

Design and synthesis of spiro-linked azacycloalkane–dihydropyrano[4,3-*d*]pyrimidine compounds

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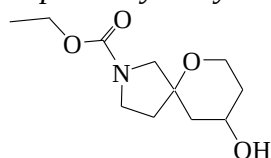
General information

Commercially available reagents and solvents were used without further purification. NMR spectra were recorded using a Bruker DPX-300 spectrometer (^1H : 300 MHz; ^{13}C : 75 MHz). Chemical shifts are reported as parts per million (δ , ppm). The residual solvent peak (CDCl_3 or $\text{DMSO-}d_6$) was used as the internal standard: 7.28 or 2.51 ppm for ^1H and 77.07 or 40.00 ppm for ^{13}C . Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, tt = triplet of triplets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets. Coupling constants, *J*, are reported in Hz. Mass spectra were recorded using a Bruker microTOF spectrometer (ionization by electrospray, positive ion detection). Analytical thin-layer chromatography (TLC) was carried out on UV254 silica gel plates. Visualization was accomplished by short-wavelength UV light. Column chromatography was performed with 230–400-mesh silica gel Merk grade 60 (0.040–0.063 mm).

The starting compounds **1** and **2** were synthesized according to the previously described protocol [A. Lukin, D. Bagnyukova, N. Kalinchenkova, N. Zhurilo and M. Krasavin, *Tetrahedron Lett.*, 2016, 57, 3311; <https://doi.org/10.1016/j.tetlet.2016.06.054>].

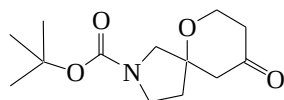
Synthesis and characterization of compound 8

Step 1. Ethyl 9-hydroxy-6-oxa-2-azaspiro[4.5]decane-2-carboxylate (**6**)



To a vigorously stirred mixture of ethyl 3-oxopyrrolidine-1-carboxylate (**5**) (5.0 g, 31.8 mmol) and but-3-en-1-ol (2.5 g, 35.0 mmol) at 0°C was slowly added 70% H_2SO_4 solution (10.8 mL). Stirring was continued overnight, after which the mixture was diluted with water (40 mL), and the pH was adjusted to 9–10 with saturated aqueous NaOH. The mixture was extracted with ethyl acetate (2×100 mL), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was chromatographed on silica gel using 0–10% MeOH in dichloromethane as the eluent. Yield 2.2 g (30%). The physicochemical characteristics matched those previously described [A. Lukin, D. Bagnyukova, N. Kalinchenkova, N. Zhurilo and M. Krasavin, *Tetrahedron Lett.*, 2016, 57, 3311; <https://doi.org/10.1016/j.tetlet.2016.06.054>].

Step 2. *tert*-Butyl 9-hydroxy-6-oxa-2-azaspiro[4.5]decane-2-carboxylate (**8**)

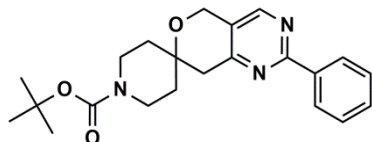


Alcohol **6** (2.2 g, 9.6 mmol) and KOH (10.8 g, 192 mmol) were added to a mixture of ethanol (18 ml) and water (7.5 ml). The mixture was heated under reflux for 4 h. The resulting mixture was neutralized with concentrated HCl. Then it was filtrated, the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol, then di-*tert*-butyl dicarbonate (11.5 mmol) and triethylamine (38.4 mmol) were added. The mixture was stirred for 18 h. Then it was concentrated *in vacuo*, the resulting residue was dissolved in ethyl acetate (30 ml). The organic phase was washed with 3% HCl (20 ml x 2) and water (20 ml), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with 5% MeOH in CH₂Cl₂. Yield of intermediate **7** 1.59 g (64%).

To a solution of compound **7** (1.59 g, 6.2 mmol) in 50 mL of dichloromethane were added 3 g of 3Å molecular sieves and a few drops of acetic acid, then pyridinium dichromate (4.9 g, 12.4 mmol) was added portionwise with stirring. The reaction mixture was stirred at room temperature for 18 h, filtered through a Celite layer, and the filter cake was washed with dichloromethane (50 mL). The filtrate was washed with 5% HCl, then dried over anhydrous Na₂SO₄, filtered, and evaporated. The residue was purified by column chromatography on silica gel eluting chloroform. Yield 3.54 g (76%). ¹H NMR (300 MHz, CDCl₃) δ 3.99 (td, J = 6.2, 2.0 Hz, 2H), 3.66 – 3.50 (m, 1H), 3.50 – 3.36 (m, 2H), 3.20 (t, J = 10.5 Hz, 1H), 2.62 – 2.43 (m, 4H), 2.13 (dtd, J = 12.8, 5.6, 1.5 Hz, 1H), 1.86 – 1.72 (m, 1H), 1.44 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 205.82, 154.36, 83.81, 82.96, 79.69, 79.60, 61.96, 55.09, 54.60, 49.15, 49.09, 44.20, 43.80, 41.68, 35.22, 34.45, 28.44. LCMS (ESI): m/z (M+H) calcd, 256.2; found, 256.2.

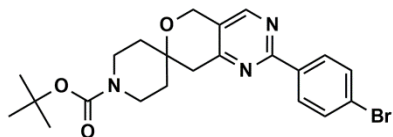
Synthesis and characterization of compounds **3**, **4** and **9**

General synthesis procedure 1 for the azaspirocyclic derivatives of dihydropyrano[4,3-*d*]pyrimidine **3, **4**, and **9** exemplified by the synthesis of *tert*-butyl 2'-phenyl-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (**3a**)**



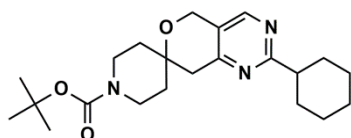
Ketone **1** (0.30 g, 1.1 mmol) was dissolved in 3 mL of dimethylformamide dimethyl acetal and heated under reflux for 2 h. Then the volatiles were removed *in vacuo*, and the residue was co-evaporated with toluene (10 mL). The residue was dissolved in 10 mL of methanol and then added to a methanolic solution (30 mL) of benzenecarboximidamide hydrochloride (0.20 g, 1.67 mmol) and sodium methoxide (60 mg, 2.2 mmol). The resulting mixture was heated at reflux for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with 5% aqueous citric acid (50 mL x 2) and water (50 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 33% ethyl acetate in hexane. Yield 0.190 g (45%). ¹H NMR (300 MHz, CDCl₃) δ 8.49 (s, 1H, Pyr), 8.46 – 8.39 (m, 2H), 7.52 – 7.46 (m, 3H), 4.83 (s, 2H, OCH₂Pyr), 3.91 – 3.76 (m, 2H), 3.26 (t, J = 12.3 Hz, 2H), 2.89 (s, 2H), 1.83 (d, J = 14.5 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.48 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 163.34, 161.53, 154.75, 152.84, 137.47, 130.46, 128.47, 127.93, 124.57, 79.54, 70.67, 59.08, 41.58, 39.32, 34.08, 28.38. LCMS (ESI): m/z (M+H) calcd, 382.2; found, 382.1.

***tert*-Butyl 2'-(4-bromophenyl)-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (3b)**



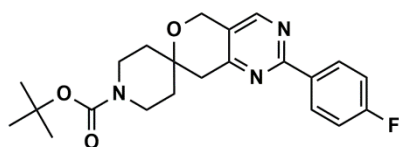
The compound was synthesized according to general procedure 1 from ketone **1** (0.30 g, 1.1 mmol) and 4-bromobenzenecarboximidamide (0.33 g, 1.67 mmol). Yield 0.19 g (37%). ¹H NMR (300 MHz, CDCl₃) δ 8.48 (s, 1H, Pyr), 8.34 – 8.29 (m, 2H), 7.64 – 7.59 (m, 2H), 4.83 (s, 2H, OCH₂Pyr), 3.84 (d, *J* = 13.2 Hz, 2H), 3.27 (t, *J* = 12.2 Hz, 2H), 2.88 (s, 2H), 1.83 (d, *J* = 13.7 Hz, 2H), 1.69 – 1.64 (m, 1H), 1.63 – 1.58 (m, 1H), 1.49 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 162.39, 161.69, 154.76, 152.90, 136.37, 131.68, 129.53, 125.26, 124.91, 79.62, 70.66, 59.06, 41.55, 39.32, 34.05, 28.39. LCMS (ESI): *m/z* (*M*+*H*) calcd, 460.1; found, 460.2.

***tert*-Butyl 2'-cyclohexyl-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (3c)**



The compound was synthesized according to general procedure 1 from ketone **1** (0.30 g, 1.1 mmol) and cyclohexanecarboximidamide (0.21 g, 1.67 mmol). Yield 0.22 g (51%). ¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 1H, Pyr), 4.75 (s, 2H, OCH₂Pyr), 3.88 – 3.71 (m, 2H), 3.23 (t, *J* = 12.3 Hz, 2H), 2.87 – 2.78 (m, 1H), 2.77 (s, 2H), 2.01 – 1.93 (m, 2H), 1.88 – 1.81 (m, 2H), 1.77 – 1.70 (m, 2H), 1.64 – 1.52 (m, 4H), 1.46 (s, 9H), 1.43 – 1.24 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 173.06, 161.00, 154.72, 152.61, 123.73, 79.54, 70.55, 58.91, 47.28, 41.34, 39.35, 34.04, 31.89, 28.36, 26.18, 25.86. LCMS (ESI): *m/z* (*M*+*H*) calcd, 388.3; found, 388.3.

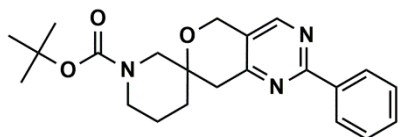
***tert*-Butyl 2'-(4-fluorophenyl)-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (3d)**



The compound was synthesized according to general procedure 1 from ketone **1** (0.30 g, 1.1 mmol) and 4-fluorobenzenecarboximidamide (0.23 g, 1.67 mmol). Yield 0.09 g (20%). ¹H NMR (300 MHz, CDCl₃) δ 8.47 (s, 1H, Pyr), 8.46 – 8.39 (m, 2H), 7.20 – 7.12 (m, 2H), 4.82 (s, 2H, OCH₂Pyr), 3.94 – 3.75 (m, 2H), 3.26 (t, *J* = 12.4 Hz, 2H), 2.87 (d, *J* = 1.1 Hz, 2H), 1.83 (d, *J* = 13.7 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.49 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 164.52 (d, ¹*J*_{CF} = 250.5 Hz), 162.38, 161.61, 154.76, 152.88, 133.62 (d, ⁴*J*_{CF} = 3.0 Hz), 130.02 (d, ³*J*_{CF} = 8.7 Hz), 124.49, 115.45 (d, ²*J*_{CF} = 21.6 Hz), 79.60, 70.64, 59.04, 41.56, 28.38. LCMS (ESI): *m/z* (*M*+*H*) calcd, 400.2; found, 400.2.

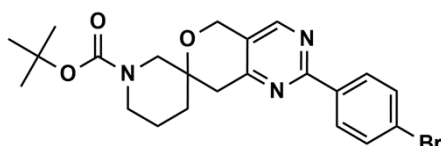
***tert*-Butyl
carboxylate (4a)**

2'-phenyl-5',8'-dihydrospiro[piperidine-3,7'-pyrano[4,3-*d*]pyrimidine]-1-



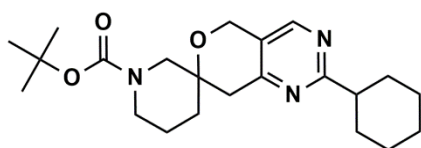
The compound was synthesized according to general procedure 1 from ketone **2** (0.50 g, 1.9 mmol) and benzenecarboximidamide (0.34 g, 2.8 mmol). Yield 0.22 g (30%). ¹H NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H, Pyr), 8.39 (s, 2H), 7.50 – 7.42 (m, 3H), 5.05 – 4.72 (m, 2H, OCH₂Pyr), 4.13 – 3.77 (m, 1H), 3.69 – 3.53 (m, 1H), 3.25 (s, 1H), 3.06 – 2.88 (m, 1H), 2.85 (s, 2H), 1.91 – 1.59 (m, 4H), 1.40 (d, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 163.28, 161.45, 154.53, 152.92, 137.53, 130.52, 128.57, 127.98, 124.96, 79.82, 70.90, 59.74, 50.20, 48.69, 44.40, 43.33, 39.40, 38.61, 34.89, 28.35, 21.05. LCMS (ESI): m/z (M+H) calcd, 382.2; found, 382.2.

***tert*-Butyl 2'-(4-bromophenyl)-5',8'-dihydrospiro[piperidine-3,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (4b)**



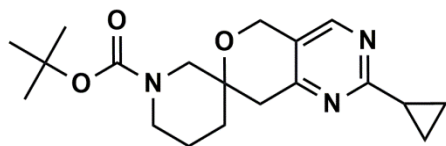
The compound was synthesized according to general procedure 1 from ketone **2** (0.12 g, 0.45 mmol) and 4-bromobenzenecarboximidamide (0.13 g, 0.67 mmol). Yield 0.065 g (32%). ¹H NMR (300 MHz, CDCl₃) δ 8.43 (s, 1H, Pyr), 8.27 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 5.03 – 4.74 (m, 2H, OCH₂Pyr), 4.04 – 3.51 (m, 2H), 3.34 – 2.88 (m, 2H), 2.83 (s, 2H), 1.90 – 1.79 (m, 2H), 1.69 – 1.52 (m, 2H), 1.49 – 1.33 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 162.44, 161.58, 154.74, 153.09, 136.62, 131.80, 129.71, 125.43, 125.34, 79.91, 71.00, 59.85, 50.35, 48.84, 44.43, 43.49, 39.36, 38.72, 35.05, 28.46, 21.17. LCMS (ESI): m/z (M+H) calcd, 460.1; found, 460.1.

***tert*-Butyl 2'-cyclohexyl-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (4c)**



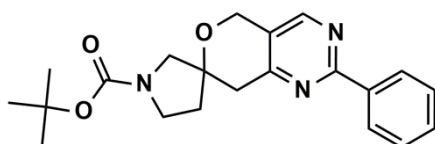
The compound was synthesized according to general procedure 1 from ketone **2** (0.25 g, 0.93 mmol) and cyclohexanecarboximidamide (0.18 g, 1.4 mmol). Yield 0.11 g (31%). ¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 1H, Pyr), 4.75 (s, 2H, OCH₂Pyr), 3.88 – 3.71 (m, 2H), 3.23 (t, J = 12.3 Hz, 2H), 2.87 – 2.78 (m, 1H), 2.77 (s, 2H), 2.01 – 1.93 (m, 2H), 1.88 – 1.81 (m, 2H), 1.77 – 1.70 (m, 2H), 1.64 – 1.52 (m, 4H), 1.46 (s, 9H), 1.43 – 1.24 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 173.06, 161.00, 154.72, 152.61, 123.73, 79.54, 70.55, 58.91, 47.28, 41.34, 39.35, 34.04, 31.89, 28.36, 26.18, 25.86. LCMS (ESI): m/z (M+H) calcd, 388.3; found, 388.3.

