Supporting Information

Design, synthesis and evaluation of (*R*)-3-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile as a JAK1-selective inhibitor

Chieyeon Chough[a, +], Sunmin Lee[b, +], Misuk Joung[b], Jaemin Lee[b], Jong Hoon Kim[c] and B. Moon Kim[a, *]

[a] Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 08876, South Korea

[b] Yang Ji Chemical Co., Ltd., Gyeonggi Bio-Center, Suwon, Gyeonggi-do 16229, South Korea

[c] Han Wha Pharma Co., Ltd., 109, Yagam-gil, Nam-myeon, Chuncheon, Gangwon-do 24468, South Korea

[+] These two individuals contributed equally to this work.

Corresponding author's email address: kimbm@snu.ac.kr

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Synthetic methods

All reagents for the syntheses were obtained from commercially available sources and used without any further purification. A diastereomeric pair of the key starting material, 5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine, was purchased from custom-synthesis through Sundia Meditech, China. All final products were purified by flash column chromatography and Merck silica gel 60 (0.040-0.063 mm) was used for flash column chromatography. The structures of the compounds were identified through ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry (MS) analyses. NMR spectra were taken from Agilent NMR system 400 MHz DD2MR400, Bruker Biospin AVANCE II 400, and Varian NMR System 500 MHz. Bruker Compact Ultra High Resolution ESI Q-TOF mass spectrometer was used for the MS data. The purities of synthesized compounds were analyzed through the use of 256 nm-wavelength absorption spectra on Agilent HPLC 1100 and 1260 infinity with 6120 Quadrupole LC/MS detector. Additionally, their optical rotation data were obtained from JASCO's P-1030 Polarimeter.

Synthesis of ethyl ((R)-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)carbamate, ***(R)-2c***

Potassium carbonate (25.9 g, 187 mmol) in 140 mL of deionized water was added to (*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine **(*R*)-1c** (20.1 g, 92.9 mmol) solution in 250 mL of tetrahydrofuran and the mixture was stirred at room temperature for 10 minutes. Ethyl chloroformate (9.46 mL, 99.4 mmol) was then added and the mixture was stirred at room temperature overnight. After the reaction, the solution was evaporated and the residue was extracted with dichloromethane three times. The combined organic layers were dried over anhydrous sodium sulfate and the solid was filtered off. The filtered solution was evaporated. Removing the solvent in vacuo provided 26.7 g of ethyl ((*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)carbamate (quantitatively yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.20 (d, *J* = 8.9 Hz, 1H), 4.04 (dd, *J* = 14.2, 7.1 Hz, 2H), 3.82 (ddd, *J* = 8.7, 5.8, 2.8 Hz, 1H), 3.21 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.84 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.78 (d, *J* = 8.9 Hz, 1H), 2.46 (dd, *J* = 9.6, 2.5 Hz, 1H), 2.30 (d, *J* = 8.8 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.75 (m, 2H), 0.59 (m, 1H), 0.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 144.8, 128.5, 127.2, 125.5, 77.5, 77.2, 76.9, 65.6, 61.0, 60.8, 60.7, 56.1, 26.4, 22.7, 14.7, 14.2, 8.9.

Synthesis of (R)-N-methyl-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine, ***(R)-3c***

An ethyl ((*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)carbamate **(*R*)-2c** (26.6 g, 92.2 mmol) solution in 345 mL of tetrahydrofuran was placed in a 1 L round bottom flask. After it was cooled at -40 °C, lithium aluminum hydride (7.01 g, 185 mmol) was slowly added to the stirred mixture. The reaction mixture was refluxed for 4 hours then cooled down to -40 °C. The reaction was quenched with 40 mL of deionized water, 40 mL of 15% sodium hydroxide solution, and 40 mL of deionized water. Then, celite 545 was added and the mixture was stirred for 30 minutes before being filtered through a celite 545 pad. The filtered solution was evaporated and extracted with dichloromethane three times. Combined organic layers were dried over anhydrous sodium sulfate and the solid was filtered off. And the filtered solution was evaporated. Removing the solvent in vacuo provided 19.4 g of (*R*)-*N*-methyl-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine (91.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 3.22 (q, *J* = 6.6 Hz, 1H), 3.11 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.86 (t, *J* = 5.5 Hz, 1H), 2.61 (d, *J* = 8.9 Hz, 1H), 2.39 (m, 1H), 2.30 (d, *J* = 4.9 Hz, 3H), 2.28 (d, *J* = 9.0 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 0.78 (m, 1H), 0.56 (dd, *J* = 8.6, 7.1 Hz, 2H), 0.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 128.4, 127.3, 127.0, 66.2, 63.8, 61.9, 59.8, 34.4, 25.9, 23.0, 14.1, 7.3.

Synthesis of N-methyl-N-((R)-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***(R)-4c***

A solution of (*R*)-*N*-methyl-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine **(*R*)-3c** (18.3 g, 79.4 mmol) in 330 mL of deionized water was placed in a 500 mL round bottom flask. Consequently, 6-chloro-7-deazapurine (12.8 g, 83.3 mmol) and potassium carbonate (22.0 g, 159 mmol) were added and the mixture was refluxed for 18 hours. After the reaction, it was cooled at room temperature and the aqueous mixture was extracted with 250 mL of dichloromethane three times. The combined organic layers were dried over anhydrous sodium sulfate and the solid was filtered off while the filtered solution was evaporated. Removing the solvent in vacuo provided 27.7 g of *N*-methyl-*N*-((*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (quantitatively yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.20 (s, 1H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (dd, *J* = 13.4, 6.2 Hz, 1H), 7.03 (t, *J* = 3.7 Hz, 1H), 6.53 (d, *J* = 3.4 Hz, 1H), 5.52 (s, 1H), 3.49 (s, 3H), 3.18 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.87 (t, *J* = 9.5 Hz, 2H), 2.73 (dd, *J* = 10.5, 2.8 Hz, 1H), 2.45 (d, *J* = 8.8 Hz, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 0.94 (m, 1H), 0.63 (m, 2H), 0.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 151.8, 150.6, 145.5, 128.6, 127.1, 127.1, 120.2, 102.7, 102.2, 66.2, 62.1, 59.7, 58.6, 33.8, 24.5, 23.2, 12.6, 11.6.

Synthesis of (R)-N-methyl-N-(5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***(R)-5c***

A *N*-methyl-*N*-((*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-4c** (27.7 g, 79.7 mmol) solution in 890 mL of methanol was placed in a 2 L round bottom flask. Then, 10w/w% palladium on charcoal (14.0 g, 5 wt%) and 10.1 g of ammonium formate (10.1 g, 160 mmol) were added and the reaction mixture was stirred at 60~70 °C overnight. After the reaction, it was filtered through a celite 545 pad

before the solution was evaporated. Removing the solvent in vacuo provided 22.2 g of (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (quantitatively yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 8.25 (s, 1H), 7.08 (t, *J* = 6.0 Hz, 1H), 6.54 (d, *J* = 3.4 Hz, 1H), 5.35 (m, 1H), 4.52 (s, 1H), 3.64 (dd, *J* = 12.2, 8.2 Hz, 1H), 3.48 (t, *J* = 8.4 Hz, 1H), 3.41 (s, 3H), 3.27 (d, *J* = 10.9 Hz, 1H), 2.96 (m, 1H), 0.91 (d, *J* = 9.8 Hz, 1H), 0.71 (m, 2H), 0.62 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.5, 120.7, 103.1, 102.1, 62.4, 56.2, 51.3, 34.8, 25.1, 14.9, 9.4.

Syntheses of the 3-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile enantiomers

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (210 mg, 0.863 mmol) solution in 2.50 mL of *n*-butanol in a 5 mL round bottom flask, ethyl cyanoacetate (0.918 mL, 8.63 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0654 mL, 0.437 mmol) were added and the mixture was heated at 80 °C for 24 hours. The reaction solution was evaporated and the residue was purified with flash column chromatography (methanol:dichloromethane = 2:98) to provide 238 mg of (*R*)-3-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile (88.8% yield).

In the cases of racemic mixture and (*S*)-enantiomer, the racemic mixture and the (*S*)-enantiomer of 5-(1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine were purchased at Sundia Meditech, China. The processes similar to the synthesis of (*R*)-form was employed in the synthesis of racemic and (*S*)-isomer.

(R)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, ***(R)-6c***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.13 (s, 1H), 6.56 (d, *J* = 8.6 Hz, 1H), 5.44 (dd, *J* = 41.1, 5.6 Hz, 1H), 4.26 – 4.00 (m, 1H), 3.98 – 3.70 (m, 2H), 3.58 – 3.32 (m, 6H), 1.16 – 0.94 (m, 1H), 0.82 (dd, *J* = 21.5, 10.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 151.9, 150.3, 120.9, 113.8, 103.1, 101.8, 77.4, 77.1, 76.8, 61.5, 54.8, 51.3, 33.5, 25.7, 22.6, 16.7, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd 311.1616. $[\alpha]_D$ +51.6° (*c* 1.49, $CHCl_3$).

3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, ***6c***

96.8% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.26 (d, *J* = 6.1 Hz, 1H), 7.13 (s, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 5.56 – 5.27 (m, 1H), 4.25 – 4.02 (m, 1H), 4.00 – 3.70 (m, 2H), 3.60 – 3.29 (m, 6H), 1.15 – 0.94 (m, 1H), 0.82 (dd, *J* = 19.5, 9.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.3, 151.7, 150.1, 120.5, 113.3, 102.8, 101.6, 61.4, 54.6, 52.6, 33.2, 25.4, 22.5, 16.5, 8.0. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd: 311.1616.

(S)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, ***(S)-6c***

97.4% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.18 (s, 1H), 8.26 (s, 1H), 7.12 (s, 1H), 6.55 (s, 1H), 5.38 (t, *J* = 37.8 Hz, 1H), 4.10 (d, *J* = 42.3 Hz, 1H), 3.82 (dd, *J* = 74.7, 15.0 Hz, 2H), 3.63 – 3.18 (m, 6H), 1.02 (d, *J* = 32.1 Hz, 1H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.5, 151.9, 150.2, 120.9, 113.9, 103.1, 101.8, 61.5, 54.8, 51.3, 33.4, 25.7, 22.6, 16.7, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd: 311.1616. $[\alpha]_D$ +35.6° (*c* 0.980, $CHCl_3$).

In the cases of **6a**, **6b** and **6d** – **6g**, the desired products were synthesized with 4-amino-1-benzylpiperidine, (*R*)-3-amino-1-benzylpiperidine, ethyl (5-benzyl-5-azaspiro[2.4]heptan-7-yl)carbamate, (*R*,*R*)-6-benzyl-octahydro-pyrrolo[3,4-*b*]pyridine dihydrochloride, 4-hydroxypiperidine, and 3-hydroxymethylpiperidine, respectively, instead of (*R*)-5-((*R*)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine according to the aforementioned process (vide supra).

3-(4-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, ***6a***

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.65 (s, 1H), 8.38 (s, 1H), 7.43 (s, 1H), 6.90 (d, *J* = 1.6 Hz, 1H), 4.75 (s, 1H), 4.52 (d, *J* = 12.8 Hz, 1H), 4.08 (s, 2H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.27 – 3.20 (m, 3H), 2.82 – 2.75 (m, 1H), 2.03 – 1.91 (m, 1H), 1.77 (s, 2H), 1.23 – 1.18 (m, 2H). LRMS (ESI) calcd for $C_{15}H_{19}N_6O$: 299.2. Obsd: 299.1.

(R)-3-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, ***6b***

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (d, *J* = 84 Hz, 1H), 8.32 (s, 1H), 7.13 – 7.12 (m, 1H), 6.62 – 6.59 (m, 1H), 4.79 – 4.72 (m, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 3.91 – 3.55 (m, 3H), 3.38 (s, 2H), 3.27 (s, 1H), 3.12 (q, *J* = 13.2, 11.2 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.11 – 2.08 (m, 1H), 2.02 – 1.69 (m, 3H). LRMS (ESI) calcd for $C_{15}H_{19}N_6O$: 299.2. Obsd: 299.1.

N-(5-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-azaspiro[2.4]heptan-7-yl)-2-cyanoacetamide, ***6d***

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.68 (d, J = 7.2 Hz, 1H), 8.18 (s, 1H), 7.13 (s, 1H), 6.55 (s, 1H), 3.99 (s, 2H), 3.85 (d, J = 10.0 Hz, 1H), 3.64 (s, 2H), 3.62 – 3.55 (m, 1H), 3.16 – 3.10 (m, 1H), 0.84 – 0.70 (m, 4H). LRMS (ESI) calcd for $C_{15}H_{17}N_6O$: 297.1. Obsd: 297.1.

3-((4aR,7aR)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl)-3-oxopropanenitrile, ***6e***

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.36 (d, J = 2.8 Hz, 1H), 7.15 – 7.08 (m, 1H), 6.58 – 6.54 (m, 1H), 5.65 – 5.51 (m, 1H), 4.65 – 4.57 (m, 1H), 4.01 – 3.49 (m, 4H), 3.46 (d, J = 3.6 Hz, 2H), 3.41 – 3.20 (m, 1H), 2.53 – 2.39 (m, 1H), 2.01 – 1.94 (m, 2H), 1.80 – 1.69 (m, 1H), 1.54 – 1.42 (m, 1H). LRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.2. Obsd: 311.1.

3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)piperidin-1-yl)-3-oxopropanenitrile, ***6f***

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 8.34 (s, 1H), 7.35 (t, J = 3.2 Hz, 1H), 6.47 (q, J = 3.6, 2.0 Hz, 1H), 5.58 – 5.43 (m, 1H), 4.08 (s, 2H), 3.90 – 3.86 (m, 1H), 3.63 – 3.59 (m, 1H), 3.47 – 3.32 (m, 2H), 2.09 – 2.00 (m, 2H), 1.82 – 1.77 (m, 1H), 1.69 – 1.61 (m, 1H). LRMS (ESI) calcd for $C_{14}H_{16}N_5O_2$: 286.1. Obsd: 286.1.

3-(3-(((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)methyl)piperidin-1-yl)-3-oxopropanenitrile, ***6g***

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.34 (s, 1H), 7.36 (s, 1H), 6.54 – 6.46 (m, 1H), 4.43 – 4.39 (m, 1H), 4.35 – 4.26 (m, 2H), 4.06 – 4.02 (m, 2H), 3.07 – 3.01 (m, 1H), 2.76 – 2.67 (m, 2H), 1.98 – 1.91 (m, 1H), 1.90 – 1.84 (m, 1H), 1.74 – 1.66 (m, 1H), 1.45 – 1.37 (m, 2H). LRMS (ESI) calcd for $C_{15}H_{18}N_5O_2$: 300.1. Obsd: 300.1.

Synthesis of (R)-N-(5-ethyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***7***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (70.0 mg, 0.288 mmol) solution in 1.00 mL of dichloromethane in a 5 mL round-bottom flask, bromoethane (0.0320 mL, 0.432 mmol) and *N*,*N*-diisopropylethylamine (0.100 mL, 0.574 mmol) were added. The reaction mixture was stirred at room temperature overnight then evaporated. The residue was purified by column chromatography (methanol:dichloromethane=2:98) to provide 23.9 mg of (*R*)-*N*-(5-ethyl-5-azaspiro[2.4]heptan-7-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (30.7% yield).

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.24 (s, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.57 (s, 1H), 5.58 (s, 1H), 3.46 (d, J = 2.8 Hz, 3H), 3.08 (s, 1H), 2.94 (s, 1H), 2.80 (d, J = 5.9 Hz, 1H), 2.58 (d, J = 5.4 Hz, 2H), 1.19 – 1.12 (m, 3H), 0.90 (dd, J = 21.8, 5.3 Hz, 2H), 0.68 (s, 2H), 0.50 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.5, 120.0, 102.6, 102.0, 63.3, 59.9, 58.3, 50.4, 33.9, 24.1, 13.4, 13.2, 10.4. HRMS (ESI) calcd for $C_{15}H_{22}N_5$: 272.1875. Obsd: 272.1872. $[\alpha]_D$ +43.2° (*c* 0.560, $CHCl_3$).

In the cases of compounds **8** and **9**, the desired products were synthesized through substitution reactions with *n*-butyl bromide and benzyl bromide, respectively, instead of ethyl bromide according to the aforementioned process (vide supra).

(R)-N-(5-Butyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***8***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.24 (s, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.58 (d, J = 3.4 Hz, 1H), 5.55 (s, 1H), 3.48 (s, 3H), 3.02 (s, 2H), 2.86 (s, 1H), 2.67 – 2.40 (m, 3H), 1.65 – 1.47 (m, 2H), 1.38 (dq, J = 14.4, 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 4H), 0.69 (s, 2H), 0.52 (t, J = 10.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 151.9, 150.7, 119.9, 102.6, 102.2, 63.4, 60.0, 58.6, 56.2, 34.1, 30.3, 24.0, 20.6, 14.0, 13.1, 10.6. HRMS (ESI) calcd for $C_{17}H_{26}N_5$: 300.2188. Obsd: 300.2188. $[\alpha]_D$ +55.6° (*c* 0.410, $CHCl_3$).

(R)-N-(5-Benzyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***9***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H), 8.21 (s, 1H), 7.44 – 7.21 (m, 5H), 7.03 (d, J = 3.5 Hz, 1H), 6.56 (d, J = 3.4 Hz, 1H), 5.57 (s, 1H), 3.64 (dd, J = 31.2, 12.9 Hz, 2H), 3.52 (s, 3H), 3.01 – 2.87 (m, 2H), 2.76 (d, J = 8.9 Hz, 1H), 2.51 (d, J = 8.9 Hz, 1H), 1.01 – 0.90 (m, 1H), 0.70 – 0.56 (m, 2H), 0.51 – 0.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.7, 138.9, 128.6, 128.3, 127.0, 119.7, 102.2, 63.3, 60.6, 59.1, 33.7, 24.4, 12.5, 11.2. HRMS (ESI) calcd for $C_{20}H_{24}N_5$: 334.2032. Obsd: 334.2025. $[\alpha]_D$ +52.9° (*c* 3.07, $CHCl_3$).

Synthesis of (R)-3-methyl-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)butan-1-one, ***11***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (60.0 mg, 0.247 mmol) solution in 1.00 mL of *N*,*N*-dimethylformamide in a 5 mL round-bottom flask, isovaleryl chloride (46.6 mg, 0.386 mmol) and *N*,*N*-diisopropylethylamine (0.0860 mL, 0.494 mmol) were added. The reaction mixture was stirred at room temperature overnight and then evaporated. The residue was purified by column

chromatography (methanol:dichloromethane=2:98) to provide 32.0 mg of (*R*)-3-methyl-1-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)butan-1-one (39.1% yield).

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (d, *J* = 16.4 Hz, 1H), 8.27 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 9.6 Hz, 1H), 6.56 (d, *J* = 9.9 Hz, 1H), 5.37 (t, *J* = 38.6 Hz, 1H), 4.05 (ddd, *J* = 43.9, 27.1, 11.7 Hz, 2H), 3.82 (dd, *J* = 66.1, 11.9 Hz, 1H), 3.65 (dd, *J* = 178.8, 11.3 Hz, 1H), 3.45 – 3.33 (m, 3H), 2.20 (d, *J* = 13.8 Hz, 3H), 0.99 (s, 6H), 0.78 (t, *J* = 21.2 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 157.5, 151.8, 150.2, 120.4, 102.8, 101.6, 61.6, 55.1, 52.5, 43.3, 33.1, 25.4, 24.8, 22.6, 16.6, 8.0. HRMS (ESI) calcd for $C_{18}H_{26}N_5O$: 328.2137. Obsd: 328.2126. $[\alpha]_D$ +45.2° (*c* 1.21, $CHCl_3$).

In the cases of **12**, **13**, and **17** – **24**, the desired products were synthesized through substitution reactions with isobutyryl chloride, cyclopropane carbonyl chloride, 2-furoyl chloride, benzoyl chloride, nicotinoyl chloride hydrochloride, isonicotinoyl chloride hydrochloride, 3-cyanobenzoyl chloride, 4-cyanobenzoyl chloride, 2-(trifluoromethyl)benzoyl chloride, and 3-(trifluoromethyl)benzoyl chloride, respectively, instead of isovaleryl chloride according to the aforementioned process (vide supra).

(R)-2-Methyl-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)propan-1-one, ***12***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (d, *J* = 17.4 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.11 (d, *J* = 10.0 Hz, 1H), 6.56 (d, *J* = 10.8 Hz, 1H), 5.37 (dd, *J* = 42.3, 38.0 Hz, 1H), 4.23 – 3.74 (m, 3H), 3.43 (t, *J* = 21.8 Hz, 4H), 2.79 – 2.56 (m, 1H), 1.16 (dd, *J* = 9.8, 5.6 Hz, 6H), 1.10 – 0.94 (m, 1H), 0.79 (td, *J* = 25.2, 8.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 157.2, 151.9, 150.3, 120.4, 102.9, 101.7, 61.6, 54.2, 50.3, 32.8, 32.0, 24.9, 18.7, 16.8, 8.0. HRMS (ESI) calcd for $C_{17}H_{24}N_5O$: 314.1981. Obsd: 314.1971. $[\alpha]_D$ +50.0° (*c* 1.12, $CHCl_3$).

(R)-Cyclopropyl(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)methanone, ***13***

93.1% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.28 (d, *J* = 15.5 Hz, 1H), 8.28 (d, *J* = 10.3 Hz, 1H), 7.12 (d, *J* = 10.0 Hz, 1H), 6.56 (d, *J* = 14.6 Hz, 1H), 5.44 (d, *J* = 15.0 Hz, 1H), 4.40 – 4.24 (m, 1H), 4.11 – 3.92 (m, 2H), 3.74 (dd, *J* = 141.4, 10.9 Hz, 2H), 3.45 (t, *J* = 21.3 Hz, 3H), 1.63 (d, *J* = 40.6 Hz, 1H), 1.16 – 0.94 (m, 3H), 0.80 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 157.7, 152.0, 150.4, 120.6, 103.0, 101.8, 61.5, 54.5, 52.3, 33.2, 22.9, 16.8, 12.4, 12.3, 7.7. HRMS (ESI) calcd for $C_{17}H_{22}N_5O$: 312.1824. Obsd: 312.1823. $[\alpha]_D$ +60.0° (*c* 1.31, $CHCl_3$).

(R)-Furan-2-yl(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)methanone, ***17***

99.2% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.28 (s, 1H), 7.52 (s, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.10 (d, *J* = 3.4 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.51 (s, 1H), 5.48 (s, 1H), 4.60 – 4.41 (m, 1H), 4.25 (d, *J* = 10.0 Hz, 2H), 4.18 – 4.02 (m, 1H), 3.72 (dd, *J* = 70.6, 11.6 Hz, 1H), 3.44 (s, 2H), 1.06 (s, 1H), 0.83 (dd, *J* = 22.6, 14.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.6, 151.5, 150.2, 144.4, 144.3, 120.5, 116.6, 111.5, 102.9, 102.1, 61.8, 58.5, 51.8, 33.3, 25.5, 16.7, 8.0. HRMS (ESI) calcd for $C_{18}H_{20}N_5O_2$: 338.1617. Obsd: 338.1616. $[\alpha]_D$ +56.0° (*c* 0.360, $CHCl_3$).

(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(phenyl)methanone, ***18***

95.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 8.25 (d, *J* = 25.1 Hz, 1H), 7.54 (s, 2H), 7.39 (s, 2H), 7.28 (s, 1H), 7.06 (s, 1H), 6.53 (d, *J* = 21.5 Hz, 1H), 5.45 (d, *J* = 74.9 Hz, 1H), 4.40 – 3.97 (m, 2H), 3.89 – 3.54 (m, 2H), 3.42 (d, *J* = 20.4 Hz, 3H), 1.01 (s, 1H), 0.79 (dd, *J* = 26.4, 14.3 Hz, 2H), 0.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 157.5, 151.9, 150.1, 136.1, 130.1, 128.4, 127.0, 120.7, 102.9, 101.7, 61.4, 57.5, 50.6, 33.2, 22.9, 16.5, 8.5. HRMS (ESI) calcd for $C_{20}H_{22}N_5O$: 348.1824. Obsd: 348.1819. $[\alpha]_D$ +22.5° (*c* 2.85, $CHCl_3$).

(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(pyridin-3-yl)methanone, ***19***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.83 (s, 1H), 8.68 (d, *J* = 12.5 Hz, 1H), 8.25 (d, *J* = 31.9 Hz, 1H), 7.90 (s, 1H), 7.47 – 7.31 (m, 1H), 7.10 (d, *J* = 12.4 Hz, 1H), 6.56 (d, *J* = 27.7 Hz, 1H), 5.40 (dd, *J* = 73.5, 68.8 Hz, 1H), 4.37 – 4.03 (m, 2H), 3.94 – 3.59 (m, 2H), 3.43 (t, *J* = 15.8 Hz, 3H), 1.05 (d, *J* = 8.0 Hz, 1H), 0.96 – 0.73 (m, 2H), 0.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.5, 152.0, 151.1, 150.4, 148.0, 135.0, 131.9, 123.4, 120.6, 103.0, 101.8, 61.5, 54.5, 50.7, 33.4, 22.6, 16.5, 8.4. HRMS (ESI) calcd for $C_{19}H_{21}N_6O$: 349.1777. Obsd: 349.1764. $[\alpha]_D$ +15.1° (*c* 1.12, $CHCl_3$).

(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(pyridin-4-yl)methanone, ***20***

94.1% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.72 (d, *J* = 15.1 Hz, 2H), 8.25 (d, *J* = 31.9 Hz, 1H), 7.41 (s, 2H), 7.11 (d, *J* = 12.7 Hz, 1H), 6.55 (d, *J* = 24.5 Hz, 1H), 5.46 (d, *J* = 111.2 Hz, 1H), 4.19 (dt, *J* = 26.7, 13.8 Hz, 2H), 3.64 (d, *J* = 12.1 Hz, 1H), 3.56 (dd, *J* = 220.1, 10.6 Hz, 1H), 3.44 (d, *J* = 14.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 1H), 0.95 – 0.72 (m, 2H), 0.67 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 157.5, 152.0, 150.4, 150.3, 143.5, 121.1, 120.7, 103.0, 101.7, 61.4, 57.2, 50.6, 33.4, 22.6, 16.6, 8.5. HRMS (ESI) calcd for $C_{19}H_{21}N_6O$: 349.1777. Obsd: 349.1772. $[\alpha]_D$ +24.5° (*c* 1.16, $CHCl_3$).

(R)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)benzonitrile, ***21***

97.7% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (s, 1H), 8.27 (d, *J* = 23.4 Hz, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.76 – 7.64 (m, 1H), 7.62 – 7.46 (m, 1H), 7.11 (d, *J* = 5.6 Hz, 1H), 6.56 (d, *J* = 18.0 Hz, 1H), 5.46 (d, *J* = 82.3 Hz, 1H), 4.39 – 4.02 (m, 2H), 3.65 (t, *J* = 12.3 Hz, 1H), 3.58 (dd, *J* = 185.8, 10.4 Hz, 1H), 3.44 (d, *J* = 14.8 Hz, 3H), 1.05 (d, *J* = 10.3 Hz, 1H), 0.97 – 0.74 (m, 2H), 0.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.5, 152.0, 150.2, 137.3, 133.5, 131.4, 130.8, 129.5, 120.8, 117.9, 112.8, 103.1, 101.7, 61.5, 54.5, 50.8, 33.4, 22.6, 16.6, 8.4. HRMS (ESI) calcd for $C_{21}H_{21}N_6O$: 373.1777. Obsd: 373.1772. $[\alpha]_D$ +10.9° (*c* 0.963, $CHCl_3$).

(R)-4-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)benzonitrile, ***22***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.26 (d, *J* = 32.1 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.64 (d, *J* = 6.7 Hz, 2H), 7.11 (d, *J* = 12.4 Hz, 1H), 6.55 (d, *J* = 25.3 Hz, 1H), 5.45 (d, *J* = 116.1 Hz, 1H), 4.19 (dt, *J* = 98.3, 17.9 Hz, 2H), 3.64 (d, *J* = 12.2 Hz, 1H), 3.55 (dd, *J* = 225.6, 10.4 Hz, 1H), 3.44 (d, *J* = 17.0 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 1H), 0.97 – 0.72 (m, 2H), 0.66 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 157.5, 152.0, 150.2, 140.3, 132.4, 127.8, 120.8, 118.0, 113.8, 103.0, 101.7, 61.5, 57.3, 50.7, 33.4, 22.6, 16.6, 8.5. HRMS (ESI) calcd for $C_{21}H_{21}N_6O$: 373.1777. Obsd: 373.1766. $[\alpha]_D$ +15.7° (*c* 2.54, $CHCl_3$).

(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(2-(trifluoromethyl)-phenyl)-methanone, ***23***

98.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.19 (s, 1H), 8.30 (d, *J* = 32.9 Hz, 1H), 7.71 (dd, *J* = 13.4, 7.9 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.52 (dt, *J* = 14.8, 7.6 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 9.7, 3.5 Hz, 1H), 6.57 (dd, *J* = 18.0, 3.1 Hz, 1H), 5.69 – 5.31 (m, 1H), 4.07 (ddd, *J* = 19.1, 12.6, 7.8 Hz, 1H), 3.87 (dd, *J* = 163.0, 12.6 Hz, 1H), 4.18 – 3.35 (m, 1H), 3.45 (s, 3H), 3.31 (dd, *J* = 158.2, 10.8 Hz, 1H), 1.04 (dd, *J* = 11.7, 6.7 Hz, 1H), 0.94 – 0.68 (m, 2H), 0.68 – 0.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 157.5, 151.8, 150.0, 135.4 (d, *J* = 26.1 Hz), 132.3, 129.3 (d, *J* = 4.1 Hz), 127.1 (d, *J* = 12.0 Hz), 126.9 – 126.6 (m), 123.6 (q, *J* = 273.8 Hz), 120.7, 103.2, 101.9, 61.2, 56.6, 50.2, 33.3, 24.8, 16.8, 8.3. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_5O$: 416.1698. Obsd: 416.1695. $[\alpha]_D$ +25.1° (*c* 1.71, $CHCl_3$).

(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(3-(trifluoromethyl)-phenyl)methanone, ***24***

98.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (s, 1H), 8.27 (s, 1H), 7.82 (s, 1H), 7.71 (dd, *J* = 17.7, 7.8 Hz, 2H), 7.62 – 7.46 (m, 1H), 7.09 (s, 1H), 6.58 (d, *J* = 20.8 Hz, 1H), 5.48 (d, *J* = 77.8 Hz, 1H), 4.39 – 4.01 (m, 2H), 3.66 (t, *J* = 13.7 Hz, 1H), 3.59 (dd, *J* = 173.8, 10.5 Hz, 1H), 3.46 (d, *J* = 18.1 Hz, 3H), 1.05 (d, *J* = 10.5 Hz, 1H), 0.98 – 0.73 (m, 2H), 0.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.5, 151.4, 149.9, 136.8, 131.0 (q, *J* = 32.8 Hz), 130.4, 129.1, 126.9, 124.1, 123.6 (q, *J* = 273.0 Hz), 120.7, 103.4, 102.0, 61.5, 54.5, 50.7, 33.4, 22.8, 16.6, 8.4. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_5O$: 416.1698. Obsd: 416.1692. $[\alpha]_D$ +20.7° (*c* 0.730, $CHCl_3$).

Synthesis of (R)-2-azido-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)ethan-1-one, ***10***

To a 2-azidoacetic acid (208 mg, 2.06 mmol) solution in 6.0 mL of *N*,*N*-dimethylformamide in a 10 mL round-bottom flask, *N*,*N*'-dicyclohexylcarbodiimide (423 mg, 2.05 mmol) and *N*,*N*-diisopropylethylamine (0.716 mL, 4.11 mmol) were added and the reaction mixture was stirred for 15 minutes. In a second 25 mL round-bottom flask, (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (300 mg, 1.23 mmol) was placed and the reaction mixture of 2-azidoacetic acid was transferred to this second flask. The reaction mixture was refluxed overnight and then cooled at room temperature. The mixture was filtered through a celite 545 pad and the solution was evaporated. The residue was purified with column chromatography (methanol:dichloromethane=2:98) to provide 41.0 mg of (*R*)-2-azido-1-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)ethan-1-one (11.9% yield).

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.23 (d, *J* = 22.5 Hz, 1H), 7.10 (d, *J* = 17.0 Hz, 1H), 6.56 (s, 1H), 5.55 – 5.22 (m, 1H), 4.17 – 3.94 (m, 1H), 3.90 (d, *J* = 16.4 Hz, 2H), 3.81 – 3.47 (m, 2H), 3.38 (dd, *J* = 33.1, 19.3 Hz, 4H), 1.03 (d, *J* = 46.0 Hz, 1H), 0.91 – 0.58 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 157.5, 151.9, 150.4, 120.8, 103.1, 101.8, 61.7, 54.5, 51.6, 51.0, 33.4, 22.4, 16.8, 8.1. HRMS (ESI) calcd for $C_{15}H_{19}N_8O$: 327.1682. Obsd: 327.1673. $[\alpha]_D$ +37.3° (*c* 1.49, $CHCl_3$).

In the cases of **14** – **16**, the desired products were synthesized through amide coupling reactions with *N*-acetylglycine, 3-(methylamino)-3-oxopropanoic acid, and 1-acetyl-4-piperidinecarboxylic acid, respectively, instead of 2-azidoacetic acid according to the aforementioned process (vide supra).

(R)-N-(2-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-2-oxoethyl)acetamide, ***14***

98.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.26 (s, 1H), 7.30 (s, 1H), 7.12 (s, 1H), 6.55 (s, 1H), 5.43 (d, *J* = 11.0 Hz, 1H), 4.09 (d, *J* = 15.0 Hz, 2H), 3.88 (ddd, *J* = 47.9, 37.2, 16.8 Hz, 2H), 3.45 (dd, *J* = 42.9, 13.8 Hz, 3H), 2.04 (s, 3H), 1.26 (s, 2H), 1.15 – 0.96 (m, 1H), 0.96 – 0.61 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.0, 157.5, 151.9, 150.2, 120.9, 103.1, 101.7, 61.3, 54.4, 51.2, 42.0, 33.3, 24.6, 22.8, 16.6, 8.1. HRMS (ESI) calcd for $C_{17}H_{23}N_6O_2$: 343.1882. Obsd: 343.1879. $[\alpha]_D$ +42.2° (*c* 1.00, $CHCl_3$).

(R)-N-Methyl-3-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanamide, ***15***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (d, *J* = 30.6 Hz, 1H), 8.24 (dd, *J* = 6.6, 1.8 Hz, 1H), 8.13 (s, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.51 – 5.34 (m, 1H), 4.13 (ddd, *J* = 21.2, 12.6, 7.5 Hz, 1H), 4.00 – 3.80 (m, 2H), 3.49 (t, *J* = 11.6 Hz, 1H), 3.40 (d, *J* = 14.5 Hz, 3H), 3.35 (t, *J* = 19.8 Hz, 2H), 2.83 (dd, *J* = 4.5, 2.1 Hz, 3H), 1.11 – 0.94 (m, 1H), 0.90 – 0.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.7, 157.5, 152.0, 150.4, 120.8, 103.0, 101.7, 59.3, 55.6, 52.7, 41.3, 33.3, 26.1, 22.9, 16.3, 8.1. HRMS (ESI) calcd for $C_{17}H_{23}N_6O_2$: 343.1882. Obsd: 343.1872. $[\alpha]_D$ +37.2° (*c* 1.30, $CHCl_3$).

(R)-1-(4-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)piperidin-1-yl)ethan-1-one, ***16***

95.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.36 – 8.21 (m, 1H), 7.13 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.62 – 6.51 (m, 1H), 5.54 – 5.31 (m, 1H), 4.62 (dd, *J* = 17.9, 8.6 Hz, 1H), 4.19 (dd, *J* = 9.8, 6.5 Hz, 1H), 4.11 – 3.76 (m, 3H), 3.54 – 3.46 (m, 1H), 3.46 – 3.33 (m, 3H), 3.19 – 3.01 (m, 1H), 2.75 – 2.51 (m, 2H), 2.17 – 2.02 (m, 3H), 1.97 – 1.63 (m, 4H), 1.15 – 0.95 (m, 1H), 0.92 – 0.71 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.8, 157.5, 152.0, 150.3, 120.8, 103.1, 101.7, 61.9, 58.9, 50.6, 45.7, 40.9, 40.2, 33.4, 24.9, 21.4, 16.0, 8.1. HRMS (ESI) calcd for $C_{21}H_{29}N_6O_2$: 397.2352. Obsd: 397.2343. $[\alpha]_D$ +45.2° (*c* 1.63, $CHCl_3$).

Synthesis of (R)-3-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-thioxopropanenitrile, ***25***

To an (*R*)-3-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile **(*R*)-6c** (44.7 mg, 0.144 mmol) in 1.40 mL of dichloromethane in a 10 mL round-bottom flask, Lawesson's reagent (32.0 mg, 0.0791 mmol) was added and the mixture was stirred for 3 days before being evaporated. The residue was purified with column chromatography (methanol:dichloromethane=2:98) to provide 37.0 mg of (*R*)-3-(7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-thioxopropanenitrile (78.7% yield). 100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.27 (d, *J* = 3.4 Hz, 1H), 7.20 – 7.08 (m, 1H), 6.57 (dd, *J* = 5.7, 3.7 Hz, 1H), 5.45 (tt, *J* = 186.7, 93.9 Hz, 1H), 4.42 – 4.25 (m, 1H), 4.20 (dd, *J* = 131.3, 13.0 Hz, 1H), 4.01 (dd, *J* = 162.4, 14.4 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.90 (dd, *J* = 211.1, 11.8 Hz, 1H), 3.44 (t, *J* = 19.7 Hz, 3H), 1.16 – 1.00 (m, 1H), 0.97 – 0.74 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 157.4, 152.0, 150.2, 121.0, 114.1, 103.2, 101.8, 62.3, 59.1, 57.0, 34.2, 33.7, 25.2, 16.9, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6S$: 327.1392. Obsd: 327.1380. $[\alpha]_D$ +48.8° (*c* 1.23, $CHCl_3$).

Synthesis of isobutyl (R)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxylate, ***26***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (100 mg, 0.411 mmol) solution in 1.00 mL of *N*,*N*-dimethylformamide in a 5 mL round-bottom flask, isobutyl chloroformate (84.2 mg, 0.616 mmol) and *N*,*N*-diisopropylethylamine (0.138 mL, 0.792 mmol) were added. The reaction solution was stirred at room temperature overnight and evaporated. The residue was purified by column chromatography (methanol:dichloromethane=2:98) to provide 107.0 mg of isobutyl (*R*)-7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxylate (76.4% yield).

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.28 (s, 1H), 7.11 (s, 1H), 6.55 (s, 1H), 5.41 (s, 1H), 4.08 – 3.97 (m, 1H), 3.91 (d, *J* = 4.7 Hz, 2H), 3.85 – 3.66 (m, 2H), 3.42 (s, 3H), 3.39 – 3.29 (m, 1H), 2.02 – 1.87 (m, 1H), 1.01 (s, 1H), 0.94 (s, 6H), 0.75 (d, *J* = 9.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 154.9, 152.0, 150.3, 120.6, 102.9, 101.8, 71.4, 61.0, 54.6, 51.1, 33.0, 28.0, 23.6, 19.1, 16.5, 8.1. HRMS (ESI) calcd for $C_{18}H_{26}N_5O_2$: 344.2087. Obsd: 344.2077. $[\alpha]_D$ +33.2° (*c* 4.45, $CHCl_3$).

Synthesis of (R)-N-butyl-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***27***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (49.2 mg, 0.202 mmol) solution in 2.00 mL of dichloromethane in a 5 mL round-bottom flask, *N*,*N*-diisopropylethylamine

(0.0370 mL, 0.212 mmol) was added and the mixture was treated with 0.0241 mL of butyl isocyanate (0.0241 mL, 0.214 mmol). The reaction solution was stirred for 2 hours before being evaporated. The residue was purified by column chromatography (methanol:dichloromethane = 2:98) to provide 67.7 mg of (*R*)-*N*-butyl-7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide (97.8% yield).

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 8.26 (s, 1H), 7.10 (s, 1H), 6.54 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 4.46 (s, 1H), 3.98 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.71 (dd, *J* = 31.5, 10.3 Hz, 2H), 3.41 (s, 3H), 3.33 (d, *J* = 9.8 Hz, 1H), 3.26 (d, *J* = 5.1 Hz, 2H), 1.50 (dt, *J* = 14.5, 7.2 Hz, 2H), 1.34 (td, *J* = 14.5, 7.2 Hz, 2H), 0.99 (d, *J* = 7.7 Hz, 1H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 1H), 0.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 156.6, 151.5, 150.0, 120.7, 102.9, 101.9, 61.0, 54.4, 51.1, 40.4, 33.1, 32.5, 24.1, 20.0, 16.7, 13.8, 8.1. HRMS (ESI) calcd for $C_{18}H_{27}N_6O$: 343.2246. Obsd: 343.2241. $[\alpha]_D$ +43.2° (*c* 2.89, $CHCl_3$).

In the cases from **28** to **36**, the desired products were synthesized through substitution reactions with cyclohexyl isocyanate, phenyl isocyanate, isocyanic acid 4-fluorophenyl ester, isocyanic acid 2,4-dichlorophenyl ester, 3,4-dichlorophenyl isocyanate, 2,5-dichlorophenyl isocyanate, 2,3-dichlorophenyl isocyanate, 3-chloro-4-methylphenyl isocyanate, and 2-biphenyl isocyanate, respectively, instead of butyl isocyanate according to the aforementioned process (vide supra).

(R)-N-Cyclohexyl-7-(methyl(7H-pyrrolo[2,3-d]-pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***28***

96.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.25 (s, 1H), 8.28 (s, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.56 (s, 1H), 5.39 (d, *J* = 5.8 Hz, 1H), 4.18 (d, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 10.8, 7.5 Hz, 1H), 3.66 (t, *J* = 10.8 Hz, 2H), 3.53 (dd, *J* = 163.5, 9.8 Hz, 2H), 3.43 (s, 3H), 1.97 (d, *J* = 11.4 Hz, 2H), 1.70 (d, *J* = 9.8 Hz, 2H), 1.60 (d, *J* = 12.8 Hz, 1H), 1.36 (td, *J* = 14.2, 2.5 Hz, 2H), 1.22 – 1.04 (m, 3H), 1.03 – 0.93 (m, 1H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.9, 151.5, 150.0, 120.6, 103.0, 101.9, 61.0, 54.4, 51.1, 49.2, 34.1, 33.1, 25.6, 25.0, 24.0, 16.7, 8.1. HRMS (ESI) calcd for $C_{20}H_{29}N_6O$: 369.2403. Obsd: 369.2398. $[\alpha]_D$ +39.1° (*c* 2.39, $CHCl_3$).

(R)-7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-phenyl-5-azaspiro[2.4]heptane-5-carboxamide, ***29***

98.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.29 (s, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.29 (s, 2H), 7.09 (s, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 45.2 Hz, 2H), 5.43 (s, 1H), 4.11 (s, 1H), 3.84 (dd, *J* = 21.3, 10.0 Hz, 2H), 3.68 – 3.25 (m, 1H), 3.46 (s, 3H), 1.04 (d, *J* = 8.6 Hz, 1H), 0.95 – 0.69 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.7, 150.9, 149.6, 138.8, 128.9, 123.1, 120.7, 119.7, 103.1, 102.2, 61.2, 54.6, 51.4, 33.3, 24.0, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{23}N_6O$: 363.1933. Obsd: 363.1928. $[\alpha]_D$ +38.0° (*c* 0.707, $CHCl_3$).

(R)-N-(4-Fluorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***30***

99.2% purity by HPLC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.41 – 8.28 (m, 1H), 8.18 (s, 1H), 7.52 (dd, *J* = 6.9, 5.2 Hz, 2H), 7.26 (s, 1H), 7.07 (t, *J* = 7.9 Hz, 2H), 6.72 (s, 1H), 5.20 (s, 1H), 4.03 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.80 (t, *J* = 10.6 Hz, 2H), 3.49 (d, *J* = 68.5 Hz, 10H), 3.37 (s, 9H), 0.95 (d, *J* = 10.2 Hz, 1H), 0.84 (d, *J* = 13.6 Hz, 2H), 0.68 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.7 (d, *J* = 237.8 Hz), 154.2, 149.9, 148.6, 137.1 (d, *J* = 2.4 Hz), 122.2, 121.5 (d, *J* = 7.6 Hz), 115.2 (d, *J* = 22.0 Hz), 102.9, 102.5, 61.6, 54.5, 51.5, 33.6, 24.2, 16.5, 8.2. HRMS (ESI) calcd for $C_{20}H_{22}FN_6O$: 381.1839. Obsd: 381.1835. $[\alpha]_D$ +54.3° (*c* 0.223, MeOH).

(R)-N-(2,4-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***31***

97.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.01 (s, 1H), 8.28 (d, *J* = 8.9 Hz, 2H), 7.40 – 7.31 (m, 1H), 7.22 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.82 (s, 1H), 6.59 (s, 1H), 5.53 (d, *J* = 6.3 Hz, 1H), 4.16 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.87 (dd, *J* = 23.7, 10.4 Hz, 2H), 3.48 (s, 3H), 3.42 (s, 1H), 1.08 (d, *J* = 10.3 Hz, 1H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.6, 151.5, 150.0, 134.4, 128.3, 127.9, 127.4, 122.3, 121.2, 120.7, 103.0, 102.0, 60.7, 54.4, 51.1, 33.2, 24.1, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1146. $[\alpha]_D$ +47.8° (*c* 0.970, $CHCl_3$).

