Supporting Information

Design, synthesis and pharmacological evaluation of 3*H*-spiro[benzofuran-2,4'-piperidine] IRAK4 inhibitors for the treatment of diffuse large B-cell lymphoma

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Table of Contents

Synthesis of intermediates **A1**–**A9**, **B1**, **C1**, **E5**, **F3**, **F4**, **G1**, **G2**, **H4**, and **I1**. 2

^{1}H NMR spectra for intermediates. 12

^{1}H NMR, ^{13}C NMR, and HRMS spectra for target compounds **1**–**21** and DW18134. 25

HPLC determination of target compounds **1**–**21** and DW18134. 47

The binding models of compounds **3**–**7** with IRAK4. 70

References. 70

Synthesis of intermediates A1–A9, B1, C1, E5, F3, F4, G1, G2, H4, and I1.

General procedure for the preparation of A1–A6.

Synthesis of intermediate **A1**

Step A: a mixture of ethyl 2-chlorooxazole-4-carboxylate (**A10**) (100 mg, 0.57 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy) methyl)-1*H*-pyrazole (221 mg, 0.68 mmol), $Pd(dppf)_2Cl_2$ (83 mg, 0.11 mmol), and sodium carbonate (181 mg, 1.71 mmol) in 1,2-dimethoxyethane/water (4.0 mL/0.4 mL) was heated to 80 ºC under an argon atmosphere for 6 hours. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 25% petroleum ether in ethyl acetate to afford **A11** as a white solid (181 mg, 94%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.19 – 8.18 (m, 2H), 8.08 (s, 1H), 5.47 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.59 (t, *J* = 8.0 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 2H), -0.02 (s, 9H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{15}H_{24}N_3O_4Si$: 338.2, found: 338.1.

Step B: a mixture of **A11** (160 mg, 0.47 mmol) and sodium hydroxide (56 mg, 1.40 mmol) in tetrahydrofuran/methanol/water (1 mL/4 mL/2 mL) was stirred at room temperature for 30 minutes. The solvent was removed in vacuo. The residue was adjusted pH to 4 with 1 M hydrochloric acid upon which precipitate formed. The precipitate was filtered off and dried to afford **A1** as a white solid (107 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (brs, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 8.07 (s, 1H), 5.48 (s, 2H), 3.58 (t, *J* = 8.0 Hz, 2H), 0.85 (t, *J* = 8.0 Hz, 2H), -0.05 (s, 9H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}N_3O_4Si$: 310.1, found: 310.3.

Synthesis of intermediate **A2**

Intermediate **A2** was prepared from ethyl 2-chlorooxazole-4-carboxylate (**A10**) and 2-(difluoromethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine according to the general procedure for the preparation of **A1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (brs, 1H), 9.02 (s, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 7.82 (d, *J* = 5.0 Hz, 1H), 7.78 (t, *J* = 72.0 Hz, 1H), 7.55 (s, 1H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{10}H_7F_2N_2O_4$: 257.0, found: 257.0.

Synthesis of intermediate **A3**

Intermediate **A3** was prepared from ethyl 2-chlorooxazole-4-carboxylate (**A10**) and (3-sulfamoylphenyl)boronic acid according to the general procedure for the preparation of **A1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.51 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.76 (t, J = 7.9 Hz, 1H), 7.61 (s, 2H).

Synthesis of intermediate **A4**

Intermediate **A4** was prepared from ethyl 2-chlorooxazole-4-carboxylate (**A10**) and *tert*-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)(2,2,2-trifluoroethyl)carbamate according to the general procedure for the preparation of **A1**. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.51 (d, J = 5.1 Hz, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 7.78 (d, J = 5.1 Hz, 1H), 4.88–4.79 (m, 2H), 1.55 (s, 9H).

Synthesis of intermediate **A5**

Intermediate **A5** was prepared from ethyl 2-chlorooxazole-4-carboxylate (**A10**) and (6-(benzyloxy)pyridin-3-yl)boronic acid according to the general procedure for the preparation of **A1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (brs, 1H), 8.84 (s, 1H), 8.81 (s, 1H), 8.27 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.43 – 7.30 (m, 3H), 7.07 (d, J = 8.7 Hz, 1H), 5.44 (s, 2H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}N_2O_4$: 297.1, found: 297.0.

Synthesis of intermediate **A6**

Intermediate **A6** was prepared from ethyl 2-chlorooxazole-4-carboxylate (**A10**) and *tert*-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate according to the general procedure for the preparation of **A1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 10.16 (s, 1H), 8.96 (s, 1H), 8.56–8.26 (m, 2H), 7.55 (d, J = 5.1 Hz, 1H), 1.50 (s, 9H).

Synthesis of intermediate **A7**

Step A: a mixture of ethyl oxazole-4-carboxylate (**A17**) (230 mg, 1.63 mmol),

4-bromo-2-(difluoromethyl)pyridine (407 mg, 1.95 mmol), $Pd(OAc)_2$ (37 mg, 0.16 mmol), tri-*o*-tolylphosphine (98 mg, 0.32 mmol), and cesium carbonate (98 mg, 0.32 mmol) in DMF (8.0 mL) was heated to 70 °C under an argon atmosphere for 4 hours. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 14% petroleum ether in ethyl acetate to afford **A19** as a white solid (305 mg, 70%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.81 (d, *J* = 4.4 Hz, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.08 (d, *J* = 4.4 Hz, 1H), 6.70 (t, *J* = 55.2 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}F_2N_2O_3$: 269.1, found: 269.0.

Step B: intermediate **A7** was prepared from **A19** according to the procedure for the preparation of **A1** (76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.40 (brs, 1H), 9.03 (s, 1H), 8.91 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 8.11 (d, *J* = 5.1 Hz, 1H), 7.10 (t, *J* = 54.6 Hz, 1H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{10}H_7F_2N_2O_3$: 241.0, found: 241.1.

Synthesis of intermediate **A8**

Step A: a mixture of *tert*-butyl 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (211 mg, 0.71 mmol), ethyl oxazole-4-carboxylate (**A17**) (200 mg, 1.42 mmol), $Pd(OAc)_2$ (16 mg, 0.07 mmol), tri-*o*-tolylphosphine (43 mg, 0.14 mmol), and cesium carbonate (462 mg, 1.42 mmol) in diethyl carbonate (6.0 mL) was heated to 110 °C under an argon atmosphere for 20 hours. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 15% ethyl acetate in petroleum ether to afford crude **A21** as a yellow solid (65 mg). ESI-LRMS m/z $[M+H]^+$ calcd for $C_{18}H_{20}N_3O_5$: 358.1, found: 358.2.

Step B: a mixture of **A21** (60 mg, 0.168 mmol), lithium hydroxide monohydrate (22 mg, 0.524 mmol) in tetrahydrofuran/methanol/water (3.0 mL/1.5 mL/0.7 mL) was stirred at room temperature for 1 hour. The solvent was removed in vacuo. The residue was added water (5 mL) and cooled in an ice bath. Then the mixture was adjusted pH to 5 with 1 M hydrochloric acid upon which precipitate formed. The precipitate was filtered off and dried to afford crude **A8** as a yellow solid (20 mg). ^{1}H

NMR (400 MHz, methanol-d_4) δ 8.41 (s, 1H), 8.30 (d, J = 5.1 Hz, 1H), 7.78 (d, J = 5.0 Hz, 1H), 7.54 (d, J = 3.4 Hz, 1H), 7.29 (d, J = 3.0 Hz, 1H).

Synthesis of intermediate **A9**

Step A: a mixture of ethyl oxazole-4-carboxylate (**A17**) (4.1 g, 29.1 mmol), 4-bromopyridin-2-amine (2.5 g, 14.4 mmol), $Pd(OAc)_2$ (338 mg, 1.5 mmol), [1,1'-biphenyl]-2-yldicyclohexylphosphane (1.0 g, 2.9 mmol), and cesium carbonate (9.4 g, 28.9 mmol) in diethyl carbonate (51 mL) was heated to 110 °C under an argon atmosphere for 20 hours. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 20% petroleum ether in ethyl acetate to afford **A23** as a yellow solid (452 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.05 (s, 1H), 6.99 (d, J = 5.3 Hz, 1H), 6.32 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{11}H_{12}N_3O_3$: 234.1, found: 234.1.

Step B: a mixture of **A23** (919 mg, 3.9 mmol) and lithium hydroxide monohydrate (500 mg, 11.9 mmol) in tetrahydrofuran/methanol/water (14.0 mL/7.0 mL/3.5 mL) was stirred at room temperature for 1 hour. The solvent was removed in vacuo. The residue was added water (10 mL) and adjusted pH to 5 with 1 M hydrochloric acid upon which precipitate formed. The precipitate was filtered off and dried to afford **A9** as a yellow solid (769 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 8.88 (s, 1H), 8.07 (d, J = 5.2 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 5.2 Hz, 1H), 6.32 (s, 2H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_9H_8N_3O_3$: 206.1, found: 206.0.

Synthesis of intermediate **B1**

Step A: intermediate **B3**–**B6** was synthesized according to our previously reported procedure.[1]

Step B: a mixture of **B6** (3.7 g, 16.3 mmol), pyridin-4-ylboronic acid (4.0 g, 32.6 mmol), cesium carbonate (10.6 g, 32.6 mmol), and $Pd(dppf)_2Cl_2$ (1.2 g, 1.6 mmol) in 1,4-dioxane/water (90 mL/9 mL) was heated to 100 °C under an argon atmosphere for 16 hours. The mixture was cooled to room temperature and concentrated. The residue

was purified by silica gel chromatography eluting with 33% ethyl acetate in petroleum ether to afford **B7** as a yellow solid (4.1 g, 94%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.63 (dd, *J* = 4.5, 1.8 Hz, 2H), 7.92 (s, 1H), 7.19 (dd, *J* = 4.5, 1.8 Hz, 2H), 6.60 (s, 1H), 3.12 (s, 2H), 1.54 (s, 6H).

Step C: **B7** (6.5 g, 24.1 mmol) was dissolved in ethanol (163 mL) followed by the addition of iron powder (33.0 g, 590.9 mmol), ammonium chloride (31.1 g, 581.3 mmol), and water (54 mL). The mixture was heated to 50 °C under an argon atmosphere for 3 hours and then filtered through Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel eluting with 70% ethyl acetate in petroleum ether to afford **B1** as a yellow solid (4.7 g, 82%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.64 (d, *J* = 6.0 Hz, 2H), 7.40 (d, *J* = 6.0 Hz, 2H), 6.64 (s, 1H), 6.53 (s, 1H), 2.98 (s, 2H), 1.47 (s, 6H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1, found: 241.1.

Synthesis of intermediate **C1**

Step A: to a solution of magnesium (6.9 g, 284.0 mmol) and iodine (650 mg, 2.5 mmol) in diethyl ether (150 mL) at reflux was slowly added 1-(bromomethyl)-4-chloro-2-fluorobenzene (**C2**) (25.0 g, 112 mmol), and the resulting mixture was stirred for 30 minutes. This solution was then added to *tert*-butyl 4-oxopiperidine-1-carboxylate (18.8 g, 94 mmol) in diethyl ether (400 mL) at -78 °C prior to warming to room temperature for 2 hours. A saturated aqueous solution of ammonium chloride (800 mL) and ethyl acetate (800 mL) were added, and the organic phase was separated. The organic phase was concentrated and the residue was purified by silica gel chromatography with 15% ethyl acetate in petroleum ether to afford crude **C3** (22.3 g) as a white solid. ESI-LRMS m/z $[M+Na]^+$ calcd for $C_{17}H_{24}ClFNNaO_3$: 366.1, found: 366.1.

Step B: a mixture of crude **C3** (22.3 g) and potassium *tert*-butanolate (18.3 g, 163 mmol) in THF (131 mL) was stirred at 65 °C for 3 hours. A saturated aqueous solution of ammonium chloride (500 mL) was added, and the mixture was extracted with ethyl acetate (500 mL X 3). The organic phase was isolated and concentrated.

The residue was purified by silica gel chromatography with 10% ethyl acetate in petroleum ether to afford **C4** (15.4 g, 50% yield for two steps) as a white solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.03 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.75 (s, 1H), 3.88 – 3.64 (m, 2H), 3.52 – 3.31 (m, 2H), 2.94 (s, 2H), 1.95 – 1.84 (m, 2H), 1.73 – 1.64 (m, 2H), 1.47 (s, 9H).

Step C: a mixture of **C4** (2.55 g, 7.9 mmol) in dichloromethane (40 mL) and trifluoroacetic acid (8 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated under reduced pressure, and the resulting residue was slurried with diethyl ether (30 mL) for 10 minutes. The The solid was collected by filtration and dried in vacuo to afford **C5** as a white solid (2.20 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.88 – 6.83 (m, 2H), 3.23 – 3.08 (m, 4H), 3.05 (s, 2H), 2.02 – 1.84 (m, 4H).

Step D: a mixture of **C5** (50 mg, 0.15 mmol), trifluoroacetic anhydride (90 μL, 0.65 mmol), and DIPEA (110 μL, 0.64 mmol) in dichloromethane (2 mL) was stirred at room temperature for 3 hours. Then the mixture was diluted with dichloromethane, washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford **C6** as a yellow solid (42 mg, 87%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.06 (d, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 4.39 – 4.30 (m, 1H), 3.92 – 3.83 (m, 1H), 3.70 – 3.59 (m, 1H), 3.41 – 3.31 (m, 1H), 2.98 (s, 2H), 2.09 – 2.00 (m, 2H), 1.83 – 1.72 (m, 2H).

Step E: To a solution of **C6** (100 mg, 0.31 mmol) in dichloromethane (4.0 mL) was slowly added fuming nitric acid (1.9 mL). The mixture was stirred at room temperature for 10 hours. Then water (10 mL) was added and the mixture was extracted with dichloromethane (10 mL X 3). The organic phase was washed with brine and concentrated. The residue was purified by silica gel chromatography with 25% ethyl acetate in petroleum ether to afford **C7** (68 mg, 60%) as a yellow oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86 (s, 1H), 6.92 (s, 1H), 4.43 – 4.35 (m, 1H), 3.96 – 3.87 (m, 1H), 3.69 – 3.58 (m, 1H), 3.40 – 3.30 (m, 1H), 3.08 (s, 2H), 2.13 – 2.04 (m, 2H), 1.89 – 1.78 (m, 2H).

Step F: a mixture of **C7** (34 mg, 0.09 mmol) and potassium carbonate (48 mg,

0.35 mmol) in methanol/water (2 mL/0.7 mL) was stirred at room temperature for 40 minutes. Then the mixture was diluted with dichloromethane, washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford **C8** as a yellow oil (24 mg, 99%). ESI-LRMS m/z $[M+H]^+$ calcd for $C_{12}H_{14}ClN_2O_3$: 269.1, found: 269.1.

Step G: a mixture of **C8** (716 mg, 2.66 mmol) and di-*tert*-butyl dicarbonate (700 mg, 3.20 mmol) in 1,4-dioxane (8 mL) was stirred at room temperature for 2 hours. The solvent was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography eluting with 25% ethyl acetate in petroleum ether to afford **C9** as a yellow solid (563 mg, 57%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (s, 1H), 6.87 (s, 1H), 3.84 – 3.71 (m, 2H), 3.41 – 3.30 (m, 2H), 3.03 (s, 2H), 1.95 – 1.88 (m, 2H), 1.78 – 1.70 (m, 2H), 1.46 (s, 9H).

Step H: a mixture of **C9** (405 mg, 1.10 mmol), pyridin-4-ylboronic acid (540 mg, 4.39 mmol), cesium carbonate (716 mg, 2.20 mmol), and $Pd(dppf)_2Cl_2$ (80 mg, 0.11 mmol) in 1,4-dioxane/water (20 mL/2 mL) was heated to 100 °C under an argon atmosphere overnight. The mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with ethyl acetate, washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 30% ethyl acetate in petroleum ether to afford **C1** as a yellow solid (291 mg, 76%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.65 (d, *J* = 5.8 Hz, 2H), 7.94 (s, 1H), 7.19 (d, *J* = 5.8 Hz, 2H), 6.67 (s, 1H), 3.88 – 3.74 (m, 2H), 3.43 – 3.34 (m, 2H), 3.11 (s, 2H), 2.00 – 1.92 (m, 2H), 1.83 – 1.72 (m, 2H), 1.48 (s, 9H).

Synthesis of intermediate **E5**

Step A: a mixture of **E1** (224 mg, 0.97 mmol) and diethylaminosulfur trifluoride (321 μL, 2.43 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by chromatography on

silica gel eluting with petroleum ether to afford **E2** as a colorless oil (180 mg, 73%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.61 (t, *J* = 8.1 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.23 – 7.19 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

Step B: to a stirred solution of **E2** (180 mg, 0.71 mmol) in dry THF (5 mL) was added methyl magnesium bromide (3M in ethyl ether, 0.72 mL) dropwise at –75 °C and the mixture was stirred for additional 10 minutes. Then the mixture was warmed and stirred at room temperature for 2 hours. The reaction was quenched with saturated ammonium chloride solution, extracted with ethyl acetate and washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford **E3** as a colorless oil (163 mg, 96%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 (t, *J* = 8.1 Hz, 1H), 7.23–7.13 (m, 2H), 2.01 (s, 1H), 1.33 (q, *J* = 1.3 Hz, 6H).

Step C: a mixture of **E3** (162 mg, 0.70 mmol) and potassium *tert*-butoxide (191 mg, 1.70 mmol) in dry THF (8 mL) was heated to reflux for 2.5 hours. The mixture was concentrated, diluted with ethyl acetate, and washed with brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford **E4** as a yellow oil (128 mg, 84%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 (dt, *J* = 8.1, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.86 (q, *J* = 1.7 Hz, 1H), 1.49 (t, *J* = 2.0 Hz, 6H).

Step D: to a stirred solution of **E4** (64 mg, 0.29 mmol) in dichloromethane (3 mL) was slowly added fuming nitric acid (0.2 mL) at room temperature and stirred for 30 minutes. Then the mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by prep-TLC (5% ethyl acetate in petroleum ether) to afford **E5** as a yellow oil (18 mg, 23%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.17 (t, *J* = 1.5 Hz, 1H), 7.03 (t, *J* = 1.5 Hz, 1H), 1.54 (t, *J* = 2.1 Hz, 6H).

Synthesis of intermediate **F3** and **F4**

Step A: a mixture of **C1** (282 mg, 0.685 mmol) in dichloromethane (3 mL) and trifluoroacetic acid (1 mL) was stirred at room temperature for 1 hour. The solvents

were removed under reduced pressure to yield a residue, which was dissolved in methanol (1 mL). The solution was neutralized with ammonium hydroxide, and the resulting mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were concentrated to afford **F3** as a yellow solid (149 mg, 70%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.65 (d, *J* = 5.0 Hz, 2H), 7.94 (s, 1H), 7.19 (d, *J* = 5.0 Hz, 2H), 6.67 (s, 1H), 3.25 – 3.00 (m, 6H), 2.08 – 1.93 (m, 4H).

Step B: To a solution of **F3** (47 mg, 0.15 mmol) in methanol (3 mL) was added formaldehyde (37 wt % in water, 116 μL) at room temperature. The reaction solution was stirred for 1 h at room temperature. Sodium borohydride (115 mg, 3.02 mmol) was added slowly, and the reaction was stirred for 1 hour at room temperature. Saturated ammonium chloride solution (60 μL) was added, and the mixture was concentrated. The residue was purified by chromatography on silica gel eluting with 12% methanol in dichloromethane to afford **F4** (30 mg, 61%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.57 (d, *J* = 4.7 Hz, 2H), 8.03 (s, 1H), 7.36 (d, *J* = 4.7 Hz, 2H), 6.78 (s, 1H), 3.22 (s, 2H), 2.84 – 2.70 (m, 4H), 2.45 (s, 3H), 2.13 – 2.04 (m, 2H), 2.02 – 1.95 (m, 2H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}N_3O_3$: 326.2, found: 326.2.

General procedure for the preparation of G1 and G2

Synthesis of intermediate **G1**

A mixture of **C8** (4.45 g, 16.56 mmol), 2,2-difluoroethyl trifluoromethanesulfonate (7.10 g, 33.12 mmol), and DIPEA (11.54 mL, 66.24 mmol) in THF (100 mL) was stirred at room temperature for 2.5 hours. The solvent was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography eluting with 25% ethyl acetate in petroleum ether to afford **G1** as a yellow oil (2.84 g, 52%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (s, 1H), 6.87 (s, 1H), 5.89 (tt, *J* = 56.0, 4.3 Hz, 1H), 3.02 (s, 2H), 2.80 (td, *J* = 15.0, 4.3 Hz, 2H), 2.76 – 2.67 (m, 4H), 2.03 – 1.94 (m, 2H), 1.91 – 1.82 (m, 2H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}ClF_2N_2O_3$: 333.1, found: 333.1.

Synthesis of intermediate **G2**

Intermediate **G2** was prepared from **C8** and 2,2,2-trifluoroethyl trifluoromethanesulfonate according to the general procedure for the preparation of **G1**. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (s, 1H), 6.87 (s, 1H), 3.08 – 2.96 (m, 4H), 2.90 – 2.75 (m, 4H), 2.05 – 1.94 (m, 2H), 1.91 – 1.84 (m, 2H).

Synthesis of intermediate **H4**

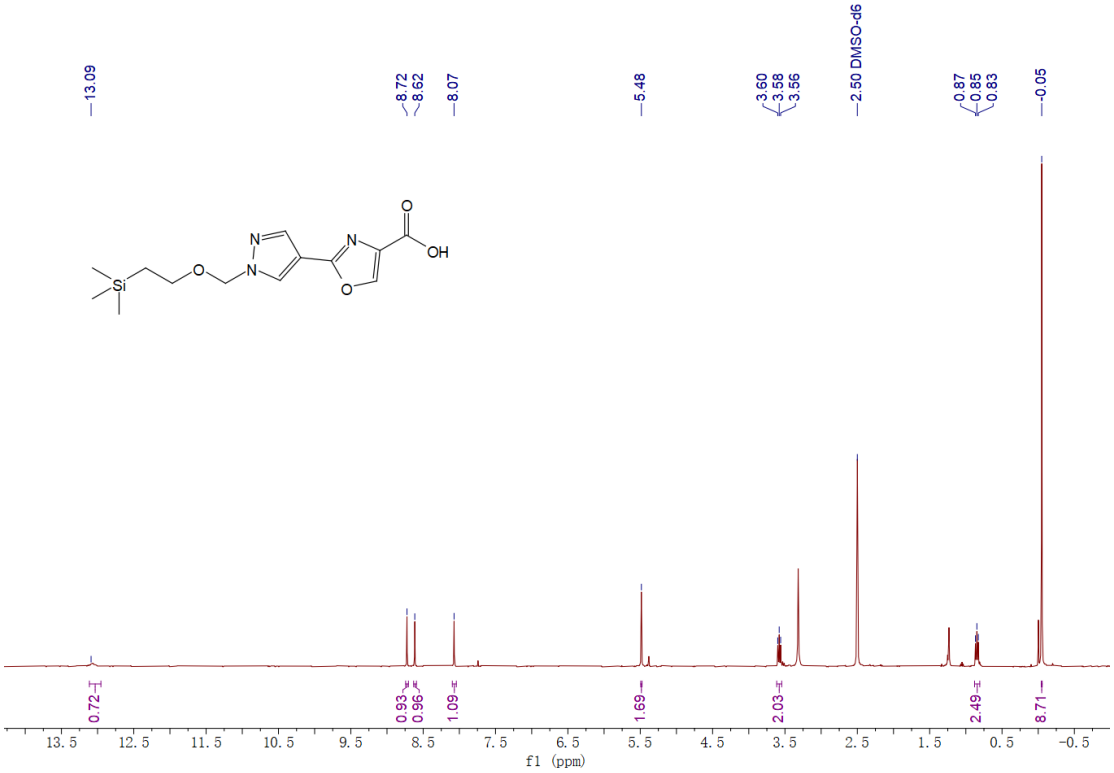
A mixture of **F3** (158 mg, 0.51 mmol), 2-bromothiazole (167 mg, 1.02 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), *rac*-BINAP (62 mg, 0.10 mmol), and cesium carbonate (664 mg, 2.04 mmol) in 1,4-dioxane (3.5 mL) was heated to 80 °C under an argon atmosphere for 20 hours. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 40% petroleum ether in ethyl acetate to afford **H4** as a yellow solid (62 mg, 31%). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.57 (d, J = 6.2 Hz, 2H), 8.04 (s, 1H), 7.37 (d, J = 6.2 Hz, 2H), 7.15 (d, J = 3.7 Hz, 1H), 6.81 (s, 1H), 6.75 (d, J = 3.7 Hz, 1H), 3.82 – 3.72 (m, 2H), 3.65 – 3.55 (m, 2H), 3.25 (s, 2H), 2.13 – 1.96 (m, 4H). ESI-LRMS *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}N_4O_3S$: 395.1, found: 395.0.

Synthesis of intermediate **I1**

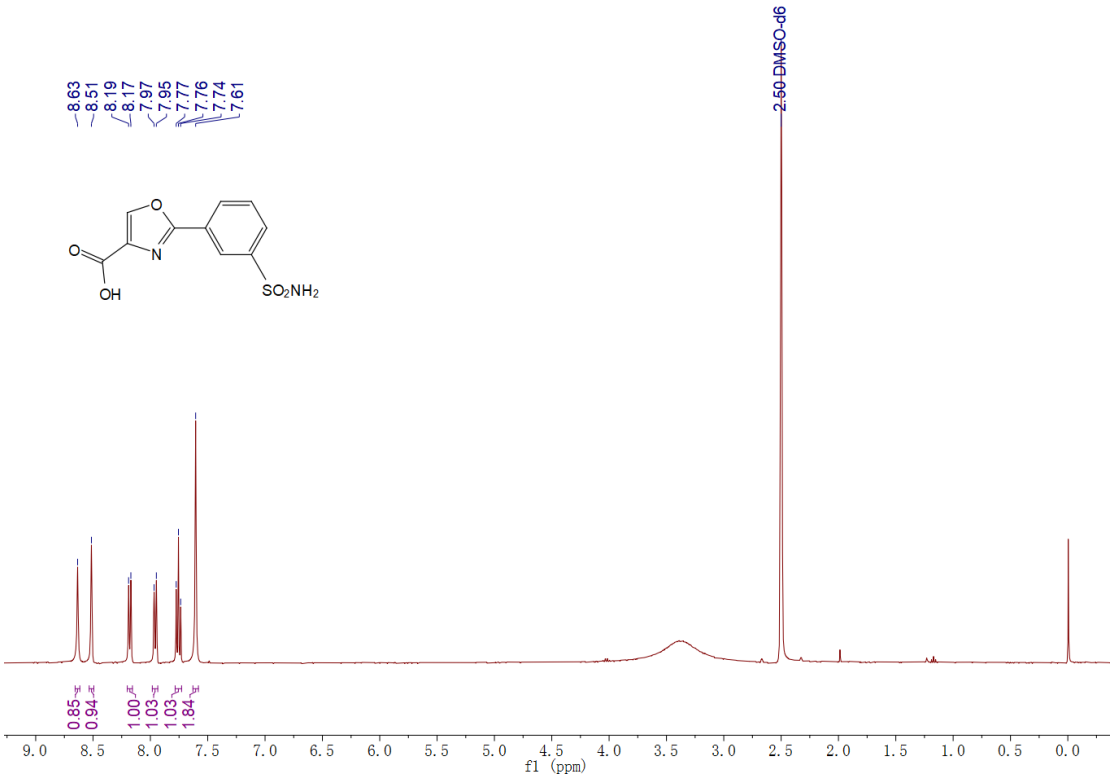
A mixture of **C8** (3.13 g, 11.65 mmol), acetic anhydride (3.57 g, 34.97 mmol) DMAP (142 mg, 1.17 mmol), and TEA (8.09 mL, 58.24 mmol) in dichloromethane (20 mL) was stirred at room temperature for 12 hours. Then the mixture was diluted with dichloromethane, washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 4% methanol in dichloromethane to afford **I1** as a yellow oil (3.50 g, 97%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.85 (s, 1H), 6.90 (s, 1H), 4.33 – 4.25 (m, 1H), 3.71 – 3.52 (m, 2H), 3.31 – 3.21 (m, 1H), 3.05 (s, 2H), 2.14 (s, 3H), 2.04 – 1.94 (m, 2H), 1.78 – 1.74 (m, 2H).

^{1}H NMR spectra for intermediates.