***tert*-Butyl 2'-cyclopropyl-5',8'-dihydrospiro[piperidine-3,7'-pyrano[4,3-*d*]pyrimidine]-1-carboxylate (4d)**



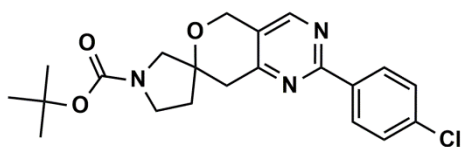
The compound was synthesized according to general procedure 1 from ketone **2** (0.25 g, 0.93 mmol) and cyclopropanecarboximidamide (0.12 g, 1.4 mmol). Yield 0.07 g (22%). ¹H NMR (300 MHz, CDCl₃) δ 8.24 (s, 1H, Pyr), 4.98 – 4.70 (m, 2H, OCH₂Pyr), 4.04 – 3.49 (m, 2H), 3.34 – 2.81 (m, 2H), 2.73 (s, 2H), 2.19 (ddd, *J* = 13.4, 8.1, 4.8 Hz, 1H), 1.89 – 1.78 (m, 2H), 1.69 – 1.52 (m, 2H), 1.43 (s, 9H), 1.13 – 1.00 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 170.51, 160.76, 154.74, 152.70, 123.65, 79.87, 70.88, 59.73, 50.39, 48.82, 44.46, 43.48, 38.58, 35.02, 28.48, 21.17, 18.00, 10.54, 10.42. LCMS (ESI): *m/z* (M+H) calcd, 346.2; found, 346.2.

***tert*-Butyl 2-phenyl-5,8-dihydrospiro[pyrano[4,3-*d*]pyrimidine-7,3'-pyrrolidine]-1'-carboxylate (9a)**



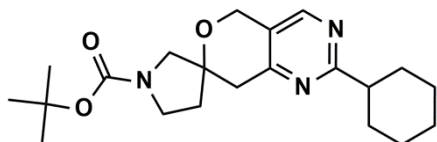
The compound was synthesized according to general procedure 1 from ketone **8** (0.36 g, 1.4 mmol) and benzenecarboximidamide (0.25 g, 2.1 mmol). Yield 0.11 g (21%). ¹H NMR (300 MHz, CDCl₃) δ 8.52 (s, 1H, Pyr), 8.47 – 8.38 (m, 2H), 7.54 – 7.46 (m, 3H), 4.90 (s, 2H, OCH₂Pyr), 3.75 – 3.51 (m, 3H), 3.30 (d, *J* = 11.9 Hz, 1H), 3.17 – 3.00 (m, 2H), 2.27 – 2.15 (m, 1H), 1.98 – 1.81 (m, 1H), 1.49 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 163.33, 161.38, 154.51, 153.20, 137.42, 130.62, 128.57, 128.04, 124.45, 80.15, 79.60, 79.30, 60.34, 54.96, 53.96, 44.41, 44.10, 38.19, 35.18, 33.87, 28.50. LCMS (ESI): *m/z* (M+H) calcd, 368.2; found, 368.2.

***tert*-Butyl 2-(4-chlorophenyl)-5,8-dihydrospiro[pyrano[4,3-*d*]pyrimidine-7,3'-pyrrolidine]-1'-carboxylate (9b)**



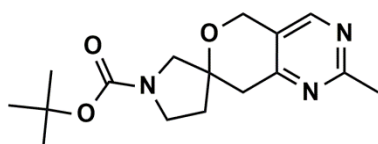
The compound was synthesized according to general procedure 1 from ketone **8** (0.15 g, 0.59 mmol) and 4-chlorobenzenecarboximidamide (0.14 g, 0.88 mmol). Yield 0.04 g (17%). ¹H NMR (300 MHz, CDCl₃) δ 8.47 (s, 1H, Pyr), 8.37 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 4.87 (s, 2H, OCH₂Pyr), 3.73 – 3.50 (m, 3H), 3.28 (d, *J* = 11.8 Hz, 1H), 3.12 – 2.95 (m, 2H), 2.23 – 2.14 (m, 1H), 1.95 – 1.80 (m, 1H), 1.47 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 162.37, 161.58, 154.59, 153.35, 136.95, 135.97, 129.48, 128.90, 124.80, 80.22, 79.82, 79.75, 79.38, 60.52, 60.36, 55.04, 53.98, 44.50, 44.19, 38.19, 35.24, 33.87, 28.61. LCMS (ESI): *m/z* (M+H) calcd, 402.2; found, 402.2.

***tert*-Butyl 2-cyclohexyl-5,8-dihydrospiro[pyrano[4,3-*d*]pyrimidine-7,3'-pyrrolidine]-1'-carboxylate (9c)**



The compound was synthesized according to general procedure 1 from ketone **8** (0.15 g, 0.59 mmol) and cyclohexanecarboximidamide (0.11 g, 0.88 mmol). Yield 0.065 g (30%). ¹H NMR (300 MHz, CDCl₃) δ 8.37 (s, 1H, Pyr), 4.82 (s, 2H, OCH₂Pyr), 3.69 – 3.49 (m, 3H), 3.26 (d, J = 11.9 Hz, 1H), 3.07 – 2.90 (m, 2H), 2.84 (tt, J = 11.9, 3.4 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.07 – 1.96 (m, 2H), 1.91 – 1.71 (m, 4H), 1.70 – 1.57 (m, 2H), 1.48 (s, 9H), 1.44 – 1.25 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 173.26, 161.00, 153.06, 123.78, 80.24, 79.70, 79.38, 60.52, 60.30, 55.12, 54.05, 47.48, 44.54, 44.24, 38.17, 35.44, 34.01, 32.10, 28.65, 26.40, 26.11. LCMS (ESI): m/z (M+H) calcd, 374.2; found, 374.2.

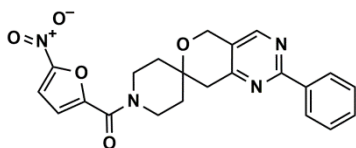
***tert*-Butyl 2-methyl-5,8-dihydrospiro[pyrano[4,3-*d*]pyrimidine-7,3'-pyrrolidine]-1'-carboxylate (9d)**



The compound was synthesized according to general procedure 1 from ketone **8** (0.15 g, 0.59 mmol) and acetamidine (0.05 g, 0.88 mmol). Yield 0.060 g (33%). ¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 1H, Pyr), 4.82 (s, 2H, OCH₂Pyr), 3.68 – 3.47 (m, 3H), 3.24 (d, J = 11.8 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.70 (s, 3H), 2.21 – 2.12 (m, 1H), 1.93 – 1.75 (m, 1H), 1.46 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 166.41, 160.93, 154.33, 152.83, 123.43, 79.90, 79.42, 79.03, 60.14, 59.94, 54.83, 53.66, 44.24, 43.95, 37.77, 35.13, 33.64, 28.37, 25.58. LCMS (ESI): m/z (M+H) calcd, 306.2; found, 306.2.

Synthesis and characterization of compounds 10-12

General synthesis procedure 2 for compounds 10-12 exemplified by synthesis of 1-(5-nitro-2-furoyl)-2'-phenyl-5',8'-dihydrospiro[piperidine-4,7'-pyrano[4,3-*d*]pyrimidine] (10)

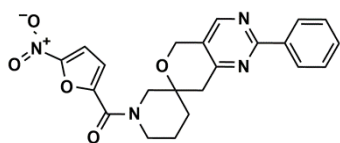


To a solution of 5-nitrofuranic acid (0.035 g, 0.222 mmol) in DMF (3 mL), CDI (0.048 g, 0.296 mmol) was added at 0°C, and the mixture was stirred at 0°C for 1 h.

Compound **3a** (0.28 mmol) was dissolved in 4M HCl in dioxane (1.5 mL); the resulting mixture was stirred for 3 h. The volatiles were removed *in vacuo*, and the residue was dissolved in DMF (3 mL). Triethylamine (125 μL, 0.9 mmol) was added; the solution was stirred for 30 min and added dropwise to the above mixture of 5-nitrofuranic acid and CDI. The reaction was stirred at room temperature for 18 h, poured into water (25 mL), and then extracted with ethyl acetate (3×20 mL). The organic layers were combined and washed with brine, then dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10% methanol in dichloromethane. Yield 0.025 g (26%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (s, 1H, Pyr), 8.40 – 8.35 (m, 2H), 7.76 (d, J = 3.9 Hz, 1H), 7.54 – 7.49 (m, 3H), 7.26 (d, J = 3.9 Hz, 1H), 4.86 (s, 2H, OCH₂Pyr), 4.22 – 3.90 (m, 2H), 3.69 – 3.34 (m, 2H), 2.91 (s, 2H), 1.87 (d, J = 14.0 Hz, 2H),

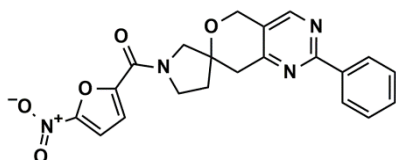
1.81 – 1.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.10, 161.62, 157.03, 154.14, 151.54, 148.29, 137.51, 130.99, 129.05, 127.88, 125.76, 117.11, 113.30, 70.76, 58.92, 41.06, 34.63, 33.28. LCMS (ESI): m/z ($M+H$) calcd, 420.1; found, 420.1.

1-(5-Nitro-2-furoyl)-2'-phenyl-5',8'-dihydrospiro[piperidine-3,7'-pyrano[4,3-*d*]pyrimidine] (11)



The compound was synthesized according to general procedure 2 from compound **4a**. Yield 0.067 g (35%). ^1H NMR (300 MHz, DMSO- d_6) δ 8.67 and 8.59 (2s, 1H, Pyr), 8.36 (s, 2H), 7.73 (d, J = 25.1 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.32 – 7.24 (m, 1H), 4.91 – 4.68 (m, 2H, OCH_2Pyr), 4.29 (t, J = 14.1 Hz, 1H), 4.03 (t, J = 14.6 Hz, 1H), 3.29 – 3.13 (m, 1H), 3.09 – 2.71 (m, 3H), 1.98 – 1.60 (m, 4H). ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.18, 161.24, 158.08, 157.32, 154.06, 151.53, 148.15, 137.48, 130.98, 129.01, 127.89, 125.68, 117.32, 113.18, 71.37, 59.54, 59.07, 54.58, 48.10, 46.85, 43.10, 33.61, 30.74, 21.71, 20.52. LCMS (ESI): m/z ($M+H$) calcd, 420.1; found, 420.1.

1-(5-Nitro-2-furoyl)-2'-phenyl-5',8'-dihydrospiro[pyrano[4,3-*d*]pyrimidine-7,3'-pyrrolidine] (12)



The compound was synthesized according to general procedure 2 from compound **9a**. Yield 0.029 g (30%). ^1H NMR (300 MHz, CDCl_3) δ 8.54 (s, 1H, Pyr), 8.50 – 8.38 (m, 2H), 7.57 – 7.45 (m, 3H), 7.41 – 7.29 (m, 2H), 4.92 (m, 2H, OCH_2Pyr), 4.29 – 4.07 (m, 2H), 3.99 – 3.50 (m, 2H), 3.32 – 3.05 (m, 2H), 2.51 – 2.30 (m, 1H), 2.15 – 1.84 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.52, 161.00, 160.89, 156.16, 156.11, 153.47, 151.54, 148.85, 137.40, 137.36, 130.86, 128.74, 128.16, 124.24, 124.16, 118.26, 118.07, 111.92, 80.64, 77.91, 60.47, 60.36, 57.01, 55.59, 46.39, 46.07, 37.70. LCMS (ESI): m/z ($M+H$) calcd, 406.1; found, 406.1.

NMR Spectra

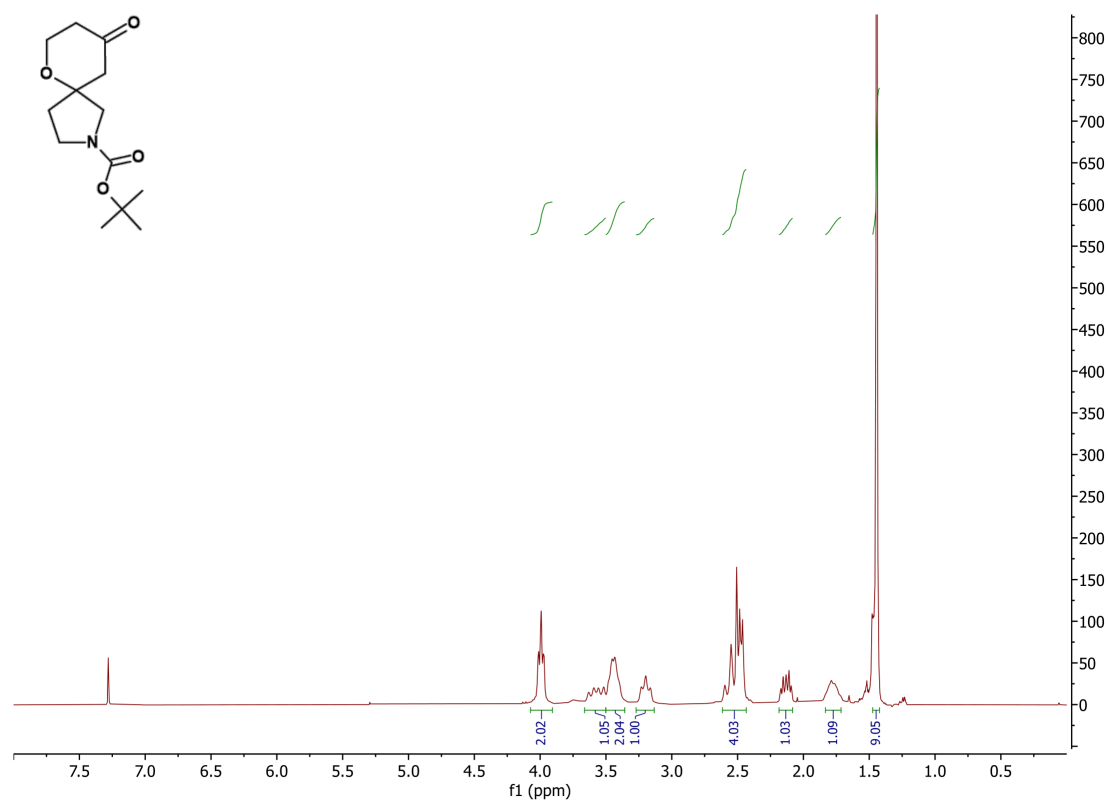


Figure S1 ¹H NMR spectrum of **8** in CDCl₃.

