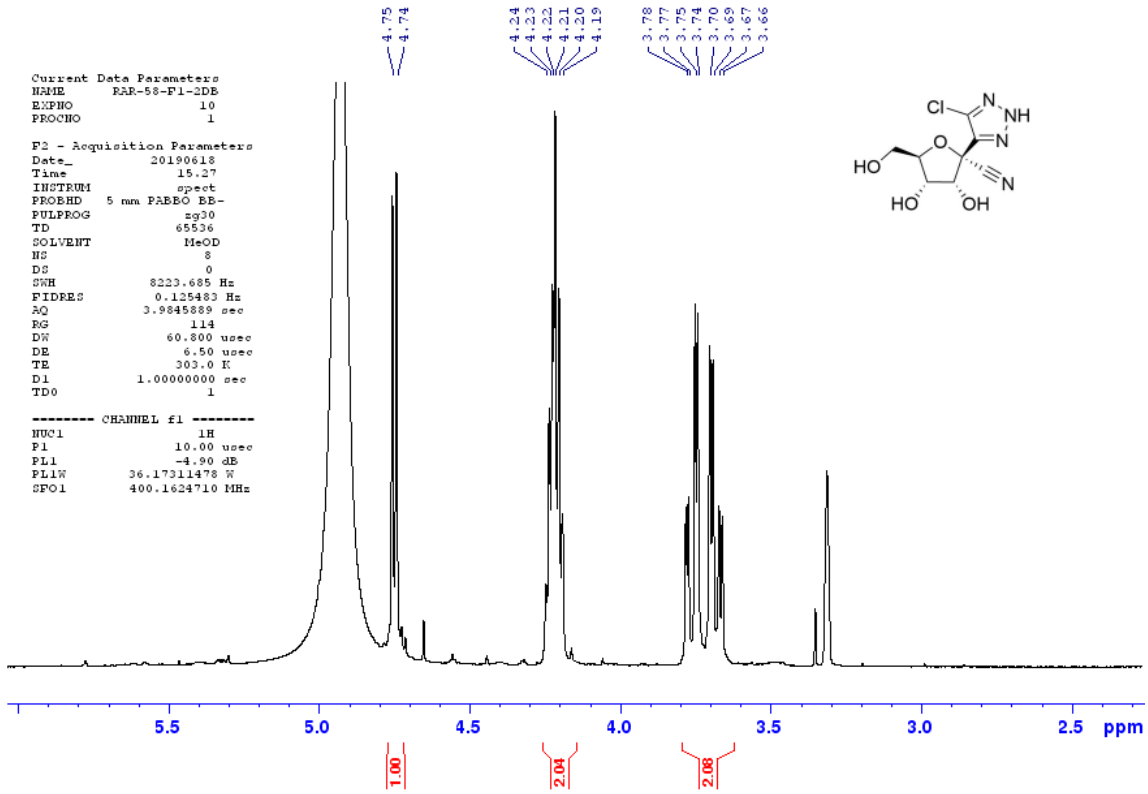


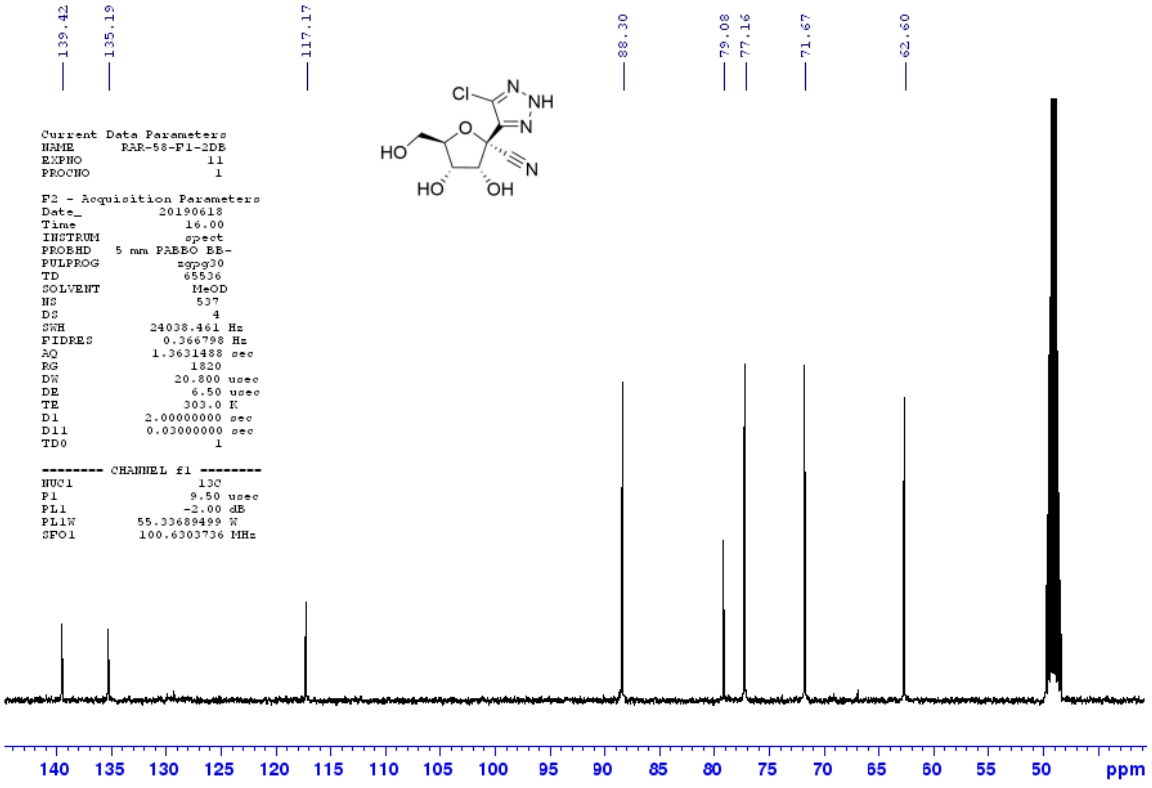
^{1}H and ^{13}C NMR spectra of compound (5b)



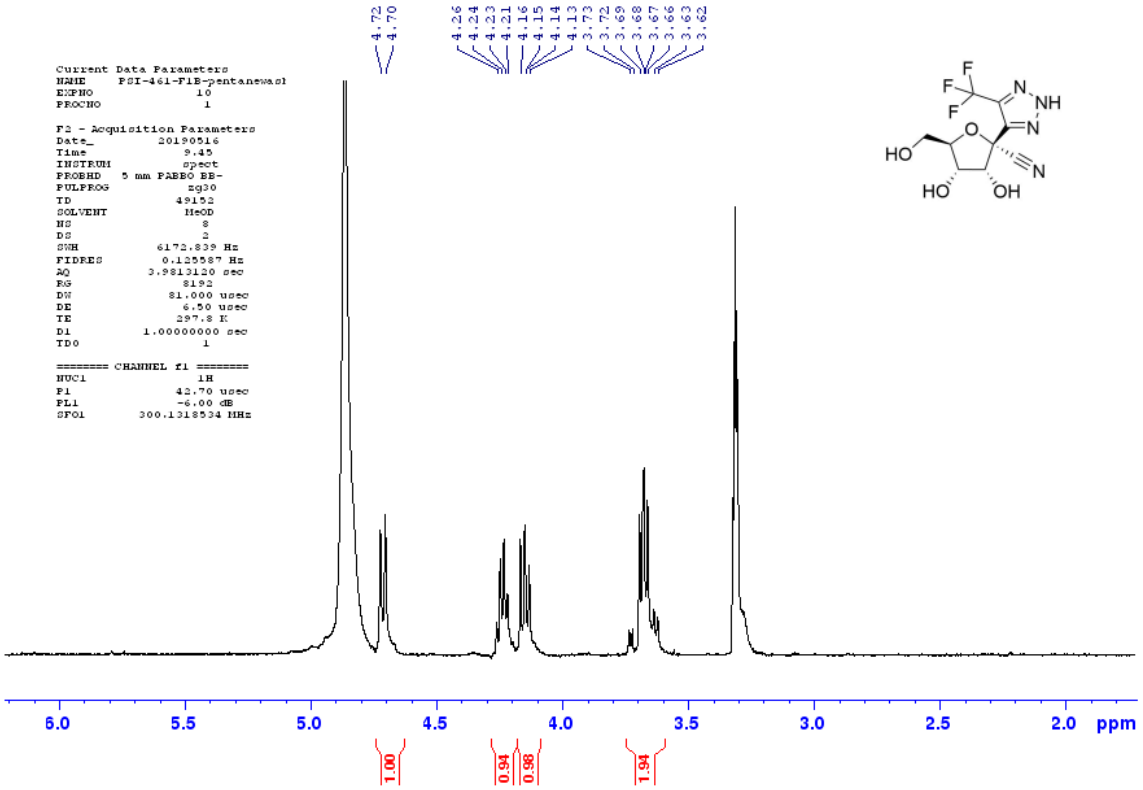


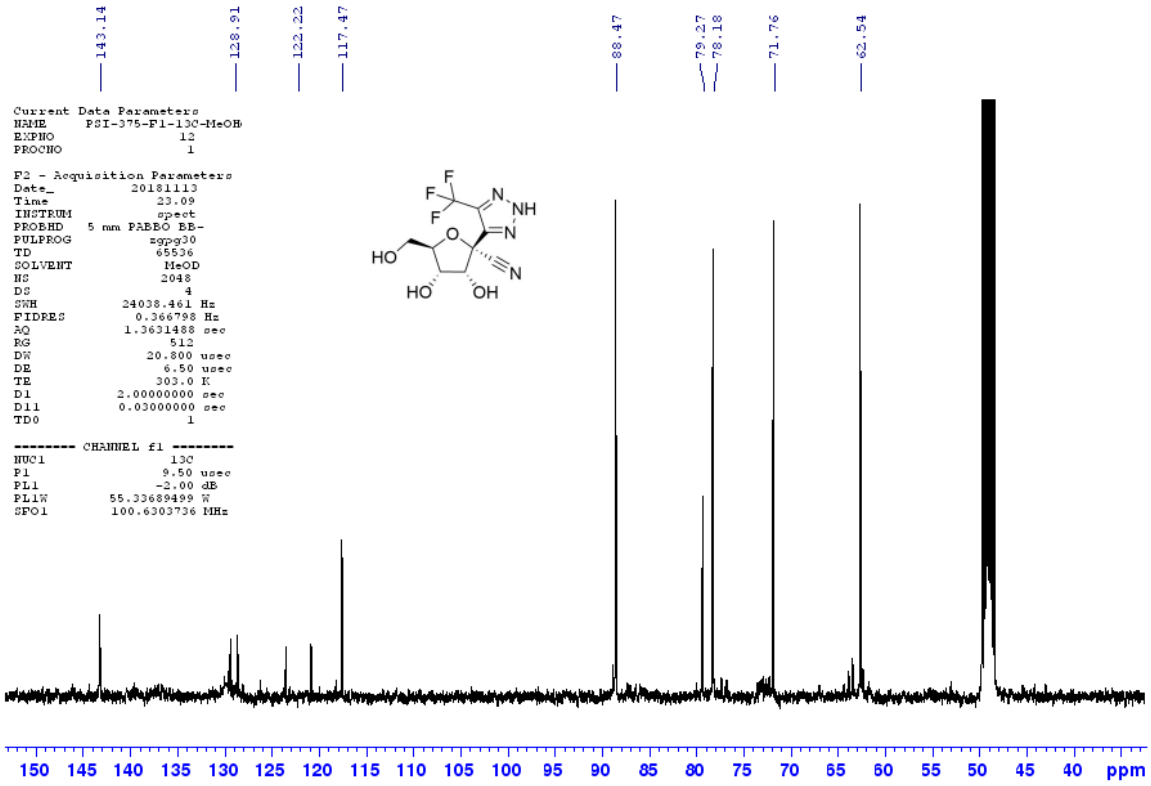
