Electronic Supplementary Information

An efficient labeling strategy of drug like molecules with functionalized alkyl linkers using CH-activation

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General information and materials

When it was required, non-dry solvents were distilled before use. If reactions were performed under exclusion of water and oxygen, solvents and reagents were degassed and dried with common methods and stored under inert gas over molecular sieves. Raney-Nickel 2800 was purchased from Sigma Aldrich as black slurry in water. After finishing a hydrogenation reaction, Raney-Nickel was removed by filtration through a pad of celite or silica gel under an inert atmosphere (N_2 or Ar). The catalytic residue (pyrophoric!) was removed from the filter pad and immediately stored under water. This slurry was disposed of as hazardous waste. Reactions were monitored by thin layer chromatography (TLC) on commercial silica gel plates (TLC aluminum foil, Merck, 60 F_{254}). Melting points were determined with a Mel-Temp® melting point apparatus with integrated microscopical support from Electrothermal in open capillary tubes and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer (300.36 MHz for ^{1}H NMR, 75.53 MHz for ^{13}C NMR) with autosampler. The residual solvent peak was set as internal standard. If necessary, APT spectra and additional 1D and 2D spectra (HSQC, HMBC, HMQC, COSY) were measured to confirm the structure. Infrared spectra were collected using a Bruker Tensor 37 FT-IR spectrophotometer (4000-600 cm^{-1}) with integrated ATR module. GC-MS data were collected using a HP 7890A GC system (from Agilent Technologies) with the mass selective detector 5975C MSD (EI, 70 eV). The components were separated on a capillary column HP-5MS (30 m x 0.25 mm, film: 0.25 µm) with the following temperature program: 1 min at 50 °C, ramp 40 °C/min linear to 300 °C, hold for 5 min. As no standards were used during the measurements, all data are relative values. Analytical high performance liquid chromatography (HPLC) data were obtained on a Shimadzu Nexera HPLC-MS system with two Nexera LC-30AD pump modules, Nexera SIL-30AC auto sampler, CTO-20AC prominence column oven, SPD-M20A prominence diode array detector, CBM-20A prominence communications bus module, FCV-20AH$_2$ valve unit and LCMS-2020 quadrupole mass detector. The following methods were used for analytical HPLC: Method A: Poroshell 120 EC-C18, 100x3 mm, 2.7 µm, Agilent, A: 0.01% HCOOH in H_2O, B: acetonitrile, 40 °C, 0.7 mL/min, 0-6 min: 2-60% B, 6-8 min: 60% B constant, ESI^+, λ 254, 210 nm. Method B: Nucleodur C18 ec 150/4, 100x5 mm, Macherey-Nagel, A: 0.01% HCOOH in H_2O, B: MeOH, 30 °C, 0.7 mL/min, 0-7 min: 15% B constant, 7-9 min: 15-100% B, 9-14 min: 100% B constant, λ 254, 210 nm. Semi-preparative high performance liquid chromatography was performed on an instrument from Knauer Technologies consisting of a smartline pump 1000 V7603, smartline DAD UV detector 2600, smartline manager 5000

V7602, smartline autosampler 3800 V9759 or manual 6 port injection ventil and fraction collector Teledyne Isco Foxy Jr. FC100. The compounds were separated on a C18-reversed phase VP 125/21 Nucleodur 100-5 C18ec column from Macherey & Nagel with VP 20/16 Nucleodur C18ec pre-column and detected with a UV diode array detector in the wavelength range of 200-400 nm. High resolution mass spectrometry (HRMS) was performed using a Waters GCT premier micromass with electron impact ionization (EI) at 70 eV. The probes were submitted to HRMS either by direct inlet or by GC 7890A from Agilent Technologies with capillary column DB-5MS (30 m x 0.25 mm, film: 0.25 µm). For molecules with a high molecular weight, a Micromass Tofspec 3E spectrometer with matrix assisted laser desorption ionisation (MALDI), α-cyano-4-hydroxycinnamic acid as matrix and a time of flight mass analyzer (TOF) was used.

Experimental data

2-((*E*)-2-Nitroethenyl)thiophene (1d)

Compound **1d** was prepared using a modified synthesis procedure of Trost and Muller.[3]

In a 250 mL two-necked round-bottom flask, heat dried under vacuum and flushed with N_2, 2-thiophencarbaldehyde (2.0 mL, 22.3 mmol, 1.0 eq) and nitromethane (1.2 mL, 22.3 mmol, 1.0 eq) were dissolved in methanol (5 mL). To the colorless solution NaOH (1.09 g, 26.8 mmol, 1.2 eq), dissolved in H_2O (1.5 mL), were added dropwise at 0 °C. The yellow solution was diluted with methanol (2.5 mL) and stirred at 0 °C for 2.5 h. TLC control was difficult due to nearly similar R_f-values. After the reaction seemed to be complete according to TLC analysis, the yellow solution was diluted with H_2O (15 mL) and the reaction mixture (pH 12) was poured into a solution of HCl conc. (10 mL) in H_2O (15 mL) (pH 1) and stirred for 30 min. Subsequently, this mixture was extracted with dichloromethane (3x10 mL), dried over $MgSO_4$, filtrated and the solvent was evaporated under reduced pressure. The brown solid was recrystallized from ethanol (5 mL) to yield the title compound as a brownish crystals (1.76 g, 11.4 mmol, 51%). R_f 0.77 (cyclohexane/ethyl acetate 2:1); mp 70 °C. (lit., [3] 78-79 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* =13.2 Hz, 1H, C<u>H</u>=CH-NO_2), 7.57 (d, *J* =5.1 Hz, 1H, Ar-H), 7.52-7.43 (m, 2H, 1x Ar-H, 1x CH-NO_2), 7.15 (dd, *J*= 5.1, *J*= 5.1 Hz, 1H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 134.6, 133.8, 132.1, 131.6, 128.9 ppm. NMR data are consistent with the reported data.[3]

tert-Butyl _N_-(thiophen-2-ylmethyl)carbamate (1f)

In a 50 mL round-bottom flask sodium carbonate (237 mg, 2.24 mmol, 2.5 eq) was dissolved in H_2O (2 mL) and 2-aminomethylthiophene (**1e**) (92 µL, 0.89 mmol, 1.0 eq) was added. At 0 °C, 1,4-dioxane (2 mL) and (314 mg, 1.44 mmol, 1.6 eq) di-*tert*-butyl-dicarbonate were added to the reaction mixture and it was stirred for 2 h until TLC indicated complete conversion. The crude product was concentrated under reduced pressure. The residue was diluted with dichloromethane (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic layers were extracted with 1 M HCl (3x10 mL), dried over Na_2SO_4, filtrated and the solvent was evaporated under reduced pressure. The crude colorless oil was purified by flash chromatography (20 g silica gel, cyclohexane/ethyl acetate 4:1) to yield the title compound as a colorless solid (187 mg, 0.46 mmol, 98%). R_f 0.43 (cyclohexane/ethyl acetate 4:1); mp 47 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, *J* =4.2, *J* =6.3 Hz, 1H, Ar-H), 6.98-6.91 (m, 2H, 2x Ar-H), 4.88 (bs, 1H, NH), 4.48 (d, *J* =3.3 Hz, 2H, CH_2-N), 1.46 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 141.9, 126.8, 125.4, 124.9, 79.7, 39.6, 28.4 ppm; GC-MS: t_R 5.82 min, *m/z* 213 (M^+, 2%), 97 (100). NMR data are consistent with the reported data.[1]

Benzyl _N_-(thiophen-2-ylmethyl)carbamate (1g)

In a 50 mL round-bottom flask sodium carbonate (3.93 g, 36 mmol, 2.3 eq) was dissolved in H_2O (92 mL) and 2-aminomethylthiophene (**1e**) (2.0 mL, 16 mmol, 1.0 eq) was added. At 0 °C, 1,4-dioxane (91 mL) and benzyl chloroformate (4.8 mL, 23 mmol, 1.4 eq) were added to the reaction mixture and it was stirred for 1 h until TLC indicated complete conversion. The solvents were evaporated and the residue was diluted with dichloromethane (60 mL) and H_2O (60 mL). The aqueous layer was extracted with dichloromethane (3x15 mL). The combined organic layers were extracted with 1 M HCl (3x15 mL), dried over Na_2SO_4, filtrated and the product **1g** was concentrated under reduced pressure to yield the title compound as a colorless solid (4.79 g, 19 mmol, quantitative). R_f 0.64 (cyclohexane/ethyl acetate 2:1); mp 33-36 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.22 (m, 5H, 5x Ar-H), 7.13 (dd, *J* =4.5 Hz, *J* =4.8 Hz, 1H, Ar-H), 6.90-6.81 (m, 2H, 2x Ar-H), 5.19 (bs, 1H, NH), 5.04 (s, 2H, CH_2-O), 4.44 (d, *J* =5.7 Hz, 2H, CH_2-N) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 141.2, 136.3, 128.4, 128.1, 128.0, 126.8, 125.7, 125.0, 66.8, 39.8 ppm; GC-MS: t_R 7.38 min, *m/z* 156 (M^+, 100%). NMR data are consistent with the reported data.[2]

2-((Benzyloxy)methyl)thiophene (1j)

In a 50 mL Schlenk tube, heat dried under vacuum and flushed with N_2, 2-thiophenemethanol (**1i**) (1.21 mL, 11.4 mmol, 1.0 eq) was dissolved in dry THF (9 mL). At 0 °C, sodium hydride (60% dispersion) (688 mg, 17.2 mmol, 1.5 eq) was added portionwise. The yellow suspension was allowed to warm up to rt under stirring for 20 min. Subsequently, benzyl bromide (4.2 mL, 17.1 mmol, 1.5 eq) was added dropwise at 0 °C followed by stirring at rt for 3 h. As GC-MS control indicated full conversion methanol (10 mL) was added to the white suspension. After evaporation of the solvents under reduced pressure the residue was diluted with dichloromethane (15 mL), H_2O (15 mL) and saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with dichloromethane (3x7 mL). The combined organic layers were dried over Na_2SO_4, filtrated and the product **1j** was concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (100 g silica gel, cyclohexane, then cyclohexane/ethyl acetate 50:1) to yield the title compound as a colorless liquid (2.31 g, 11.3 mmol, 99%). R_f 0.25 (cyclohexane/ethyl acetate 50:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.34 (m, 4H, 4x Ar-H), 7.33-7.27 (m, 2H, 2x Ar-H), 7.03-6.96 (m, 2H, 2x Ar-H), 4.72 (s, 2H, CH_2), 4.57 (s, 2H, CH_2) ppm; ^{13}C NMR (75MHz, $CDCl_3$): δ 141.0, 137.9, 128.4 (2xC), 127.7 (2xC), 126.6, 126.5, 125.8, 71.7, 66.5 ppm; GC-MS: t_R 6.21 min, *m/z* 204 (M^+, 2%), 97 (100).

1,3,7-Trimethyl-8-(5-methylthiophen-2-yl)-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (3a)

Compound **3a** was prepared according to the procedure of Xi *et al*.[5] In a 20 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (2.8 mg, 0.0125 mmol, 0.025 eq), copper acetate monohydrate (150 mg, 0.75 mmol, 1.50 eq) and caffeine (**77**) (97.1 mg, 0.50 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (0.6 mL). After addition of pyridine (40.8 µL, 0.50 mmol, 1.00 eq) the blue suspension was degassed in three vacuum-N_2 cycles. 2-Methylthiophene (**84**) (145 µL, 1.50 mmol, 3.00 eq) was added and the reaction mixture was heated at 120 °C for 24 h until GC-MS control indicated complete conversion. The green-black suspension was filtrated through a pad of celite and a pad of silica gel and rinsed with dichloromethane (17 mL). After evaporation of the solvent under reduced pressure the light green solid was purified by flash chromatography (6 g silica gel, dichloromethane/acetone 30:1) to yield the title compound as a light yellow powder (133 mg, 0.46 mmol, 92%). R_f 0.29 (dichloromethane/acetone 30:1); mp 188-190 °C, (lit., [5] 185-188 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* =3.6 Hz, 1H, Ar-H), 6.84 (dd, *J* =3.6 Hz, *J* =0.9 Hz, 1H, Ar-H), 4.16 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 2.56 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 151.6, 148.2, 146.8, 144.6, 128.9, 128.1, 126.5, 108.1, 33.6, 29.8, 27.9,

15.3 ppm; GC-MS: t_R 9.47 min, *m/z* 290 (M^+, 100%). NMR data are consistent with the reported data.[5]

5-(1,3,7-Trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophene-2-carbonitrile (3b)

Compound **3b** was prepared according to the procedure of Xi *et al*[5] using palladium acetate (1.6 mg, 0.006 mmol, 0.01 eq), copper acetate monohydrate (154 mg, 0.772 mmol, 1.50 eq), caffeine (**2**) (101 mg, 0.516 mmol, 1.00 eq), dry 1,4-dioxane (1.0 mL), pyridine (42 µL, 0.516 mmol, 1.00 eq) and 2-thiophencarbonitrile (**1b**) (143 µL, 1.545 mmol, 3.00 eq) to yield the title compound as a yellow solid (79 mg, 0.26 mmol, 50%). R_f 0.56 (dichloromethane/acetone 15:1); mp 268 °C (lit., [5] 298-301 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.67 (d, *J* =4.2 Hz, 1H, Ar-H), 7.54 (d, *J* =4.2 Hz, 1H, Ar-H), 4.24 (s, 3H, CH_3-N), 3.60 (s, 3H, CH_3-N), 3.42 (s, 3H, CH_3-N) ppm. NMR data are consistent with the reported data.[5]

1,3,7-Trimethyl-8-(5-nitrothiophen-2-yl)-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**3c**)

In a 20 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (11.2 mg, 0.05 mmol, 0.025 eq), copper acetate monohydrate (600 mg, 3.00 mmol, 1.50 eq) and caffeine (**2**) (389 mg, 2.00 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (2.4 mL). After addition of pyridine (0.16 mL, 2.00 mmol, 1.00 eq) the blue suspension was degassed in five vacuum-N_2 cycles. 2-Nitrothiophene (**1c**) (775 mg, 6.00 mmol, 3.00 eq) (85% pure, contains 15% 3-nitrothiophene) was added and the reaction mixture was heated at 120 °C for 19 h. GC-MS control was not sufficient as the product **3c** was not detectable on GC-MS. TLC indicated incomplete conversion. Therefore, the black suspension was stirred at 120 °C for further 6 d. Since TLC control still indicated incomplete conversion and a metal mirror on the Schlenk tube wall already occurred, the reaction mixture was filtrated through a pad of celite and rinsed with dichloromethane (15x5 mL). After evaporation of the solvent, the black solid was purified by flash chromatography (80 g silica gel, dichloromethane/acetone 9:1) to yield the title compound as a red-brownish powder (160 mg, 0.50 mmol, 25%). R_f 0.53 (dichloromethane/acetone 9:1); mp 287 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.24 (d, *J* =4.2 Hz, 1H, Ar-H), 7.81 (d, *J* =4.5 Hz, 1H, Ar-H), 4.21 (s, 3H, CH_3-N), 3.45 (s, 3H, CH_3-N), 3.25 (s, 3H, CH_3-N) ppm. As product **3c** precipitated from all tested solvents, no ^{13}C NMR could be measured. HPLC (Method A): t_R 5.90 min, $[M+H]^+$ 322; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{12}H_{12}N_5O_4S^+$ $[M+H]^+$: 322.0610, found 322.0632.

tert-Butyl _N_-((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1_H_-purin-8-yl) thiophen-2-yl)methyl)carbamate (3f)

In a 15 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (7 mg, 0.03 mmol, 0.03 eq), copper acetate monohydrate (385 mg, 1.93 mmol, 1.51 eq), CuCl (25 mg, 0.26 mmol, 0.20 eq) and caffeine (**2**) (249 mg, 1.28 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (2.2 mL). After addition of pyridine (100 µL, 1.30 mmol, 1.02 eq) the blue suspension was degassed in three vacuum-N_2 cycles. *tert*-Butyl (thiophen-2-ylmethyl)carbamate (**1f**) (822 mg, 3.85 mmol, 3.00 eq) was added and the reaction mixture was stirred at 120 °C for 20 h until TLC control indicated complete conversion. The suspension was diluted with 50 mL dichloromethane, filtrated through a pad of celite and rinsed with dichloromethane (4x20 mL). After evaporation of the solvent under reduced pressure the green solid was purified by filtration through a 2 cm pad of silica gel (dichloromethane/acetone 15:1) to yield the title compound as a colorless solid (514 mg, 1.27 mmol, 99%). R_f 0.13 (dichloromethane/acetone 15:1); mp 169-170 °C; IR (neat): ν_{max} 3320 (w), 2980 (w), 1694 (s), 1652 (s), 1537 (m), 1503 (m), 1450 (m), 1248 (m), 1163 (s), 745 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* =3.6 Hz, 1H, Ar-H), 7.02 (d, *J* =3.6 Hz, 1H, Ar-H), 5.00 (bs, 1H, NH), 4.52 (d, *J* =5.7 Hz, 2H, CH_2-N), 4.17 (s, 3H, CH_3-N), 3.61 (s, 3H, CH_3-N), 3.42 (s, 3H, CH_3-N), 1.47 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 155.4, 151.6, 148.1, 146.8, 146.4, 129.7, 128.6, 126.2, 108.3, 80.2, 39.6, 33.6, 29.8, 28.4, 28.0 ppm; HPLC (Method A): t_R 6.53 min, $[M+H]^+$ 406, $[M+Na]^+$ 428, $[M+K]^+$ 444; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{18}H_{24}N_5O_4S^+$ $[M+H]^+$: 406.1549, found 406.1559.