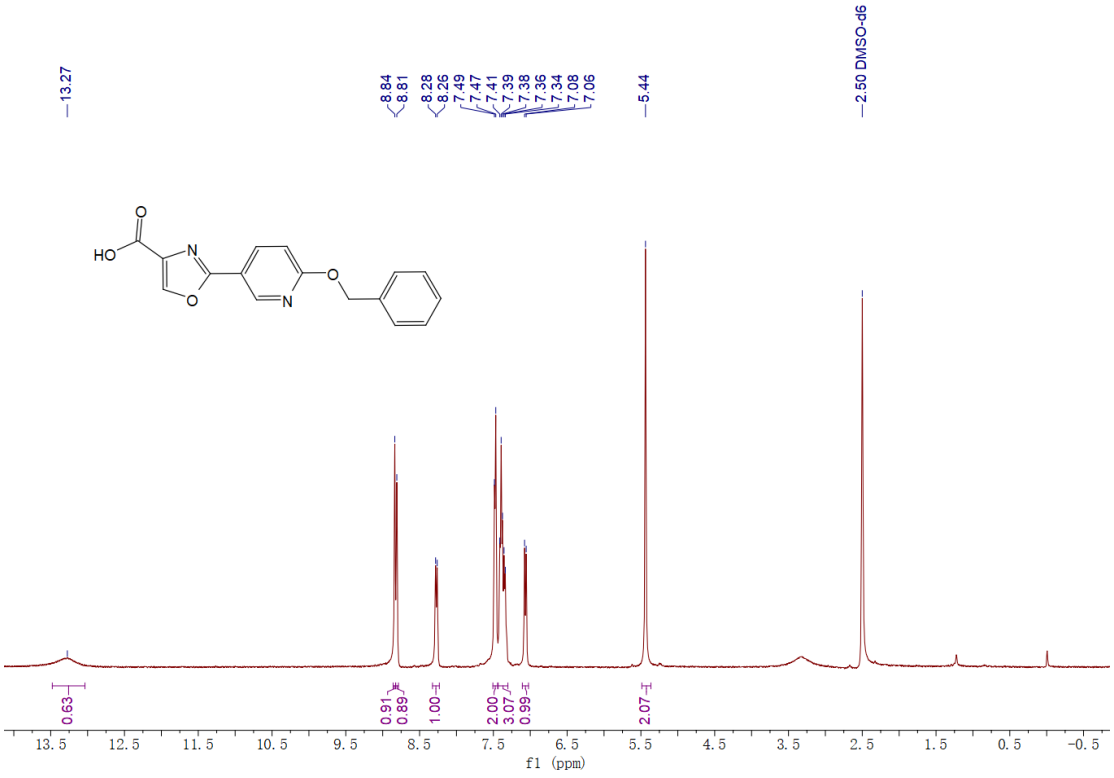
2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)oxazole-4-carboxylic acid (**A1**)



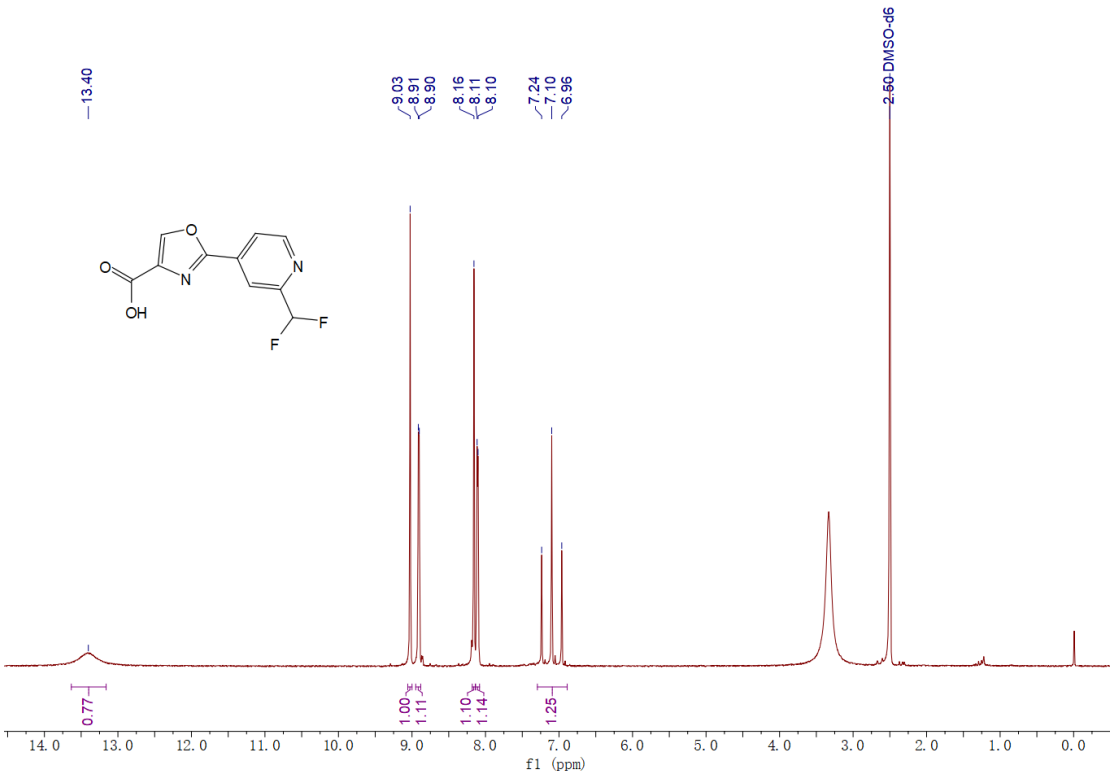
2-(3-sulfamoylphenyl)oxazole-4-carboxylic acid (**A3**)



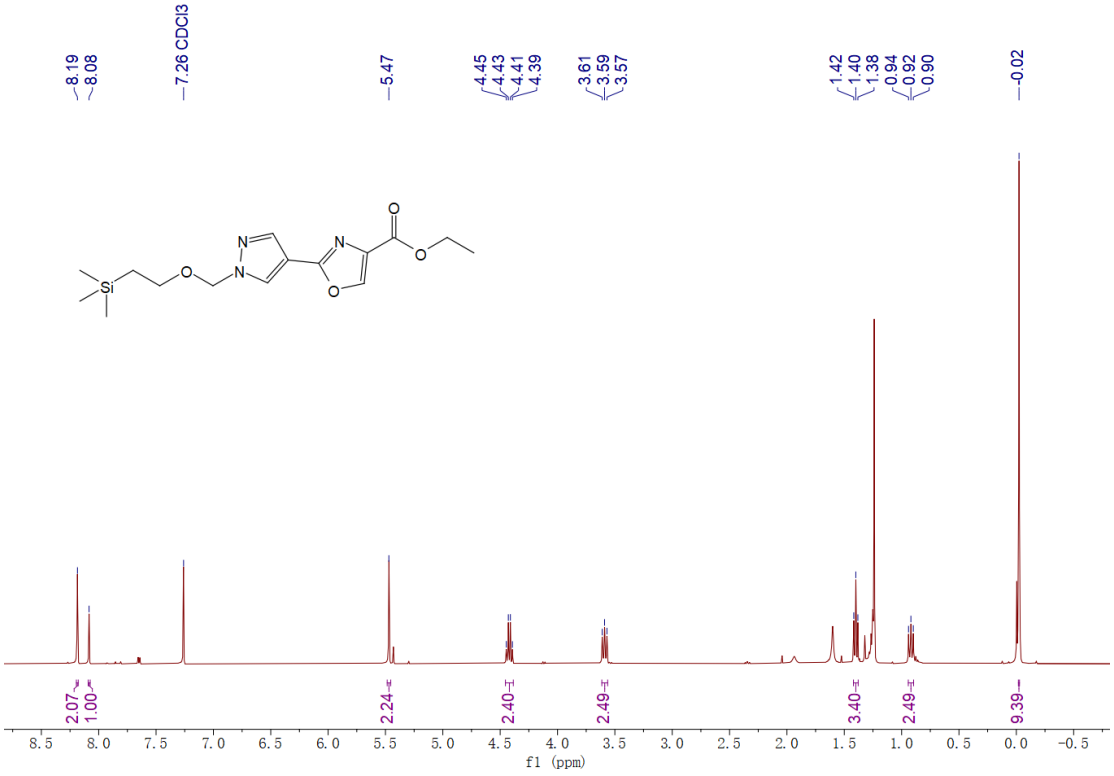
2-(6-(benzyloxy)pyridin-3-yl)oxazole-4-carboxylic acid (**A5**)



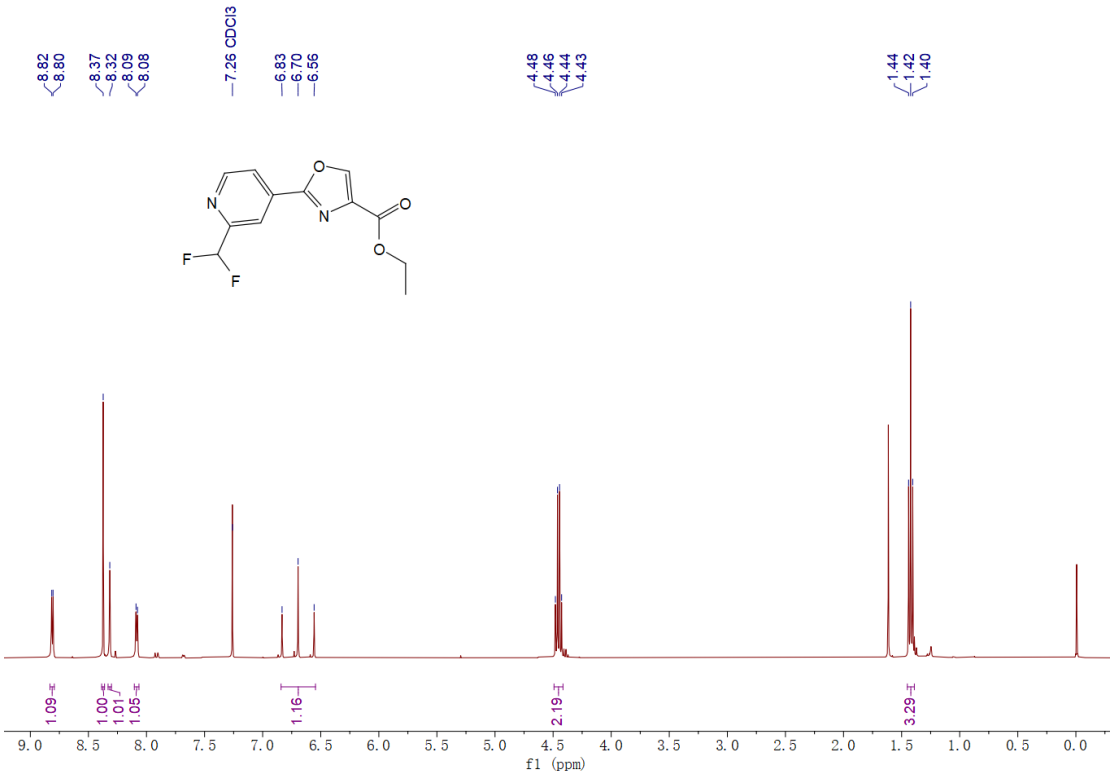
2-(2-(difluoromethyl)pyridin-4-yl)oxazole-4-carboxylic acid (**A7**)



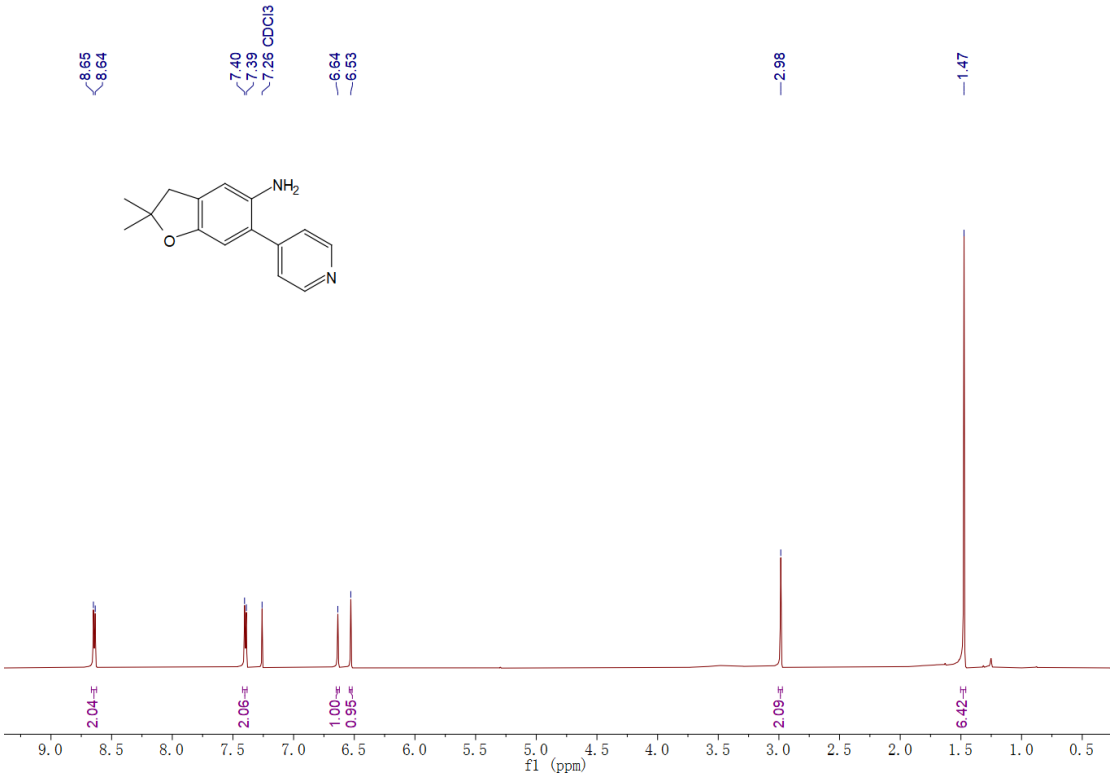
ethyl 2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)oxazole-4-carboxylate (**A11**)



ethyl 2-(2-(difluoromethyl)pyridin-4-yl)oxazole-4-carboxylate (**A19**)

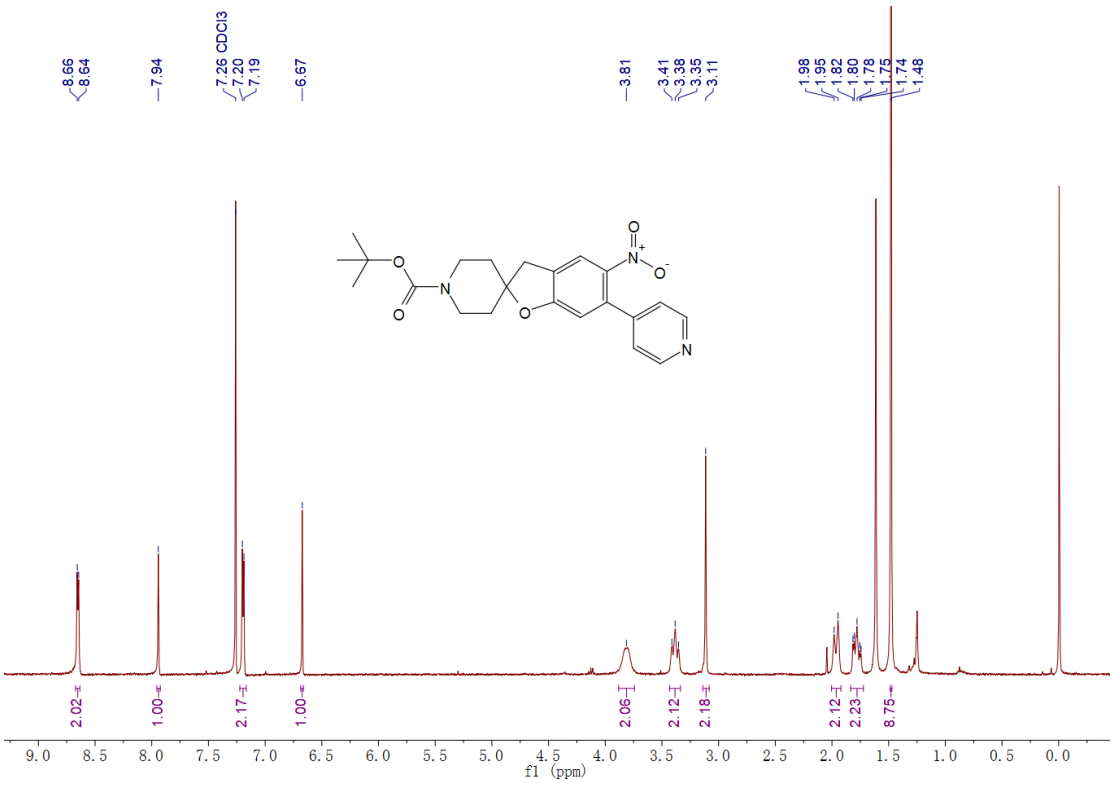


2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-amine (**B1**)



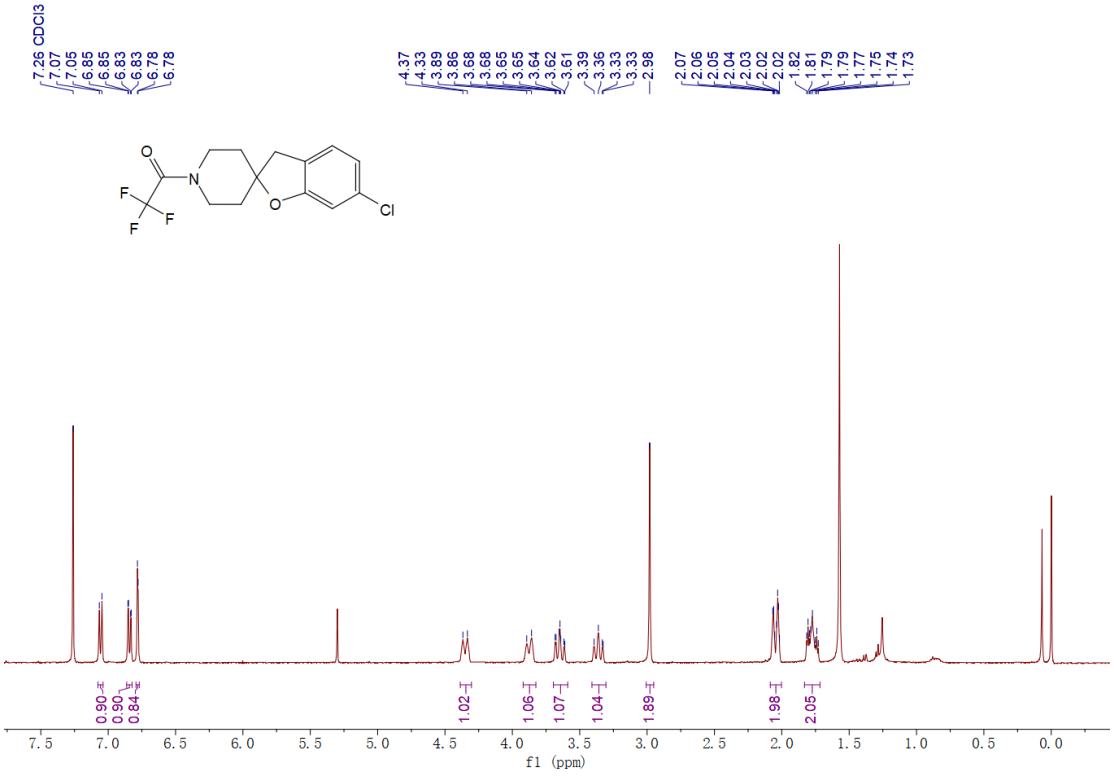
4-(2,2-dimethyl-5-nitro-2,3-dihydrobenzofuran-6-yl)pyridine (**B7**)

tert-butyl 5-nitro-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidine]-1'-carboxylate (**C1**)

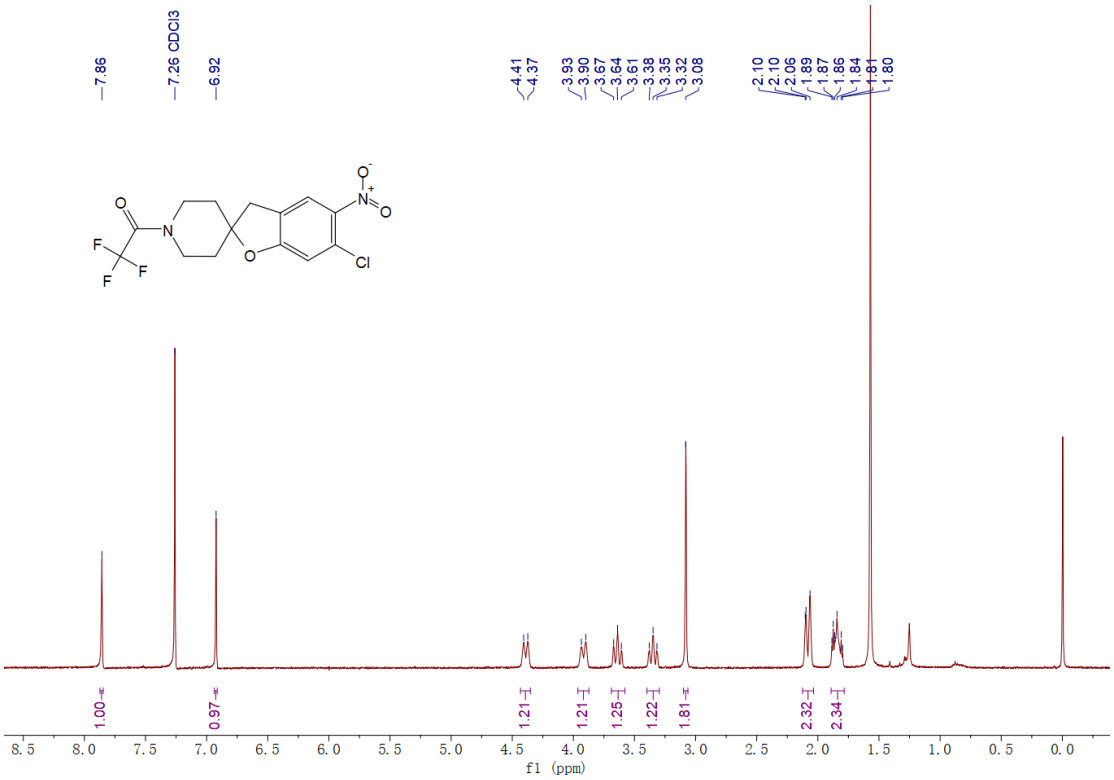


tert-butyl 6-chloro-3*H*-spiro[benzofuran-2,4'-piperidine]-1'-carboxylate (**C4**)

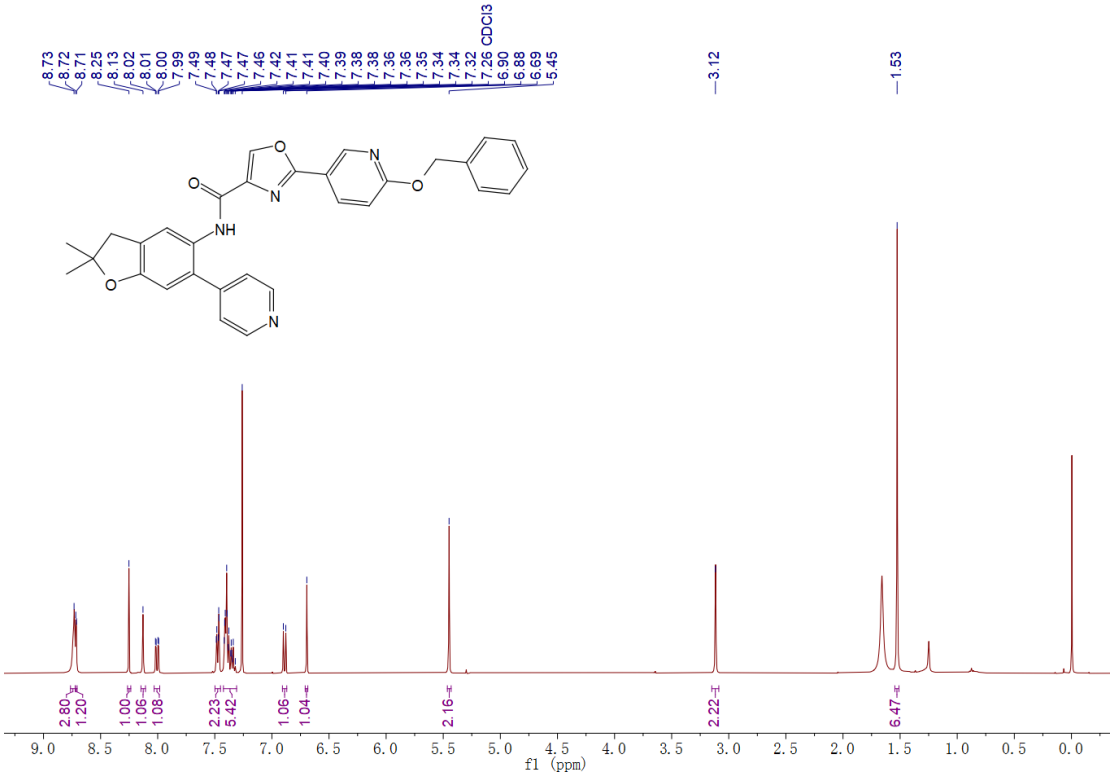
1-(6-chloro-3*H*-spiro[benzofuran-2,4'-piperidin]-1'-yl)-2,2,2-trifluoroethan-1-one (**C6**)



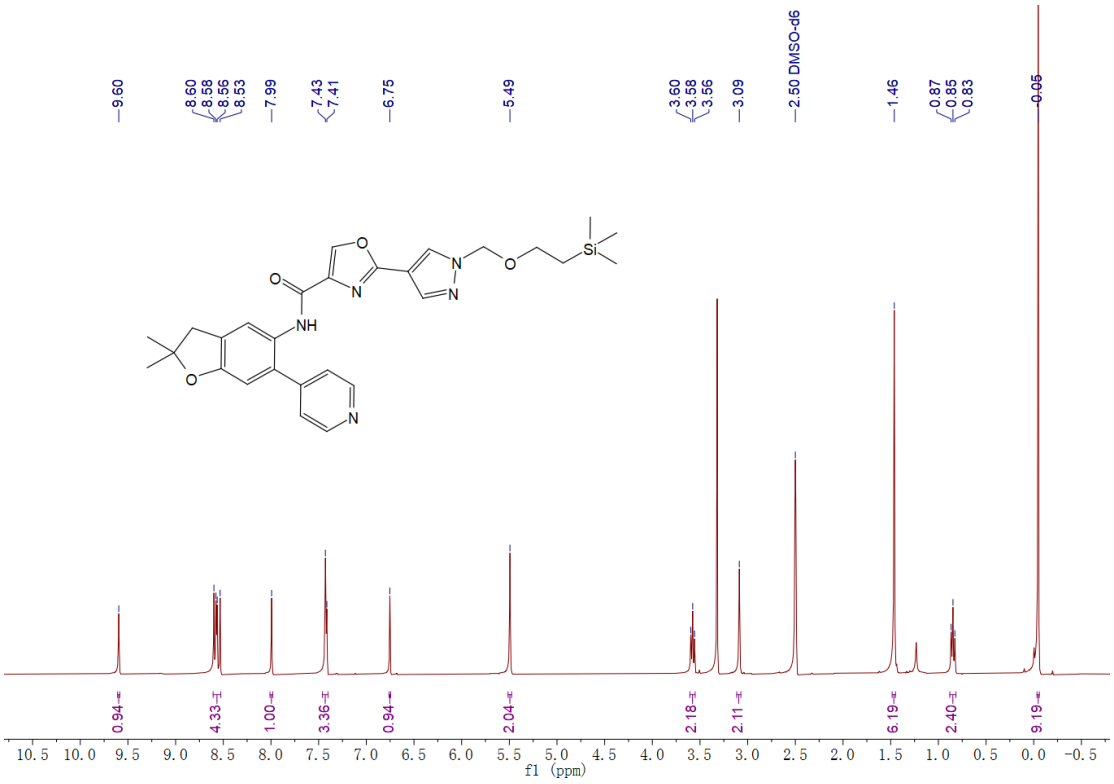
1-(6-chloro-5-nitro-3*H*-spiro[benzofuran-2,4'-piperidin]-1'-yl)-2,2,2-trifluoroethan-1-one (**C7**)



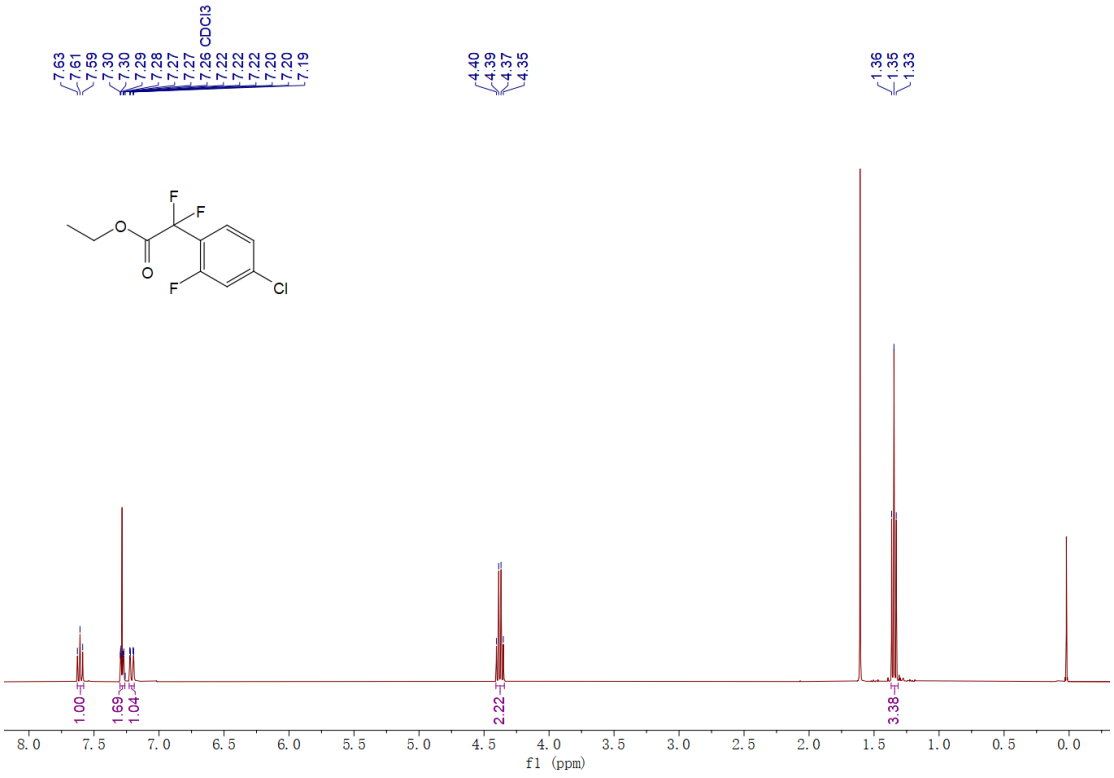
2-(6-(benzyloxy)pyridin-3-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**D1**)



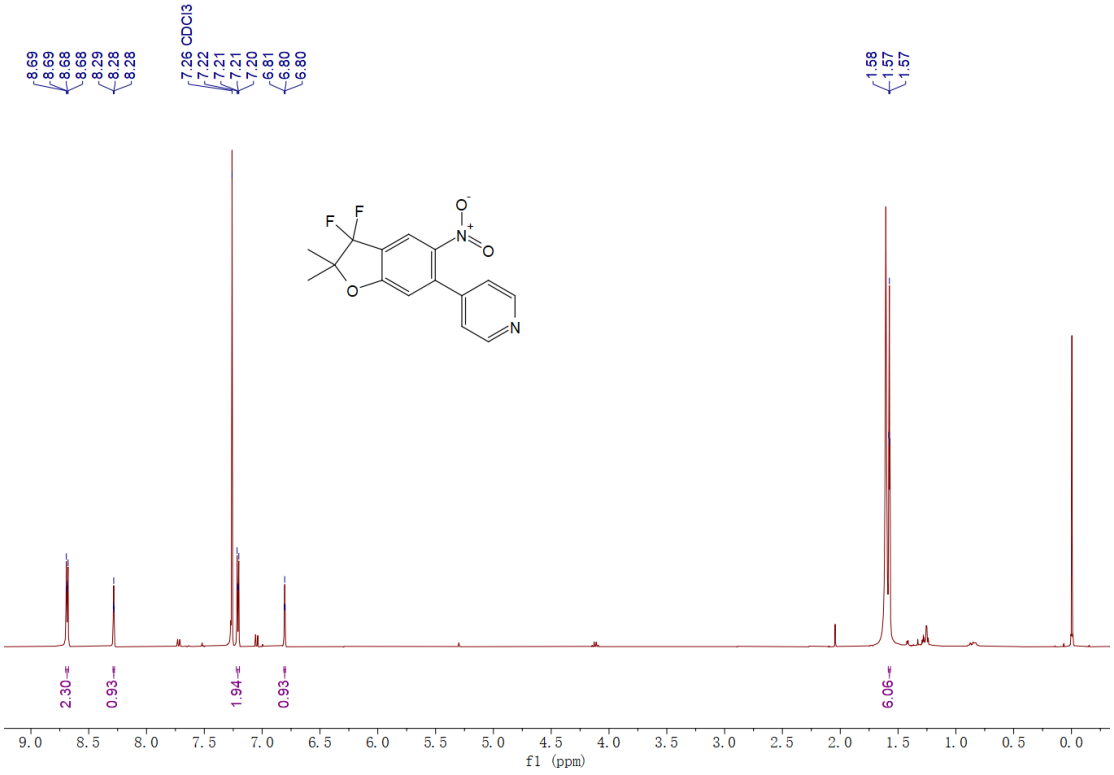
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)oxazole-4-carboxamide (**D3**)



