Supporting Information

for

Bicyclic Nucleoside Analogues: Synthesis of Thiazolopyrimidine-based Nucleosides via Copper-Catalysed Tandem Reaction of 5-Iodocytidine with Isothiocyanates

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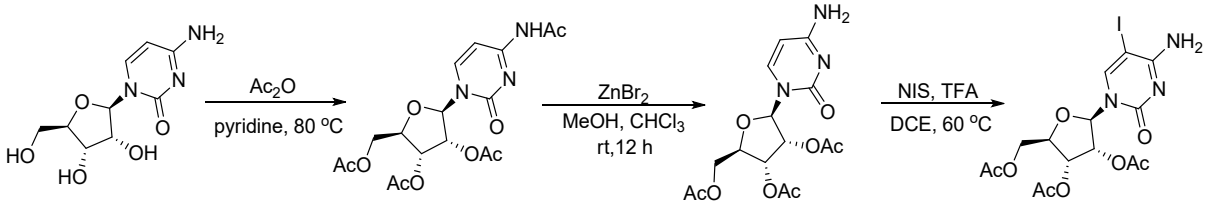
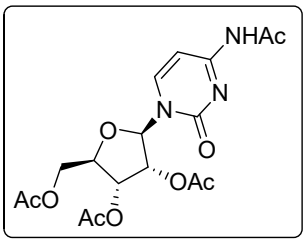
1. General Experimental Methods

All reactions were conducted in oven-dried glass wares. Solvents used for the experiments were distilled and degassed with Argon. All other reagents were purchased from local suppliers. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Enholm yellow solution. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane- ethyl acetate were used for elution. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{^{1}H} NMR). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C{^{1}H} NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer.

2. Synthesis of iodo-substituted triacetylated cytidine



*(2R,3R,4R,5R)-2-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-5-(acetoxymethyl)tetrahydrofuran-3,4-diyl diacetate (**1a'**)*: Cytidine (3 g, 10 mmol) was stirred with Ac_2O (10 mL, 100 mmol) and pyridine (20 mL) for 12 h at 80 °C. Volatiles were evaporated in vacuo, and to the residue, water was added and the aqueous layer was extracted thrice with DCM. The combined organic extracts were washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated in vacuo to give **1a'** as a white amorphous solid (3.65 g, 89%).



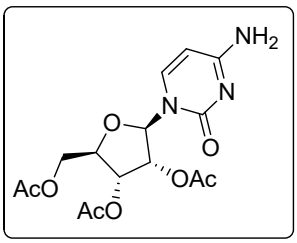
Analytical data of **1a'**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.84 (s, 1H), 7.85 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 6.5 Hz, 1H), 6.02 (s, 1H), 5.36 (s, 1H), 5.25 (s, 1H), 4.35-4.33 (m, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 2.03 (d, *J* = 8.0 Hz, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.2, 169.6, 169.4, 163.2, 154.9, 143.9, 97.3, 89.3, 79.8, 73.8, 69.7, 62.7, 24.9, 20.8, 20.5 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{17}H_{22}N_3O_9$ 412.1351, found 412.1353.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (**1a"**)*: A solution of **1a'** (3.65 g, 10 mmol) and $ZnBr_2$ (54 mg, 2.4 mmol) in MeOH/$CHCl_3$ (10/12 mL) was stirred at room temperature for 12 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer was extracted thrice with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo to give **1a"** as a white amorphous solid (3.54 g, 96%).



Analytical data of **1a"**:

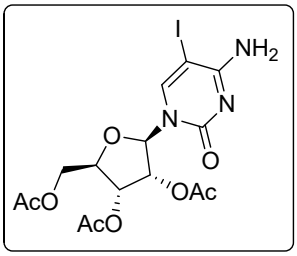
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.47 (d, *J* = 7.5 Hz, 1H), 6.28 (d, *J* = 7.5 Hz, 1H), 5.84 (d, *J* = 4.5 Hz, 1H), 5.20 (t, *J* = 5.0 Hz, 1H), 5.15 (t, *J* = 4.5 Hz, 1H), 4.24-4.20 (m, 3H), 1.99 (s, 3H), 1.97 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.5, 169.8, 169.7, 165.8, 141.1, 95.9, 89.6, 79.3, 73.5, 70.0, 63.1, 20.8, 20.6, 20.5 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{15}H_{20}N_3O_8$ 370.1245, found 370.1258.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(4-amino-5-iodo-2-oxopyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diacetate (**1a**)*: A mixture of the deacetylated compound **1a"**(3.54 g, 10 mmol) and NIS (4.5 g, 20 mmol) was dissolved in DCE (25 ml). Separately, 758 µL of trifluoroacetic acid was added and the reaction mixture was stirred at 60 °C. After completion of the reaction, as indicated from the TLC, the volatiles were removed under vacuum. To the remaining residue

saturated sodium thiosulphate solution was added and the aqueous layer was extracted thrice with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford **1a** as a pale yellow solid (2.52 g, 51%).



Analytical data of **1a**:

MP : 198-200 °C

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.82 (s, 1H), 6.02 (d, *J* = 2.5 Hz, 1H), 5.29 (t, *J* = 4.0 Hz, 1H), 5.24 (s, 1H), 4.31 (s, 3H), 2.16 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.2, 169.60, 169.56, 162.4, 152.9, 146.8, 88.7, 79.9, 73.7, 69.7, 62.7, 57.4, 21.2, 20.5 ppm.

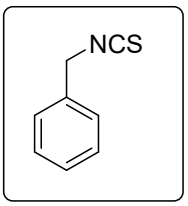
HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{15}H_{19}IN_3O_8$ 496.0211, found 496.0231.

3. General procedure for the synthesis of isothiocyanate

Absolute ethanol was added to the amine (1 equiv.). To this 1 equiv. of triethylamine was added and cooled to 0 °C using an ice bath. CS_2 (2 equiv.) was added dropwise using a pressure equalizer while stirring, resulting in the precipitation of the dithiocarbamate. After complete addition of CS_2, the ice bath was removed and then stirred for 2 h. A catalytic amount of DMAP (3 mol%) and $(Boc)_2O$ (0.99 equiv.) was added and the reaction mixture was stirred for one hour. After completion of the reaction, as indicated from the TLC, water was added and the aqueous layer was extracted thrice with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: hexane) to afford the desired product as colorless liquid.

*(isothiocyanatomethyl)benzene (**2a**):* The reaction was performed according to the general procedure with benzylamine (4 g, 37 mmol) in EtOH (40 ml), followed by addition of triethylamine (5.2 ml, 37 mmol), CS_2 (4.5 ml, 74 mmol), DMAP (137 mg, 1.1 mmol) and $(Boc)_2O$ (8.5 ml, 36 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O

mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2a** as a colorless liquid. (3.7 g, 66%).

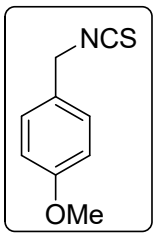


Analytical data of **2a**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.43 (t, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 4.74 (s, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 134.3, 129.0, 128.4, 126.9, 48.7 ppm.

*1-(isothiocyanatomethyl)-4-methoxybenzene (**2b**):* The reaction was performed according to the general procedure with 4-methoxy benzyl amine (3g, 21 mmol) in EtOH (30 ml), followed by addition of triethylamine (3.0 ml, 21 mmol), CS_2 (2.6 ml, 43 mmol), DMAP (80 mg, 0.6 mmol) and $(Boc)_2O$ (5.0 ml, 21 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford **2b** as a colorless liquid. (2.19 g, 65%).

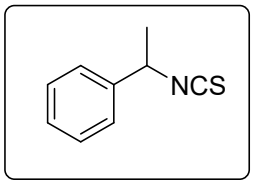


Analytical data of **2b**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 7.5 Hz, 2H), 4.62 (s, 2H), 3.81 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.7, 128.5, 126.4, 114.4, 55.4, 48.3 ppm.

*1-(isothiocyanatoethyl)benzene (**2c**):* The reaction was performed according to the general procedure with 1-phenylethan-1-amine (3 g, 24 mmol) in EtOH (30 ml), followed by addition of triethylamine (3.5 ml, 24 mmol), CS_2 (3.0 ml, 50 mmol), DMAP (91 mg, 0.7 mmol) and $(Boc)_2O$ (5.6 ml, 24 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2c** as a colorless liquid. (2.95 g, 73%).

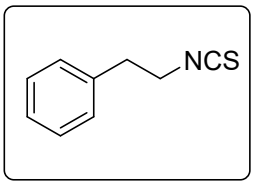


Analytical data of **2c**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.43 (t, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 3H), 4.96-4.92 (m, 1H), 1.70 (d, *J* = 7 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.3, 129.0, 128.3, 125.5, 57.1, 25.1 ppm.

*1-(isothiocyanatoethyl)benzene (**2d**):* The reaction was performed according to the general procedure with 2-phenylethan-1-amine (3 g, 24 mmol) in EtOH (30 ml), followed by addition of triethylamine (3.5 ml, 24 mmol), CS_2 (3.0 ml, 49 mmol), DMAP (90 mg, 0.7 mmol) and $(Boc)_2O$ (5.6 ml, 24 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2d** as a colorless liquid. (1.89 g, 47%).

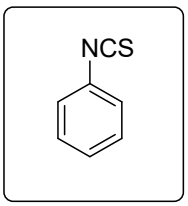


Analytical data of **2d**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.38 (t, *J* = 7.0 Hz, 2H), 7.33-7.24 (m, 3H), 3.75 (t, *J* = 7.0 Hz, 2H), 3.02 (t, *J* = 7.0 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 137.0, 128.8, 127.2, 46.4, 36.5 ppm.

*Phenyl isothiocyanate (**2e**):* The reaction was performed according to the general procedure with phenyl amine (3 g, 32 mmol) in EtOH (30 ml), followed by addition of triethylamine (4.5 ml, 32 mmol), CS_2 (3.9 ml, 64 mmol), DMAP (118 mg, 0.9 mmol) and $(Boc)_2O$ (7.3 ml, 31 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2e** as a colorless liquid. (1.5 g, 34%).

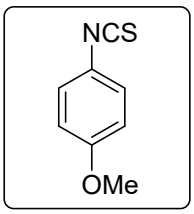


Analytical data of **2e**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.27 (d, *J* = 7.0 Hz, 2H), 7.22-7.19 (m, 1H), 7.15 (d, *J* = 7.0 Hz, 2H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 129.6, 127.3, 125.8 ppm.

*Phenyl isothiocyanate (**2f**):* The reaction was performed according to the general procedure with 4-methoxy phenyl amine (2 g, 16 mmol) in EtOH (30 ml), followed by addition of triethylamine (2.3 ml, 16 mmol), CS_2 (2.0 ml, 32 mmol), DMAP (59 mg, 0.4 mmol) and $(Boc)_2O$ (3.7 ml, 16 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2f** as a colorless liquid. (1.67 g, 62%).

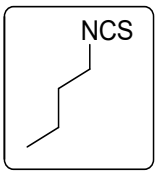


Analytical data of **2f**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.14 (d, *J* = 6.0 Hz, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 3.80 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 158.6, 127.0, 123.5, 114.8, 55.6 ppm.

*1-isothiocyanatobutane (**2g**):* The reaction was performed according to the general procedure with butyl amine (3g, 41 mmol) in EtOH (30 ml), followed by addition of triethylamine (5.7 ml, 41 mmol), CS_2 (4.9 ml, 82 mmol), DMAP (150 mg, 1.2 mmol) and $(Boc)_2O$ (9.3 ml, 41 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2g** as a colorless liquid. (1.4 g, 30%).



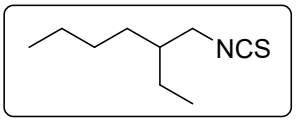
Analytical data of **2g**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.52-3.49 (m, 2H), 1.66-1.65 (m, 2H), 1.44-1.42 (m, 2H), 0.94-0.91 (m, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 44.8, 31.9, 19.8, 13.2 ppm.

*(3-isothiocyanato methyl)heptane (**2h**):* The reaction was performed according to the general procedure with ethylhexyl amine (3 g, 23 mmol) in EtOH (30 ml), followed by addition of

triethylamine (3.2 ml, 23 mmol), CS_2 (2.8 ml, 46 mmol), DMAP (85 mg, 0.6 mmol) and $(Boc)_2O$ (5.3 ml, 22 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2h** as a colorless liquid. (2.5 g, 63%).

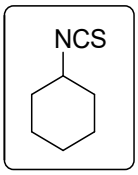


Analytical data of **2h**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.40 (d, J = 5.0 Hz, 2H), 1.54-1.49 (m, 1H), 1.40-1.18 (m, 8H), 0.84 (t, J = 7.0 Hz, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 47.9, 40.4, 30.9, 28.8, 24.3, 22.8, 14.0, 10.9 ppm.

*isothiocyanatocyclohexane (**2i**):* The reaction was performed according to the general procedure with cyclohexyl amine (3g, 30.2 mmol) in EtOH (30 ml), followed by addition of triethylamine (4.2 ml, 30.2 mmol), CS_2 (3.7 ml, 60.4 mmol), DMAP (110 mg, 0.9 mmol) and $(Boc)_2O$ (6.9 ml, 30.2 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford **2i** as a colorless liquid. (2.2 g, 52%).

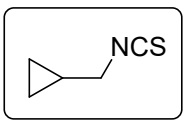


Analytical data of **2i**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.63 (s, 1H), 1.83 (s, 2H), 1.65-1.58 (m, 4H), 1.43-1.41 (m, 1H), 1.32 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 55.4, 33.2, 25.1, 23.2 ppm.

*(Isothiocyanatomethyl)cyclopropane (**2j**):* The reaction was performed according to the general procedure with cyclopropylmethanamine (1.7 g, 23 mmol) in EtOH (20 ml), followed by addition of triethylamine (3.3 ml, 23 mmol), CS_2 (2.9 ml, 47 mmol), DMAP (87 mg, 0.7 mmol) and $(Boc)_2O$ (5.4 ml, 24 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford the **2j** as a colorless liquid. (1.45 g, 54%).

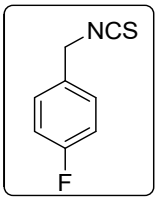


Analytical data of **2j**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.38 (d, *J* = 7.0 Hz, 2H), 1.20-1.18 (m, 1H), 0.61 (d, *J* = 7.5 Hz, 2H), 0.30 (d, *J* = 4.5 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 49.9, 11.4, 3.80 ppm.

*1-fluoro-4-(isothiocyanatomethyl)benzene (**2k**):* The reaction was performed according to the general procedure with 4-fluoro-benzylamine (3g, 23 mmol) in EtOH (30 ml), followed by addition of triethylamine (3.3 ml, 23 mmol), CS_2 (2.9 ml, 47 mmol), DMAP (87 mg, 0.7 mmol) and $(Boc)_2O$ (5.4 ml, 23 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford **2k** as a colorless liquid. (2.09 g, 52%).

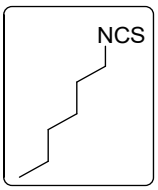


Analytical data of **2k**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.21-7.19 (m, 2H), 6.98 (t, *J* = 8.0 Hz, 2H), 4.59 (s, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.6, 161.6, 130.2, 130.1, 128.82, 128.76, 116.0, 115.9, 48.1 ppm.

*1-isothiocyanatohexane (**2l**):* The reaction was performed according to the general procedure with hexylamine (3g, 41 mmol) in EtOH (30 ml), followed by addition of triethylamine (4.1 ml, 29.6 mmol), CS_2 (3.6 ml, 59.2 mmol), DMAP (108 mg, 0.88 mmol) and $(Boc)_2O$ (6.8 ml, 29.6 mmol). The work-up of the reaction mixture was done using EtOAc/H_2O mixture. After workup, the residue was purified by silica gel column chromatography (hexane) to afford **2l** as a colorless liquid. (2.5 g, 59%).



Analytical data of **2l**:

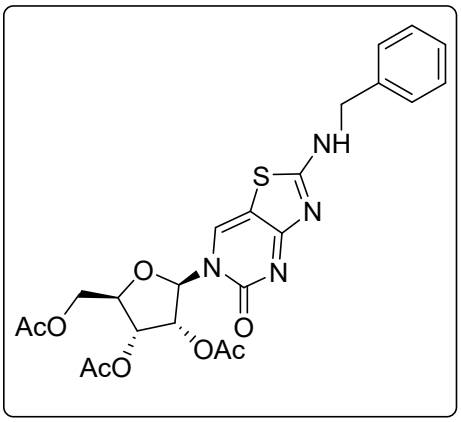
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 3.44 (t, *J* = 6.5 Hz, 2H), 1.66-1.60 (m, 2H), 1.38-1.32 (m, 2H), 1.28-1.24 (m, 4H), 0.84 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 45.1, 31.0, 29.9, 26.2, 22.4, 13.9 ppm.

4. General procedure for the synthesis of thiazolopyrimidine analogues of triacetylated cytidine

An oven dried Schlenk tube was charged with iodo-substituted triacetylated cytidine (1 equiv.), isothiocyanate (2 equiv.), CuBr (10 mol%), 1,10-phenanthroline (20 mol%) and K_2CO_3 (1 equiv.). The schlenk tube was sealed with a rubber septum and degassed followed by the addition of dry DMSO under Argon atmosphere. The reaction mixture was then allowed to stir in an oil bath at 80 °C for 36 h. After completion of the reaction, as indicated from the TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the desired product.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(benzylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3a**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), (isothiocyanatomethyl)benzene **2a** (181 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3a** as a yellow amorphous solid (235 mg, 75%).



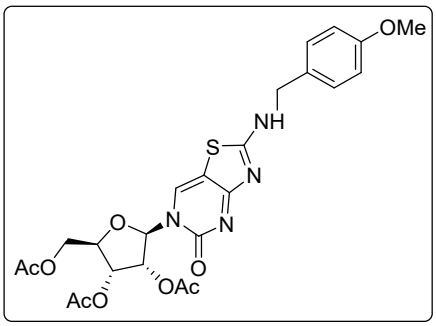
Analytical data of **3a:**

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.99 (s, 1H), 7.79 (s, 1H), 7.24-7.21 (m, 3H), 7.09-7.07 (m, 2H), 6.00 (s, 1H), 5.40 (s, 1H), 5.26 (s, 1H), 4.71 (s, 1H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.30 (s, 3H), 2.00 (d, *J* = 5.5 Hz, 9H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.4, 169.59, 169.55, 136.9, 128.8, 128.5, 128.1, 127.6, 79.6, 73.9, 69.6, 62.8, 49.0, 20.9, 20.5, 20.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_8S$ 517.1388, found 517.1409.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-((4-methoxybenzyl)amino)-5-oxothiazolo[4,5-d] pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3b**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), 1-(isothiocyanatomethyl)-4-methoxybenzene **2b** (217 mg, 1.21 mmol), CuCl (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3b** as an amorphous yellow solid (265 mg, 80%).



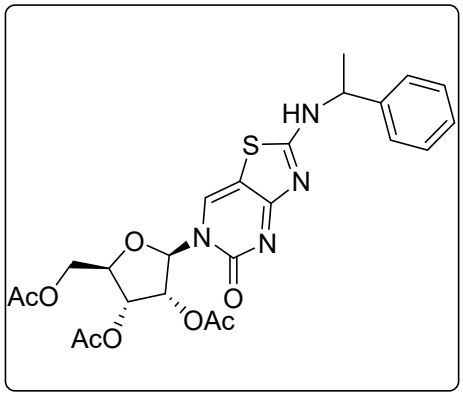
Analytical data of **3b**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.88 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 6.5 Hz, 2H), 6.12 (s, 1H), 5.35 (t, *J* = 3.5 Hz, 1H), 5.24 (t, *J* = 5.0 Hz, 1H), 4.48 (s, 2H), 4.35-4.32 (m, 3H), 3.72 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 170.4, 170.3, 169.61, 169.58, 159.5, 159.0, 129.7, 129.5, 129.2, 114.2, 113.8, 79.6, 74.0, 69.6, 69.5, 62.8, 60.4, 55.3, 21.1, 20.9, 20.6, 20.5 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{24}H_{27}N_4O_9S$ 547.1493, found 547.1507.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-((1-phenylethyl)amino)-5-oxothiazolo[4,5-d] pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3c**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), (isothiocyanatoethyl)benzene **2c** (198 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanathroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (70% ethyl acetate/hexane) to afford **3c** as an amorphous yellow solid (280 mg, 87%).



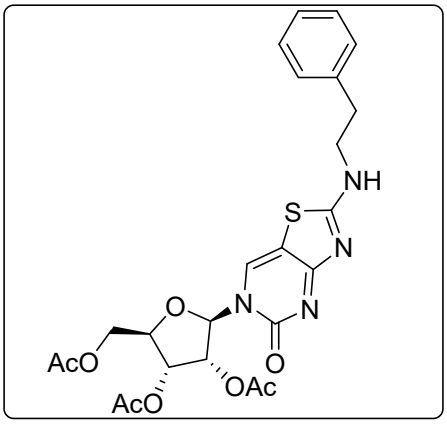
Analytical data of **3c**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.89 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.26 (s, 3H), 6.06 (s, 1H), 5.39-5.37 (m, 1H), 5.24 (s, 1H), 4.33 (d, *J* = 8.0 Hz, 3H), 2.10 (s, 1H), 2.05-2.01 (m, 9H), 2.00 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 173.5, 169.7, 169.6, 129.0, 126.2, 89.6, 79.4, 73.9, 69.4, 62.7, 50.6, 40.8, 29.7, 22.6, 20.8, 20.48, 20.46 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{24}H_{27}N_4O_8S$ 531.1544, found 531.1564.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(phenethylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3d**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), (2-isothiocyanatoethyl)benzene **2d** (198 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanathroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3d** as an amorphous yellow solid (193 mg, 60%).



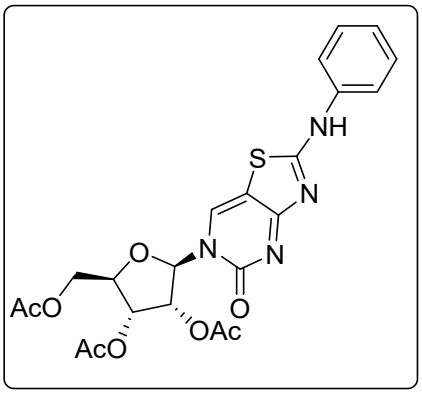
Analytical data of **3d**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.98-7.95 (m, 1H), 7.20-7.17 (m, 2H), 7.09(s, 3H), 6.05 (s, 1H), 5.41 (d, *J* = 7.5 Hz, 1H), 5.27 (s, 1H), 4.34-4.32 (m, 3H), 3.82 (s, 1H), 3.56 (s, 1H), 3.04-2.92 (m, 2H), 2.07-2.01 (m, 9H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 170.6, 169.8, 169.7, 139.0, 129.3, 129.2, 128.9, 126.9, 109.5, 90.5, 79.6, 73.5, 70.0, 63.5, 46.3, 34.7, 21.1, 20.8, 20.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{24}H_{27}N_4O_8S$ 531.1544, found 531.1543.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(phenylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3e**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), 1-isothiocyanatobenzene **2e** (164 mg, 1.21 mmol), CuBr(9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3e** as an amorphous yellow solid (136 mg, 45%).



Analytical data of **3e:**

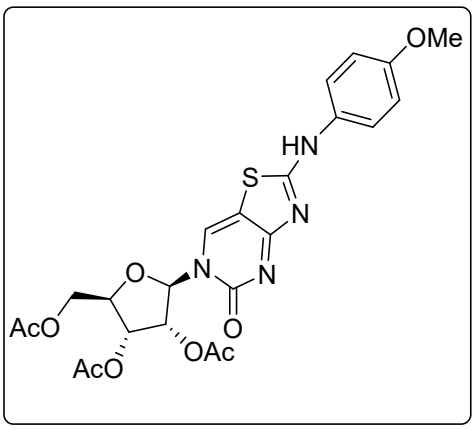
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.94 (s, 1H), 7.54 (s, 2H), 7.20 (s, 2H), 7.07 (s, 1H), 6.04 (s, 1H), 5.43 (s, 1H), 5.24 (s, 1H), 4.35-4.32 (m, 3H), 2.03 (s, 6H), 2.00 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.3, 169.6, 169.5, 154.7, 138.6, 133.4, 129.1, 90.5, 79.5, 74.0, 69.2, 62.6, 20.9, 20.5, 20.4 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{22}H_{23}N_4O_8S$ 503.1231, found 503.1256.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(4-methoxyphenyl)amino)-5-oxothiazolo[4,5-d] pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3f**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), 1-isothiocyanat-4-methoxybenzene **2f** (200 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanathroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel

chromatography (80% ethyl acetate/hexane) to afford **3f** as an amorphous yellow solid (239 mg,74%).



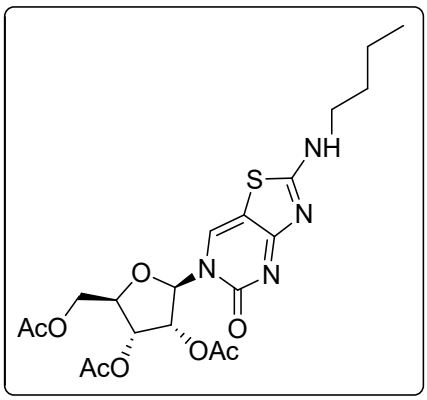
Analytical data of **3f**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.90 (s, 1H), 7.40 (s, 2H), 6.86 (s, 2H), 6.11 (d, *J* = 3.0 Hz, 1H), 5.39 (s, 1H), 5.24 (t, *J* = 5.0 Hz, 1H), 4.35-4.31 (m, 3H), 3.74 (s, 3H), 2.04 (s, 6H), 2.01 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 170.6, 169.8, 169.7, 136.8, 122.0, 114.8, 109.0, 90.7, 79.6, 73.6, 70.0, 63.5, 55.8, 55.4, 21.1, 20.76, 20.75 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_9S$ 533.1337, found 533.1352.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(butylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3g**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), 1-isothiocyanatobutane **2g** (140 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3g** as an yellow amorphous solid (193 mg, 66%).



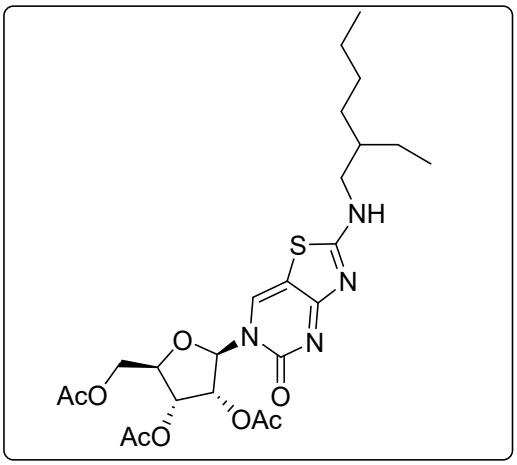
Analytical data of **3g**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.96 (s, 1H), 6.11 (s, 1H), 5.39 (s, 1H), 5.26 (s, 1H), 4.34-4.32 (m, 3H), 3.61 (s, 1H), 3.32 (t, *J* = 6.0 Hz, 1H), 2.09-2.05 (m, 6H), 2.02 (s, 3H), 1.72 (t, *J* = 6.5 Hz, 1H), 1.61 (s, 1H), 1.39-1.35 (m, 2H), 0.90-0.84 (m, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.64, 169.56, 132.4, 108.7, 89.8, 79.4, 74.0, 69.4, 62.7, 46.6, 30.8, 20.9, 20.53, 20.48, 20.0, 13.6 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{27}N_4O_8S$ 483.1544, found 483.1540.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(2-ethylhexyl)amino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3h**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), 4-(isothiocyanatomethyl)heptane **2h** (208 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3h** as an amorphous yellow solid (245 mg, 75%).



