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Spirocyclic azetidines for drug discovery: novel Boc-protected 7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidines]

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Contents

General

All commercial reagents and solvents were used without further purification, unless otherwise noted. THF for the synthesis was distilled over Na and stored under nitrogen over freshly activated molecular sieves 4 Å. The NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm)) (Bruker, Billerica, MA, USA); the residual solvent peaks were used as internal standards: 7.28 and 2.50 ppm for ^{1}H in $CDCl_3$ and DMSO-*d*$_6$, respectively, 40.01 and 77.02 ppm for ^{13}C in DMSO-*d*$_6$ and $CDCl_3$, respectively. Mass spectra were recorded on a Bruker Maxis HRMS-ESI-qT spectrometer (ESI ionization) (Bruker, Billerica, MA, USA). The melting points were determined in open capillary tubes on a Stuart SMP30 Melting Point Apparatus (Staffordshire, UK). Analytical thin-layer chromatography was carried out on Silufol UV-254 silica gel plates (Chemapol, Czech Republic) using appropriate mixtures of ethyl acetate and hexane. The compounds were visualized with short-wavelength UV light. Column chromatography was performed on silica gel 60 (230–400 mesh).

***tert*-Butyl 3-(2-ethoxy-2-oxoethylidene)azetidine-1-carboxylate (2)**

To a suspension of NaH (60% dispersion in mineral oil, 1.88 g, 0.047 mol, 1.15 equiv.) in THF (150 mL) at 0 °C was added triethyl phosphonoacetate (11 g, 0.054 mol, 1.2 equiv.). The resulting mixture was allowed to warm to room temperature and stirred at that temperature for 30 min. Then it was cooled back to 0 °C at which point a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (7 g, 0.041 mol, 1 equiv.) in THF (50 mL) was added. The mixture was allowed to reach room temperature and was stirred at that temperature for 18 h. It was then diluted with ethyl acetate (100 mL), washed with sat. aq. $NaHCO_3$, water and brine. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 0→10% ethyl acetate in hexane to give the title compound as a clear oil. Yield 9 g (92%), colorless oil. Spectral characteristics of the product matched the ones reported in the literature [C. Le Manach *et al*., *J. Med. Chem.* 2021, **64**, 2291]. ^{1}H NMR (300 MHz, CDCl3) δ 5.74 (dd, *J* = 4.5, 2.2 Hz, 1H), 4.80 (dd, *J* = 6.3, 2.9 Hz, 2H), 4.57 (dt, *J* = 5.3, 2.7 Hz, 2H), 4.31 – 4.02 (m, 2H), 1.45 (s, 8H), 1.26 (t, *J* = 7.1 Hz, 4H); LCMS (ESI): m/z (M + H) calcd, 242.3; found, 242.2.

***tert*-Butyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (3)**

To a suspension of NaH (60% dispersion in mineral oil, 4.2 g, 0.105 mol) in dry ether (150 mL), methyl glycolate (8.1 mL, 105 mmol) was added dropwise under argon. The resulting mixture was stirred at room temperature for 30 min whereupon it was concentrated *in vacuo*. Dry DMSO (200 mL) was added, and the solution was cooled to 0 °C. A solution of compound **2** (21 g, 87.2 mmol) in dry DMSO (20 mL) was added. The mixture was allowed to reach room temperature and stirred at that temperature for 18 h. It was then diluted with 5% HCl (50 mL) and ether (200 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to leave yellowish oil. The latter was dissolved in a mixture of DMSO (300 mL) and water (30 mL) containing NaCl (10.2 g, 175 mmol). The resulting mixture was heated at 120 °C for 2 h under argon. After cooling to room temperature, the mixture was diluted with brine (100 mL) and ether (100 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic phases were washed with water (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give yellowish oil. The latter was purified by column chromatography on silica gel eluting with 1:4.5 ethyl acetate – hexane to give the title compound as a yellowish waxy solid. Yield 12 g (61%). Spectral characteristics of the product matched the ones reported in the literature [D. B. Li *et al*., *Org. Lett.*, 2013, **15**, 4766]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.06 – 3.81 (m, 6H), 2.78 (s, 2H), 1.36 (s, 9H); LCMS (ESI): m/z (M + H) calcd, 228.3; found, 228.2.

***tert*-Butyl 2'-cyclopropyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidine]-1-carboxylate (5a) – General procedure 1 for the synthesis of compounds 5a-e**

Ketone **3** (2.24 g, 0.01 mol, 1 equiv.) was dissolved in dimethylformamide dimethyl acetal (13 mL, 10 equiv.) and was heated under reflux for 18 h. The volatiles were removed on a rotary evaporator, and the residue was co-evaporated again with toluene. The residue was dissolved in methanol (10 mL) and the solution was added dropwise to a 0 °C solution of cyclopropanecarboximidamide hydrochloride (1.24 g, 0.015 mol, 1.5 equiv) and sodium methoxide (0.9 g, 0.017 mol, 1.7 equiv.) in methanol (30 mL), and the resulting solution was heated at reflux for 8 h. The volatiles were removed *in vacuo* and the residue was partitioned between 5% aqueous citric acid (50 mL) and dichloromethane (100 mL). The organic phase was separated, washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 50% → 100% ethyl acetate in hexane. Yield 1.6 g (54%), white solid, m.p. 66-67 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 4.96 (s, 2H), 4.35 – 4.29 (m, 2H), 4.15 – 4.08 (m, 2H), 2.40 – 2.06 (m, 1H), 1.59 –

1.36 (m, 9H), 1.23 – 0.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.04, 169.20, 156.27, 149.45, 129.12, 80.64, 80.19, 71.69, 63.71, 28.25, 18.22, 11.24; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_3O_3$ [M+H$^+$] 304.3636, found 304.3638.

tert-Butyl 2'-phenyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidine]-1-carboxylate (5b)

Prepared according to General Procedure 1. Yield 2.13 g (63%), white solid, m. p. 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.51 – 8.40 (m, 2H), 7.59 – 7.37 (m, 3H), 5.11 (s, 2H), 4.39 (dd, *J* = 9.6, 0.9 Hz, 2H), 4.28 – 4.14 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.83, 165.40, 156.32, 149.94, 136.93, 131.07, 130.25, 128.64, 128.32, 80.72, 80.29, 71.87, 63.76, 28.29.; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_3O_3$ [M+H$^+$] 340.1655, found 340.1658.

tert-Butyl 2'-methyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidine]-1-carboxylate (5c)

Prepared according to General Procedure 1. Yield 1.58 g (57%), white solid, m.p. 88-89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 5.01 (s, 1H), 4.34 (d, *J* = 9.6 Hz, 2H), 4.15 (t, *J* = 10.0 Hz, 2H), 2.77 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.54, 168.71, 156.26, 149.64, 129.66, 80.64, 80.26, 71.73, 63.69, 28.24, 25.73; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}N_3O_3$ [M+H$^+$] 278.1499, found 278.1503.

tert-Butyl 2'-propyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidine]-1-carboxylate (5d)

Prepared according to General Procedure 1. Yield 1.67 g (55%), white solid, m.p. 54-55 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 4.99 (s, 2H), 4.31 (dd, *J* = 9.5, 0.9 Hz, 2H), 4.15 – 4.09 (m, 2H), 3.06 – 2.80 (m, 2H), 1.92 – 1.75 (m, 2H), 1.46 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.08, 169.46, 156.31, 149.68, 129.73, 80.71, 80.27, 71.83, 41.27, 28.31, 22.20, 13.87; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}N_3O_3$ [M+H$^+$] 306.1812, found 306.1816.

tert-Butyl 2'-cyclohexyl -1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]pyrimidine]-1-carboxylate (5e)

Prepared according to General Procedure 1. Yield 2.3 g (67%), white solid, m.p. 72-73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 5.02 (s, 2H), 4.34 (dd, J = 9.5, 0.9 Hz, 2H), 4.23 – 4.06 (m, 2H), 2.94 (tt, J = 11.7, 3.5 Hz, 1H), 2.11 – 1.82 (m, 5H), 1.79 – 1.54 (m, 4H), 1.49 (s, 9H), 1.47 – 1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.38, 169.34, 156.29, 149.64, 129.69, 80.67, 80.23, 71.83, 63.73, 47.45, 31.93, 28.26, 26.11, 25.80; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}N_3O_3$ [M+H$^+$] 346.2125, found 346.2128.

1-[(5-Nitrofuran-2-yl)carbonyl]-2'-cyclopropyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]-pyrimidine] (6a) – General Procedure 2 for the preparation of compounds 6a-e

Solution **A**. To a solution of 5-nitrofuranoic acid (75 mg, 0.47 mmol) in DMF (3 mL), CDI (97 mg, 0.6 mmol) was added at 0 °C, and the solution was stirred at this temperature for 1 h.

Solution **B**. To a solution of compound **5a** (0.18 g, 0.6 mmol) in dichloromethane (5 mL), trifluoroacetic acid (1 mL) was added dropwise at 0 °C, and the resulting solution was stirred for 1 h. The volatiles were removed *in vacuo* (bath temperature < 30 °C), and the residue was dissolved in DMF (3 mL). Triethylamine (0.19 g, 1.9 mmol) was added, the mixture was stirred for 30 min and added dropwise to solution A. The mixture was stirred at room temperature for 18 h, poured into water (25 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10:1 dichloromethane-methanol. Yield 68 mg (42%), white solid, m.p. 84-85 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.81 (d, J = 3.9 Hz, 1H), 7.39 (d, J = 3.9 Hz, 1H), 5.00 (s, 2H), 4.87 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 34.8 Hz, 2H), 4.41 (ABq, J_{AB} = 11.4 Hz, $\Delta\nu_{AB}$ = 55.3 Hz, 2H), 2.36 – 2.09 (m, 1H), 1.23 – 0.83 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.09, 169.87, 156.82, 151.86, 151.45, 147.77, 128.58, 117.54, 113.57, 81.98, 71.36, 66.64, 63.28, 18.34, 11.14; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_4O_5$ [M+H$^+$] 343.1037, found 343.1041.

