

Supporting Information

Design, synthesis, and biological evaluation of 2-anilino-4-triazolpyrimidine derivatives as CDK4/HDACs inhibitors

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I. Supplementary Figure S1

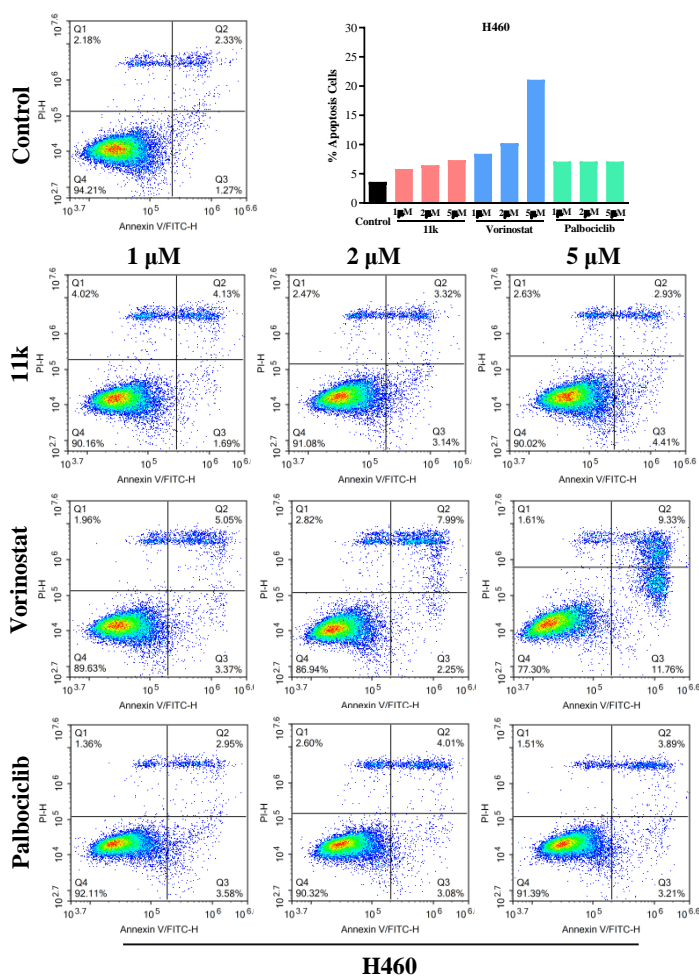


Figure S1 Effects of **11k**, vorinostat and palbociclib on the induction of cell apoptosis in H460 cell line. H460 cells were exposed to **11k**, vorinostat and palbociclib for 48 h. Cells were analyzed by flow cytometry with Annexin-V/FITC/PI staining. The percentage of apoptosis cells was defined as the sum of early- and late-stage apoptosis.

II. Chemistry

2-chloro-4-((trimethylsilyl)ethynyl)pyrimidine (**2a**)

Reaction time: 3h, yellow solid, yield: 57%.

2-chloro-5-fluoro-4-((trimethylsilyl)ethynyl)pyrimidine (**2b**)

Reaction time: 10 min, yellow solid, yield: 62%. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 0.31 (s, 9H). ESI-MS: m/z = 229 [M+H]⁺.

General synthetic procedure of ethynylpyrimidine derivatives (**3a**, **3b**)

To the solution of ethynylpyrimidine derivatives (**2a** or **2b**, 4.7 mmol) in MeOH (10 mL), a

solution of KOH (0.003 g, 0.05 mmol) in MeOH (5 mL) was added. After reacting for about 0.5 h at rt, the mixture was concentrated and the residue was purified by silica gel column chromatography to get pure intermediate **3a** or **3b**.

2-chloro-4-ethynylpyrimidine (3a)

White solid, yield: 90%.

2-chloro-4-ethynyl-5-fluoropyrimidine (3b)

White solid, yield: 91%. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 3.78 (s, 1H). ESI-MS: m/z = 157 [M+H]⁺.

2-chloro-4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidine (4a)

White solid; Yield: 81%; ¹H NMR (500 MHz, CDCl₃): δ = 8.67 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.33 (s, 1H, triazole-H), 8.07 (d, 1H, *J* = 6.5 Hz, Ar-H), 5.07-5.00 (m, 1H, CH), 2.36-2.30 (m, 2H, CH₂), 2.12-2.07 (m, 2H, CH₂), 1.97-1.90 (m, 2H, CH₂), 1.84-1.78 (m, 2H, CH₂); ESI-MS: m/z = 250 [M+H]⁺.

2-chloro-4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidine (4b)

White solid; Yield: 79%. ¹H NMR (500 MHz, CDCl₃): δ = 8.66 (d, 1H, *J* = 6.5 Hz, Ar-H), 8.34 (s, 1H, triazole-H), 8.06 (d, 1H, *J* = 6.5 Hz, Ar-H), 4.58-4.52 (m, 1H, CH), 2.30-2.26 (m, 2H, CH₂), 1.99-1.94 (m, 2H, CH₂), 1.82-1.72 (m, 3H, CH₂), 1.53-1.41 (m, 2H, CH₂), 1.32-1.29 (m, 1H, CH₂); ESI-MS: m/z = 264 [M+H]⁺.

2-chloro-4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidine (4c)

White solid; Yield: 74%. ¹H NMR (500 MHz, CDCl₃): δ = 8.56 (d, 1H, *J* = 3.0 Hz, Ar-H), 8.31 (s, 1H, triazole-H), 4.63-4.55 (m, 1H, CH), 2.31-2.27 (m, 2H, CH₂), 1.99-1.95 (m, 2H, CH₂), 1.85-1.76 (m, 3H, CH₂), 1.55-1.46 (m, 2H, CH₂), 1.37-1.32 (m, 1H, CH₂); ESI-MS: m/z = 282 [M+H]⁺.

2-chloro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidine (4d)

White solid; Yield: 55%. ¹H NMR (500 MHz, CDCl₃): δ = 8.67 (d, 1H, *J* = 6.5 Hz, Ar-H), 8.35 (s, 1H, triazole-H), 8.07 (d, 1H, *J* = 6.5 Hz, Ar-H), 4.97-4.89 (m, 1H, CH), 1.65 (d, 6H, *J* = 6.5 Hz, CH₃); ESI-MS: m/z = 224 [M+H]⁺.

2-chloro-5-fluoro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidine (4e)

White solid; Yield: 46%. ¹H NMR (500 MHz, CDCl₃): δ = 8.57 (d, 1H, *J* = 3.0 Hz, Ar-H), 8.33 (s, 1H, triazole-H), 5.01-4.94 (m, 1H, CH), 1.67 (d, 6H, *J* = 8.5 Hz, CH₃); ESI-MS: m/z

= 242 [M+H]⁺.

2-chloro-5-fluoro-4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidine (4f)

White solid; Yield: 78%; ¹H NMR (500 MHz, CDCl₃): δ = 8.56 (d, 1H, *J* = 3.0 Hz, Ar-H), 8.31 (s, 1H, triazole-H), 5.08-5.02 (m, 1H, CH), 2.42-2.31 (m, 2H, CH₂), 2.17-2.05 (m, 2H, CH₂), 1.99-1.92 (m, 2H, CH₂), 1.87-1.79 (m, 2H, CH₂); ESI-MS: *m/z* = 268 [M+H]⁺.

4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine (6a)

Yellow solid, yield: 47%. ¹H NMR (400 MHz, MeOD) δ 8.40 (s, 1H), 8.30 (d, *J* = 5.1 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.21 (d, *J* = 5.1 Hz, 1H), 6.92 – 6.83 (m, 2H), 5.02 – 4.90 (m, 1H), 3.12 – 2.99 (m, 4H), 2.62 – 2.47 (m, 4H), 2.27 (s, 3H), 2.25 – 2.13 (m, 2H), 2.06-1.96 (m, 2H), 1.89 – 1.78 (m, 2H), 1.75 – 1.63 (m, 2H). ¹³C NMR (100 MHz, MeOD) δ 162.05, 159.82, 159.12, 148.08, 147.48, 134.62, 124.48, 122.25 (2C), 118.30 (2C), 107.90, 63.68, 55.98 (2C), 50.78 (2C), 45.99, 34.31 (2C), 25.08 (2C). ESI-MS: *m/z* = 405 [M+H]⁺. HRMS (ESI): *m/z* calcd for (C₂₂H₂₈N₈ + H)⁺: 405.2510; found: 405.2519.

4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine (6b)

Yellow solid, yield: 51%. ¹H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 8.31 (d, *J* = 5.1 Hz, 1H), 7.58 – 7.45 (m, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 6.98 – 6.83 (m, 2H), 4.46 (tt, *J* = 11.6, 3.7 Hz, 1H), 3.29 – 3.04 (m, 8H), 2.70 (s, 3H), 1.89 – 1.66 (m, 5H), 1.44-1.38 (m, 2H), 1.30-1.12 (m, 3H). ¹³C NMR (100 MHz, MeOD) δ 162.00, 159.83, 159.15, 147.25, 146.92, 135.42, 123.83, 122.13 (2C), 118.73 (2C), 108.09, 61.91, 55.18 (2C), 54.82, 47.90, 44.26, 34.41 (2C), 26.21 (2C), 26.17. ESI-MS: *m/z* = 419 [M+H]⁺. HRMS (ESI): *m/z* calcd for (C₂₃H₃₀N₈ + H)⁺: 419.2666; found: 419.2663.

4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)-5-fluoro-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine (6c)

Yellow solid, yield: 42%. ¹H NMR (400 MHz, MeOD) δ 8.45 (d, *J* = 2.1 Hz, 1H), 8.28 (d, *J* = 2.7 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.1 Hz, 2H), 4.57 – 4.40 (m, 1H), 3.11 – 2.99 (m, 4H), 2.62 – 2.47 (m, 4H), 2.26 (s, 3H), 2.16 – 2.05 (m, 2H), 1.90 – 1.64 (m, 5H), 1.52 – 1.23 (m, 3H). ¹³C NMR (100 MHz, MeOD) δ 157.20, 148.73 (d, *J*_{C-F} = 252.9 Hz), 146.45, 146.11 (d, *J*_{C-F} = 23.5 Hz), 144.44 (d, *J*_{C-F} = 11.9 Hz), 140.65 (d, *J*_{C-F} = 6.3 Hz),

133.61, 124.71 (d, J_{C-F} = 8.8 Hz), 120.04 (2C), 116.96 (2C), 60.62, 54.61 (2C), 49.49 (2C), 44.63, 32.96 (2C), 24.82 (2C), 24.76. ESI-MS: m/z = 437 [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₃H₂₉FN₈ + H)⁺: 437.2572; found: 437.2570.

4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzenesulfonamide (6d)

White solid, yield: 67%. ¹H NMR (400 MHz, MeOD) δ 8.62 (s, 1H), 8.56 (d, J = 5.1 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 5.0 Hz, 1H), 4.68 – 4.54 (m, 1H), 2.32 – 2.18 (m, 2H), 2.07 – 1.74 (m, 6H), 1.68 – 1.34 (m, 4H). ¹³C NMR (100 MHz, MeOD) δ 161.46, 160.06, 159.14, 145.48, 137.03, 128.22 (2C), 124.03, 119.28 (2C), 109.50, 107.76, 62.00, 34.42 (2C), 26.23 (2C), 26.19. HRMS (ESI): m/z calcd for (C₁₈H₂₁N₇O₂S + H)⁺: 400.1550; found: 400.1558.

Methyl

7-(4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)heptanoate (10a)

Yellow solid; Yield: 65%. ¹H NMR (500 MHz, CDCl₃): δ = 8.45 (d, 1H, J = 6.5 Hz, Ar-H), 8.13 (s, 1H, triazole-H), 7.51-7.48 (m, 3H, Ar-H), 7.02 (s, 1H, NH), 6.90 (d, 2H, J = 11.0 Hz, Ar-H), 4.93-4.89 (m, 1H, CH), 3.96 (t, 2H, J = 8.0 Hz, CH₂), 3.67 (s, 3H, CH₃), 2.33 (t, 2H, J = 9.0 Hz, CH₂), 1.81-1.76 (m, 2H, CH₂), 1.71-1.64 (m, 8H, 2CH₃+CH₂), 1.52-1.45 (m, 2H, CH₂), 1.44-1.40 (m, 2H, CH₂); ESI-MS: m/z = 439 [M+H]⁺.

Methyl

7-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)heptanoate (10b)

Yellow solid; Yield: 58%; ¹H NMR (500 MHz, CDCl₃): δ = 8.46 (d, 1H, J = 6.5 Hz, Ar-H), 8.12 (s, 1H, triazole-H), 7.51-7.48 (m, 3H, Ar-H), 6.99 (s, 1H, NH), 6.90 (d, 2H, J = 11.0 Hz, Ar-H), 5.05-4.98 (m, 1H, CH), 3.96 (t, 2H, J = 8.0 Hz, CH₂), 3.68 (s, 3H, CH₃), 2.36-2.27 (m, 4H, CH₂), 2.16-2.05 (m, 2H, CH₂), 1.97-1.90 (m, 2H, CH₂), 1.82-1.76 (m, 4H, CH₂), 1.69-1.63 (m, 2H, CH₂), 1.52-1.46 (m, 2H, CH₂), 1.45-1.36 (m, 2H, CH₂); ESI-MS: m/z = 465 [M+H]⁺.

Methyl

7-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)heptanoate (10c)

Yellow solid; Yield: 71%; ¹H NMR (500 MHz, CDCl₃): δ = 8.47 (d, 1H, J = 6.5 Hz, Ar-H),

8.15 (s, 1H, triazole-H), 7.52-7.50 (m, 3H, Ar-H), 7.03 (s, 1H, NH), 6.92 (d, 2H, $J = 11.5$ Hz, Ar-H), 4.58-4.51 (m, 1H, CH), 3.98 (t, 2H, $J = 8.0$ Hz, CH₂), 3.69 (s, 3H, CH₃), 2.37-2.27 (m, 4H, CH₂), 2.00-1.96 (m, 2H, CH₂), 1.84-1.77 (m, 4H, CH₂), 1.71-1.65 (m, 2H, CH₂), 1.53-1.44 (m, 4H, CH₂), 1.35-1.28 (m, 4H, CH₂); ESI-MS: $m/z = 479$ [M+H]⁺.

Methyl

7-(4-((5-fluoro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)heptanoate (10d)

Yellow solid; Yield: 69%; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.35$ (d, 1H, $J = 3.0$ Hz, Ar-H), 8.16 (d, 1H, $J = 3.0$ Hz, triazole-H), 7.48 (d, 2H, $J = 11.5$ Hz, Ar-H), 7.18 (s, 1H, NH), 6.89 (d, 2H, $J = 11.5$ Hz, Ar-H), 5.00-4.94 (m, 1H, CH), 3.95 (t, 2H, $J = 8.0$ Hz, CH₂), 3.67 (s, 3H, CH₃), 2.33 (t, 2H, $J = 9.0$ Hz, CH₂), 1.81-1.77 (m, 2H, CH₂), 1.68-1.62 (m, 8H, 2CH₃+CH₂), 1.49-1.45 (m, 2H, CH₂), 1.44-1.38 (m, 2H, CH₂); ESI-MS: $m/z = 457$ [M+H]⁺.

Methyl

7-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenoxy)heptanoate (10e)

Yellow solid; Yield: 57%; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.33$ (d, 1H, $J = 3.5$ Hz, Ar-H), 8.15 (d, 1H, $J = 3.0$ Hz, triazole-H), 7.48 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.17 (s, 1H, NH), 6.89 (d, 2H, $J = 11.0$ Hz, Ar-H), 5.09-5.02 (m, 1H, CH), 3.95 (t, 2H, $J = 8.0$ Hz, CH₂), 3.67 (s, 3H, CH₃), 2.35-2.29 (m, 4H, CH₂), 2.16-2.08 (m, 2H, CH₂), 2.00-1.91 (m, 2H, CH₂), 1.85-1.74 (m, 4H, CH₂), 1.68-1.63 (m, 2H, CH₂), 1.49-1.33 (m, 4H, CH₂); ESI-MS: $m/z = 483$ [M+H]⁺.

Methyl

7-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenoxy)heptanoate (10f)

Yellow solid; Yield: 63%; ¹H NMR (500 MHz, CDCl₃): $\delta = 8.33$ (d, 1H, $J = 3.0$ Hz, Ar-H), 8.15 (d, 1H, $J = 3.0$ Hz, triazole-H), 7.48 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.18 (s, 1H, NH), 6.89 (d, 2H, $J = 11.0$ Hz, Ar-H), 4.63-4.55 (m, 1H, CH), 3.95 (t, 2H, $J = 8.0$ Hz, CH₂), 3.67 (s, 3H, CH₃), 2.35-2.28 (m, 4H, CH₂), 2.00-1.92 (m, 2H, CH₂), 1.84-1.72 (m, 5H, CH₂), 1.68-1.61 (m, 2H, CH₂), 1.52-1.45 (m, 4H, CH₂), 1.44-1.31 (m, 3H, CH₂); ESI-MS: $m/z = 497$ [M+H]⁺.

Methyl

7-(4-(4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)

l)heptanoate (10g)

Pale yellow solid; Yield: 67%; ¹H NMR (500 MHz, CDCl₃): δ = 8.47 (d, 1H, *J* = 6.5 Hz, Ar-H), 8.16 (s, 1H, triazole-H), 7.52-7.49 (m, 3H, Ar-H), 7.03 (s, 1H, NH), 6.97 (d, 2H, *J* = 6.0 Hz, Ar-H), 4.96-4.89 (m, 1H, CH), 3.69 (s, 3H, CH₃), 3.23-3.20 (m, 4H, CH₂), 2.69-2.65 (m, 4H, CH₂), 2.43 (t, 2H, *J* = 9.5 Hz, CH₂), 2.34 (t, 2H, *J* = 9.5 Hz, CH₂), 1.76-1.54 (m, 10H, 2CH₃+CH₂), 1.40-1.32 (m, 4H, CH₂); ESI-MS: *m/z* = 507 [M+H]⁺.

Methyl**7-(4-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)heptanoate (10h)**

Pale yellow solid; Yield: 70%; ¹H NMR (500 MHz, CDCl₃): δ = 8.44 (d, 1H, *J* = 6.0 Hz, Ar-H), 8.12 (s, 1H, triazole-H), 7.50-7.46 (m, 3H, Ar-H), 7.03 (s, 1H, NH), 6.95 (d, 2H, *J* = 6.0 Hz, Ar-H), 5.04-4.97 (m, 1H, CH), 3.67 (s, 3H, CH₃), 3.20-3.17 (m, 4H, CH₂), 2.64-2.60 (m, 4H, CH₂), 2.39 (t, 2H, *J* = 9.5 Hz, CH₂), 2.30 (t, 2H, *J* = 9.5 Hz, CH₂), 2.15-2.04 (m, 2H, CH₂), 1.96-1.90 (m, 2H, CH₂), 1.71-1.50 (m, 8H, CH₂), 1.38-1.29 (m, 4H, CH₂); ESI-MS: *m/z* = 533 [M+H]⁺.

Methyl**7-(4-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)heptanoate (10i)**

Pale yellow solid; Yield: 68%; ¹H NMR (500 MHz, CDCl₃): δ = 8.46 (d, 1H, *J* = 6.5 Hz, Ar-H), 8.15 (s, 1H, triazole-H), 7.52-7.48 (m, 3H, Ar-H), 7.00 (s, 1H, NH), 6.97 (d, 2H, *J* = 6.5 Hz, Ar-H), 4.58-4.50 (m, 1H, CH), 3.69 (s, 3H, CH₃), 3.22-3.19 (m, 4H, CH₂), 2.66-2.62 (m, 4H, CH₂), 2.43-2.23 (m, 6H, CH₂), 2.01-1.95 (m, 2H, CH₂), 1.85-1.76 (m, 3H, CH₂), 1.59-1.46 (m, 6H, CH₂), 1.41-1.30 (m, 5H, CH₂); ESI-MS: *m/z* = 547 [M+H]⁺.

Methyl**7-(4-(4-((5-fluoro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)heptanoate (10j)**

Yellow solid; Yield: 73%; ¹H NMR (500 MHz, CDCl₃): δ = 8.34 (d, 1H, *J* = 3.0 Hz, Ar-H), 8.16 (d, 1H, *J* = 2.5 Hz, triazole-H), 7.48 (d, 2H, *J* = 11.0 Hz, Ar-H), 7.20 (s, 1H, NH), 6.94 (d, 2H, *J* = 11.0 Hz, Ar-H), 4.99-4.92 (m, 1H, CH), 3.67 (s, 3H, CH₃), 3.19-3.16 (m, 4H, CH₂), 2.62-2.59 (m, 4H, CH₂), 2.39 (t, 2H, *J* = 9.5 Hz, CH₂), 2.32 (t, 2H, *J* = 9.0 Hz, CH₂),

1.68-1.64 (m, 8H, 2CH₃+CH₂), 1.57-1.51 (m, 2H, CH₂), 1.39-1.31 (m, 4H, CH₂); ESI-MS: m/z = 525 [M+H]⁺.

Methyl

7-(4-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenyl)perazin-1-yl)heptanoate (10k)

Yellow solid; Yield: 69%; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 9.51 (s, 1H, NH), 8.66 (d, 1H, *J* = 2.0 Hz, triazole-H), 8.53 (d, 1H, *J* = 3.5 Hz, Ar-H), 7.64 (d, 2H, *J* = 11.5 Hz, Ar-H), 6.87 (d, 2H, *J* = 11.5 Hz, Ar-H), 5.14-5.08 (m, 1H, CH), 3.58 (s, 3H, CH₃), 3.06-3.02 (m, 4H, CH₂), 2.52-2.46 (m, 4H, CH₂), 2.33-2.19 (m, 6H, CH₂), 2.10-2.02 (m, 2H, CH₂), 1.89-1.81 (m, 2H, CH₂), 1.76-1.68 (m, 2H, CH₂), 1.55-1.37 (m, 4H, CH₂), 1.31-1.24 (m, 4H, CH₂); ESI-MS: m/z = 551 [M+H]⁺.

