Supplementary Information

Discovery of Anilinopyrimidine-Based Naphthamide Derivatives as Potent VEGFR-2 Inhibitors

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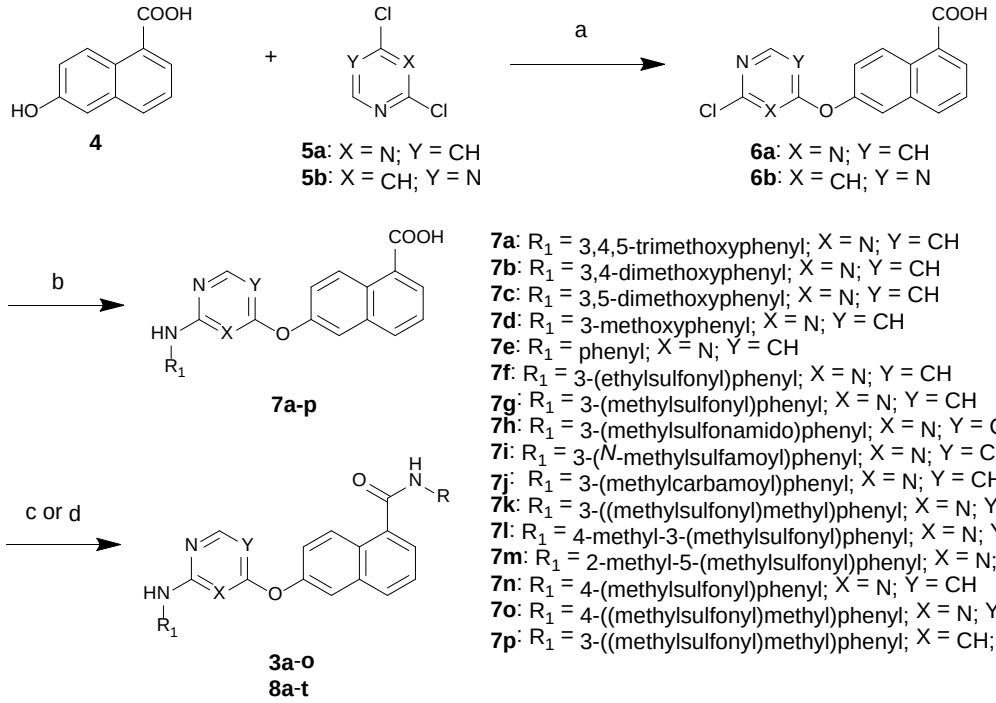
Synthesis of compounds

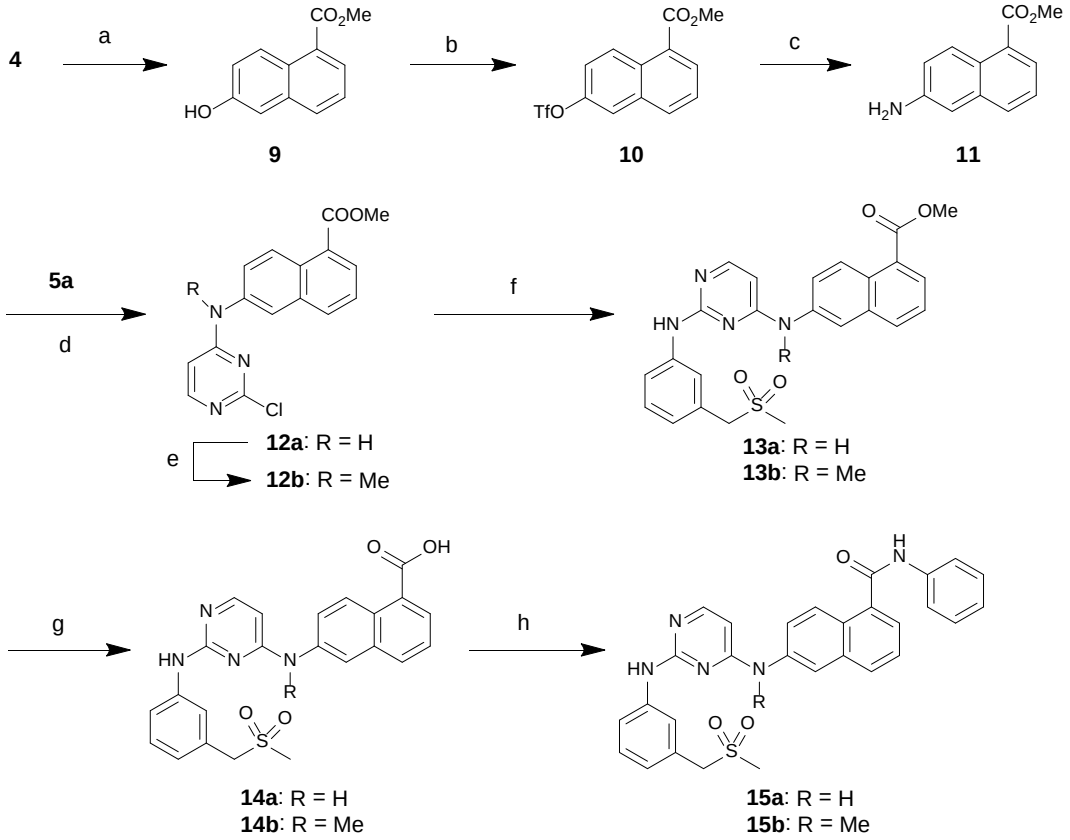
The compounds listed in Tables 1−4 were synthesized according to the following Schemes.

Scheme 1 Synthesis of Naphthamides **3a-o**, **8a-t**[a]



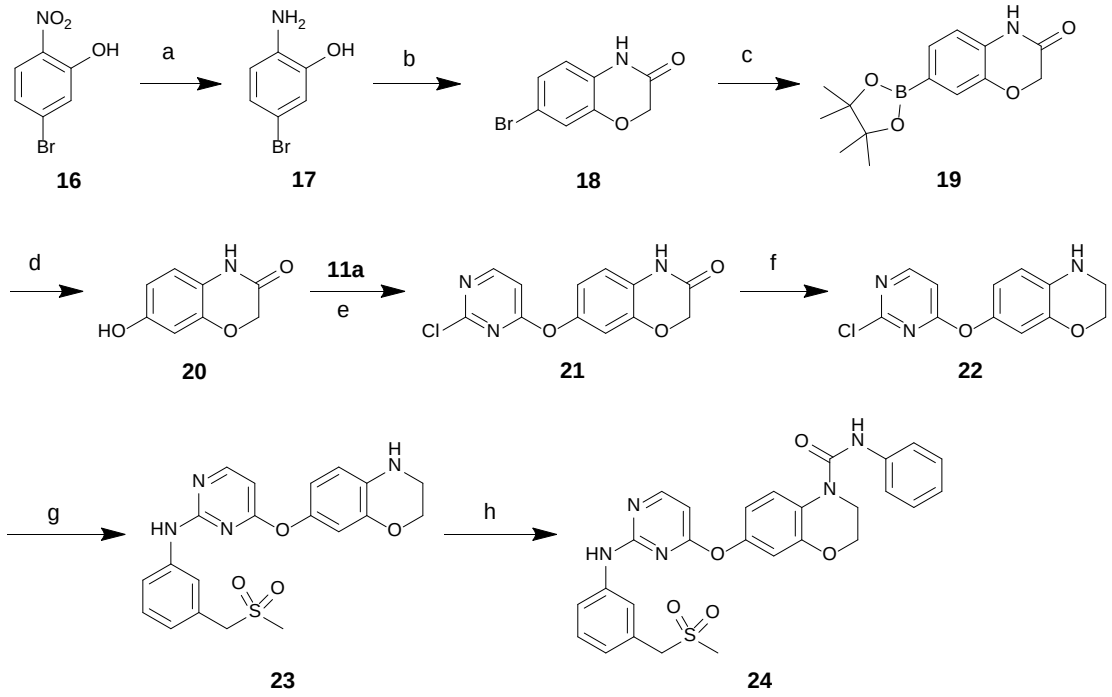
Scheme 1 Synthesis of Naphthamides **3a-o**, **8a-t**. [a]*Reagents and conditions*: (a) DBU, DMSO, rt, 60-76%; (b) R_1NH_2, conc. HCl, *i*-PrOH, reflux, 43-97%; (c) RNH_2, T3P, Et_3N, DMAP, DMF, rt, 33-94%; (d) CDI, DMF, 60 °C, 0.5 h; ammonium hydroxide, rt, 75%.

Scheme 2 Synthesis of Naphthamides **15a-b**[a]



Scheme 2 Synthesis of Naphthamides **15a-b**. [a]*Reagents and conditions*: (a) $SOCl_2$, MeOH, reflux, 99%; (b) Tf_2O, DIPEA, DCM, -78 °C, 93%; (c) $Pd_2(dba)_3$, K_3PO_4, 2-(dicyclohexylphosphino)biphenyl, benzophenone imine, DME, 90 °C, 3h; then 2 N aqueous HCl, rt, 76%; (d) DIPEA, *i*-PrOH, 120 °C, 74%; (e) MeI, Cs_2CO_3, DMF, rt, 95%; (f) 3-((methylsulfonyl)methyl)aniline, conc. HCl, *i*-PrOH, reflux, 75-98%; (g) 6 N aqueous NaOH, DMF, 80 °C, 86-94%; (h) $PhNH_2$, T3P, Et_3N, DMAP, DMF, rt, 57-74%.

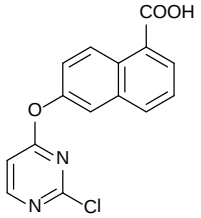
Scheme 3 Synthesis of 2,3-Dihydro-1,4-benzoxazine **24**[a]



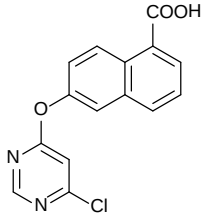
Scheme 3 Synthesis of 2,3-Dihydro-1,4-benzoxazine **24**. [a]*Reagents and conditions*: (a) Fe, NH_4Cl, EtOH, H_2O, 70 °C, 70%; (b) chloroacetylchloride, Cs_2CO_3, MeCN, rt, 82%; (c) $Pd(dppf)Cl_2$, AcOK, bis(pinacolato)-diboron, dioxane, 100 °C, 88%; (d) aqueous H_2O_2, HOAc, rt, 89%; (e) DBU, DMSO, rt, 89%; (f) BH_3·THF, THF, reflux, 55%; (g) 3-((methylsulfonyl)methyl)aniline, conc. HCl, *i*-PrOH, reflux, 55%; (h) PhNCO, Et_3N, DMF, 70 °C, 62%.