1-[(5-Nitrofuran-2-yl)carbonyl]-2'-phenyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]-pyrimidine] (6b)

Yield 78 mg (44%), white solid, m.p. 120-121 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.24 (s, 1H), 8.42 (dd, J = 6.3, 2.8 Hz, 2H), 7.82 (d, J = 3.9 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.41 (d, J = 3.9 Hz, 1H), 5.16 (s, 2H), 4.94 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 42.8 Hz, 2H), 4.49 (ABq, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 65.7 Hz, 2H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.69, 164.15, 156.85, 152.10, 151.89, 147.80, 137.09, 131.54, 129.94, 129.22, 128.31, 117.58, 113.59, 82.09, 71.59, 66.65, 63.26; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_4O_5$ [M+H$^+$] 378.0964, found 378.0969.

1-[(5-Nitrofuran-2-yl)carbonyl]-2'-methyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]-pyrimidine] (6c)

Yield 61 mg (41%), white solid, m.p. 115-116 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.79 (d, J = 3.9 Hz, 1H), 7.38 (d, J = 3.9 Hz, 1H), 5.02 (s, 2H), 4.87 (ABq, J_{AB} = 10.6 Hz, $\Delta\nu_{AB}$ = 35.1 Hz, 2H), 4.41 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 55.1 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.99, 168.06, 156.85, 151.87, 151.57, 147.77, 128.84, 117.54, 113.58, 81.98,

71.38, 66.62, 63.28, 25.85; HRMS (ESI) *m/z* calcd for $C_{14}H_{13}N_4O_5$ [M+H$^+$] 317.0880, found 317.0883.

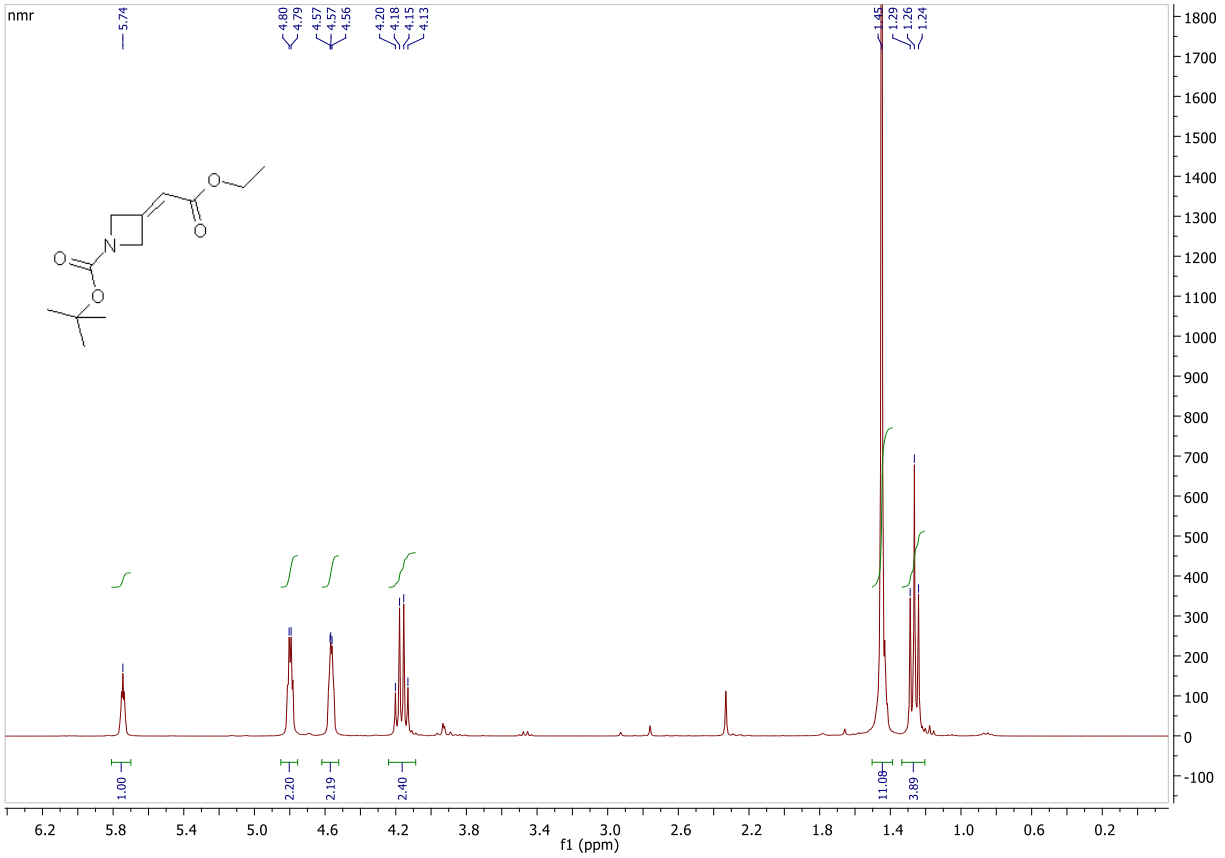
1-[(5-Nitrofuran-2-yl)carbonyl]-2'-propyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]-pyrimidine] (6d)

Yield 59 mg (36%), white solid, m.p. 78-79 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.81 (d, J = 3.9 Hz, 1H), 7.39 (d, J = 3.9 Hz, 1H), 5.05 (s, 2H), 4.89 (ABq, J_{AB} = 10.3 Hz, $\Delta\nu_{AB}$ = 37.6 Hz, 2H), 4.43 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 57.9 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H), 1.88 – 1.64 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.07, 169.95, 156.84, 151.54, 147.78, 128.99, 117.53, 113.56, 82.00, 71.43, 66.66, 63.26, 21.74, 14.07; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}N_4O_5$ [M+H$^+$] 345.1193, found 345.1188.

1-[(5-Nitrofuran-2-yl)carbonyl]-2'-cyclohexyl-1*H*,7'*H*-spiro[azetidine-3,5'-furo[3,4-*d*]-pyrimidine] (6e)

Yield 65 mg (36%), white solid, m.p. 92-93 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.81 (d, J = 3.8 Hz, 1H), 7.39 (d, J = 3.8 Hz, 1H), 5.05 (s, 2H), 4.88 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 39.8 Hz, 2H), 4.43 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 60.7 Hz, 2H), 2.86 (t, J = 9.8 Hz, 1H), 1.99 – 1.09 (m, 11H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.36, 169.91, 156.83, 151.59, 147.76, 129.08, 117.53, 113.57, 82.00, 71.47, 66.67, 63.27, 46.97, 31.97, 26.03; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_4O_5$ [M+H$^+$] 385.1506, found 385.1502.