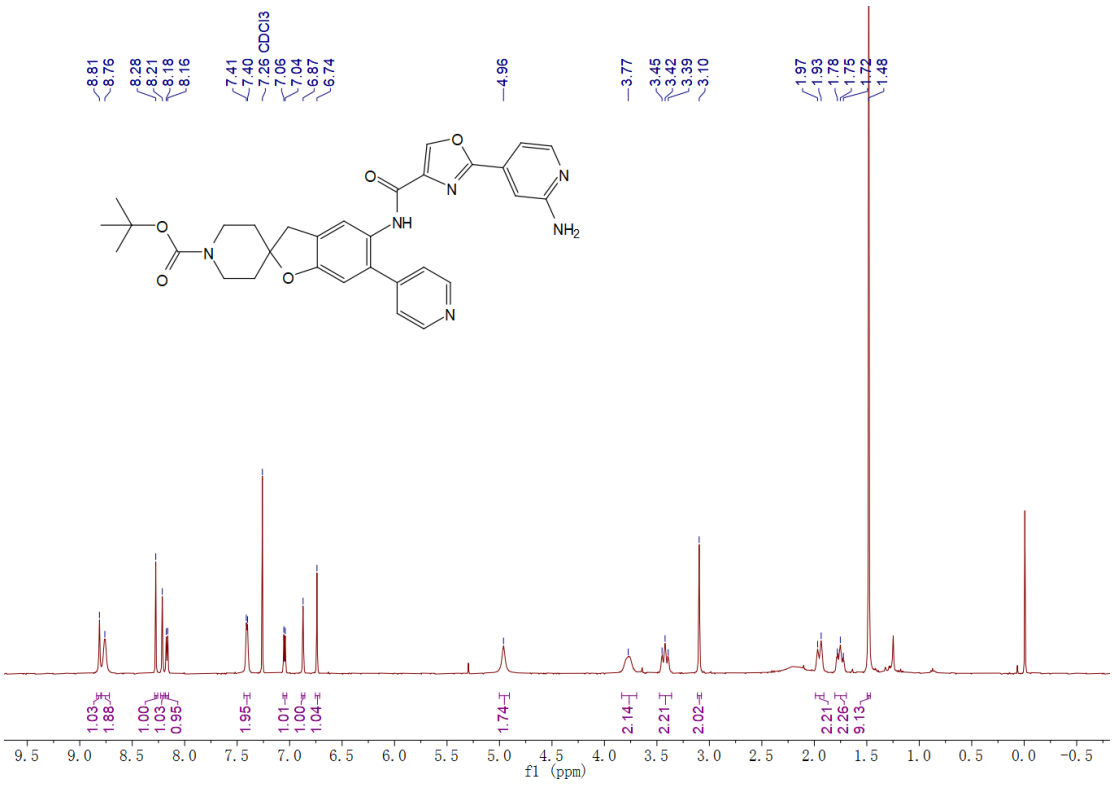
ethyl 2-(4-chloro-2-fluorophenyl)-2,2-difluoroacetate (**E2**)



4-(3,3-difluoro-2,2-dimethyl-5-nitro-2,3-dihydrobenzofuran-6-yl)pyridine (**E6**)

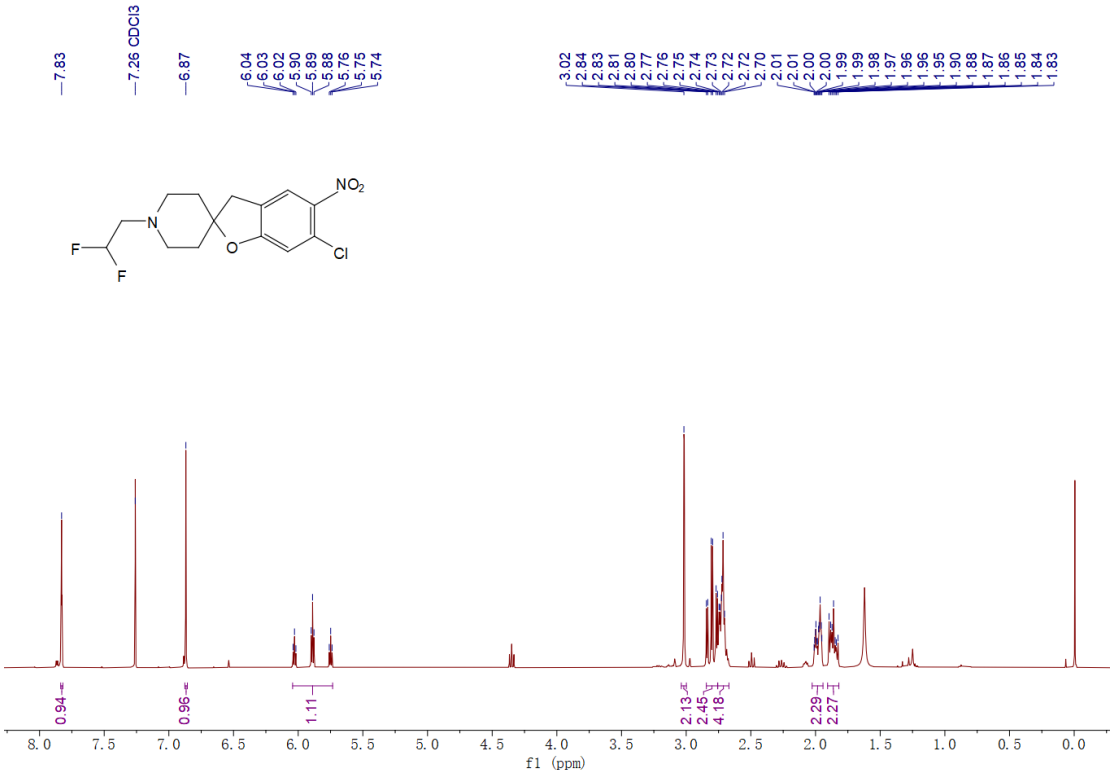


tert-butyl 5-(2-(2-aminopyridin-4-yl)oxazole-4-carboxamido)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidine]-1'-carboxylate (**F2**)

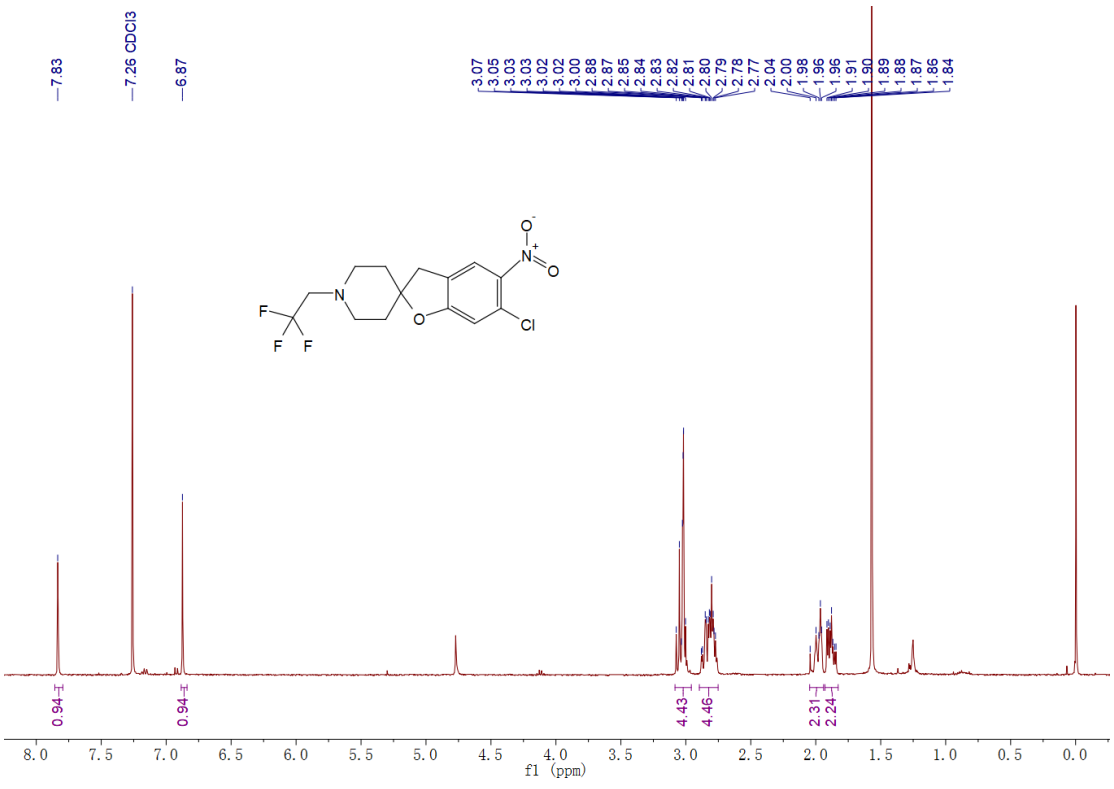


1'-methyl-5-nitro-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidine] (**F4**)

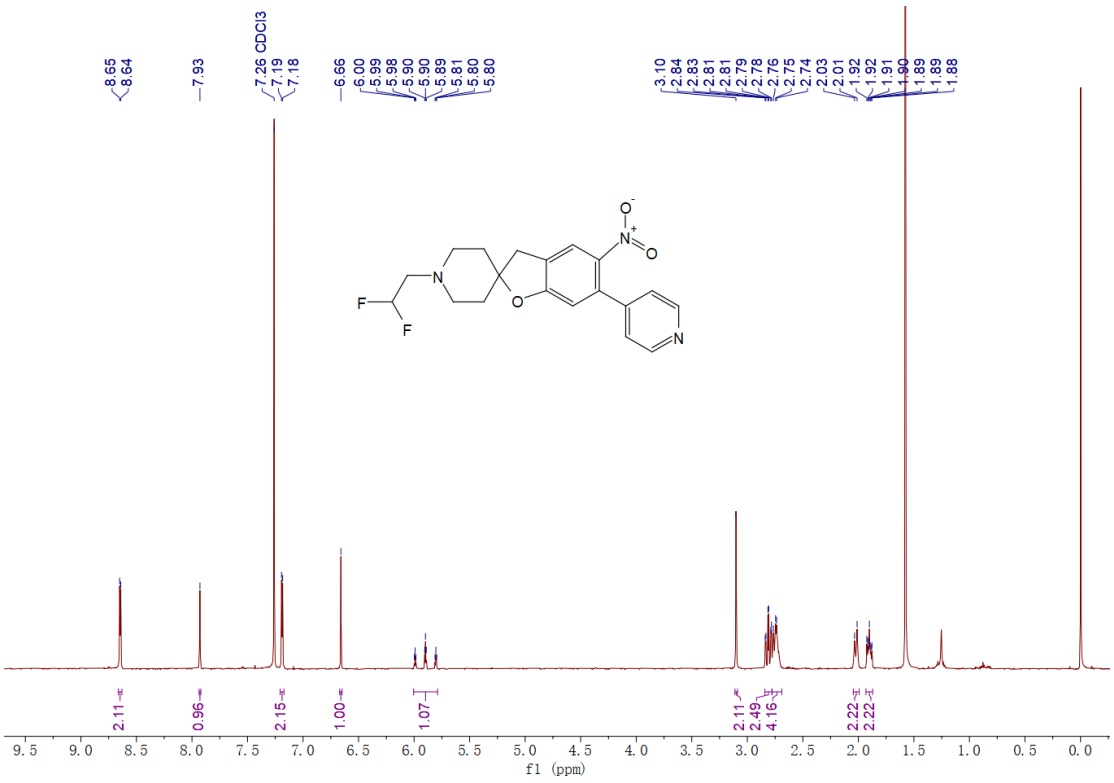
6-chloro-1'-(2,2-difluoroethyl)-5-nitro-3*H*-spiro[benzofuran-2,4'-piperidine] (**G1**)



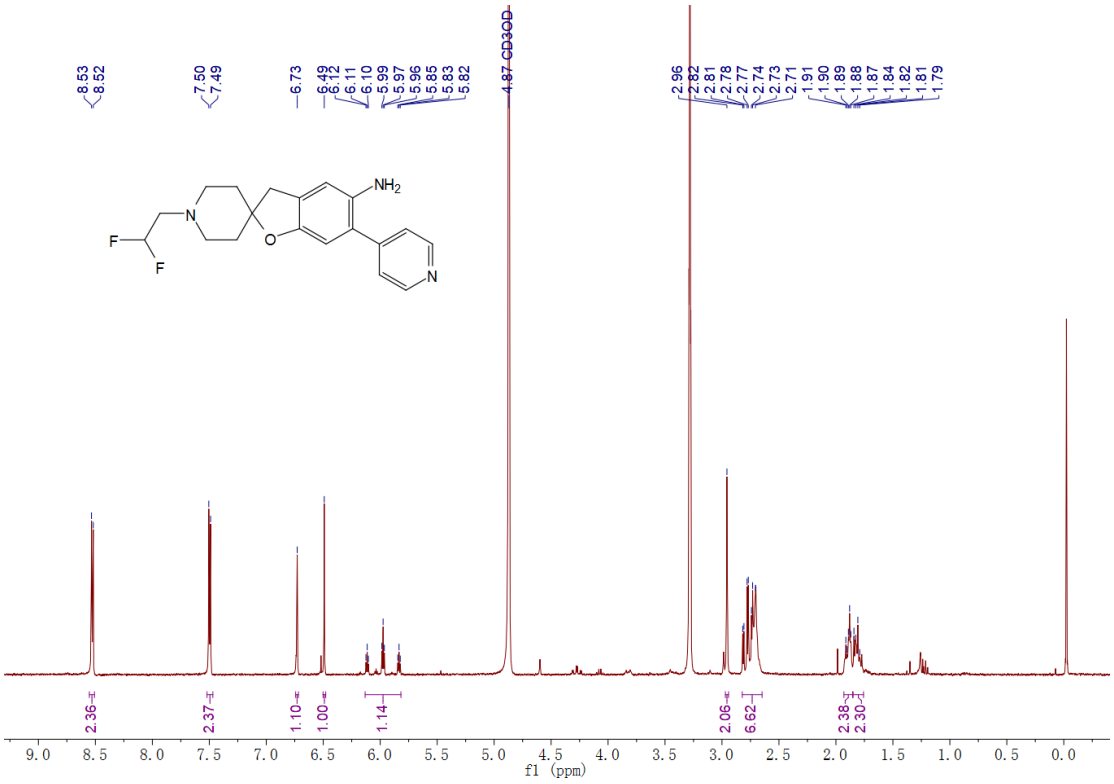
6-chloro-5-nitro-1'-(2,2,2-trifluoroethyl)-3*H*-spiro[benzofuran-2,4'-piperidine] (**G2**)



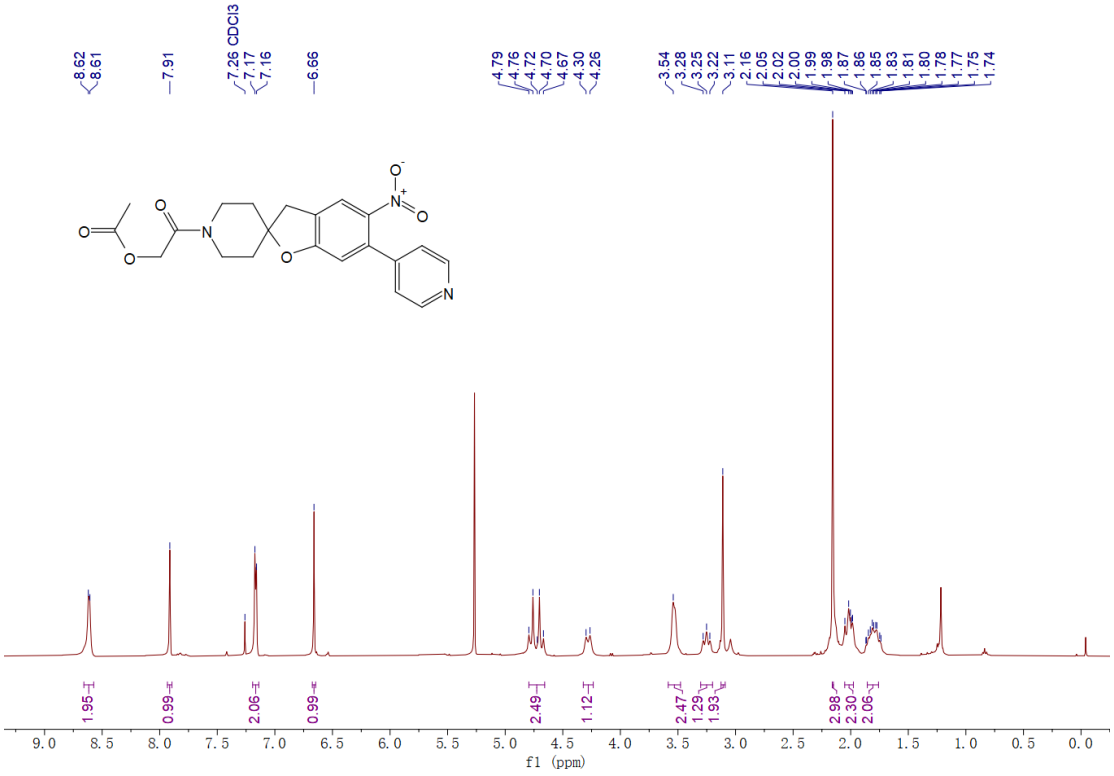
1'-(2,2-difluoroethyl)-5-nitro-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidine] (**G3**)



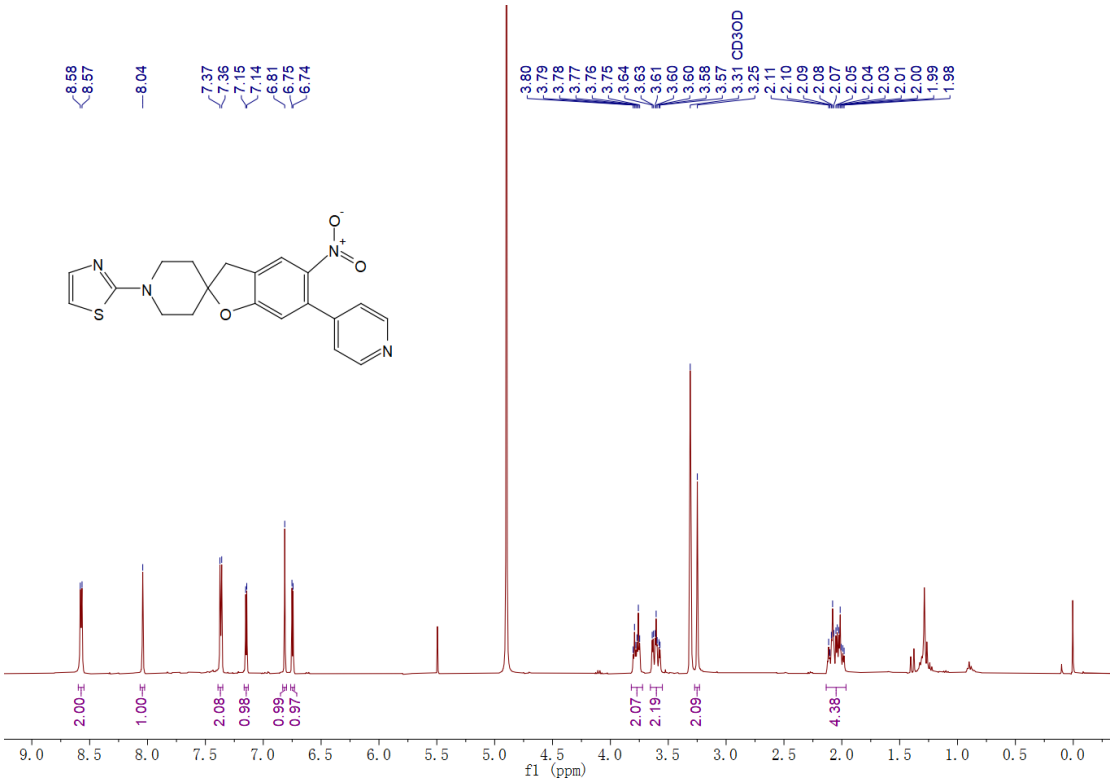
1'-(2,2-difluoroethyl)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-amine (**G5**)



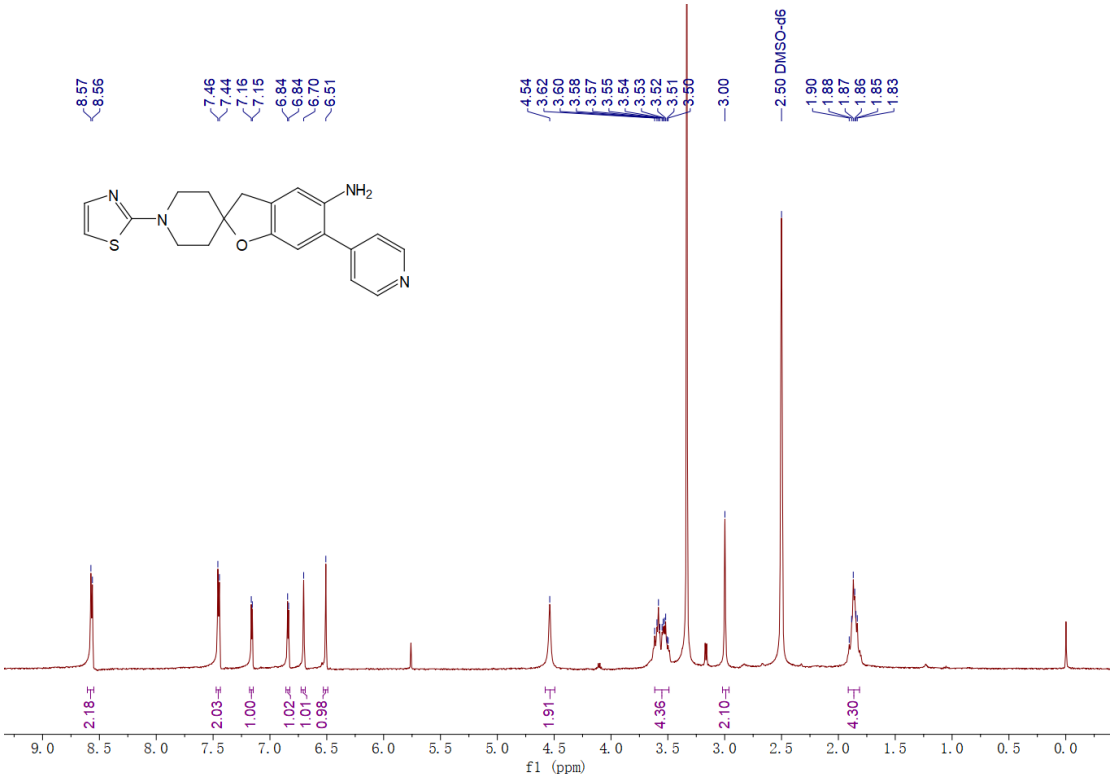
2-(5-nitro-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-1'-yl)-2-oxoethyl acetate (**H1**)



5-nitro-6-(pyridin-4-yl)-1'-(thiazol-2-yl)-3*H*-spiro[benzofuran-2,4'-piperidine] (**H4**)

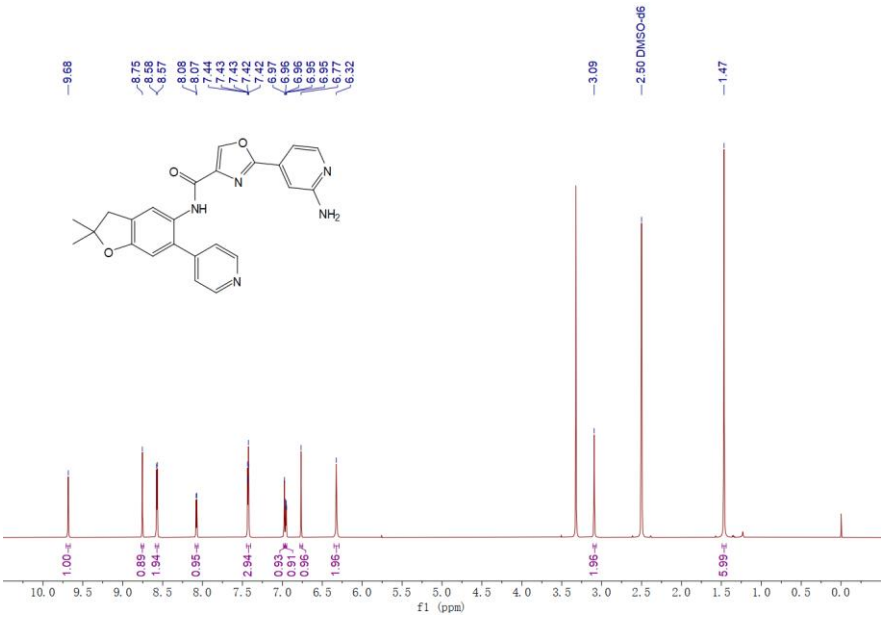


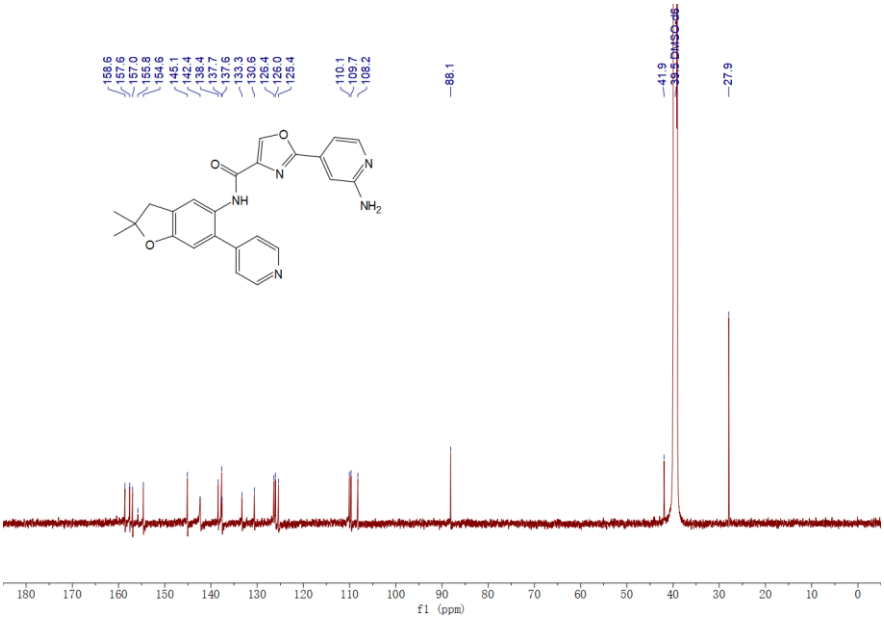
6-(pyridin-4-yl)-1'-(thiazol-2-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-amine (**H5**)

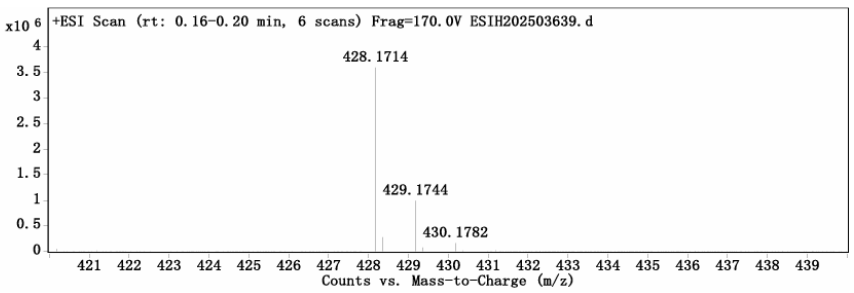


^{1}H NMR, ^{13}C NMR, and HRMS spectra for target compounds 1–21 and DW18134.

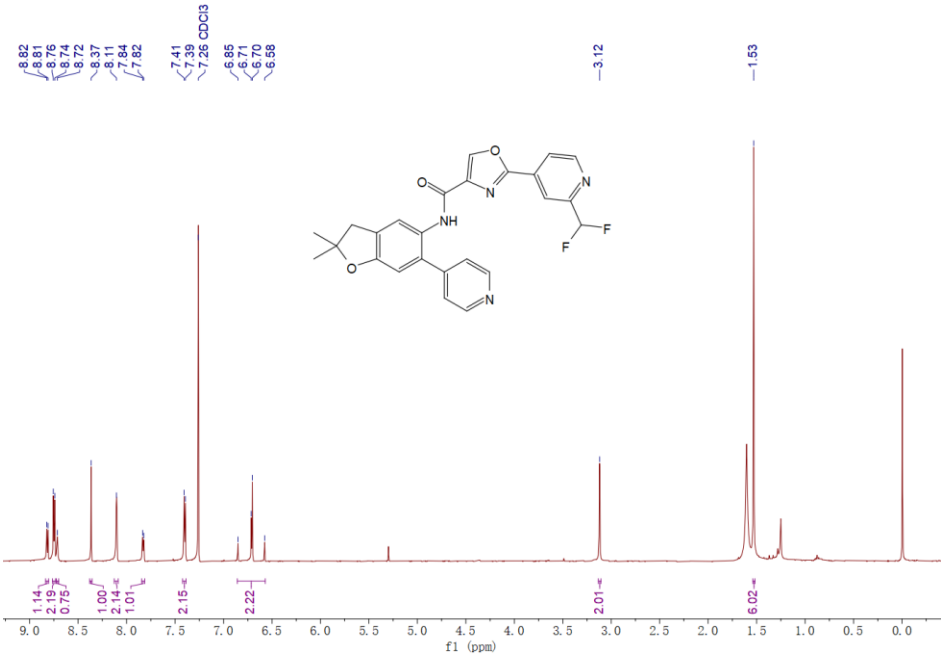
2-(2-aminopyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (DW18134)

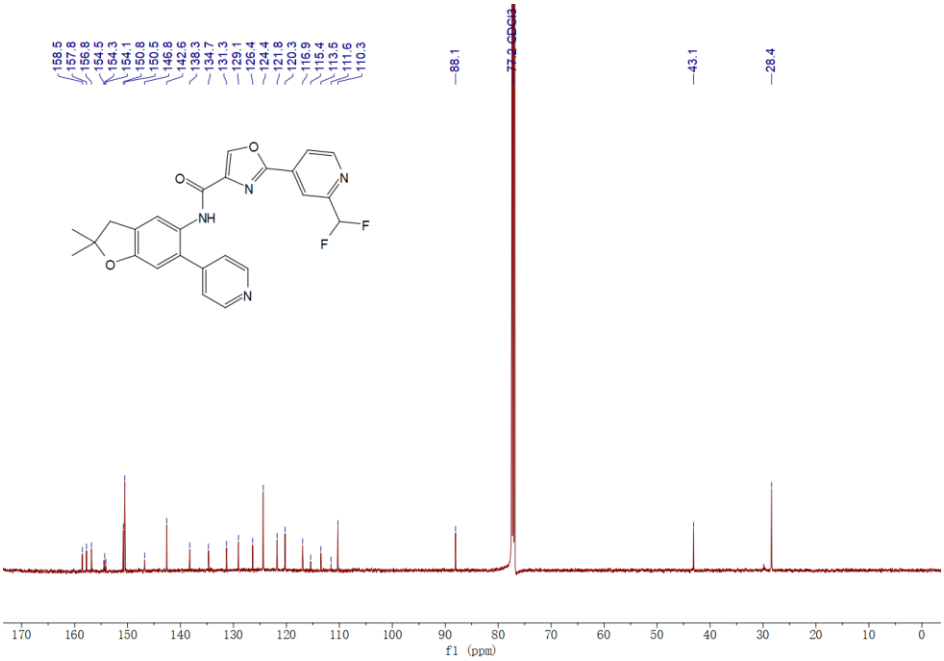


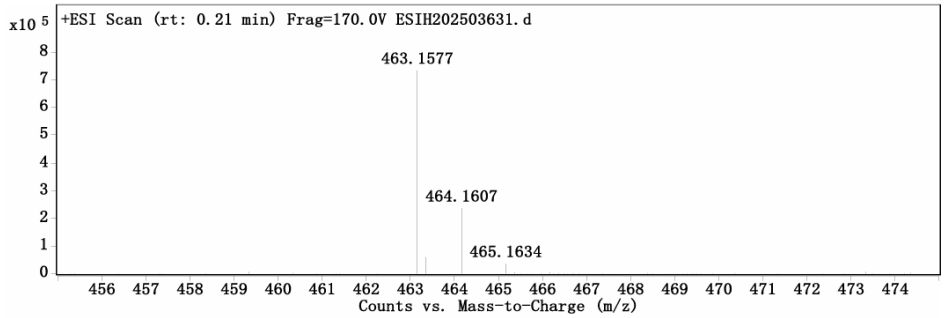




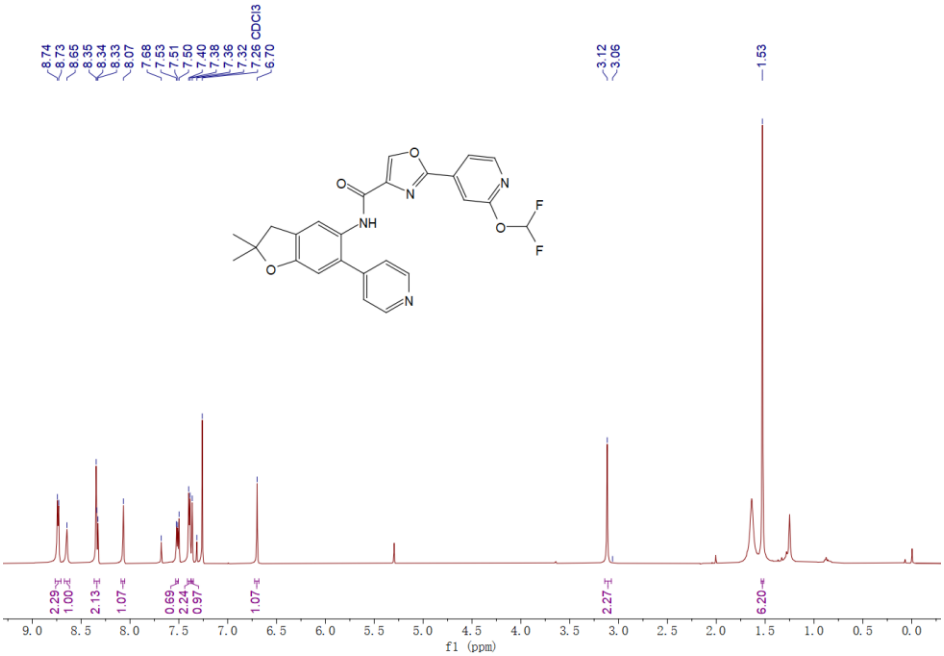
2-(2-(difluoromethyl)pyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**1**)

