

Supporting Information.

An Efficient and Diastereoselective Synthesis of PSI-6130: A Clinically Efficacious Inhibitor of HCV NS5B Polymerase

Peiyuan Wang, Byoung-Kwon Chun, Suguna Rachakonda, Jinfa Du, Noshena Khan, Junxing Shi, Wojciech Stec, Darryl Cleary, Bruce S. Ross, and Michael J. Sofia

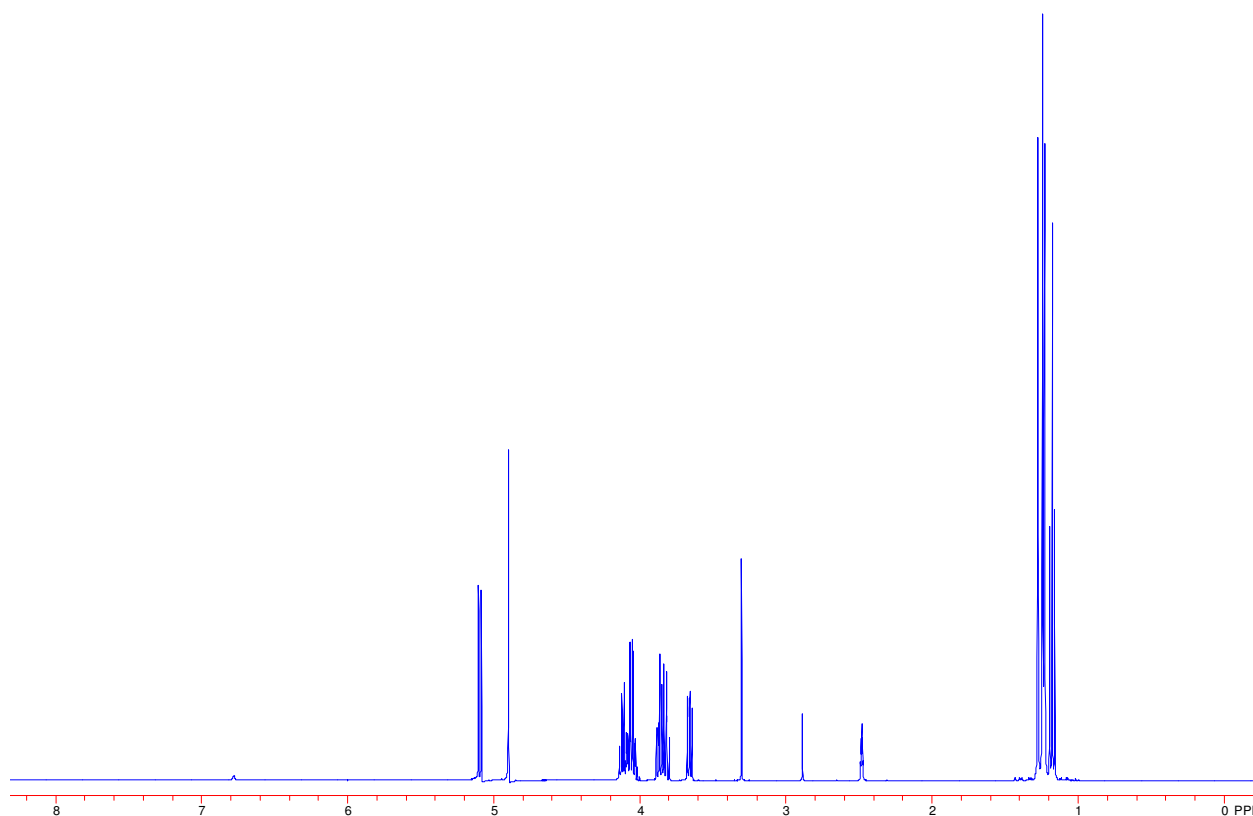
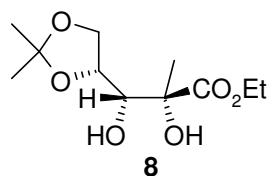
Pharmasset, Inc., 303A College Road E., Princeton, NJ 08540

Table of Contents:

1) General Methods	1
2) ¹ H-NMR Spectrum of Compound 8	2
3) ¹³ C-NMR Spectrum of Compound 8	3
4) ¹ H-NMR Spectrum of Compound 12	4
5) ¹³ C-NMR Spectrum of Compound 12	5
6) ¹ H-NMR Spectrum of Compound 15	6
7) ¹³ C-NMR Spectrum of Compound 15	7
8) ¹ H-NMR Spectrum of Compound 1	8
9) ¹³ C-NMR Spectrum of Compound 1	9