(R)-N-(3,4-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***32***

99.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (d, *J* = 18.4 Hz, 1H), 8.24 (s, 1H), 7.64 (s, 1H), 7.26 (d, *J* = 4.1 Hz, 2H), 7.07 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 12.8 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 5.37 (d, *J* = 4.8 Hz, 1H), 4.05 (dd, *J* = 10.6, 7.0 Hz, 1H), 3.79 (dd, *J* = 25.3, 10.5 Hz, 2H), 3.40 (s, 4H), 1.00 (s, 1H), 0.82 (d, *J* = 42.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 153.2, 151.8, 150.3, 138.5, 132.4, 130.2, 125.9, 121.2, 120.6, 118.9, 103.0, 101.9, 61.0, 54.6, 51.5, 33.2, 23.8, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +48.5° (*c* 0.850, $CHCl_3$).

(R)-N-(2,5-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***33***

98.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H), 8.36 (d, *J* = 53.7 Hz, 2H), 7.12 (s, 1H), 7.07 (dd, *J* = 124.5, 8.5 Hz, 2H), 6.88 (s, 1H), 6.57 (s, 1H), 5.53 (d, *J* = 5.8 Hz, 1H), 4.24 – 4.07 (m, 1H), 3.87 (dd, *J* = 21.7, 10.3 Hz, 2H), 3.48 (s, 1H), 3.46 (s, 3H), 1.07 (d, *J* = 8.7 Hz, 1H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.4, 152.1, 150.3, 136.5, 133.5, 129.3, 122.9, 120.7, 120.2, 119.9, 103.0, 101.8, 60.6, 54.4, 51.0, 33.2, 24.1, 16.7, 8.1. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +34.6° (*c* 2.36, DMSO).

(R)-N-(2,3-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***34***

98.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.36 (s, 1H), 8.45 – 8.16 (m, 2H), 7.23 – 7.06 (m, 3H), 6.97 (s, 1H), 6.58 (s, 1H), 5.54 (d, *J* = 5.8 Hz, 1H), 4.17 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.88 (dd, *J* = 19.3, 10.4 Hz, 2H), 3.50 (s, 1H), 3.47 (s, 3H), 1.07 (d, *J* = 8.0 Hz, 1H), 0.86 (d, *J* = 18.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.6, 151.7, 150.0, 137.3, 132.3, 127.7, 123.7, 120.8, 120.4, 118.4, 103.1, 101.9, 60.7, 54.4, 51.1, 33.2, 24.2, 16.7, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +31.7° (*c* 3.17, $CHCl_3$).

(R)-N-(3-Chloro-4-methylphenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***35***

98.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.24 (s, 1H), 7.49 (s, 1H), 7.20 (d, *J* = 6.6 Hz, 1H), 7.13 – 6.98 (m, 2H), 6.87 (s, 1H), 6.49 (s, 1H), 5.36 (s, 1H), 4.04 (s, 1H), 3.79 (d, *J* = 8.2 Hz, 2H), 3.42 (d, *J* = 32.5 Hz, 1H), 3.36 (s, 3H), 2.25 (s, 3H), 0.97 (d, *J* = 8.3 Hz, 1H), 0.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.8, 151.5, 150.0, 137.9, 134.1, 130.7, 130.3, 120.7, 120.5, 118.4, 103.0, 101.9, 61.0, 54.5, 51.3, 33.2, 23.9, 19.3, 16.6, 8.1. HRMS (ESI) calcd for $C_{21}H_{24}ClN_6O$: 411.1700. Obsd: 411.1694. $[\alpha]_D$ +41.1° (*c* 3.38, $CHCl_3$).

(R)-N-([1,1'-Biphenyl]-2-yl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***36***

97.9% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.24 (s, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.30 (m, 6H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.10 (dd, *J* = 9.2, 5.5 Hz, 2H), 6.55 (d, *J* = 2.9 Hz, 1H), 6.38 (s, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 3.82 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 3.48 (d, *J* = 10.1 Hz, 1H), 3.38 (s, 3H), 3.20 (d, *J* = 9.9 Hz, 1H), 1.04 – 0.95 (m, 1H), 0.78 – 0.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 153.4, 149.6, 148.6, 138.5, 135.8, 131.5, 129.6, 129.2, 129.1, 128.5, 128.0, 123.0, 120.9, 120.6, 102.5, 61.1, 54.2, 50.9, 31.9, 22.7, 16.8, 8.1. HRMS (ESI) calcd for $C_{26}H_{27}N_6O$: 439.2246. Obsd: 439.2242. $[\alpha]_D$ +29.2° (*c* 0.587, $CHCl_3$).

Synthesis of (R)-N-(3,5-bis(trifluoromethyl)phenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro-[2.4]heptane-5-carbothioamide, ***37***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (49.8 mg, 0.205 mmol) solution in 2.00 mL of dichloromethane in a 5 mL round-bottom flask, *N*,*N*-diisopropylethylamine (0.0374 mL, 0.215 mmol) was added and the mixture was treated with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.0400 mL, 0.219 mmol). The reaction solution was stirred for 2 hours before being evaporated. The residue was purified by column chromatography (methanol:dichloromethane=2:98) to provide 109.8 mg of (*R*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-7-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbothioamide (quantitatively yield).

99.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.27 (s, 1H), 7.97 (s, 2H), 7.69 (s, 1H), 7.62 (s, 1H), 7.08 (s, 1H), 6.55 (s, 1H), 5.42 (s, 1H), 4.30 (s, 1H), 4.15 (s, 2H), 3.72 (s, 1H), 3.43 (s, 3H), 1.03 (s, 1H), 0.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 157.5, 151.4, 149.7, 140.7, 131.6 (q, *J* = 33.6 Hz), 124.8, 123.0 (q, *J* = 272.9 Hz), 120.9, 118.6, 103.4, 102.0, 61.0, 55.3, 33.4, 29.7, 23.3, 16.8, 8.0. HRMS (ESI) calcd for $C_{22}H_{21}F_6N_6S$: 515.1453. Obsd: 515.1446. $[\alpha]_D$ +51.4° (*c* 3.37, $CHCl_3$).

Synthesis of (R)-N-(5-(ethylsulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***38***

To an (*R*)-*N*-methyl-*N*-(5-azaspiro[2.4]heptan-7-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **(*R*)-5c** (70.0 mg, 0.288 mmol) solution in 0.700 mL of *N*,*N*-dimethylformamide in a 5 mL round bottom flask, ethanesulfonyl chloride (55.5 mg, 0.432 mmol) and *N*,*N*-diisopropylethylamine (0.208 mL, 1.19 mmol) were added. Then, the reaction solution was stirred at room temperature overnight before being evaporated. The residue was purified by flash column chromatography (methanol:dichloromethane=2:98) to provide 80.0 mg of (*R*)-*N*-(5-(ethylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-*N*-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (82.5% yield).

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.26 (s, 1H), 7.12 (s, 1H), 6.56 (s, 1H), 5.55 (s, 1H), 3.92 (t, *J* = 9.1 Hz, 1H), 3.68 (d, *J* = 9.9 Hz, 2H), 3.48 (s, 3H), 3.33 (d, *J* = 9.8 Hz, 1H), 3.14 – 3.03 (m, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 9.9 Hz, 1H), 0.77 (d, *J* = 11.9 Hz, 2H), 0.73 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 152.0, 150.2, 120.7, 103.0, 101.8, 60.5, 55.9, 52.4, 44.2, 33.5, 24.4, 15.4, 9.2, 7.9. HRMS (ESI) calcd for $C_{15}H_{22}N_5O_2S$: 336.1494. Obsd: 336.1485. $[\alpha]_D$ +34.7° (*c* 3.25, $CHCl_3$).

In the cases from **39** to **56**, the desired products were synthesized through substitution reactions with 2-propanesulfonyl chloride, 1-propanesulfonyl chloride, benzenesulfonyl chloride, 2-fluorobenzene-1-sulfonyl chloride, 3-fluorobenzene-1-sulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 2-cyanobenzenesulfonyl chloride, 3-cyanobenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 2-nitrobenzenesulfonyl chloride, 3-nitrobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 3-toluenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 4-(trifluoromethyl)benzenesulfonyl chloride, 2-naphthalenesulfonyl chloride, piperidine-1-sulfonyl chloride, and morpholine-4-sulfonyl chloride, respectively, instead of ethylsulfonyl chloride according to the aforementioned process (vide supra).

(R)-N-(5-(Isopropylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***39***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.26 (s, 1H), 7.11 (s, 1H), 6.57 (s, 1H), 5.51 (s, 1H), 3.99 (t, *J* = 8.2 Hz, 1H), 3.71 (d, *J* = 8.7 Hz, 2H), 3.48 (s, 3H), 3.38 (d, *J* = 9.6 Hz, 1H), 3.28 (d, *J* = 4.9 Hz, 1H), 1.40 (s, 6H), 1.03 (d, *J* = 8.7 Hz, 1H), 0.85 – 0.69 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 151.9, 150.3, 120.5, 102.9, 101.8, 60.6, 56.4, 53.4, 52.9, 33.5, 24.4, 16.6, 15.5, 8.9. HRMS (ESI) calcd for $C_{16}H_{24}N_5O_2S$: 350.1651. Obsd: 350.1639. $[\alpha]_D$ +36.0° (*c* 1.82, $CHCl_3$).

(R)-N-Methyl-N-(5-(propylsulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***40***

99.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.29 (s, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.59 (s, 1H), 5.65 – 5.46 (m, 1H), 3.91 (dd, *J* = 10.9, 7.6 Hz, 1H), 3.77 – 3.61 (m, 2H), 3.49 (s, 3H), 3.32 (d, *J* = 9.8 Hz, 1H), 3.11 – 2.94 (m, 2H), 1.91 (dd, *J* = 15.4, 7.6 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H), 1.07 – 0.98 (m, 1H), 0.76 (dt, *J* = 11.3, 9.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 151.8, 150.1, 120.7, 103.1, 101.9, 60.5, 55.8, 52.3, 51.3, 33.6, 24.4, 17.0, 15.4, 13.1, 9.2. HRMS (ESI) calcd for $C_{16}H_{24}N_5O_2S$: 350.1651. Obsd: 350.1650. $[\alpha]_D$ +34.9° (*c* 1.97, $CHCl_3$).

(R)-N-Methyl-N-(5-(phenylsulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***41***

99.4% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.22 (s, 1H), 8.11 (s, 1H), 7.75 (s, 2H), 7.56 (s, 1H), 7.48 (s, 2H), 7.00 (s, 1H), 6.42 (s, 1H), 5.34 (s, 1H), 3.51 (s, 2H), 3.43 (d, *J* = 8.4 Hz, 1H), 3.24 (s, 3H), 2.99 (d, *J* = 8.3 Hz, 1H), 0.79 (s, 1H), 0.64 (s, 1H), 0.52 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 152.0, 150.2, 135.1, 133.0, 129.1, 127.9, 120.6, 102.9, 101.8, 59.9, 56.0, 52.7, 33.3, 23.9, 14.5, 9.6. HRMS (ESI) calcd for $C_{19}H_{22}N_5O_2S$: 384.1494. Obsd: 384.1483. $[\alpha]_D$ -3.5° (*c* 2.73, $CHCl_3$).

(R)-N-(5-((2-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***42***

97.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.21 (s, 1H), 7.91 (t, *J* = 7.3 Hz, 1H), 7.68 – 7.56 (m, 1H), 7.39 – 7.20 (m, 2H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 5.47 (d, *J* = 5.4 Hz, 1H), 3.82 (dd, *J* = 10.9, 7.8 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.48 (dd, *J* = 160.2, 9.9 Hz, 2H), 3.41 (s, 3H), 0.98 – 0.89 (m, 1H), 0.76 (dt, *J* = 13.1, 6.5 Hz, 1H), 0.72 – 0.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (d, *J* = 255.8 Hz), 157.6, 151.7, 150.2, 135.2 (d, *J* = 8.4 Hz), 131.5, 125.0 (d, *J* = 14.8 Hz), 124.5 (d, *J* = 3.8 Hz), 120.6, 117.3 (d, *J* = 22.0 Hz), 102.9, 102.0, 60.3, 55.7, 52.3, 33.4, 24.2, 14.9, 9.3. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1393. $[\alpha]_D$ -7.2° (*c* 0.803, $CHCl_3$).

(R)-N-(5-((3-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***43***

99.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H), 8.20 (s, 1H), 7.67 – 7.62 (m, 1H), 7.56 (dt, *J* = 13.4, 6.6 Hz, 2H), 7.36 (ddd, *J* = 10.0, 5.3, 1.5 Hz, 1H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.53 (d, *J* = 3.4 Hz, 1H), 5.44 (t, *J* = 5.0 Hz, 1H), 3.62 (d, *J* = 5.2 Hz, 2H), 3.37 (s, 3H), 3.33 (dd, *J* = 185.2, 9.6 Hz, 2H), 0.96 – 0.85 (m, 1H), 0.77 (dd, *J* = 10.2, 4.9 Hz, 1H), 0.69 – 0.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* = 252.1 Hz), 157.6, 151.7, 150.1, 137.4 (d, *J* = 6.5 Hz), 130.9 (d, *J* = 7.7 Hz), 123.6 (d, *J* = 3.4 Hz), 120.6, 120.2 (d, *J* = 21.2 Hz), 115.1 (d, *J* = 24.1 Hz), 102.9, 101.9, 60.0, 56.0, 52.8, 33.4, 23.9, 14.6, 9.7. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1391. $[\alpha]_D$ -6.7° (*c* 0.880, $CHCl_3$).

(R)-N-(5-((4-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***44***

96.3% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (s, 1H), 8.11 (d, *J* = 3.9 Hz, 1H), 7.78 (ddd, *J* = 8.8, 4.6, 2.0 Hz, 2H), 7.22 – 7.11 (m, 2H), 7.02 (d, *J* = 3.5 Hz, 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 5.35 (s, 1H), 3.51

(d, *J* = 5.1 Hz, 2H), 3.44 (d, *J* = 9.6 Hz, 1H), 3.28 (s, 3H), 2.98 (d, *J* = 9.6 Hz, 1H), 0.87 – 0.77 (m, 1H), 0.71 – 0.61 (m, 1H), 0.60 – 0.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (d, *J* = 255.8 Hz), 157.1, 151.5, 149.8, 130.9, 130.1 (d, *J* = 9.0 Hz), 120.1, 115.9 (d, *J* = 21.4 Hz), 102.4, 101.4, 59.5, 55.6, 52.3, 33.0, 23.4, 14.1, 9.2. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1388. $[\alpha]_D$ -3.0° (*c* 2.17, $CHCl_3$).

(R)-2-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***45***

99.2% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.05 (s, 1H), 8.12 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.3 Hz, 1H), 7.66 (dt, *J* = 22.3, 7.4 Hz, 2H), 7.02 (d, *J* = 3.1 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 3.74 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.68 (d, *J* = 9.8 Hz, 1H), 3.61 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.32 (s, 3H), 3.29 (d, *J* = 9.8 Hz, 1H), 0.88 (t, *J* = 7.0 Hz, 1H), 0.72 (dd, *J* = 8.7, 5.5 Hz, 1H), 0.69 – 0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 150.2, 140.0, 135.6, 133.0, 132.9, 130.3, 120.7, 116.4, 110.9, 103.0, 101.8, 60.3, 56.1, 52.6, 33.5, 24.1, 14.9, 9.3. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1435. $[\alpha]_D$ +2.2° (*c* 1.91, $CHCl_3$).

(R)-3-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***46***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.03 (s, 1H), 8.19 (s, 1H), 8.14 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 5.40 (s, 1H), 3.65 (t, *J* = 5.1 Hz, 2H), 3.60 (d, *J* = 9.8 Hz, 1H), 3.36 (s, 3H), 3.10 (d, *J* = 9.7 Hz, 1H), 0.90 (dd, *J* = 9.8, 4.4 Hz, 1H), 0.83 – 0.74 (m, 1H), 0.73 – 0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.2, 137.5, 136.0, 131.6, 131.2, 130.2, 120.7, 117.1, 113.8, 103.0, 101.8, 60.1, 56.1, 52.8, 33.5, 23.8, 14.8, 9.6. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1435. $[\alpha]_D$ -7.5° (*c* 1.82, $CHCl_3$).

(R)-4-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***47***

94.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.18 (s, 1H), 8.00 – 7.90 (m, 2H), 7.89 – 7.81 (m, 2H), 7.08 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 5.36 (dd, *J* = 5.7, 4.4 Hz, 1H), 3.65 (s, 1H), 3.64 (d, *J* = 1.9 Hz, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.34 (s, 3H), 3.10 (d, *J* = 9.7 Hz, 1H), 0.91 (ddd, *J* = 10.2, 6.2, 4.0 Hz, 1H), 0.82 – 0.75 (m, 1H), 0.73 – 0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.2, 134.0, 132.9, 128.3, 120.8, 117.2, 116.7, 103.0, 101.8, 60.2, 56.0, 52.9, 33.5, 23.8, 14.9, 9.5. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1433. $[\alpha]_D$ -12.7° (*c* 1.66, $CHCl_3$).

(R)-N-Methyl-N-(5-((2-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***48***

96.9% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (s, 1H), 8.23 (s, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.69 (dd, *J* = 16.0, 7.9 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.10 (s, 1H), 6.53 (s, 1H), 5.50 (d, *J* = 6.2 Hz, 1H), 4.03 – 3.87 (m, 1H), 3.75 (d, *J* = 9.6 Hz, 2H), 3.39 (s, 3H), 3.38 – 3.27 (m, 1H), 0.96 (d, *J* = 5.5 Hz, 1H), 0.91 – 0.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.0, 150.2, 148.4, 133.9, 131.6, 130.8, 124.1, 120.7, 103.0, 101.8, 60.4, 55.9, 52.6, 33.4, 24.2, 15.1, 9.2. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1340. $[\alpha]_D$ +6.1° (*c* 2.21, $CHCl_3$).

(R)-N-Methyl-N-(5-((3-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***49***

94.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.67 (d, *J* = 1.4 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.16 (d, *J* = 3.4 Hz, 2H), 7.78 (td, *J* = 8.1, 3.3 Hz, 1H), 7.06 (s, 1H), 6.52 (s, 1H), 5.47 – 5.32 (m, 1H), 3.79 – 3.57 (m, 3H), 3.37 (d, *J* = 3.2 Hz, 3H), 3.14 (d, *J* = 9.7 Hz, 1H), 0.90 (dd, *J* = 6.2, 3.2 Hz, 1H), 0.84 – 0.74 (m, 1H), 0.74 – 0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.0, 150.6, 148.4, 138.1, 133.2, 130.5, 127.4, 122.7, 120.3, 102.8, 102.1, 60.1, 56.1, 52.9, 33.6, 23.8, 14.8, 9.6. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1339. $[\alpha]_D$ -6.4° (*c* 0.117, $CHCl_3$).

(R)-N-Methyl-N-(5-((4-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***50***

97.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 1H), 8.50 – 8.30 (m, 2H), 8.19 (d, *J* = 3.4 Hz, 1H), 8.02 (s, 2H), 7.09 (s, 1H), 6.50 (s, 1H), 5.36 (d, *J* = 3.5 Hz, 1H), 3.67 (s, 2H), 3.65 – 3.56 (m, 1H), 3.36 (d, *J* = 3.5 Hz, 3H), 3.19 – 3.05 (m, 1H), 0.83 – 0.75 (m, 1H), 0.67 (dd, *J* = 14.9, 9.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.0, 150.3, 150.2, 141.6, 128.9, 124.3, 120.6, 103.0, 101.9, 60.2, 56.1, 52.9, 33.5, 23.8, 14.9, 9.5. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1338. $[\alpha]_D$ -19.0° (*c* 1.38, $CHCl_3$).

(R)-N-Methyl-N-(5-(m-tolylsulfonyl)-5-azaspiro[2.4]-heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***51***

98.0% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 8.22 (d, *J* = 4.7 Hz, 1H), 7.65 (s, 2H), 7.43 (s, 2H), 7.10 (s, 1H), 6.50 (s, 1H), 5.41 (s, 1H), 3.61 (s, 2H), 3.52 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.33 (d, *J* = 4.3 Hz, 3H), 3.08 (dd, *J* = 9.3, 4.5 Hz, 1H), 2.42 (d, *J* = 4.3 Hz, 3H), 0.87 (d, *J* = 4.6 Hz, 1H), 0.75 (d, *J* = 9.6 Hz,

1H), 0.61 (d, *J* = 2.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 150.1, 139.3, 134.9, 133.8, 129.0, 128.2, 125.0, 120.7, 102.9, 101.8, 60.0, 56.0, 52.8, 33.3, 23.9, 21.4, 14.4, 9.7. HRMS (ESI) calcd for $C_{20}H_{24}N_5O_2S$: 398.1651. Obsd: 398.1645. $[\alpha]_D$ -5.6° (*c* 3.88, $CHCl_3$).

(R)-N-(5-((4-Methoxyphenyl)sulfonyl)-5-azaspiro-[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***52***

96.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.19 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 3.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 3.1 Hz, 1H), 5.43 (t, *J* = 4.7 Hz, 1H), 3.89 (s, 3H), 3.56 (d, *J* = 4.9 Hz, 2H), 3.36 (s, 3H), 3.27 (dd, *J* = 174.5, 9.5 Hz, 2H), 0.95 – 0.84 (m, 1H), 0.78 – 0.68 (m, 1H), 0.62 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 157.6, 151.7, 150.2, 130.1, 126.6, 120.5, 114.2, 102.9, 102.0, 59.9, 56.0, 55.6, 52.7, 33.4, 23.9, 14.3, 9.9. HRMS (ESI) calcd for $C_{20}H_{24}N_5O_3S$: 414.1600. Obsd: 414.1591. $[\alpha]_D$ -14.2° (*c* 0.983, $CHCl_3$).

(R)-N-Methyl-N-(5-((4-(trifluoromethyl)phenyl)-sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]-pyrimidin-4-amine, ***53***

97.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1H), 8.23 (s, 1H), 7.90 (dd, *J* = 54.7, 8.2 Hz, 4H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.54 (s, 1H), 5.41 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.65 (dd, *J* = 15.1, 4.8 Hz, 2H), 3.37 (s, 3H), 3.34 (dd, *J* = 191.6, 9.6 Hz, 2H), 0.99 – 0.87 (m, 1H), 0.82 – 0.72 (m, 1H), 0.71 – 0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.5, 149.9, 139.1, 134.7 (q, *J* = 33.1 Hz), 128.3, 126.3 (q, *J* = 3.6 Hz), 123.2 (q, *J* = 272.9 Hz), 120.7, 103.1, 102.0, 60.2, 56.0, 52.8, 33.5, 23.9, 14.7, 9.7. HRMS (ESI) calcd for $C_{20}H_{21}F_3N_5O_2S$: 452.1368. Obsd: 452.1361. $[\alpha]_D$ -6.8° (*c* 0.970, $CHCl_3$).

(R)-N-Methyl-N-(5-(naphthalen-2-ylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***54***

98.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.42 (s, 1H), 8.19 (d, *J* = 1.7 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.93 – 7.77 (m, 2H), 7.62 (dt, *J* = 16.4, 7.3 Hz, 2H), 7.06 (s, 1H), 6.43 (s, 1H), 5.39 (s, 1H), 3.67 (d, *J* = 3.8 Hz, 2H), 3.36 (dd, *J* = 171.8, 9.6 Hz, 2H), 3.30 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 1H), 0.71 (d, *J* = 4.6 Hz, 1H), 0.57 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.1, 134.9, 132.3, 132.1, 129.3, 129.2, 128.9, 127.9, 127.6, 123.1, 120.7, 102.9, 101.8, 60.0, 56.1, 52.9, 33.4, 23.9, 14.5, 9.7. HRMS (ESI) calcd for $C_{23}H_{24}N_5O_2S$: 434.1651. Obsd: 434.1644. $[\alpha]_D$ -17.1° (*c* 4.58, $CHCl_3$).

(R)-N-Methyl-N-(5-(piperidin-1-ylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***55***

95.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 8.25 (s, 1H), 7.09 (s, 1H), 6.58 (s, 1H), 5.56 (d, *J* = 5.8 Hz, 1H), 3.92 – 3.76 (m, 1H), 3.54 (d, *J* = 9.5 Hz, 2H), 3.48 (s, 4H), 3.28 (d, *J* = 4.5 Hz, 4H), 1.61 (dd, *J* = 26.6, 3.9 Hz, 6H), 1.03 (d, *J* = 9.7 Hz, 1H), 0.76 (d, *J* = 9.9 Hz, 2H), 0.69 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 150.6, 120.3, 102.8, 102.0, 60.2, 56.6, 52.9, 47.2, 33.5, 25.5, 24.0, 23.8, 15.1, 9.5. HRMS (ESI) calcd for $C_{18}H_{27}N_6O_2S$: 391.1916. Obsd: 391.1913. $[\alpha]_D$ +32.7° (*c* 0.297, $CHCl_3$).

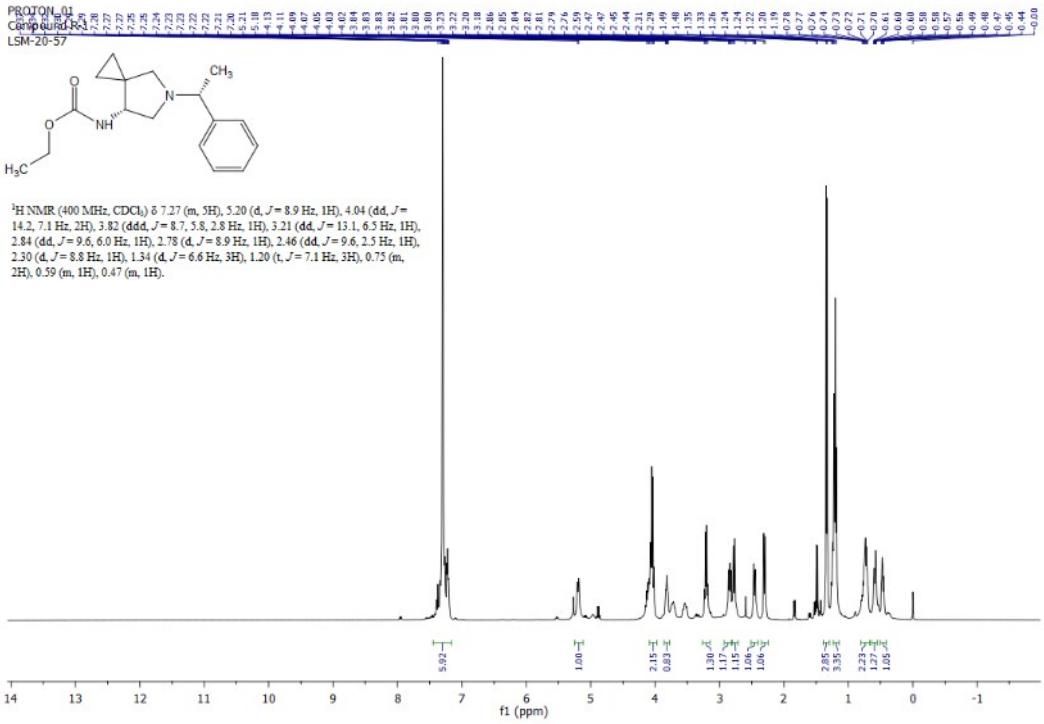
(R)-N-Methyl-N-(5-(morpholinosulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***56***

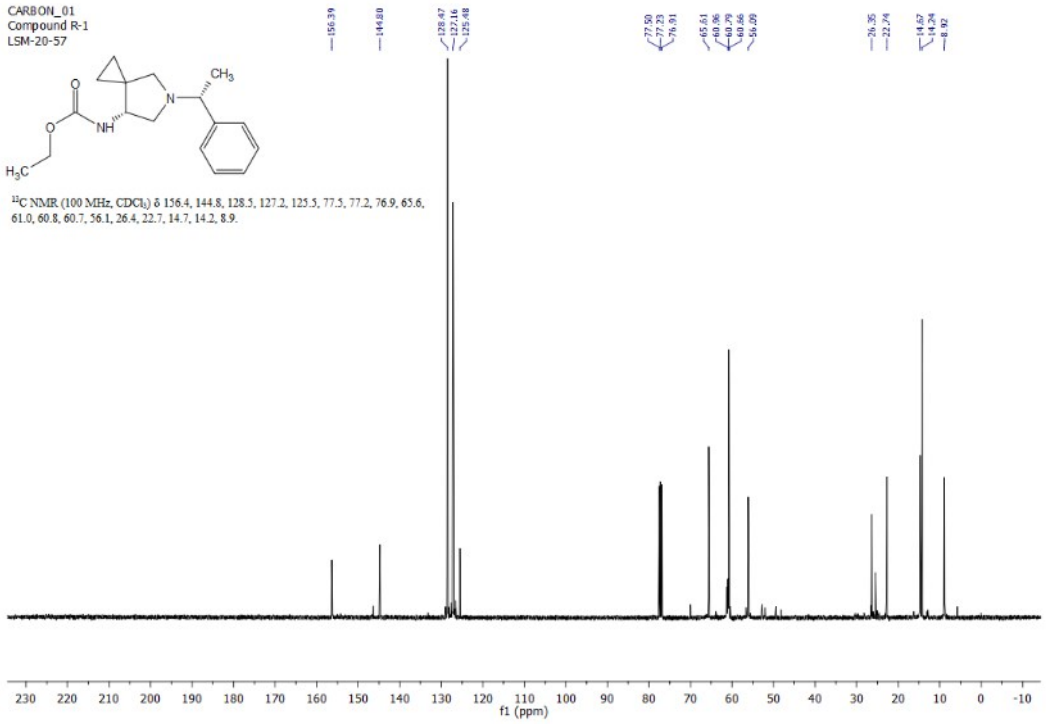
94.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 8.27 (d, *J* = 2.8 Hz, 1H), 7.13 (s, 1H), 6.57 (s, 1H), 5.63 – 5.51 (m, 1H), 3.90 (ddd, *J* = 10.6, 7.6, 2.7 Hz, 1H), 3.75 (dd, *J* = 5.8, 3.1 Hz, 4H), 3.65 – 3.55 (m, 2H), 3.48 (d, *J* = 2.8 Hz, 3H), 3.37 – 3.22 (m, 5H), 1.04 (d, *J* = 9.6 Hz, 1H), 0.85 – 0.75 (m, 2H), 0.75 – 0.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 150.3, 120.7, 102.9, 101.8, 66.4, 60.2, 56.8, 53.1, 46.4, 33.5, 24.0, 15.3, 9.3. HRMS (ESI) calcd for $C_{17}H_{25}N_6O_3S$: 393.1709. Obsd: 393.1704. $[\alpha]_D$ +32.9° (*c* 1.57, $CHCl_3$).

NMR spectra

Ethyl ((R)-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)carbamate, ***(R)-2c***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.20 (d, *J* = 8.9 Hz, 1H), 4.04 (dd, *J* = 14.2, 7.1 Hz, 2H), 3.82 (ddd, *J* = 8.7, 5.8, 2.8 Hz, 1H), 3.21 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.84 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.78 (d, *J* = 8.9 Hz, 1H), 2.46 (dd, *J* = 9.6, 2.5 Hz, 1H), 2.30 (d, *J* = 8.8 Hz, 1H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.75 (m, 2H), 0.59 (m, 1H), 0.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 144.8, 128.5, 127.2, 125.5, 77.5, 77.2, 76.9, 65.6, 61.0, 60.8, 60.7, 56.1, 26.4, 22.7, 14.7, 14.2, 8.9.

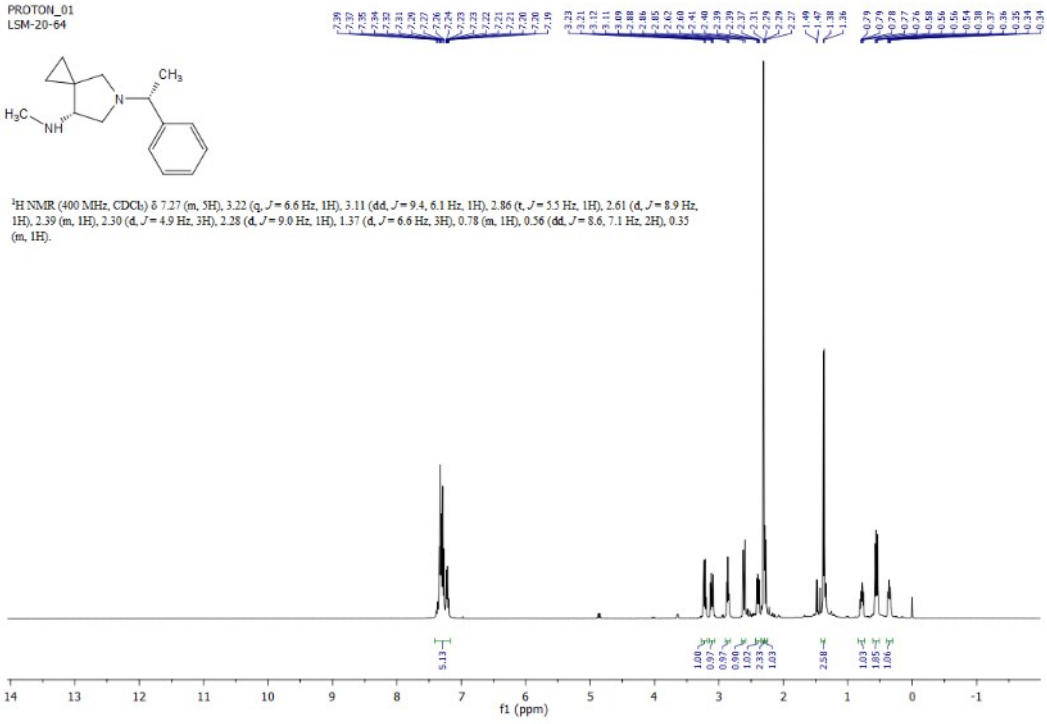




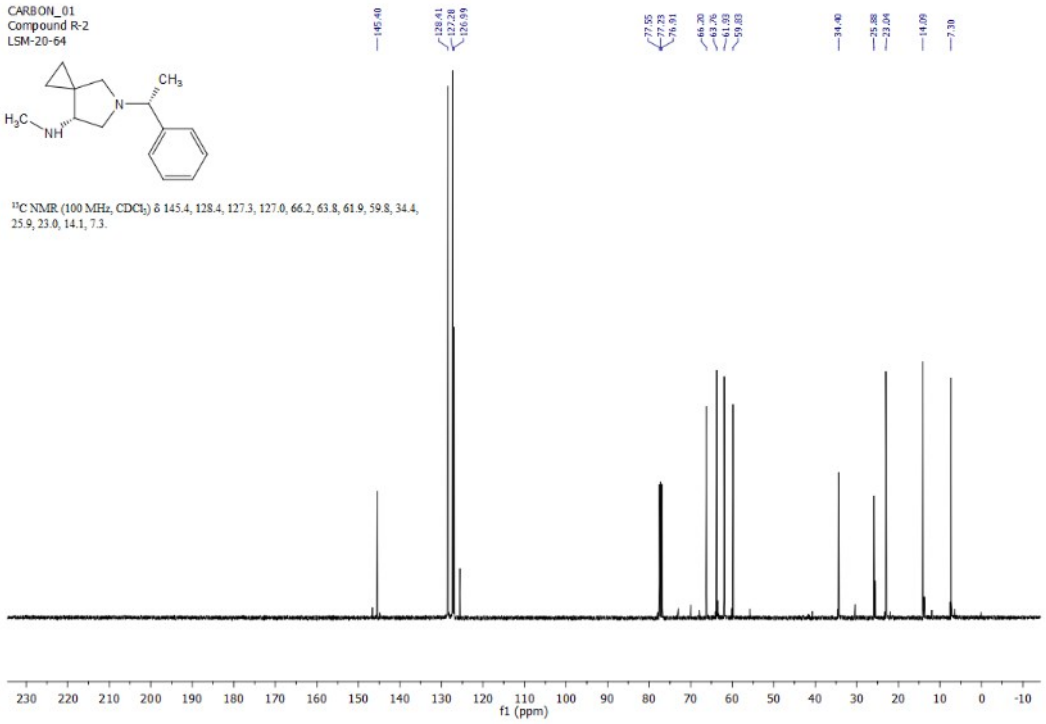
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 144.8, 128.5, 127.2, 125.5, 77.5, 77.2, 76.9, 65.6, 61.0, 60.8, 60.7, 56.1, 26.4, 22.7, 14.7, 14.2, 8.9.

(R)-N-Methyl-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-amine, ***(R)-3c***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 3.22 (q, *J* = 6.6 Hz, 1H), 3.11 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.86 (t, *J* = 5.5 Hz, 1H), 2.61 (d, *J* = 8.9 Hz, 1H), 2.39 (m, 1H), 2.30 (d, *J* = 4.9 Hz, 3H), 2.28 (d, *J* = 9.0 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 0.78 (m, 1H), 0.56 (dd, *J* = 8.6, 7.1 Hz, 2H), 0.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 128.4, 127.3, 127.0, 66.2, 63.8, 61.9, 59.8, 34.4, 25.9, 23.0, 14.1, 7.3.

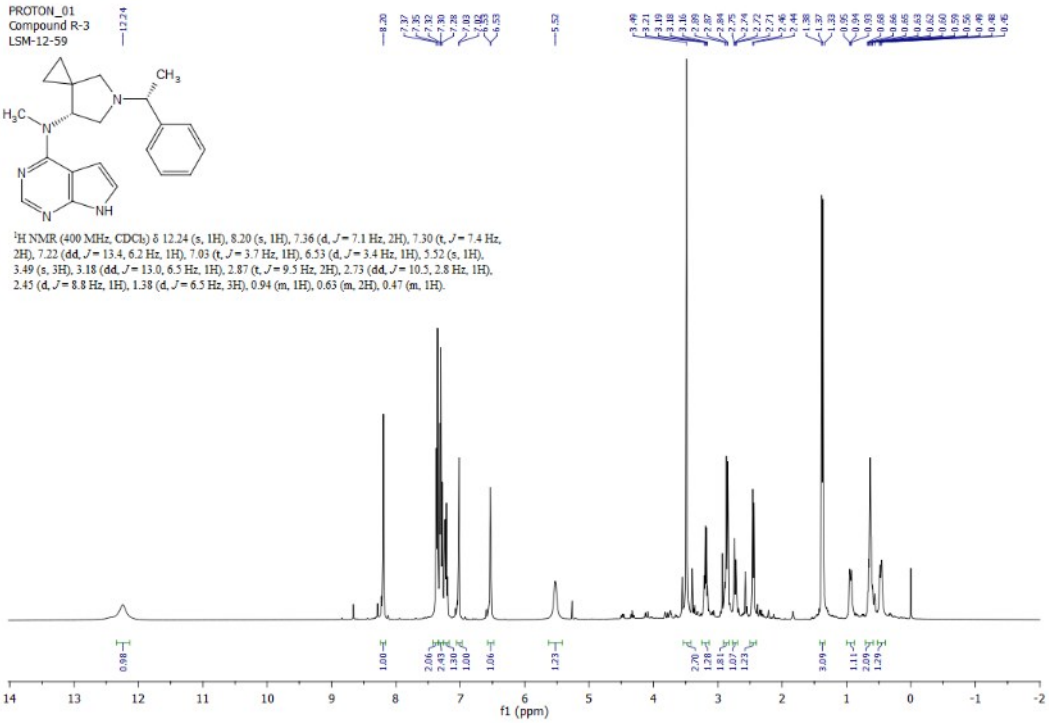


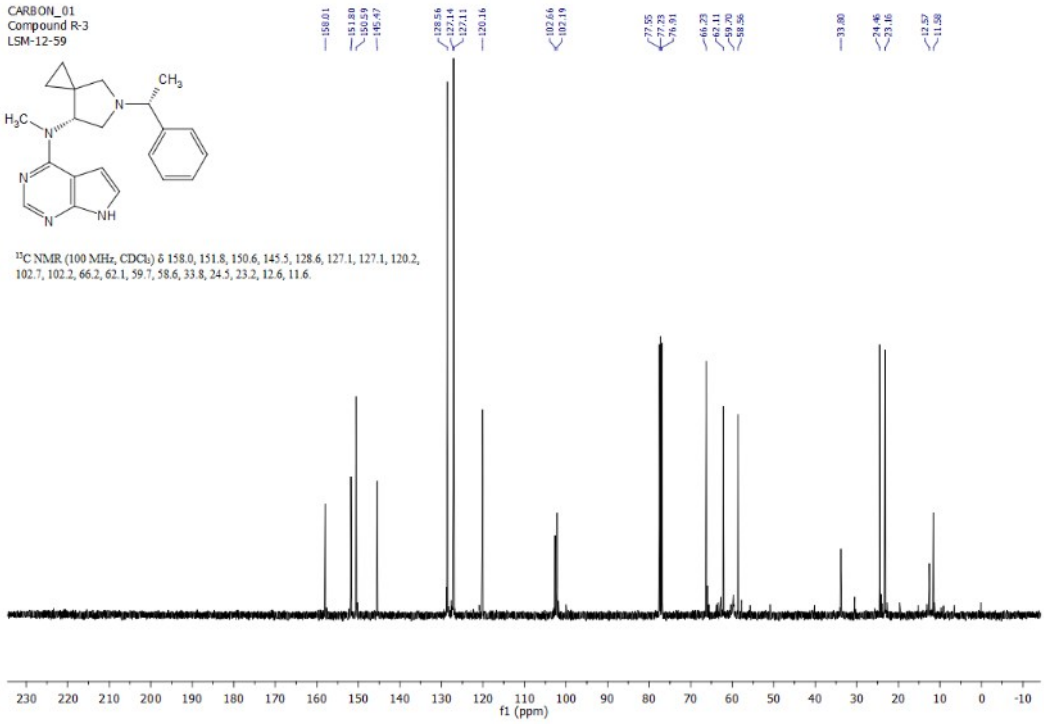
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 3.22 (q, *J* = 6.6 Hz, 1H), 3.11 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.86 (t, *J* = 5.5 Hz, 1H), 2.61 (d, *J* = 8.9 Hz, 1H), 2.39 (m, 1H), 2.30 (d, *J* = 4.9 Hz, 3H), 2.28 (d, *J* = 9.0 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 0.78 (m, 1H), 0.56 (dd, *J* = 8.6, 7.1 Hz, 2H), 0.35 (m, 1H).



N-Methyl-N-((R)-5-((R)-1-phenylethyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***(R)-4c***

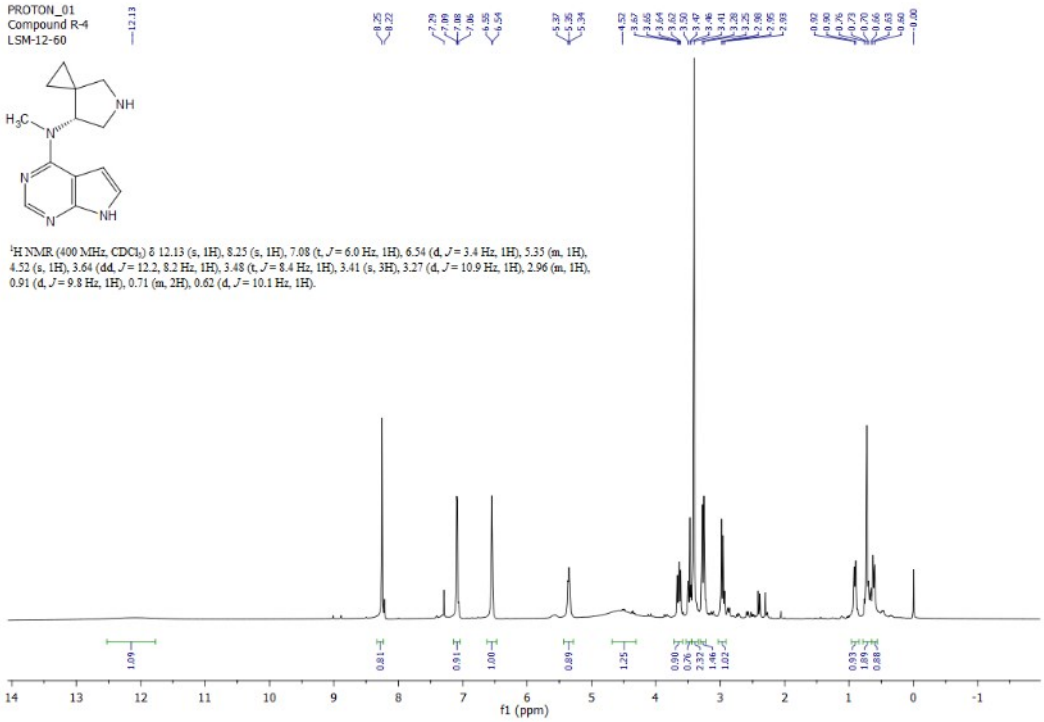
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (s, 1H), 8.20 (s, 1H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (dd, *J* = 13.4, 6.2 Hz, 1H), 7.03 (t, *J* = 3.7 Hz, 1H), 6.53 (d, *J* = 3.4 Hz, 1H), 5.52 (s, 1H), 3.49 (s, 3H), 3.18 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.87 (t, *J* = 9.5 Hz, 2H), 2.73 (dd, *J* = 10.5, 2.8 Hz, 1H), 2.45 (d, *J* = 8.8 Hz, 1H), 1.38 (d, *J* = 6.5 Hz, 3H), 0.94 (m, 1H), 0.63 (m, 2H), 0.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 151.8, 150.6, 145.5, 128.6, 127.1, 127.1, 120.2, 102.7, 102.2, 66.2, 62.1, 59.7, 58.6, 33.8, 24.5, 23.2, 12.6, 11.6.

