Supporting Information

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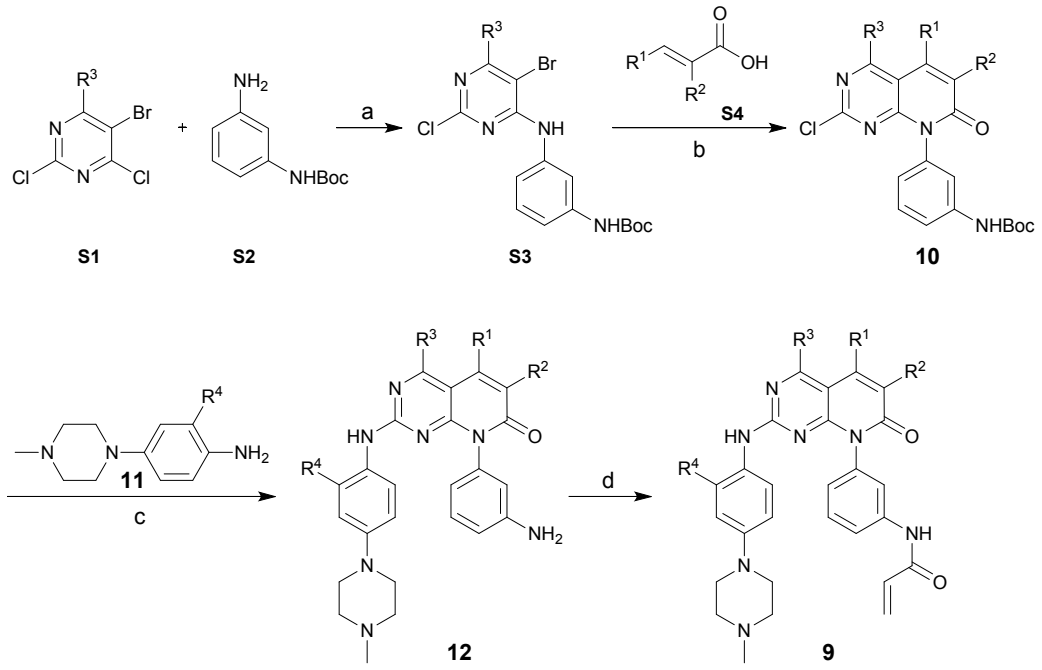
Synthesis of compounds 9

General Methods for Chemistry

All reagents and solvents were purchased from suppliers without further purification. Analytical TLC was carried out on silica gel plates with fluorescence F254 and UV light visualization. ^{1}H NMR spectra were recorded on a Bruker AV-400 spectrometer at 400 MHz. ^{13}CNMR spectra were recorded on a Bruker AV-500 spectrometer at 125 MHz. Chemical shifts(δ) of NMR are reported in parts per million (ppm) units relative to residual undeuterated solvent, and coupling constants (*J* values) are given in hertz (Hz). Splitting patterns and apparent multiplicities are described as below: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad signal), dd (doublet of doublets). High-resolution mass spectra (HRMS) were measured by an Applied Biosystems Q-STAR Elite ESI-LC-MS/MS mass spectrometer. Purity of the final compounds were determined with reverse-phase HPLC analysis to be over 95% (SI). HPLC instrument: Dionex Summit HPLC (Column: Diamonsil C18, 5.0μm, 4.6 × 250 mm (Agilent Technologies); detector: PDA-100 photodiode array; injector: ASI-100 autoinjector; pump: p-680A). A flow rate of 1.0 mL/min was used with mobile phase of MeOH in H_2O with 0.1% modifier (ammonia, v/v).



a) $R^1 = R^2 = R^3 = H$; R^4 = MeO
b) $R^1 = R^3 = H$; R^2 = Me; R^4 = MeO
f) R^1 = Me; $R^2 = R^3 = H$; R^4 = MeO
g) R^1 = Et; $R^2 = R^3 = H$; R^4 = MeO
h) R^1 = n-Pr; $R^2 = R^3 = H$; R^4 = MeO
o) $R^1 = R^3$ = Me; $R^2 = H$; R^4 = MeO
p) R^1 = Me; $R^2 = R^3 = R^4 = H$
q) $R^1 = R^4$ = Me; $R^2 = R^3 = H$
r) R^1 = Me; $R^2 = R^3 = H$; R^4 = EtO
s) R^1 = Me; $R^2 = R^3 = H$; R^4 = n-PrO
t) R^1 = Me; $R^2 = R^3 = H$; R^4 = iso-PrO

Scheme S1. Synthesis of Compounds **9**. Reagents and conditions: a) K_2CO_3, DMF, rt, 60–84.2%. b) i) Compounds **13**, $Pd(PhCN)_2Cl_2$, $(o\text{-}MeC_6H_4)_3P$, DIPEA, THF, 70 °C, Ar; ii) Ac_2O, 80 °C, 20–30%; (two steps). c) i) Compounds **15**, TFA, 2-Butanol, 100 °C; ii) TFA, DCM, rt, 60-80% (two steps). d) acryloyl chloride, DIPEA, DCM, 0 °C, 55-70%.

tert-Butyl (3-((5-bromo-2-chloropyrimidin-4-yl)amino)phenyl)carbamate (**S3a**). To a solution of 5-bromo-2, 4-dichloropyrimidine (0.45 g, 2.0 mmol) and *tert*-butyl (3-aminophenyl)carbamate (0.42 g, 2.0 mmol) in DMF (3 mL), K_2CO_3 (0.55 g, 4.0 mmol) was added. The suspension was stirred overnight. 20 mL of water was added to the reaction mixture and the precipitate was collected by filtration. The solid was washed with ether and dried to yield compound **S3a** (0.67 g, 84.2%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1 H), 7.78 (s, 1 H), 7.45 (d, 1 H, *J* = 7.2 Hz), 7.32-7.28 (m, 2 H), 7.03 (dd, 1 H, *J* = 1.2, 8.0 Hz), 6.56 (s, 1 H), 1.53 (s, 9 H).

tert-Butyl (3-(2-chloro-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)carbamate (**10a**). Compound **S3a** (2.57 g, 6.43 mmol) and acrylic acid (2.22 mL, 64.3 mmol) were mixed in THF (40 mL) and DIPEA (11.2 mL) under argon. The slurry was stirred, evacuated and refilled with argon before bis(benzonitrile)palladium(II) dichloride (0.12 g, 5%) and tri-o-tolylphosphine (96 mg, 5%) were added. The mixture was then heated and stirred at 70 ℃ for 24 hrs and then 1.5 mL of Ac_2O was added. The reaction mixture was heated and stirred at 80 ℃ for an additional 24 hrs. The solvent was removed under reduced pressure and the residue was diluted with DCM. The organic layer was separated and washed with 1N HCl (100 mL) and brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica gel chromatography to afford compound **10a** (0.71g, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1 H), 9.07 (s, 1 H), 8.13 (d, 1 H, *J* = 9.6 Hz), 7.50 (s, 1 H), 7.45-7.39 (m, 2 H), 6.92-6.89 (m, 1 H), 6.85 (d, 1 H, *J* = 9.6 Hz), 1.46 (s, 9 H).

8-(3-Aminophenyl)-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12a**). To a solution of compound **10a** (260.9 mg, 0.7 mmol) in 2-butanol (8 mL), 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (162.6 mg, 0.7 mmol) and trifluoroacetic acid (56.0 μL, 0.7 mmol) were added in a sealed tube. The reaction was heated to 95 ℃ for 12 hrs. The reaction mixture was then allowed to cool to room temperature. The mixture was transferred to a round-bottom flask and then the solvent was removed under reduced pressure. The residue was dissolved in DCM (3.0 mL) and TFA (3.0 mL), and the resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was neutralized with saturated $NaHCO_3$ solution. The water layer was extracted with DCM. The organic layer was combined and washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **12a** as a yellow solid (250 mg, 78% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1 H), 8.08 (s, 1 H), 7.87 (d, 1 H, *J* = 9.6 Hz), 7.44 (d, 1 H, *J* = 8.8 Hz), 7.18 (t, 1 H, *J* = 8.0 Hz),

6.70 (d, 1 H, *J* = 8.4 Hz), 6.55 (d, 1 H, *J* = 2.4 Hz), 6.41-6.36 (m, 3 H), 6.15 (br, 1 H), 5.25 (br, 2 H), 3.79 (s, 3 H), 3.06 (t, 4 H, *J* = 4.8 Hz), 2.45 (t, 4 H, *J* = 4.8 Hz), 2.23 (s, 3 H).

N-(3-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9a**). Acryloyl chloride (45.4 µL, 0.55 mmol) was added dropwise to a mixture of **12a** (250 mg, 0.55 mmol) and DIPEA (96.1 µL, 0.55 mmol) in dry DCM (10 mL) at 0 °C. The reaction mixture was stirred at 0 ℃ for 1.0 hr and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography to afford **9a** as a yellow solid (182.9 mg, 65%)**.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1 H), 8.74 (s, 1 H), 8.15 (s, 1 H), 7.92-7.86 (m, 2 H), 7.60 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.27 (d, 1 H, *J* = 8.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.52 (s,1 H), 6.47-6.41 (m, 2 H), 6.27-6.23 (s,1 H), 6.03 (br, 1 H), 5.78-5.75 (m, 1 H), 3.77 (s, 3 H), 3.03 (m, 4 H), 2.43 (m, 4 H), 2.22 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.5, 158.7, 156.4, 139.9, 137.5, 136.9, 131.7, 129.4, 127.0, 123.9, 119.6, 118.8, 117.2, 106.2, 105.7, 99.6, 55.7, 54.5, 48.5, 45.7. HRMS (ESI) for $C_{28}H_{29}N_7O_3$ $[M + H]^+$, calcd: 512.2405, found: 512.2400.

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-methyl-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9b**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s ,1 H), 8.68 (s, 1 H), 8.01 (s, 1 H), 7.87 (d, 1 H, *J* = 8.0 Hz), 7.78 (s, 1 H), 7.60 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.30 (d, 1 H, *J* = 8.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.52 (s, 1 H), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.27-6.23 (m, 1 H), 6.01 (br, 1 H), 5.77-5.75 (m, 1 H), 3.77 (s, 3 H), 3.02 (m, 4 H), 2.44 (m, 4 H), 2.23 (s, 3 H), 2.11 (s, 3 H). ^{13}C NMR (125 MHz, Acetic-d_4) δ 166.2, 166.0, 157.7, 157.3, 157.0, 150.8, 146.8, 140.4, 138.2, 135.3, 132.0, 131.0, 129.1, 128.4, 125.8, 123.1, 121.7, 121.6, 109.5, 107.7, 101.8, 56.4, 54.0, 48.3, 43.7, 17.2. HRMS (ESI) for $C_{29}H_{32}N_7O_3$ $[M + H]^+$, calcd: 526.2561, found: 526.2564.

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9f**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1 H), 8.80 (s, 1 H), 8.10 (s, 1 H), 7.88 (d, 1 H, *J* = 8.0 Hz), 7.56 (s, 1 H), 7.50 (t, 1 H, *J* = 8.0 Hz), 7.26 (d, 1 H, *J* = 8.8 Hz), 6.97 (d, 1 H, *J* = 7.6 Hz), 6.52 (s, 1 H), 6.43 (dd,

1 H, *J* = 10.0, 16.8 Hz), 6.32 (s, 1 H), 6.27-6.23 (m, 1 H), 5.99 (br, 1 H), 5.78-5.75 (m, 1 H), 3.77 (s, 3 H), 3.02 (m, 4 H), 2.46-2.43 (m, 7 H), 2.22 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.1, 156.5, 156.3, 146.9, 139.9, 137.0, 131.7, 129.4, 127.1, 124.0, 119.7, 118.7, 116.5, 106.2, 106.1, 99.6, 55.7, 54.6, 48.5, 45.7, 17.0. HRMS (ESI) for $C_{29}H_{31}N_7O_3$ $[M + H]^+$, calcd: 526.2561, found: 526.2558.

N-(3-(5-ethyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9g**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1 H), 8.85 (s, 1 H), 8.09 (s, 1 H), 7.87 (d, 1 H, *J* = 7.2Hz), 7.57 (s, 1 H), 7.50 (t, 1 H, *J* = 8.0Hz), 7.26 (d, 1 H, *J* = 8.8Hz), 6.98 (d, 1 H, *J* = 8.0Hz), 6.52 (s, 1 H), 6.43 (dd, 1 H, *J* = 10.0Hz, 16.8Hz), 6.30 (s, 1 H), 6.27-6.23 (m, 1 H), 6.00 (br, 1 H), 5.78-5.75 (m, 1 H), 3.77 (s, 3 H), 3.02 (m, 4 H), 2.88 (q, 2 H, *J* = 7.2 Hz), 2.43 (m, 4 H),2.22 (s, 3 H), 1.28 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 162.7, 156.9, 165.5, 152.4, 140.3, 137.5, 132.1, 129.9, 127.5, 124.4, 120.1, 119.1, 115.0, 106.6, 105.7, 100.0, 56.1, 55.0, 49.0, 46.2, 23.4, 13.3. HRMS (ESI) for $C_{30}H_{33}N_7O_3$ $[M + H]^+$, calcd: 540.2718, found: 540.2714.

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-5-propylpyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9h**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1 H), 8.86(s, 1 H), 8.09 (s, 1 H), 7.87 (d, 1 H, *J* = 7.6 Hz), 7.57 (s, 1 H), 7.50 (t, 1 H, *J* = 8.0 Hz), 7.25 (d, 1 H, *J* = 8.8 Hz), 6.99-6.97 (m, 1 H), 6.51 (d, 1 H, *J* = 2.0 Hz), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.29 (s, 1 H), 6.25 (dd, 1 H, *J* = 2.0, 17.2 Hz), 5.99 (br, 1 H), 5.76 (dd, 1 H, *J* = 1.6, 10.0 Hz), 3.77 (s, 3 H), 3.02 (m, 4 H), 2.81 (t, 2 H, *J* = 7.2 Hz), 2.42 (t, 4 H, *J* = 4.8 Hz), 2.21 (s, 3 H), 1.74-1.64 (m, 2 H), 1.01 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.4, 167.4, 161.7, 155.7, 145.1, 142.3, 136.9, 134.7, 132.3, 129.2, 124.9, 123.9, 120.7, 111.4, 110.5, 104.8, 60.9, 59.8, 53.8, 51.0, 37.0, 27.1, 18.9. HRMS (ESI) for $C_{31}H_{35}N_7O_3$ $[M + H]^+$, calcd: 554.2874, found: 554.2875.

N-(3-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-4,5-dimethyl-7-oxopyrido [2,3-d]pyrimidin-8(7H)-yl)phenyl)acrylamide (**9o**). ^{1}H NMR (400 MHz, DMSO-

d_6) δ 10.33 (s, 1 H), 7.91 (d, 1 H, *J* = 8.4 Hz), 7.84 (s, 1 H), 7.52-7.48 (m, 2 H), 7.16 (d, 1 H, *J* = 7.2 Hz), 6.92 (d, 1 H, *J* = 7.6 Hz), 6.50 (s, 1 H), 6.42 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.31 (s, 1 H), 6.27-6.22 (m, 1 H), 5.95 (br, 1 H), 5.77-5.74 (m, 1 H), 3.78 (s, 3 H), 3.00 (m, 4 H), 2.77 (s, 3 H), 2.62 (s, 3 H), 2.42 (m, 4 H), 2.22 (s, 3 H). ^{13}C NMR (125 MHz, Acetic-d_4) δ 169.0, 166.1, 165.1, 158.9, 156.9, 151.2, 150.7, 146.7, 140.5, 138.8, 132.0, 131.1, 129.1, 125.7, 123.0, 121.5, 121.4, 119.4, 109.5, 107.9, 101.6, 56.4, 54.0, 48.3, 43.7, 25.9, 25.0. HRMS (ESI) for $C_{30}H_{34}N_7O_3$ $[M + H]^+$, calcd: 540.2718, found: 540.2720.

N-(3-(5-Methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9p**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1 H), 9.84 (s, 1 H), 8.82 (s, 1 H), 7.93-7.91 (m, 1 H), 7.57 (s, 1 H), 7.53 (t, 1 H, *J* = 8.0 Hz), 7.18 (d, 2 H, *J* = 6.0 Hz), 6.99 (d, 1 H, *J* = 8.4 Hz), 6.54 (d, 2 H, *J* = 6.8 Hz), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.30(s, 1 H), 6.25 (dd, 1 H, *J* = 2.0, 16.8 Hz), 5.76 (dd, 1 H, *J* = 1.6, 10.0 Hz), 2.95-2.94 (m, 4 H), 2.46 (s, 3 H), 2.41 (t, 4 H, *J* = 4.8 Hz), 2.20 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 162.4, 158.5, 156.6, 147.2, 146.3, 140.1, 137.4, 131.8, 131.7, 129.8, 127.4, 124.2, 119.8, 118.9, 116.4, 115.4, 106.0, 54.7, 48.7, 45.9, 17.1. HRMS (ESI) for $C_{28}H_{29}N_7O_2$ [M + H]+, calcd: 496.2456, found: 496.2456.

N-(3-(5-Methyl-2-((2-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9q**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1 H), 8.83 (s, 1 H), 8.75 (s, 1 H), 7.73 (d, 1 H, *J* = 8.4 Hz), 7.54 (s, 1 H), 7.41 (t, 1 H, *J* = 8.0 Hz), 7.07 (s, 1 H)， 6.91 (d, *J* = 6.4 Hz, 1 H), 6.63 (s, 1 H), 6.45 (dd, 1 H, *J* = 10.0, 17.2 Hz), 6.28-6.23 (m, 2 H), 5.77 (dd, 1 H, *J* = 2.0, 10.0 Hz), 2.99 (m, 4 H), 2.43-2.40 (m, 7 H), 2.21 (s, 3 H), 2.08 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4, 162.4, 156.7, 156.3, 147.0, 139.8, 136.9, 131.8, 129.2, 128.8, 127.2, 124.2, 119.8, 118.6, 117.1, 116.1, 112.7, 106.1, 54.63, 48.7, 45.8, 18.3, 17.0. HRMS (ESI) for $C_{29}H_{31}N_7O_2$ [M + H]+, calcd: 510.2612, found: 510.2603.

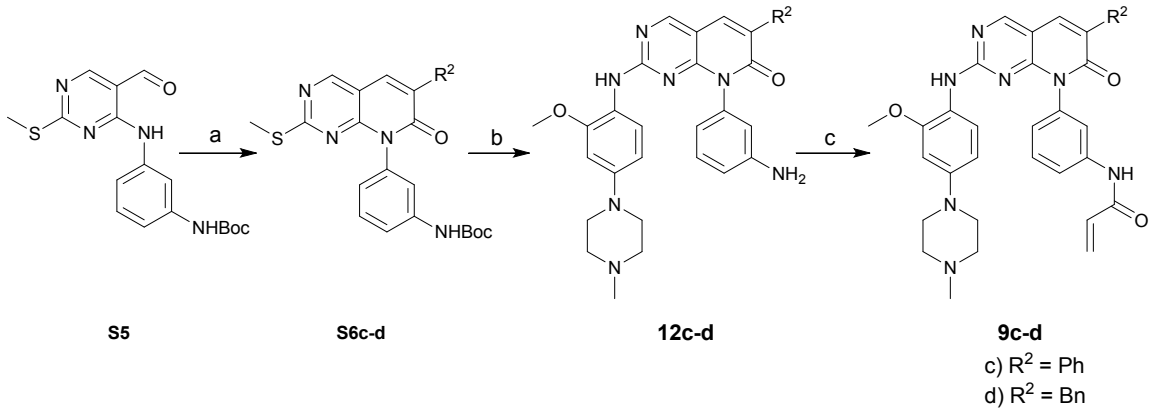
N-(3-(2-((2-Ethoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9r**). ^{1}H NMR (400 MHz, DMSO-

d_6) δ 10.35 (s, 1 H), 8.80 (s, 1 H), 8.02 (s, 1 H), 7.89 (d, 1 H, *J* = 7.2 Hz), 7.57 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.28 (d, 1 H, *J* = 8.8 Hz), 6.98 (d, 1 H, *J* = 8.4 Hz), 6.51 (d, 1 H, *J* = 2.4 Hz), 6.45 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.33 (s, 1 H), 6.25 (dd, 1 H, *J* = 2.0, 16.8 Hz), 5.99 (br, 1 H), 5.76 (dd, 1 H, *J* = 2.0, 10.0 Hz), 4.04 (q, 2 H, *J* = 6.8 Hz), 3.00 (m, 4 H), 2.46 (s, 3 H), 2.42 (t, 4 H, *J* = 4.8 Hz), 2.21 (s, 3 H), 1.32 (t, 3 H, *J* = 6.8 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.1, 156.5, 156.3, 146.8, 139.9, 137.0, 131.7, 129.5, 127.1, 124.0, 120.0, 119.6, 118.7, 116.6, 106.2, 106.1, 100.4, 63.9, 54.6, 48.6, 45.8, 17.0, 16.6. HRMS (ESI) for $C_{30}H_{33}N_7O_3$ [M + H]+, calcd: 540.27176, found: 540.27173.

N-(3-(5-Methyl-2-((4-(4-methylpiperazin-1-yl)-2-propoxyphenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9s**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1 H), 8.80 (s, 1 H), 8.00 (s, 1 H), 7.88 (d, 1 H, *J* = 8.0 Hz), 7.57 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.27 (d, 1 H, *J* = 8.8 Hz), 6.98 (d, 1 H, *J* = 7.2 Hz), 6.51 (d, 1 H, *J* = 2.4 Hz), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.33 (s, 1 H), 6.25 (dd, 1 H, *J* = 2.0, 17.2 Hz), 5.99 (br, 1 H), 5.76 (dd, 1 H, *J* = 2.0, 10.4 Hz), 3.94 (t, 1 H, *J* = 6.4 Hz), 3.00 (m, 4 H), 2.46 (s, 3 H), 2.42 (t, 4 H, *J* = 4.8 Hz), 2.22 (s, 3 H), 1.75-1.70 (m, 2 H), 0.95 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.1, 156.5, 156.3, 146.8, 139.9, 137.0, 131.7, 129.4, 127.0, 124.0, 120.0, 119.6, 118.7, 116.6, 106.3, 106.1, 100.5, 69.7, 54.6, 48.6, 45.8, 22.0, 17.0, 10.4. HRMS (ESI) for $C_{31}H_{35}N_7O_3$ [M + H]+, calcd: 554.28741, found: 554.28711.

N-(3-(2-((2-Isopropoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9t**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1 H), 8.80 (s, 1 H), 7.93-7.90 (m, 2 H), 7.58 (s, 1 H), 7.52 (t, 1 H, *J* = 8.0 Hz), 7.31 (d, 1 H, *J* = 9.2 Hz), 6.99 (d, 1 H, *J* = 8.4 Hz), 6.54 (d, 1 H, *J* = 2.4 Hz), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.34 (d, 1 H, *J* = 1.2 Hz), 6.25 (dd, 1 H, *J* = 2.0, 16.8 Hz), 5.99 (br, 1 H), 5.76 (dd, 1 H, *J* = 2.0, 10.0 Hz), 4.66-4.60 (m, 1 H), 2.99-2.98 (m, 4 H), 2.46 (s, 3 H), 2.42 (t, 4 H, *J* = 4.8 Hz), 2.21 (s, 3 H), 1.25 (d, 6 H, *J* = 6.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.0, 156.5, 156.3, 146.8, 139.9, 137.1, 131.7, 129.5, 127.1, 124.0, 121.0, 119.7,

118.7, 116.6, 106.6, 106.1, 102.1, 70.7, 54.6, 48.6, 45.8, 21.8, 17.0. HRMS (ESI) for $C_{31}H_{35}N_7O_3$ [M + H]+, calcd: 554.2874, found: 554.2874.



Scheme S2. Synthesis of Compounds **9c-d**. Reagents and conditions: a) R^2CH_2COOEt (**18**), LHDMS (1M in THF), THF, -78 °C to rt, 36-40%. b) 1) m-CPBA, DCM, 0 °C to rt; 2) 2-methoxy-4-(4-methylpiperazin-1-yl)aniline, TFA, 2-Butanol, 110 °C; 3) TFA, DCM, rt, 30-40%. c) acryloyl chloride, DIPEA, DCM, 0 °C, 58-75%.