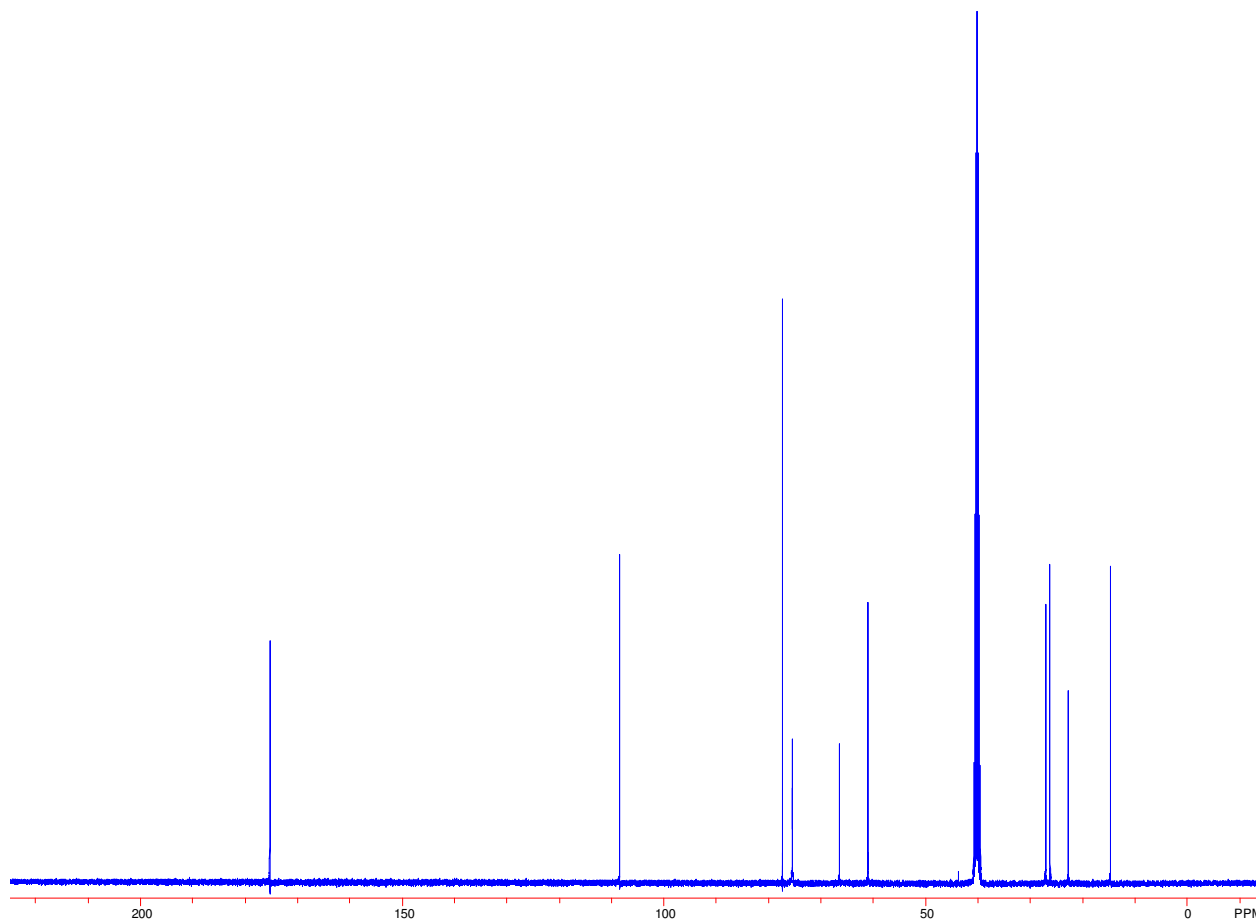
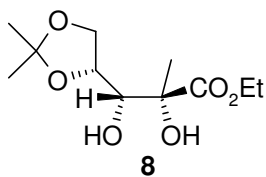
General Methods. Reactions were monitored by thin layer chromatography with Analtech Uniplate 250 micron and visualized by UV light or by charring in 5% sulfuric acid in methanol. All solvents and reagents were used as received from Aldrich or Fisher Scientific. NMR spectra were recorded in CDCl₃ or DMSO-d₆ as noted on a Varian Mercuryplus 400 MHz spectrometer. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR through a universal reflectance accessory. Optical rotations were measured using a Perkin Elmer Model 341 Polarimeter at ambient temperature and 589 nm. Low resolution mass spectra were recorded on a Waters Micromass QuattroMicro API. High resolution mass spectra were performed at the Emory University Mass Spectrometry Center (Atlanta, GA, USA) using FAB ionization. HPLC were obtained on a Waters Alliance 2695 HPLC using a Waters Atlantis C18 column and a gradient of 50mM triethylamine-acetic acid buffer and acetonitrile. Melting points were recorded on a Stanford Research Systems EZ-Melt and are uncorrected.