Benzyl _N_-((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1_H_-purin-8-yl) thiophen-2-yl)methyl)carbamate (3g)

In a 50 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (30 mg, 0.14 mmol, 0.02 eq), copper acetate monohydrate (1.70 g, 8.51 mmol, 1.50 eq), 1,10-phenanthroline (0.10 g, 0.55 mmol, 0.1 eq) and caffeine (**2**) (1.10 g, 5.66 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (8 mL). After addition of pyridine (0.5 mL, 6.19 mmol, 1.00 eq) the blue suspension was degassed in three vacuum-N_2 cycles. Benzyl (thiophen-2-ylmethyl)carbamate (**1g**) (4.25 g, 17.18 mmol, 3.00 eq) was added and the reaction mixture was stirred at 120 °C for 20 h until TLC control indicated complete conversion. The suspension was filtrated through a pad of celite and rinsed with dichloromethane (40 mL). After evaporation of the solvent under reduced pressure, the green solid was purified by flash chromatography (400 g silica gel, cyclohexane/ethyl acetate 1:2 up to ethyl acetate/methanol

2:1) to yield the title compound as a pale yellow solid (2.16 g, 4.92 mmol, 87%). R_f 0.65 (cyclohexane/ethyl acetate 2:1); mp 140-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* =3.6 Hz, 1H, Ar-H), 7.39-7.32 (m, 5H, 5x Ar-H), 7.04 (d, *J* =5.1 Hz, 1H, Ar-H), 5.26 (bs, 1H, NH), 5.15 (s, 2H, CH_2-O), 4.59 (d, *J* =6.0 Hz, 2H, CH_2-N), 4.16 (s, 3H, CH_3-N), 3.60 (s, 3H, CH_3-N), 3.42 (s, 3H, CH_3-N) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.4, 151.6, 148.1, 146.3, 146.0, 136.1, 130.1, 128.6 (2xC), 128.5, 128.3, 128.2 (2xC), 126.5, 108.3, 67.2, 40.0, 33.6, 29.8, 28.0 ppm; HPLC (Method A): t_R 6.31 min, $[M+H]^+$ 440, $[M+Na]^+$ 462; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{21}H_{22}N_5O_4S^+$ $[M+H]^+$: 440.1393, found 440.1384.

8-(5-(Hydroxymethyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (3i)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, caffeine (**2**) (50.3 mg, 0.259 mmol, 1.00 eq), CuCl (5.5 mg, 0.056 mmol, 0.22 eq), palladium acetate (1.5 mg, 0.006 mmol, 0.02 eq) and copper acetate monohydrate (77.8 mg, 0.389 mmol, 1.50 eq) were suspended in dry 1,4-dioxane (0.45 mL) and pyridine (20 µL, 0.259 mmol, 1.00 eq). After 10 min stirring at rt 2-thiophenemethanol (**1i**) (0.11 mL, 0.770 mmol, 2.97 eq) was added and the green suspension was stirred at 120 °C for 19 h. As HPLC indicated complete conversion the reaction mixture was diluted with dichloromethane (30 mL), filtrated through a pad of celite and rinsed with dichloromethane (4x25 mL). After evaporation of the solvent the crude product **3i** was purified by flash chromatography (26 g silica gel, dichloromethane) to yield the title compound as a colorless solid (50 mg, 0.163 mmol, 63%). R_f 0.62 (dichloromethane/acetone 2:1); mp 220 °C; IR (neat): ν_{max} 3405 (w), 2925 (w), 1684 (m), 1647 (s), 1538 (m), 1505 (w), 1452 (m), 1414 (w), 1359 (m), 1224 (m), 1164 (m), 1048 (m), 1029 (s), 1006 (m), 973 (m), 827 (w), 758 (s), 744 (s), 680 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* =3.9 Hz, 1H, Ar-H), 7.08 (d, *J* =3.9 Hz, 1H, Ar-H), 4.91 (s, 2H, CH_2), 4.20 (s, 3H, CH_3-N), 3.62 (s, 3H, CH_3-N), 3.43 (s, 3H, CH_3-N) ppm; HPLC (Method A): t_R 4.07 min, $[M+H]^+$ 307; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{13}H_{15}N_4O_3S^+$ $[M+H]^+$: 307.0865, found 307.0884.

8-(5-((Benzyloxy)methyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (3j)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, caffeine (**2**) (202 mg, 1.040 mmol, 1.00 eq), palladium acetate (5.2 mg, 0.023 mmol, 0.02 eq) and copper acetate monohydrate (311 mg, 1.555 mmol, 1.50 eq) were suspended in dry 1,4-dioxane (2.0 mL) and

pyridine (80 µL, 1.040 mmol, 1.00 eq). After stirring at rt for 10 min 2-((benzyloxy)methyl) thiophene (**1j**) (637 mg, 3.117 mmol, 3.00 eq) was added and the dark green suspension was stirred at 120 °C for 1 d. After HPLC control indicated full conversion the mixture was filtrated through a pad of celite and rinsed with methanol (8x20 mL). The precipitating product **3j** was collected from the blue filtrate by filtration under reduced pressure and washed with methanol (3x5 mL). The product was dried under high vacuum to yield the title compound as a colorless solid (367 mg, 0.926 mmol, 89%). R_f 0.27 (dichloromethane/acetone 5:1); mp 142-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* =3.6 Hz, 1H, Ar-H), 7.40-7.25 (m, 5H, 5x Ar-H), 7.04 (d, *J* =3.6 Hz, 1H, Ar-H), 4.72 (s, 2H, CH_2-O), 4.59 (s, 2H, CH_2-O), 4.17 (s, 3H, CH_3-N), 3.59 (s, 3H, CH_3-N), 3.40 (s, 3H, CH_3-N) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 151.8, 148.3, 146.7, 145.9, 137.7, 130.7, 128.7 (2xC), 128.7, 128.1, 128.1 (2xC), 127.0, 108.5, 72.4, 66.6, 33.8, 30.0, 28.2 ppm; HPLC (Method A): t_R 6.85 min, $[M+H]^+$ 397, $[M+Na]^+$ 419, $[M+K]^+$ 435; HRMS (TOF MS EI$^+$): *m/z* calculated for $C_{20}H_{20}N_4O_3S^+$ M^+: 396.1256, found 396.1248.

1,3,7-Trimethyl-8-pentyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (4a)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, 1,3,7-trimethyl-8-(5-methylthiophen-2-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**3a**) (116 mg, 0.40 mmol, 1.0 eq) was suspended in dry THF (2.0 mL). The yellow suspension was degassed in eight vacuum-N_2 cycles. An ethanolic black suspension of Raney-Ni (0.5 mL) was added to the reaction mixture, which was then flushed with H_2 in five vacuum-H_2 cycles and stirred under H_2 from an orsat balloon at rt. After 15 h, GC-MS indicated ~ 1/3 conversion. Therefore, further 0.5 mL Raney-Ni were added, the grey suspension underwent three vacuum-H_2 cycles and was then stirred at rt for 17 h. As GC-MS indicated 2/3 conversion another 0.5 mL Raney-Ni were added, the grey suspension was subjected to three vacuum-H_2 cycles and then stirred at rt for 18 h. As GC-MS now indicated nearly complete conversion the reaction mixture was filtrated through a pad of celite, rinsed with methanol (6x10 mL) and the solvents were evaporated under reduced pressure. The crude, green solid was purified by flash chromatography (60 g silica gel, dichloromethane/acetone 98:2 up to 94:6) to yield the title compound as a pale yellow solid (90 mg, 0.34 mmol, 85%). 17 mg (0.06 mmol, 15%) starting material (pale yellow solid) could be reisolated. R_f 0.18 (dichloromethane/acetone 30:1); mp 79-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H, CH_3-N), 3.57 (s, 3H, CH_3-N), 3.40 (s, 3H, CH_3-N), 2.73 (t, *J* =7.5 Hz, 2H, CH_2), 1.81-1.67 (m, 2H, CH_2), 1.41-1.32 (m, 4H, 2x CH_2), 0.91 (t, *J* 6.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 154.5, 151.7, 147.9, 107.3, 31.7,

31.5, 29.7, 27.8, 27.3, 26.8, 22.3, 13.9 ppm; GC-MS (JR_50_S): t_R 7.93 min, *m/z* 264 (M^+, 60%), 208 (100); HRMS (TOF MS EI^+): *m/z* calculated for $C_{13}H_{20}N_4O_2^+$ $[M]^+$: 264.1586, found 264.1602.

5-(1,3,7-Trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentan-1-amine (4b)

Via reduction with Raney-Nickel (general procedure):

In a Schlenk tube equipped with reflux condenser, heat dried under vacuum and flushed with N_2, 1.00 eq of starting material was suspended in THF. After degassing of the reaction mixture in three vacuum-N_2 cycles an aqueous Raney-Ni suspension was added. In three vacuum-H_2 cycles the mixture was flushed with H_2. The mixture was stirred at 60 °C for 22 h under H_2 from an orsat balloon. When TLC indicated complete conversion the reaction mixture was filtrated through a pad of celite and rinsed with methanol (15 mL). After evaporation of the organic solvents under reduced pressure the product **4b** was freeze dried at the lyophilisator. Finally, the crude solid was purified by preparative HPLC to yield the product as formate.

From **3b**: 5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophene-2-carbonitrile (**3b**) (60 mg, 0.20 mmol); aqueous Raney-Ni (4 mL); THF (1.5 mL).
Yield: colorless solid (1.5 mg, 0.005 mmol, 3%).

From **3g**: benzyl ((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl) methyl)carbamate (**3g**) (200 mg, 0.46 mmol); aqueous Raney-Ni (10 mL); THF (4 mL).
Yield: colorless solid (51 mg, 0.18 mmol, 40%).

Via Boc-deprotection:

In a 25 mL round-bottom flask with magnetic stirring bar *tert*-butyl (5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentyl) carbamate (**4f**) (16.4 mg, 0.045 mmol, 1 eq) was dissolved in dichloromethane (0.5 mL). After addition of TFA (200 µL, 2.250 mmol, 50 eq), the slightly yellow solution was stirred at rt for 1 h. When TLC and HPLC indicated complete conversion, the product **4b** was concentrated under N_2 flow. The crude sticky residue was purified by semi-preparative HPLC (A: 0.01% HCOOH in H_2O, B: MeOH, rt, 16 mL/min, 0-7 min: 17% B constant, 7-9 min: 17-100% B, 9-14 min: 100% B constant, λ 254 nm. t_R 4.8 min) to obtain the title compound as a colorless solid as trifluoroacetate (14.3 mg,

0.044 mmol, 98%). Mp 252-254 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 8.46 (s, 1H, $HCOO^-$), 3.86 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 2.90 (t, *J* =7.5 Hz, 2H, CH_2), 2.78 (t, *J* 7.5 Hz, 2H, CH_2), 1.84-1.61 (m, 4H, 2x CH_2), 1.53-1.41 (m, 2H, CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 170.3, 156.5, 156.1, 153.1, 149.2, 108.5, 40.5, 32.3, 30.1, 28.3, 28.3, 27.8, 27.1, 27.0 ppm; HPLC (Method A): t_R 2.58 min, $[M+H]^+$ 280, $[M+K]^+$ 318; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{13}H_{22}N_5O_2^+$ $[M+H]^+$: 280.1773, found 280.1782.

8-(4-Aminobutyl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (4c)

In a 10 mL Schlenk tube, equipped with reflux condenser, heat dried under vacuum and flushed with N_2, 1,3,7-trimethyl-8-(5-nitrothiophen-2-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (**3c**) (100 mg, 0.31 mmol, 1.00 eq) was suspended in THF (2 mL). After degassing of the reaction mixture in three vacuum-N_2 cycles, aqueous Raney-Ni suspension (6 mL) was added. In three vacuum-H_2 cycles the mixture was flushed with H_2. The reaction mixture was stirred at 60 °C for 22 h under H_2 from an orsat balloon. After TLC indicated complete conversion the mixture was filtrated through a pad of celite and rinsed with methanol (15 mL). After evaporation of the organic solvents under reduced pressure, the product **4c** was freeze dried at the lyophilisator. Finally the crude product was purified by semi-preparative HPLC (A: 0.01% HCOOH in H_2O, B: MeOH, rt, 16 mL/min, 0-7 min: 12% B constant, 7-9 min: 12-100% B, 9-14 min: 100% B constant. λ 254 nm. t_R 5.6 min) to yield the title compound as a colorless solid (1.6 mg, 0.006 mmol, 2%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.44 (bs, 2H, NH_2), 3.93 (s, 3H, CH_3-N), 3.53 (s, 3H, CH_3-N), 3.35 (s, 3H, CH_3-N), 2.98 (t, *J* =7.5 Hz, 2H, CH_2), 2.87 (t, *J* = 6.9 Hz, 2H, CH_2), 1.95-1.72 (m, 4H, 2x CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 156.8, 155.7, 154.0, 149.4, 101.6, 40.5, 32.4, 30.2, 28.4, 28.3, 26.8, 25.1 ppm; HPLC (Method B): t_R 6.44 min, $[M+H]^+$ 266.

***tert*-Butyl *N*-(5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl) pentyl)carbamate (4f)**

In a 50 mL Schlenk tube, heat dried under vacuum and flushed with N_2, t*ert*-butyl *N*-((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl)methyl)carbamate (**3f**) (140 mg, 0.345 mmol, 1.00 eq) was suspended in THF (5 mL). After degassing of the reaction mixture in three vacuum-N_2 cycles, aqueous Raney-Ni suspension (4 mL) was added. In three vacuum-H_2 cycles the mixture was flushed with H_2. Afterwards, the mixture was stirred at rt for 24 h under H_2 from an orsat balloon until another 1 mL of Raney-Ni suspension was added. After further 24 h stirring under H_2 atmosphere, TLC indicated

complete conversion. The mixture was filtrated through a pad of celite and rinsed with methanol (30 mL) and dichloromethane (30 mL). After concentration of the crude product **4f** under reduced pressure, it was purified by filtration through 3 cm silica gel (eluent methanol) to yield the title compound as a colorless solid (109 mg, 0.287 mmol, 83%). R_f 0.25 (dichloromethane/acetone 9:1); mp 106 °C; IR (neat): ν_{max} 3320 (w), 2931 (m), 1698 (s), 1651 (s), 1542 (m), 1441 (m), 1405 (w), 1276 (m), 1220 (m), 1169 (s), 1037 (m), 977 (m), 748 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (bs, 1H, NH), 3.91 (s, 3H, CH_3-N), 3.57 (s, 3H, CH_3-N), 3.40 (s, 3H, CH_3-N), 3.15 (q, *J* =4.5 Hz, 2H, CH_2-N), 2.73 (t, *J* =7.5 Hz, 2H, CH_2-C(sp^2)), 1.78 (p, *J* =7.2 Hz, 2H, CH_2), 1.68-1.50 (m, 4H, 2x CH_2), 1.43 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 154.3, 150.9, 147.3, 106.5, 77.3, 40.4, 31.4, 29.6, 28.5, 28.2, 27.4, 26.4, 26.1 (2xC) ppm; HPLC (Method A): t_R 5.59 min, $[M+H]^+$ 380, $[M+Na]^+$ 402, $[M+K]^+$ 418; HRMS (TOF MS EI^+): *m/z* calculated for $C_{18}H_{29}N_5O_4^+$ M^+: 379.2220, found 379.2229.

8-(5-Hydroxypentyl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (4i)

*From 8-(5-(hydroxymethyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (**3i**):*

In a 15 mL Schlenk tube, heat dried under vacuum and flushed with N_2, 8-(5-(hydroxymethyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**3i**) (35.7 mg, 0.116 mmol, 1.0 eq) was dissolved in THF (3 mL). After degassing in three vacuum-N_2 cycles, Raney-Ni suspension in water (2 mL) was added and the Schlenk tube was flushed with H_2 in three vacuum-H_2 cycles. The black suspension was stirred under H_2 from an orsat balloon at rt for 1 d until TLC indicated full consumption of the starting material **3i**. The reaction mixture was filtrated through a pad of celite and rinsed with methanol (2x30 mL) and dichloromethane (2x30 mL). After evaporation of the solvents under reduced pressure, the crude product was purified by silica gel filtration (20 g silica gel, dichloromethane) to yield the title compound as a colorless solid (12.8 mg, 0.046 mmol, 40%).