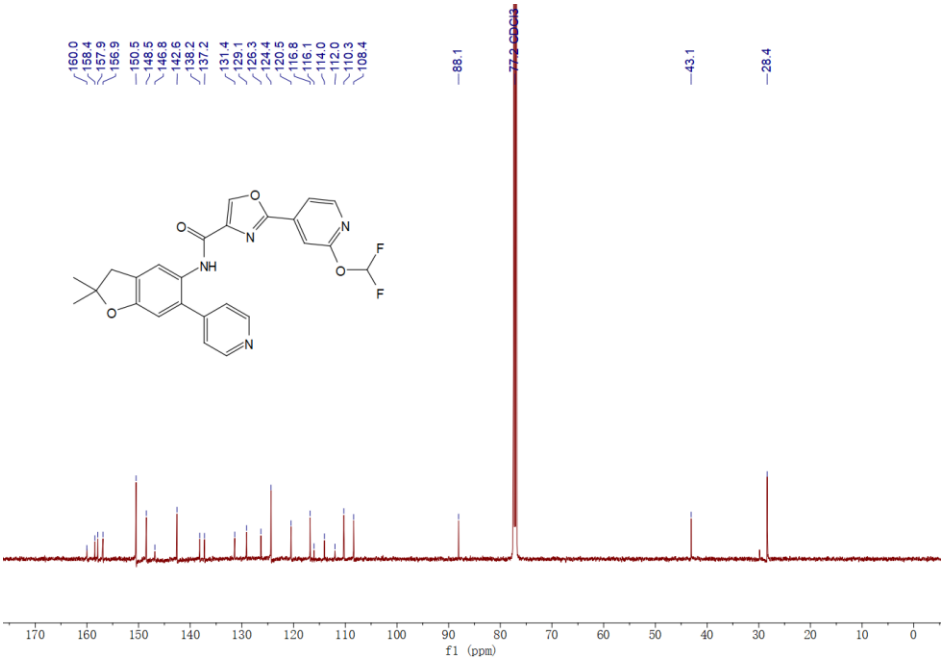


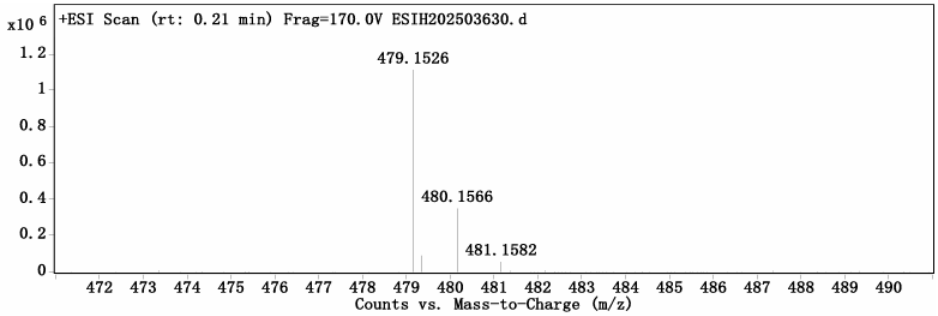




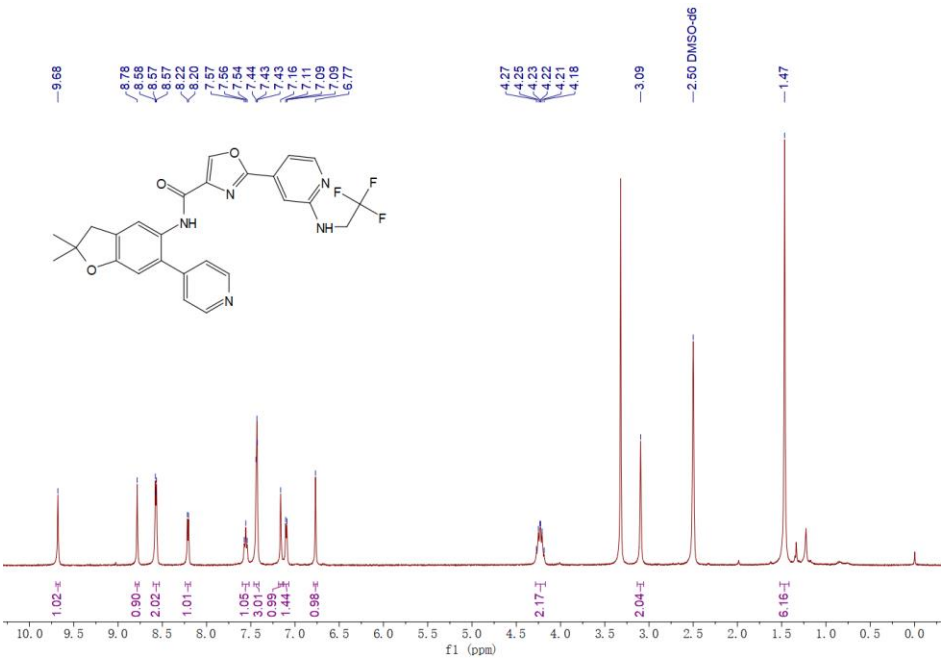
2-(2-(difluoromethoxy)pyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydroben zofuran-5-yl)oxazole-4-carboxamide (**2**)

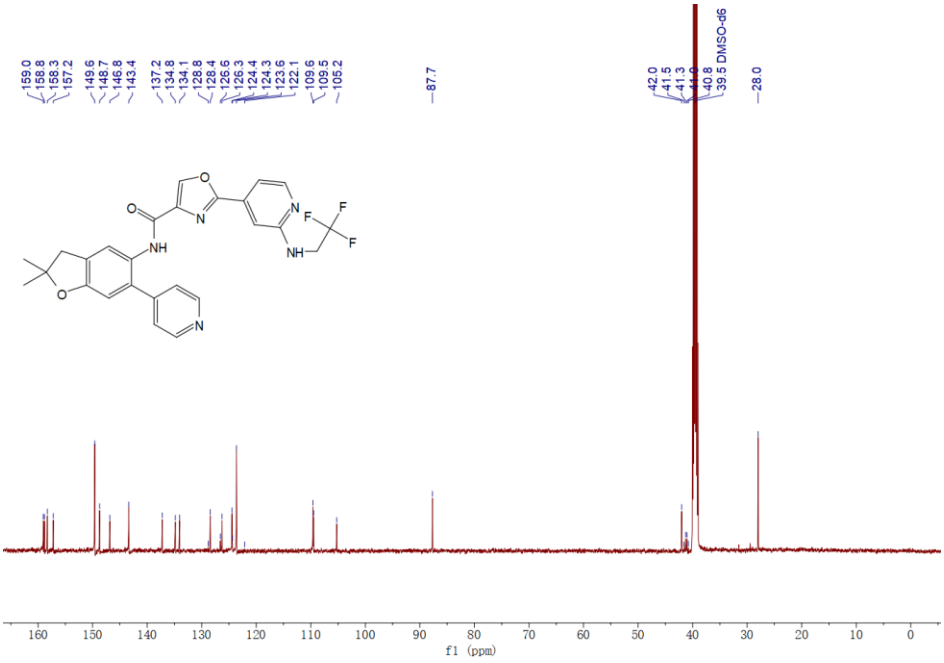


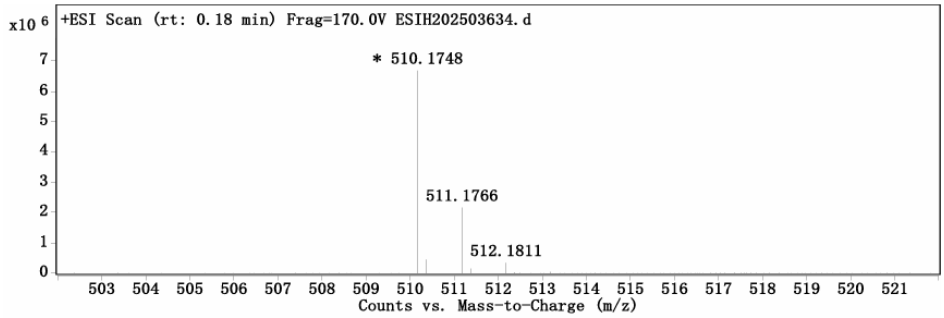




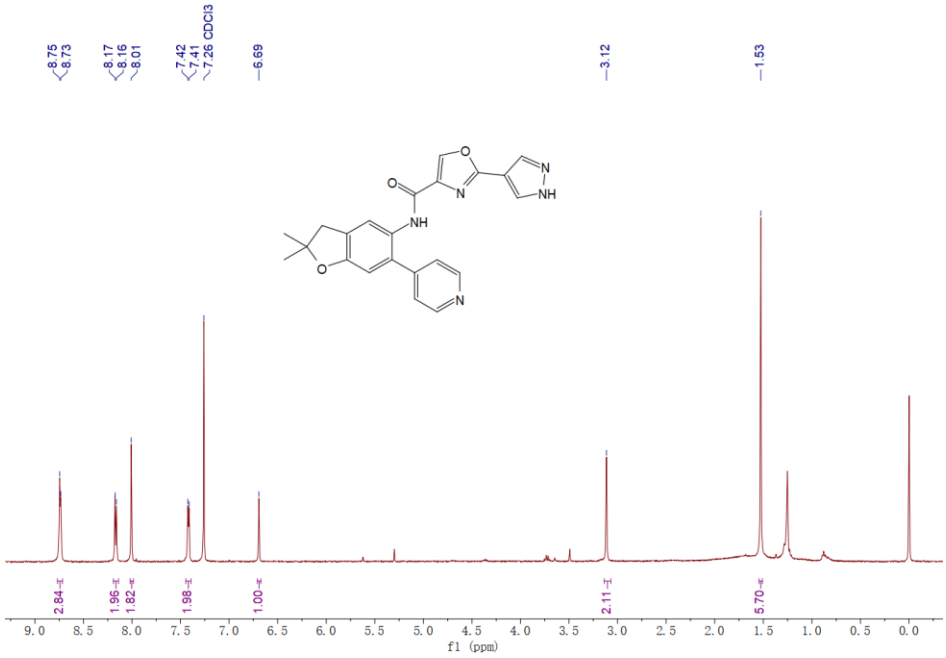
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(2-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)oxazole-4-carboxamide (**3**)

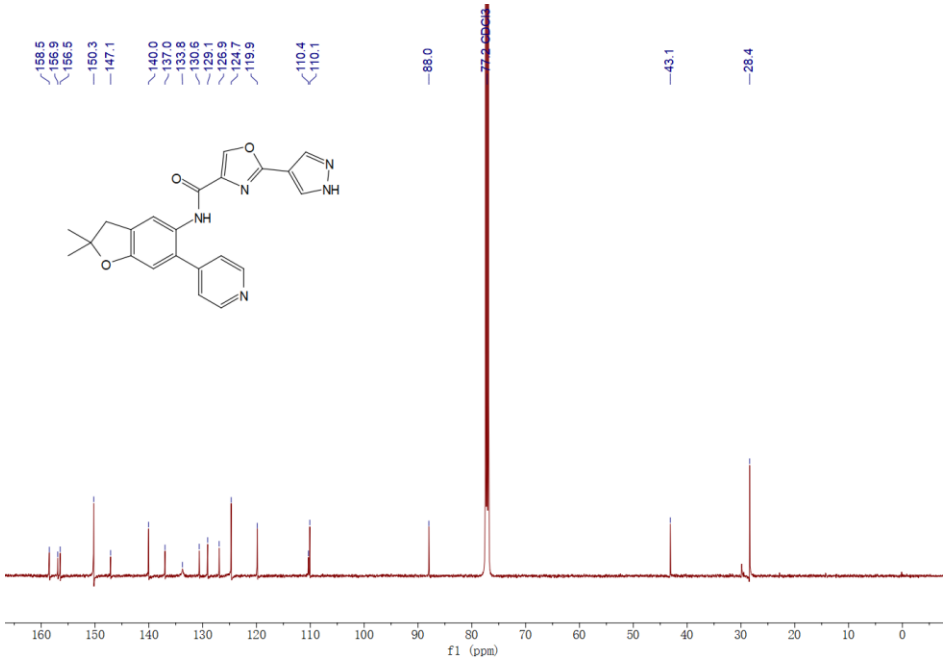


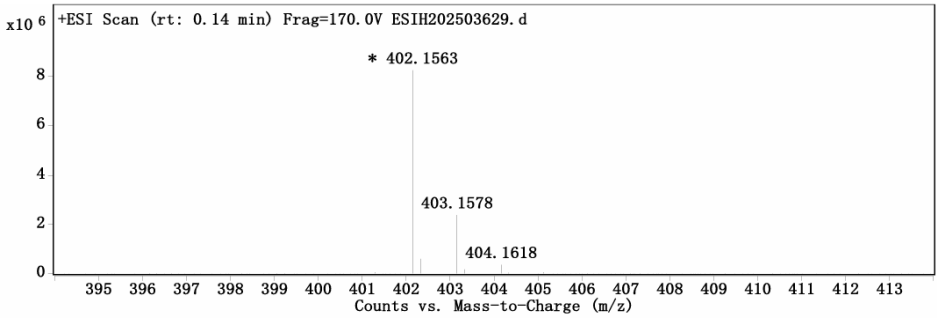




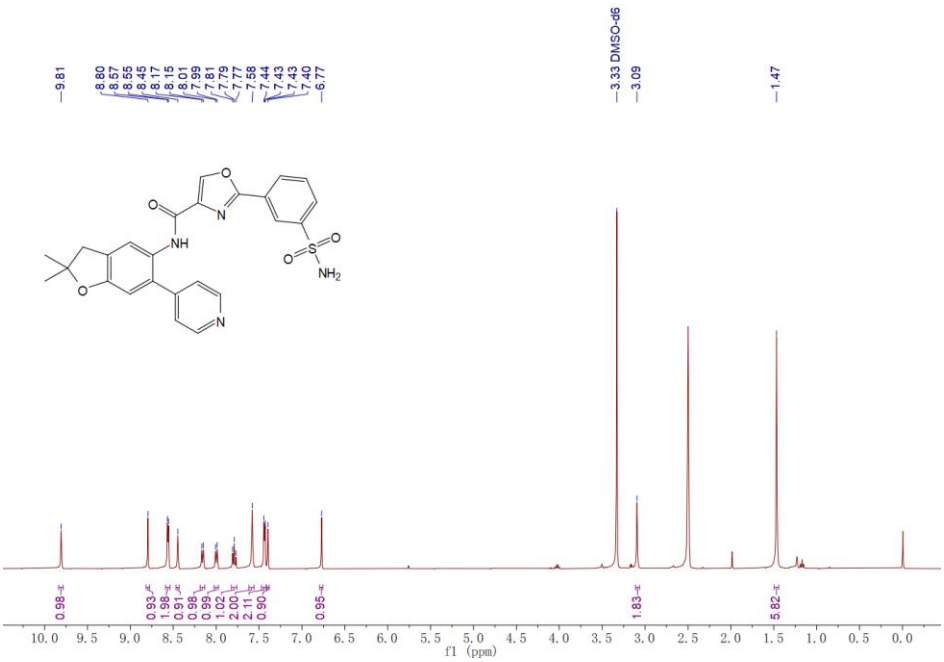
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-pyrazol-4-yl)oxazole-4-carboxamide (**4**)

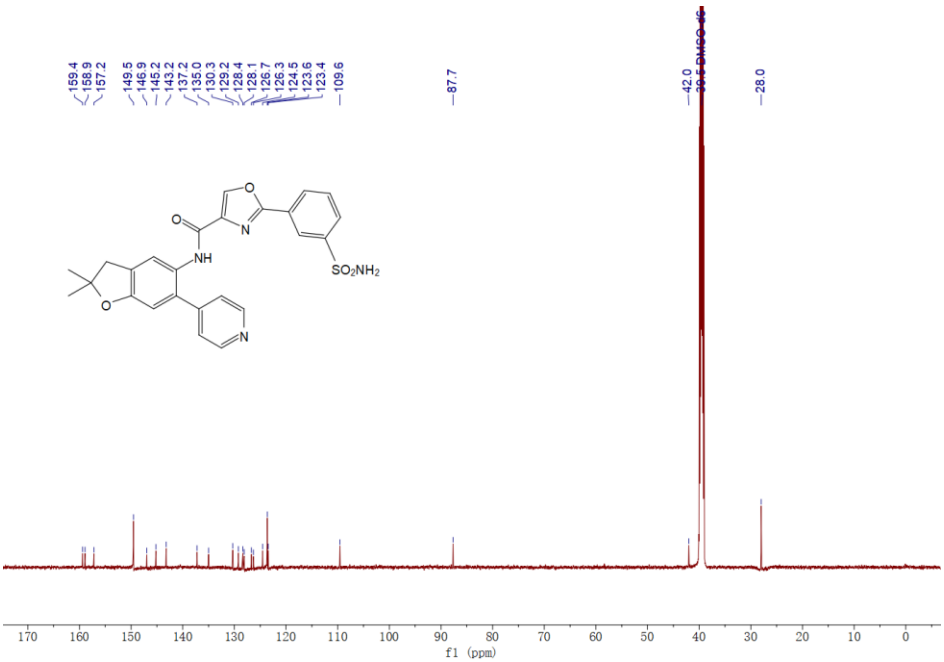


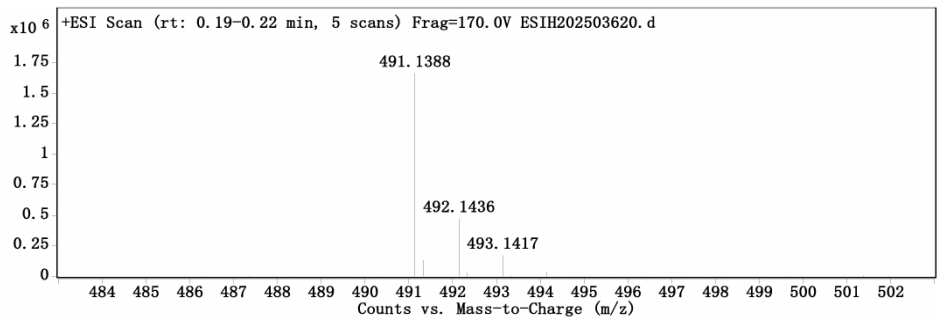




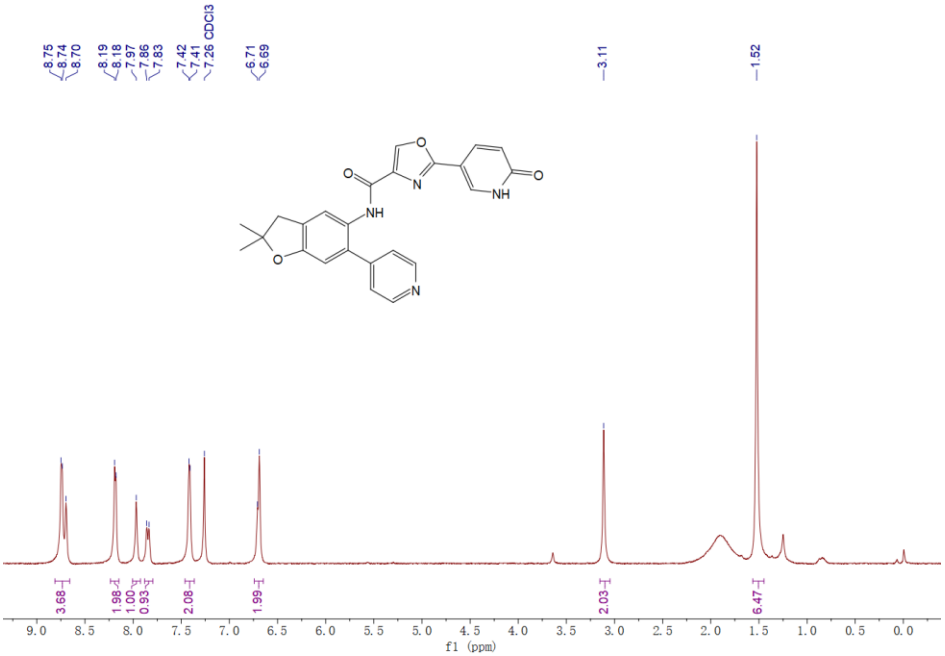
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(3-sulfamoylphenyl) oxazole-4-carboxamide (**5**)

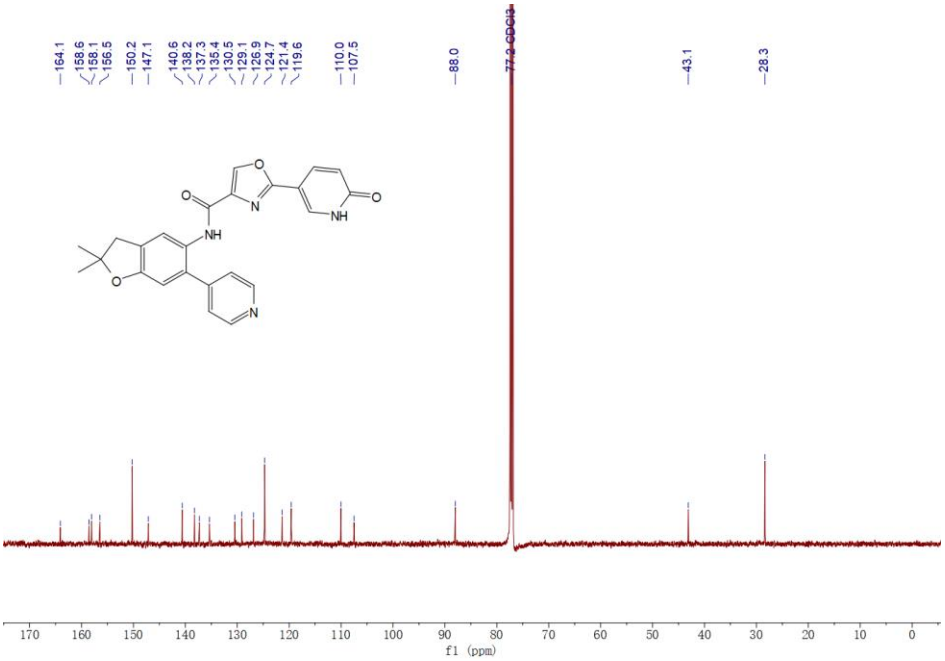


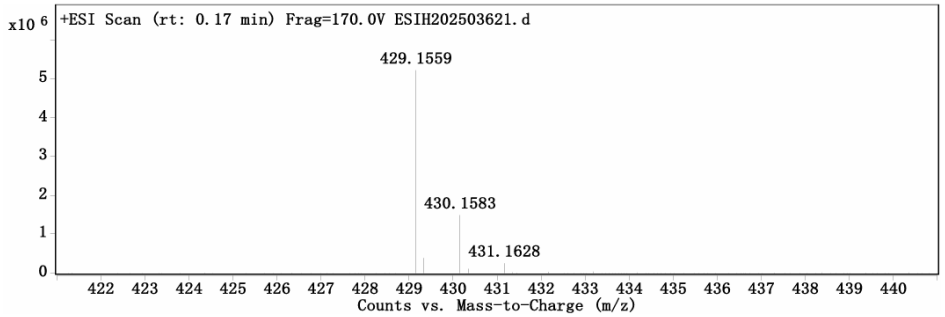




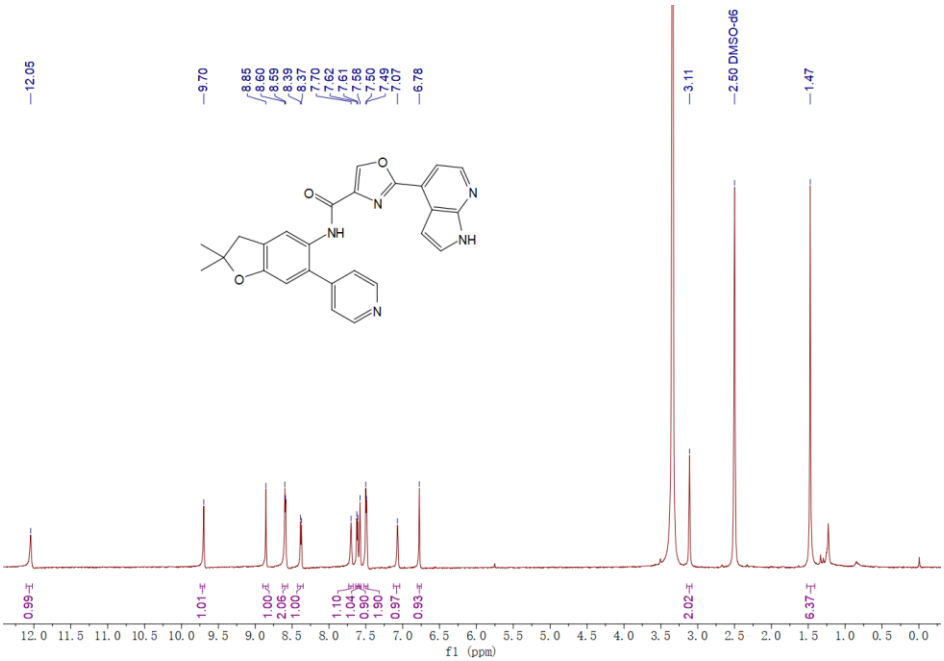
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(6-oxo-1,6-dihydropyridin-3-yl)oxazole-4-carboxamide (**6**)

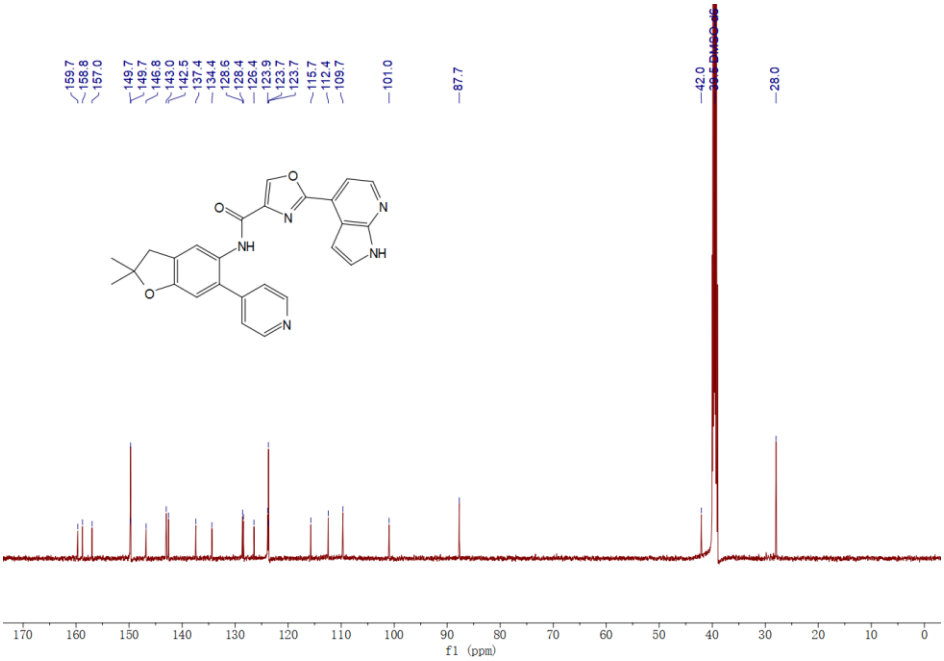


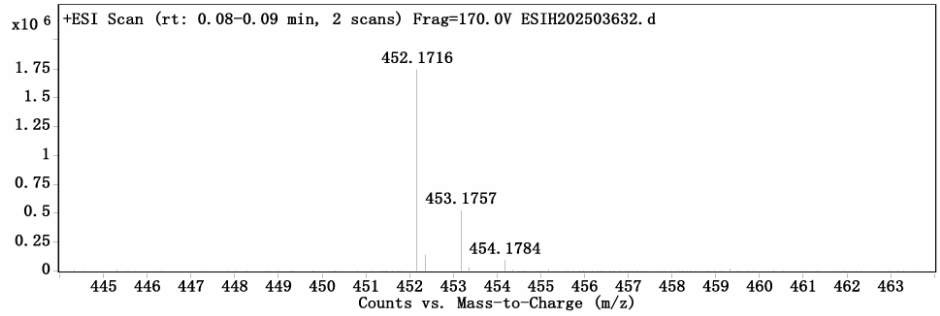




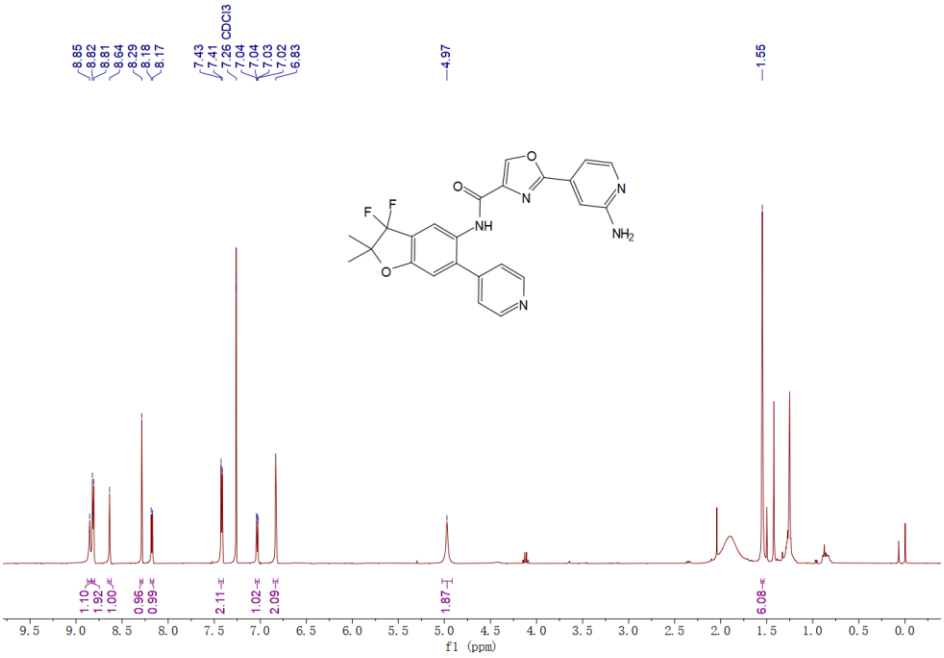
N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxazole-4-carboxamide (**7**)