Analytical data of **3h**:

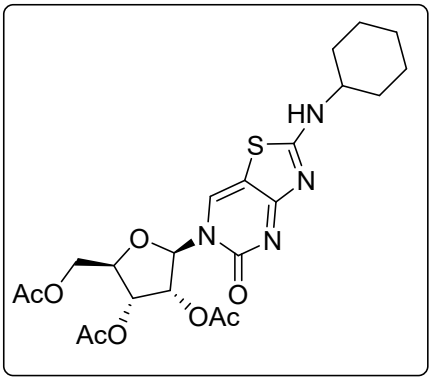
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.92 (s, 1H), 6.14 (s, 1H), 5.37 (s, 1H), 5.29-5.25 (m, 1H), 4.34-4.31 (m, 4H), 3.23 (s, 1H), 2.09 (s, 1H), 2.04-2.02 (m, 9H), 1.34-1.19 (m, 8H), 0.85-0.80 (m, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.4, 170.2, 169.6, 169.5, 89.9, 79.4, 74.0, 69.6, 69.4, 62.9, 62.7, 39.2, 30.72, 30.67, 28.6, 24.1, 23.9, 23.0, 20.9, 20.52, 20.48, 14.0, 10.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{24}H_{35}N_4O_8S$ 539.2170, found 539.2183.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-(cyclohexylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3i**):* The reaction was performed according to the

general procedure with iodo-substituted triacetylated cytidine **1a** (300 mg, 0.6 mmol), isothiocyanatocyclohexane **2i** (171 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under Argon atmosphere at 80 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3i** as an amorphous yellow solid (234 mg, 76%).



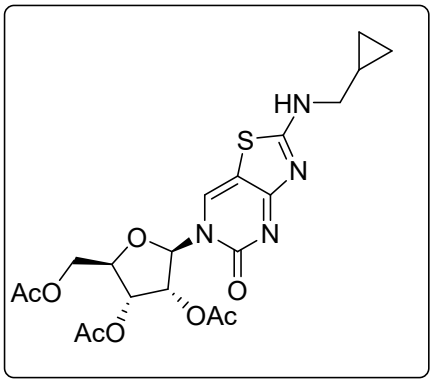
Analytical data of **3i**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.95 (s, 1H), 6.11 (s, 1H), 5.40 (t, *J* = 4.0 Hz, 1H), 5.26 (s, 1H), 4.34 (s, 3H), 3.68 (s, 1H), 2.09 (s, 2H), 2.04-2.01 (m, 9H), 1.78-1.58 (m, 4H), 1.28-1.19 (m, 4H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.65, 169.57, 89.8, 79.4, 74.0, 69.5, 69.3, 63.8, 60.4, 57.4, 32.3, 24.8, 21.1, 20.9, 20.53, 20.48, 14.2 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{22}H_{29}N_4O_8S$ 509.1701, found 509.1713.

*(2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-((cyclopropylmethyl)amino)-5-oxothiazolo[4,5-d] pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (**3j**):* The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (137 mg, 0.6 mmol), (isothiocyanatomethyl)cyclopropane **2j** (108 mg, 1.21 mmol), CuBr (9 mg, 0.06 mmol), 1,10-phenanthroline (22 mg, 0.12 mmol) and K_2CO_3 (83 mg, 0.6 mmol) and DMSO under argon atmosphere at 60 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3j** as yellow solid (105 mg, 36%).



Analytical data of **3j**:

MP: 137-139 ^{o}C

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.03 (s, 1H), 6.07 (s, 1H), 5.44-5.42 (m, 1H), 5.28 (s, 1H), 4.34 (s, 3H), 3.46 (s, 1H), 3.21 (s, 1H), 2.10-2.05 (m, 6H), 2.01 (s, 3H), 0.81 (s, 1H), 0.54-0.43 (m, 2H), 0.33-0.24 (m, 2H) ppm.

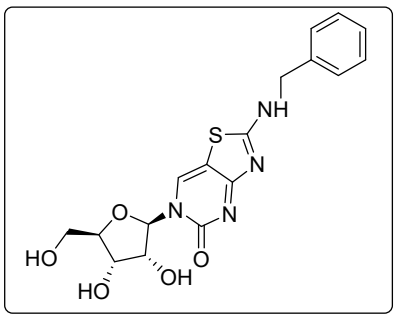
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.4, 170.2, 169.62, 169.56, 155.7, 132.9, 131.8, 90.2, 79.4, 73.9, 62.8, 62.7, 40.8, 20.9, 20.5, 20.47, 10.5, 3.9, 3.7 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{20}H_{25}N_4O_8S$ 481.1388, found 481.1413.

5. Deprotection of the thiazolopyrimidine-fused cytidine

The corresponding benzothiazole fused cytidine was dissolved in 10 ml of NH_3/MeOH and stirred at room temperature for 12 h. After completion of the reaction, as indicated from the TLC, volatiles were evaporated in vacuo. The residue then underwent sequential washing with diethyl ether, then DCM, and finally with ethyl acetate. Subsequently, it was dried under vacuum to afford the desired product.

*2-(benzylamino)-6-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-thiazolo[4,5-d]pyrimidin-5(6H)-one (**4a**):* The reaction was performed according to the general procedure with benzathiazole fused cytidine **3a** (235 mg, 0.22 mmol). in NH_3/ MeOH (10 ml) and stirred at room temperature for 12 h. Sequential washing and drying afforded **4a** as yellow solid (102 mg, 61%).



Analytical data of **4a**:

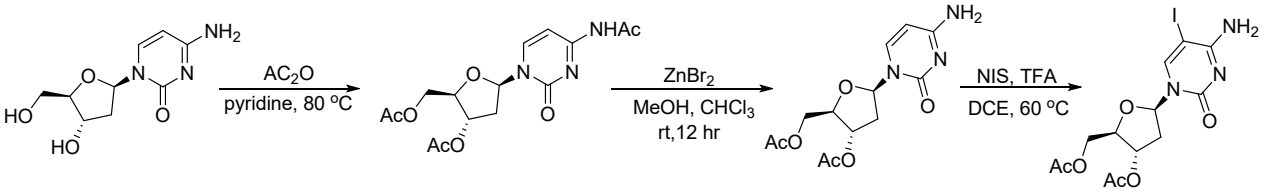
MP: 154-156 ^{o}C

^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 8.50 (s, 1H), 7.38-7.35 (m, 5H), 5.83 (s, 1H), 5.46 (s, 1H), 5.11 (s, 1H), 5.02 (s, 1H), 4.70 (s, 2H), 3.94-3.88 (m, 3H), 3.73-3.71 (m, 1H), 3.60-3.58 (m, 1H) ppm.

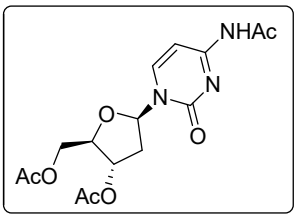
^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 175.1, 155.8, 138.0, 134.6, 129.0, 128.1, 128.0, 90.9, 84.6, 75.0, 69.3, 60.7, 60.2, 48.1ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{17}H_{18}N_4NaO_5S$ 413.0890, found 413.0888.

6. Synthesis of iodo-substituted diacetylated deoxycytidine



*(2R,3S,5R)-5-(4-acetamido-2-oxopyrimidin-1(2H)-yl)-2-(acetoxymethyl)tetrahydrofuran-3-yl acetate (**1b'**)*: Deoxycytidine (3 g, 10 mmol) was stirred with Ac_2O (10 mL, 100 mmol) and pyridine (20 mL) for 12 h at 80 °C. Volatiles were evaporated in vacuo, and to the residue, water was added and the aqueous layer was extracted thrice with DCM. The combined organic extracts were washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated in vacuo to give **1b'** as a white amorphous solid (3.18 g, 90%).



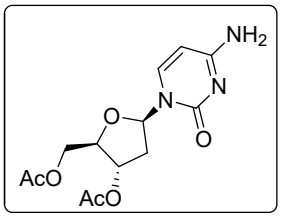
Analytical data of **1b'**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.94 (d, *J* = 7.0 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 6.17 (s, 1H), 5.14 (s, 1H), 4.30 (s, 3H), 2.74-2.71 (m, 1H), 2.22 (s, 3H), 2.03 (d, *J* = 8.5 Hz, 7H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.4, 170.2, 163.1, 154.9, 143.4, 96.9, 87.3, 83.0, 74.2, 63.7, 38.9, 24.8, 20.85, 20.76 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{15}H_{19}N_3NaO_7$ 376.1115, found 376.1132.

*((2R,3S,5R)-3-acetoxy-5-(4-amino-2-oxopyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**1b"**)*: A solution of **1b'** (3.18 g, 10 mmol) and $ZnBr_2$ (540 mg, 2.4 mmol) in MeOH/$CHCl_3$ (8/10 mL) was stirred at room temperature for 12 h. After completion of the reaction as indicated from the TLC, water was added and the aqueous layer was extracted thrice with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give **1b"** as a white amorphous solid (2.95 g, 95%).



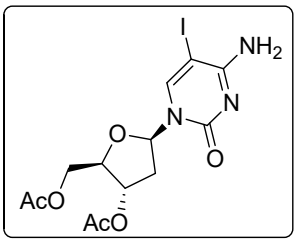
Analytical data of **1b"**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.53 (d, *J* = 7.5 Hz, 1H), 6.19 (t, *J* = 6.0 Hz, 1H), 5.81 (d, *J* = 7 Hz, 1H), 5.13 (d, *J* = 5.5 Hz, 1H), 4.26-4.21 (m, 3H), 2.61-2.58 (m, 1H), 2.03 (d, *J* = 6.5 Hz, 7H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 165.3, 155.3, 140.2, 94.9, 86.6, 82.4, 74.4, 63.9, 38.5, 20.9, 20.8 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{13}H_{18}N_3O_6$ 312.1190, found 312.1186.

*((2R,3S,5R)-3-acetoxy-5-(4-amino-5-iodo-2-oxopyrimidin-1(2H)-yl)tetrahydrofuran-2-yl) methyl acetate (**1b**)*: A mixture of the deacetylated compound **1b"** (2.95 g, 10 mmol) and NIS (4.5 g, 20 mmol) was dissolved in DCE (20 ml). Separately, 631 µL of trifluoroacetic acid was added and the reaction mixture was stirred at 60 °C. After completion of the reaction, as indicated from the TLC, the volatiles were removed under vacuum. To the remaining residue saturated sodium thiosulphate solution was added and the aqueous layer was extracted thrice with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford **1b** a pale yellow solid (2.4 g, 55%).



Analytical data of **1b**:

MP : 170-172 °C

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.87 (s, 1H), 6.16 (t, *J* = 6.0 Hz, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.29-4.24 (m, 3H), 2.60-2.56 (m, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 2.00 (s, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.4, 170.2, 163.8, 154.3, 146.1, 86.6, 82.6, 74.1, 63.7, 56.9, 38.9, 21.0, 20.9 ppm.

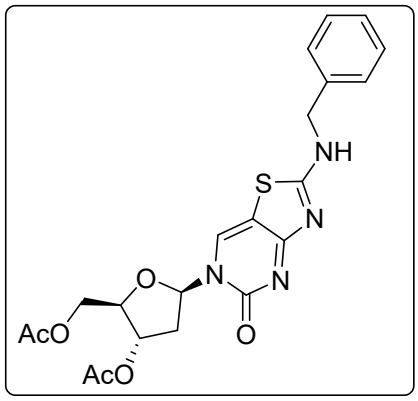
HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{13}H_{17}IN_3O_6$ 438.0157, found 438.0155.

7. General procedure for the synthesis of thiazolopyrimidine analogues of diacetylated deoxycytidine

An oven dried Schlenk tube was charged with iodo-substituted diacetylated deoxycytidine (1 equiv.), isothiocyanate (2 equiv.), CuBr (10 mol%), 1,10-phenanathroline (20 mol%) and K_2CO_3 (1 equiv.). The schlenk tube was sealed with a rubber septum and degassed followed by the addition of dry DMSO under argon atmosphere. The reaction mixture was then allowed to stir in an oil bath at 80 °C for 36 h. After completion of the reaction, as indicated from the

TLC, water was added and the aqueous layer was extracted thrice with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (silica gel, eluent: mixtures of ethyl acetate/hexanes) to afford the desired product.

*((2R,3S,5R)-3-acetoxy-5-(2-(benzylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl) tetrahydrofuran-2-yl)methyl acetate (**3k**):* The reaction was performed according to the general procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), isothiocyanatomethylbenzene **2a** (205 mg, 1.37 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanthroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under argon atmosphere at 80 ^oC for 36 h. After workup, the residue was purified with silica gel chromatography (70% ethyl acetate/hexane) to afford **3k** as an amorphous yellow solid (194 mg, 62%).



Analytical data of **3k**:

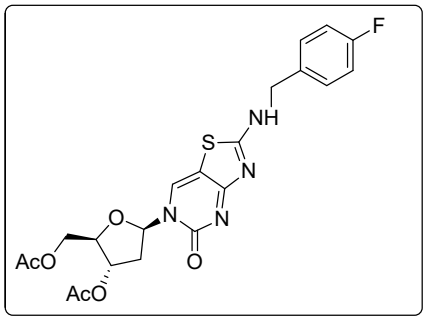
^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.96 (s, 1H), 7.30 (s, 5H), 6.22 (t, *J* = 6.0 Hz, 1H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.73 (s, 1H), 4.56 (s, 1H), 4.29-4.27 (m, 4H), 2.75-2.72 (m, 1H), 2.03 (s, 3H), 1.98 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ 170.7, 170.5, 138.0, 134.7, 129.1, 128.1, 128.0, 108.9, 87.3, 82.4, 74.6, 64.2, 48.1, 37.9, 21.2, 21.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{22}N_4NaO_6S$ 481.1152, found 481.1155.

*((2R,3S,5R)-3-acetoxy-5-(2-((4-fluorobenzyl)amino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl)tetrahydrofuran-2-yl)methyl acetate (**3l**):* The reaction was performed according to the general procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), 1-fluoro-4-(isothiocyanatomethyl)benzene **2k** (229 mg, 1.37 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanathroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under argon atmosphere at 80 ^oC for 36 h. After workup, the residue was purified with silica

gel chromatography (80% ethyl acetate/hexane) to afford **3l** as an amorphous yellow solid (261 mg, 80%).



Analytical data of **3l**:

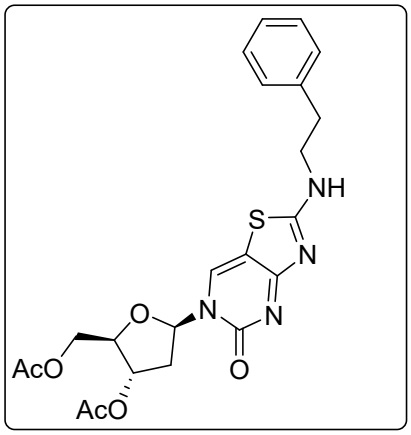
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 9.87 (s, 1H), 8.01-7.87 (m, 1H), 7.26 (s, 2H), 6.92-6.79 (m, 2H), 6.20 (t, *J* = 6.0 Hz, 1H), 5.13 (s, 1H), 4.70-4.53 (m, 2H), 4.28-4.26 (m, 3H), 2.71 (d, *J* = 9.5 Hz, 1H), 2.54 (s, 1H), 2.03 (s, 3H), 1.98 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 175.7 (d, *J* = 33.8 Hz), 170.6, 170.5, 155.5, 134.5, 130.2 (d, *J* = 8.7 Hz), 115.8 (d, *J* = 21.2), 108.8, 87.2, 82.3, 74.6, 64.2, 47.3, 37.9, 21.2, 21.1 ppm.

^{19}F NMR (471 MHz, DMSO-d_6): δ -115.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{21}H_{21}FN_4NaO_6S$ 499.1058, found 499.1082.

*((2R,3S,5R)-3-acetoxy-5-(2-(phenethylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl) tetrahydrofuran-2-yl)methyl acetate (**3m**):* The reaction was performed according to the general procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), (2-isothiocyanatoethyl)benzene **2d** (224 mg, 1.37 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanthroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under argon atmosphere at 80 °C for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3m** as an amorphous yellow solid (227 mg, 70%).



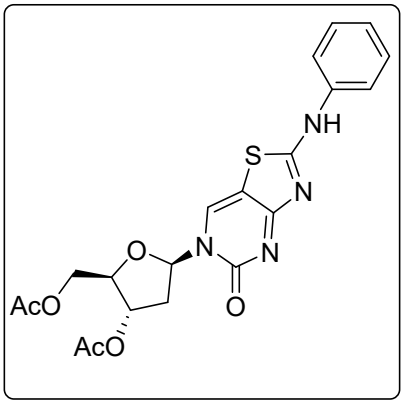
Analytical data of **3m**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.99 (s, 1H), 7.20-7.12 (m, 5H), 6.24 (t, *J* = 6.0 Hz, 1H), 5.14 (d, *J* = 6.5 Hz, 1H), 4.31-4.29 (m, 3H), 3.55 (s, 2H), 3.03 (s, 2H), 2.92 (s, 1H), 2.80-2.76 (m, 1H), 2.04 (s, 3H), 2.00 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 128.8, 128.7, 128.3, 126.9, 126.3, 87.9, 82.9, 74.2, 74.0, 63.8, 38.8, 35.1, 29.7, 21.1, 20.91, 20.87 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$ calcd for $C_{22}H_{25}N_4O_6S$ 473.1489, found 473.1496.

*((2R,3S,5R)-3-acetoxy-5-(2-(phenylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl) tetrahydrofuran-2-yl)methyl acetate (**3n**):* The reaction was performed according to the general procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), isothiocyanatobenzene **2e** (186 mg, 1.3 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanathroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under argon atmosphere at 80 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3n** as a white solid (160 mg, 52%).



Analytical data of **3n**:

MP : 253-256 °C

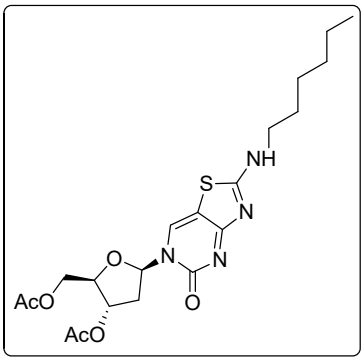
^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 11.4 (s, 1H), 8.50 (s, 1H), 7.72 (s, 2H), 7.42 (t, *J* = 7 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.20 (t, *J* = 6 Hz, 1H), 5.20 (s, 1H), 4.31-4.26 (m, 4H), 2.33-2.27 (s, 1H), 2.07 (s, 3H), 2.00 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 170.7, 170.6, 136.8, 129.8, 127.2, 82.5, 74.6, 64.2, 31.2, 21.2, 21.1 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + H)^+$calcd for $C_{20}H_{20}N_4O_6S$ 445.1176, found 445.1179.

*((2R,3S,5R)-3-acetoxy-5-(2-(hexylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl) tetrahydrofuran-2-yl)methyl acetate (**3o**):* The reaction was performed according to the general

procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), 1-iso thiocyanatohexane **2l** (197 mg, 1.37 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanathroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under argon atmosphere at 80 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3o** as an amorphous yellow solid (218 mg, 70%).



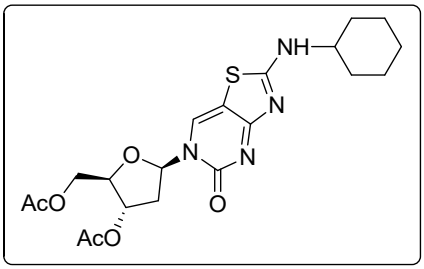
Analytical data of **3o**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.03 (s, 1H), 6.25 (t, *J* = 6 Hz, 1H), 5.15 (s, 1H), 4.32-4.29 (m, 3H), 3.31 (d, *J* = 6.0 Hz, 1H), 2.78 (s, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.71 (s, 2H), 1.32-1.18 (m, 8H), 0.81 (m, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 155.7, 87.8, 82.9, 74.1, 63.8, 46.8, 39.1, 31.2, 28.8, 26.4, 22.5, 21.1, 20.92, 20.88, 14.0 ppm.

HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{20}H_{28}N_4NaO_6$ 475.1622, found 475.1644.

*((2R,3S,5R)-3-acetoxy-5-(2-(cyclohexylamino)-5-oxothiazolo[4,5-d]pyrimidin-6(5H)-yl) tetrahydrofuran-2-yl)methyl acetate (**3p**):* The reaction was performed according to the general procedure with iodo-substituted diacetylated deoxycytidine **1b** (300 mg, 0.68 mmol), isothiocyanatocyclohexane **2i** (194 mg, 1.37 mmol), CuBr (10 mg, 0.068 mmol), 1,10-phenanathroline (25 mg, 0.13 mmol) and K_2CO_3 (95 mg, 0.68 mmol) and DMSO under Argon atmosphere at 80 °C for 48 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3p** as an amorphous yellow solid (195 mg, 63%).



Analytical data of **3p**:

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.01 (s, 1H), 6.25 (t, *J* = 6.5 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.32-4.29 (m, 3H), 3.14 (s, 1H), 2.78 (s, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.98 (s, 1H), 1.77 (s, 2H), 1.58 (s, 2H), 1.32-1.18 (m, 6H) ppm.

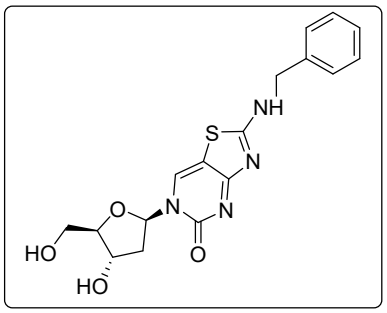
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 132.3, 88.0, 83.0, 74.2, 63.8, 42.7, 32.3, 24.8, 20.93, 20.91 ppm.

HRMS (ESI-Orbitrap) m/z:. $(M + H)^+$ calcd for $C_{20}H_{27}N_4O_6S$ 451.1646, found 451.1658.

8. Deprotection of the thiazolopyrimidine-fused deoxycytidine

The corresponding benzothiazole fused deoxycytidine was dissolved in 10 ml of NH_3/MeOH and stirred at room temperature for 12h. After completion of the reaction, as indicated from the TLC, volatiles were evaporated in vacuo. The residue then underwent sequential washing with diethyl ether, then DCM, and finally with ethyl acetate. Subsequently, it was dried under vacuum to afford the desired product.

*2-(benzylamino)-6-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl) thiazolo[4,5-d]pyrimidin-5(6H)-one (**4k**):* The reaction was performed according to the general procedure with benzathiazole fused deoxycytidine **3k** (194 mg, 0.32 mmol). in NH_3/ MeOH (10 ml) and stirred at room temperature for 12h. Sequential washing and drying afforded **4k** as yellow solid (109 mg, 69%).



Analytical data of **4k**:

MP: 187-189 °C

^{1}H NMR (500 MHz, DMSO-d_6, TMS): δ 8.46 (s, 1H), 7.36 (s, 5H), 7.31 (s, 1H), 6.19 (d, *J* = 6.0 Hz, 1H), 5.28 (d, *J* = 9.0 Hz, 1H), 5.02 (s, 1H), 4.71 (s, 2H), 4.21 (s, 1H), 3.85 (s, 1H), 3.60 (s, 3H) ppm.

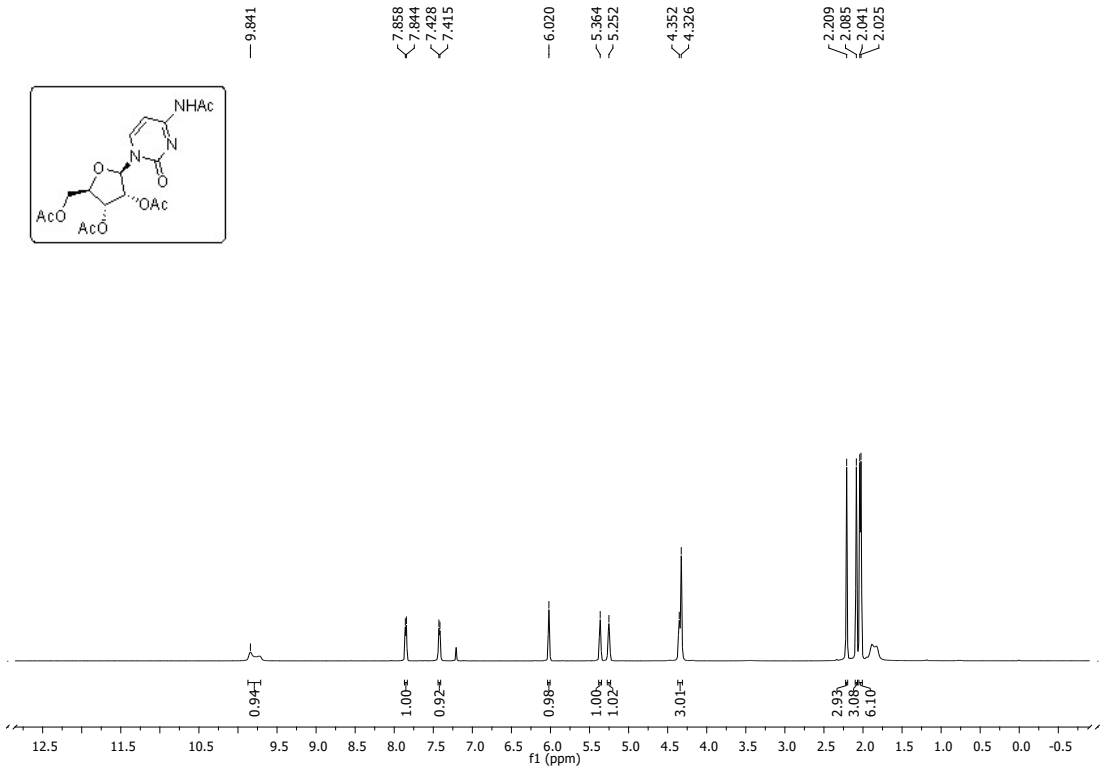
^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ 155.7, 138.0, 134.4, 129.0, 128.1, 128.0, 88.2, 87.0, 70.5, 61.6, 48.0, 41.4 ppm.