^{1}H NMR spectrum of compound **2**



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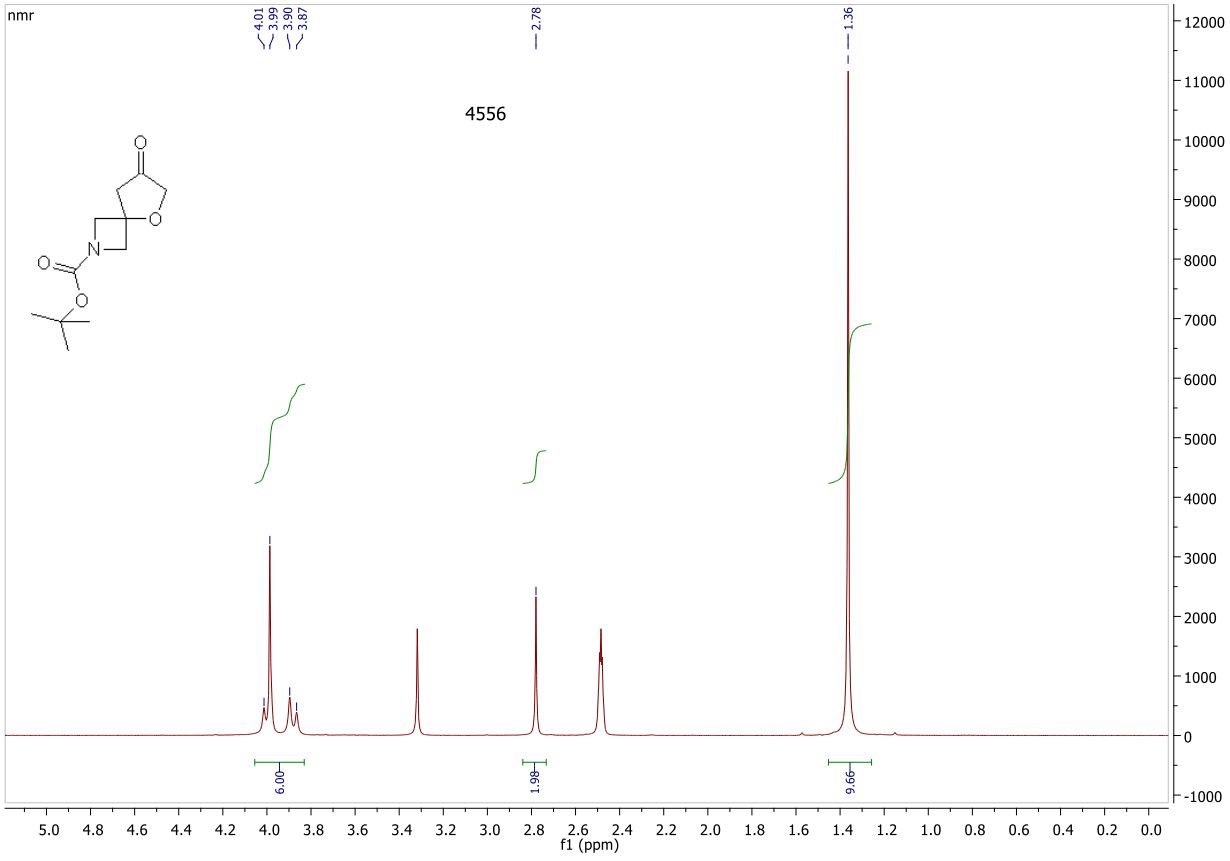
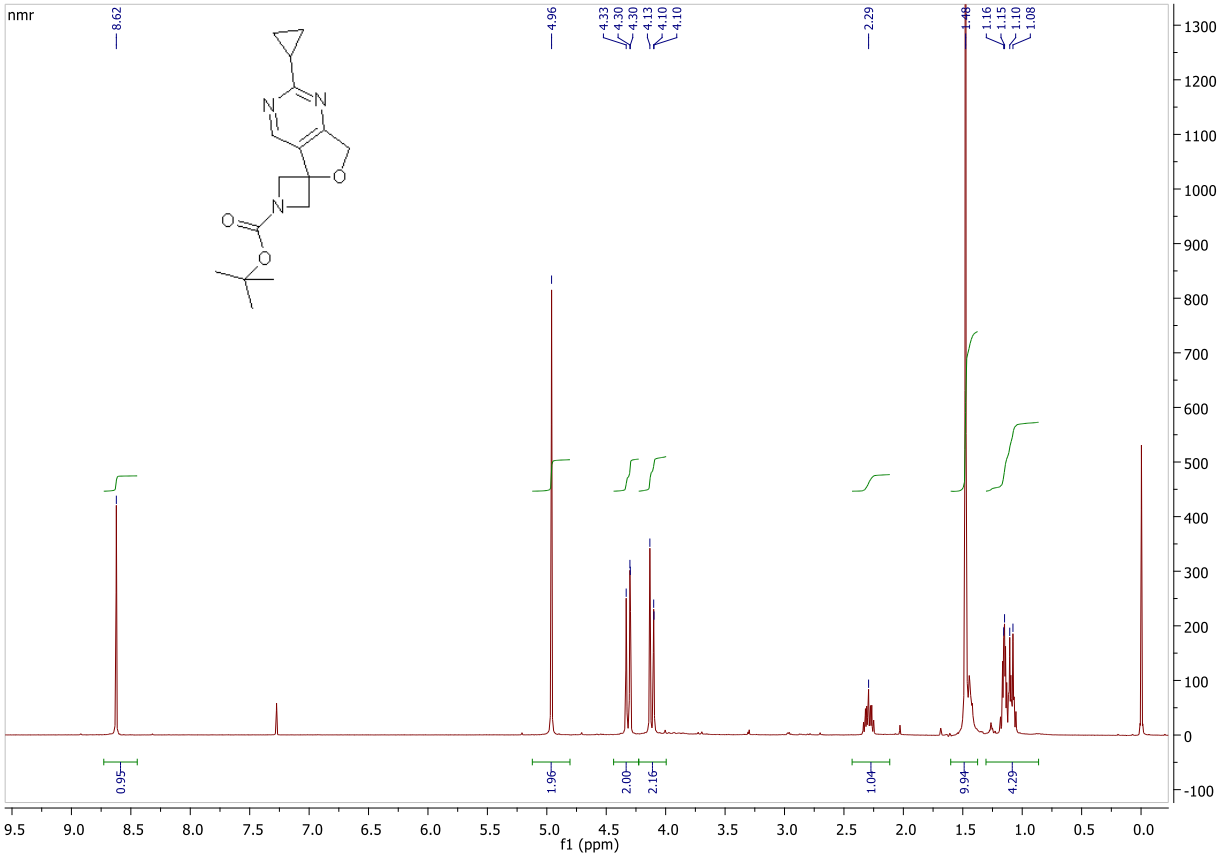
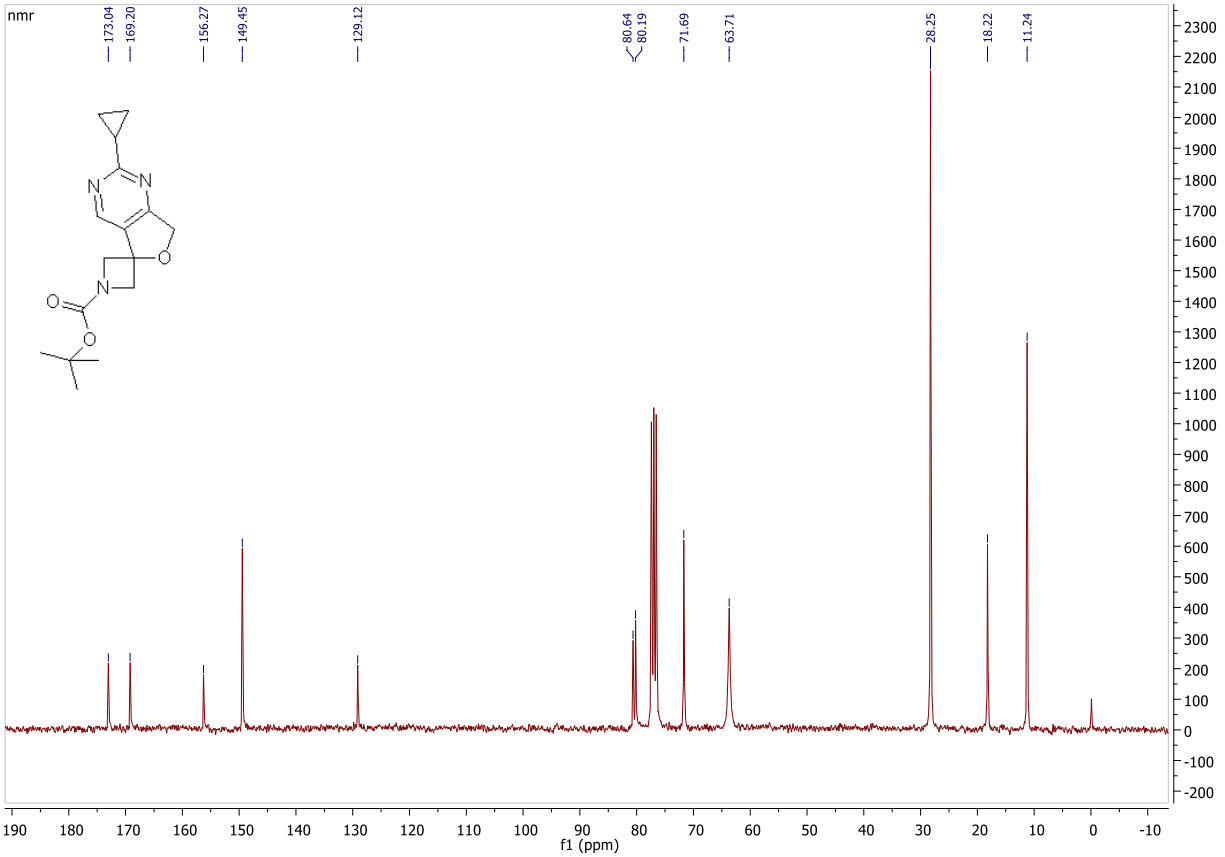
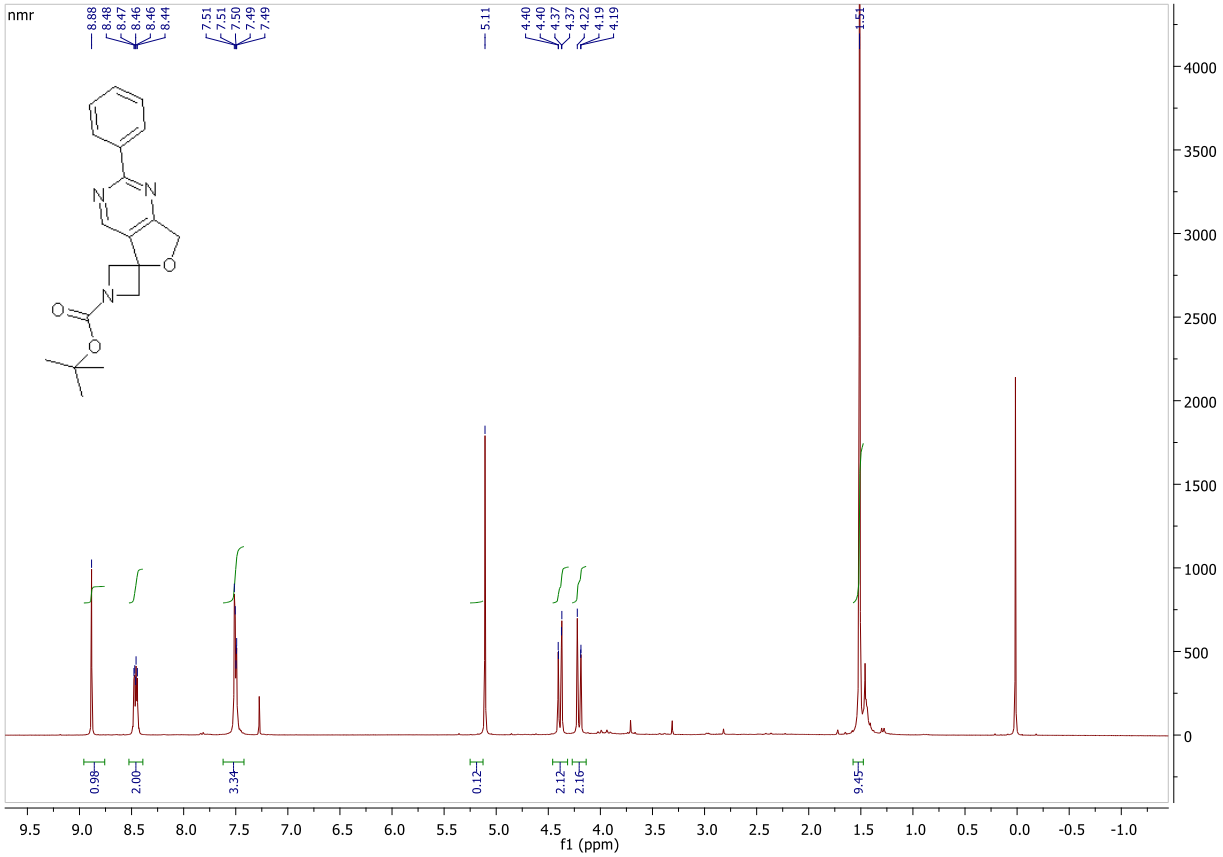