*From 8-(5-((benzyloxy)methyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (**3j**):*

In a 15 mL Schlenk tube, heat dried under vacuum and flushed with N_2, 8-(5-((benzyloxy)methyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**3j**) (119 mg, 0.30 mmol, 1.0 eq) was dissolved in THF (5 mL). After degassing in three

vacuum-N_2 cycles, Raney-Ni suspension in water (6 mL) was added and the Schlenk tube was flushed with H_2 in four vacuum-H_2 cycles. The black suspension was stirred under H_2 from an orsat balloon at rt for 3 d. Since HPLC indicated incomplete conversion, another 4 mL aqueous Raney-Ni suspension was added. After additional four vacuum-H_2 cycles the black suspension was stirred at rt for another day until full conversion could be monitored. The reaction mixture was filtrated through a pad of celite and rinsed with methanol (4x25 mL) and dichloromethane (1x30 mL). After evaporation of the solvents under reduced pressure, the crude product **4i** was purified by silica gel filtration (3 g silica gel, dichloromethane) to yield the title compound as a colorless solid (83 mg, 0.30 mmol, 99%). R_f 0.31 (dichloromethane/acetone 9:1); mp 119-120 °C; IR (neat): ν_{max} 3456 (m), 2936 (m), 1694 (s), 1655 (s), 1541 (m), 1497 (w), 1460 (s), 1411 (m), 1335 (w), 1282 (m), 1220 (m), 1049 (s), 1037 (m), 1007 (m), 978 (m), 761 (m), 746 (s) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 3.90 (s, 3H, CH_3-N), 3.56 (t, *J* =6.3 Hz, 2H, CH_2-O), 3.49 (s, 3H, CH_3-N), 3.30 (s, 3H, CH_3-N), 2.80 (t, *J* =7.5 Hz, 2H, CH_2-N), 1.85-1.71 (m, 2H, CH_2), 1.64-1.40 (m, 4H, 2x CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 156.7, 156.6, 153.3, 149.3, 108.6, 62.8, 33.4, 32.4, 30.2, 28.5, 28.3, 27.5, 26.8 ppm; HPLC (Method A): t_R 3.57 min, $[M+H]^+$ 281, $[M+Na]^+$ 303, $[M+K]^+$ 319; HRMS (TOF MS EI^+): *m/z* calculated for $C_{13}H_{20}N_4O_3^+$ M^+: 280.1535, found 280.1533.

1-Methyl-1*H*-1,3-benzodiazole (**5d**)

In a 15 mL Schlenk tube, heat dried under vacuum and flushed with N_2, benzimidazole (1.17 g, 9.91 mmol, 1.00 eq) was dissolved in dry THF (4 mL). While stirring at 0 °C, sodium hydride (60% dispersion) (608 mg, 15.21 mmol, 1.53 eq) was added carefully and the suspension was allowed to warm up to rt within 30 min. Again at 0 °C, methyl iodide (0.90 mL, 14.39 mmol, 1.45 eq) was added dropwise. After stirring the white suspension at rt for 3 h TLC indicated complete conversion. The reaction mixture was poured into ice cold water in one portion. The mixture was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine (3x50 mL), dried over Na_2SO_4, filtrated and then the solvent was removed under reduced pressure. The crude product **5d** was purified by flash chromatography (35 g silica gel, cyclohexane/ethyl acetate 3:1, 2:1, 1:1, then ethyl acetate) to yield the title compound as a beige solid (1.11 g, 8.40 mmol, 85%). R_f 0.09 (ethyl acetate); mp 50 °C (lit., [4] 57-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (bs, 1H, Ar-H), 7.80 (dd, *J* = 6.0, 1.8 Hz, 1H, Ar-H), 7.40 (dd, *J* =6.3 Hz, *J* =2.1 Hz, 1H, Ar-H), 7.36-7.28 (m, 2H, 2x Ar-H), 3.84 (s, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 143.5, 134.5, 123.0, 122.2,

120.3, 109.4, 31.1 ppm; GC-MS: t_R 5.50 min, *m/z* 132 (M^+, 100%). NMR data are consistent with the reported data.[4]

tert-Butyl _N_-((5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1_H_-purin-8-yl) thiophen-2-yl)methyl)carbamate (6a)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (1.9 mg, 0.009 mmol, 0.03 eq), copper acetate monohydrate (84.9 mg, 0.425 mmol, 1.54 eq), CuCl (5.7 mg, 0.058 mmol, 0.21 eq) and theobromine (**5a**) (49.8 mg, 0.276 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (0.8 mL). After addition of pyridine (23 µL, 0.278 mmol, 1.01 eq) the blue suspension was degassed in three vacuum-N_2 cycles. *tert*-Butyl (thiophen-2-ylmethyl)carbamate (**1f**) (178.0 mg, 0.835 mmol, 3.02 eq) was added and the reaction mixture was stirred at 120 °C for 5 d until TLC and HPLC control indicated no further conversion. The suspension was filtrated through a pad of celite and rinsed with dichloromethane (1000 mL). After evaporation of the solvent the green solid was dissolved in methanol (50 mL) from which the title compound precipitated as a pale yellow solid (71 mg, 0.181 mmol, 66%). R_f 0.27 (dichloromethane/acetone 4:1); mp 305 °C (decomposition); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (bs, 1H, NH), 7.42 (d, *J* =3.9 Hz 1H, Ar-H), 7.03 (d, *J* =3.9 Hz 1H, Ar-H), 4.99 (bs, 1H, NH), 4.52 (d, *J* =5.4 Hz, 2H, CH_2), 4.15 (s, 3H, CH_3-N), 3.56 (s, 3H, CH_3-N), 1.48 (s, 9H, 3xCH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 154.9, 150.8, 149.1, 147.9, 145.7, 129.0, 128.4, 126.0, 108.0, 78.3, 78.2, 39.5, 28.5, 28.2 ppm; HPLC (Method A): t_R 5.36 min, $[M+H]^+$ 392, $[M+Na]^+$ 414, $[M+K]^+$ 430; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{17}H_{22}N_5O_4S^+$ $[M+H]^+$: 392.1393, found 392.1423.

tert-Butyl _N_-((5-(1-methyl-1_H_-1,3-benzodiazol-2-yl)thiophen-2-yl)methyl) carbamate (6d)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, 1-methyl-benzimidazole (**5d**) (50.6 mg, 0.428 mmol, 1.00 eq), palladium acetate (3.0 mg, 0.013 mmol, 0.03 eq), copper acetate monohydrate (130.0 mg, 0.651 mmol, 1.52 eq) and CuCl (8.4 mg, 0.085 mmol, 0.20 eq) were suspended in dry 1,4-dioxane (0.8 mL) and pyridine (34 µL, 0.428 mmol, 1.00 eq). After stirring at rt for 10 min, *tert*-butyl (thiophen-2-ylmethyl)carbamate (**1f**) (271.5 mg, 1.272 mmol, 2.99 eq) was added and the blue suspension was stirred at 120 °C for 5 d. As TLC and HPLC control indicated full conversion the reaction mixture was filtrated through a pad of celite and rinsed with dichloromethane (4x20 mL). After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography (25 g

silica gel, cyclohexane/ethyl acetate 4:1 up to ethyl acetate/methanol 100:1) to yield the title compound as a yellow solid (75.0 mg, 0.219 mmol, 51%). R_f 0.38 (cyclohexane/ethyl acetate 20:1); mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.75 (m, 1H, Ar-H), 7.44 (d, *J* =3.6 Hz, 1H, Ar-H), 7.37-7.27 (m, 2H, 2x Ar-H), 7.02 (d, *J* =3.3 Hz, 1H, Ar-H), 6.96-6.92 (m, 1H, Ar-H), 5.10 (bs, 1H, NH), 4.59 (d, *J* =5.4 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3-N), 1.47 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.1, 144.0, 141.5, 136.3, 131.6, 128.8, 126.4, 126.4, 124.0, 121.0, 109.8, 79.0, 40.0, 31.8, 28.8 ppm; HPLC (Method A): t_R 5.93 min, $[M+H]^+$ 344, $[M+Na]^+$ 366, $[M+K]^+$ 382; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{18}H_{22}N_3O_2S^+$ $[M+H]^+$: 344.1433, found 344.1417.

tert-Butyl _N_-((5-(1,3-benzoxazol-2-yl)thiophen-2-yl)methyl)carbamate (6e)

In a 10 mL Schlenk tube, heat dried under vacuum and flushed with N_2, copper acetate monohydrate (77.8 mg, 0.389 mmol, 1.51 eq), palladium acetate (1.5 mg, 0.006 mmol, 0.03 eq), benzoxazole (**5e**) (29.5 mg, 0.258 mmol, 1.00 eq), CuCl (5.3 mg, 0.052 mmol, 0.20 eq) and dry pyridine (21 µL, 0.257 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (0.45 mL). This suspension was stirred at rt for 10 min until *tert*-butyl (thiophen-2-ylmethyl)carbamate (**1f**) (167 mg, 0.783 mmol, 3.02 eq) was added. The blue suspension was stirred at 120 °C for 6 d until HPLC control indicated no further conversion. The reaction mixture was allowed to cool down to rt. Subsequently, it was diluted with 15 mL methanol, filtrated through a pad of celite and rinsed with methanol (2x40 mL) and acetonitrile (2x5 mL). After evaporation of the solvents under reduced pressure, the green residue was purified by flash chromatography (7 g silica gel, cyclohexane/ethyl acetate 4:1) to yield the title compound as a pale yellow solid (5 mg, 0.015 mmol, 6%). R_f 0.28 (cyclohexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.70 (m, 2H, 2x Ar-H), 7.56-7.51 (m, 1H, Ar-H) 7.36-7.31 (m, 2H, 2x Ar-H), 7.02 (d, *J* =3.6 Hz, 1H, Ar-H), 5.01 (bs, 1H, NH), 4.54 (d, *J* =5.7 Hz , CH_2-N), 1.48 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 149.8, 149.7, 141.3 (2xC), 129.6, 126.8, 125.7, 124.8, 124.4, 119.0, 110.2, 78.7, 39.5, 28.0 ppm; HPLC (Method A): t_R 7.94 min, $[M+H]^+$ 331, $[M+Na]^+$ 353, $[M+K]^+$ 369.

2-(5-(((_tert_-Butoxycarbonyl)amino)methyl)thiophen-2-yl)-4-phenylpyridine 1-oxide (6f)

In a 15 mL Schlenk tube, heat dried under vacuum and flushed with N_2, palladium acetate (1.6 mg, 0.007 mmol, 0.03 eq), copper acetate monohydrate (88.0 mg, 0.440 mmol, 1.50 eq) and 4-phenylpyridine 1-oxide (**5f**) (50.2 mg, 0.293 mmol, 1.00 eq) were suspended in dry 1,4-dioxane (0.45 mL). After addition of pyridine (23 µL, 0.292 mmol, 1.00 eq) the green

suspension was degassed in three vacuum-N_2 cycles. *tert*-Butyl (thiophen-2-ylmethyl) carbamate (**1f**) (187.3 mg, 0.878 mmol, 3.00 eq) was added and the reaction mixture was stirred at 120 °C for 2 d until TLC and HPLC control indicated no further conversion. The suspension was filtrated through a pad of celite and rinsed with methanol (4x25 mL). After evaporation of the solvent under reduced pressure the green solid was purified by flash chromatography (25 g silica gel, cyclohexane/ethyl acetate 3:1 up to ethyl acetate, then methanol) to yield the title compound as a brown solid (58 mg, 0.152 mmol, 51%). R_f 0.67 (ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD): δ 8.38 (bs, 2H, 2xAr-H), 8.10 (d, *J* =3.9 Hz, 1H, Ar-H), 7.84-7.70 (m, 3H, 3x Ar-H), 7.60-7.40 (m, 4H, 4x Ar-H), 7.13 (d, *J* =3.9 Hz, 1H, Ar-H), 4.47 (s, 2H, CH_2-N), 1.47 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 150.8, 144.6, 142.7, 140.7, 140.6, 137.6, 130.6 (2xC), 130.5 (2xC), 128.1, 128.0 (2xC), 127.9, 125.8, 80.6, 40.2, 28.9 ppm; HPLC (Method A): t_R 6.95 min, $[M+H]^+$ 383, $[M+Na]^+$ 405, $[M+K]^+$ 421.

***tert*-Butyl *N*-(5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentyl) carbamate (7a)**

In a 50 mL Schlenk tube, heat dried under vacuum and flushed with N_2, t*ert*-butyl *N*-((5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl)methyl)carbamate (**6a**) (105 mg, 0.268 mmol, 1.00 eq) was suspended in THF (5 mL). After degassing of the reaction mixture in three vacuum-N_2 cycles, aqueous Raney-Ni suspension (8 mL) was added. In four vacuum-H_2 cycles the mixture was flushed with H_2. Afterwards, the mixture was stirred at rt for 24 h under H_2 from an orsat balloon until HPLC indicated complete conversion. The mixture was filtrated through a pad of celite and rinsed with methanol (120 mL) and dichloromethane (30 mL). The product **7a** was concentrated under reduced pressure and lyophilized to dryness to yield the title compound as a colorless solid (55 mg, 0.151 mmol, 56%). R_f 0.53 (dichloromethane/acetone 4:1); mp 156-158 °C; IR (neat): ν_{max} 3420 (w), 2971 (w), 1685 (s), 1550 (w), 1511 (m), 1441 (s), 1426 (s), 1406 (s), 1365 (m), 1161 (s), 751 (m), 621 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.98 (bs, 1H, NH), 6.78 (bs, 1H, NH), 3.80 (s, 3H, CH_3-N), 3.31 (s, 3H, CH_3-N), 2.90 (q, *J* =6.0 Hz, 2H, CH_2-N), 2.70 (t, *J* =7.5 Hz, 2H, CH_2-C(sp^2)), 1.70-1.50 (m, 4H, 2x CH_2), 1.45-1.37 (m, 2H, CH_2), 1.36 (s, 9H, ^{t}Bu) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.6, 155.3, 154.0, 148.9, 106.9, 77.3, 37.8, 31.2, 28.9, 28.4, 28.2, 26.4, 25.8, 25.8 ppm; HPLC (Method A): t_R 5.00 min, $[M+H]^+$ 366, $[M+Na]^+$ 388, $[M+K]^+$ 404; HRMS (EI^+): *m/z* calculated for $C_{17}H_{27}N_5O_4^+$ $[M]^+$: 365.2063, found 365.2065.

5-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentan-1-aminium trifluoroacetate (8a)

A 25 mL round-bottom flask with magnetic stirring bar was charged with *tert*-butyl *N*-(5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentyl) carbamate (**7a**) (11.0 mg, 0.030 mmol, 1 eq). After addition of TFA (150 µL, 1.505 mmol, 50 eq), the yellow solution was stirred at rt for 1 h. When TLC and HPLC indicated complete conversion, the product **8a** was concentrated under N_2-flow and dried under high vacuum to yield the title compound as a colorless solid (11.4 mg, 0.030 mmol, quantitative). Mp 149-150 °C; IR (neat): ν_{max} 2360 (w), 1373 (s), 1431 (w), 1177 (s), 1128 (s), 839 (m), 800 (m), 723 (m), 677 (w), 638 (w), 617 (w) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 3.90 (s, 3H, CH_3-N), 3.46 (s, 3H, CH_3-N), 2.95 (t, *J* =7.5 Hz, 2H, CH_2-N), 2.82 (t, *J* =7.5 Hz, 2H, CH_2-C(sp^2)), 1.90-1.65 (m, 4H, 2x CH_2), 1.55-1.45 (m, 2H, CH_2) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ 161.2, 156.5, 153.2, 151.0, 115.6, 109.1, 40.7, 32.4, 29.3, 28.4, 27.9, 27.1, 27.1 ppm; HPLC (Method A): t_R 2.25 min, $[M+H]^+$ 266, $[M+Na]^+$ 288, $[M+K]^+$ 304; HRMS (TOF MS LD$^+$): *m/z* calculated for $C_{12}H_{20}N_5O_2^+$ $[M+H]^+$: 266.1617, found 266.1610.

References

1 J. E. Klare, I. P. Murray, J. Goldberger and S. I. Stupp, *Chem. Commun.* 2009, 3705.

2 R. N. Salvatore, F. Chu, A. S. Nagle, E. A. Kapxhiu, R. M. Cross and K. W. Jung, *Tetrahedron* 2002, **58**, 3329.

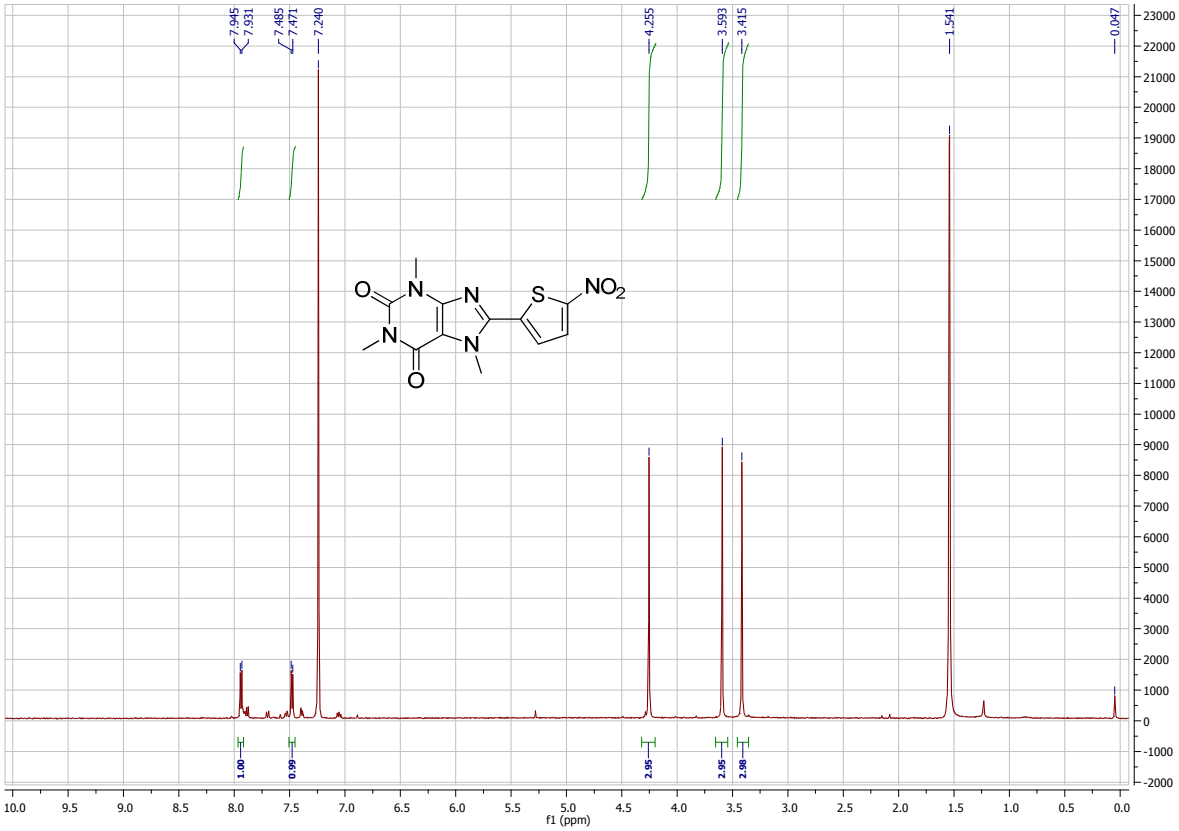
3 B. Trost and C. Muller, *J. Am. Chem. Soc.* 2008, **130**, 2438.