Methyl 4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoate (13a)

White solid; Yield: 84%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 8.77 (s, 1H), 8.64 (d, *J* = 5.1 Hz, 1H), 8.09 – 7.89 (m, 4H), 7.50 (d, *J* = 5.1 Hz, 1H), 5.12 (p, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 2.34 – 2.17 (m, 2H), 2.16 – 2.00 (m, 2H), 1.96 – 1.80 (m, 2H), 1.81 – 1.62 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.05, 159.70, 159.13, 157.45, 145.15, 145.13, 130.26 (2C), 123.83, 121.67, 117.74 (2C), 108.26, 61.46, 51.66, 32.82 (2C), 23.66 (2C). ESI-MS: m/z = 365 [M+H]⁺.

Methyl 4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoate (13b)

White solid; Yield: 83%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.19 (s, 1H), 8.78 (s, 1H), 8.63 (d, *J* = 5.0 Hz, 1H), 7.99 (dd, *J* = 24.6, 8.7 Hz, 4H), 7.50 (d, *J* = 5.0 Hz, 1H), 4.77 – 4.48 (m, 1H), 3.83 (s, 3H), 2.25 – 2.06 (m, 2H), 1.98 – 1.80 (m, 4H), 1.78 – 1.63 (m, 1H), 1.58 – 1.39 (m, 2H), 1.37 – 1.19 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.55, 160.18, 159.67, 157.94, 145.63, 145.46, 130.81 (2C), 123.69, 122.10, 118.21 (2C), 108.70, 60.05, 52.08, 33.17 (2C), 25.14 (2C), 25.08. ESI-MS: m/z = 379 [M+H]⁺.

Methyl 4-((4-(1-isobutyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoate (13c)

White solid; Yield: 80%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (s, 1H), 8.79 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 7.99 (dd, *J* = 25.8, 8.9 Hz, 4H), 7.50 (d, *J* = 5.1 Hz, 1H), 4.97 (hept, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.06, 159.70, 159.14, 157.48, 145.13 (2C), 130.29 (2C), 122.97, 121.66, 117.74 (2C),

108.23, 52.90, 51.66, 22.53 (2C). ESI-MS $m/z = 339$ $[M+H]^+$.

Methyl 7-(4-nitrophenoxy)heptanoate (8a)

Yellow solid, yield: 65%. ^1H NMR (400 MHz, DMSO-*d*6) δ 8.26 – 8.13 (m, 2H), 7.19 – 7.05 (m, 2H), 4.11 (t, $J = 6.5$ Hz, 2H), 3.58 (s, 3H), 2.31 (t, $J = 7.4$ Hz, 2H), 1.81 – 1.65 (m, 2H), 1.62 – 1.47 (m, 2H), 1.47 – 1.24 (m, 4H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 173.82, 164.50, 141.13, 126.36 (2C), 115.43 (2C), 68.99, 51.65, 33.63, 28.66, 28.57, 25.49, 24.79. ESI-MS: $m/z = 282$ $[M+H]^+$.

Methyl 7-(4-(4-nitrophenyl)piperazin-1-yl)heptanoate (8b)

Yellow solid, yield: 76%. ^1H NMR (400 MHz, DMSO-*d*6) δ 8.05 (d, $J = 7.7$ Hz, 2H), 7.02 (d, $J = 7.9$ Hz, 2H), 3.58 (s, 3H), 3.50 – 3.36 (m, 4H), 2.52 – 2.40 (m, 4H), 2.30 (m, 4H), 1.58 – 1.48 (m, 2H), 1.52 – 1.36 (m, 2H), 1.36 – 1.21 (m, 4H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 173.86, 155.22, 137.25, 126.19 (2C), 113.02 (2C), 58.08, 52.80 (2C), 51.65, 46.76 (2C), 33.70, 28.84, 27.04, 26.49, 24.88. ESI-MS: $m/z = 350$ $[M+H]^+$.

Methyl 7-(4-aminophenoxy)heptanoate (9a)

Yellow solid, yield: 100%. ^1H NMR (400 MHz, CDCl_3) δ 6.78 – 6.69 (m, 2H), 6.67 – 6.58 (m, 2H), 3.87 (t, $J = 6.5$ Hz, 2H), 3.66 (s, 3H), 2.32 (t, $J = 7.5$ Hz, 2H), 1.82 – 1.57 (m, 4H), 1.52 – 1.29 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.24, 152.29, 139.87, 116.42 (2C), 115.69 (2C), 68.52, 51.47, 34.01, 29.24, 28.90, 25.75, 24.87. ESI-MS: $m/z = 252$ $[M+H]^+$.

Methyl 7-(4-(4-aminophenyl)piperazin-1-yl)heptanoate (9b)

Yellow solid, yield: 100%. ^1H NMR (400 MHz, CDCl_3) δ 6.81 (dd, $J = 8.5, 1.3$ Hz, 2H), 6.65 (dd, $J = 8.6, 1.9$ Hz, 2H), 3.67 (s, 3H), 3.18 – 2.96 (m, 4H), 2.68 – 2.52 (m, 4H), 2.44 – 2.28 (m, 4H), 1.70 – 1.44 (m, 4H), 1.42 – 1.25 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.26, 144.58, 140.07, 118.56 (2C), 116.23 (2C), 58.68, 53.43 (2C), 51.47, 50.87 (2C), 34.02, 29.06, 27.24, 26.67, 24.87. ESI-MS: $m/z = 320$ $[M+H]^+$.

N-hydroxy-7-(4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)heptanamide (11a)

Pale yellow solid; Yield: 77%; ^1H NMR (500 MHz, DMSO-*d*6): $\delta = 10.35$ (s, 1H, NH), 9.44 (s, 1H, OH), 8.71-8.65 (m, 2H, NH+ triazole-H), 8.49 (d, 1H, $J = 6.0$ Hz, Ar-H), 7.69 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.32 (d, 1H, $J = 6.0$ Hz, Ar-H), 6.89 (d, 2H, $J = 11.0$ Hz, Ar-H), 4.97-4.91 (m, 1H, CH), 3.92 (t, 2H, $J = 8.0$ Hz, CH_2), 1.96 (t, 2H, $J = 8.0$ Hz, CH_2), 1.71-1.69 (m, 2H,

CH₂), 1.57 (d, 6H, *J* = 8.0 Hz, CH₃), 1.54-1.48 (m, 2H, CH₂), 1.45-1.36 (m, 2H, CH₂), 1.35-1.26 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 174.34, 165.47, 164.11, 162.64, 158.84, 150.67, 138.78, 127.87, 125.83 (2C), 119.67 (2C), 111.98, 72.80, 58.05, 37.43, 33.91, 33.57, 30.50, 30.29, 27.77 (2C); ESI-MS: *m/z* = 440 [M+H]⁺. HRMS (ESI): *m/z* calcd for (C₂₂H₂₉N₇O₃ + H)⁺: 440.2405; found: 440.2417.

7-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)-N-hydroxy heptanamide (11b)

Pale yellow solid; Yield: 83%. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 10.36 (s, 1H, NH), 9.48 (s, 1H, OH), 8.69 (s, 1H, NH), 8.64 (s, 1H, triazole-H), 8.49 (d, 1H, *J* = 6.5 Hz, Ar-H), 7.69 (d, 2H, *J* = 11.0 Hz, Ar-H), 7.31 (d, 1H, *J* = 6.5 Hz, Ar-H), 6.88 (d, 2H, *J* = 11.0 Hz, Ar-H), 5.11-5.07 (m, 1H, CH), 3.92 (t, 2H, *J* = 8.0 Hz, CH₂), 2.25-2.21 (m, 2H, CH₂), 2.06-2.03 (m, 2H, CH₂), 1.95 (t, 2H, *J* = 8.0 Hz, CH₂), 1.86-1.82 (m, 2H, CH₂), 1.71-1.64 (m, 4H, CH₂), 1.55-1.48 (m, 2H, CH₂), 1.42-1.37 (m, 4H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 169.08, 160.20, 158.73, 157.34, 153.55, 145.48, 133.54, 123.32, 120.52 (2C), 114.32 (2C), 106.69, 67.51, 61.36, 32.83 (2C), 32.21, 28.68, 28.35, 25.27, 25.06, 23.67 (2C); ESI-MS: *m/z* = 466 [M+H]⁺. HRMS (ESI): *m/z* calcd for (C₂₄H₃₁N₇O₃ + H)⁺: 466.2561; found: 466.2583.

7-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)-N-hydroxyheptanamide (11c)

Pale yellow solid; Yield: 79%. ¹H NMR (500MHz, DMSO-*d*₆): δ = 10.37 (s, 1H, NH), 9.48 (s, 1H, OH), 8.75 (s, 1H, NH), 8.64 (s, 1H, triazole-H), 8.48 (d, 1H, *J* = 6.5 Hz, Ar-H), 7.69 (d, 2H, *J* = 11.0 Hz, Ar-H), 7.31 (d, 1H, *J* = 6.5 Hz, Ar-H), 6.88 (d, 2H, *J* = 11.0 Hz, Ar-H), 4.62-4.57 (m, 1H, CH), 3.92 (t, 2H, *J* = 8.0 Hz, CH₂), 2.13-2.10 (m, 2H, CH₂), 1.95 (t, 2H, *J* = 8.0 Hz, CH₂), 1.91-1.82 (m, 4H, CH₂), 1.72-1.67 (m, 3H, CH₂), 1.54-1.42 (m, 6H, CH₂), 1.32-1.25 (m, 3H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 169.58, 160.68, 159.38, 157.84, 154.03, 145.74, 134.01, 123.27, 121.00 (2C), 114.87 (2C), 107.20, 67.99, 59.95, 33.18 (2C), 32.67, 29.16, 28.82, 25.76, 25.55, 25.11 (2C), 25.08; ESI-MS: *m/z* = 480 [M+H]⁺. HRMS (ESI): *m/z* calcd for (C₂₅H₃₃N₇O₃ + H)⁺: 480.2718; found: 480.2722.

7-(4-((5-fluoro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenoxy)-N-hydroxyheptanamide (11d)

Yellow solid; Yield: 89%. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 10.34 (s, 1H, NH), 9.59 (s,

1H, OH), 8.71 (s, 1H, triazole-H), 8.66 (s, 1H, NH), 8.56 (d, 1H, $J = 3.0$ Hz, Ar-H), 7.69 (d, 2H, $J = 11.0$ Hz, Ar-H), 6.86 (d, 2H, $J = 11.0$ Hz, Ar-H), 5.00-4.94 (m, 1H, CH), 3.91 (t, 2H, $J = 8.0$ Hz, CH₂), 1.96 (t, 2H, $J = 8.0$ Hz, CH₂), 1.73-1.68 (m, 2H, CH₂), 1.58 (d, 6H, $J = 8.0$ Hz, CH₃), 1.54-1.51 (m, 2H, CH₂), 1.43-1.39 (m, 2H, CH₂), 1.34-1.27 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*6): $\delta = 169.58, 157.21, 154.04, 148.74$ (d, $J_{C-F} = 252.9$ Hz), 147.18 (d, $J_{C-F} = 23.2$ Hz), 144.83 (d, $J_{C-F} = 11.1$ Hz), 140.97 (d, $J_{C-F} = 6.7$ Hz), 134.16, 125.37 (d, $J_{C-F} = 7.8$ Hz), 120.59 (2C), 114.81 (2C), 68.02, 53.32, 32.71, 29.17, 28.84, 25.76, 25.55, 23.00 (2C).; ESI-MS: $m/z = 458$ [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₂H₂₈FN₇O₃ + H)⁺: 458.2310; found: 458.2319.

7-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-hydroxyheptanamide (11e)

Yellow solid; Yield: 75%. ¹H NMR (500 MHz, DMSO-*d*6): $\delta = 10.35$ (s, 1H, NH), 9.59 (s, 1H, OH), 8.69-8.66 (m, 2H, NH+ triazole-H), 8.57 (d, 1H, $J = 1.5$ Hz, Ar-H), 7.68 (d, 2H, $J = 10.5$ Hz, Ar-H), 6.87 (d, 2H, $J = 10.0$ Hz, Ar-H), 5.14-5.10 (m, 1H, CH), 3.92 (t, 2H, $J = 8.0$ Hz, CH₂), 2.24-2.19 (m, 2H, CH₂), 2.09-2.01 (m, 2H, CH₂), 1.95 (t, 2H, $J = 8.0$ Hz, CH₂), 1.86-1.80 (m, 2H, CH₂), 1.72-1.62 (m, 4H, CH₂), 1.54-1.48 (m, 2H, CH₂), 1.43-1.35 (m, 2H, CH₂), 1.34-1.25 (m, 2H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*6): $\delta = 169.59, 157.19$ (d, $J_{C-F} = 2.1$ Hz), 154.05, 148.74 (d, $J_{C-F} = 253.2$ Hz), 147.34 (d, $J_{C-F} = 23.3$ Hz), 144.75 (d, $J_{C-F} = 11.1$ Hz), 141.00 (d, $J_{C-F} = 6.9$ Hz), 134.14, 126.27 (d, $J_{C-F} = 7.6$ Hz), 120.64 (2C), 114.87 (2C), 68.03, 61.88, 33.32 (2C), 32.67, 29.14, 28.81, 25.74, 25.53, 24.18 (2C).ESI-MS: $m/z = 484$ [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₄H₃₀FN₇O₃ + H)⁺: 484.2467; found: 484.2494.

7-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-hydroxyheptanamide (11f)

Yellow solid; Yield: 74%. ¹H NMR (500 MHz, DMSO-*d*6): $\delta = 10.35$ (s, 1H, NH), 9.58 (s, 1H, OH), 8.72-8.66 (m, 2H, NH+ triazole-H), 8.58 (s, 1H, Ar-H), 7.68 (d, 2H, $J = 10.0$ Hz, Ar-H), 6.87 (d, 2H, $J = 10.0$ Hz, Ar-H), 4.63-4.60 (m, 1H, CH), 3.92 (t, 2H, $J = 8.0$ Hz, CH₂), 2.16-2.08 (m, 2H, CH₂), 1.95 (t, 2H, $J = 8.0$ Hz, CH₂), 1.90-1.82 (m, 4H, CH₂), 1.72-1.64 (m, 3H, CH₂), 1.54-1.25 (m, 9H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*6): $\delta = 169.54, 157.19, 154.05, 148.74$ (d, $J_{C-F} = 253.5$ Hz), 147.34 (d, $J_{C-F} = 22.5$ Hz), 144.71 (d, $J_{C-F} = 2.8$ Hz), 140.83 (d, $J_{C-F} = 6.6$ Hz), 134.14, 125.63 (d, $J_{C-F} = 7.9$ Hz), 120.62 (2C), 114.87 (2C), 68.02, 59.98, 33.15 (2C),

32.66, 29.14, 28.81, 25.74, 25.54, 25.10 (2C), 25.06. ESI-MS: $m/z = 498 [M+H]^+$. HRMS (ESI): m/z calcd for $(C_{25}H_{32}FN_7O_3 + H)^+$: 498.2623; found: 498.2633.

N-hydroxy-7-(4-(4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)heptanamide (11g)

Pale yellow solid; Yield: 85%. 1H NMR (500 MHz, *DMSO-d6*): $\delta = 10.33$ (s, 1H, NH), 9.38 (s, 1H, OH), 8.66 (s, 1H, NH), 8.64 (s, 1H, triazole-H), 8.47 (d, 1H, $J = 6.5$ Hz, Ar-H), 7.65 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.30 (d, 1H, $J = 6.0$ Hz, Ar-H), 6.90 (d, 2H, $J = 11.0$ Hz, Ar-H), 4.97-4.91 (m, 1H, CH), 3.08-3.05 (m, 4H, CH₂), 2.54-2.50 (m, 4H, CH₂), 2.30 (t, 2H, $J = 9.0$ Hz, CH₂), 1.94 (t, 2H, $J = 9.5$ Hz, CH₂), 1.57 (d, 6H, $J = 8.5$ Hz, CH₃), 1.50-1.39 (m, 4H, CH₂), 1.29-1.26 (m, 4H, CH₂); ^{13}C NMR (100 MHz, *DMSO-d6*): $\delta = 169.59, 160.74, 159.31, 157.87, 146.68, 145.96, 133.09, 123.02, 120.66$ (2C), 116.39 (2C), 107.03, 58.36, 53.35 (2C), 53.28, 49.58 (2C), 32.72, 29.01, 27.17, 26.68, 25.58, 23.03 (2C). ESI-MS: $m/z = 508 [M+H]^+$. HRMS (ESI): m/z calcd for $(C_{26}H_{37}N_9O_2 + H)^+$: 508.3143; found: 508.3153.

7-(4-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)-N-hydroxyheptanamide (11h)

Pale yellow solid; Yield: 89%. 1H NMR (500 MHz, *DMSO-d6*): $\delta = 10.34$ (s, 1H, NH), 9.39 (s, 1H, OH), 8.67 (s, 1H, NH), 8.62 (s, 1H, triazole-H), 8.47 (d, 1H, $J = 6.5$ Hz, Ar-H), 7.64 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.30 (d, 1H, $J = 6.0$ Hz, Ar-H), 6.90 (d, 2H, $J = 11.0$ Hz, Ar-H), 5.11-5.08 (m, 1H, CH), 3.10-3.02 (m, 4H, CH₂), 2.43-2.32 (m, 4H, CH₂), 2.28-2.19 (m, 2H, CH₂), 2.07-1.98 (m, 2H, CH₂), 1.93 (t, 2H, $J = 8.0$ Hz, CH₂), 1.88-1.81 (m, 2H, CH₂), 1.76-1.68 (m, 2H, CH₂), 1.54-1.41 (m, 4H, CH₂), 1.32-1.20 (m, 6H, CH₂); ^{13}C NMR (100 MHz, *DMSO-d6*): $\delta = 169.66, 160.77, 159.36, 157.86, 146.69, 146.04, 133.12, 123.83, 120.69$ (2C), 116.44 (2C), 107.11, 61.93 (2C), 57.81, 53.18 (2C), 49.41, 33.31 (2C), 32.75, 28.90, 27.05, 26.50, 25.51, 24.09 (2C). ESI-MS: $m/z = 534 [M+H]^+$. HRMS (ESI): m/z calcd for $(C_{28}H_{39}N_9O_2 + H)^+$: 534.3299; found: 534.3298.

7-(4-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)-N-hydroxyheptanamide (11i)

Pale yellow solid; Yield: 77%. 1H NMR (500 MHz, *DMSO-d6*): $\delta = 10.33$ (s, 1H, NH), 9.36 (s, 1H, OH), 8.63 (s, 1H, NH), 8.60 (s, 1H, triazole-H), 8.45 (d, 1H, $J = 6.5$ Hz, Ar-H), 7.65 (d, 2H, $J = 11.0$ Hz, Ar-H), 7.30 (d, 1H, $J = 6.0$ Hz, Ar-H), 6.89 (d, 2H, $J = 11.0$ Hz, Ar-H),

4.63-4.56 (m, 1H, CH), 3.08-3.03 (m, 4H, CH₂), 2.48-2.42 (m, 4H, CH₂), 2.31-2.24 (m, 2H, CH₂), 2.16-2.09 (m, 2H, CH₂), 1.95-1.80 (m, 6H, CH₂), 1.72-1.65 (m, 1H, CH₂), 1.52-1.39 (m, 6H, CH₂), 1.31-1.16 (m, 5H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 169.59, 160.73, 159.20, 157.86, 146.64, 145.82, 133.13, 123.10, 120.62 (2C), 116.39 (2C), 106.99, 59.95, 58.38, 53.36 (2C), 49.62 (2C), 33.20 (2C), 32.74, 29.04, 27.18, 26.71, 25.59, 25.13 (2C), 25.10. ESI-MS: m/z = 548 [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₉H₄₁N₉O₂ + H)⁺: 548.3456; found: 548.3468.

7-(4-(4-((5-fluoro-4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)-N-hydroxyheptanamide (11j)

Yellow solid; Yield: 87%; ¹H NMR (500 MHz, DMSO-*d*₆): δ = 10.33 (s, 1H, NH), 9.52 (s, 1H, OH), 8.70 (d, 1H, J = 2.0 Hz, triazole-H), 8.65 (s, 1H, NH), 8.54 (d, 1H, J = 3.5 Hz, Ar-H), 7.64 (d, 2H, J = 11.0 Hz, Ar-H), 6.88 (d, 2H, J = 11.0 Hz, Ar-H), 5.00-4.93 (m, 1H, CH), 3.09-3.05 (m, 4H, CH₂), 2.48-2.42 (m, 4H, CH₂), 2.30 (t, 2H, J = 8.5 Hz, CH₂), 1.95 (t, 2H, J = 8.0 Hz, CH₂), 1.58 (d, 6H, J = 8.0 Hz, CH₃), 1.52-1.44 (m, 4H, CH₂), 1.28-1.21 (m, 4H, CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 169.10, 156.76, 148.16 (d, J_{C-F} = 252.8 Hz), 146.68 (d, J_{C-F} = 22.7 Hz), 146.16, 144.30 (d, J_{C-F} = 11.2 Hz), 140.52 (d, J_{C-F} = 7.0 Hz), 132.74, 124.84 (d, J_{C-F} = 7.5 Hz), 119.76 (2C), 115.86 (2C), 57.87, 52.85 (2C), 52.81, 49.10 (2C), 32.24, 28.53, 26.67, 26.20, 25.08, 22.51 (2C). ESI-MS: m/z = 526 [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₆H₃₆FN₉O₂ + H)⁺: 526.3049; found: 526.3070.