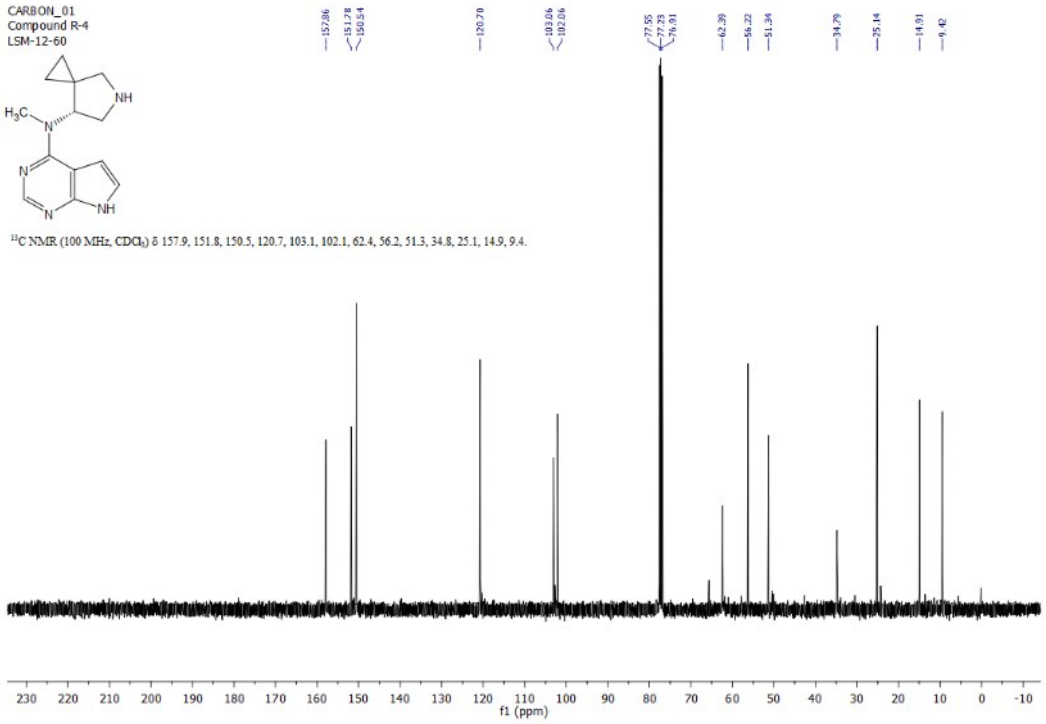




(R)-N-Methyl-N-(5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***(R)-5c***

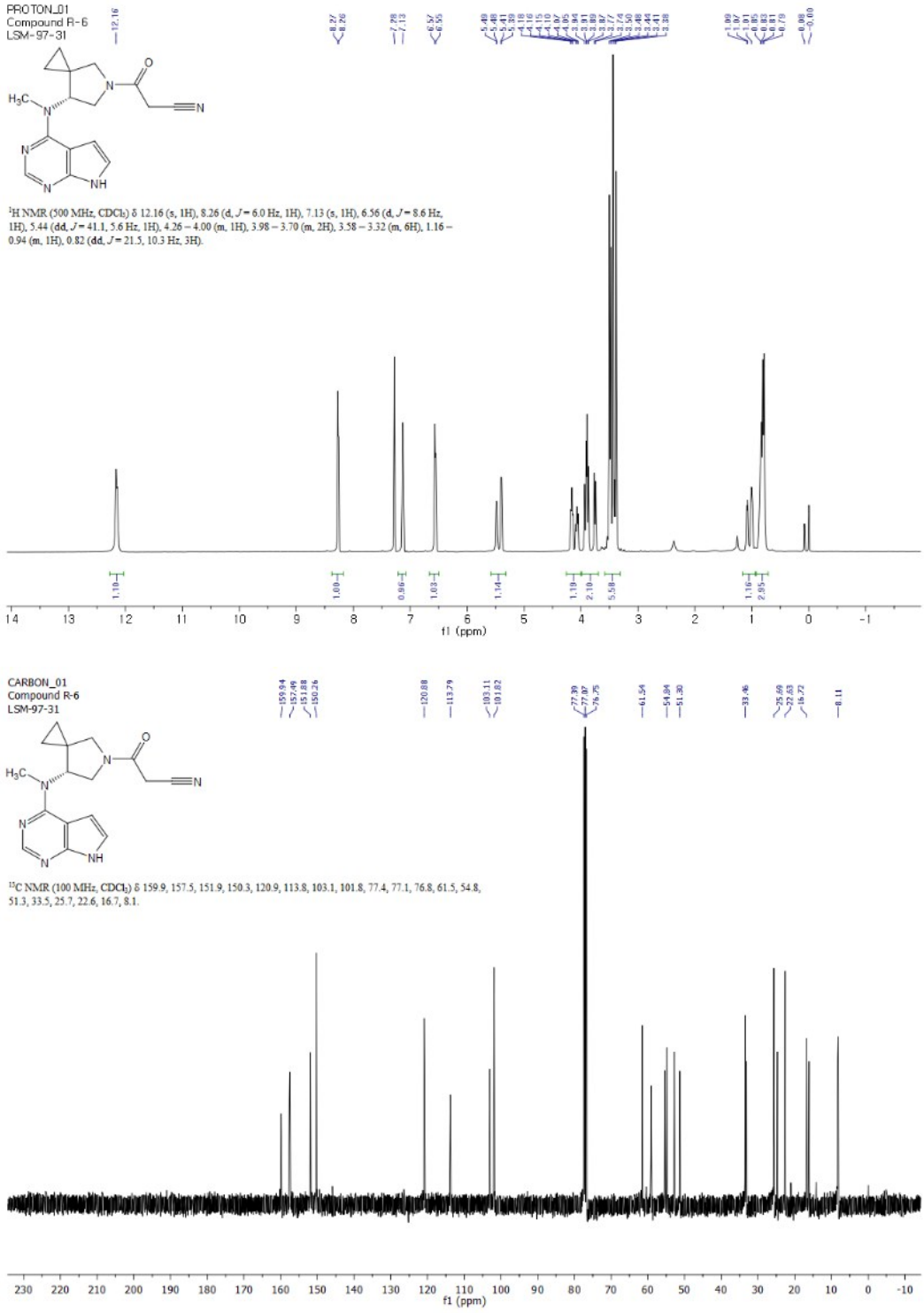
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 8.25 (s, 1H), 7.08 (t, *J* = 6.0 Hz, 1H), 6.54 (d, *J* = 3.4 Hz, 1H), 5.35 (m, 1H), 4.52 (s, 1H), 3.64 (dd, *J* = 12.2, 8.2 Hz, 1H), 3.48 (t, *J* = 8.4 Hz, 1H), 3.41 (s, 3H), 3.27 (d, *J* = 10.9 Hz, 1H), 2.96 (m, 1H), 0.91 (d, *J* = 9.8 Hz, 1H), 0.71 (m, 2H), 0.62 (d, *J* = 10.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.5, 120.7, 103.1, 102.1, 62.4, 56.2, 51.3, 34.8, 25.1, 14.9, 9.4.





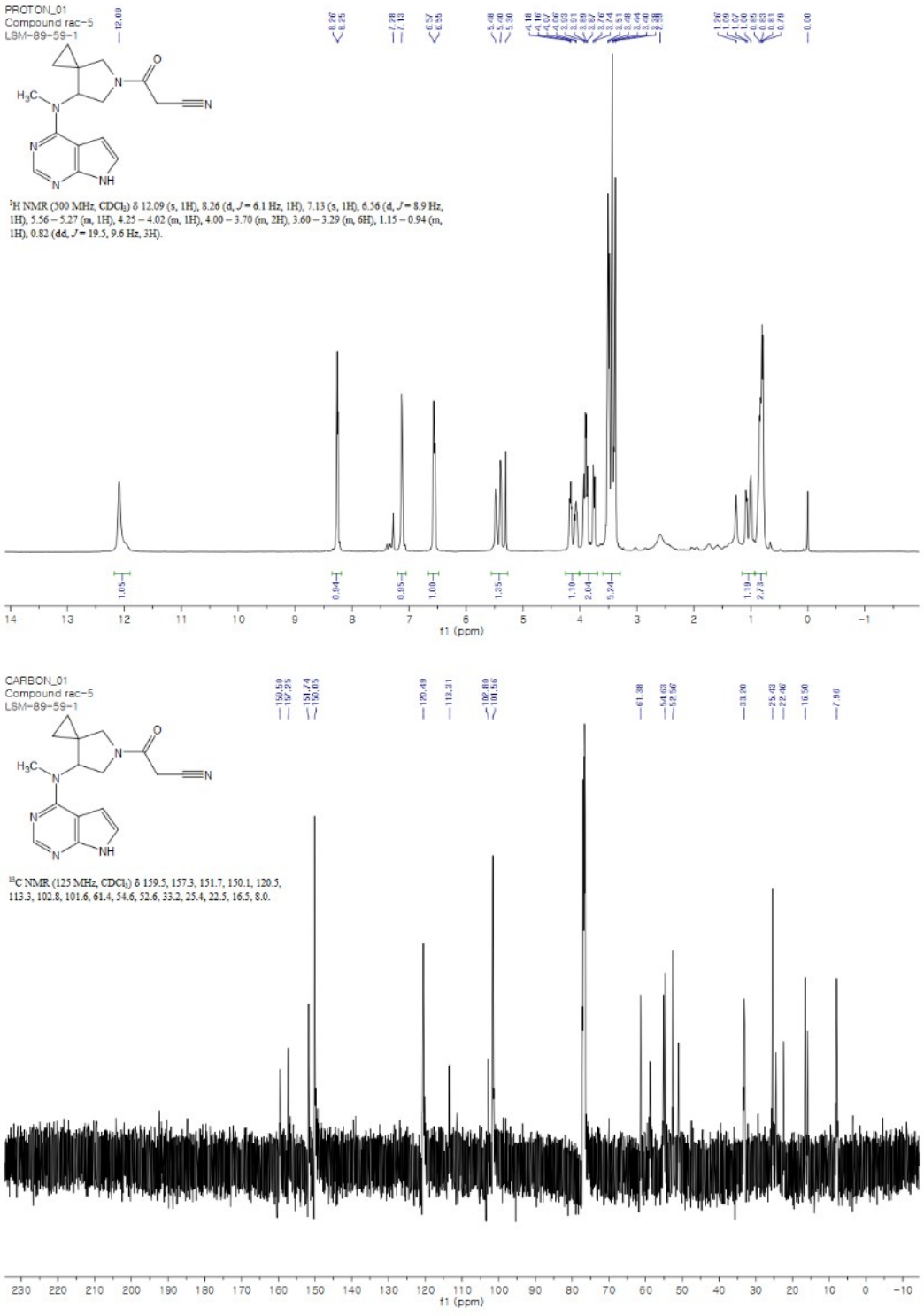
(R)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, **(*R*)-6c**

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.26 (d, *J* = 6.0 Hz, 1H), 7.13 (s, 1H), 6.56 (d, *J* = 8.6 Hz, 1H), 5.44 (dd, *J* = 41.1, 5.6 Hz, 1H), 4.26 – 4.00 (m, 1H), 3.98 – 3.70 (m, 2H), 3.58 – 3.32 (m, 6H), 1.16 – 0.94 (m, 1H), 0.82 (dd, *J* = 21.5, 10.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 151.9, 150.3, 120.9, 113.8, 103.1, 101.8, 77.4, 77.1, 76.8, 61.5, 54.8, 51.3, 33.5, 25.7, 22.6, 16.7, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd 311.1616. $[\alpha]_D$ +51.6° (*c* 1.49, $CHCl_3$).



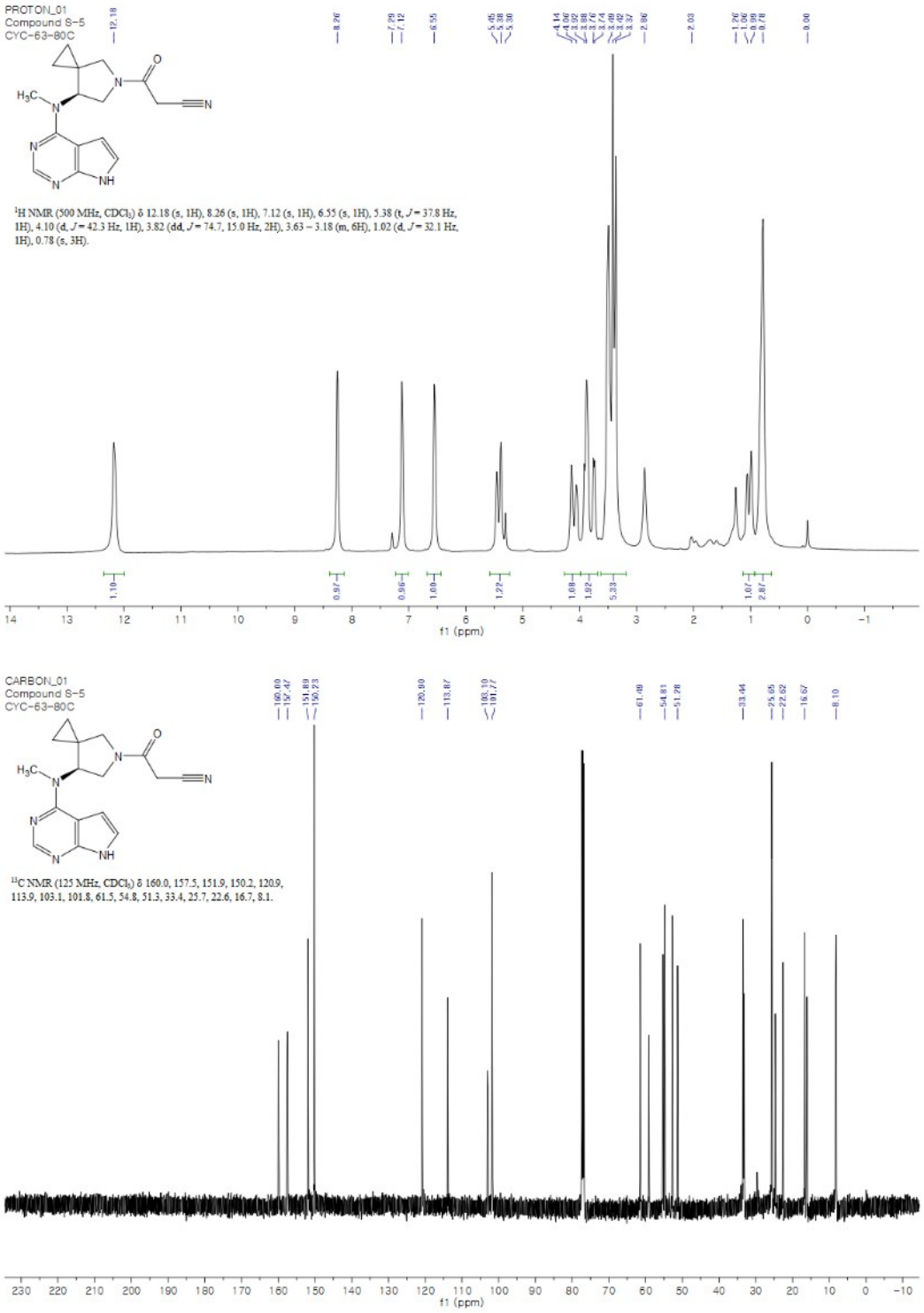
3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, ***6c***

96.8% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.26 (d, J = 6.1 Hz, 1H), 7.13 (s, 1H), 6.56 (d, J = 8.9 Hz, 1H), 5.56 – 5.27 (m, 1H), 4.25 – 4.02 (m, 1H), 4.00 – 3.70 (m, 2H), 3.60 – 3.29 (m, 6H), 1.15 – 0.94 (m, 1H), 0.82 (dd, J = 19.5, 9.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.3, 151.7, 150.1, 120.5, 113.3, 102.8, 101.6, 61.4, 54.6, 52.6, 33.2, 25.4, 22.5, 16.5, 8.0. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd: 311.1616.



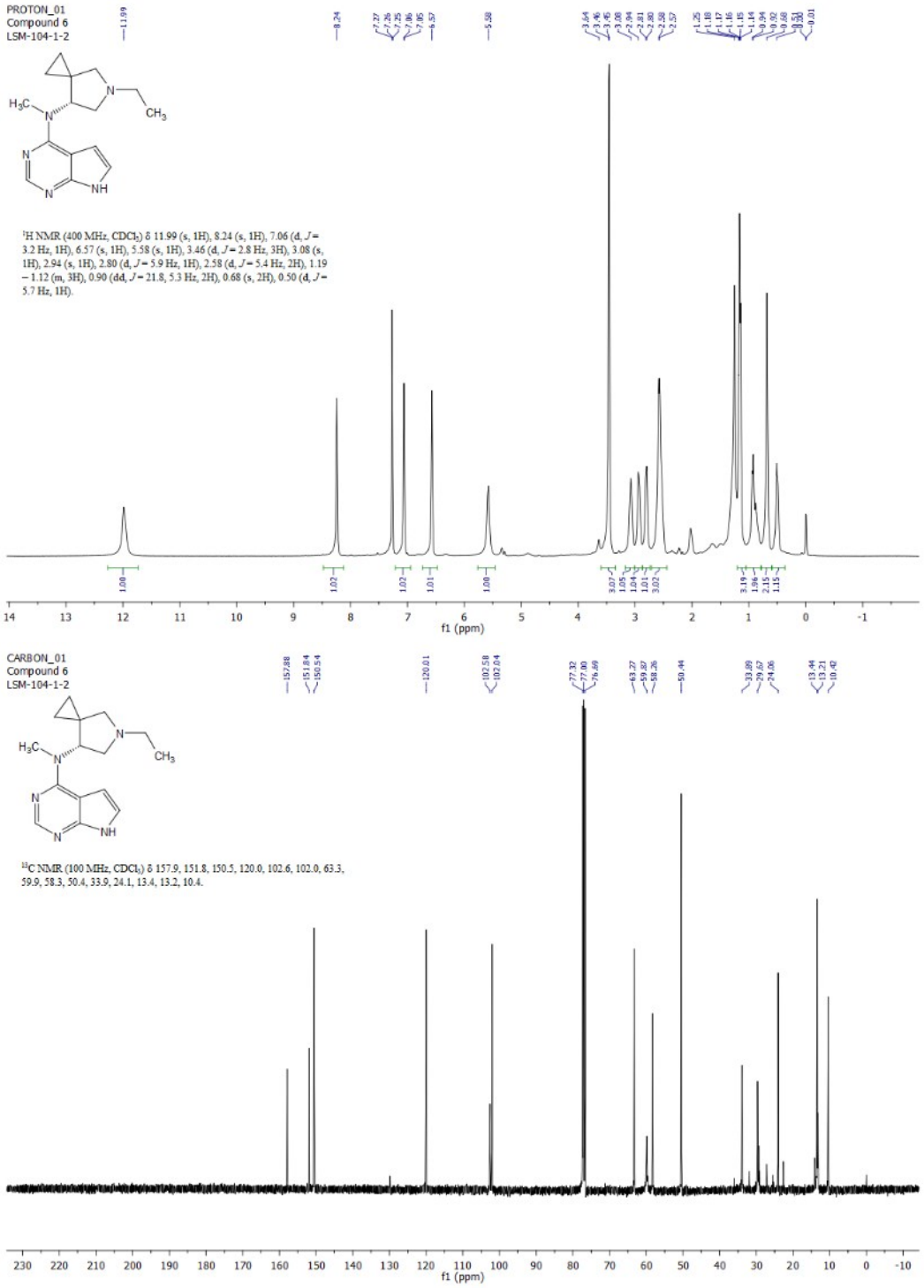
(S)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile, **(*S*)-6c**

97.4% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.18 (s, 1H), 8.26 (s, 1H), 7.12 (s, 1H), 6.55 (s, 1H), 5.38 (t, J = 37.8 Hz, 1H), 4.10 (d, J = 42.3 Hz, 1H), 3.82 (dd, J = 74.7, 15.0 Hz, 2H), 3.63 – 3.18 (m, 6H), 1.02 (d, J = 32.1 Hz, 1H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.5, 151.9, 150.2, 120.9, 113.9, 103.1, 101.8, 61.5, 54.8, 51.3, 33.4, 25.7, 22.6, 16.7, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6O$: 311.1620. Obsd: 311.1616. $[\alpha]_D$ +35.6° (*c* 0.980, $CHCl_3$).



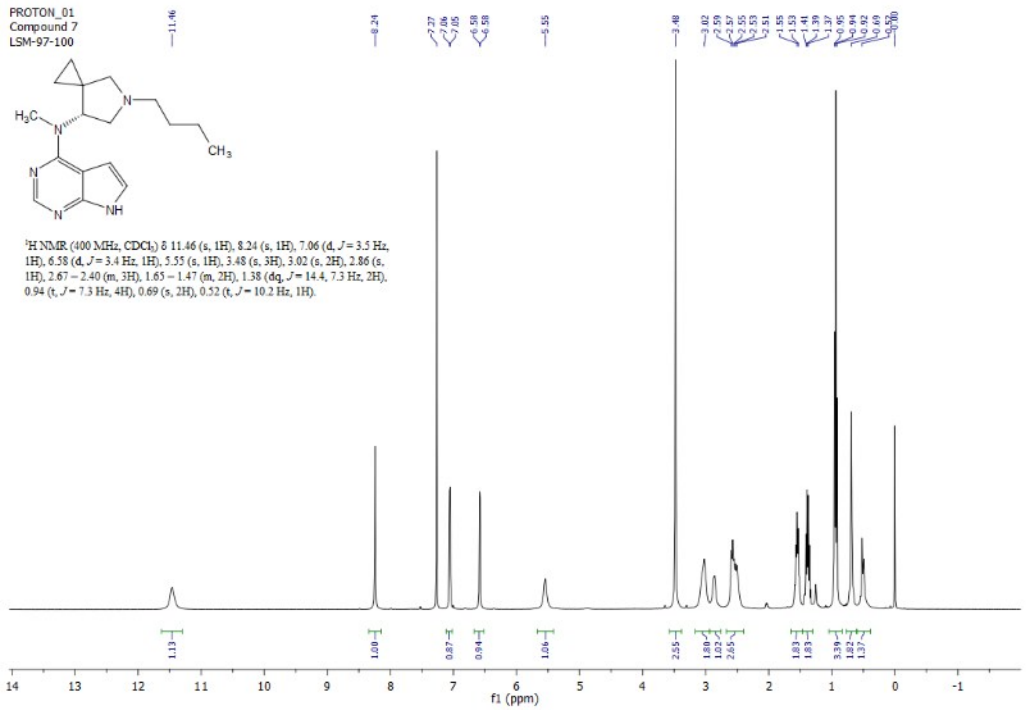
(R)-N-(5-Ethyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, 7

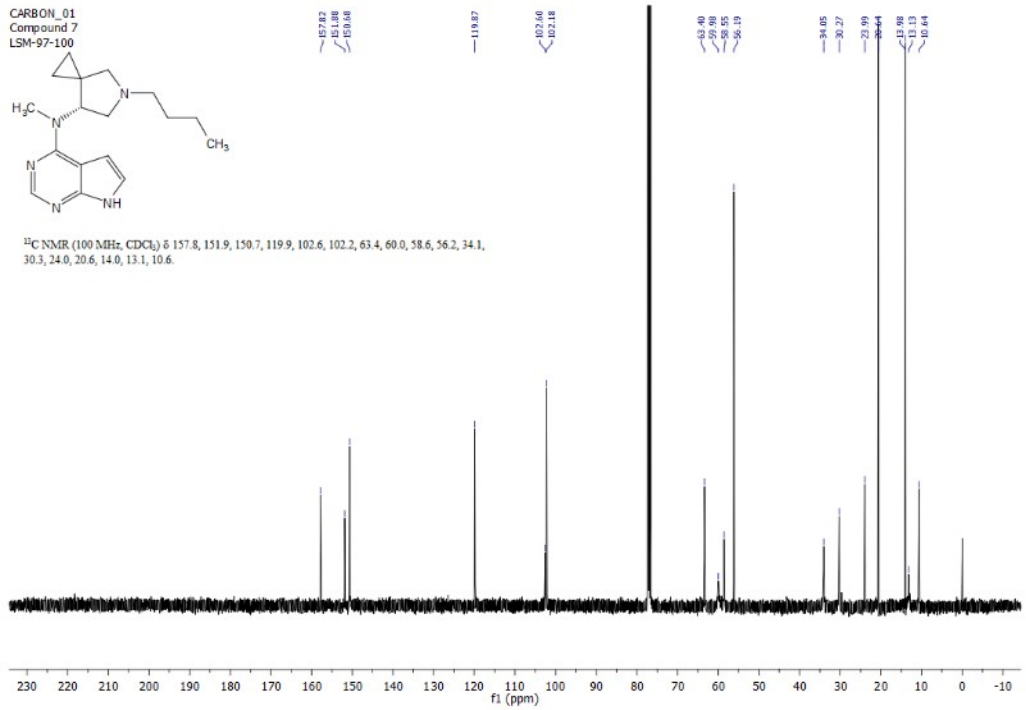
100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 8.24 (s, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.57 (s, 1H), 5.58 (s, 1H), 3.46 (d, J = 2.8 Hz, 3H), 3.08 (s, 1H), 2.94 (s, 1H), 2.80 (d, J = 5.9 Hz, 1H), 2.58 (d, J = 5.4 Hz, 2H), 1.19 – 1.12 (m, 3H), 0.90 (dd, J = 21.8, 5.3 Hz, 2H), 0.68 (s, 2H), 0.50 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.5, 120.0, 102.6, 102.0, 63.3, 59.9, 58.3, 50.4, 33.9, 24.1, 13.4, 13.2, 10.4. HRMS (ESI) calcd for $C_{15}H_{22}N_5$: 272.1875. Obsd: 272.1872. $[\alpha]_D$ +43.2^o (*c* 0.560, $CHCl_3$).



(R)-N-(5-Butyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***8***

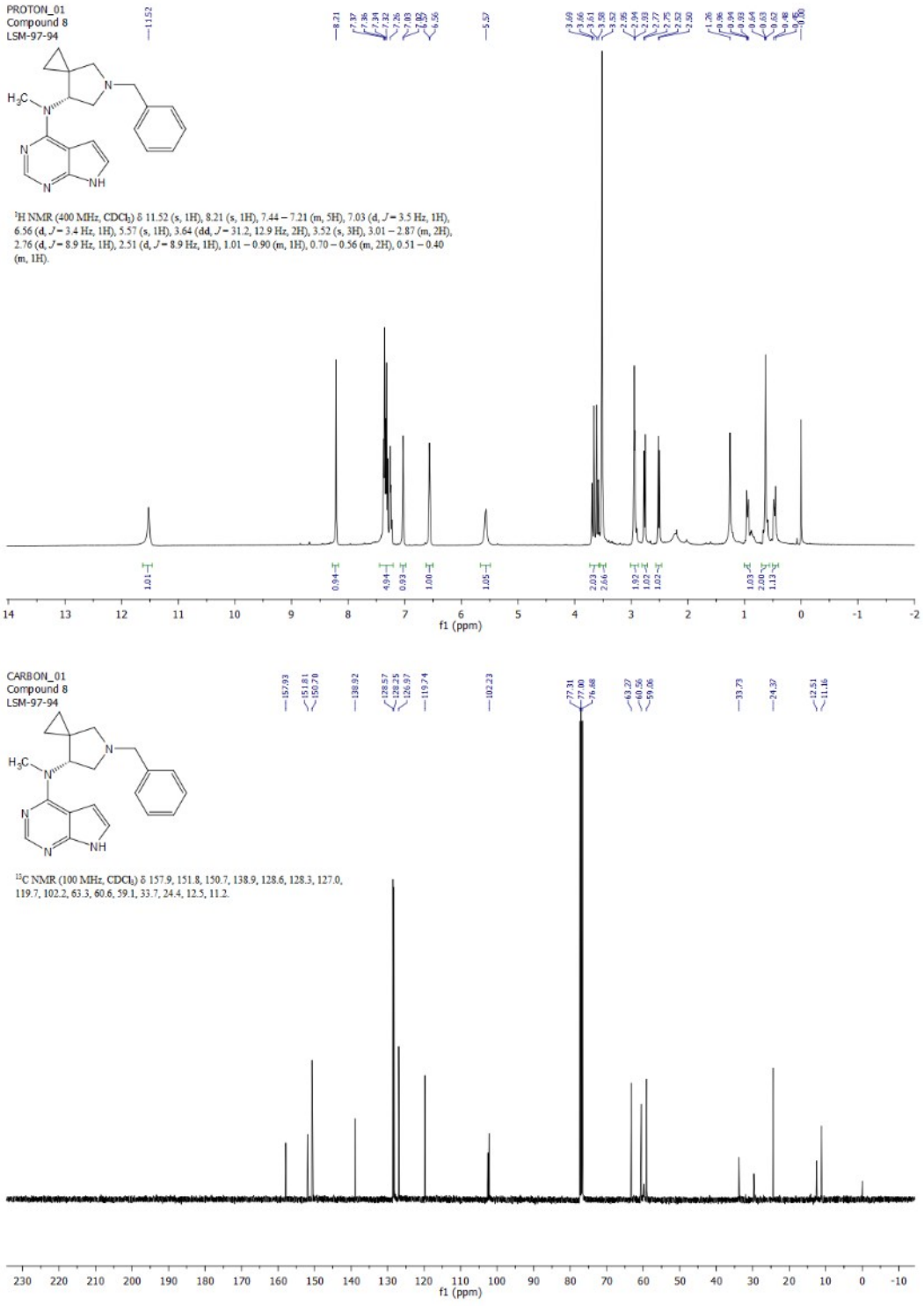
100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.24 (s, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.58 (d, J = 3.4 Hz, 1H), 5.55 (s, 1H), 3.48 (s, 3H), 3.02 (s, 2H), 2.86 (s, 1H), 2.67 – 2.40 (m, 3H), 1.65 – 1.47 (m, 2H), 1.38 (dq, J = 14.4, 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 4H), 0.69 (s, 2H), 0.52 (t, J = 10.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 151.9, 150.7, 119.9, 102.6, 102.2, 63.4, 60.0, 58.6, 56.2, 34.1, 30.3, 24.0, 20.6, 14.0, 13.1, 10.6. HRMS (ESI) calcd for $C_{17}H_{26}N_5$: 300.2188. Obsd: 300.2188. $[\alpha]_D$ +55.6° (c 0.410, $CHCl_3$).





(R)-N-(5-Benzyl-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***9***

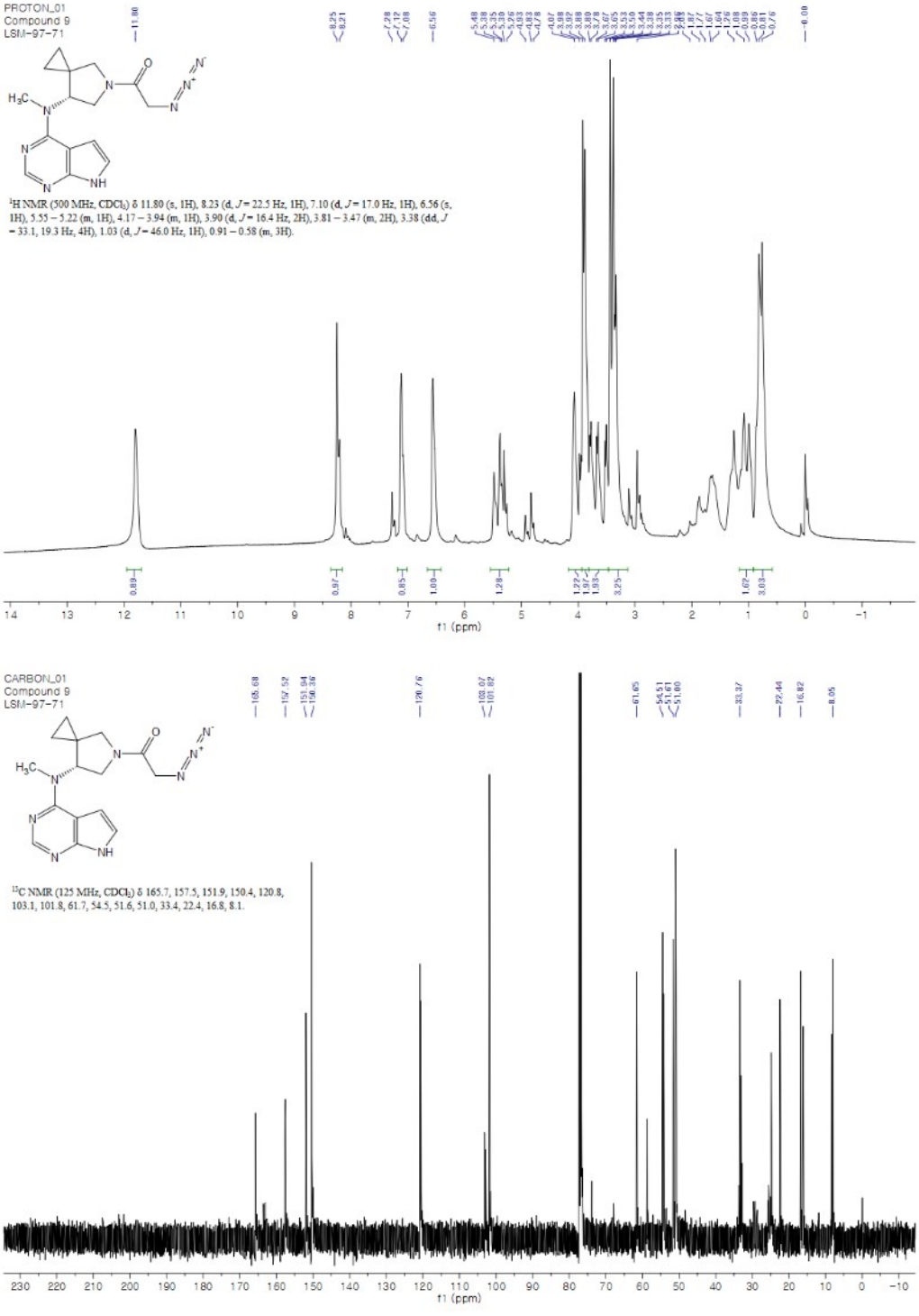
100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H), 8.21 (s, 1H), 7.44 – 7.21 (m, 5H), 7.03 (d, J = 3.5 Hz, 1H), 6.56 (d, J = 3.4 Hz, 1H), 5.57 (s, 1H), 3.64 (dd, J = 31.2, 12.9 Hz, 2H), 3.52 (s, 3H), 3.01 – 2.87 (m, 2H), 2.76 (d, J = 8.9 Hz, 1H), 2.51 (d, J = 8.9 Hz, 1H), 1.01 – 0.90 (m, 1H), 0.70 – 0.56 (m, 2H), 0.51 – 0.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 150.7, 138.9, 128.6, 128.3, 127.0, 119.7, 102.2, 63.3, 60.6, 59.1, 33.7, 24.4, 12.5, 11.2. HRMS (ESI) calcd for $C_{20}H_{24}N_5$: 334.2032. Obsd: 334.2025. $[\alpha]_D$ +52.9° (*c* 3.07, $CHCl_3$).



(R)-2-Azido-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)ethan-1-one, ***10***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.80 (s, 1H), 8.23 (d, J = 22.5 Hz, 1H), 7.10 (d, J = 17.0 Hz, 1H), 6.56 (s, 1H), 5.55 – 5.22 (m, 1H), 4.17 – 3.94 (m, 1H), 3.90 (d, J = 16.4 Hz, 2H), 3.81 – 3.47 (m, 2H), 3.38 (dd, J = 33.1, 19.3 Hz, 4H), 1.03 (d, J = 46.0 Hz, 1H), 0.91 – 0.58 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 157.5, 151.9, 150.4, 120.8, 103.1, 101.8, 61.7, 54.5, 51.6, 51.0, 33.4,

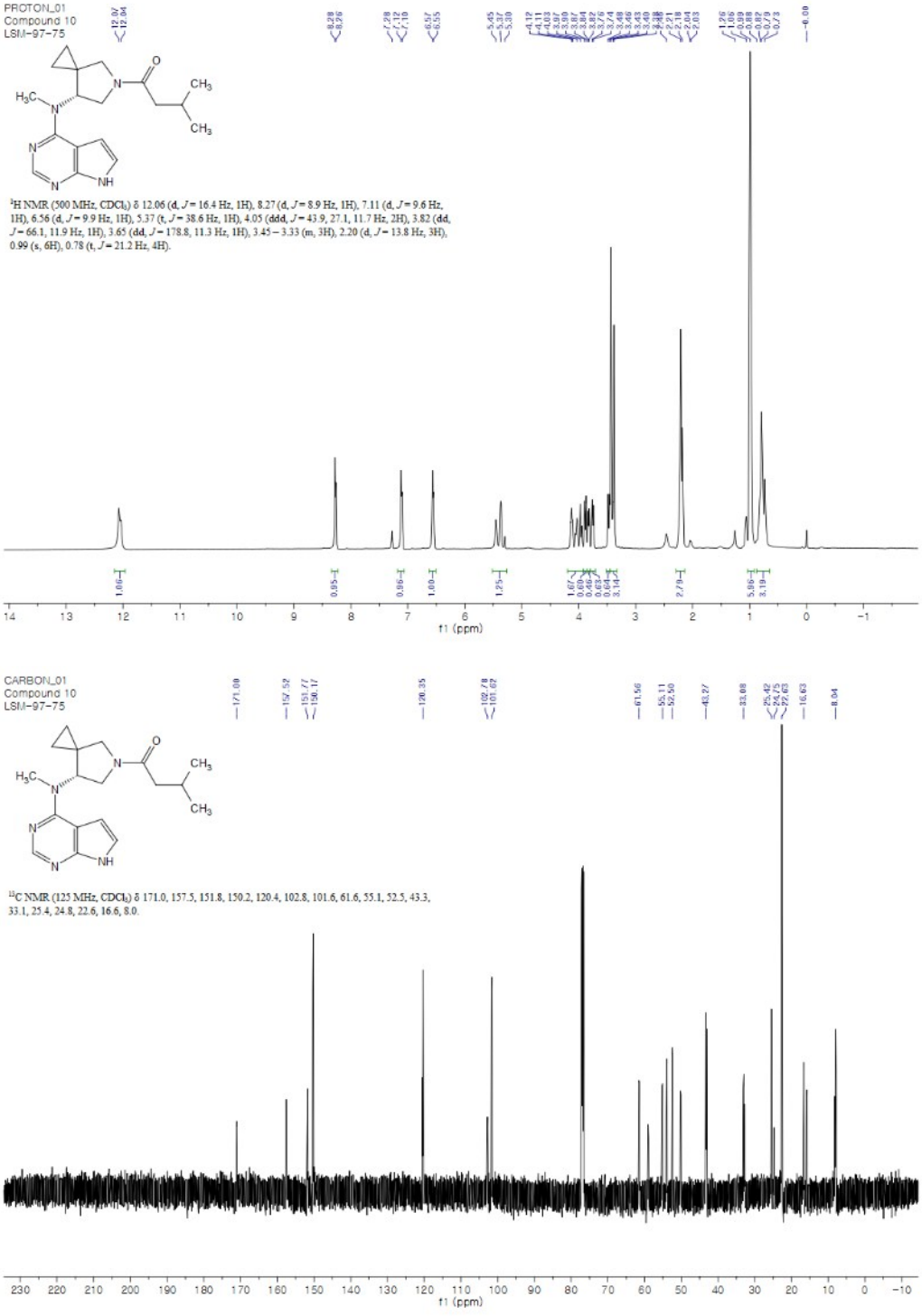
22.4, 16.8, 8.1. HRMS (ESI) calcd for $C_{15}H_{19}N_8O$: 327.1682. Obsd: 327.1673. $[\alpha]_D$ +37.3° (*c* 1.49, $CHCl_3$).



(R)-3-Methyl-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)butan-1-one, ***11***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (d, *J* = 16.4 Hz, 1H), 8.27 (d, *J* = 8.9 Hz, 1H), 7.11 (d, *J* = 9.6 Hz, 1H), 6.56 (d, *J* = 9.9 Hz, 1H), 5.37 (t, *J* = 38.6 Hz, 1H), 4.05 (ddd, *J* = 43.9, 27.1, 11.7 Hz, 2H), 3.82 (dd, *J* = 66.1, 11.9 Hz, 1H), 3.65 (dd, *J* = 178.8, 11.3 Hz, 1H), 3.45 – 3.33 (m, 3H), 2.20 (d, *J* = 13.8 Hz, 3H), 0.99 (s, 6H), 0.78 (t, *J* = 21.2 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

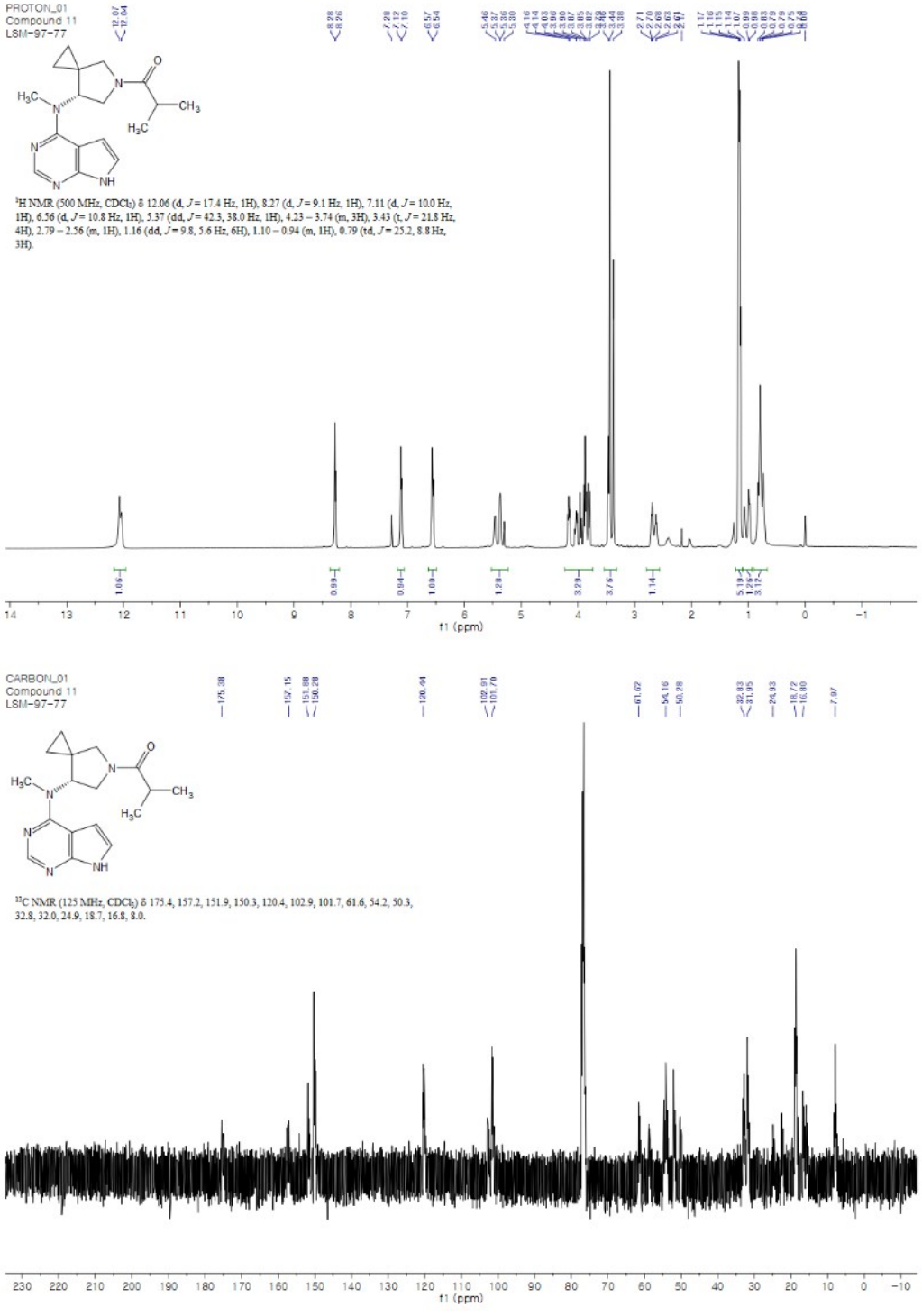
171.0, 157.5, 151.8, 150.2, 120.4, 102.8, 101.6, 61.6, 55.1, 52.5, 43.3, 33.1, 25.4, 24.8, 22.6, 16.6, 8.0. HRMS (ESI) calcd for $C_{18}H_{26}N_5O$: 328.2137. Obsd: 328.2126. $[\alpha]_D$ +45.2° (*c* 1.21, $CHCl_3$).