Experimental details

Unless otherwise noted, all starting materials and reagents were obtained commercially and used without further purification. Melting points (uncorrected) were measured on a Büchi B-510 melting point apparatus. ^{1}H NMR spectra were recorded on either a Varian Mercury 300 NMR or a Varian Mercury 400 NMR spectrometer. ^{13}C NMR were recorded on a Bruker AVANCE III 500 NMR spectrometer. Chemical shifts are given in unit of δ (ppm), and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; br s, broad singlet; m, multiplet. Trimethylsilane and the residual solvent signals were used as internal standards. Low-resolution mass spectra (ESI or EI) were recorded at an Agilent HPLC-MS (1260-6120B) spectrometer or an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Waters Q-Tof Ultima apparatus. The purity of the bioactive analogues were determined on an Agilent Technologies 1260 series HPLC system using a Agilent Eclipse Plus column (C18, 4.6×150 mm, 3.5 μm) eluting with an MeOH/H_2O gradient; flow rate: 1.0 mL/min; detection: UV 254 nM; all tested analogues have purity more than 95 %.

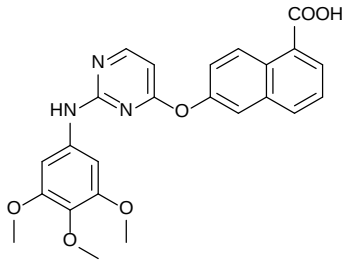


6-(2-Chloropyrimidin-4-yloxy)-1-naphthoic Acid (6a). To a stirred solution of 6-hydroxy-1-naphthoic acid (**4**, 2 g, 10.63 mmol) and 2,4-dichloropyrimidine (**5a**, 3.17 g, 21.26 mmol) in 30 mL of DMSO was added DBU (4.8 mL, 31.88 mmol) dropwise. The mixture was stirred at room temperature for 30 min. EtOAc (300mL) was added, and the mixture was extracted with 2N aqueous NaOH (3×60mL). The aqueous layer was washed with EtOAc (2×60mL) then acidified with 6N aqueous HCl to provide a white suspension. The resulting precipitate was filtered and washed with water, dried in vacuo to provide the title compound (1.92 g, 60%) as a pale yellow solid. Mp 210-212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.28 (d, J = 6.3 Hz, 1H), 7.57 (dd, J = 9.6, 2.4 Hz, 1H), 7.63-7.68 (m, 1H), 7.93 (d, J = 2.4 Hz, 1H), 8.16-8.19 (m, 2H), 8.66 (d, J = 5.4 Hz, 1H), 8.97 (d, J = 9.3 Hz, 1H), 13.25 (br, 1H); MS (ESI) m/z 299.0 $[M - H]^-$.



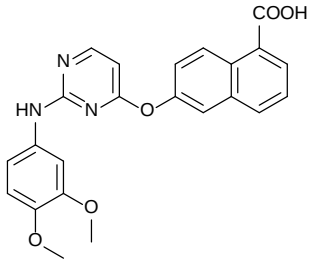
6-(6-Chloropyrimidin-4-yloxy)-1-naphthoic Acid (6b). The title compound was prepared from 4,6-dichloropyrimidine (**5b**) using a method analogous to the

preparation of compound **6a**, as an off-white solid (1.22 g, 76%); mp 180-181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.53 (d, J = 0.8 Hz, 1H), 7.57 (dd, J = 9.6, 2.8 Hz, 1H), 7.63-7.67 (m, 1H), 7.92 (d, J = 2.4 Hz, 1H), 8.16-8.19 (m, 2H), 8.67 (d, J = 0.8 Hz, 1H), 8.98 (d, J = 9.2 Hz, 1H), 13.30 (br s, 1H); MS (ESI) m/z 299.0 $[M - H]^-$.

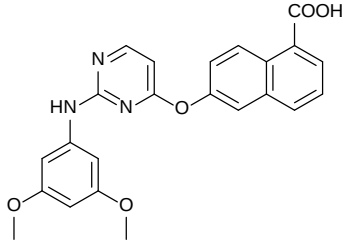


6-(2-((3,4,5-Trimethoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7a). To a solution of 6-(2-chloropyrimidin-4-yloxy)-1-naphthoic acid (**6a**, 100 mg, 0.33 mmol) and 3,4,5-trimethoxyaniline (91 mg, 0.50 mmol) in *i*-PrOH (5 mL) was added 1 drop of conc. HCl and the mixture heated to refluxfor 10 h.The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with a 100:2:0.2 (V/V/V) mixture of CH_2Cl_2/MeOH/HOAc to give the title compound (98 mg, 66%) as an off-white solid; mp 214-216 °C; ^{1}H NMR (400 MHz, DMSO-d_6 and D_2O) δ (ppm): 3.26 (s, 6H), 3.49 (s, 3H), 6.57 (d, J = 5.6 Hz, 1H), 6.87 (s, 2H), 7.53 (dd, J = 9.2, 2.4 Hz, 1H), 7.61-7.65 (m, 1H), 7.88 (d, J = 2.4 Hz, 1H), 8.12-8.14 (m, 2H), 8.41 (d, J = 5.6 Hz, 1H), 8.92 (d, J = 9.6 Hz, 1H); MS (ESI) m/z 446.1 $[M - H]^-$.

The following compounds **7b-o** were similarly prepared using the corresponding anilines.

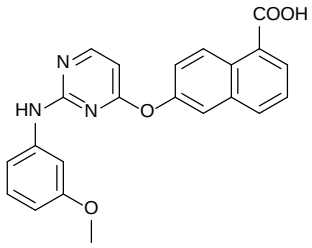


6-(2-((3,4-Dimethoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7b). Pink solid (88 mg, 63%); mp 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.29 (s, 3H), 3.57 (s, 3H), 6.43 (s, 1H), 6.51 (d, J = 5.6 Hz, 1H), 6.94 (s, 1H), 7.11 (s, 1H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.62-7.66 (m, 1H), 7.90 (d, J = 2.4 Hz, 1H), 8.15-8.17 (m, 2H), 8.37 (d, J = 5.6 Hz, 1H), 8.95 (d, J = 9.6 Hz, 1H), 9.35 (s, 1H), 13.26 (br s, 1H); MS (ESI) m/z 416.1 $[M - H]^-$.

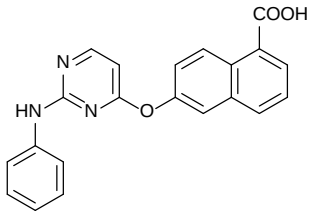


6-(2-((3,5-Dimethoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7c).

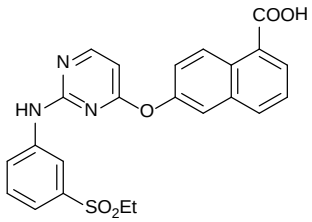
Brown yellow solid (135 mg,97%); mp 204-206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.38 (s, 6H), 5.96 (s, 1H), 6.57 (d, J = 5.6 Hz, 1H), 6.76 (s, 2H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.61-7.65 (m, 1H), 7.89 (d, J = 2.8 Hz, 1H), 8.15-8.17 (m, 2H), 8.42 (d, J = 5.6 Hz, 1H), 8.96 (d, J = 9.6 Hz, 1H), 9.51 (s, 1H); MS (ESI) m/z 416.0 $[M - H]^-$.



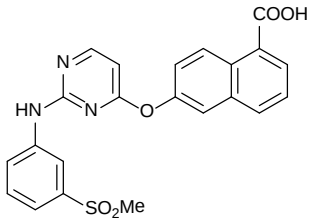
6-(2-((3-Methoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7d). Brown yellow solid (80 mg, 62%); mp 232-234 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.17 (s, 3H), 6.36 (dd, J = 8.1, 1.8 Hz, 1H), 6.56 (d, J = 5.7 Hz, 1H), 6.81 (t, J = 8.1 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 7.56 (dd, J = 9.3, 2.4 Hz, 1H), 7.61-7.66 (m, 1H), 7.91 (d, J = 2.1 Hz, 1H), 8.15-8.18 (m, 2H), 8.41 (d, J = 5.7 Hz, 1H), 8.98 (d, J = 9.3 Hz, 1H), 9.52 (s, 1H); MS (ESI) m/z 386.1 $[M - H]^-$.



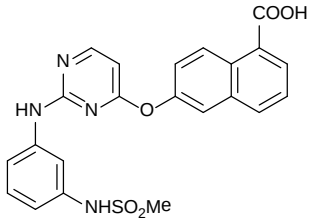
6-(2-(Phenylamino)pyrimidin-4-yloxy)-1-naphthoic Acid (7e). White solid (51 mg, 43%); mp 230-232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.56 (d, J = 5.6 Hz, 1H), 6.76 (m, 1H), 6.88 (m, 2H), 7.41-7.42 (m, 2H), 7.59 (dd, J = 9.6, 2.8 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 8.17-8.20 (m, 2H), 8.40 (d, J = 5.6 Hz, 1H), 8.99 (d, J = 9.2 Hz, 1H), 9.57 (s, 1H); MS (ESI) m/z 356.0 $[M - H]^-$.



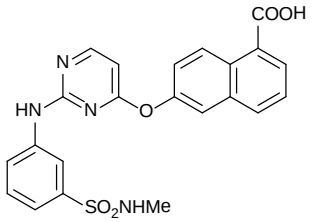
6-(2-((3-(Ethylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7f). White solid (109 mg, 73%); mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.02 (t, J = 7.2 Hz, 3H), 3.08 (q, J = 7.2 Hz, 2H), 6.64 (d, J = 5.6 Hz, 1H), 7.14 (m, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.59 (dd, J = 9.6, 2.4 Hz, 1H), 7.63-7.67 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.93 (d J = 2.4 Hz, 1H), 7.59 (dd, J = 9.6, 2.4 Hz, 1H), 7.63-7.67 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 8.10 (s, 1H), 8.17-8.19 (m, 2H), 8.47 (d, J = 5.6 Hz, 1H), 8.98 (d, J = 9.2 Hz, 1H), 9.95 (s, 1H), 13.27 (br s, 1H); MS (ESI) m/z 448.1 $[M - H]^-$.