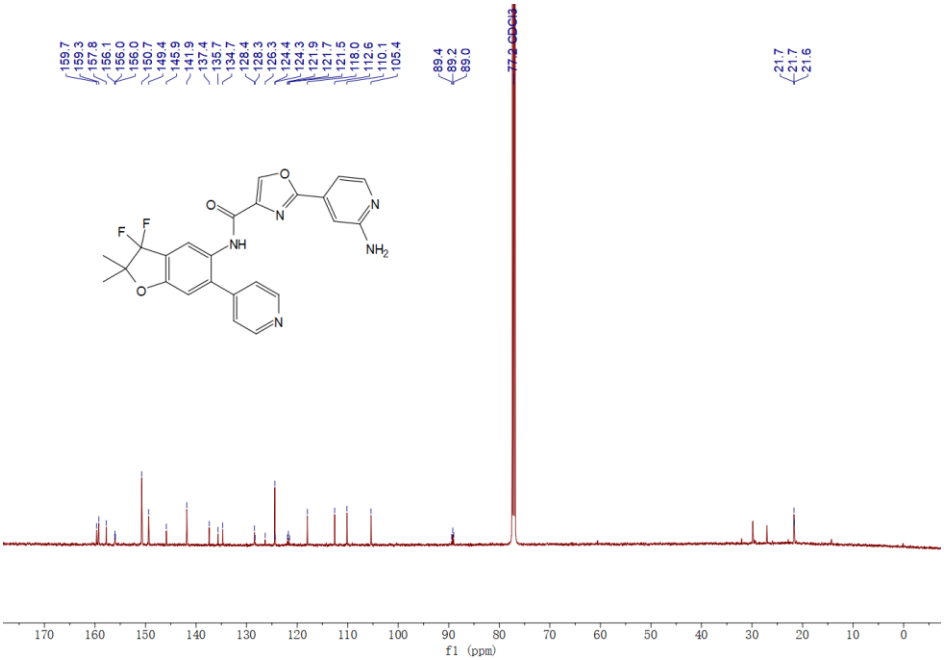


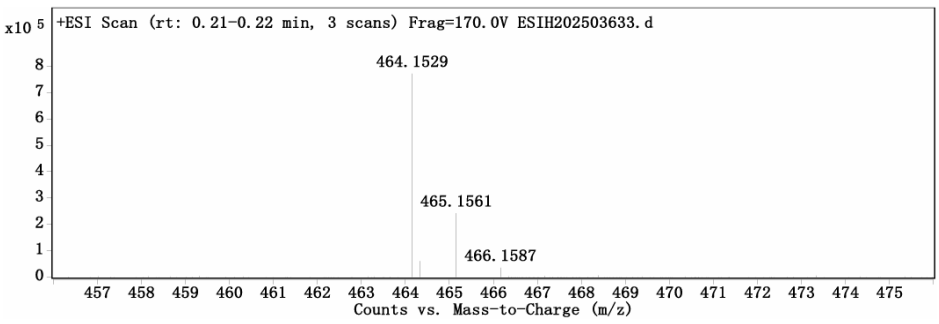




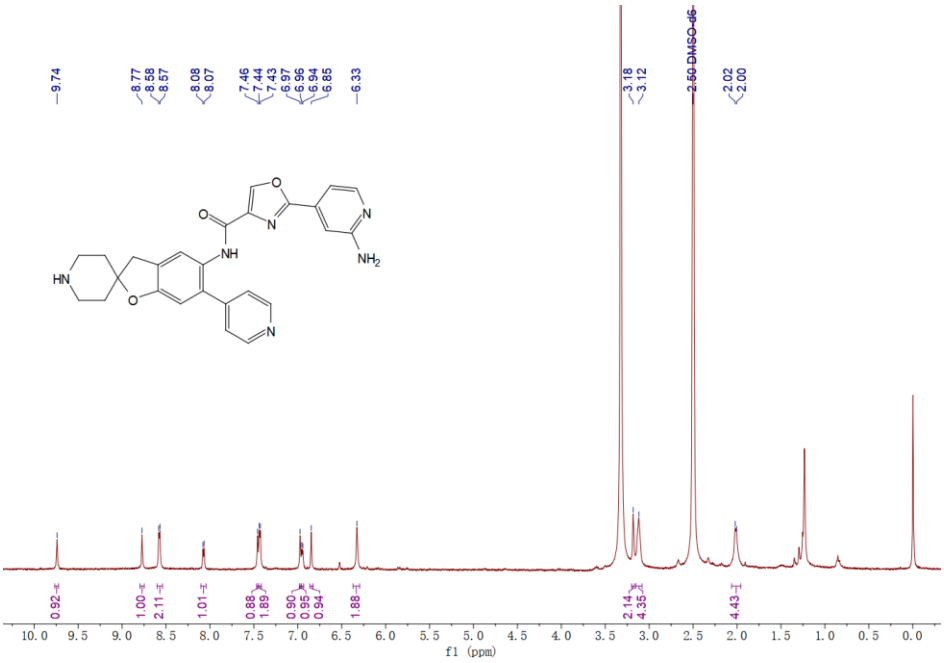
2-(2-aminopyridin-4-yl)-*N*-(3,3-difluoro-2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**8**)

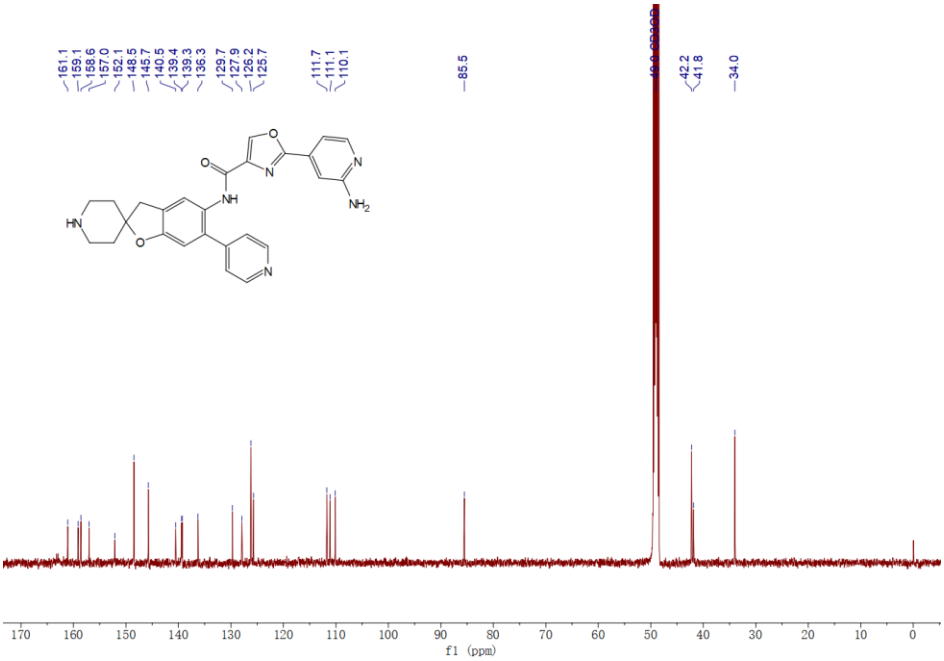


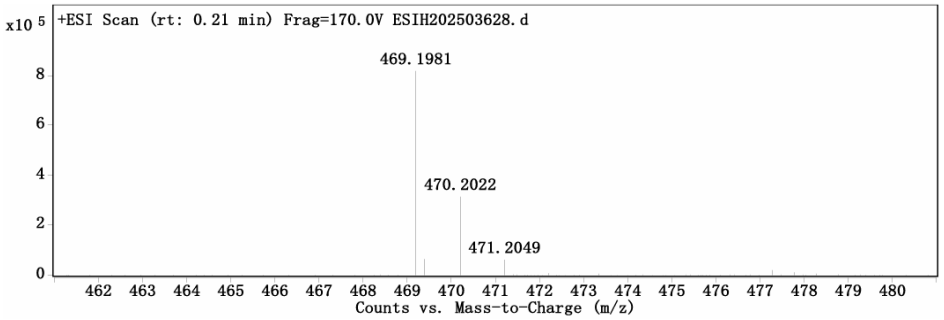




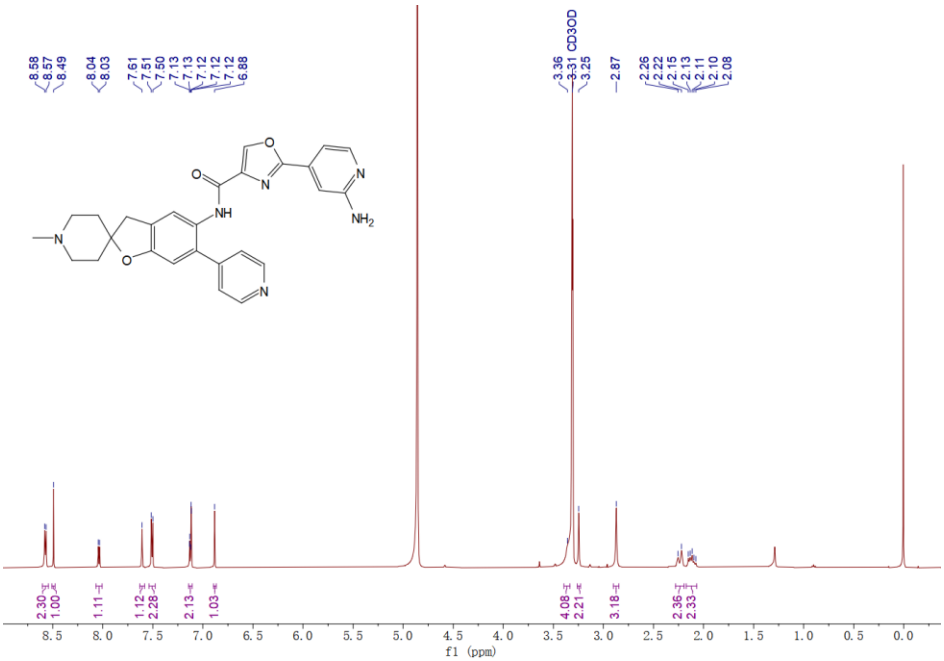
2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**9**)

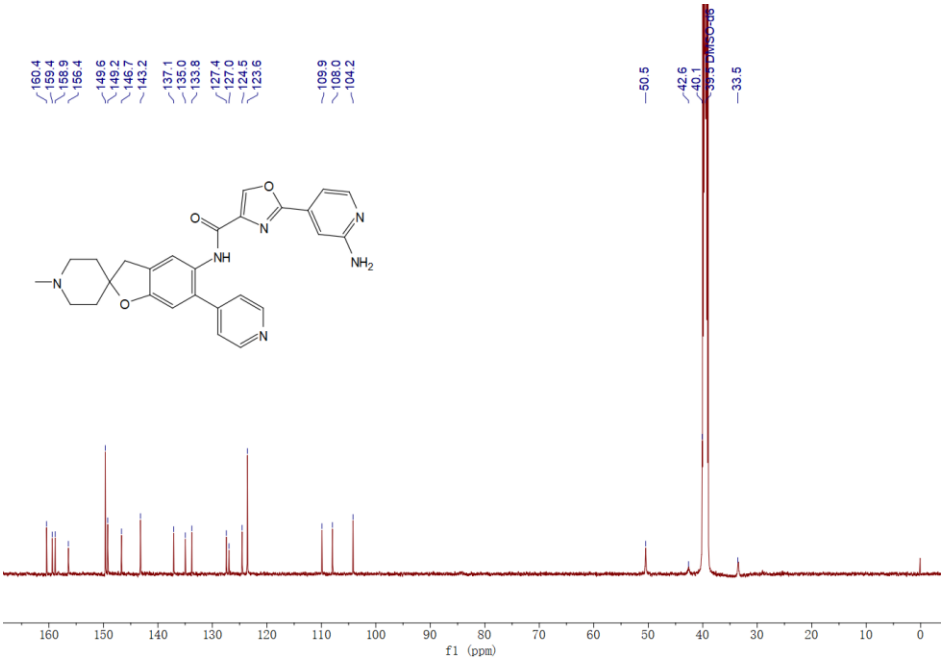


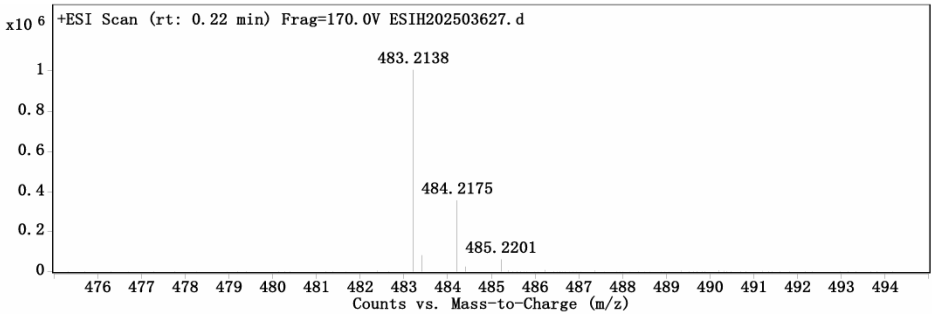




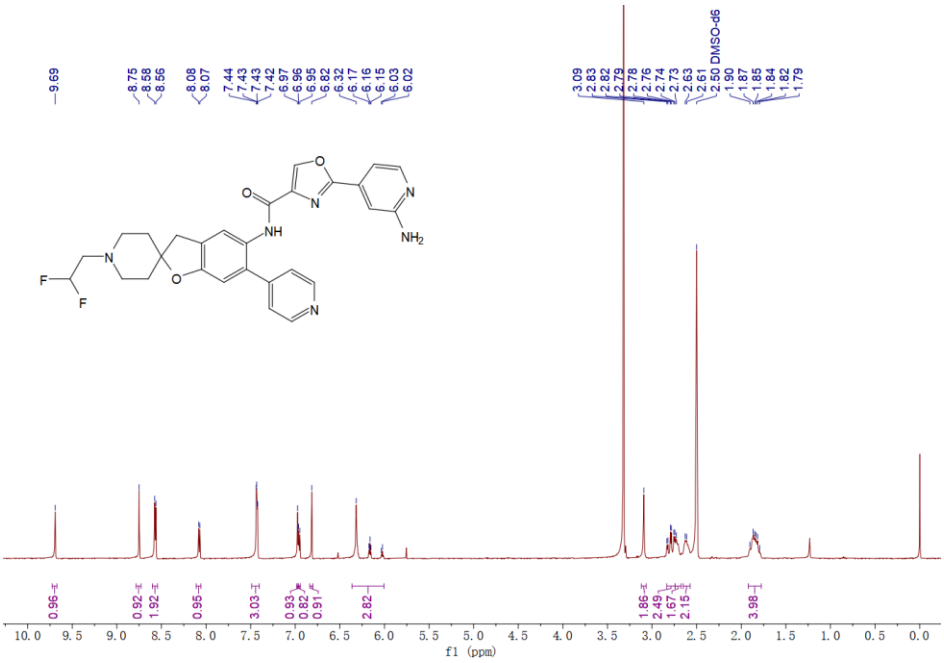
2-(2-aminopyridin-4-yl)-*N*-(1'-methyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**10**)

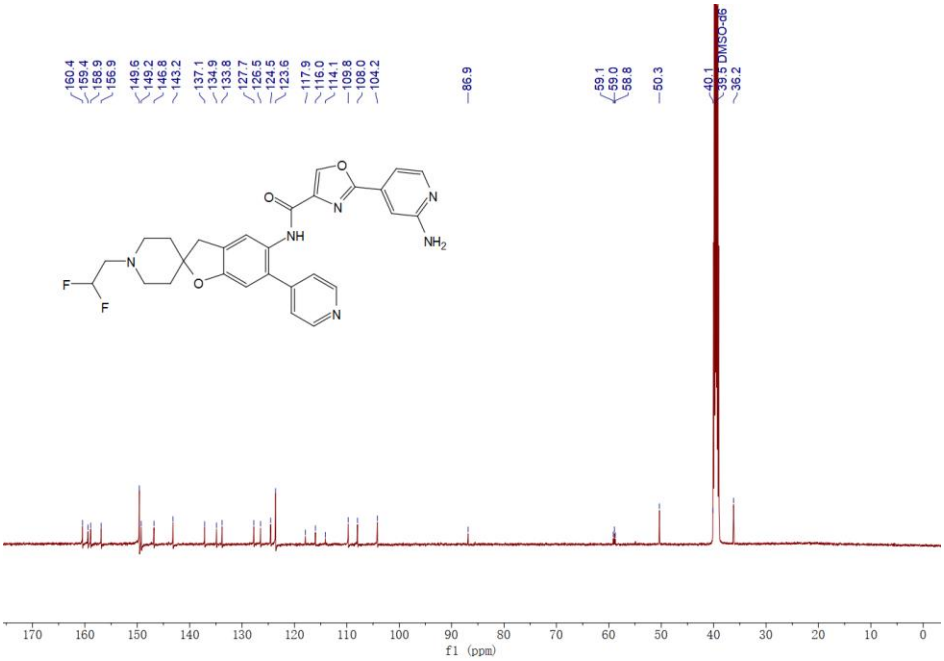


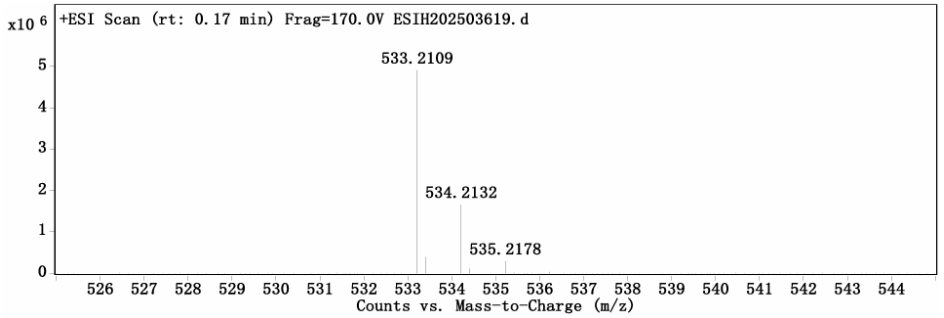




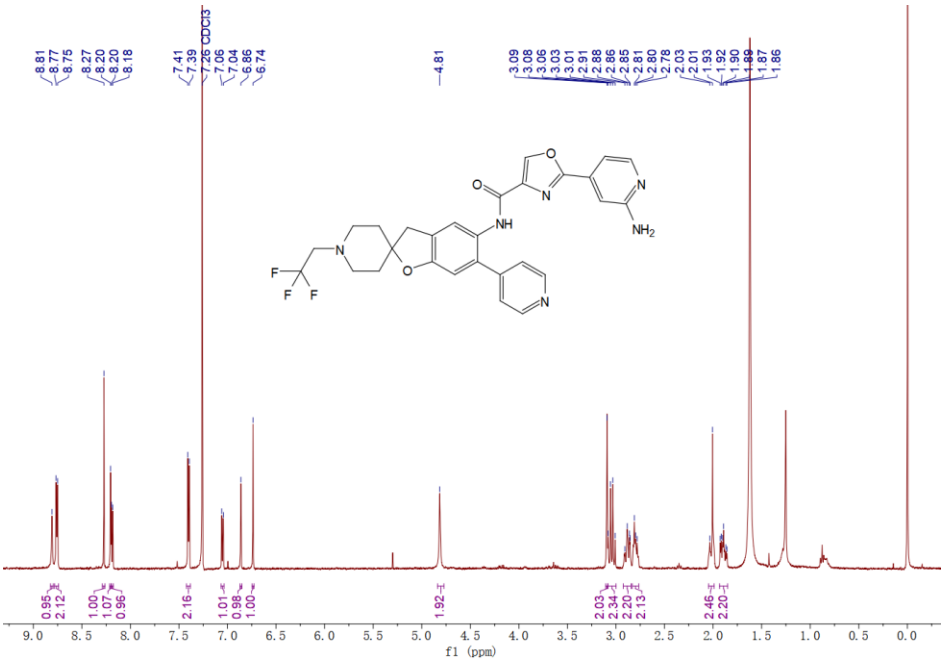
2-(2-aminopyridin-4-yl)-*N*-(1'-(2,2-difluoroethyl)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**11**)

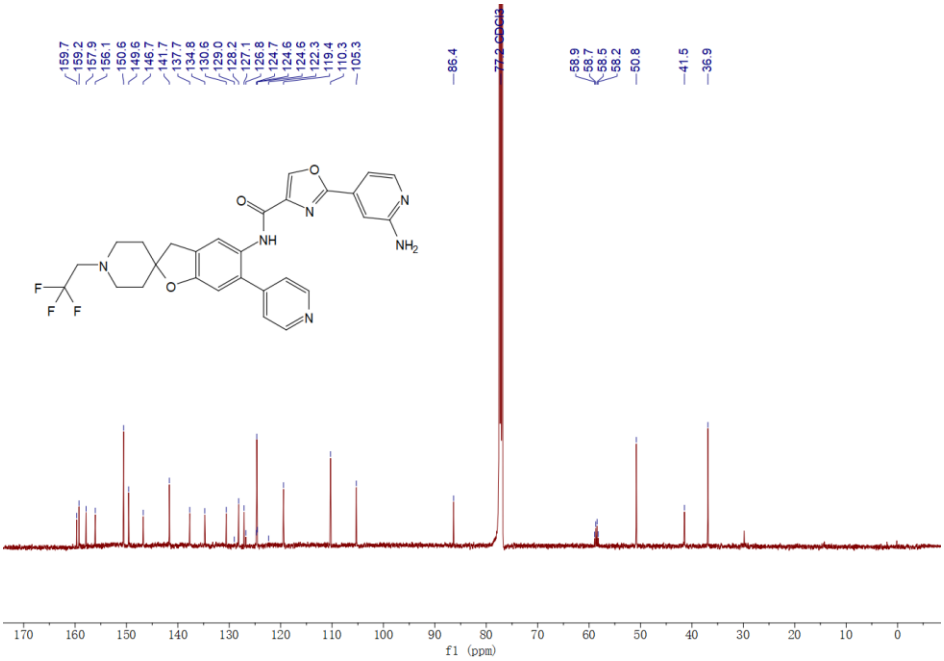


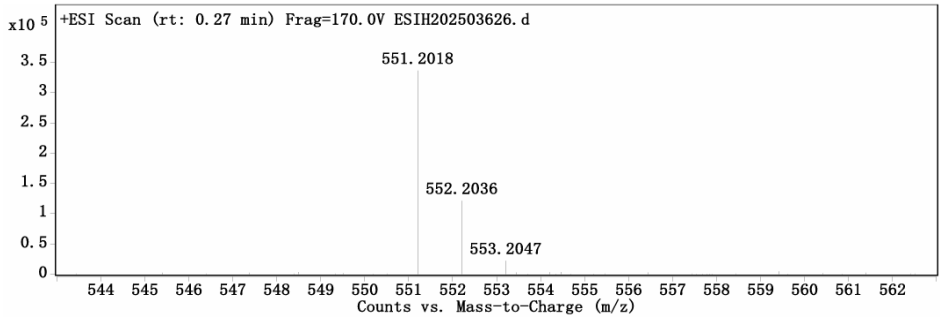




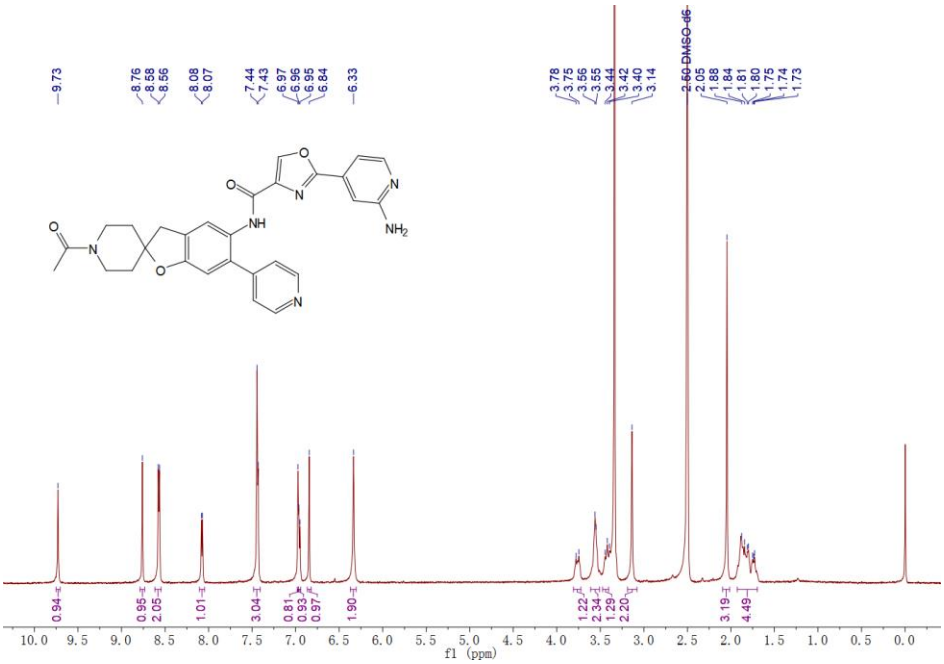
2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-1'-(2,2,2-trifluoroethyl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**12**)

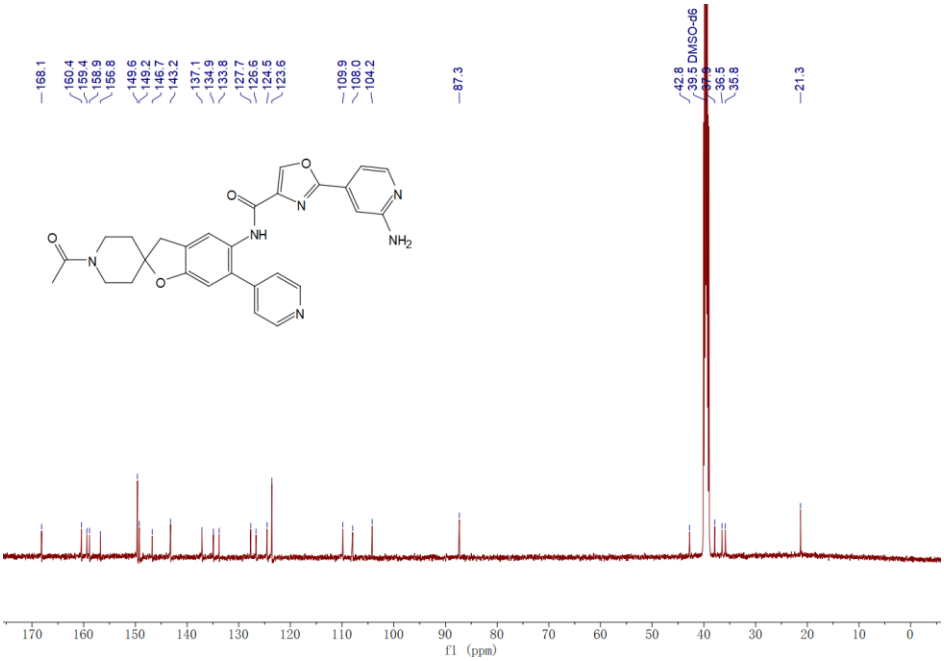


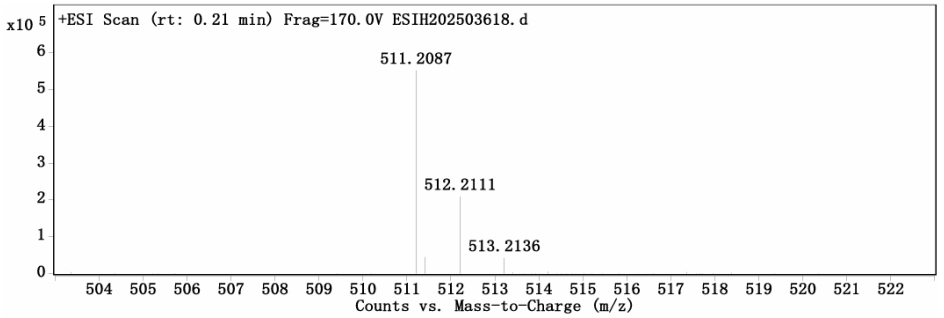




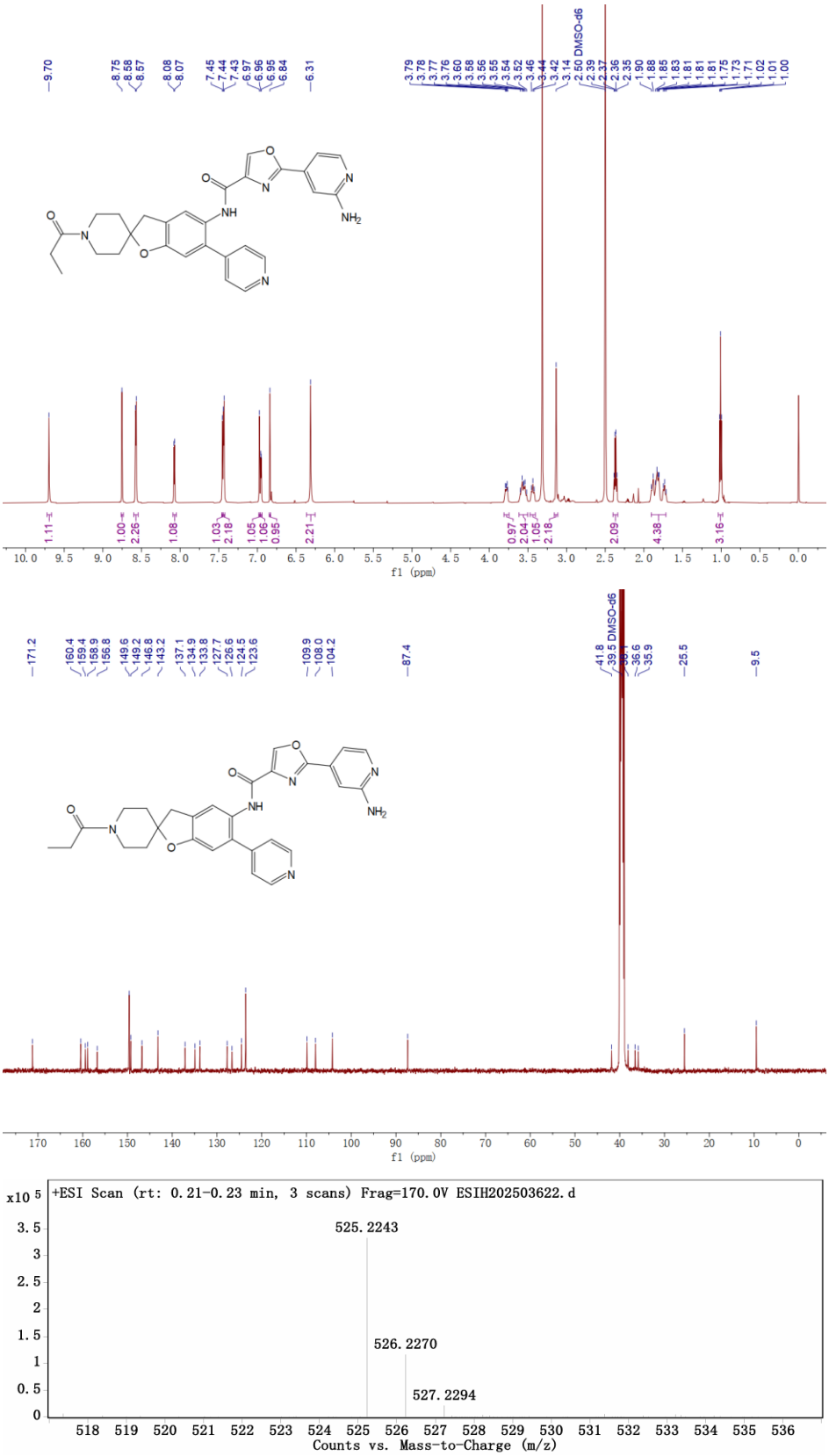
N-(1'-acetyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**13**)