7-(4-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)-5-fluoropyrimidin-2-yl)amino)phenyl)piperazin-1-yl)-N-hydroxyheptanamide (11k)

Yellow solid; Yield: 91%. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 10.33 (s, 1H, NH), 9.53 (s, 1H, OH), 8.68-8.66 (m, 2H, NH+ triazole-H), 8.54 (d, 1H, J = 3.5 Hz, Ar-H), 7.64 (d, 2H, J = 11.0 Hz, Ar-H), 6.87 (d, 2H, J = 11.0 Hz, Ar-H), 5.14-5.09 (m, 1H, CH), 3.05-3.01 (m, 4H, CH₂), 2.46-2.41 (m, 4H, CH₂), 2.35-2.19 (m, 4H, CH₂), 2.09-2.02 (m, 2H, CH₂), 1.93 (t, 2H, J = 8.0 Hz, CH₂), 1.91-1.83 (m, 2H, CH₂), 1.77-1.68 (m, 2H, CH₂), 1.52-1.48 (m, 4H, CH₂), 1.31-1.20 (m, 4H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 169.60, 157.25, 148.67 (d, J_{C-F} = 252.7 Hz), 147.28 (d, J_{C-F} = 6.5 Hz), 147.09 (d, J_{C-F} = 1.7 Hz), 146.61 (d, J_{C-F} = 5.1 Hz), 141.05 (d, J_{C-F} = 6.7 Hz), 133.29, 126.17 (d, J_{C-F} = 7.7 Hz), 120.25 (2C), 116.39 (2C), 61.85 (2C), 58.28, 53.27 (2C),

49.51, 33.33 (2C), 32.73, 29.01, 27.13, 26.60, 25.57, 24.20 (2C). ESI-MS: $m/z = 552 [M+H]^+$. HRMS (ESI): m/z calcd for $(C_{28}H_{38}FN_9O_2 + H)^+$: 552.3205; found: 552.3220.

4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoic acid (14a)

White solid. 1H NMR (400 MHz, DMSO-*d*6) δ 10.13 (s, 1H), 8.79 (s, 1H), 8.62 (d, $J = 5.1$ Hz, 1H), 7.95 (dd, $J = 26.7, 8.8$ Hz, 4H), 7.48 (d, $J = 5.1$ Hz, 1H), 5.12 (p, $J = 6.9$ Hz, 1H), 2.33 – 2.17 (m, 2H), 2.13 – 1.97 (m, 2H), 1.92 – 1.78 (m, 2H), 1.77 – 1.61 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 167.27, 159.74, 159.10, 157.42, 145.15, 144.64, 130.35 (2C), 123.90, 123.87, 117.66 (2C), 108.13, 61.42, 32.82 (2C), 23.66 (2C). ESI-MS: $m/z = 351 [M+H]^+$.

4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoic acid (14b)

White solid. 1H NMR (400 MHz, DMSO-*d*6) δ 12.56 (s, 1H), 10.13 (s, 1H), 8.77 (s, 1H), 8.62 (d, $J = 5.1$ Hz, 1H), 7.96 (dd, $J = 22.2, 8.7$ Hz, 4H), 7.48 (d, $J = 5.1$ Hz, 1H), 4.78 – 4.50 (m, 1H), 2.23 – 2.06 (m, 2H), 2.01 – 1.80 (m, 4H), 1.77 – 1.62 (m, 1H), 1.46 (q, $J = 13.2$ Hz, 2H), 1.37 – 1.13 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 167.68, 160.23, 159.64, 157.94, 145.49, 145.24, 130.93 (2C), 123.66, 123.32, 118.14 (2C), 108.60, 60.03, 33.17 (2C), 25.14 (2C), 25.08. ESI-MS $m/z = 365 [M+H]^+$.

4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzoic acid (14c)

White solid. 1H NMR (400 MHz, DMSO-*d*6) δ 10.11 (s, 1H), 8.78 (s, 1H), 8.63 (d, $J = 5.0$ Hz, 1H), 7.96 (dd, $J = 22.9, 8.7$ Hz, 4H), 7.49 (d, $J = 5.1$ Hz, 1H), 5.04 – 4.88 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*6) δ 167.18, 159.75, 159.11, 157.49, 145.15, 144.73, 130.40 (2C), 122.94, 122.90, 117.67 (2C), 108.13, 52.89, 22.52 (2C). ESI-MS: $m/z = 325 [M+H]^+$.

General synthetic procedure of compounds 15a~15c.

Tert-butyl

**(2-(4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamido)phenyl)c
arbamate (15a)**

White solid, yield: 74%. 1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.54 (d, $J = 5.1$ Hz, 1H), 8.17 (s, 1H), 7.97 (d, $J = 8.7$ Hz, 2H), 7.83 – 7.71 (m, 3H), 7.61 (d, $J = 5.1$ Hz, 1H), 7.51 (s, 1H), 7.33 – 7.28 (m, 1H), 7.24 – 7.12 (m, 2H), 6.96 (s, 1H), 5.09 – 4.94 (m, 1H), 2.39 – 2.25 (m, 2H), 2.20 – 2.06 (m, 2H), 2.03 – 1.89 (m, 2H), 1.87 – 1.76 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.30, 159.60, 158.84, 158.12, 154.61, 146.27, 143.12, 131.02,

130.13, 128.57 (2C), 127.47, 125.89, 125.87, 125.76, 124.55, 122.07, 118.16 (2C), 109.02, 81.22, 62.28, 33.49 (2C), 28.31 (3C), 24.06 (2C). ESI-MS $m/z = 541 [M+H]^+$.

Tert-butyl

(2-(4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamido)phenyl)carbamate (15b)

White solid, yield: 74%. ^1H NMR (400 MHz, CDCl_3) δ 9.23 (s, 1H), 8.52 (d, $J = 5.0$ Hz, 1H), 8.18 (s, 1H), 8.07 – 7.91 (m, 3H), 7.76 (d, $J = 7.5$ Hz, 2H), 7.70 (d, $J = 7.1$ Hz, 1H), 7.58 (t, $J = 10.9$ Hz, 1H), 7.47 – 7.31 (m, 2H), 7.22 – 7.05 (m, 2H), 4.68 – 4.36 (m, 1H), 2.36 – 2.15 (m, 2H), 2.00 – 1.72 (m, 4H), 1.63 – 1.40 (m, 11H), 1.39 – 1.21 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.48, 159.63, 158.74, 158.12, 154.62, 146.02, 143.20, 130.83 (2C), 130.43, 128.60, 127.35, 125.84, 125.74, 125.61, 124.52, 121.40, 118.18 (2C), 108.88, 81.00, 60.52, 38.60 (2C), 33.49, 28.32 (2C), 25.11(2C), 25.00. ESI-MS: $m/z = 555 [M+H]^+$.

Tert-butyl

(2-(4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamido)phenyl)carbamate (15c)

White solid, yield: 71%. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.10 (s, 1H), 9.76 (s, 1H), 8.79 (s, 1H), 8.69 (s, 1H), 8.63 (d, $J = 5.1$ Hz, 1H), 8.00 (dd, $J = 25.5, 8.8$ Hz, 4H), 7.61 – 7.50 (m, 2H), 7.49 (d, $J = 5.1$ Hz, 1H), 7.26 – 7.11 (m, 2H), 4.97 (hept, $J = 6.7$ Hz, 1H), 1.60 (s, 3H), 1.58 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 165.46, 160.29, 159.65, 157.97, 153.96, 145.69, 144.46, 132.02, 130.54 (2C), 129.05, 126.74, 126.40, 125.85, 124.64, 124.38, 123.40, 118.19 (2C), 108.58, 80.15, 53.40, 28.50 (3C), 23.05 (2C). ESI-MS: $m/z = 515 [M+H]^+$.

N-(2-aminophenyl)-4-((4-(1-cyclopentyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamide (16a)

White solid, yield: 100%. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 10.10 (s, 1H), 9.98 (s, 1H), 8.76 (s, 1H), 8.64 (d, $J = 5.1$ Hz, 1H), 8.11 – 7.95 (m, 4H), 7.49 (d, $J = 5.1$ Hz, 1H), 7.35 (d, $J = 7.3$ Hz, 1H), 7.25 – 6.97 (m, 3H), 5.18 – 5.07 (m, 1H), 2.32 – 2.19 (m, 2H), 2.14 – 1.98 (m, 2H), 1.96 – 1.81 (m, 2H), 1.80 – 1.64 (m, 2H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 165.29, 159.81, 159.08, 157.48, 145.21, 143.88, 128.84 (2C), 126.65, 126.48, 126.12, 123.73, 122.13, 120.02, 117.68, 117.60 (3C), 108.16, 61.45, 32.83 (2C), 23.66 (2C). ESI-MS: $m/z = 441$

[M+H]⁺. HRMS (ESI): m/z calcd for (C₂₄H₂₄N₈O + H)⁺: 441.2146; found: 441.2150.

N-(2-aminophenyl)-4-((4-(1-cyclohexyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamide (16b)

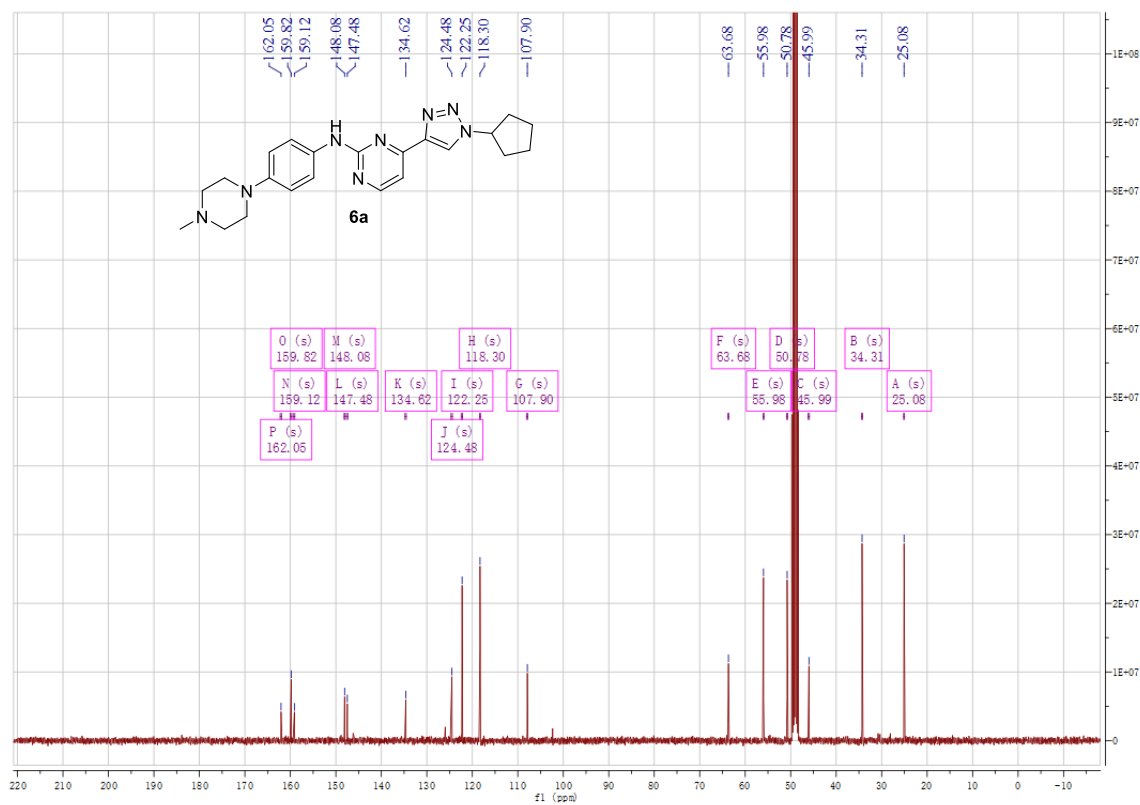
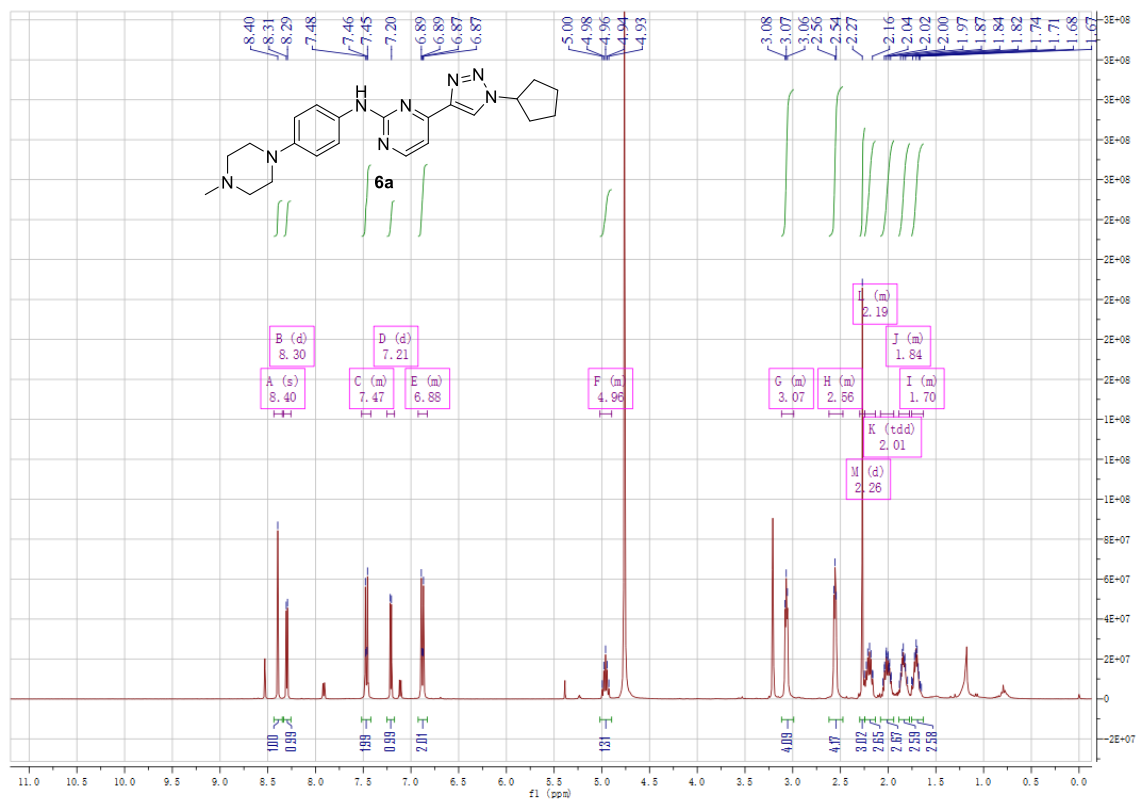
White solid, yield: 100%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.04 (s, 1H), 9.55 (s, 1H), 8.77 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 8.01 (s, 4H), 7.48 (d, *J* = 5.1 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.07 – 6.92 (m, 1H), 6.90 – 6.74 (m, 1H), 6.74 – 6.49 (m, 1H), 4.91 (s, 2H), 4.73 – 4.52 (m, 1H), 2.24 – 2.07 (m, 2H), 1.97 – 1.79 (m, 4H), 1.79 – 1.64 (m, 1H), 1.58 – 1.39 (m, 2H), 1.38 – 1.22 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 164.91, 159.84, 159.10, 157.47, 145.06, 143.49, 143.04, 128.67 (2C), 126.82, 126.54, 126.23, 123.73, 123.05, 117.60 (2C), 116.33, 116.18, 107.97, 59.53, 32.69, 24.62 (2C), 24.60. ESI-MS: m/z = 455 [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₅H₂₆N₈O + H)⁺: 455.2302; found: 455.2307.

N-(2-aminophenyl)-4-((4-(1-isopropyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-yl)amino)benzamide (16c)

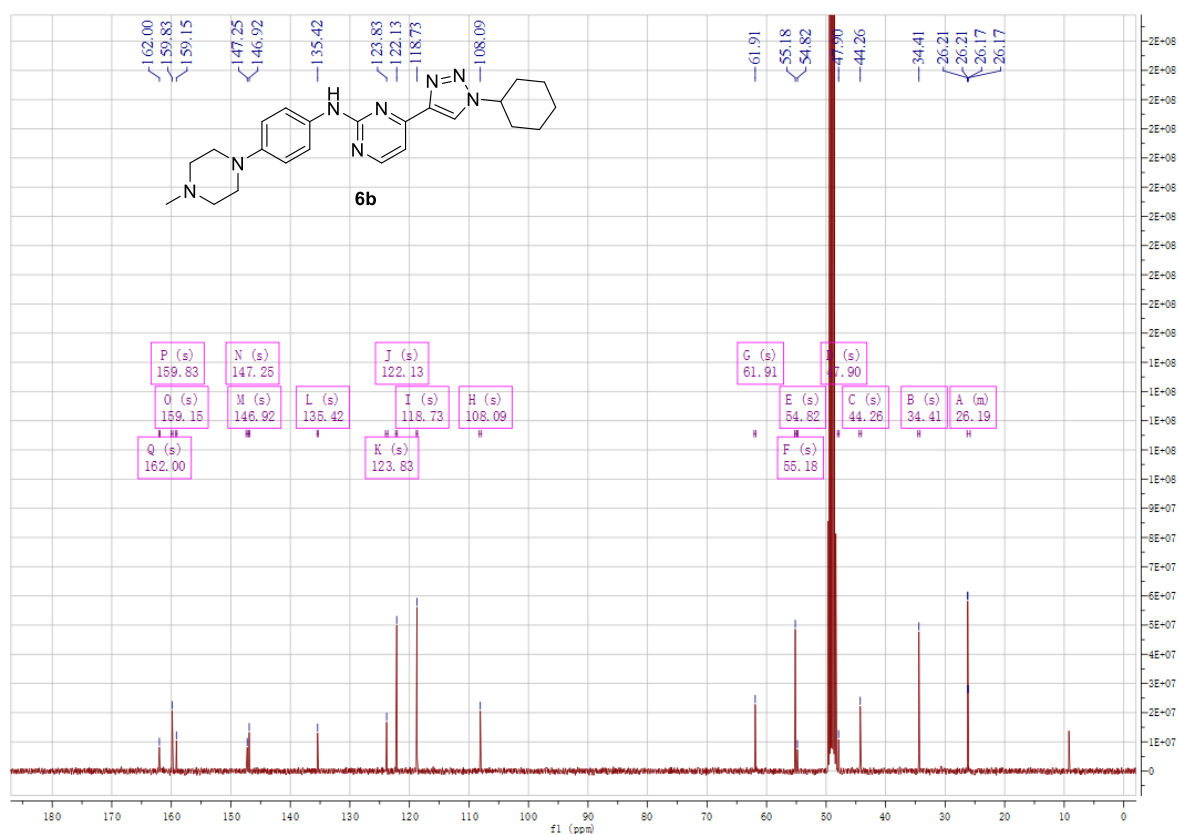
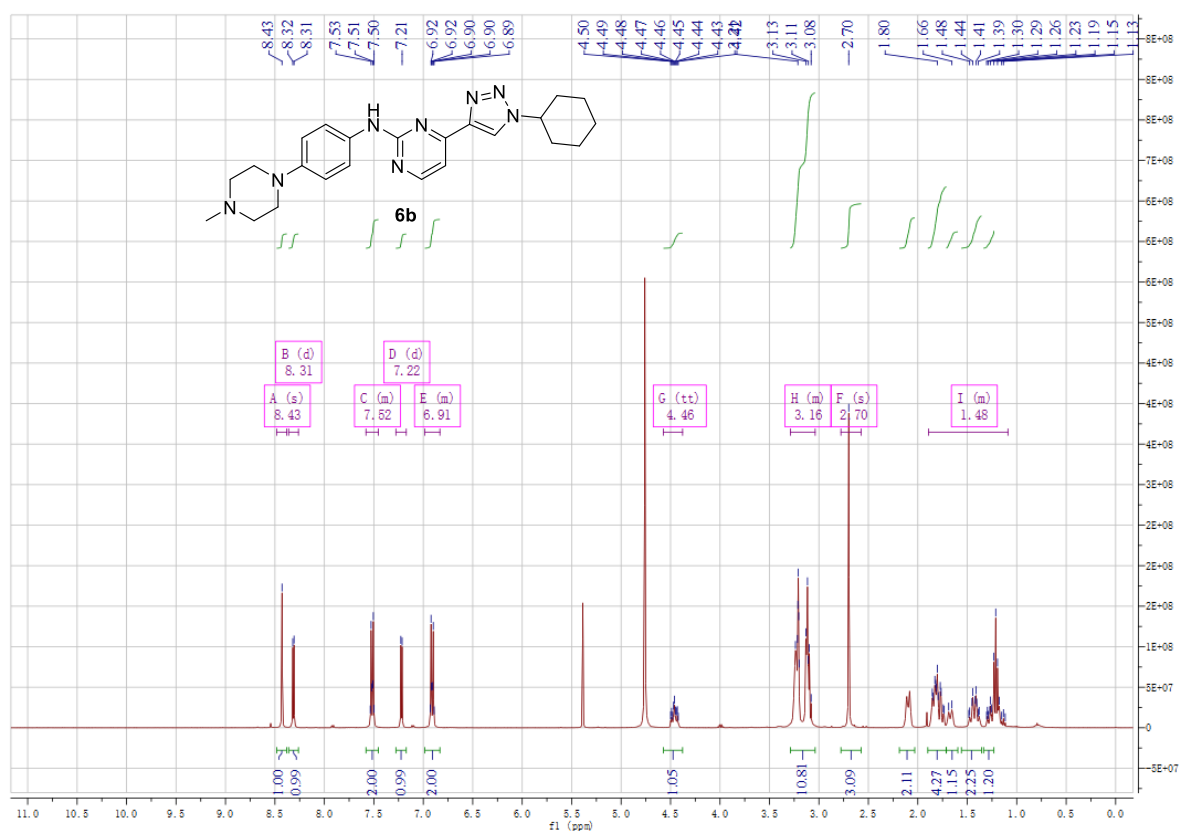
White solid, yield: 100%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.04 (s, 1H), 9.58 (s, 1H), 8.77 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H), 7.98 (s, 4H), 7.47 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 5.08 – 4.73 (m, 3H), 1.59 (s, 3H), 1.57 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 165.46, 160.31, 159.62, 157.95, 145.69, 143.97, 143.54, 129.17 (2C), 127.25, 127.08, 126.80, 124.14, 123.39, 118.09 (2C), 116.87, 116.68, 108.48, 53.41, 23.03 (2C). ESI-MS: m/z = 415 [M+H]⁺. HRMS (ESI): m/z calcd for (C₂₂H₂₂N₈O + H)⁺: 415.1989; found: 415.1995.