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-6-phenylpyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9c**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1 H), 8.82 (s, 1 H), 8.21 (s, 1 H), 8.13 (s, 1 H), 7.90 (d, 1 H, *J* = 7.2 Hz), 7.71 (d, 1 H, *J* = 7.6 Hz), 7.66 (s, 1 H), 7.53 (t, 1 H, *J* = 8.0 Hz), 7.43 (t, 1 H, *J* = 8.0 Hz), 7.36 (t, 1 H, *J* = 7.2Hz), 7.33 (d, 1 H, *J* = 8.8 Hz), 7.08 (d, 1 H, *J* = 7.6 Hz), 6.53 (d, 1 H, *J* = 2.0 Hz), 6.49 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.28 (dd, 1 H, *J* = 2.0, 16.8 Hz), 6.04 (br, 1 H), 5.78 (dd, 1 H, *J* = 2.0,10.0 Hz), 3.78 (s, 3 H), 3.06 (m, 4 H), 2.29 (m, 4 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.3, 161.7, 158.9, 155.7, 140.0, 137.3, 136.1, 135.1, 131.8, 129.5, 128.6, 128.0, 127.7, 127.4, 127.1, 124.0, 120.0, 119.7, 118.8, 106.3, 106.1, 99.8, 55.7, 53.9, 47.8, 44.7. HRMS (ESI) for $C_{34}H_{34}N_7O_3$ $[M + H]^+$, calcd: 588.2718, found: 588.2717.

tert-Butyl (3-(6-benzyl-2-(methylthio)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl) carbamate (**S6d**). LHMDS (1.0 M in THF, 6 mL, 6.0 mmol) was added into dry THF (5 mL) under argon protection, and then the mixture was stirred at -78 °C. Ethyl 3-phenylpropanoate (1.06 mL, 6.0 mmol) was then slowly added to the mixture and stirred for 20 min. Compound **S5** (720.0 mg, 2.0 mmol) dissolved in dry THF (5 mL) was

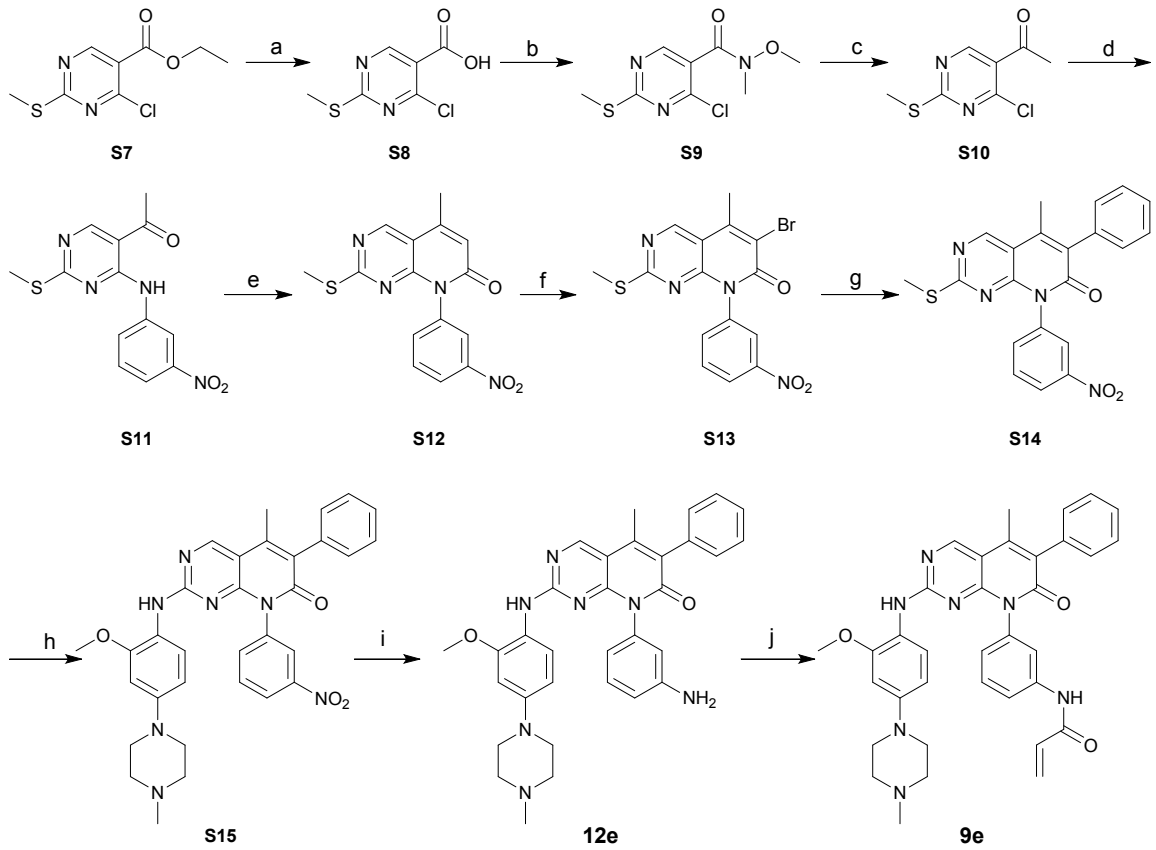
added to the mixture and stirred for another 1.0 hr at -78 ℃. The reaction mixture slowly warmed to room temperature, stirred overnight. The reaction was quenched with saturated NH_4Cl solution and was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated to afford the crude product. The crude product was recrystallized from ethyl acetate to give a light yellow product **S6d** (347 mg, 36.6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1 H), 8.87 (s, 1 H), 7.72 (s, 1 H), 7.46 (s, 1 H), 7.44-7.37 (m, 2 H), 7.35-7.32 (m, 4 H), 7.27-7.22 (m, 1 H), 6.89 (d, 1 H, *J* = 7.2 Hz), 3.86 (s, 2 H), 2.19 (s, 3 H), 1.45 (s, 9 H).

8-(3-Aminophenyl)-6-benzyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino) pyrido [2,3-d] pyrimidin-7(8H)-one (**12d**) To a solution of compound **S6d** (118.6 mg, 0.25 mmol) in DCM (5 mL), 75% m-CPBA (172.6 mg, 0.75 mmol) was added dropwise at 0 ℃. The mixture was slowly warmed to room temperature and stirred for 4.5 hrs. Subsequently, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (three times), and brine. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl (3-(6-benzyl-2-(methylsulfonyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)phenyl)carbamate as a crude product which was used in the next step without further purification.

To a solution of the crude product in 2-butanol (5.0 mL), 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (55.3 mg, 0.25 mmol) and trifluoroacetic acid (19.5 µL, 0.25 mmol) were added in a sealed tube. The reaction was heated to 110 ℃ for 24 hrs. The reaction mixture was allowed to cool to room temperature. The mixture was transferred to a round-bottom flask and then the solvent was removed under reduced pressure to afford the crude product. The crude product was then dissolved in DCM (2 mL) and TFA (2 mL), and the resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was neutralized by saturated $NaHCO_3$ solution. The water layer was extracted with DCM. The

organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **12d** as a solid (47.9 mg, total yield of three steps 35.0 %). ^{1}H NMR (400 MHz, DMSO) δ 8.65 (s, 1 H), 8.00 (s, 1 H), 7.61 (s, 1 H), 7.44 (d, 1 H, *J* = 8.0 Hz), 7.34-7.30 (m, 4 H), 7.24-7.21 (m, 1 H), 7.17 (t, 1 H, *J* = 8.0 Hz), 6.70 (d, 1H, *J* = 8.0 Hz), 6.54 (d, 1 H, *J* = 2.4 Hz), 6.39-6.36 (m, 2 H), 6,15 (br, 1 H), 5.24 (s, 2 H), 3.81 (s, 2 H), 3.78 (s, 3 H), 3.05 (t, 4 H, *J* = 4.8 Hz), 2.45 (t, 4 H, *J* = 4.8 Hz), 2.22(s, 3 H).

N-(3-(6-Benzyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9d**). The synthetic procedure of **9d** from **12d** was similar to that of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1 H), 8.69 (s, 1 H), 8.06 (s, 1 H), 7.86 (d, 1 H, *J* = 6.8 Hz), 7.65 (s, 1 H), 7.58 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.33-7.23 (m, 6 H), 7.00 (d, 1 H, *J* = 7.2 Hz), 6.51 (s, 1 H), 6.43 (dd, 1 H, *J* = 9.6, 16.8 Hz), 6.26-6.22 (m, 1 H), 6.02 (brs, 1 H), 5.77-5.75 (m, 1 H), 3.83 (s, 2 H), 3.76 (s, 3 H), 3.02 (m, 4 H), 2.42 (m, 4 H), 2.22(s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.2, 162.5, 158.1, 155.5, 139.9, 139.3, 137.2, 133.9, 131.7, 129.4, 128.8, 128.4, 127.1, 126.2, 124.0, 119.8, 119.5, 118.8, 106.2, 105.6, 99.6, 55.7, 54.6, 48.6, 45.7, 35.7. HRMS (ESI) for $C_{35}H_{36}N_7O_3$ $[M + H]^+$, calcd: 602.2874, found: 602.2876.



Scheme S3. Synthesis of Compounds **9e.** .Reagents and conditions: a) $LiOH{\cdot}H_2O$, $THF:H_2O$ (1:1, v:v), 60 ℃, 85%. b) *N*, *O*-dimethylhydroxylamine hydrochloride, DMTMM, CH_3CN, rt, 60.6%. c) Methylmagnesium bromide (1M in THF), THF, -78 ℃ to -10 ℃, 49.3%. d) 3-nitroaniline, DIPEA, CH_3CN， 50 ℃, 32.8%. e) $Ph_3PCHCOOMe$, toluene, 110 ℃, Ar, 78%. f) Br_2, DCM, 0 ℃ to rt, 58.9%. g) Phenyboronic acid, $Pd(dppf)_2DCM{\cdot}Cl_2$， Et_3N, $DME:H_2O$ (10:1, v:v), rt, 83%. h) 1) m-CPBA, DCM, 0 ℃ to rt, ii) 2-methoxy-4-(4-methylpiperazin-1-yl)aniline, TFA, 2-Butanol, 110 ℃, 63.2% (two steps). i) Pd/C, H_2 (1 atmo), AcOH, rt, 46.3%. j) acryloyl chloride, DIPEA, DCM, 0 ℃, 74.5%.

4-Chloro-2-(methylthio)pyrimidine-5-carboxylic acid (**S8**). $LiOH{\cdot}H_2O$ (2.52 g, 60 mmol) was slowly added into a mixed solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (11.64 g, 50.0 mmol) in THF (50 mL and H_2O (50 mL), then the mixture was heated and stirred at 60 °C overnight. The solution was acidified with 1M HCl after THF was partly removed under reduced pressure. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4, filtered,

concentrated to give **S8** as a white solid (8.70 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1 H), 2.58 (s, 3 H).

4-Chloro-*N*-methoxy-*N*-methyl-2-(methylthio)pyrimidine-5-carboxamide (**S9**). To a mixture of compound **S8** (204.6 mg, 1 mmol), DMTMM (276.7 mg, 1 mmol) and *N*, *O*-dimethylhydroxylamine hydrochloride (97.5 mg, 1 mmol) in acetonitrile (5 mL) was slowly added DIPEA (0.17mL, 1 mmol). The reaction mixture was stirred at room temperature for 1h and then the solvent was removed under reduced pressure. DCM was added to dissolve the crude product, and then the organic layer was washed with water, brine once and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S9** as a white solid (150.0 mg, 60.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1 H), 3.55 (s, 3 H), 3.37 (s, 3 H), 2.59 (s, 3 H).

1-(4-Chloro-2-(methylthio)pyrimidin-5-yl)ethanone (**S10**). Methylmagnesium bromide (1M in THF, 2.00 mL, 2.0 mmol) was slowly added to a solution of compound **S9** (495.4 mg, 2.0 mmol) in dry THF (5 mL) under Ar condition at -78 ℃. The resulting mixture was slowly warmed to -10 ℃, and then stirred for 1h. The reaction was quenched with 1*N* HCl (2 mL) and then partitioned between water and DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S10** (200.0 mg, 49.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 2.69 (s, 3 H), 2.61 (s, 3 H).

1-(2-(Methylthio)-4-((3-nitrophenyl)amino)pyrimidin-5-yl)ethanone (**S11**). To a solution of 1-(4-chloro-2-(methylthio)pyrimidin-5-yl)ethanone (202.7 mg, 1.0 mmol) and 3-nitroaniline (138.1 mg,1.0 mmol) in 5 mL of acetonitrile was added DIPEA (0.17 mL, 1 mmol). The suspention was stirred at 50 ℃ overnight. The reaction mixture was allowed to cool to room temperature. The precipitate was filtered to give **S11** as a light yellow solid (100.0 mg, 32.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1 H), 9.00-8.99 (m, 2 H), 7.99 (d, 1 H, J = 8.4 Hz), 7.91 (d, 1 H, J = 8.0 Hz), 7.66 (t, 1 H, J = 8.0 Hz), 2.64 (s, 3 H), 2.58 (s, 3 H).

5-Methyl-2-(methylthio)-8-(3-nitrophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**S12**). A mixture of compound **S11** (918.0 mg, 3.0 mmol) and methyl (triphenylphosphoranylidene)acetate (1.21 g, 3.6 mmol) in dry toluene (10 mL) was heated to reflux under argon for 48 hrs and then the solvent was removed under reduced pressure. The resulting crude product was purified by silica gel chromatography to afford compound **S12** (776.0 mg, 78.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1 H), 8.37-8.34 (m, 2 H), 7.88-7.82 (m, 2 H), 6.62 (d, 1 H, *J* = 1.2 Hz), 2.52 (s, 3 H), 2.15 (s, 3 H).

6-Bromo-5-methyl-2-(methylthio)-8-(3-nitrophenyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**S13**). Bromine (0.12 mL, 2.36 mmol) was slowly added dropwise to a solution of compound **S12** (776.0 mg, 2.36 mmol) at 0 ℃ under argon. The reaction mixture was stirred overnight at room temperature. Subsequently, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$. The organic layer was separated and washed with water, then brine. The combined organic layer was dried over Na_2SO_4, filtered, concentrated and purified by silica gel chromatography to afford **S13** as a white solid (567.0 mg, 58.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1 H), 8.41-8.36 (m, 2 H), 7.91-7.84 (m, 2 H), 2.72 (s, 3 H), 2.14 (s, 3 H).

5-Methyl-2-(methylthio)-8-(3-nitrophenyl)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**S14**). Compound **S13** (407.2mg, 1mmol), phenylboronic acid (182.9mg, 1.5mmol), $Pd(dppf)_2DCM{\cdot}Cl_2$ (81.6mg, 0.1 mmol) and Et_3N (0.42mL, 3.0 mmol) were added to a mixture solution of DME (8 mL) and H_2O (0.8 mL). The mixture was evacuated and refilled with argon and then heated to 90 ℃, stirred for 24 hrs. The mixture was diluted with DCM and partitioned between water and DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S14** as a white solid (337.0 mg, 83.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1 H), 8.40 (t, 1 H, *J* = 2.0 Hz), 8.37-8.34 (m, 1 H), 7.93-7.91 (m, 1H), 7.85 (t, 1 H, *J* = 8.0 Hz), 7.46 (t, 2 H, *J* = 7.2 Hz), 7.40 (t, 1 H, *J* = 7.6 Hz), 7.33-7.31 (m, 2 H), 2.36 (s, 3 H), 2.18 (s, 3 H).

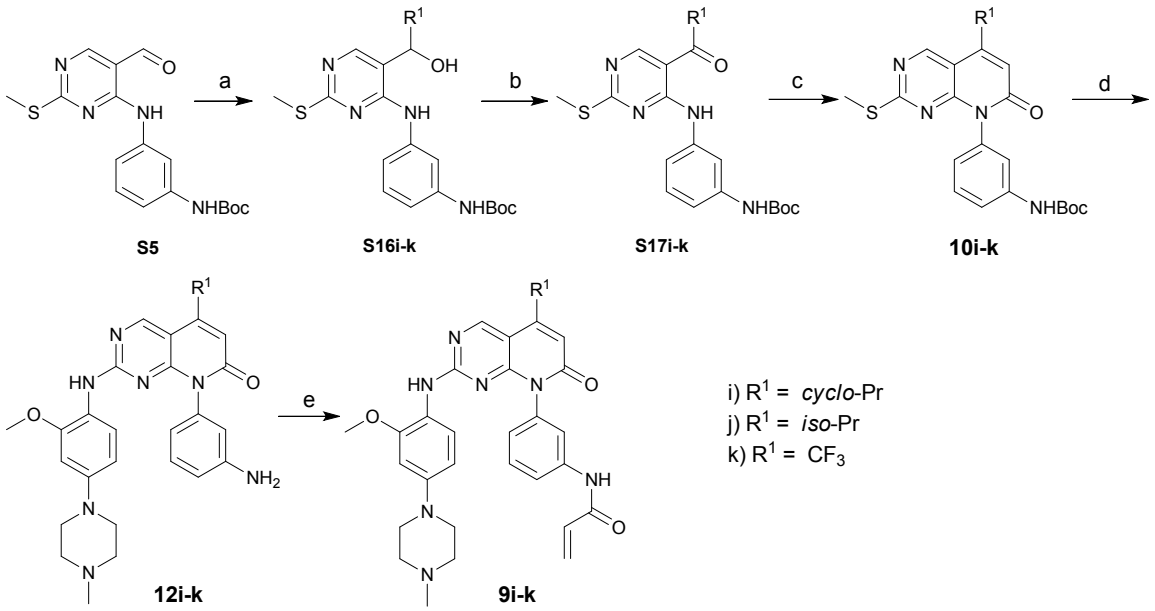
2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-8-(3-nitrophenyl)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**S15**). To a solution of compound **S14** (337.0 mg， 0.83 mmol) in DCM (10mL), 75% m-CPBA(507.0 mg，2.52 mmol) was added dropwise at 0 ℃. The mixture was slowly warmed to room temperature and stirred for 4 hrs. Subsequently, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (three times), then brine. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 5-methyl-2-(methylsulfonyl)-8-(3-nitrophenyl)-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one as a crude product which was used in the next step without further purification.

To a solution of the crude product in 2-butanol (8 mL), 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (183.3 mg, 0.83 mmol) and TFA (66.5 μL, 0.83 mmol) were added in a sealed tube (25 mL). The mixture was heated to 110 ℃, and then stirred for 24 hrs. The mixture was allowed to cool to room temperature and was transferred to a round-bottom flask. The solvent was removed under reduced pressure and the resulting crude product was dissolved in DCM, and then washed with saturated aqueous $NaHCO_3$ solution and brine. The combined organic layer was dried over Na_2SO_4, filtered, concentrated and purified by silica gel chromatography to give **S15** as a yellow solid (303.0 mg, 63.2%.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1 H), 8.37-8.32 (m, 3 H), 7.87-7.81 (m, 2 H), 7.44 (t, 2 H, J = 7.2 Hz), 7.38-7.34 (m, 1 H), 7.31-7.29 (m, 2 H), 7.05 (br, 1H), 6.49 (s, 1 H), 5.99 (br, 1 H), 3.74 (s, 3 H), 3.04 (m, 4 H), 2.45 (t, 4 H, J = 4.4 Hz), 2.31 (s, 3 H), 2.23 (s, 3 H).

8-(3-Aminophenyl)-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**12e**). A suspension of compound **S15** (303.0 mg, 0.52 mmol) and Pd/C (20 mg) in glacial acetic acid (10 mL) at room temperature was stirred under 1 atom H_2 for 6 hrs. The suspension was then filtered through Dicalite, and the filtrate was collected, concentrated under reduced pressure.

The resulting residue was neutralized by saturated $NaHCO_3$ solution. The water layer was extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered and concentrated to give compound **12e** as a yellow solid (241.0 mg, 46.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1 H), 8.04 (s, 1 H), 7.49-7.41 (m, 3 H), 7.35 (t, 1 H, *J* = 7.6 Hz), 7.37-7.34 (m, 2 H), 7.18 (t, 1 H, *J* = 8.0 Hz), 6.70 (d, 1 H, *J* = 8.0 Hz), 6.56 (d, 1 H, *J* = 2.4 Hz), 6.44-6.43 (m, 1 H), 6.41-6.39 (m, 1 H), 6.15 (br s, 1 H), 5.25 (s, 2 H), 3.81 (s, 3 H), 3.06-3.05 (m, 4 H), 2.45 (t, 4 H, *J* = 4.8 Hz), 2.27 (s, 3 H), 2.23 (s, 3 H).

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxo-6-phenylpyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9e**). The synthetic procedure of **9e** is similar to that of **9a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1 H), 8.89 (s, 1 H), 8.10 (s, 1 H), 7.86 (d, 1 H, *J* = 8.0 Hz), 7.64 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.44 (t, 1 H, *J* = 7.2 Hz), 7.38-7.34 (m, 1 H), 7.31-7.29 (m, 3 H), 7.03 (d, 1 H, *J* = 8.0 Hz,), 6.53 (s, 1 H), 6.43 (dd, 1 H, *J* = 10.0, 17.2 Hz), 6.27-6.23 (m, 1 H), 6.02 (br, 1 H), 5.78-5.75 (m, 1 H), 3.79 (s, 3 H), 3.03 (m, 4 H), 2.45-2.44 (m, 4 H), 2.30 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 162.2, 157.4, 155.8, 142.7, 140.3, 137.8, 135.9, 132.2, 130.9, 129.9, 127.8, 127.5, 124.5, 120.3, 120.1, 119.1, 106.7, 106.7, 100.0, 56.1, 55.0, 49.0, 46.2, 15.7. HRMS (ESI) for $C_{35}H_{35}N_7O_3$ $[M + H]^+$, calcd: 602.2874, found: 602.2873.



Scheme S4. Synthesis of **9i**-**k**. Reagents and conditions: a) R^1MgBr (in THF), THF, -78 °C, Ar, 57.8-60% or CF_3TMS, THF, 0 °C to rt, Ar, 27%. b) MnO_2, DCM, reflux, 80-86.6%. c) $Ph_3PCHCOOMe$, toluene, 110 °C, 40-50%. d) 1) m-CPBA, DCM, 0 °C to rt; 2) 2-methoxy-4-(4-methylpiperazin-1-yl)aniline, TFA, 2-Butanol, 110 °C; 3) TFA, DCM, rt, 30-40%. e) acryloyl chloride, DIPEA, DCM, 0 °C, 70-75%.

tert-Butyl (3-((5-(cyclopropyl(hydroxy)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (**S16i**). Compound **S5** (1.44 g, 4 mmol) was dissolved in dry THF (10 mL) under Ar then cooled to -78°C, to which cyclopropylmagnesium bromide (20 mL, 10 mmol, 0.5M in THF) was slowly added and stirred for 4h. The reaction was quenched with 1N HCl (10 mL) and then partitioned between water and DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S16i** (0.93 g, 57.8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.93 (s, 1 H), 8.11 (s, 1 H), 7.80 (s, 1 H), 7.35 (d, 1H, *J* = 8.0 Hz), 7.19 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 8.0 Hz), 6.04 (d, 1 H, *J* = 3.2 Hz), 4.11-4.09 (m, 1 H), 2.45 (s, 3 H), 1.47 (s, 9 H), 0.60-0.55 (m, 1H), 0.47-0.42 (m, 1 H), 0.32-0.31 (m, 1 H).

tert-Butyl (3-((2-(methylthio)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrimidin-4-yl)amino)phenyl)carbamate (**S16k**). To a mixture of compound **S5** (1.8 g, 5 mmol) and CsF (10 mg) in dry THF (25 mL) was added CF_3TMS (2.95 mL, 20 mmol) under Ar. The

reaction mixture was then stirred at room temperature for 48 h. The reaction was quenched with 0.5N HCl and partitioned between water and DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S16k** (0.58 g, 27%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (s, 1 H), 8.93 (s, 1 H), 8.24 (s, 1 H), 7.81 (s, 1H), 7.39 (d, 1 H, *J* = 5.6 Hz), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.20 (t, 1 H, *J* = 8.0 Hz), 7.06 (d, 1 H, *J* = 7.6 Hz), 5.66-5.63 (m, 1 H), 3.33 (s, 1 H), 2.41 (s, 3 H), 1.47 (s, 1 H).

tert-Butyl (3-((5-(cyclopropanecarbonyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl) carbamate (**S17i**). To a solution of compound **S16i** (0.93 g, 2.31 mmol) in DCM (20 mL), MnO_2 (2.01 g, 23.1 mmol) was added. The reaction mixture was then heated to reflux for 24 hrs. The solids was filtered off through a Celite pad and washed with DCM (3 × 10 mL). The filtrate was dried over Na_2SO_4, filtered, concentrated to afford **S17i** (0.80g, 86.6.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1 H), 9.43 (s, 1 H), 9.22 (s, 1 H), 7.89 (s, 1 H), 7.36 (d, 1 H, *J* = 8.0 Hz), 7.24 (t, 1 H, *J* = 8.0 Hz), 7.11 (d, 1 H, *J* = 8.0 Hz), 3.01-2.96 (m, 1 H), 2.53 (s, 3 H), 1.48 (s, 9 H), 1.14-1.04 (m, 4 H).