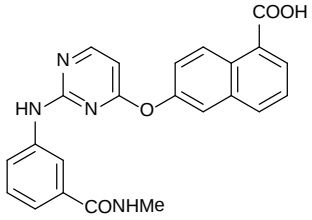
6-(2-((3-(Methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7g). White solid (79 mg, 54%); mp 196-197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.03 (s, 3H), 6.64 (d, J = 6.0 Hz, 1H), 7.10 (m, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.59 (dd, J = 9.6, 2.0 Hz, 1H), 7.62-7.67 (m, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 8.10-8.21 (m, 3H), 8.47 (d, J = 5.6 Hz, 1H), 8.98 (d, J = 9.2 Hz, 1H), 9.95 (s, 1H); MS (ESI) m/z 434.0 $[M - H]^-$.



6-(2-((3-(Methylsulfonamido)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7h). Off-white solid (92 mg, 61%); mp 190-191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.93 (s, 3H), 6.53 (d, J = 5.2 Hz, 1H), 6.66-6.68 (m, 1H), 6.79 (m, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.57 (dd, J = 9.6, 2.8 Hz, 1H), 7.62-7.66 (m, 1H), 7.92 (d, J = 2.8 Hz, 1H), 8.16-8.19 (m, 2H), 8.39 (d, J = 5.6 Hz, 1H), 8.97 (d, J = 9.2 Hz, 1H), 9.58 (s, 1H), 9.60 (s, 1H); MS (ESI) m/z 451.1 $[M + H]^+$.

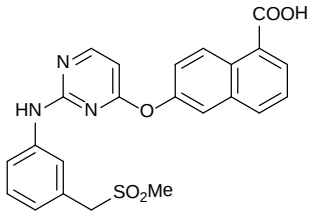


6-(2-((3-(*N*-Methylsulfamoyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7i). White solid (109 mg, 73%); mp 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.36 (d, J = 4.8 Hz, 3H), 6.61 (d, J = 5.6 Hz, 1H), 7.06 (m, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.34 (q, J = 4.8 Hz, 1H), 7.59 (dd, J = 9.2, 2.4 Hz, 1H), 7.63-7.67 (m, 1H), 7.78 (dd, J = 8.0, 1.2 Hz, 1H), 7.93 (d, J = 2.8 Hz, 1H), 8.03 (s, 1H), 8.16-8.19 (m, 2H), 8.45 (d, J = 5.6 Hz, 1H), 8.98 (d, J = 9.6 Hz, 1H), 9.88 (s, 1H); MS (ESI) m/z 449.1 $[M - H]^-$.



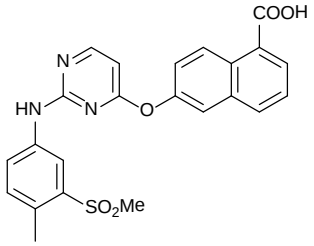
6-(2-((3-(Methylcarbamoyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic

Acid(7j). White solid (114 mg, 83%); mp 216-218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.71 (d, J = 4.5 Hz, 3H), 6.56 (d, J = 5.4 Hz, 1H), 6.87-6.91 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.58 (dd, J = 9.3, 2.7 Hz, 1H), 7.61-7.66 (m, 2H), 7.91-7.92 (m, 2H), 8.15-8.17 (m, 2H), 8.22 (q, J = 4.2 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H), 8.97 (d, J = 9.3 Hz, 1H), 9.67 (s, 1H); MS (ESI) m/z 413.1 $[M - H]^-$.



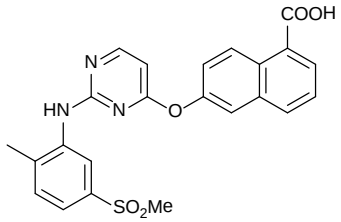
6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7k). Brown yellow solid (480 mg, 64%); mp 202-204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.80 (s, 3H), 4.10 (s, 2H), 6.57 (d, J = 5.4 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.87-6.94 (m, 1H), 7.45-7.48 (m, 2H), 7.58 (dd, J = 9.3, 2.4 Hz, 1H), 7.62-7.67 (m, 1H), 7.92 (d, J = 2.7 Hz, 1H), 8.16-8.19 (m, 2H), 8.41 (d, J = 5.7 Hz, 1H), 9.98 (d, J = 9.6 Hz, 1H), 9.66 (s, 1H); MS (ESI) m/z 450.1 $[M + H]^+$.

The corresponding 3-((methylsulfonyl)methyl)aniline used was prepared according to the literature procedure.[1]



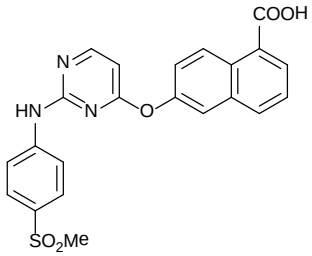
6-(2-((4-Methyl-3-(methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7l). Off-white solid (122 mg, 82%); mp 210-211 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.42 (s, 3H), 3.05 (s, 3H), 6.57 (d, J = 5.4 Hz, 1H), 6.87 (m, 1H), 7.55-7.69 (m, 3H), 7.90 (s, 1H), 8.09-8.17 (m, 3H), 8.41 (d, J = 5.4 Hz, 1H), 8.94 (d, J = 9.3 Hz, 1H), 9.81 (s, 1H); MS (ESI) m/z 448.1 $[M - H]^-$.

The corresponding4-methyl-3-(methylsulfonyl)anilineused was prepared according to the literature procedure.[2]

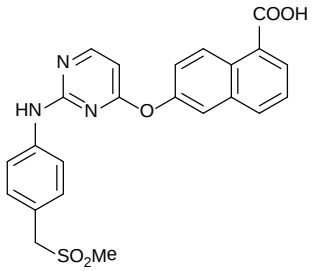


6-(2-((2-Methyl-5-(methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7m). White solid (65 mg, 44%); mp 178-180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.24 (s, 3H), 3.01 (s, 3H), 6.46 (d, J = 5.7 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.50-7.56 (m, 2H), 7.62 (m, 1H), 7.86 (d, J = 2.7 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 8.12-8.15 (m, 2H), 8.32 (d, J = 5.4 Hz, 1H), 8.91 (d, J = 9.3 Hz, 1H), 9.02 (s, 1H); MS (ESI) m/z 448.0 $[M - H]^-$.

The corresponding 2-methyl-5-(methylsulfonyl)aniline used was prepared according to the literature procedure.[3]

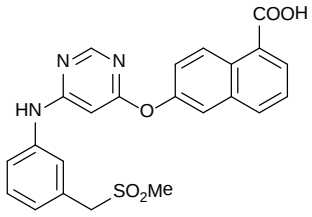


6-(2-((4-(Methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7n). Slightly yellow solid (98 mg, 68%); mp 222-224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.04 (s, 3H), 6.70 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.59-7.70 (m, 4H), 7.96 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 7.8 Hz, 2H), 8.50 (d, J = 5.7 Hz, 1H), 9.01 (d, J = 9.3 Hz, 1H), 10.10 (s, 1H), 13.25 (br s, 1H); MS (ESI) m/z 434.1 $[M - H]^-$.

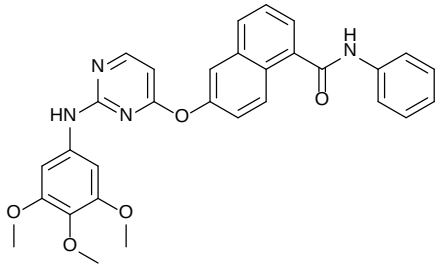


6-(2-((4-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7o). White solid (98 mg, 66%); mp 260-262 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.77 (s, 3H), 4.26 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 7.00 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 9.2, 2.4 Hz, 1H), 7.62-7.66 (m, 1H), 7.94 (d, J = 2.4 Hz, 1H), 8.17-8.18 (m, 2H), 8.42 (d, J = 6.0 Hz, 1H), 8.98 (d, J = 9.6 Hz, 1H), 9.66 (s, 1H); MS (ESI) m/z 448.0 $[M - H]^-$.

The corresponding 4-((methylsulfonyl)methyl)aniline used was prepared according to the literature procedure.[1]

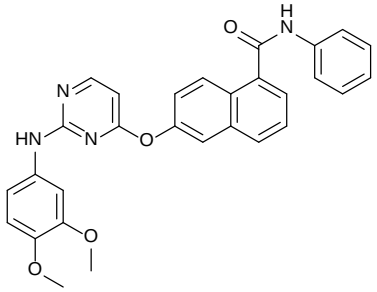


6-(6-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic Acid (7p). The title compound was prepared from 6-(6-chloropyrimidin-4-yloxy)-1-naphthoic acid (**6b**) using a method analogous to the preparation of compound **7k**, as a slightly yellow solid (106mg, 71%). Mp 234-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.93 (s, 3H), 4.48 (s, 2H), 6.24 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.33-7.37 (m, 1H), 7.53 (dd, J = 9.6, 2.4 Hz, 1H), 7.59-7.69 (m, 3H), 7.87 (d, J = 2.4 Hz, 1H), 8.15-8.19 (m, 2H), 8.38 (s, 1H), 8.96 (d, J = 9.2 Hz, 1H), 9.72 (s, 1H), 13.25 (br s, 1H); MS (ESI) m/z 448.1 $[M - H]^-$.



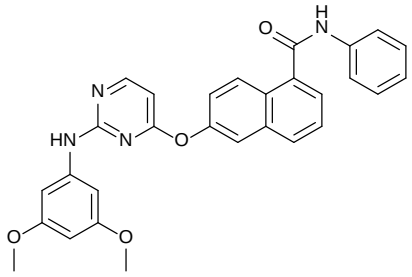
***N*-phenyl-6-(2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (3a).** To a solution of 6-(2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yloxy)-1-naphthoic acid (**7a**, 20 mg, 0.043 mmol) and aniline (6 μL, 0.064 mmol) in 0.5 mL DMF was added Et_3N (89 μL, 0.64 mmol) followed by propylphosphonic anhydride (50% T3P in EtOAc, 76 μL, 0.13 mmol) and DMAP (3 mg, 0.021 mmol). After the mixture was stirred for 5 h, water (10 mL) was added to provide a white suspension. The resulting precipitate was filtered, washed with water, and dried in vacuo to provide the title compound (19 mg, 86%) as a white solid. Mp 98-100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.31 (s, 6H), 3.50 (s, 3H), 6.56 (d, J = 5.6 Hz, 1H), 6.92 (s, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.51 (dd, J = 9.2, 2.4 Hz, 1H), 7.64-7.67 (m, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H), 7.90 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 9.2 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H), 9.44 (s, 1H), 10.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 55.08, 59.88 (2C), 96.36, 98.70 (2C), 118.38, 119.79 (2C), 122.44, 123.67, 125.09, 125.77, 127.20, 127.40, 128.63 (2C), 129.66, 132.01, 134.07, 134.43, 136.05, 139.14, 150.33, 152.32 (2C), 159.67, 159.99, 166.94, 169.03; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{26}N_4O_5Na$ $[M + Na]^+$, 545.1801, found, 545.1802. HPLC purity: 98.73%.