400 MHz ^1H -NMR in DMSO- d_6 of (2S,3R)-ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydroxy-2-methylpropanoate



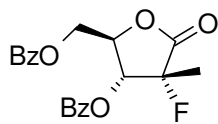
δ 1.18 (t, 3H, $J=7.2\text{Hz}$, CH_2CH_3), 1.23 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.28 (s, 3H, 2- CH_3), 3.66 (dd, 1H, $J=7.4\text{ Hz}$, 3-H), 3.80-3.89 (m, 2H, 5-H), 4.05 (dt, 2H, 7.2 and 2 Hz, CH_2CH_3), 4.11 (q, 1H, 6.4 Hz, 4-H), 4.90 (s, 1H, 2-OH), 5.09 (d, 1H, $J=7.4\text{Hz}$, 3-OH).

100 MHz ^{13}C -NMR in DMSO-*d*6 of (2S,3R)-ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-dihydroxy-2-methylpropanoate

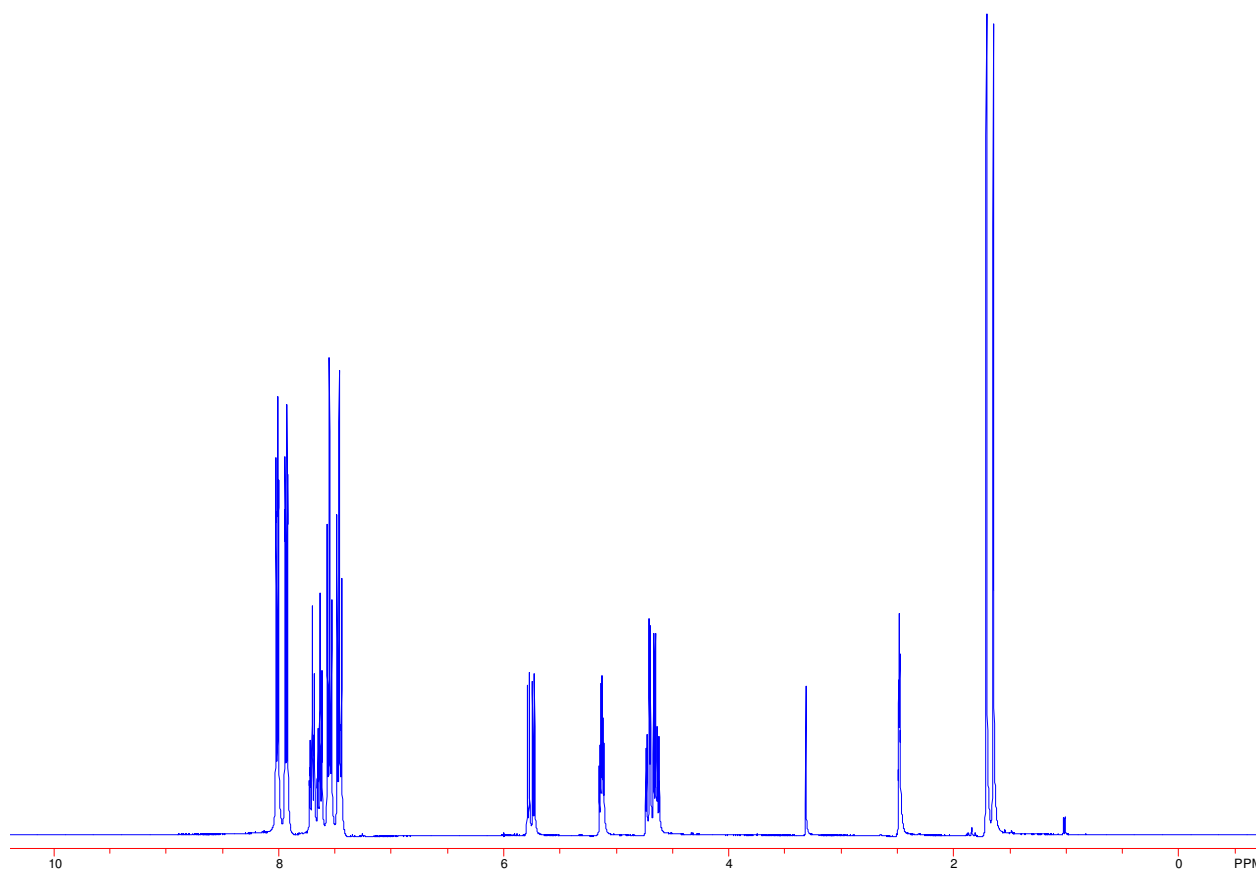


δ 14.73, 22.74, 26.23, 27.11, 61.00, 66.51, 75.44, 75.48, 77.35, 108.52, 175.33.