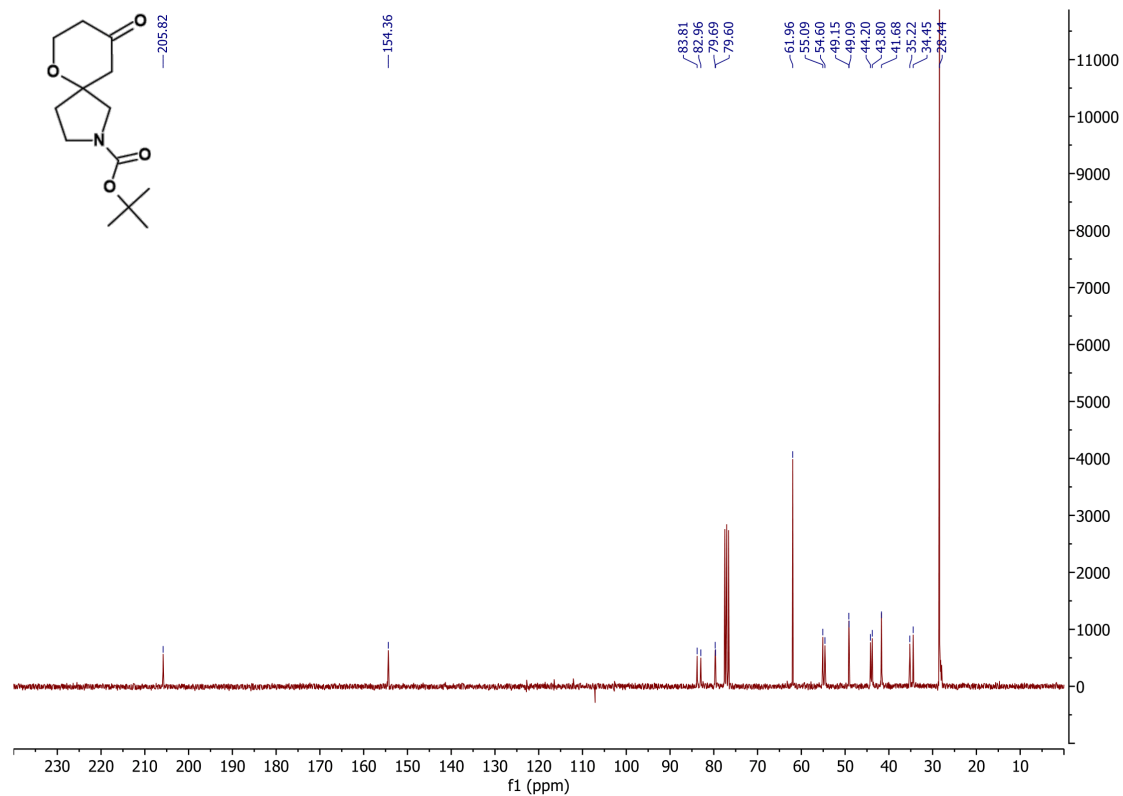


Figure S2 ¹³C NMR spectrum of **8** in CDCl₃.

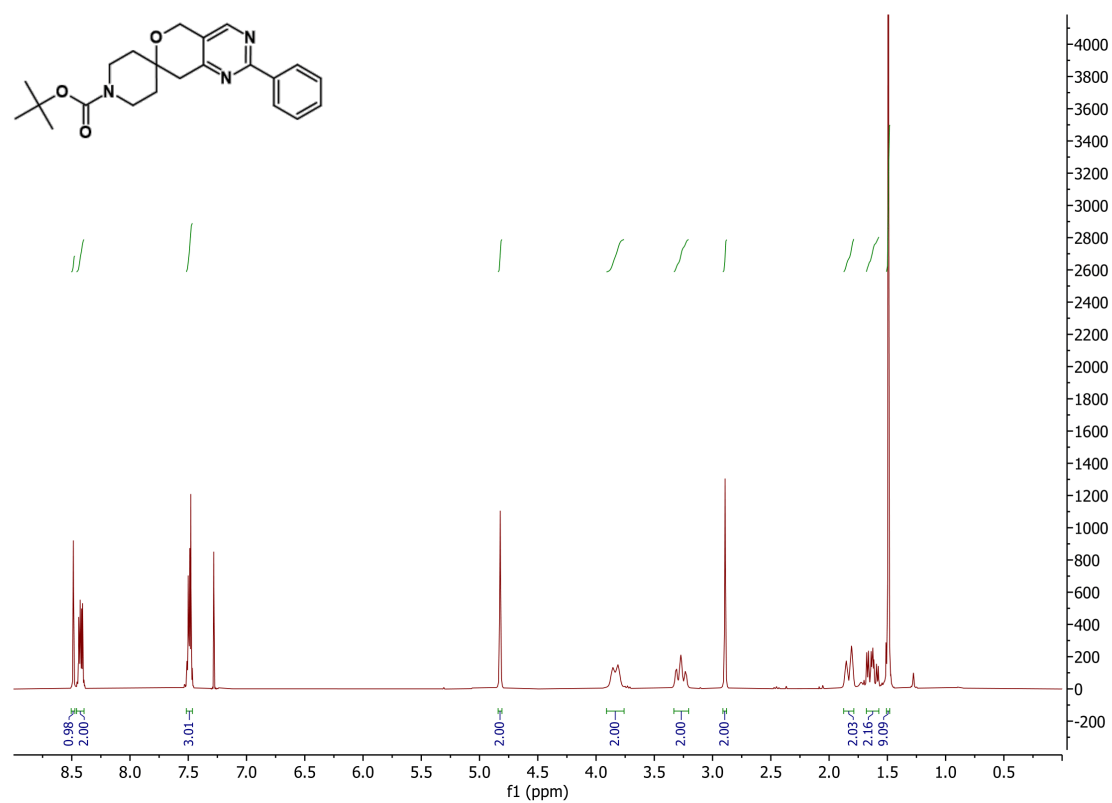


Figure S3 ¹H NMR spectrum of **3a** in CDCl₃.

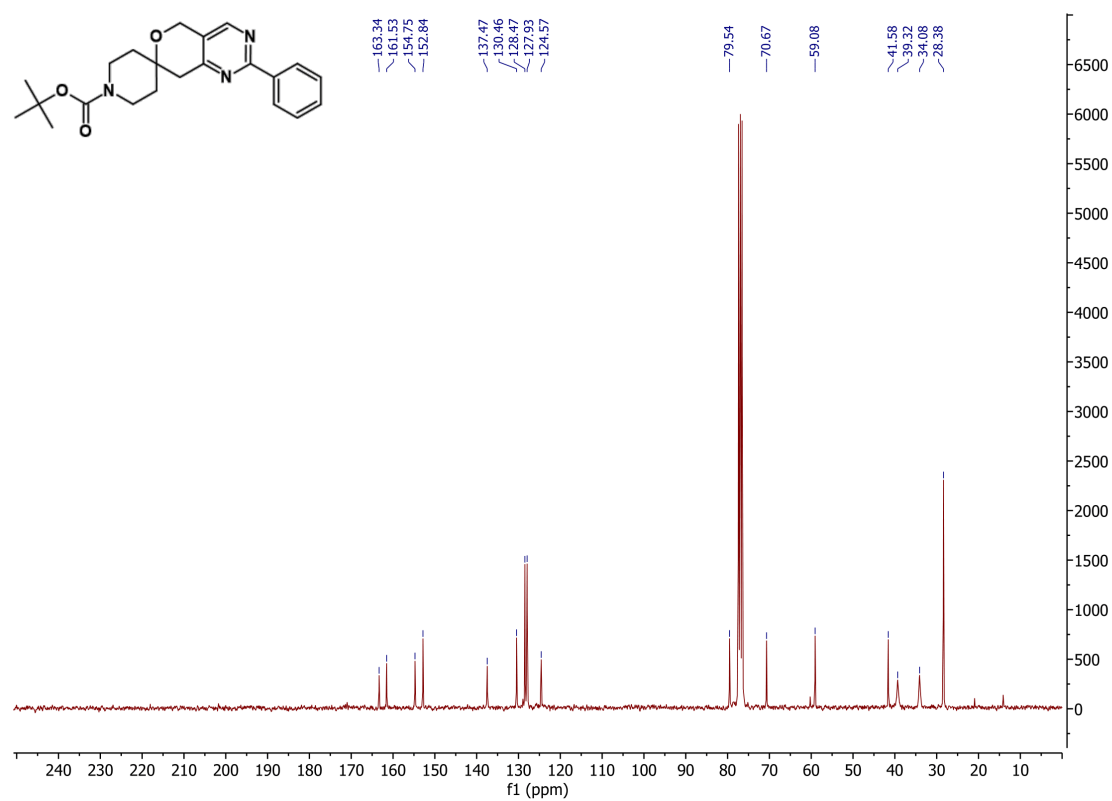


Figure S4 ¹³C NMR spectrum of **3a** in CDCl₃.

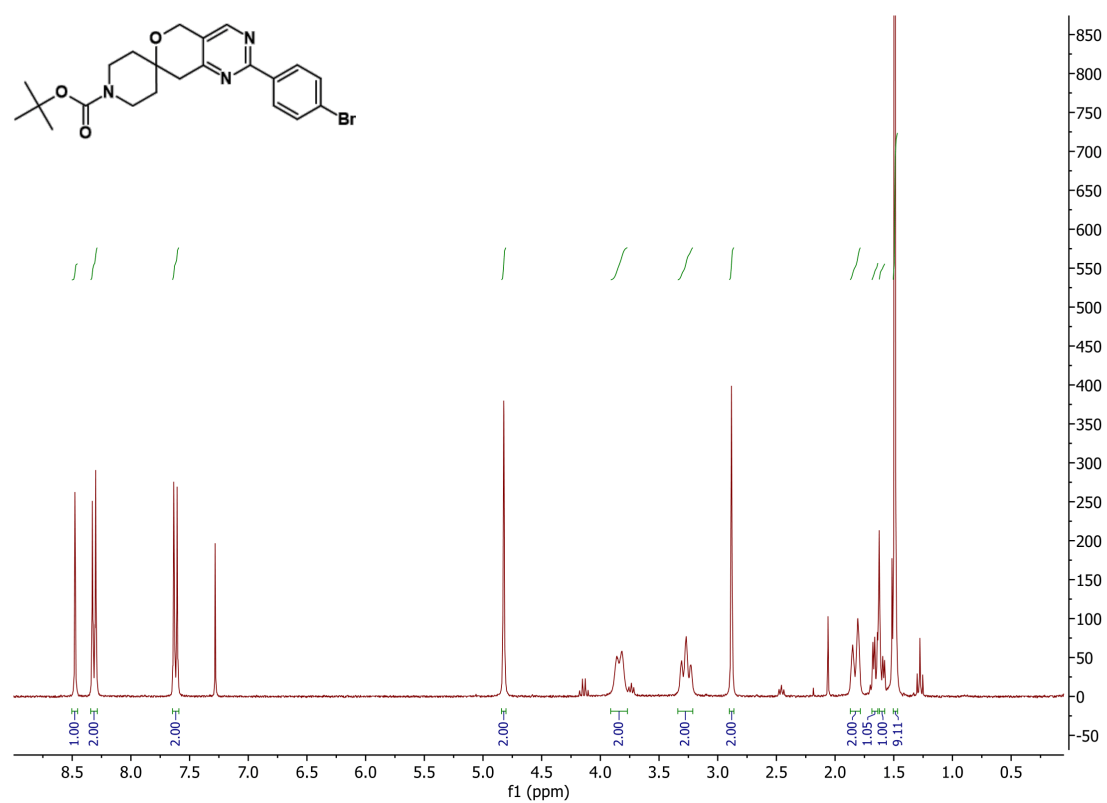


Figure S5 ¹H NMR spectrum of **3b** in CDCl₃.

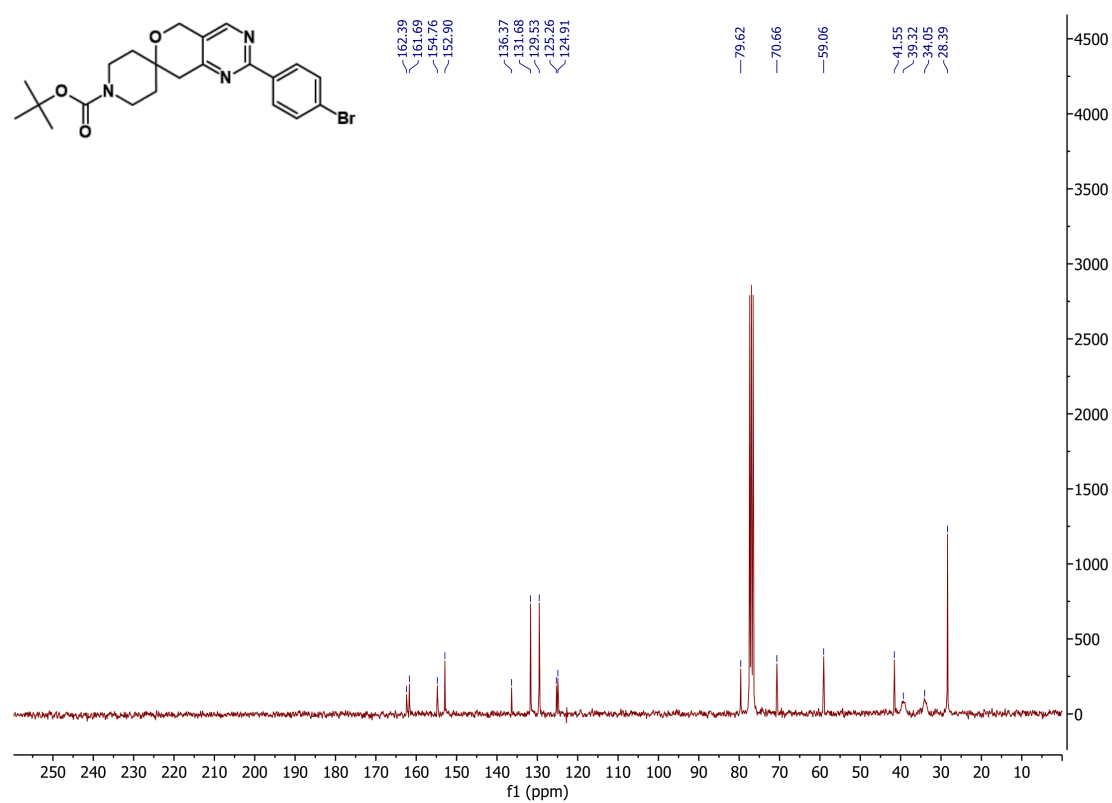


Figure S6 ¹³C NMR spectrum of **3b** in CDCl₃.