(R)-2-Methyl-1-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)propan-1-one, ***12***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (d, *J* = 17.4 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.11 (d, *J* = 10.0 Hz, 1H), 6.56 (d, *J* = 10.8 Hz, 1H), 5.37 (dd, *J* = 42.3, 38.0 Hz, 1H), 4.23 – 3.74 (m, 3H), 3.43 (t, *J* = 21.8 Hz, 4H), 2.79 – 2.56 (m, 1H), 1.16 (dd, *J* = 9.8, 5.6 Hz, 6H), 1.10 – 0.94 (m, 1H), 0.79 (td, *J* = 25.2, 8.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 157.2, 151.9, 150.3, 120.4,

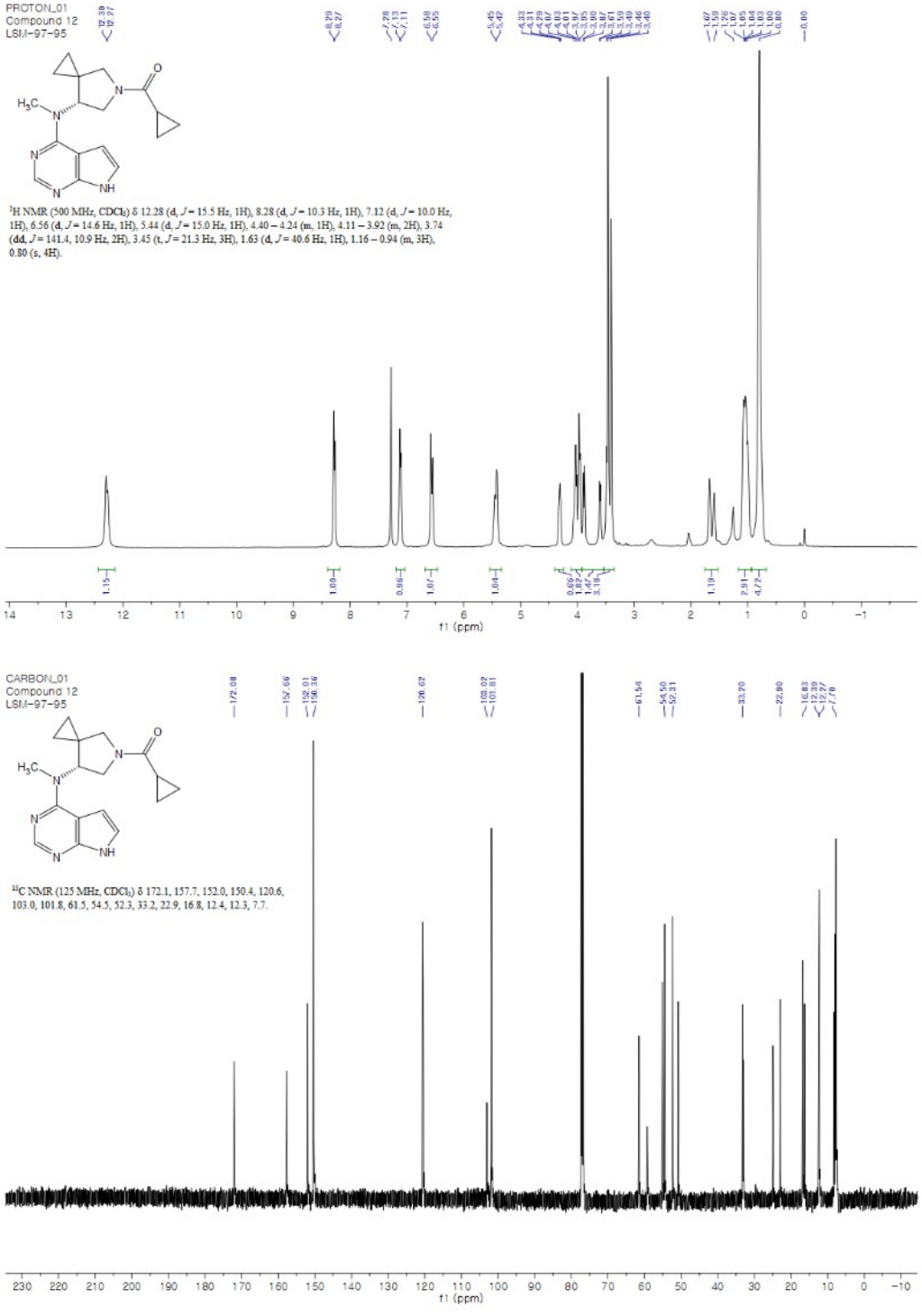
102.9, 101.7, 61.6, 54.2, 50.3, 32.8, 32.0, 24.9, 18.7, 16.8, 8.0. HRMS (ESI) calcd for $C_{17}H_{24}N_5O$: 314.1981. Obsd: 314.1971. $[\alpha]_D$ +50.0° (*c* 1.12, $CHCl_3$).



(R)-Cyclopropyl(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)methanone, ***13***

93.1% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.28 (d, *J* = 15.5 Hz, 1H), 8.28 (d, *J* = 10.3 Hz, 1H), 7.12 (d, *J* = 10.0 Hz, 1H), 6.56 (d, *J* = 14.6 Hz, 1H), 5.44 (d, *J* = 15.0 Hz, 1H), 4.40 – 4.24 (m, 1H), 4.11 – 3.92 (m, 2H), 3.74 (dd, *J* = 141.4, 10.9 Hz, 2H), 3.45 (t, *J* = 21.3 Hz, 3H), 1.63 (d, *J* = 40.6 Hz, 1H), 1.16 – 0.94 (m, 3H), 0.80 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 157.7, 152.0, 150.4,

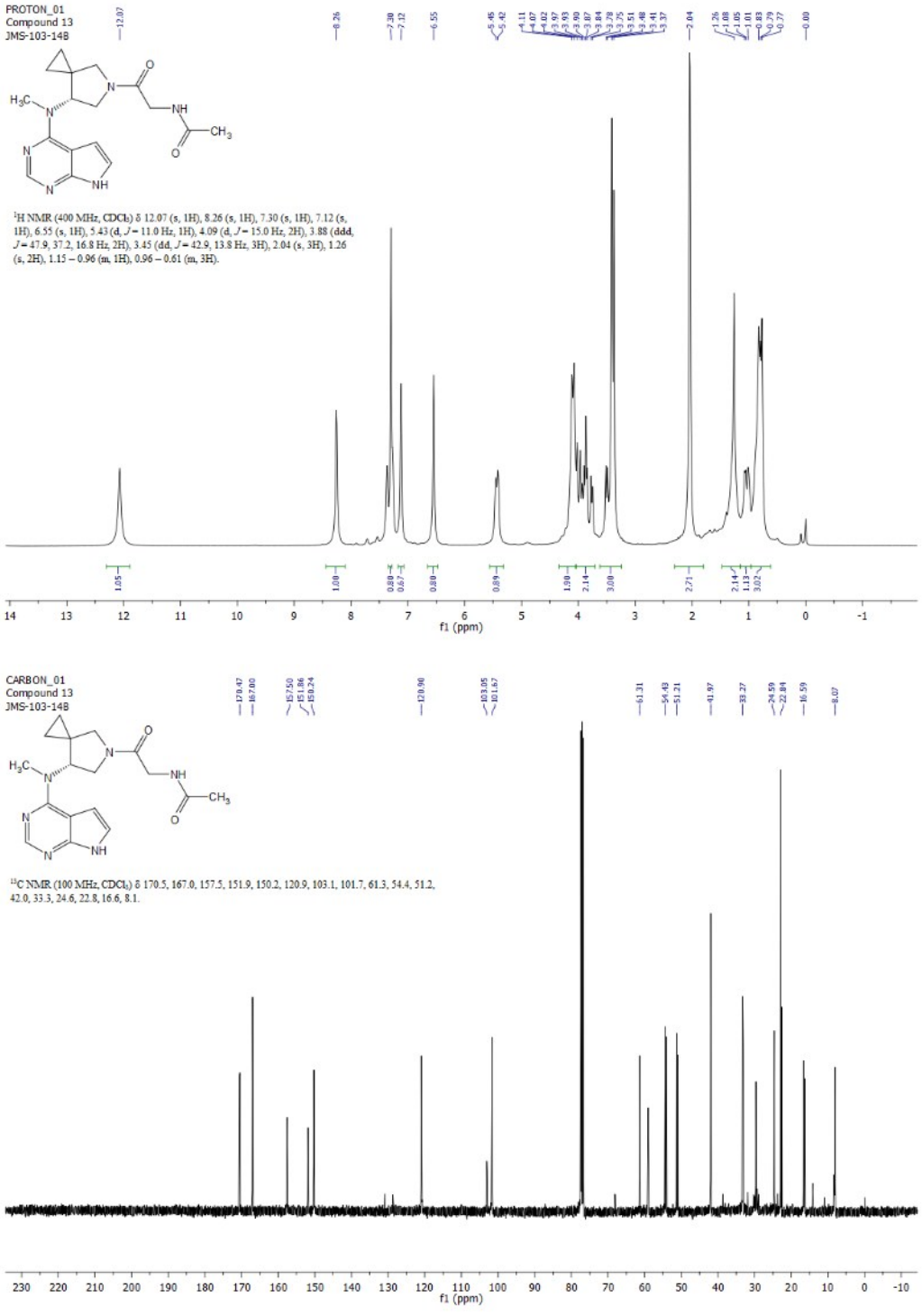
120.6, 103.0, 101.8, 61.5, 54.5, 52.3, 33.2, 22.9, 16.8, 12.4, 12.3, 7.7. HRMS (ESI) calcd for $C_{17}H_{22}N_5O$: 312.1824. Obsd: 312.1823. $[\alpha]_D$ +60.0° (*c* 1.31, $CHCl_3$).



(R)-N-(2-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-2-oxoethyl)acetamide, ***14***

98.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.26 (s, 1H), 7.30 (s, 1H), 7.12 (s, 1H), 6.55 (s, 1H), 5.43 (d, *J* = 11.0 Hz, 1H), 4.09 (d, *J* = 15.0 Hz, 2H), 3.88 (ddd, *J* = 47.9, 37.2, 16.8 Hz, 2H), 3.45 (dd, *J* = 42.9, 13.8 Hz, 3H), 2.04 (s, 3H), 1.26 (s, 2H), 1.15 – 0.96 (m, 1H), 0.96 – 0.61 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.0, 157.5, 151.9, 150.2, 120.9, 103.1, 101.7,

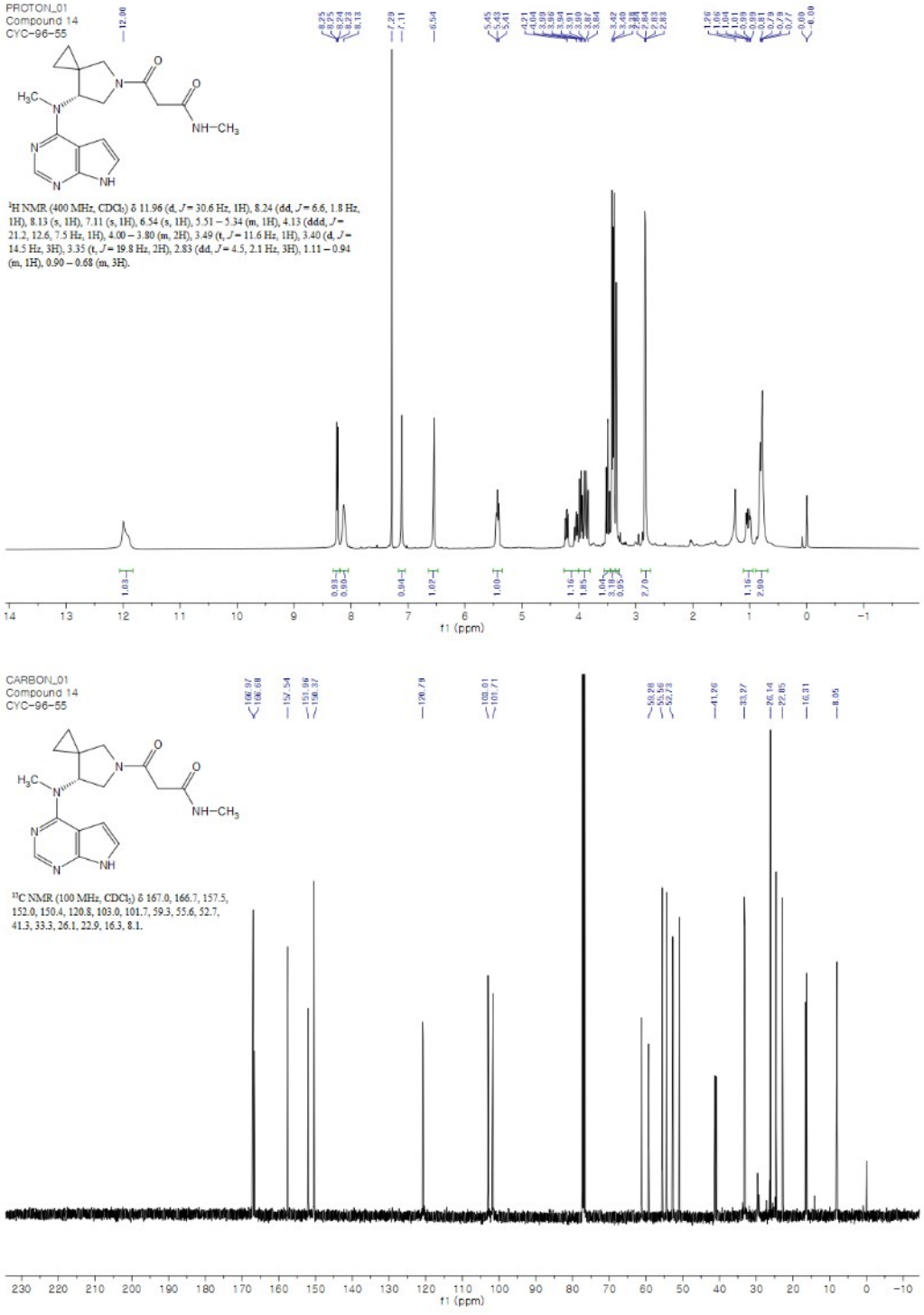
61.3, 54.4, 51.2, 42.0, 33.3, 24.6, 22.8, 16.6, 8.1. HRMS (ESI) calcd for $C_{17}H_{23}N_6O_2$: 343.1882. Obsd: 343.1879. $[\alpha]_D$ +42.2° (*c* 1.00, $CHCl_3$).



(R)-N-Methyl-3-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanamide, ***15***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (d, *J* = 30.6 Hz, 1H), 8.24 (dd, *J* = 6.6, 1.8 Hz, 1H), 8.13 (s, 1H), 7.11 (s, 1H), 6.54 (s, 1H), 5.51 – 5.34 (m, 1H), 4.13 (ddd, *J* = 21.2, 12.6, 7.5 Hz, 1H), 4.00 – 3.80 (m, 2H), 3.49 (t, *J* = 11.6 Hz, 1H), 3.40 (d, *J* = 14.5 Hz, 3H), 3.35 (t, *J* = 19.8 Hz, 2H), 2.83 (dd, *J* = 4.5, 2.1 Hz, 3H), 1.11 – 0.94 (m, 1H), 0.90 – 0.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)

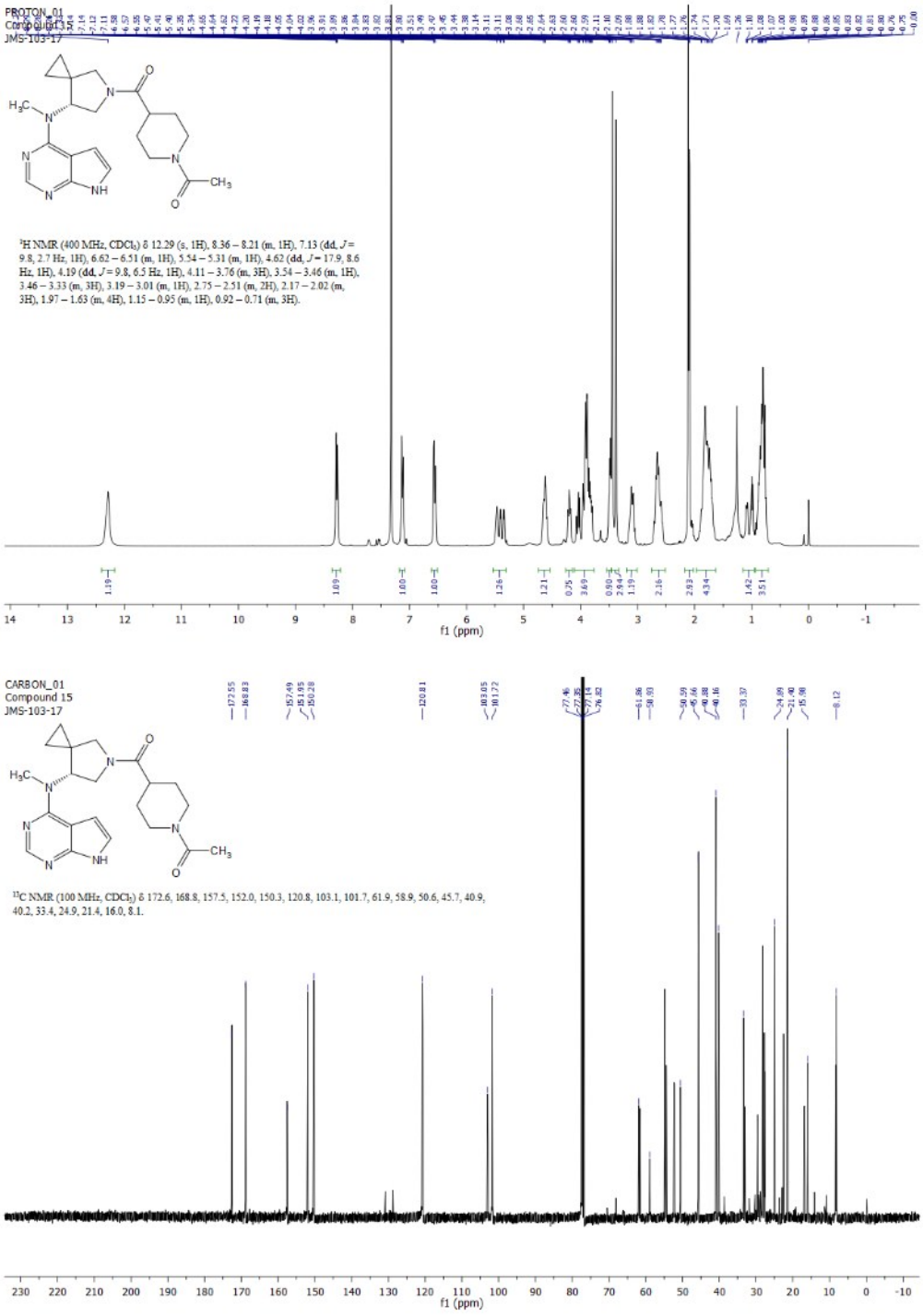
δ 167.0, 166.7, 157.5, 152.0, 150.4, 120.8, 103.0, 101.7, 59.3, 55.6, 52.7, 41.3, 33.3, 26.1, 22.9, 16.3, 8.1. HRMS (ESI) calcd for $C_{17}H_{23}N_6O_2$: 343.1882. Obsd: 343.1872. $[\alpha]_D$ +37.2° (*c* 1.30, $CHCl_3$).



(R)-1-(4-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)piperidin-1-yl)ethan-1-one, ***16***

95.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.36 – 8.21 (m, 1H), 7.13 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.62 – 6.51 (m, 1H), 5.54 – 5.31 (m, 1H), 4.62 (dd, *J* = 17.9, 8.6 Hz, 1H), 4.19 (dd, *J* = 9.8, 6.5 Hz, 1H), 4.11 – 3.76 (m, 3H), 3.54 – 3.46 (m, 1H), 3.46 – 3.33 (m, 3H), 3.19 – 3.01 (m, 1H), 2.75 – 2.51 (m, 2H), 2.17 – 2.02 (m, 3H), 1.97 – 1.63 (m, 4H), 1.15 – 0.95 (m, 1H), 0.92 – 0.71

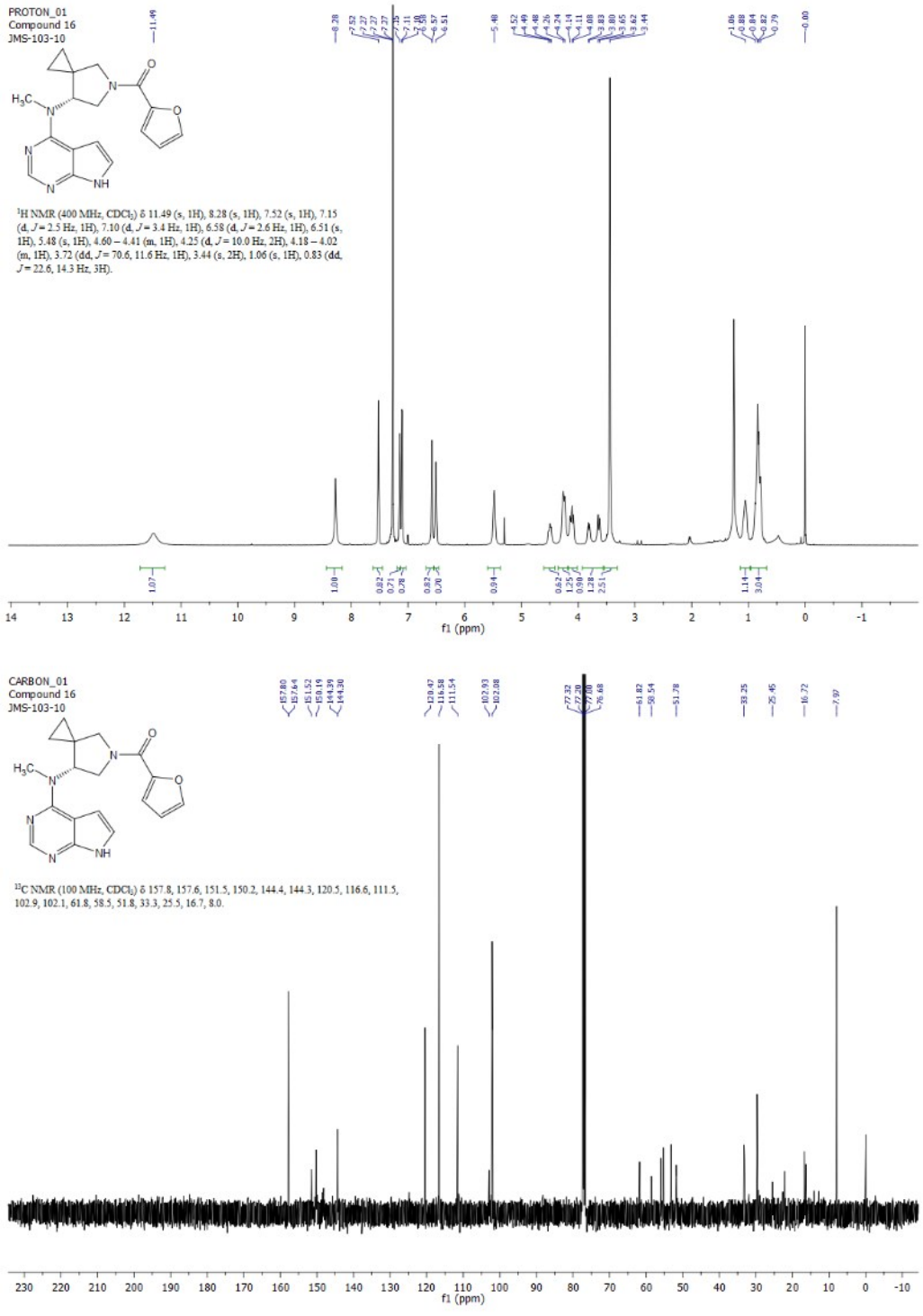
(m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 168.8, 157.5, 152.0, 150.3, 120.8, 103.1, 101.7, 61.9, 58.9, 50.6, 45.7, 40.9, 40.2, 33.4, 24.9, 21.4, 16.0, 8.1. HRMS (ESI) calcd for $C_{21}H_{29}N_6O_2$: 397.2352. Obsd: 397.2343. $[\alpha]_D$ +45.2° (*c* 1.63, $CHCl_3$).



(R)-Furan-2-yl(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)methanone, ***17***

99.2% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.28 (s, 1H), 7.52 (s, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.10 (d, *J* = 3.4 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.51 (s, 1H), 5.48 (s, 1H), 4.60 – 4.41 (m, 1H), 4.25 (d, *J* = 10.0 Hz, 2H), 4.18 – 4.02 (m, 1H), 3.72 (dd, *J* = 70.6, 11.6 Hz, 1H), 3.44 (s, 2H), 1.06 (s, 1H), 0.83 (dd, *J* = 22.6, 14.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.6, 151.5,

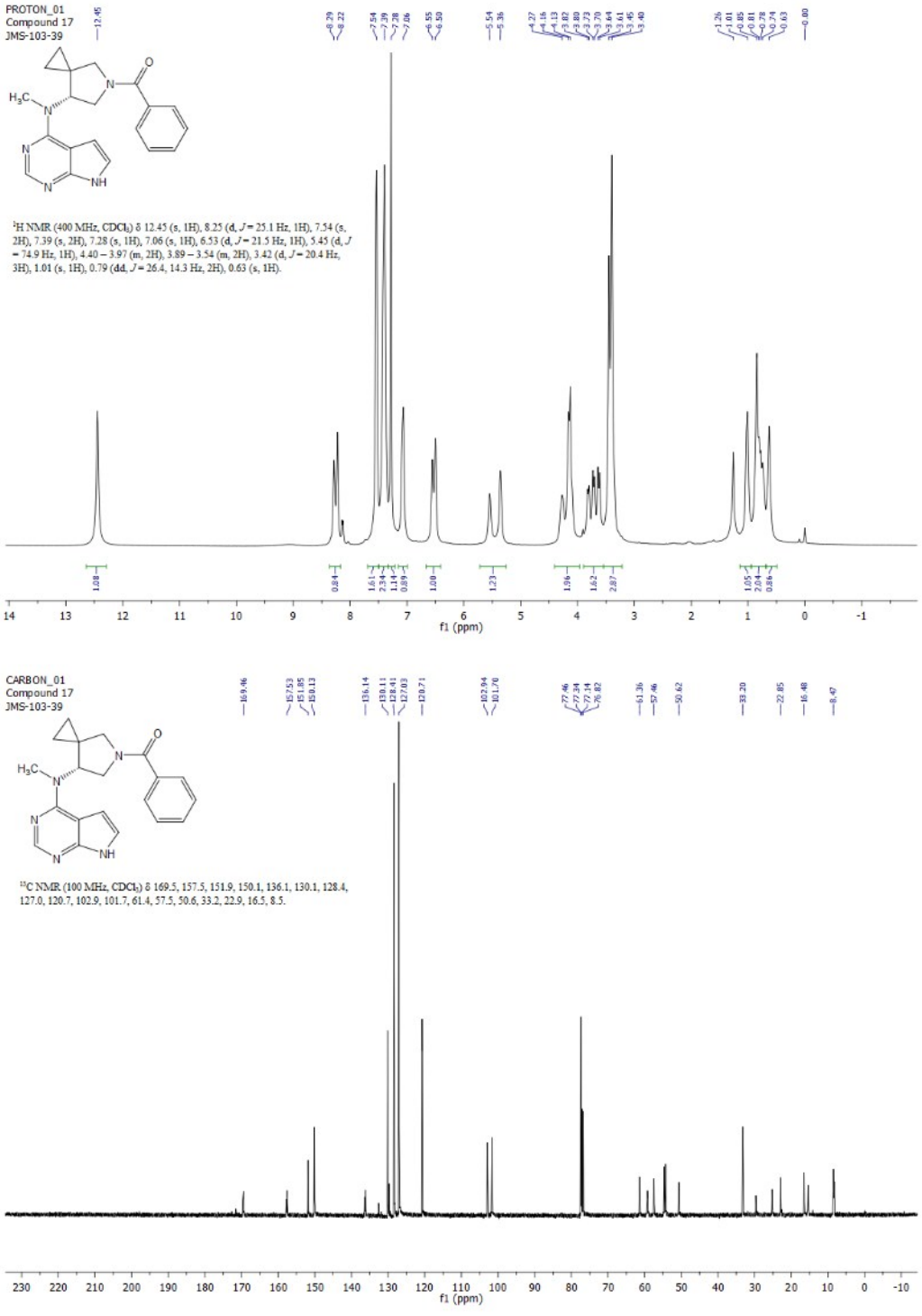
150.2, 144.4, 144.3, 120.5, 116.6, 111.5, 102.9, 102.1, 61.8, 58.5, 51.8, 33.3, 25.5, 16.7, 8.0. HRMS (ESI) calcd for $C_{18}H_{20}N_5O_2$: 338.1617. Obsd: 338.1616. $[\alpha]_D$ +56.0° (*c* 0.360, $CHCl_3$).



(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(phenyl)methanone, ***18***

95.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 8.25 (d, *J* = 25.1 Hz, 1H), 7.54 (s, 2H), 7.39 (s, 2H), 7.28 (s, 1H), 7.06 (s, 1H), 6.53 (d, *J* = 21.5 Hz, 1H), 5.45 (d, *J* = 74.9 Hz, 1H), 4.40 – 3.97 (m, 2H), 3.89 – 3.54 (m, 2H), 3.42 (d, *J* = 20.4 Hz, 3H), 1.01 (s, 1H), 0.79 (dd, *J* = 26.4, 14.3 Hz, 2H), 0.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 157.5, 151.9, 150.1, 136.1, 130.1,

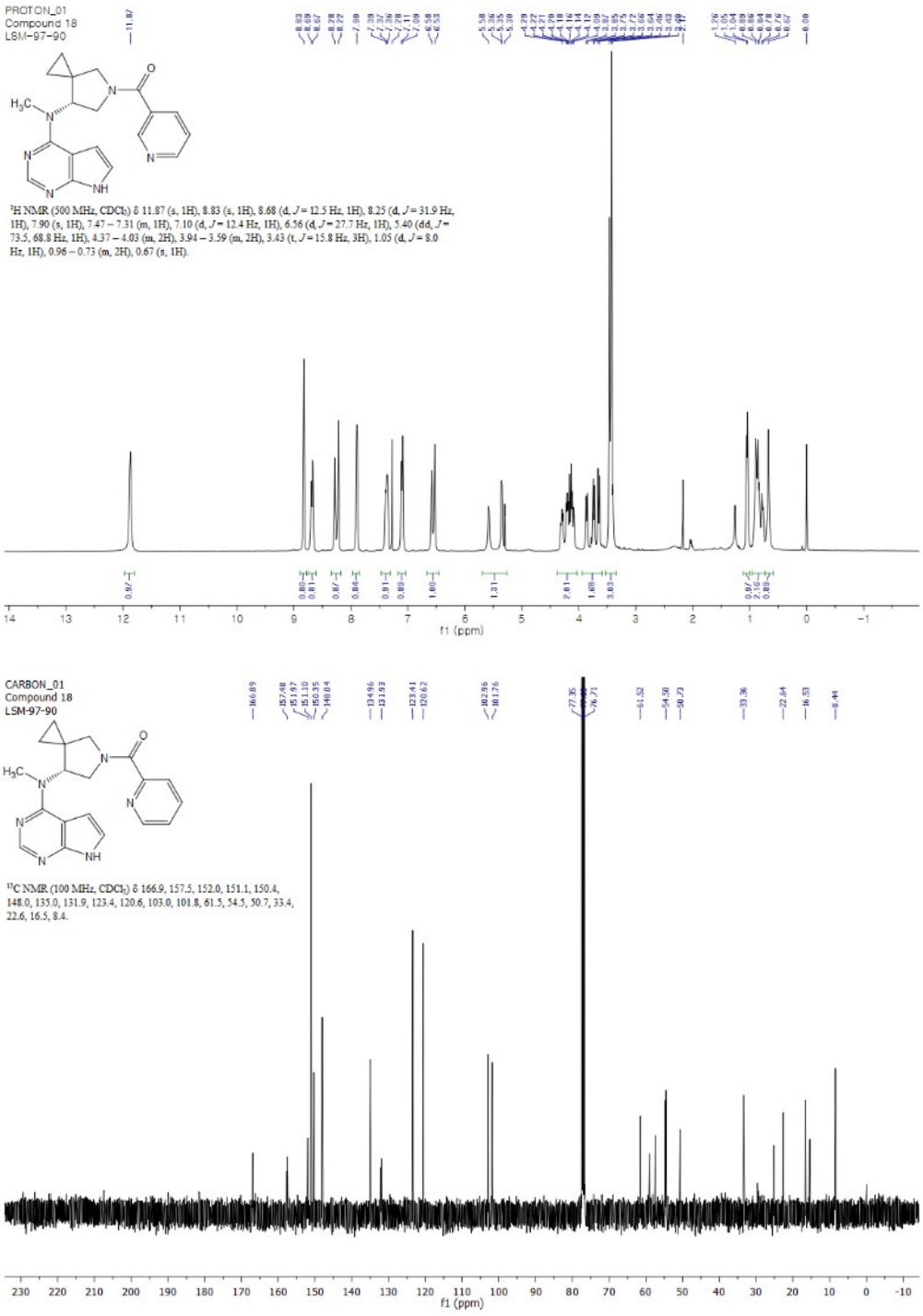
128.4, 127.0, 120.7, 102.9, 101.7, 61.4, 57.5, 50.6, 33.2, 22.9, 16.5, 8.5. HRMS (ESI) calcd for $C_{20}H_{22}N_5O$: 348.1824. Obsd: 348.1819. $[\alpha]_D$ +22.5° (*c* 2.85, $CHCl_3$).



(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(pyridin-3-yl)methanone, ***19***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.87 (s, 1H), 8.83 (s, 1H), 8.68 (d, *J* = 12.5 Hz, 1H), 8.25 (d, *J* = 31.9 Hz, 1H), 7.90 (s, 1H), 7.47 – 7.31 (m, 1H), 7.10 (d, *J* = 12.4 Hz, 1H), 6.56 (d, *J* = 27.7 Hz, 1H), 5.40 (dd, *J* = 73.5, 68.8 Hz, 1H), 4.37 – 4.03 (m, 2H), 3.94 – 3.59 (m, 2H), 3.43 (t, *J* = 15.8 Hz, 3H), 1.05 (d, *J* = 8.0 Hz, 1H), 0.96 – 0.73 (m, 2H), 0.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$)

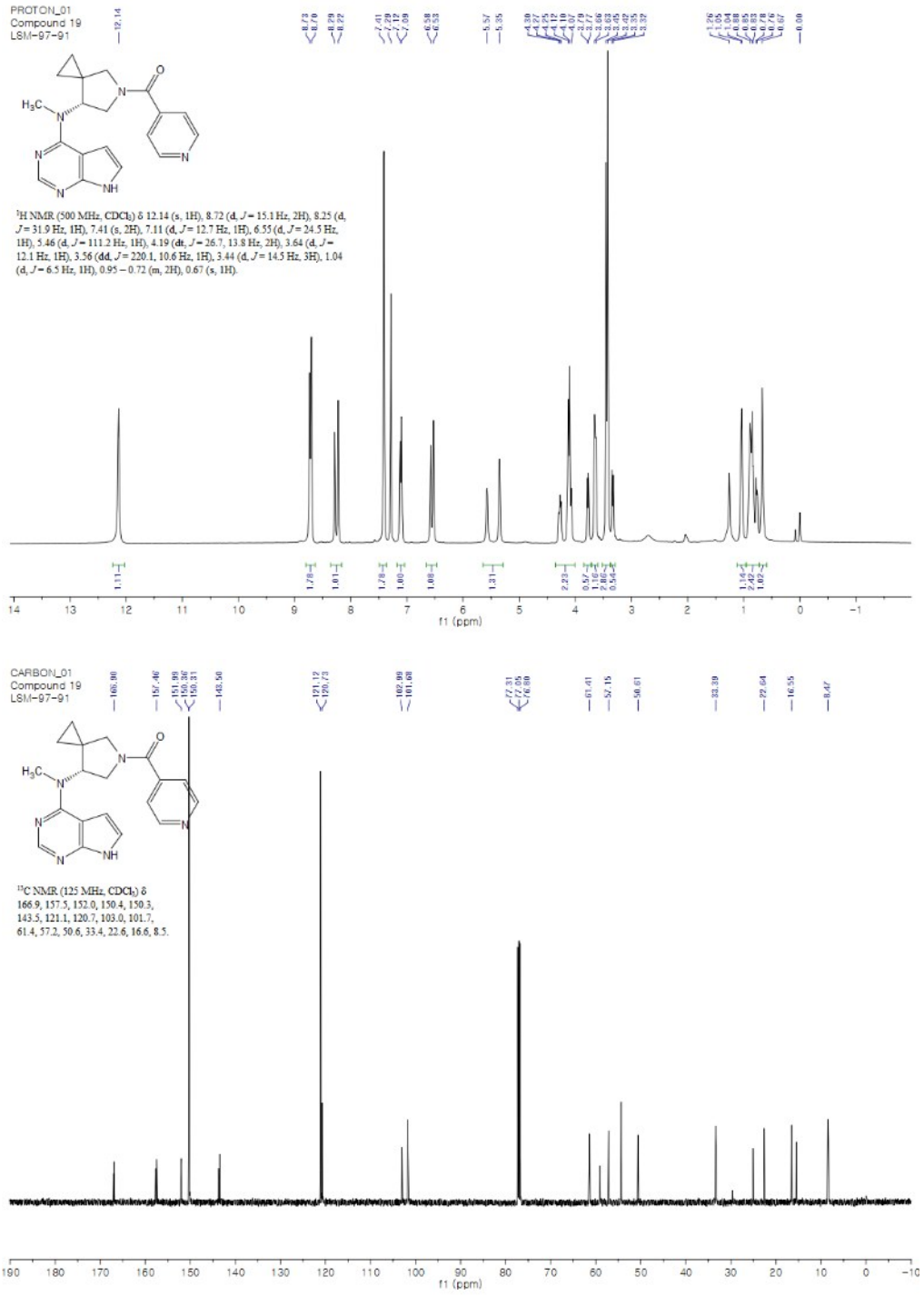
δ 166.9, 157.5, 152.0, 151.1, 150.4, 148.0, 135.0, 131.9, 123.4, 120.6, 103.0, 101.8, 61.5, 54.5, 50.7, 33.4, 22.6, 16.5, 8.4. HRMS (ESI) calcd for $C_{19}H_{21}N_6O$: 349.1777. Obsd: 349.1764. $[\alpha]_D$ +15.1° (*c* 1.12, $CHCl_3$).



(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(pyridin-4-yl)methanone, ***20***

94.1% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.72 (d, *J* = 15.1 Hz, 2H), 8.25 (d, *J* = 31.9 Hz, 1H), 7.41 (s, 2H), 7.11 (d, *J* = 12.7 Hz, 1H), 6.55 (d, *J* = 24.5 Hz, 1H), 5.46 (d, *J* = 111.2 Hz, 1H), 4.19 (dt, *J* = 26.7, 13.8 Hz, 2H), 3.64 (d, *J* = 12.1 Hz, 1H), 3.56 (dd, *J* = 220.1, 10.6 Hz, 1H), 3.44 (d, *J* = 14.5 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 1H), 0.95 – 0.72 (m, 2H), 0.67 (s, 1H). ^{13}C NMR

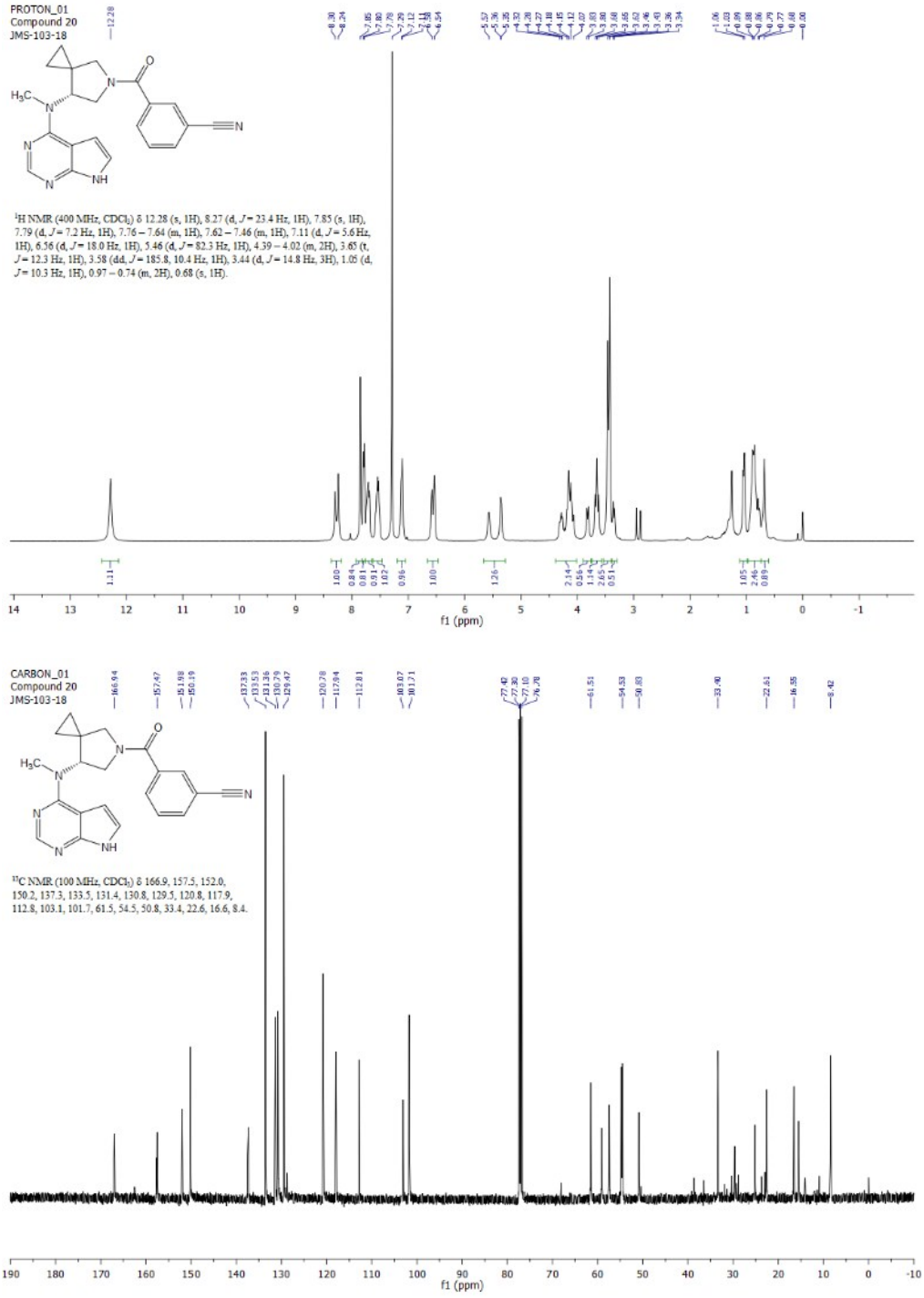
(125 MHz, $CDCl_3$) δ 166.9, 157.5, 152.0, 150.4, 150.3, 143.5, 121.1, 120.7, 103.0, 101.7, 61.4, 57.2, 50.6, 33.4, 22.6, 16.6, 8.5. HRMS (ESI) calcd for $C_{19}H_{21}N_6O$: 349.1777. Obsd: 349.1772. $[\alpha]_D$ +24.5° (*c* 1.16, $CHCl_3$).



(R)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)benzonitrile, ***21***

97.7% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (s, 1H), 8.27 (d, *J* = 23.4 Hz, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.76 – 7.64 (m, 1H), 7.62 – 7.46 (m, 1H), 7.11 (d, *J* = 5.6 Hz, 1H), 6.56 (d, *J* = 18.0 Hz, 1H), 5.46 (d, *J* = 82.3 Hz, 1H), 4.39 – 4.02 (m, 2H), 3.65 (t, *J* = 12.3 Hz, 1H), 3.58 (dd, *J* = 185.8, 10.4 Hz, 1H), 3.44 (d, *J* = 14.8 Hz, 3H), 1.05 (d, *J* = 10.3 Hz, 1H), 0.97 – 0.74 (m, 2H),

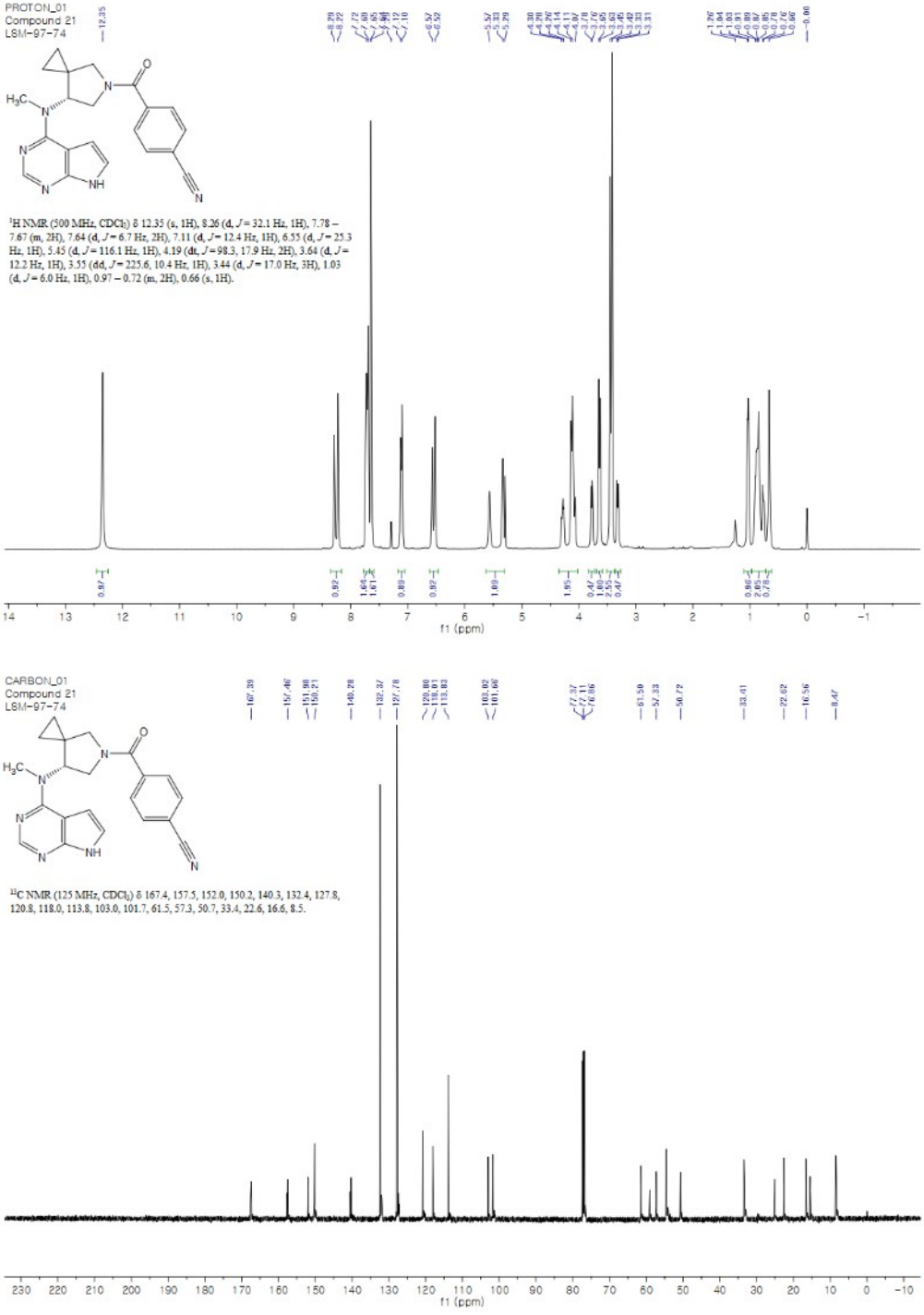
0.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 157.5, 152.0, 150.2, 137.3, 133.5, 131.4, 130.8, 129.5, 120.8, 117.9, 112.8, 103.1, 101.7, 61.5, 54.5, 50.8, 33.4, 22.6, 16.6, 8.4. HRMS (ESI) calcd for $C_{21}H_{21}N_6O$: 373.1777. Obsd: 373.1772. $[\alpha]_D$ +10.9° (*c* 0.963, $CHCl_3$).