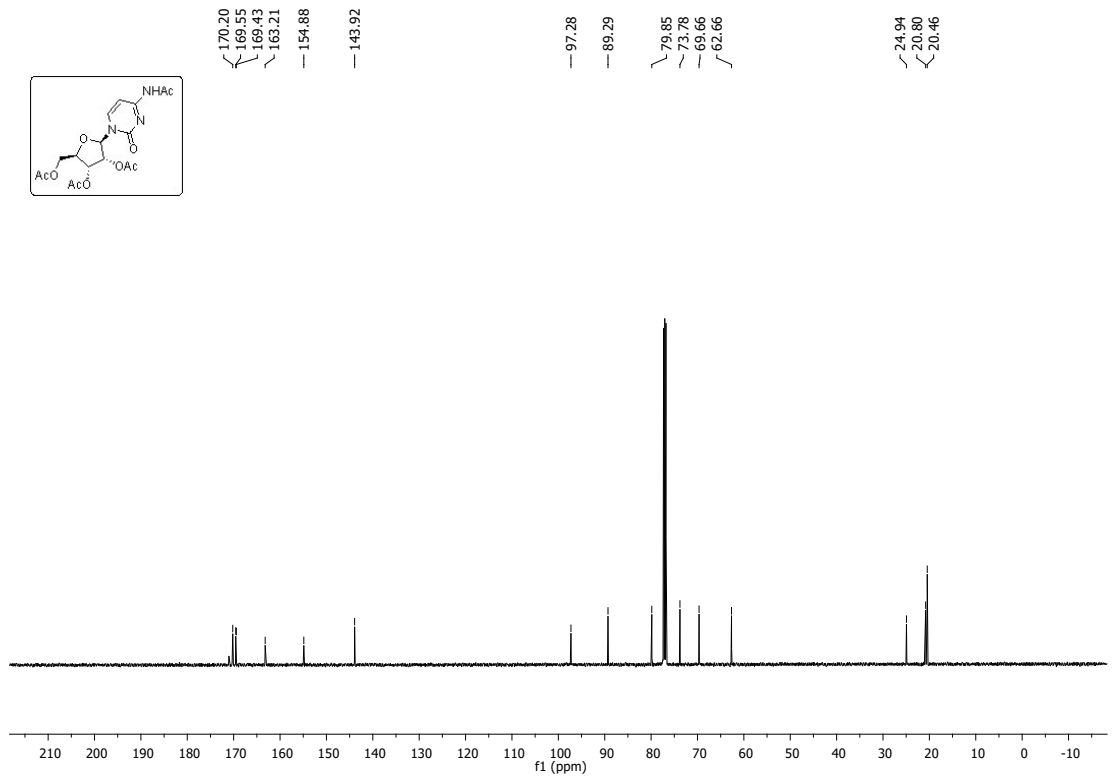
HRMS (ESI-Orbitrap) m/z: $(M + Na)^+$ calcd for $C_{17}H_{18}N_4NaO_4S$ 397.0941, found 397.0954.

9. Gram Scale Synthesis of (2R,3R,4R,5R)-2-(acetoxymethyl)-5-(2-((4-methoxybenzyl)amino)-5-oxothiazolo[4,5-d] pyrimidin-6(5H)-yl)tetrahydrofuran-3,4-diyl diacetate (3b): The reaction was performed according to the general procedure with iodo-substituted triacetylated cytidine **1a** (1 g, 2.02 mmol), 1-(isothiocyanatomethyl)-4-methoxybenzene **2b** (724 mg, 4.03 mmol), CuCl (29 mg, 0.2 mmol), 1,10-phenanthroline (73 mg, 0.4 mmol) and K_2CO_3 (279 mg, 2.02 mmol) and DMSO under argon atmosphere at 80 ^oC for 36 h. After workup, the residue was purified with silica gel chromatography (80% ethyl acetate/hexane) to afford **3b** as an amorphous yellow solid (762 mg, 69%).

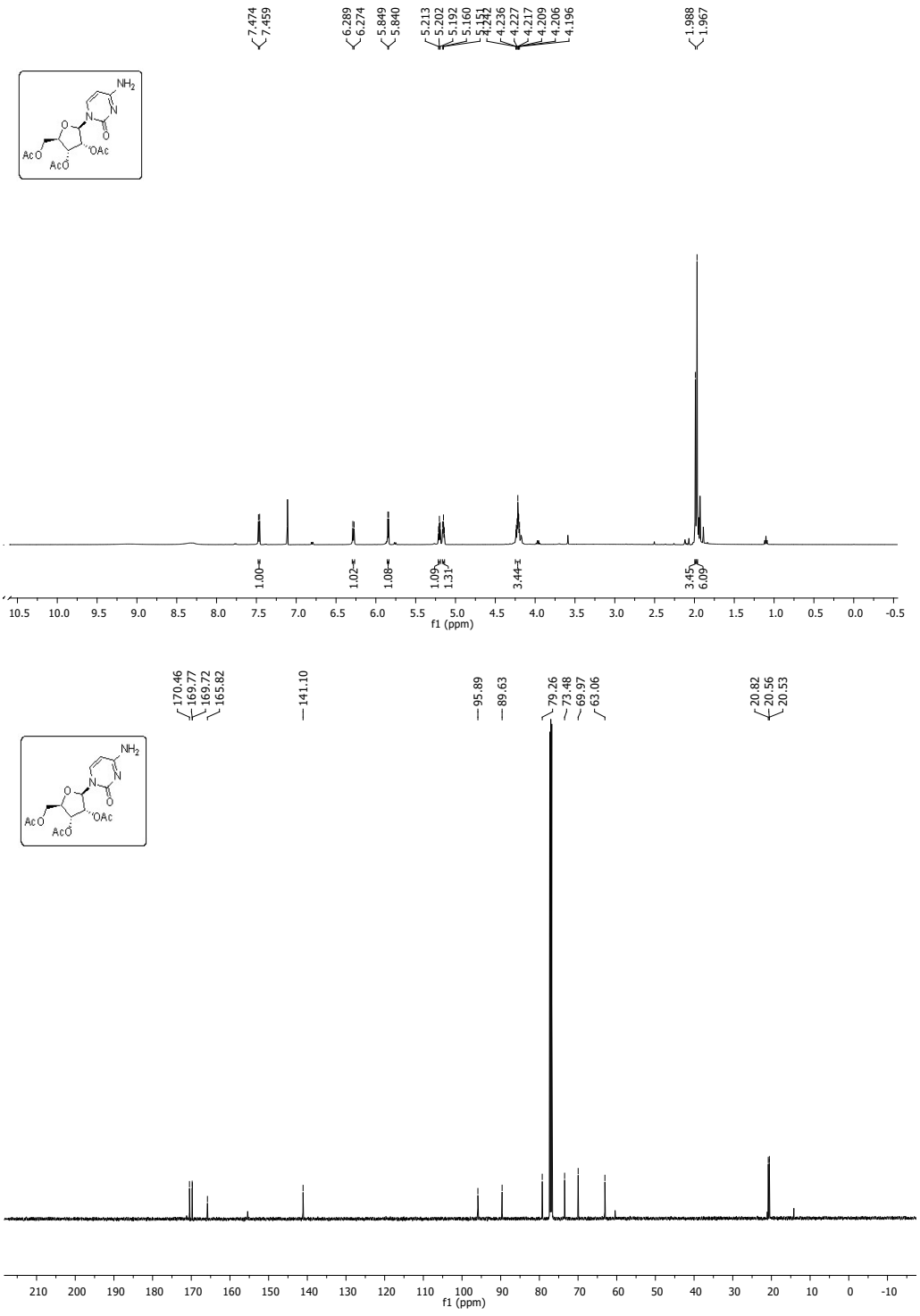
^{1}H NMR & ^{13}C NMR Spectra

^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1a'**

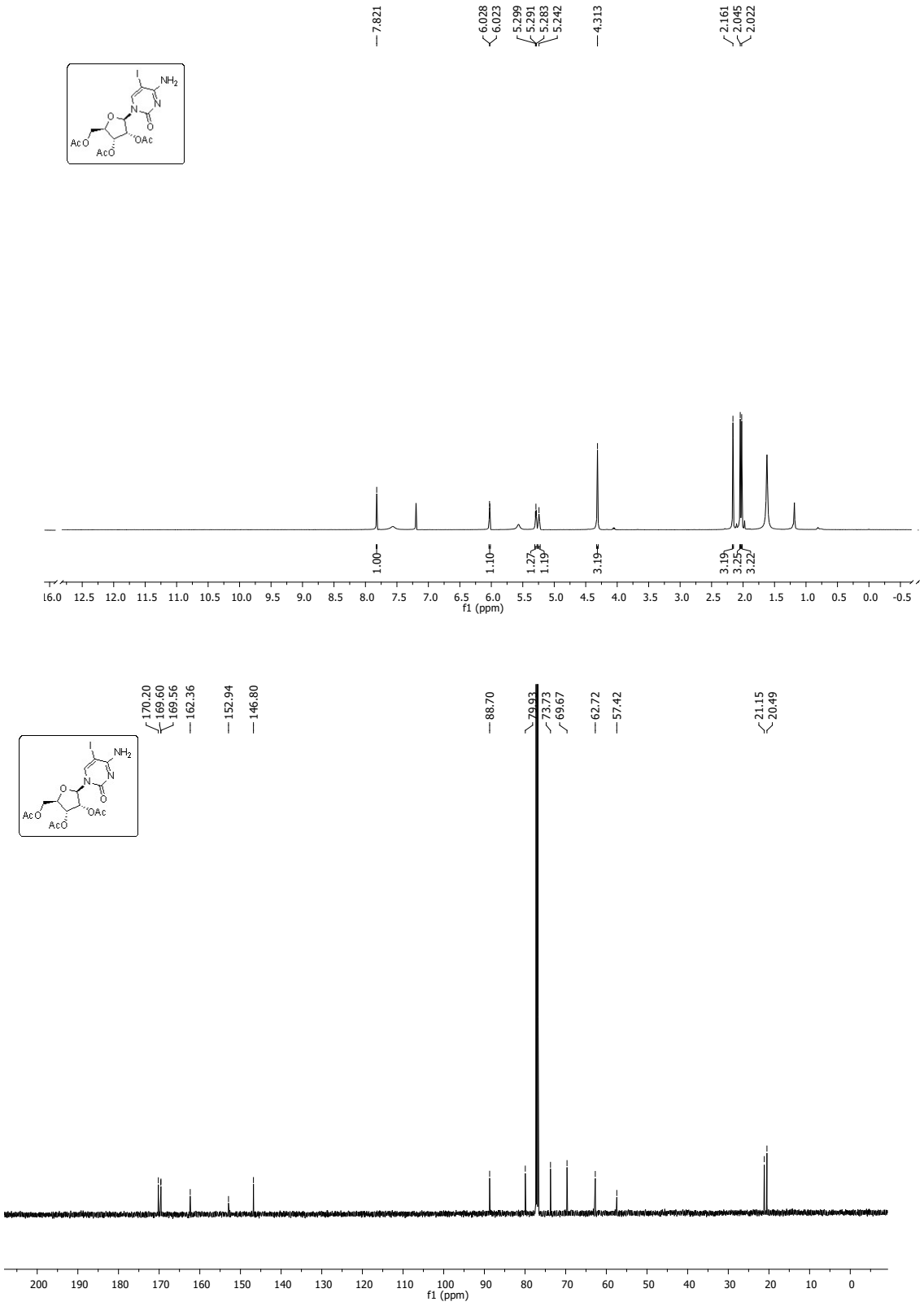




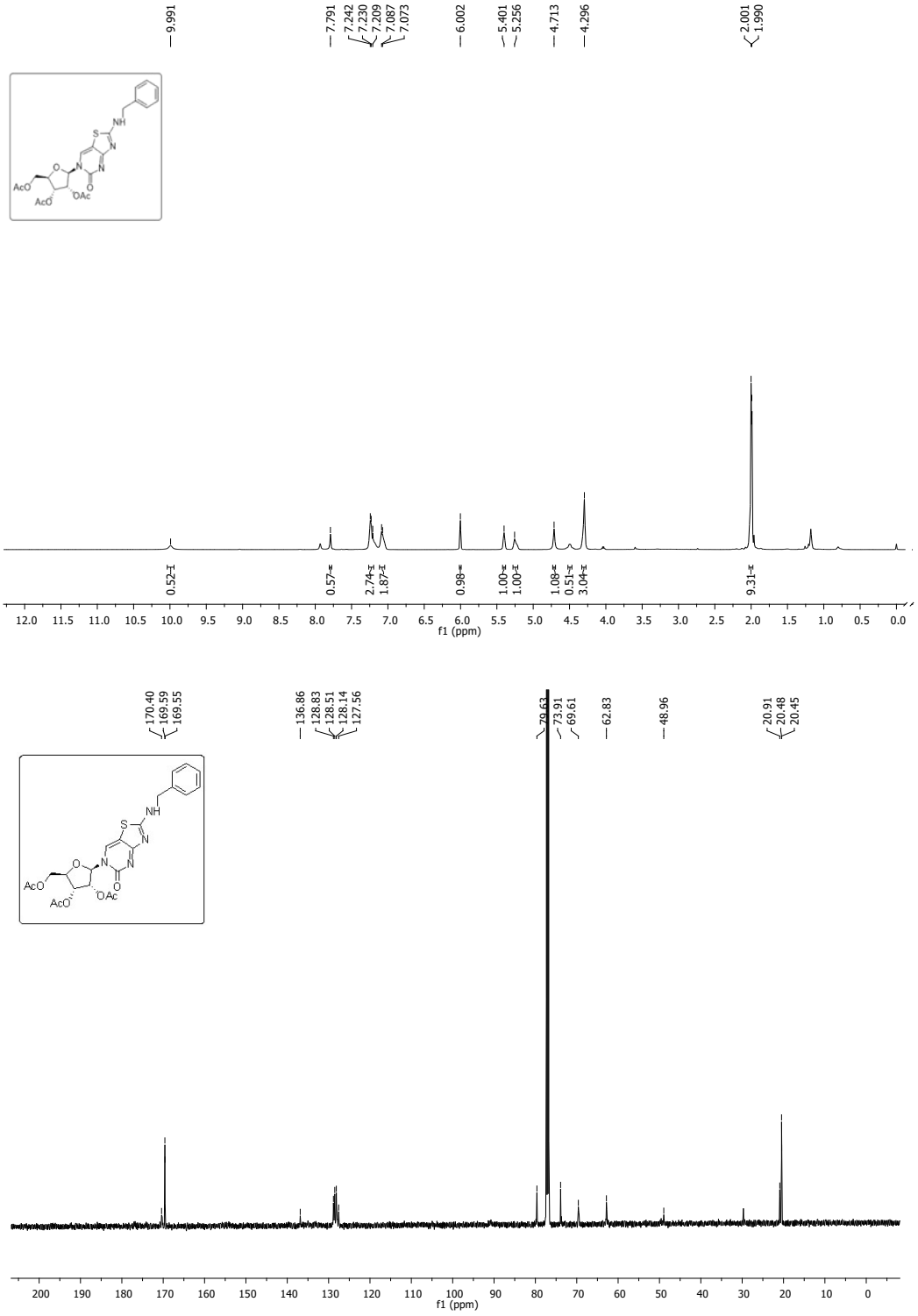
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1a"**



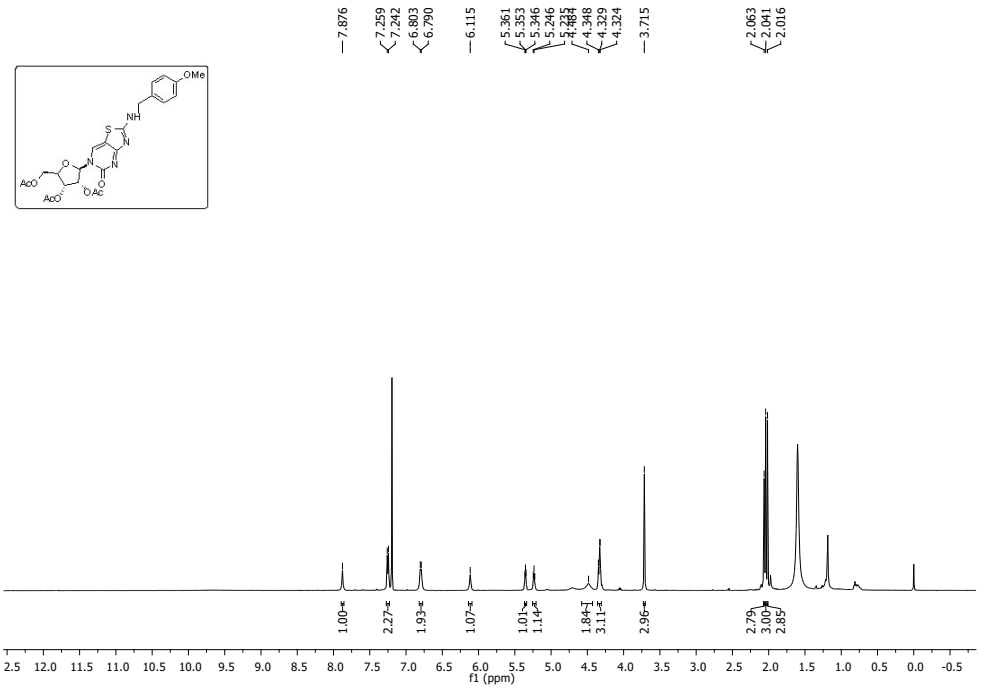
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1a**

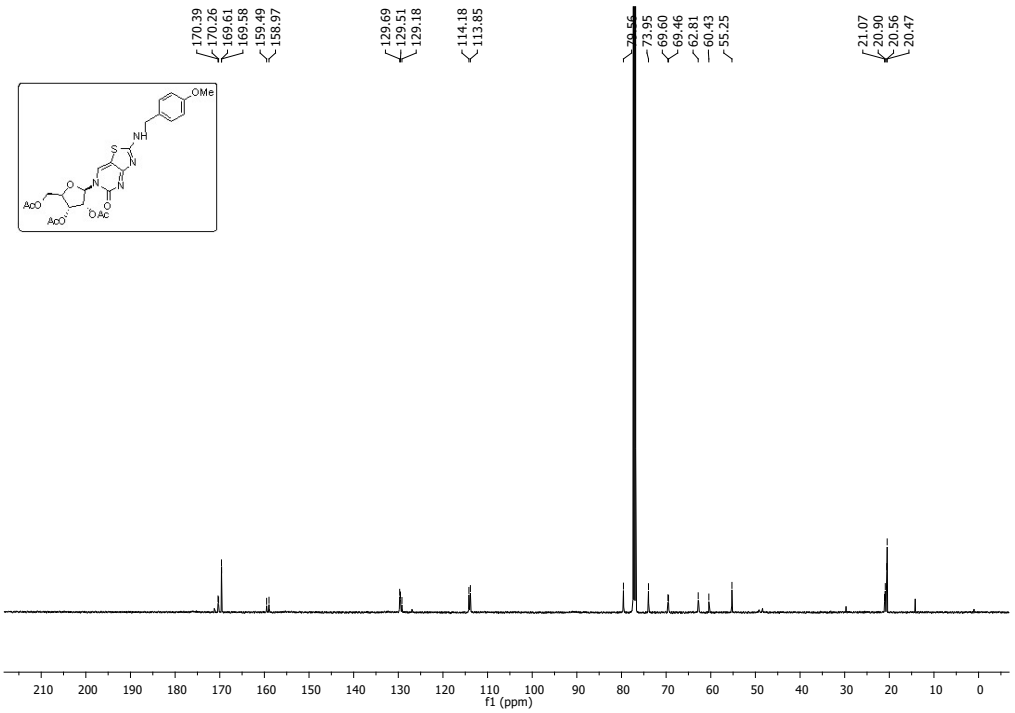


^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3a**

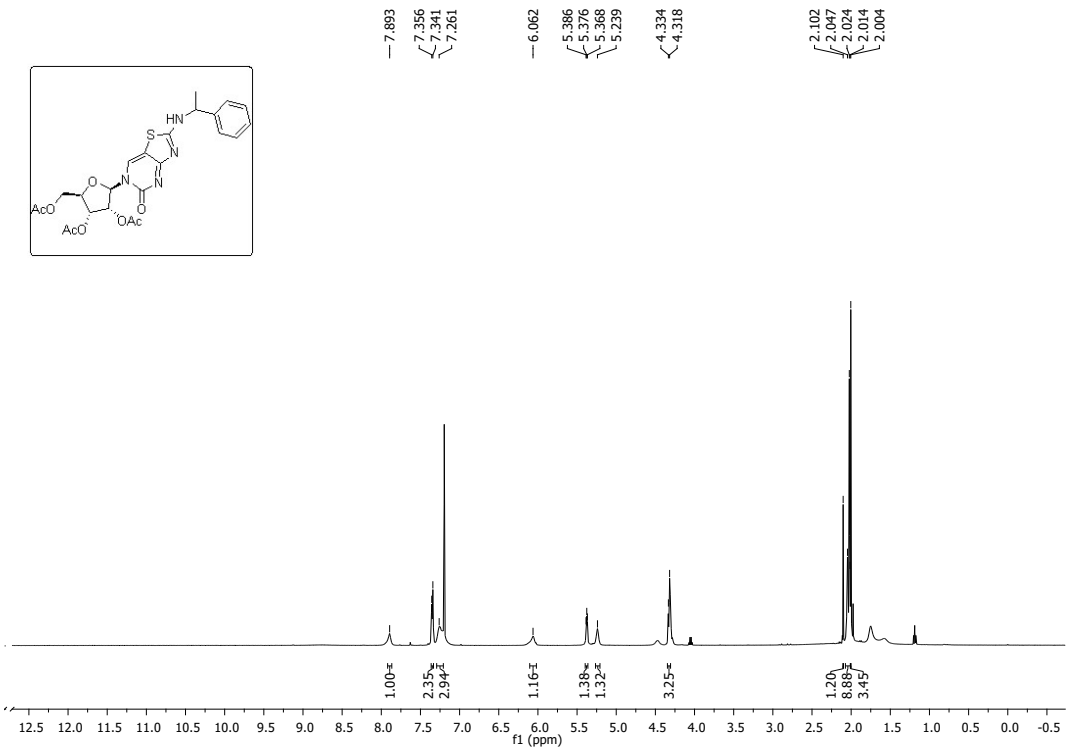


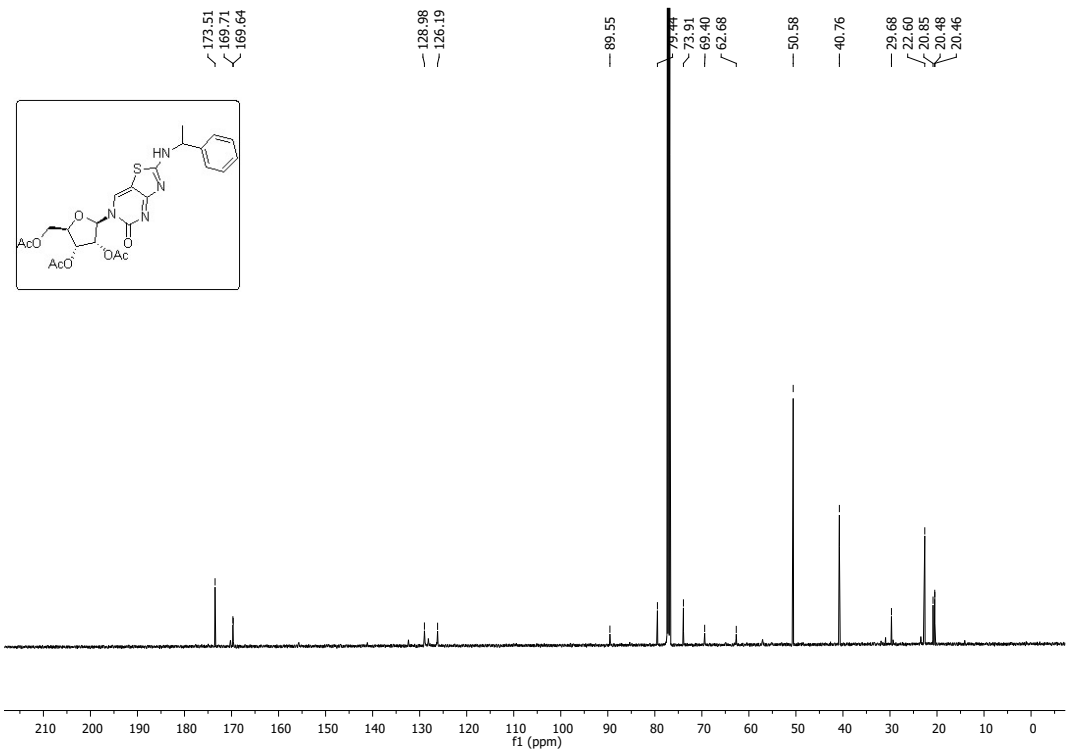
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3b**