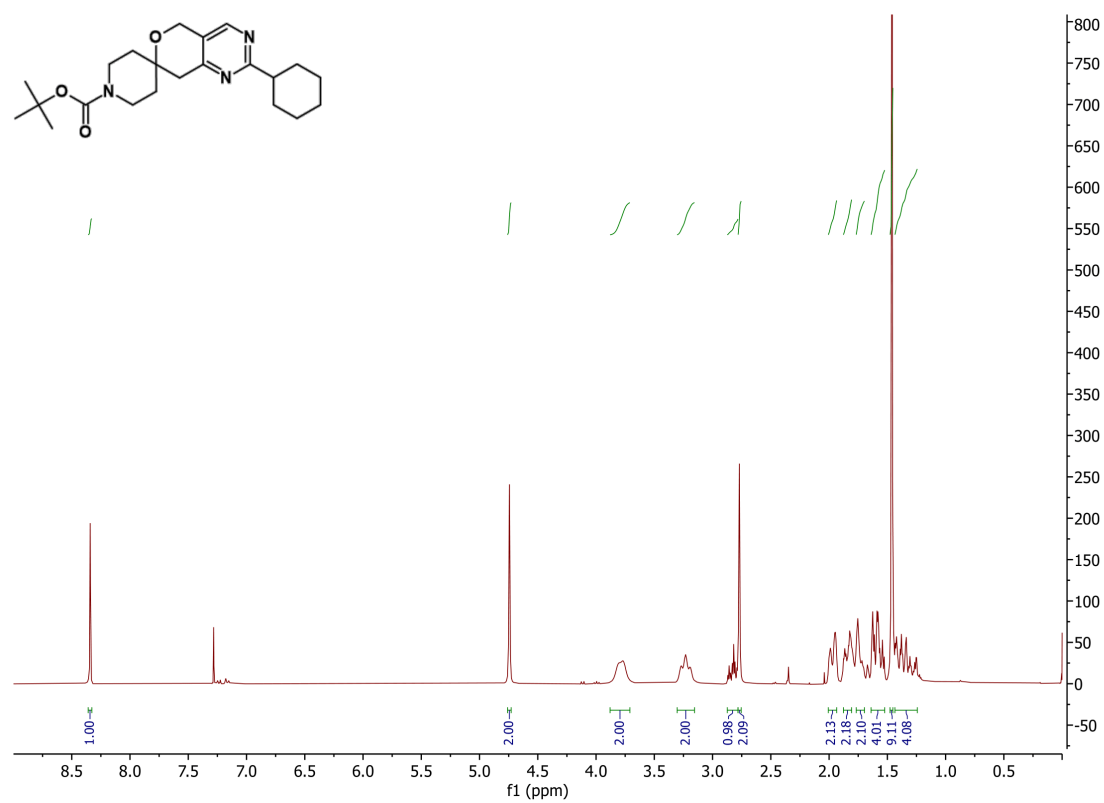


Figure S7 ¹H NMR spectrum of **3c** in CDCl₃.

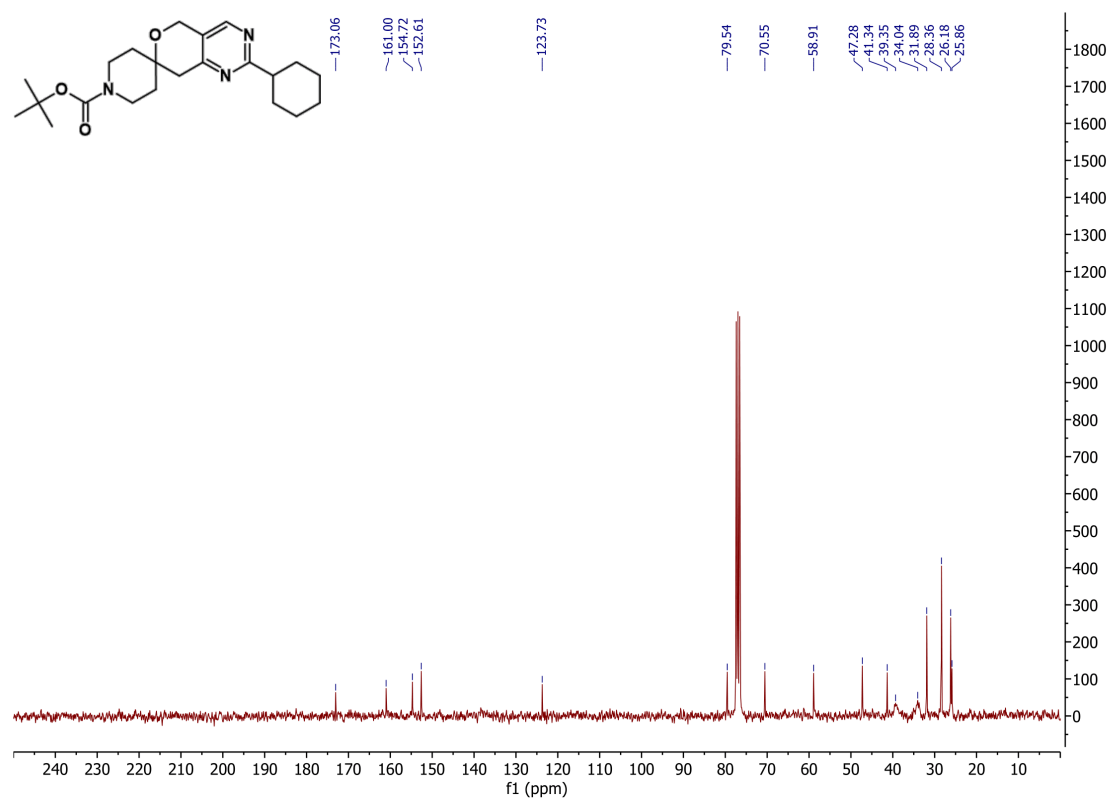


Figure S8 ¹³C NMR spectrum of **3c** in CDCl₃.

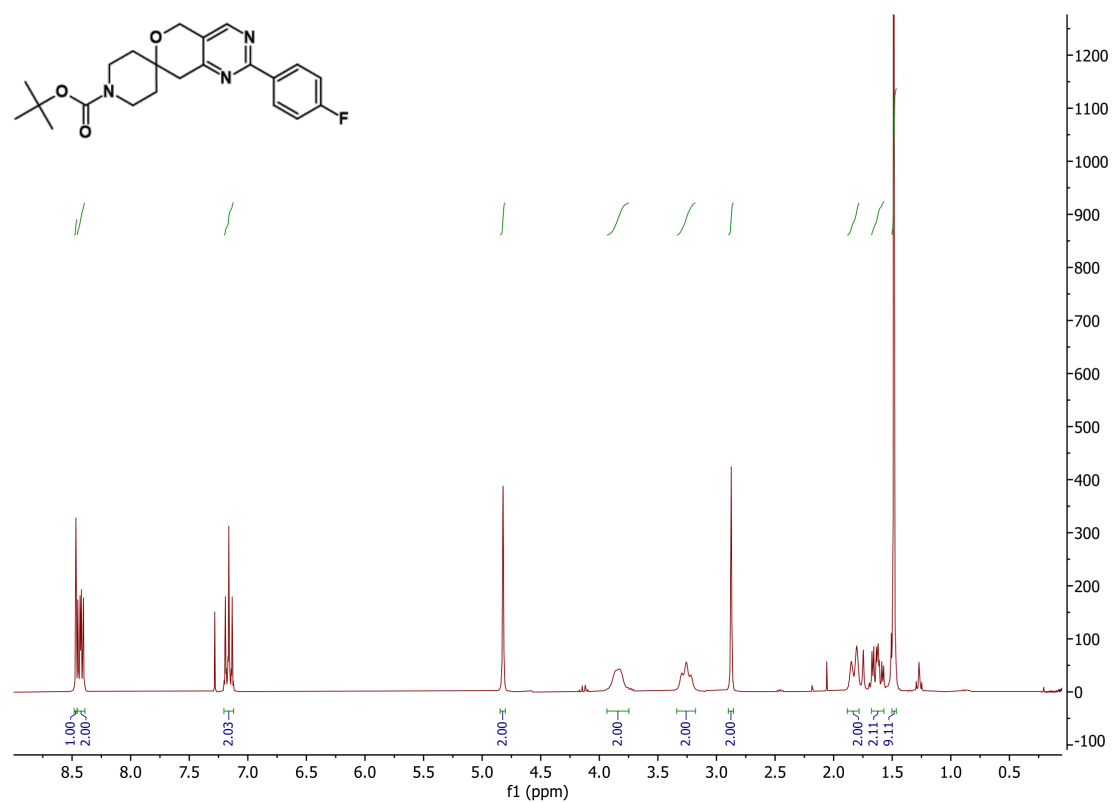


Figure S9 ¹H NMR spectrum of **3d** in CDCl₃.

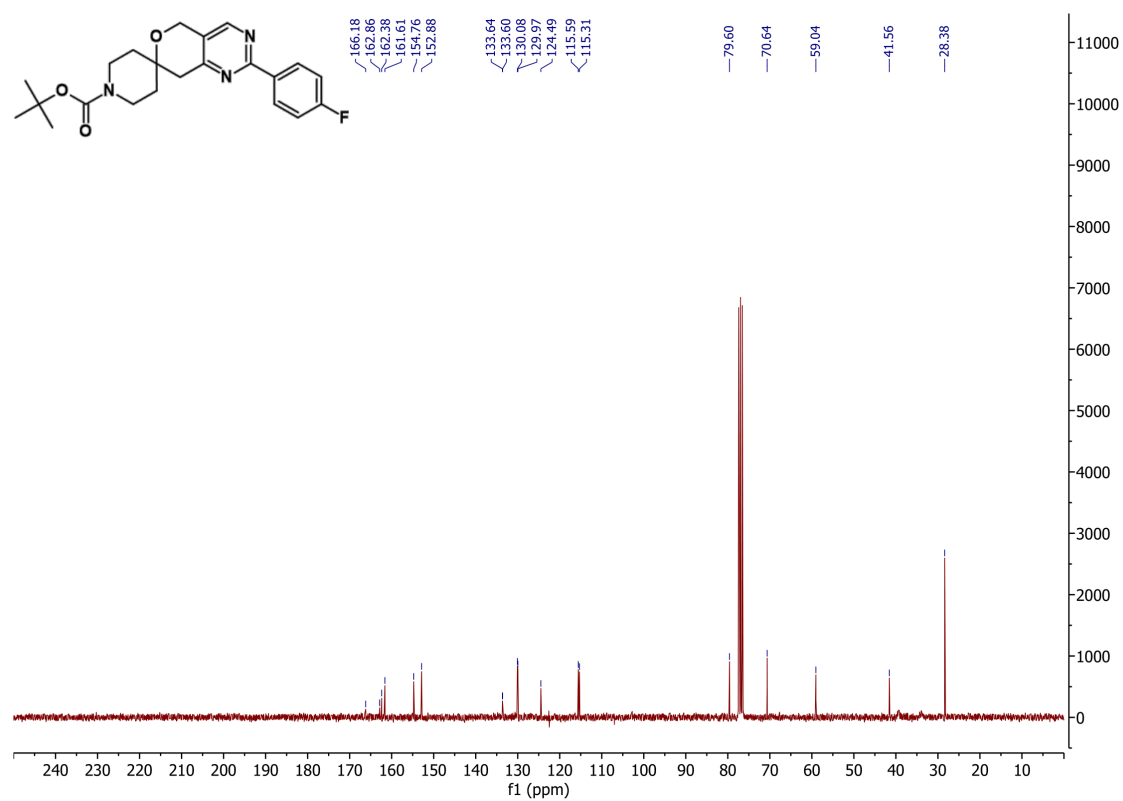


Figure S10 ¹³C NMR spectrum of **3d** in CDCl₃.

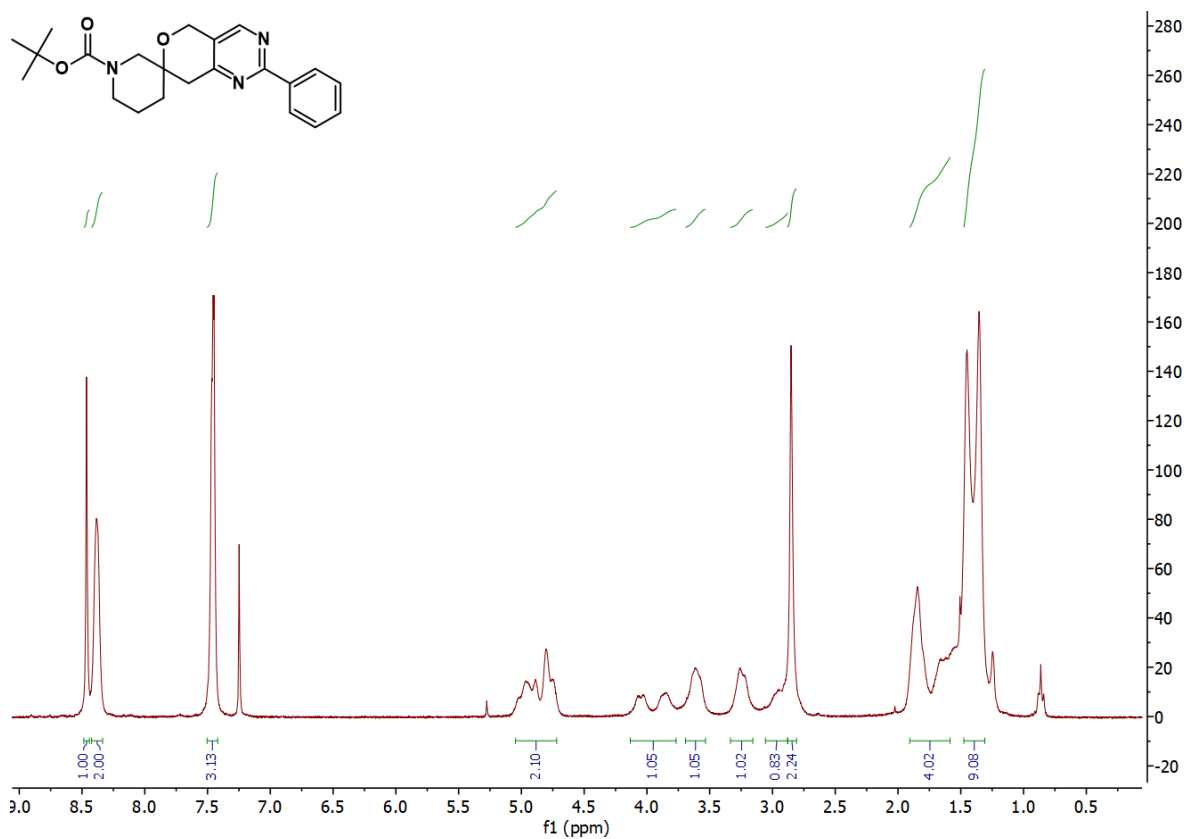


Figure S11 ¹H NMR spectrum of **4a** in CDCl₃.