The following compounds **3b**-**o**, **8a**-**r**, and **8t** were similarly prepared using the corresponding acids **7b**-**p** and appropriate amine.

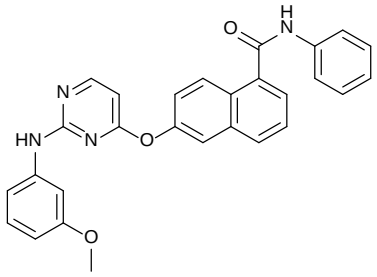


6-(2-((3,4-Dimethoxyphenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3b). Slightly yellow solid (20 mg, 42%); mp 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.35 (s, 3H), 3.59 (s, 3H), 6.50 (d, J = 5.6 Hz, 1H), 6.55-6.57 (m, 1H), 6.99-6.70 (m, 1H), 7.12-7.15 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.64-7.68 (m, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 9.36 (s, 1H), 10.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 54.87, 55.51, 97.91, 104.21, 110.78, 111.71, 118.67, 119.74 (2C), 122.85, 123.65, 125.00, 125.68, 127.02, 127.41, 128.63 (2C), 129.67, 133.48, 134.03, 134.55, 139.15, 143.56, 148.14, 150.27, 159.63, 159.96, 167.02, 169.13; HRMS (ESI) *m*/*z* calcd for

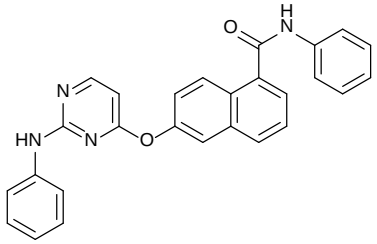
$C_{29}H_{24}N_4O_4Na$ $[M + Na]^+$, 515.1695, found, 515.1683. HPLC purity: 98.25%.



6-(2-((3,5-Dimethoxyphenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3c). White solid (21 mg, 87%); mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.42 (s, 6H), 5.98 (s, 1H), 6.56 (d, J = 5.6 Hz, 1H), 6.82 (s, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.53 (dd, J = 9.2, 2.4 Hz, 1H), 7.64-7.68 (m, 1H), 7.79 (d, J = 6.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H), 9.52 (s, 1H), 10.62 (s, 1H); HRMS (ESI) m/z calcd for $C_{29}H_{25}N_4O_4$ $[M + H]^+$, 493.1876, found, 493.1886. HPLC purity: 95.12%.

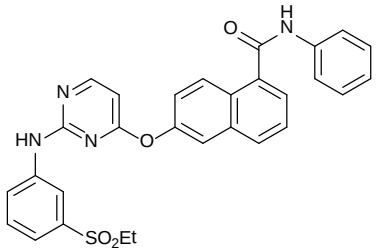


6-(2-((3-Methoxyphenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3d). Slightly yellow solid (34 mg, 94%); mp 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.45 (s, 3H), 6.39 (dd, J = 8.1, 2.1 Hz, 1H), 6.55 (d, J = 5.7 Hz, 1H), 6.88 (t, J = 8.1 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.54 (dd, J = 9.3, 3.0 Hz, 1H), 7.63-7.68 (m, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.91 (d, J = 2.7 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 5.7 Hz, 1H), 9.53 (s, 1H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 54.46, 98.51, 104.49, 106.55, 111.10, 118.72, 119.75 (2C), 122.73, 123.65, 125.05, 125.66, 127.16, 127.45, 128.64 (2C), 128.80, 129.72, 134.05, 134.52, 139.16, 141.07, 150.19, 159.19, 159.53, 159.95, 167.02, 169.15; HRMS (ESI) m/z calcd for $C_{28}H_{23}N_4O_3$ $[M + H]^+$, 463.1770, found, 463.1781. HPLC purity: 99.25%.

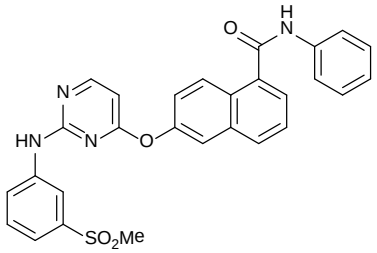


***N*-Phenyl-6-(2-(phenylamino)pyrimidin-4-yloxy)-1-naphthamide (3e).** White solid (11 mg, 46%); mp 216-218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.55 (d, J = 5.7 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 2H), 7.14 (t, J = 7.5 Hz, 1H),

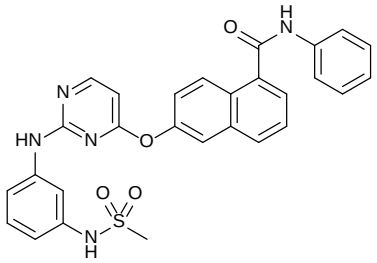
7.37 (d, *J* = 8.4 Hz, 2H), 7.42-7.46 (m, 2H), 7.54 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.64-7.69 (m, 1H), 7.79-7.81 (m, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 9.6 Hz, 1H), 8.40 (d, *J* = 5.4 Hz, 1H), 9.56 (s, 1H), 10.65 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 98.22, 118.62 (2C), 118.98, 119.77 (2C), 121.23, 122.97, 123.65, 125.04, 125.68, 127.04, 127.44, 128.03 (2C), 128.64 (2C), 129.68, 134.02, 134.59, 139.17, 139.87, 150.19, 159.49, 160.00, 167.05, 169.26; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{20}N_4O_2Na$ $[M + Na]^+$, 455.1484, found, 455.1477. HPLC purity: 99.88%.



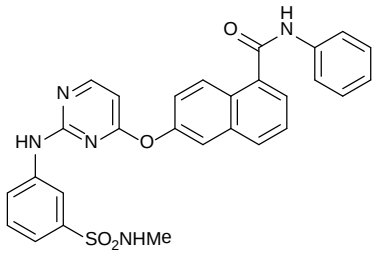
6-(2-((3-(Ethylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3f). White solid (19 mg, 83%); mp 190-192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.03 (t, *J* = 7.2 Hz, 3H), 3.10 (q, *J* = 7.2 Hz, 2H), 6.63 (d, *J* = 5.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.21-7.23 (m, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.80-7.85 (m, 4H), 7.93 (d, *J* = 2.4 Hz, 1H), 8.09-8.11 (m, 2H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 9.95 (s, 1H), 10.64 (s, 1H); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{24}N_4O_4SNa$ $[M + Na]^+$, 547.1416, found, 547.1406. HPLC purity: 99.56%.



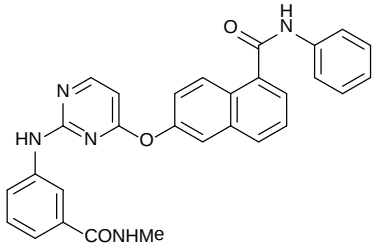
6-(2-((3-(Methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3g). White solid (16 mg, 70%); mp 188-190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.04 (s, 3H), 6.63 (d, *J* = 5.6 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.18-7.22 (m, 1H), 7.35-7.41 (m, 3H), 7.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.80-7.85 (m, 4H), 7.93 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.14 (m, 1H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.48 (d, *J* = 5.6 Hz, 1H), 9.96 (s, 1H), 10.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 43.33, 99.44, 116.34, 118.82, 119.28, 119.78 (2C), 122.74, 122.99, 123.68, 125.13, 125.76, 127.21, 127.49, 128.64 (2C), 129.20, 129.73, 134.05, 134.56, 139.13, 140.84, 140.87, 150.10, 159.22, 160.05, 167.02, 169.30; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{22}N_4O_4NaS$ $[M + Na]^+$, 533.1259, found, 533.1268. HPLC purity: 97.88%.



6-(2-((3-(Methylsulfonamido)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3h). White solid (17 mg, 74%); mp 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.94 (s, 3H), 6.53 (d, J = 5.6 Hz, 1H), 6.67-6.69 (m, 1H), 6.87 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.37-7.41 (m, 3H), 7.54 (dd, J = 9.2, 2.4 Hz, 1H), 7.65-7.68 (m, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 2.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 9.2 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 9.59 (s, 2H), 10.63 (s, 1H); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{23}N_5O_4NaS$ $[M + Na]^+$, 548.1368, found, 548.1353. HPLC purity: 98.32%.

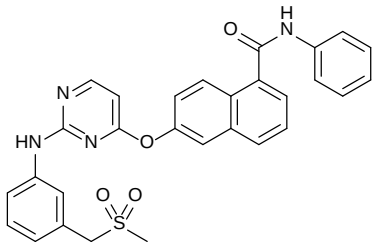


6-(2-((3-(*N*-Methylsulfamoyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3i). White solid (15 mg, 65%); mp 194-196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.37 (d, J = 5.2 Hz, 3H), 6.61 (d, J = 5.6 Hz, 1H), 7.12-7.16 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.35-7.41 (m, 3H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.78-7.82 (m, 2H), 7.84 (d, J = 7.6 Hz, 2H), 7.94 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.2 Hz, 1H), 8.45 (d, J = 5.6 Hz, 1H), 9.90 (s, 1H), 10.66 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{28}H_{23}N_5O_4NaS$ $[M + Na]^+$, 548.1368, found, 548.1373. HPLC purity: 95.00%.