(R)-4-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbonyl)benzonitrile, ***22***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.26 (d, *J* = 32.1 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.64 (d, *J* = 6.7 Hz, 2H), 7.11 (d, *J* = 12.4 Hz, 1H), 6.55 (d, *J* = 25.3 Hz, 1H), 5.45 (d, *J* = 116.1 Hz, 1H), 4.19 (dt, *J* = 98.3, 17.9 Hz, 2H), 3.64 (d, *J* = 12.2 Hz, 1H), 3.55 (dd, *J* = 225.6, 10.4 Hz, 1H), 3.44 (d, *J* = 17.0 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 1H), 0.97 – 0.72 (m, 2H), 0.66 (s, 1H). ^{13}C NMR

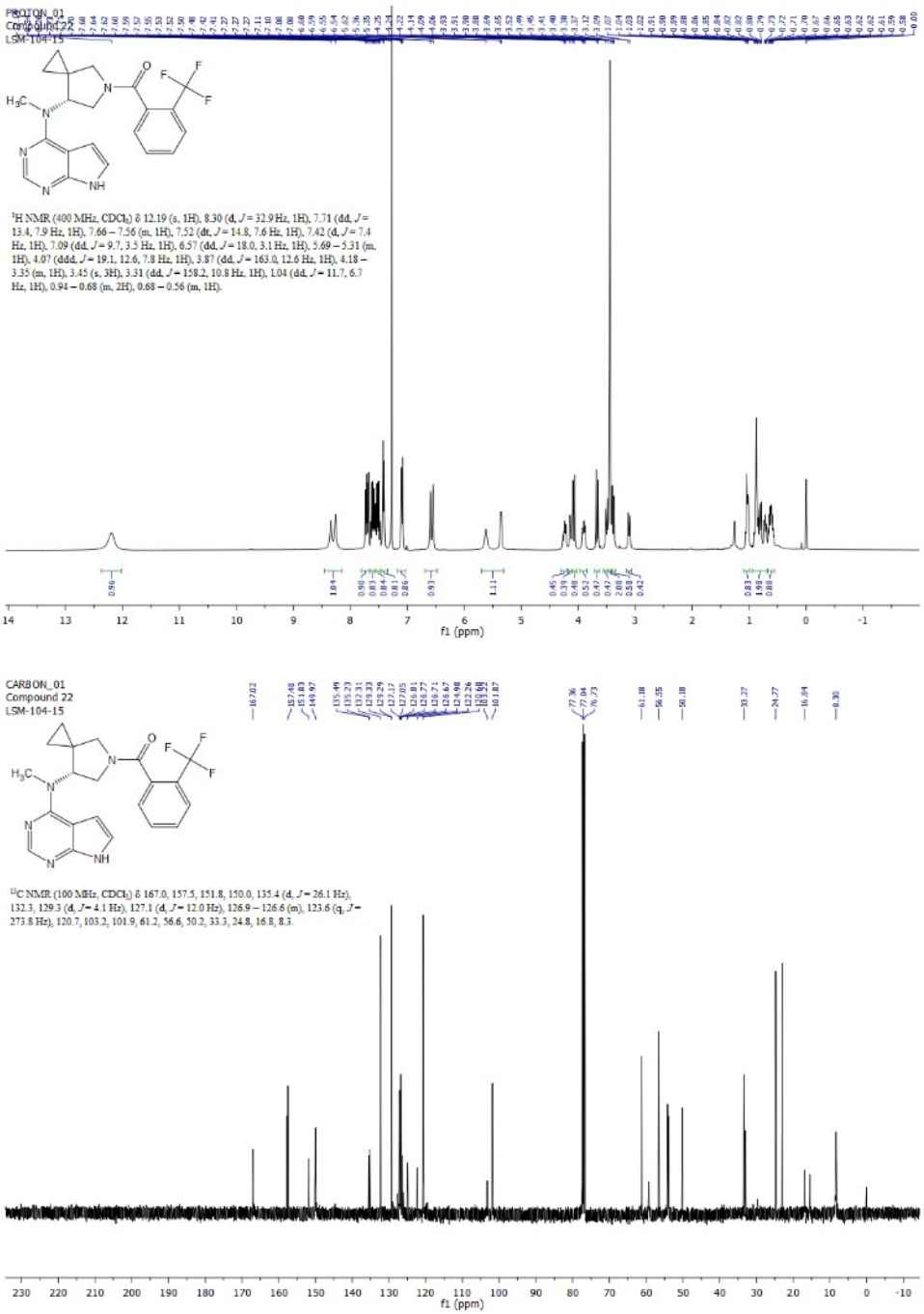
(125 MHz, $CDCl_3$) δ 167.4, 157.5, 152.0, 150.2, 140.3, 132.4, 127.8, 120.8, 118.0, 113.8, 103.0, 101.7, 61.5, 57.3, 50.7, 33.4, 22.6, 16.6, 8.5. HRMS (ESI) calcd for $C_{21}H_{21}N_6O$: 373.1777. Obsd: 373.1766. $[\alpha]_D$ +15.7° (*c* 2.54, $CHCl_3$).



(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(2-(trifluoromethyl)phenyl)methanone, ***23***

98.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.19 (s, 1H), 8.30 (d, *J* = 32.9 Hz, 1H), 7.71 (dd, *J* = 13.4, 7.9 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.52 (dt, *J* = 14.8, 7.6 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 9.7, 3.5 Hz, 1H), 6.57 (dd, *J* = 18.0, 3.1 Hz, 1H), 5.69 – 5.31 (m, 1H), 4.07 (ddd, *J* = 19.1, 12.6, 7.8 Hz, 1H), 3.87 (dd, *J* = 163.0, 12.6 Hz, 1H), 4.18 – 3.35 (m, 1H), 3.45 (s, 3H), 3.31 (dd, *J* =

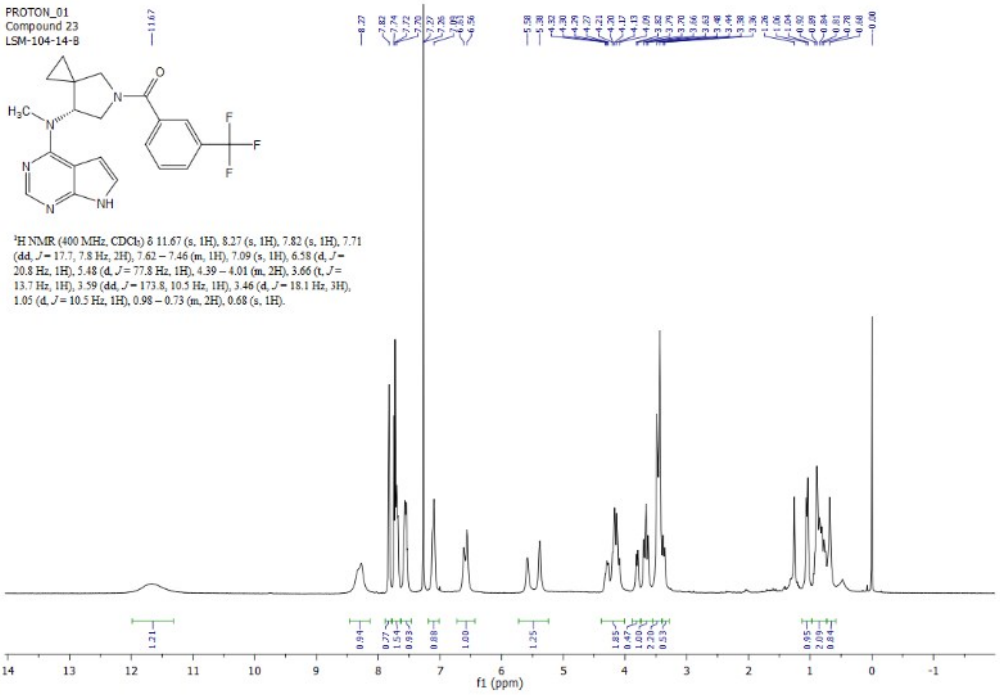
158.2, 10.8 Hz, 1H), 1.04 (dd, *J* = 11.7, 6.7 Hz, 1H), 0.94 – 0.68 (m, 2H), 0.68 – 0.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 157.5, 151.8, 150.0, 135.4 (d, *J* = 26.1 Hz), 132.3, 129.3 (d, *J* = 4.1 Hz), 127.1 (d, *J* = 12.0 Hz), 126.9 – 126.6 (m), 123.6 (q, *J* = 273.8 Hz), 120.7, 103.2, 101.9, 61.2, 56.6, 50.2, 33.3, 24.8, 16.8, 8.3. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_5O$: 416.1698. Obsd: 416.1695. $[\alpha]_D$ +25.1° (*c* 1.71, $CHCl_3$).

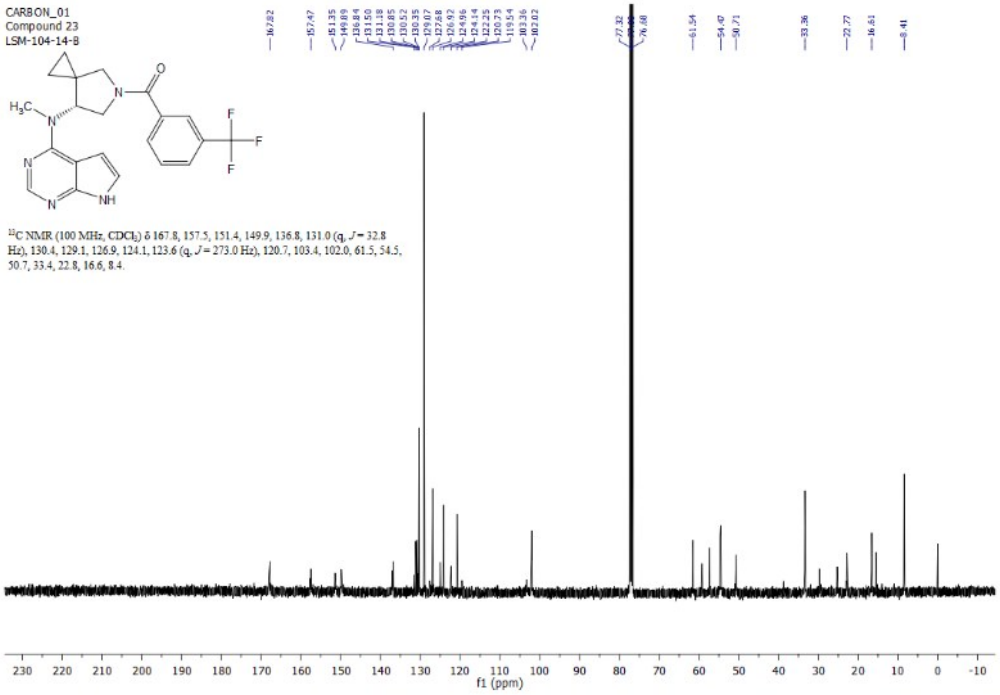


(R)-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)(3-(trifluoromethyl)phenyl)methanone, ***24***

98.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.67 (s, 1H), 8.27 (s, 1H), 7.82 (s, 1H), 7.71 (dd, *J* = 17.7, 7.8 Hz, 2H), 7.62 – 7.46 (m, 1H), 7.09 (s, 1H), 6.58 (d, *J* = 20.8 Hz, 1H), 5.48 (d, *J* = 77.8 Hz, 1H), 4.39 – 4.01 (m, 2H), 3.66 (t, *J* = 13.7 Hz, 1H), 3.59 (dd, *J* = 173.8, 10.5 Hz, 1H), 3.46 (d, *J* =

18.1 Hz, 3H), 1.05 (d, J = 10.5 Hz, 1H), 0.98 – 0.73 (m, 2H), 0.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.5, 151.4, 149.9, 136.8, 131.0 (q, J = 32.8 Hz), 130.4, 129.1, 126.9, 124.1, 123.6 (q, J = 273.0 Hz), 120.7, 103.4, 102.0, 61.5, 54.5, 50.7, 33.4, 22.8, 16.6, 8.4. HRMS (ESI) calcd for $C_{21}H_{21}F_3N_5O$: 416.1698. Obsd: 416.1692. $[\alpha]_D$ +20.7° (*c* 0.730, $CHCl_3$).

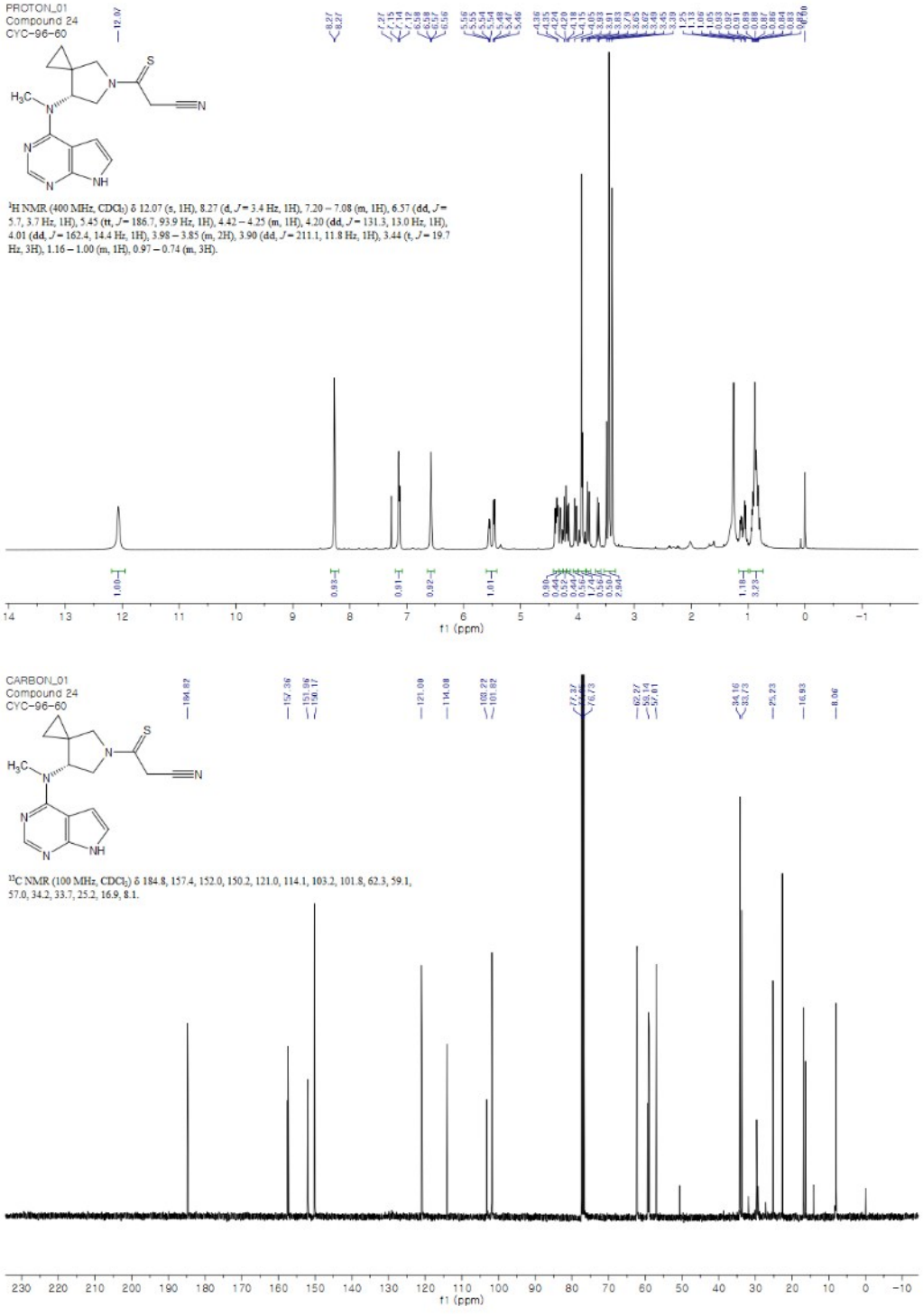




(R)-3-(7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-thioxopropanenitrile, ***25***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.27 (d, J = 3.4 Hz, 1H), 7.20 – 7.08 (m, 1H), 6.57 (dd, J = 5.7, 3.7 Hz, 1H), 5.45 (tt, J = 186.7, 93.9 Hz, 1H), 4.42 – 4.25 (m, 1H), 4.20 (dd, J = 131.3, 13.0 Hz, 1H), 4.01 (dd, J = 162.4, 14.4 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.90 (dd, J = 211.1,

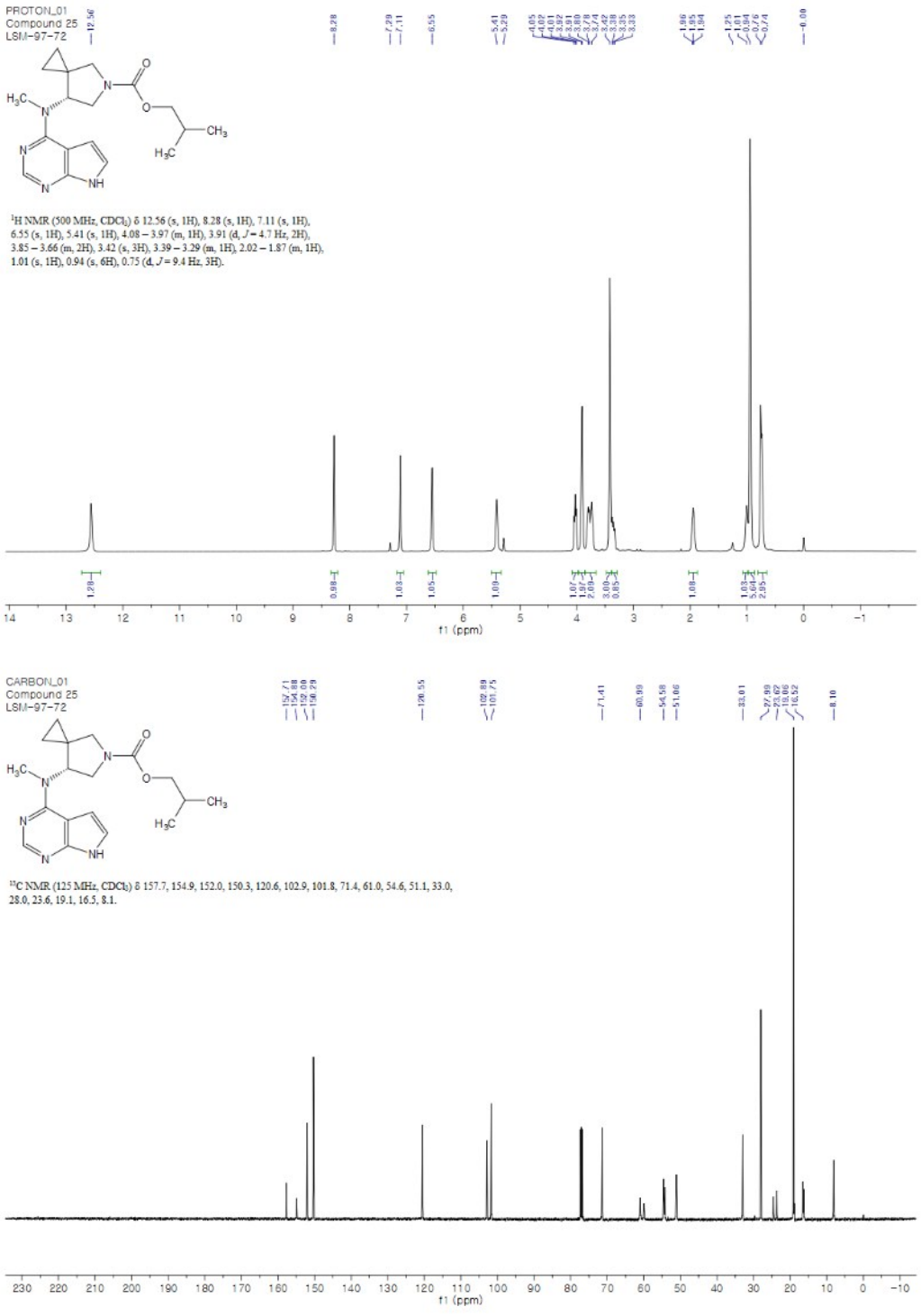
11.8 Hz, 1H), 3.44 (t, J = 19.7 Hz, 3H), 1.16 – 1.00 (m, 1H), 0.97 – 0.74 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 157.4, 152.0, 150.2, 121.0, 114.1, 103.2, 101.8, 62.3, 59.1, 57.0, 34.2, 33.7, 25.2, 16.9, 8.1. HRMS (ESI) calcd for $C_{16}H_{19}N_6S$: 327.1392. Obsd: 327.1380. $[\alpha]_D$ +48.8° (*c* 1.23, $CHCl_3$).



Isobutyl (R)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxylate, ***26***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.28 (s, 1H), 7.11 (s, 1H), 6.55 (s, 1H), 5.41 (s, 1H), 4.08 – 3.97 (m, 1H), 3.91 (d, J = 4.7 Hz, 2H), 3.85 – 3.66 (m, 2H), 3.42 (s, 3H), 3.39 – 3.29 (m, 1H), 2.02 – 1.87 (m, 1H), 1.01 (s, 1H), 0.94 (s, 6H), 0.75 (d, J = 9.4 Hz, 3H). ^{13}C NMR (125

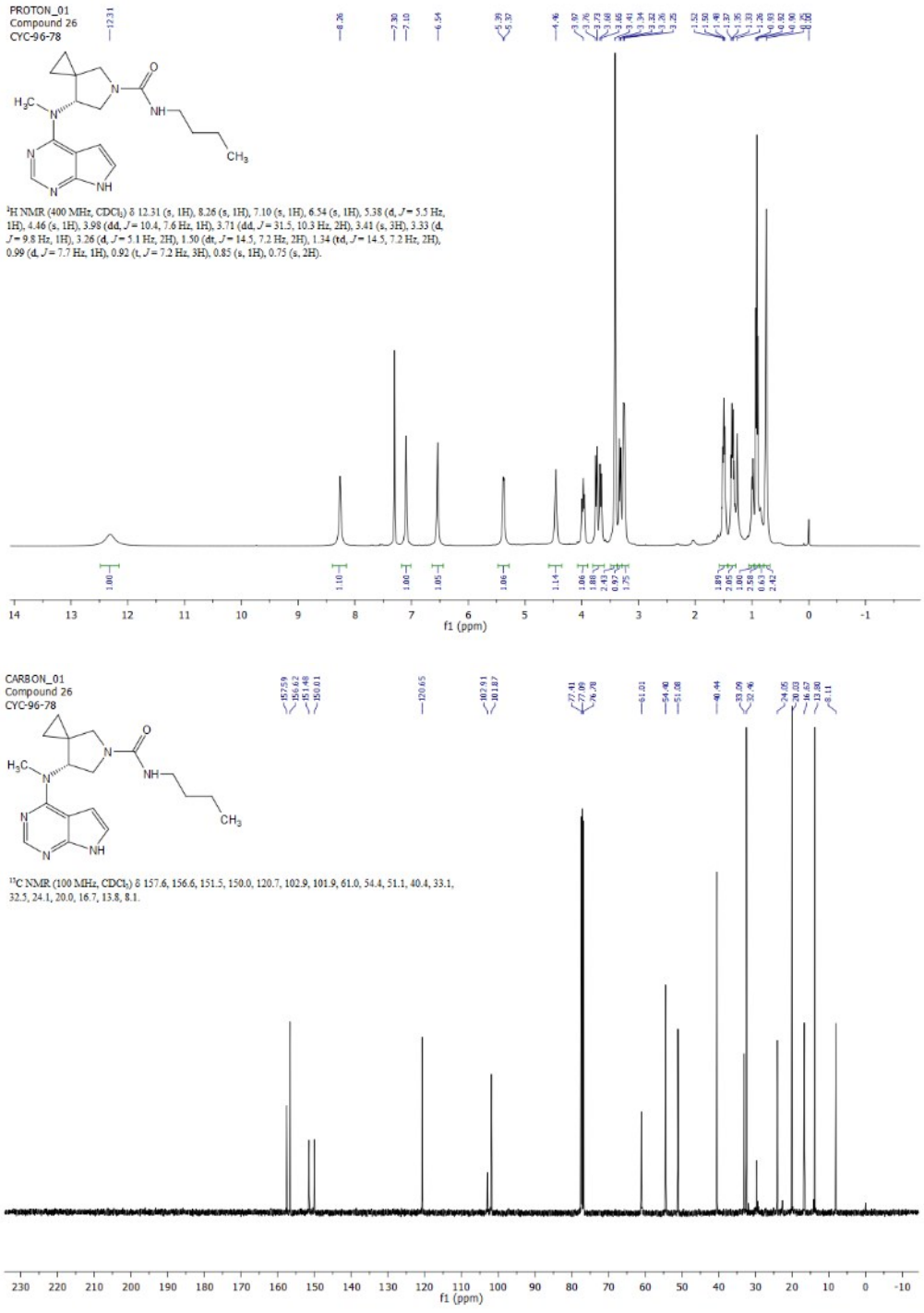
MHz, $CDCl_3$) δ 157.7, 154.9, 152.0, 150.3, 120.6, 102.9, 101.8, 71.4, 61.0, 54.6, 51.1, 33.0, 28.0, 23.6, 19.1, 16.5, 8.1. HRMS (ESI) calcd for $C_{18}H_{26}N_5O_2$: 344.2087. Obsd: 344.2077. $[\alpha]_D$ +33.2° (*c* 4.45, $CHCl_3$).



(R)-N-Butyl-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***27***

100% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.31 (s, 1H), 8.26 (s, 1H), 7.10 (s, 1H), 6.54 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 4.46 (s, 1H), 3.98 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.71 (dd, *J* = 31.5, 10.3 Hz, 2H), 3.41 (s, 3H), 3.33 (d, *J* = 9.8 Hz, 1H), 3.26 (d, *J* = 5.1 Hz, 2H), 1.50 (dt, *J* = 14.5, 7.2 Hz, 2H),

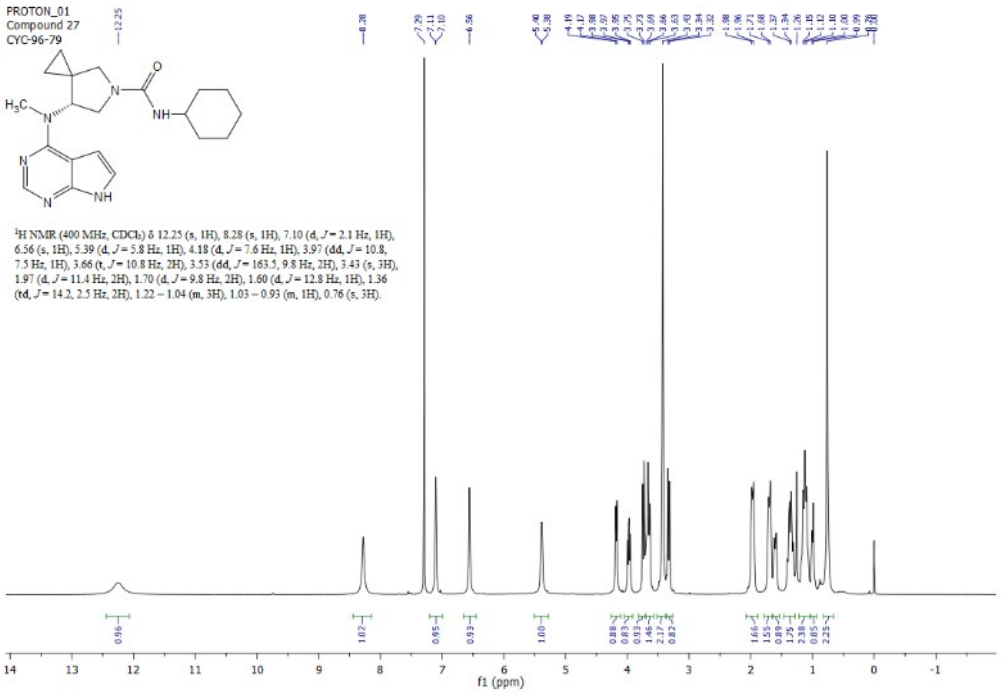
1.34 (td, J = 14.5, 7.2 Hz, 2H), 0.99 (d, J = 7.7 Hz, 1H), 0.92 (t, J = 7.2 Hz, 3H), 0.85 (s, 1H), 0.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 156.6, 151.5, 150.0, 120.7, 102.9, 101.9, 61.0, 54.4, 51.1, 40.4, 33.1, 32.5, 24.1, 20.0, 16.7, 13.8, 8.1. HRMS (ESI) calcd for $C_{18}H_{27}N_6O$: 343.2246. Obsd: 343.2241. $[\alpha]_D$ +43.2° (*c* 2.89, $CHCl_3$).

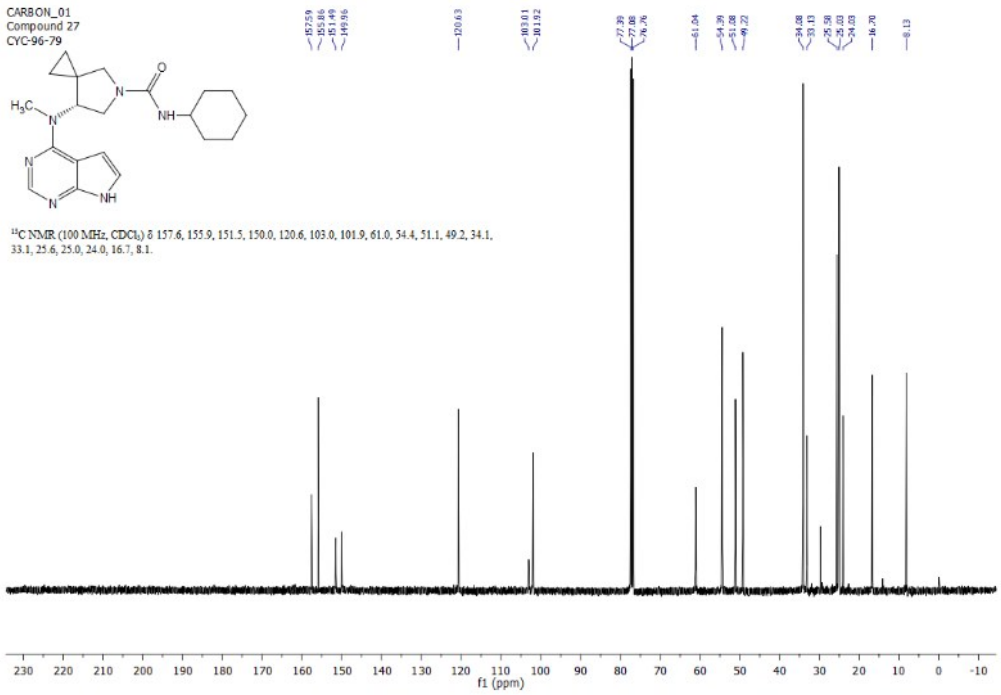


(R)-N-Cyclohexyl-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***28***

96.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.25 (s, 1H), 8.28 (s, 1H), 7.10 (d, J = 2.1 Hz, 1H), 6.56 (s, 1H), 5.39 (d, J = 5.8 Hz, 1H), 4.18 (d, J = 7.6 Hz, 1H), 3.97 (dd, J = 10.8, 7.5 Hz, 1H), 3.66 (t, J = 10.8 Hz, 2H), 3.53 (dd, J = 163.5, 9.8 Hz, 2H), 3.43 (s, 3H), 1.97 (d, J = 11.4 Hz, 2H), 1.70

(d, J = 9.8 Hz, 2H), 1.60 (d, J = 12.8 Hz, 1H), 1.36 (td, J = 14.2, 2.5 Hz, 2H), 1.22 – 1.04 (m, 3H), 1.03 – 0.93 (m, 1H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.9, 151.5, 150.0, 120.6, 103.0, 101.9, 61.0, 54.4, 51.1, 49.2, 34.1, 33.1, 25.6, 25.0, 24.0, 16.7, 8.1. HRMS (ESI) calcd for $C_{20}H_{29}N_6O$: 369.2403. Obsd: 369.2398. $[\alpha]_D$ +39.1° (*c* 2.39, $CHCl_3$).

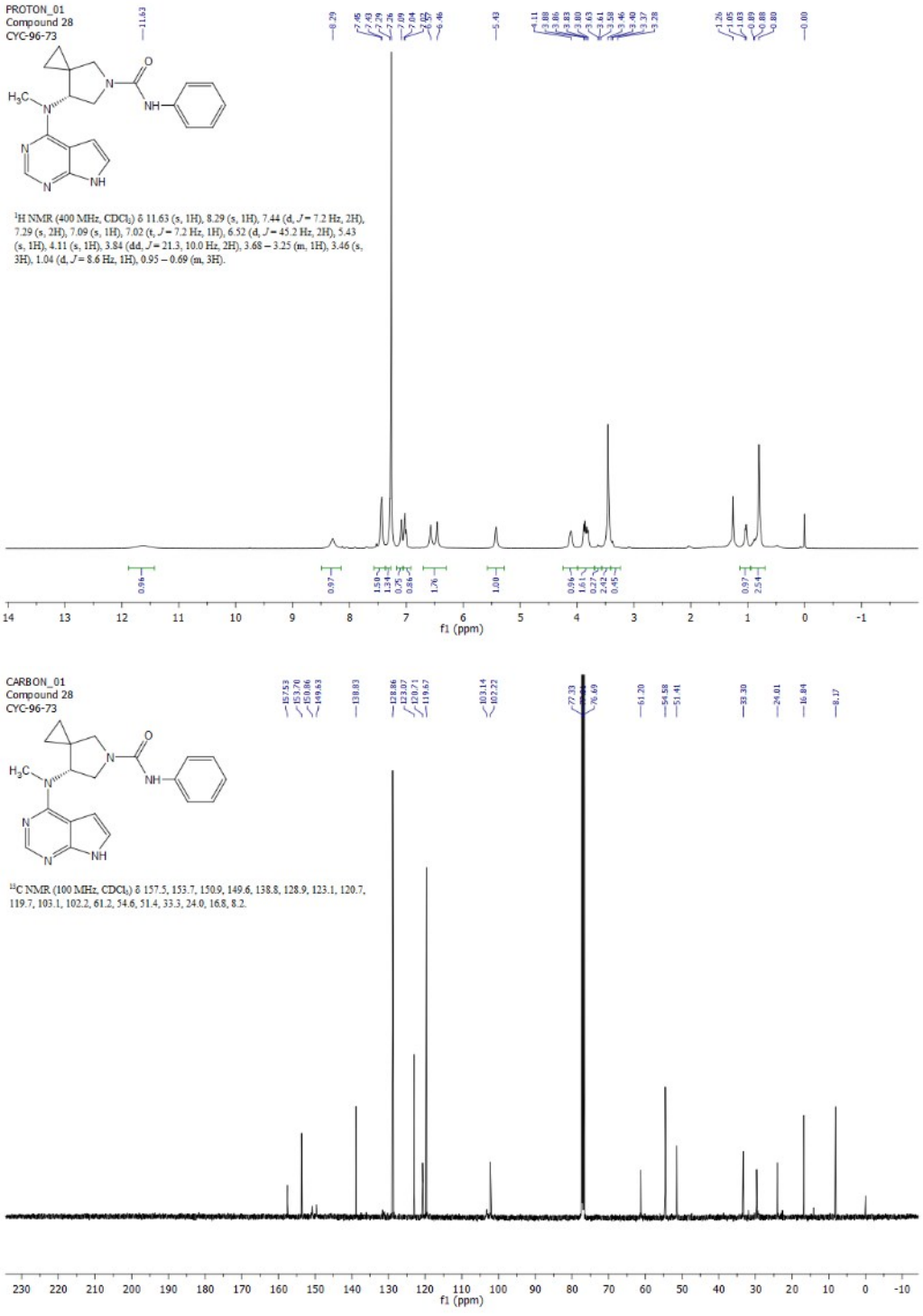




(R)-7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-N-phenyl-5-azaspiro[2.4]heptane-5-carboxamide, ***29***

98.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 8.29 (s, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.29 (s, 2H), 7.09 (s, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 45.2 Hz, 2H), 5.43 (s, 1H), 4.11 (s, 1H), 3.84 (dd, J = 21.3, 10.0 Hz, 2H), 3.68 – 3.25 (m, 1H), 3.46 (s, 3H), 1.04 (d, J = 8.6 Hz, 1H), 0.95

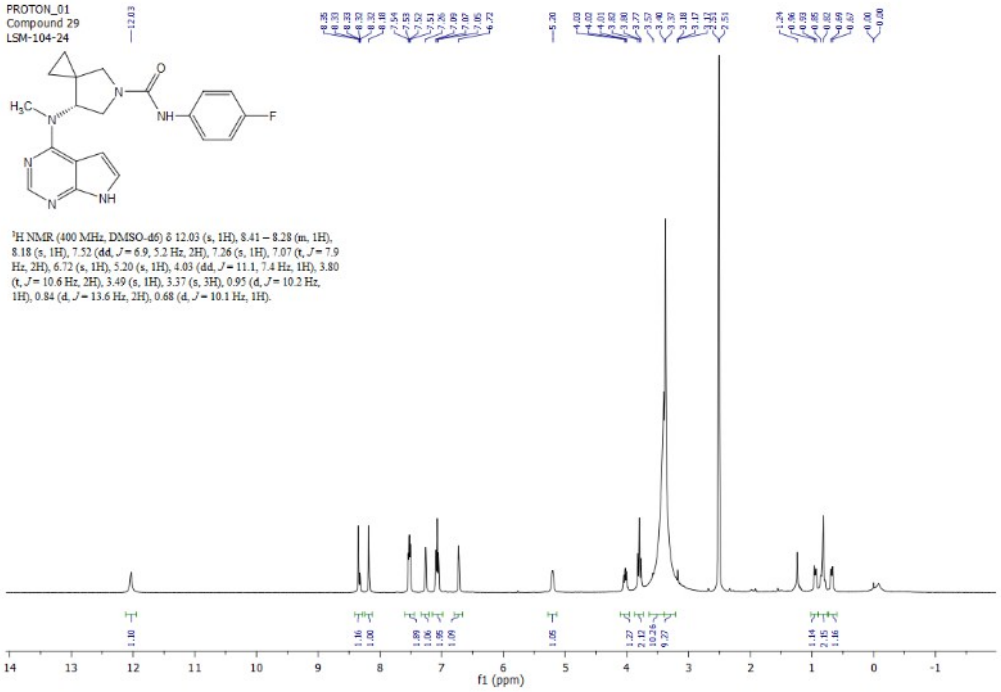
– 0.69 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.7, 150.9, 149.6, 138.8, 128.9, 123.1, 120.7, 119.7, 103.1, 102.2, 61.2, 54.6, 51.4, 33.3, 24.0, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{23}N_6O$: 363.1933. Obsd: 363.1928. $[\alpha]_D$ +38.0° (*c* 0.707, $CHCl_3$).

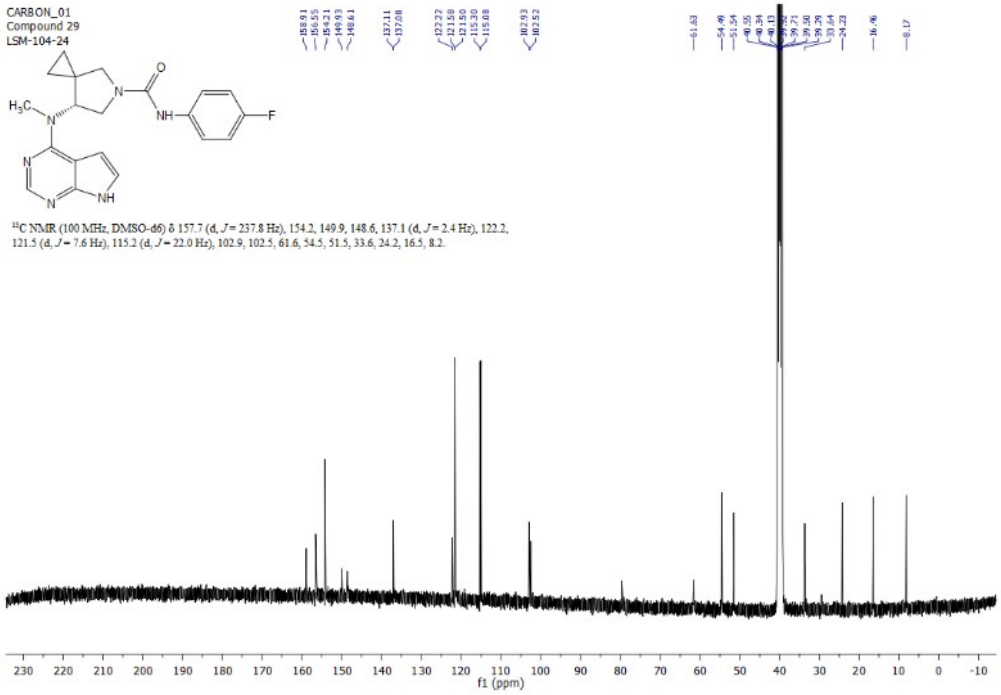


(R)-N-(4-Fluorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***30***

99.2% purity by HPLC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.41 – 8.28 (m, 1H), 8.18 (s, 1H), 7.52 (dd, *J* = 6.9, 5.2 Hz, 2H), 7.26 (s, 1H), 7.07 (t, *J* = 7.9 Hz, 2H), 6.72 (s, 1H), 5.20 (s, 1H), 4.03 (dd, *J* = 11.1, 7.4 Hz, 1H), 3.80 (t, *J* = 10.6 Hz, 2H), 3.49 (d, *J* = 68.5 Hz, 10H), 3.37 (s, 9H), 0.95

(d, J = 10.2 Hz, 1H), 0.84 (d, J = 13.6 Hz, 2H), 0.68 (d, J = 10.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.7 (d, J = 237.8 Hz), 154.2, 149.9, 148.6, 137.1 (d, J = 2.4 Hz), 122.2, 121.5 (d, J = 7.6 Hz), 115.2 (d, J = 22.0 Hz), 102.9, 102.5, 61.6, 54.5, 51.5, 33.6, 24.2, 16.5, 8.2. HRMS (ESI) calcd for $C_{20}H_{22}FN_6O$: 381.1839. Obsd: 381.1835. $[\alpha]_D$ +54.3° (*c* 0.223, MeOH).