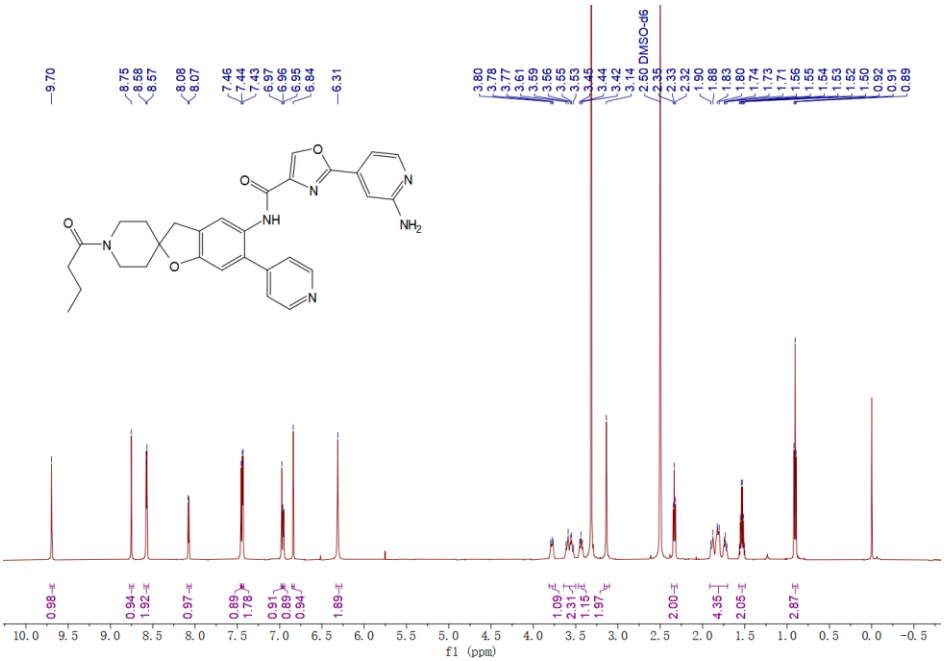


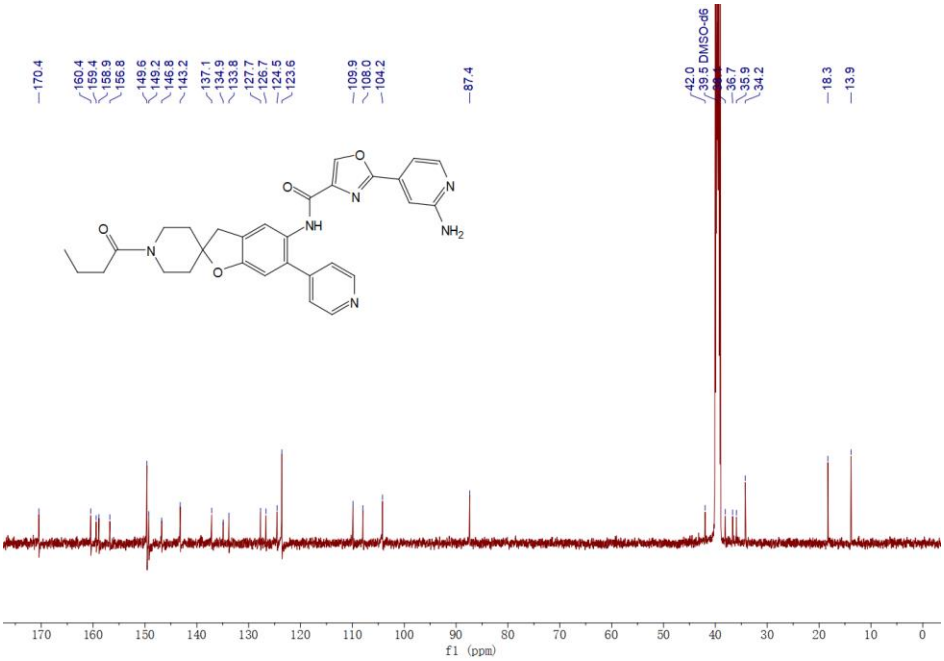


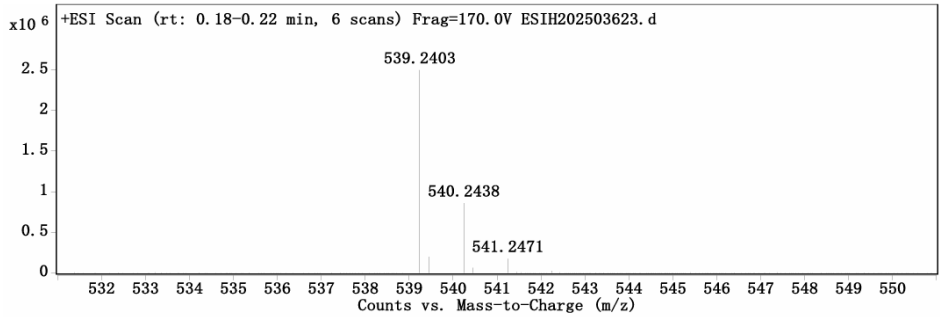
2-(2-aminopyridin-4-yl)-*N*-(1'-propionyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**14**)



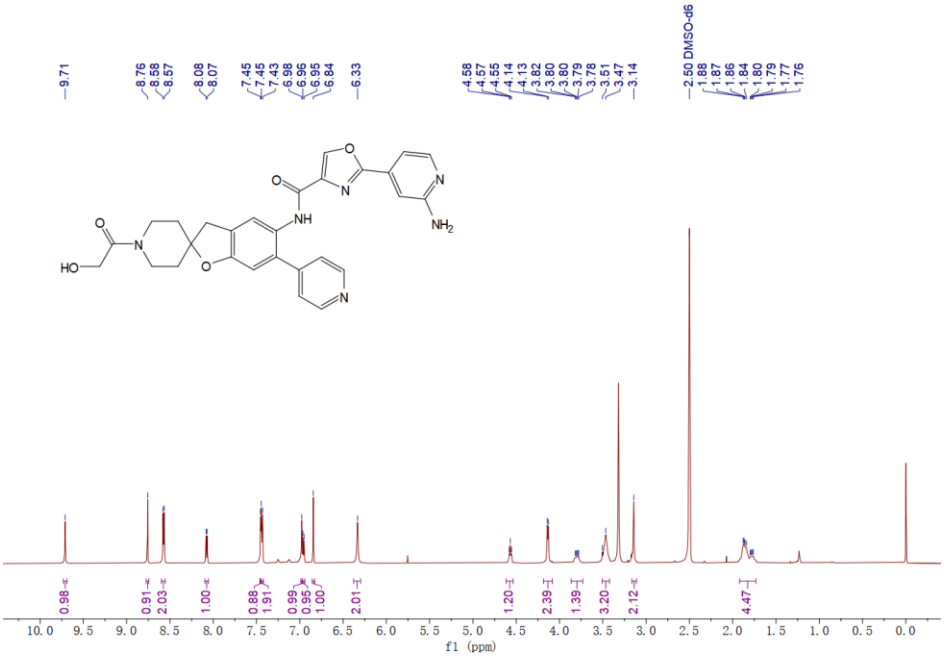
2-(2-aminopyridin-4-yl)-*N*-(1'-butyryl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**15**)

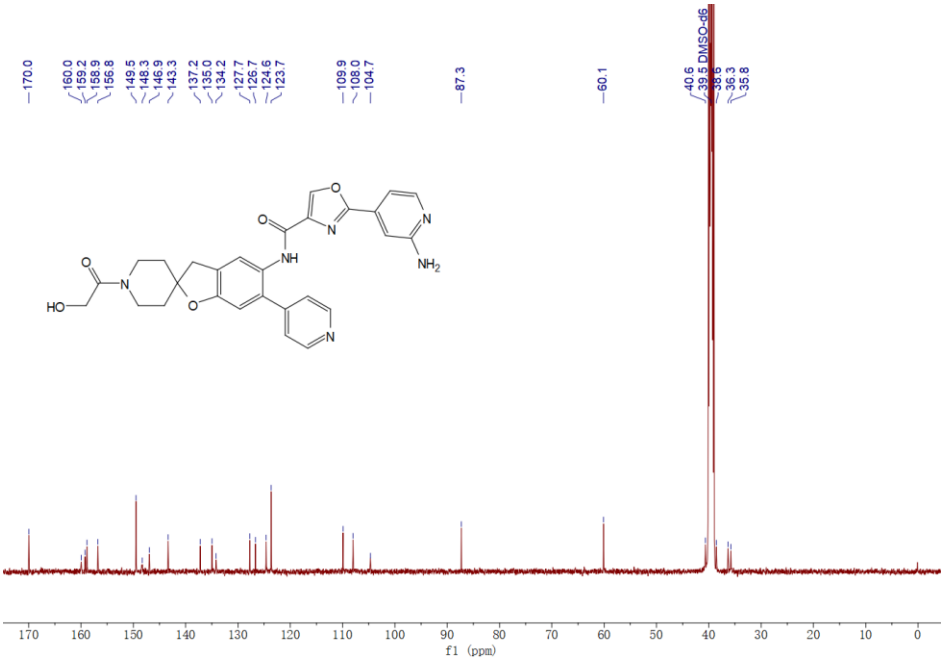


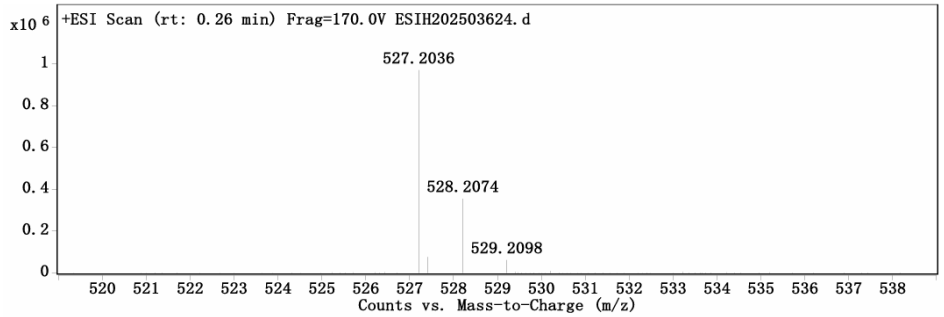




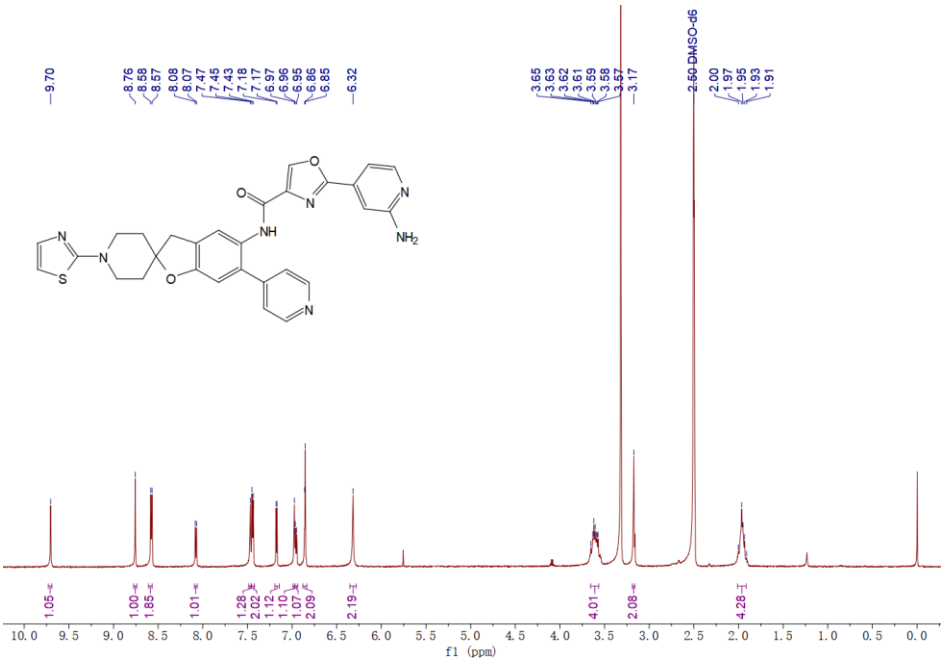
2-(2-aminopyridin-4-yl)-*N*-(1'-(2-hydroxyacetyl)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**16**)

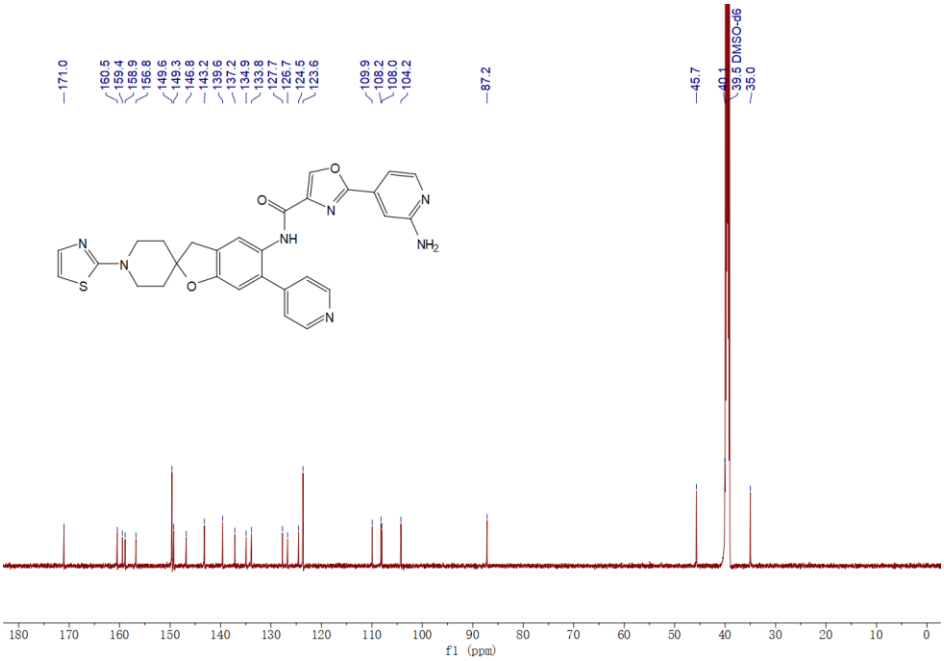


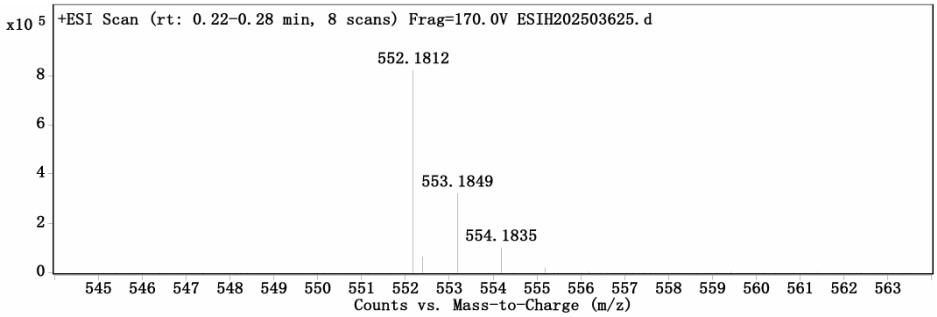




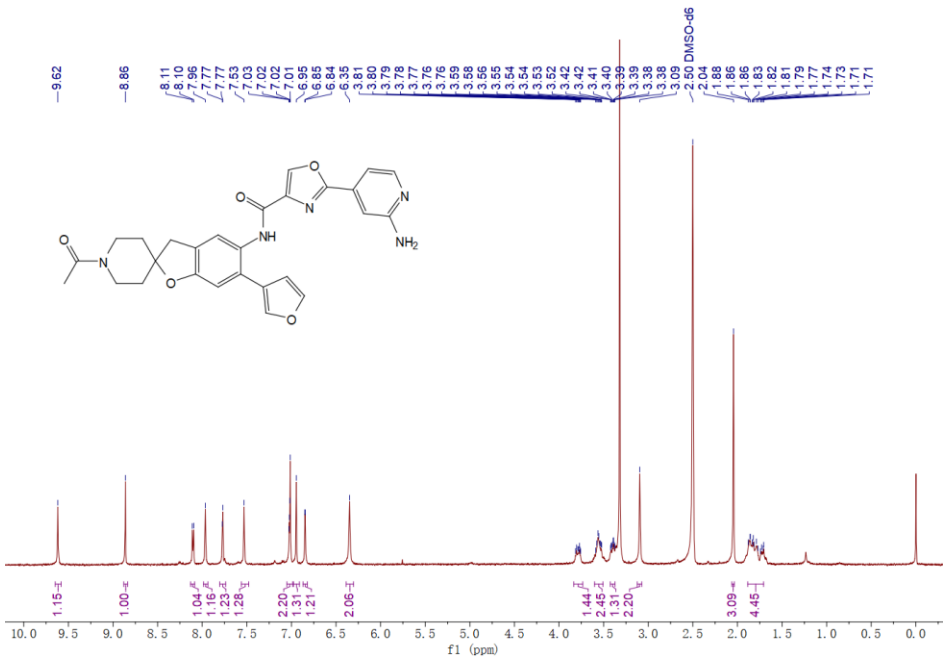
2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-1'-(thiazol-2-yl)-3*H*-spiro[benzofuran-2, 4'-piperidin]-5-yl)oxazole-4-carboxamide (**17**)

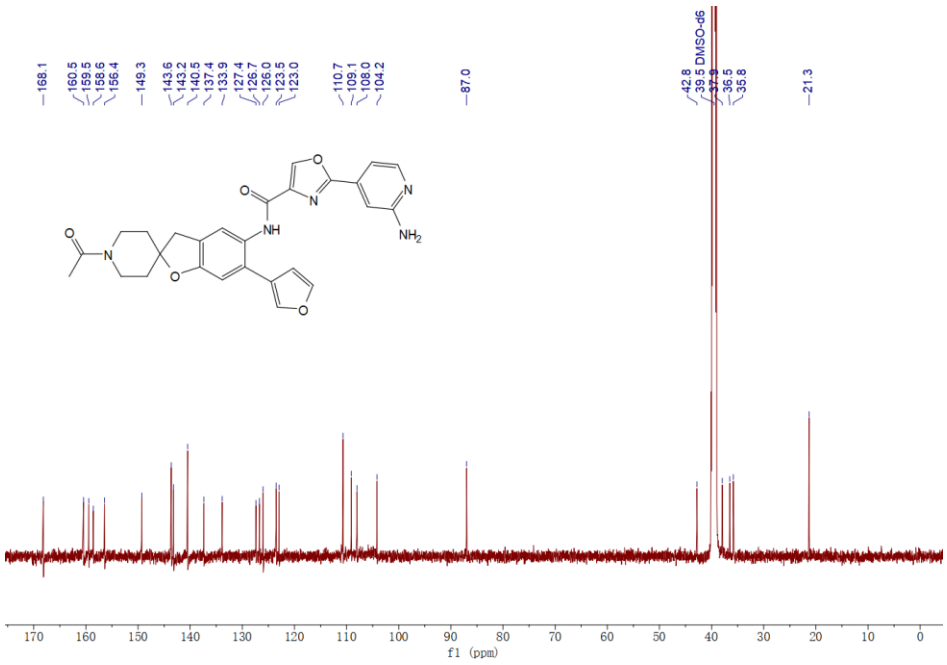


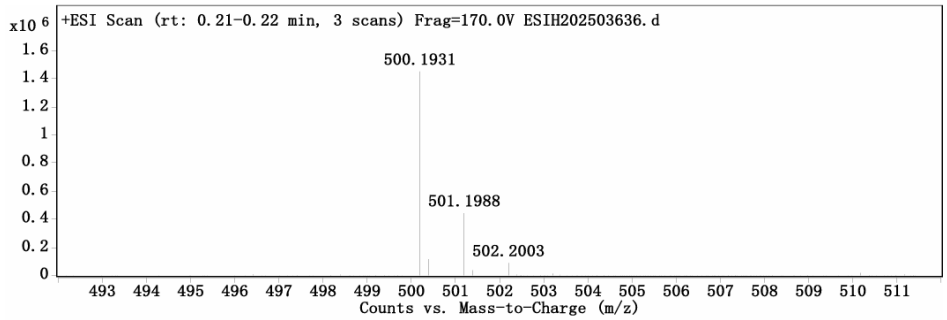




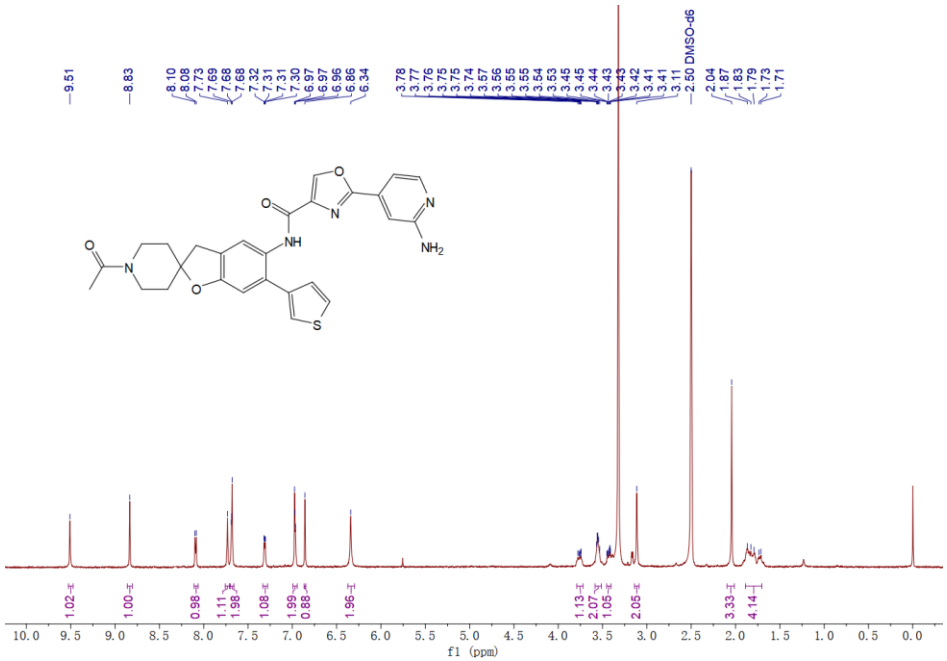
N-(1'-acetyl-6-(furan-3-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**18**)

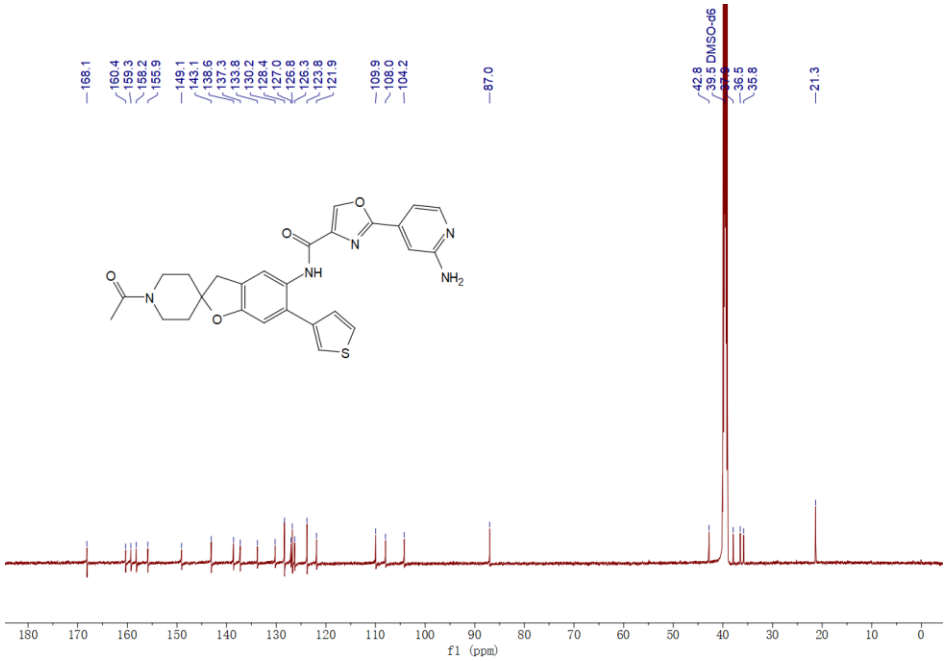


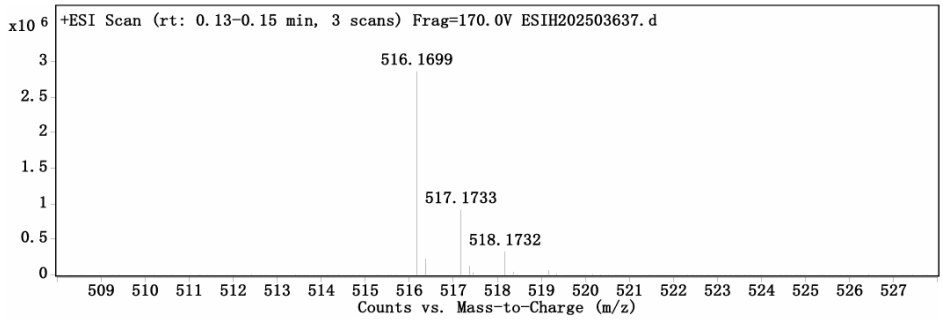




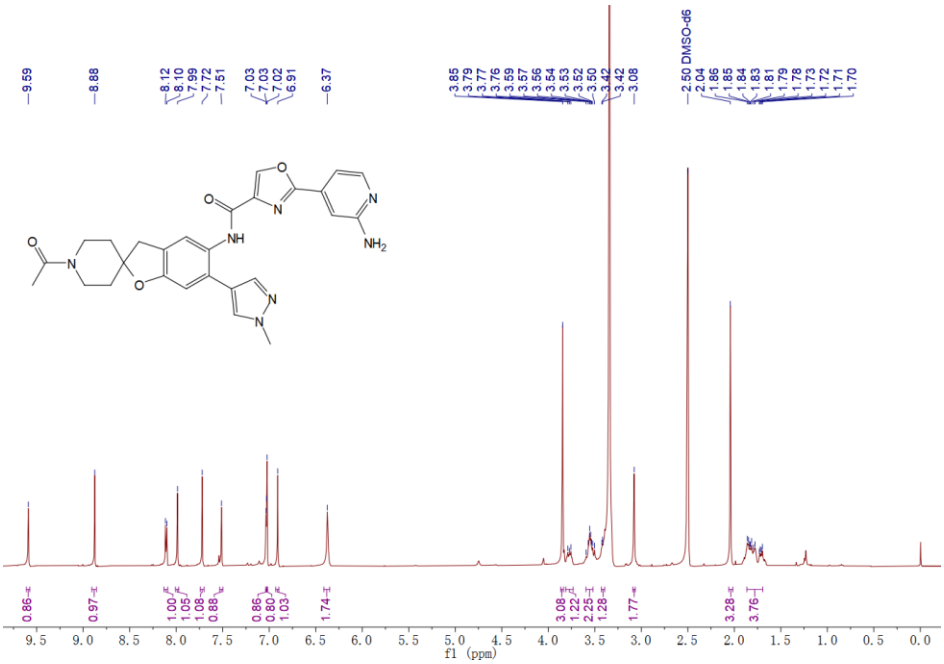
N-(1'-acetyl-6-(thiophen-3-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**19**)

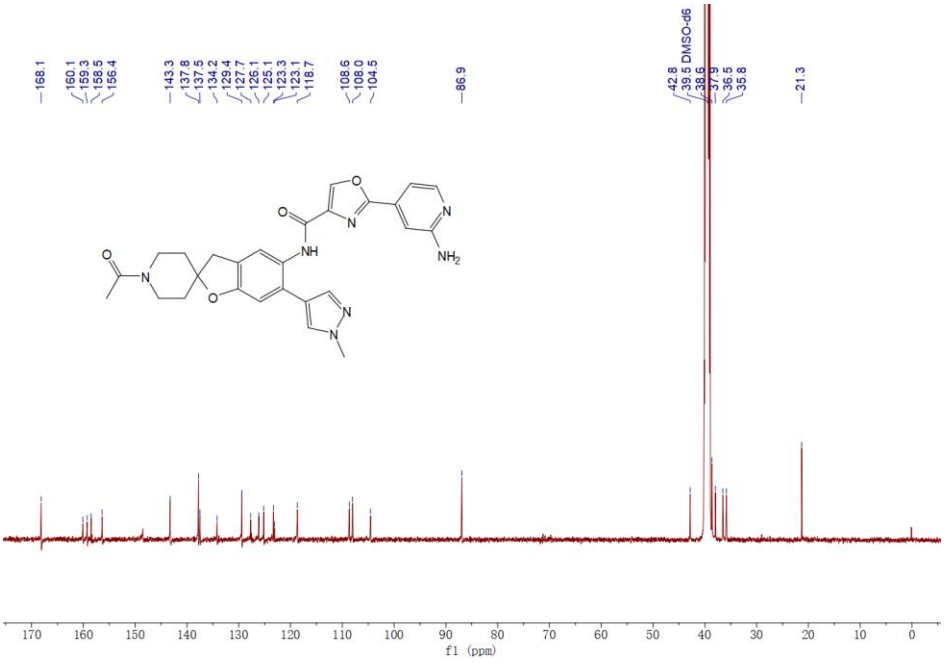


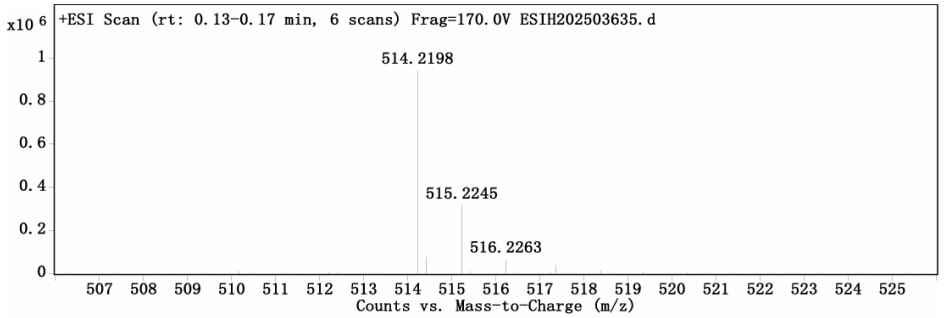




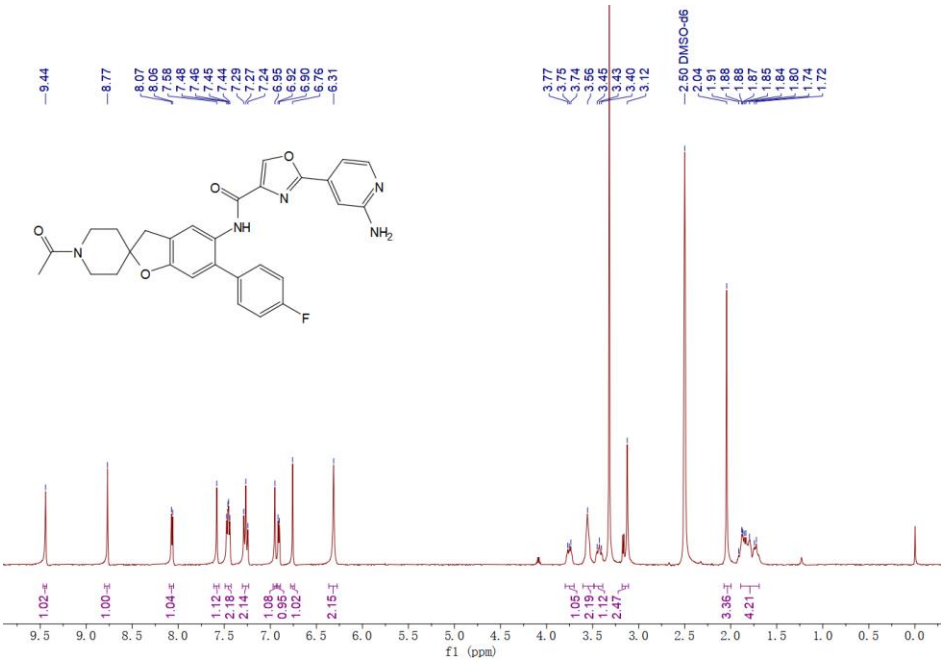
N-(1'-acetyl-6-(1-methyl-1*H*-pyrazol-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**20**)

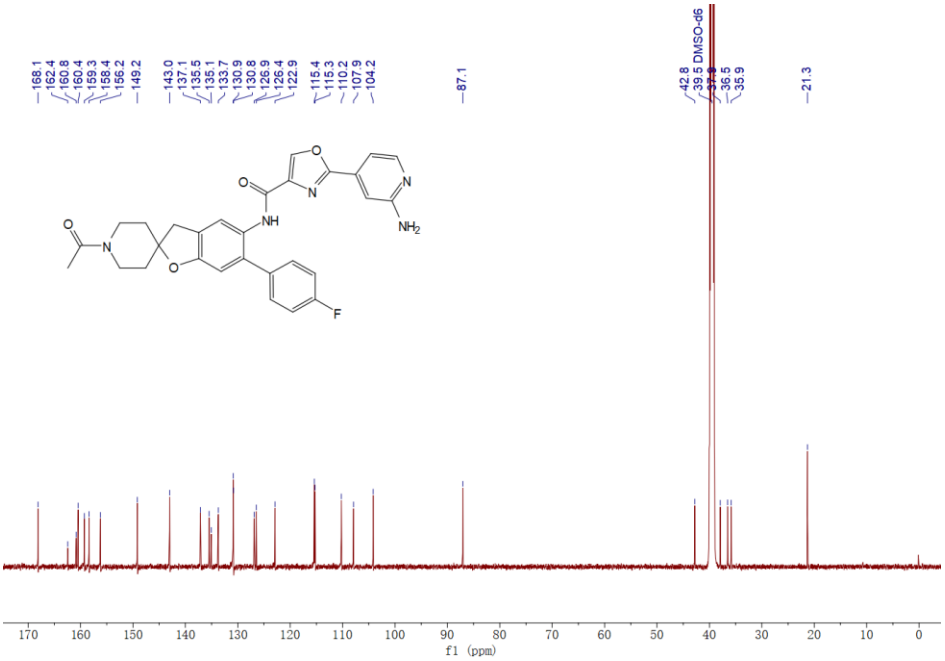


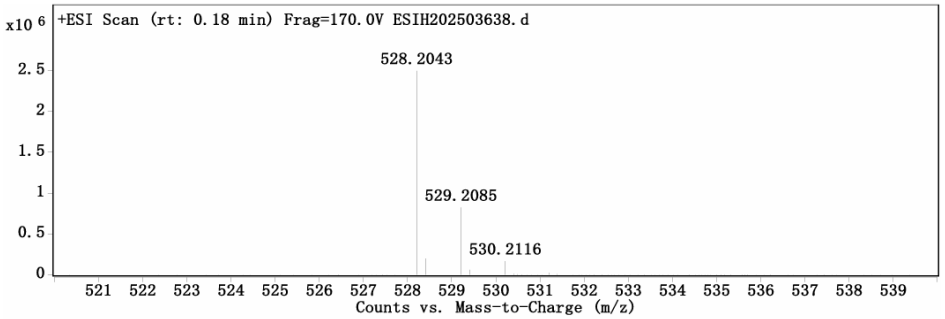




N-(1'-acetyl-6-(4-fluorophenyl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-amino pyridin-4-yl)oxazole-4-carboxamide (**21**)







HPLC determination of target compounds 1–21 and DW18134.