NMR spectrum

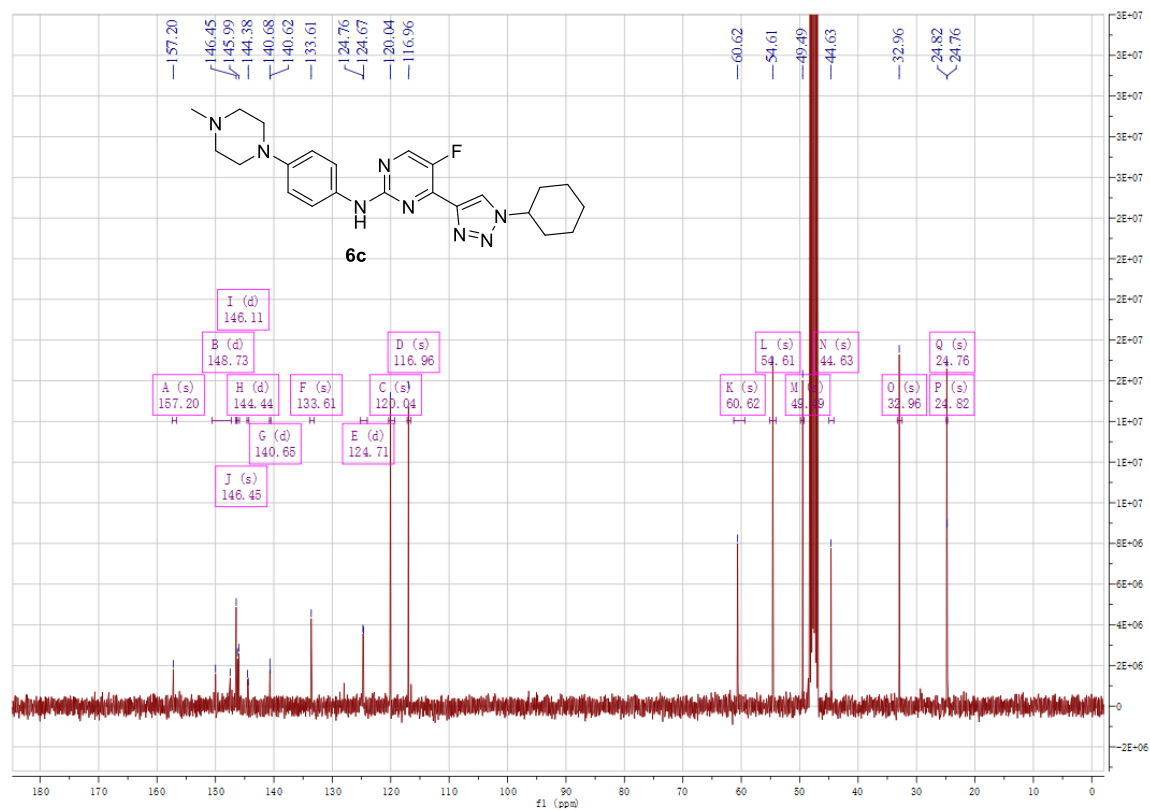
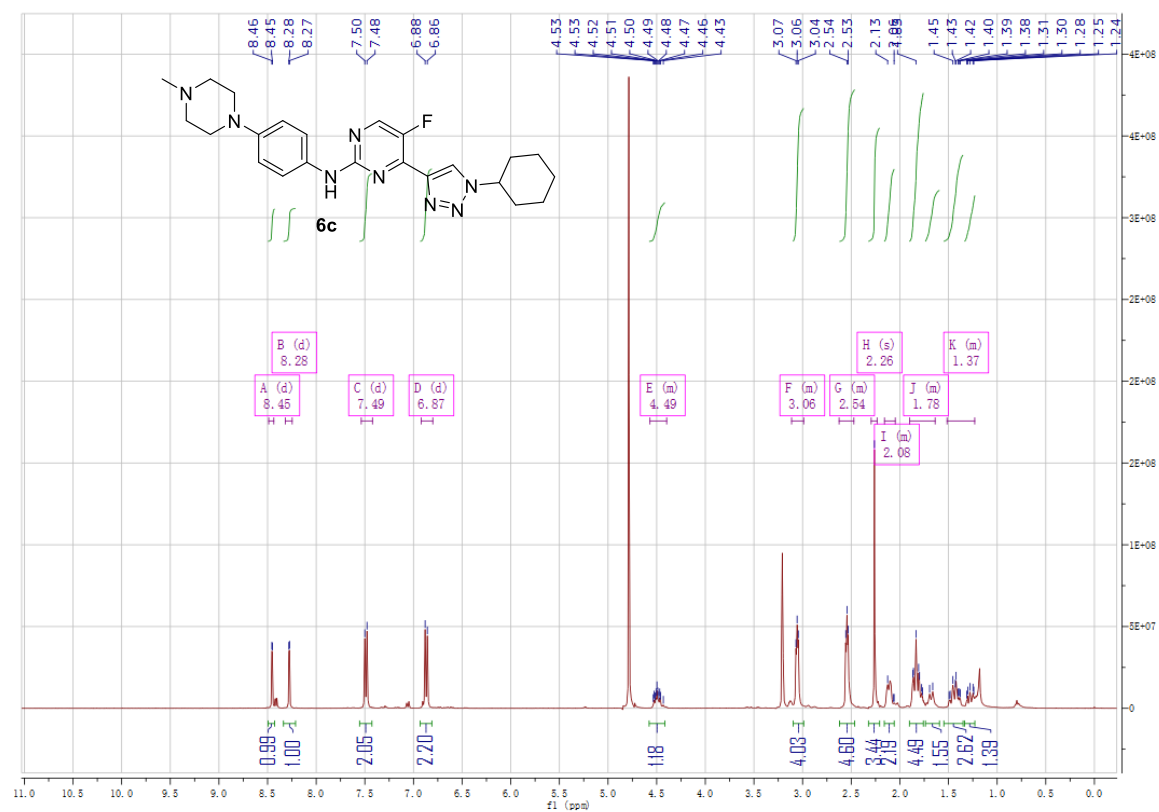
6a



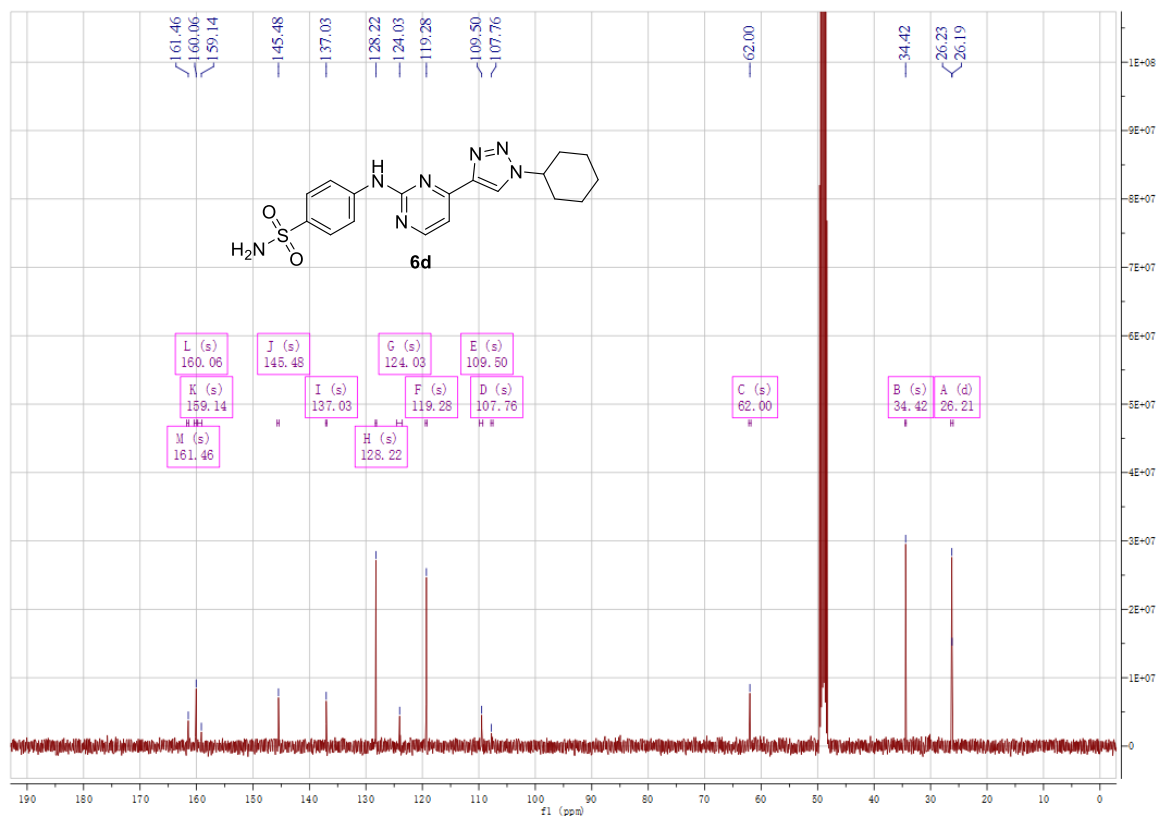
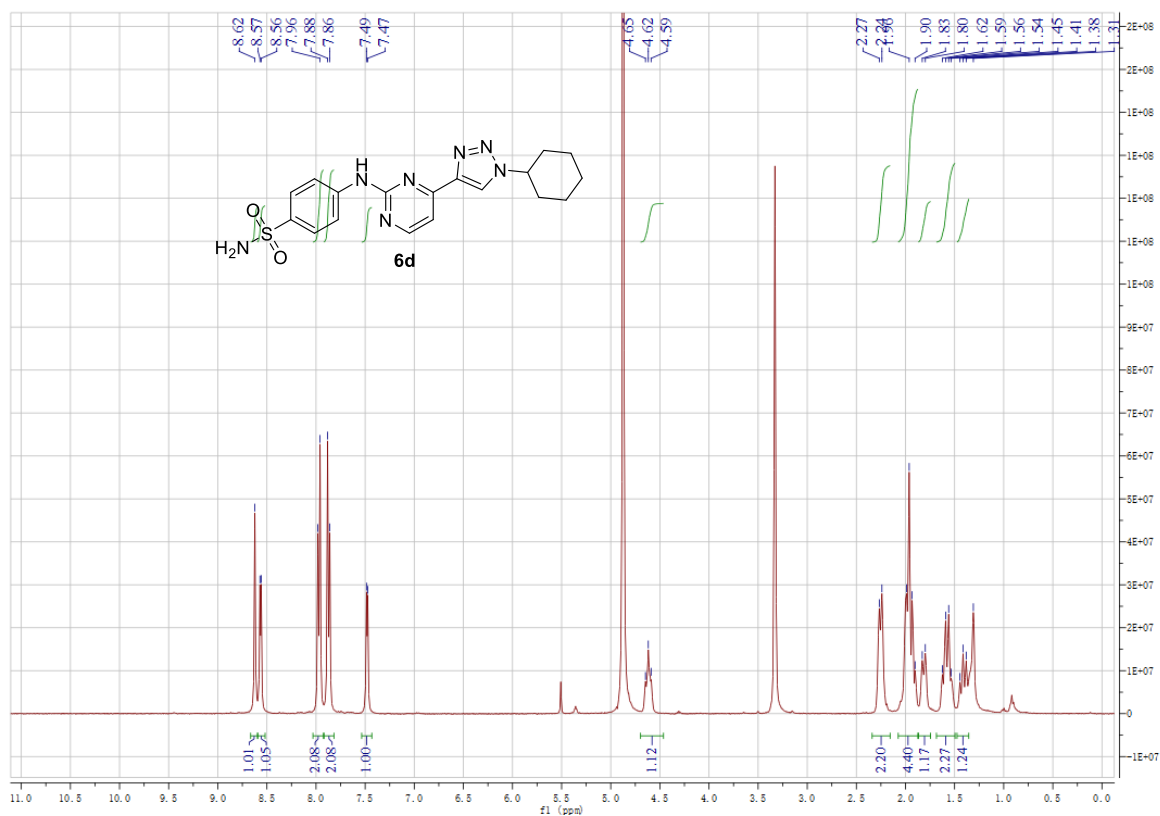
6b



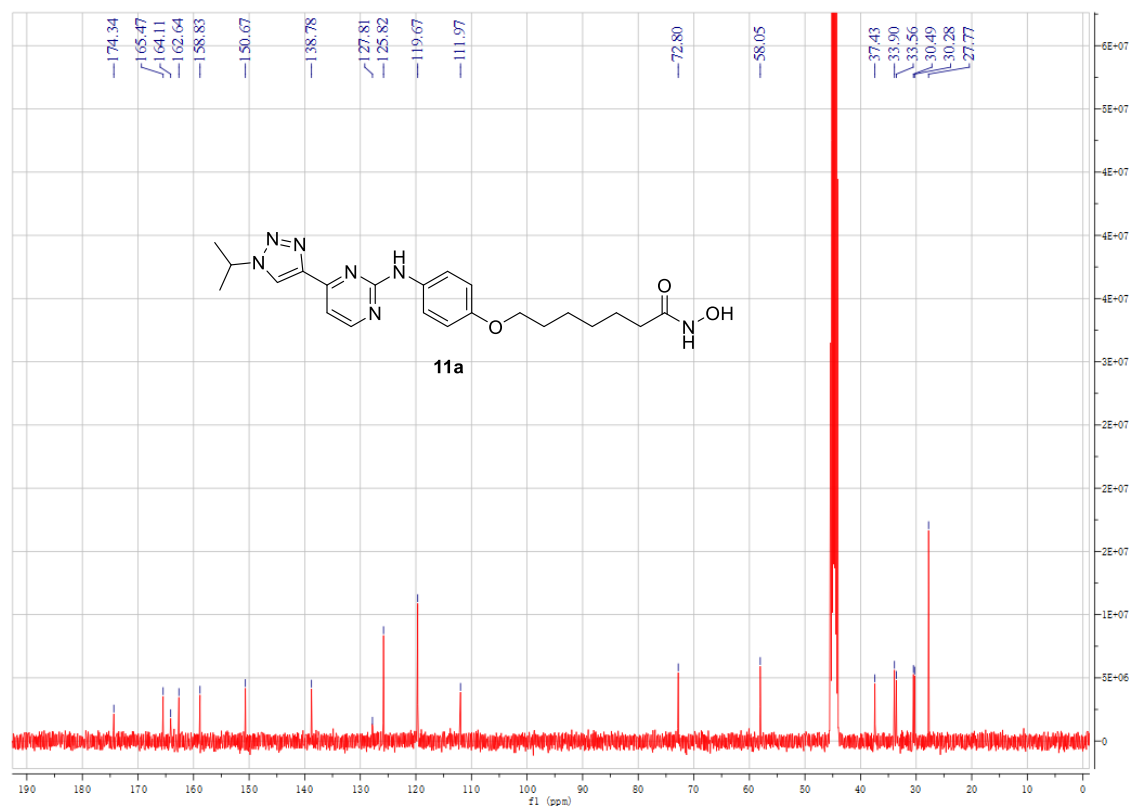
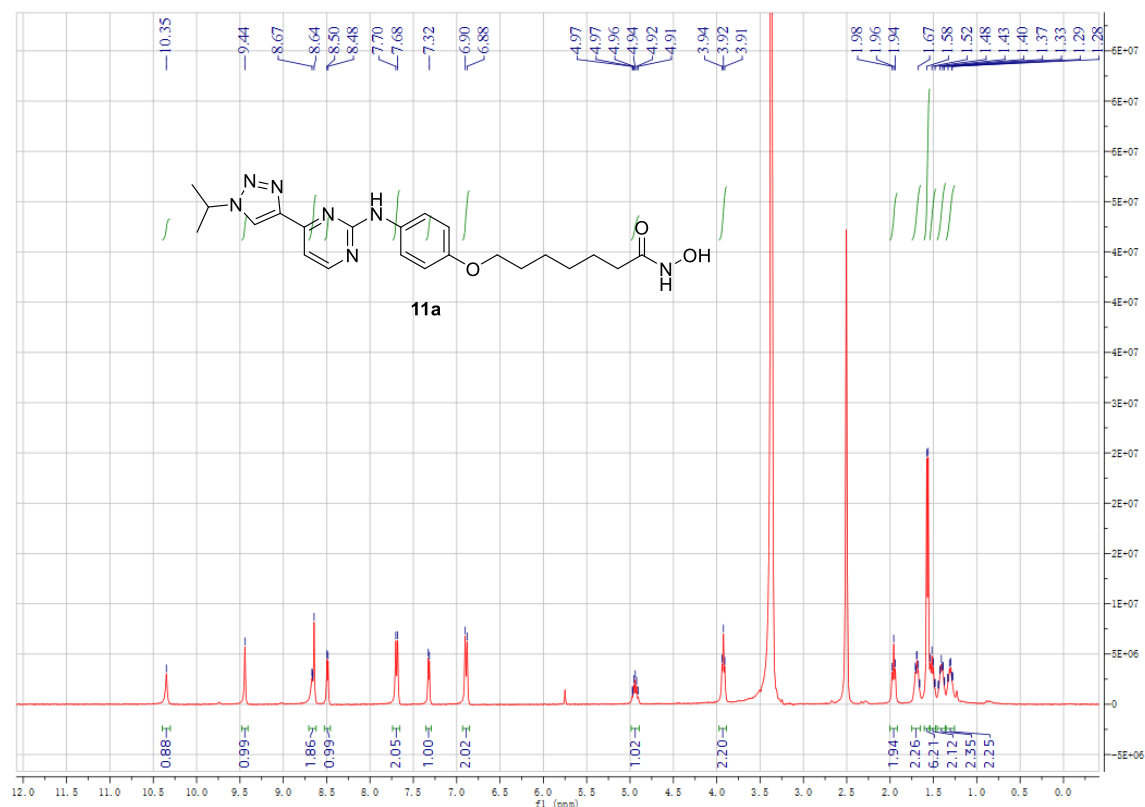
6c



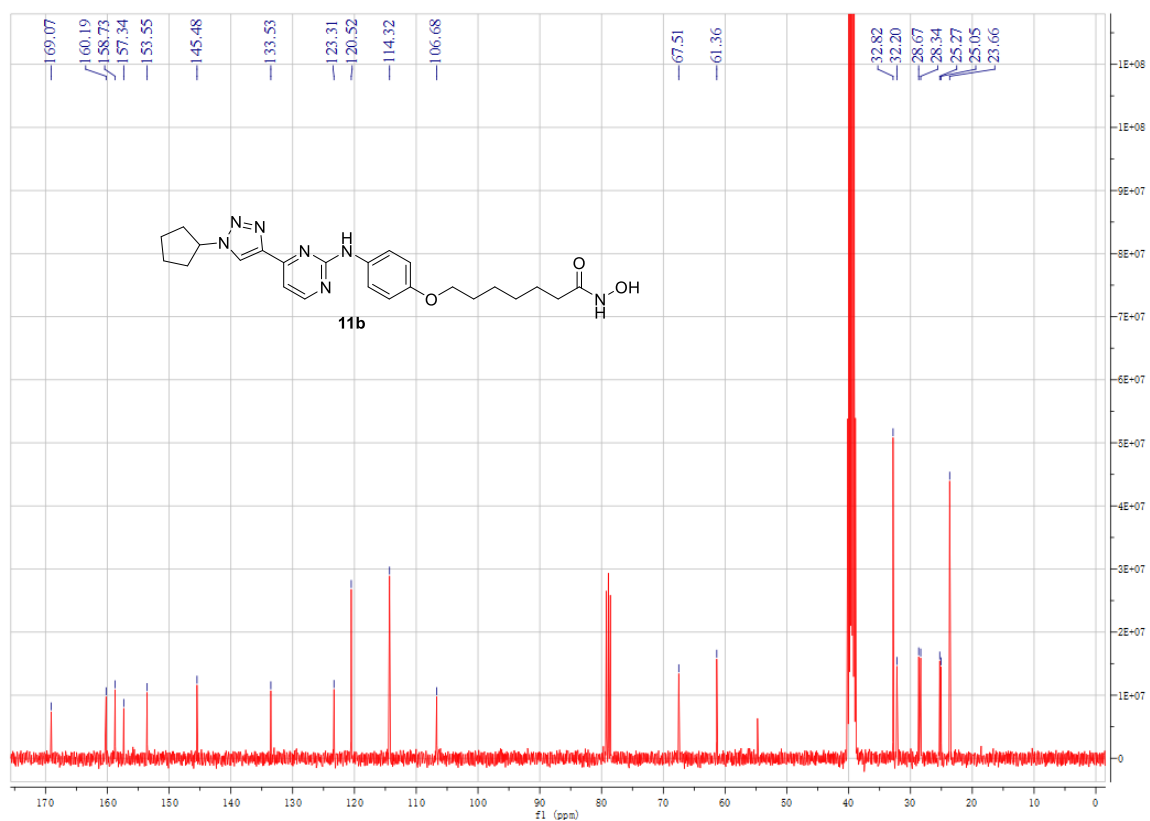
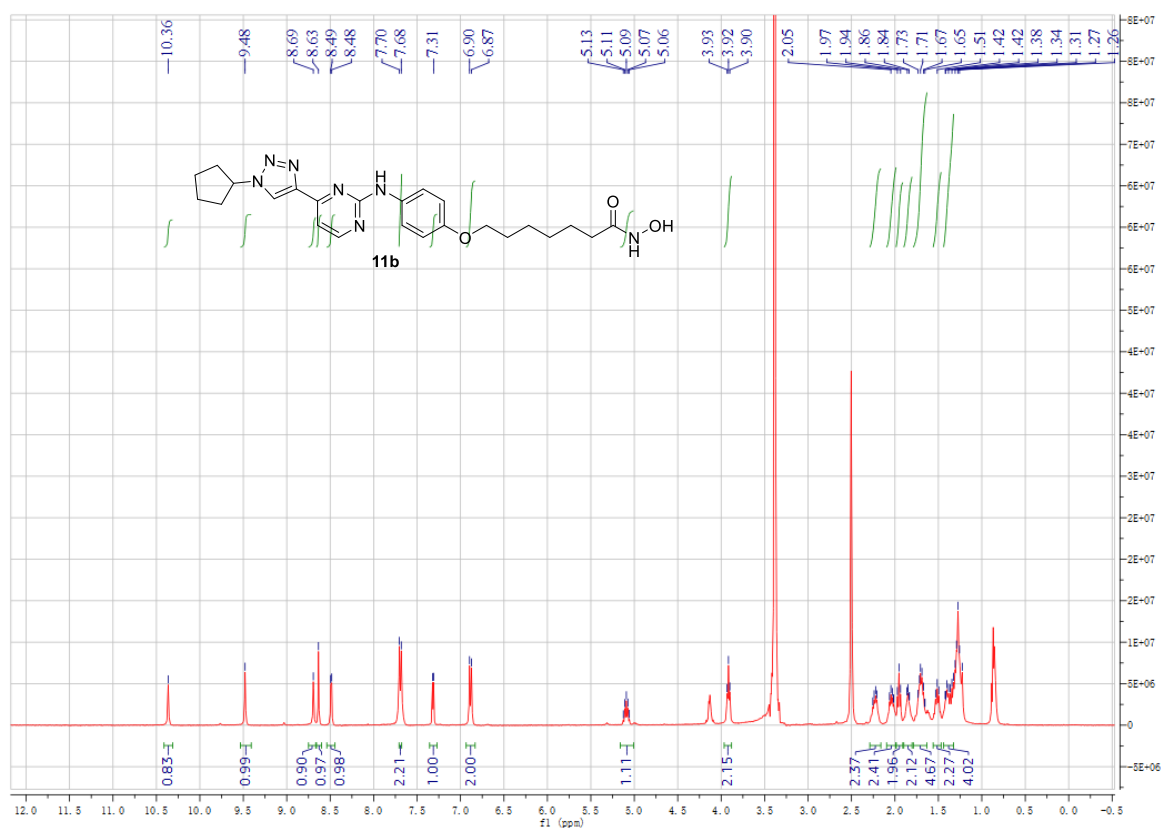
6d