400 MHz ^1H -NMR in DMSO- d_6 of ((2R,3R,4R)-3-(benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl benzoate

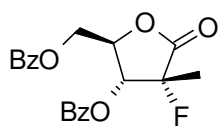


12

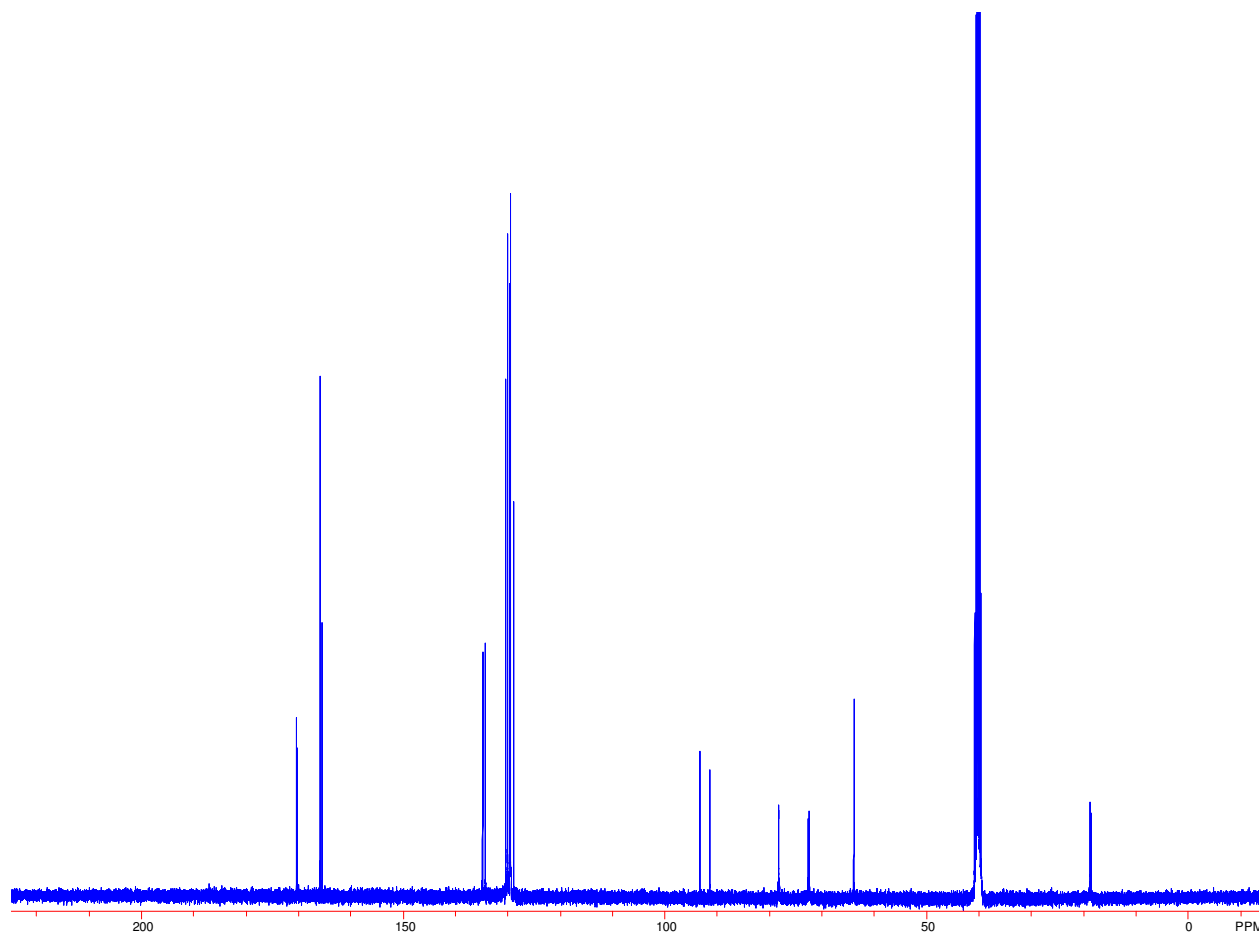


δ 1.68 (d, 3H, J = 24.2 Hz, CH_3), 4.62-4.74 (m, 2H, H-5, 5'), 5.11-5.15 (m, 1H, H-4), 5.76 (dd, 1H, J = 7.0, 18.4 Hz, H-3), 7.46 (m, 2H, m-Ar), 7.55 (m, 2H, m-Ar), 7.62 (m, 1H, p-Ar), 7.70 (m, 1H, p-Ar), 7.93 (m, 2H, o-Ar), 8.06 (m, 2H, p-Ar), 8.08 (m, 2H, Ar).