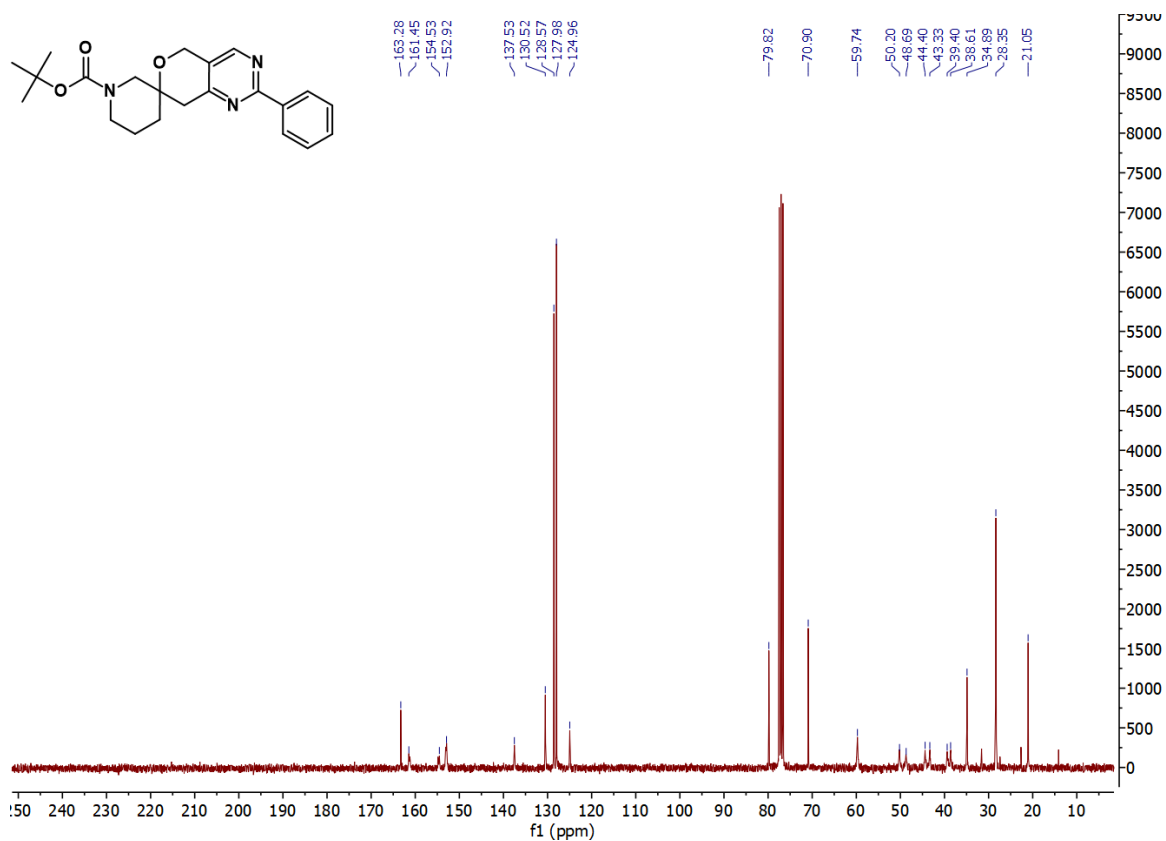


Figure S12 ¹³C NMR spectrum of **4a** in CDCl₃.

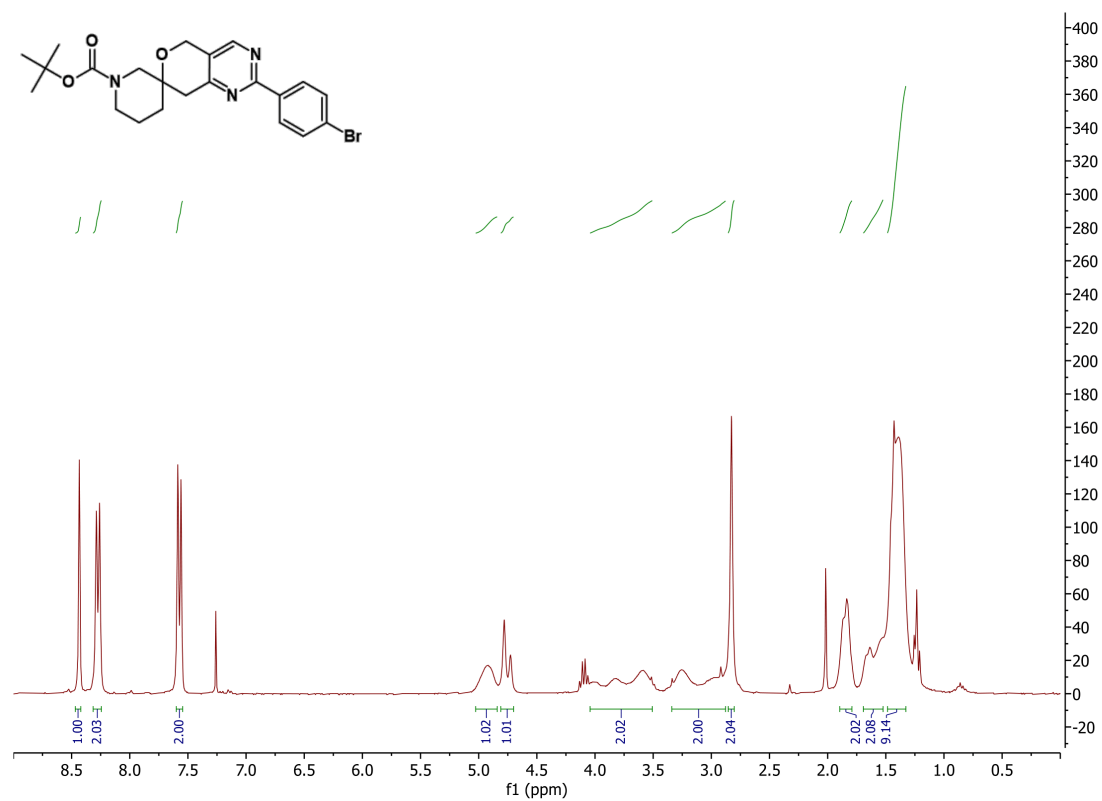


Figure S13 ¹H NMR spectrum of **4b** in CDCl₃.

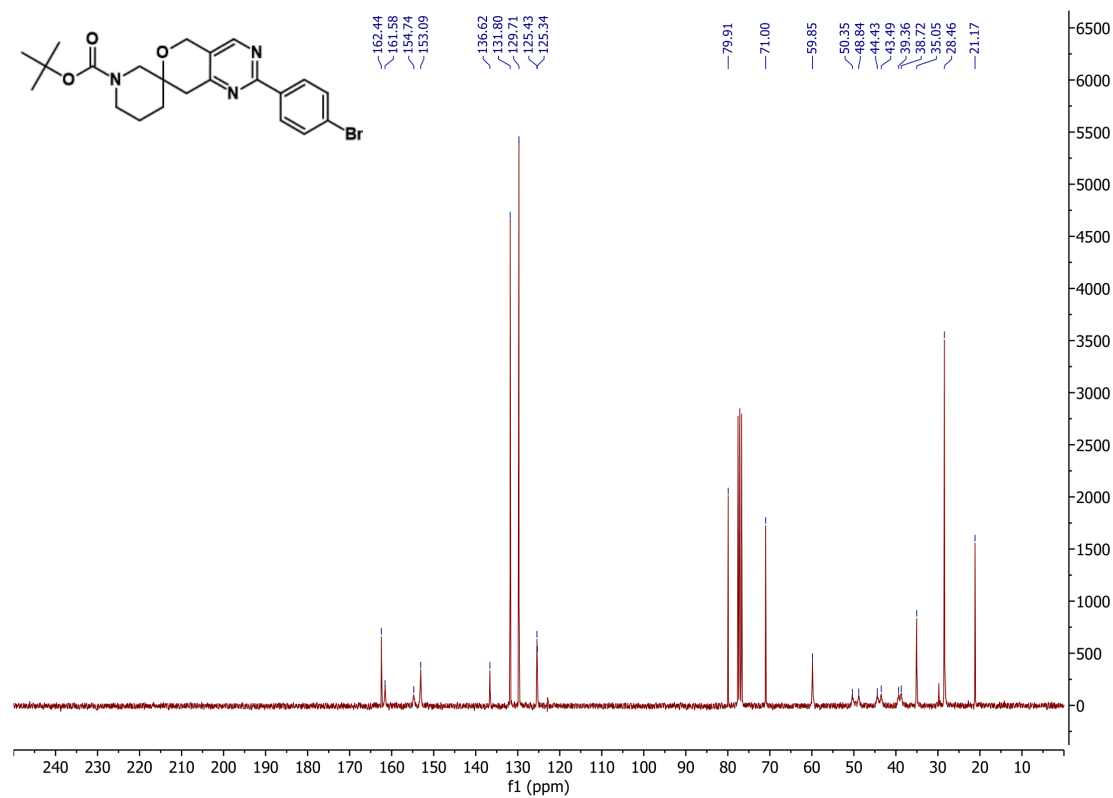


Figure S14 ¹³C NMR spectrum of **4b** in CDCl₃.

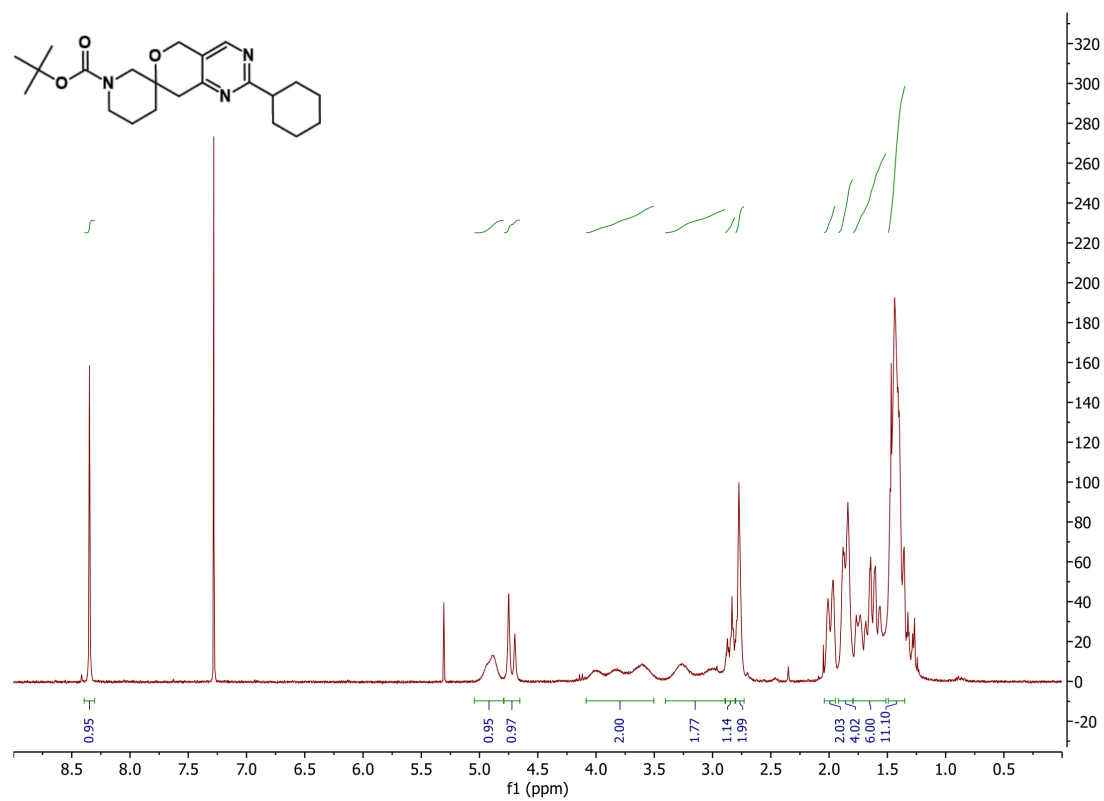


Figure S15 ¹H NMR spectrum of **4c** in CDCl₃.

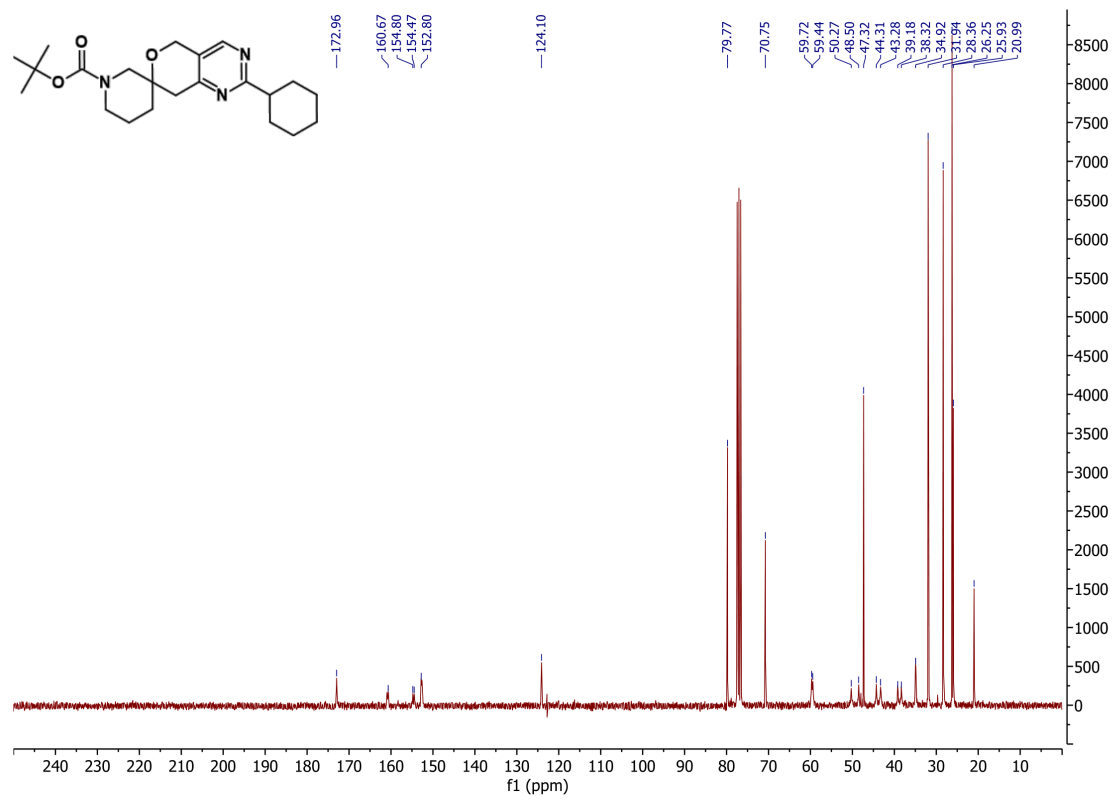


Figure S16 ¹³C NMR spectrum of **4c** in CDCl₃.