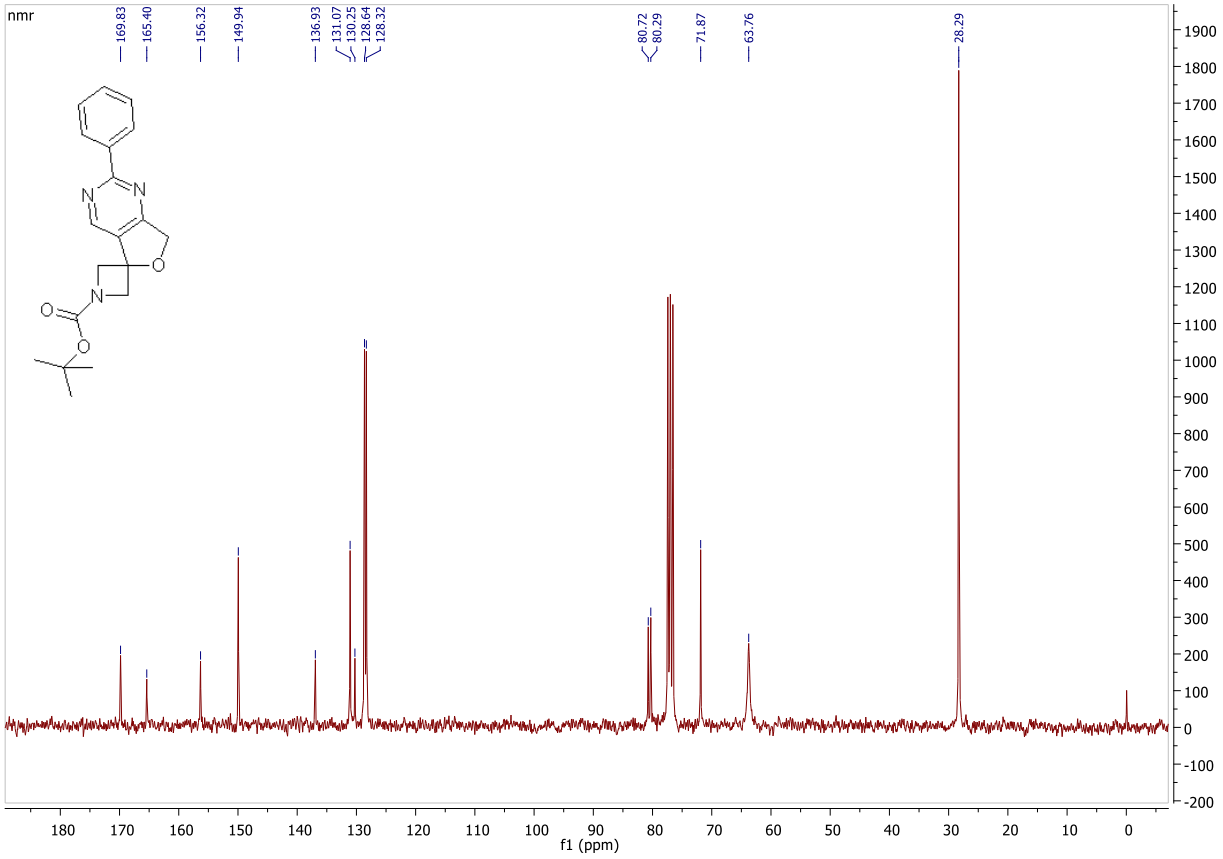
^{1}H and ^{13}C NMR spectra of compound **5a**





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





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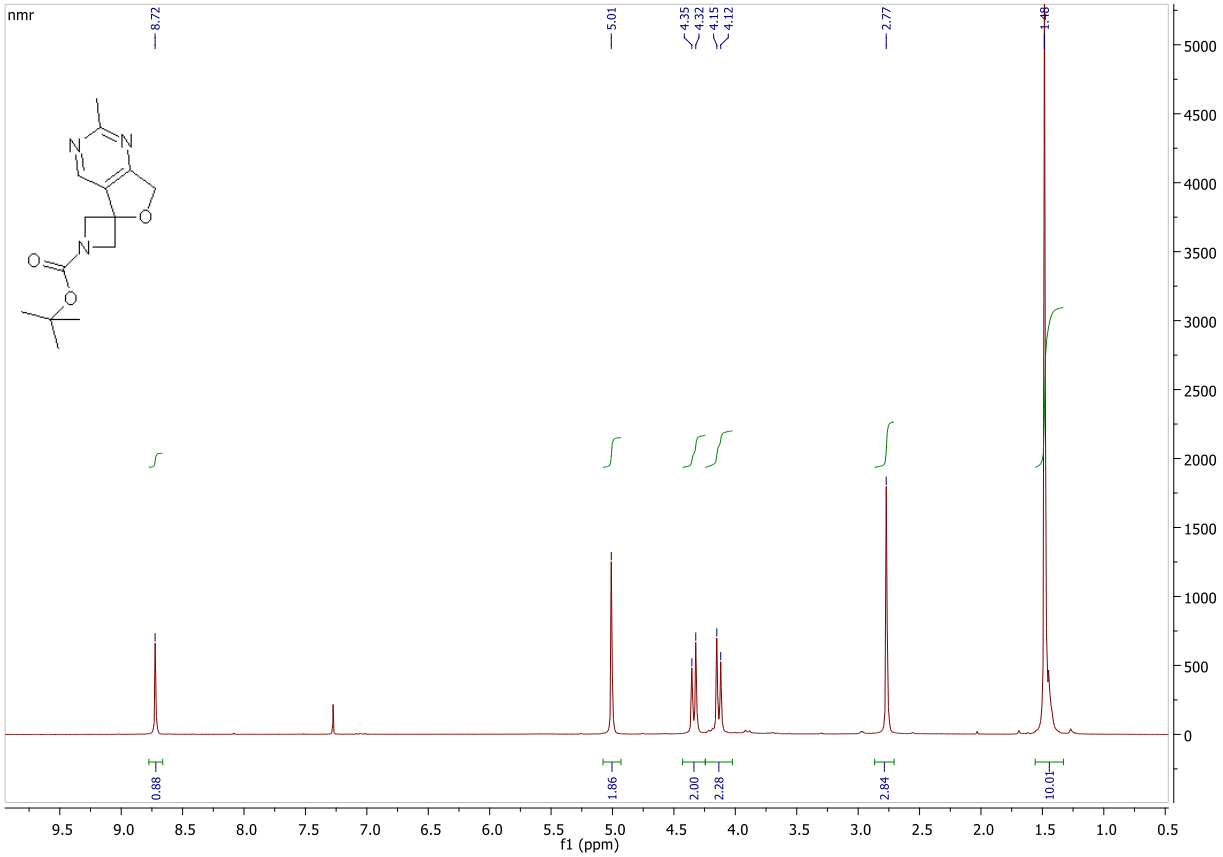