4 J. Bergman and P. Sand, *Tetrahedron Lett.* 1984, **25**, 1957.

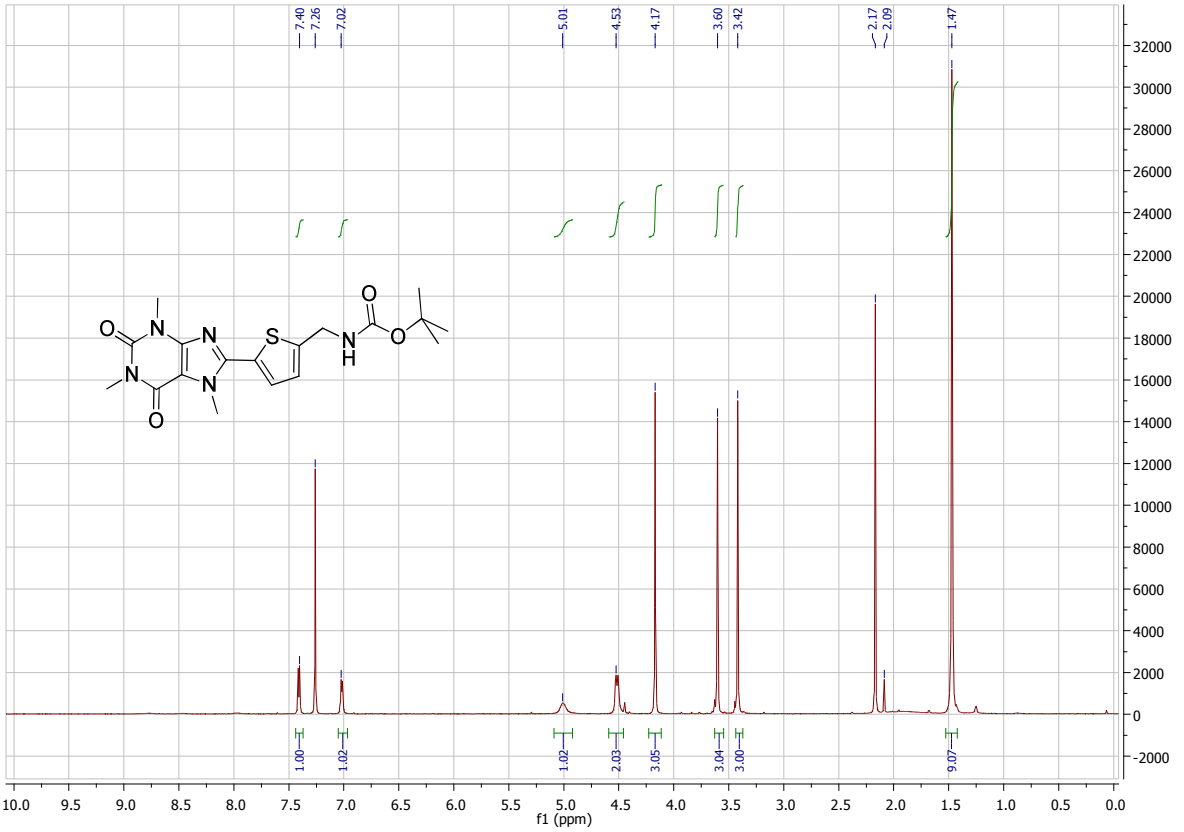
5 P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.* 2010, **132**, 1822.

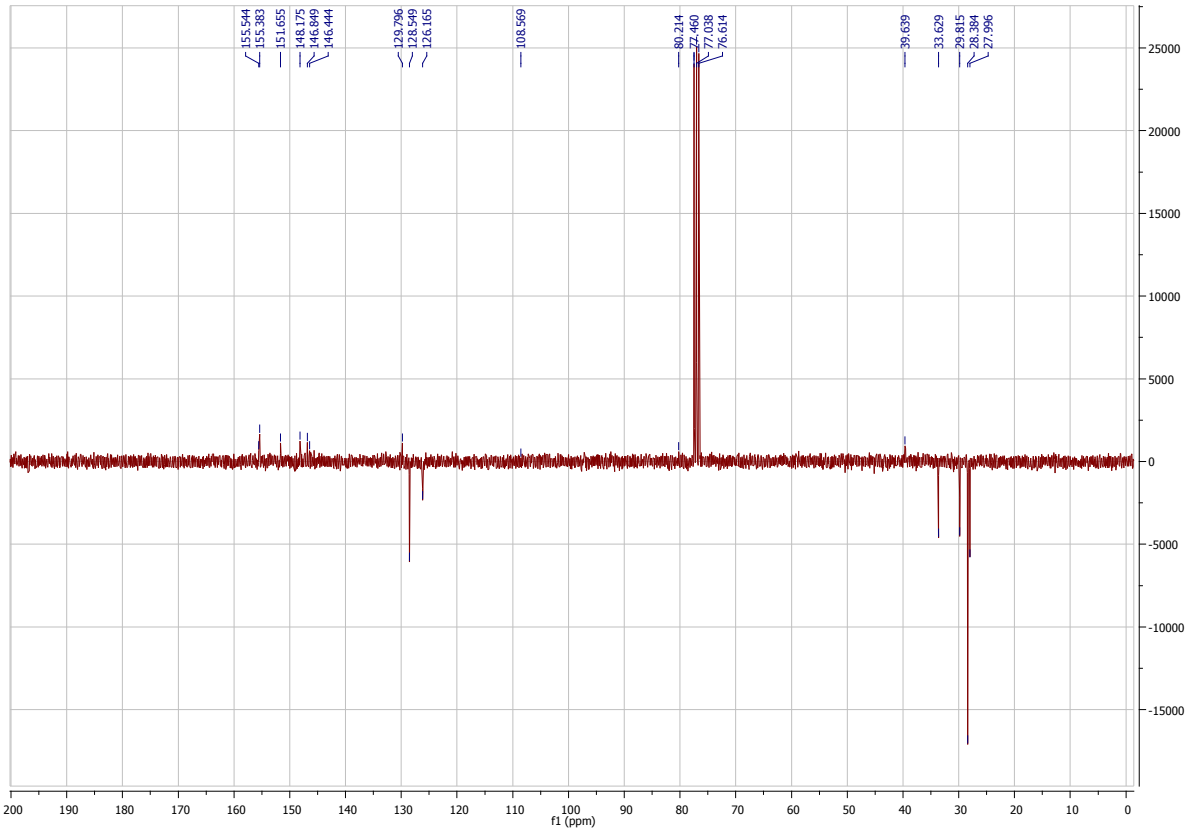
^{1}H and ^{13}C NMR spectra

1,3,7-Trimethyl-8-(5-nitrothiophen-2-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione **3c**

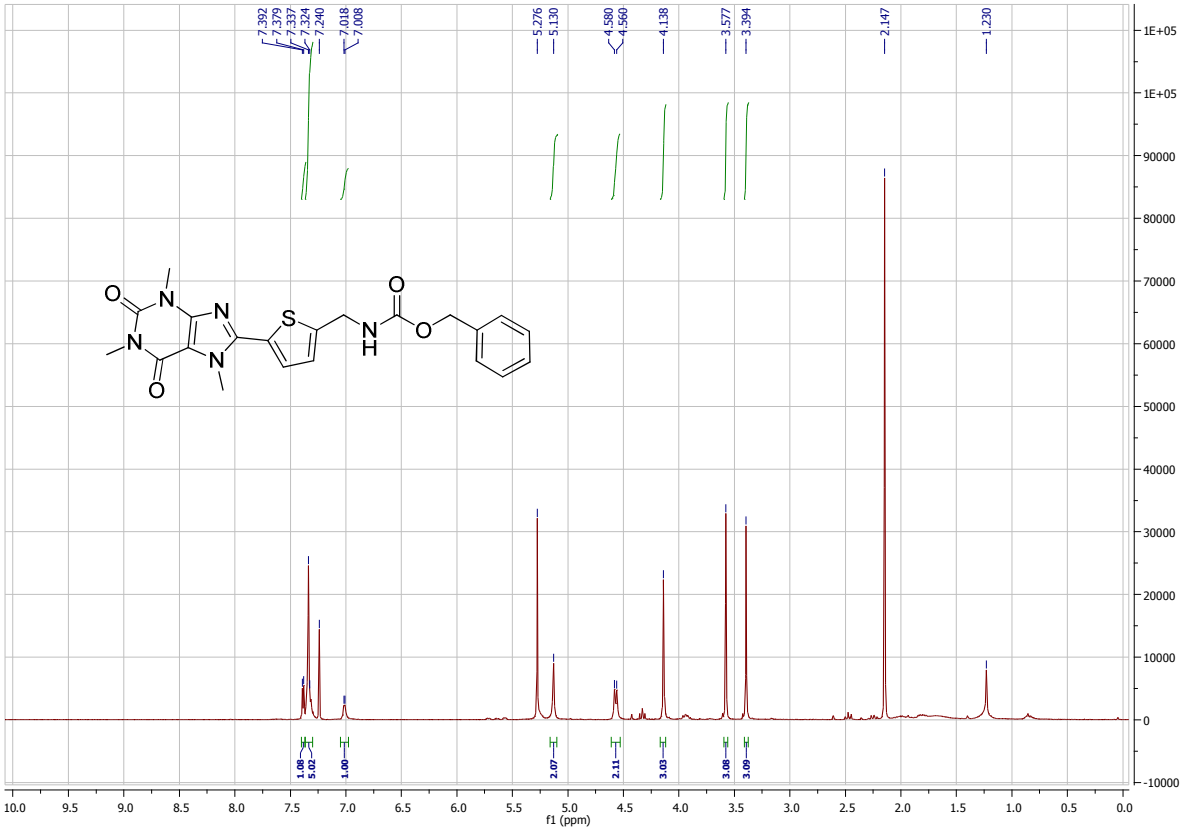


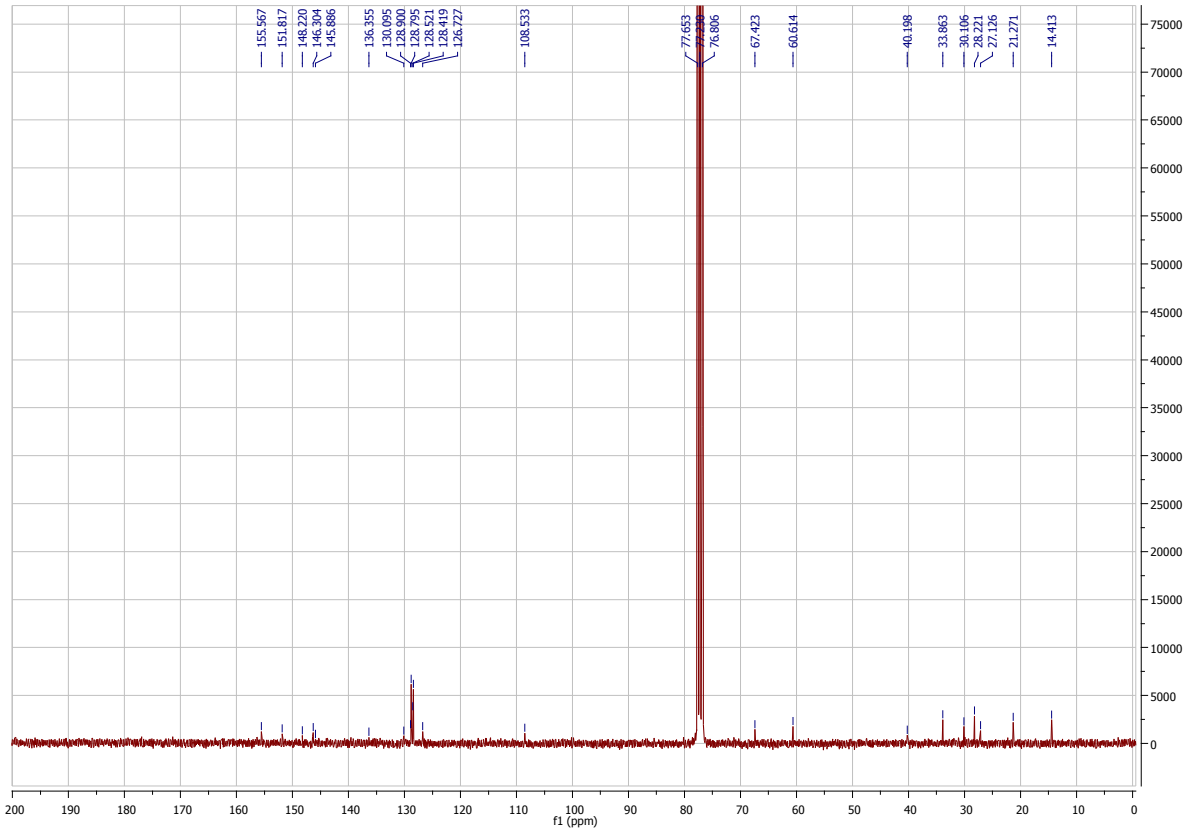
Tert-butyl ((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl) methyl)carbamate (**3f**)



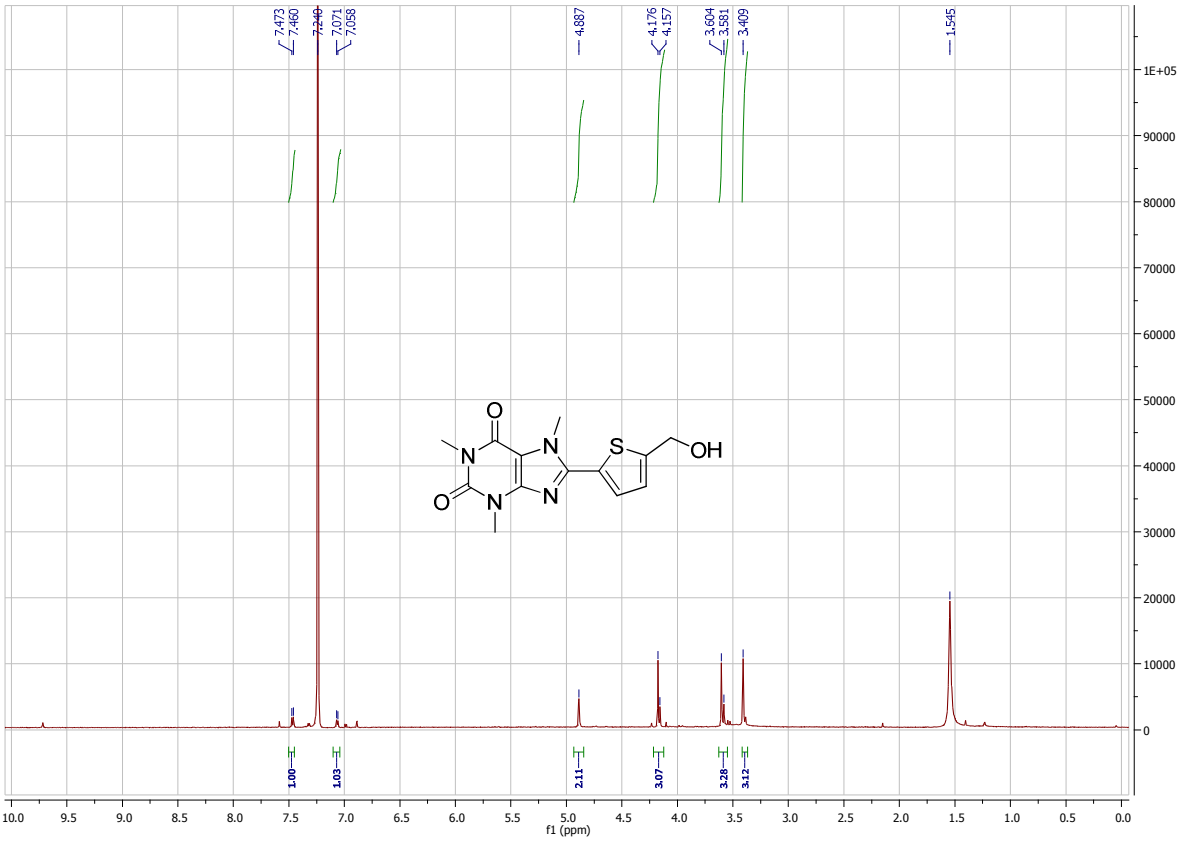


Benzyl ((5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl) methyl)carbamate (**3g**)