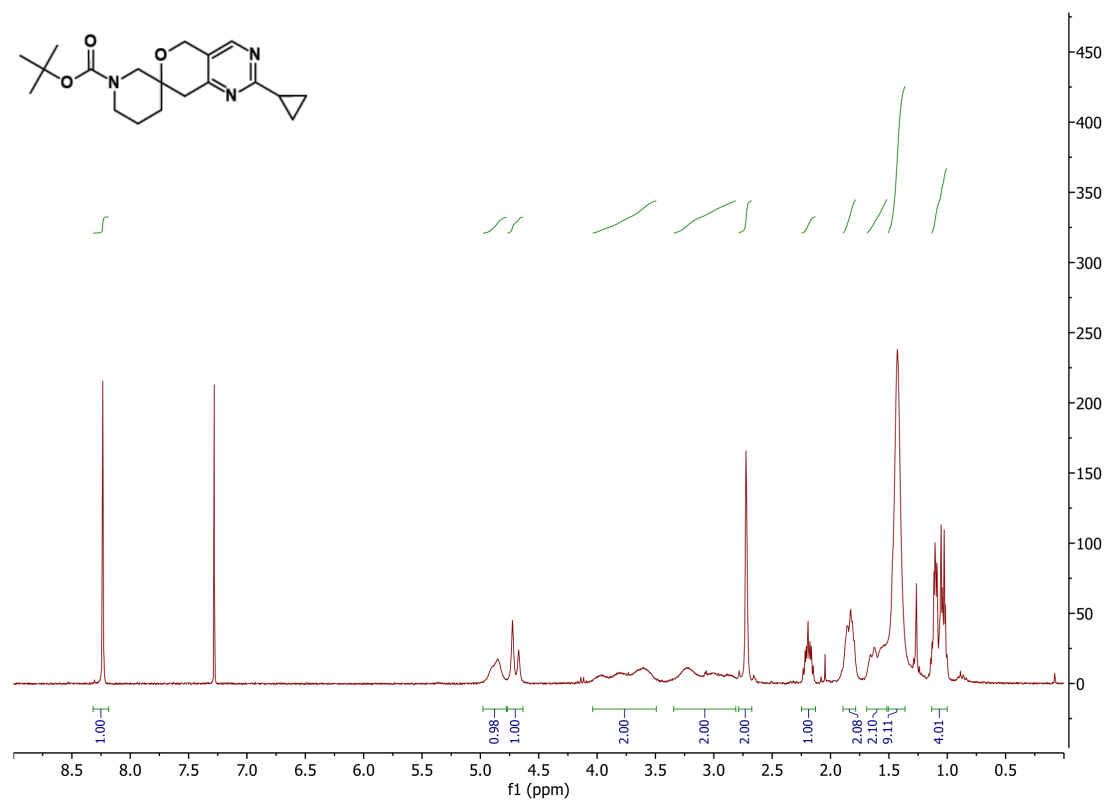


Figure S17 ¹H NMR spectrum of **4d** in CDCl₃.

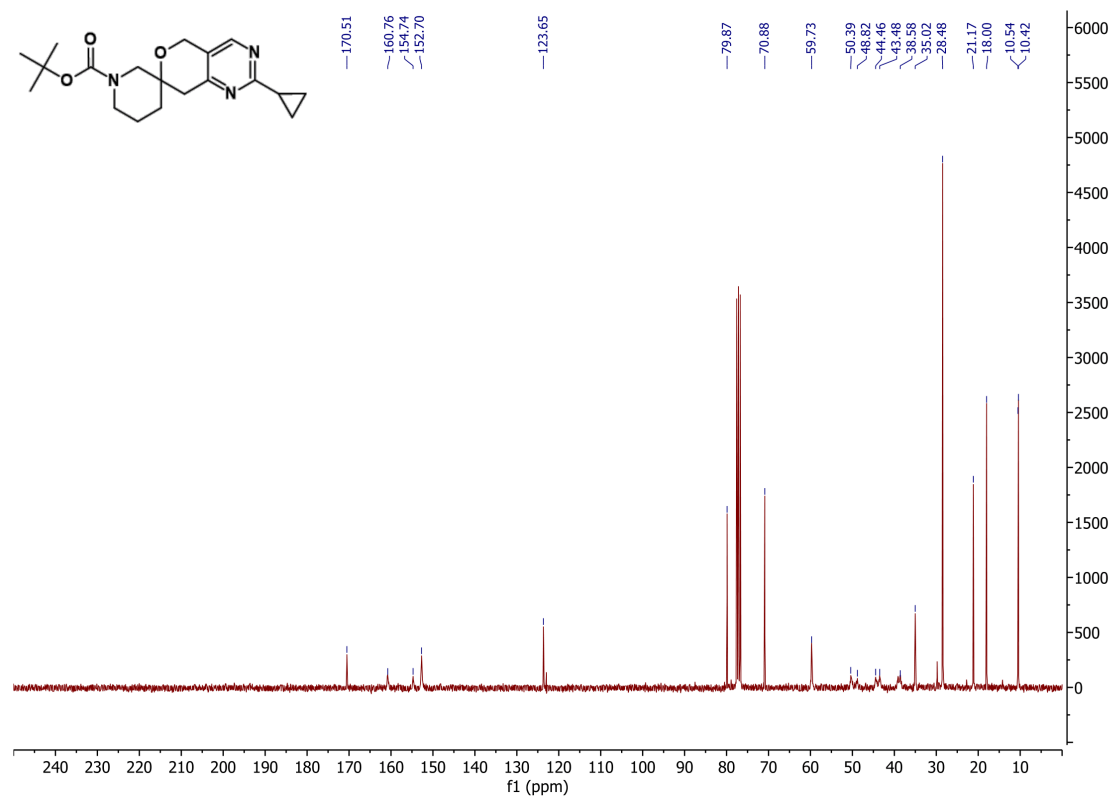


Figure S18 ¹³C NMR spectrum of **4d** in CDCl₃.

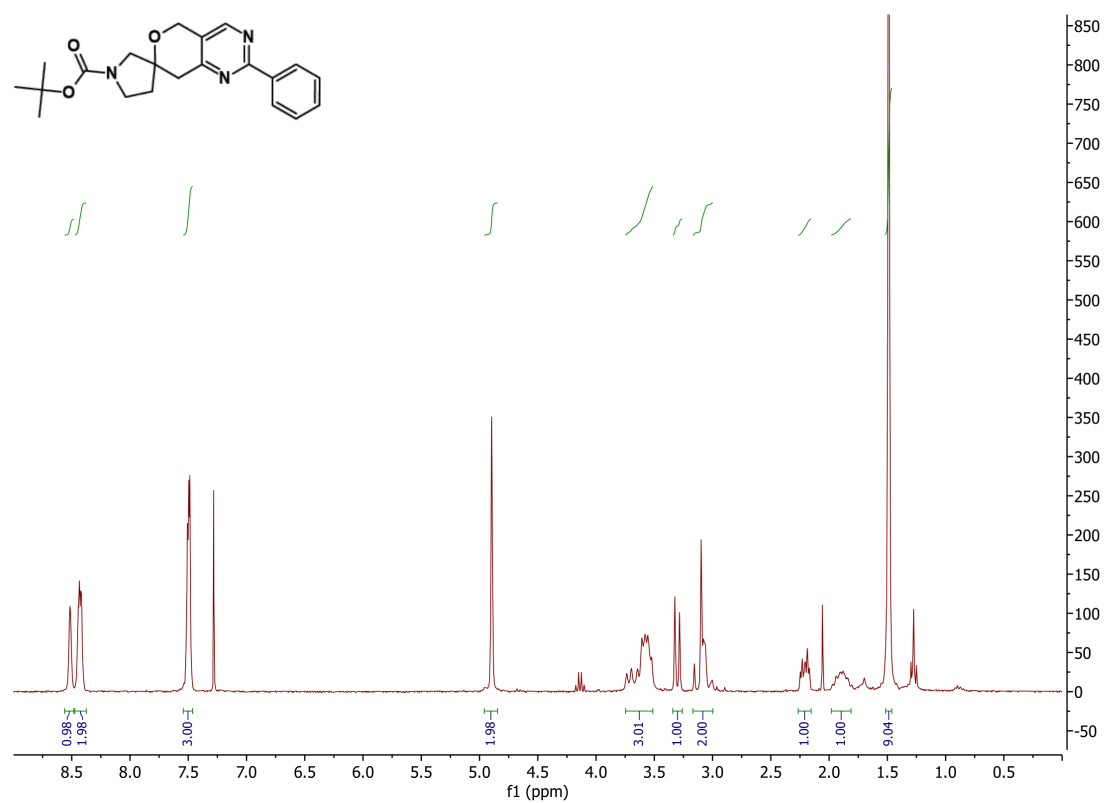


Figure S19 ¹H NMR spectrum of **9a** in CDCl₃.

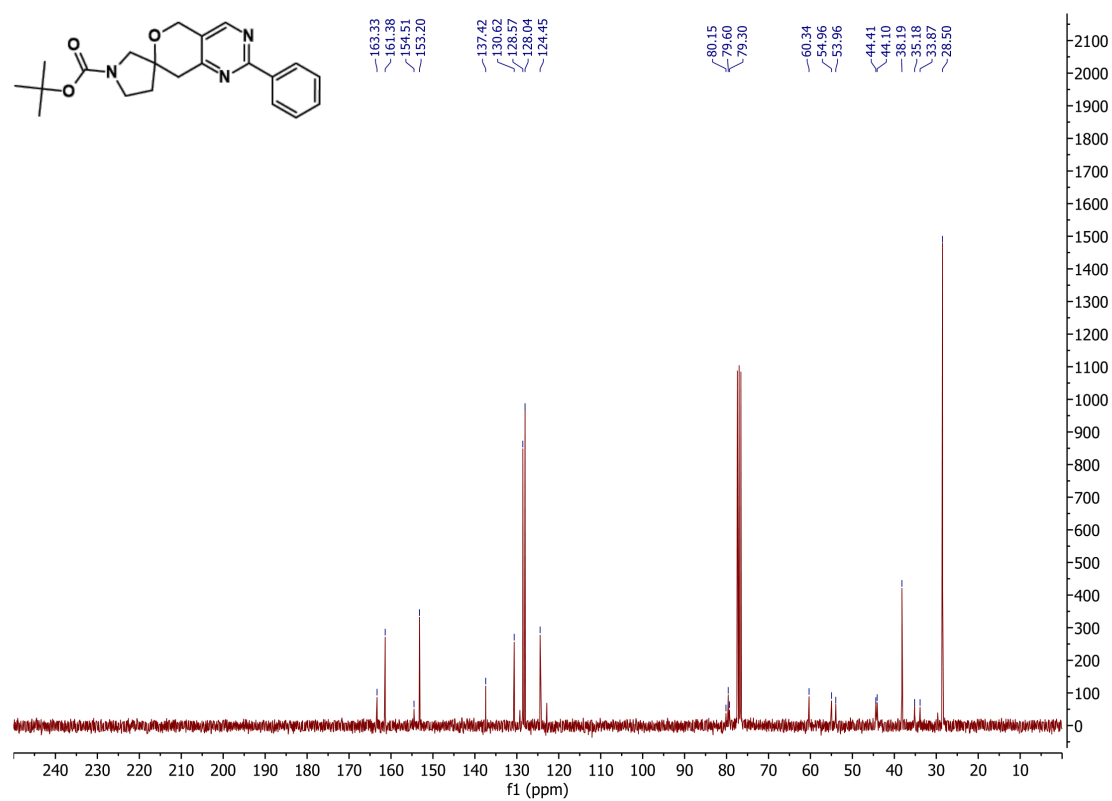


Figure S20 ¹³C NMR spectrum of **9a** in CDCl₃.

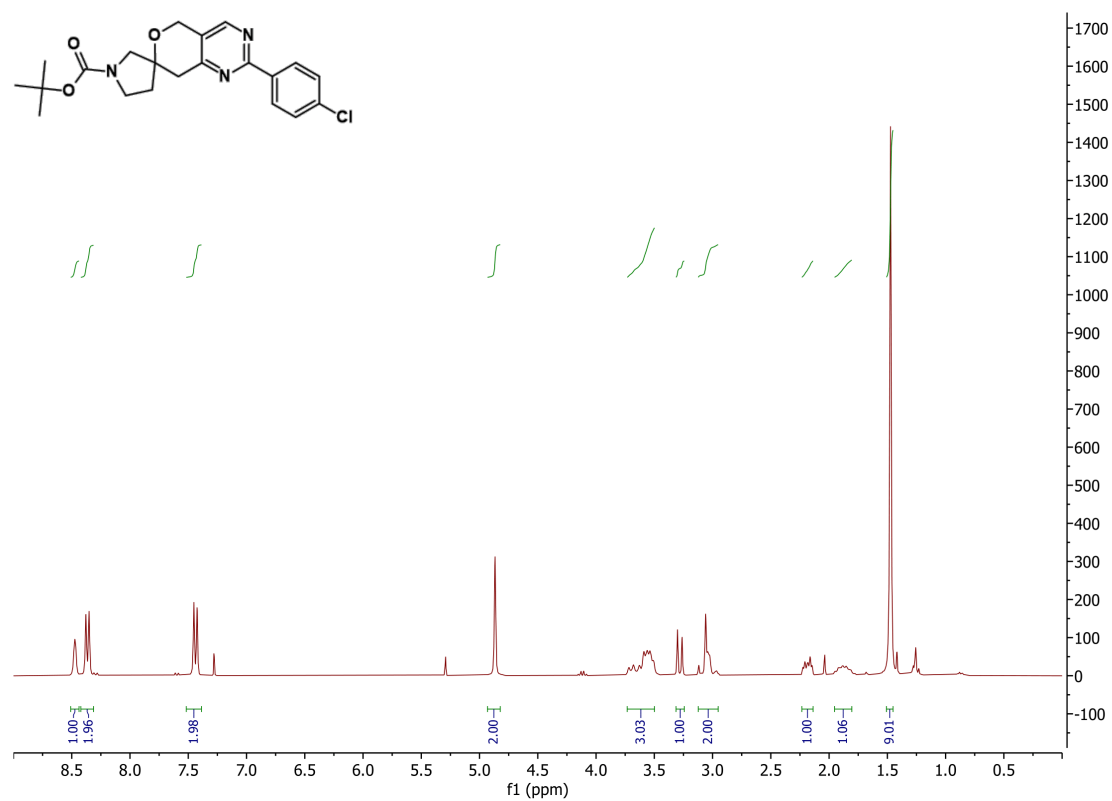


Figure S21 ¹H NMR spectrum of **9b** in CDCl₃.

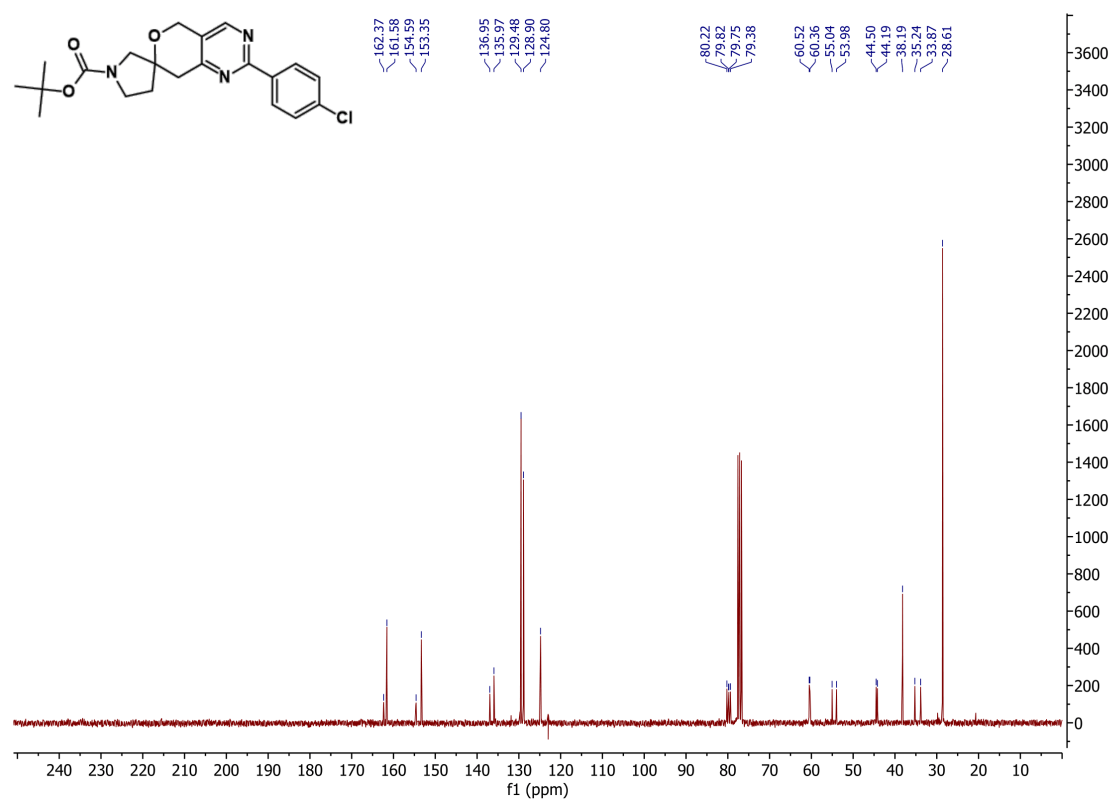


Figure S22 ¹³C NMR spectrum of **9b** in CDCl₃.