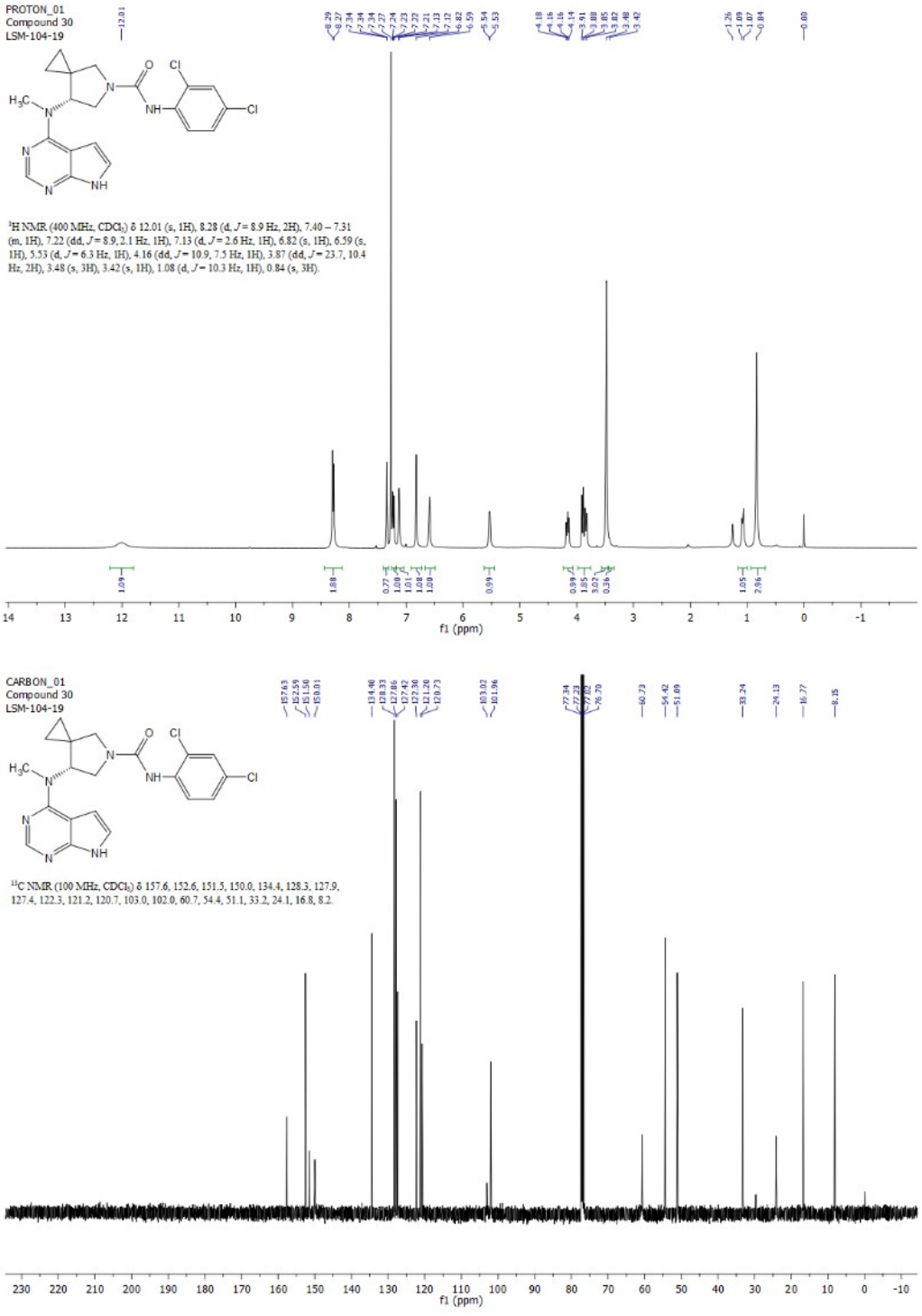




(R)-N-(2,4-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***31***

97.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.01 (s, 1H), 8.28 (d, J = 8.9 Hz, 2H), 7.40 – 7.31 (m, 1H), 7.22 (dd, J = 8.9, 2.1 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 6.82 (s, 1H), 6.59 (s, 1H), 5.53 (d, J = 6.3 Hz, 1H), 4.16 (dd, J = 10.9, 7.5 Hz, 1H), 3.87 (dd, J = 23.7, 10.4 Hz, 2H), 3.48 (s, 3H), 3.42

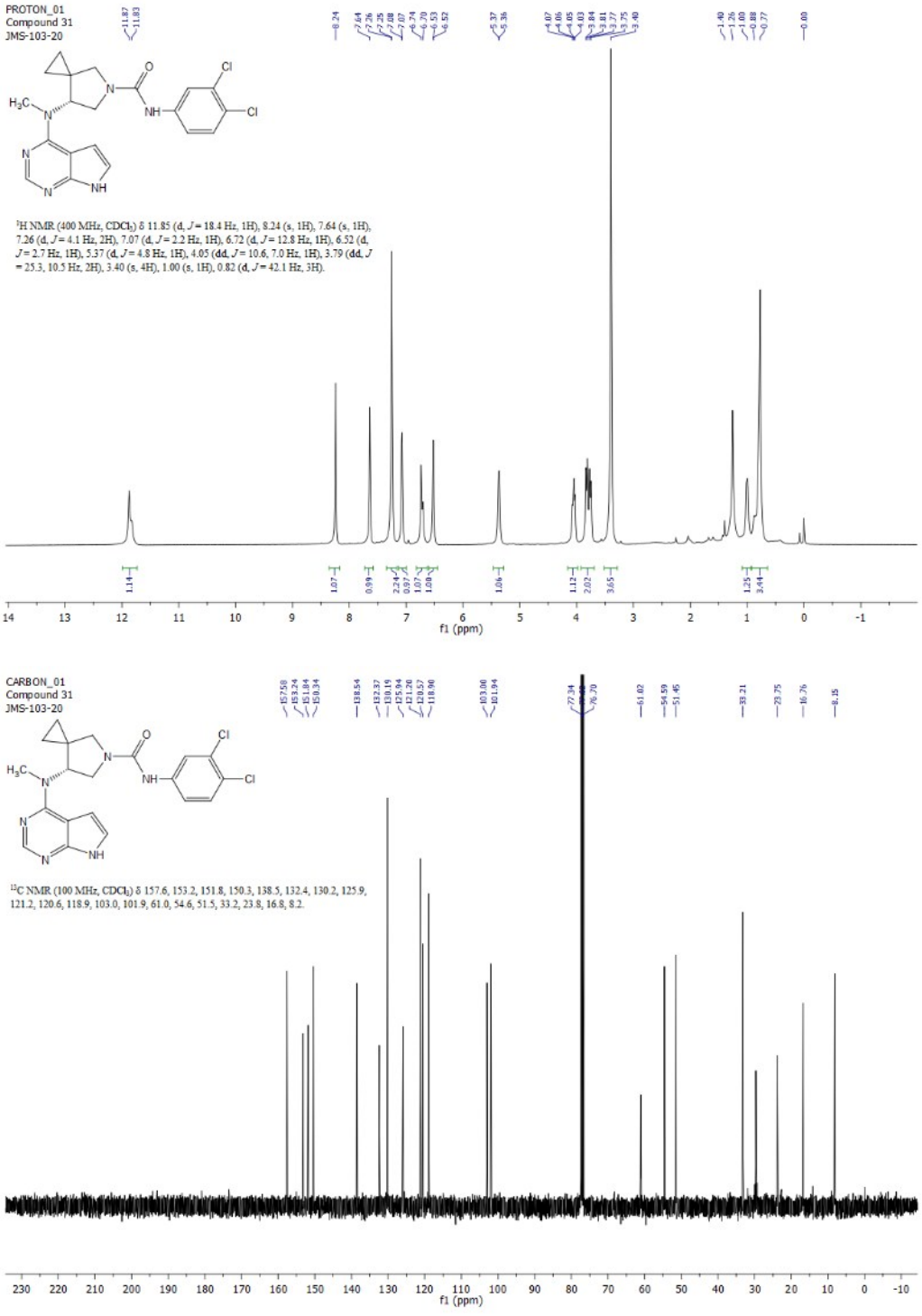
(s, 1H), 1.08 (d, J = 10.3 Hz, 1H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.6, 151.5, 150.0, 134.4, 128.3, 127.9, 127.4, 122.3, 121.2, 120.7, 103.0, 102.0, 60.7, 54.4, 51.1, 33.2, 24.1, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1146. $[\alpha]_D$ +47.8° (*c* 0.970, $CHCl_3$).



(R)-N-(3,4-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***32***

99.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (d, J = 18.4 Hz, 1H), 8.24 (s, 1H), 7.64 (s, 1H), 7.26 (d, J = 4.1 Hz, 2H), 7.07 (d, J = 2.2 Hz, 1H), 6.72 (d, J = 12.8 Hz, 1H), 6.52 (d, J = 2.7 Hz, 1H), 5.37 (d, J = 4.8 Hz, 1H), 4.05 (dd, J = 10.6, 7.0 Hz, 1H), 3.79 (dd, J = 25.3, 10.5 Hz, 2H), 3.40

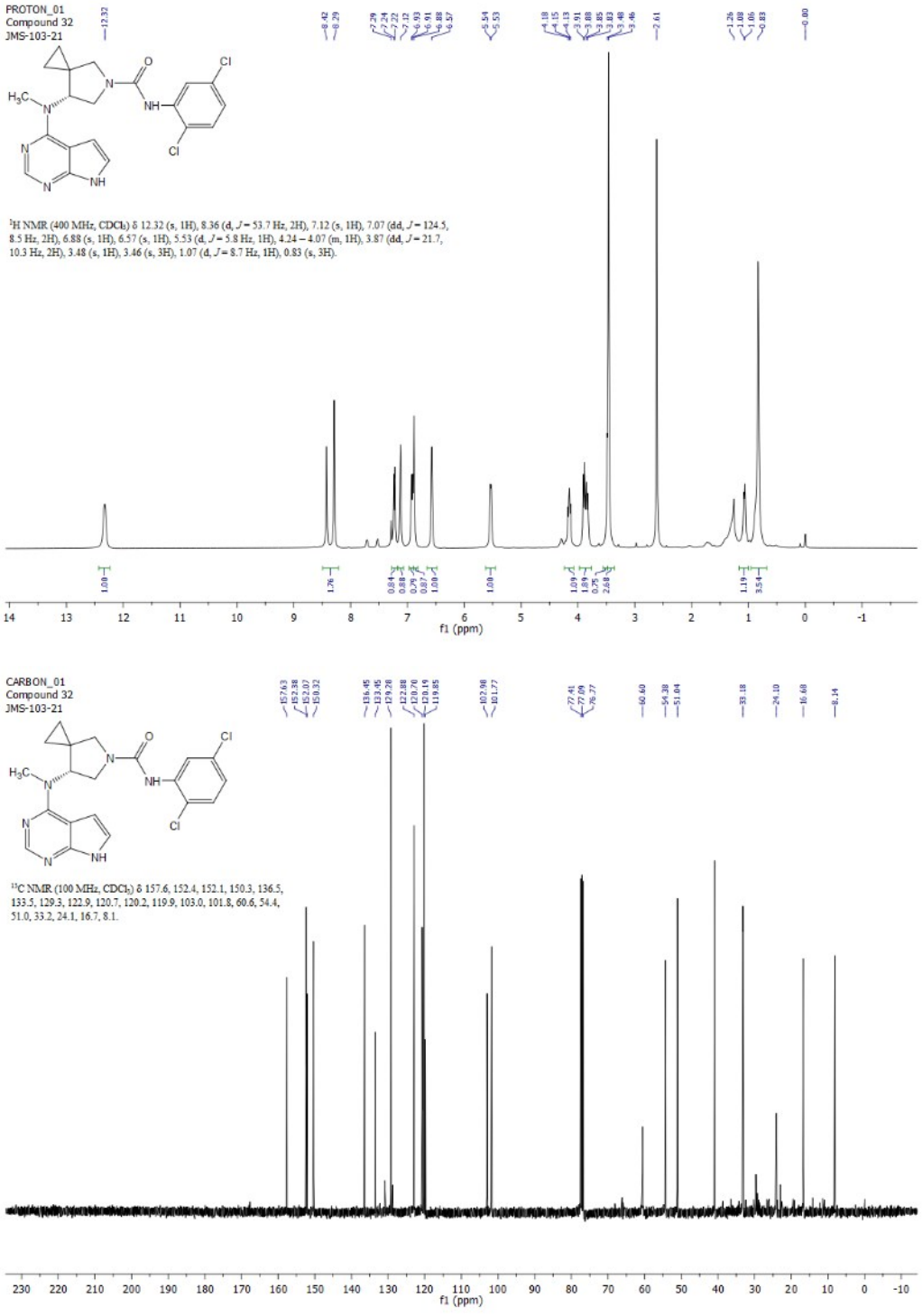
(s, 4H), 1.00 (s, 1H), 0.82 (d, J = 42.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 153.2, 151.8, 150.3, 138.5, 132.4, 130.2, 125.9, 121.2, 120.6, 118.9, 103.0, 101.9, 61.0, 54.6, 51.5, 33.2, 23.8, 16.8, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +48.5° (c 0.850, $CHCl_3$).



(R)-N-(2,5-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***33***

98.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H), 8.36 (d, J = 53.7 Hz, 2H), 7.12 (s, 1H), 7.07 (dd, J = 124.5, 8.5 Hz, 2H), 6.88 (s, 1H), 6.57 (s, 1H), 5.53 (d, J = 5.8 Hz, 1H), 4.24 – 4.07 (m, 1H), 3.87 (dd, J = 21.7, 10.3 Hz, 2H), 3.48 (s, 1H), 3.46 (s, 3H), 1.07 (d, J = 8.7 Hz, 1H), 0.83 (s,

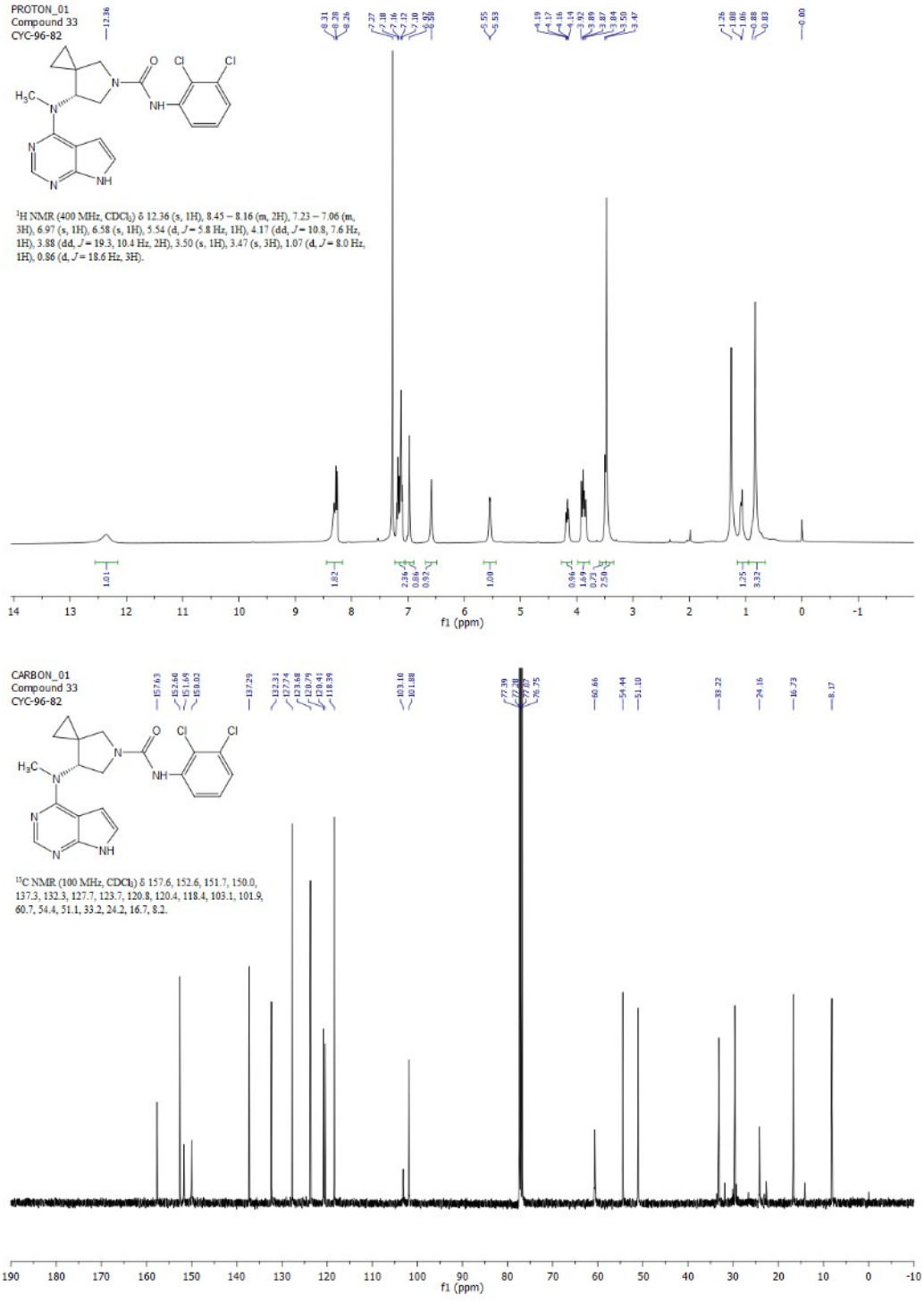
3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.4, 152.1, 150.3, 136.5, 133.5, 129.3, 122.9, 120.7, 120.2, 119.9, 103.0, 101.8, 60.6, 54.4, 51.0, 33.2, 24.1, 16.7, 8.1. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +34.6° (*c* 2.36, DMSO).



(R)-N-(2,3-Dichlorophenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***34***

98.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.36 (s, 1H), 8.45 – 8.16 (m, 2H), 7.23 – 7.06 (m, 3H), 6.97 (s, 1H), 6.58 (s, 1H), 5.54 (d, *J* = 5.8 Hz, 1H), 4.17 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.88 (dd, *J* = 19.3, 10.4 Hz, 2H), 3.50 (s, 1H), 3.47 (s, 3H), 1.07 (d, *J* = 8.0 Hz, 1H), 0.86 (d, *J* = 18.6 Hz, 3H).

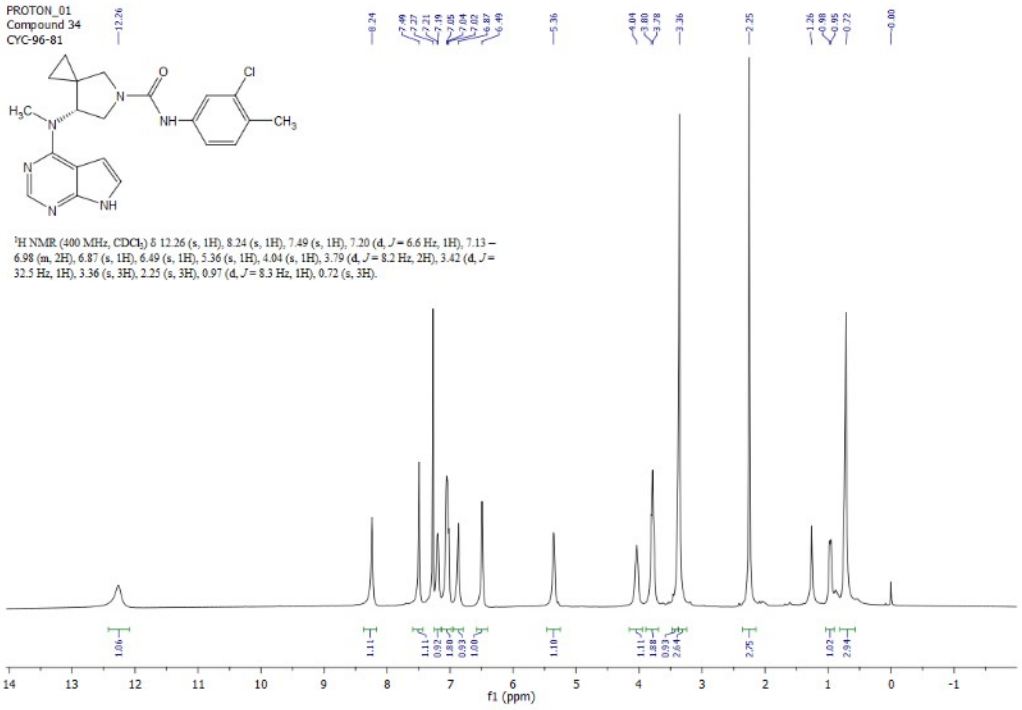
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.6, 151.7, 150.0, 137.3, 132.3, 127.7, 123.7, 120.8, 120.4, 118.4, 103.1, 101.9, 60.7, 54.4, 51.1, 33.2, 24.2, 16.7, 8.2. HRMS (ESI) calcd for $C_{20}H_{21}Cl_2N_6O$: 431.1154. Obsd: 431.1148. $[\alpha]_D$ +31.7° (*c* 3.17, $CHCl_3$).

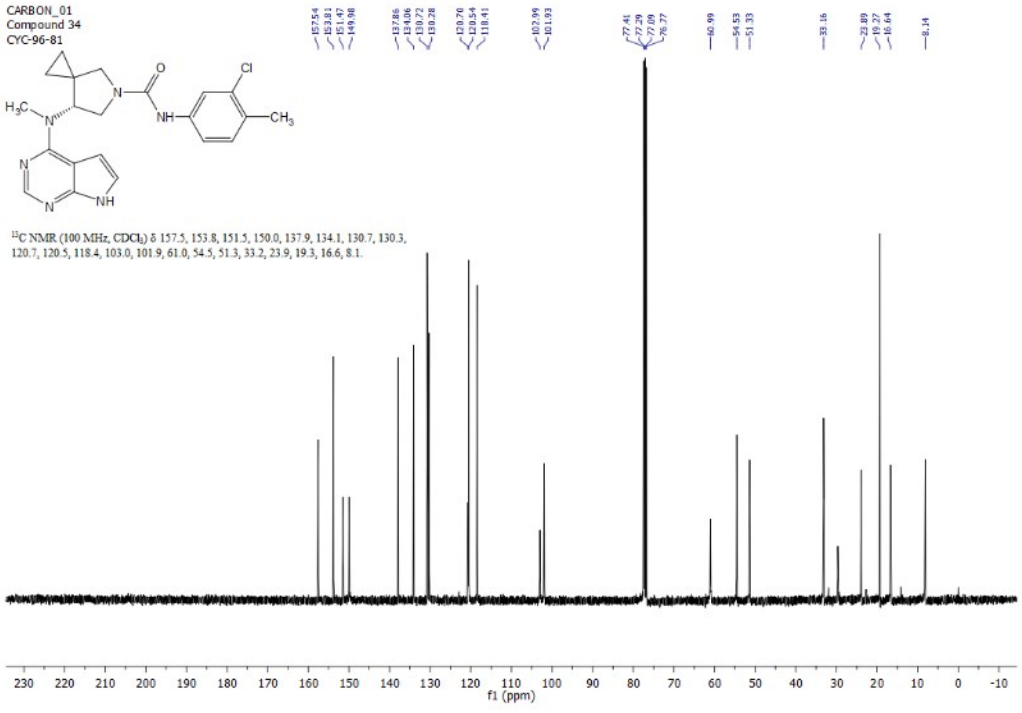


(R)-N-(3-Chloro-4-methylphenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***35***

98.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.24 (s, 1H), 7.49 (s, 1H), 7.20 (d, *J* = 6.6 Hz, 1H), 7.13 – 6.98 (m, 2H), 6.87 (s, 1H), 6.49 (s, 1H), 5.36 (s, 1H), 4.04 (s, 1H), 3.79 (d, *J* = 8.2 Hz, 2H), 3.42 (d, *J* = 32.5 Hz, 1H), 3.36 (s, 3H), 2.25 (s, 3H), 0.97 (d, *J* = 8.3 Hz, 1H), 0.72 (s,

3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.8, 151.5, 150.0, 137.9, 134.1, 130.7, 130.3, 120.7, 120.5, 118.4, 103.0, 101.9, 61.0, 54.5, 51.3, 33.2, 23.9, 19.3, 16.6, 8.1. HRMS (ESI) calcd for $C_{21}H_{24}ClN_6O$: 411.1700. Obsd: 411.1694. $[\alpha]_D$ +41.1° (*c* 3.38, $CHCl_3$).

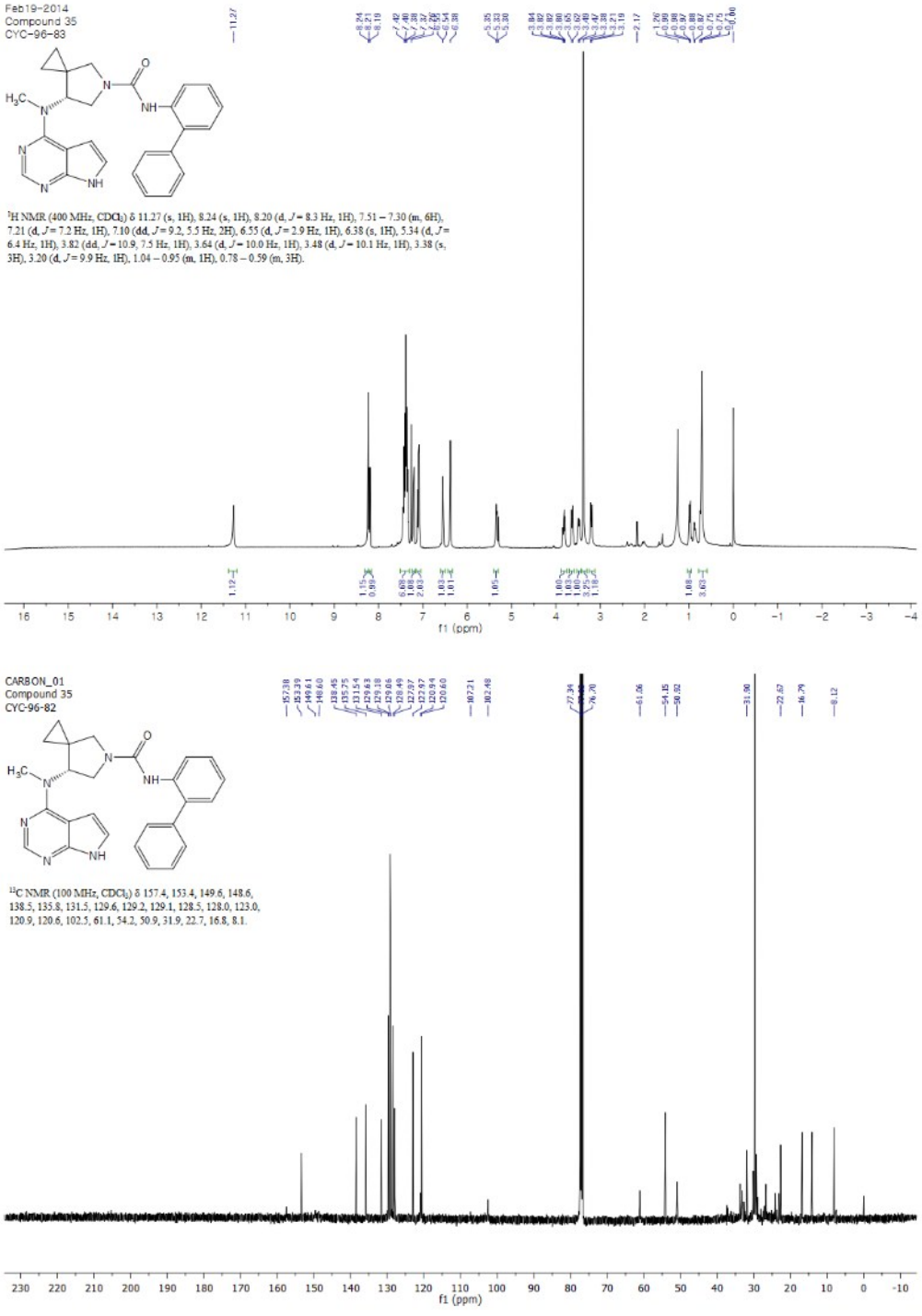




(R)-N-([1,1'-Biphenyl]-2-yl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carboxamide, ***36***

97.9% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.24 (s, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.30 (m, 6H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.10 (dd, *J* = 9.2, 5.5 Hz, 2H), 6.55 (d, *J* = 2.9 Hz, 1H), 6.38 (s, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 3.82 (dd, *J* = 10.9, 7.5 Hz, 1H), 3.64 (d, *J* = 10.0 Hz, 1H),

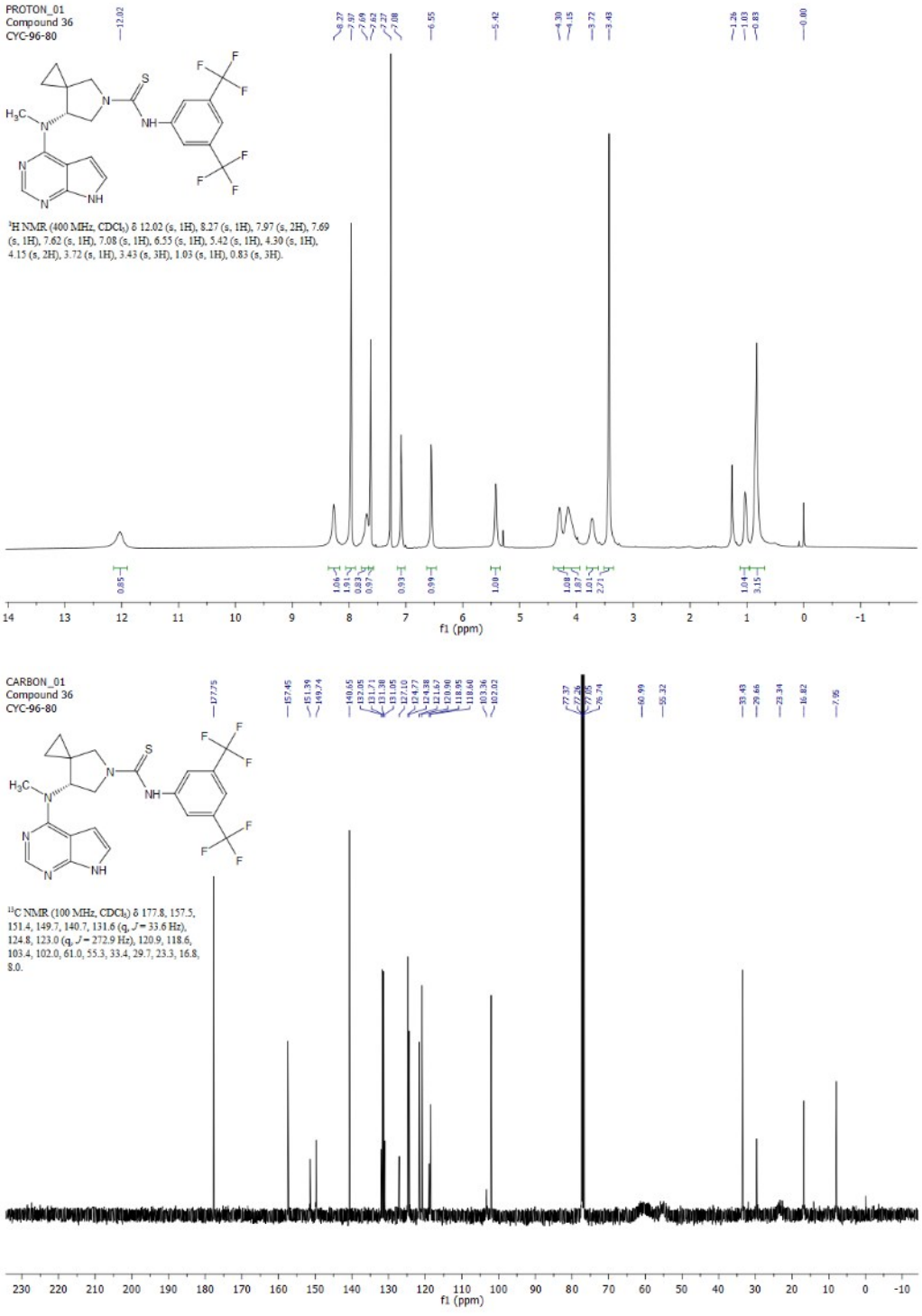
3.48 (d, J = 10.1 Hz, 1H), 3.38 (s, 3H), 3.20 (d, J = 9.9 Hz, 1H), 1.04 – 0.95 (m, 1H), 0.78 – 0.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 153.4, 149.6, 148.6, 138.5, 135.8, 131.5, 129.6, 129.2, 129.1, 128.5, 128.0, 123.0, 120.9, 120.6, 102.5, 61.1, 54.2, 50.9, 31.9, 22.7, 16.8, 8.1. HRMS (ESI) calcd for $C_{26}H_{27}N_6O$: 439.2246. Obsd: 439.2242. $[\alpha]_D$ +29.2° (c 0.587, $CHCl_3$).



(R)-N-(3,5-Bis(trifluoromethyl)phenyl)-7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptane-5-carbothioamide, ***37***

99.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.27 (s, 1H), 7.97 (s, 2H), 7.69 (s, 1H), 7.62 (s, 1H), 7.08 (s, 1H), 6.55 (s, 1H), 5.42 (s, 1H), 4.30 (s, 1H), 4.15 (s, 2H), 3.72 (s, 1H), 3.43 (s, 3H), 1.03 (s, 1H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 157.5, 151.4, 149.7,

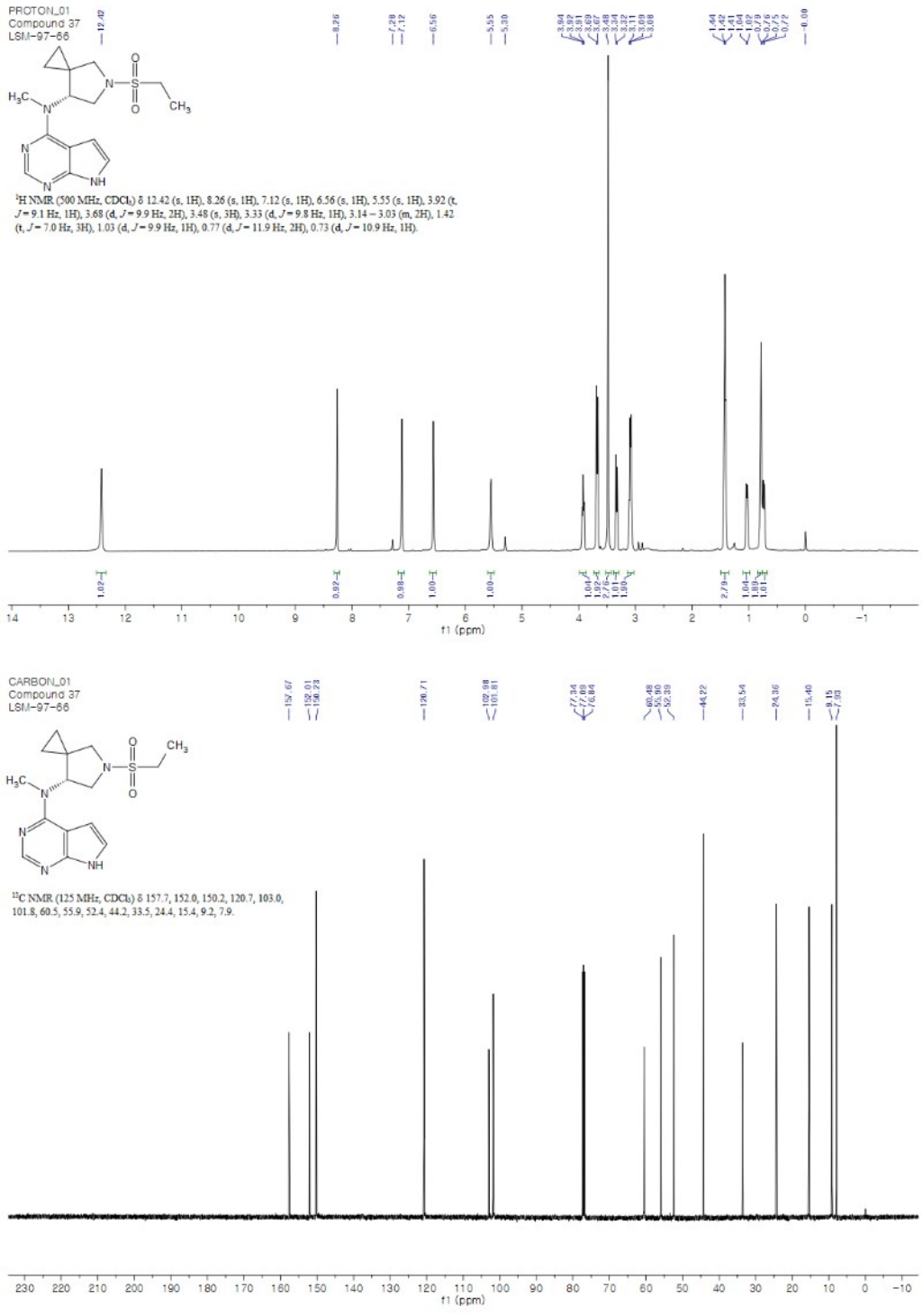
140.7, 131.6 (q, J = 33.6 Hz), 124.8, 123.0 (q, J = 272.9 Hz), 120.9, 118.6, 103.4, 102.0, 61.0, 55.3, 33.4, 29.7, 23.3, 16.8, 8.0. HRMS (ESI) calcd for $C_{22}H_{21}F_6N_6S$: 515.1453. Obsd: 515.1446. $[\alpha]_D$ +51.4° (*c* 3.37, $CHCl_3$).



(R)-N-(5-(ethylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***38***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.26 (s, 1H), 7.12 (s, 1H), 6.56 (s, 1H), 5.55 (s, 1H), 3.92 (t, J = 9.1 Hz, 1H), 3.68 (d, J = 9.9 Hz, 2H), 3.48 (s, 3H), 3.33 (d, J = 9.8 Hz, 1H), 3.14 – 3.03 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.03 (d, J = 9.9 Hz, 1H), 0.77 (d, J = 11.9 Hz, 2H),

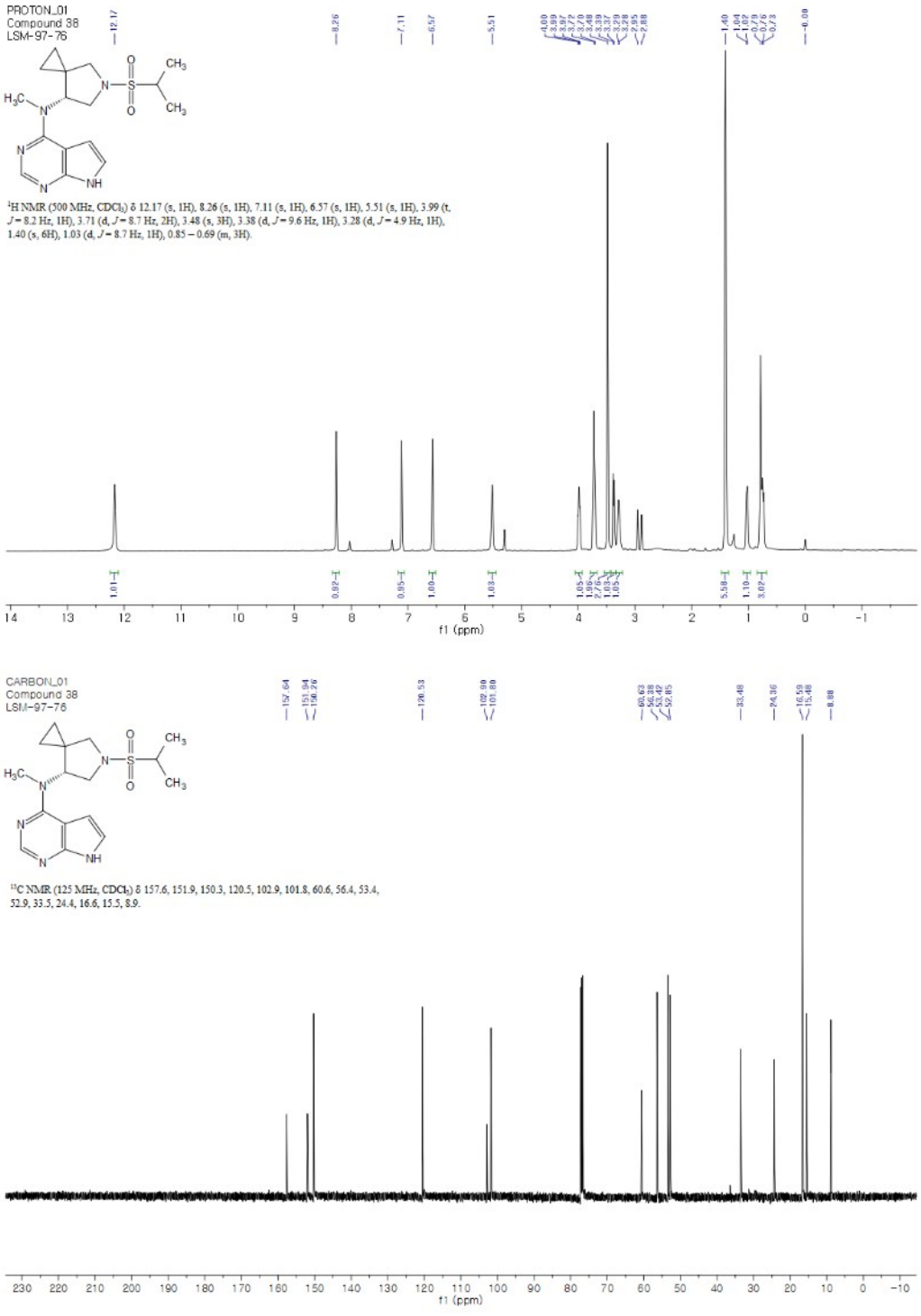
0.73 (d, J = 10.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 152.0, 150.2, 120.7, 103.0, 101.8, 60.5, 55.9, 52.4, 44.2, 33.5, 24.4, 15.4, 9.2, 7.9. HRMS (ESI) calcd for $C_{15}H_{22}N_5O_2S$: 336.1494. Obsd: 336.1485. $[\alpha]_D$ +34.7° (c 3.25, $CHCl_3$).



(R)-N-(5-(Isopropylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***39***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.26 (s, 1H), 7.11 (s, 1H), 6.57 (s, 1H), 5.51 (s, 1H), 3.99 (t, J = 8.2 Hz, 1H), 3.71 (d, J = 8.7 Hz, 2H), 3.48 (s, 3H), 3.38 (d, J = 9.6 Hz, 1H), 3.28 (d, J = 4.9 Hz, 1H), 1.40 (s, 6H), 1.03 (d, J = 8.7 Hz, 1H), 0.85 – 0.69 (m, 3H). ^{13}C NMR

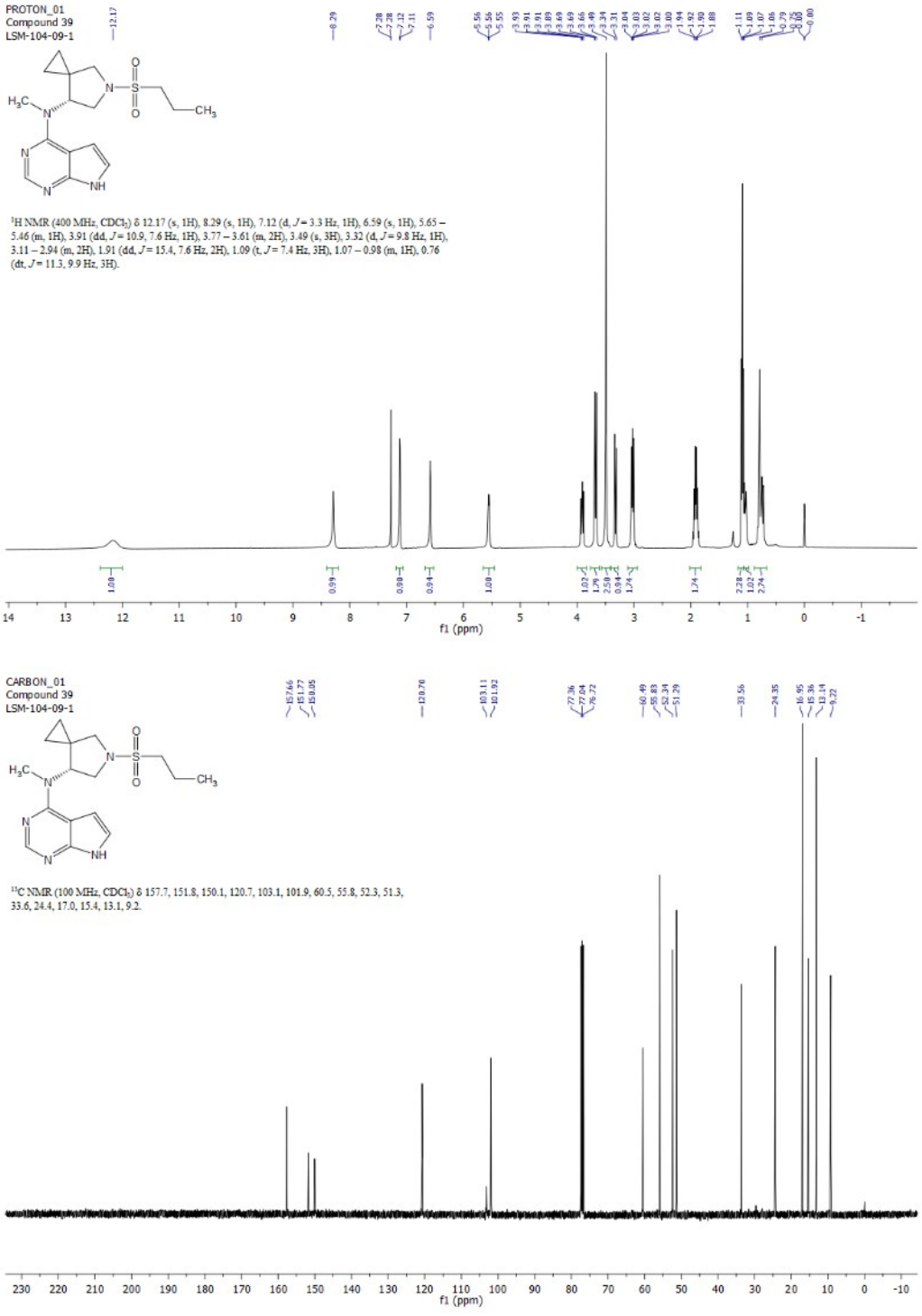
(125 MHz, $CDCl_3$) δ 157.6, 151.9, 150.3, 120.5, 102.9, 101.8, 60.6, 56.4, 53.4, 52.9, 33.5, 24.4, 16.6, 15.5, 8.9. HRMS (ESI) calcd for $C_{16}H_{24}N_5O_2S$: 350.1651. Obsd: 350.1639. $[\alpha]_D$ +36.0° (*c* 1.82, $CHCl_3$).



(R)-N-Methyl-N-(5-(propylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***40***

99.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.29 (s, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 6.59 (s, 1H), 5.65 – 5.46 (m, 1H), 3.91 (dd, *J* = 10.9, 7.6 Hz, 1H), 3.77 – 3.61 (m, 2H), 3.49 (s, 3H), 3.32 (d, *J* = 9.8 Hz, 1H), 3.11 – 2.94 (m, 2H), 1.91 (dd, *J* = 15.4, 7.6 Hz, 2H), 1.09 (t, *J* = 7.4 Hz,

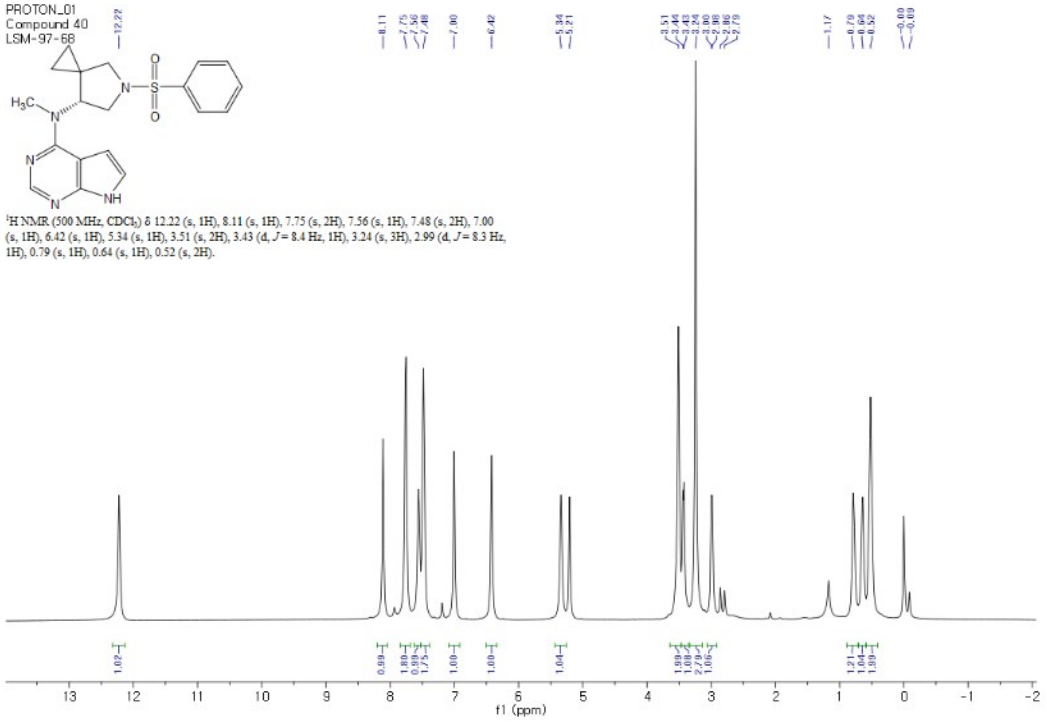
3H), 1.07 – 0.98 (m, 1H), 0.76 (dt, J = 11.3, 9.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 151.8, 150.1, 120.7, 103.1, 101.9, 60.5, 55.8, 52.3, 51.3, 33.6, 24.4, 17.0, 15.4, 13.1, 9.2. HRMS (ESI) calcd for $C_{16}H_{24}N_5O_2S$: 350.1651. Obsd: 350.1650. $[\alpha]_D$ +34.9° (*c* 1.97, $CHCl_3$).