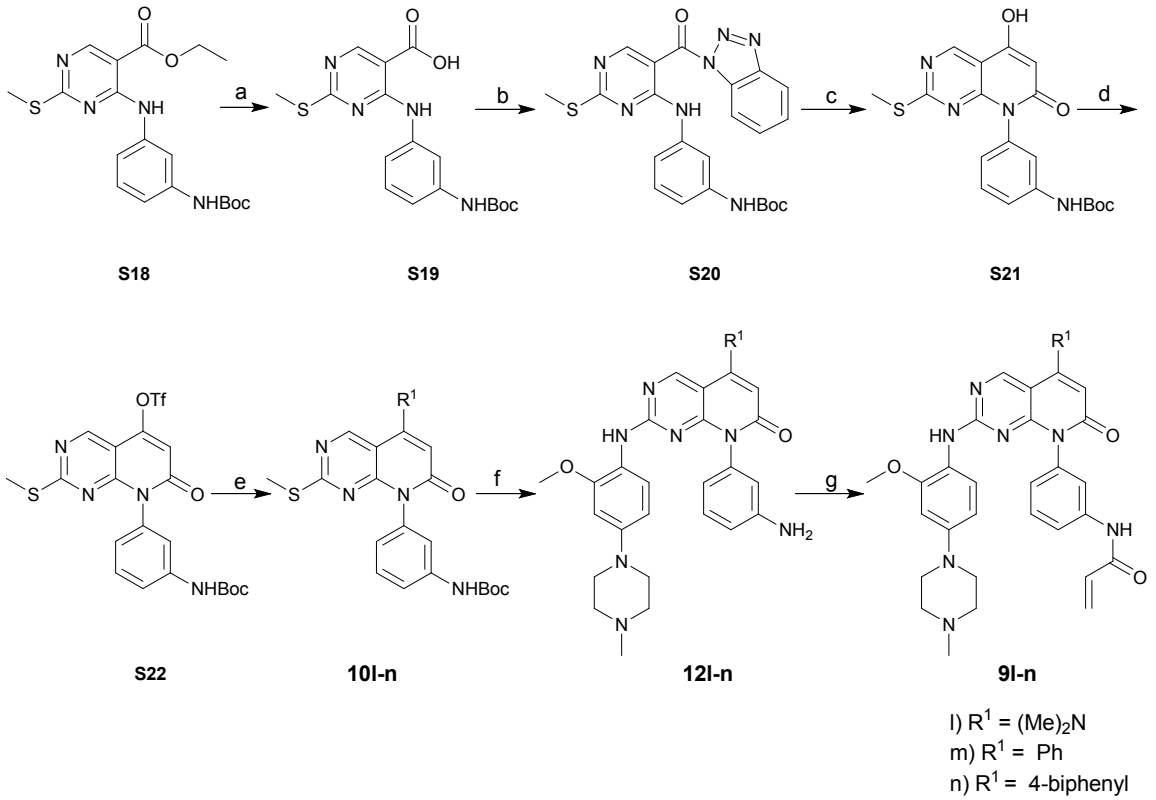
tert-Butyl (3-(5-cyclopropyl-2-(methylthio)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl) carbamate (**10i**). A mixture of compound **S17i** (0.8 g, 2.0 mmol) and methyl (triphenylphosphoranylidene)acetate (1.0 g, 3.0 mmol) in toluene (10 mL) was heated to reflux under argon for 48 hrs and then the solvent was removed under reduced pressure. The resulting crude product was purified by silica gel chromatography to afford **10i** (0.35 g, 40.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1 H), 9.25 s, 1 H), 7.44-7.36 (m, 3 H), 7.87(d, 1 H, *J* = 7.6 Hz), 6.31 (s, 1 H), 2.41-2.38 (m, 1 H), 2.20 (s, 3 H), 1.46 (s, 9 H), 1.12-1.09 (m, 2 H), 0.87-0.84 (m, 2 H).

N-(3-(5-Cyclopropyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido [2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9i**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.09 (s, 1 H), 8.11 (s, 1 H), 7.86 (d, 1 H, *J* = 7.6 Hz), 7.56 (s, 1 H), 7.49(t, 1 H, *J* = 8.0 Hz), 7.26 (d, 1 H, *J* = 9.2 Hz), 6.97 (d, 1 H, *J* = 8.4 Hz), 6.52 (d, 1 H, *J* = 2.4 Hz),

6.45 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.25 (dd, 1 H, *J* = 2.0, 16.8 Hz), 6.05-5.99 (m, 2 H), 5.76 (dd, 1 H, *J* = 2.0, 10.0 Hz), 3.77 (s, 3 H), 3.01 (m, 4 H), 2.43-2.37 (m, 5 H), 2.22 (s, 3 H), 1.09-1.07 (m, 2 H), 0.92-0.89 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 162.9, 156.6, 152.7, 140.1, 137.3, 131.8, 129.8, 127.6, 124.3, 120.0, 119.9, 119.0, 111.1, 106.7, 106.5, 99.8, 56.0, 54.7, 48.7, 45.9, 10.7, 8.6. HRMS (ESI) for $C_{31}H_{33}N_7O_3$ $[M + H]^+$, calcd: 552.2718, found: 552.2712.

N-(3-(5-Isopropyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9j**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1 H), 8.92 (s, 1 H), 8.09 (s, 1 H), 7.86 (d, 1 H, *J* = 8.4 Hz), 7.58 (s, 1 H), 7.50 (t, 1 H, *J* = 8.0 Hz), 7.25 (d, 1 H, *J* = 8.8 Hz), 6.99-6.97 (m, 2 H), 6.51 (s, 1 H), 6.43 (dd ,1 H, *J* = 10.0, 16.8 Hz), 6.32 (s, 1 H), 6.27-6.23 (m, 1 H), 5.99 (br, 1 H), 5.77-5.75 (m, 1 H), 3.77 (s, 3 H), 3.50-3.47 (m, 1 H), 3.02 (m, 4 H), 2.43 (m, 4 H), 2.22 (s, 3 H), 1.29 (d, 6 H, *J* = 6.8 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 162.8, 156.8, 156.7, 156.1, 140.0, 137.3, 131.8, 129.7, 127.5, 124.2, 119.9, 119.8, 118.9, 112.6, 106.4, 104.9, 99.7, 55.9, 54.7, 48.6, 45.8, 27.1, 22.2. HRMS (ESI) for $C_{31}H_{35}N_7O_3$ $[M + H]^+$, calcd: 554.2874, found: 554.2873.

N-(3-(2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-5-(trifluoromethyl) pyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9k**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1 H), 8.71 (s, 1 H), 8.47 (s, 1 H), 7.88 (s, 1 H), 7.63 (s, 1 H), 7.51 (t, 1 H, *J* = 8.0 Hz), 7.16 (d, 1 H, *J* = 8.8 Hz), 7.04 (d, 1 H, *J* = 8.4 Hz), 6.89 (s, 1 H), 6.50(s, 1 H), 6.44 (dd, 1 H, *J* = 10.0, 16.8 Hz), 5.96 (br, 1 H), 5.77 (dd, 1 H, *J* = 2.0, 10.4 Hz), 3.76 (s, 3 H), 3.03 (m, 4 H), 2.42 (t, 4 H, *J* = 4.8 Hz), 2.22 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 161.3, 157.4, 155.5, 140.2, 136.7, 135.0, 134.8, 131.8, 129.9, 127.5, 125.6, 123.4, 121.2, 119.1 (q, 1C, *J* = 275 Hz), 123.9, 119.6, 119.3, 116.8, 106.2, 100.6, 99.6, 55.9, 54.7, 48.5, 45.9. HRMS (ESI) for $C_{29}H_{28}F_3N_7O_3$ $[M + H]^+$, calcd: 580.2279, found: 580.2272.



Scheme S5. Synthesis of **9l-n**. Reagents and conditions: a) NaOH (1 M in H_2O), THF, 50 °C, 95%. b) 1H-benzo[*d*][1,2,3]triazole, EDCI, DCM, rt, 85%. c) EA, KHMDS (1 M in THF), THF, -78 °C to rt, Ar, 17.5%. d) Tf_2O, Et_3N, DCM, -78 °C, 82.9%. e) $Me_2NH{\cdot}HCl$, DIPEA, THF, 40 °C, 98.3% or $R_1B(OH)_2$, $Pd(PPh_3)_2Cl_2$ (5%), K_2CO_3, THF/H_2O (5:1, v:v), r.t., Ar, 58-60%. f) 1) m-CPBA, DCM, 0 °C to rt; 2) 2-methoxy-4-(4-methylpiperazin-1-yl)aniline, TFA, 2-Butanol, 110 °C; 3) TFA, DCM, rt, 30-45%. g) acryloyl chloride, DIPEA, DCM, 0 °C, 60-77%.

4-((3-((Tert-butoxycarbonyl)amino)phenyl)amino)-2-(methylthio)pyrimidine-5-carboxylic acid (**S19**). 1 M NaOH (20 mL, 20 mmol) was slowly added into a solution of compound **S18** (4.0 g, 10 mmol) in 20 mL THF, then the mixture was heated at 50 °C for 4 h. The solution was acidified with 1M HCl after the solvent was partly removed under reduced pressure. The formed solid was collected by filtration and dried in a vacuum oven to give **S19** as a white solid (3.5 g, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (br, 1 H), 9.34 (s, 1 H), 8.58 (s, 1 H), 7.78 (s, 1 H), 7.47 (d, 1 H, *J* = 8.0 Hz), 7.19 (t, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 8.0 Hz).

tert-Butyl (3-((5-(1H-benzo[*d*][1,2,3]triazole-1-carbonyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (**S20**). To a mixture of compound **S19** (43.55 g, 115.7 mmol) and EDCI (19.1 g, 115.7 mmol) in dry DCM (400 mL) was added benzotriazole (11.91 g, 115.7 mmol). The reaction mixture was stirred at room temperature for 4h and then the mixture was purified by silica gel chromatography to afford **S20** (46.96 g, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1 H), 9.42 (s, 1 H), 8.77 (s, 1 H), 8.29 (t, 1H, *J* = 8.0 Hz), 7.84 (t, 1 H, *J* = 7.6 Hz), 7.65 (t, 1 H, *J* = 8.0 Hz), 7.27-7.20 (m, 2 H), 7.10 (d, 1 H, *J* = 8.0 Hz), 2.52 (s, 3 H), 1.47 (s, 9 H).

tert-Butyl (3-(5-hydroxy-2-(methylthio)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)carbamate (**S21**). A solution of potassium hexamethyldisilazide (KHMDS, 1M in THF, 87.8 mL, 87.8 mmol) was slowly added to a solution of EA (8.54 mL, 87.8 mmol) in dry THF (100 mL) under Ar at -78 °C. The reaction mixture was stirred at -78 ℃ for 0.5 h and then a solution of compound **S20** (16.76 g, 35.1 mmol) in dry THF (200 mL) was slowly added to the mixture during 0.5h. The resulting mixture was stirred at -78 ℃ for another hour and then slowly warmed to room temperature, stirred for 10h. The reaction was quenched with 1*N* HCl and then treated with 6N HCl until pH = 2. The resulting mixture was stirred for another hour, was then diluted with DCM and partitioned between water and DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S21** (2.2 g, 15.7%).^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (br, 1 H), 9.52 (s, 1 H), 8.89 (s, 1 H), 7.42-7.35 (s, 1 H), 6.85 (d, 1 H, *J* = 6.0 Hz), 5.84 (s, 1 H), 2.19 (s, 3 H), 1.46 (s, 9 H).

8-(3-((*tert*-Butoxycarbonyl)amino)phenyl)-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*] pyrimidin-5-yl trifluoromethanesulfonate (**S22**). To a solution of compound **S21** (2.2 g, 5.51 mmol) and Et_3N (2.30 mL, 11.02 mmol) in dry DCM (30 mL), Tf_2O (0.98 mL, 5.51 mmol) was added at -78 ℃. The mixture was stirred at -78 ℃ for 2 hrs and then the reaction was treated with H_2O. The organic layer was separated and

washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **S22** (2.43g , 82.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1 H), 8.88 (s, 1 H), 7.59 (s, 1 H), 7.42-7.40 (m, 2 H), 6.98-6.95 (m, 2 H), 1.46 (s, 9 H).

tert-butyl (3-(5-(dimethylamino)-2-(methylthio)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl) phenyl)carbamate (**10l**). To a solution of compound **S22** (668.0 mg, 1.25 mmol) in THF (15 mL) dimethylamine hydrochloride (153.5 mg, 1.88 mmol) and DIPEA (0.67 mL, 3.75 mmol) were added. The mixture was heated at 40 ℃ overnight. The solvent was then removed under reduced pressure. 15.0 mL of DCM was added to the resulting crude product. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **10l** as a white solid (525.0 mg, 98.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 7.46 (s, 1 H), 7.39 (t, 1 H, *J* = 8.0 Hz), 7.29 (s, 1 H), 7.28 (s, 1 H), 6.91 (d, 1 H, *J* = 7.6 Hz), 6.64 (s, 1 H), 5.92 (s, 1 H), 2.15 (s, 3 H), 3.02 (s, 6 H), 1.49 (s, 9 H).

N-(3-(5-(dimethylamino)-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9l**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1 H), 8.78 (s, 1 H), 8.03 (s, 1 H), 7.85 (d, 1 H, *J* = 6.4 Hz), 7.54(s, 1 H), 7.48(t, 1 H, *J* = 8.0 Hz), 7.24(d, 1 H, *J* = 8.8 Hz), 6.93 (d, 1 H, *J* = 7.6 Hz), 6.51 (s, 1 H), 6.43 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.23-6.27 (m, 1 H), 5.99 (br, 1 H), 5.78-5.75 (m, 1 H), 5.59 (s, 1 H), 3.77 (s, 1 H), 3.00 (m, 10 H), 2.43 (m, 4 H), 2.22 (s, 3 H). ^{13}C NMR (125 MHz, Acetic-d_4) δ 166.5, 166.1, 158.7, 158.4, 157.5, 156.9, 150.7, 146.9, 140.4, 138.2, 132.0, 130.9, 129.0, 126.0, 122.7, 122.0, 121.7, 109.5, 103.6, 101.6, 56.4, 54.0, 48.2, 43.7, 43.5. HRMS (ESI) for $C_{30}H_{35}N_8O_3$ $[M + H]^+$, calcd: 555.2827, found: 555.2824.

tert-Butyl (3-(2-(methylthio)-7-oxo-5-phenylpyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl) carbamate (**10m**). Compound **S22** (0.61 g, 1.14 mmol), phenylboronic acid (153.6 mg, 1.26 mmol), Bis(triphenylphosphine)palladium(II) dichloride (40.53 mg, 5%) and K_2CO_3 (473.6 mg, 3.43 mmol) were added to a mixture solution of THF (10 mL) and H_2O (2 mL). The mixture was stirred, evacuated, refilled with argon and then stirred at room

temperature for 24 hrs. The mixture was diluted with DCM. The organic layer was washed with brine and dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography to afford **10m** (300 mg, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59(s, 1 H), 8.57 (s, 1 H), 7.63-7.59 (m, 5 H), 7.54 (s, 1 H), 7.47-7.41 (m, 2 H), 6.97 (d, 1 H, *J* = 5.6 Hz), 6.64 (s, 1 H), 2.20 (s, 3 H), 1.47 (s, 9 H).

N-(3-(2-((2-Methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-5-phenylpyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9m**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1 H), 8.42 (s, 1 H), 8.27 (s, 1 H), 7.90 (s, 1 H), 7.64-7.51 (m, 7 H), 7.28 (d, 1 H, *J* = 8.8 Hz), 7.06 (d, 1 H, *J* = 7.6 Hz), 6.57 (s, 1 H), 6.48 (dd, 1 H, *J* = 10.0, 16.8 Hz), 6.38 (s, 1 H), 6.29-6.25 (m, 1 H), 6.03 (br, 1 H), 5.79-5.76 (m, 1 H), 3.78 (s, 3 H), 3.12-2.97 (m, 4 H), 2.67 (m, 4 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.3, 161.9, 157.3, 156.9, 149.5, 140.0, 137.1, 134.8, 131.8, 129.5, 129.4, 129.0, 128.7, 127.2, 124.0, 119.6, 118.9, 116.5, 106.5, 105.0, 100.1, 55.8, 52.9, 46.7. HRMS (ESI) for $C_{34}H_{33}N_7O_3$ $[M + H]^+$, calcd: 588.2718, found: 588.2717.

N-(3-(5-([1,1'-Biphenyl]-4-yl)-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)phenyl)acrylamide (**9n**). ^{1}H NMR (400 MHz, Acetic-d_4) δ 8.70 (s, 1H), 8.15 (d, 1 H, *J* = 8.0 Hz), 7.88 (d, 2 H, *J* = 8.4 Hz), 7.75 (d, 2 H, *J* = 7.6 Hz), 7.71 (d, 2 H, *J* = 8.0 Hz), 7.64-7.59 (m, 2 H), 7.52-7.39 (m, 4 H), 7.20 (d, 1 H, *J* = 7.6 Hz), 6.77 (s, 1 H), 6.59 (d, 1 H, *J* = 2.0 Hz), 6.45 (d, 2 H, *J* = 5.6 Hz), 6.21 (d, 1 H, *J* = 8.8 Hz), 5.80 (t, 1 H, *J* = 5.6 Hz), 3.85 (s, 3 H), 3.71 (m, 4 H), 3.22 (m, 4 H), 2.95 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.3, 161.9, 157.3, 156.9, 149.1, 140.0, 139.3, 137.1, 133.8, 131.7, 129.6, 129.4, 129.1, 127.9, 127.2, 126.8, 123.9, 119.6, 118.8, 116.3, 106.1, 104.9, 99.6, 55.7, 54.6, 48.5, 45.8. HRMS (ESI) for $C_{40}H_{37}N_7O_3$ $[M + H]^+$, calcd: 664.3031, found: 664.3028.

Table S1. Purity of the synthesized compounds **9**.

Compd.	MeOH:H_2O (v:v)	Ret. time (min)	Purity (%)
9a	80:20	6.09	98.9
9b	85:15	5.22	99.3
9c	85:15	6.67	98.9
9d	85:15	8.68	96.9
9e	85:15	6.82	98.9
9f	85:15	5.50	98.8
9g	75:25	10.68	98.7
9h	85:15	6.96	95.0
9i	85:15	6.32	96.3
9j	85:15	6.67	96.9
9k	85:15	7.37	98.5
9l	85:15	5.29	99.4
9m	85:15	5.50	97.1
9n	85:15	13.35	96.7
9o	75:25	10.66	97.8
9p	85:15	4.48	97.5
9q	85:15	4.67	96.8
9r	85:15	5.97	97.4
9s	85:15	6.88	97.9
9t	85:15	6.30	98.2

Method:Dionex Summit, Column: Diamonsil C18, 5.0μm, 4.6 × 250 mm (Agilent Technologies); detector: PDA-100 photodiode array; pump: p-680A). A flow rate of 1.0 mL/min was used with mobile phase of MeOH in H2O with 0.1% modifier (ammonia, v/v)

Enzyme-linked immunosorbent assay (ELISA) kinase assay

Poly (Glu, Tyr)$_{4:1}$ (Sigma, St. Louis, MO) (20 μg/mL) was precoated in 96-well ELISA plates as the substrate. The active kinases were incubated with indicated compounds in 1×reaction buffer (50 mmol/L HEPES pH 7.4, 20 mmol/L $MgCl_2$, 0.1 mmol/L $MnCl_2$, 0.2 mmol/L Na_3VO_4, 1 mmol/L DTT) containing 5 μmol/L ATP at 37 °C for 1 h. After incubation, the wells was washed with PBS, and then incubated with anti-phosphotyrosine (PY99) antibody (Santa Cruz, CA) and horseradish peroxidase (HRP) – conjugated secondary antibody in sequence. The wells were visualized using o-phenylenediamine (OPD) and read using a multiwell spectrophotometer (VERSAmax™, Molecular Devices, Sunnyvale, CA, USA) at 492 nm.

Kinase profiling study and K_d determination.

The kinase profiling study and K_d determination were conducted using the DiscoveRx Kinome screening platform (http://www..com).

For most assays, kinase-tagged T7 phage strains were prepared in an E. coli host derived from the BL21 strain. E. coli were grown to log-phase and infected with T7 phage and incubated with shaking at 32°C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). All reactions were performed in polystyrene 96-well plates in a final volume of 0.135 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

An 11-point 3-fold serial dilution of each test compound was prepared in 100% DMSO at 100x final test concentration and subsequently diluted to 1x in the assay (final DMSO concentration = 1%). Most Kds were determined using a compound top concentration = 30,000 nM. If the initial Kd determined was < 0.5 nM (the lowest concentration tested), the measurement was repeated with a serial dilution starting at a lower top concentration. A Kd value reported as 40,000 nM indicates that the Kd was determined to be >30,000 nM.

Binding constants (Kds) were calculated with a standard dose-response curve using the Hill equation:

$$\text{Response} = \text{Background} + \frac{\text{Signal - Background}}{1 + (\text{Kd}^{\text{Hill Slope}} / \text{Dose}^{\text{Hill Slope}})}$$

The Hill Slope was set to -1.

Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

Western blot analysis

Western blotting was conducted as previously reported. In brief, cells were seeded to six-well plates and incubated overnight, and then starved with serum-free medium for 24 h. Starved cells were treated with or without different concentrations of compounds for 2 h and then stimulated with or without EGF (50 ng/ml) for 15 min. Cell samples were then lysed in 1×SDS lysis buffer. Proteins were resolved by SDS-PAGE and transferred onto polyvinylidene difluoride membranes (Millipore), which were blocked with nonfat milk and hybridized with specific primary antibodies. The bands were visualized using an enhanced chemiluminescence reagent (GE Healthcare) after hybridization with a HRP-conjugated secondary antibody. For the washing-out experiments, cells were seeded in 96-well plates and incubated overnight. After the treatment of compounds at indicated concentration for 2 h, cells were collected at indicated time points and processed for Western blot analysis.

Irreversibility assessments for compounds

The mobility shift assay were used to examine irreversible binding mode of compound **9f** with EGFR $^{L858R/T790M}$. Compound **4** as used as positive control in this assay. The EGFR $^{L858R/T790M}$ protein and compound **9f** or **4** are incubated together for 30 min, and then diluted into standard enzyme assay mixtures containing ATP and substrate peptide (5-FAM-EEPLYWSFPAKKK-$CONH_2$, 1.5 □M). Meanwhile, control reactions with inhibitor added to the reaction mix without being incubated with enzyme were also conducted. The microplate was then placed in the EZ Reader (Caliper Life Sciences, MA) and wells were continuously sampled for 120 min.

In general, preincubation of a reversible inhibitor with the protein results in similar kinase activiy with that of none preinbubation control, whereas, preincubation of an irreversible inhibitor will dramatically decreased the kinase activity compared with control. The results in Figure S1 showed that preincubation of the EGFR$^{L858R/T790M}$ protein with **9f** caused an obvious decrease of kinase activity relative to the non-incubation sample, which is quite similar to that of compound **4**, supporting the irreversible binding of **9f** with the protein.