General method for HPLC analysis: HPLC analysis was conducted according to different eluents. The retention time (t_R) is expressed in min at UV detection of 254 nM. HPLC analysis was performed on an Agilent Eclipse Plus column (4.6 × 150 mm, 5 μm) at 35 °C. Flow rate: 1.0 mL/min.

Compound	Retention Time (Min)	Purity (%)
1	4.978[a]	99.95
2	7.908[a]	99.89
3	7.998[f]	99.47
4	6.256[c]	99.94
5	6.396[h]	99.53
6	4.944[e]	99.10
7	6.615[f]	97.44
8	5.328[f]	98.83
9	6.728[a]	99.87
10	5.696[b]	99.62
11	8.581[h]	99.99
12	5.265[a]	98.91
13	5.183[d]	99.45
14	9.200[i]	98.35
15	8.010[h]	98.26
16	8.026[h]	98.55
17	4.948[f]	98.03
18	4.931[g]	97.95
19	7.261[g]	98.43
20	5.408[d]	96.19
21	8.492[g]	99.43
DW18134	7.196[h]	99.87

[a] CH_3OH/H_2O (0.1% TEA) = 70/30 (v/v);

[b] CH_3OH/H_2O (0.1% TEA) = 65/35 (v/v);

[c] CH_3OH/H_2O (0.1% TEA) = 60/40 (v/v);

[d] CH_3OH/H_2O (0.1% TEA) = 55/45 (v/v);

[e] CH_3OH/H_2O (0.1% TFA) = 45/55 (v/v);

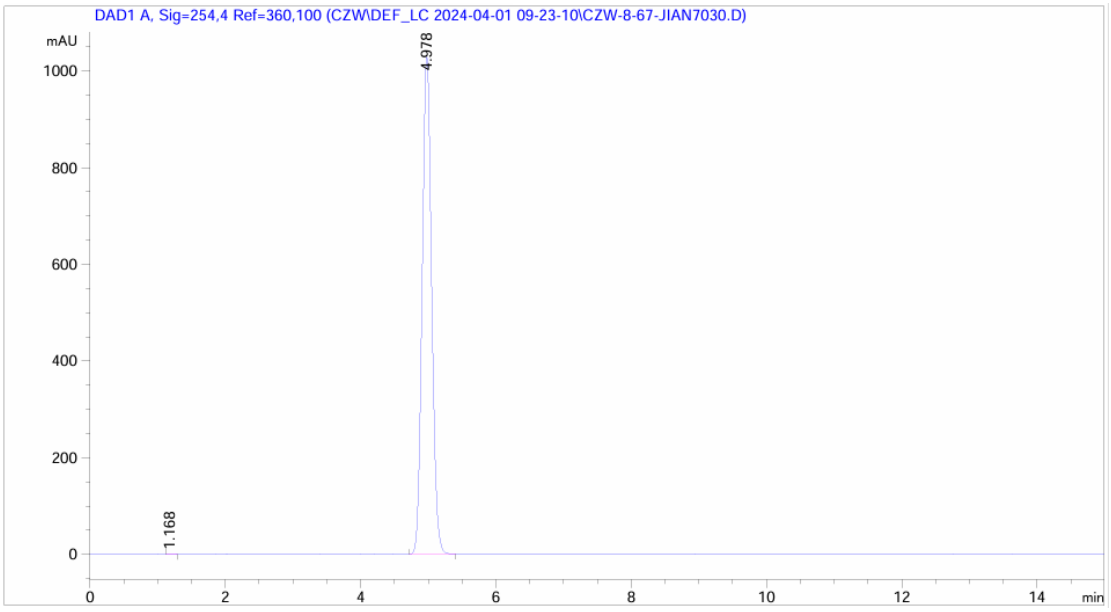
[f] CH_3OH/H_2O = 70/30 (v/v);

[g] CH_3OH/H_2O = 65/35 (v/v);

[h] CH_3OH/H_2O = 60/40 (v/v);

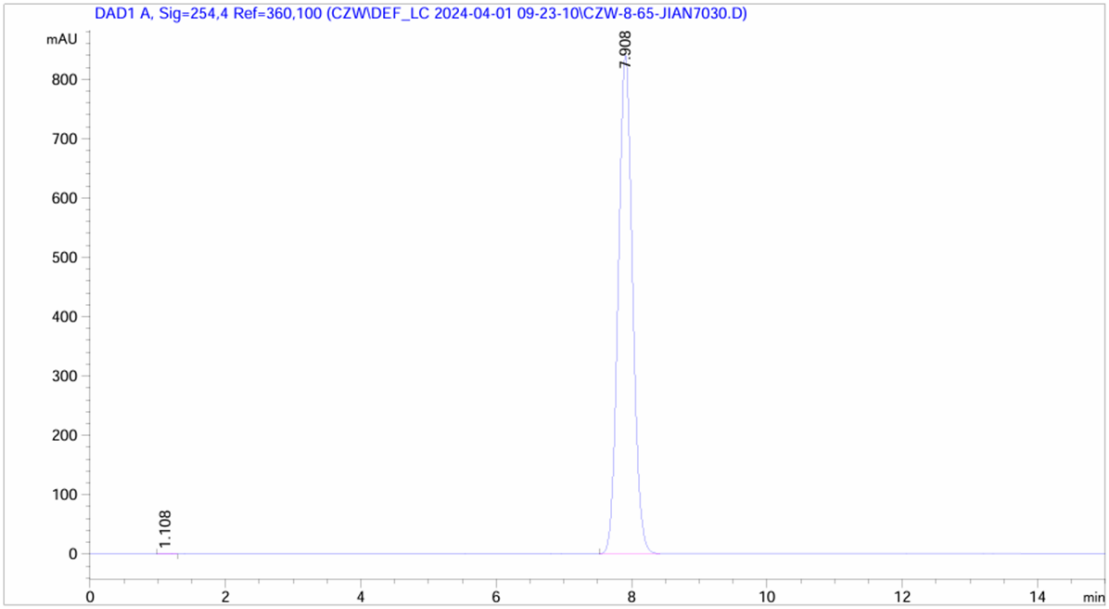
[i] CH_3OH/H_2O = 55/45 (v/v).

2-(2-(difluoromethyl)pyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**1**)



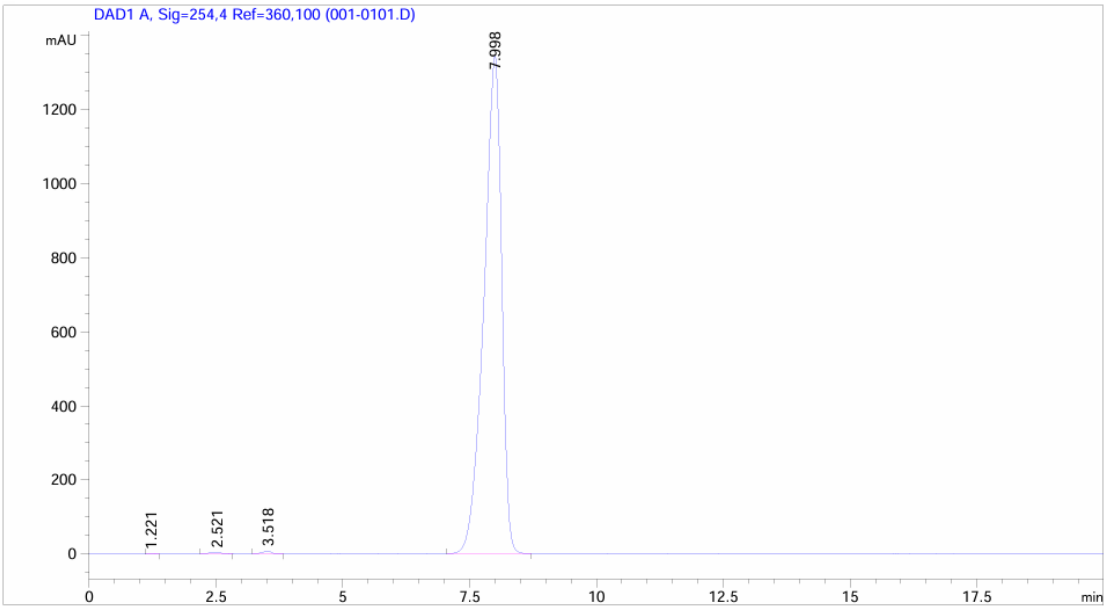
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.168	0.0671	5.34346	1.17366	0.0533
2	4.978	0.1495	1.00150e4	1029.19836	99.9467
Totals			1.00204e4	1030.37203	

2-(2-(difluoromethoxy)pyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**2**)



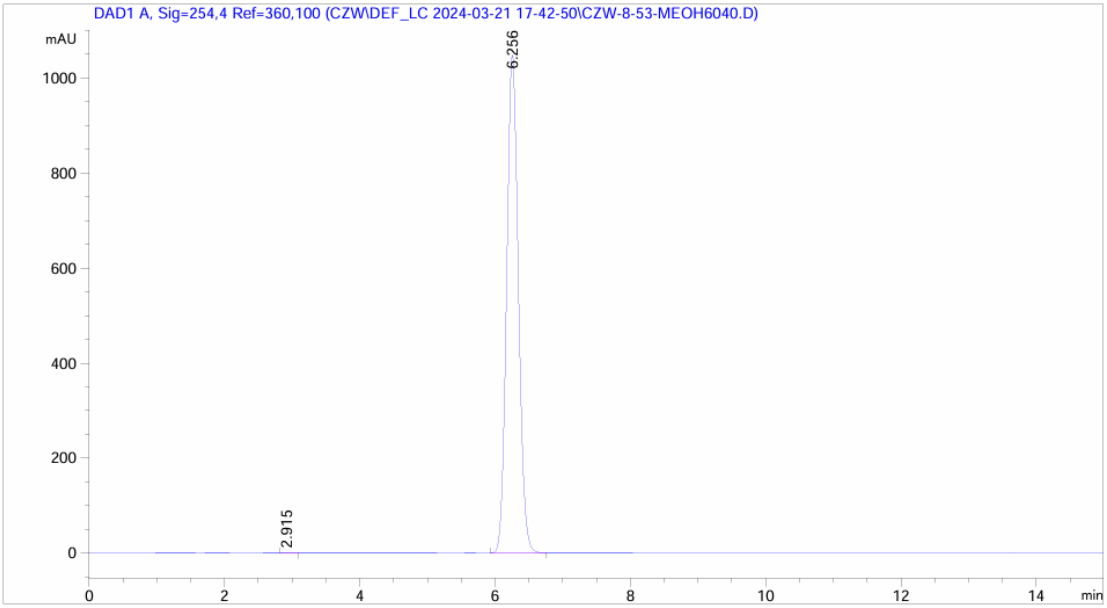
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.108	0.1151	13.26876	1.62815	0.1076
2	7.908	0.2271	1.23237e4	840.11731	99.8924
Totals			1.23369e4	841.74546	

N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(2-((2,2,2-trifluoroethyl)amino)pyridin-4-yl)oxazole-4-carboxamide (**3**)



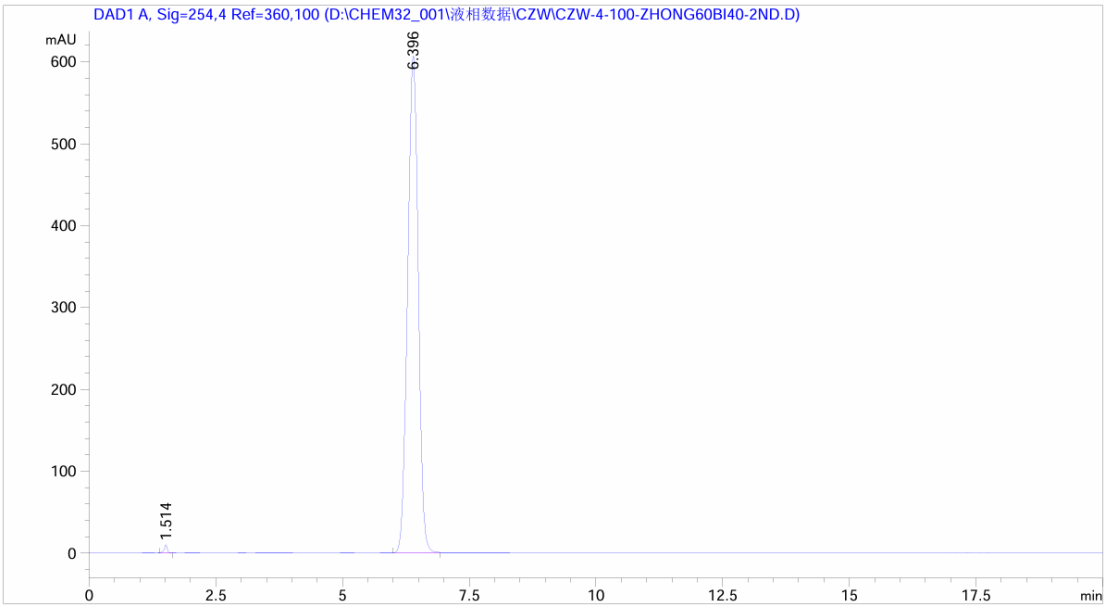
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.221	0.0932	7.58720	1.14726	0.0231
2	2.521	0.1719	63.13881	5.04800	0.1923
3	3.518	0.1753	102.99205	8.75075	0.3138
4	7.998	0.3657	3.26521e4	1342.95386	99.4708
Totals			3.28258e4	1357.89986	

N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-pyrazol-4-yl)oxazole-4-carboxamide (**4**)



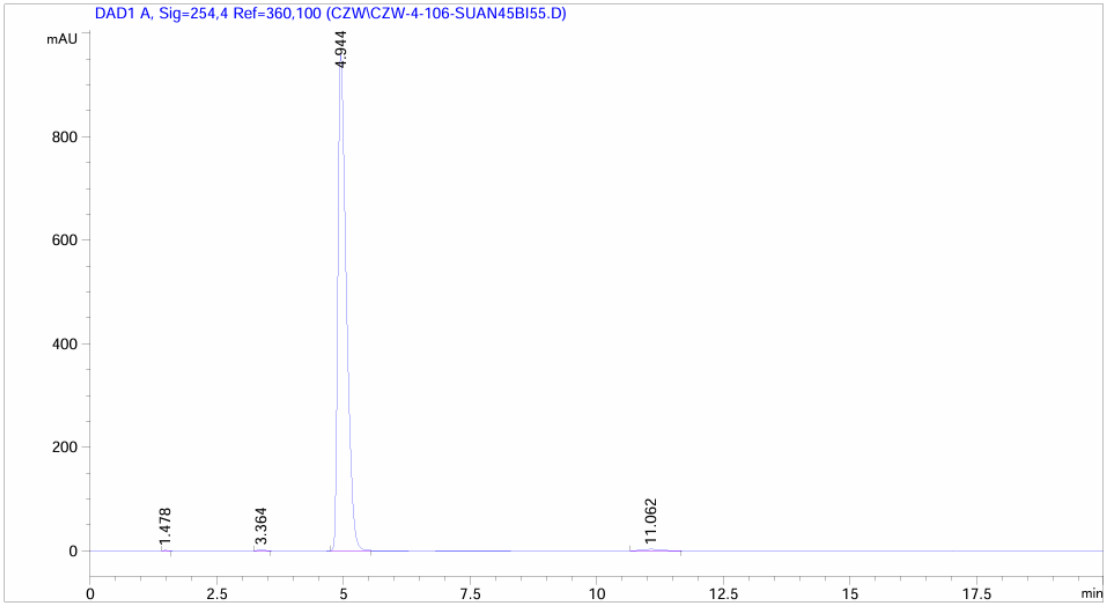
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	2.915	0.0984	8.14081	1.24249	0.0645
2	6.256	0.1864	1.26173e4	1048.61072	99.9355
Totals			1.26254e4	1049.85320	

N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(3-sulfamoylphenyl) oxazole-4-carboxamide (**5**)



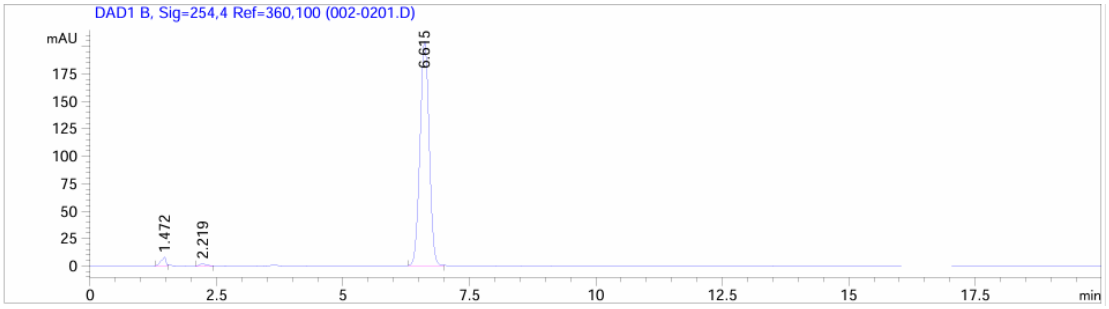
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.514	0.0604	41.48970	9.99302	0.4674
2	6.396	0.2298	8834.61914	607.09369	99.5326
Totals			8876.10884	617.08671	

N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(6-oxo-1,6-dihydropyridin-3-yl)oxazole-4-carboxamide (**6**)



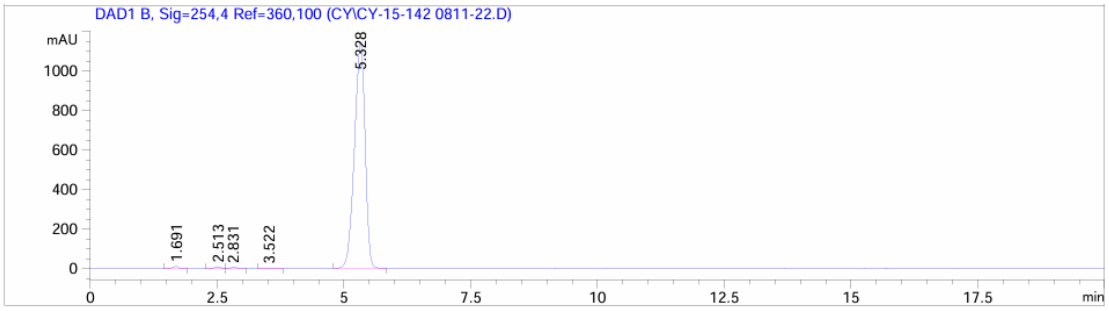
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.478	0.0746	9.40688	1.80997	0.0840
2	3.364	0.1217	17.98340	2.23999	0.1606
3	4.944	0.1750	1.10951e4	958.68994	99.0999
4	11.062	0.3630	73.38122	3.06806	0.6554
Totals			1.11959e4	965.80796	

N-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)oxazole-4-carboxamide (**7**)



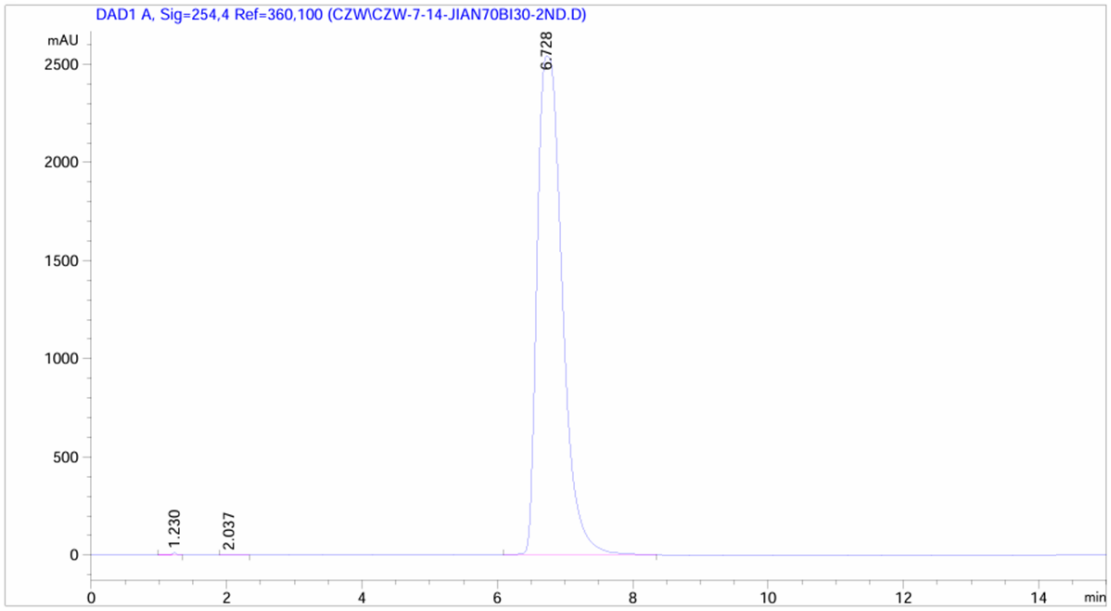
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.472	0.0884	52.19584	7.97314	1.9652
2	2.219	0.1145	15.88582	2.09516	0.5981
3	6.615	0.1977	2587.93311	204.39383	97.4367
Totals			2656.01476	214.46213	

2-(2-aminopyridin-4-yl)-*N*-(3,3-difluoro-2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (**8**)



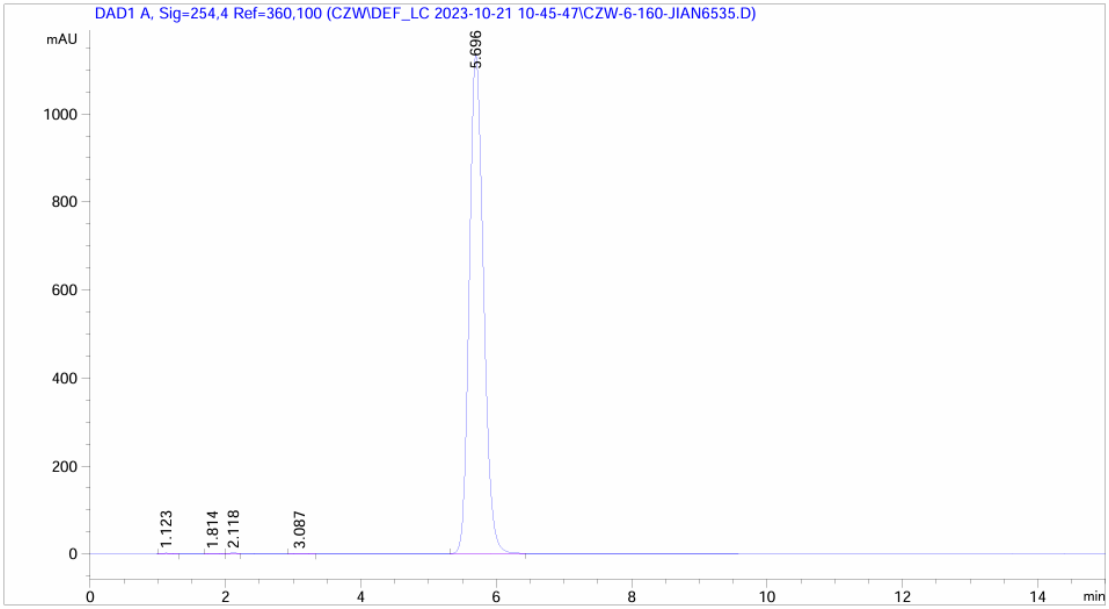
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.691	0.0997	81.41309	11.34933	0.4816
2	2.513	0.1213	59.18854	7.24898	0.3501
3	2.831	0.1558	39.29405	3.76258	0.2324
4	3.522	0.1704	17.69357	1.58337	0.1047
5	5.328	0.2283	1.67078e4	1144.71619	98.8312
Totals			1.69054e4	1168.66045	

2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**9**)



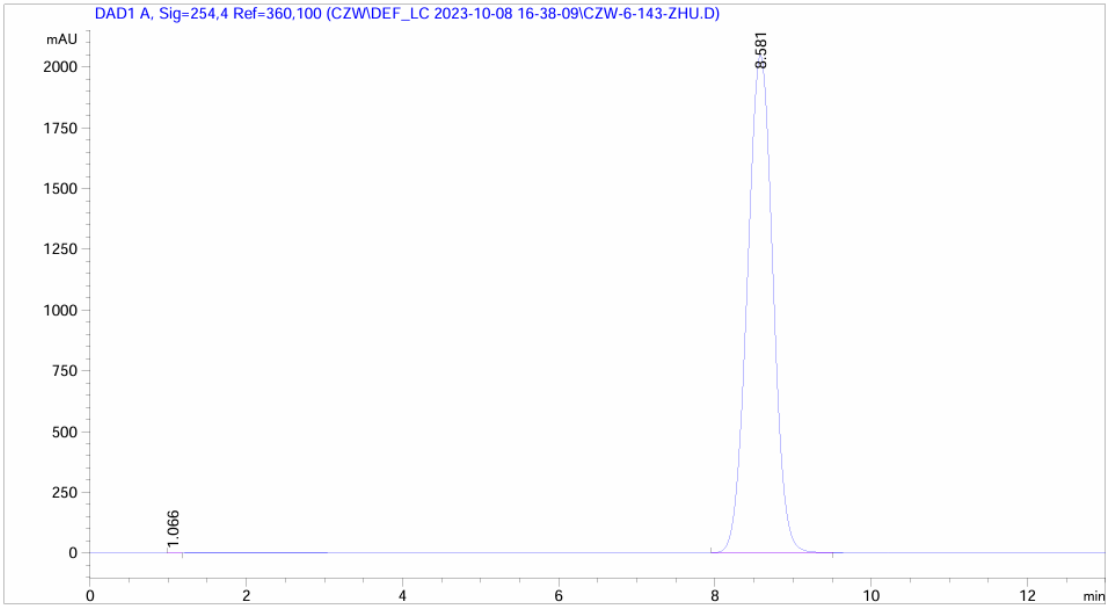
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.230	0.0802	70.41953	12.41711	0.1081
2	2.037	0.1430	14.34328	1.27771	0.0220
3	6.728	0.3448	6.50335e4	2539.61816	99.8698
Totals			6.51182e4	2553.31298	

2-(2-aminopyridin-4-yl)-*N*-(1'-methyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**10**)