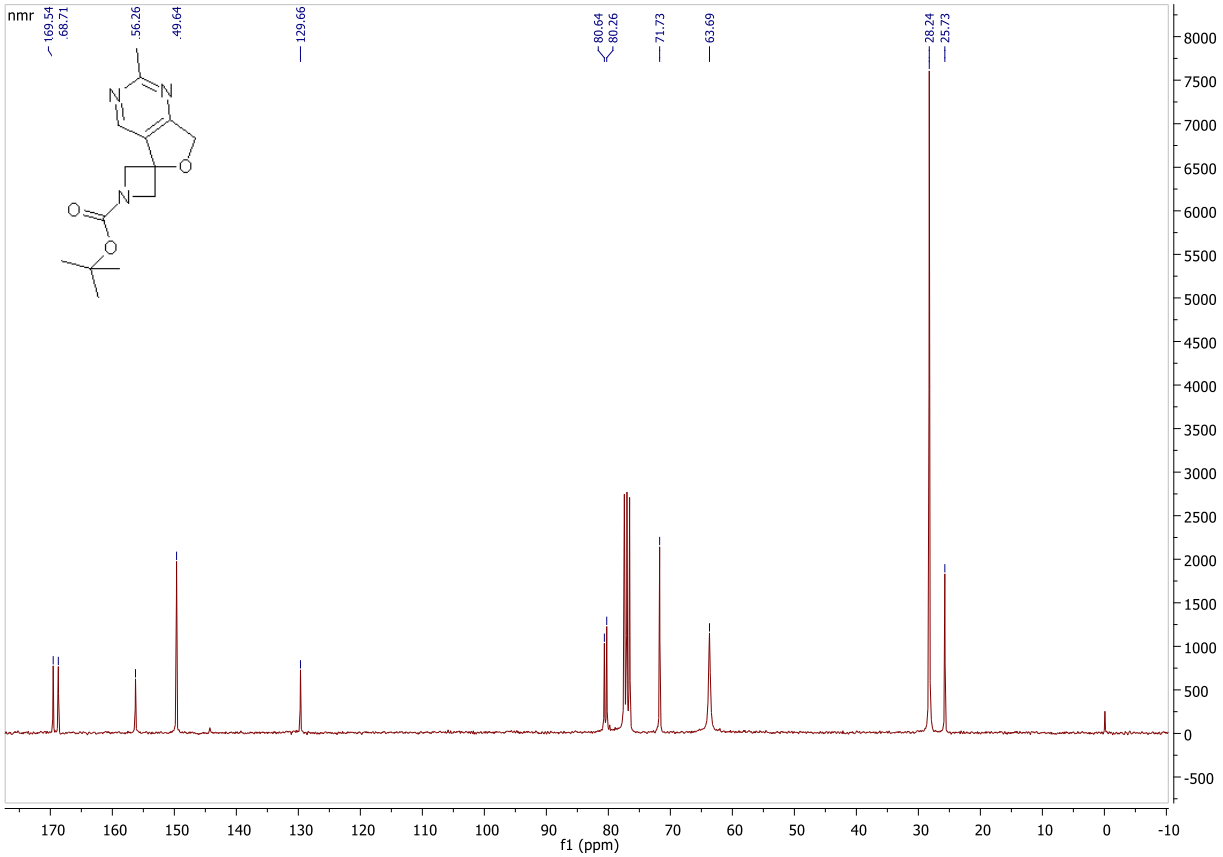

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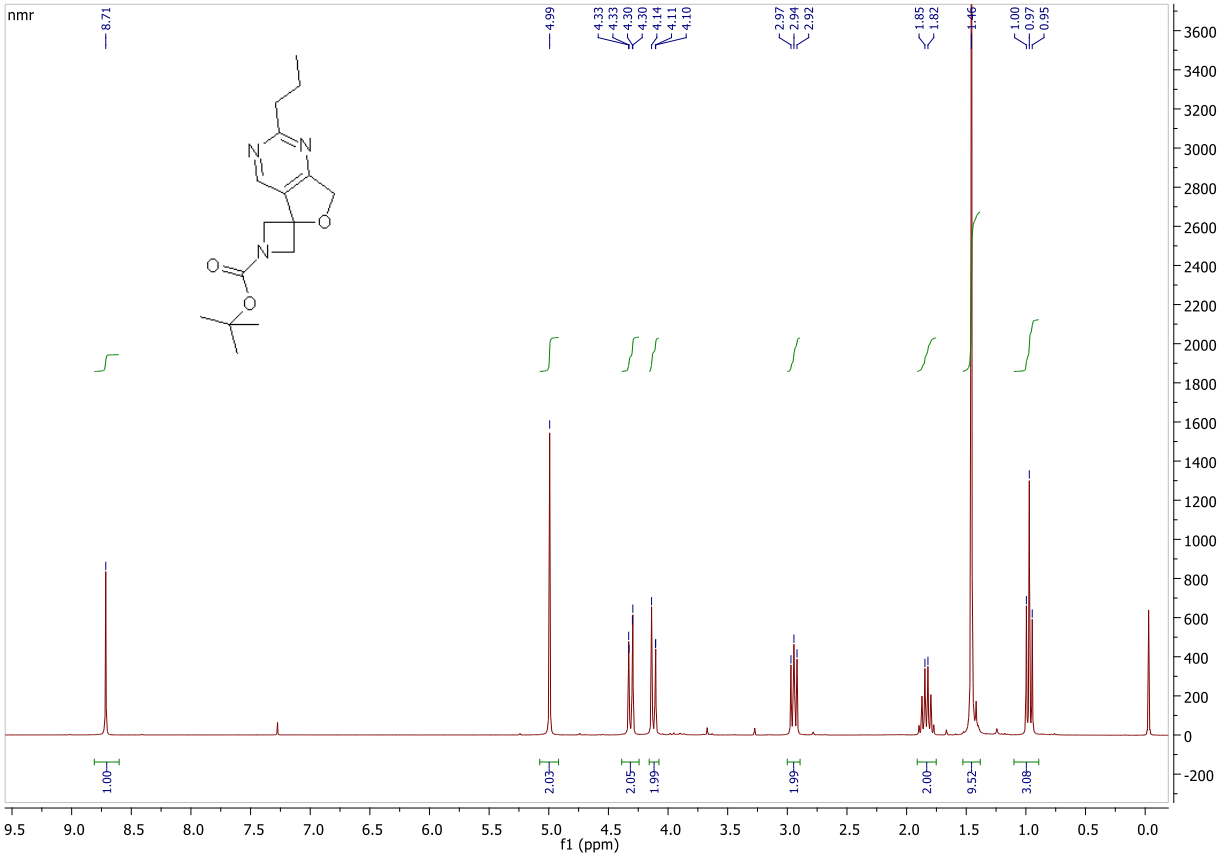
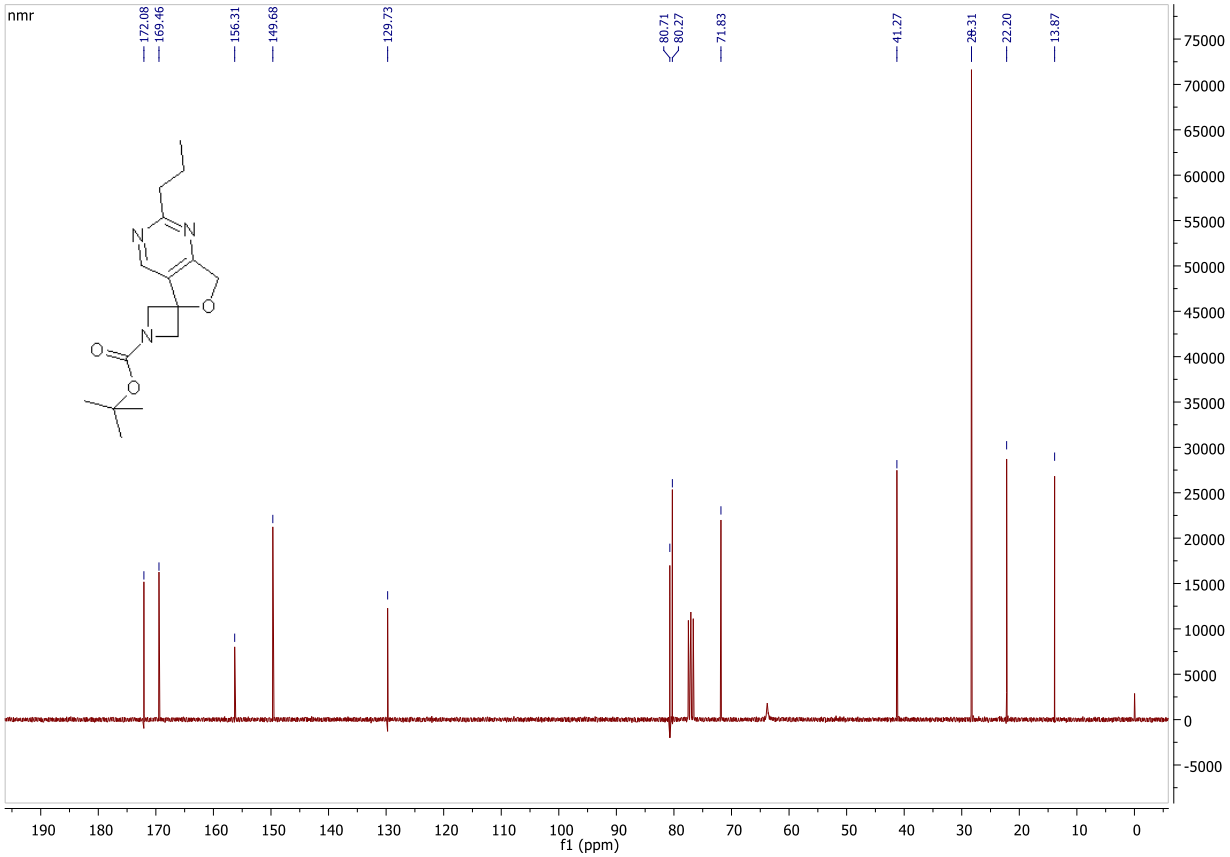
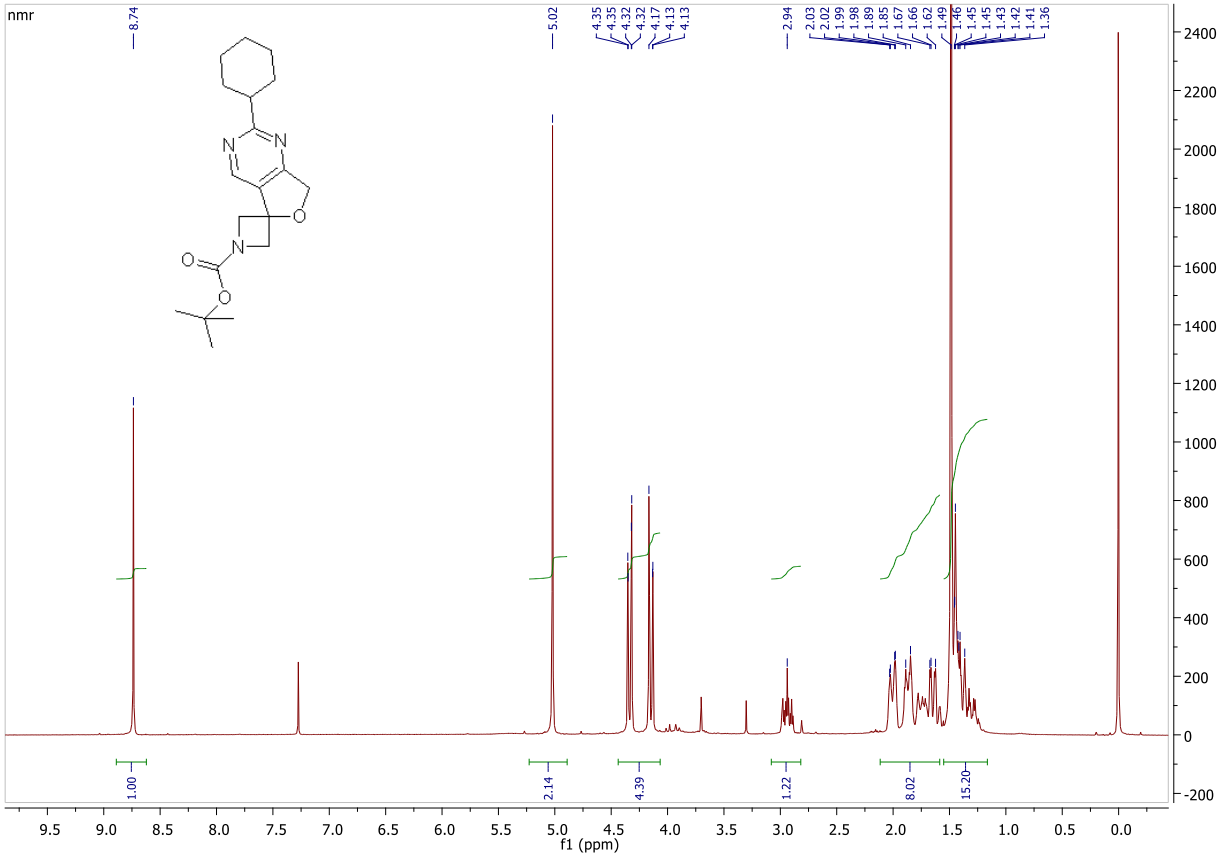
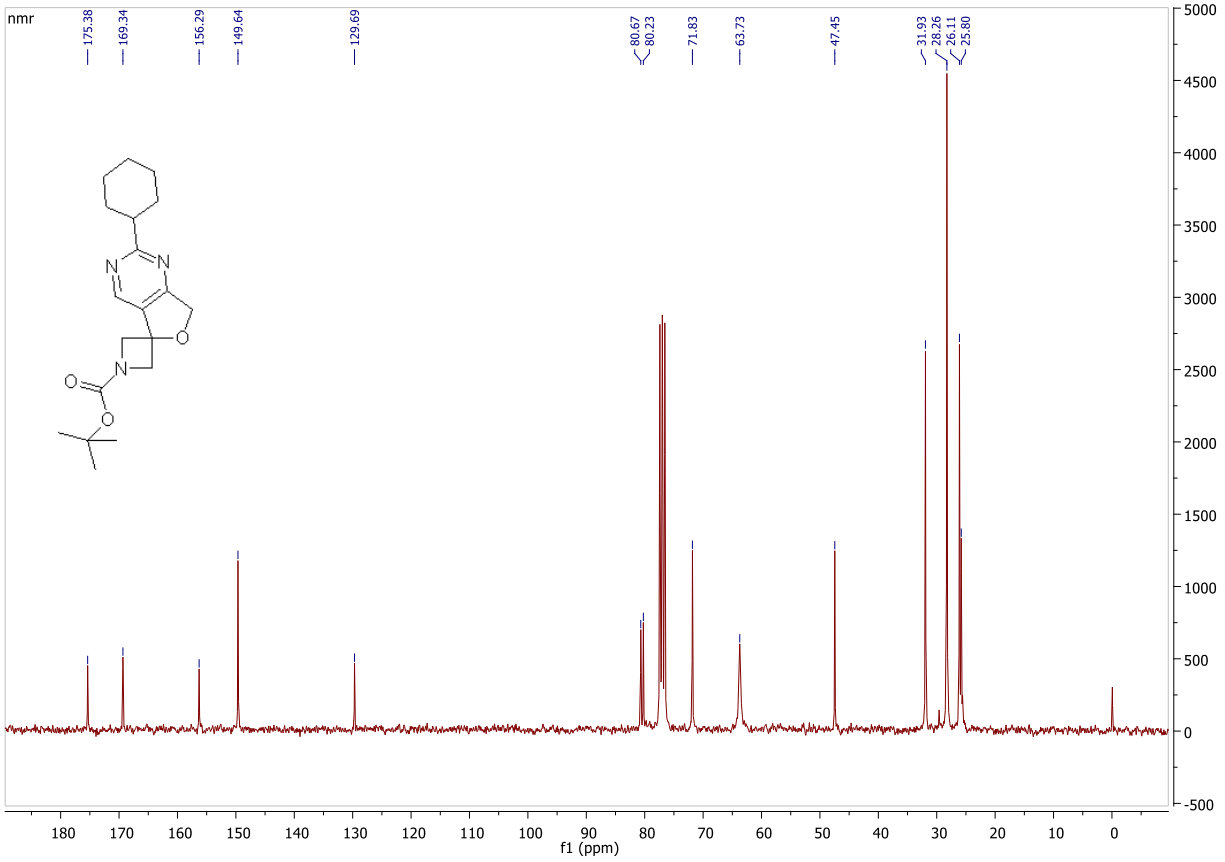