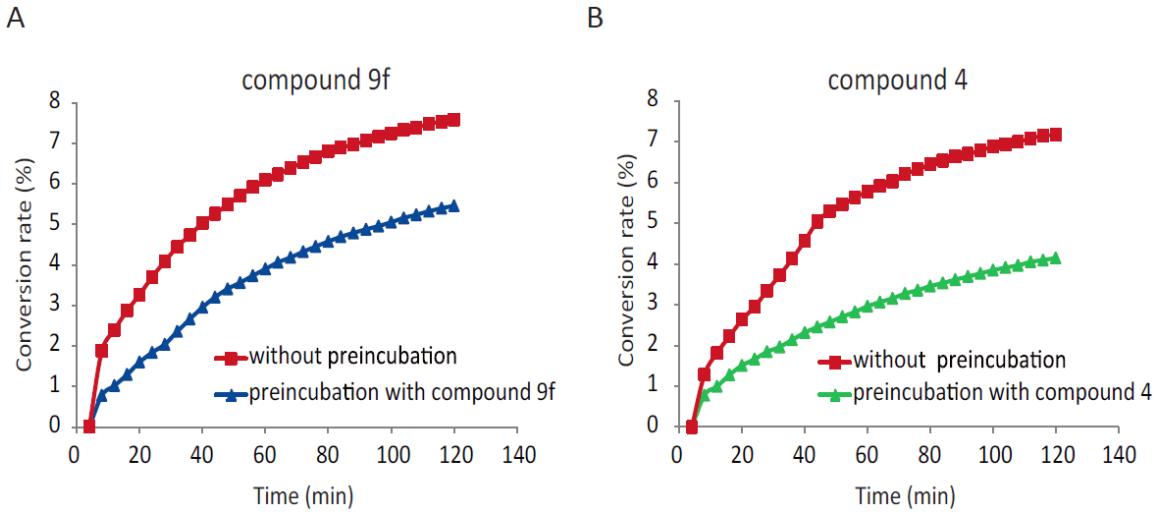


Fig. S1. **9f** irreversibly binds with EGFR$^{L858R/T790M}$.

Cell lines and proliferation assay

NCI-H1975，A431 cancer cells and, GES-1, LO2, WI-38 and MCF-10A normal cell lines were obtained from American Type Culture Collection (ATCC, Rockville, MD) and maintained in strict accordance with the instruction and established procedures. The cell proliferation assay was evaluated using SRB (Sulforhodamine B) assay treated for 72 hrs with different concentrations of compounds.

Table S2. Anti-proliferative activities of the new EGFR T790M mutant inhibitors. [a]

Cpds	Anti-proliferation (IC_{50}, nM)		
	H1975	A431	Selectivity Ratio[b]
9a	3.7 ± 2.7	<16	<5.0
9e	28.9 ± 11.6	236.8 ± 165.2	8.2
9f	2.8 ± 2.0	865.6 ± 426.1	311.3
9i	24.8 ± 17.2	4250.8 ± 2602.0	171.5
9n	>10000	>50000	NA
9p	6.8 ± 0.4	1104.0 ± 589.8	162.8
9r	5.3 ± 1.2	2186.5 ± 575.4	415.1
9t	11.6 ± 10.2	7468.7 ± 948.4	645.2

9u	16.1 ± 10.0	562.9 ± 124.6	35.0
9v	21.0 ± 9.4	687.4 ± 35.3	32.7
3	69.8 ± 43.9	16.7 ± 4.0	0.2
4	50.1 ± 23.2	5550.4 ± 1680.3	110.7
5	43.1 ± 12.1	10117.1 ± 2919.5	274.0

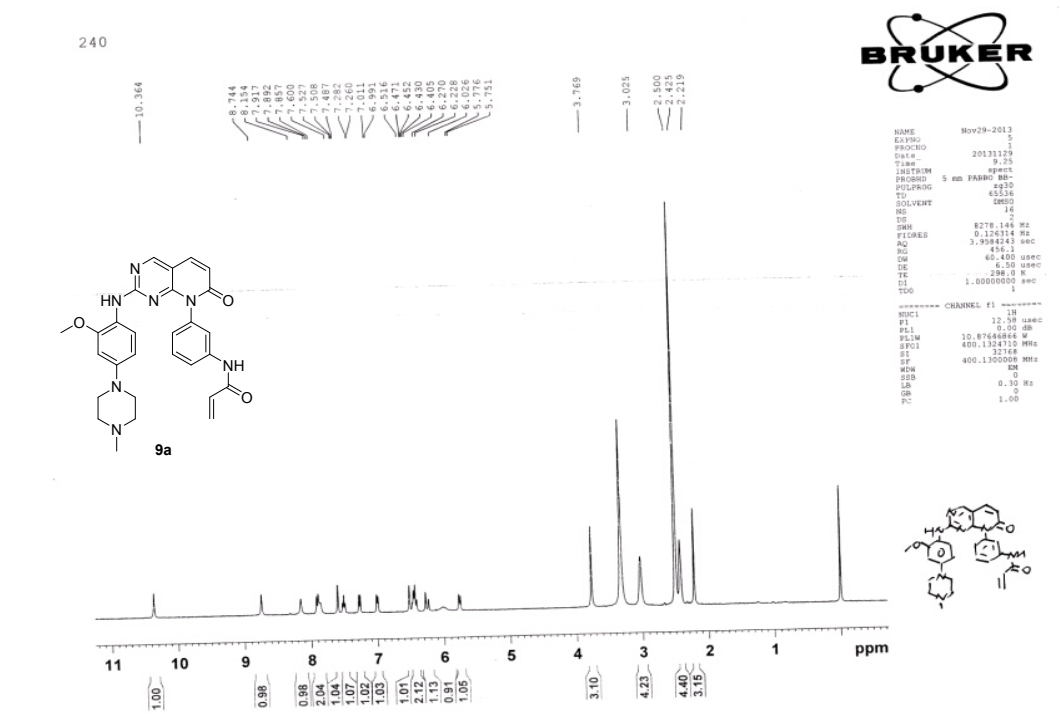
[a] The anti-proliferative activities of the compounds were evaluated using SRB assay. The data were means from at least four independent experiments. [b] Ratio = IC_{50} (A431) / IC_{50} (H1975). NA means not available.

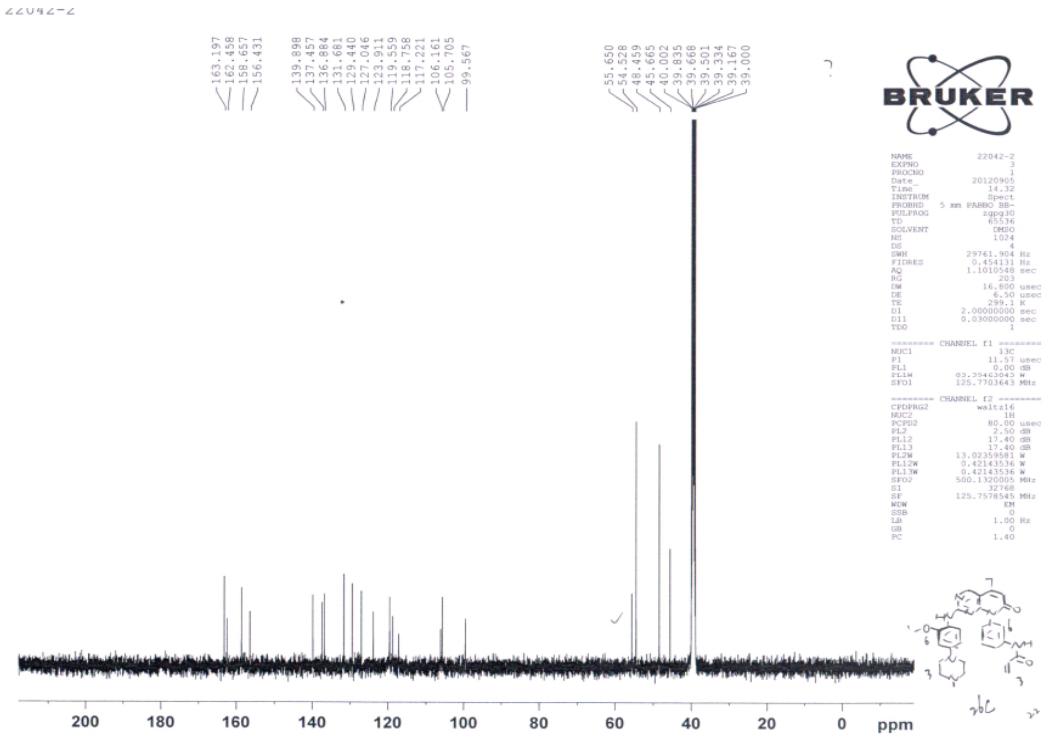
Table S3. Anti-proliferative activities of **9f** against a panel of normal cell lines.

Cpds	Anti-proliferation (IC_{50}, μM)			
	GES-1	LO2	WI-38	MCF-10A
9f	4.591±0.248	2.493±0.683	7.231±0.489	2.016±0.316

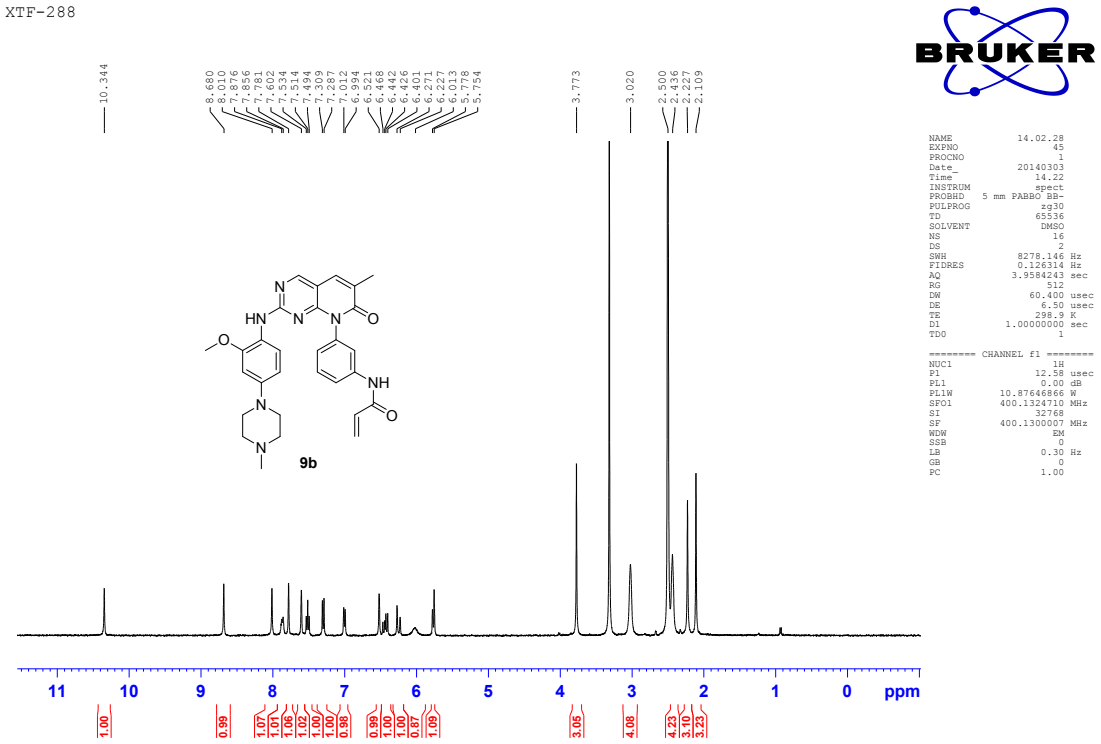
^{1}H NMR and ^{13}C NMR spectra of compounds 9

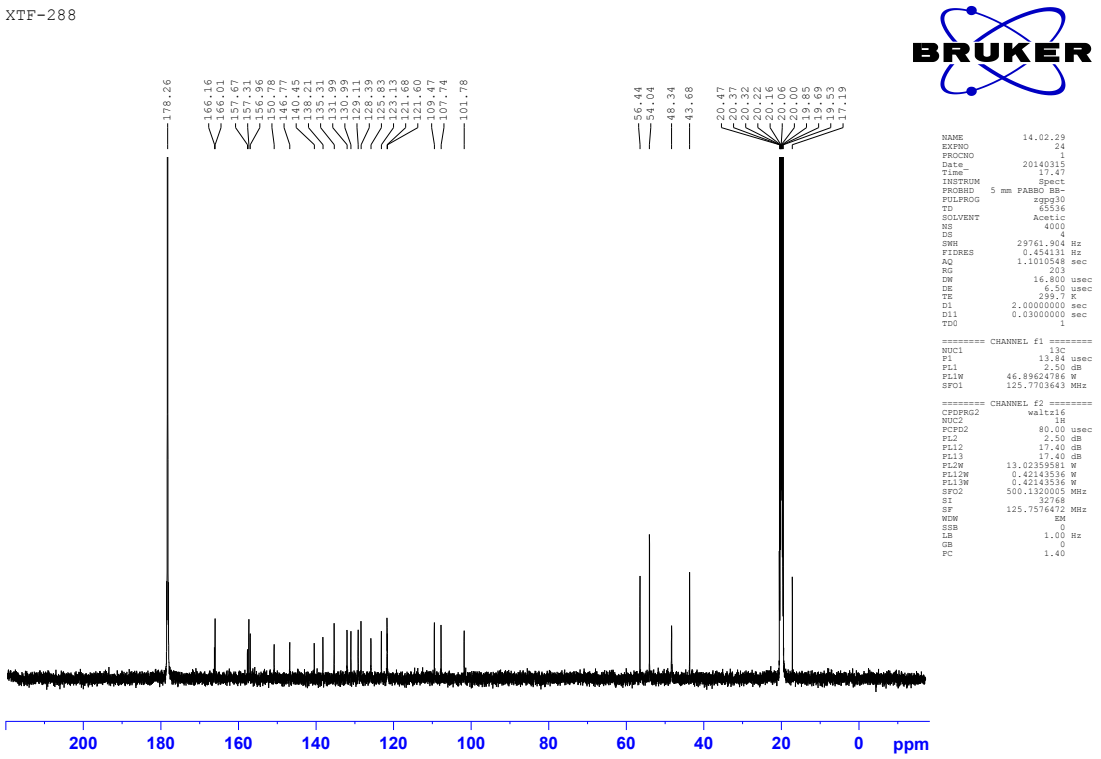
^{1}H, ^{13}C NMR spectra of compound **9a**



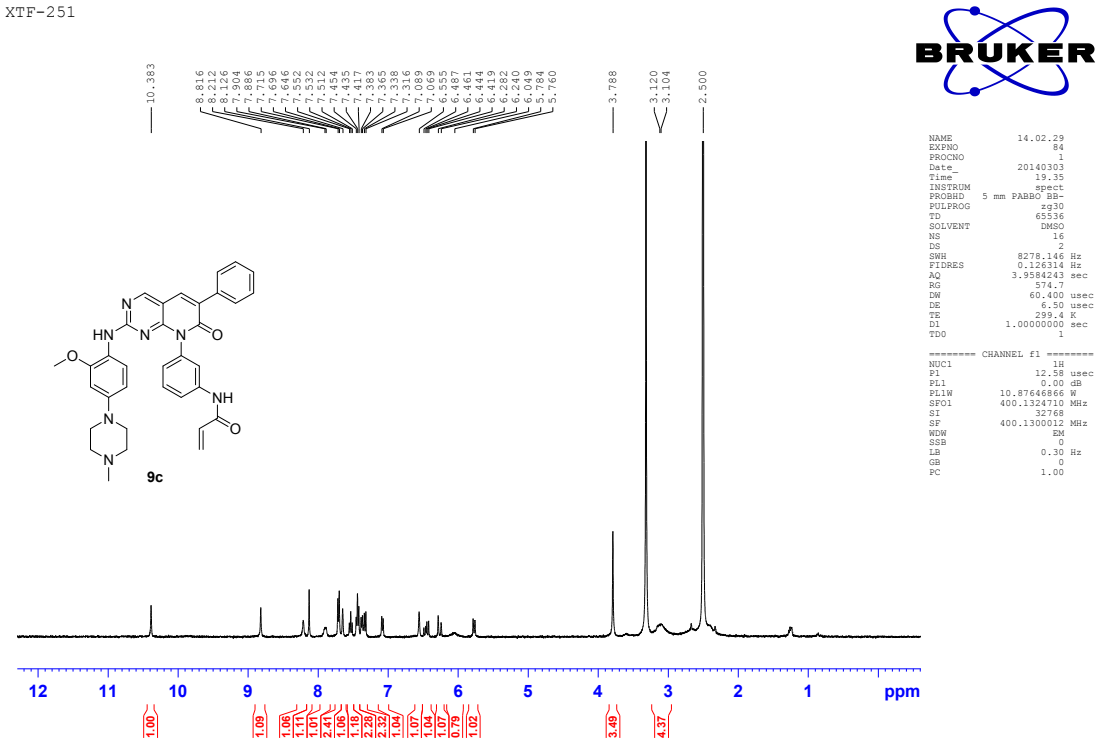


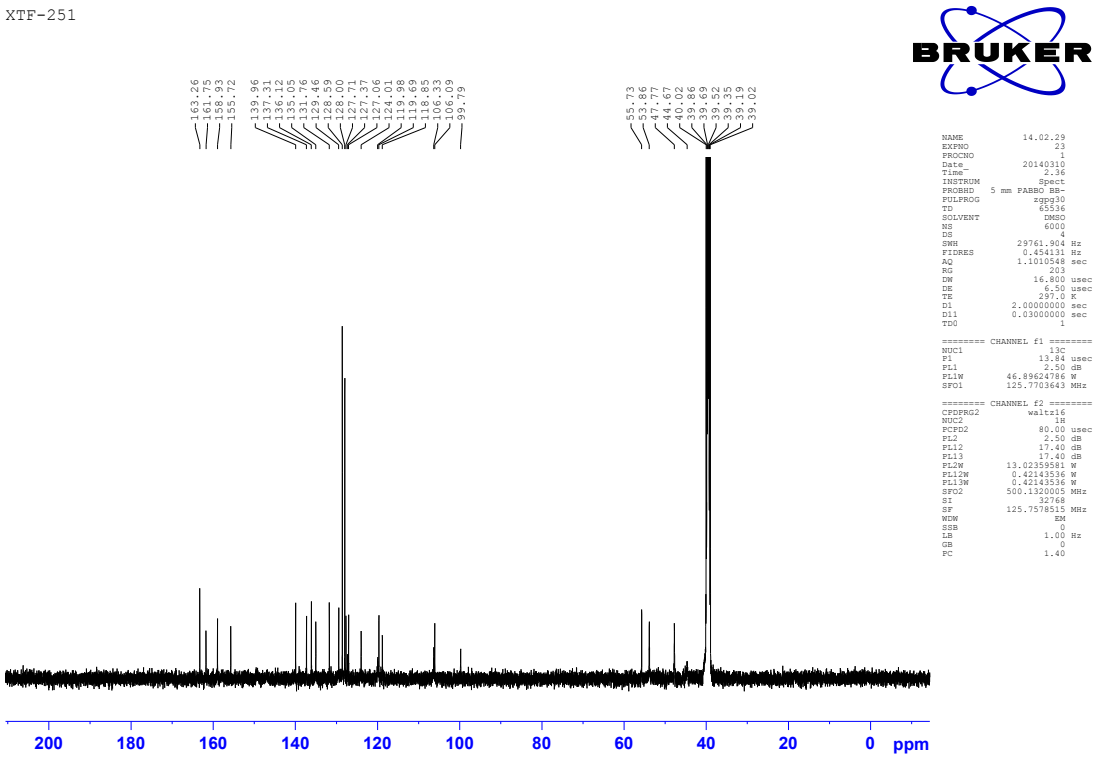
^{1}H, ^{13}C NMR spectra of compound **9b**





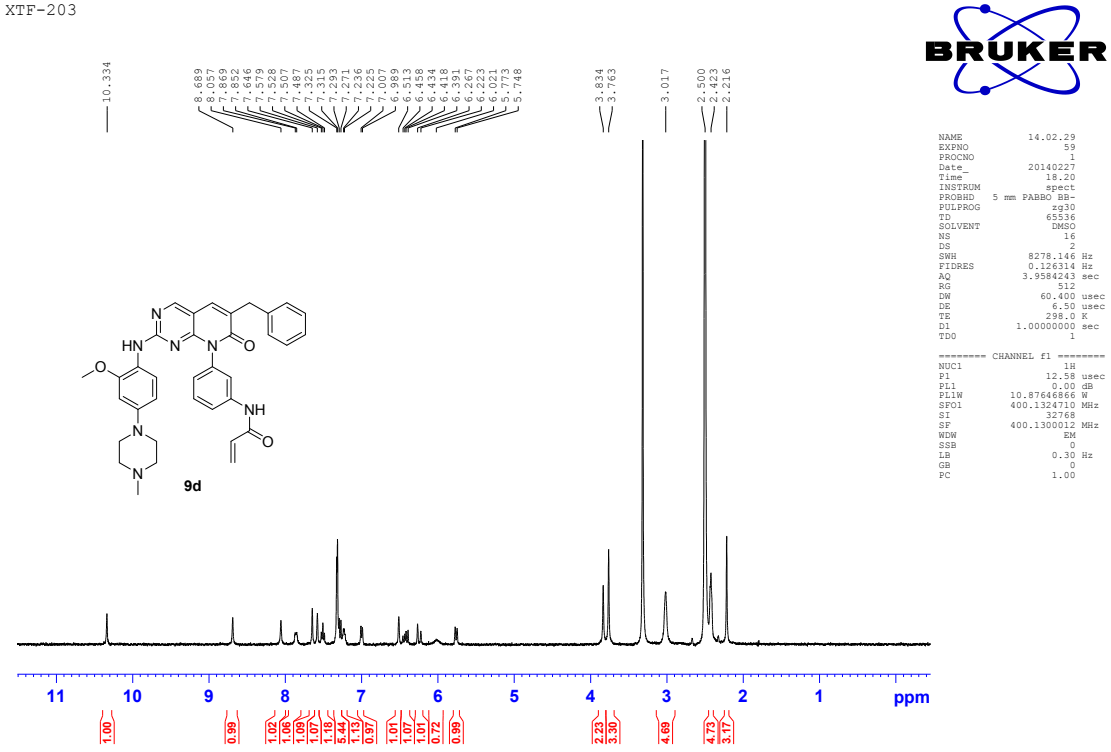
^{1}H, ^{13}C NMR spectra of compound **9c**