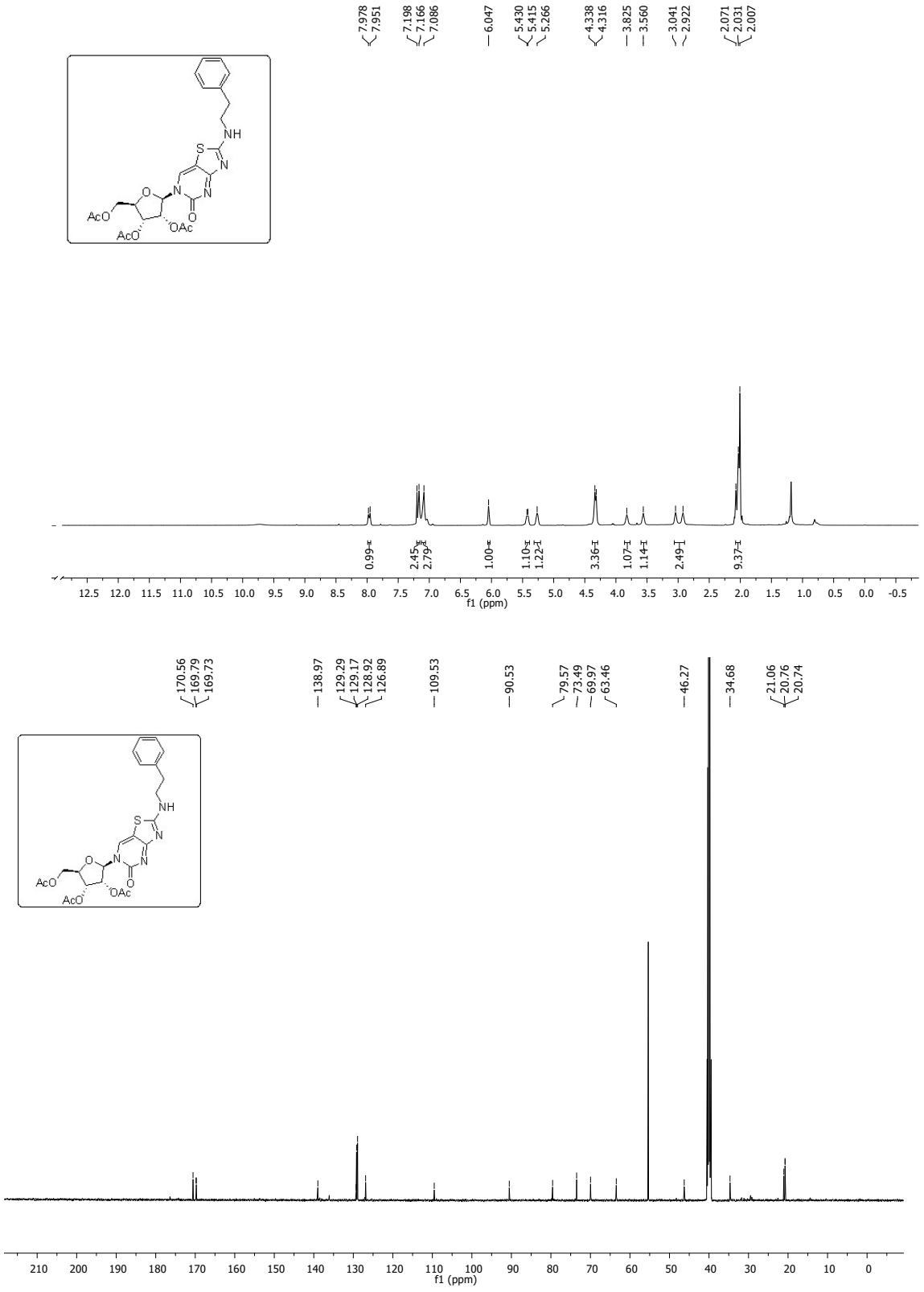


^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3c**

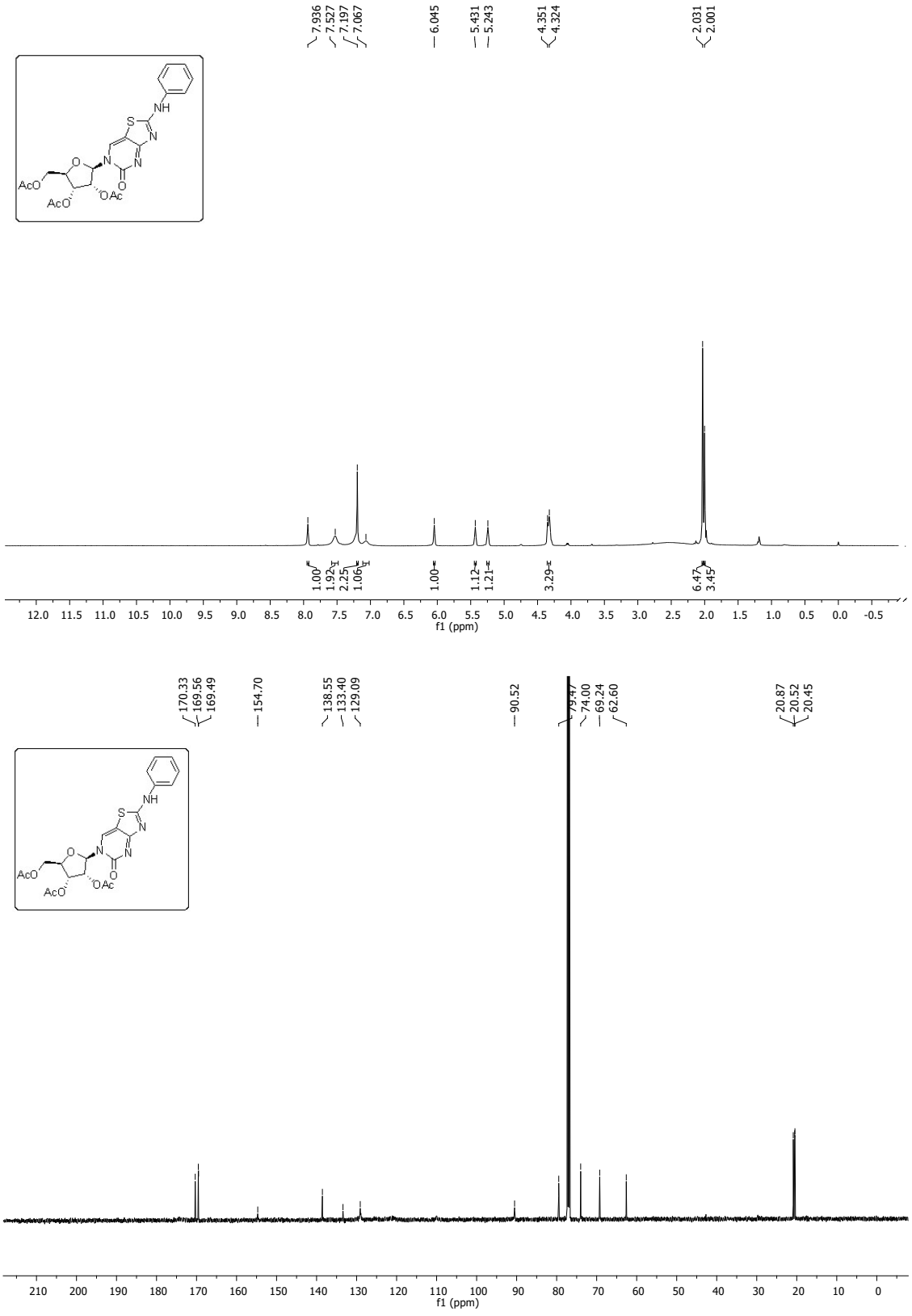




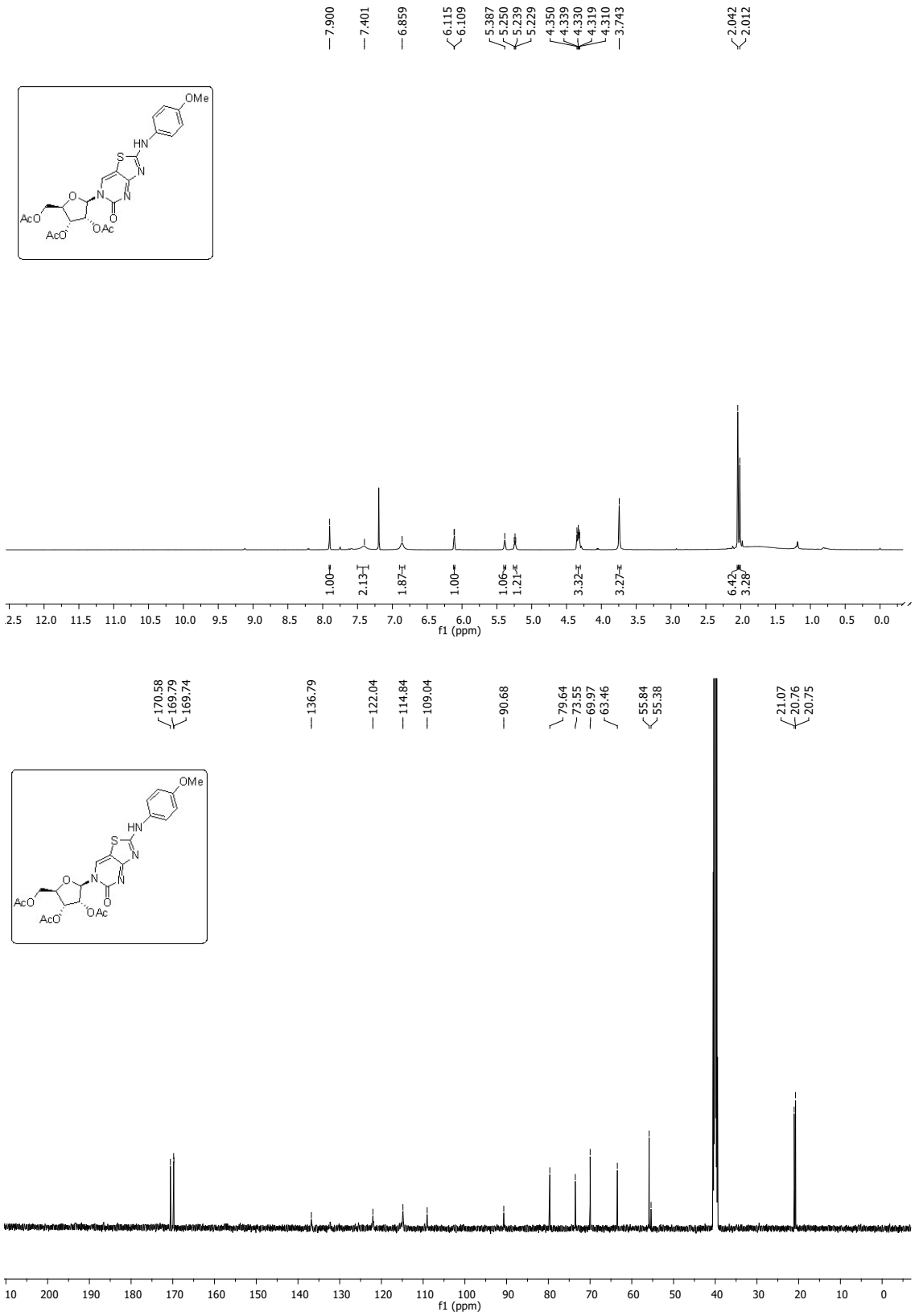
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **3d**



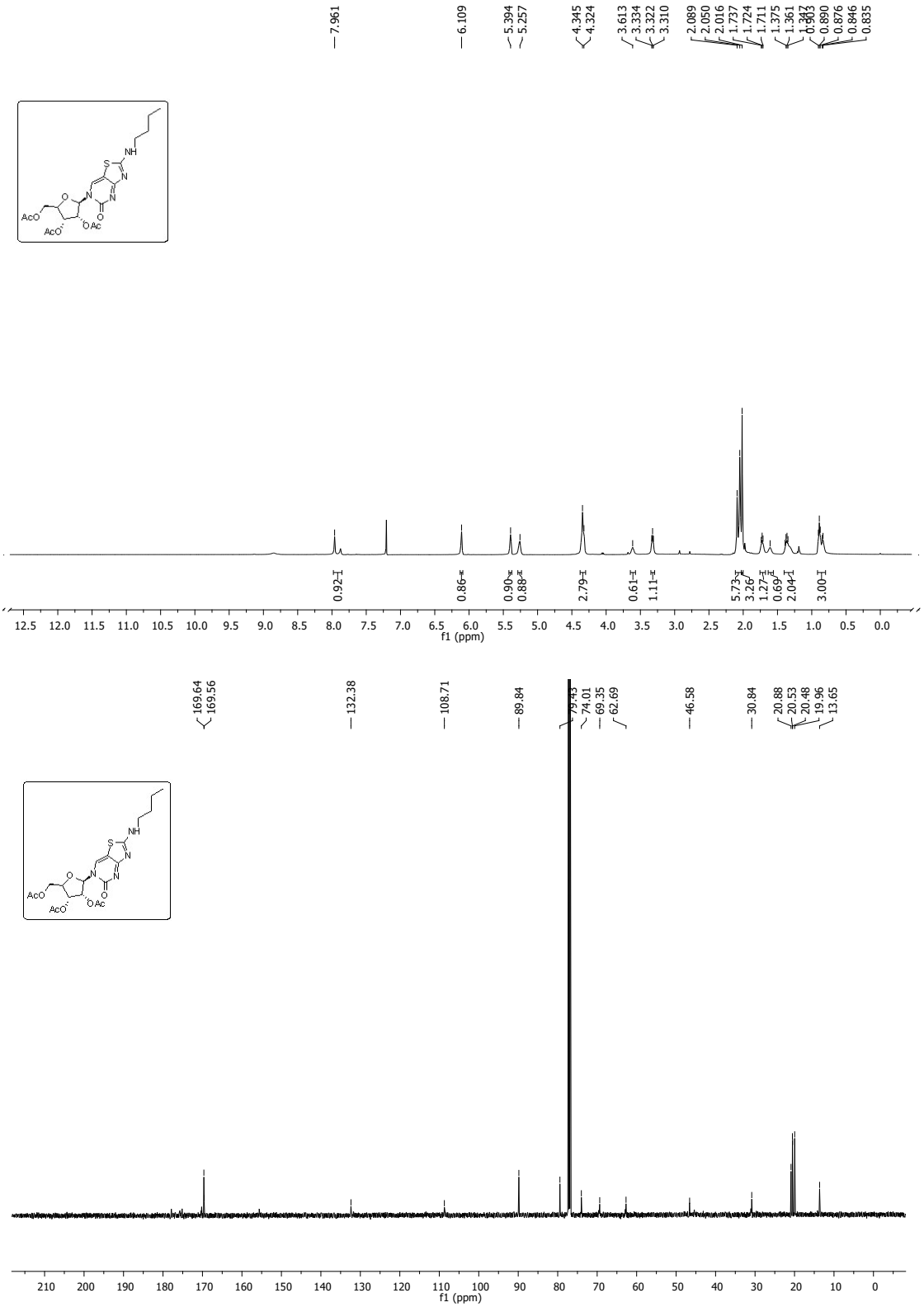
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3e**



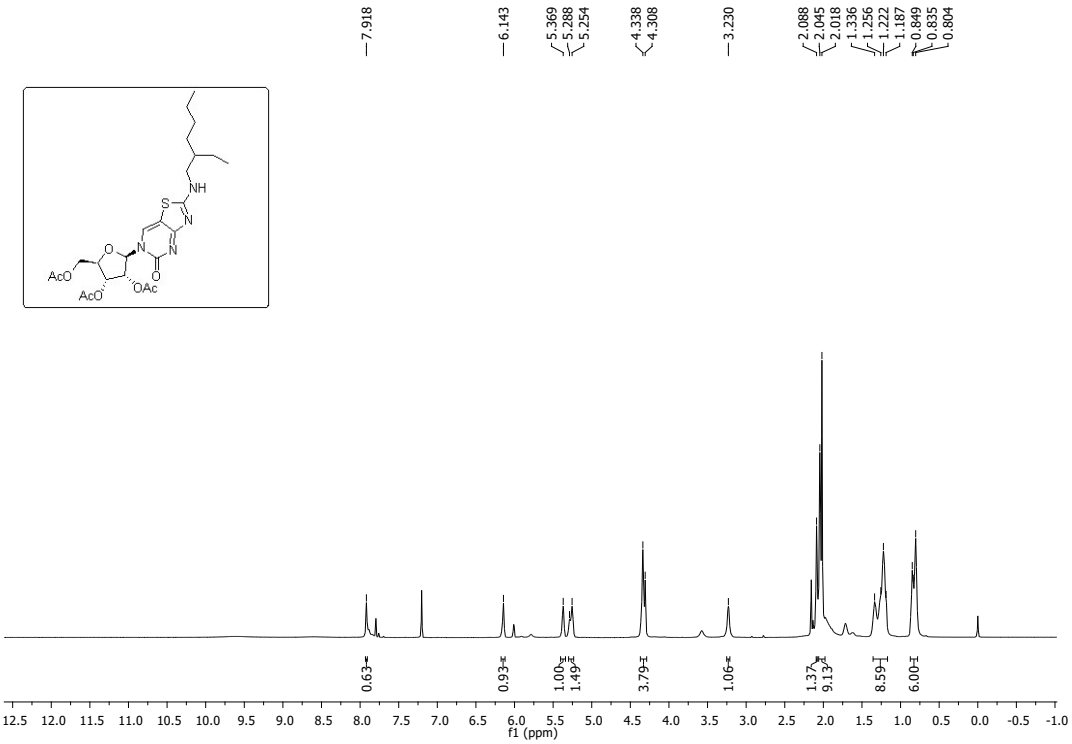
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **3f**

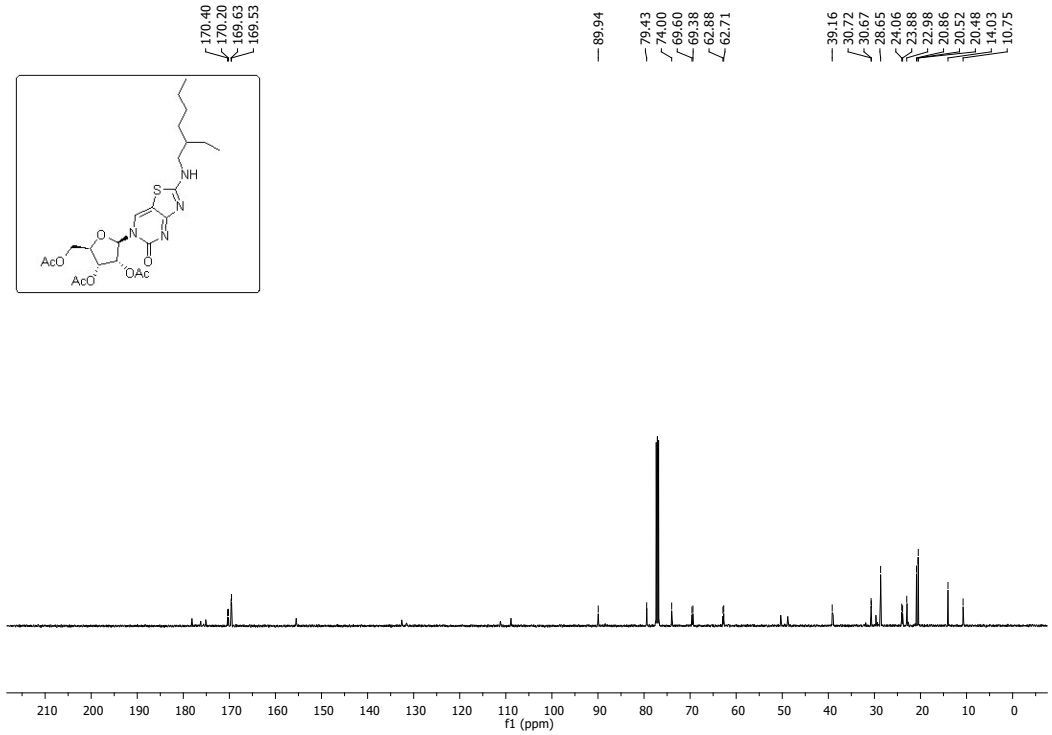


^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3g**

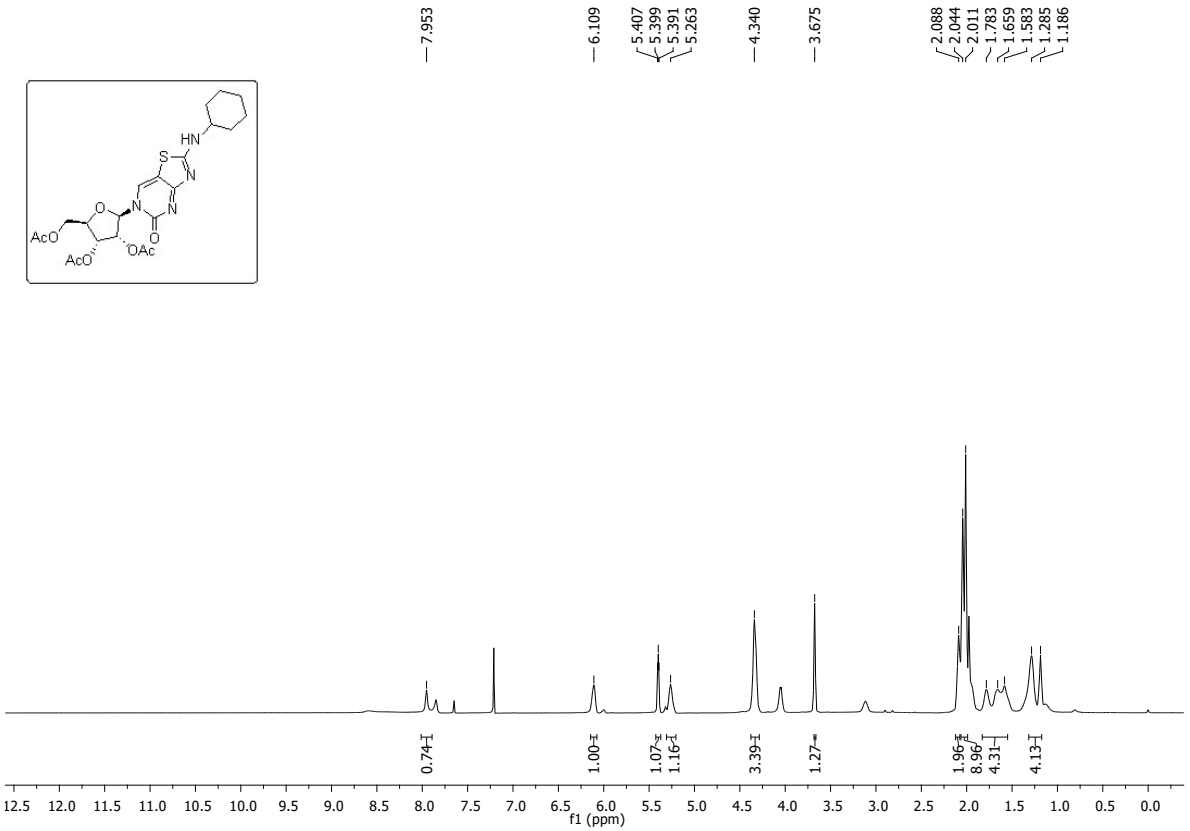


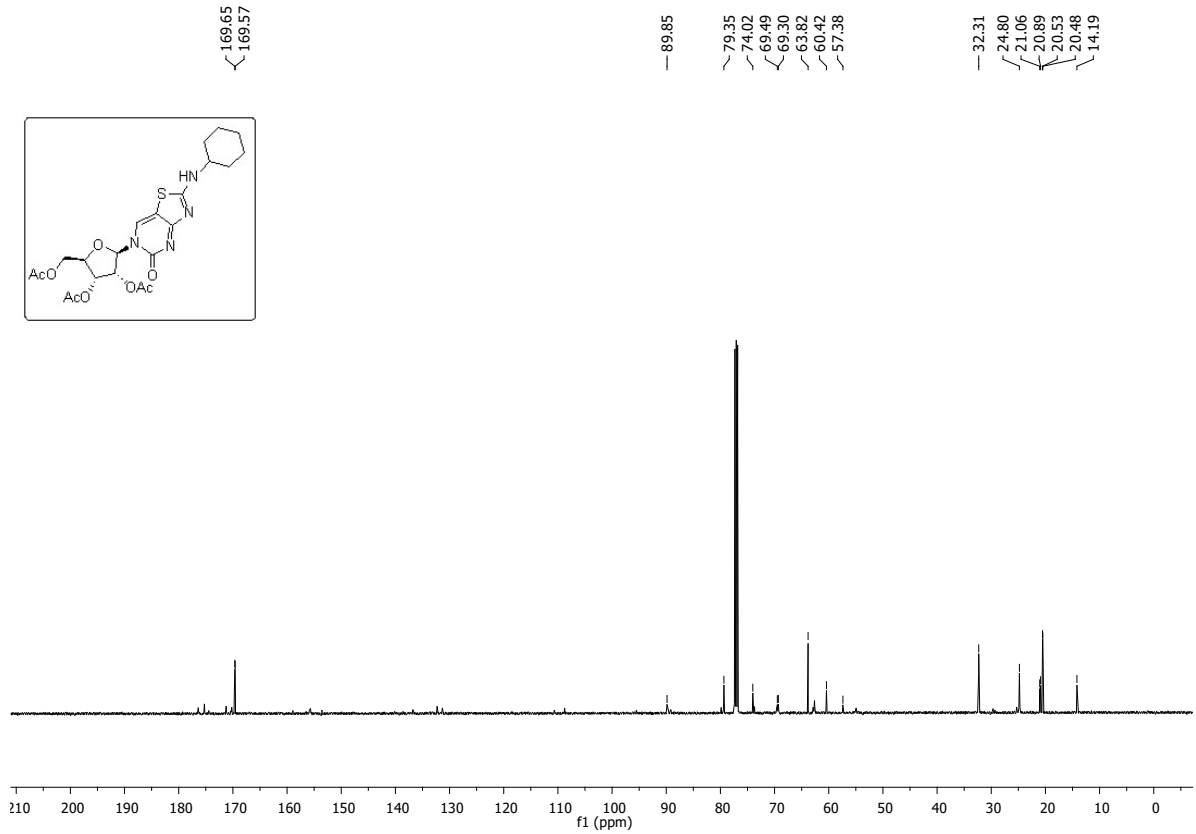
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3h**



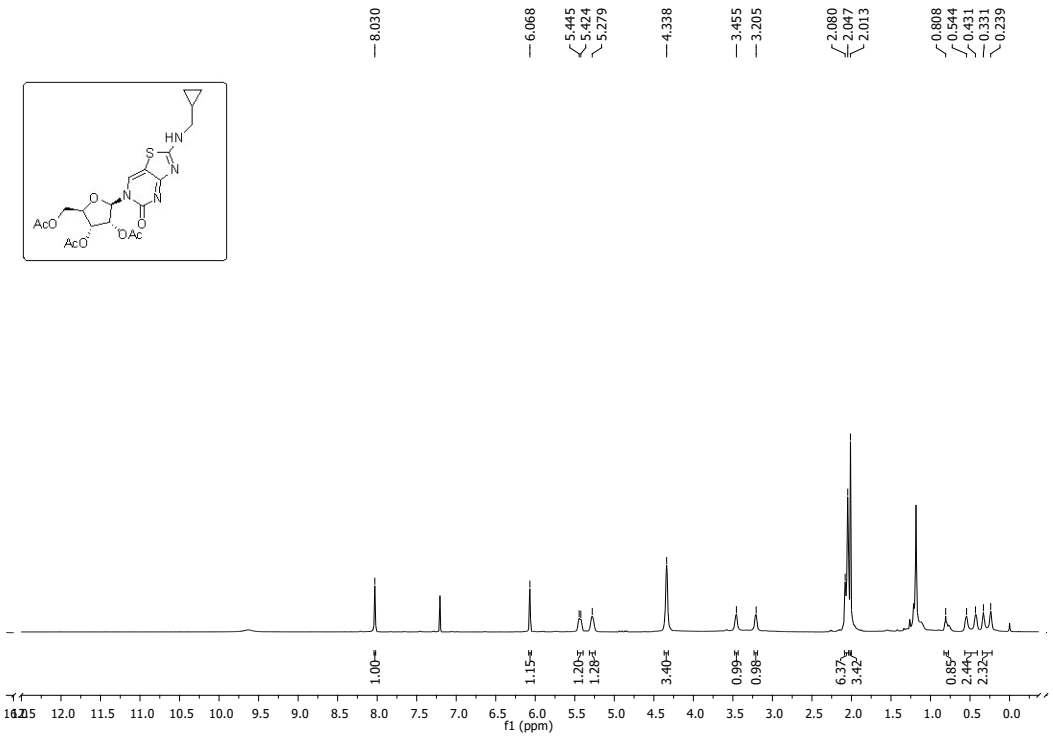


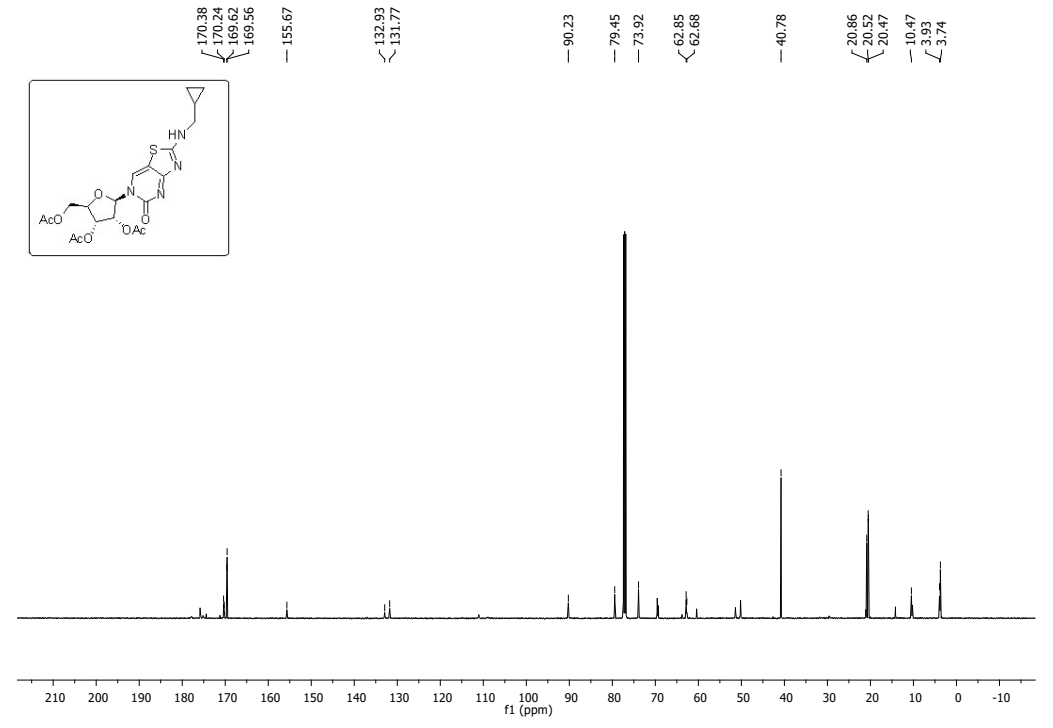
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3i**