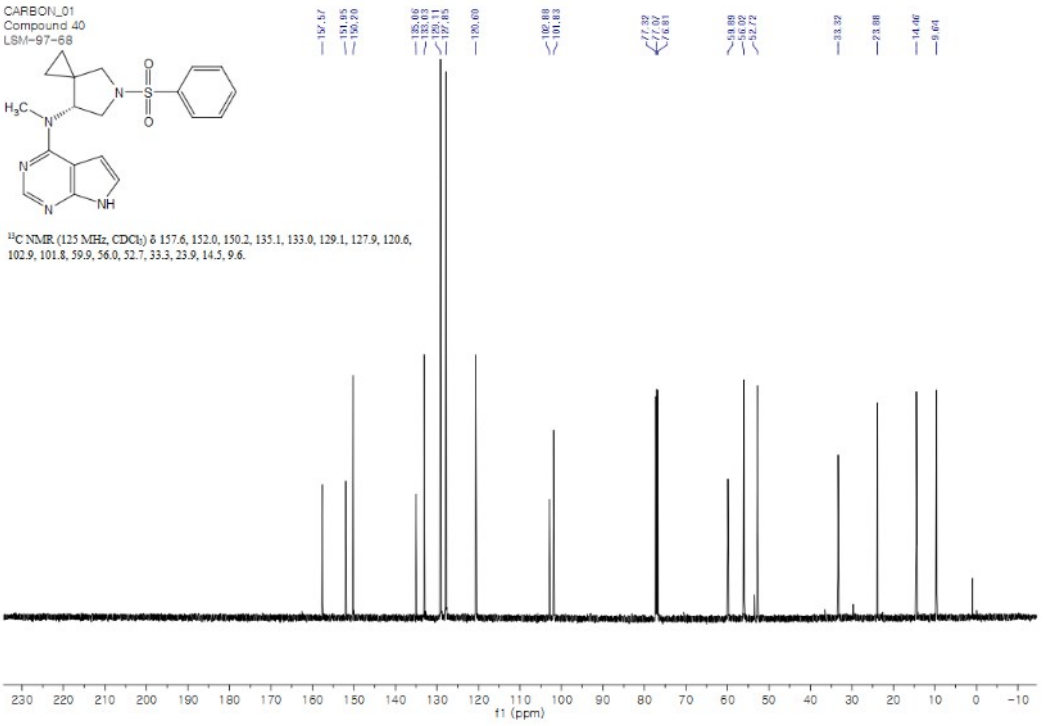


(R)-N-Methyl-N-(5-(phenylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***41***

99.4% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.22 (s, 1H), 8.11 (s, 1H), 7.75 (s, 2H), 7.56 (s, 1H), 7.48 (s, 2H), 7.00 (s, 1H), 6.42 (s, 1H), 5.34 (s, 1H), 3.51 (s, 2H), 3.43 (d, J = 8.4 Hz, 1H), 3.24 (s, 3H), 2.99 (d, J = 8.3 Hz, 1H), 0.79 (s, 1H), 0.64 (s, 1H), 0.52 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$)

δ 157.6, 152.0, 150.2, 135.1, 133.0, 129.1, 127.9, 120.6, 102.9, 101.8, 59.9, 56.0, 52.7, 33.3, 23.9, 14.5, 9.6. HRMS (ESI) calcd for $C_{19}H_{22}N_5O_2S$: 384.1494. Obsd: 384.1483. $[\alpha]_D$ -3.5° (*c* 2.73, $CHCl_3$).

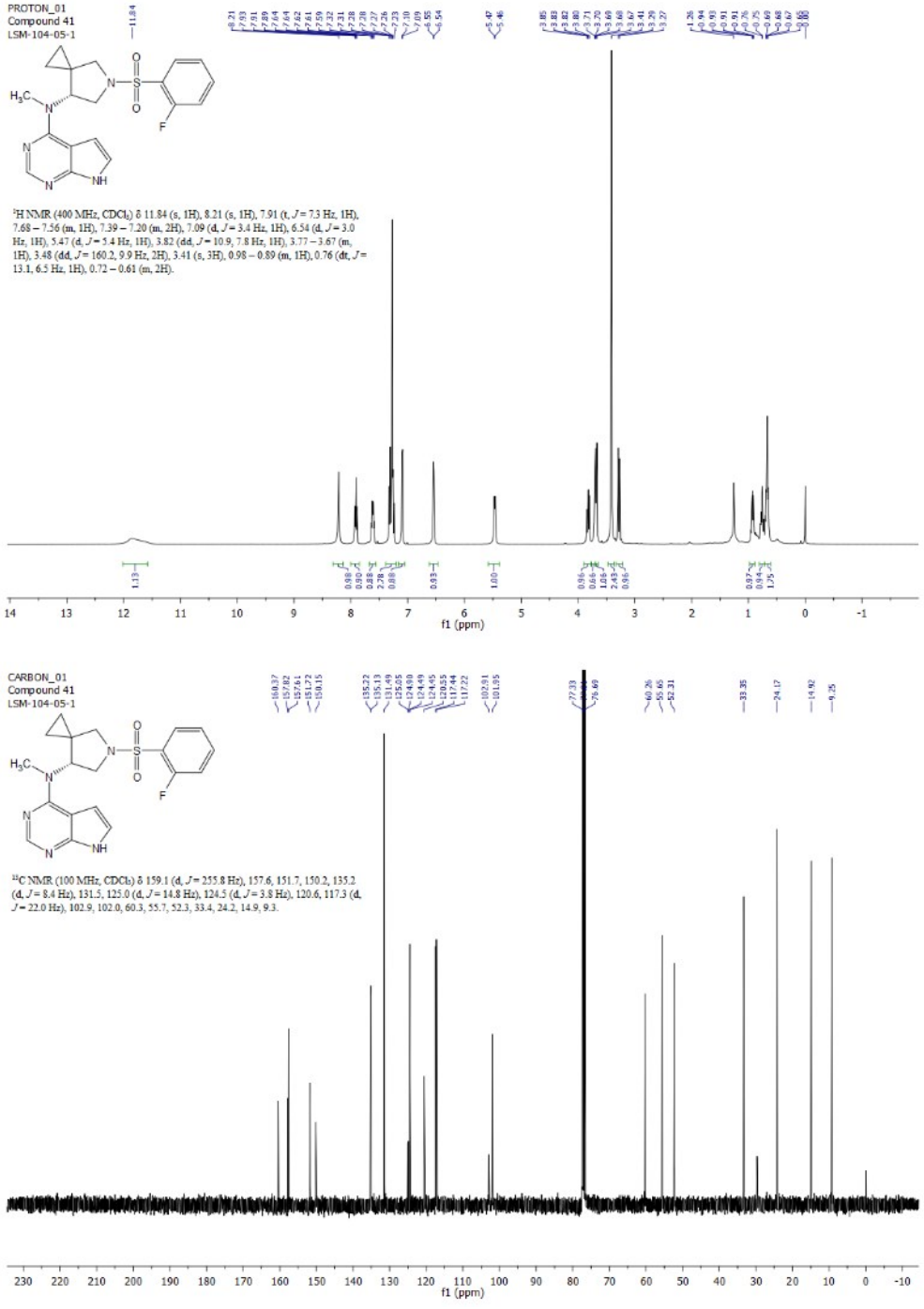




(R)-N-(5-((2-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***42***

97.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.21 (s, 1H), 7.91 (t, *J* = 7.3 Hz, 1H), 7.68 – 7.56 (m, 1H), 7.39 – 7.20 (m, 2H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 5.47 (d, *J* = 5.4 Hz, 1H), 3.82 (dd, *J* = 10.9, 7.8 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.48 (dd, *J* = 160.2, 9.9 Hz,

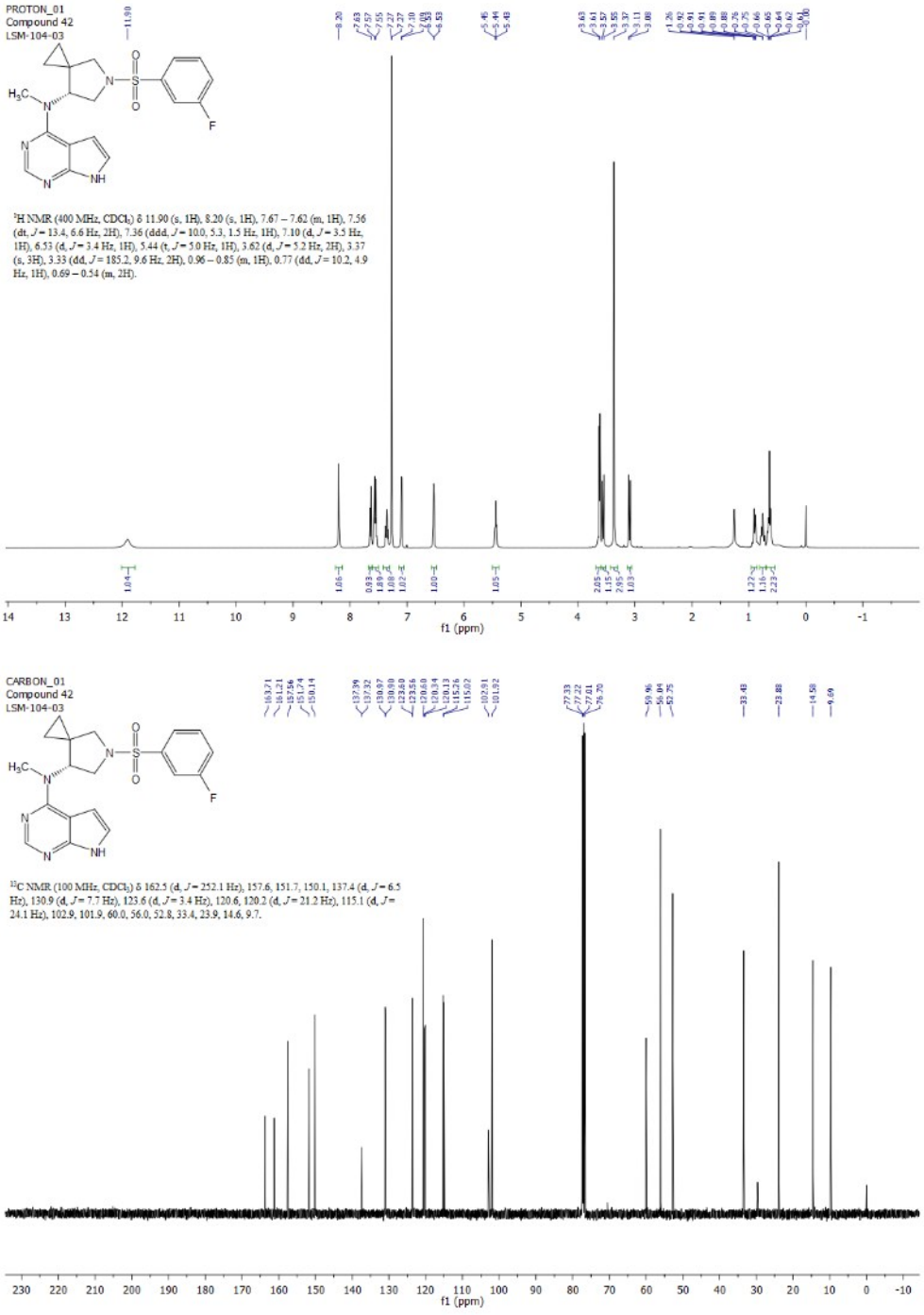
2H), 3.41 (s, 3H), 0.98 – 0.89 (m, 1H), 0.76 (dt, *J* = 13.1, 6.5 Hz, 1H), 0.72 – 0.61 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (d, *J* = 255.8 Hz), 157.6, 151.7, 150.2, 135.2 (d, *J* = 8.4 Hz), 131.5, 125.0 (d, *J* = 14.8 Hz), 124.5 (d, *J* = 3.8 Hz), 120.6, 117.3 (d, *J* = 22.0 Hz), 102.9, 102.0, 60.3, 55.7, 52.3, 33.4, 24.2, 14.9, 9.3. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1393. $[\alpha]_D$ -7.2° (*c* 0.803, $CHCl_3$).



(R)-N-(5-((3-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***43***

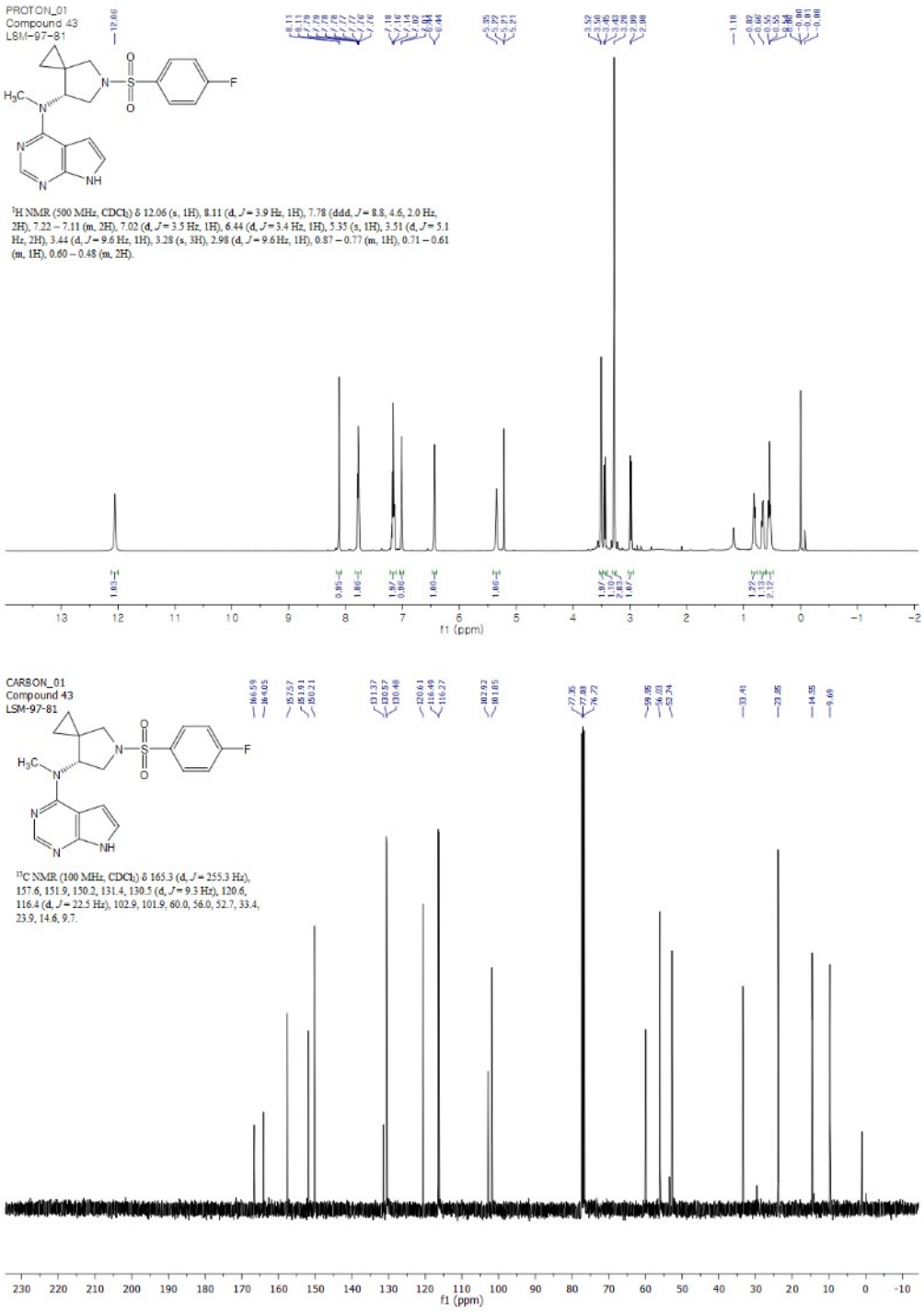
99.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H), 8.20 (s, 1H), 7.67 – 7.62 (m, 1H), 7.56 (dt, *J* = 13.4, 6.6 Hz, 2H), 7.36 (ddd, *J* = 10.0, 5.3, 1.5 Hz, 1H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.53 (d,

J = 3.4 Hz, 1H), 5.44 (t, *J* = 5.0 Hz, 1H), 3.62 (d, *J* = 5.2 Hz, 2H), 3.37 (s, 3H), 3.33 (dd, *J* = 185.2, 9.6 Hz, 2H), 0.96 – 0.85 (m, 1H), 0.77 (dd, *J* = 10.2, 4.9 Hz, 1H), 0.69 – 0.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* = 252.1 Hz), 157.6, 151.7, 150.1, 137.4 (d, *J* = 6.5 Hz), 130.9 (d, *J* = 7.7 Hz), 123.6 (d, *J* = 3.4 Hz), 120.6, 120.2 (d, *J* = 21.2 Hz), 115.1 (d, *J* = 24.1 Hz), 102.9, 101.9, 60.0, 56.0, 52.8, 33.4, 23.9, 14.6, 9.7. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1391. $[\alpha]_D$ -6.7° (*c* 0.880, $CHCl_3$).



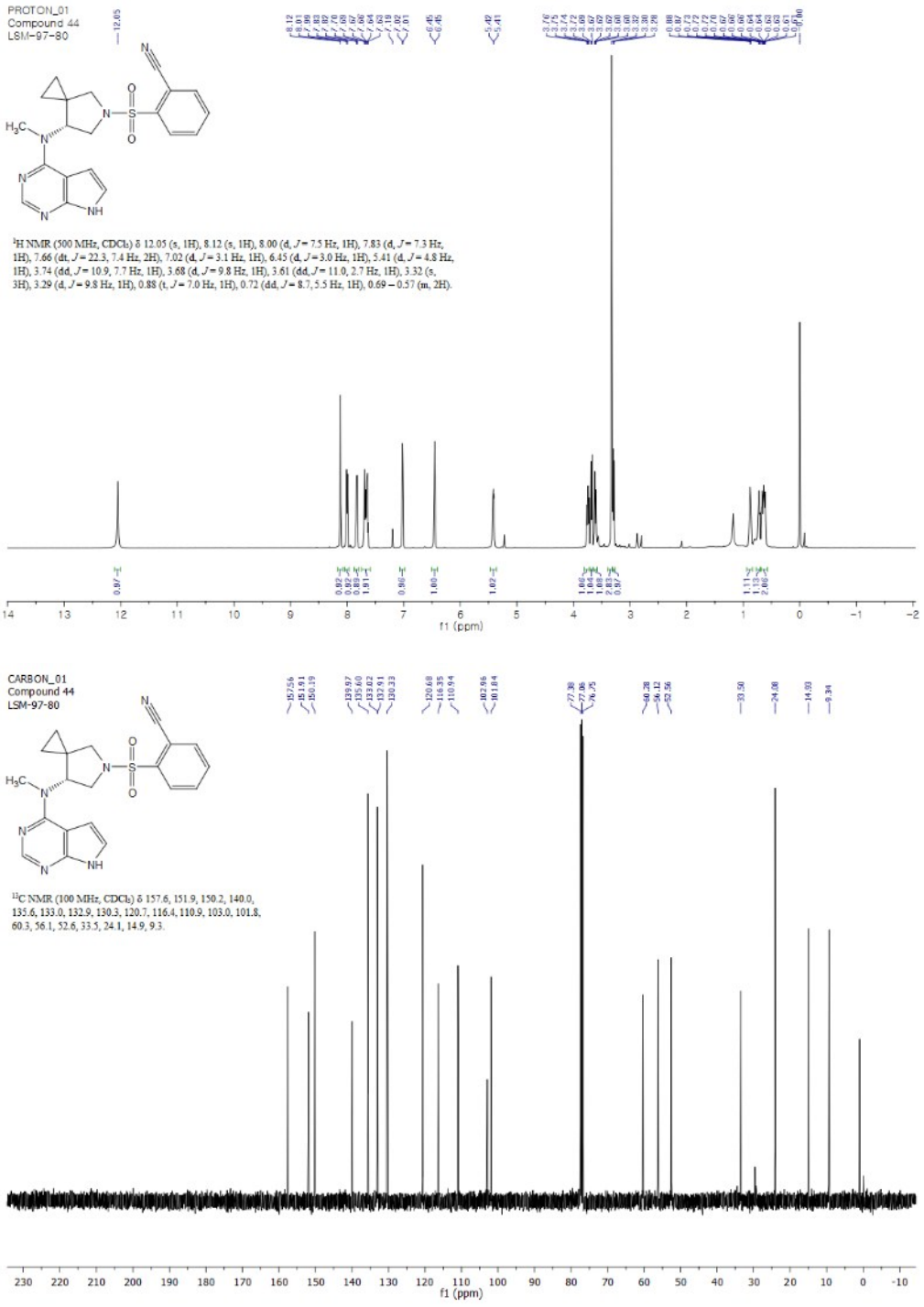
(R)-N-(5-((4-Fluorophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***44***

96.3% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.06 (s, 1H), 8.11 (d, *J* = 3.9 Hz, 1H), 7.78 (ddd, *J* = 8.8, 4.6, 2.0 Hz, 2H), 7.22 – 7.11 (m, 2H), 7.02 (d, *J* = 3.5 Hz, 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 5.35 (s, 1H), 3.51 (d, *J* = 5.1 Hz, 2H), 3.44 (d, *J* = 9.6 Hz, 1H), 3.28 (s, 3H), 2.98 (d, *J* = 9.6 Hz, 1H), 0.87 – 0.77 (m, 1H), 0.71 – 0.61 (m, 1H), 0.60 – 0.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (d, *J* = 255.8 Hz), 157.1, 151.5, 149.8, 130.9, 130.1 (d, *J* = 9.0 Hz), 120.1, 115.9 (d, *J* = 21.4 Hz), 102.4, 101.4, 59.5, 55.6, 52.3, 33.0, 23.4, 14.1, 9.2. HRMS (ESI) calcd for $C_{19}H_{21}FN_5O_2S$: 402.1400. Obsd: 402.1388. $[\alpha]_D$ -3.0° (*c* 2.17, $CHCl_3$).



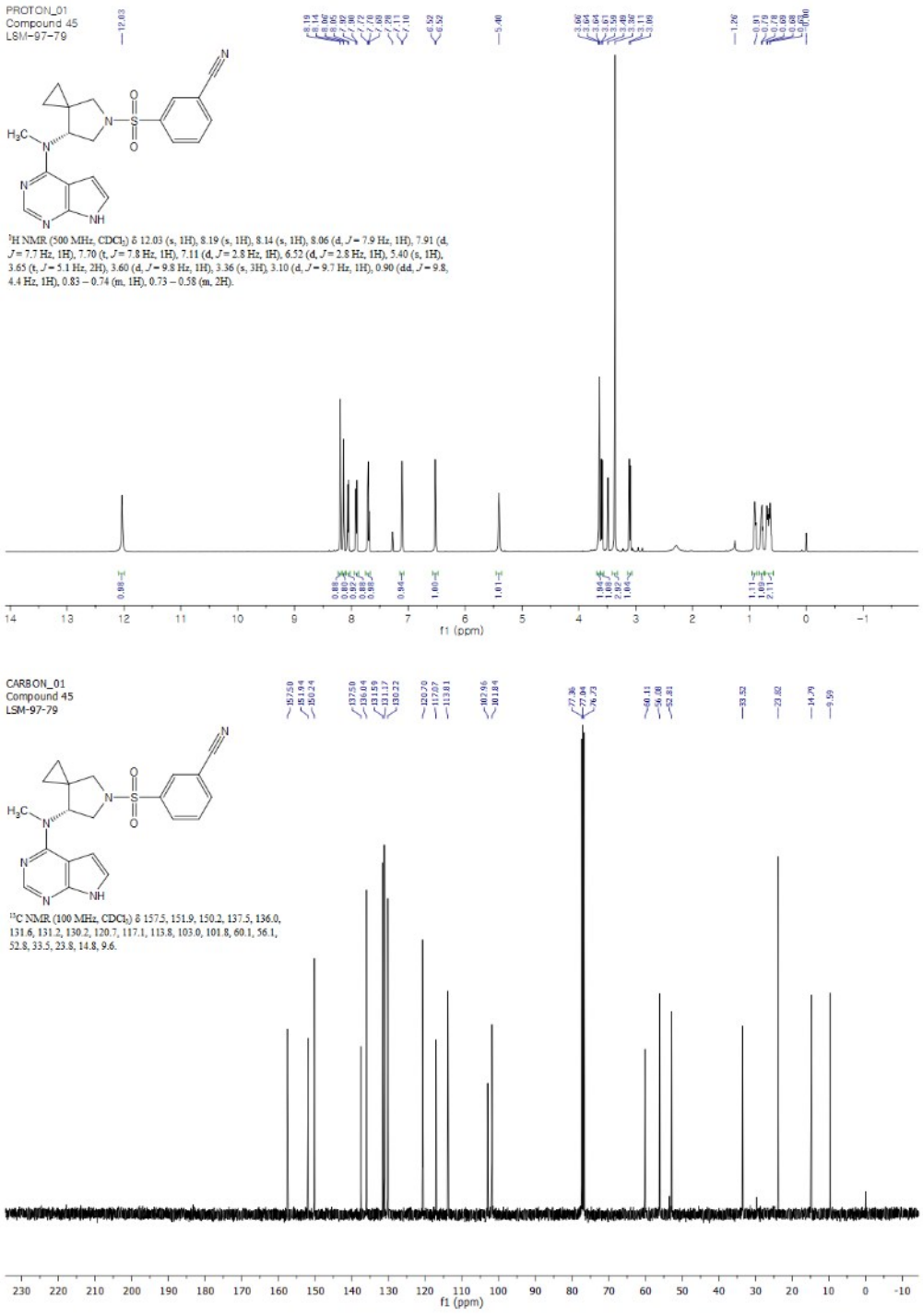
(R)-2-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***45***

99.2% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.05 (s, 1H), 8.12 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.3 Hz, 1H), 7.66 (dt, *J* = 22.3, 7.4 Hz, 2H), 7.02 (d, *J* = 3.1 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 3.74 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.68 (d, *J* = 9.8 Hz, 1H), 3.61 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.32 (s, 3H), 3.29 (d, *J* = 9.8 Hz, 1H), 0.88 (t, *J* = 7.0 Hz, 1H), 0.72 (dd, *J* = 8.7, 5.5 Hz, 1H), 0.69 – 0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 150.2, 140.0, 135.6, 133.0, 132.9, 130.3, 120.7, 116.4, 110.9, 103.0, 101.8, 60.3, 56.1, 52.6, 33.5, 24.1, 14.9, 9.3. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1435. $[\alpha]_D$ +2.2° (*c* 1.91, $CHCl_3$).



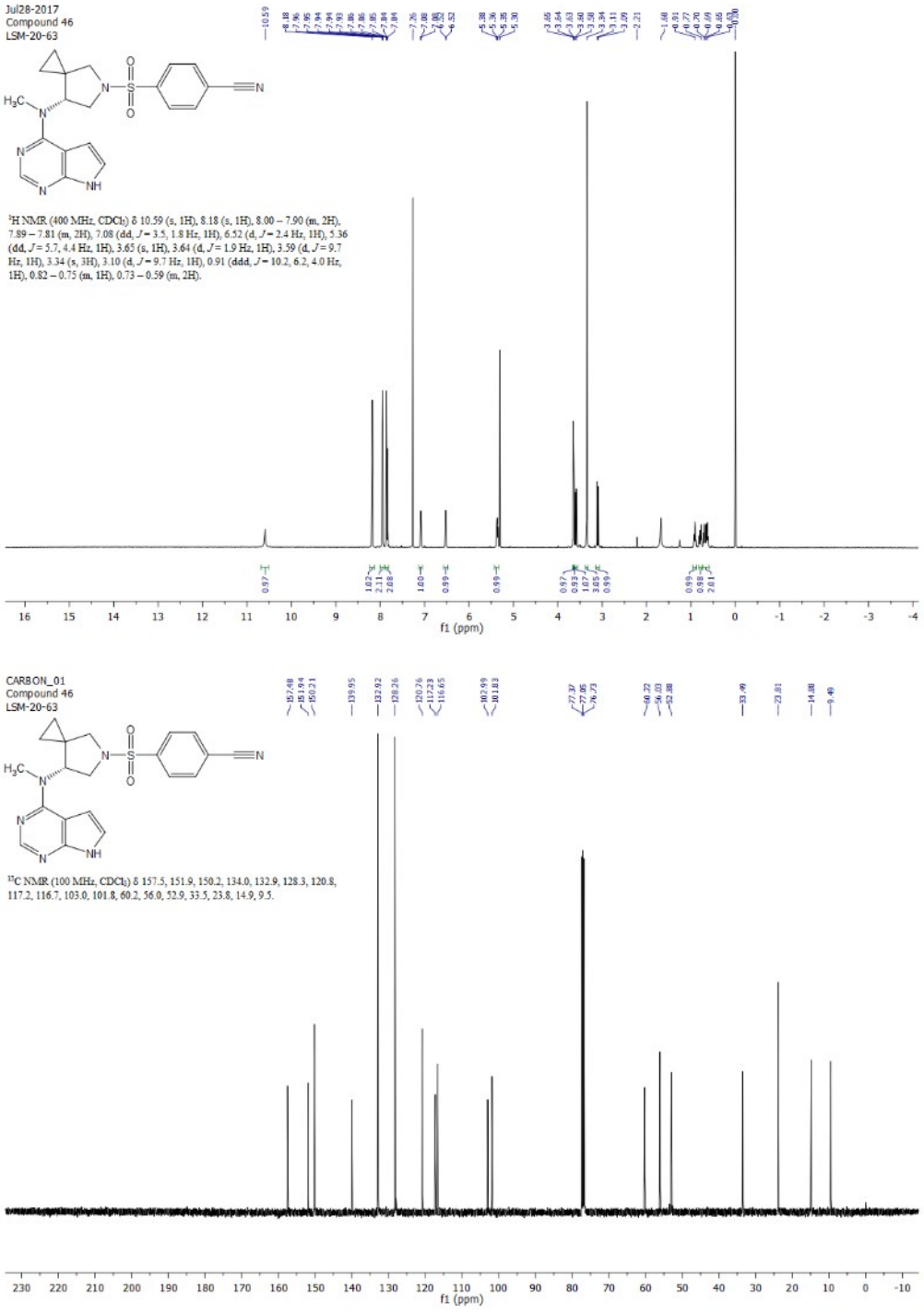
(R)-3-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***46***

100% purity by HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.03 (s, 1H), 8.19 (s, 1H), 8.14 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 5.40 (s, 1H), 3.65 (t, *J* = 5.1 Hz, 2H), 3.60 (d, *J* = 9.8 Hz, 1H), 3.36 (s, 3H), 3.10 (d, *J* = 9.7 Hz, 1H), 0.90 (dd, *J* = 9.8, 4.4 Hz, 1H), 0.83 – 0.74 (m, 1H), 0.73 – 0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.2, 137.5, 136.0, 131.6, 131.2, 130.2, 120.7, 117.1, 113.8, 103.0, 101.8, 60.1, 56.1, 52.8, 33.5, 23.8, 14.8, 9.6. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1435. $[\alpha]_D$ -7.5° (*c* 1.82, $CHCl_3$).



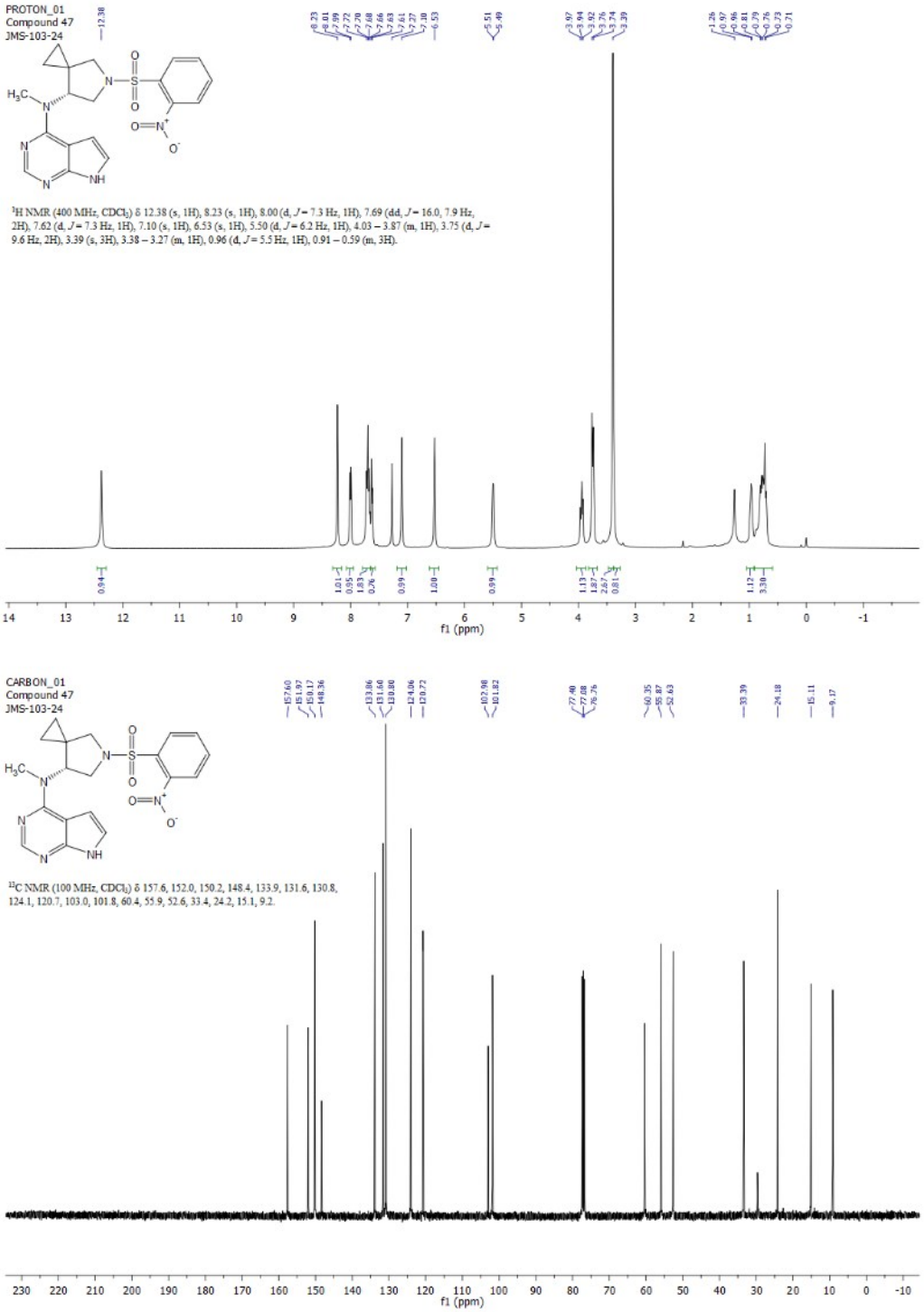
(R)-4-((7-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)sulfonyl)benzonitrile, ***47***

94.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.18 (s, 1H), 8.00 – 7.90 (m, 2H), 7.89 – 7.81 (m, 2H), 7.08 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 5.36 (dd, *J* = 5.7, 4.4 Hz, 1H), 3.65 (s, 1H), 3.64 (d, *J* = 1.9 Hz, 1H), 3.59 (d, *J* = 9.7 Hz, 1H), 3.34 (s, 3H), 3.10 (d, *J* = 9.7 Hz, 1H), 0.91 (ddd, *J* = 10.2, 6.2, 4.0 Hz, 1H), 0.82 – 0.75 (m, 1H), 0.73 – 0.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.2, 134.0, 132.9, 128.3, 120.8, 117.2, 116.7, 103.0, 101.8, 60.2, 56.0, 52.9, 33.5, 23.8, 14.9, 9.5. HRMS (ESI) calcd for $C_{20}H_{21}N_6O_2S$: 409.1447. Obsd: 409.1433. $[\alpha]_D$ -12.7° (*c* 1.66, $CHCl_3$).



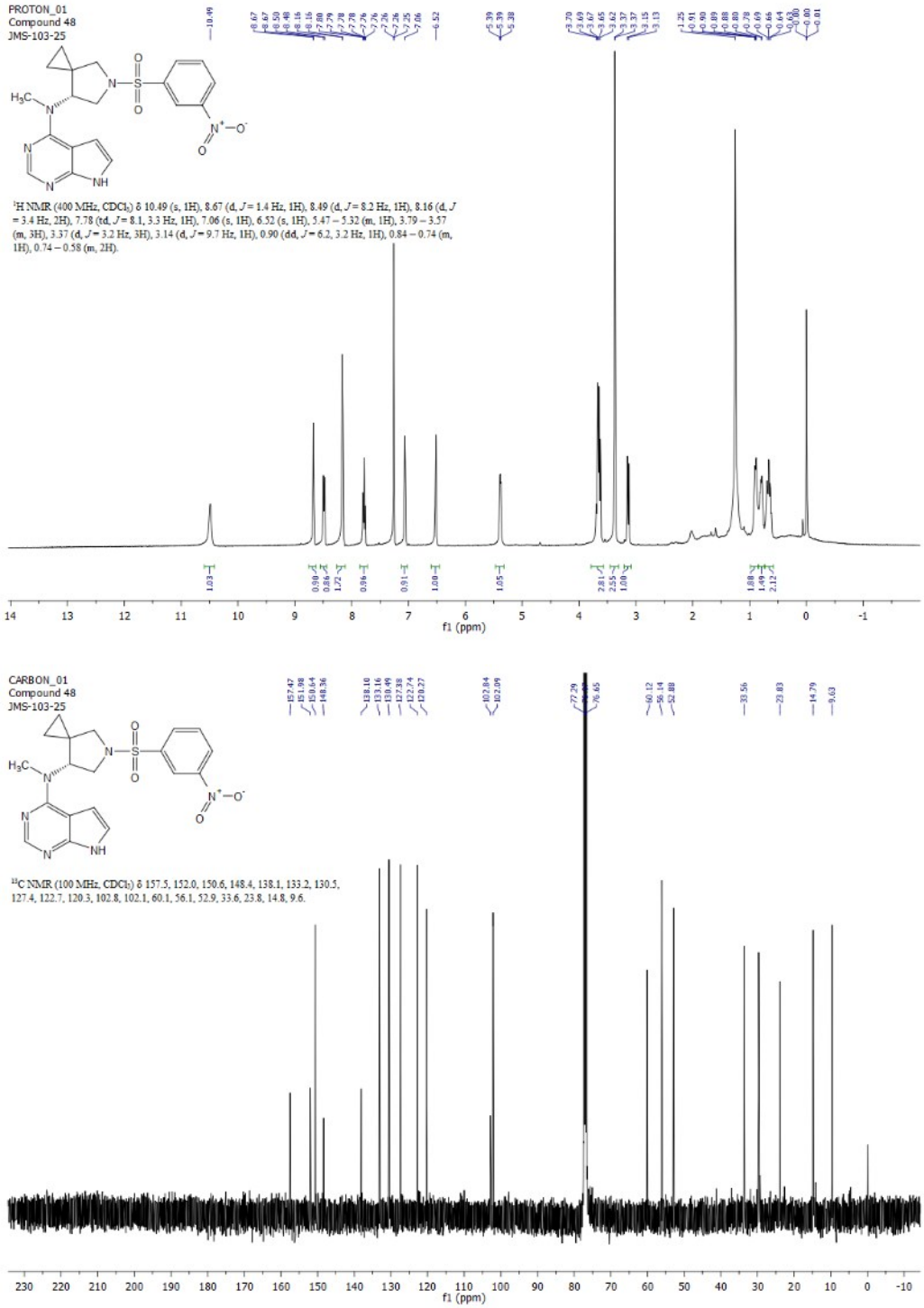
(R)-N-Methyl-N-(5-((2-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***48***

96.9% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (s, 1H), 8.23 (s, 1H), 8.00 (d, *J* = 7.3 Hz, 1H), 7.69 (dd, *J* = 16.0, 7.9 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.10 (s, 1H), 6.53 (s, 1H), 5.50 (d, *J* = 6.2 Hz, 1H), 4.03 – 3.87 (m, 1H), 3.75 (d, *J* = 9.6 Hz, 2H), 3.39 (s, 3H), 3.38 – 3.27 (m, 1H), 0.96 (d, *J* = 5.5 Hz, 1H), 0.91 – 0.59 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.0, 150.2, 148.4, 133.9, 131.6, 130.8, 124.1, 120.7, 103.0, 101.8, 60.4, 55.9, 52.6, 33.4, 24.2, 15.1, 9.2. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1340. $[\alpha]_D$ +6.1° (*c* 2.21, $CHCl_3$).



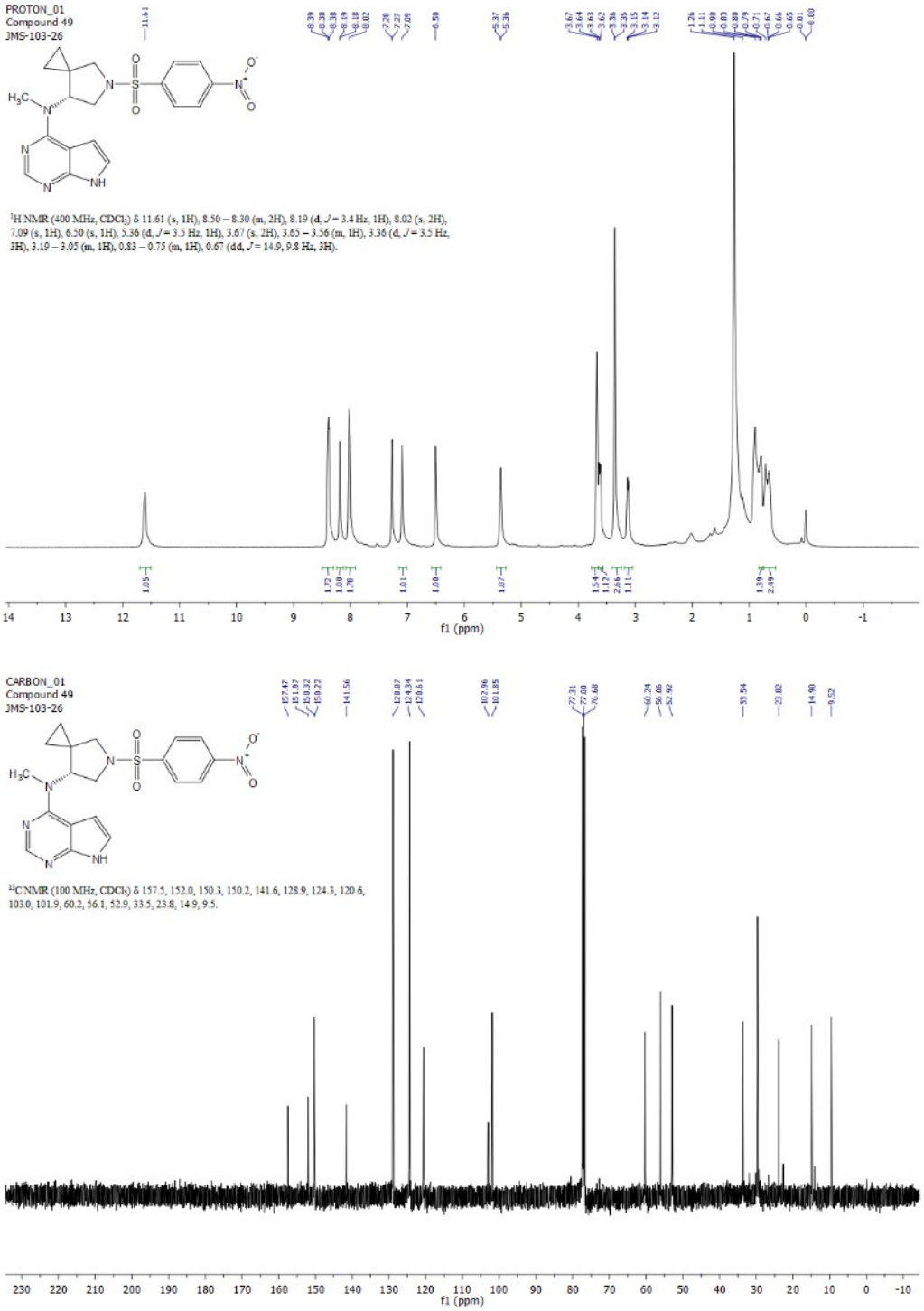
(R)-N-Methyl-N-(5-((3-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***49***

94.8% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.67 (d, *J* = 1.4 Hz, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 8.16 (d, *J* = 3.4 Hz, 2H), 7.78 (td, *J* = 8.1, 3.3 Hz, 1H), 7.06 (s, 1H), 6.52 (s, 1H), 5.47 – 5.32 (m, 1H), 3.79 – 3.57 (m, 3H), 3.37 (d, *J* = 3.2 Hz, 3H), 3.14 (d, *J* = 9.7 Hz, 1H), 0.90 (dd, *J* = 6.2, 3.2 Hz, 1H), 0.84 – 0.74 (m, 1H), 0.74 – 0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.0, 150.6, 148.4, 138.1, 133.2, 130.5, 127.4, 122.7, 120.3, 102.8, 102.1, 60.1, 56.1, 52.9, 33.6, 23.8, 14.8, 9.6. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1339. $[\alpha]_D$ -6.4° (*c* 0.117, $CHCl_3$).