^{1}H, ^{13}C NMR spectra of compound **9d**

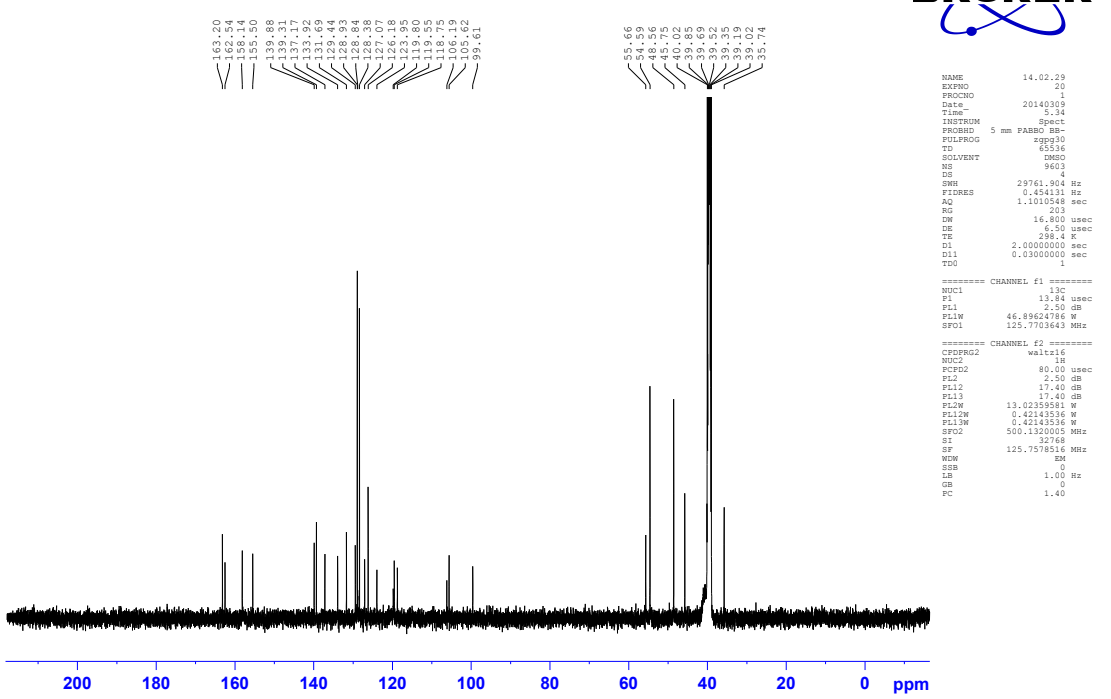
XTF-203



BRUKER

```
NAME                14.02.29
EXPNO                     59
PROCNO                     1
Date_               20140227
Time                   18.20
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       512
DW                  60.400 usec
DE                   6.50 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1                     0.00 dB
PL1W           10.87646866 W
SFO1           400.1324710 MHz
SI                        32768
SF             400.1300012 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

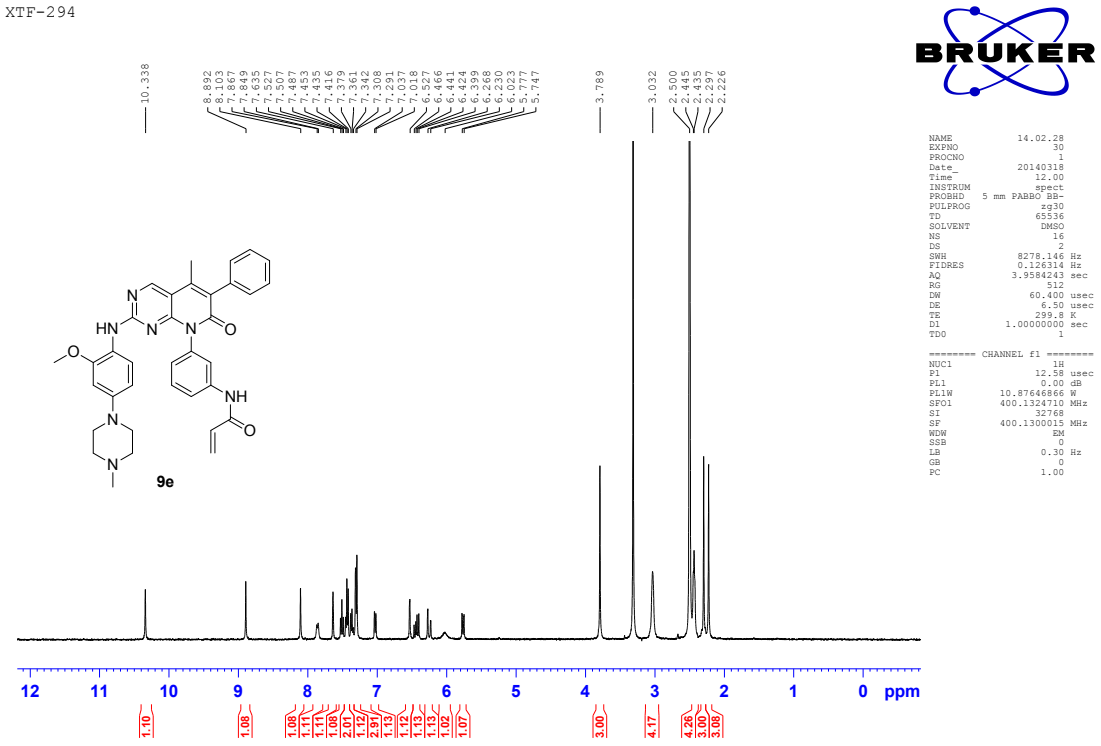
XTF-203

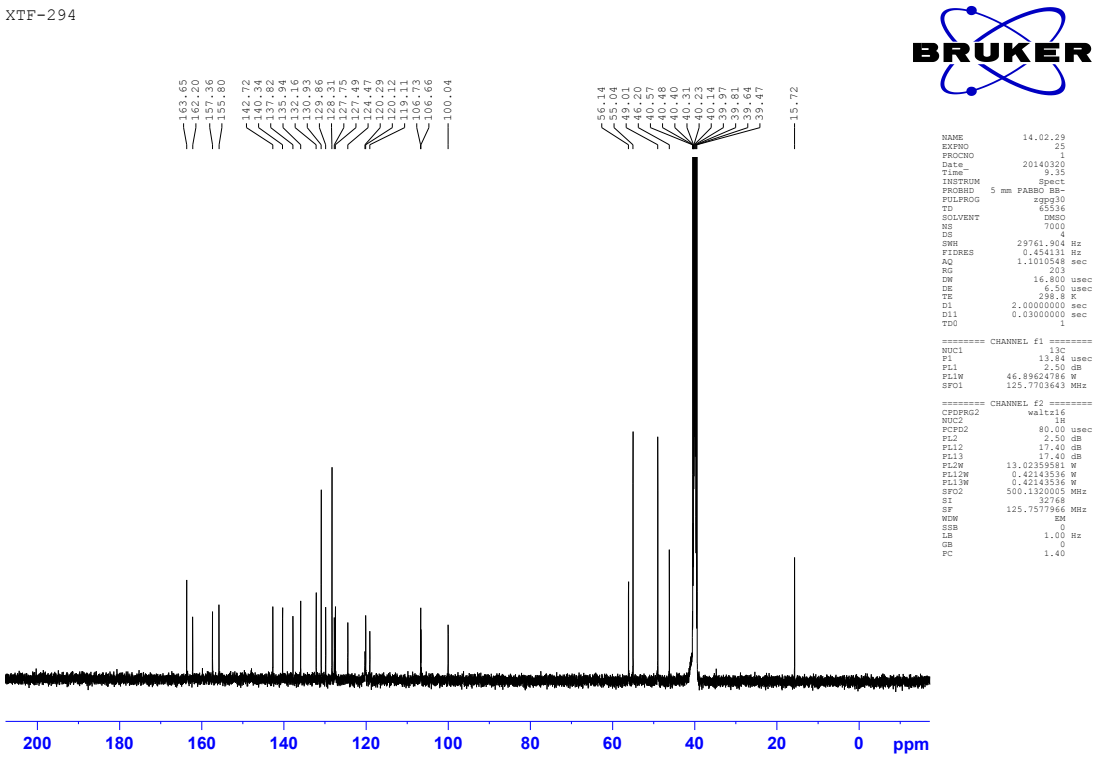


BRUKER

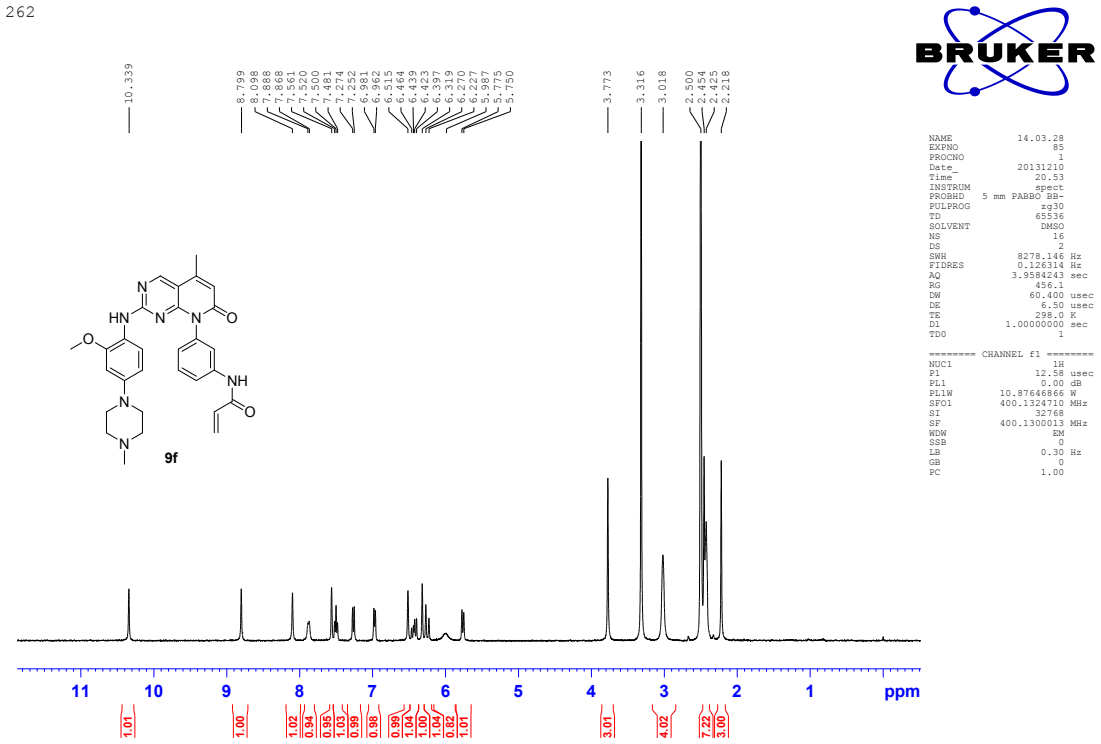
```
NAME                14.02.29
EXPNO                     20
PROCNO                     1
Date_               20140309
Time                    5.34
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      9603
DS                         4
SWH               29761.904 Hz
FIDRES            0.454131 Hz
AQ                1.1010548 sec
RG                       203
DW                  16.800 usec
DE                   6.50 usec
TE                   298.4 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                     13.84 usec
PL1                     2.50 dB
PL1W           46.89624786 W
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2                80.00 usec
PL2                     2.50 dB
PL12                   17.40 dB
PL13                   17.40 dB
PL2W           13.02359581 W
PL12W           0.42143536 W
PL13W           0.42143536 W
SFO2           500.1320005 MHz
SI                        32768
SF             125.7578516 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

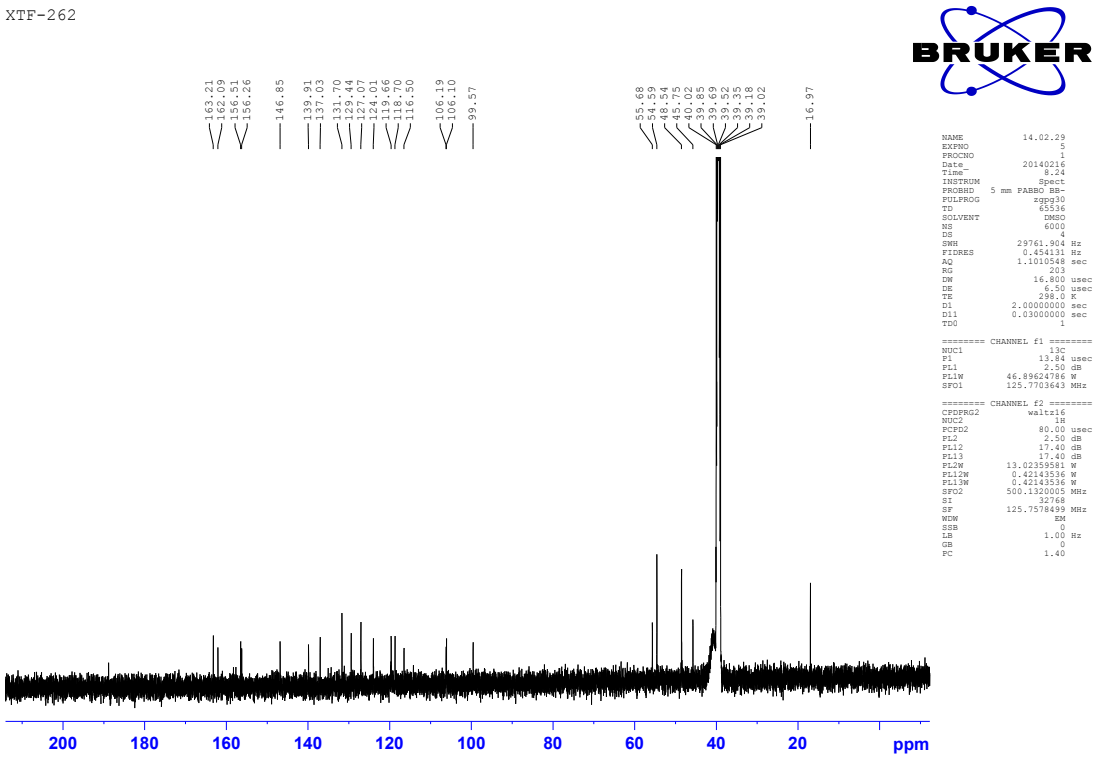
^{1}H, ^{13}C NMR spectra of compound **9e**





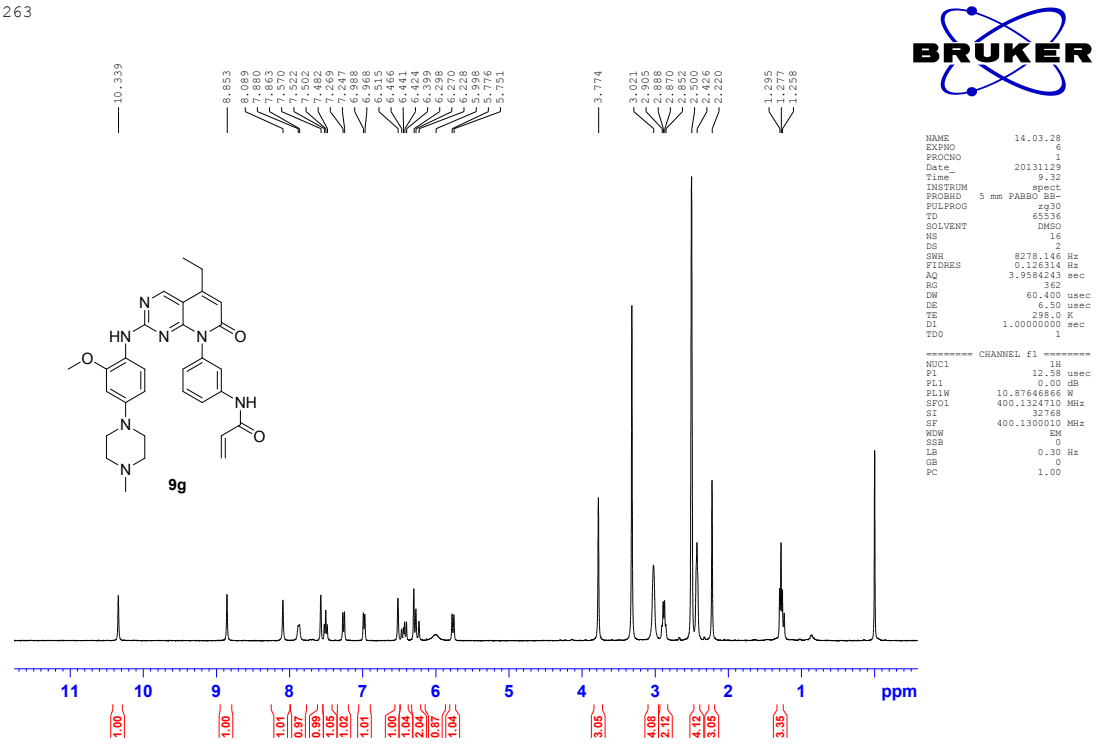
^{1}H, ^{13}C NMR spectra of compound **9f**





^{1}H, ^{13}C NMR spectra of compound **9g**

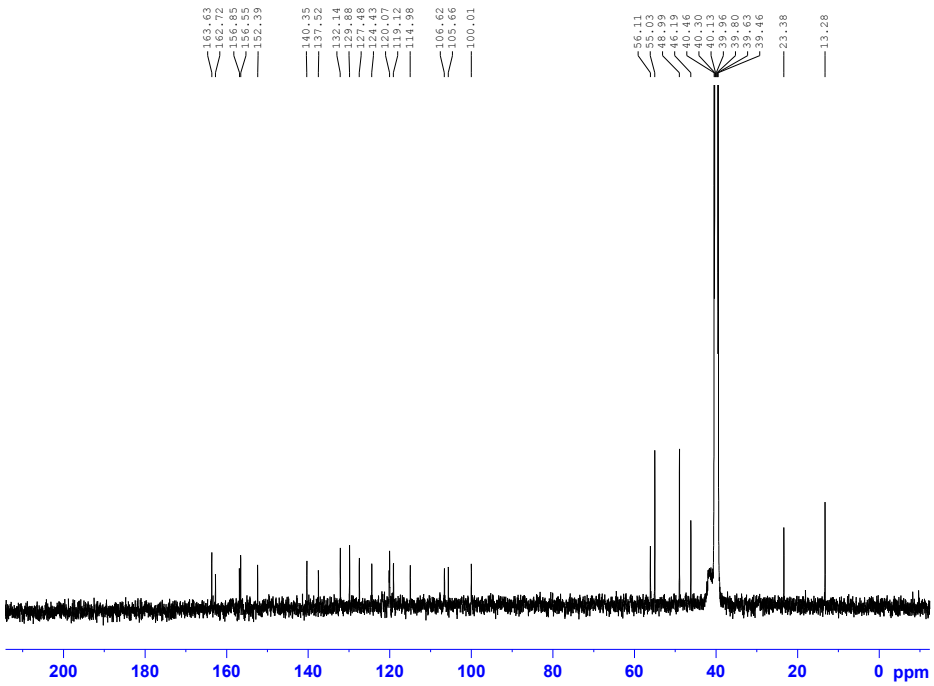
263



NAME 14.03.28
EXPNO 6
PROCNO 1
Date_ 20131129
Time_ 9.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300010 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-263



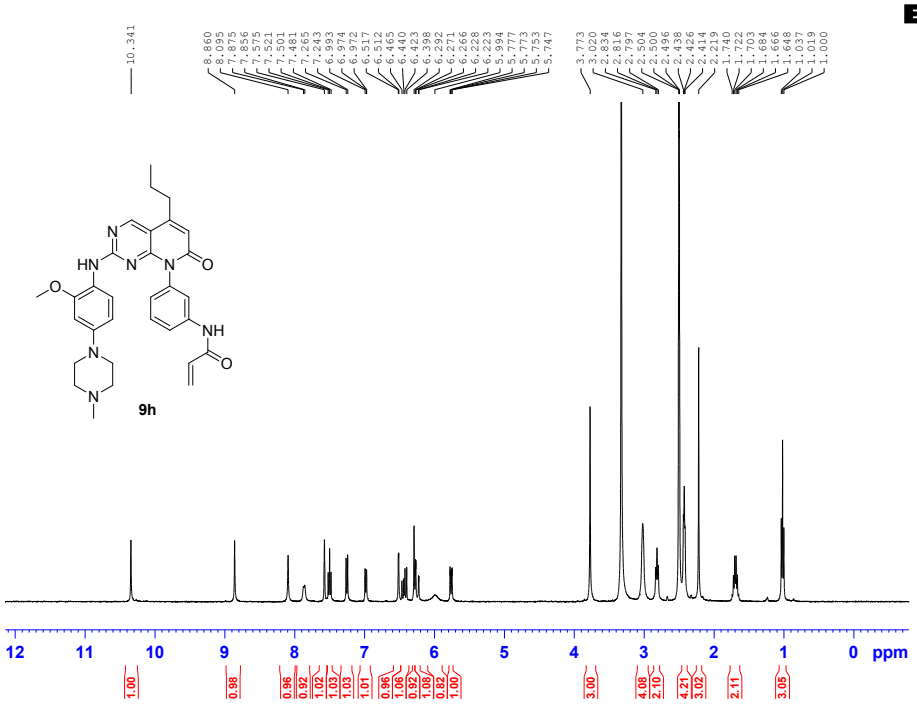
NAME 14.02.29
EXPNO 263
PROCNO 1
Date_ 20140212
Time_ 20.57
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 3489
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7577966 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40

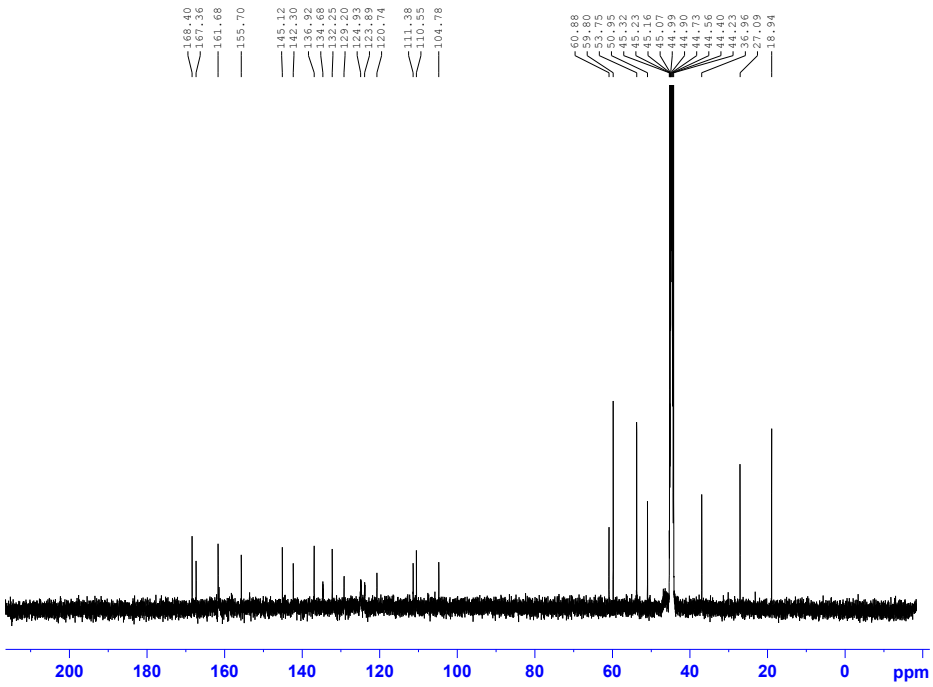
^{1}H, ^{13}C NMR spectra of compound **9h**

35841-1




```
NAME                14.02.28
EXPNO                     58
PROCNO                     1
Date_               20130502
Time_                 16.17
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       362
DW                  60.400 usec
DE                   6.50 usec
TE                   297.4 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    12.58 usec
PL1                    0.00 dB
PL1W          10.87646866 W
SFO1          400.1324710 MHz
SI                      32768
SF            400.1300022 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                      1.00
```

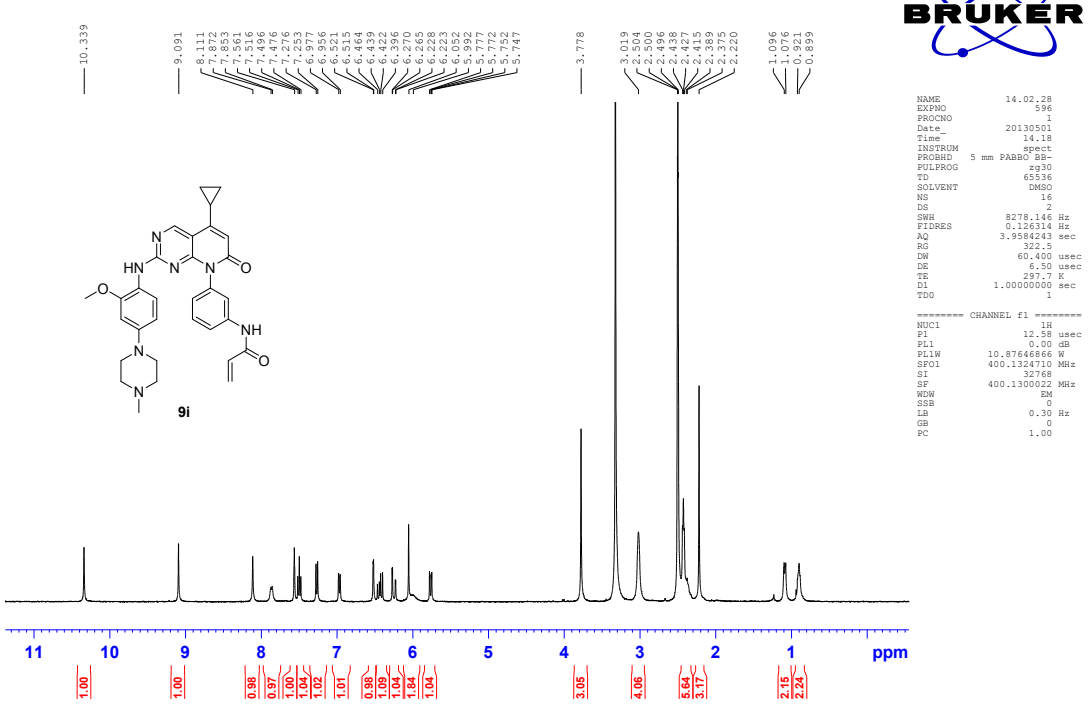
XTF-264




```
NAME                14.02.29
EXPNO                    264
PROCNO                     1
Date_               20140213
Time_                 3.40
INSTRUM               Spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      5120
DS                         4
SWH                29761.904 Hz
FIDRES             0.454131 Hz
AQ                1.1010548 sec
RG                       203
DW                  16.800 usec
DE                   6.50 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                    13.84 usec
PL1                    2.50 dB
PL1W          46.89624786 W
SFO1          125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                    2.50 dB
PL12                  17.40 dB
PL13                  17.40 dB
PL2W          13.02359581 W
PL12W          0.42143536 W
PL13W          0.42143536 W
SFO2          500.1320005 MHz
SI                      32768
SF            125.7577966 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                      1.40
```