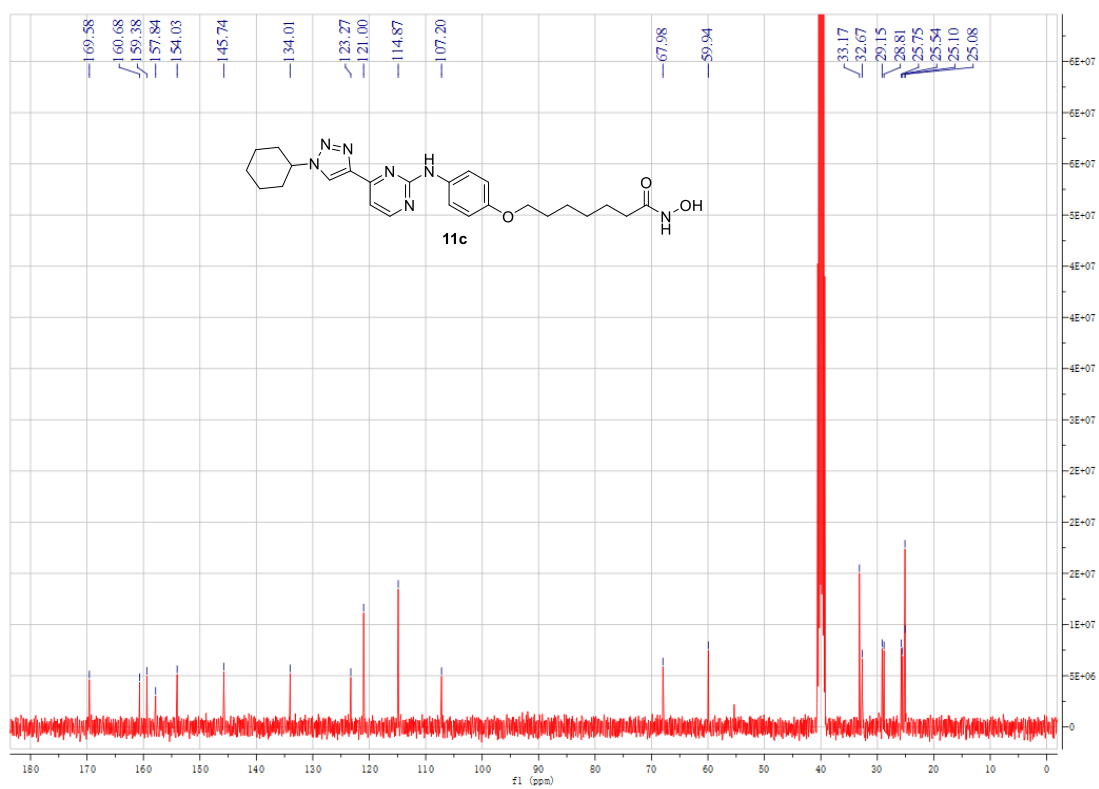
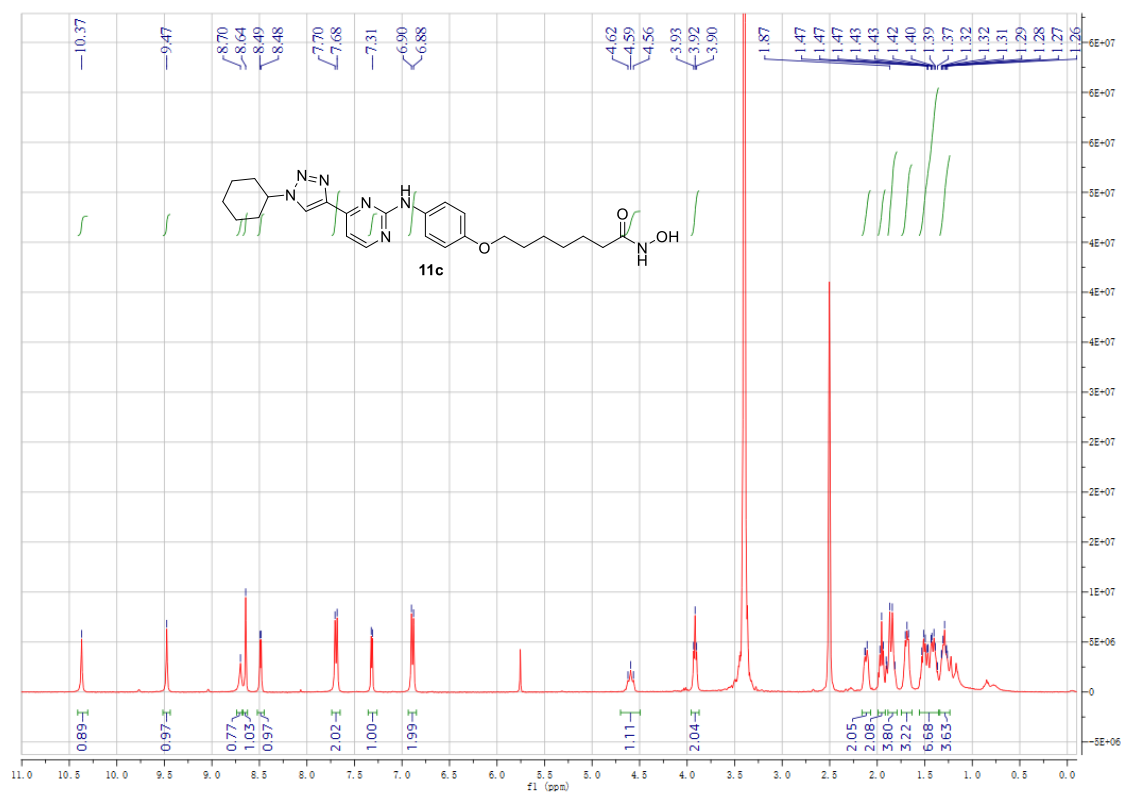
11a



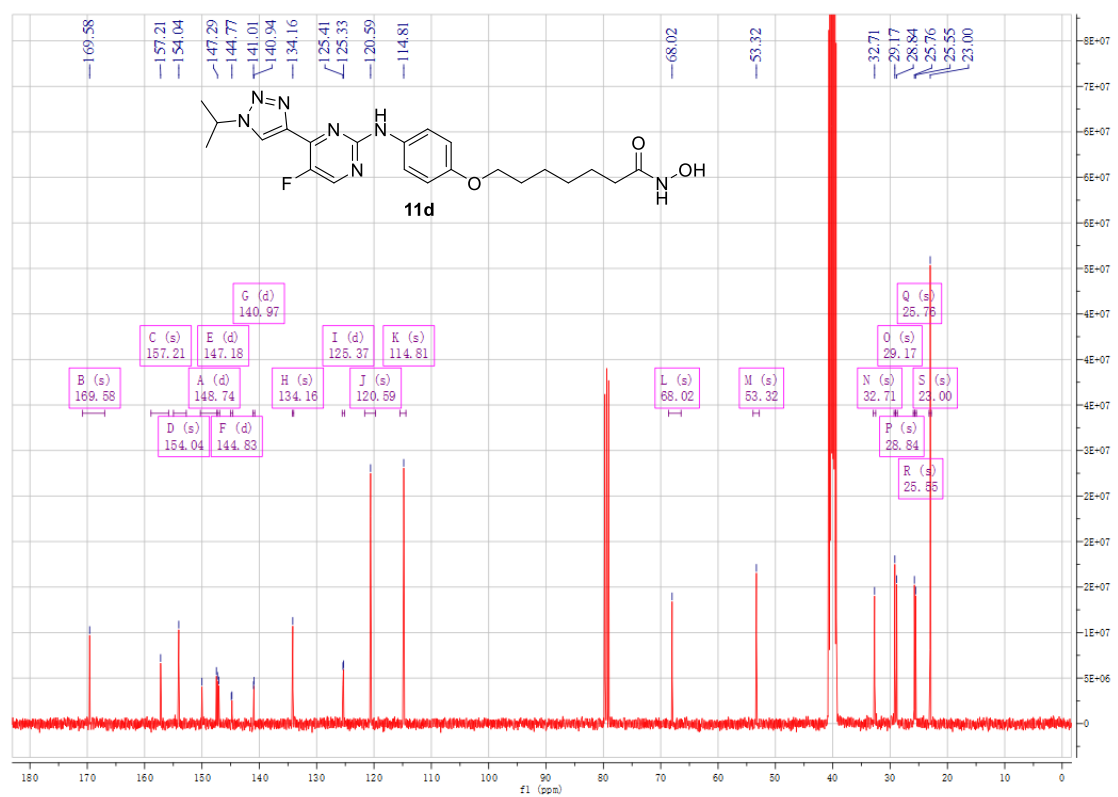
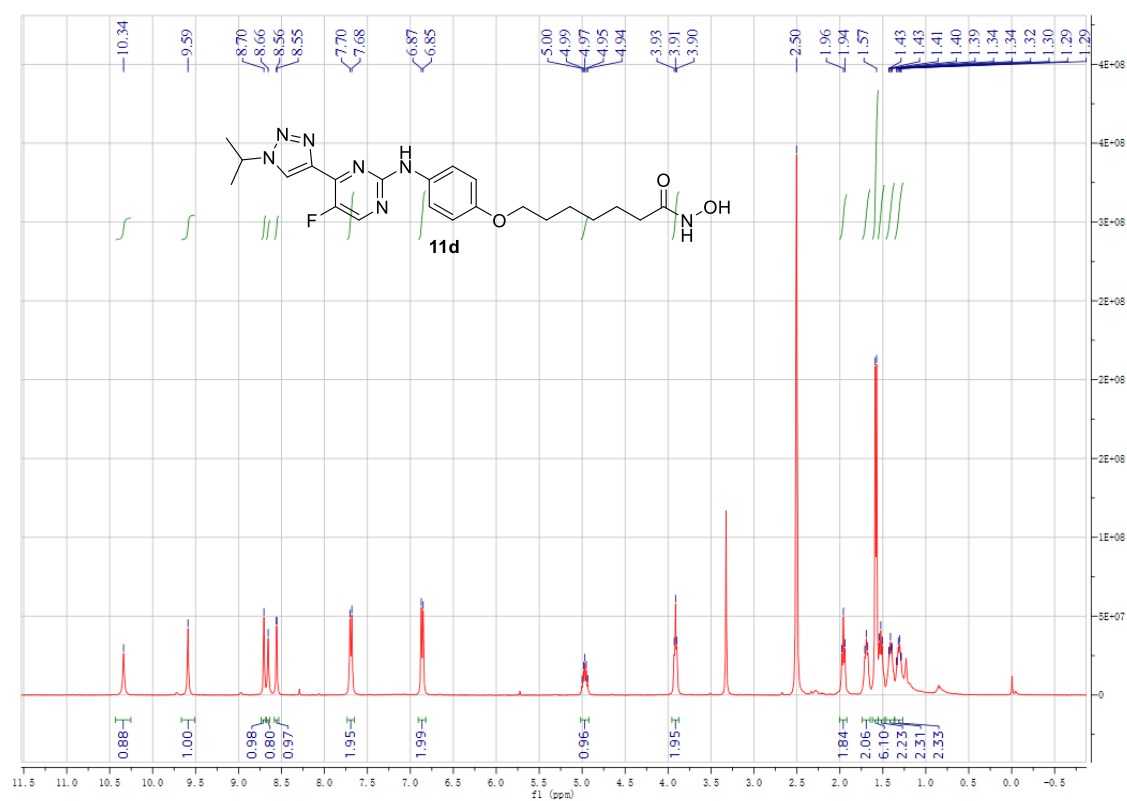
11b



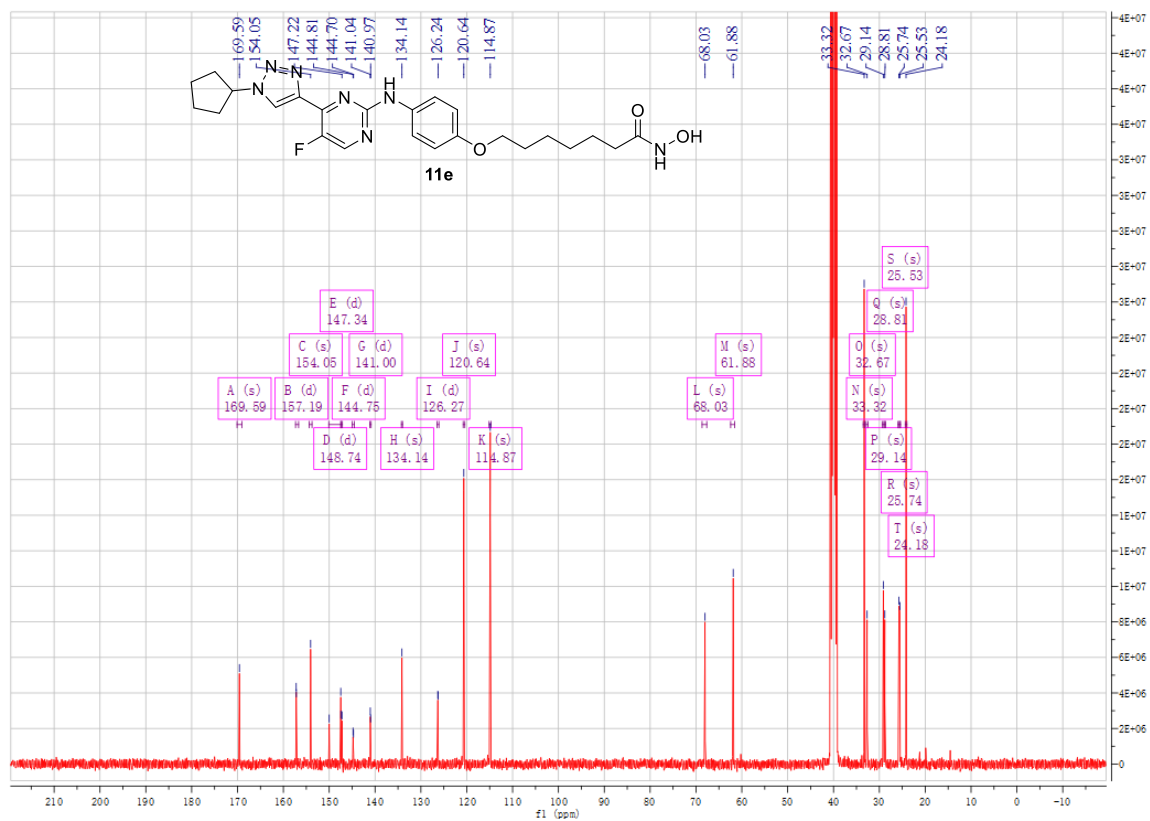
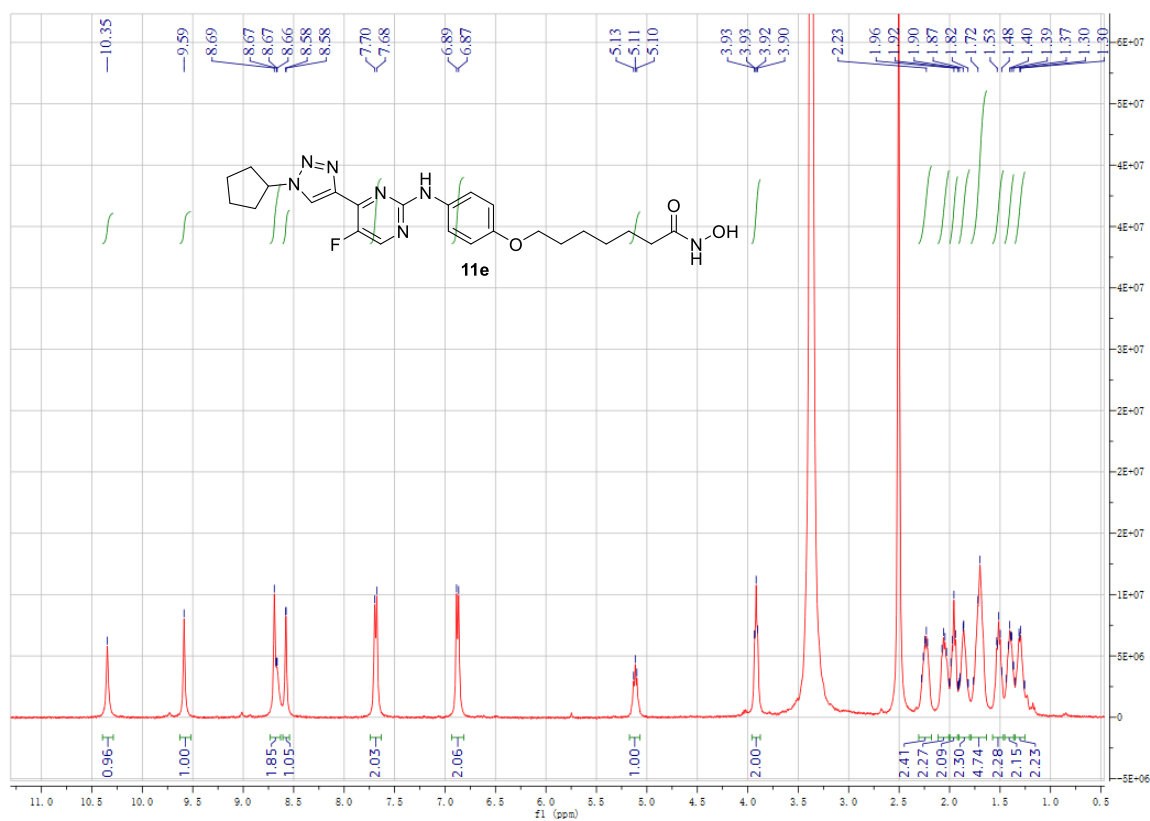
11c