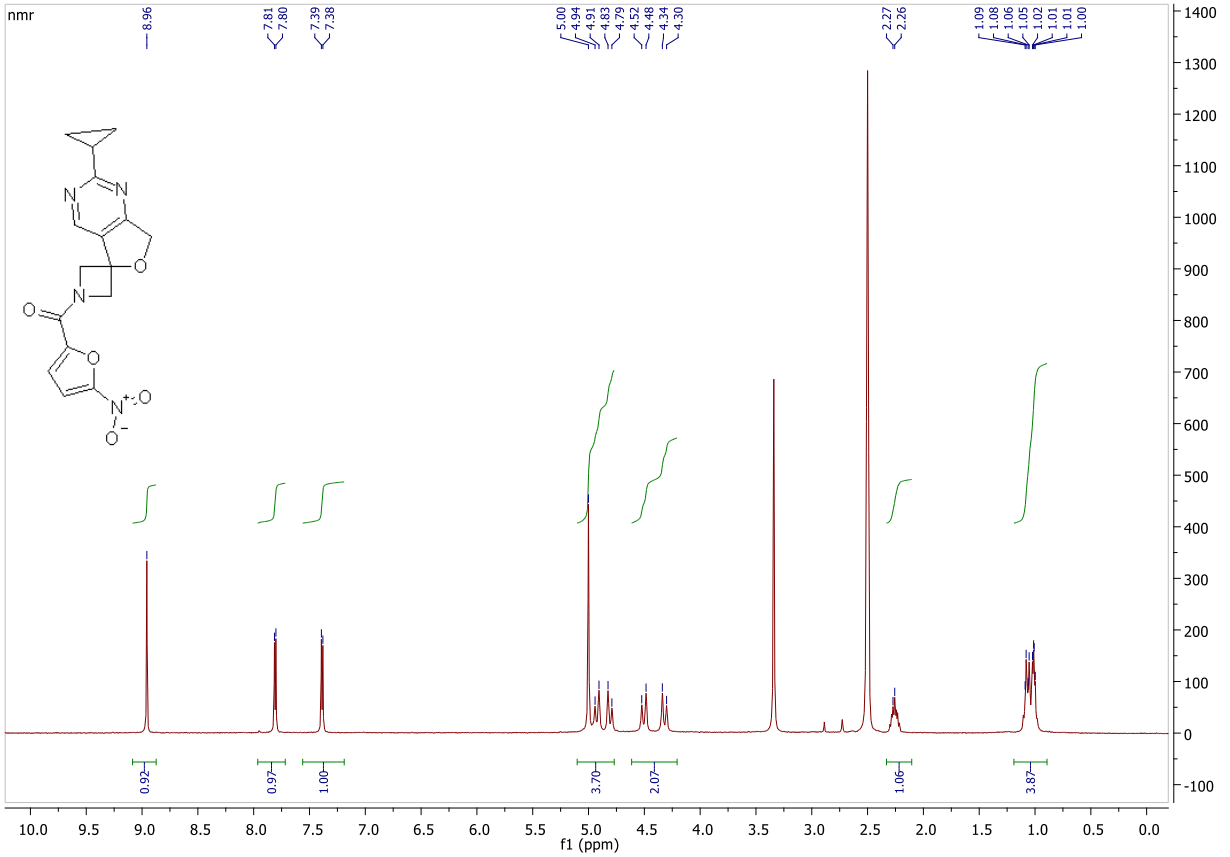


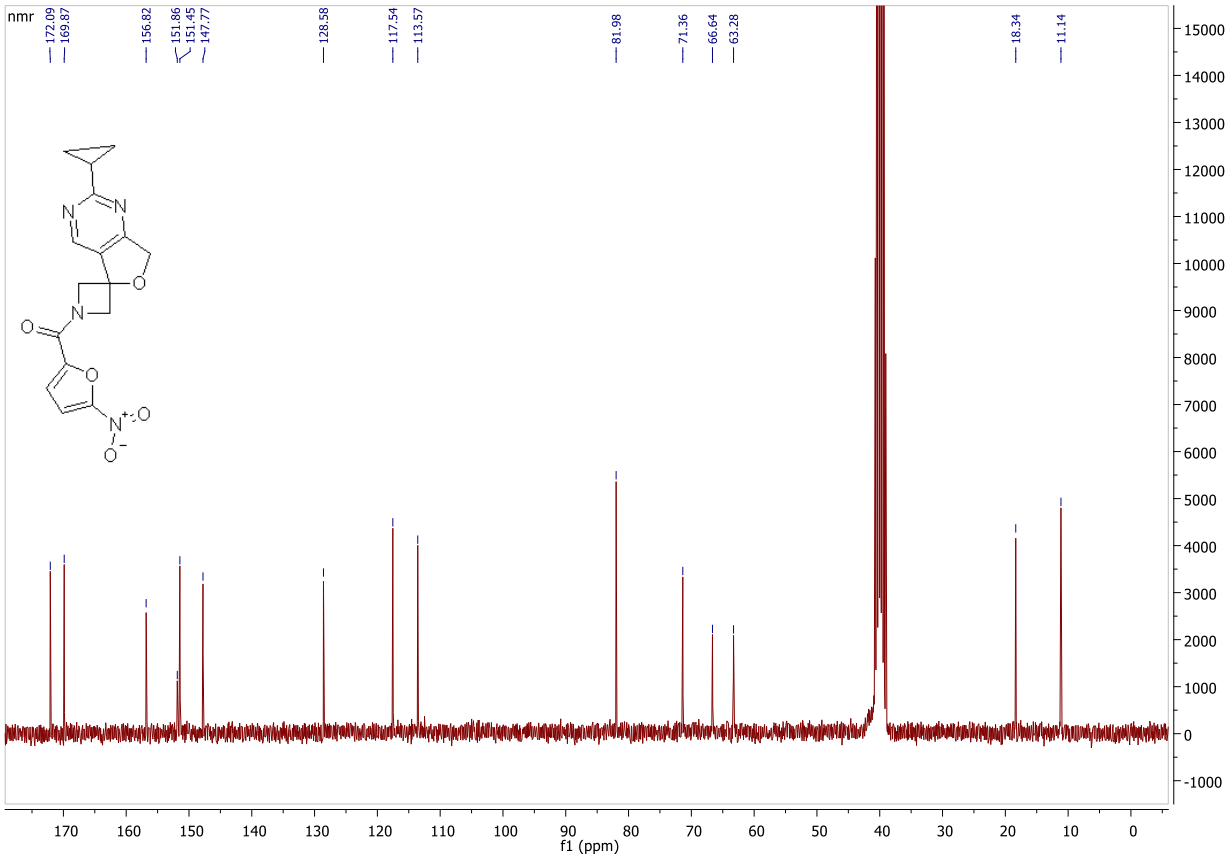
^{1}H and ^{13}C NMR spectra of compound **5e**