^{1}H, ^{13}C NMR spectra of compound **9i**

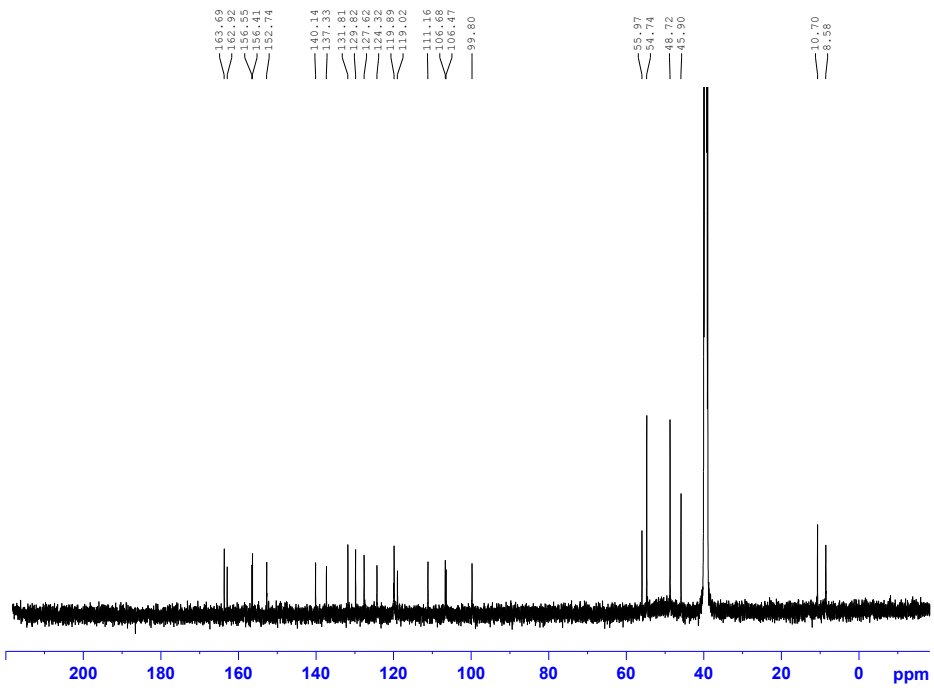
XTF-278



NAME 14.02.28
EXPNO 596
PROCNO 1
Date_ 20130501
Time_ 14.18
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 322.5
DW 60.400 usec
DE 6.50 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-278



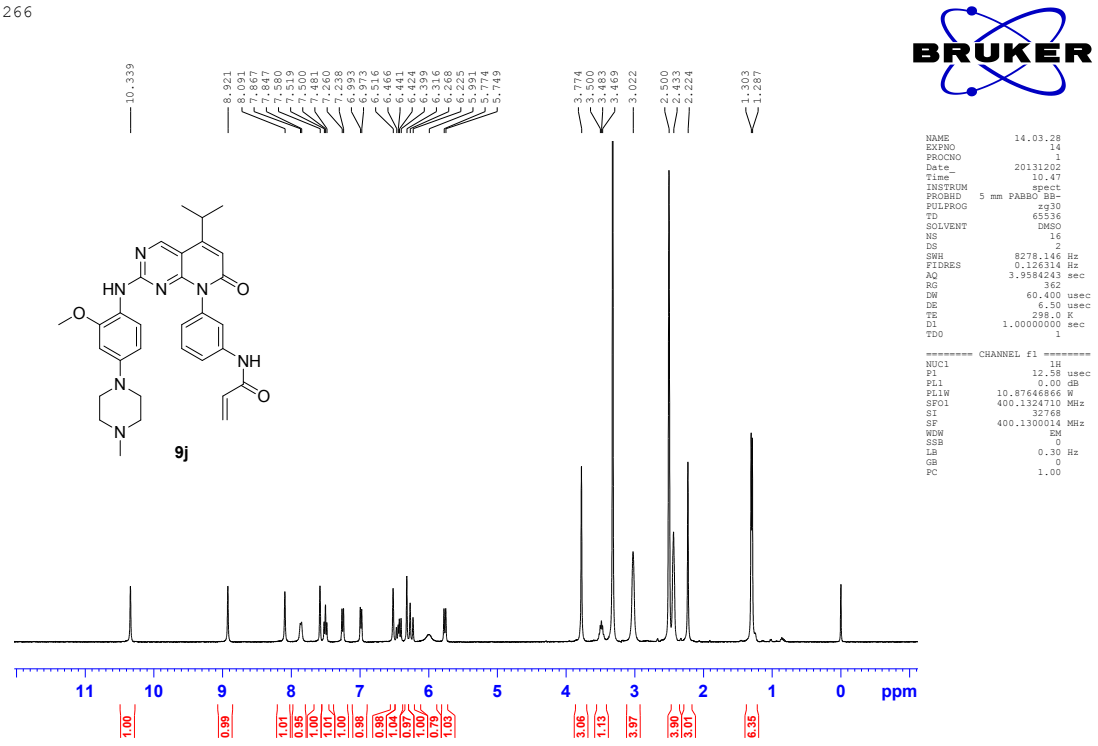
NAME 14.02.29
EXPNO 6
PROCNO 1
Date_ 20140216
Time_ 21.04
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 6000
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578110 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{1}H, ^{13}C NMR spectra of compound **9j**

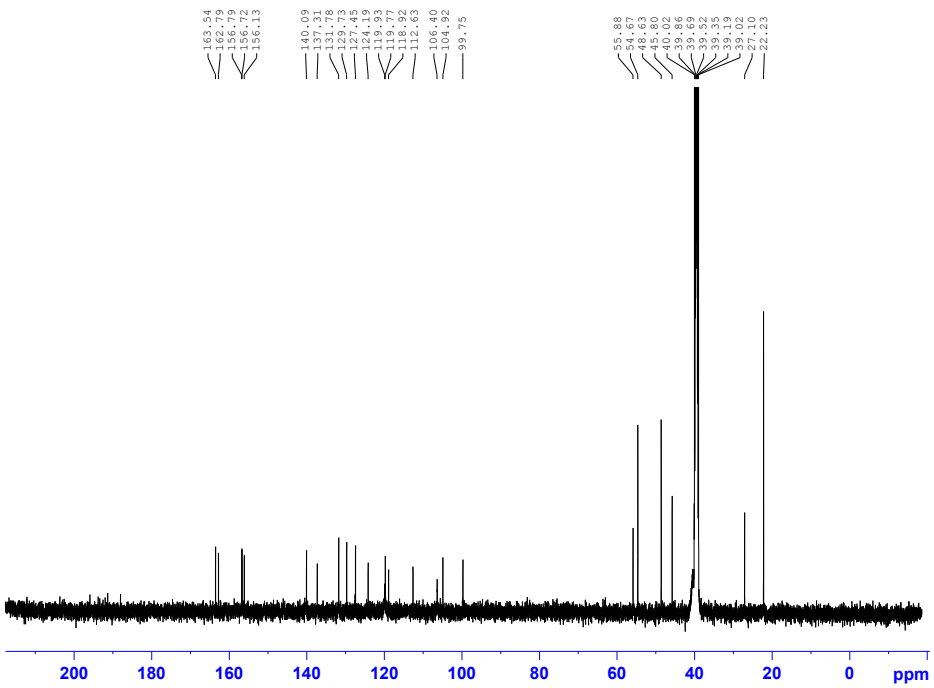
266



BRUKER

```
NAME                14.03.28
EXPNO                     14
PROCNO                     1
Date_               20131202
Time_                  10.47
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                       362
DW                  60.400 usec
DE                   6.50 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     1H
P1                   12.58 usec
PL1                   0.00 dB
PL1W          10.87646866 W
SFO1          400.1324710 MHz
SI                     32768
SF            400.1300014 MHz
WDW                       EM
SSB                        0
LB                    0.30 Hz
GB                         0
PC                    1.00
```

XTF-266

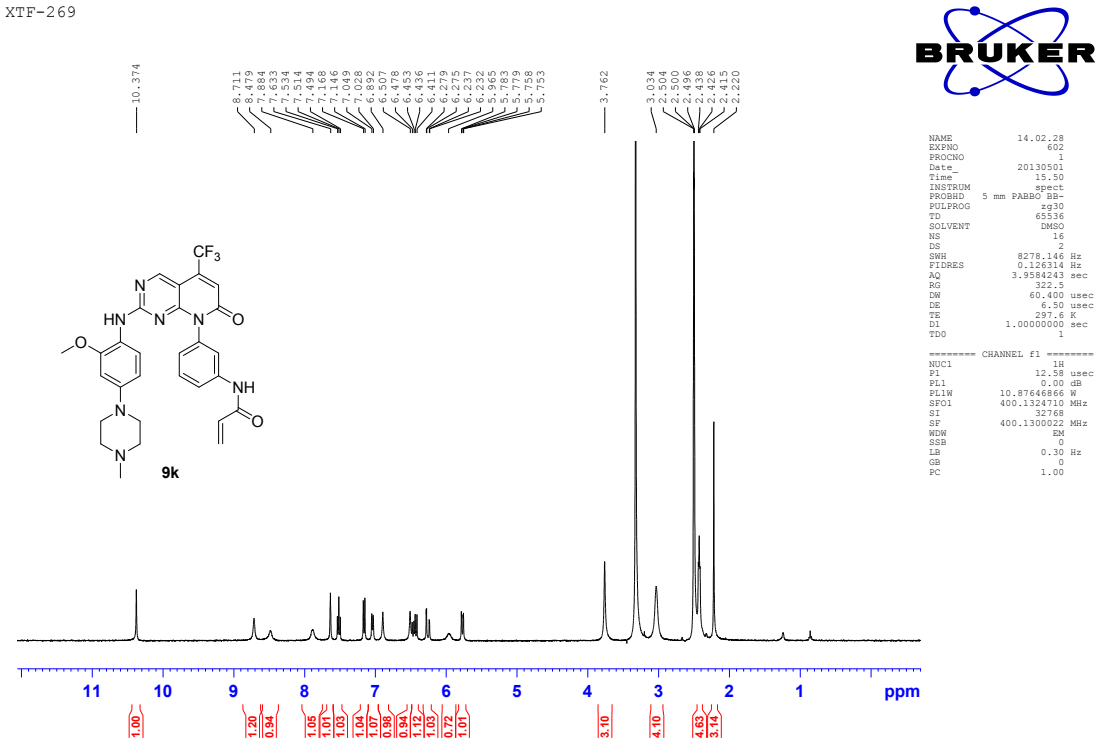


BRUKER

```
NAME                14.02.29
EXPNO                     8
PROCNO                    1
Date_               20140220
Time_                  5.53
INSTRUM               Spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      6000
DS                         4
SWH               29761.904 Hz
FIDRES            0.454131 Hz
AQ                1.1010548 sec
RG                       203
DW                  16.800 usec
DE                   6.50 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                     13C
P1                   13.84 usec
PL1                   2.50 dB
PL1W          46.89624786 W
SFO1          125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                   2.50 dB
PL12                 17.40 dB
PL13                 17.40 dB
PL2W          13.02359581 W
PL12W          0.42143536 W
PL13W          0.42143536 W
SFO2          500.1320005 MHz
SI                     32768
SF            125.7578237 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                    1.40
```

^{1}H, ^{13}C NMR spectra of compound **9k**

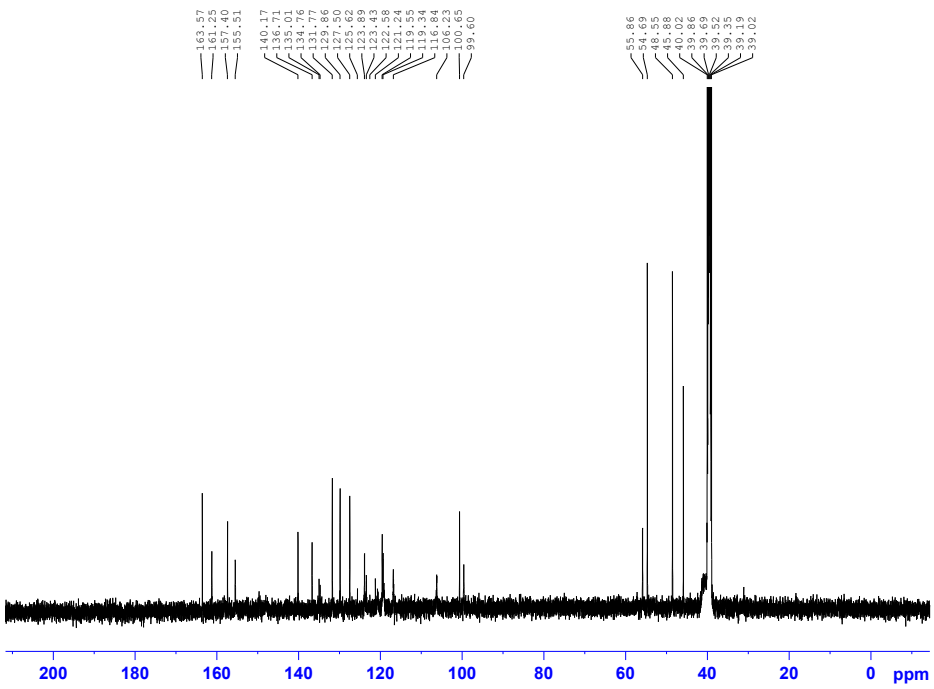
XTF-269



NAME 14.02.28
EXPNO 602
PROCNO 1
Date_ 20130501
Time_ 15.50
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 322.5
DW 60.400 usec
DE 6.50 usec
TE 297.6 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-269



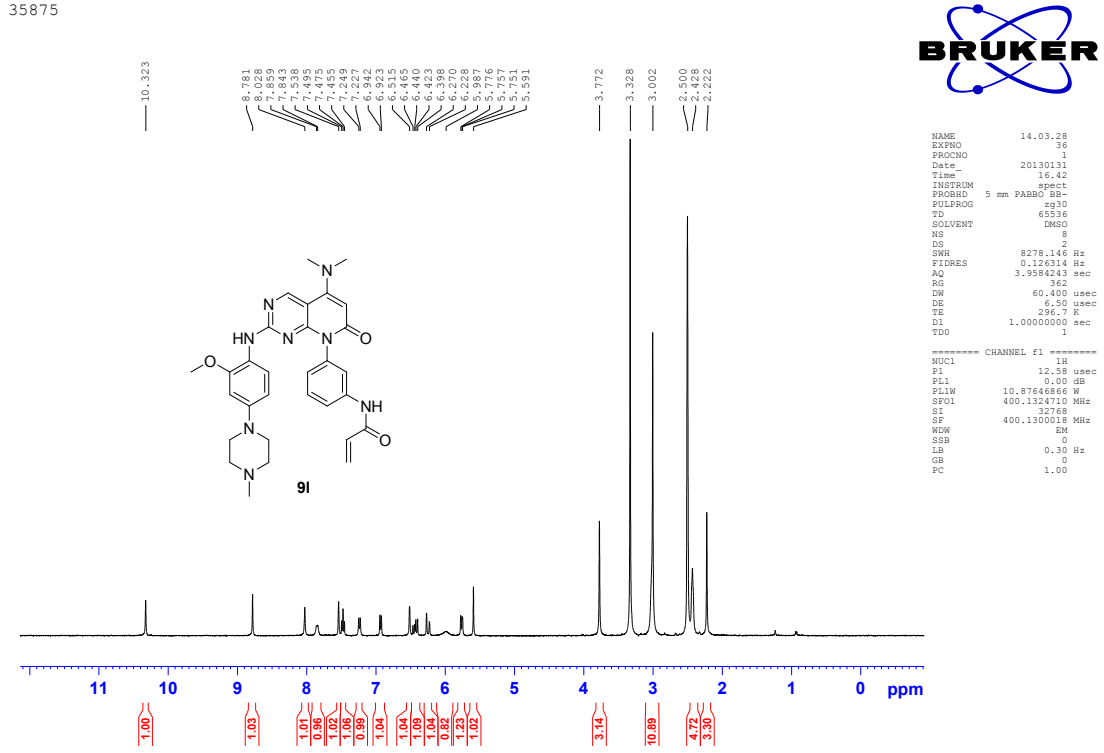
NAME 14.02.29
EXPNO 3
PROCNO 1
Date_ 20140215
Time_ 21.32
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 5120
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578215 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{1}H, ^{13}C NMR spectra of compound **9l**

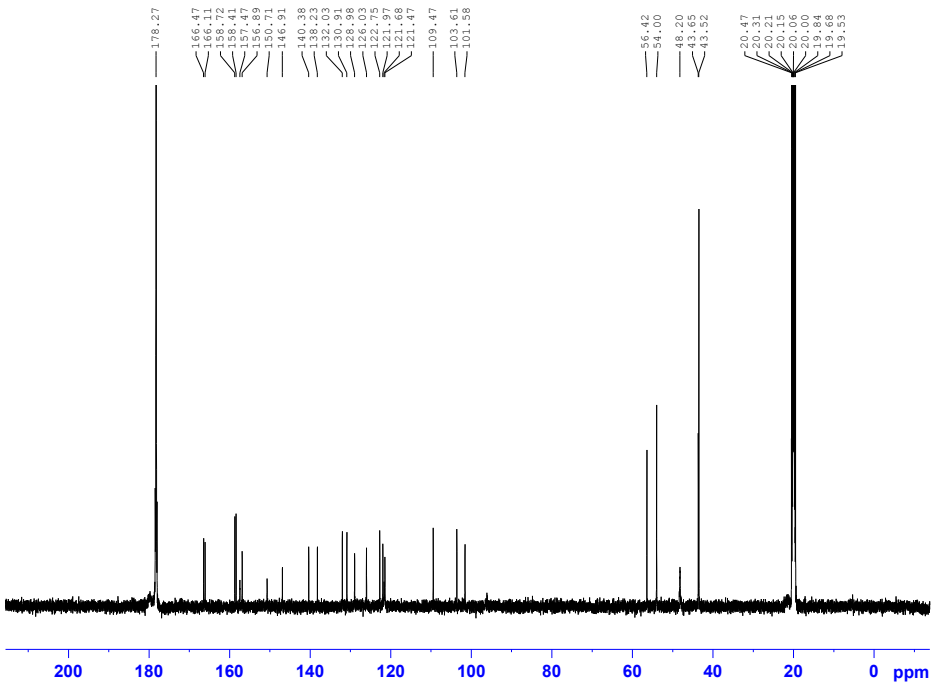
35875



NAME 14.03.28
EXPNO 36
PROCNO 1
Date_ 20130131
Time 16.42
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.50 usec
TE 296.7 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300018 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-267

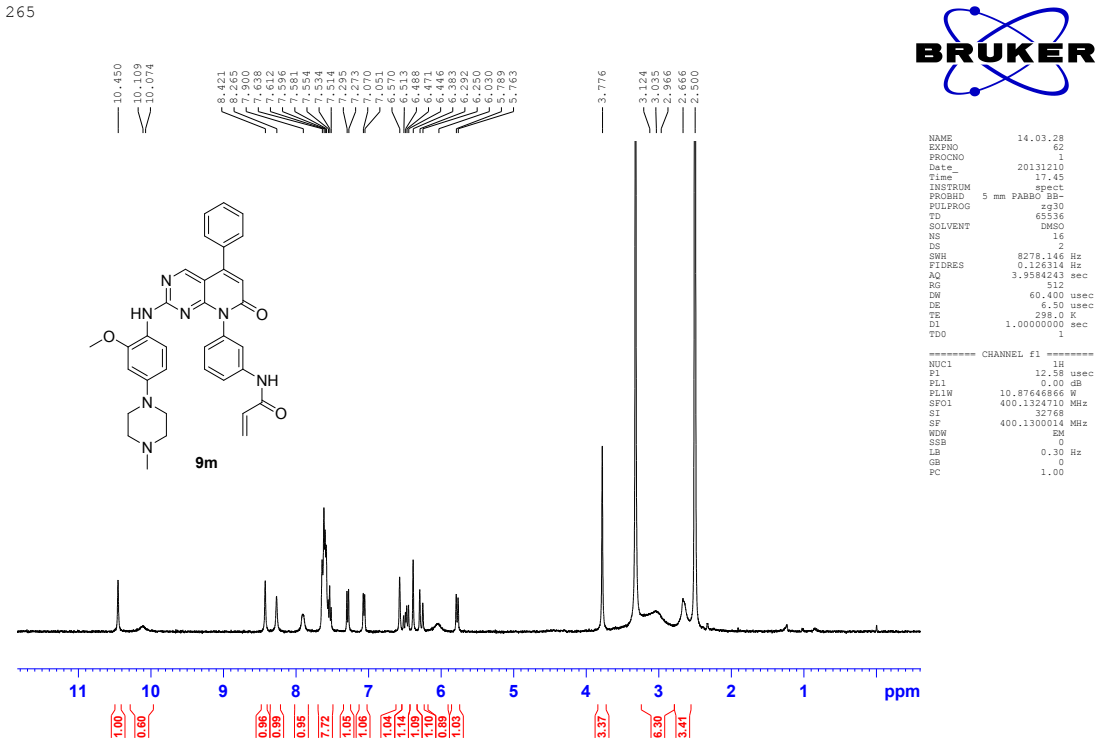


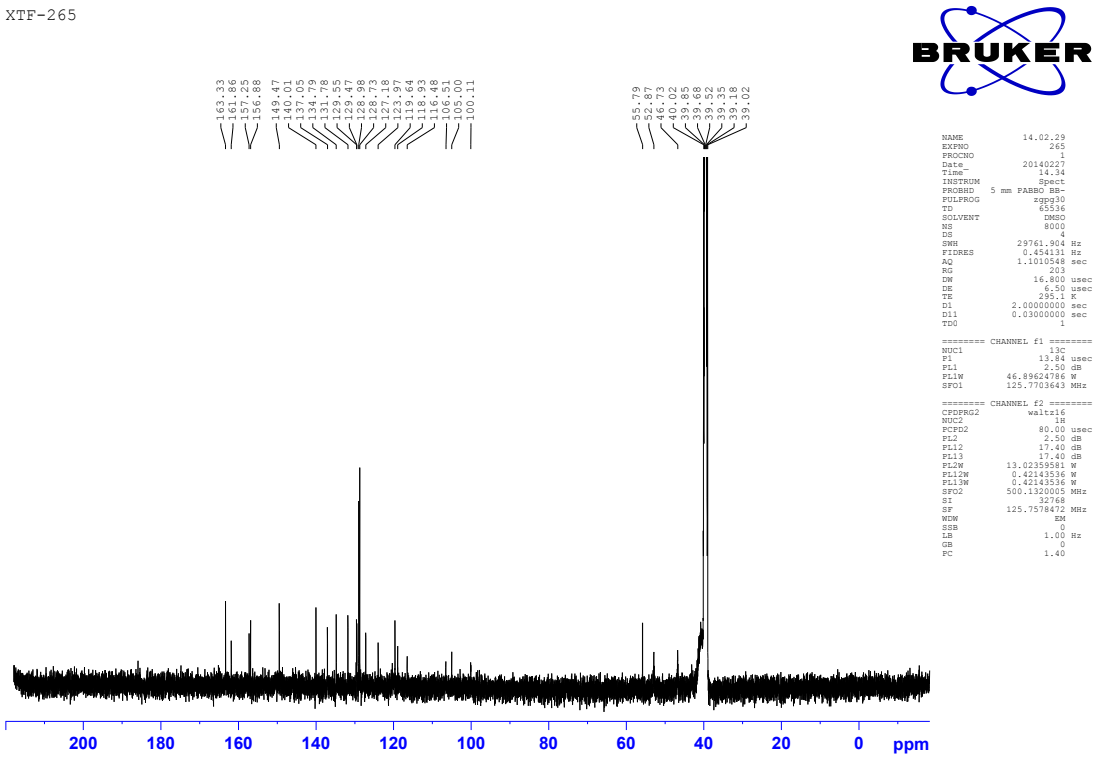
NAME 14.02.29
EXPNO 22
PROCNO 1
Date_ 20140309
Time 21.22
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT Acetic
NS 3949
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 296.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