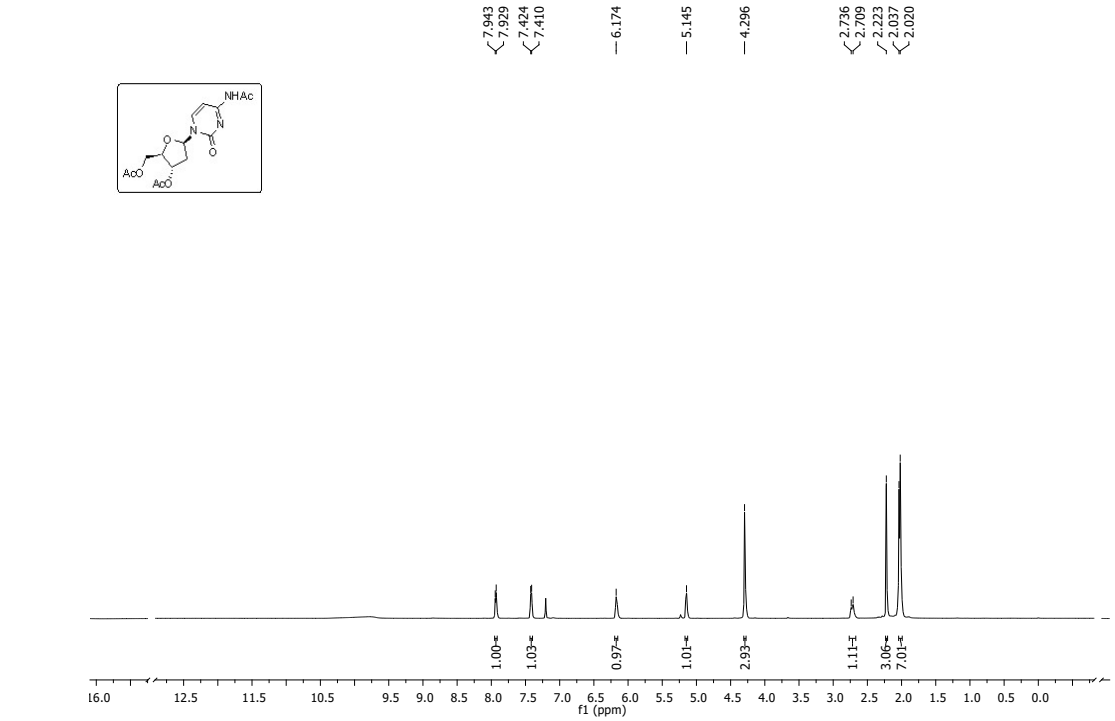


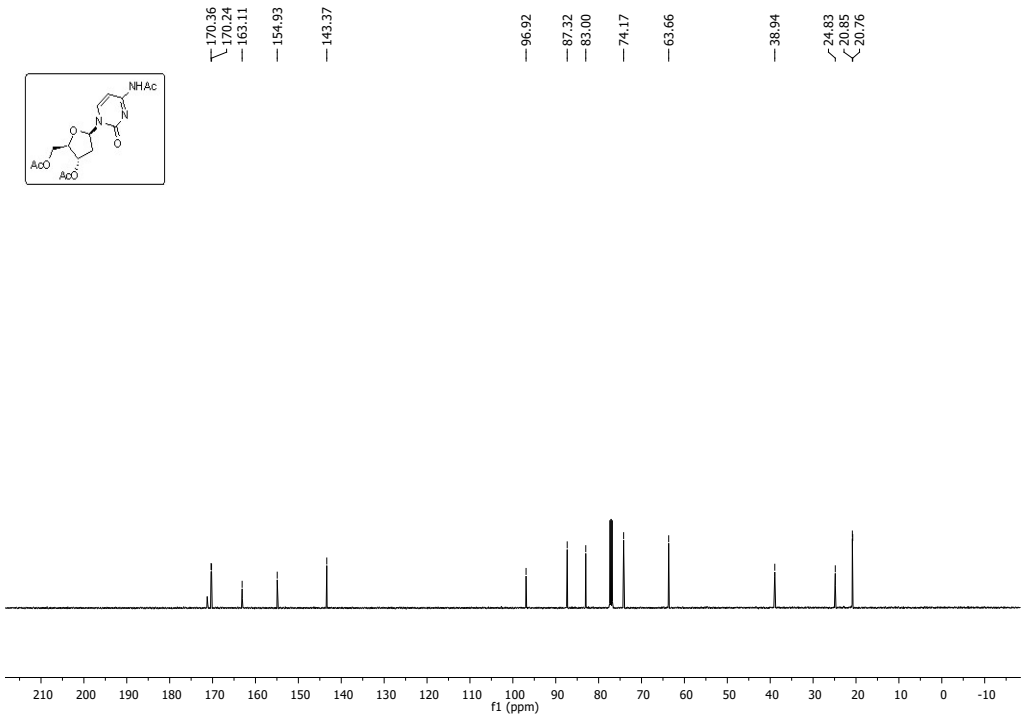
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3j**



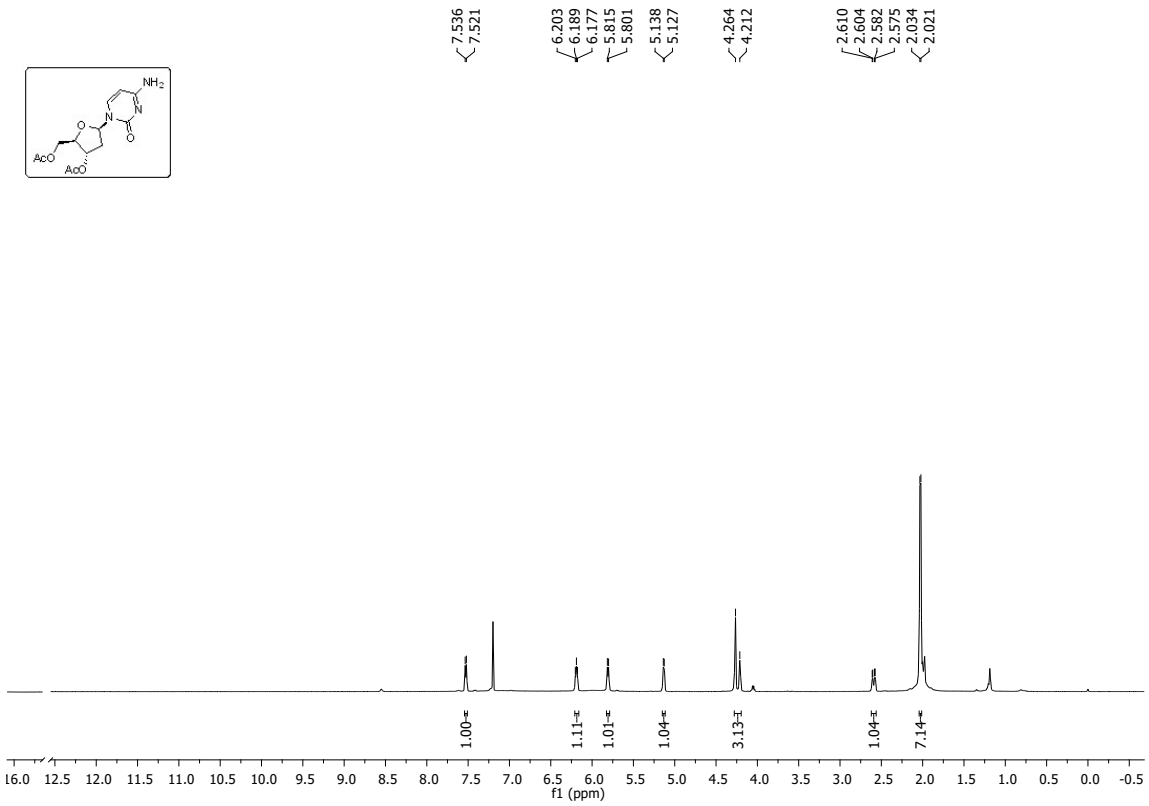


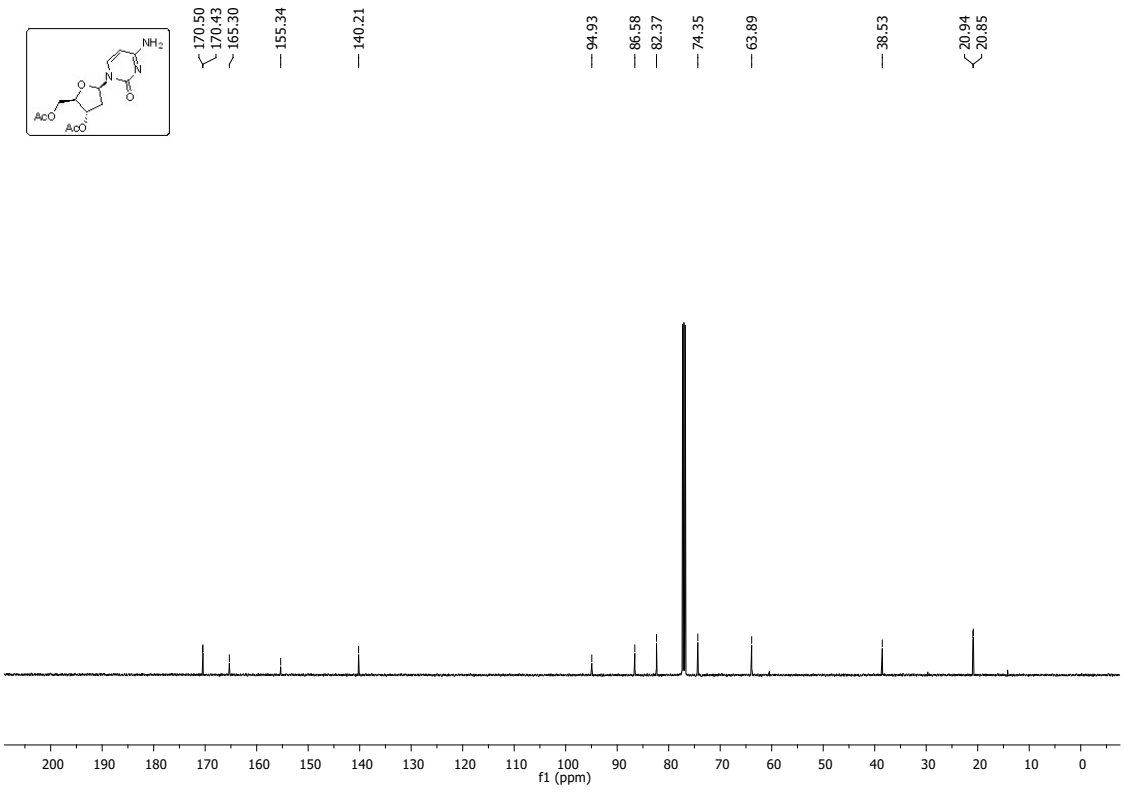
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1b'**



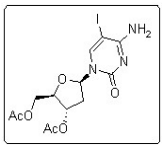


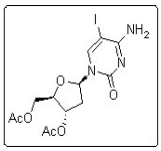
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1b”**



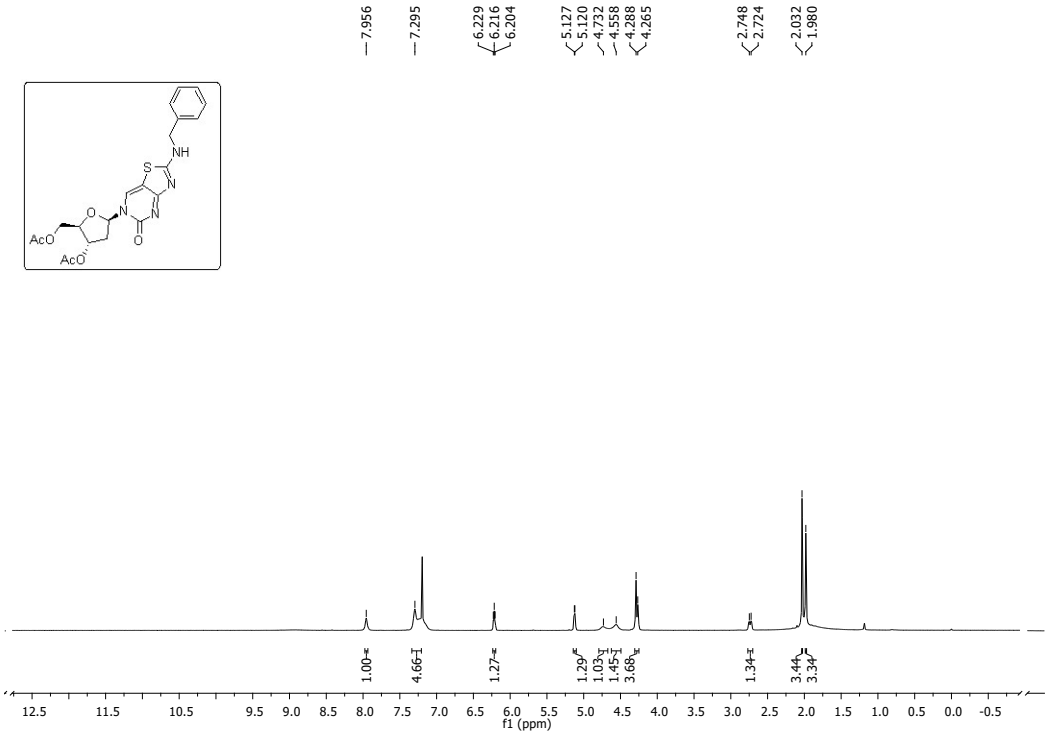


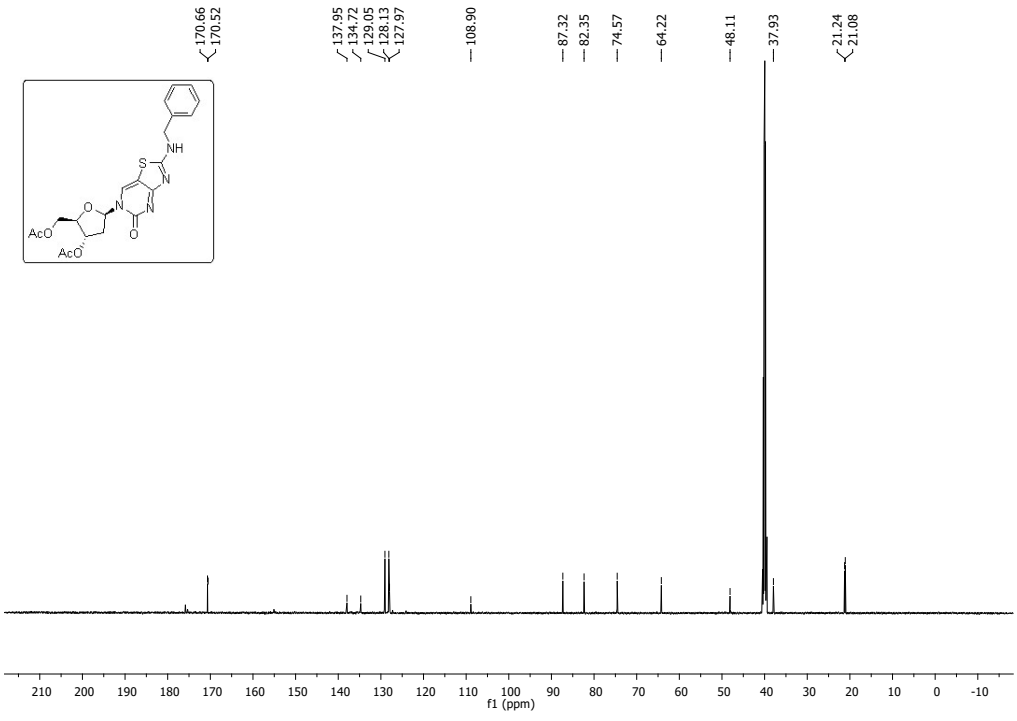
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **1b**



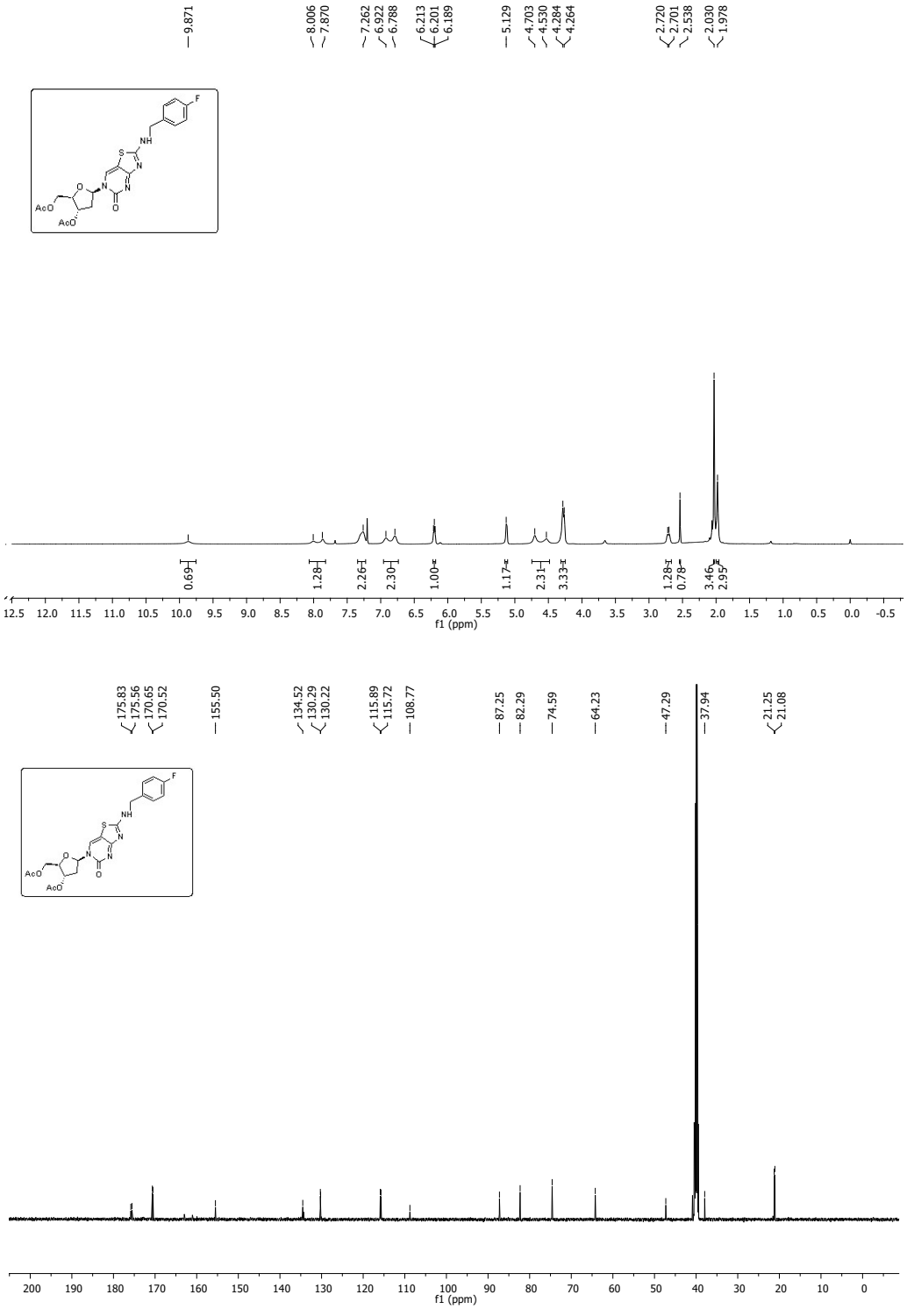


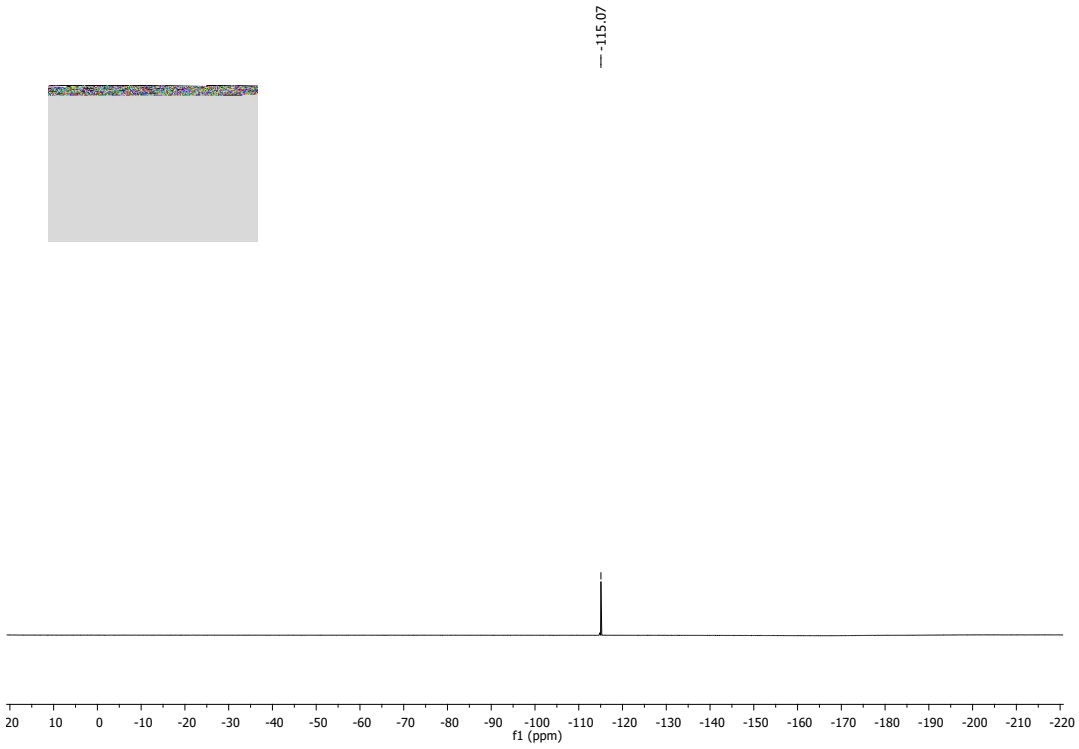
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **3k**



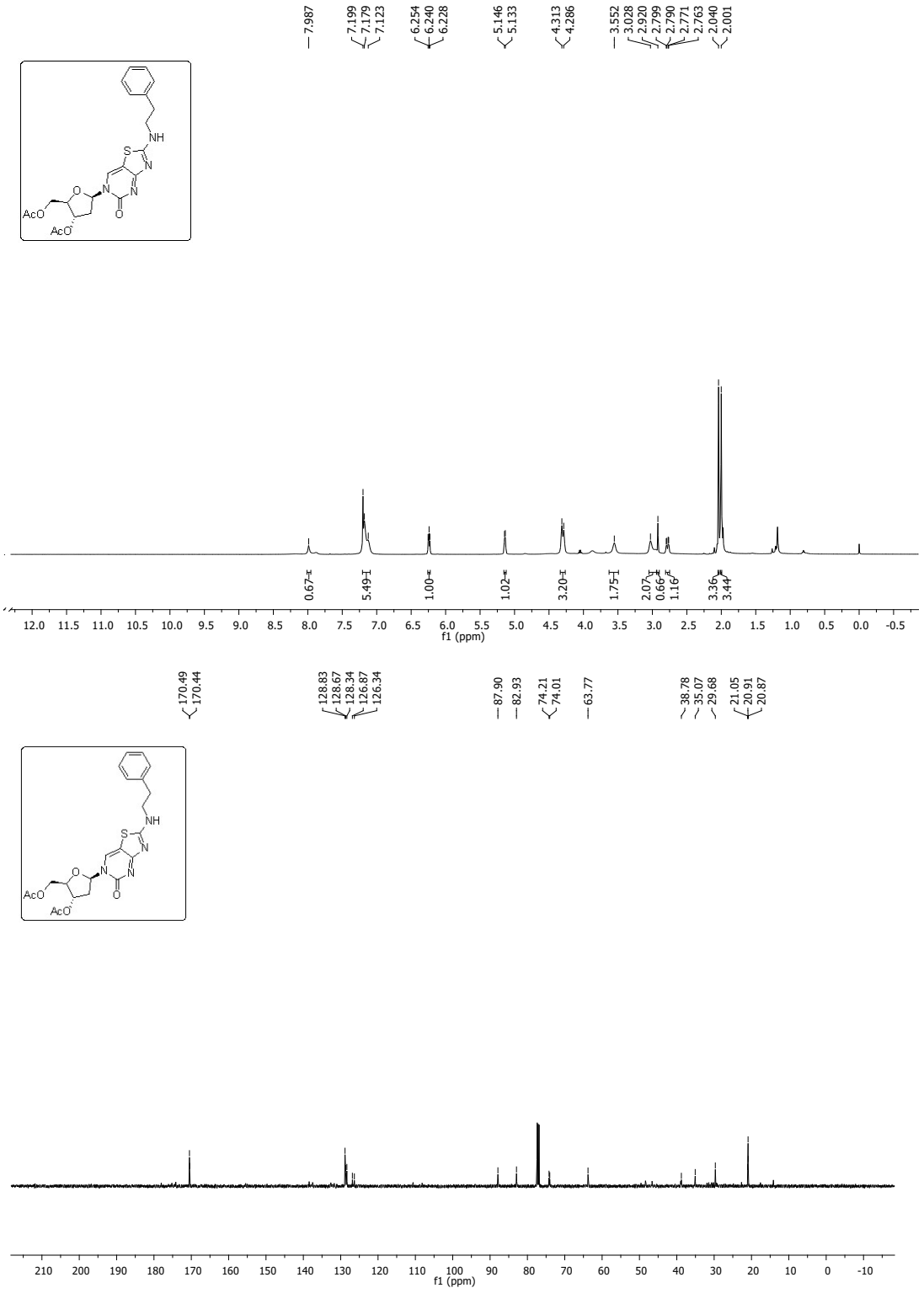


^{1}H NMR (500 MHz, $CDCl_3$) ,^{13}C{^{1}H} (125 MHz, DMSO-d_6) & ^{19}F (471 MHz, DMSO-d_6) Spectra of **3l**