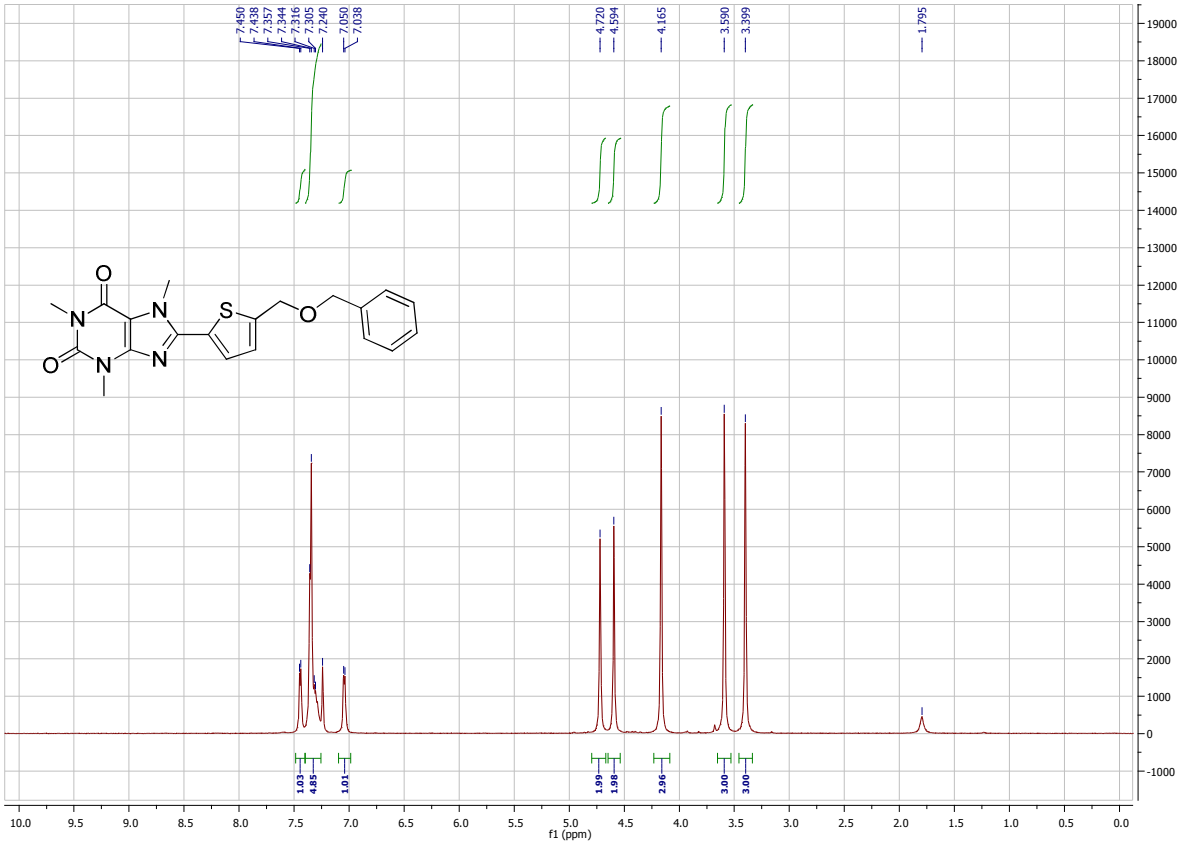


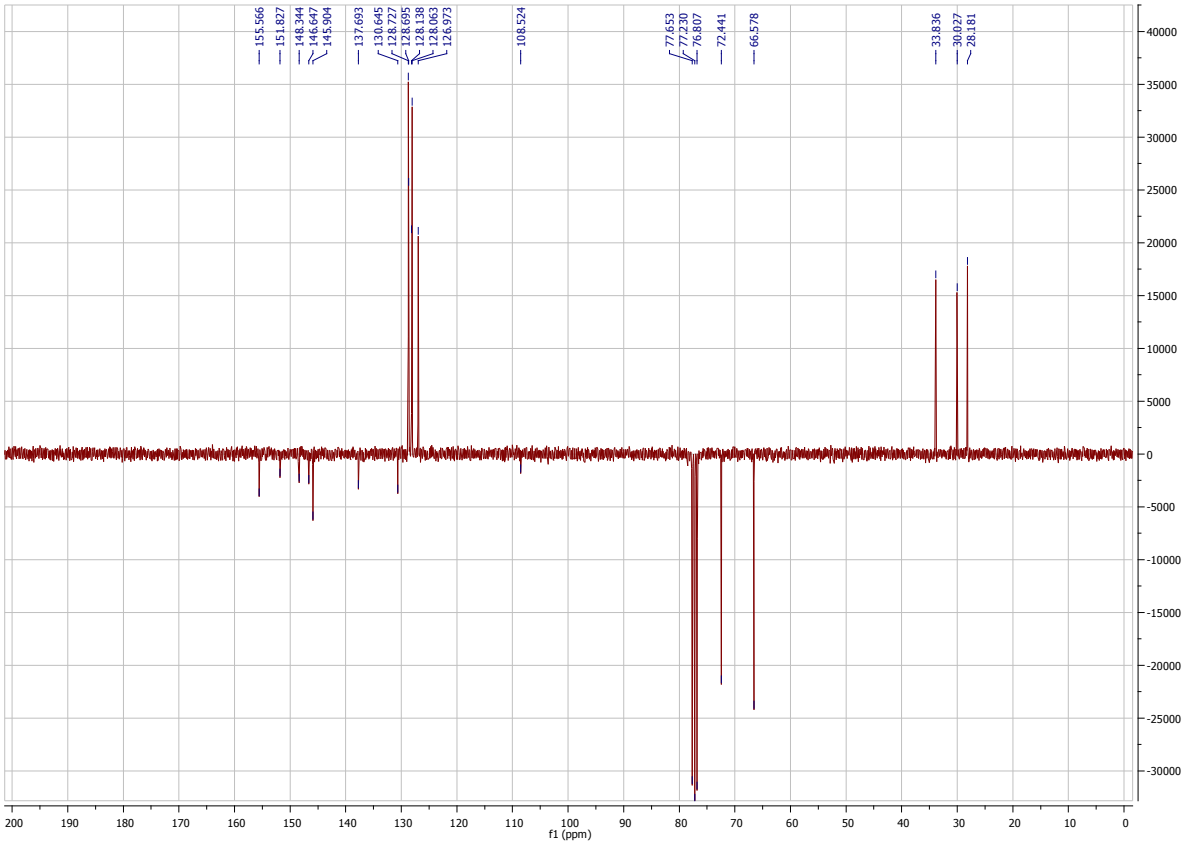


8-(5-(Hydroxymethyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**3i**)

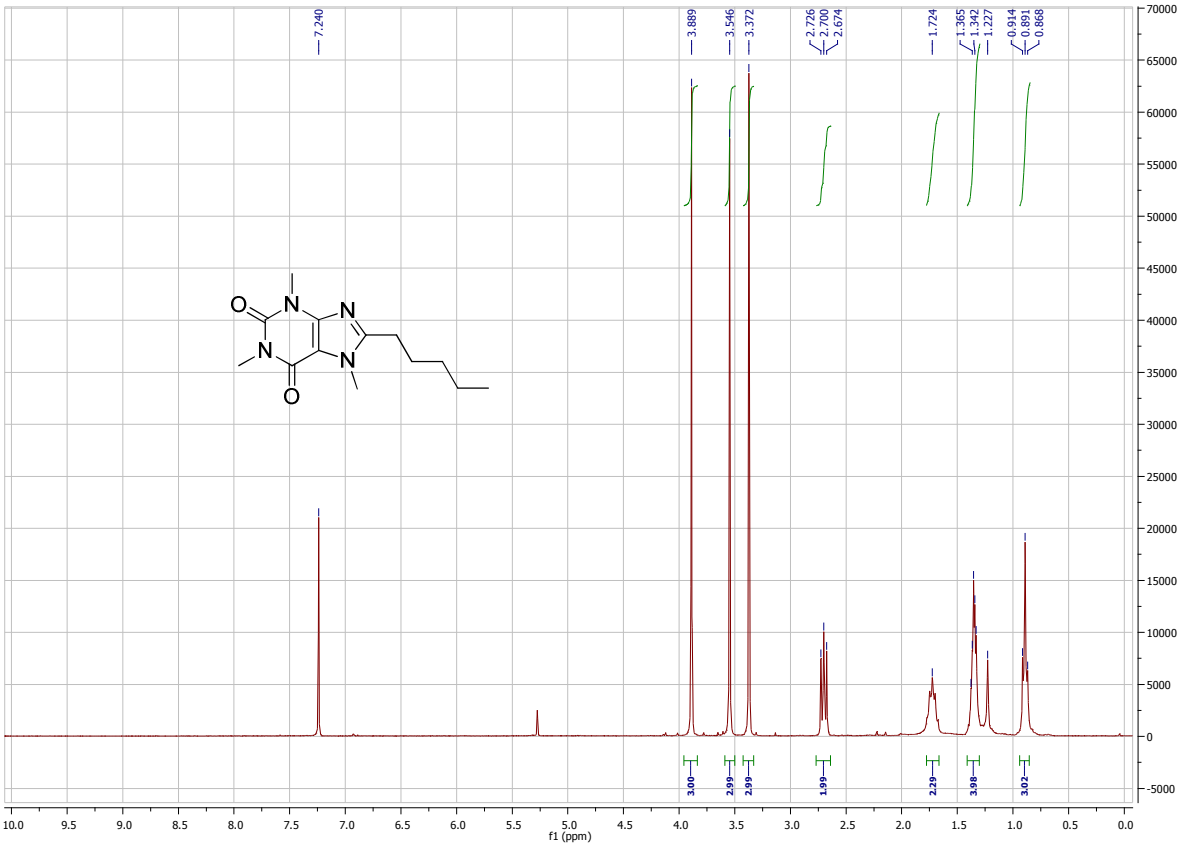


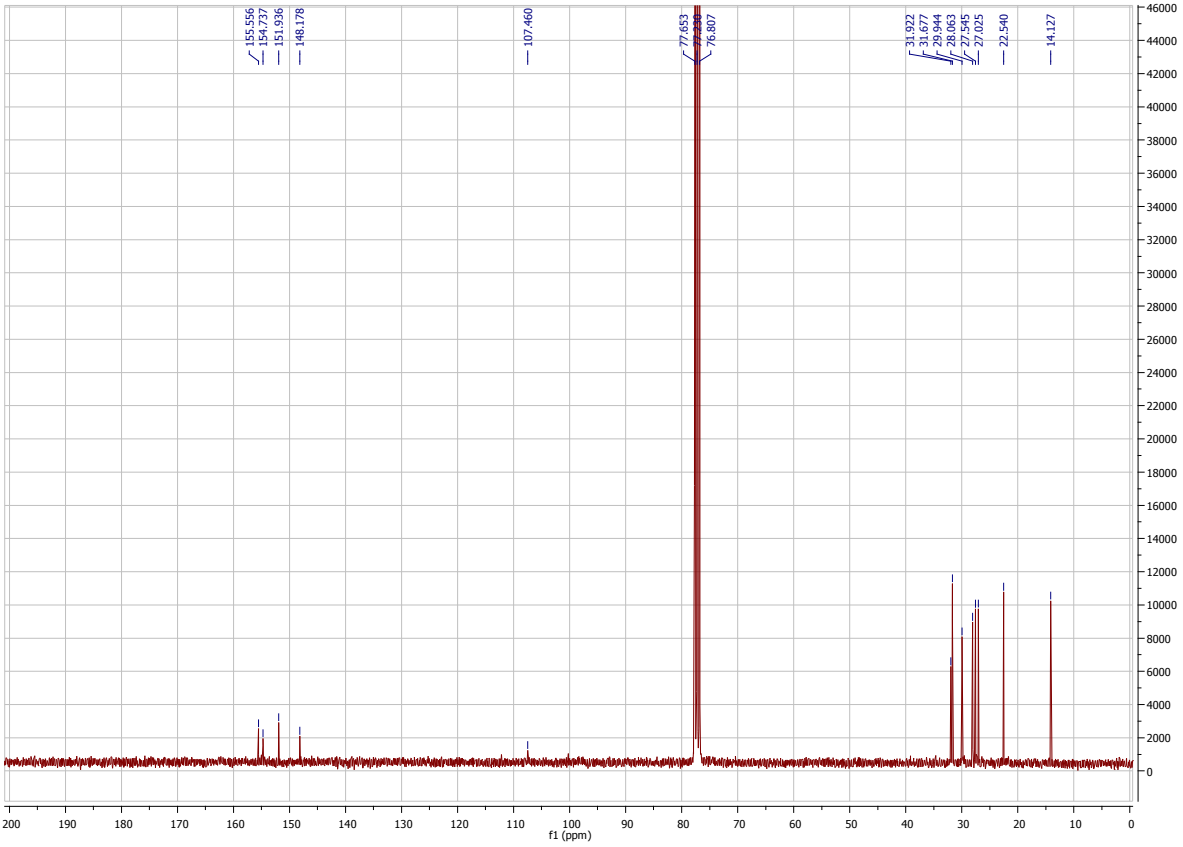
8-(5-((Benzyloxy)methyl)thiophen-2-yl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**3j**)