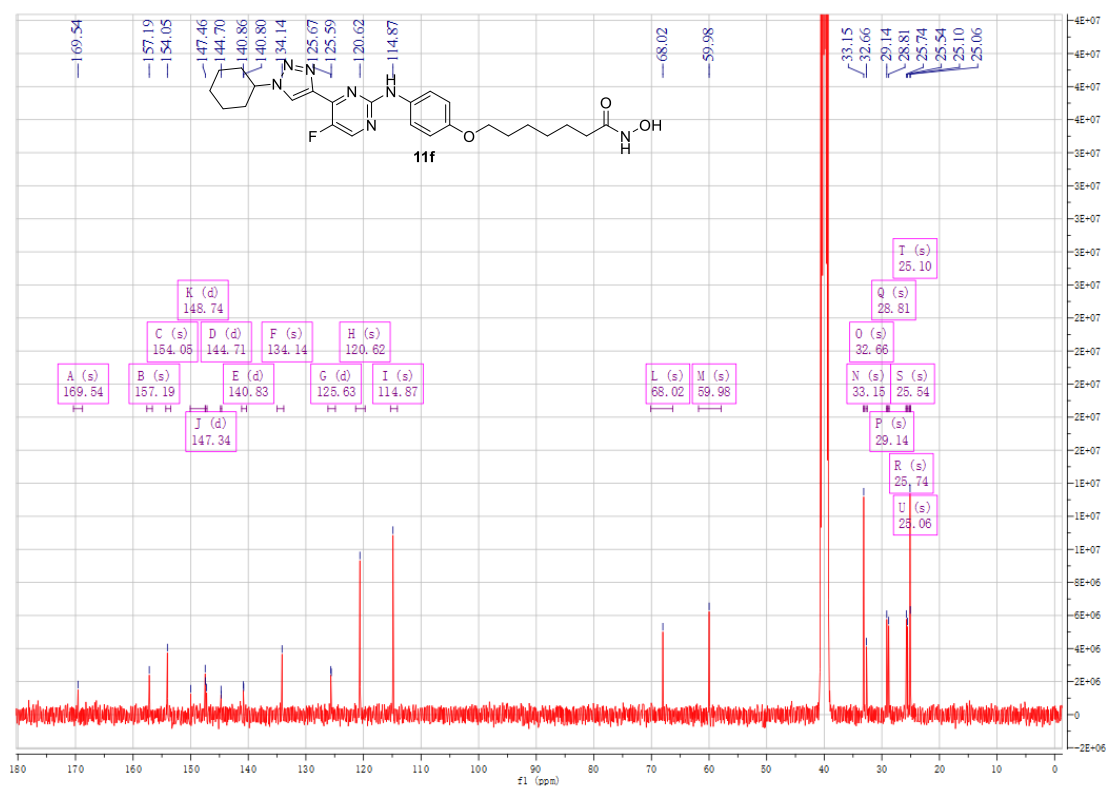
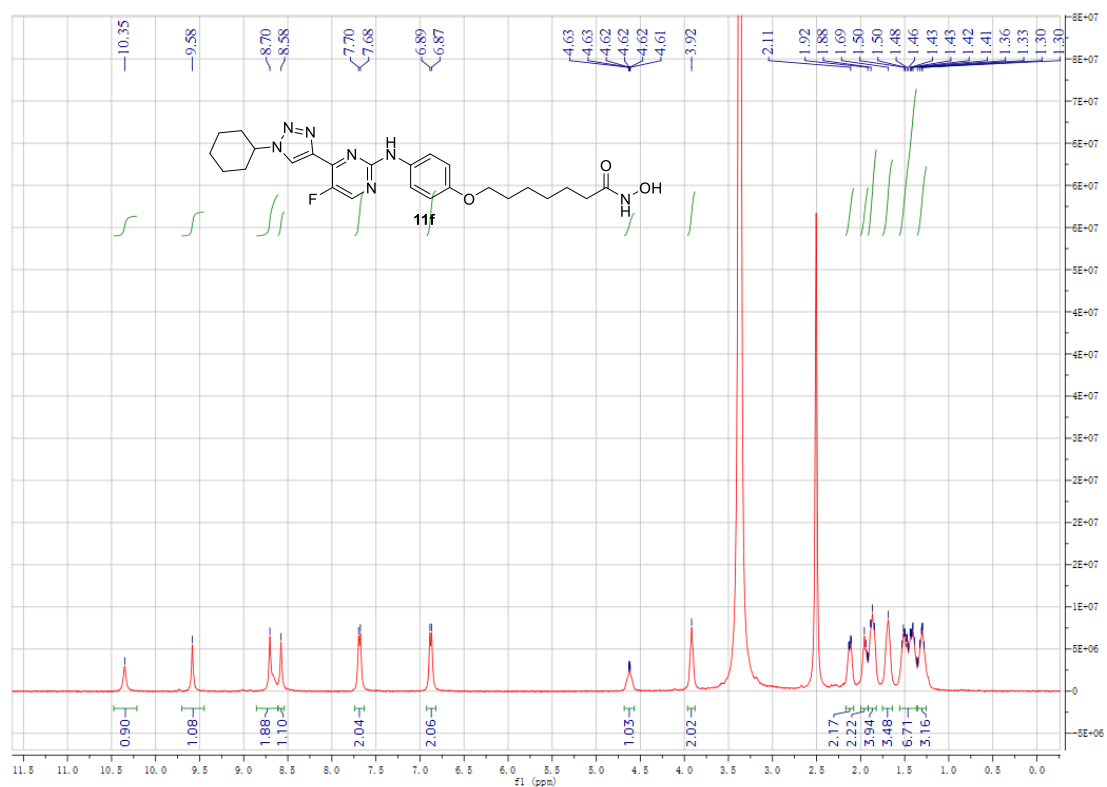
11d



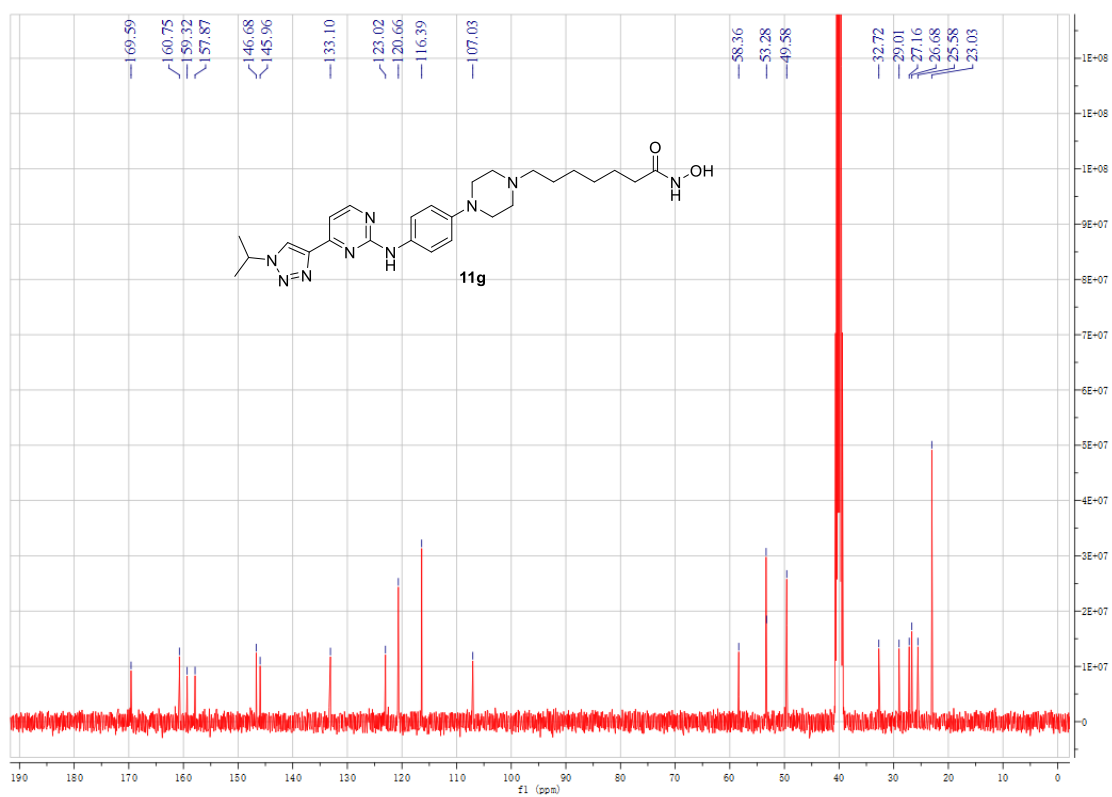
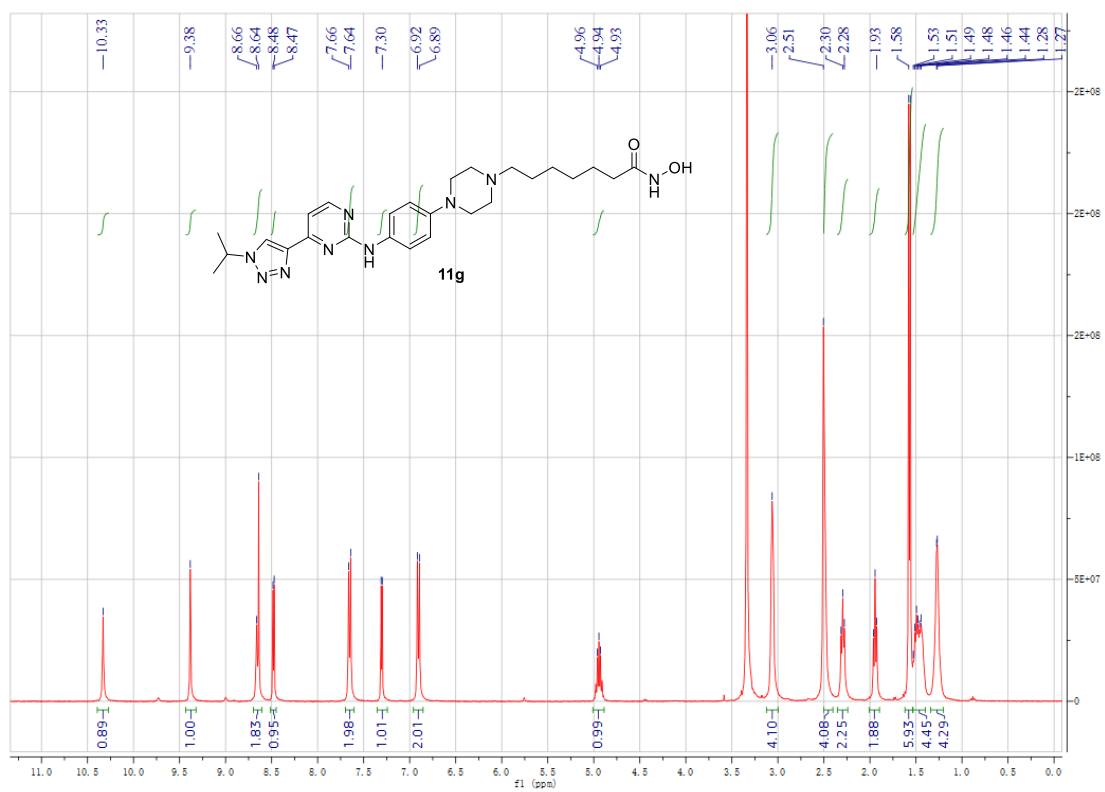
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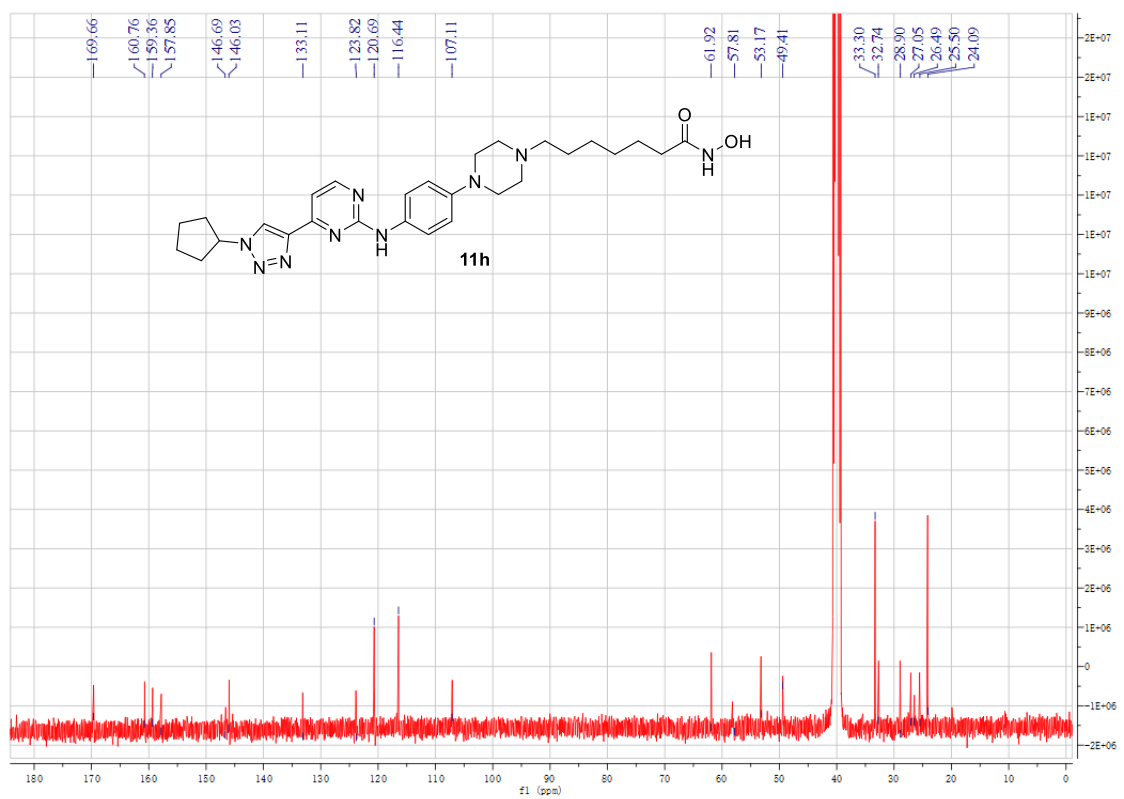
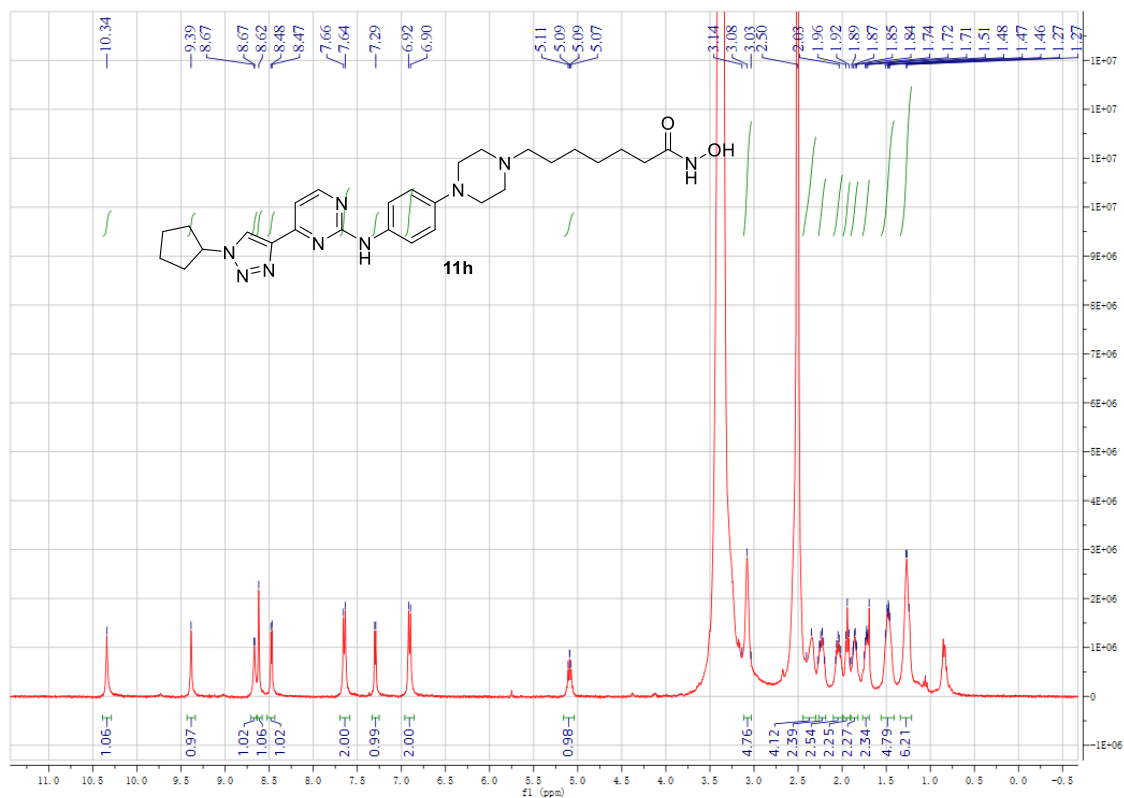
11f



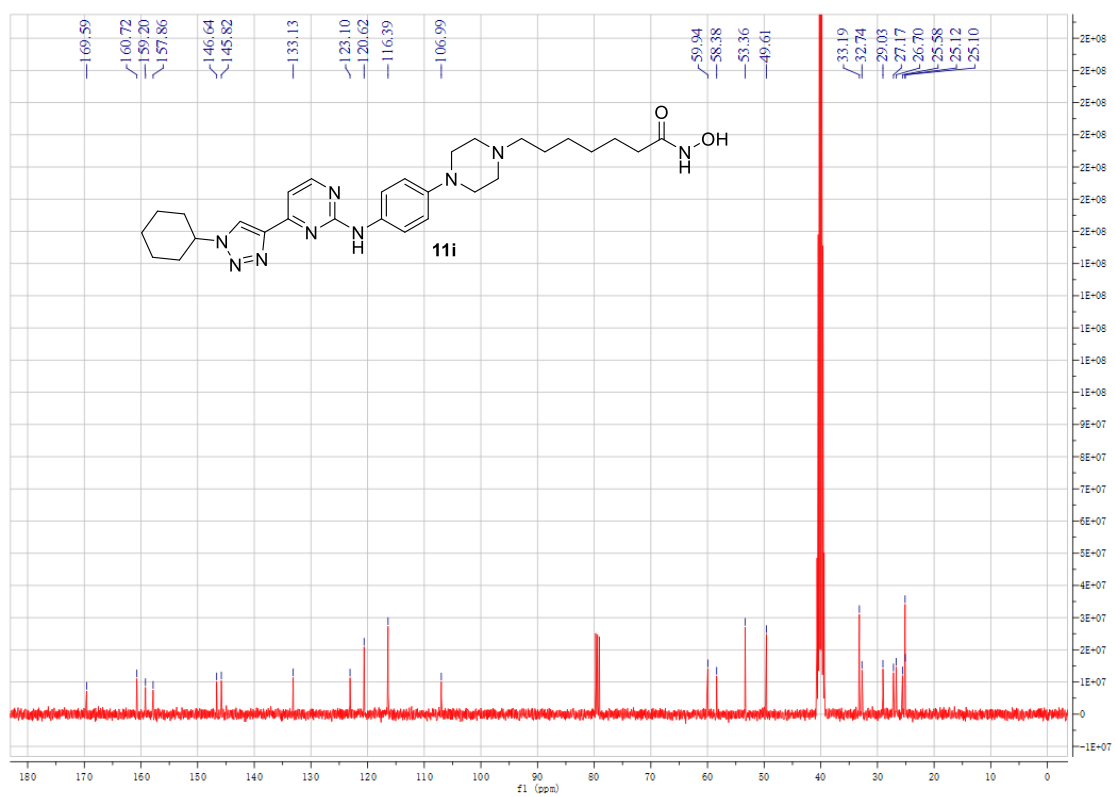
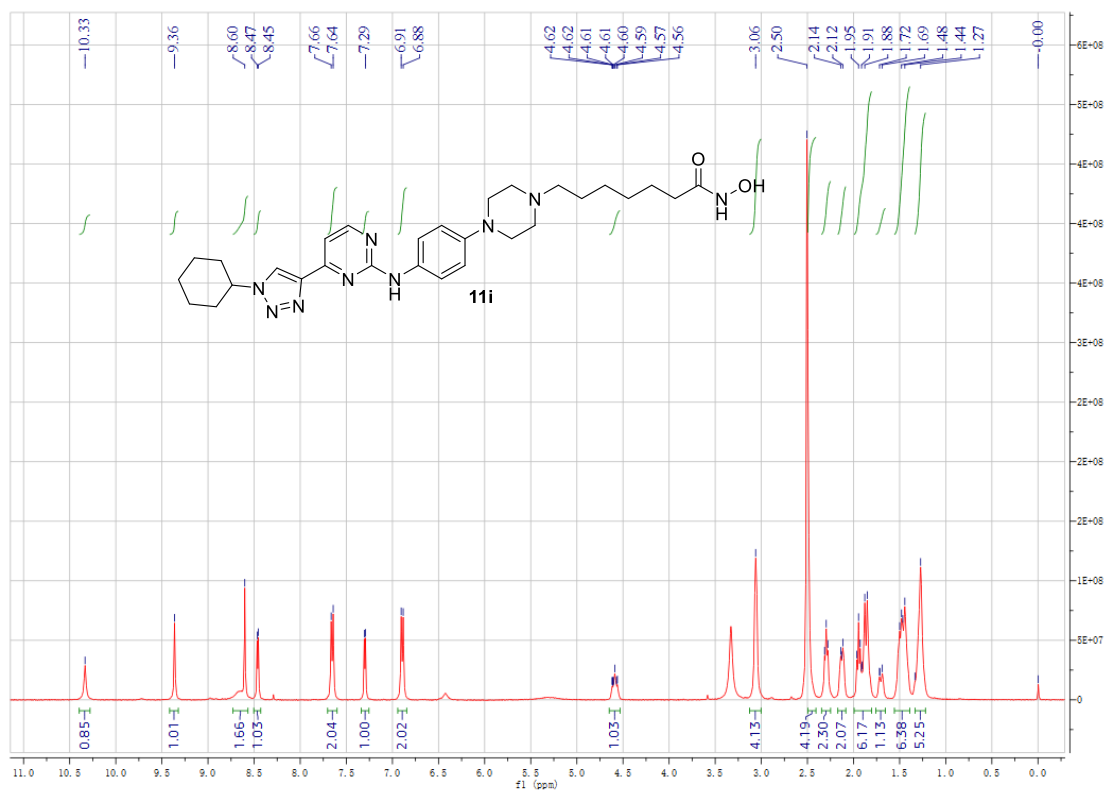
11g