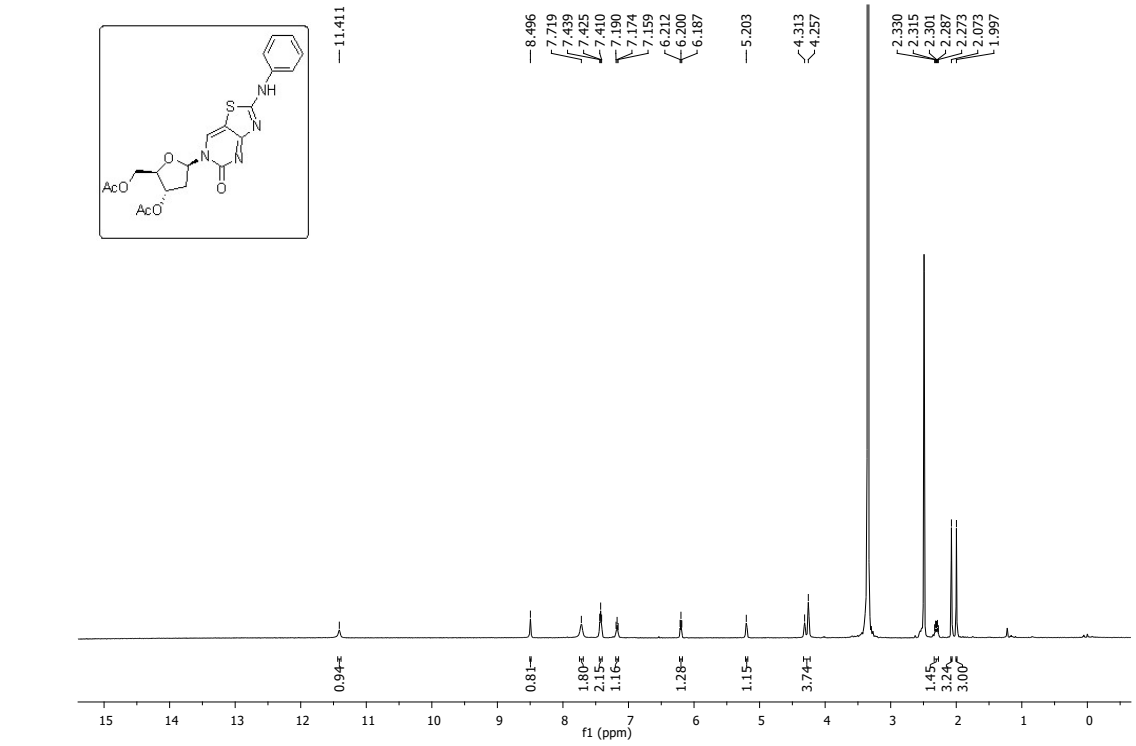


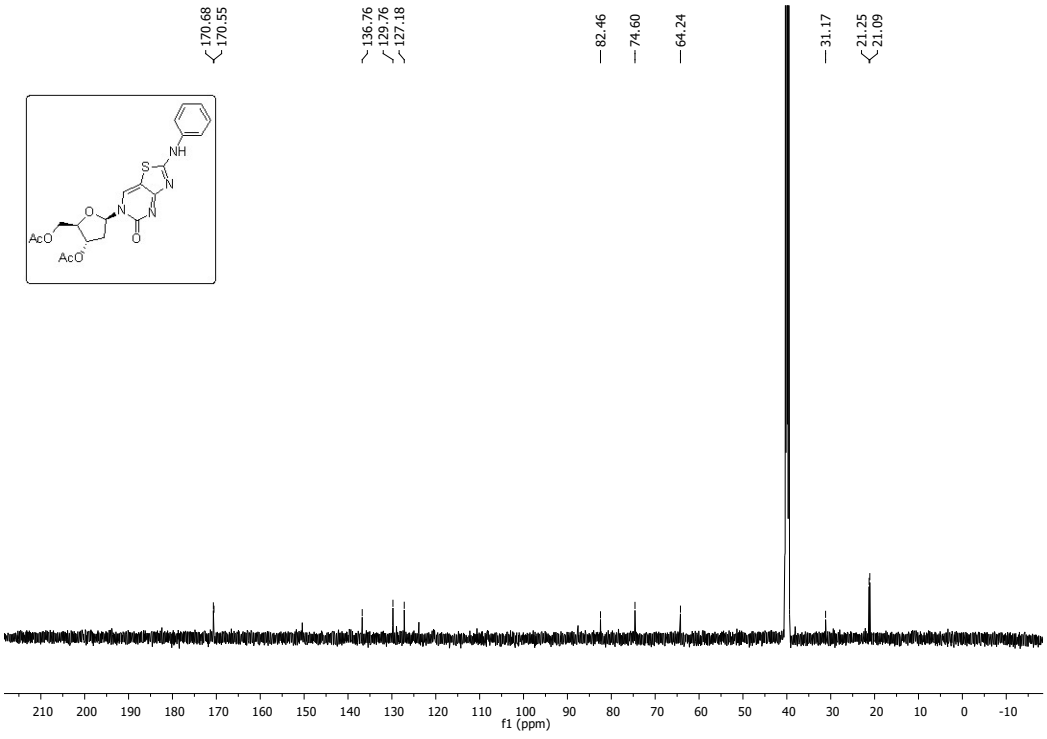

-115.07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3m**

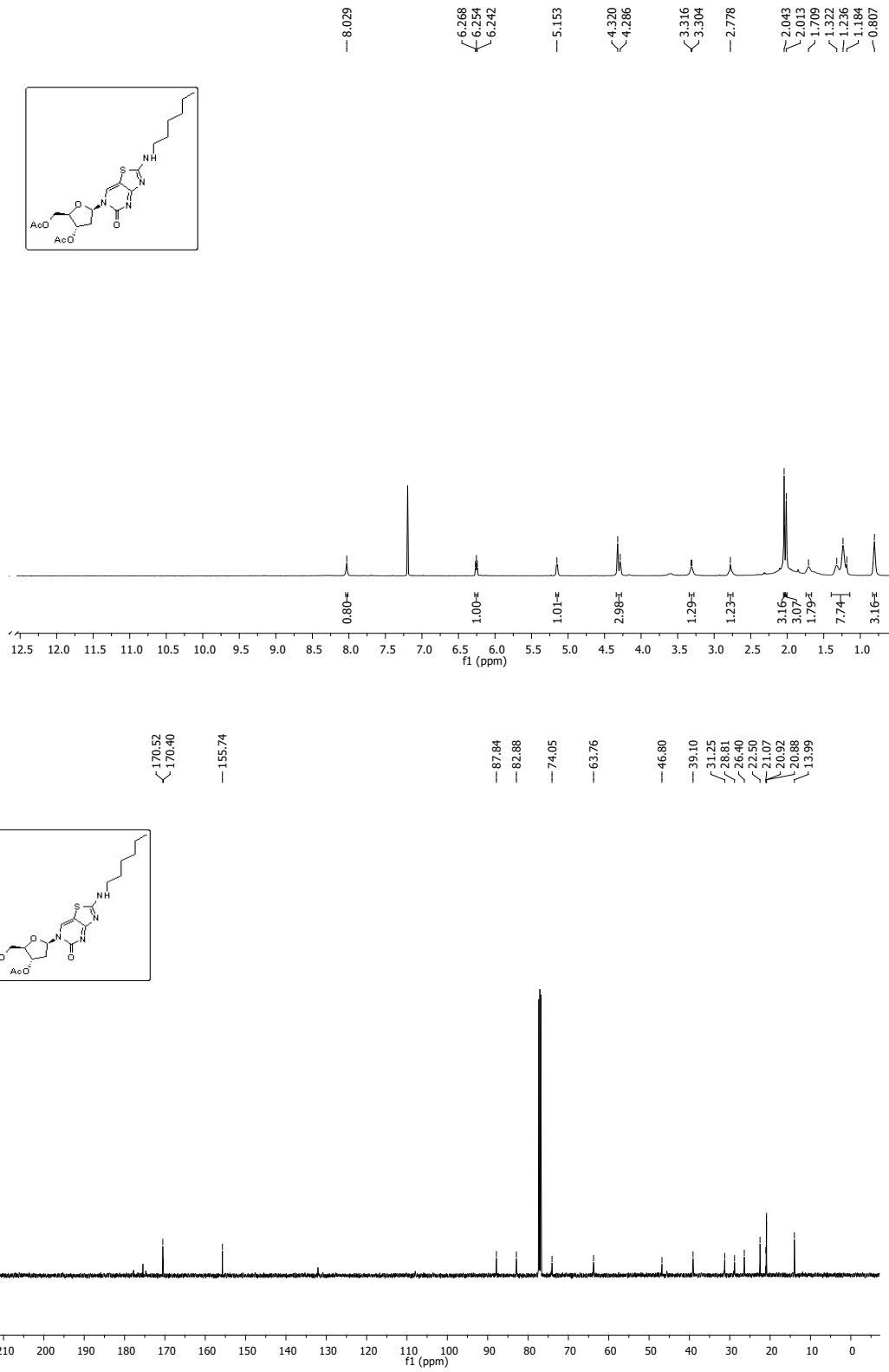


^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **3n**

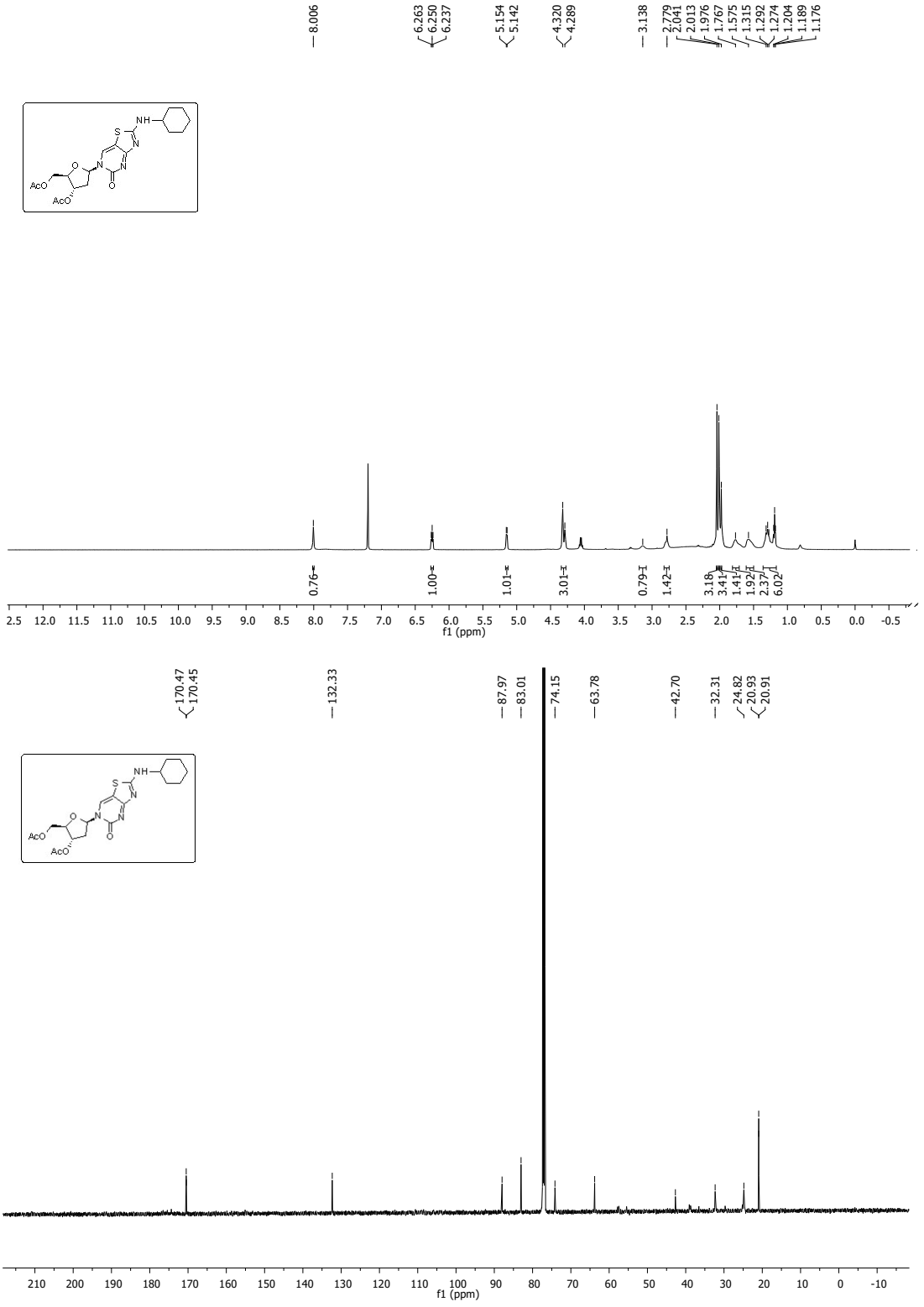




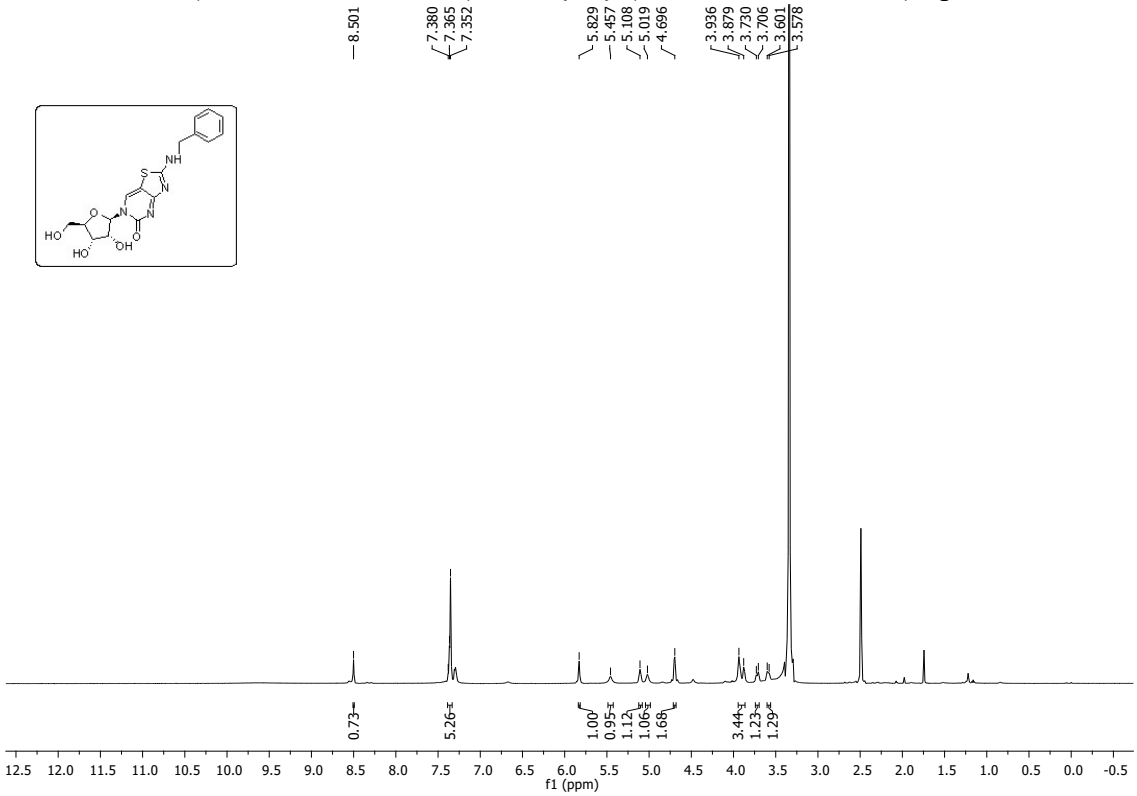
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3o**

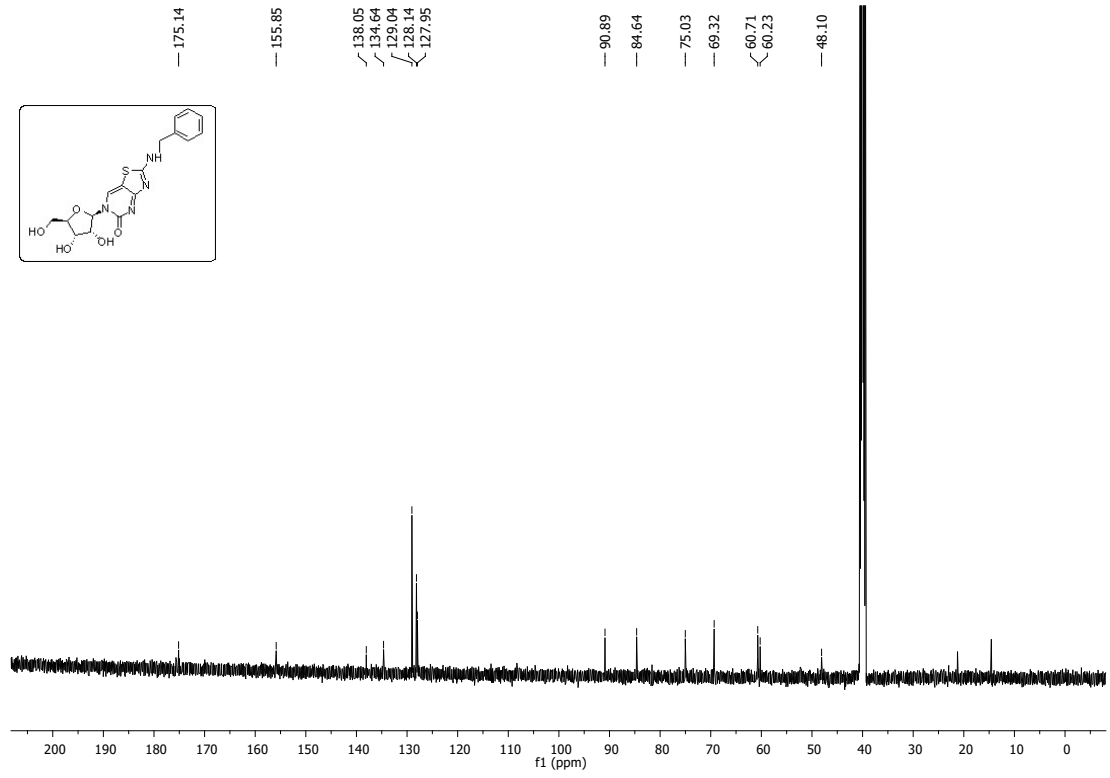


^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **3p**

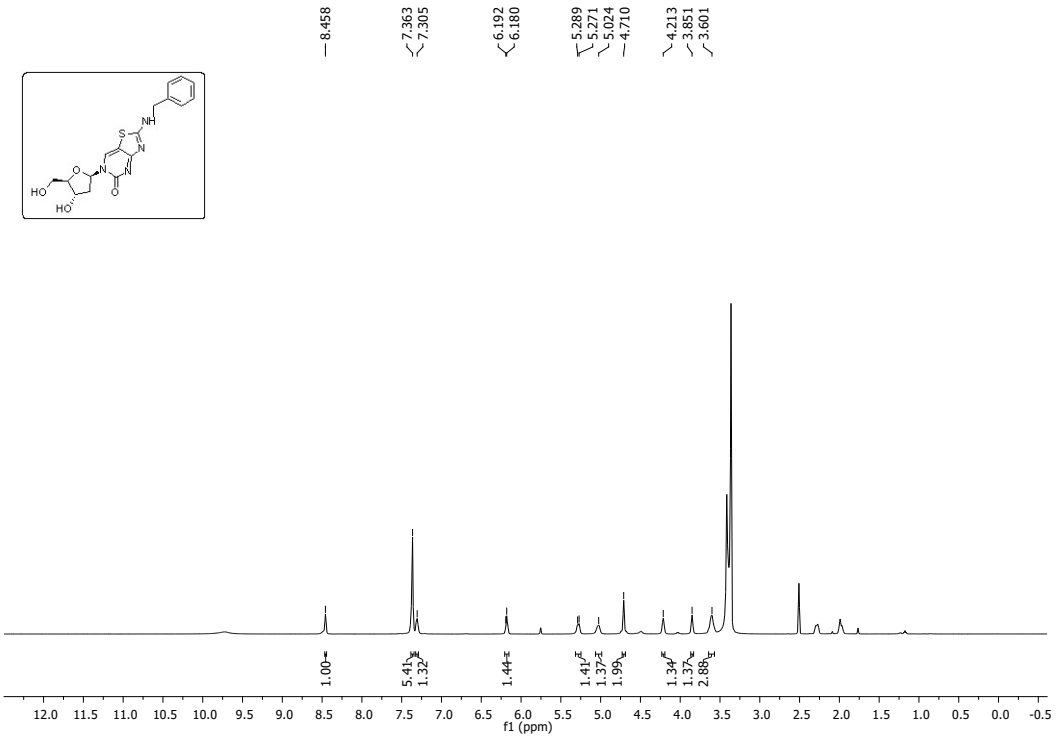


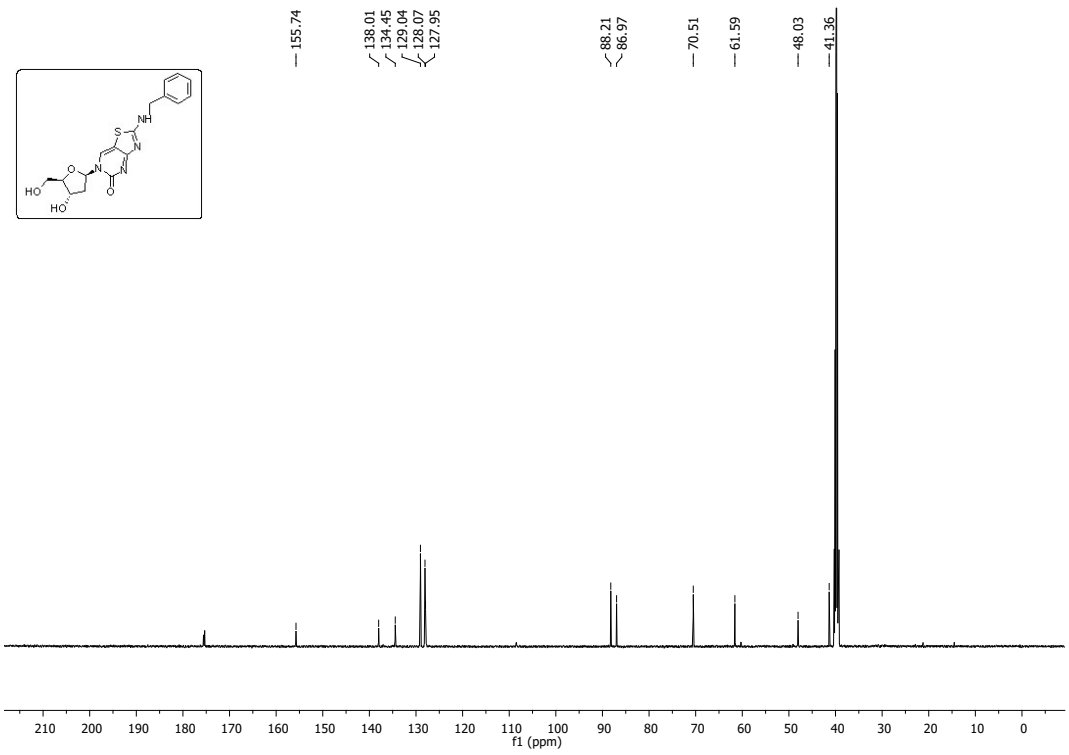
^{1}H NMR (500 MHz, DMSO-d_6) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **4a**