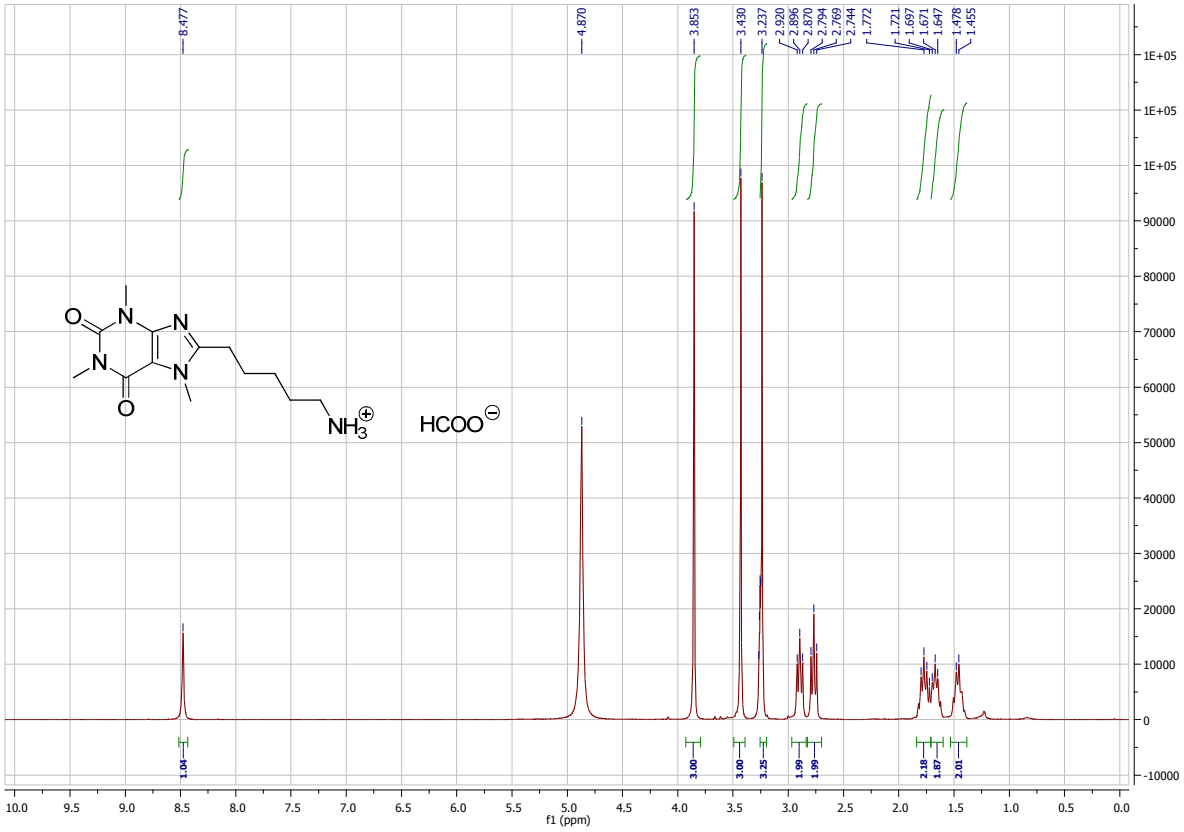


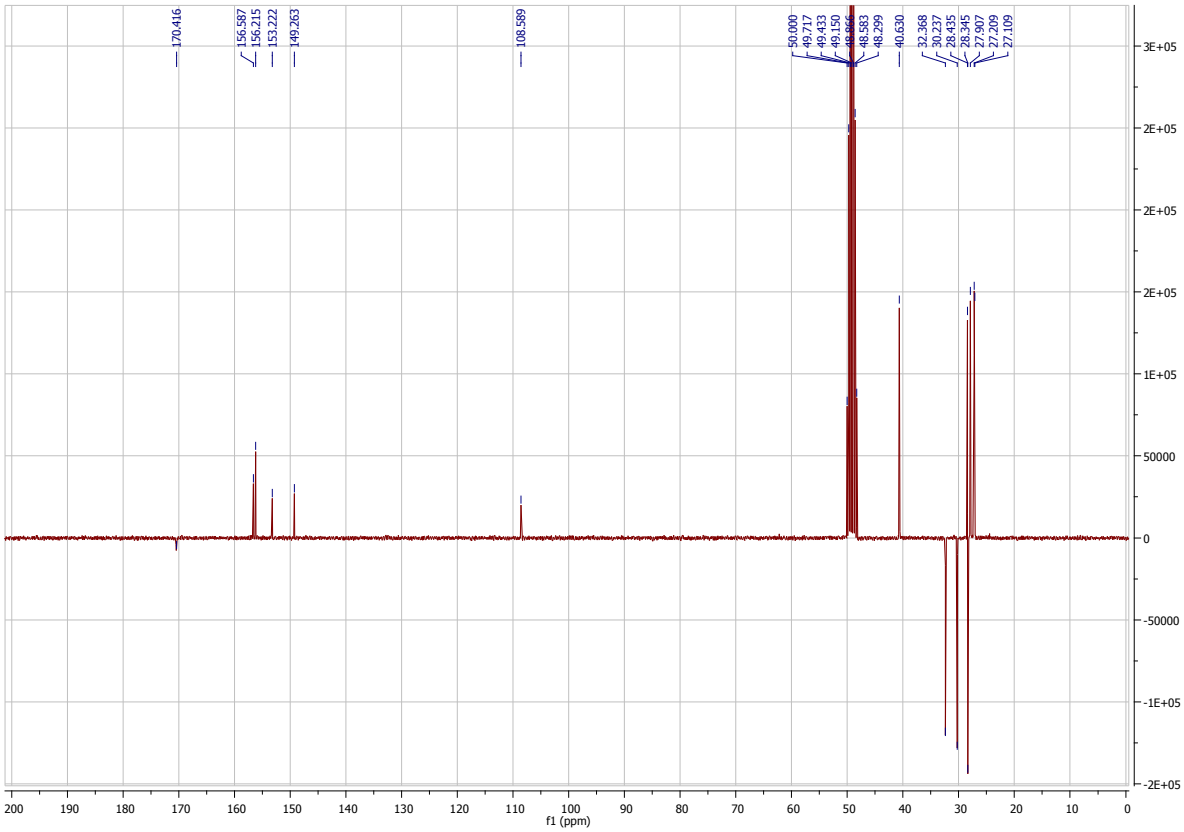
1,3,7-Trimethyl-8-(5-methylthiophen-2-yl)-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**4a**)



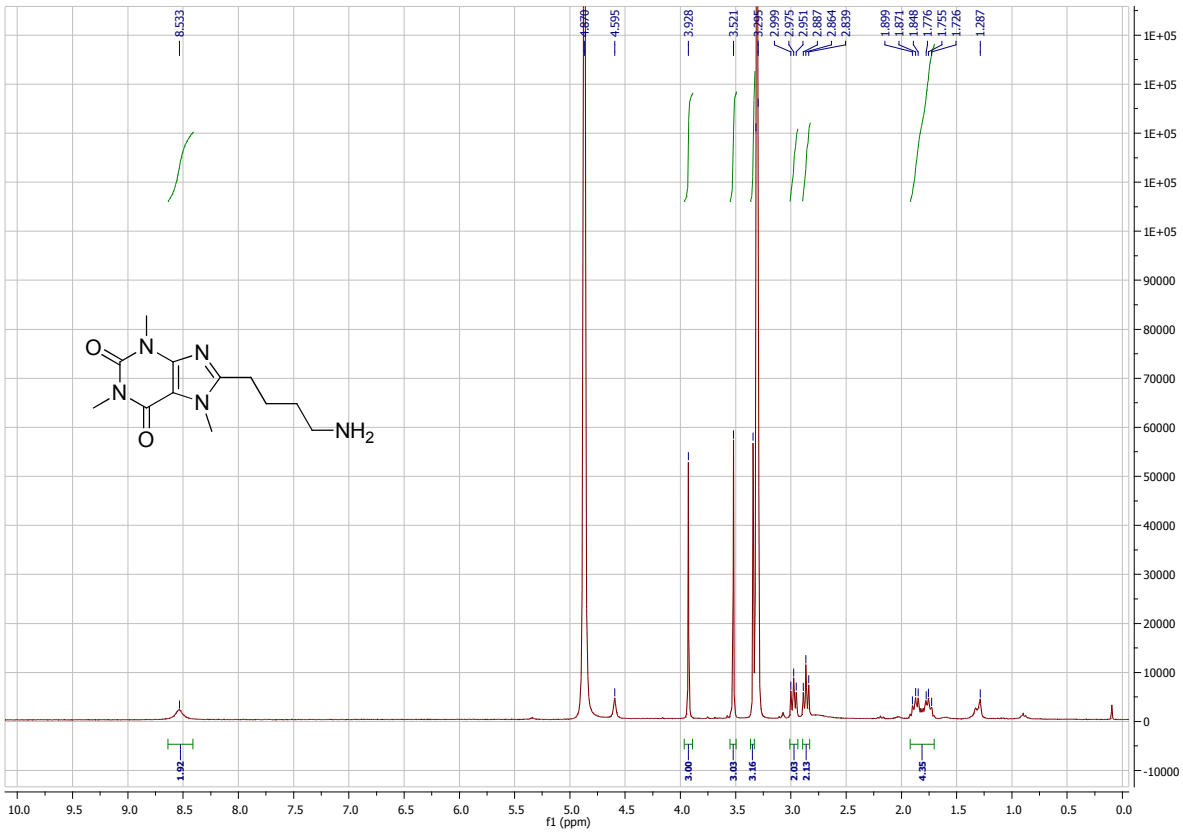


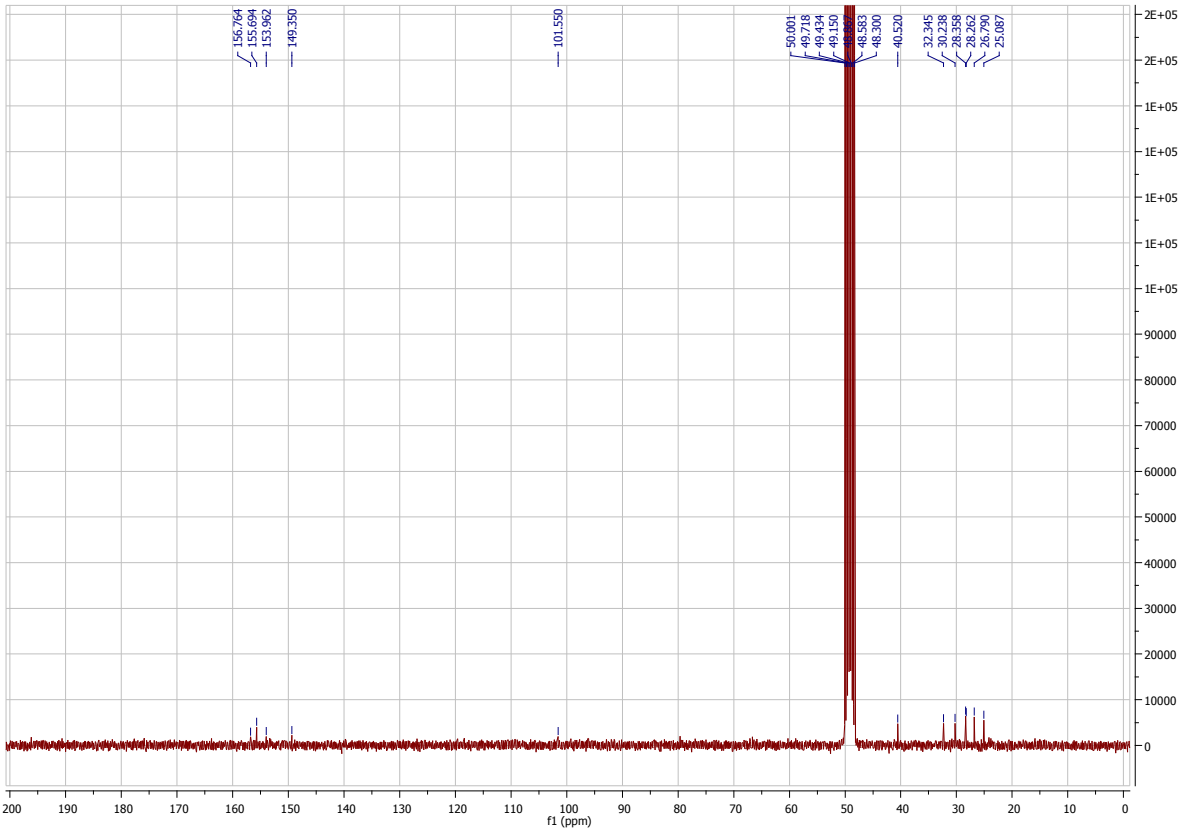
5-(1,3,7-Trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentan-1-aminium formate (**4b**)



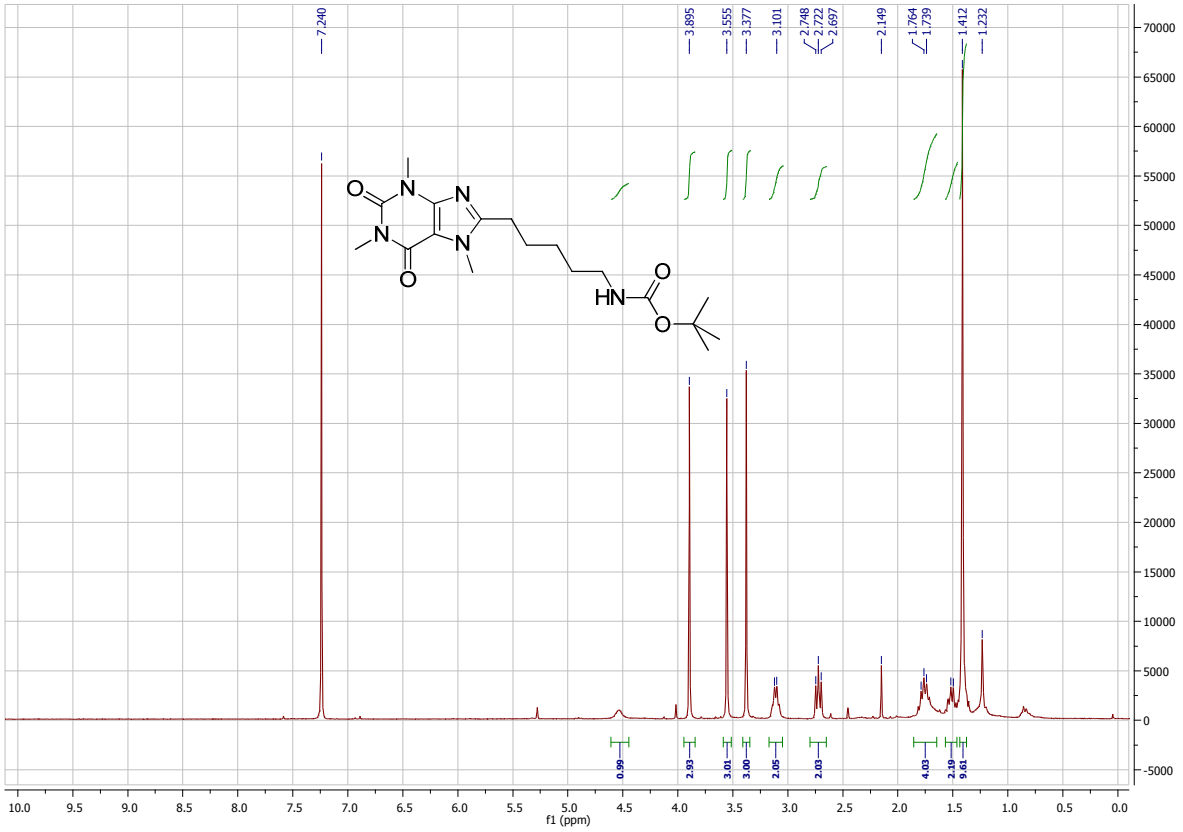


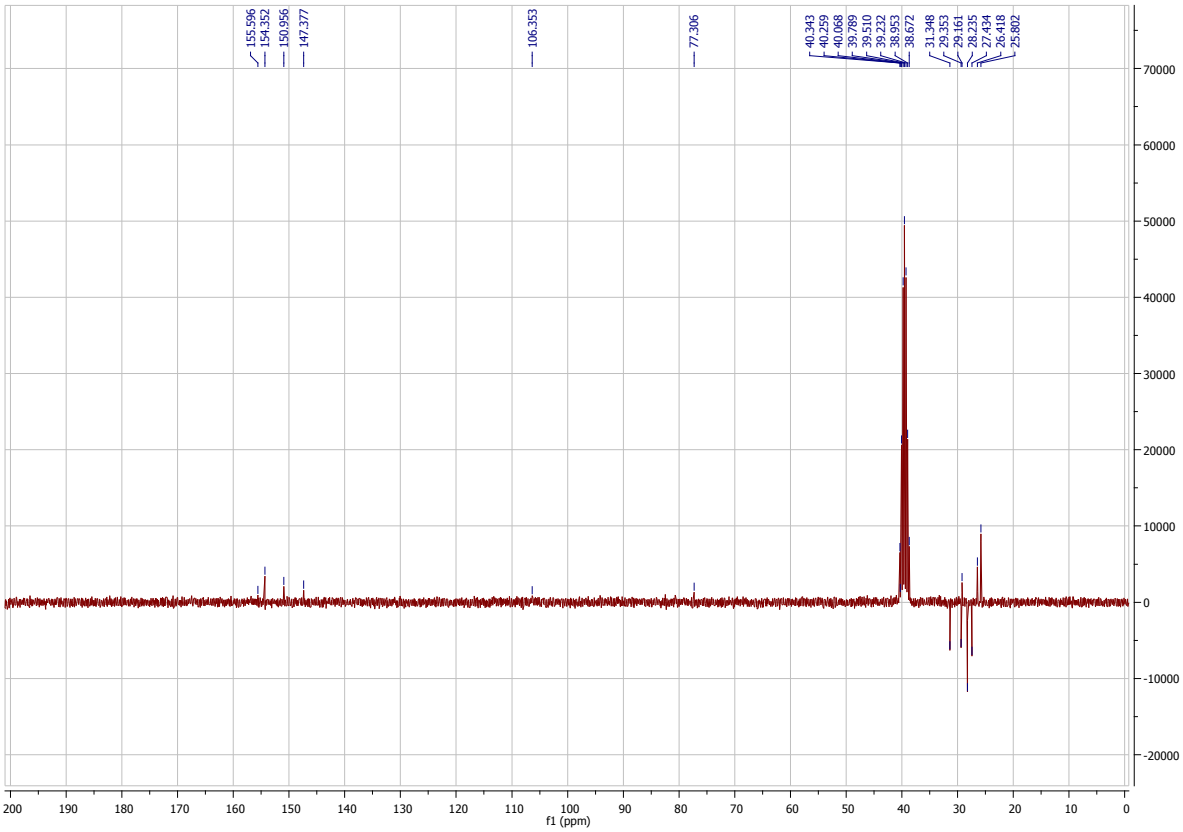
8-(4-Aminobutyl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**4c**)