^{1}H and ^{13}C NMR spectra of compound (5c)

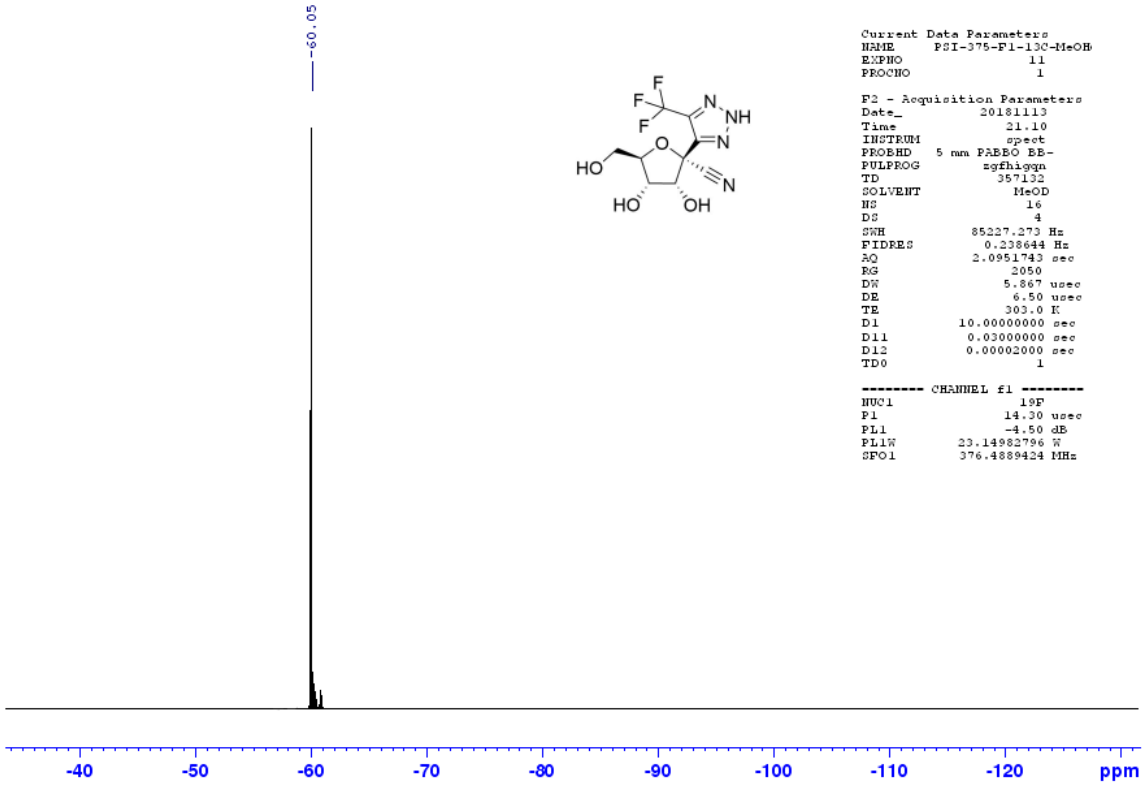




^{1}H, ^{19}F and ^{13}C NMR spectra of compound (5d)





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Current Data Parameters