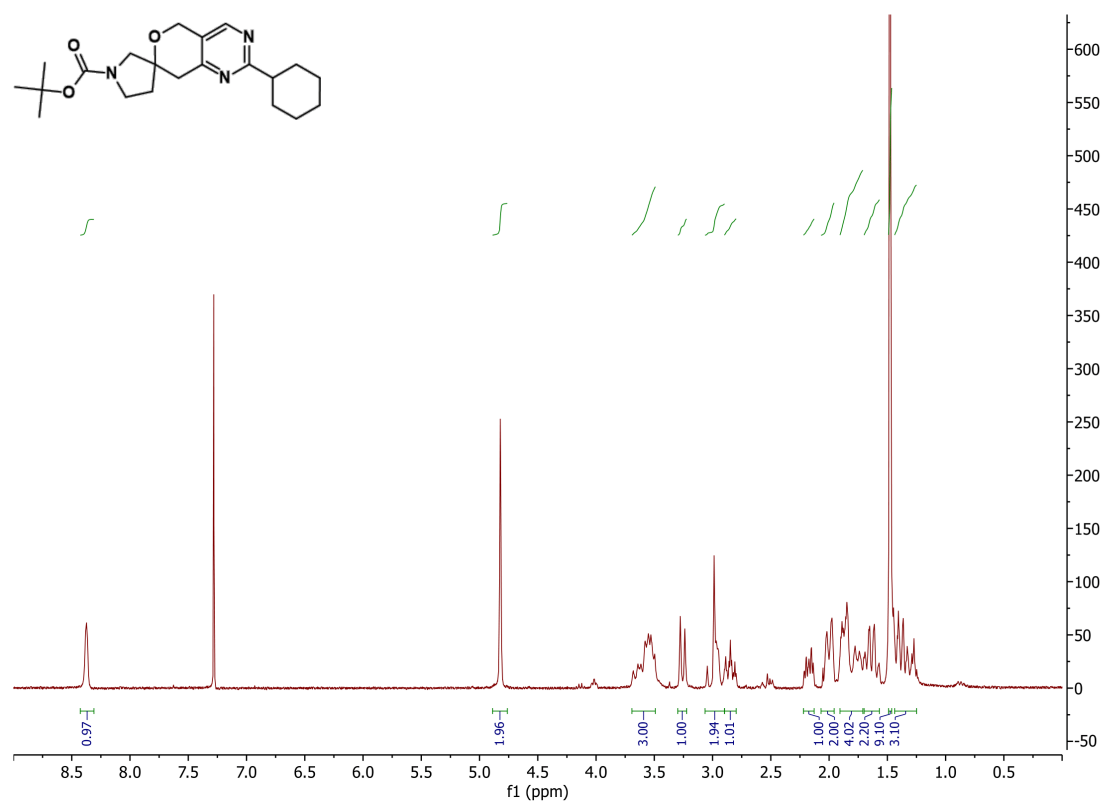


Figure S23 ¹H NMR spectrum of **9c** in CDCl₃.

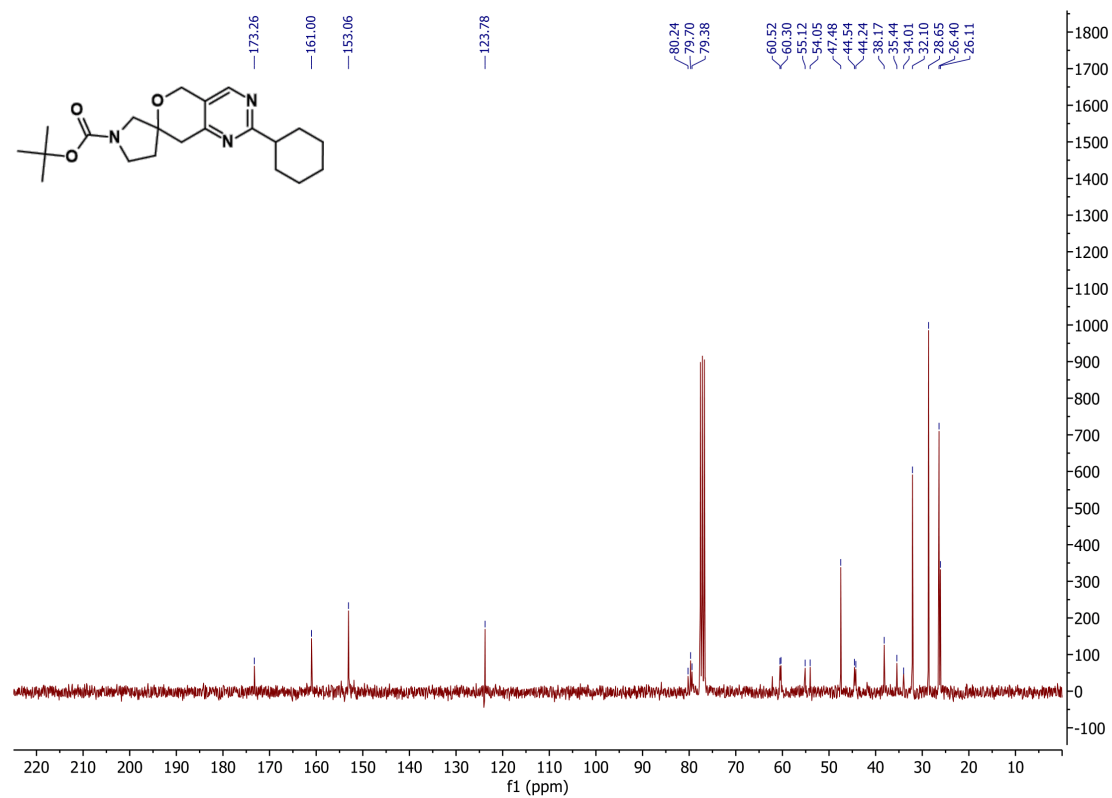


Figure S24 ¹³C NMR spectrum of **9c** in CDCl₃.

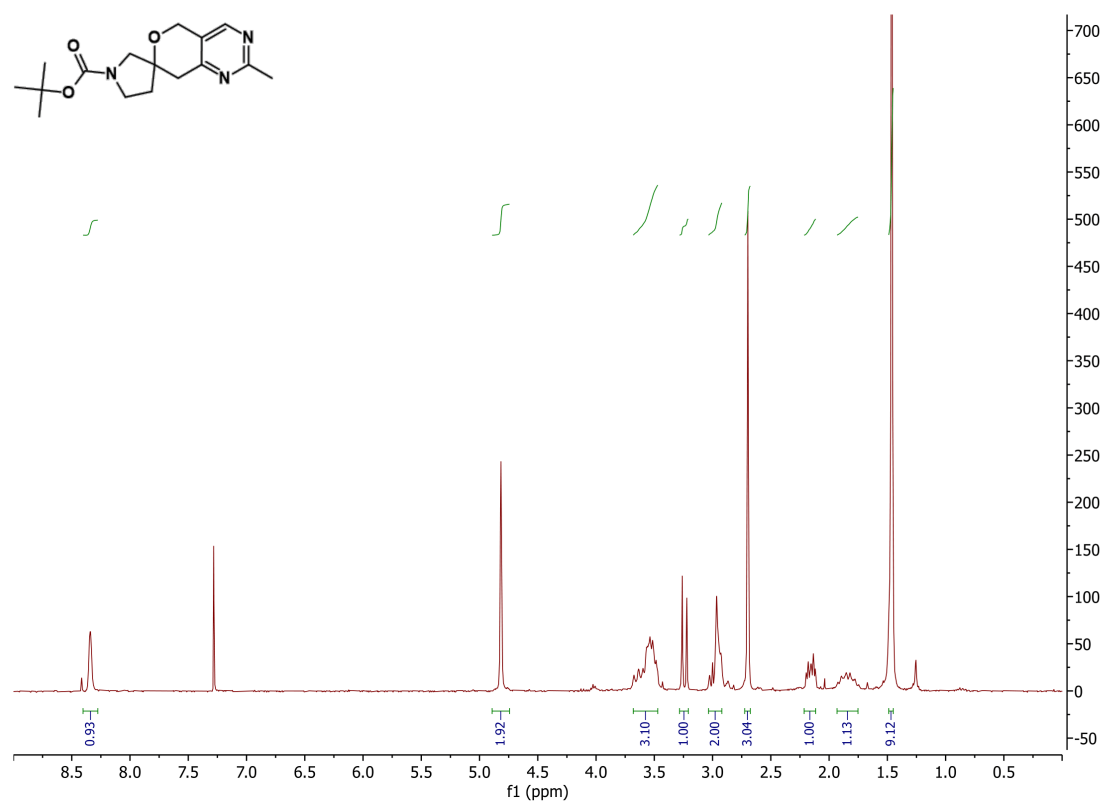


Figure S25 ¹H NMR spectrum of **9d** in CDCl₃.

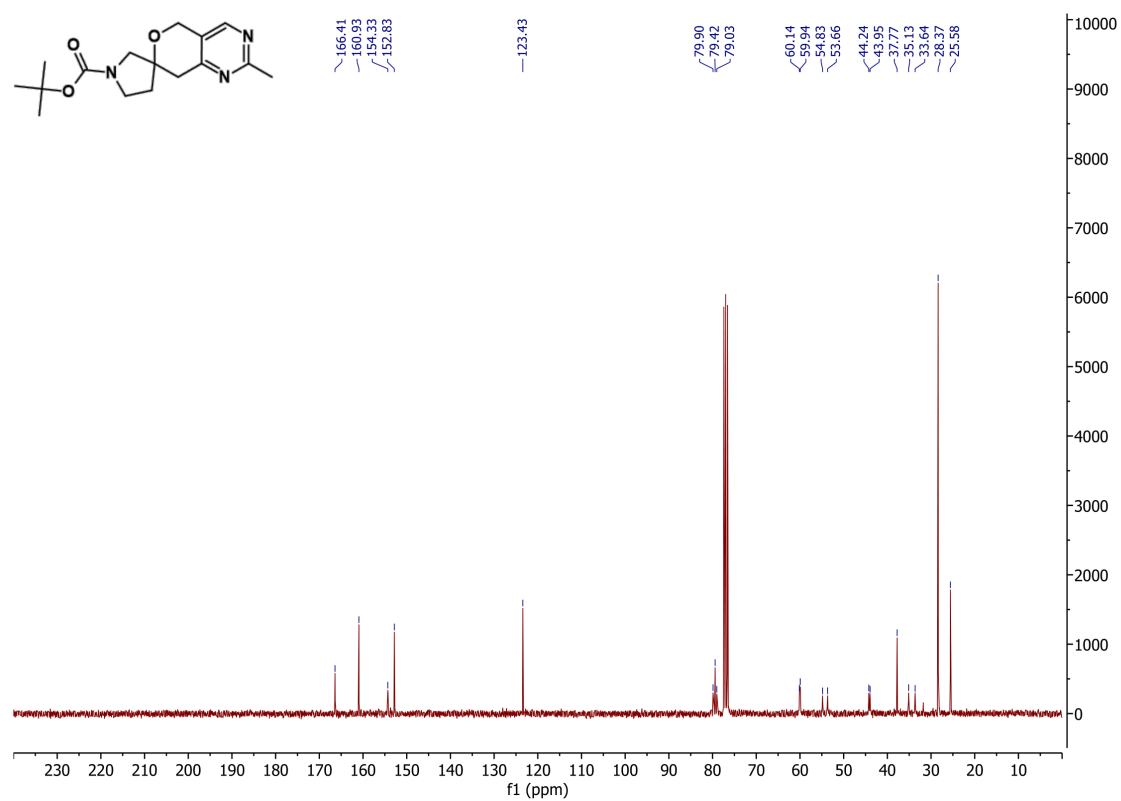


Figure S26 ¹³C NMR spectrum of **9d** in CDCl₃.

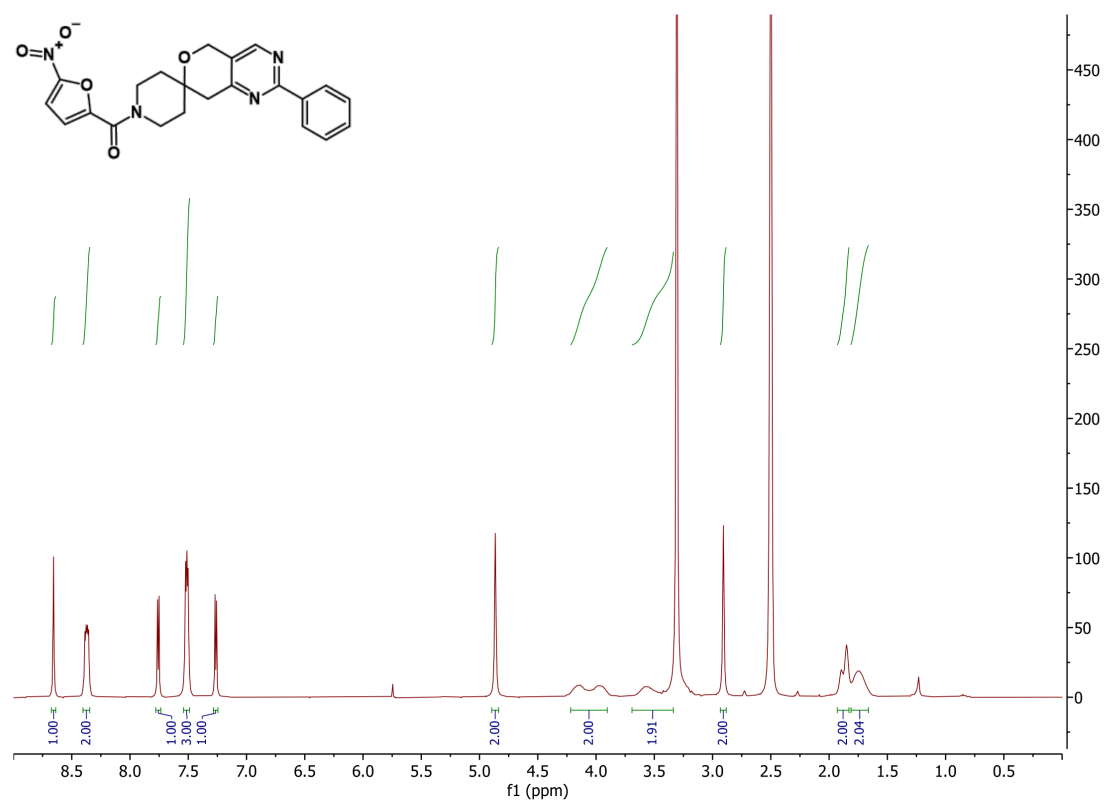


Figure S27 ¹H NMR spectrum of **10** in DMSO-d₆.