100 MHz ^{13}C -NMR in DMSO- d_6 of ((2R,3R,4R)-3-(benzoyloxy)-4-fluoro-4-methyl-5-oxotetrahydrofuran-2-yl)methyl benzoate

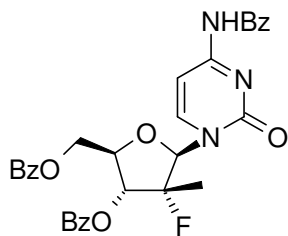


12

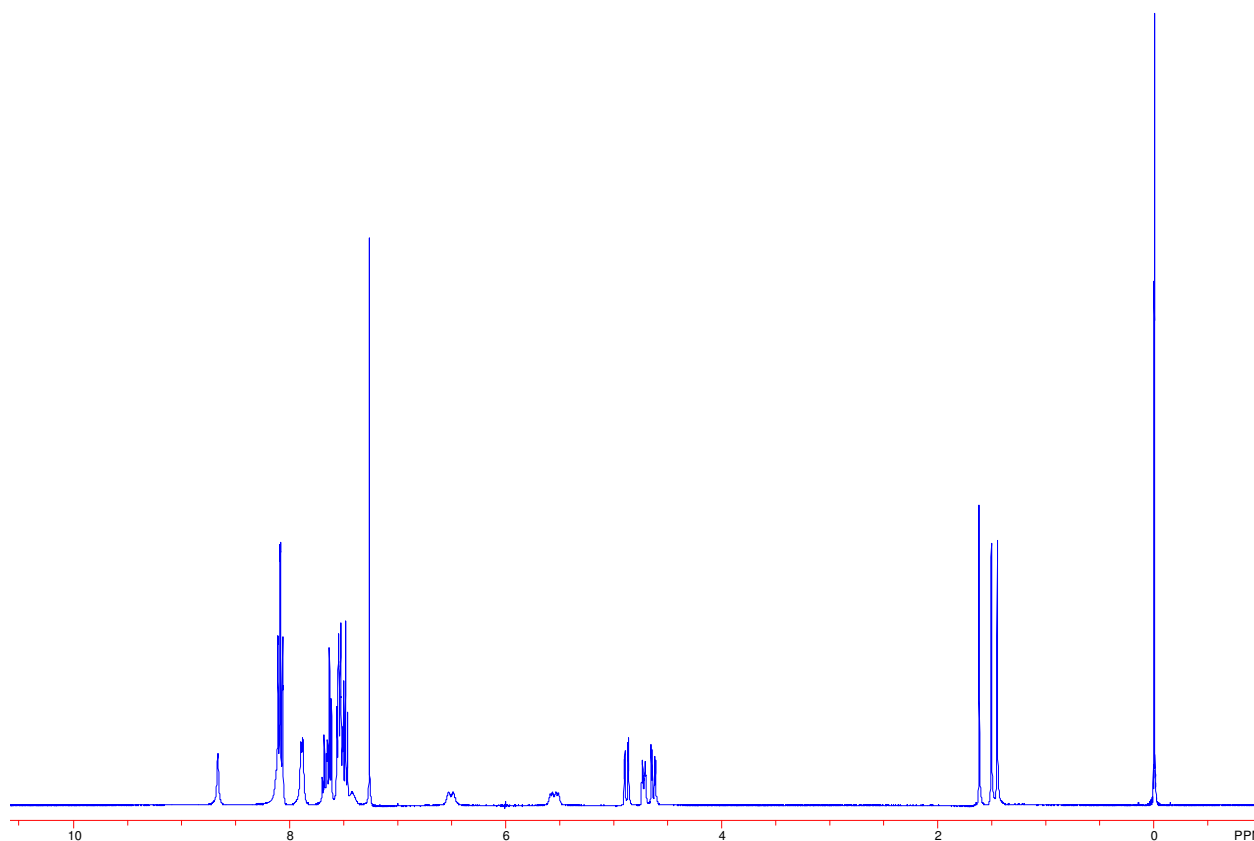


δ 18.69 (d, $J=24.3$ Hz), 63.90, 72.53 (d, $J=7.0$ Hz), 78.30, 92.38 (d, $J=183.5$ Hz), 128.95, 129.43, 129.59, 129.67, 130.00, 133.36, 134.32, 134.81, 165.47, 165.94, 170.24 (d, $J=21.4$ Hz).