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EXPNO                      11
PROCNO                      1

F2 - Acquisition Parameters
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Time                  21.10
INSTRUM               spect
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PULPROG          zgfhigqn
TD                 357132
SOLVENT              MeOD
NS                     16
DS                      4
SWH              85227.273 Hz
FIDRES           0.238644 Hz
AQ               2.0951743 sec
RG                    2050
DW                5.867 usec
DE                6.50 usec
TE                303.0 K
D1           10.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  19F
P1                14.30 usec
PL1                -4.50 dB
PL1W         23.14982796 W
SFO1         376.4889424 MHz
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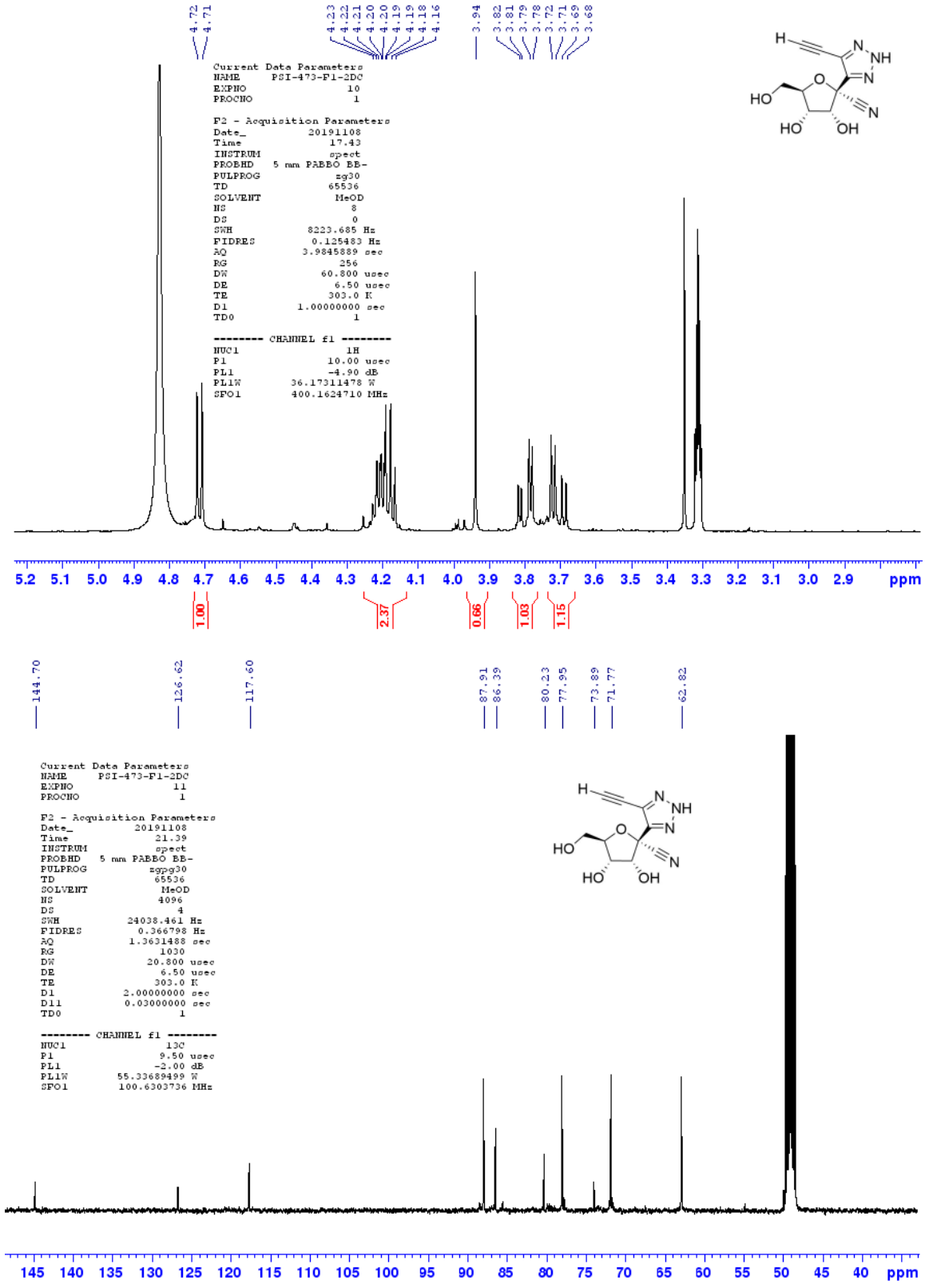