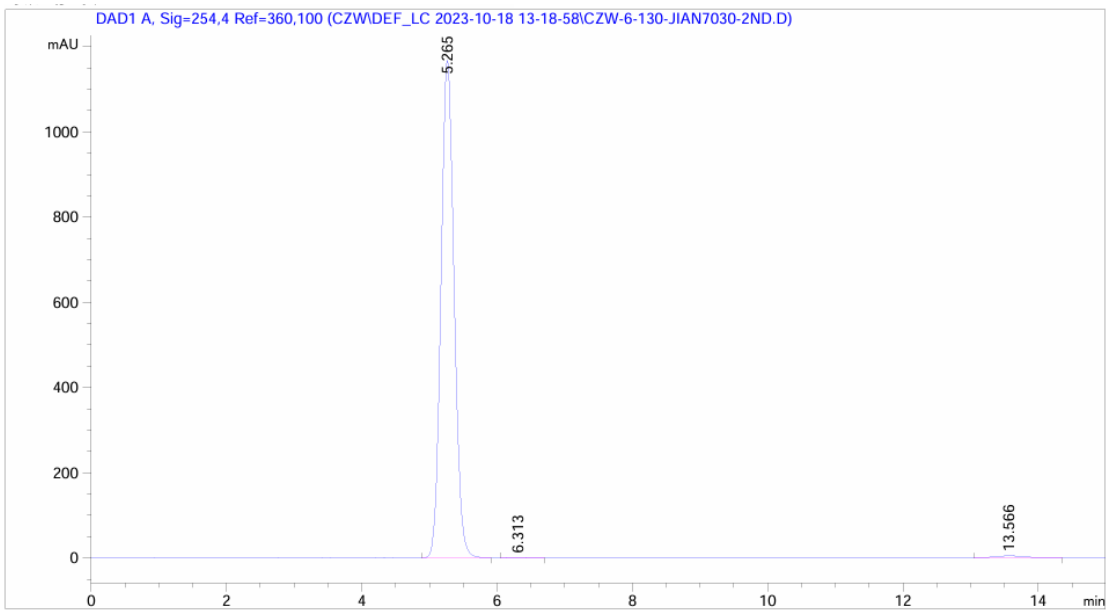
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.123	0.0965	16.76173	2.37146	0.1009
2	1.814	0.1186	14.16868	1.74660	0.0853
3	2.118	0.1163	19.07369	2.46358	0.1148
4	3.087	0.1443	12.48115	1.34416	0.0751
5	5.696	0.2283	1.65484e4	1133.49500	99.6238
Totals			1.66109e4	1141.42080	

2-(2-aminopyridin-4-yl)-*N*-(1'-(2,2-difluoroethyl)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**11**)



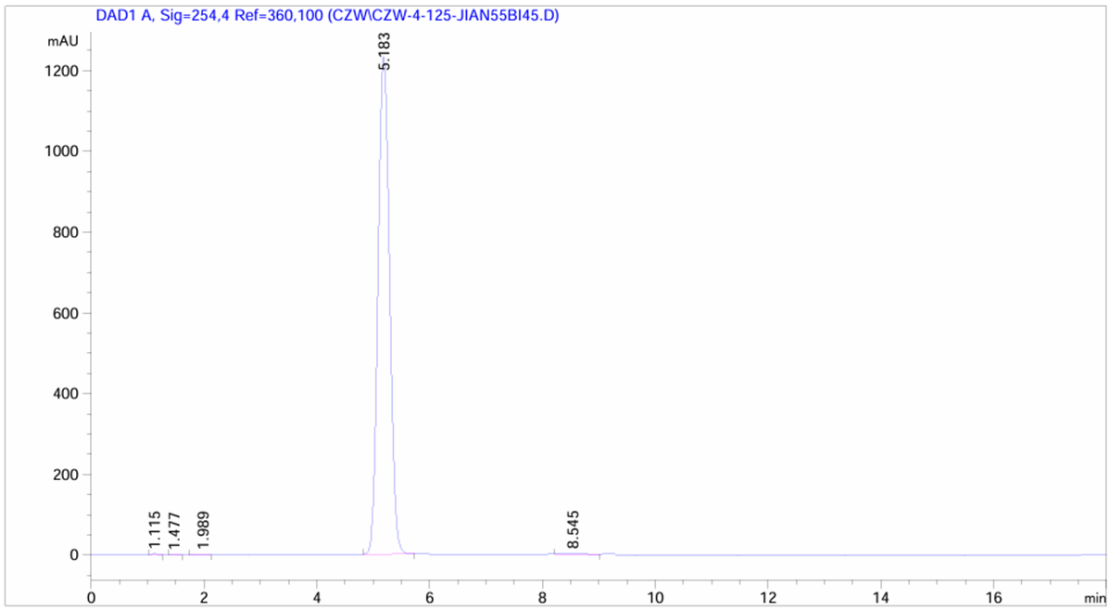
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.066	0.0833	6.41048	1.11073	0.0138
2	8.581	0.3551	4.65435e4	2048.19360	99.9862
Totals			4.65499e4	2049.30434	

2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-1'-(2,2,2-trifluoroethyl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**12**)



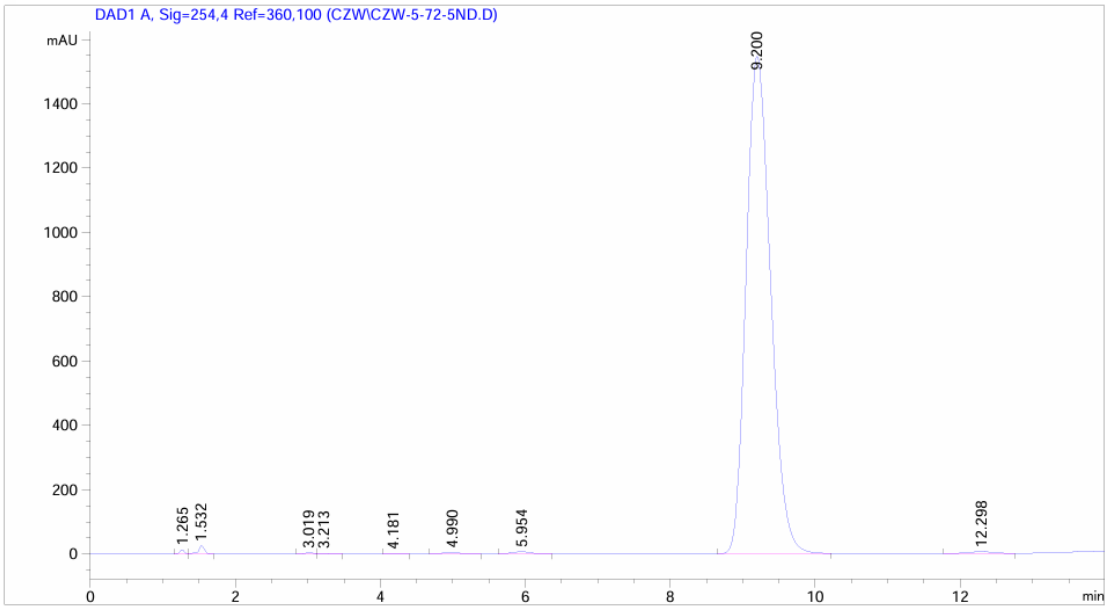
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	5.265	0.2112	1.57364e4	1168.18188	98.9075
2	6.313	0.1899	17.08642	1.18724	0.1074
3	13.566	0.4617	156.73451	5.00018	0.9851
Totals			1.59102e4	1174.36930	

N-(1'-acetyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**13**)



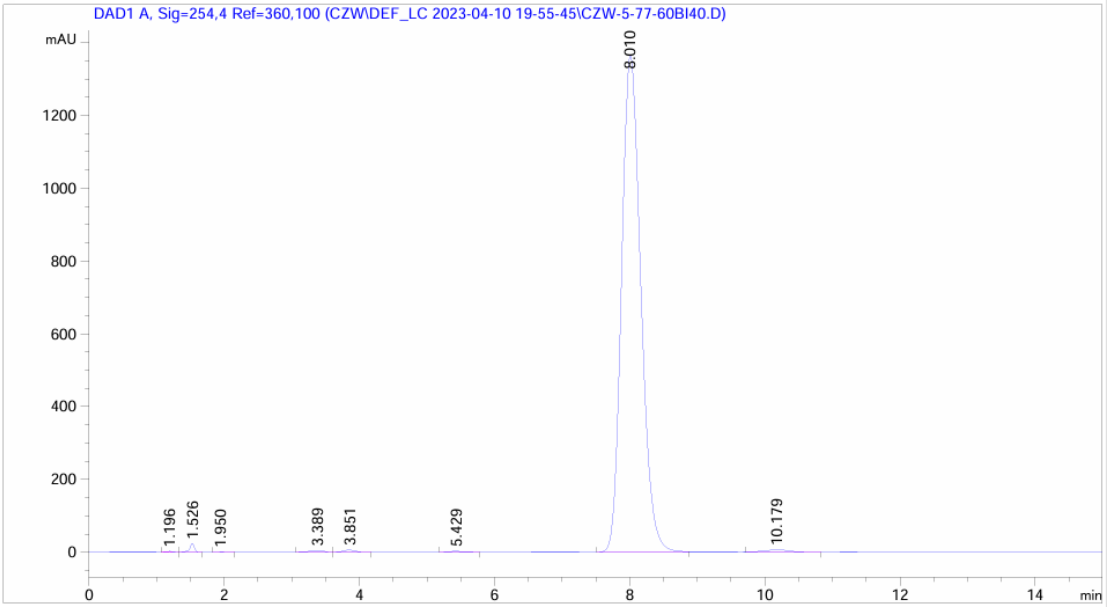
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.115	0.0829	19.08170	3.32699	0.1085
2	1.477	0.1007	8.17601	1.18188	0.0465
3	1.989	0.1558	25.26881	2.17132	0.1437
4	5.183	0.2257	1.74927e4	1231.85681	99.4469
5	8.545	0.2768	44.75562	2.47680	0.2544
Totals			1.75900e4	1241.01380	

2-(2-aminopyridin-4-yl)-*N*-(1'-propionyl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**14**)



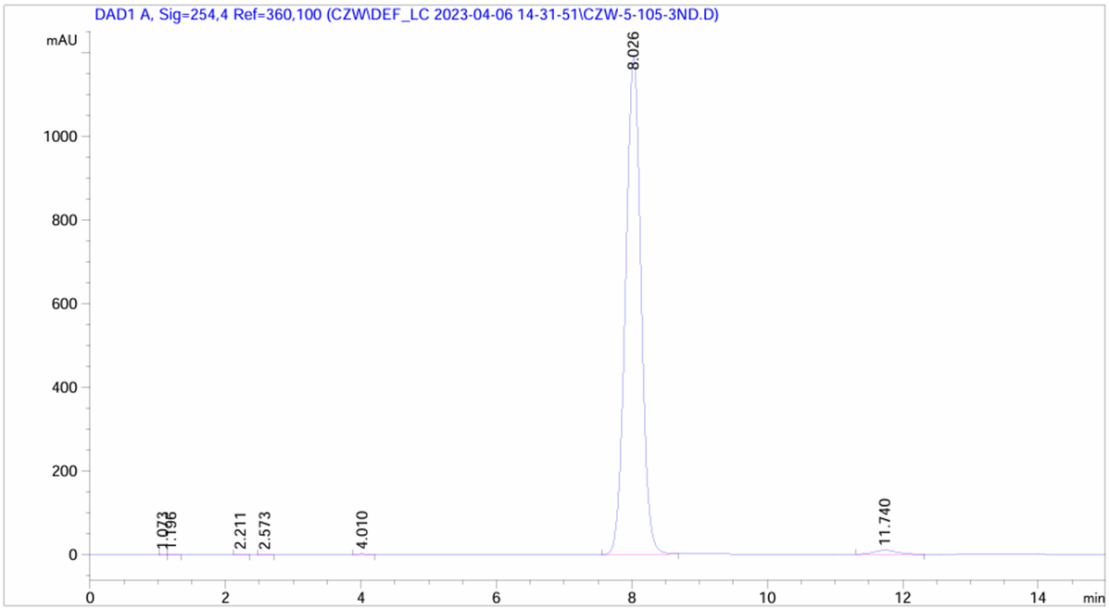
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.265	0.0619	56.51296	13.77088	0.1530
2	1.532	0.0887	143.03836	25.79211	0.3872
3	3.019	0.1316	28.26218	3.31089	0.0765
4	3.213	0.1530	24.60363	2.41227	0.0666
5	4.181	0.1367	10.02356	1.11646	0.0271
6	4.990	0.2437	78.50866	4.93183	0.2125
7	5.954	0.2470	117.80408	7.27236	0.3189
8	9.200	0.3681	3.63336e4	1546.33813	98.3503
9	12.298	0.3952	150.71513	6.08032	0.4080
Totals			3.69431e4	1611.02527	

2-(2-aminopyridin-4-yl)-*N*-(1'-butyryl-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**15**)



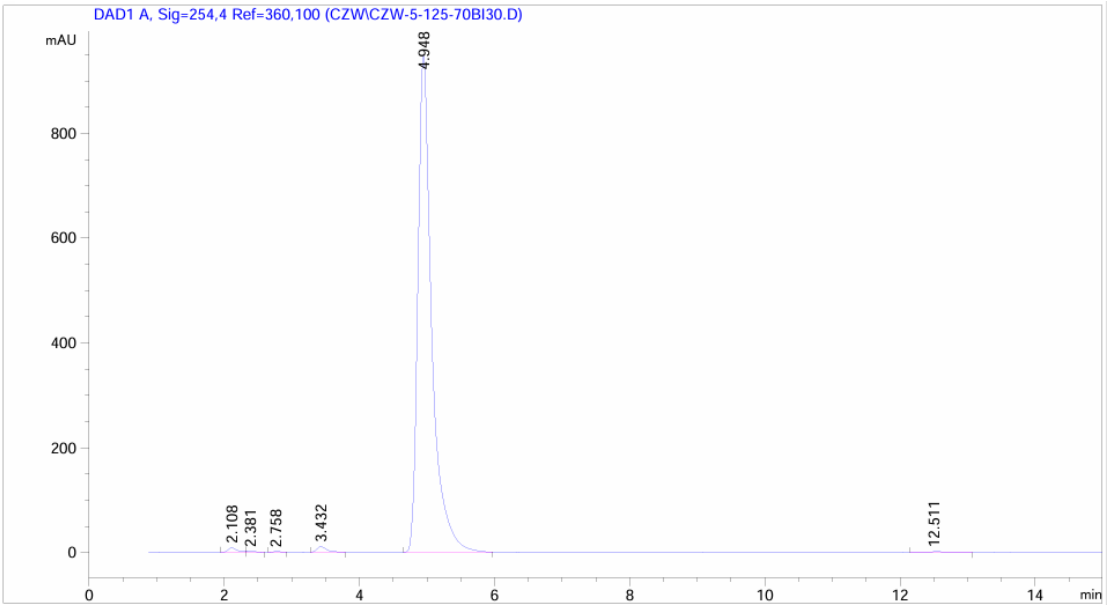
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.196	0.0840	16.81593	2.72429	0.0614
2	1.526	0.0697	116.17903	24.33755	0.4241
3	1.950	0.1063	8.08699	1.17555	0.0295
4	3.389	0.2120	65.96297	4.75101	0.2408
5	3.851	0.1918	76.43655	6.20026	0.2790
6	5.429	0.2216	41.23497	2.83625	0.1505
7	8.010	0.3081	2.69159e4	1364.56506	98.2565
8	10.179	0.3671	152.88336	6.62701	0.5581
Totals			2.73935e4	1413.21697	

2-(2-aminopyridin-4-yl)-*N*-(1'-(2-hydroxyacetyl)-6-(pyridin-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)oxazole-4-carboxamide (**16**)



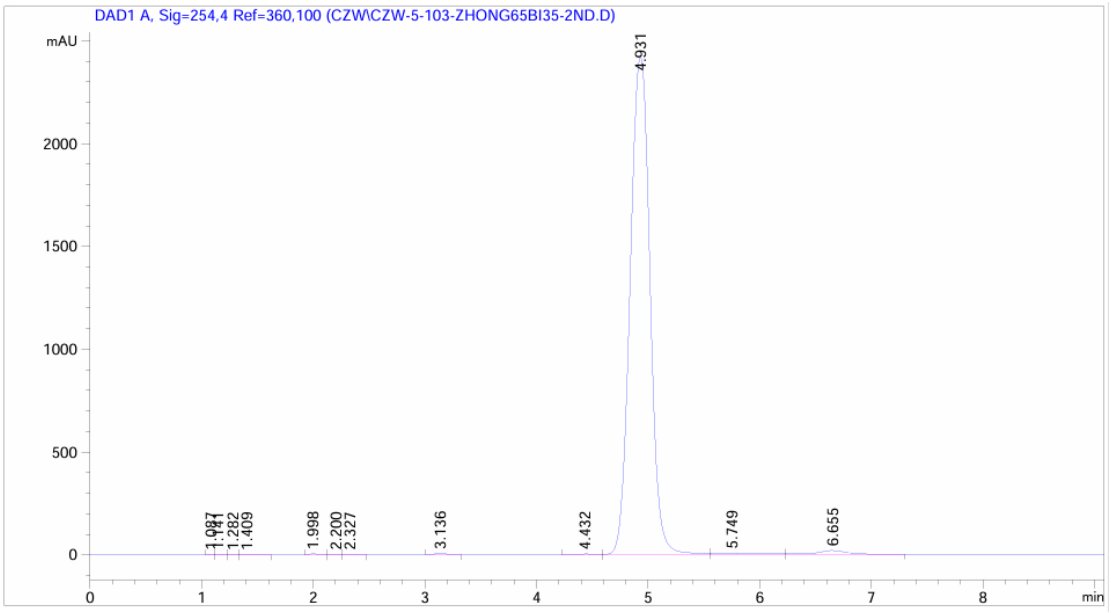
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.073	0.0535	5.61536	1.57847	0.0294
2	1.196	0.0815	5.70393	1.08208	0.0299
3	2.211	0.0879	12.16927	2.15302	0.0637
4	2.573	0.0860	8.44843	1.54000	0.0442
5	4.010	0.1173	18.82439	2.45806	0.0985
6	8.026	0.2447	1.88252e4	1189.38318	98.5536
7	11.740	0.3487	225.52705	10.01483	1.1807
Totals			1.91015e4	1208.20963	

2-(2-aminopyridin-4-yl)-*N*-(6-(pyridin-4-yl)-1'-(thiazol-2-yl)-3*H*-spiro[benzofuran-2, 4'-piperidin]-5-yl)oxazole-4-carboxamide (**17**)



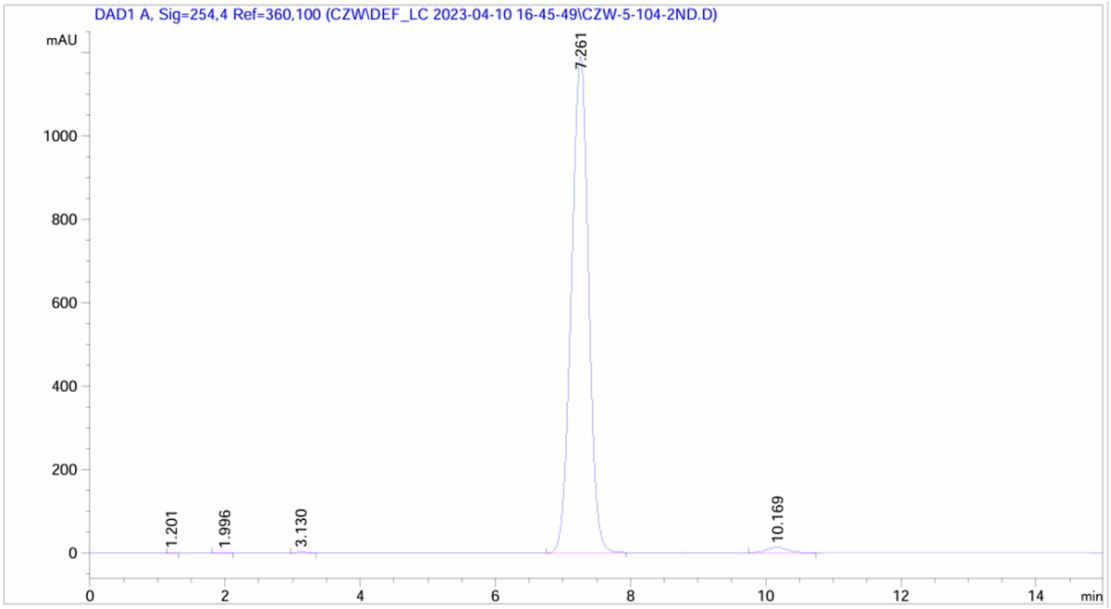
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	2.108	0.1265	77.64240	8.83603	0.5652
2	2.381	0.1321	15.35501	1.68871	0.1118
3	2.758	0.1401	11.28359	1.13393	0.0821
4	3.432	0.1508	112.85766	11.07893	0.8216
5	4.948	0.2099	1.34658e4	946.73804	98.0334
6	12.511	0.3890	52.99458	1.92628	0.3858
Totals			1.37359e4	971.40192	

N-(1'-acetyl-6-(furan-3-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**18**)



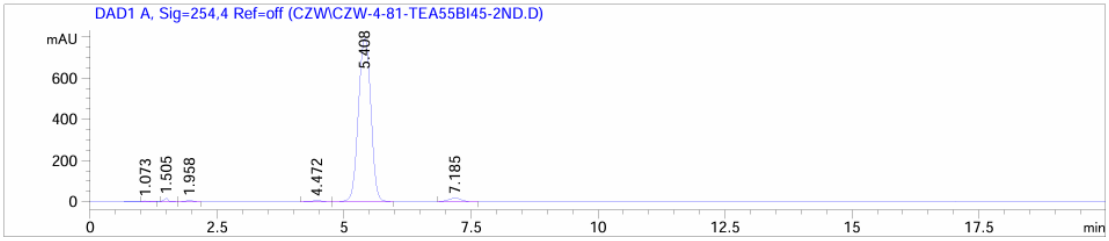
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.087	0.0463	8.14004	2.76644	0.0267
2	1.141	0.0649	11.46271	2.52637	0.0377
3	1.282	0.0771	6.14279	1.17223	0.0202
4	1.409	0.1141	13.21709	1.60518	0.0434
5	1.998	0.0699	22.95955	4.97308	0.0754
6	2.200	0.0782	8.35802	1.62094	0.0275
7	2.327	0.0797	8.80534	1.78104	0.0289
8	3.136	0.1153	34.97212	4.67145	0.1149
9	4.432	0.1715	33.61323	3.12354	0.1104
10	4.931	0.1938	2.98149e4	2418.17798	97.9521
11	5.749	0.3377	163.89183	6.83499	0.5384
12	6.655	0.2492	311.78482	18.63343	1.0243
Totals			3.04382e4	2467.88668	

N-(1'-acetyl-6-(thiophen-3-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**19**)



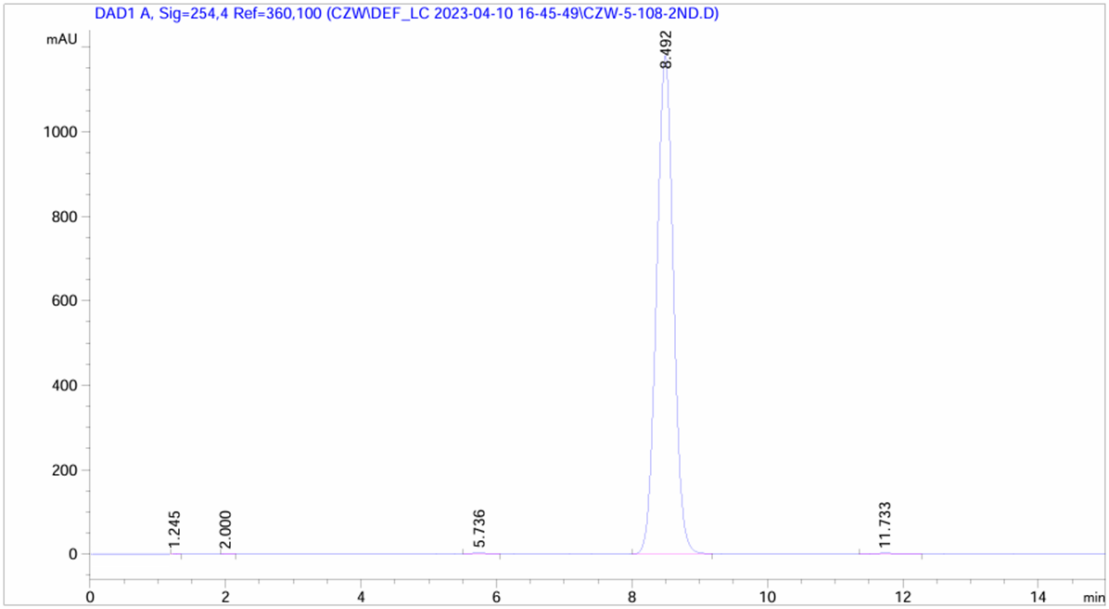
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.201	0.0559	6.97191	1.94214	0.0328
2	1.996	0.0976	9.33197	1.36804	0.0439
3	3.130	0.1311	30.51139	3.59173	0.1435
4	7.261	0.2749	2.09334e4	1191.70605	98.4292
5	10.169	0.3385	287.25403	13.27145	1.3507
Totals			2.12675e4	1211.87941	

N-(1'-acetyl-6-(1-methyl-1*H*-pyrazol-4-yl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-aminopyridin-4-yl)oxazole-4-carboxamide (**20**)



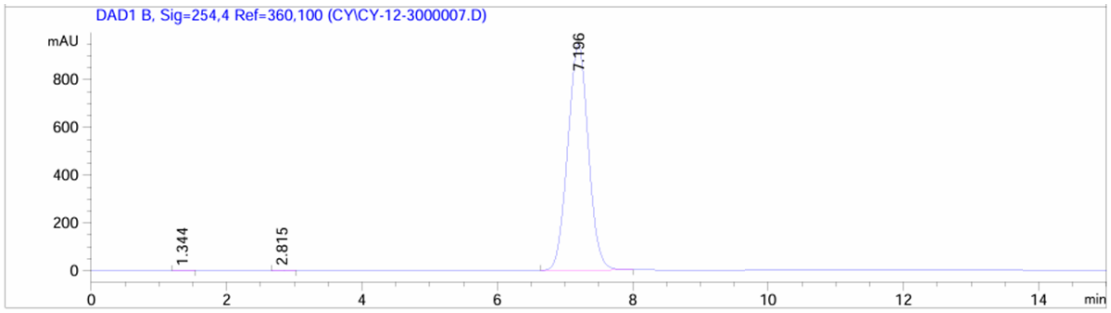
Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.073	0.1282	24.95506	2.69131	0.1780
2	1.505	0.0754	86.36100	15.90092	0.6159
3	1.958	0.1273	60.31545	7.23472	0.4301
4	4.472	0.2371	70.09052	4.66942	0.4998
5	5.408	0.2748	1.34888e4	791.42328	96.1917
6	7.185	0.2651	292.30481	17.30049	2.0845
Totals			1.40229e4	839.22014	

N-(1'-acetyl-6-(4-fluorophenyl)-3*H*-spiro[benzofuran-2,4'-piperidin]-5-yl)-2-(2-amino pyridin-4-yl)oxazole-4-carboxamide (**21**)



Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.245	0.0489	5.74512	1.81639	0.0279
2	2.000	0.0682	7.57378	1.76124	0.0368
3	5.736	0.1884	50.41125	4.18854	0.2452
4	8.492	0.2679	2.04395e4	1181.17432	99.4328
5	11.733	0.3315	52.86382	2.47196	0.2572
Totals			2.05561e4	1191.41245	

2-(2-aminopyridin-4-yl)-*N*-(2,2-dimethyl-6-(pyridin-4-yl)-2,3-dihydrobenzofuran-5-yl)oxazole-4-carboxamide (DW18134)



Peak	RetTime [min]	Width [min]	Area [mAU*s]	Height [mAU]	Area (%)
1	1.344	0.0987	10.79273	1.48710	0.0539
2	2.815	0.1256	15.24155	1.75072	0.0762
3	7.196	0.3258	1.99813e4	948.24341	99.8699
Totals			2.00073e4	951.48123	

The binding models of compounds 3–7 with IRAK4.

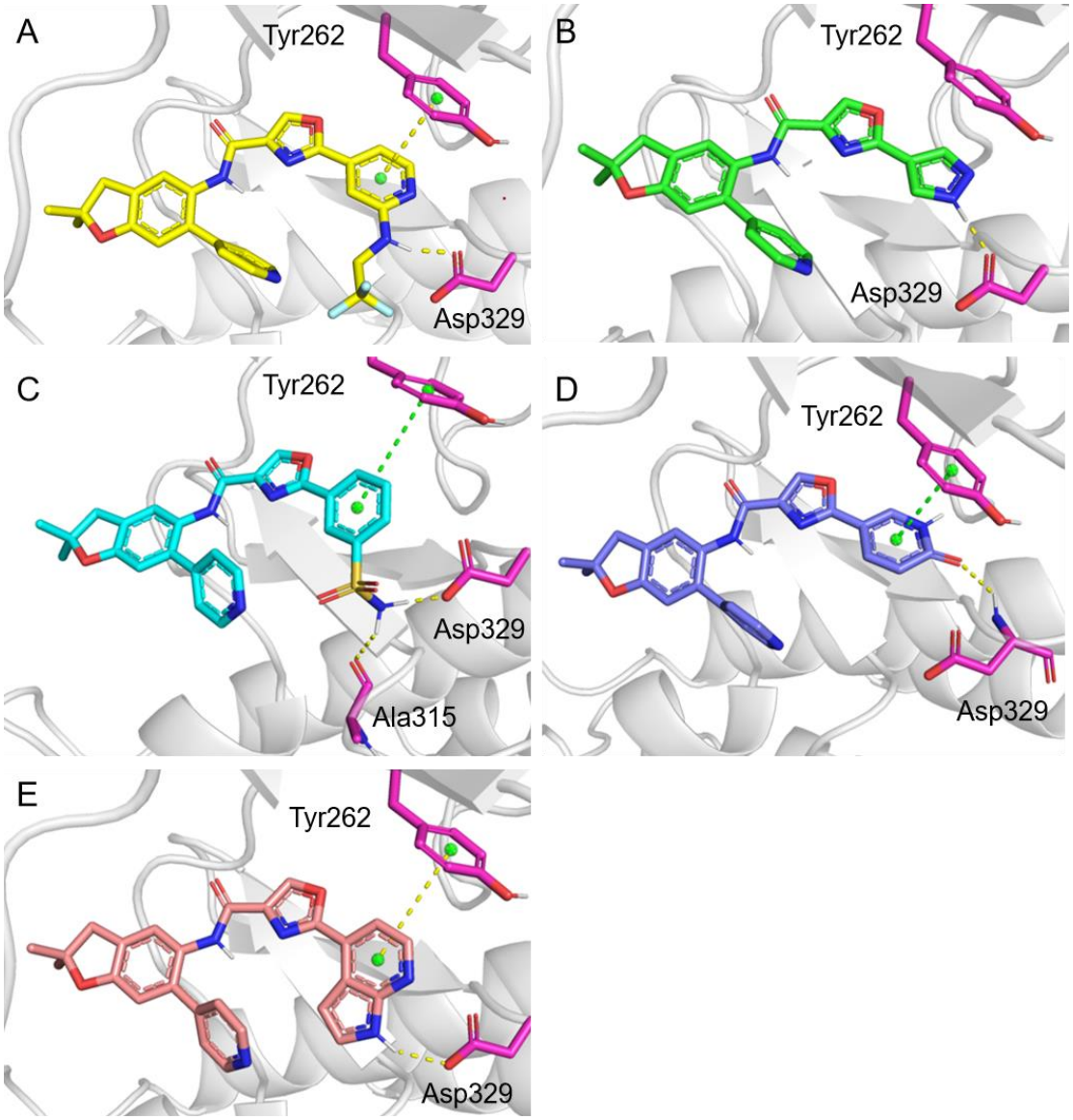


Fig S1. The binding models of compounds **3**–**7** with IRAK4. (A) the binding model of **3** with IRAK4; (B) the binding model of **4** with IRAK4; (C) the binding model of **5** with IRAK4; (D) the binding model of **6** with IRAK4; (E) the binding model of **7** with IRAK4.

References

1. Y. Chen, Y. Ning, Z. Chen, Y. Xue, Q. Wu, W. Duan, J. Ding, J. Zhou, H. Xie and H. Zhang, *Eur. J. Med. Chem.*, 2023, **256**, 115453.