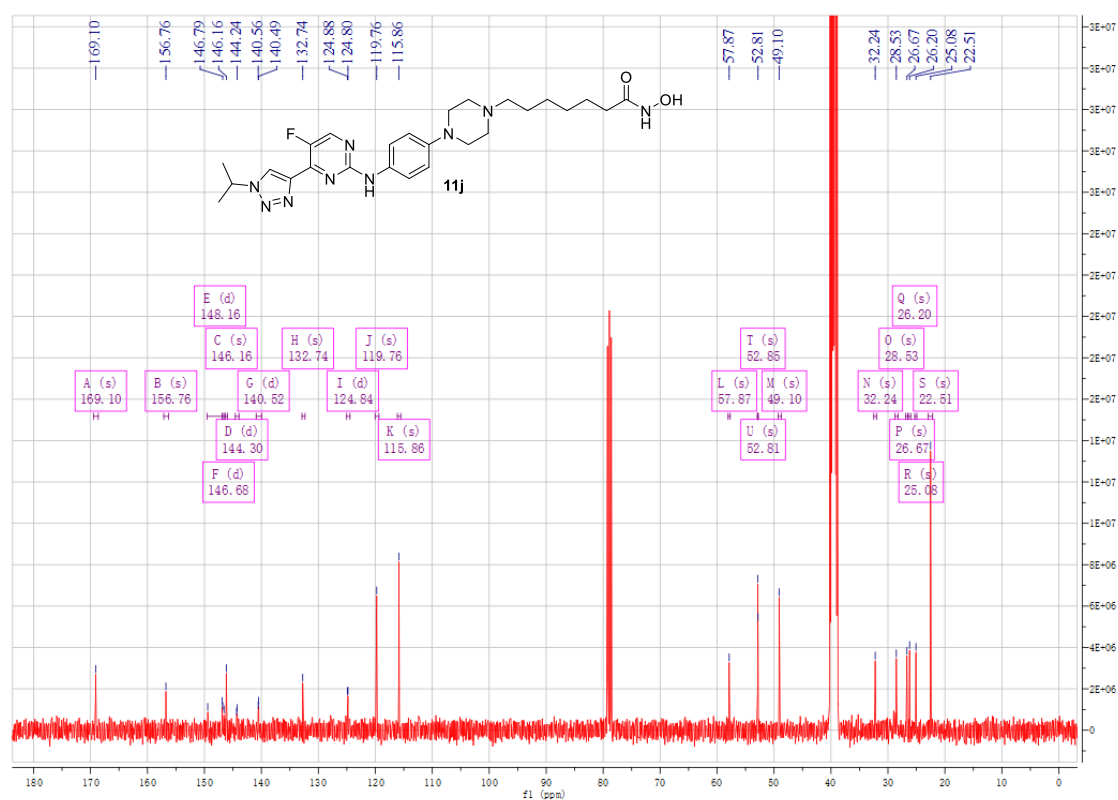
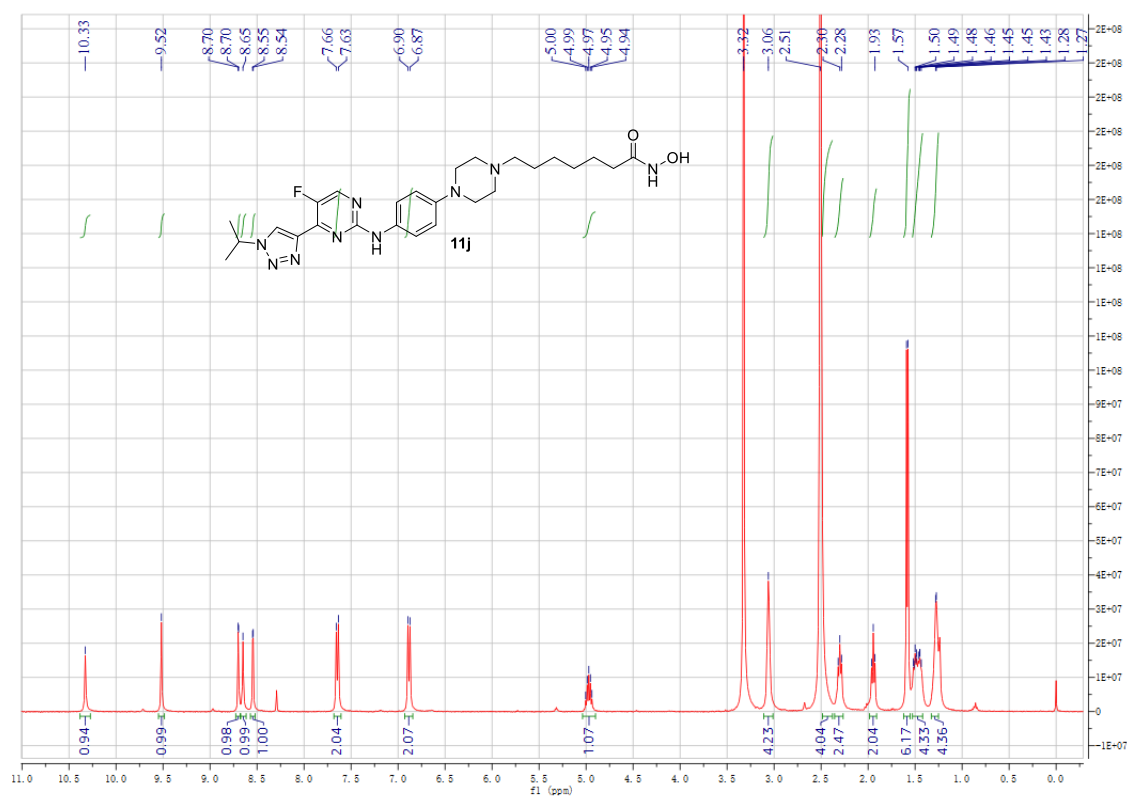
11h



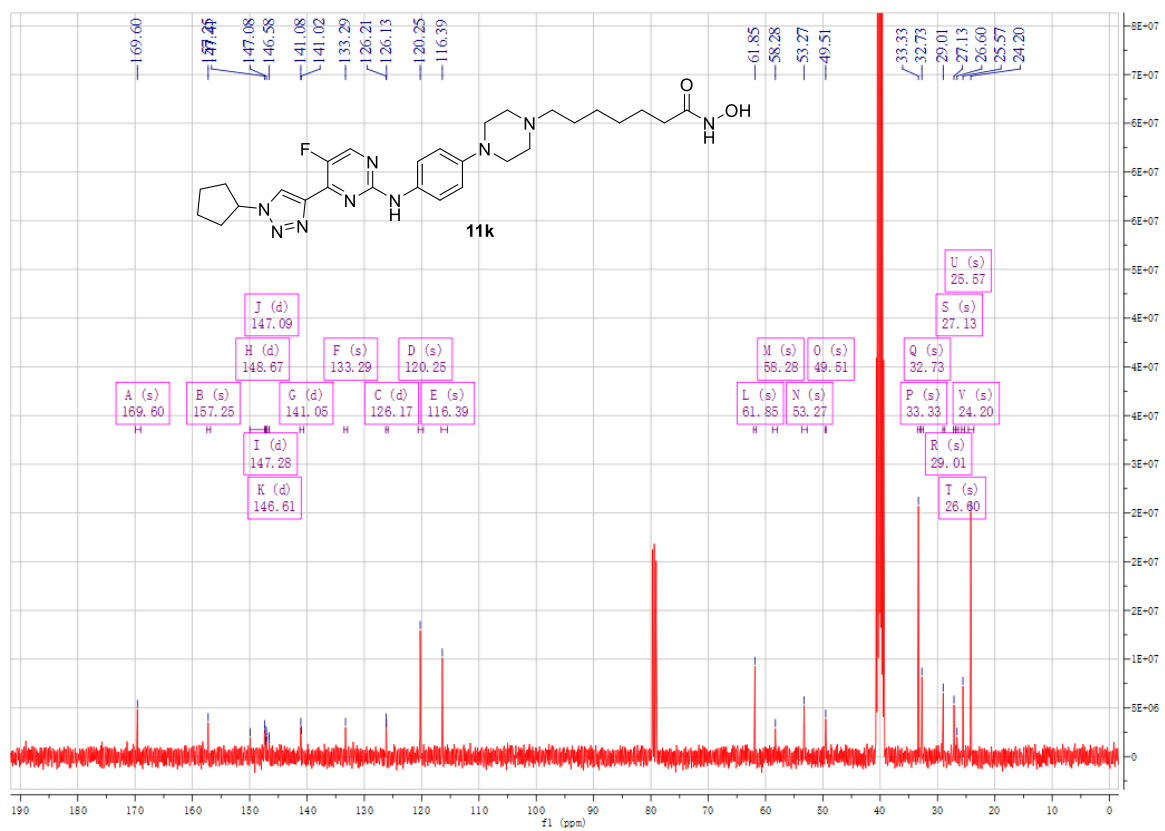
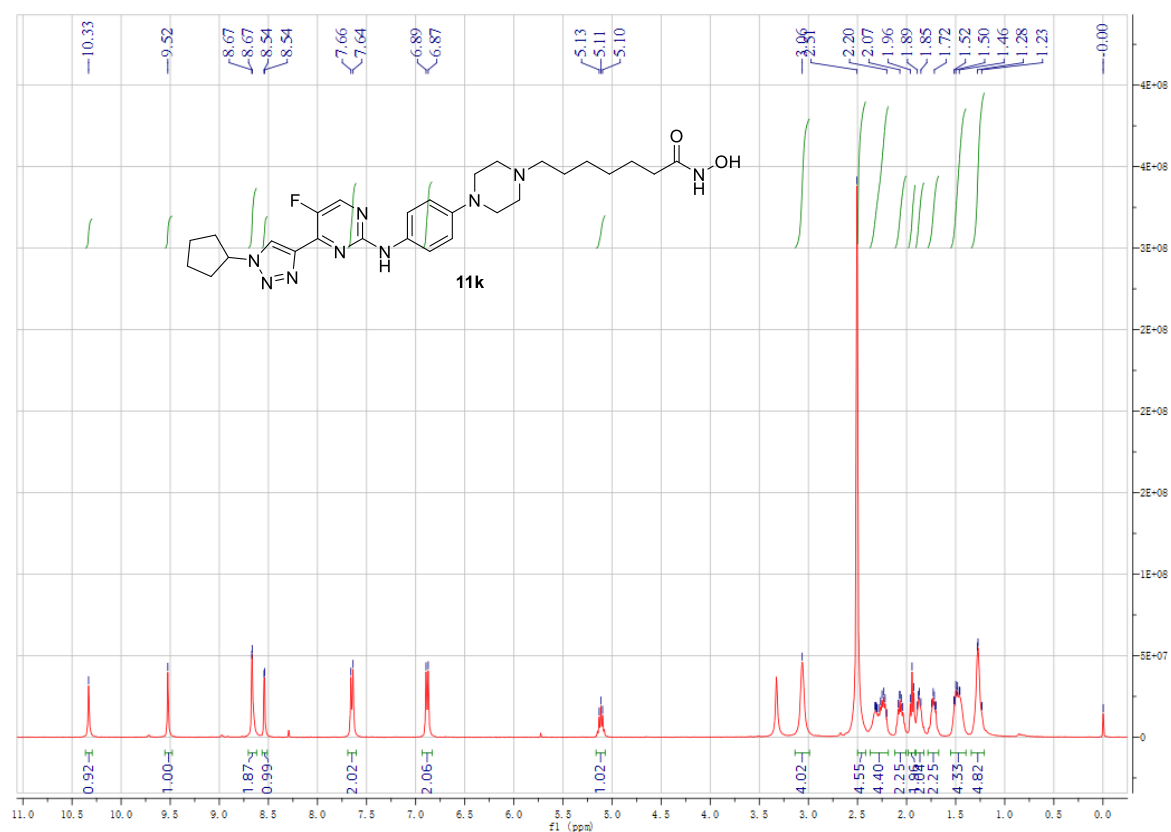
11i



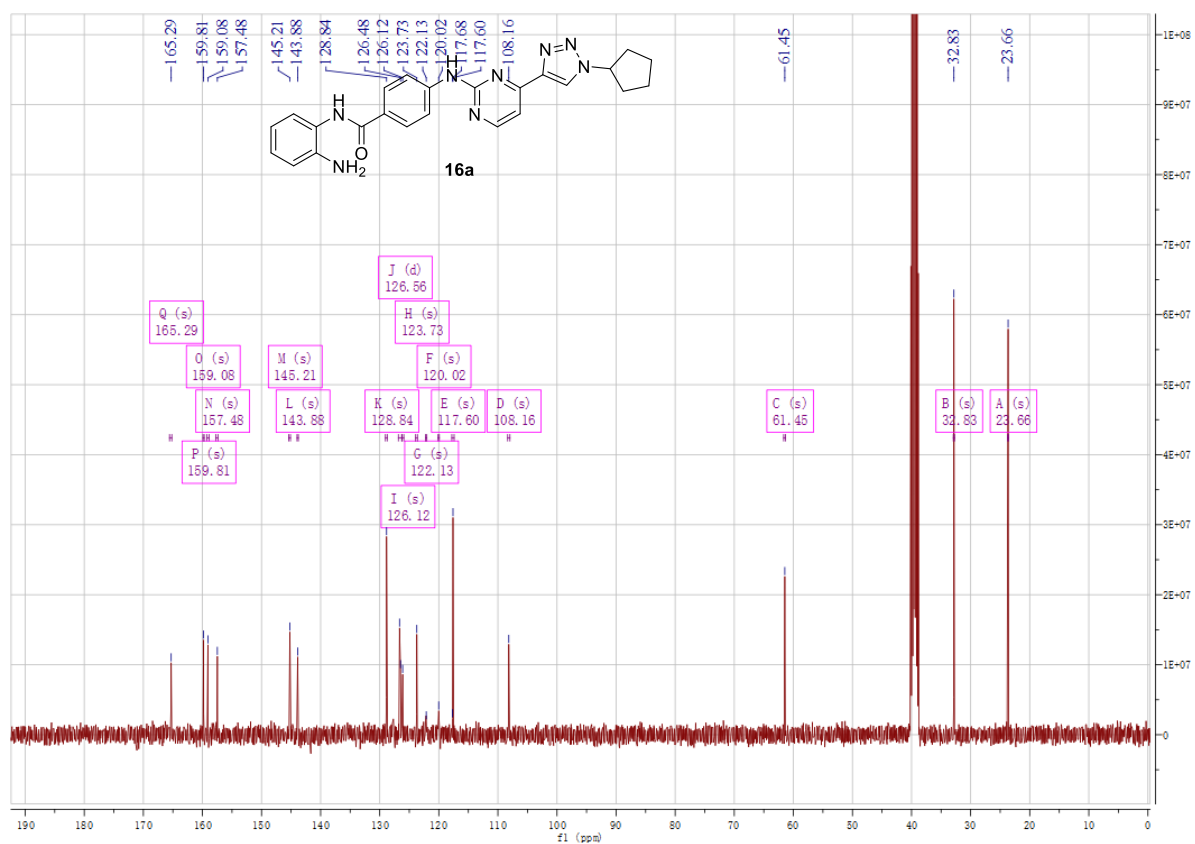
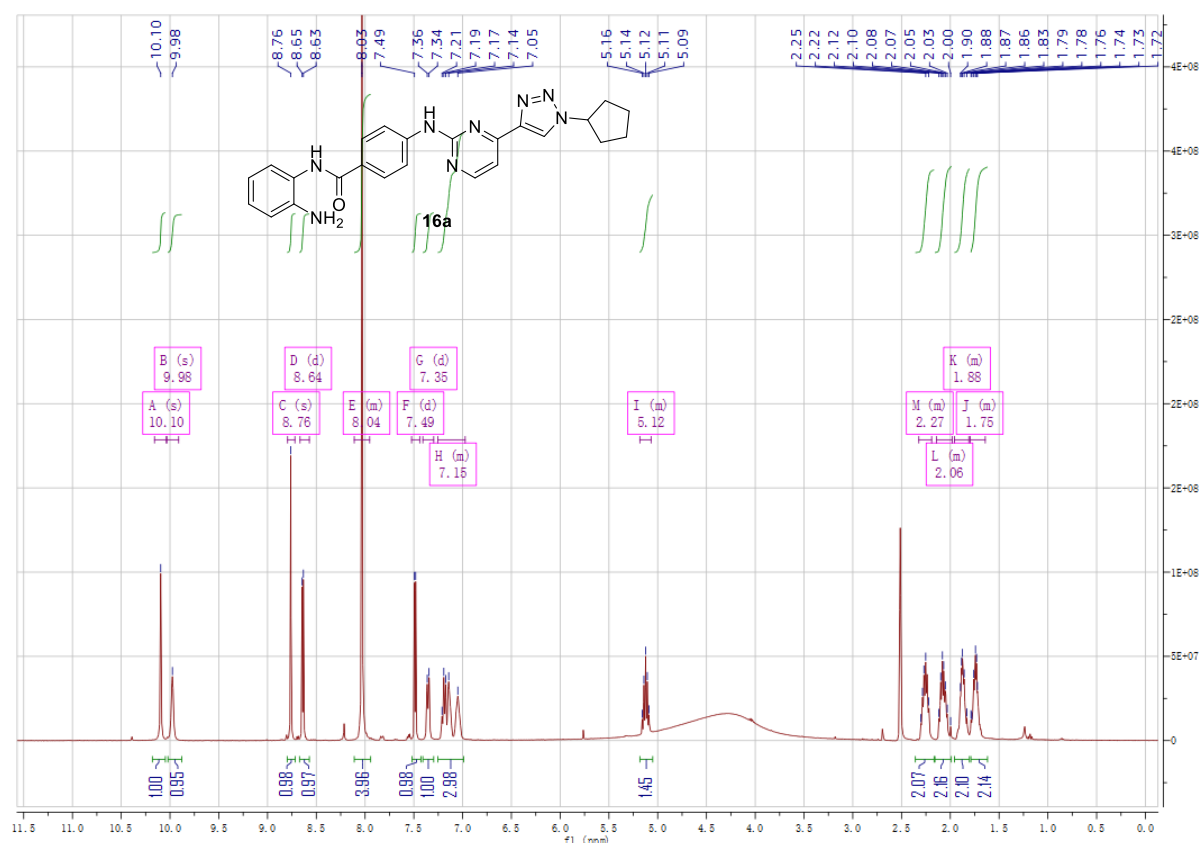
11j



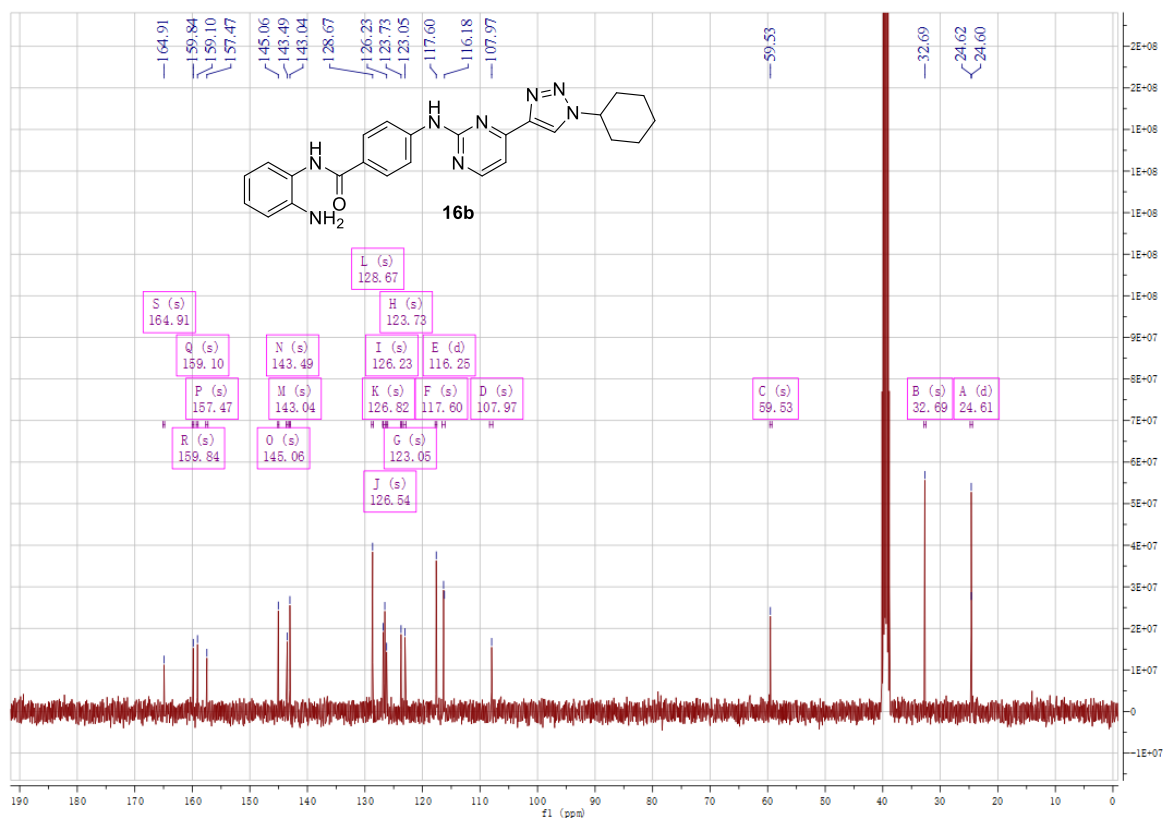
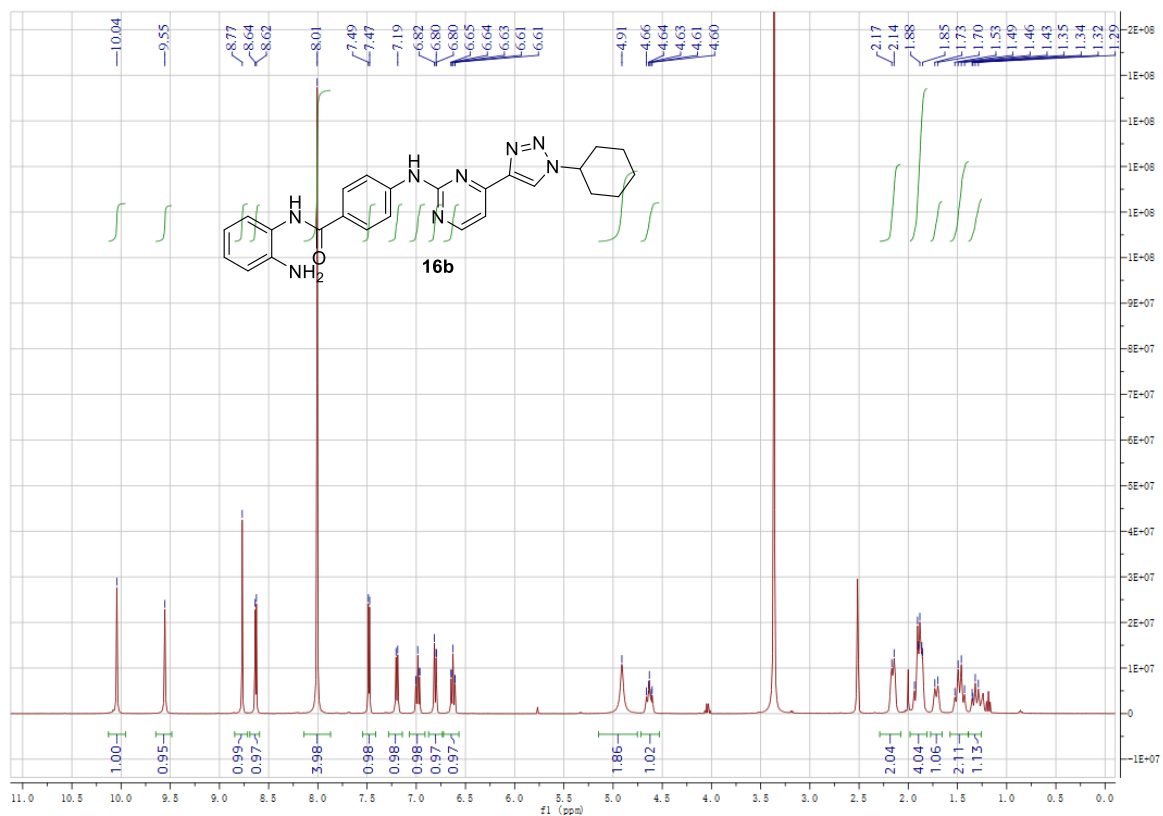
11k