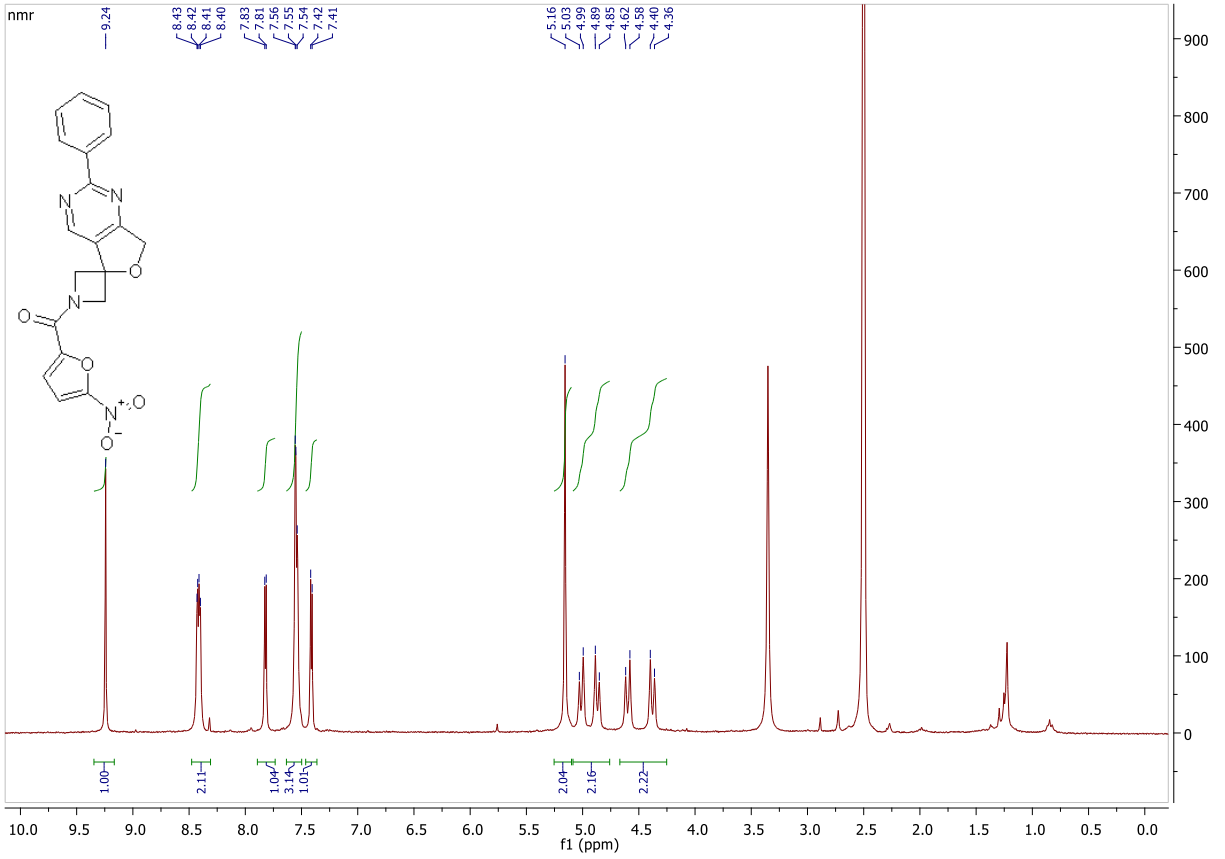


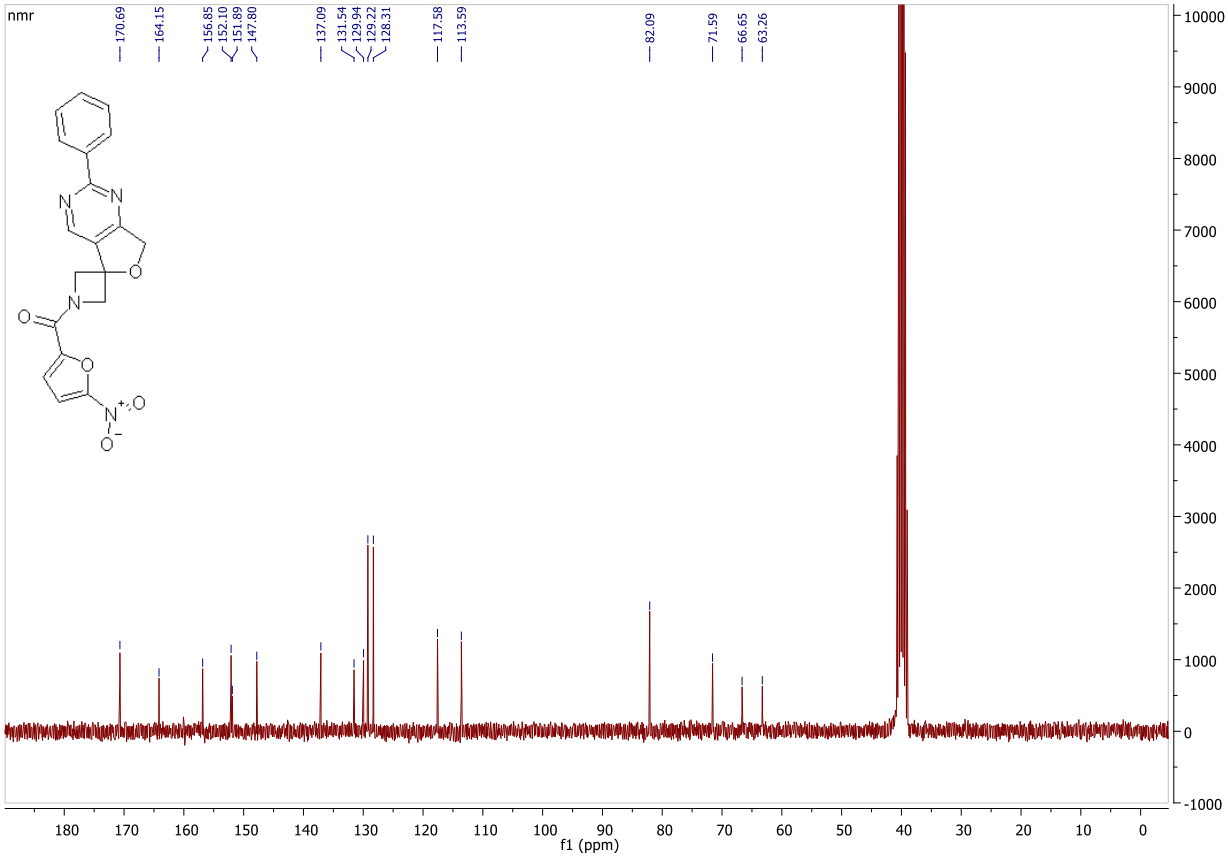
^{1}H and ^{13}C NMR spectra of compound **6a**