400 MHz ^1H -NMR in CDCl_3 of (2R,3R,4R,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(benzyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate

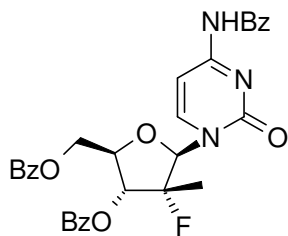


15

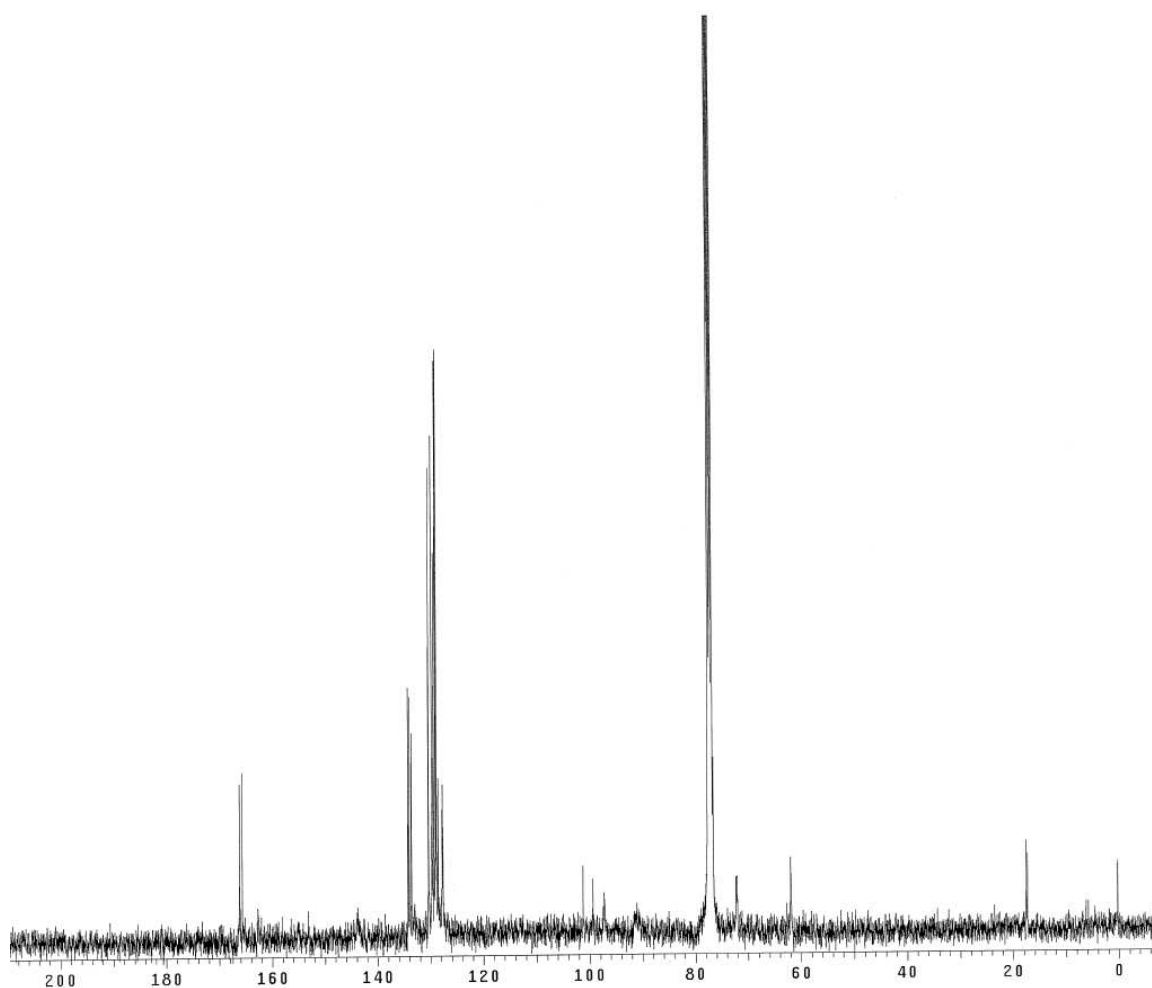


δ 1.47 (d, 3H, J = 22.3 Hz, CH_3), 4.63 (dd, 1H, J = 2.8, 12.7 Hz, H-5'), 4.72 (d, 1H, J = 9.4 Hz, H-4'), 4.87 (d, 1H, J = 12.7 Hz, H-5''), 5.55 (br dd, 1H, 8.4, 20.9 Hz, H-3'), 6.50 (br d, 1H, J = 16.8 Hz, H-1'), 7.41-7.55 (m, 7H, Ar and H-5), 7.61-7.69 (m, 3H, Ar), 7.88 (d, 1H, 6.8 Hz, H-6), 8.06-8.10 (m, 5H, Ar), 8.65 (s, 1H, NH).