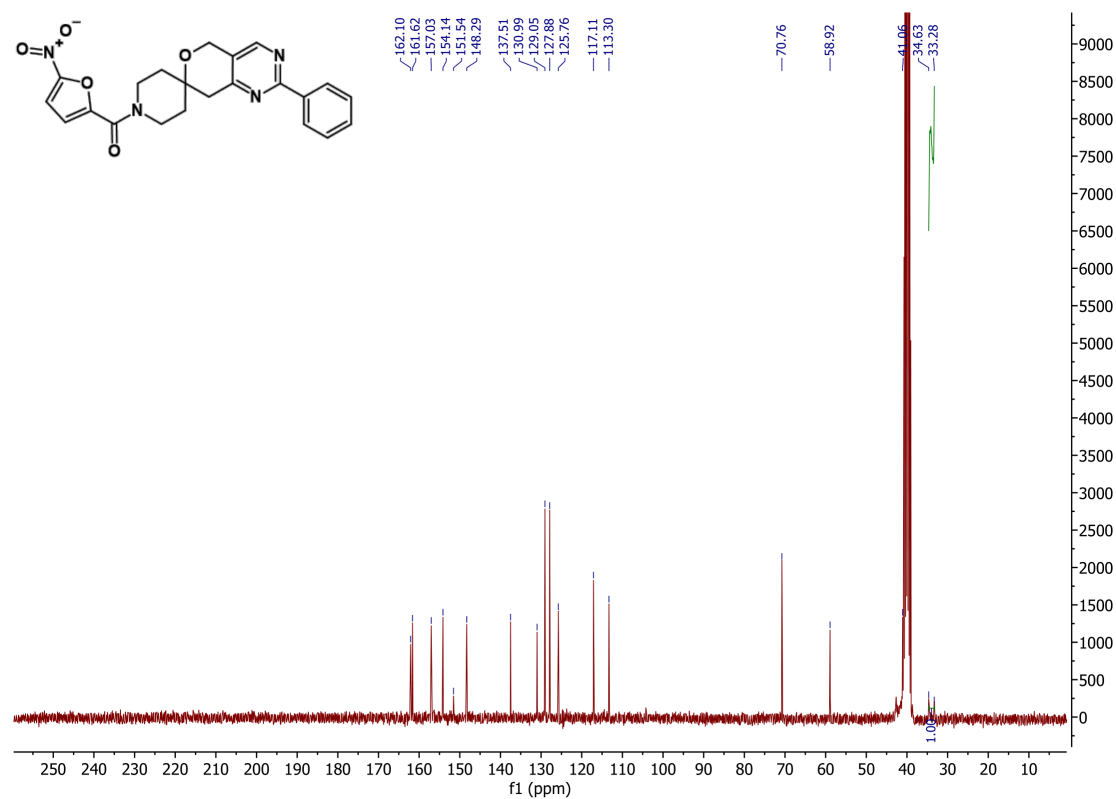


Figure S28 ¹³C NMR spectrum of **10** in DMSO-d₆.

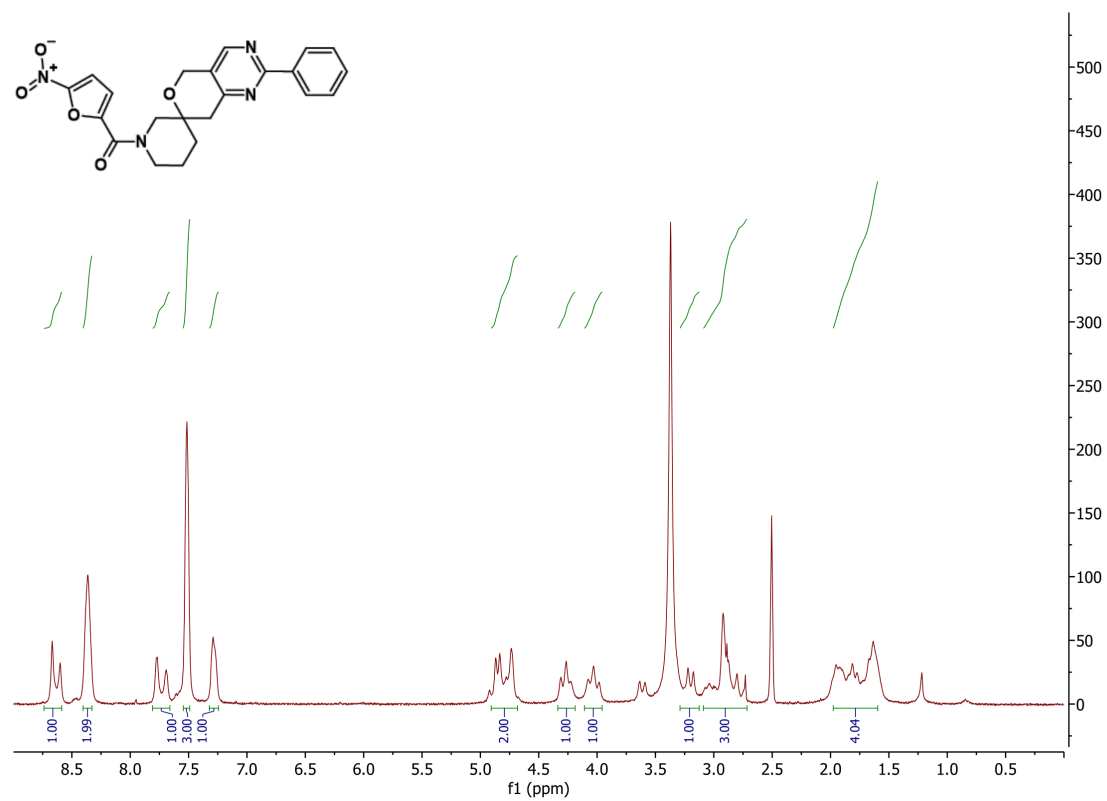


Figure S29 ¹H NMR spectrum of **11** in DMSO-d₆.

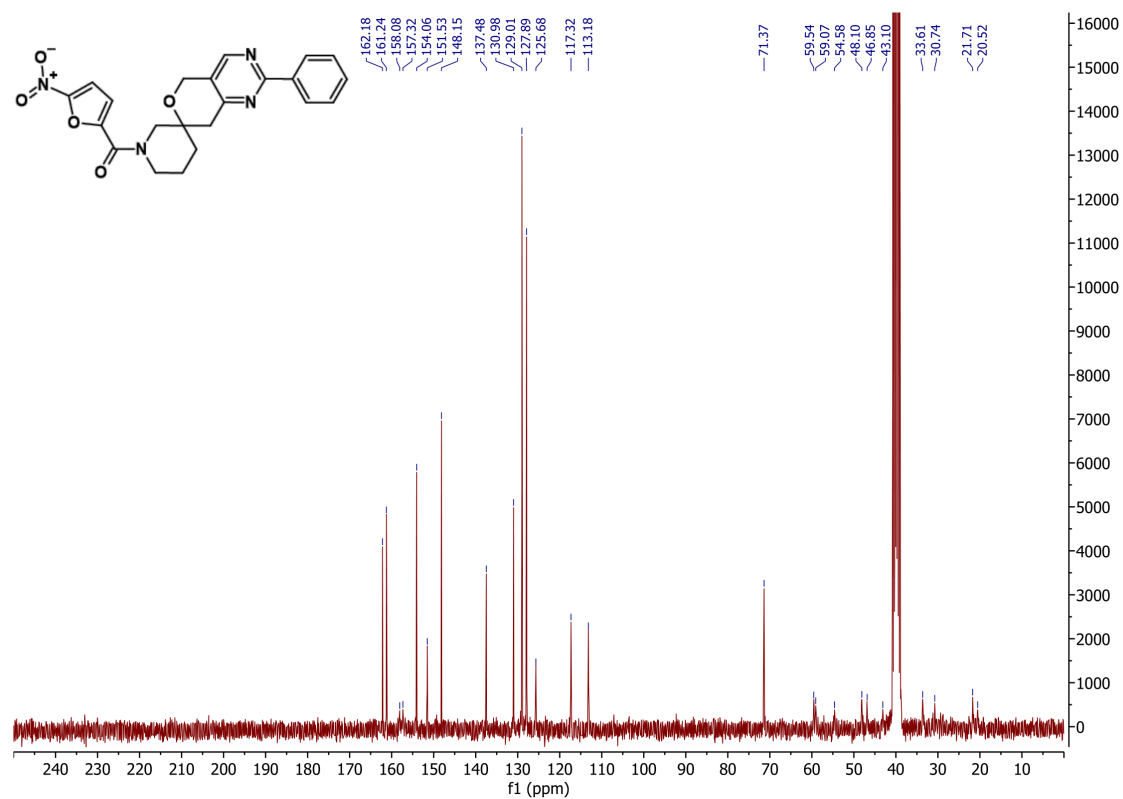


Figure S30 ¹³C NMR spectrum of **11** in DMSO-d₆.

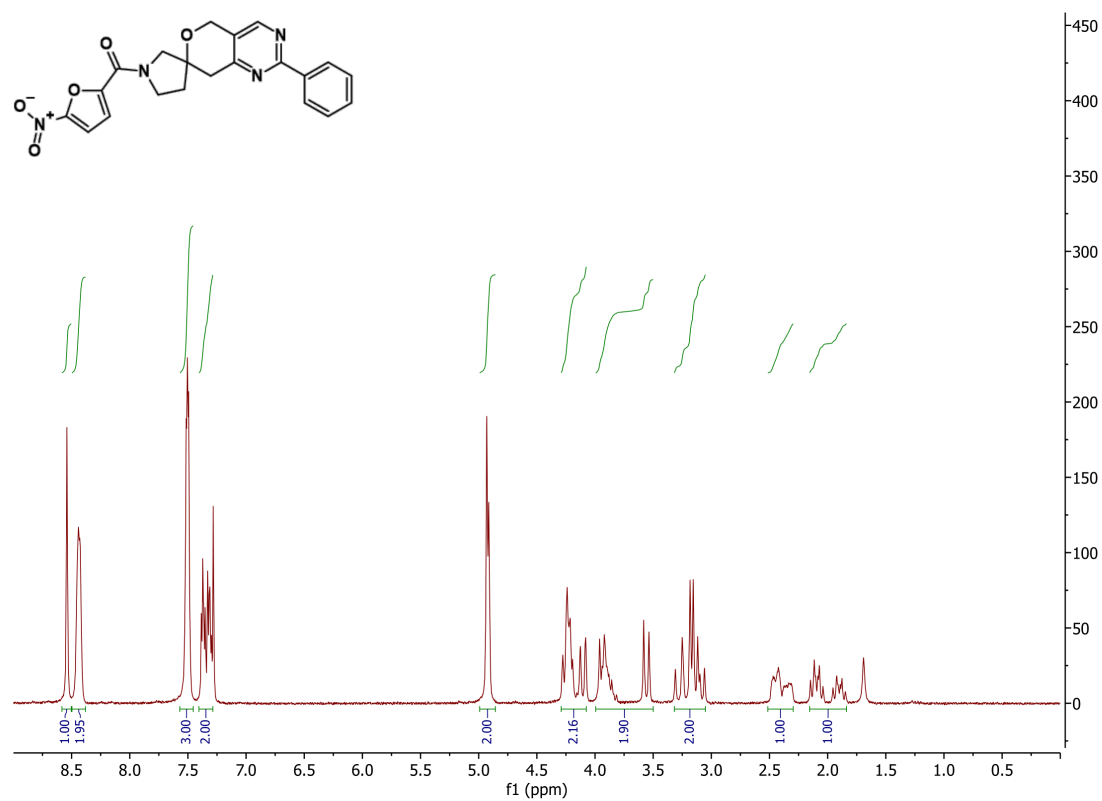


Figure S31 ¹H NMR spectrum of **12** in CDCl₃.

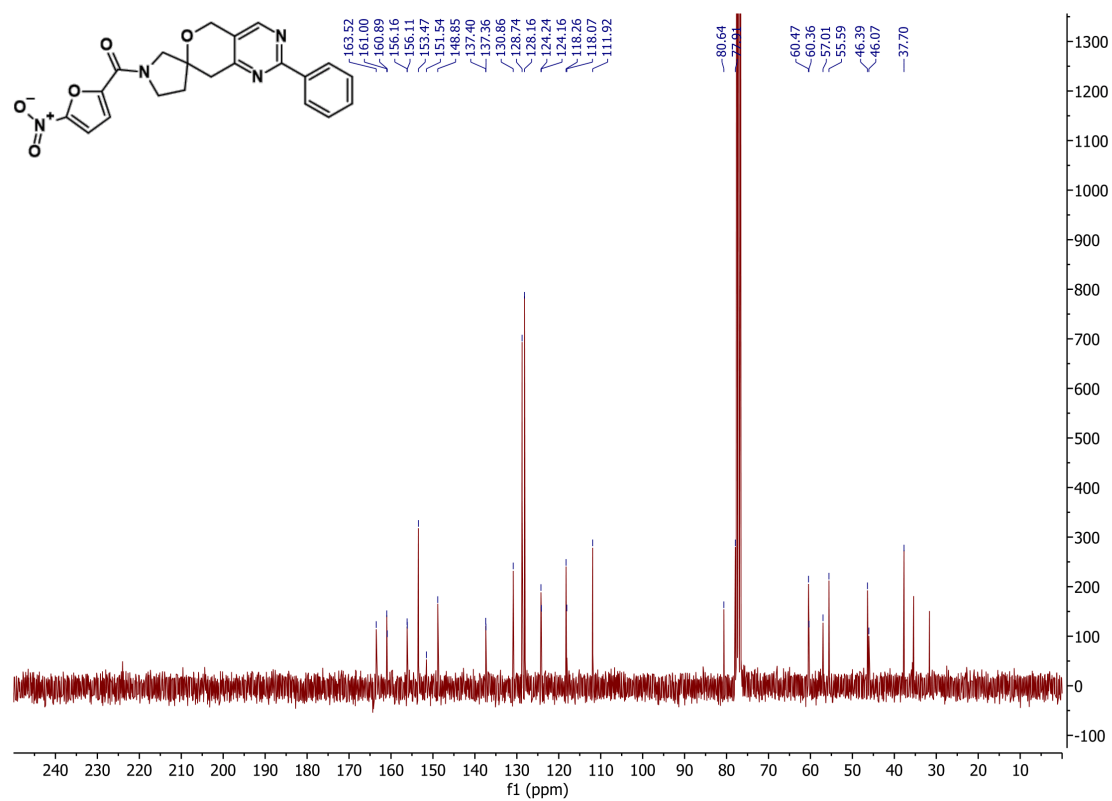


Figure S32 ¹³C NMR spectrum of **12** in CDCl₃.