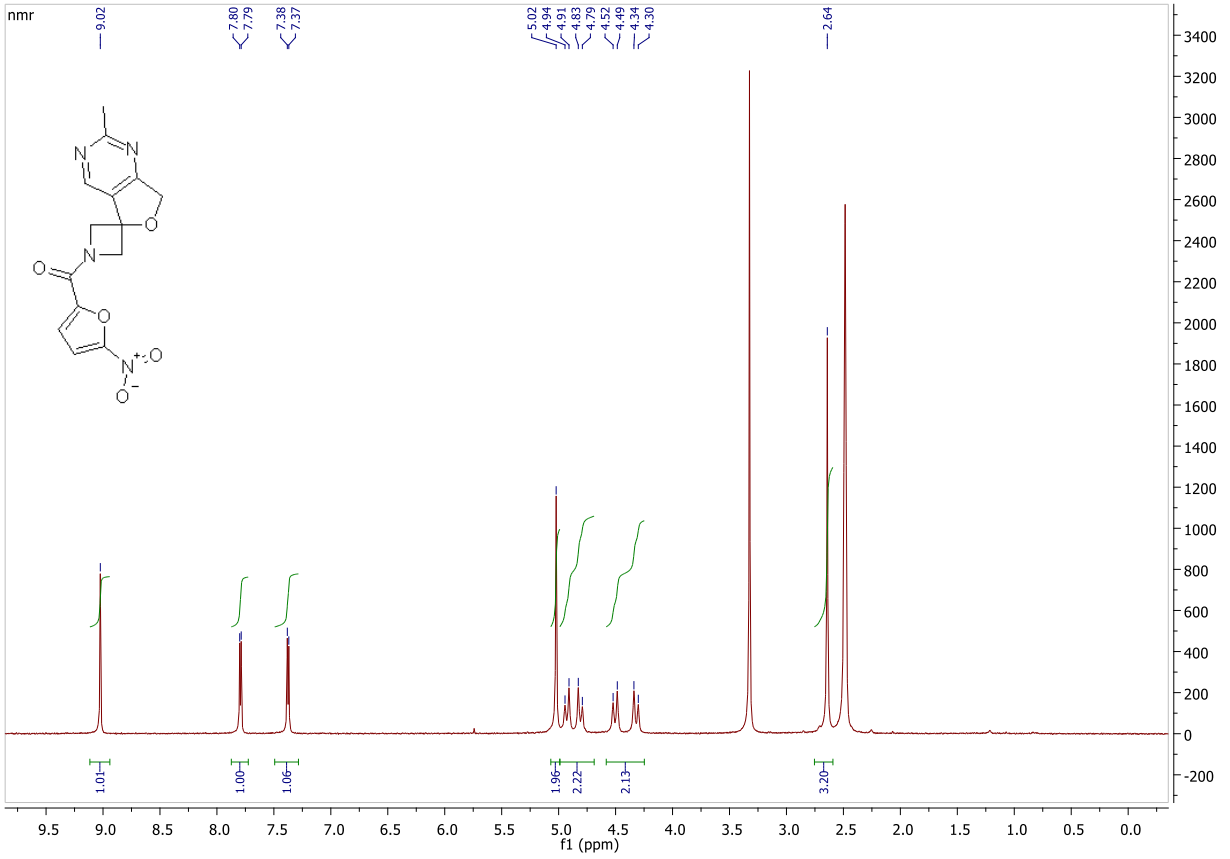


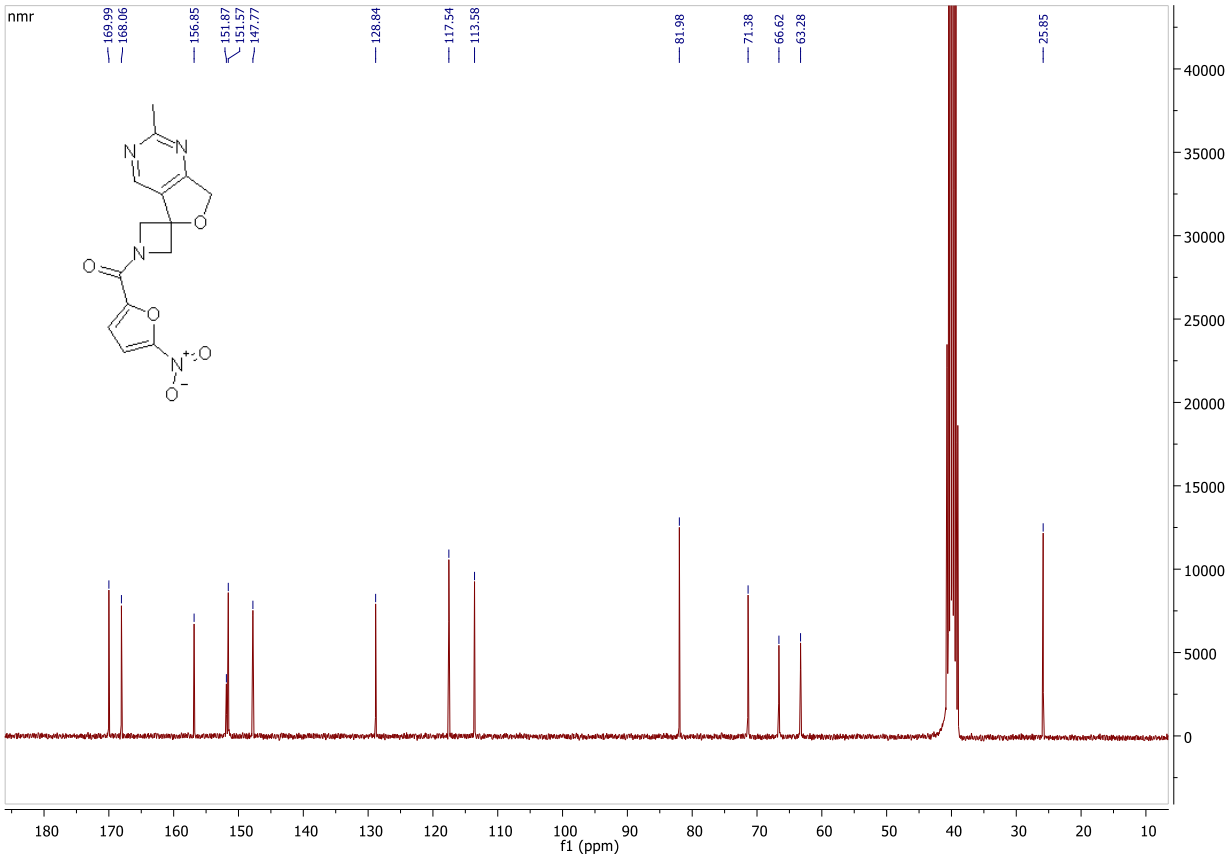
^{1}H and ^{13}C NMR spectra of compound **6b**



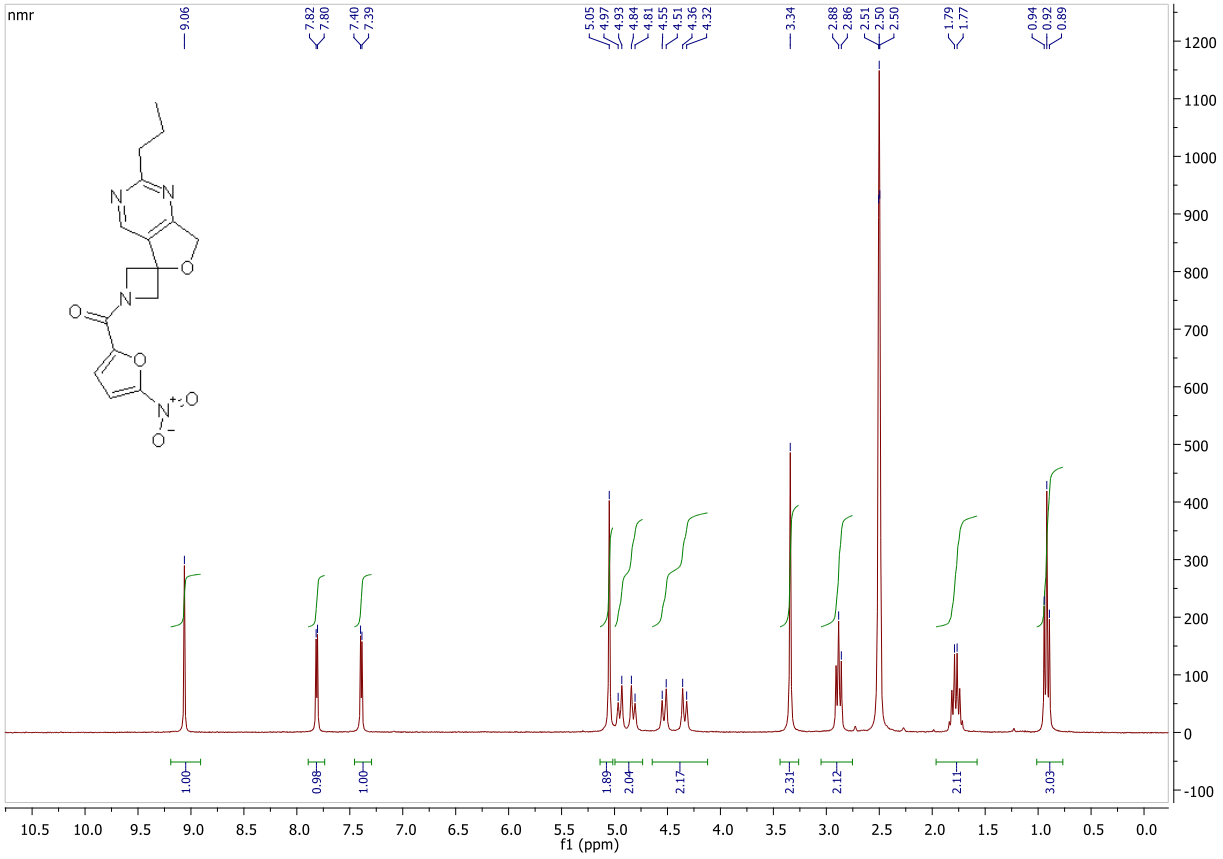


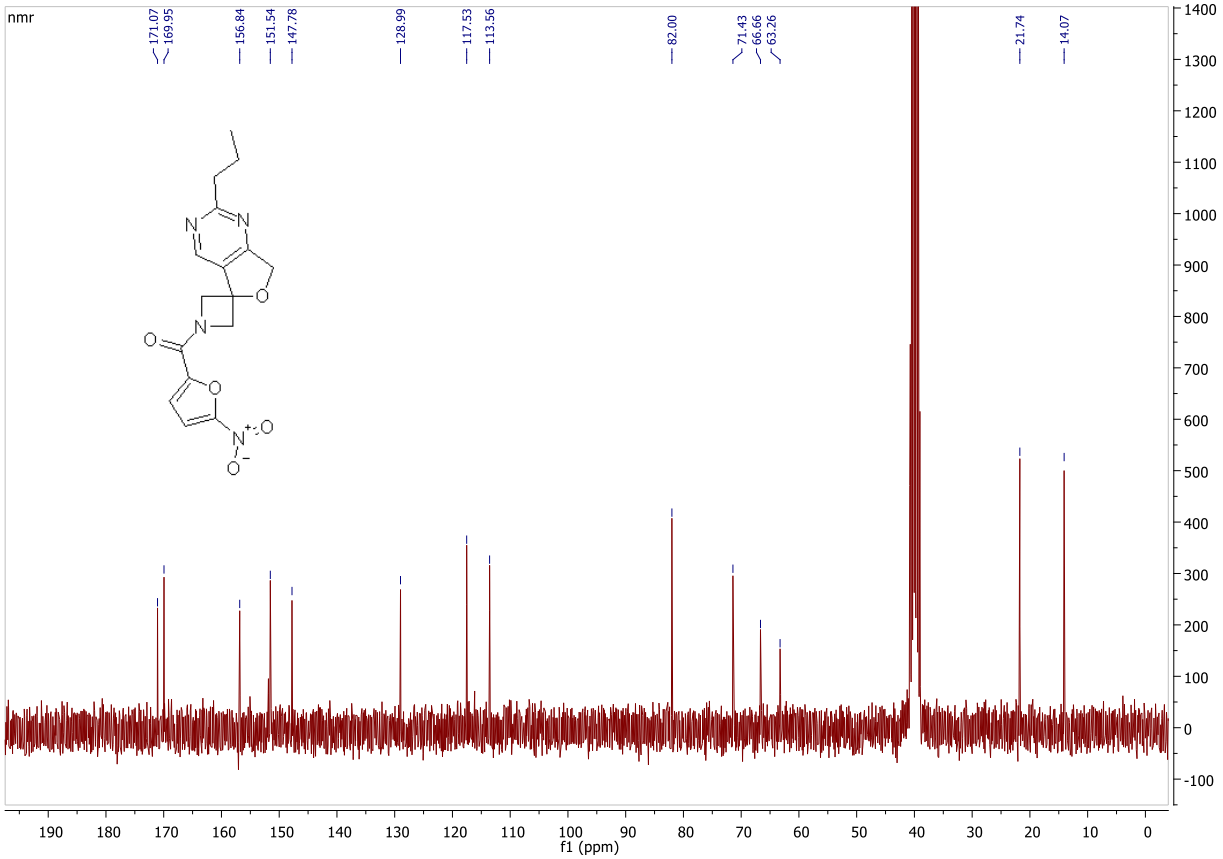
^{1}H and ^{13}C NMR spectra of compound **6c**





^{1}H and ^{13}C NMR spectra of compound **6d**





^{1}H and ^{13}C NMR spectra of compound **6e**