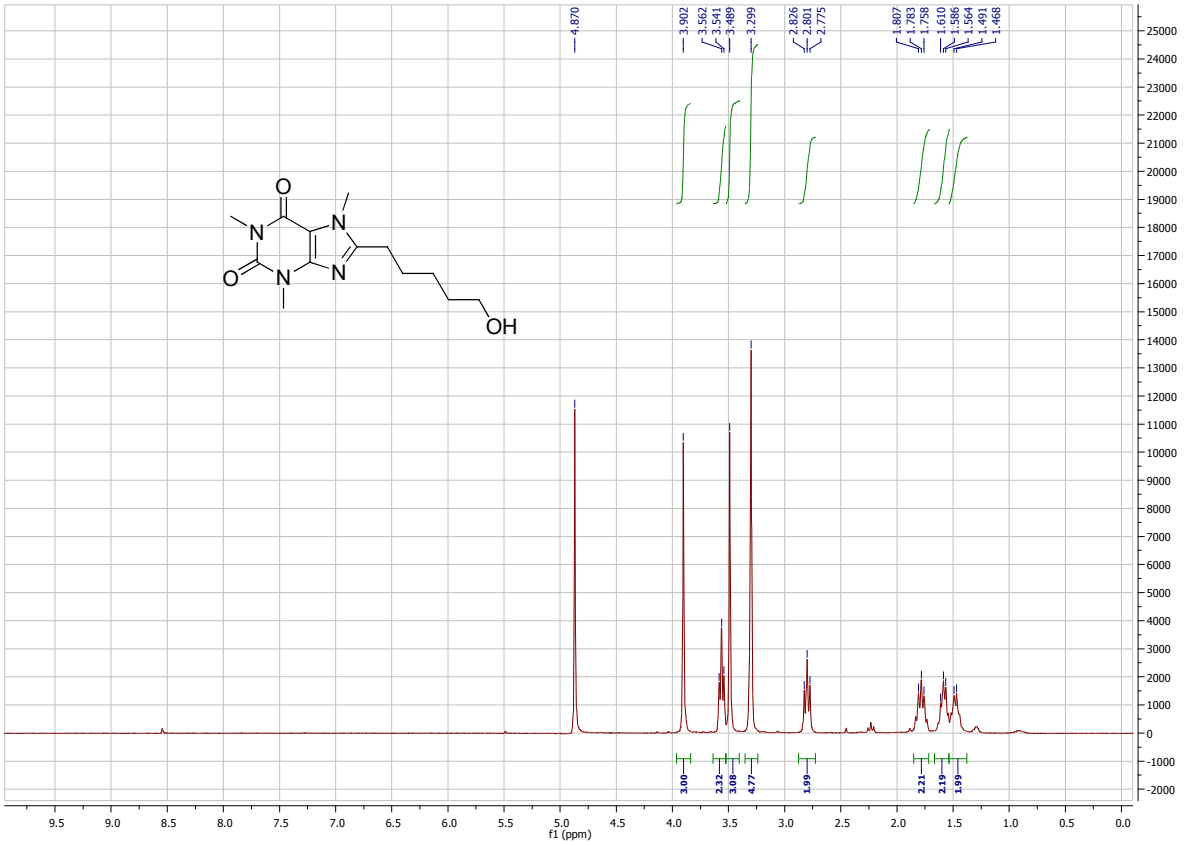


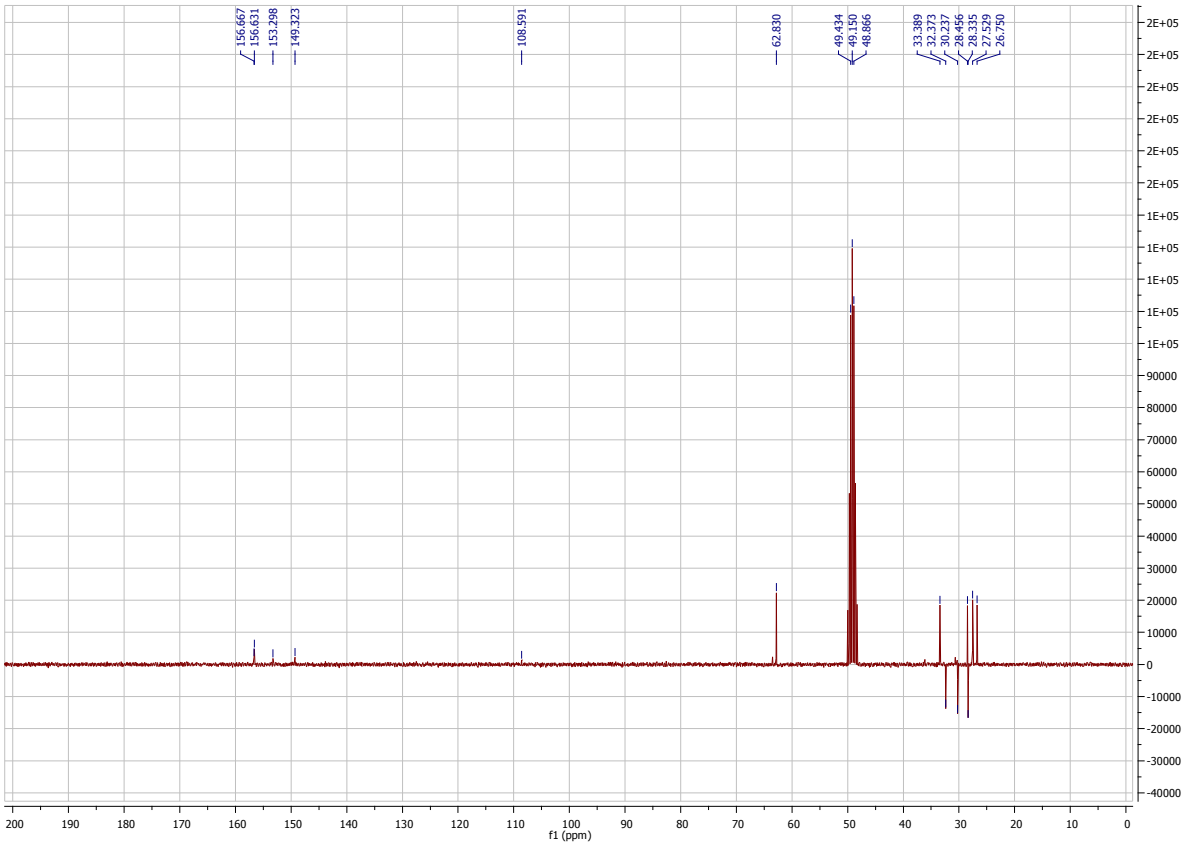
Tert-butyl *N*-(5-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentyl) carbamate (**4f**)



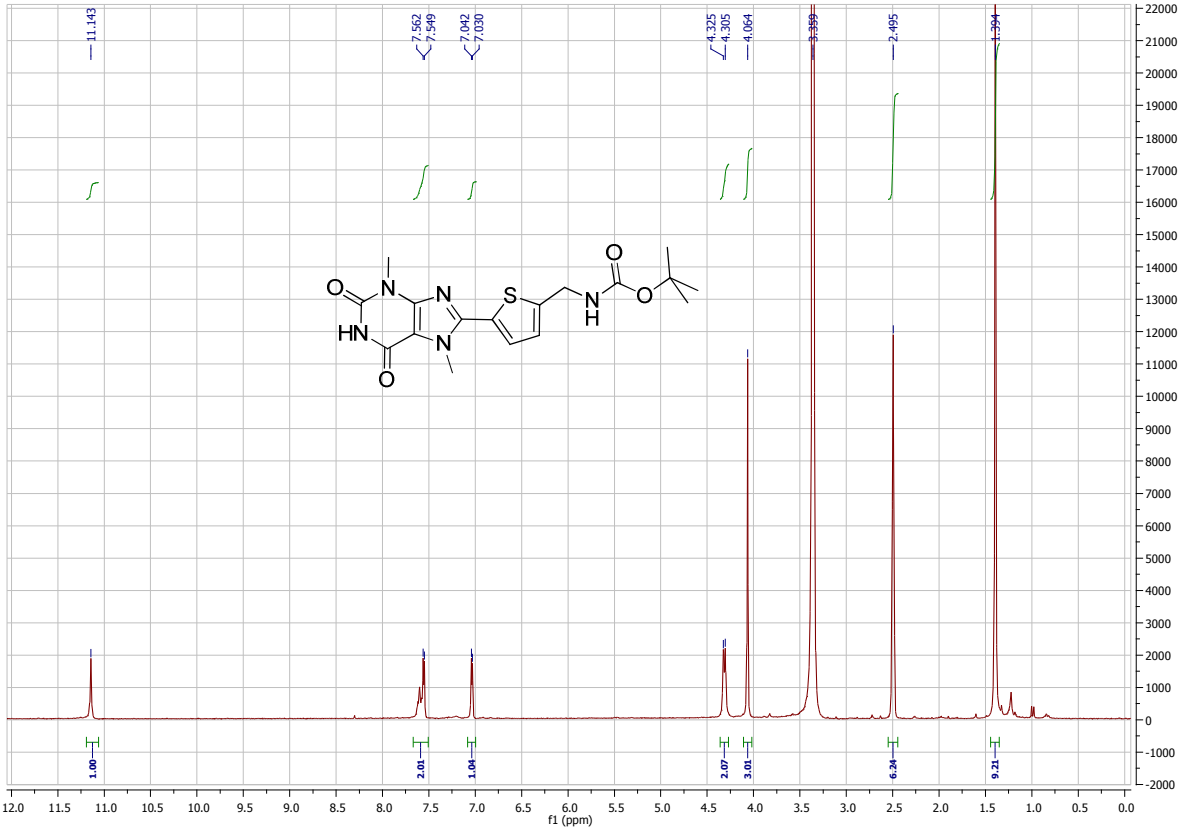


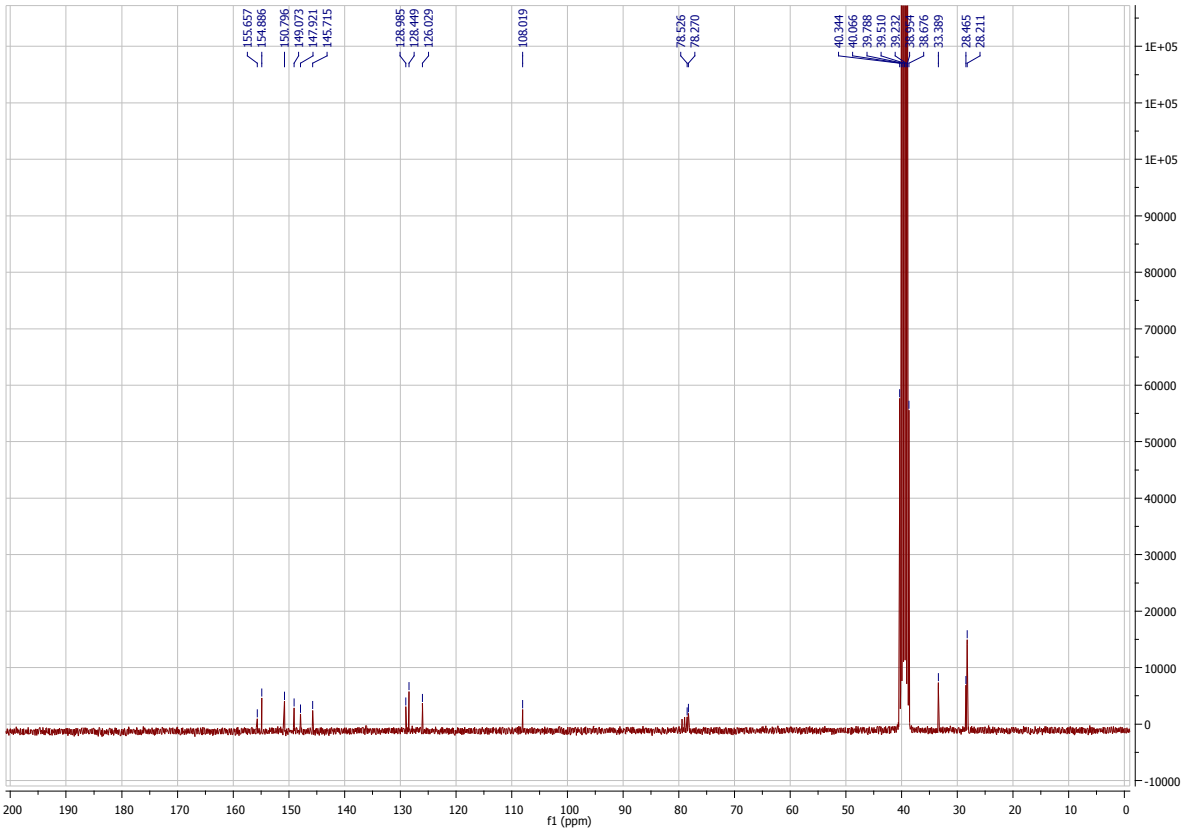
8-(5-Hydroxypentyl)-1,3,7-trimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (**4i**)



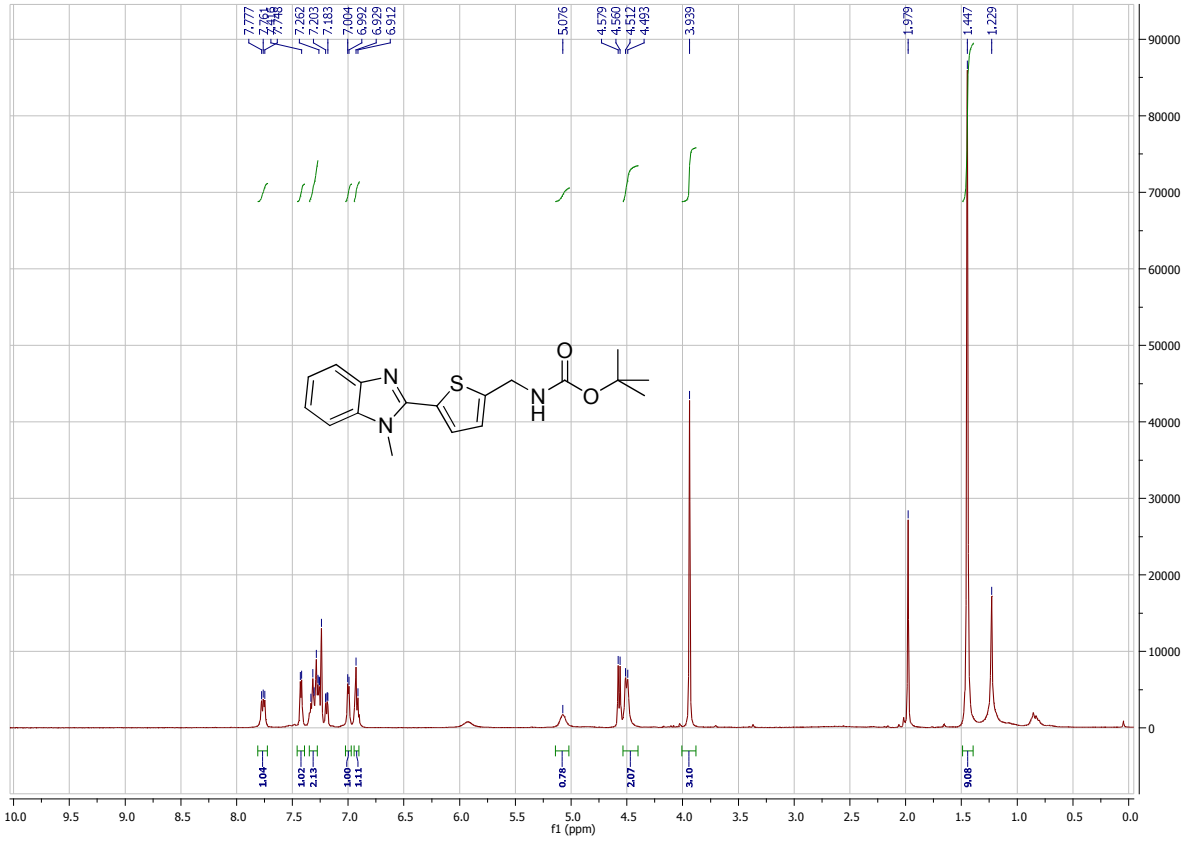


Tert-butyl *N*-((5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thiophen-2-yl)methyl)carbamate (**6a**)