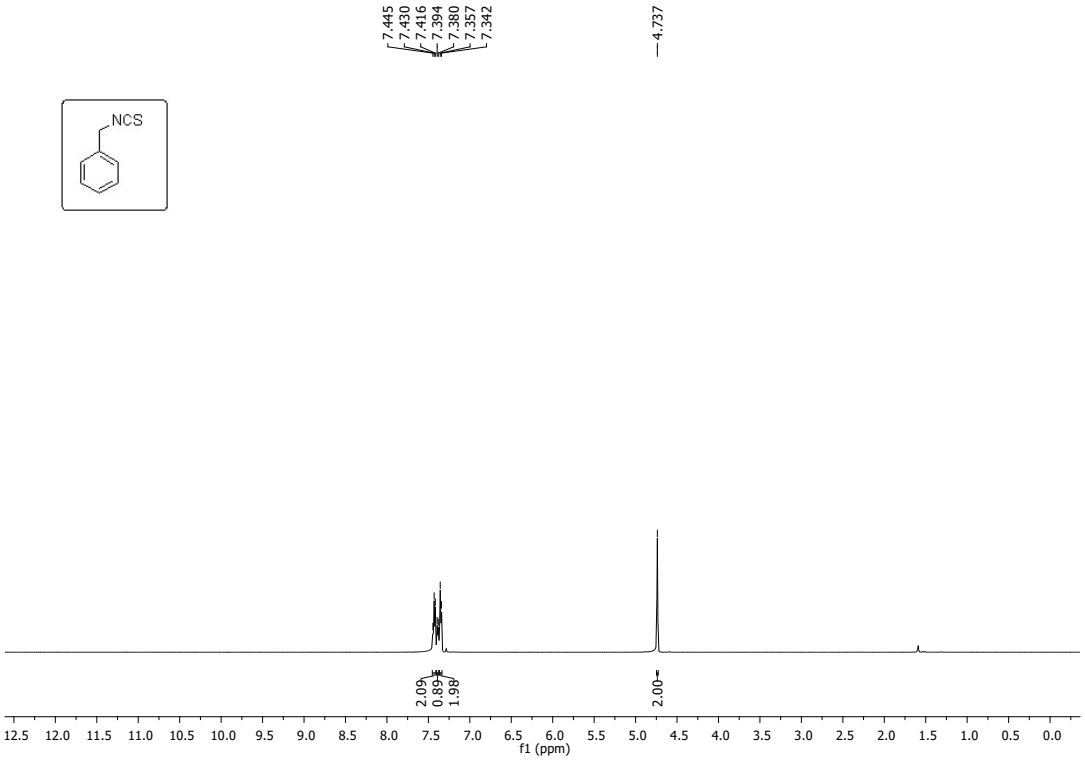


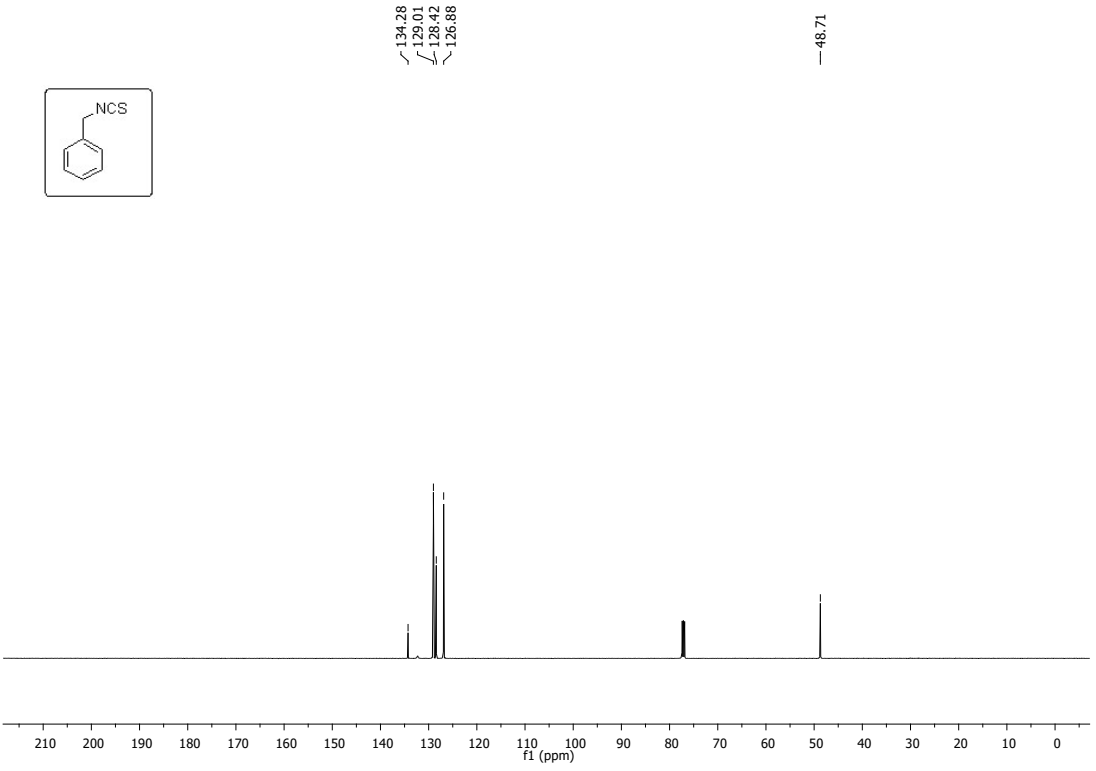
^{1}H NMR (500 MHz, DMSO-d_6) &^{13}C{^{1}H} (125 MHz, DMSO-d_6) Spectra of **4k**



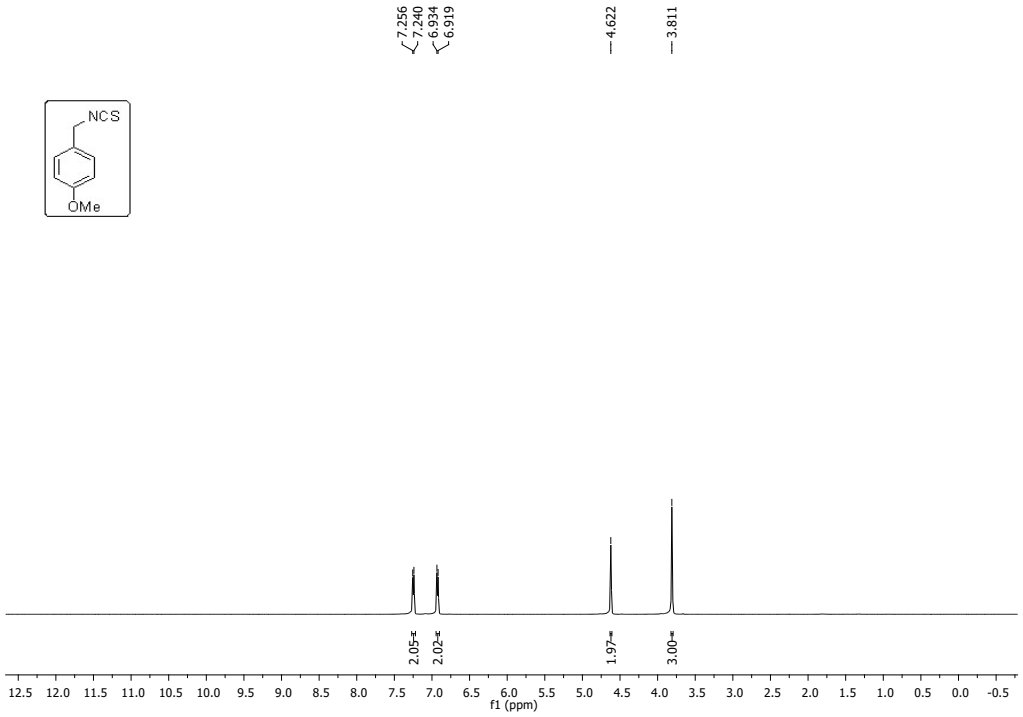


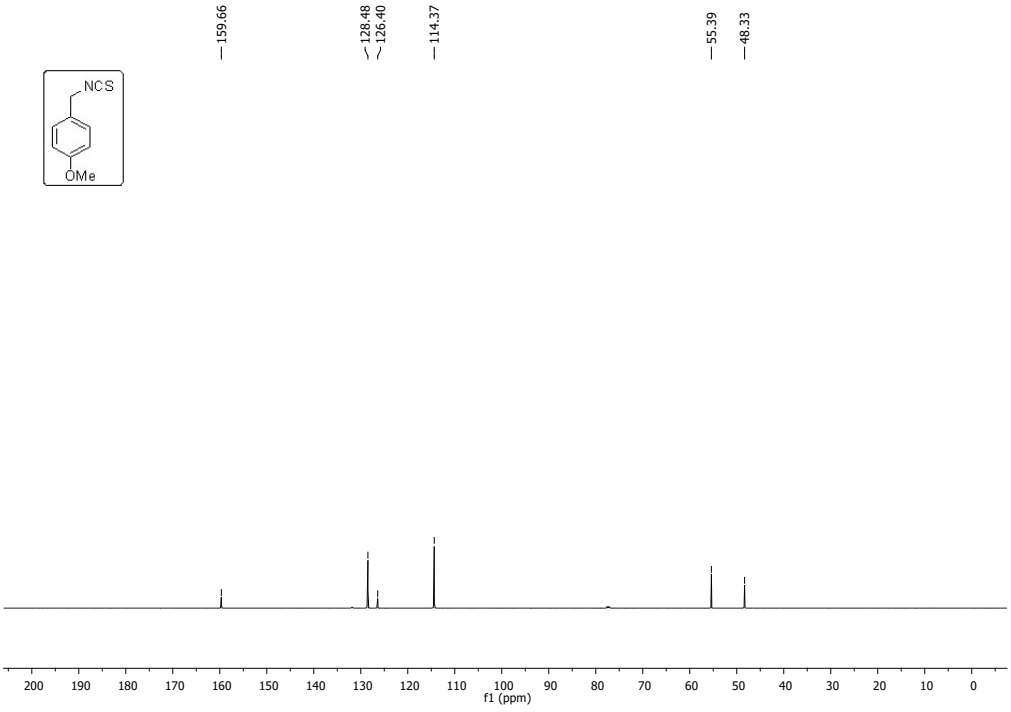
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2a**



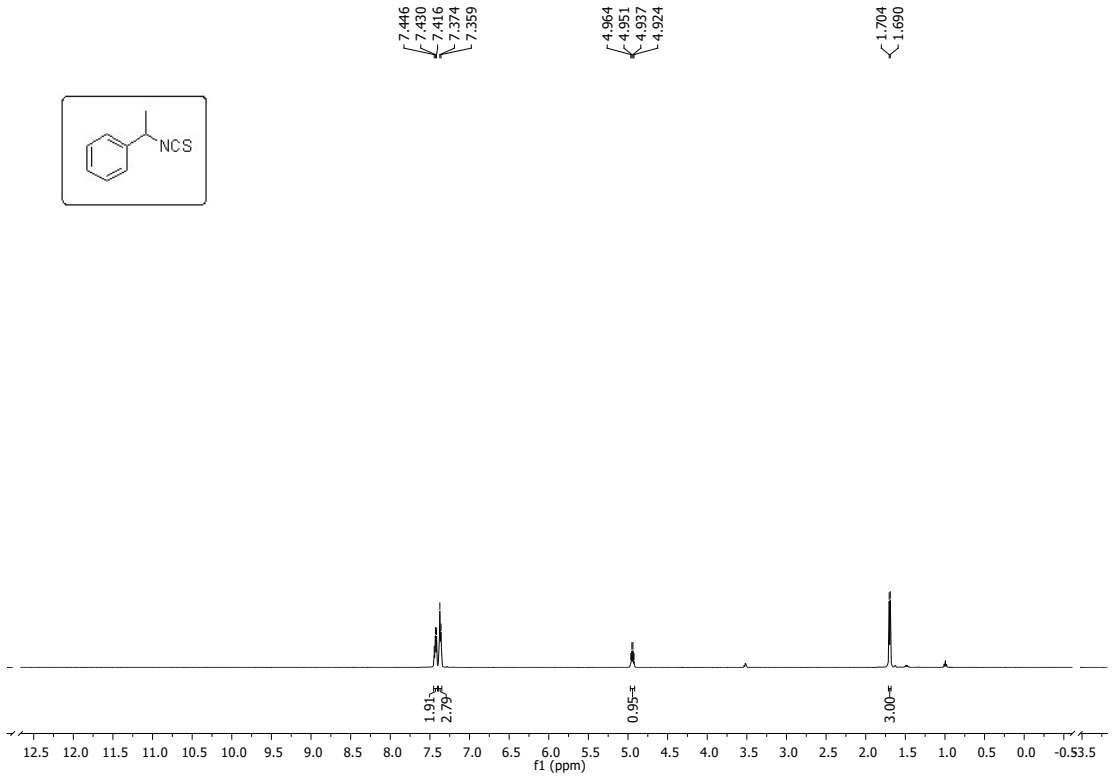


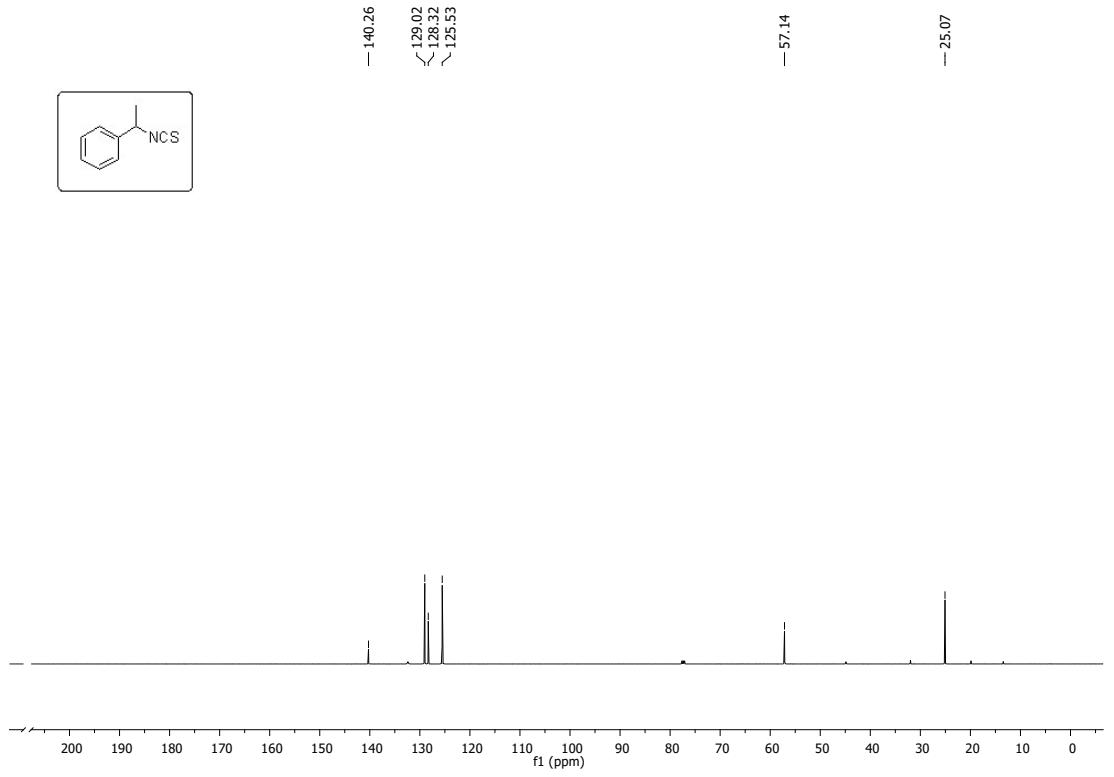
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2b**



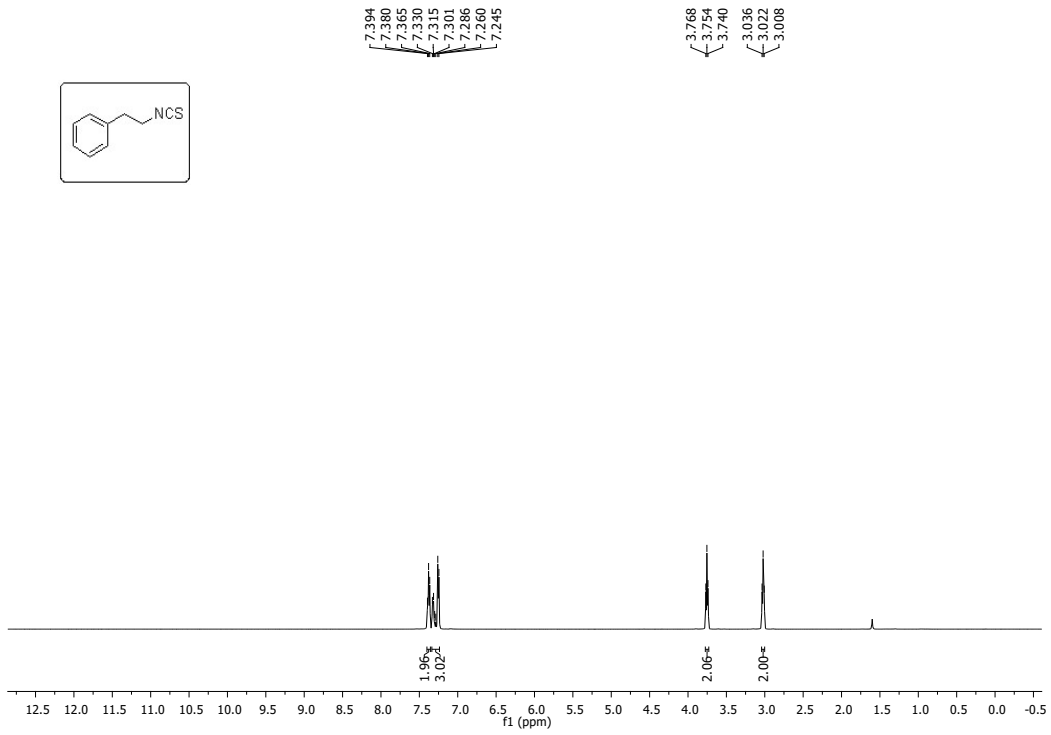


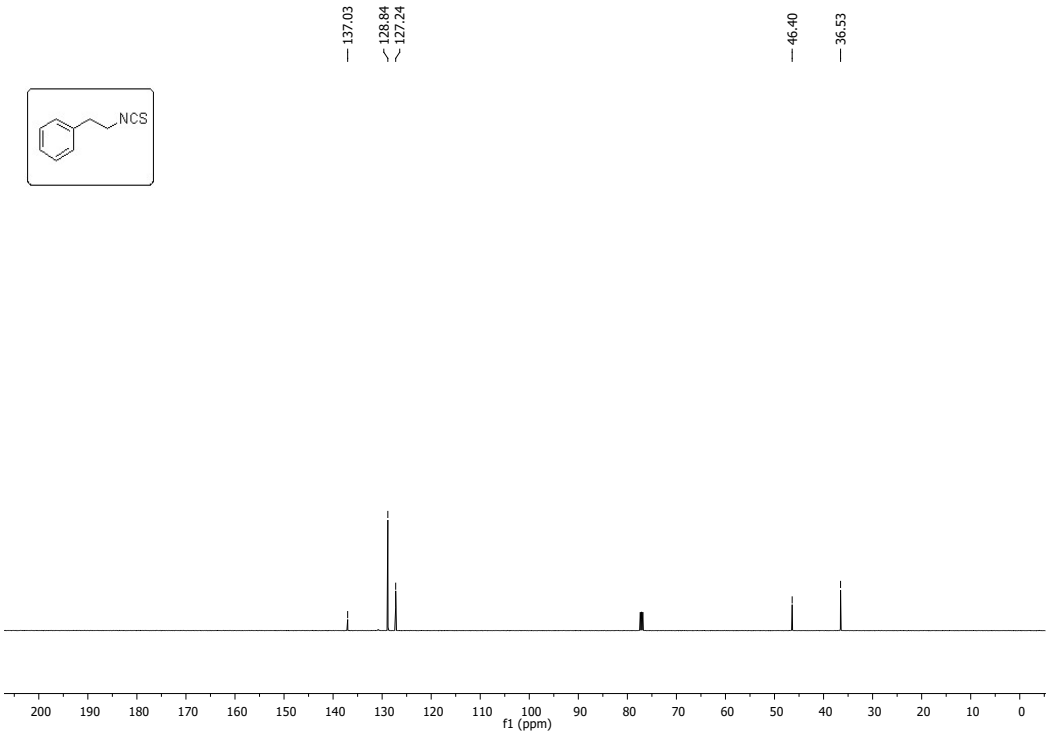
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2c**



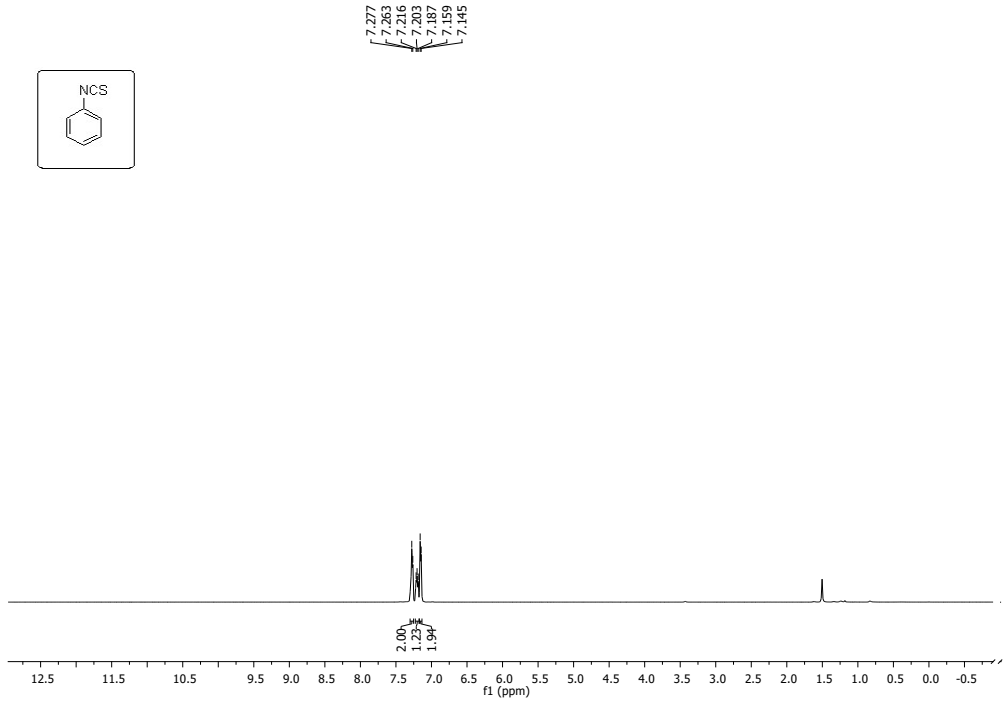


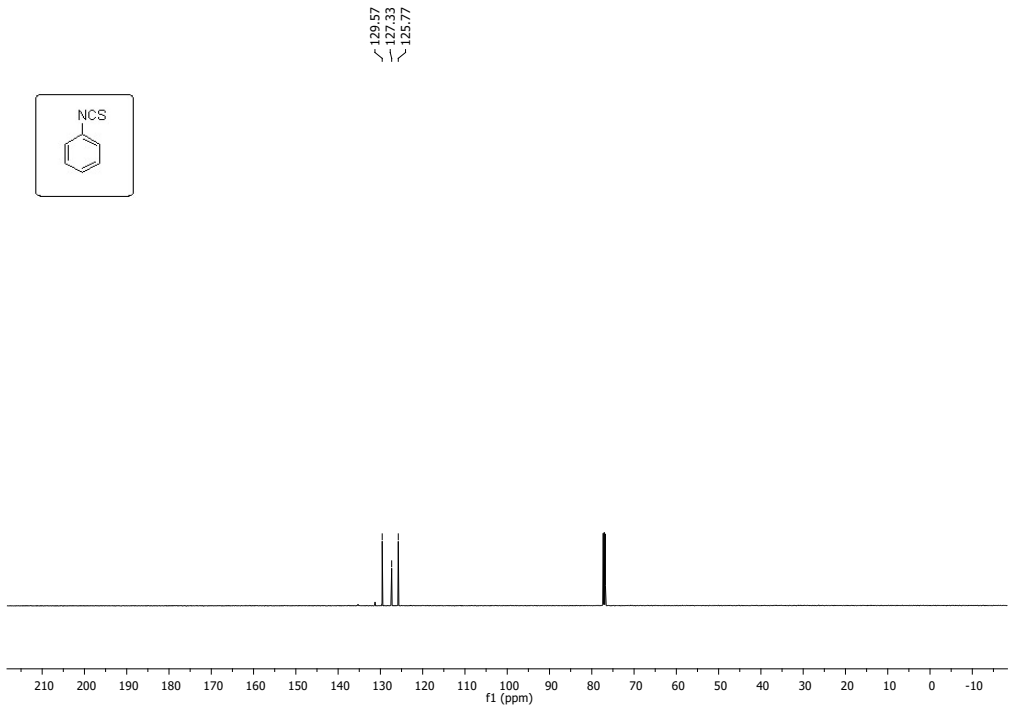
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2d**



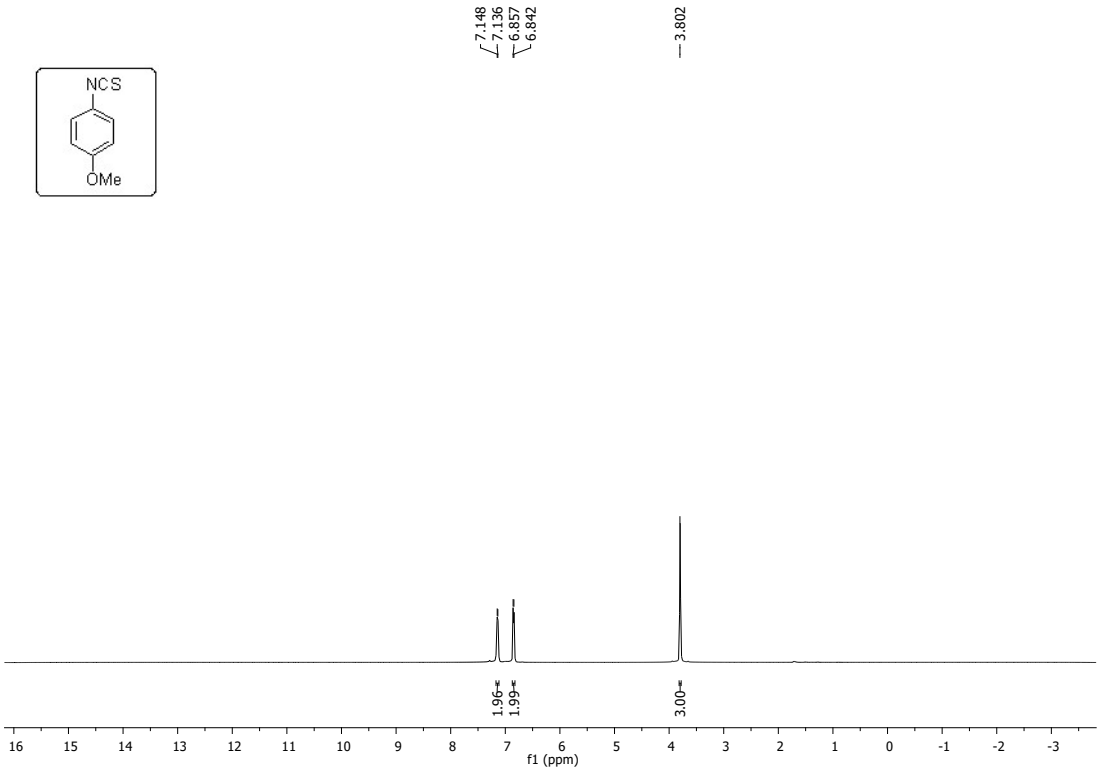


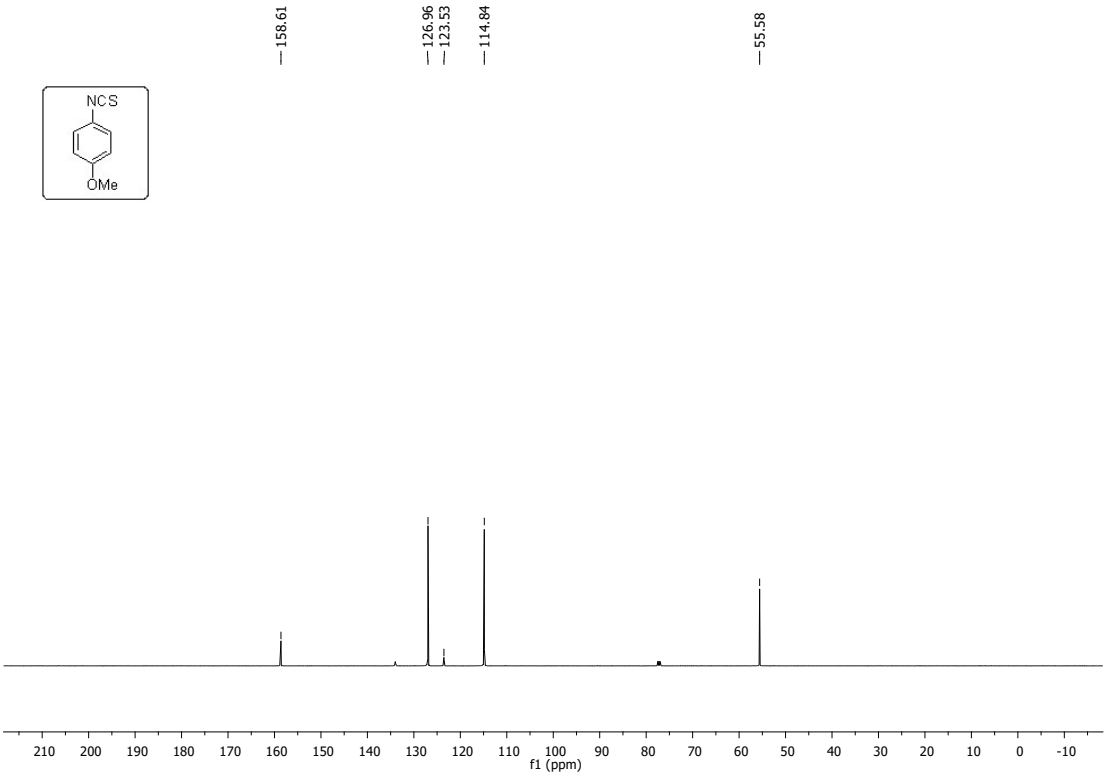
^{1}H NMR (500 MHz, $CDCl_3$) &$^{13}C\{^{1}H\}$ (125 MHz, $CDCl_3$) Spectra of **2e**