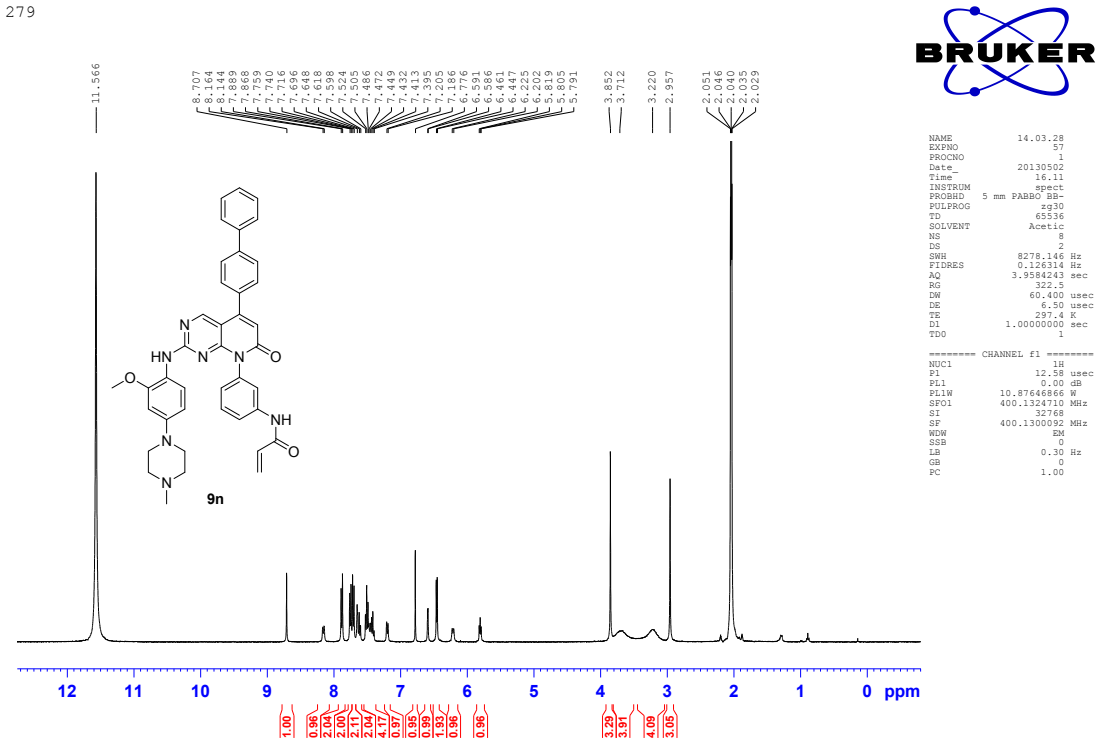
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7576507 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

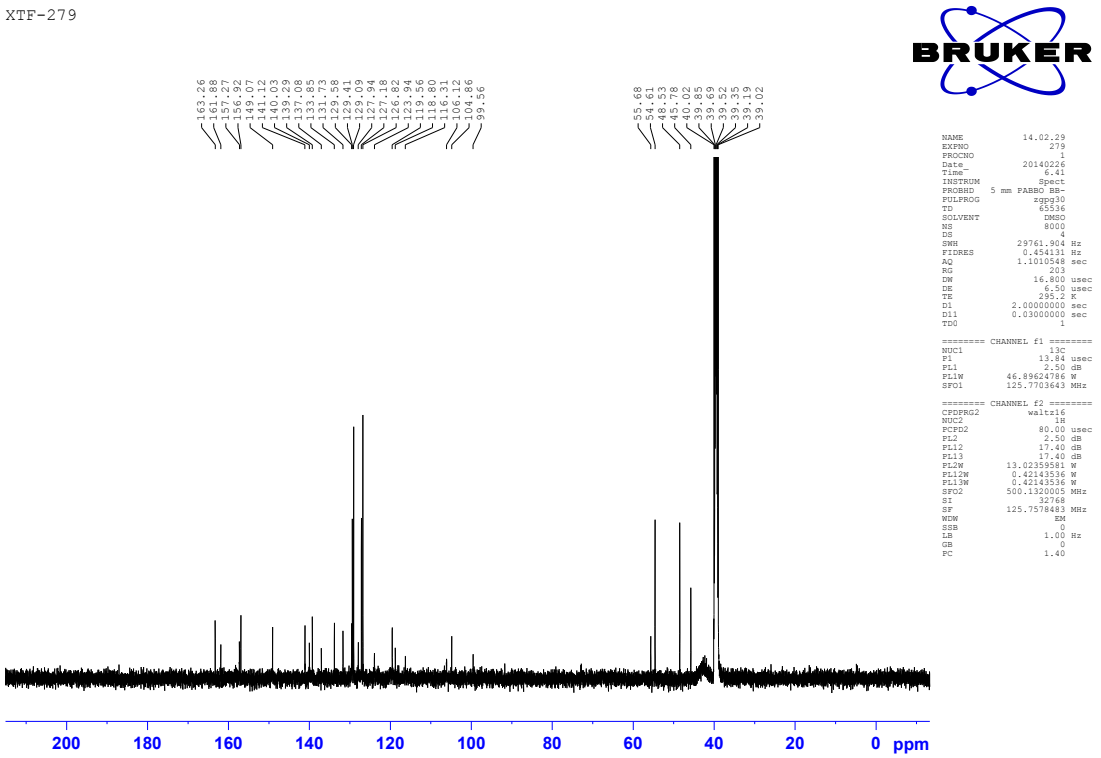
^{1}H, ^{13}C NMR spectra of compound **9m**



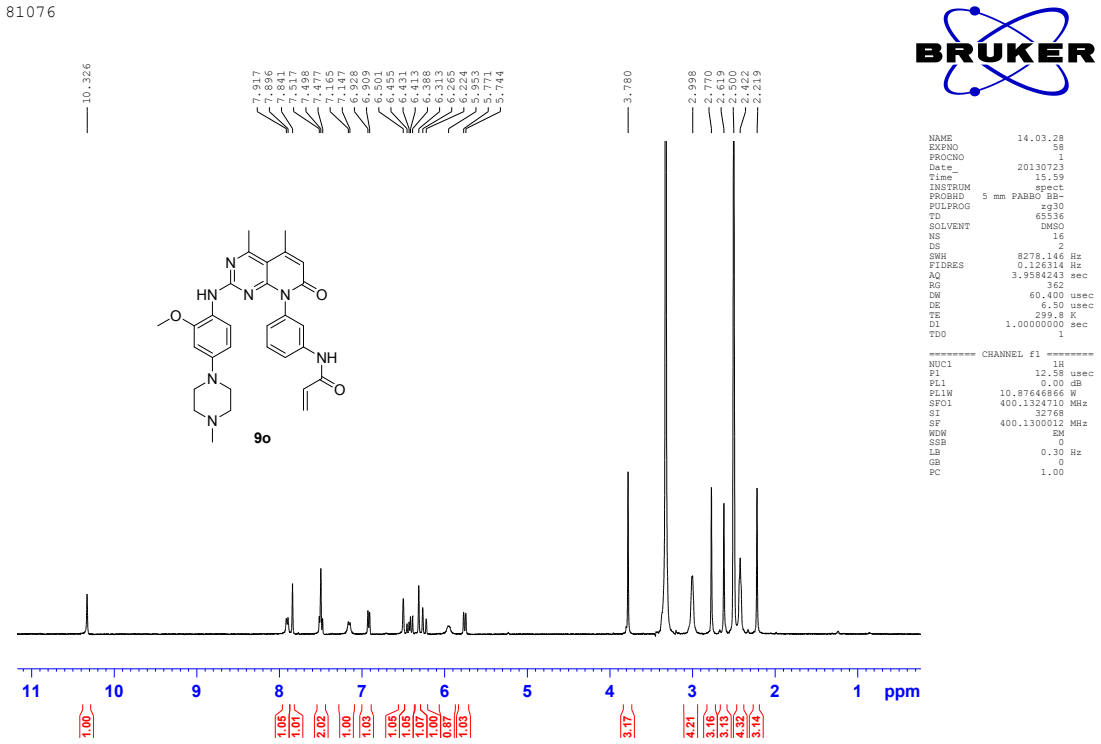


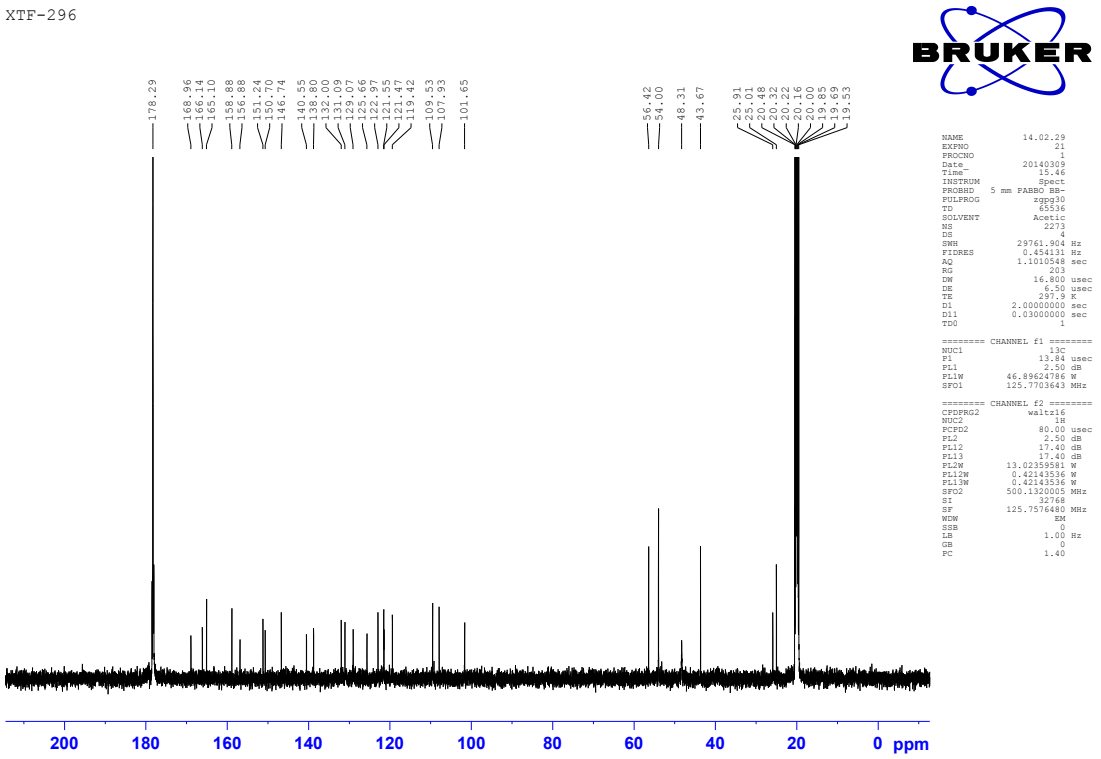
^{1}H, ^{13}C NMR spectra of compound **9n**





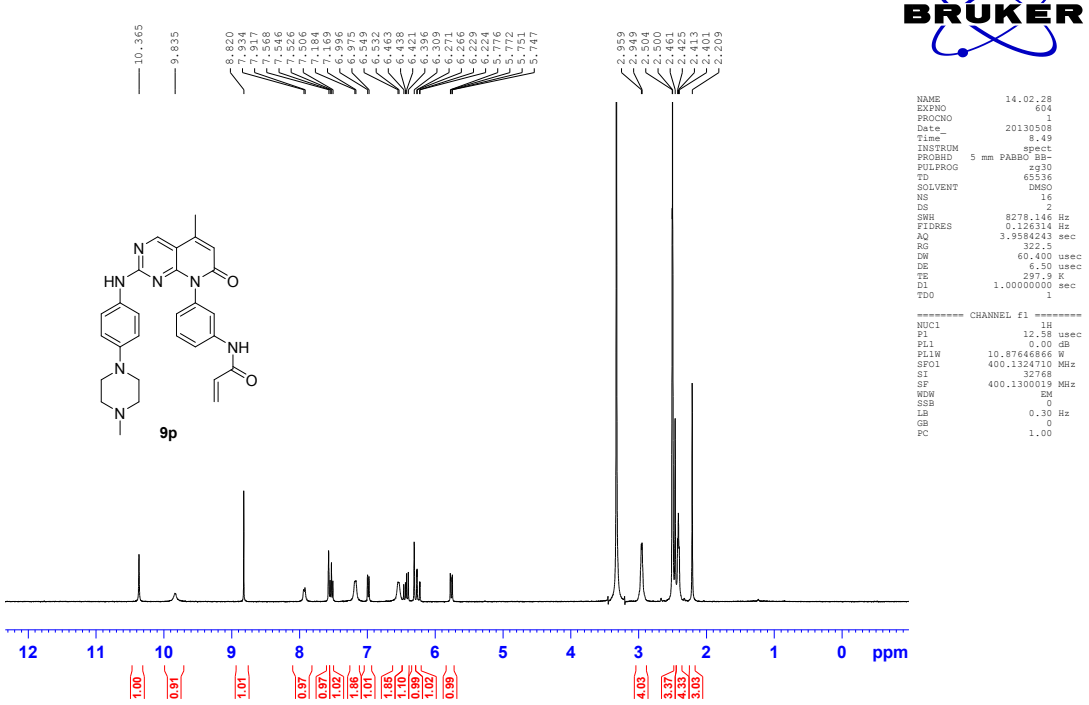
^{1}H, ^{13}C NMR spectra of compound **9o**





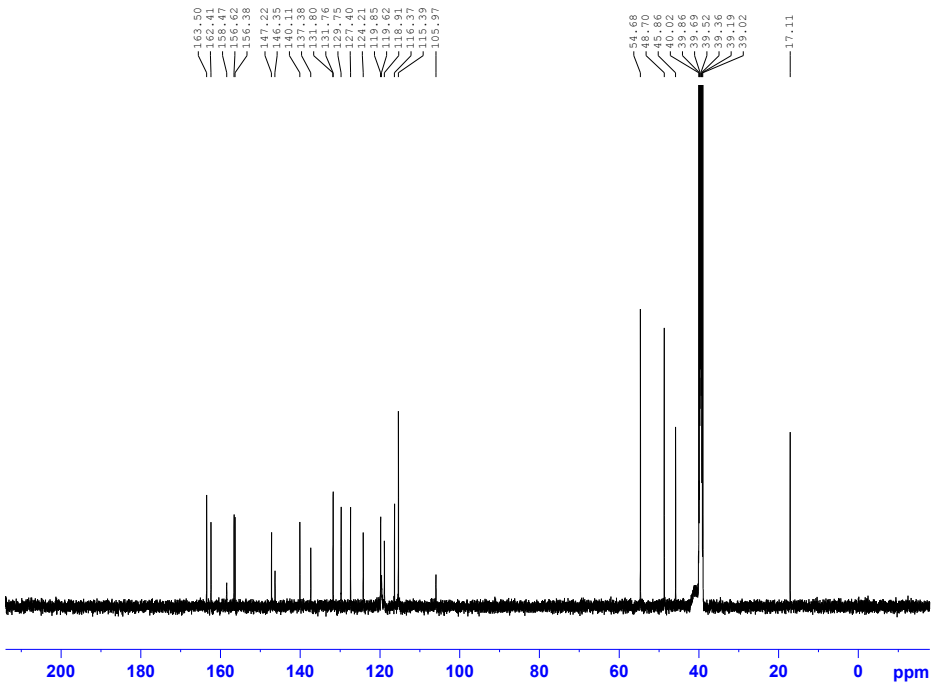
^{1}H, ^{13}C NMR spectra of compound **9p**

35984



```
NAME                14.02.28
EXPNO                    604
PROCNO                     1
Date_               20130508
Time_                   8.49
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                    322.5
DW                   60.400 usec
DE                    6.50 usec
TE                   297.9 K
D1                1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1                     0.00 dB
PL1W           10.87646866 W
SFO1           400.1324710 MHz
SI                      32768
SF             400.1300019 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

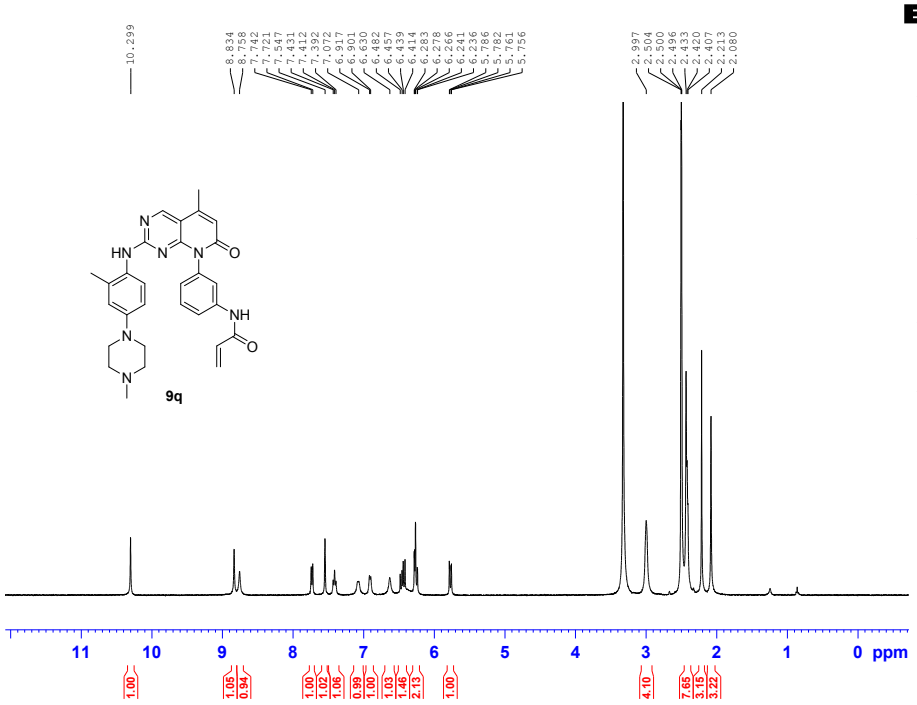
XTF-35984



```
NAME                14.02.29
EXPNO                      9
PROCNO                     1
Date_               20140221
Time_                   6.53
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                     4875
DS                        4
SWH                29761.904 Hz
FIDRES             0.454131 Hz
AQ                1.1010548 sec
RG                      203
DW                   16.800 usec
DE                    6.50 usec
TE                   297.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     13.84 usec
PL1                     2.50 dB
PL1W           46.89624786 W
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                     2.50 dB
PL12                   17.40 dB
PL13                   17.40 dB
PL2W           13.02359581 W
PL12W           0.42143536 W
PL13W           0.42143536 W
SFO2           500.1320005 MHz
SI                      32768
SF             125.7578280 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

^{1}H, ^{13}C NMR spectra of compound **9q**

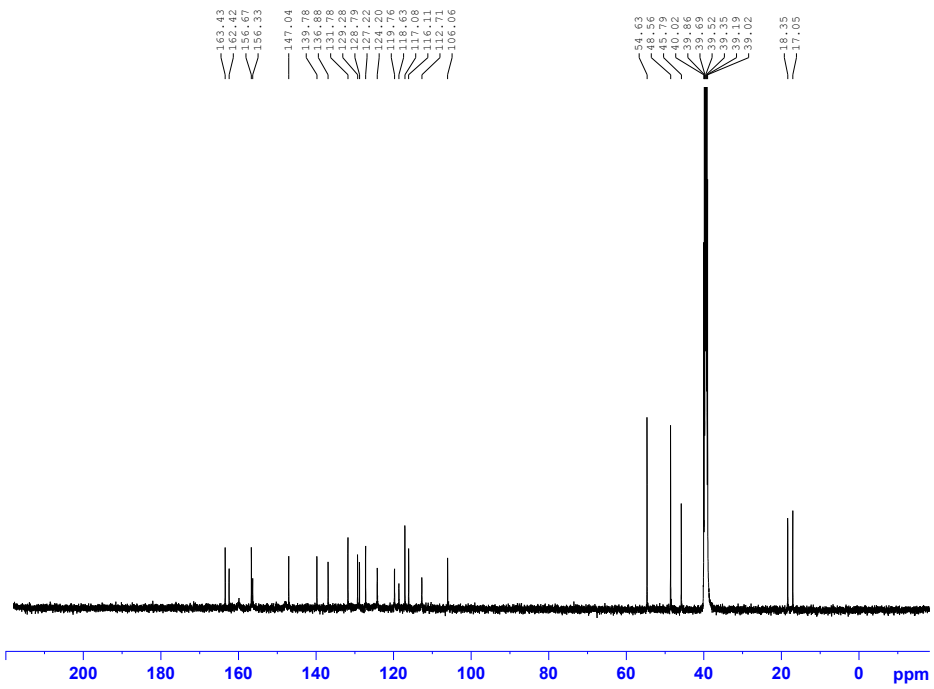
XTF-284



NAME 14.02.28
EXPNO 600
PROCNO 1
Date_ 20130501
Time_ 15.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 322.5
DW 60.400 usec
DE 6.50 usec
TE 297.7 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-284



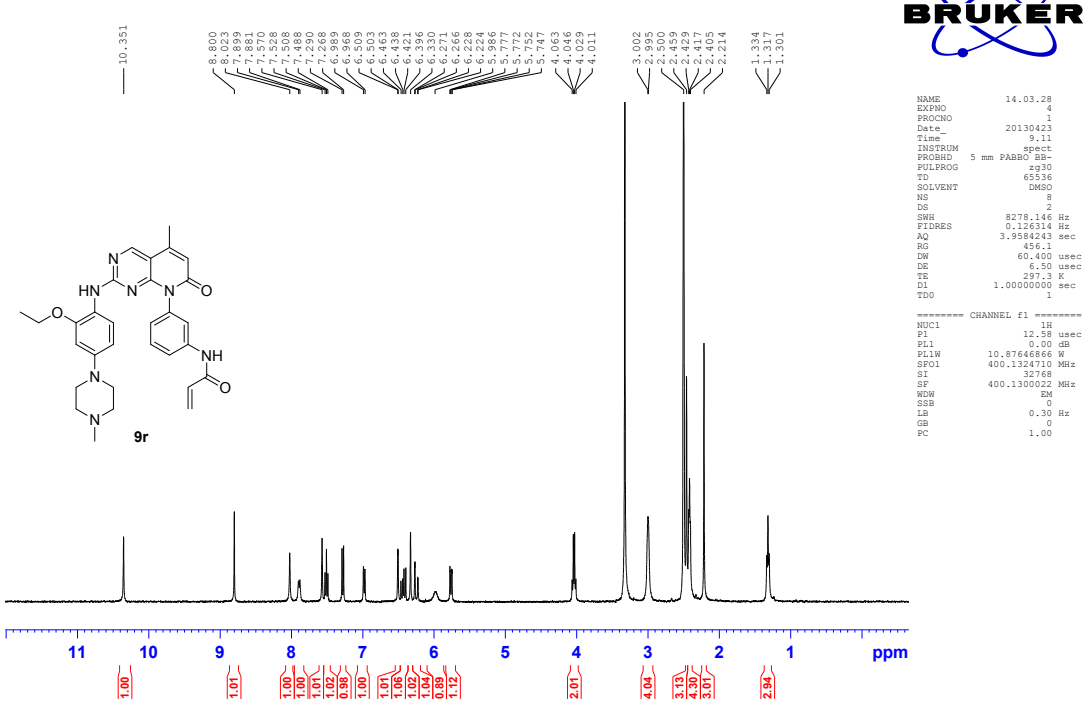
NAME 14.02.29
EXPNO 284
PROCNO 1
Date_ 20140214
Time_ 4.49
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 6144
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 305.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578354 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