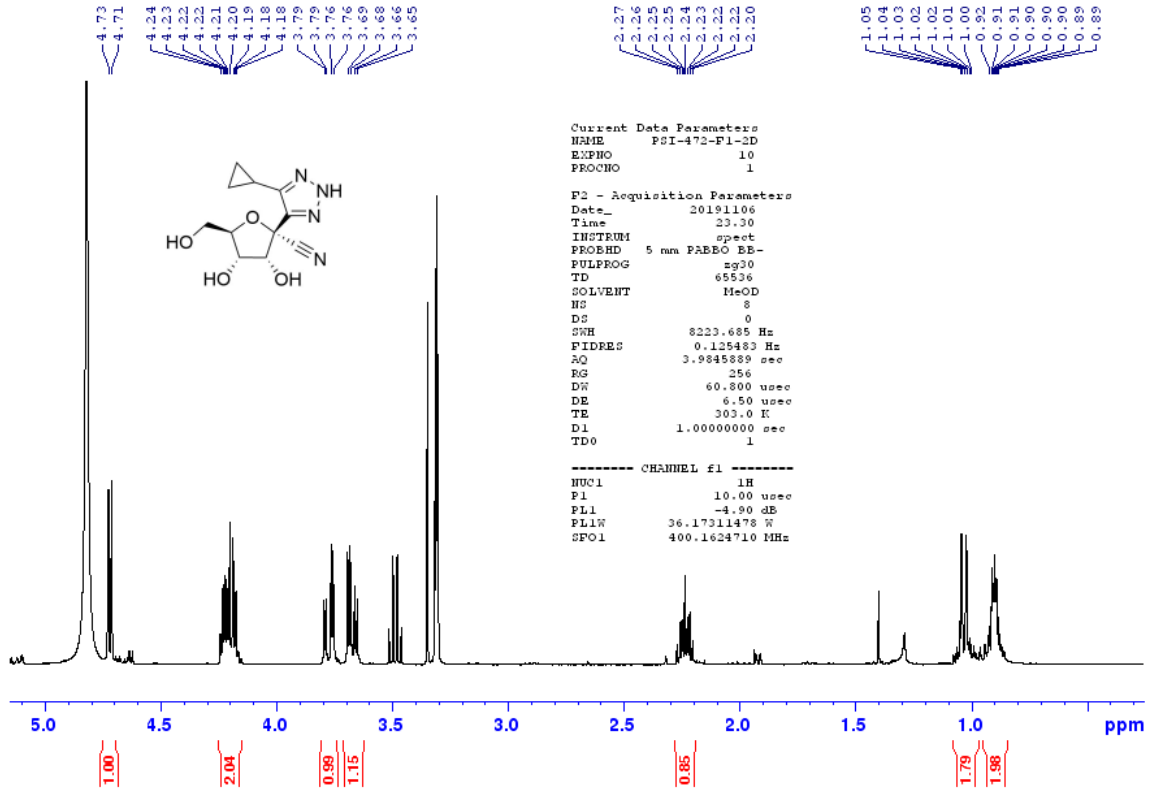
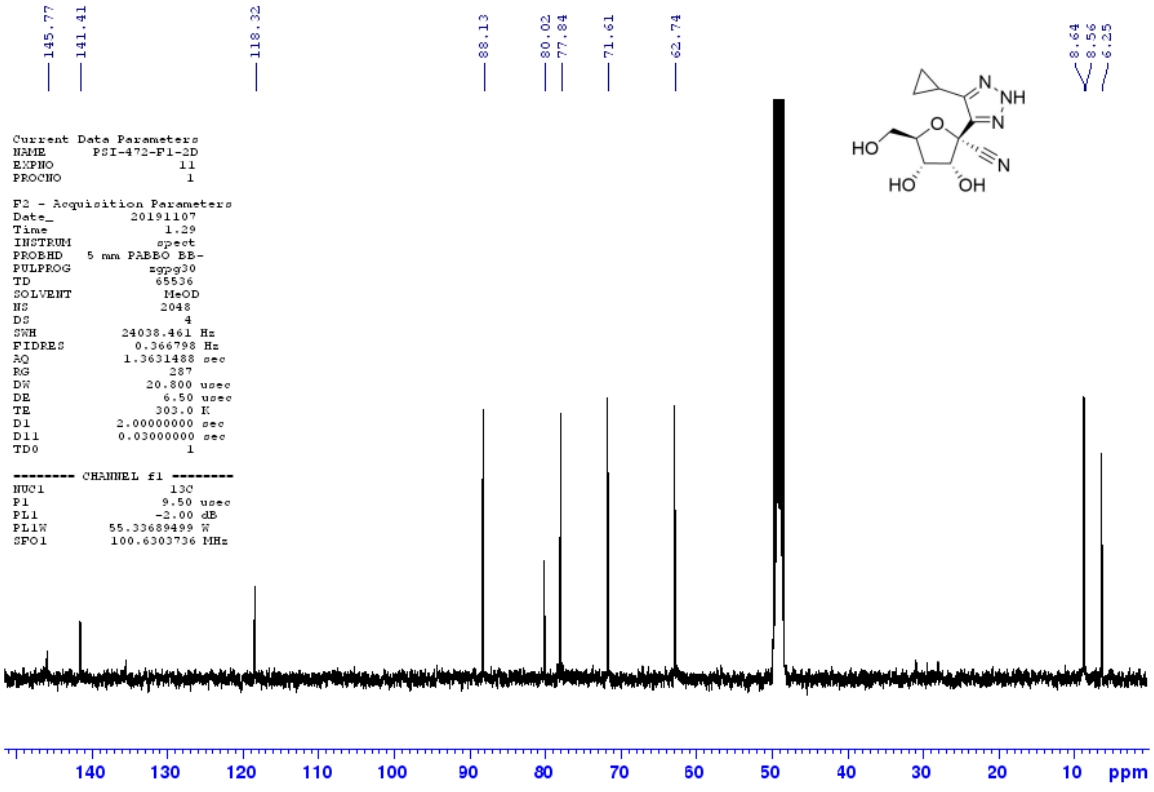
^{1}H and ^{13}C NMR spectra of compound (5e)

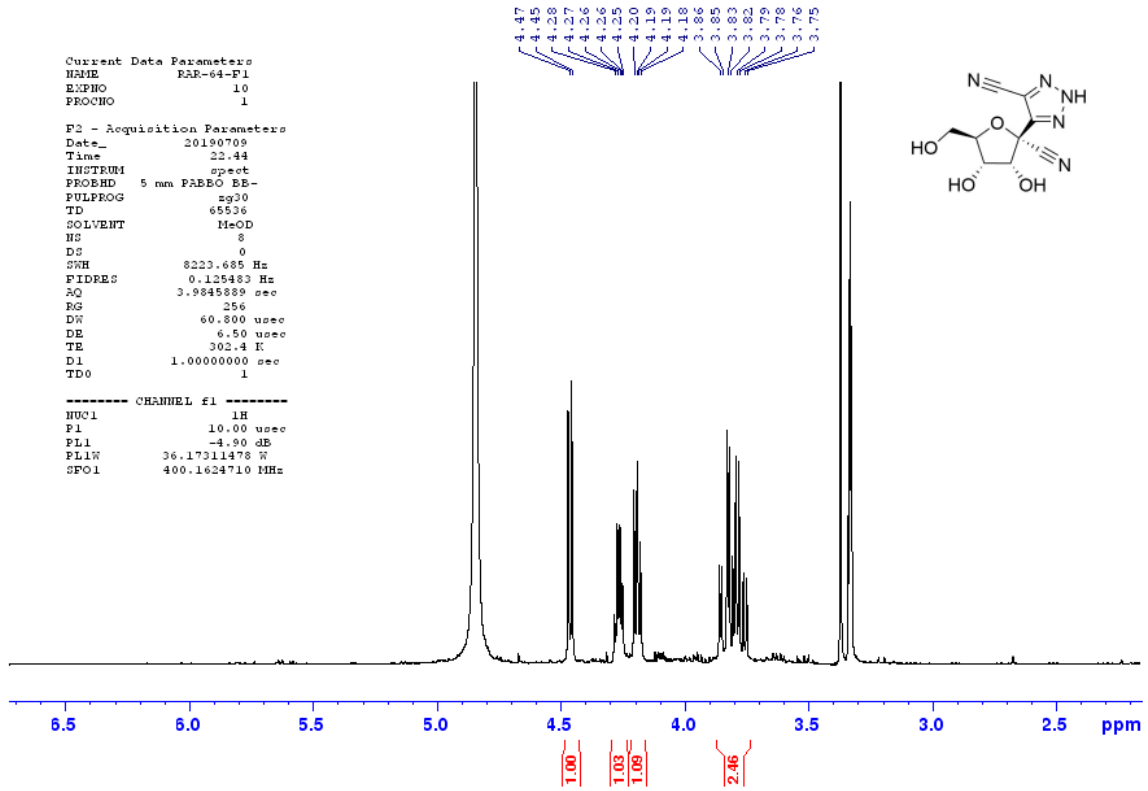


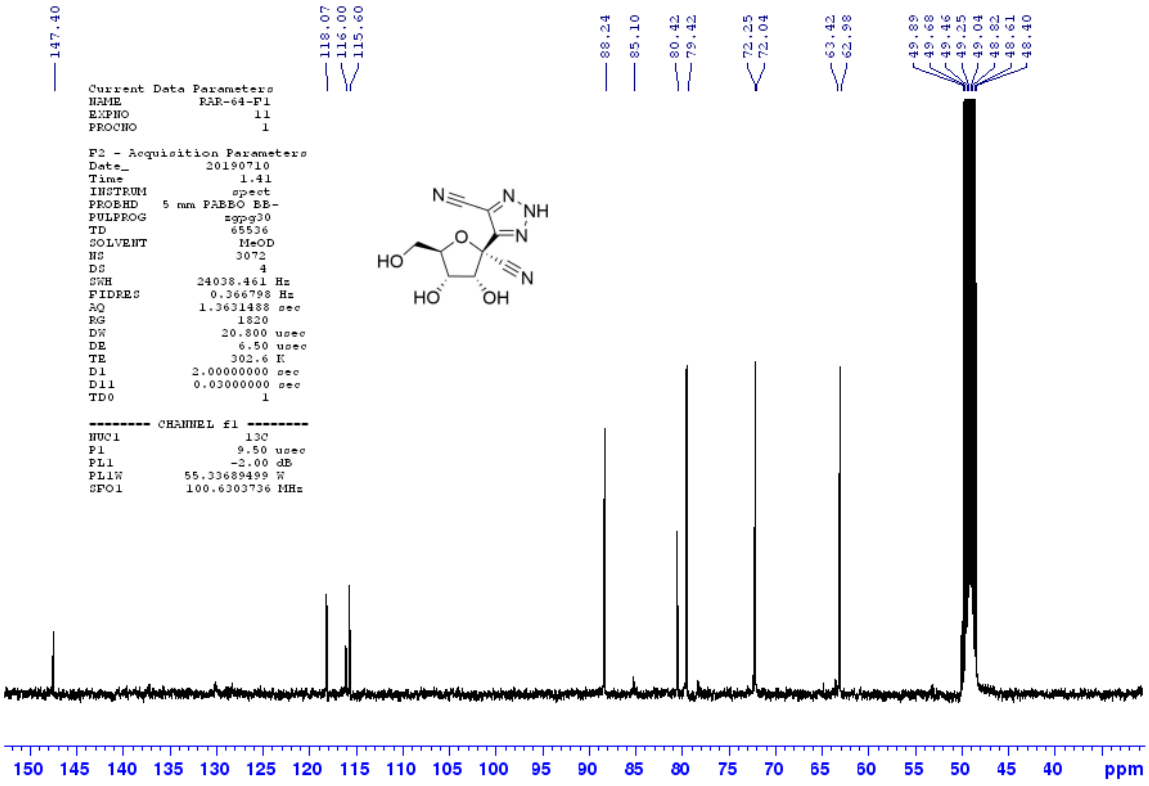