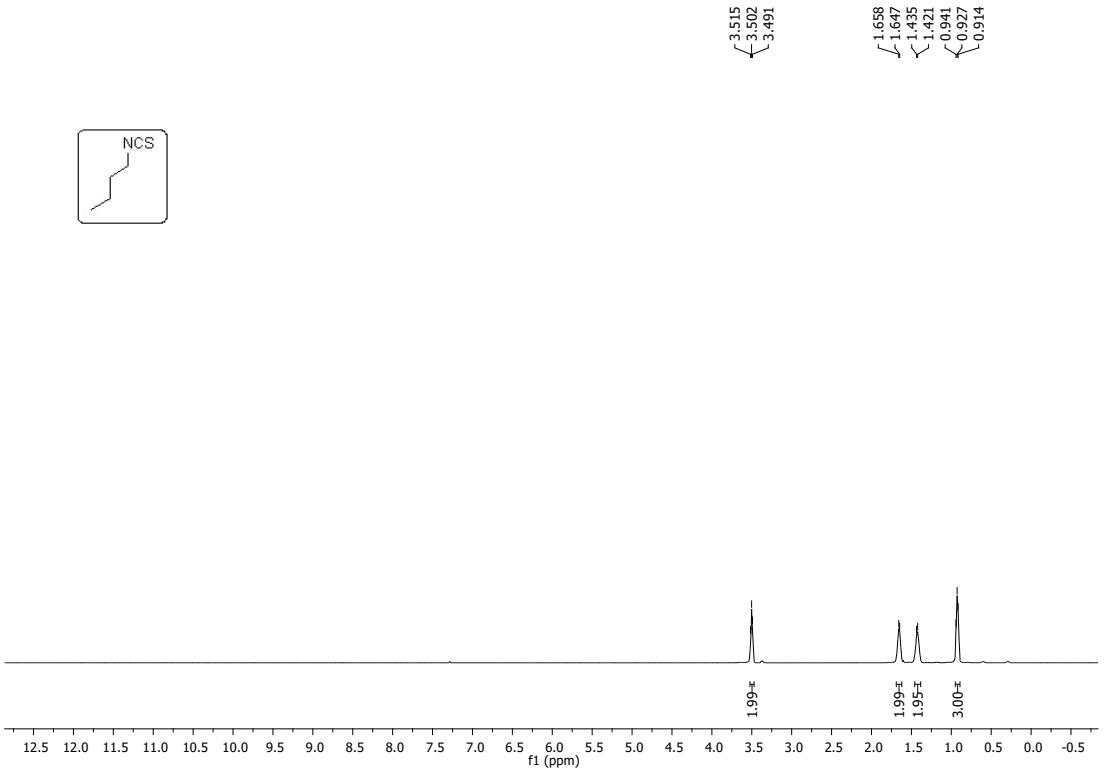


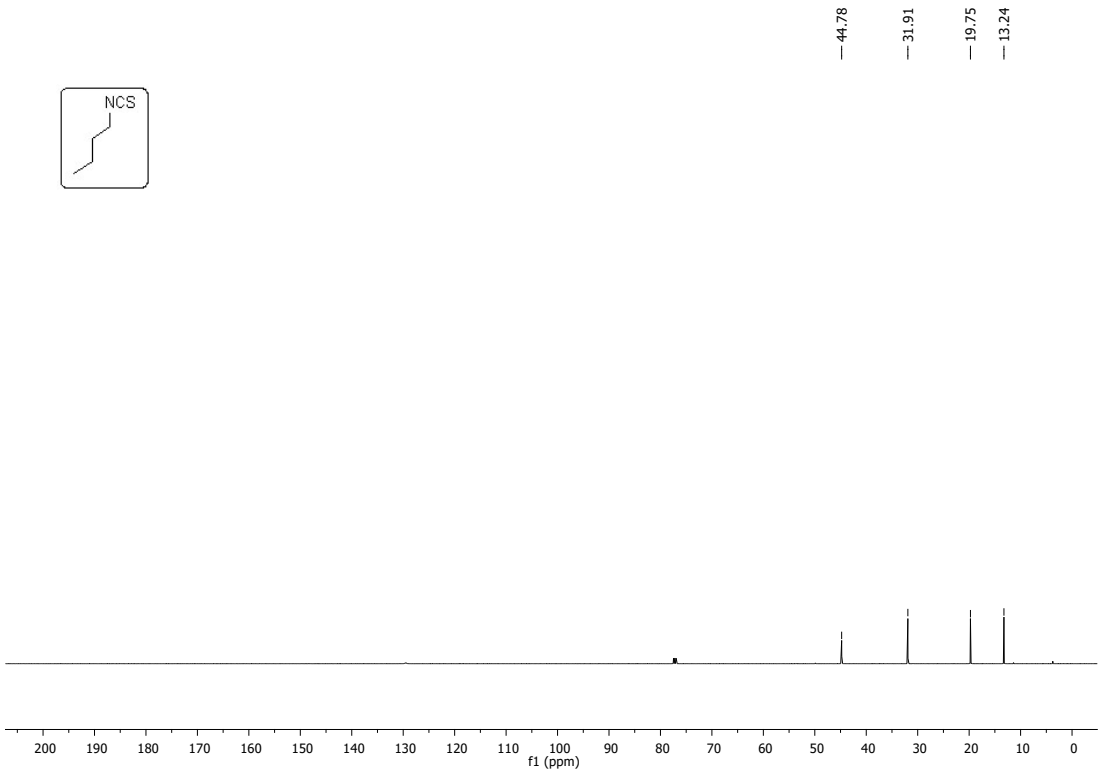
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2f**



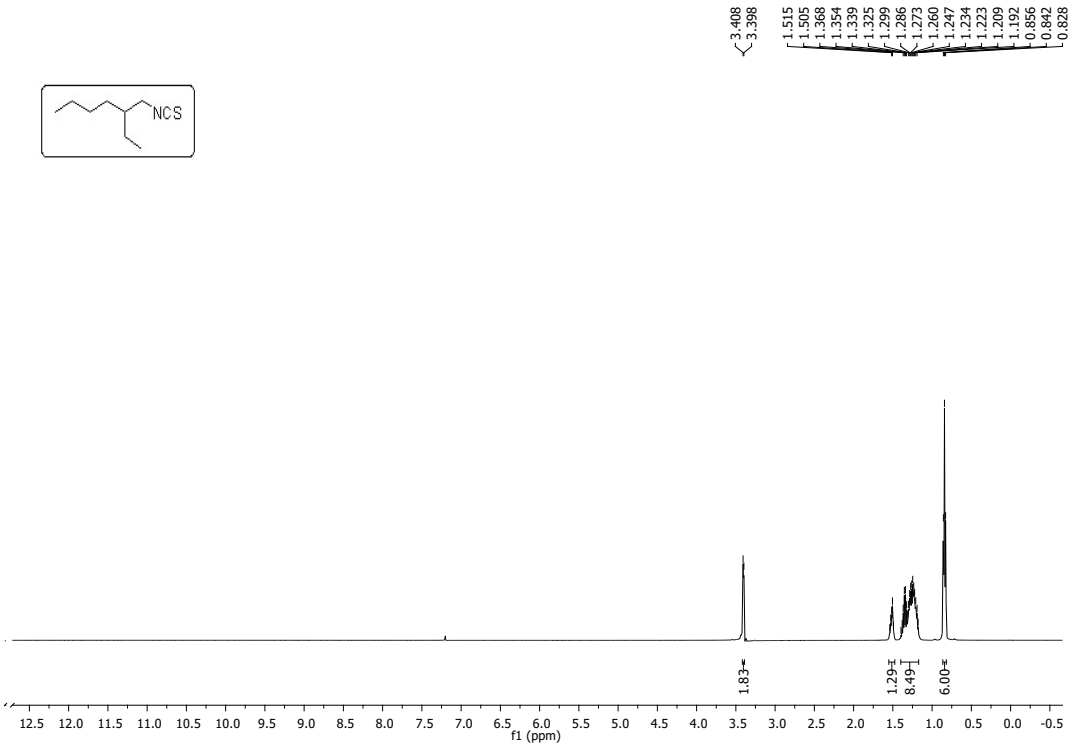


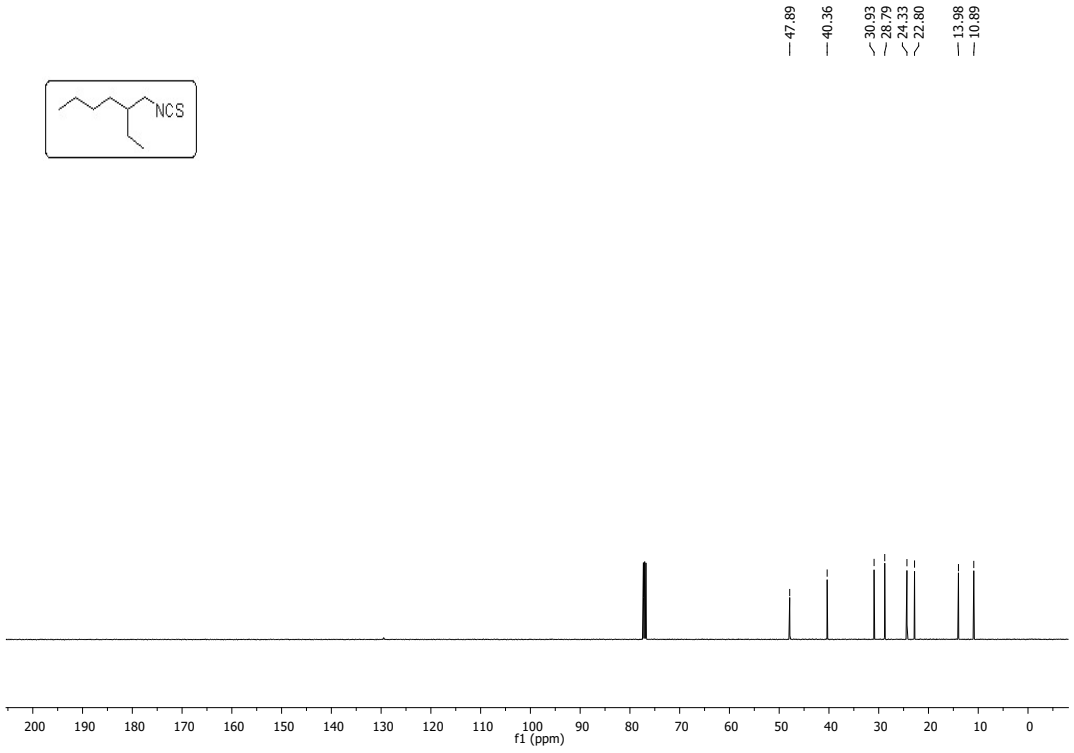
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2g**



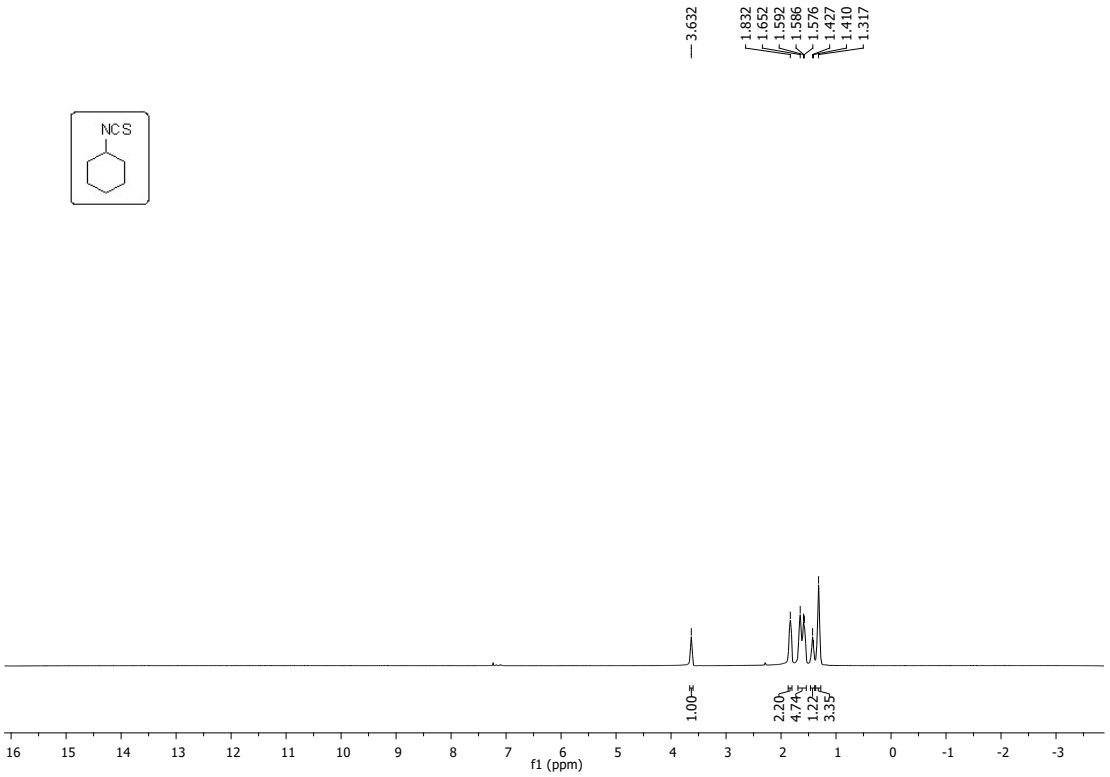


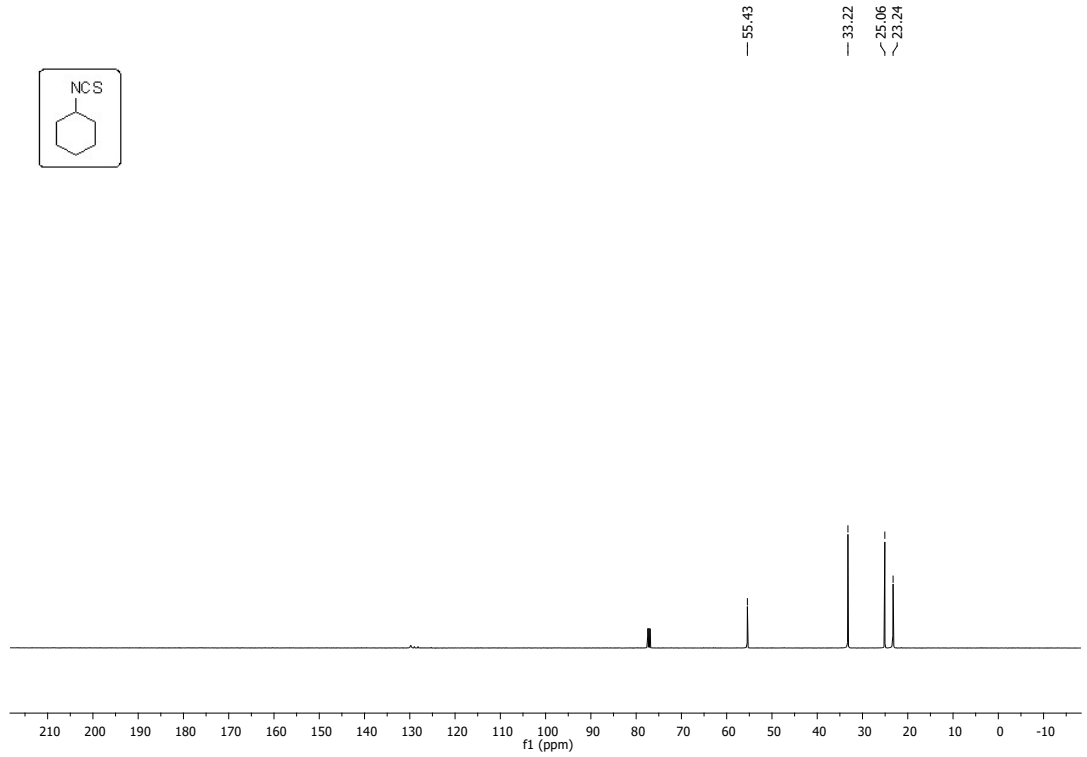
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2h**



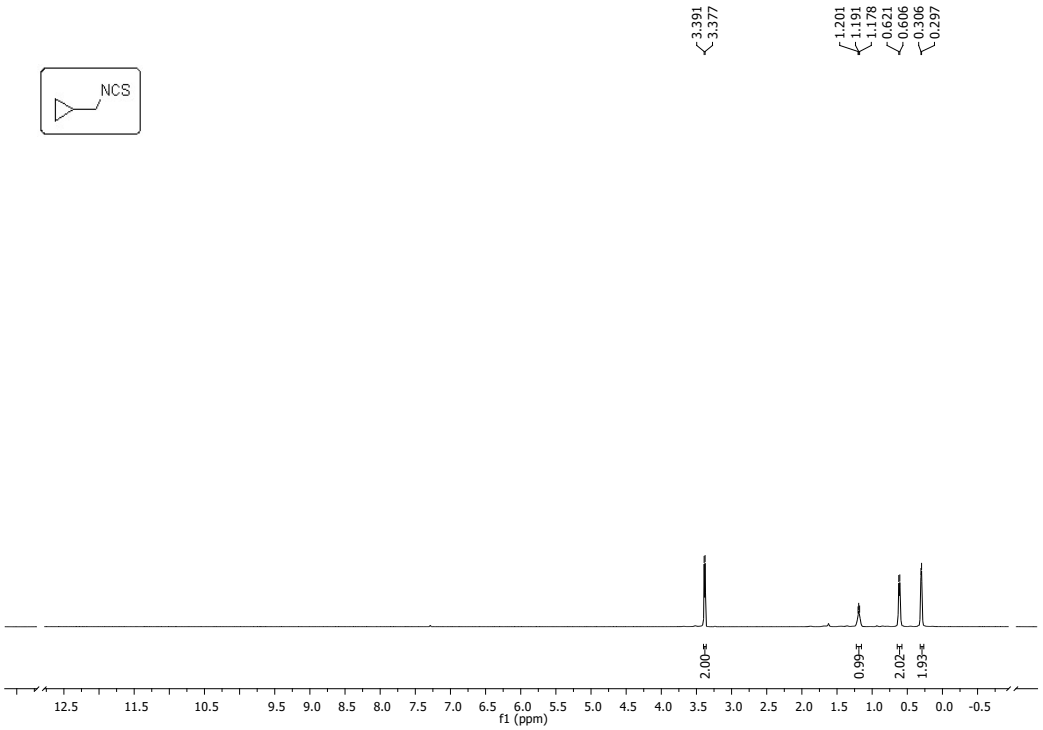


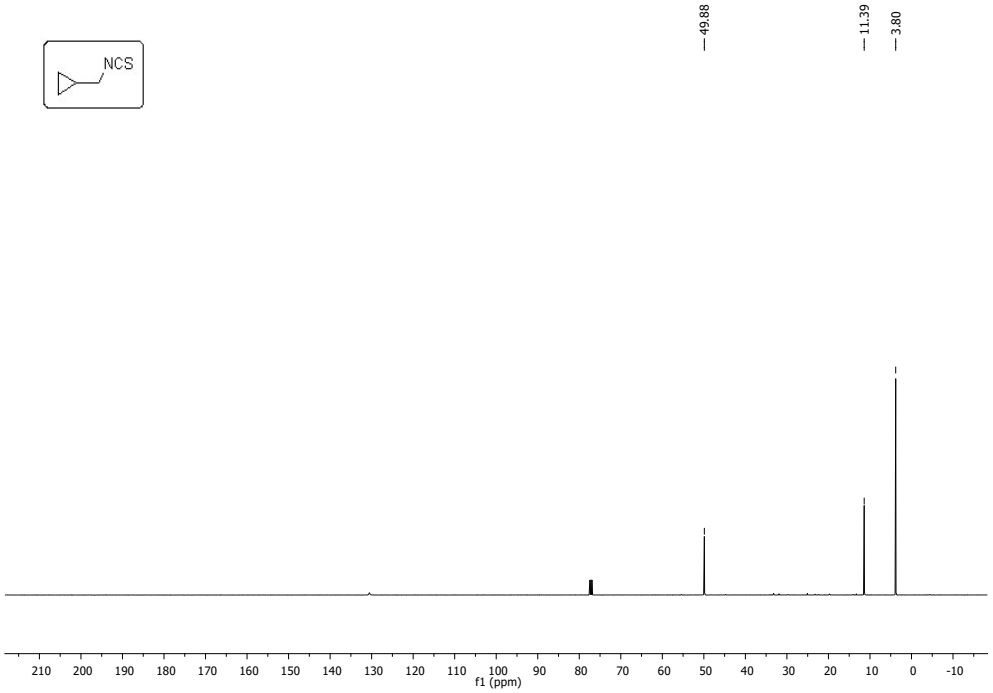
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2i**



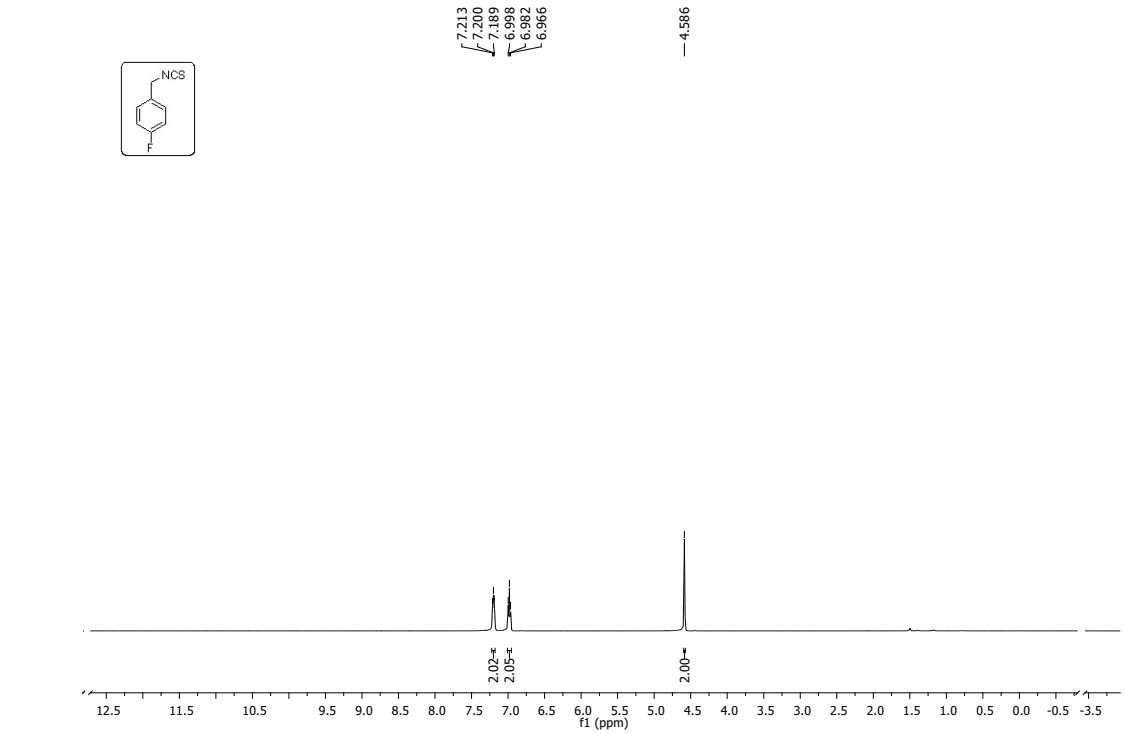


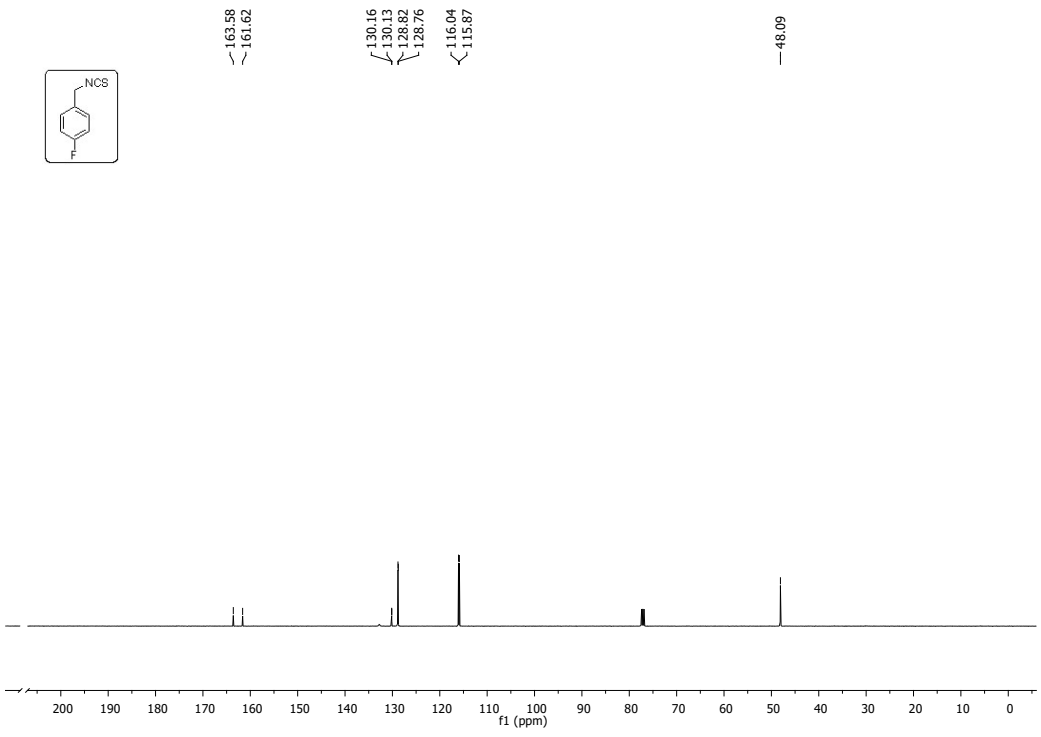
^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2j**





^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2k**





^{1}H NMR (500 MHz, $CDCl_3$) &^{13}C{^{1}H} (125 MHz, $CDCl_3$) Spectra of **2l**