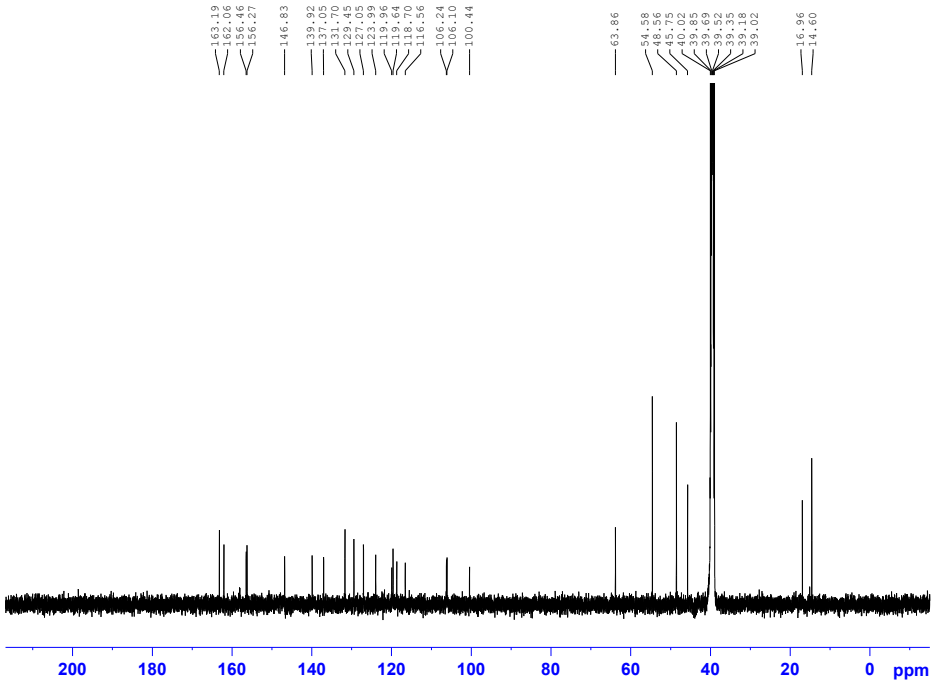
^{1}H, ^{13}C NMR spectra of compound **9r**

35970




```
NAME                14.03.28
EXPNO                      4
PROCNO                     1
Date_               20130423
Time_                   9.11
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                         8
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                     456.1
DW                  60.400 usec
DE                   6.50 usec
TE                   297.3 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     12.58 usec
PL1                     0.00 dB
PL1W           10.87646866 W
SFO1           400.1324710 MHz
SI                      32768
SF             400.1300022 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

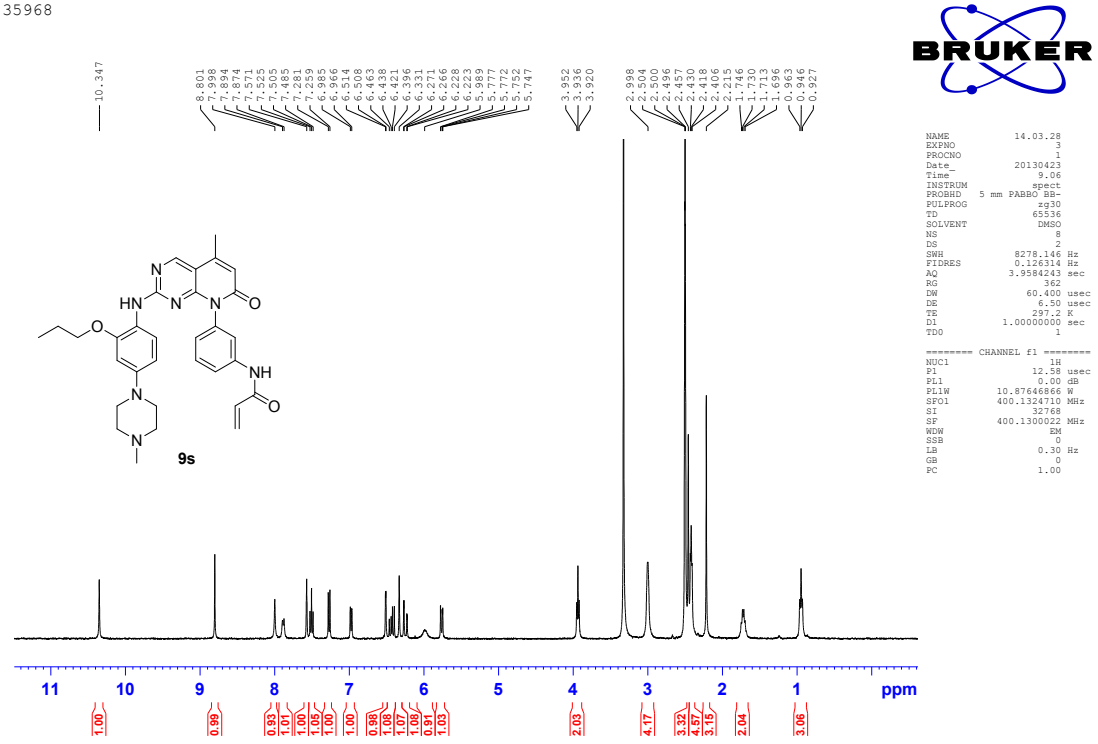
XTF-285




```
NAME                14.02.29
EXPNO                     14
PROCNO                     1
Date_               20140224
Time_                   6.03
INSTRUM                Spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      6000
DS                         4
SWH               29761.904 Hz
FIDRES            0.454131 Hz
AQ                1.1010548 sec
RG                     203
DW                  16.800 usec
DE                   6.50 usec
TE                   298.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      13C
P1                     13.84 usec
PL1                     2.50 dB
PL1W           46.89624786 W
SFO1           125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                  80.00 usec
PL2                     2.50 dB
PL12                   17.40 dB
PL13                   17.40 dB
PL2W           13.02359581 W
PL12W           0.42143536 W
PL13W           0.42143536 W
SFO2           500.1320005 MHz
SI                      32768
SF             125.7578517 MHz
WDW                       EM
SSB                        0
LB                      1.00 Hz
GB                         0
PC                      1.40
```

^{1}H, ^{13}C NMR spectra of compound **9s**

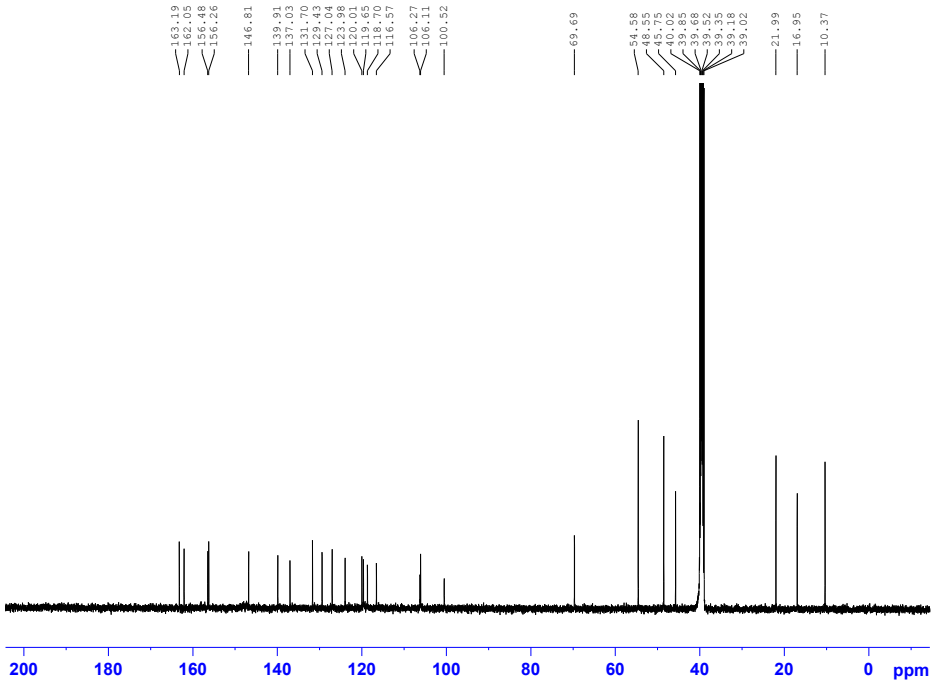
35968



NAME 14.03.28
EXPNO 3
PROCNO 1
Date_ 20130423
Time_ 9.06
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-287



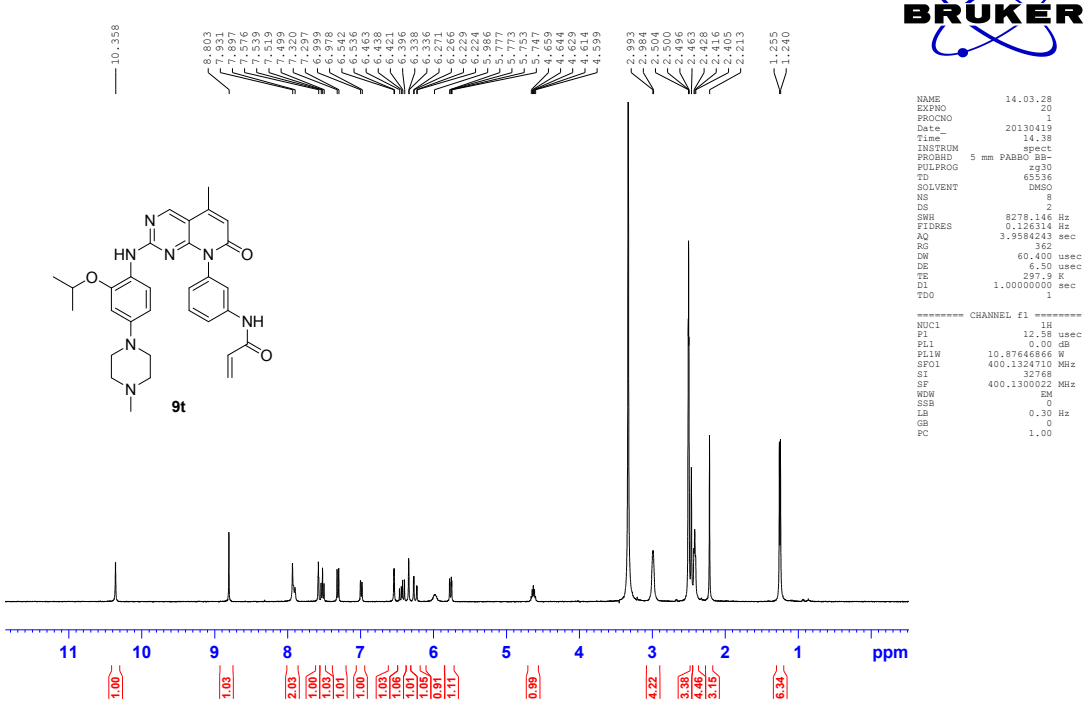
NAME 14.02.29
EXPNO 11
PROCNO 1
Date_ 20140223
Time_ 1.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 6000
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578518 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

^{1}H, ^{13}C NMR spectra of compound **9t**

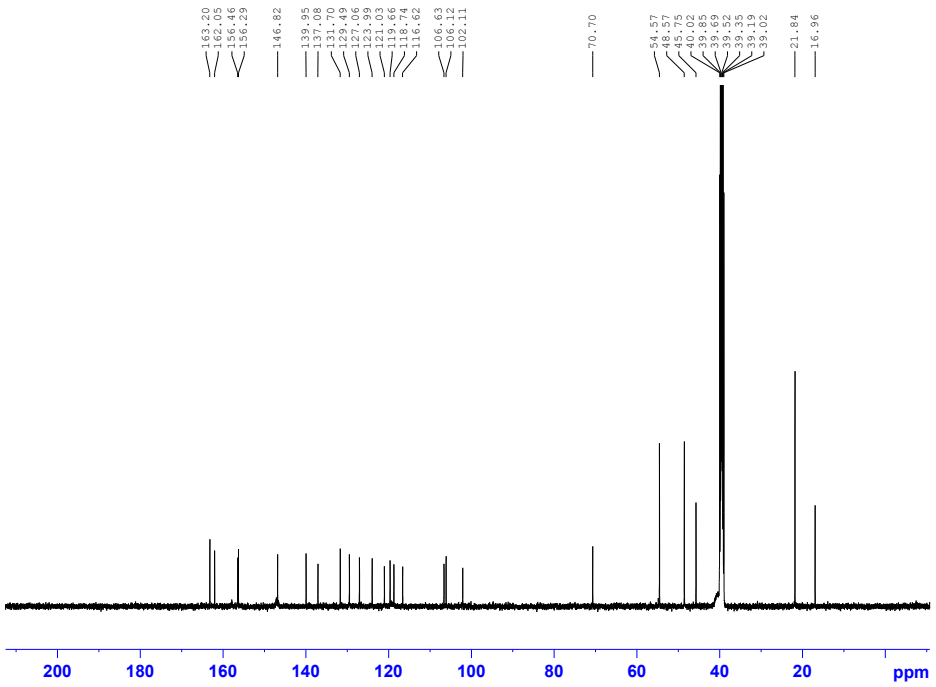
35966



NAME 14.03.28
EXPNO 20
PROCNO 1
Date_ 20130419
Time_ 14.38
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.50 usec
TE 297.9 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 12.58 usec
PL1 0.00 dB
PL1W 10.87646866 W
SFO1 400.1324710 MHz
SI 32768
SF 400.1300022 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

XTF-286



NAME 14.02.29
EXPNO 13
PROCNO 1
Date_ 20140223
Time_ 20.53
INSTRUM Spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 6000
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 13.84 usec
PL1 2.50 dB
PL1W 46.89624786 W
SFO1 125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.50 dB
PL12 17.40 dB
PL13 17.40 dB
PL2W 13.02359581 W
PL12W 0.42143536 W
PL13W 0.42143536 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578514 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

The Kinase Profiling Results of Compound 9f

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
AAK1	100
ABL1(E255K)-phosphorylated	56
ABL1(F317I)-nonphosphorylated	87
ABL1(F317I)-phosphorylated	100
ABL1(F317L)-nonphosphorylated	74
ABL1(F317L)-phosphorylated	100
ABL1(H396P)-nonphosphorylated	100
ABL1(H396P)-phosphorylated	78
ABL1(M351T)-phosphorylated	84
ABL1(Q252H)-nonphosphorylated	75
ABL1(Q252H)-phosphorylated	84
ABL1(T315I)-nonphosphorylated	82
ABL1(T315I)-phosphorylated	82
ABL1(Y253F)-phosphorylated	100
ABL1-nonphosphorylated	65
ABL1-phosphorylated	88
ABL2	92
ACVR1	92
ACVR1B	96
ACVR2A	100
ACVR2B	88
ACVRL1	95
ADCK3	86
ADCK4	95
AKT1	76
AKT2	96
AKT3	100
ALK	92
ALK(C1156Y)	75
ALK(L1196M)	100
AMPK-alpha1	100
AMPK-alpha2	85
ANKK1	98
ARK5	100
ASK1	94
ASK2	84
AURKA	98
AURKB	82
AURKC	98
AXL	100
BIKE	94
BLK	68
BMPR1A	100
BMPR1B	91
BMPR2	99
BMX	83
BRAF	92
BRAF(V600E)	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
BRK	93
BRSK1	100
BRSK2	100
BTK	100
BUB1	93
CAMK1	100
CAMK1D	100
CAMK1G	100
CAMK2A	94
CAMK2B	100
CAMK2D	100
CAMK2G	100
CAMK4	100
CAMKK1	100
CAMKK2	100
CASK	68
CDC2L1	100
CDC2L2	100
CDC2L5	99
CDK11	98
CDK2	100
CDK3	76
CDK4-cyclinD1	100
CDK4-cyclinD3	89
CDK5	100
CDK7	83
CDK8	100
CDK9	99
CDKL1	97
CDKL2	100
CDKL3	92
CDKL5	78
CHEK1	96
CHEK2	98
CIT	92
CLK1	78
CLK2	100
CLK3	100
CLK4	81
CSF1R	100
CSF1R-autoinhibited	93
CSK	100
CSNK1A1	78
CSNK1A1L	100
CSNK1D	99
CSNK1E	100
CSNK1G1	93
CSNK1G2	100
CSNK1G3	86

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
CSNK2A1	80
CSNK2A2	100
CTK	100
DAPK1	88
DAPK2	97
DAPK3	98
DCAMKL1	65
DCAMKL2	100
DCAMKL3	100
DDR1	84
DDR2	89
DLK	89
DMPK	75
DMPK2	91
DRAK1	90
DRAK2	100
DYRK1A	91
DYRK1B	100
DYRK2	90
EGFR	40
EGFR(E746-A750del)	70
EGFR(G719C)	77
EGFR(G719S)	56
EGFR(L747-E749del, A750P)	19
EGFR(L747-S752del, P753S)	33
EGFR(L747-T751del,Sins)	27
EGFR(L858R)	28
EGFR(L858R,T790M)	0.3
EGFR(L861Q)	26
EGFR(S752-I759del)	47
EGFR(T790M)	0.2
EIF2AK1	100
EPHA1	100
EPHA2	80
EPHA3	100
EPHA4	99
EPHA5	94
EPHA6	100
EPHA7	100
EPHA8	100
EPHB1	100
EPHB2	98
EPHB3	100
EPHB4	96
EPHB6	79
ERBB2	75
ERBB3	100
ERBB4	33
ERK1	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
ERK2	98
ERK3	100
ERK4	100
ERK5	100
ERK8	100
ERN1	78
FAK	100
FER	93
FES	100
FGFR1	89
FGFR2	85
FGFR3	86
FGFR3(G697C)	100
FGFR4	100
FGR	100
FLT1	98
FLT3	96
FLT3(D835H)	82
FLT3(D835Y)	100
FLT3(ITD)	100
FLT3(K663Q)	100
FLT3(N841I)	100
FLT3(R834Q)	95
FLT3-autoinhibited	94
FLT4	79
FRK	98
FYN	98
GAK	100
GCN2(Kin.Dom.2,S808G)	79
GRK1	77
GRK4	86
GRK7	85
GSK3A	100
GSK3B	98
HASPIN	88
HCK	100
HIPK1	75
HIPK2	80
HIPK3	87
HIPK4	100
HPK1	96
HUNK	95
ICK	100
IGF1R	95
IKK-alpha	92
IKK-beta	98
IKK-epsilon	100
INSR	80
INSRR	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
IRAK1	100
IRAK3	100
IRAK4	87
ITK	70
JAK1(JH1domain-catalytic)	100
JAK1(JH2domain-pseudokinase)	68
JAK2(JH1domain-catalytic)	74
JAK3(JH1domain-catalytic)	11
JNK1	73
JNK2	86
JNK3	99
KIT	97
KIT(A829P)	82
KIT(D816H)	83
KIT(D816V)	83
KIT(L576P)	87
KIT(V559D)	79
KIT(V559D,T670I)	95
KIT(V559D,V654A)	98
KIT-autoinhibited	80
LATS1	100
LATS2	91
LCK	96
LIMK1	96
LIMK2	100
LKB1	95
LOK	100
LRRK2	89
LRRK2(G2019S)	94
LTK	100
LYN	100
LZK	100
MAK	100
MAP3K1	79
MAP3K15	95
MAP3K2	73
MAP3K3	100
MAP3K4	100
MAP4K2	100
MAP4K3	100
MAP4K4	85
MAP4K5	92
MAPKAPK2	90
MAPKAPK5	100
MARK1	97
MARK2	79
MARK3	100
MARK4	92
MAST1	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
MEK1	100
MEK2	76
MEK3	73
MEK4	100
MEK5	76
MEK6	99
MELK	87
MERTK	77
MET	100
MET(M1250T)	73
MET(Y1235D)	100
MINK	100
MKK7	76
MKNK1	79
MKNK2	88
MLCK	100
MLK1	100
MLK2	100
MLK3	100
MRCKA	100
MRCKB	98
MST1	99
MST1R	100
MST2	100
MST3	100
MST4	74
MTOR	100
MUSK	85
MYLK	72
MYLK2	96
MYLK4	100
MYO3A	100
MYO3B	99
NDR1	92
NDR2	97
NEK1	100
NEK10	88
NEK11	89
NEK2	100
NEK3	74
NEK4	98
NEK5	90
NEK6	100
NEK7	100
NEK9	100
NIK	100
NIM1	100
NLK	96
OSR1	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
p38-alpha	100
p38-beta	94
p38-delta	98
p38-gamma	76
PAK1	91
PAK2	94
PAK3	100
PAK4	90
PAK6	100
PAK7	100
PCTK1	90
PCTK2	100
PCTK3	100
PDGFRA	100
PDGFRB	95
PDPK1	100
PFCDPK1(P.falciparum)	86
PFPK5(P.falciparum)	88
PFTAIRE2	100
PFTK1	91
PHKG1	100
PHKG2	94
PIK3C2B	97
PIK3C2G	88
PIK3CA	81
PIK3CA(C420R)	71
PIK3CA(E542K)	80
PIK3CA(E545A)	49
PIK3CA(E545K)	66
PIK3CA(H1047L)	97
PIK3CA(H1047Y)	54
PIK3CA(I800L)	61
PIK3CA(M1043I)	100
PIK3CA(Q546K)	81
PIK3CB	96
PIK3CD	100
PIK3CG	70
PIK4CB	100
PIM1	88
PIM2	100
PIM3	98
PIP5K1A	80
PIP5K1C	100
PIP5K2B	100
PIP5K2C	100
PKAC-alpha	99
PKAC-beta	99
PKMYT1	83
PKN1	100

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
PKN2	93
PKNB(M.tuberculosis)	100
PLK1	87
PLK2	55
PLK3	82
PLK4	82
PRKCD	88
PRKCE	100
PRKCH	95
PRKCI	100
PRKCQ	100
PRKD1	100
PRKD2	99
PRKD3	96
PRKG1	93
PRKG2	97
PRKR	81
PRKX	100
PRP4	92
PYK2	100
QSK	63
RAF1	85
RET	97
RET(M918T)	78
RET(V804L)	76
RET(V804M)	100
RIOK1	90
RIOK2	100
RIOK3	100
RIPK1	100
RIPK2	97
RIPK4	97
RIPK5	100
ROCK1	97
ROCK2	82
ROS1	100
RPS6KA4(Kin.Dom.1-N-terminal)	88
RPS6KA4(Kin.Dom.2-C-terminal)	98
RPS6KA5(Kin.Dom.1-N-terminal)	80
RPS6KA5(Kin.Dom.2-C-terminal)	100
RSK1(Kin.Dom.1-N-terminal)	100
RSK1(Kin.Dom.2-C-terminal)	100
RSK2(Kin.Dom.1-N-terminal)	78
RSK2(Kin.Dom.2-C-terminal)	99
RSK3(Kin.Dom.1-N-terminal)	100
RSK3(Kin.Dom.2-C-terminal)	100
RSK4(Kin.Dom.1-N-terminal)	67
RSK4(Kin.Dom.2-C-terminal)	98
S6K1	81

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
SBK1	86
SGK	100
SgK110	86
SGK2	99
SGK3	92
SIK	100
SIK2	100
SLK	99
SNARK	100
SNRK	96
SRC	84
SRMS	79
SRPK1	73
SRPK2	100
SRPK3	99
STK16	100
STK33	100
STK35	100
STK36	78
STK39	100
SYK	100
TAK1	88
TAOK1	100
TAOK2	49
TAOK3	83
TBK1	66
TEC	100
TESK1	100
TGFBR1	86
TGFBR2	100
TIE1	87
TIE2	97
TLK1	100
TLK2	93
TNIK	100
TNK1	100
TNK2	95
TNNI3K	100
TRKA	96
TRKB	86
TRKC	96
TRPM6	73
TSSK1B	100
TTK	94
TXK	74
TYK2(JH1domain-catalytic)	76
TYK2(JH2domain-pseudokinase)	100
TYRO3	97
ULK1	78

Target	XTF-262
Gene Symbol	%Ctrl @ 100nM
ULK2	83
ULK3	87
VEGFR2	84
VRK2	85
WEE1	98
WEE2	99
WNK1	84
WNK3	85
YANK1	100
YANK2	96
YANK3	100
YES	95
YSK1	95
YSK4	100
ZAK	100
ZAP70	89

Fig. S4. the kinase profiling results of compound **9f (XTF-262)** at 100nM.