^{1}H and ^{13}C NMR spectra of compound (5f)



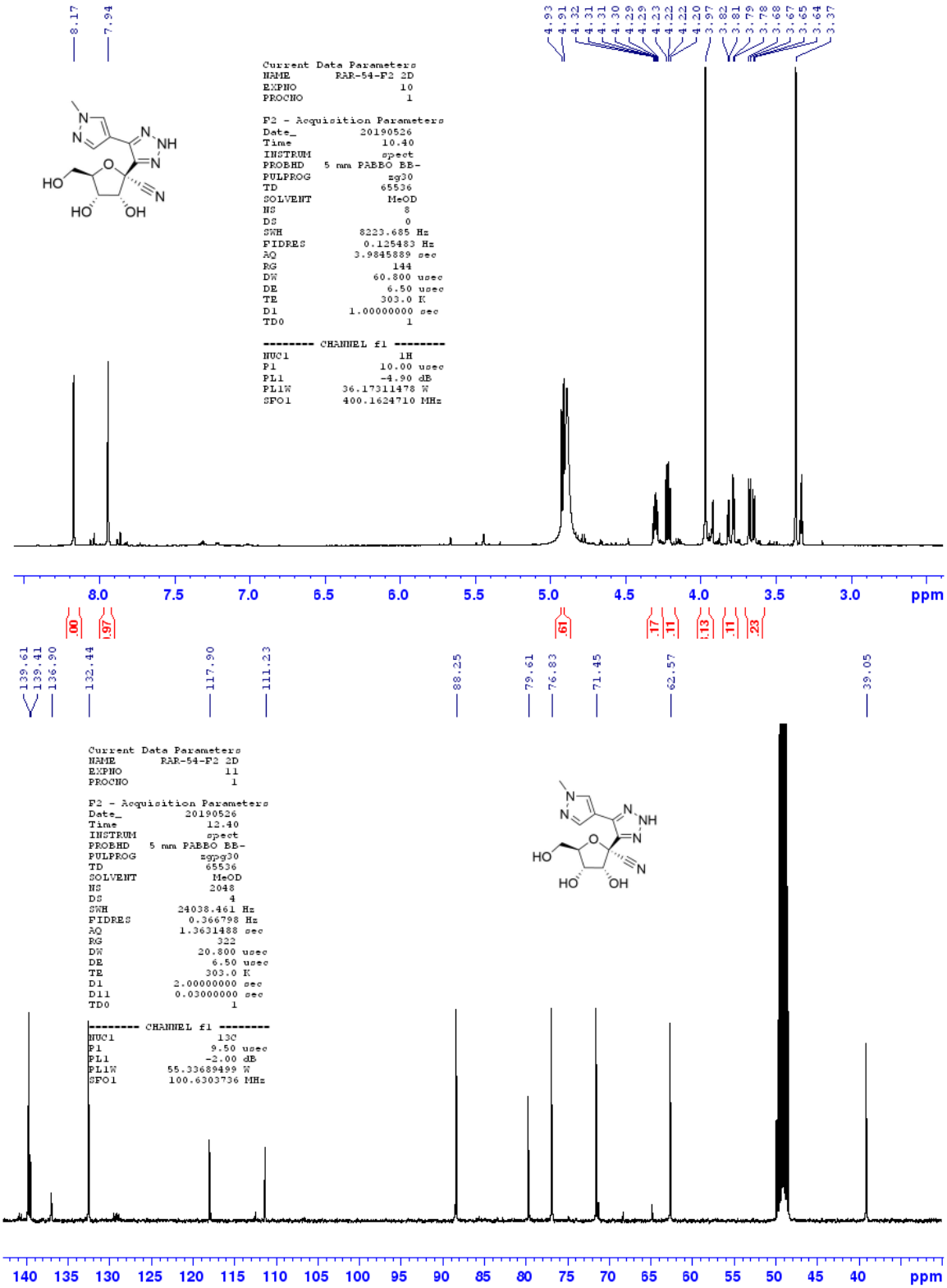


^{1}H and ^{13}C NMR spectra of compound (5g)





^{1}H and ^{13}C NMR spectra of compound (5h)



^{1}H and ^{13}C NMR spectra of compound (5i)