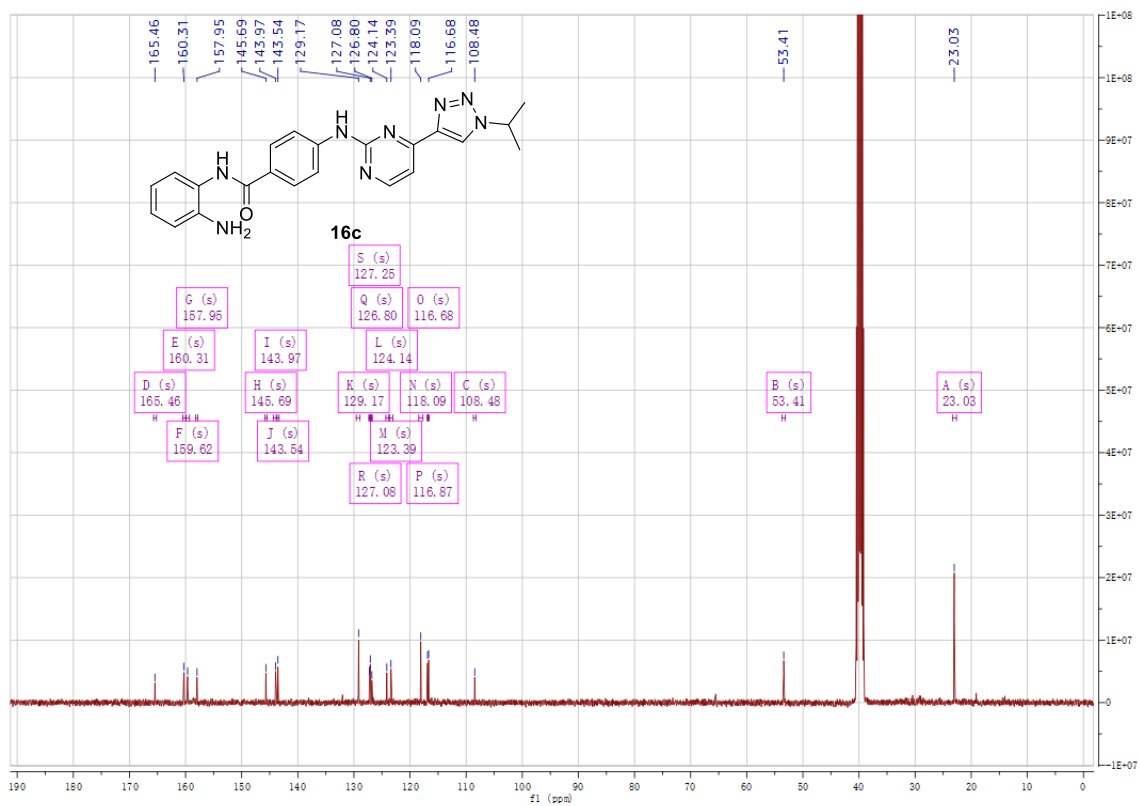
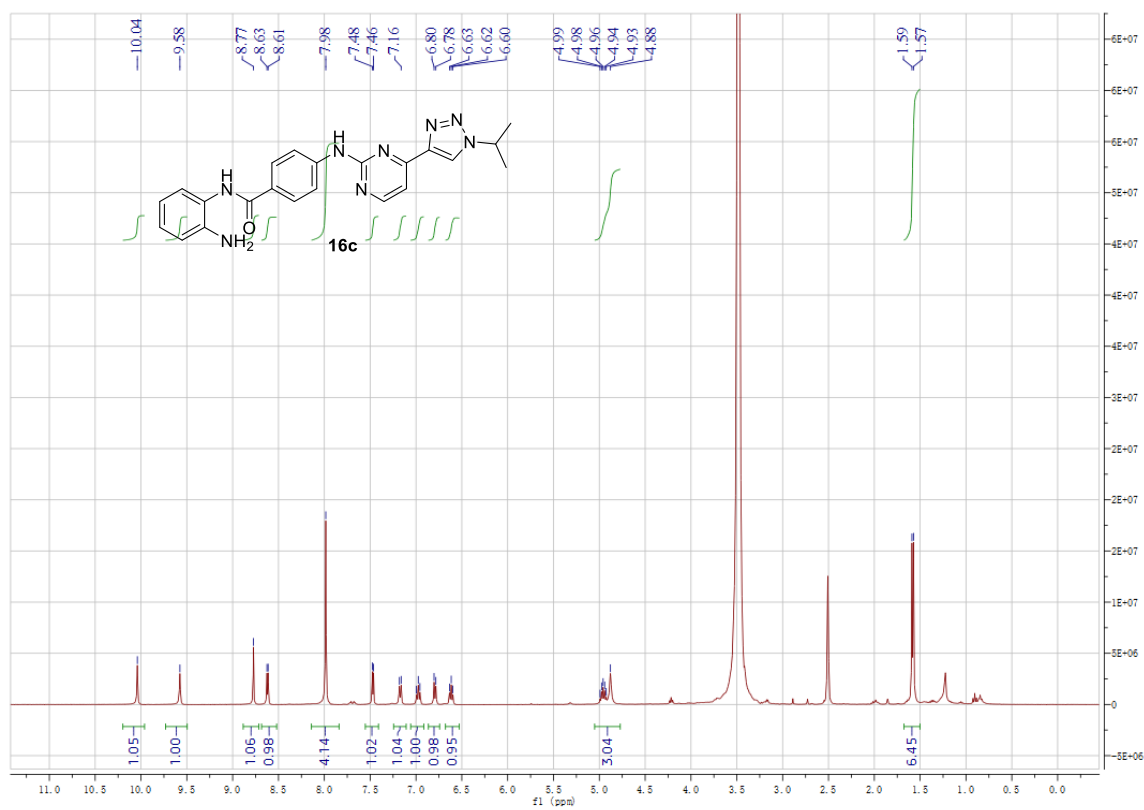
16a



16b

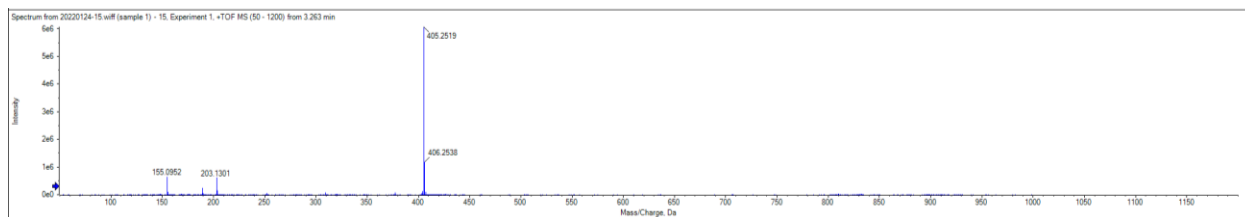


16c

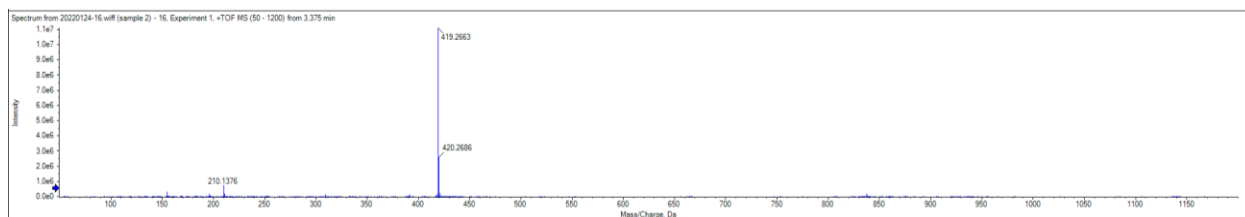


HRMS spectrum

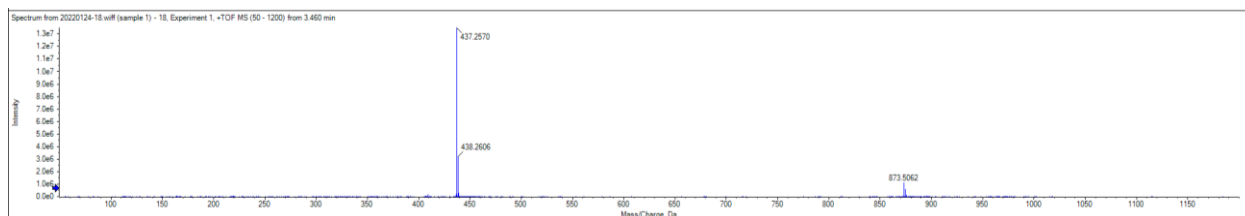
6a



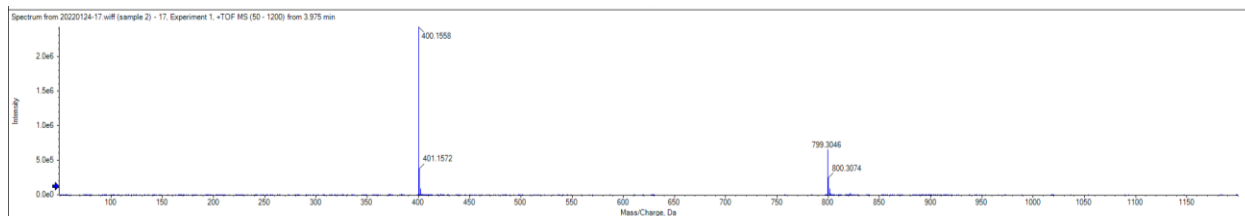
6b



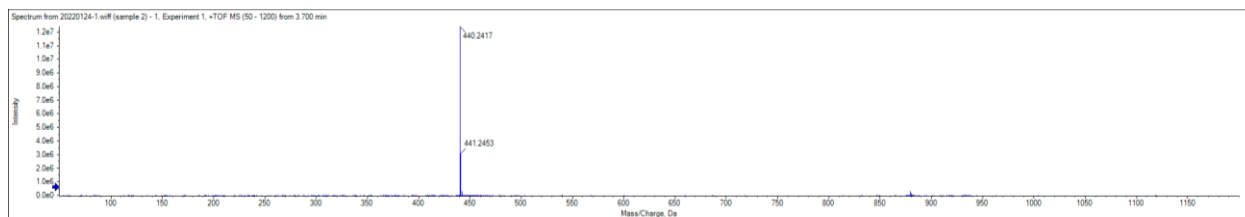
6c



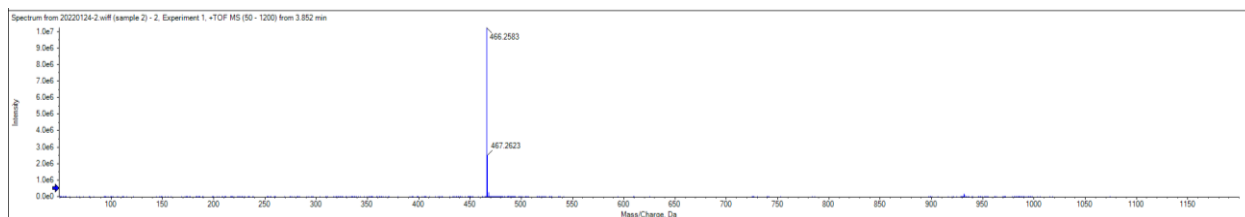
6d



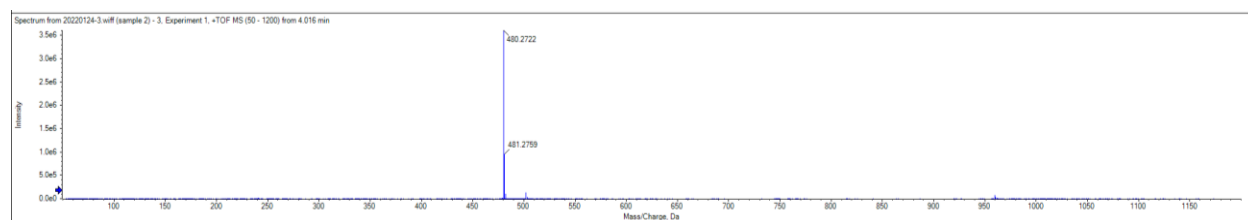
11a



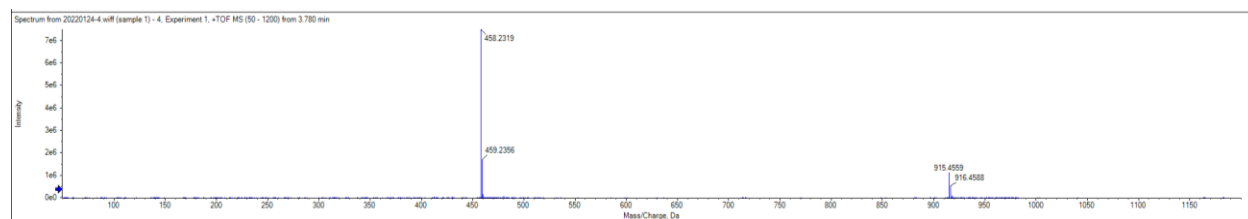
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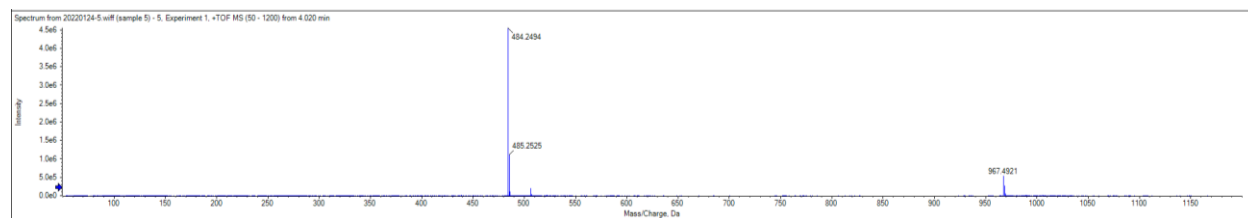
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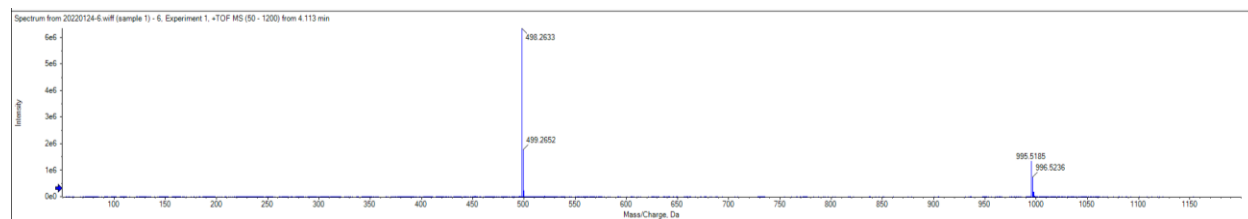
11d



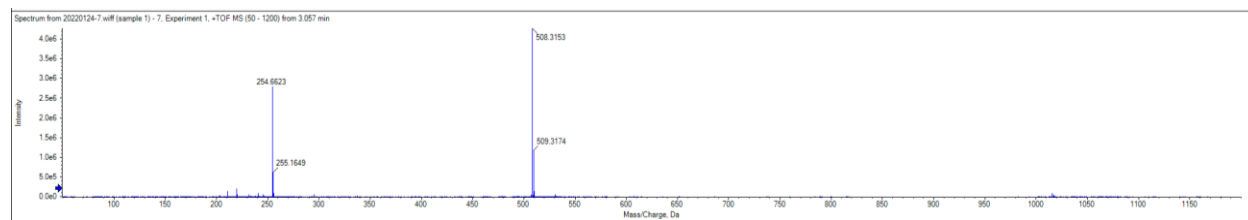
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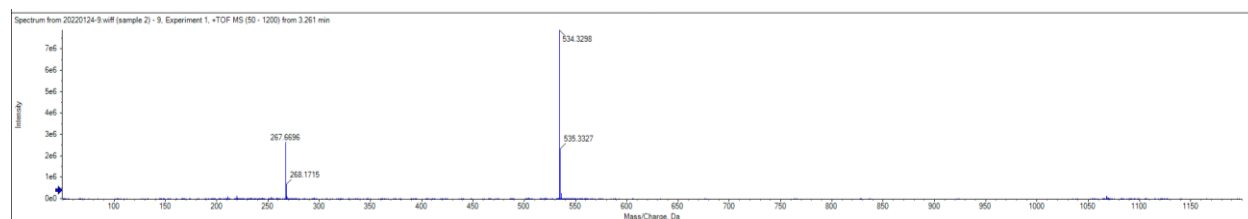
11f



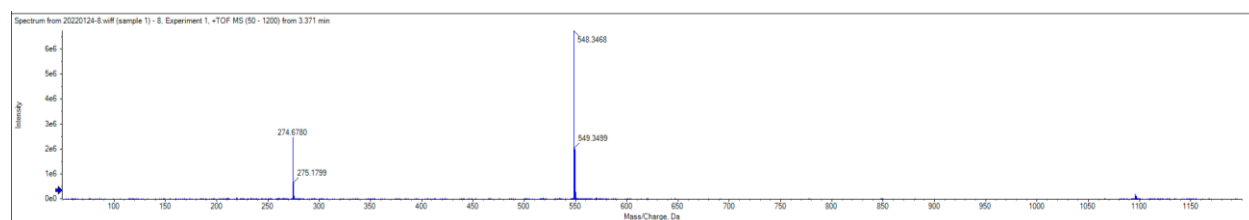
11g



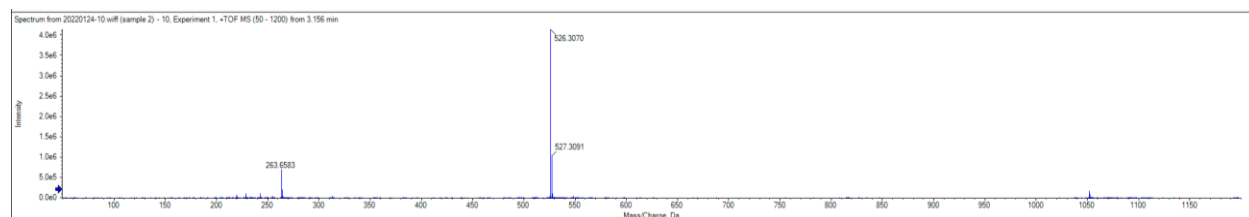
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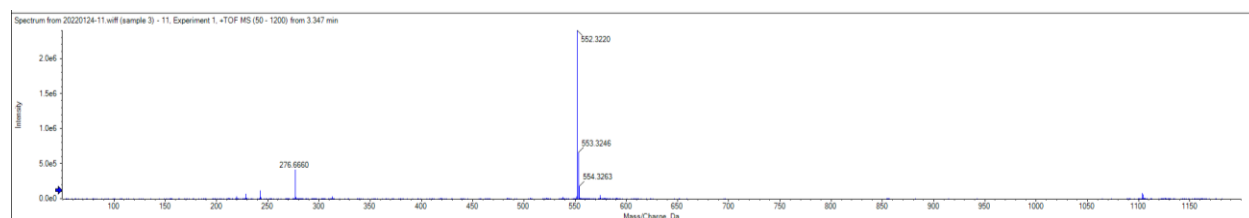
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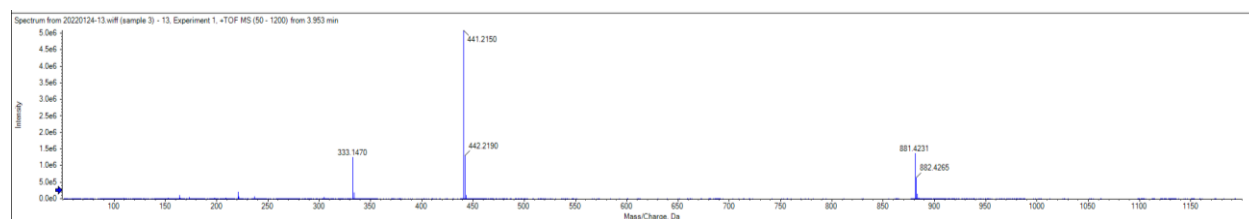
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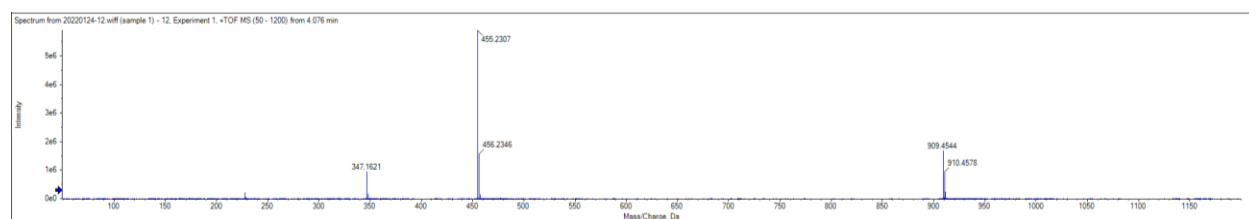
11k



16a



16b



16c