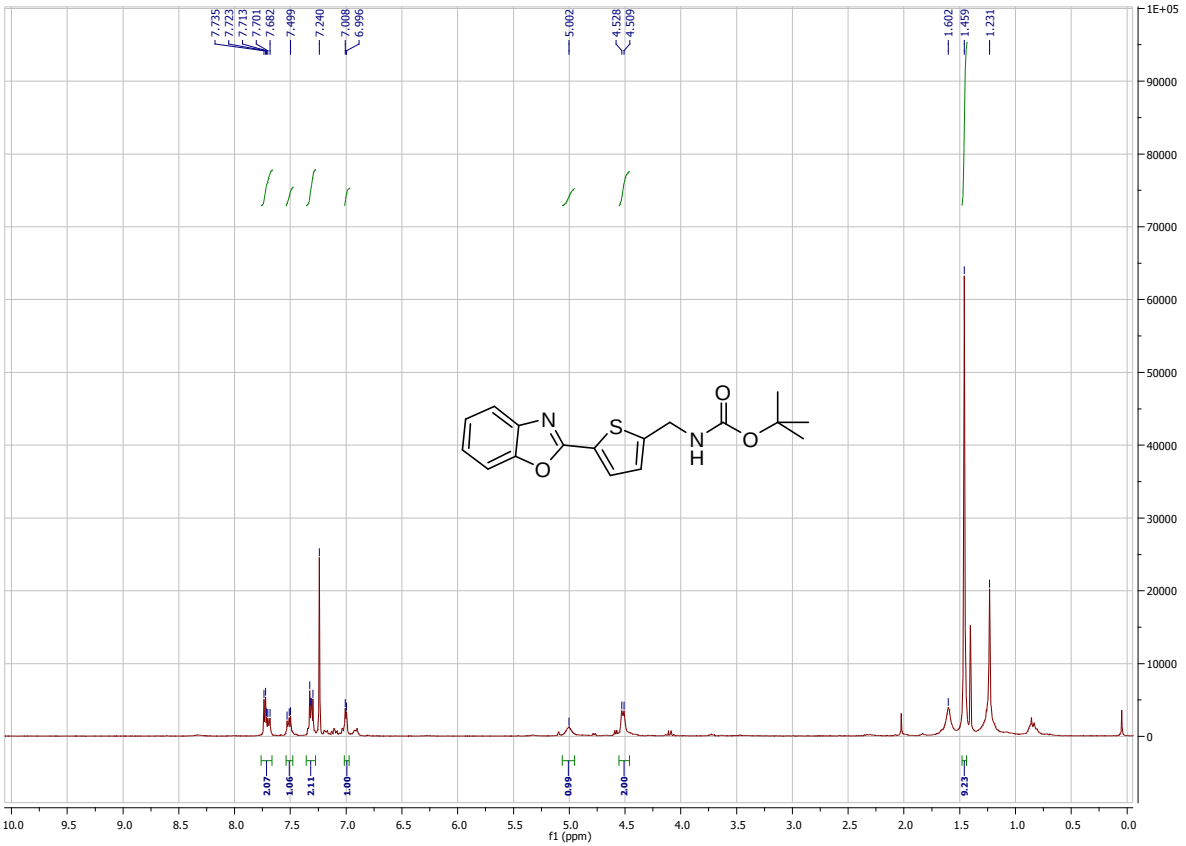


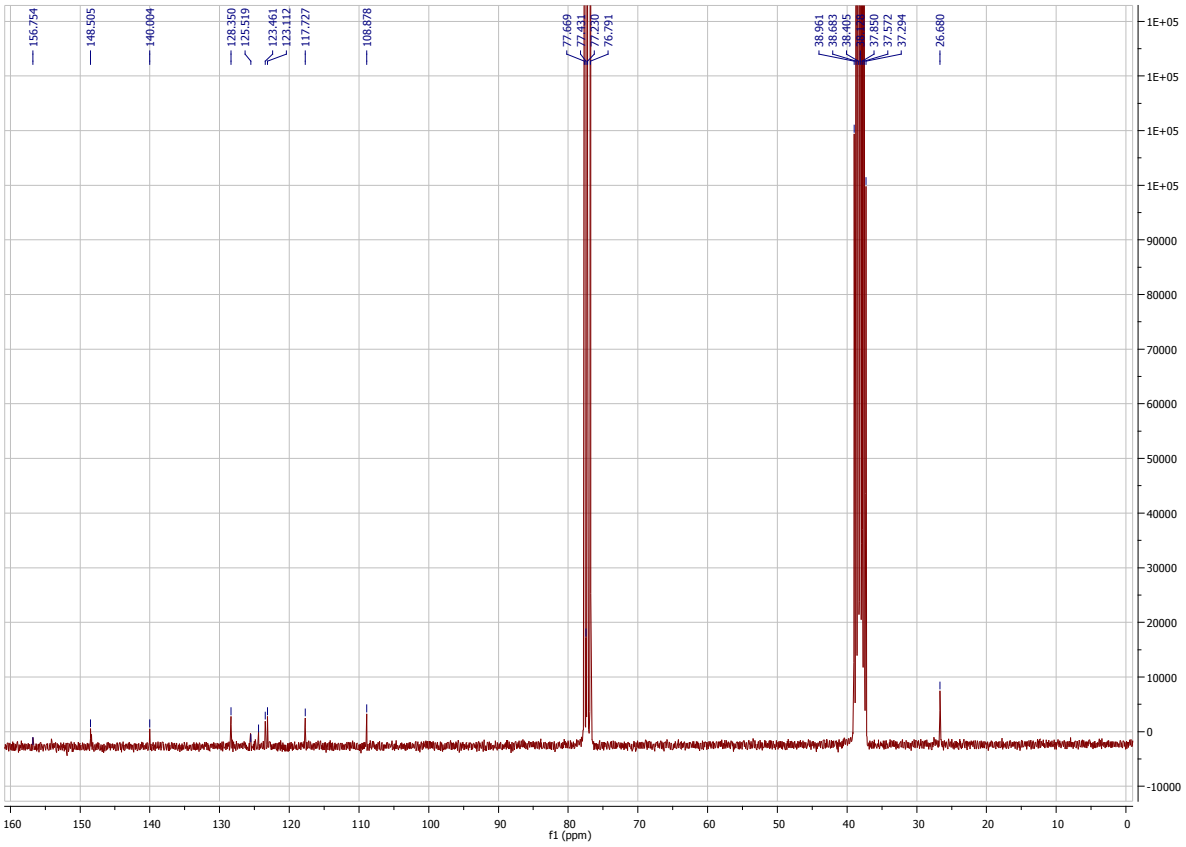


Tert-butyl *N*-((5-(1-methyl-1*H*-1,3-benzodiazol-2-yl)thiophen-2-yl)methyl)carbamate (**6d**)

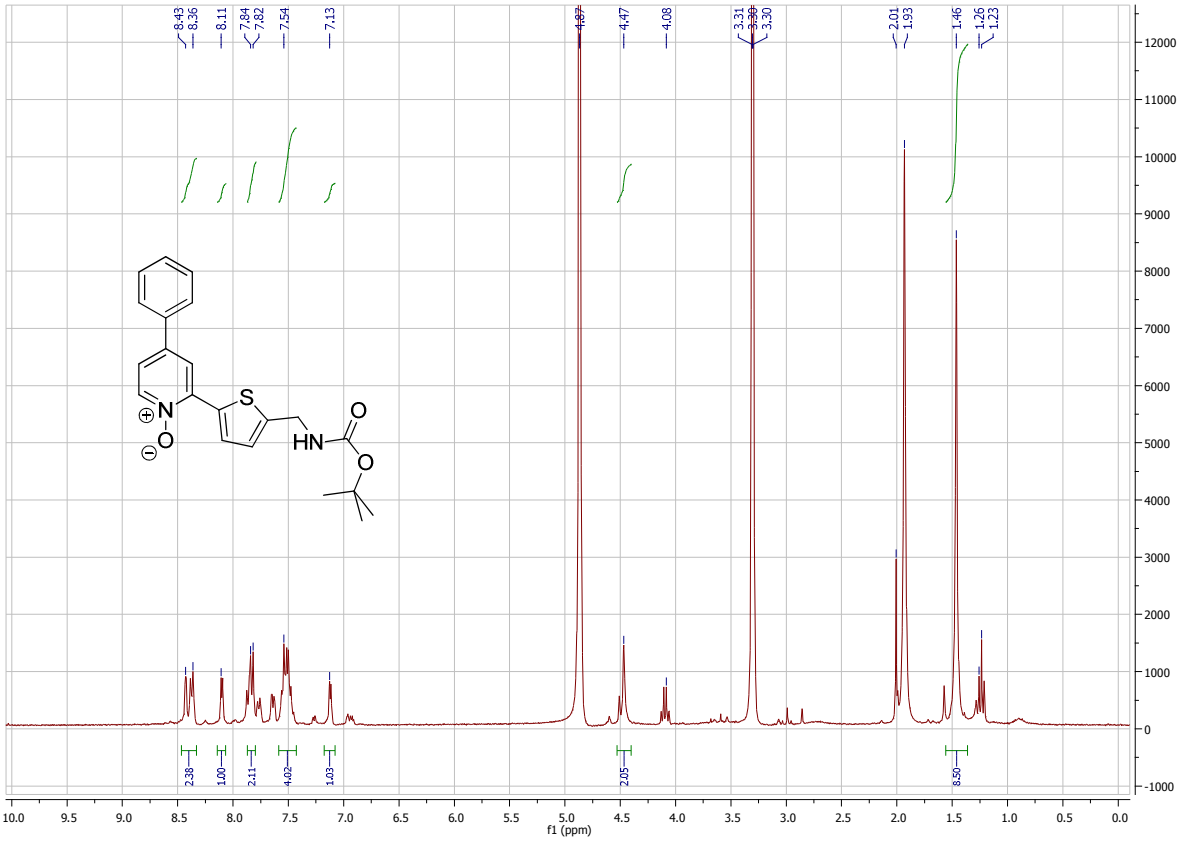


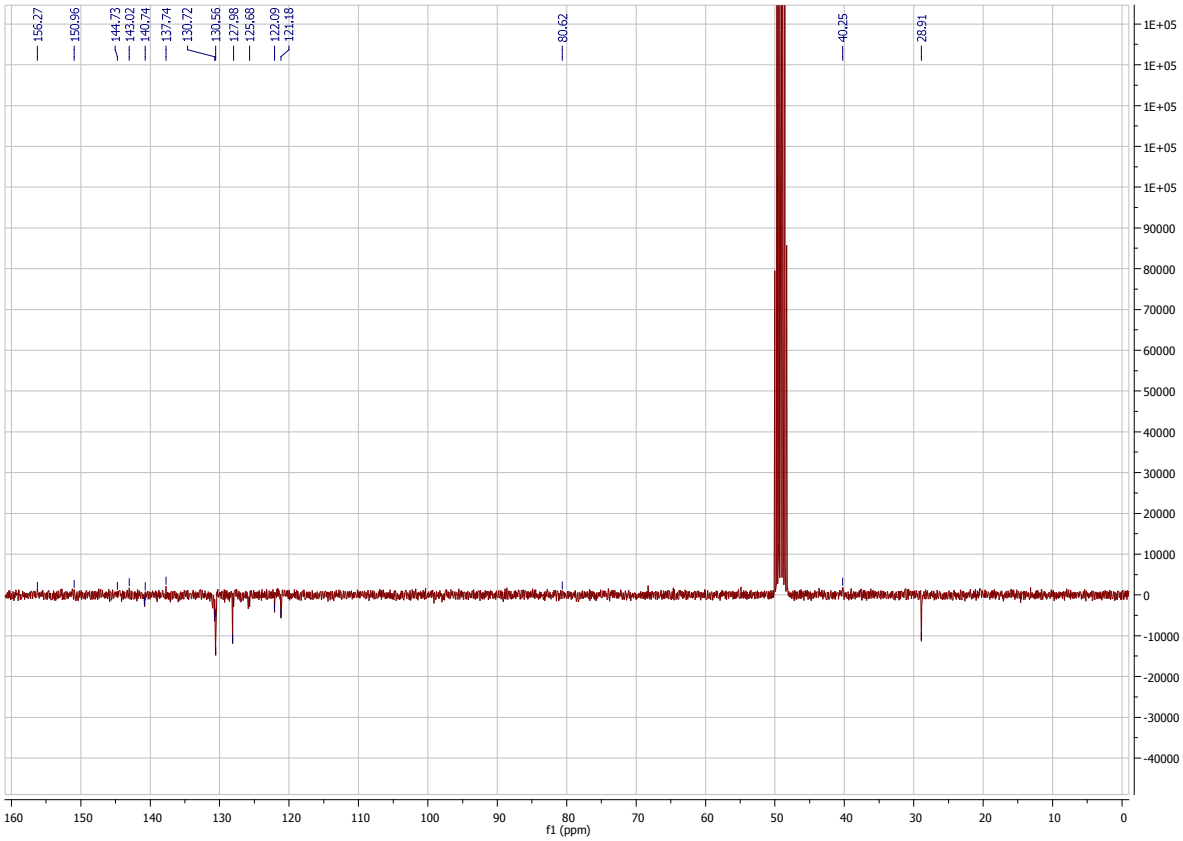
Tert-butyl *N*-((5-(1,3-benzoxazol-2-yl)thiophen-2-yl)methyl)carbamate (**6e**)



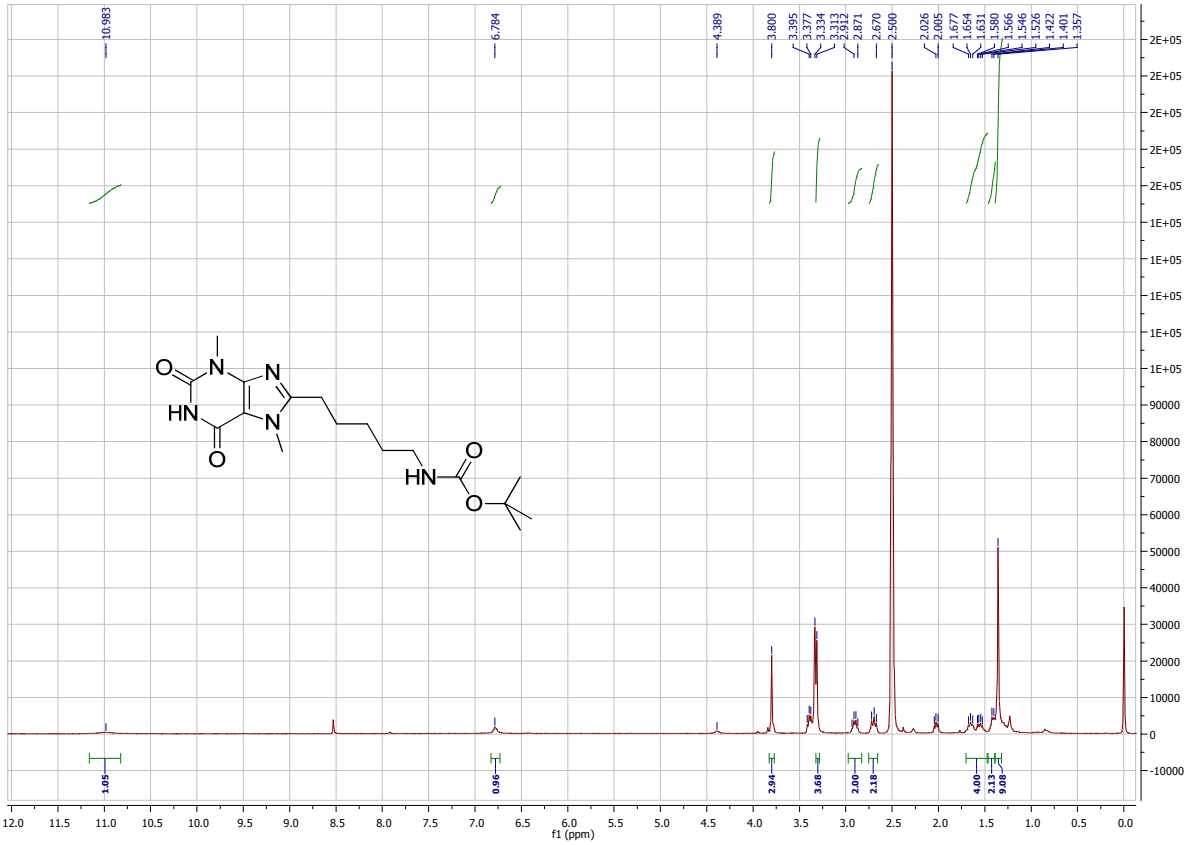


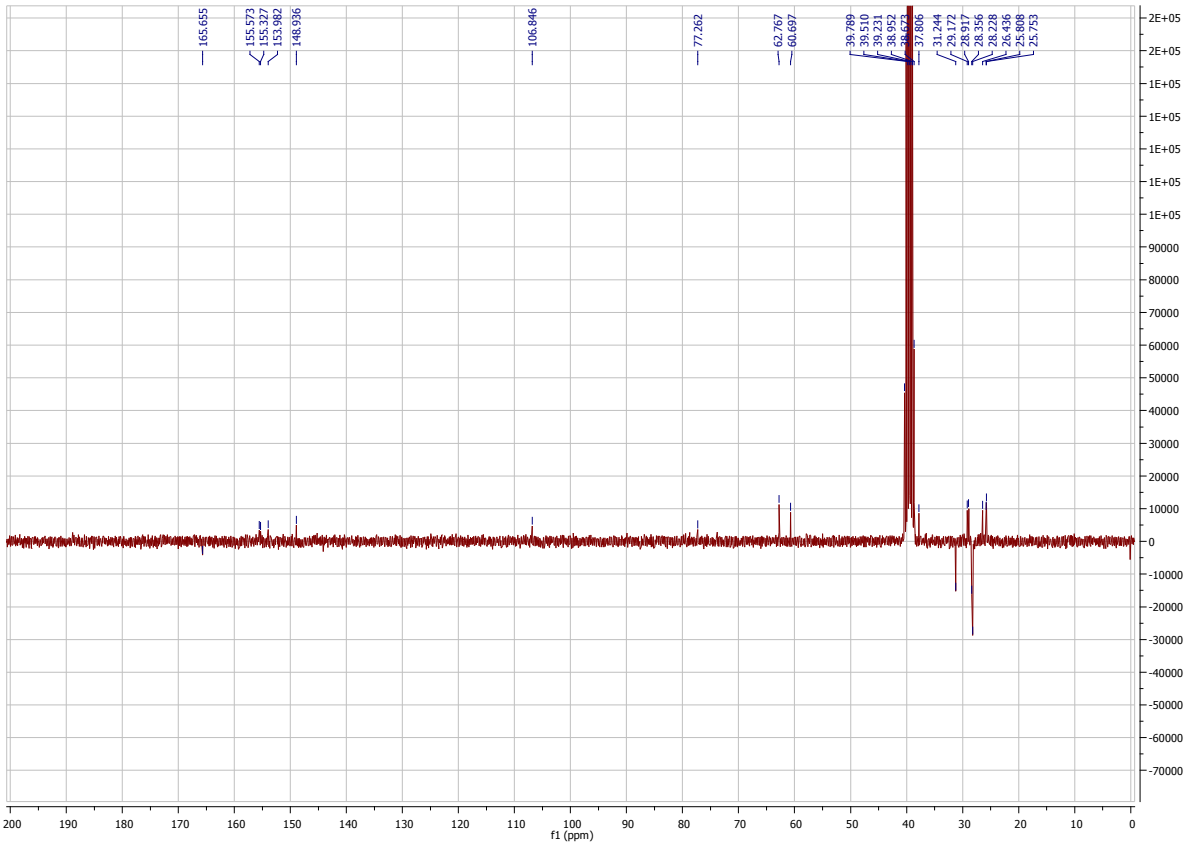
2-(5-(((*tert*-Butoxycarbonyl)amino)methyl)thiophen-2-yl)-4-phenylpyridine 1-oxide (**6f**)





Tert-butyl *N*-(5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl) pentyl) carbamate (**7a**)





5-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)pentan-1-aminium trifluoroacetate (**8a**)