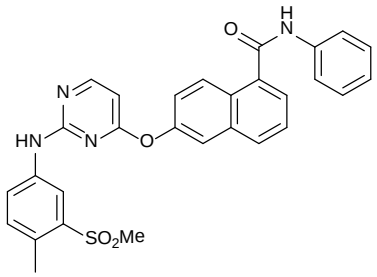


6-(2-((3-(Methylcarbamoyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3j). White solid (19 mg, 80%); mp 230-232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.70 (d, J = 4.2 Hz, 3H), 6.55 (d, J = 5.4 Hz, 1H), 6.70 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.55 (dd, J = 9.0, 2.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 2H), 7.78-7.81 (m, 1H), 7.84 (d, J = 7.8 Hz, 2H), 7.91-7.92 (m, 2H), 8.09 (d, J = 8.1 Hz, 1H), 8.24-8.25 (m, 1H), 8.30 (d, J = 9.3 Hz, 1H), 8.42 (d, J = 5.7 Hz, 1H), 9.68 (s, 1H), 10.65 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_5O_3Na$ $[M + Na]^+$, 512.1699, found, 512.1686. HPLC purity:

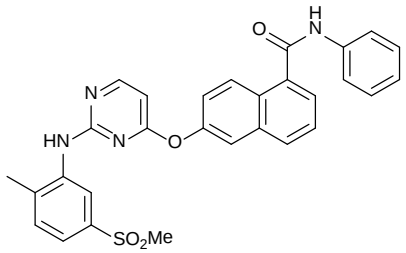
96.84%.



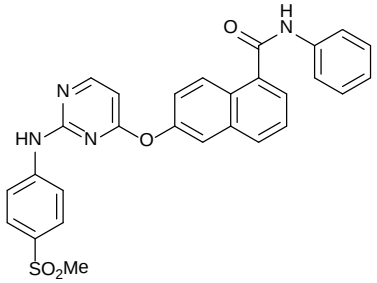
6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3k). White solid (17 mg, 74%); mp 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.56 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.97 (m, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.48-7.50 (m, 2H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.79-7.81 (m, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.41 (d, J = 6.0 Hz, 1H), 9.68 (s, 1H), 10.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.37, 59.33, 98.56, 118.84, 118.87, 119.79 (2C), 121.09, 122.93, 123.68, 124.04, 125.10, 125.76, 127.04, 127.41, 128.15, 128.63 (2C), 128.71, 129.71, 134.01, 134.55, 139.13, 140.01, 150.17, 159.49, 160.00, 167.03, 169.24; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4SNa$ $[M + Na]^+$, 547.1416, found, 547.1428. HPLC purity: 98.47%.



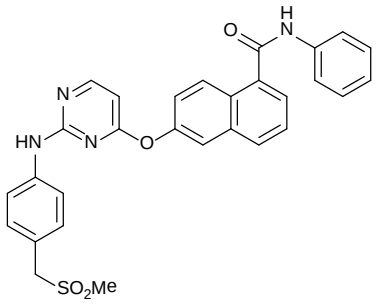
6-(2-((4-Methyl-3-(methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3l). White solid (35 mg, 86%); mp 230-232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.46 (s, 3H), 3.09 (s, 3H), 6.59 (d, J = 5.2 Hz, 1H), 6.99-7.01 (m, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.72-7.74 (m, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.92 (d, J = 2.4 Hz, 1H), 8.09-8.13 (m, 2H), 8.31 (d, J = 9.2 Hz, 1H), 8.43 (d, J = 5.6 Hz, 1H), 9.86 (s, 1H), 10.66 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 18.76, 42.99, 99.00, 118.50, 118.80, 119.76 (2C), 122.91, 123.26, 123.68, 125.06, 125.74, 127.07, 127.45, 128.64 (2C), 128.94, 129.70, 132.45, 134.03, 134.63, 138.57 (2C), 139.14, 150.12, 159.29, 160.03, 167.04, 169.26; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4NaS$ $[M + Na]^+$, 547.1416, found, 547.1409. HPLC purity: 96.56%.



6-(2-((2-Methyl-5-(methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3m). White solid (15 mg, 33%); mp 130-132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.25 (s, 3H), 3.02 (s, 3H), 6.46 (d, J = 5.2 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.37-7.42 (m, 3H), 7.49-7.54 (m, 2H), 7.63-7.67 (m, 1H), 7.77 (d, J = 6.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 2.4 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 9.04 (s, 1H), 10.60 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 18.14, 43.40, 98.69, 118.50, 119.78 (2C), 122.40, 122.53, 122.90, 123.68, 125.06, 125.72, 127.18, 127.37, 128.64 (2C), 129.70, 131.07, 133.99, 134.53, 138.20, 138.32, 138.37, 139.10, 150.70, 160.06, 160.54, 166.99, 169.47; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4NaS$ [M + Na]$^+$, 547.1416, found, 547.1407. HPLC purity: 99.03%.

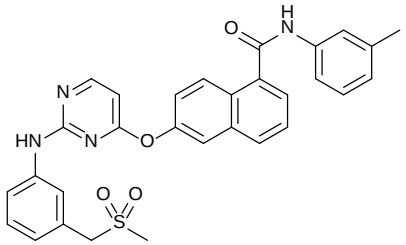


6-(2-((4-(Methylsulfonyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3n). White solid (9 mg, 39%); mp 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.08 (s, 3H), 6.68 (d, J = 5.6 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.52-7.58 (m, 3H), 7.66-7.70 (m, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.81-7.84 (m, 3H), 7.96 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 10.11 (s, 1H), 10.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 43.68, 99.82, 117.96 (2C), 118.95, 119.79 (2C), 122.83, 123.67, 125.19, 125.79, 127.24, 127.52 (2C), 128.64 (2C), 129.73, 132.29, 134.04, 134.57, 139.12, 144.64, 150.06 (2C), 158.99, 160.09, 166.98, 169.33; HRMS (ESI) *m/z* calcd for $C_{28}H_{22}N_4O_4NaS$ [M + Na]$^+$, 533.1259, found, 533.1273. HPLC purity: 97.33%.

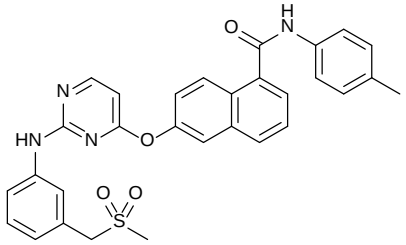


6-(2-((4-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (3o). White solid (21 mg, 91%); mp 226-228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.77 (s, 3H), 4.27 (s, 2H), 6.56 (d, J = 5.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.51-7.56 (m, 3H), 7.64-7.68 (m, 1H), 7.80 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H), 9.66 (s, 1H), 10.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 38.89, 58.95,

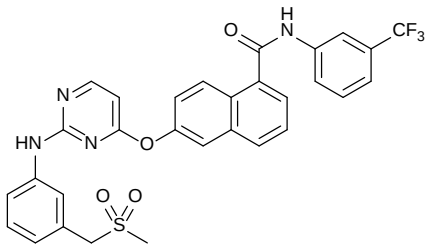
98.65, 118.69 (2C), 118.85, 119.77 (2C), 121.54, 122.85, 123.68, 125.06, 125.74, 127.08, 127.42, 128.65 (2C), 129.69, 130.70 (2C), 134.01, 134.58, 139.12, 140.11, 150.16, 159.42, 159.99, 167.05, 169.24; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4NaS$ $[M + Na]^+$, 547.1416, found, 547.1407. HPLC purity: 98.92%.



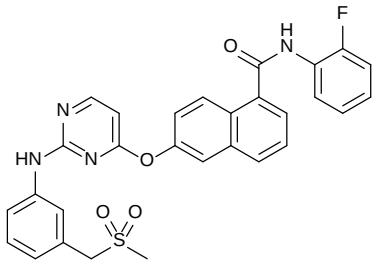
6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-(*m*-tolyl)-1-naphthamide (8a). White solid (18 mg, 75%); mp 206-208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.33 (s, 3H), 2.83 (s, 3H), 4.18 (s, 2H), 6.56 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.95-6.97 (m, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.48-7.50 (m, 2H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.64-7.68 (m, 1H), 7.71 (s, 1H), 7.78 (dd, J = 7.2, 1.2 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 9.69 (s, 1H), 10.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 12.17, 39.38, 59.32, 98.54, 117.01, 118.83, 118.86, 120.31, 121.09, 122.90, 124.04, 124.36, 125.03, 125.75, 127.03, 127.41, 128.15, 128.46, 128.71, 129.66, 134.01, 134.63, 137.81, 139.05, 140.01, 150.16, 159.49, 160.01, 166.98, 169.24; HRMS (ESI) *m/z* calcd for $C_{30}H_{26}N_4O_4NaS$ $[M + Na]^+$, 561.1572, found, 561.1559. HPLC purity: 96.14%.



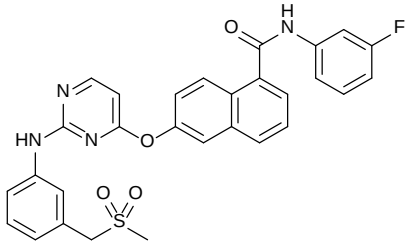
6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-(p-tolyl)-1-naphthamide (8b). White solid (16 mg, 67%); mp 218-220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H), 2.83 (s, 3H), 4.18 (s, 2H), 6.56 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.97 (m, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.48-7.50 (m, 2H), 7.54 (dd, J = 9.2, 2.8 Hz, 1H), 7.64-7.68 (m, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 6.8, 0.8 Hz, 1H), 7.91 (d, J = 2.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.2 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 9.68 (s, 1H), 10.55 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 20.42, 39.37, 59.32, 98.55, 118.85 (2C), 119.79 (2C), 121.08, 122.88, 124.04, 125.02, 125.75, 127.07, 127.43, 128.15, 128.70, 129.00 (2C), 129.63, 132.60, 134.01, 134.64, 136.63, 140.01, 150.16, 159.49, 160.01, 166.82, 169.23; HRMS (ESI) *m/z* calcd for $C_{30}H_{26}N_4O_4NaS$ $[M + Na]^+$, 561.1572, found, 561.1576. HPLC purity: 95.40%.



6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-(3-(trifluoromethyl)phenyl)-1-naphthamide (8c). White solid (19 mg, 73%); mp 188-190 °C.^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.96 (m, 1H), 7.48-7.52 (m, 3H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.62-7.71 (m, 2H), 7.86 (dd, J = 7.2, 1.2 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.34-8.36 (m, 2H), 8.41 (d, J = 5.6 Hz, 1H), 9.69 (s, 1H), 10.97 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{30}H_{23}N_4O_4NaSF_3$ $[M + Na]^+$, 615.1290, found, 615.1302. HPLC purity: 95.16%.