100 MHz ^{13}C -NMR in CDCl_3 of (2R,3R,4R,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(benzoyloxymethyl)-4-fluoro-4-methyltetrahydrofuran-3-yl benzoate

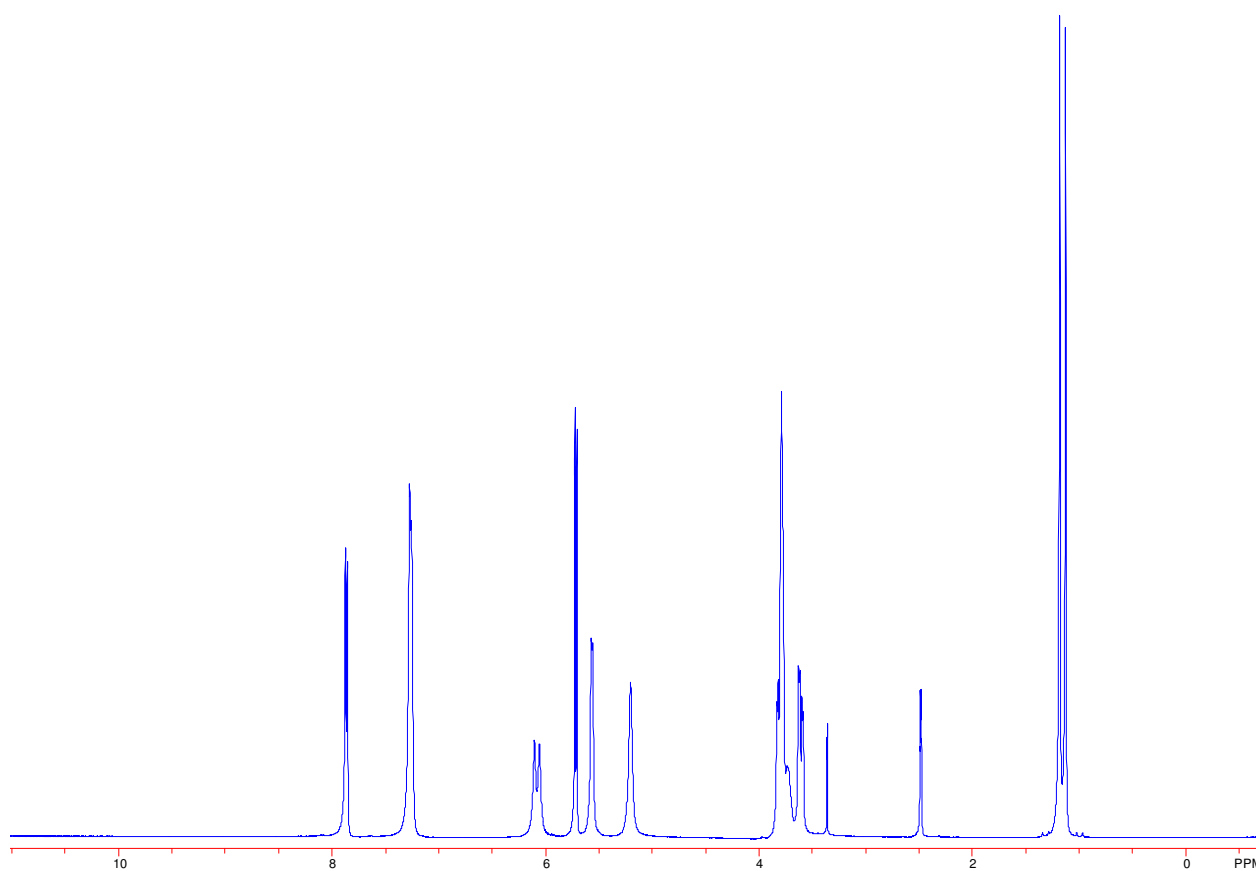
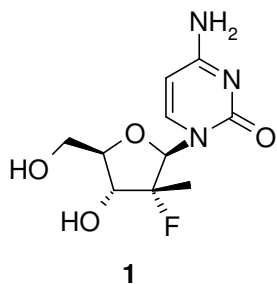