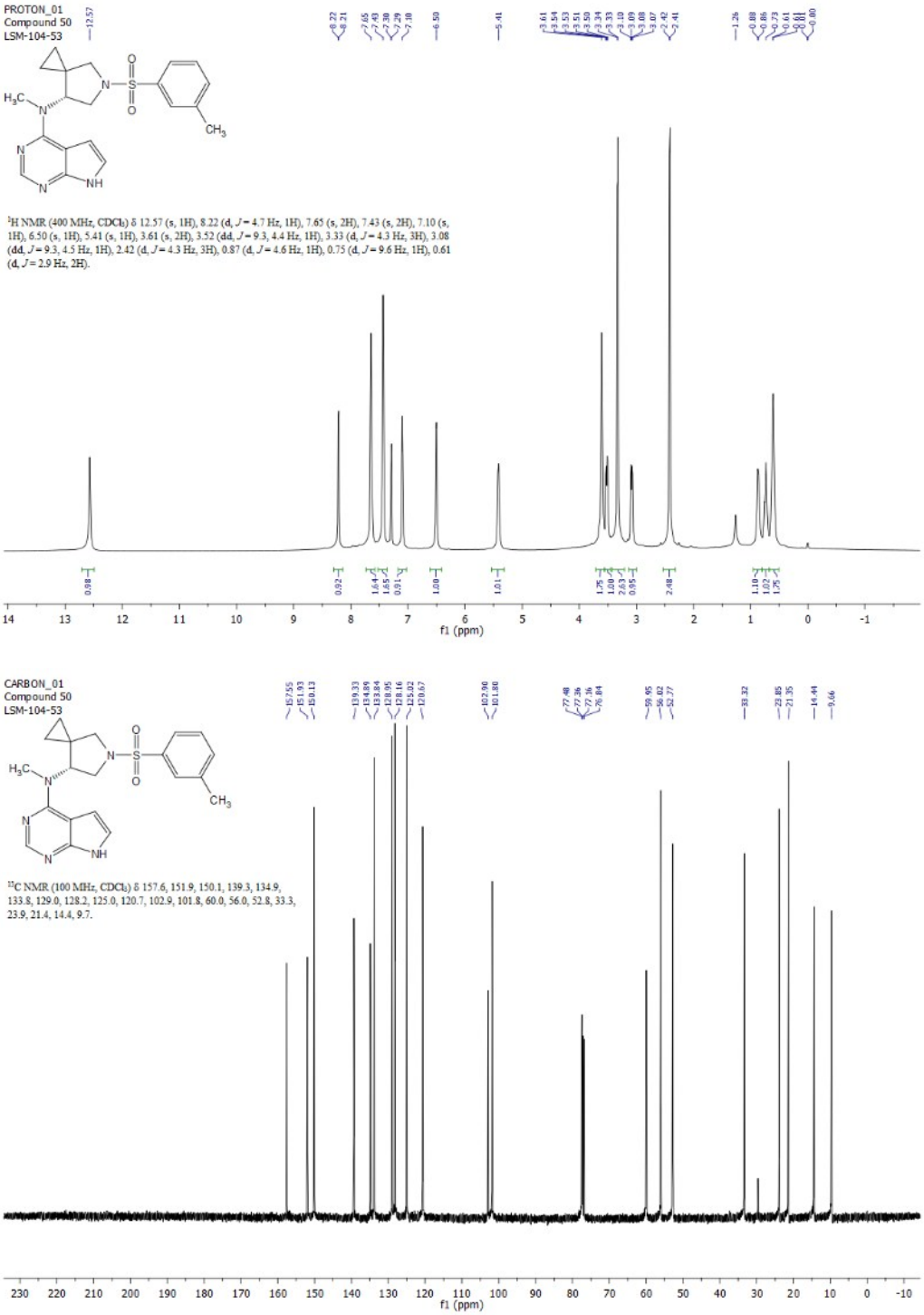
(R)-N-Methyl-N-(5-((4-nitrophenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***50***

97.1% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 1H), 8.50 – 8.30 (m, 2H), 8.19 (d, *J* = 3.4 Hz, 1H), 8.02 (s, 2H), 7.09 (s, 1H), 6.50 (s, 1H), 5.36 (d, *J* = 3.5 Hz, 1H), 3.67 (s, 2H), 3.65 – 3.56 (m, 1H), 3.36 (d, *J* = 3.5 Hz, 3H), 3.19 – 3.05 (m, 1H), 0.83 – 0.75 (m, 1H), 0.67 (dd, *J* = 14.9, 9.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.0, 150.3, 150.2, 141.6, 128.9, 124.3, 120.6, 103.0, 101.9, 60.2, 56.1, 52.9, 33.5, 23.8, 14.9, 9.5. HRMS (ESI) calcd for $C_{19}H_{21}N_6O_4S$: 429.1345. Obsd: 429.1338. $[\alpha]_D$ -19.0° (*c* 1.38, $CHCl_3$).



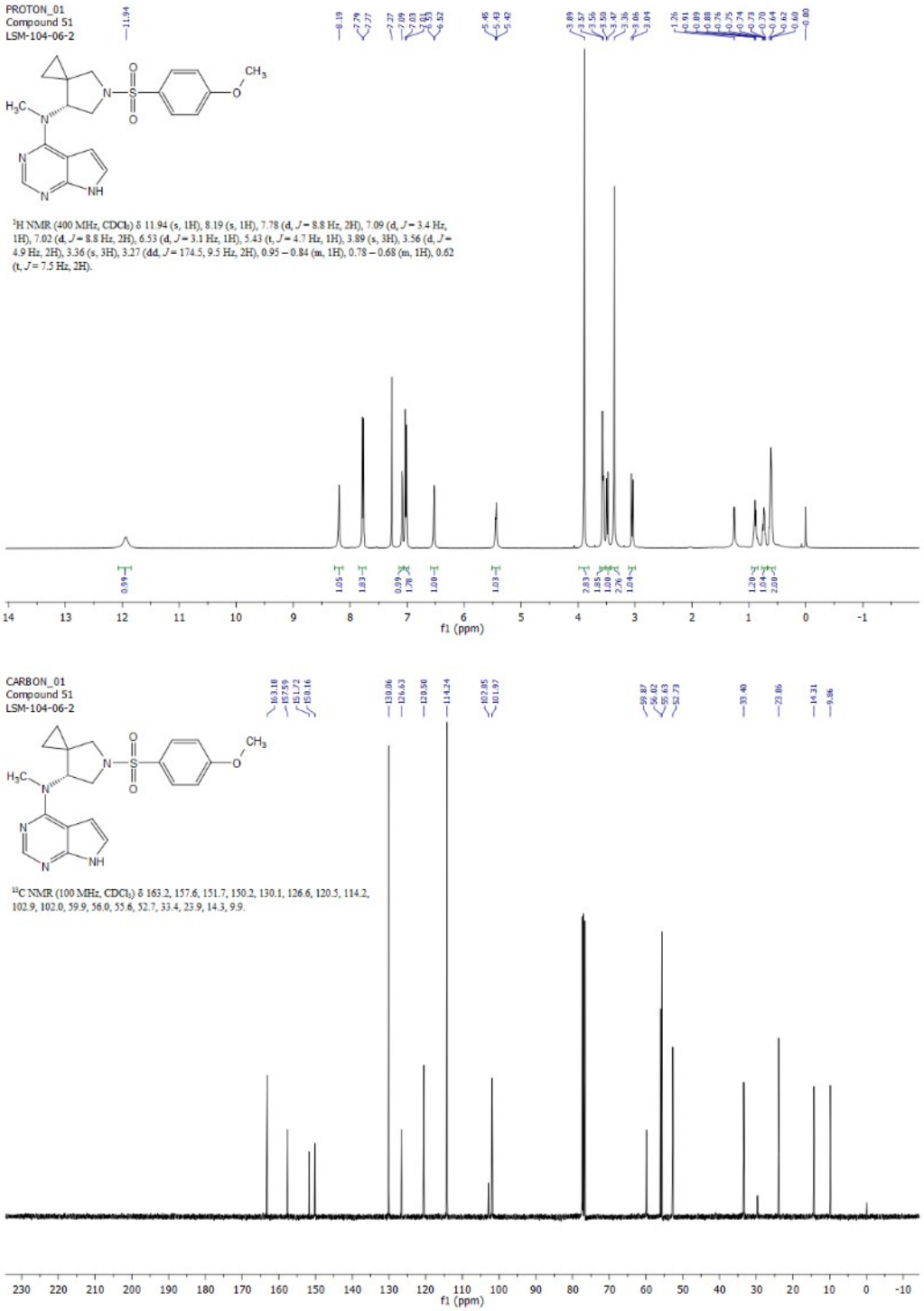
(R)-N-Methyl-N-(5-(m-tolylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***51***

98.0% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 8.22 (d, *J* = 4.7 Hz, 1H), 7.65 (s, 2H), 7.43 (s, 2H), 7.10 (s, 1H), 6.50 (s, 1H), 5.41 (s, 1H), 3.61 (s, 2H), 3.52 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.33 (d, *J* = 4.3 Hz, 3H), 3.08 (dd, *J* = 9.3, 4.5 Hz, 1H), 2.42 (d, *J* = 4.3 Hz, 3H), 0.87 (d, *J* = 4.6 Hz, 1H), 0.75 (d, *J* = 9.6 Hz, 1H), 0.61 (d, *J* = 2.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.9, 150.1, 139.3, 134.9, 133.8, 129.0, 128.2, 125.0, 120.7, 102.9, 101.8, 60.0, 56.0, 52.8, 33.3, 23.9, 21.4, 14.4, 9.7. HRMS (ESI) calcd for $C_{20}H_{24}N_5O_2S$: 398.1651. Obsd: 398.1645. $[\alpha]_D$ -5.6° (*c* 3.88, $CHCl_3$).



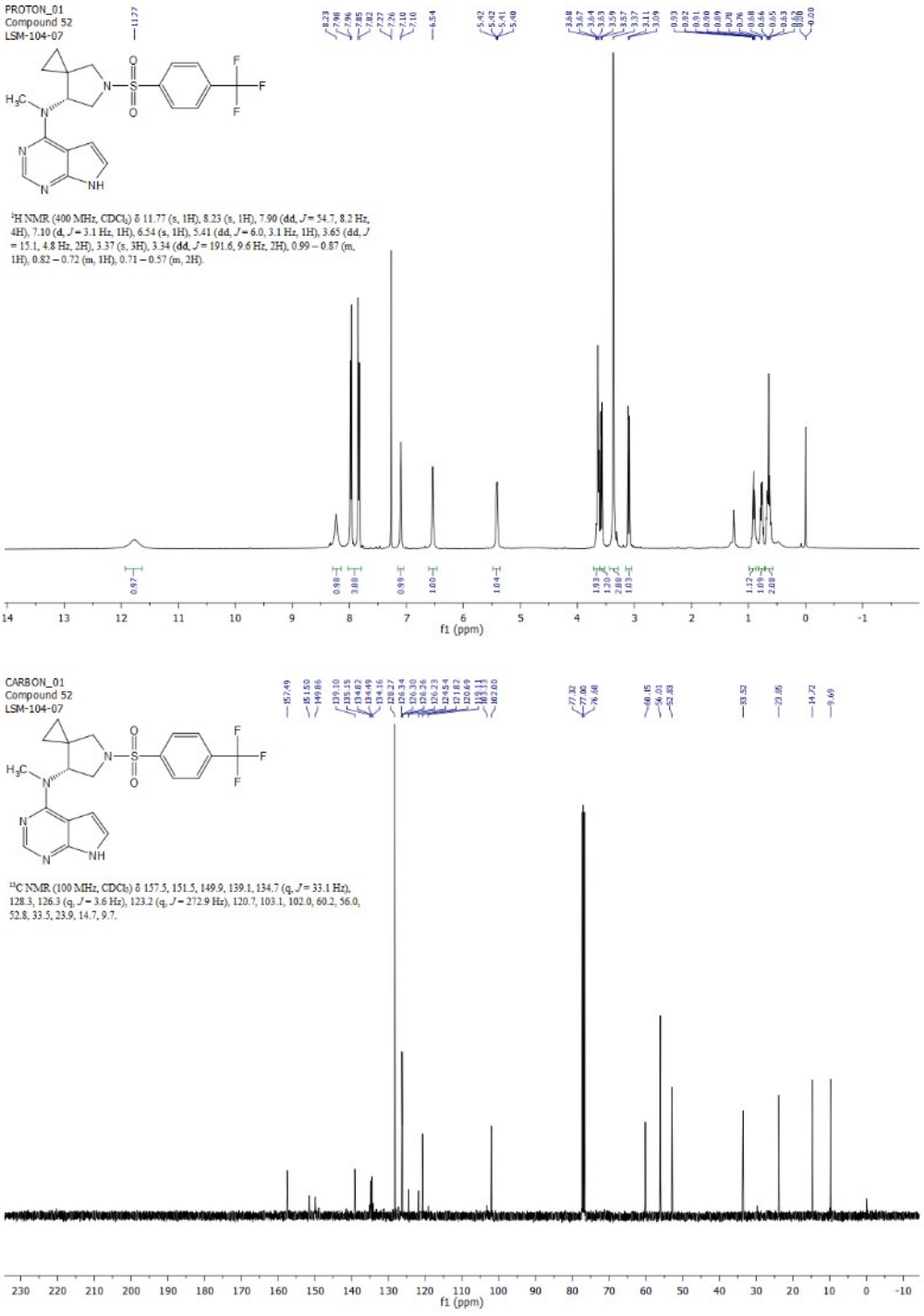
(R)-N-(5-((4-Methoxyphenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-N-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***52***

96.3% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.94 (s, 1H), 8.19 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 3.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 3.1 Hz, 1H), 5.43 (t, *J* = 4.7 Hz, 1H), 3.89 (s, 3H), 3.56 (d, *J* = 4.9 Hz, 2H), 3.36 (s, 3H), 3.27 (dd, *J* = 174.5, 9.5 Hz, 2H), 0.95 – 0.84 (m, 1H), 0.78 – 0.68 (m, 1H), 0.62 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 157.6, 151.7, 150.2, 130.1, 126.6, 120.5, 114.2, 102.9, 102.0, 59.9, 56.0, 55.6, 52.7, 33.4, 23.9, 14.3, 9.9. HRMS (ESI) calcd for $C_{20}H_{24}N_5O_3S$: 414.1600. Obsd: 414.1591. $[\alpha]_D$ -14.2° (*c* 0.983, $CHCl_3$).



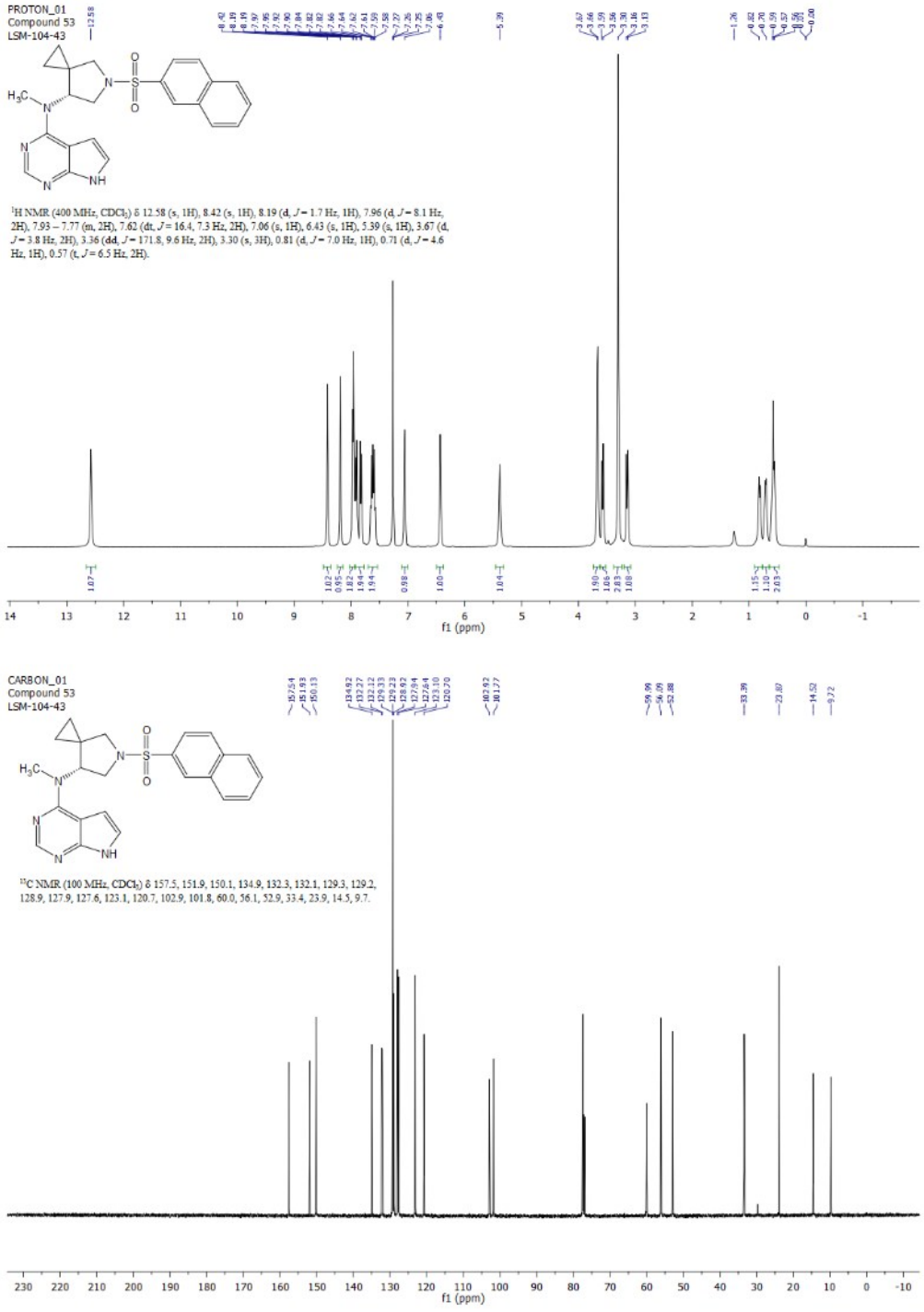
(R)-N-Methyl-N-(5-((4-(trifluoromethyl)phenyl)sulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***53***

97.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1H), 8.23 (s, 1H), 7.90 (dd, *J* = 54.7, 8.2 Hz, 4H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.54 (s, 1H), 5.41 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.65 (dd, *J* = 15.1, 4.8 Hz, 2H), 3.37 (s, 3H), 3.34 (dd, *J* = 191.6, 9.6 Hz, 2H), 0.99 – 0.87 (m, 1H), 0.82 – 0.72 (m, 1H), 0.71 – 0.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.5, 149.9, 139.1, 134.7 (q, *J* = 33.1 Hz), 128.3, 126.3 (q, *J* = 3.6 Hz), 123.2 (q, *J* = 272.9 Hz), 120.7, 103.1, 102.0, 60.2, 56.0, 52.8, 33.5, 23.9, 14.7, 9.7. HRMS (ESI) calcd for $C_{20}H_{21}F_3N_5O_2S$: 452.1368. Obsd: 452.1361. $[\alpha]_D$ -6.8° (*c* 0.970, $CHCl_3$).



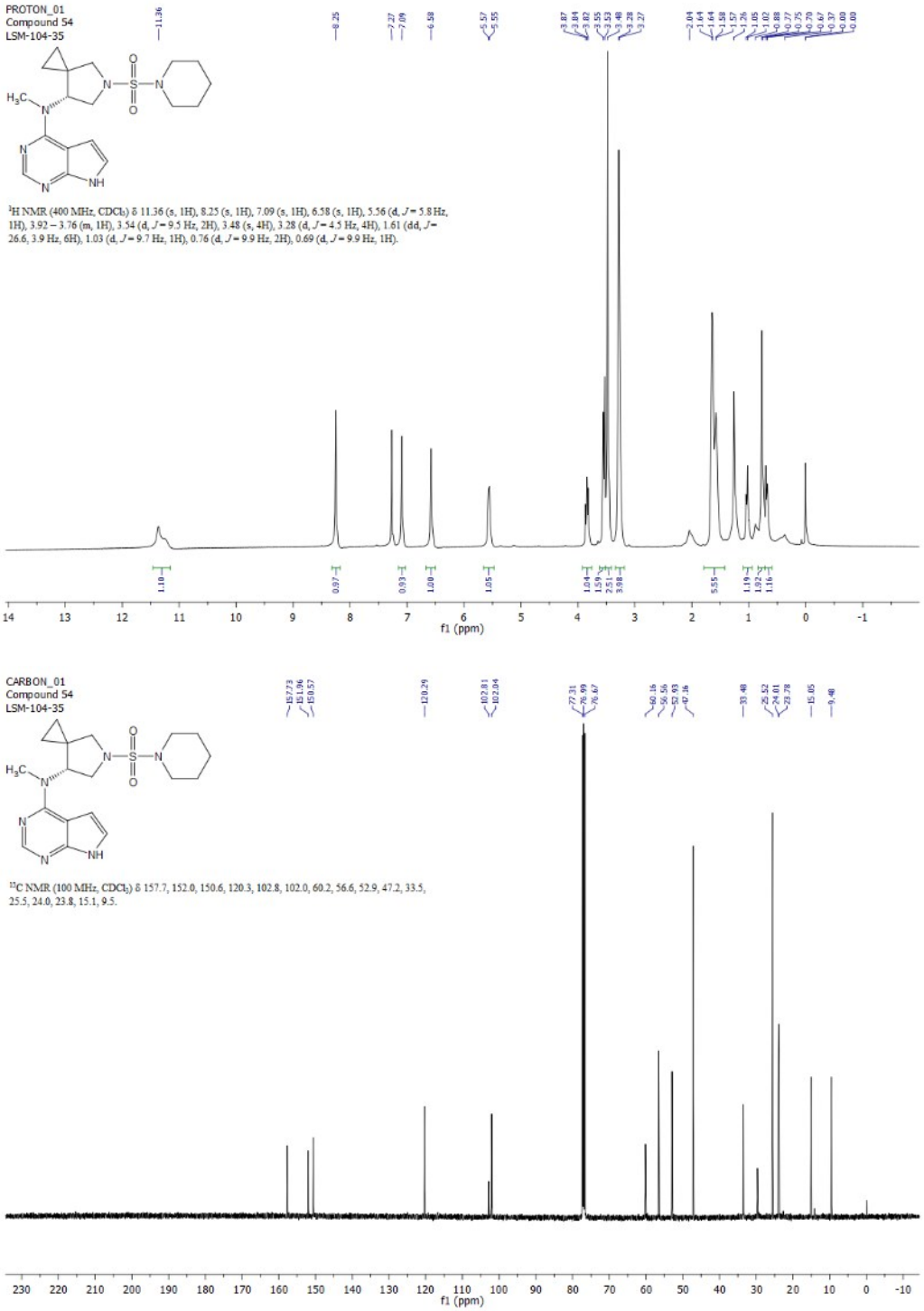
(R)-N-Methyl-N-(5-(naphthalen-2-ylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***54***

98.5% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.42 (s, 1H), 8.19 (d, *J* = 1.7 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.93 – 7.77 (m, 2H), 7.62 (dt, *J* = 16.4, 7.3 Hz, 2H), 7.06 (s, 1H), 6.43 (s, 1H), 5.39 (s, 1H), 3.67 (d, *J* = 3.8 Hz, 2H), 3.36 (dd, *J* = 171.8, 9.6 Hz, 2H), 3.30 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 1H), 0.71 (d, *J* = 4.6 Hz, 1H), 0.57 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 150.1, 134.9, 132.3, 132.1, 129.3, 129.2, 128.9, 127.9, 127.6, 123.1, 120.7, 102.9, 101.8, 60.0, 56.1, 52.9, 33.4, 23.9, 14.5, 9.7. HRMS (ESI) calcd for $C_{23}H_{24}N_5O_2S$: 434.1651. Obsd: 434.1644. $[\alpha]_D$ -17.1° (*c* 4.58, $CHCl_3$).



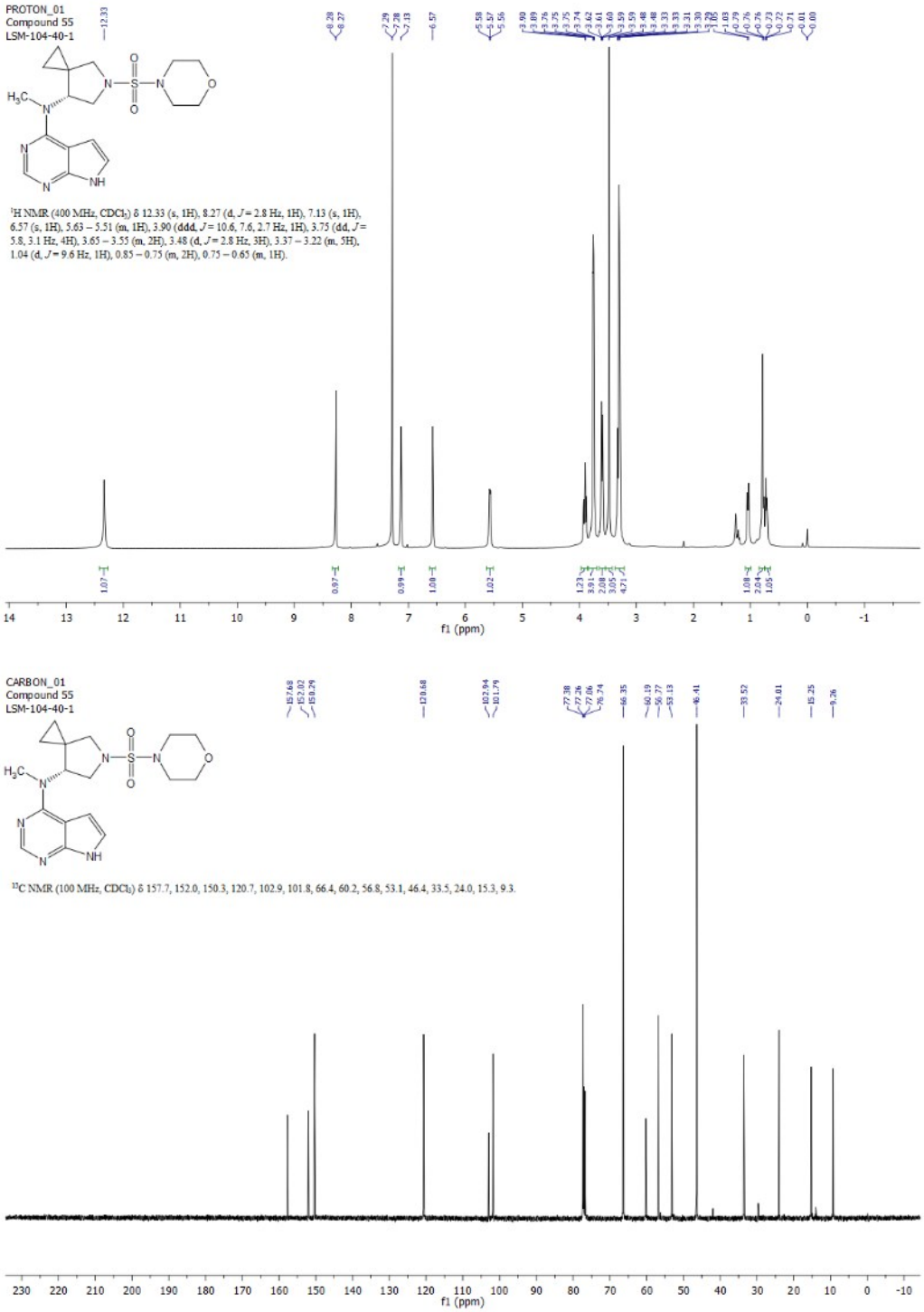
(R)-N-Methyl-N-(5-(piperidin-1-ylsulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***55***

95.4% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (s, 1H), 8.25 (s, 1H), 7.09 (s, 1H), 6.58 (s, 1H), 5.56 (d, *J* = 5.8 Hz, 1H), 3.92 – 3.76 (m, 1H), 3.54 (d, *J* = 9.5 Hz, 2H), 3.48 (s, 4H), 3.28 (d, *J* = 4.5 Hz, 4H), 1.61 (dd, *J* = 26.6, 3.9 Hz, 6H), 1.03 (d, *J* = 9.7 Hz, 1H), 0.76 (d, *J* = 9.9 Hz, 2H), 0.69 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 150.6, 120.3, 102.8, 102.0, 60.2, 56.6, 52.9, 47.2, 33.5, 25.5, 24.0, 23.8, 15.1, 9.5. HRMS (ESI) calcd for $C_{18}H_{27}N_6O_2S$: 391.1916. Obsd: 391.1913. $[\alpha]_D$ +32.7° (*c* 0.297, $CHCl_3$).



(R)-N-Methyl-N-(5-(morpholinosulfonyl)-5-azaspiro[2.4]heptan-7-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine, ***56***

94.6% purity by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 8.27 (d, *J* = 2.8 Hz, 1H), 7.13 (s, 1H), 6.57 (s, 1H), 5.63 – 5.51 (m, 1H), 3.90 (ddd, *J* = 10.6, 7.6, 2.7 Hz, 1H), 3.75 (dd, *J* = 5.8, 3.1 Hz, 4H), 3.65 – 3.55 (m, 2H), 3.48 (d, *J* = 2.8 Hz, 3H), 3.37 – 3.22 (m, 5H), 1.04 (d, *J* = 9.6 Hz, 1H), 0.85 – 0.75 (m, 2H), 0.75 – 0.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.0, 150.3, 120.7, 102.9, 101.8, 66.4, 60.2, 56.8, 53.1, 46.4, 33.5, 24.0, 15.3, 9.3. HRMS (ESI) calcd for $C_{17}H_{25}N_6O_3S$: 393.1709. Obsd: 393.1704. $[\alpha]_D$ +32.9° (*c* 1.57, $CHCl_3$).



The activity percentages for 323 kinases at 10 μM concentration of (R)-6c for kinase profiling assay

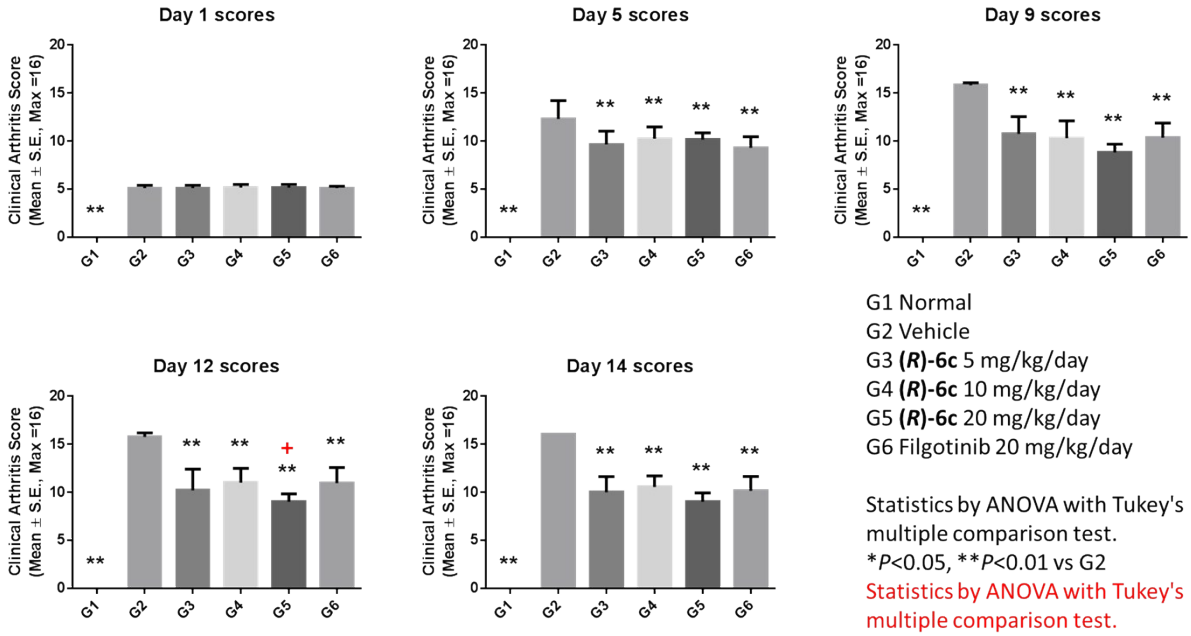
Kinase	Activity%	Kinase	Activity%
Abl(h)	94	CDK9/cyclin T1(h)	78
Abl(m)	94	CHK1(h)	91
Abl (H396P) (h)	93	CHK2(h)	84
Abl (M351T)(h)	90	CHK2(I157T)(h)	86
Abl (Q252H) (h)	92	CHK2(R145W)(h)	105
Abl(T315I)(h)	93	CK1γ1(h)	83
Abl(Y253F)(h)	94	CK1γ2(h)	67
ACK1(h)	44	CK1γ3(h)	66
ALK(h)	106	CK1δ(h)	60
ALK2(h)	102	CK1(y)	58
ALK4(h)	96	CK2(h)	98
ALK6(h)	102	CK2α2(h)	88
Arg(h)	81	CLK1(h)	55
AMPKα1(h)	87	CLK2(h)	52
AMPKα2(h)	62	CLK3(h)	96
Arg(m)	105	CLK4(h)	51
ARK5(h)	58	cKit(h)	98
ASK1(h)	99	cKit(D816V)(h)	102
Aurora-A(h)	58	cKit(D816H)(h)	97
Aurora-B(h)	93	cKit(V560G)(h)	87
Aurora-C(h)	80	cKit(V654A)(h)	79
Axl(h)	82	CSK(h)	118
Blk(h)	85	c-RAF(h)	88
Blk(m)	104	cSRC(h)	91
Bmx(h)	64	DAPK1(h)	94
BRK(h)	91	DAPK2(h)	79
BrSK1(h)	82	DCAMKL2(h)	75
BrSK2(h)	71	DDR1(h)	70
BTK(h)	113	DDR2(h)	96
BTK(R28H)(h)	87	DMPK(h)	92
B-Raf(h)	85	DRAK1(h)	87
B-Raf(V599E)(h)	85	DYRK2(h)	89
CaMKI(h)	78	eEF-2K(h)	98
CaMKIIβ(h)	87	EGFR(h)	95
CaMKIIγ(h)	47	EGFR(L858R)(h)	107
CaMKIδ(h)	58	EGFR(L861Q)(h)	102
CaMKIIδ(h)	70	EGFR(T790M)(h)	93
CaMKIV(h)	101	EGFR(T790M,L858R)(h)	93
CaMKK2(h)	79	EphA1(h)	87
CDK1/cyclinB(h)	103	EphA2(h)	73
CDK2/cyclinA(h)	75	EphA3(h)	84
CDK2/cyclinE(h)	99	EphA4(h)	104
CDK3/cyclinE(h)	69	EphA5(h)	88
CDK5/p25(h)	84	EphA7(h)	93
CDK5/p35(h)	83	EphA8(h)	76
CDK6/cyclinD3(h)	81	EphB2(h)	82
CDK7/cyclinH/MAT1(h)	100	EphB1(h)	79
EphB3(h)	107	JNK1α1(h)	92
EphB4(h)	65	JNK2α2(h)	93
ErbB2(h)	94	JNK3(h)	64

Kinase	Activity%	Kinase	Activity%
ErbB4(h)	95	KDR(h)	96
FAK(h)	81	Lck(h)	79
Fer(h)	103	Lck(h) activated	72
Fes(h)	65	LIMK1(h)	34
FGFR1(h)	86	LKB1(h)	87
FGFR1(V561M)(h)	45	LOK(h)	94
FGFR2(h)	93	Lyn(h)	92
FGFR2(N549H)(h)	76	Lyn(m)	103
FGFR3(h)	75	LRRK2(h)	57
FGFR4(h)	84	MAPK1(h)	91
Fgr(h)	85	MAPK2(h)	84
Flt1(h)	94	MAPK2(m)	101
Flt3(D835Y)(h)	141	MAPKAP-K2(h)	90
Flt3(h)	86	MAPKAP-K3(h)	101
Flt4(h)	37	MEK1(h)	109
Fms(h)	78	MARK1(h)	56
Fms(Y969C)(h)	94	MELK(h)	76
Fyn(h)	108	Mer(h)	102
GCK(h)	51	Met(h)	98
GCN2(h)	93	Met(D1246H)(h)	87
GRK1(h)	79	Met(D1246N)(h)	77
GRK5(h)	99	Met(M1268T)(h)	95
GRK6(h)	74	Met(Y1248C)(h)	99
GRK7(h)	87	Met(Y1248D)(h)	88
GSK3α(h)	67	Met(Y1248H)(h)	94
GSK3β(h)	73	MINK(h)	96
Haspin(h)	117	MKK4(m)	97
Hck(h)	67	MKK6(h)	82
Hck(h) activated	83	MKK7β(h)	100
HIPK1(h)	94	MLCK(h)	97
HIPK2(h)	82	MLK1(h)	76
HIPK3(h)	100	Mnk2(h)	106
IGF-1R(h)	100	MRCKα(h)	93
IGF-1R(h), activated	79	MRCKβ(h)	76
IKKα(h)	109	MSK1(h)	75
IKKβ(h)	72	MSK2(h)	59
IKKε(h)	84	MSSK1(h)	103
IR(h)	84	MST1(h)	95
IR(h), activated	88	MST2(h)	75
IRE1(h)	84	MST3(h)	91
IRR(h)	95	MST4(h)	81
IRAK1(h)	104	mTOR(h)	96
IRAK4(h)	68	mTOR/FKBP12(h)	75
Itk(h)	108	MuSK(h)	107
JAK1(h)	1	NEK2(h)	101
JAK2(h)	8	NEK3(h)	77
JAK3(h)	5	NEK6(h)	83
NEK7(h)	77	RIPK2(h)	105
NEK9(h)	62	ROCK-I(h)	95
NEK11(h)	102	ROCK-II(h)	16

Kinase	Activity%	Kinase	Activity%
NLK(h)	114	ROCK-II(r)	15
p70S6K(h)	49	Ron(h)	95
PAK1(h)	104	Ros(h)	115
PAK2(h)	91	Rse(h)	107
PAK4(h)	86	Rsk1(h)	80
PAK5(h)	76	Rsk1(r)	101
PAK6(h)	70	Rsk2(h)	85
PAR-1Bα(h)	54	Rsk3(h)	63
PASK(h)	104	Rsk4(h)	85
PEK(h)	98	SAPK2a(h)	81
PDGFRα(h)	104	SAPK2a(T106M)(h)	104
PDGFRα(D842V)(h)	84	SAPK2b(h)	95
PDGFRα(V561D)(h)	88	SAPK3(h)	45
PDGFRβ(h)	145	SAPK4(h)	59
PDK1(h)	84	SGK(h)	92
PhKγ2(h)	108	SGK2(h)	65
Pim-1(h)	103	SGK3(h)	69
Pim-2(h)	98	SIK(h)	85
Pim-3(h)	97	Snk(h)	96
PKA(h)	75	SNRK(h)	99
PKBα(h)	85	Src(1-530)(h)	84
PKBβ(h)	76	Src(T341M)(h)	77
PKBγ(h)	78	SRPK1(h)	78
PKCα(h)	90	SRPK2(h)	95
PKCβI(h)	63	STK25(h)	81
PKCβII(h)	102	STK33(h)	88
PKCγ(h)	65	Syk(h)	109
PKCδ(h)	34	TAK1(h)	86
PKCε(h)	80	TAO1(h)	69
PKCη(h)	78	TAO2(h)	66
PKCι(h)	95	TAO3(h)	75
PKCμ(h)	87	TBK1(h)	90
PKCθ(h)	77	Tec(h) activated	85
PKCζ(h)	69	TGFBR1(h)	104
PKD2(h)	91	Tie2 (h)	104
PKG1α(h)	77	Tie2(R849W)(h)	91
PKG1β(h)	73	Tie2(Y897S)(h)	97
Plk1(h)	93	TLK1(h)	85
Plk3(h)	115	TLK2(h)	94
PRAK(h)	69	TrkA(h)	44
PRK2(h)	79	TrkB(h)	79
PrKX(h)	93	TrkC(h)	75
PTK5(h)	74	TSSK1(h)	66
Pyk2(h)	83	TSSK2(h)	91
Ret(h)	96	Txk(h)	84
Ret (V804L)(h)	89	TYK2(h)	3
Ret(V804M)(h)	83	ULK2(h)	91
ULK3(h)	69	PI3 Kinase (p110β/p85β)(m)	86
Wee1(h)	95	PI3 Kinase (p110β/p85α)(m)	101
WNK2(h)	85	PI3 Kinase (p110δ/p85α)(m)	91

Kinase	Activity%	Kinase	Activity%
WNK3(h)	64	PI3 Kinase (p110α(E542K)/p85α)(m)	99
VRK2(h)	69	PI3 Kinase (p110α/p85α)(h)	98
Yes(h)	81	PI3 Kinase (p110α(E542K)/p85α)(h)	85
ZAP-70(h)	129	PI3 Kinase (p110α(H1047R)/p85α)(h)	93
ZIPK(h)	80	PI3 Kinase (p110α(E545K)/p85α)(h)	105
PI3 Kinase (p110β/p85α)(h)	98	PI3 Kinase (p110α/p65α)(h)	88
PI3 Kinase (p120γ)(h)	94	PI3KC2α(h)	105
PI3 Kinase (p110δ/p85α)(h)	93	PI3KC2γ(h)	75
PI3 Kinase (p110α/p85α)(m)	100	PIP4K2α(h)	91
PI3 Kinase (p110α/p65α)(m)	102	PIP5K1α(h)	83
PI3 Kinase (p110α(E545K)/p85α)(m)	105	PIP5K1γ(h)	96
PI3 Kinase (p110α(H1047R)/p85α)(m)	108		

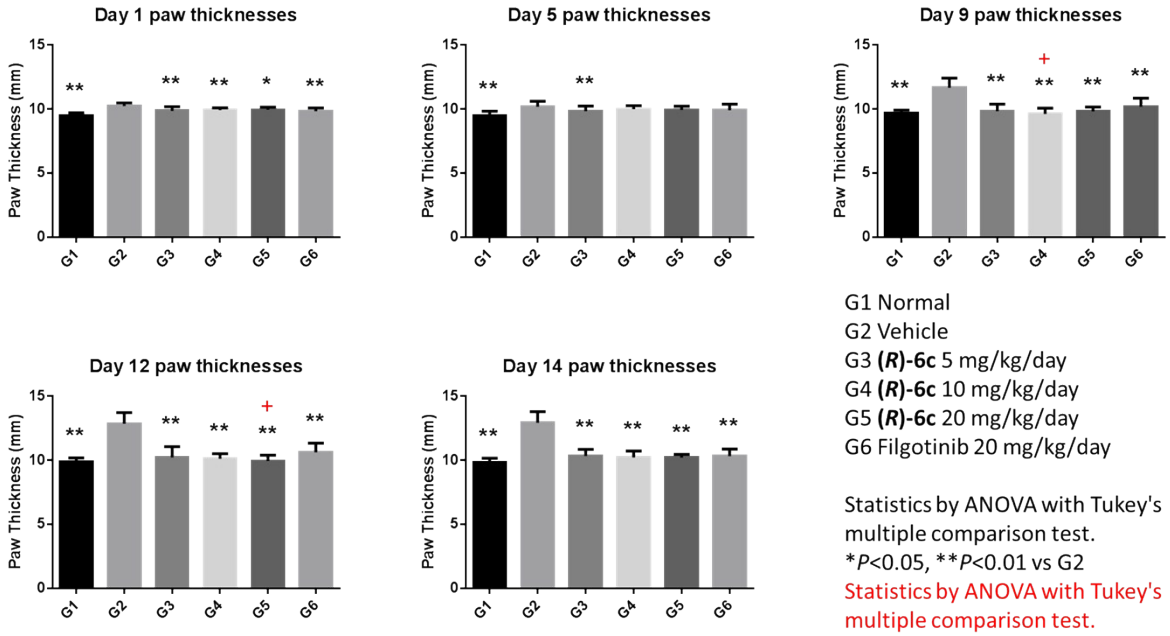
Clinical arthritis scores of (R)-6c in rat adjuvant induced arthritis (AIA) model



G1 Normal
G2 Vehicle
G3 **(*R*)-6c** 5 mg/kg/day
G4 **(*R*)-6c** 10 mg/kg/day
G5 **(*R*)-6c** 20 mg/kg/day
G6 Filgotinib 20 mg/kg/day

Statistics by ANOVA with Tukey's multiple comparison test.
**P*<0.05, ***P*<0.01 vs G2
Statistics by ANOVA with Tukey's multiple comparison test.
\+ *P*<0.05 vs G6

Paw thicknesses of (R)-6c in rat adjuvant induced arthritis (AIA) model



G1 Normal
G2 Vehicle
G3 **(*R*)-6c** 5 mg/kg/day
G4 **(*R*)-6c** 10 mg/kg/day
G5 **(*R*)-6c** 20 mg/kg/day
G6 Filgotinib 20 mg/kg/day

Statistics by ANOVA with Tukey's multiple comparison test.
**P*<0.05, ***P*<0.01 vs G2
Statistics by ANOVA with Tukey's multiple comparison test.
\+ *P*<0.05 vs G6