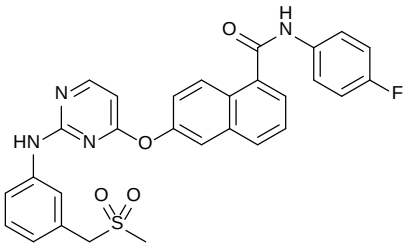


***N*-(2-Fluorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8d).** White solid (8 mg, 33%); mp 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.82 (s, 3H), 4.16 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.96 (m, 1H), 7.25-7.37 (m, 3H), 7.48-7.50 (m, 2H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.78-7.85 (m, 2H), 7.92 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 9.6 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 9.68 (s, 1H), 10.43 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4NaSF$ $[M + Na]^+$, 565.1322, found, 565.1324. HPLC purity: 99.83%.

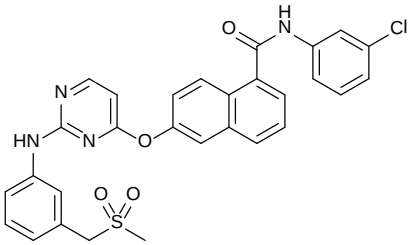


***N*-(3-Fluorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8e).** White solid (17 mg, 71%); mp 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, J = 5.2 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.96-7.00 (m, 2H), 7.40-7.50 (m, 3H), 7.54-7.59 (m, 2H), 7.66-7.70 (m, 1H), 7.81-7.84 (m, 2H), 7.93 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 9.69 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.35, 59.33, 98.54, 106.51 (d, J = 27.0 Hz), 110.15 (d, J = 20.0 Hz), 115.52, 118.81, 118.92, 121.08, 123.03, 124.04, 125.26, 125.73, 126.97, 127.33, 128.14, 128.72, 129.99, 130.30 (d, J = 8.25 Hz), 134.01,

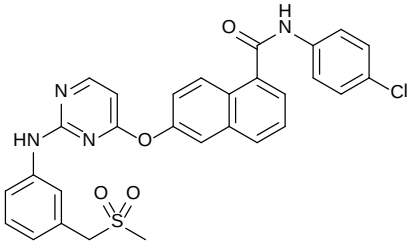
134.09, 140.01, 140.83 (d, J = 12.0 Hz), 150.22, 159.48, 160.03, 162.00 (d, J = 239.88 Hz), 167.26, 169.22; HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4FNaS$ $[M + Na]^+$, 565.1322, found, 565.1324. HPLC purity: 95.39%.



***N*-(4-Fluorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8f).** White solid (19 mg, 79%); mp 234-236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.81 (s, 3H), 4.16 (s, 2H), 6.54 (d, J = 5.7 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 6.95 (m, 1H), 7.19-7.25 (m, 2H), 7.46-7.48 (m, 2H), 7.53 (dd, J = 9.3, 3.0 Hz, 1H), 7.62-7.67 (m, 1H), 7.78-7.86 (m, 3H), 7.90 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.39 (d, J = 5.7 Hz, 1H), 9.66 (s, 1H), 10.67 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4FNaS$ $[M + Na]^+$, 565.1322, found, 565.1321. HPLC purity: 95.01%.

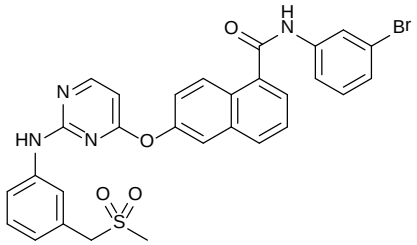


***N*-(3-Chlorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8g).** White solid (18 mg, 72%); mp 204-206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.95-6.96 (m, 1H), 7.20-7.22 (m, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.48-7.50 (m, 2H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.66-7.73 (m, 2H), 7.82 (dd, J = 6.8, 0.8 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 8.06 (t, J = 2.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 9.69 (s, 1H), 10.83 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4NaSCl$ $[M + Na]^+$, 581.1026, found, 581.1016. HPLC purity: 96.32%.

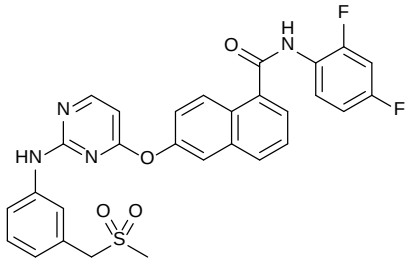


***N*-(4-chlorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8h).** White solid (20 mg, 80%); mp 236-238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.56 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 6.96 (m, 1H), 7.45-7.50 (m, 4H), 7.55 (dd, J = 9.2, 2.8 Hz, 1H), 7.65-7.69 (m, 1H), 7.81 (d, J = 6.4 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.6 Hz, 1H), 8.41 (d, J = 5.6 Hz,

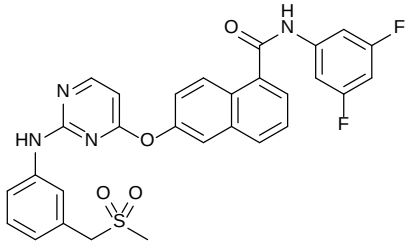
1H), 9.68 (s, 1H), 10.78 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4NaSCl$ [M + Na]$^+$, 581.1026, found, 581.1018. HPLC purity: 97.05%.



***N*-(3-Bromophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8i).** White solid (21 mg, 78%); mp 204-206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, *J* = 5.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.96 (m, 1H), 7.35-7.39 (m, 2H), 7.48-7.50 (m, 2H), 7.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.75-7.76 (m, 1H), 7.81-7.83 (m, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 9.69 (s, 1H), 10.81 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4SBr$ [M + H]$^+$, 603.0702, found, 603.0700. HPLC purity: 95.80%.

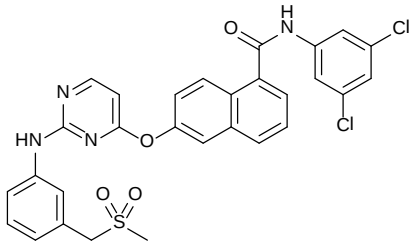


***N*-(2,4-Difluorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8j).** White solid (10 mg, 40%); mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.82 (s, 3H), 4.16 (s, 2H), 6.57 (d, *J* = 5.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.96 (m, 1H), 7.15-7.20 (m, 1H), 7.39-7.45 (m, 1H), 7.48-7.51 (m, 2H), 7.57 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.75-7.81 (m, 1H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.93 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.37 (d, *J* = 9.2 Hz, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 9.68 (s, 1H), 10.43 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{22}N_4O_4NaSF_2$ [M + Na]$^+$, 583.1228, found, 583.1226. HPLC purity: 99.69%.

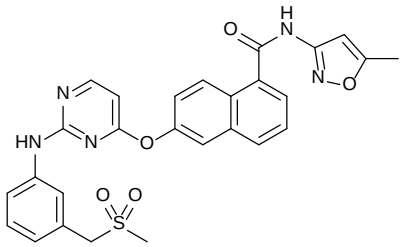


***N*-(3,5-Difluorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8k).** White solid (11 mg, 44%); mp 206-207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, *J* = 5.4 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 6.93-7.05 (m, 2H), 7.48 (s, 2H), 7.55-7.60 (m, 3H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 6.9 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 9.3 Hz, 1H), 8.41 (d, *J* = 5.7 Hz, 1H), 9.68 (s, 1H), 11.02 (s,

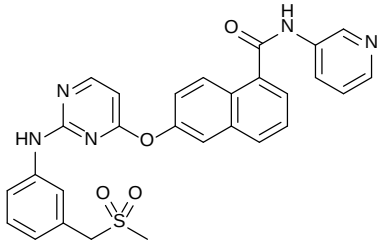
1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{23}N_4O_4SF_2$ $[M + H]^+$, 561.1408, found, 561.1419. HPLC purity: 96.08%.



***N*-(3,5-Dichlorophenyl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8l).** White solid (15 mg, 58%); mp 258-260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.17 (s, 2H), 6.57 (d, J = 6.0 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.94-6.96 (m, 1H), 7.39 (t, J = 2.0 Hz, 1H), 7.48-7.49 (m, 2H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.67-7.70 (m, 1H), 7.85 (dd, J = 7.2, 1.2 Hz, 1H), 7.93-7.94 (m, 3H), 8.13 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 5.6 Hz, 1H), 9.69 (s, 1H), 10.99 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{29}H_{22}N_4O_4NaSCl_2$ $[M + Na]^+$, 615.0637, found, 615.0644. HPLC purity: 95.71%.

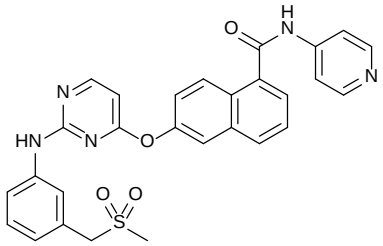


***N*-(5-methylisoxazol-3-yl)-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8m).** White solid (11 mg, 23%); mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.45 (s, 3H), 2.83 (s, 3H), 4.15 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 6.84-6.86 (m, 2H), 6.93-6.97 (m, 1H), 7.46-7.48 (m, 2H), 7.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.62-7.66 (m, 1H), 7.82 (dd, J = 6.8, 0.8 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 9.6 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 9.67 (s, 1H), 11.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 12.06, 39.37, 59.31, 96.70, 98.57, 118.83, 118.99, 121.10, 123.11, 124.02, 125.63, 125.97, 126.86, 127.41, 128.13, 128.68, 130.46, 132.56, 134.02, 140.00, 150.20, 158.24, 159.46, 160.00, 166.91, 169.24, 169.51; HRMS (ESI) *m/z* calcd for $C_{27}H_{23}N_5O_5NaS$ $[M + Na]^+$, 552.1318, found, 552.1309. HPLC purity: 97.79%.