15



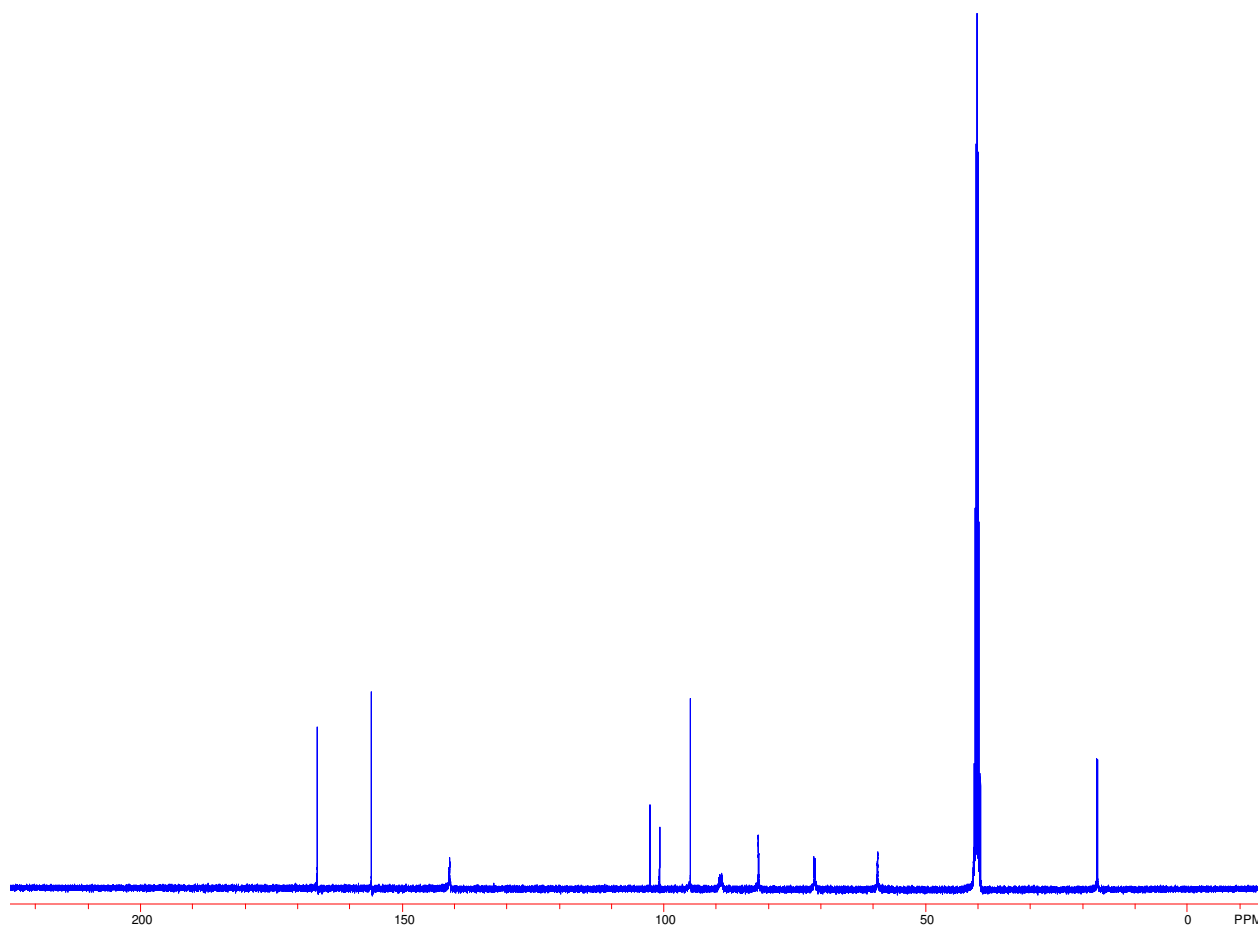
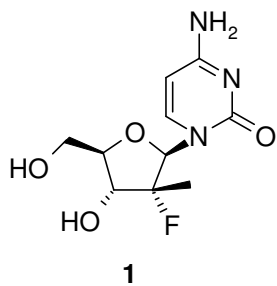
δ 17.19 (d, $J = 25.8$ Hz), 61.75 (s), 71.88 (s), 90.20 (br s), 96.98 (br s), 100.08 (d, $J = 197$ Hz), 127.51, 128.34, 128.65, 128.83, 129.14, 128.37, 129.54, 130.12, 132.80, 133.38, 133.78, 134.02, 143.80 (br s), 154.30, 157.50, 162.51, 165.43, 165.95.

400 MHz ^1H -NMR in DMSO- d_6 of 4-amino-1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidin-2(1H)-one



δ 1.15 (d, 3H, $J=22.5$ Hz, CH_3), 3.62 (m, 1H, H-5'), 3.78 (m, 3H, H-3', H-4', H-5''), 5.20 (br s, 1H, 3'-OH), 5.56 (d, 1H, $J=4.8$ Hz, 5'-OH), 5.72 (d, 1H, $J=7.6$ Hz, H-5), 6.08 (d, $J=19.2$ Hz, H-1'), 7.26 (s, 2H, NH_2), 7.86 (d, 1H, $J=7.4$ Hz, H-6).

100 MHz ^{13}C -NMR in DMSO- d_6 of 4-amino-1-((2R,3R,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)pyrimidin-2(1H)-one



δ 17.08 (d, $J=25.8$ Hz), 59.19 (s), 71.21 (d, $J=17.6$ Hz), 81.95 (s), 89.17 (d, $J=40.5$ Hz), 94.96 (s), 100.85 (s), 102.65 (s), 140.95 (s), 155.86 (s), 166.21 (s).