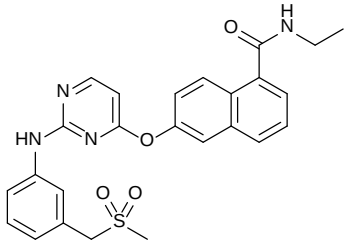


6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-(pyridin-3-yl)-1-naphthamide (8n). White solid (11 mg, 47%); mp 158-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 6.96 (m, 1H), 7.43-7.49 (m, 3H), 7.56 (dd, J = 9.2, 2.4 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.8

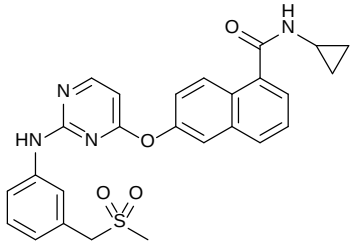
Hz, 1H), 8.27-8.29 (m, 1H), 8.34-8.36 (m, 2H), 8.41 (d, *J* = 5.6 Hz, 1H), 8.97 (s, 1H), 9.69 (s, 1H), 10.86 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.35, 59.32, 98.54, 118.81, 118.93, 121.07, 123.05, 123.57, 124.03, 125.41, 125.71, 126.76, 127.01, 127.36, 128.14, 128.72, 130.10, 133.81, 134.04, 135.79, 140.01, 141.45, 144.59, 150.23, 159.48, 160.03, 167.44, 169.23; HRMS (ESI) *m/z* calcd for $C_{28}H_{24}N_5O_4S$ $[M + H]^+$, 526.1549, found, 526.1553. HPLC purity: 96.62%.



6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-(pyridin-4-yl)-1-naphthamide (8o). White solid (20 mg, 83%); mp 150-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.18 (s, 2H), 6.57 (d, *J* = 5.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.94-6.96 (m, 1H), 7.48-7.50 (m, 2H), 7.57 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.67-7.71 (m, 1H), 7.81-7.83 (m, 2H), 7.86 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 9.2 Hz, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 8.52-8.53 (m, 2H), 9.69 (s, 1H), 11.04 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{28}H_{23}N_5O_4NaS$ $[M + Na]^+$, 548.1368, found, 548.1358. HPLC purity: 95.34%.

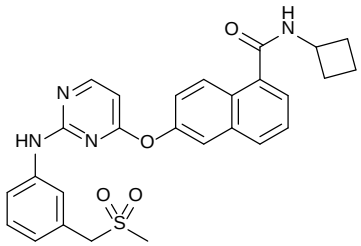


***N*-Ethyl-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8p).** White solid (15 mg, 71%); mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6 and D_2O) δ (ppm): 1.19 (t, *J* = 7.2 Hz, 3H), 2.82 (s, 3H), 3.34-3.47 (m, 2H), 4.13 (s, 2H), 6.55 (d, *J* = 5.6 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.95 (m, 1H), 7.45-7.47 (m, 2H), 7.50 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.56-7.61 (m, 2H), 7.85 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.31 (d, *J* = 9.2 Hz, 1H), 8.39 (d, *J* = 5.6 Hz, 1H), 8.61 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 14.67, 33.88, 39.37, 59.30, 98.54, 118.71, 118.81, 121.04, 122.58, 124.01, 124.59, 125.71, 127.29, 127.51, 128.14, 128.69, 129.20, 133.96, 134.87, 140.02, 150.04, 159.48, 159.97, 168.06, 169.26; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}N_4O_4NaS$ $[M + Na]^+$, 499.1416, found, 499.1404. HPLC purity: 95.58%.

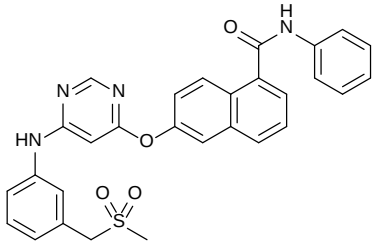


***N*-Cyclopropyl-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylox**

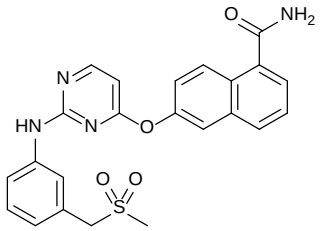
y)-1-naphthamide (8q). White solid (11 mg, 50%); mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.59-0.63 (m, 2H), 0.73-0.77 (m, 2H), 2.84 (s, 3H), 2.94-2.97 (m, 1H), 4.16 (s, 2H), 6.55 (d, J = 6.0 Hz, 1H), 6.85 (d, J = 6.8 Hz, 1H), 6.96 (m, 1H), 7.47-7.59 (m, 5H), 7.85 (d, J = 2.4 Hz, 1H), 8.00-8.03 (m, 1H), 8.31 (d, J = 9.2 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.64 (d, J = 4.4 Hz, 1H), 9.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 5.72 (2C), 22.84, 39.38, 59.32, 98.53, 118.70, 118.82, 121.04, 122.62, 124.01, 124.74, 125.65, 127.25, 127.47, 128.13, 128.69, 129.28, 133.93, 134.53, 140.01, 150.04, 159.48, 159.98, 169.25, 169.48; HRMS (ESI) *m/z* calcd for $C_{26}H_{24}N_4O_4NaS$ $[M + Na]^+$, 511.1416, found, 511.1407. HPLC purity: 98.78%.



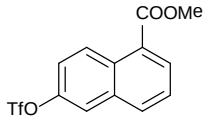
***N*-Cyclobutyl-6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy) -1-naphthamide (8r).** White solid (17 mg, 77%); mp 204-206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.68-1.74 (m, 2H), 2.05-2.11 (m, 2H), 2.28-2.30 (m, 2H), 2.84 (s, 3H), 4.16 (s, 2H), 4.49-4.53 (m, 1H), 6.55 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 7.2 Hz, 1H), 6.96 (m, 1H), 7.47-7.53 (m, 3H), 7.56-7.62 (m, 2H), 7.86 (d, J = 2.0 Hz, 1H), 8.01-8.03 (m, 1H), 8.28 (d, J = 9.2 Hz, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.85 (d, J = 7.6 Hz, 1H), 9.67 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{27}H_{26}N_4O_4NaS$ $[M + Na]^+$, 525.1572, found, 525.1567. HPLC purity: 97.49%.



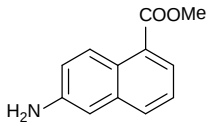
6-(6-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-1-naphthamide (8t). White solid (19 mg, 83%); mp 196-198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.93 (s, 3H), 4.48 (s, 2H), 6.26 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.33-7.41 (m, 3H), 7.48 (dd, J = 9.2, 2.4 Hz, 1H), 7.60 (s, 1H), 7.64-7.69 (m, 2H), 7.77-7.78 (m, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 2.4 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 9.2 Hz, 1H), 8.37 (s, 1H), 9.73 (s, 1H), 10.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.37, 59.22, 89.17, 118.41, 119.75 (2C), 119.81, 121.99, 122.49, 123.65, 125.04 (2C), 125.79, 127.19, 127.28, 128.62 (2C), 128.83, 129.48, 129.62, 134.01, 134.64, 139.13, 139.65, 150.38, 158.05, 162.35, 166.98, 169.13; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_4O_4NaS$ $[M + Na]^+$, 547.1416, found, 547.1427. HPLC purity: 95.75%.



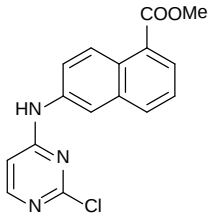
6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthamide (8s). To a solution of 6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-1-naphthoic acid (**7k**, 20 mg, 0.046 mmol) in 0.5 mL of DMF was added *N*,*N*'-Carbonyldiimidazole (CDI) (9 mg, 0.053 mmol) and the mixture was heated to 60 °C for 0.5 h. After cooling to ambient temperature, 0.2 mL aqueous ammonium hydroxide was added. The resulting mixture was stirred overnight and concentrated to dryness. A 1 mL portion of MeOH was added to the residue, and the mixture was then subjected to sonication to provide a white suspension. The resulting precipitate was filtered and washed with minimal amount of MeOH, dried in vacuo to provide the title compound (15 mg, 75%) as a white solid; mp 168-170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.83 (s, 3H), 4.14 (s, 2H), 6.55 (d, J = 5.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.95 (m, 1H), 7.46-7.53 (m, 3H), 7.58 (t, J = 8.0 Hz, 1H), 7.67-7.68 (m, 2H), 7.86 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 8.40-8.44 (m, 2H), 9.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.40, 59.29, 98.55, 118.71, 118.82, 121.05, 122.53, 124.02, 124.79, 125.66, 127.48 (2C), 128.12, 128.65, 129.39, 134.03, 134.39, 140.02, 150.01, 159.47, 159.97, 169.27, 170.34; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_4O_4NaS$ $[M + Na]^+$, 471.1103, found, 471.1111. HPLC purity: 97.23%.



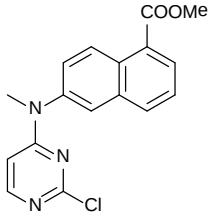
Methyl 6-(Trifluoromethylsulfonyloxy)-1-naphthoate (10). To a stirred solution of 6-hydroxy-1-naphthoic acid (**4**, 5 g, 26.57mmol) in 200 mL of MeOH was added thionyl chloride (2.8 mL, 39.86 mmol) dropwise. The mixture was heated to reflux for 2 h and concentrated to provide methyl 6-hydroxy-1-naphthoate (**9**, 5.32 g, 99%) as a brown yellow solid, which was used without further purification. To a solution of methyl 6-hydroxy-1-naphthoate (**9**, 2.5 g, 12.36 mmol) in 150 mL of CH_2Cl_2 at -78 °C was added DIPEA (6.5 mL, 37.09 mmol) and triflic anhydride (3 mL, 18.55 mmol). The mixture was stirred at this temperature for 1 h before being poured into saturated NH_4Cl (100 mL).The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification by silica gel chromatography eluting with 5% ethyl acetate in petroleum ether to provide the title compound (3.85 g, 93%) as a brown yellow solid; mp 58-60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.97 (s, 3H), 7.74-7.81 (m, 2H), 8.27 (dd, J = 7.2, 1.2 Hz, 1H), 8.30 (d, J = 3.0 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.94 (d, J = 9.3 Hz, 1H); MS (ESI) *m*/*z* 335.0 $[M + H]^+$.



Methyl 6-Amino-1-naphthoate (11). A mixture of Methyl 6-(trifluoromethylsulfonyloxy)-1-naphthoate (**10**, 1 g, 2.99 mmol), benzophenone imine (0.65 mL, 3.89 mmol), $Pd_2(dba)_3$ (274 mg, 0.30mmol), 2-(dicyclohexylphosphino)biphenyl(105 mg, 0.30 mmol), and potassium phosphate (953 mg, 4.49 mmol) in 1,2-dimethoxyethane (10 mL) was purged with bubbling argon for 3 min and then heated at 90 °C for 3 h. After cooling to room temperature, 5 mL of 2 N HCl was added and the mixture was stirred for 30 min. The mixture was added 20 mL of ethyl acetate and the pH was adjusted to 10 with 2 N NaOH. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel eluting with 25% ethyl acetate in petroleum ether chromatography to provide the title compound (460 mg, 76%) as light-yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.89 (s, 3H), 5.54 (s, 2H), 6.89 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 9.0, 2.4 Hz, 1H), 7.32-7.37 (m, 1H), 7.69 (dd, J = 7.2, 1.2 Hz, 1H), 7.75 (d, J= 8.1 Hz, 1H), 8.42 (d, J= 9.6 Hz, 1H); MS (EI) m/z 201.1 $[M]^+$.

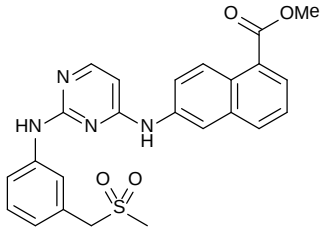


Methyl 6-(2-Chloropyrimidin-4-ylamino)-1-naphthoate (12a). A mixture of methyl 6-amino-1-naphthoate (**11**, 300 mg, 1.29 mmol), 2,4-dichloropyrimidine (**5a**, 443 mg, 2.97 mmol), and DIPEA (776 μL, 4.46 mmol) in *i*-PrOH was heated at 120 °C for 21 h in a sealed tube. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 2% MeOH in CH_2Cl_2 to provide the title compound (346 mg, 74%) as a yellow solid; mp 108-110 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.95 (s, 3H), 6.90 (d, J = 6.0 Hz, 1H), 7.57-7.62 (m, 1H), 7.78 (dd, J = 9.6, 2.7 Hz, 1H), 8.05 (dd, J = 7.2, 0.9 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 6.0 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.74 (d, J = 9.6 Hz, 1H), 10.40 (s, 1H); MS (ESI) m/z 314.3 $[M + H]^+$.

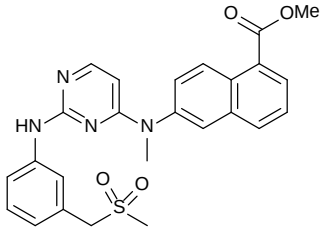


Methyl 6-((2-Chloropyrimidin-4-yl)(methyl)amino)-1-naphthoate (12b). To a stirred solution of methyl 6-(2-chloropyrimidin-4-ylamino)-1-naphthoate (**12a**, 322

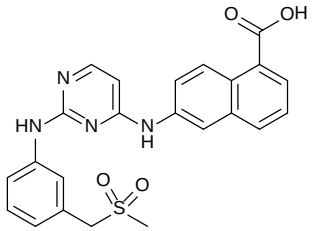
mg, 1.02 mmol) and cesium carbonate (669 mg, 2.05 mmol) in 5 mL of DMF was added iodomethane (77 μL, 1.23 mmol). The mixture was stirred at room temperature overnight. Water was added, the aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide the title compound (319 mg, 95%) as a yellow solid; mp 138-140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.50 (s, 3H), 3.96 (s, 3H), 6.47 (d, J = 6.0 Hz, 1H), 7.65-7.70 (m, 2H), 8.03 (d, J = 6.3 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 8.17-8.22 (m, 2H), 8.85 (d, J = 9.0 Hz, 1H); MS (ESI) m/z 328.3 $[M + H]^+$.



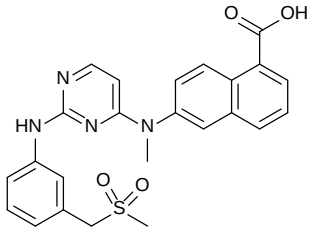
Methyl 6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylamino)-1-naphthoate (13a). To a solution of methyl 6-(2-chloropyrimidin-4-ylamino)-1-naphthoate (**12a**, 100 mg, 0.32 mmol) and 3-((methylsulfonyl)methyl)aniline (71 mg, 0.38 mmol) in *i*-PrOH (5mL) was added 1 drop of conc. HCl and the mixture heated to reflux for 2.5 h. The mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography eluting with 5% MeOH in CH_2Cl_2 to provide the title compound (145 mg, 75%) as a white solid; mp 228-230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.91 (s, 3H), 3.95 (s, 3H), 4.39 (s, 2H), 6.36 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.54-7.60 (m, 1H), 7.72 (s, 1H), 7.81 (dd, J = 9.6, 2.4 Hz, 1H), 7.88-7.92 (m, 1H), 7.99 (dd, J = 7.2, 1.2 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 5.4 Hz, 1H), 8.67 (d, J = 2.1 Hz, 1H), 8.71 (d, J = 9.3 Hz, 1H), 9.38 (s, 1H), 9.74 (s, 1H); MS (ESI) m/z 463.1 $[M + H]^+$.



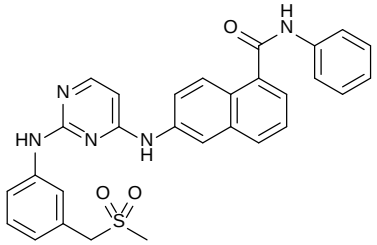
Methyl 6-(Methyl(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yl)amino)-1-naphthoate (13b). The title compound was prepared from 6-((2-chloropyrimidin-4-yl)(methyl)amino)-1-naphthoate (**12b**, 100 mg, 0.31 mmol) using a method analogous to the preparation of compound **13a**, as an off-white solid (109mg, 75%); mp 150-152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.87 (s, 3H), 3.55 (s, 3H), 3.96 (s, 3H), 4.29 (s, 2H), 6.01 (d, J = 6.3 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 7.09-7.14 (m, 1H), 7.62-7.70 (m, 3H), 7.79 (s, 1H), 7.94 (d, J = 6.0 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H), 8.15-8.22 (m, 2H), 8.82 (d, J = 9.3 Hz, 1H), 9.35 (s, 1H); MS (ESI) m/z 477.1 $[M + H]^+$.



6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylamino)-1-naphthoic Acid (14a). To a solution of methyl 6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylamino)-1-naphthoate (**13a**, 91 mg, 0.20 mmol) in 5 mL of DMF was added 1 mL of 6 N NaOH, then the reaction mixture was heated at 80 °C for 30 min. The mixture was cooled to room temperature, concentrated to dryness, and the residue was dissolved in 5 mL of water, then the pH was adjusted to 3-4 with 6 N HCl to provide a brown suspension. The resulting precipitate was filtered and washed with water, dried in vacuo to provide the title compound (76 mg, 86%) as a brown solid; mp 230-232 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.89 (s, 3H), 4.43 (s, 2H), 6.58 (d, J = 6.9 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.35-7.41 (m, 1H), 7.54-7.60 (m, 2H), 7.75 (s, 1H), 7.79 (dd, J = 9.3, 2.1 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 8.06-8.08 (m, 2H), 8.48 (s, 1H), 8.84 (d, J = 9.6 Hz, 1H), 10.47 (s, 1H), 10.96 (s, 1H); MS (ESI) m/z 449.2 $[M + H]^+$.

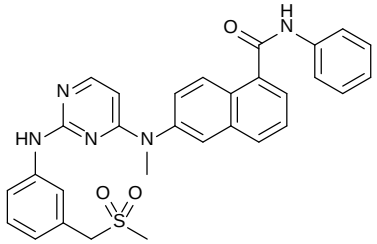


6-(Methyl(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yl)amino)-1-naphthoic Acid (14b). The title compound was prepared from methyl 6-(methyl(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yl)amino)-1-naphthoate (**13b**, 90 mg, 0.19 mmol) using a method analogous to the preparation of compound **14a**, as an off-white solid. (82mg, 94%); mp 280-282 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.88 (s, 3H), 3.57 (s, 3H), 4.32 (s, 2H), 6.02 (d, J = 6.6 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 7.11-7.17 (m, 1H), 7.61-7.67 (m, 3H), 7.78 (s, 1H), 7.94 (d, J = 6.0 Hz, 1H), 8.04 (s, 1H), 8.14-8.19 (s, 2H), 8.96 (d, J = 9.0 Hz, 1H), 9.51 (s, 1H), 13.22 (br s, 1H); MS (ESI) m/z 463.1 $[M + H]^+$.

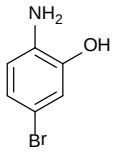


6-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylamino)-*N*-phenyl-1-naphthamide (15a). The title compound was prepared from 6-(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-ylamino)-1-naphthoic acid (**14a**, 20 mg, 0.045mmol) using a method analogous to the preparation of

compound **3a**, as a white solid. (13 mg, 57%); mp 240-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.92 (s, 3H), 4.40 (s, 2H), 6.35 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.57-7.61 (m, 2H), 7.71 (s, 2H), 7.83 (d, J = 7.6 Hz, 2H), 7.91-7.95 (m, 2H), 8.09-8.14 (m, 2H), 8.72 (s, 1H), 9.42 (s, 1H), 9.74 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.36, 59.58, 99.47, 115.06, 119.11, 119.64 (2C), 121.47, 121.57, 123.29, 123.52, 123.64, 125.23, 125.40, 125.56, 128.43, 128.62 (2C), 128.99, 129.28, 134.04, 134.50, 137.95, 139.24, 140.87, 155.96, 159.32, 160.31, 167.28; HRMS (ESI) *m/z* calcd for $C_{29}H_{25}N_5O_3SNa$ [M + Na]$^+$, 546.1576, found, 546.1582. HPLC purity: 97.36%.

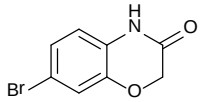


6-(Methyl(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yl)amino)-*N*-phenyl-1-naphthamide (15b). The title compound was prepared from 6-(methyl(2-((3-((methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yl)amino)-1-nap hthoic acid (**14b**, 30 mg, 0.065 mmol) using a method analogous to the preparation of compound **3a**, as a white solid. (26 mg, 74%); mp 228-230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.89 (s, 3H), 3.56 (s, 3H), 4.33 (s, 2H), 5.98 (d, J = 6.0 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.11-7.18 (m, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.58-7.70 (m, 3H), 7.77-7.84 (m, 4H), 7.94 (d, J = 5.7 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 9.31 (s, 1H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 37.89, 39.36, 59.68, 96.32, 118.47, 119.74 (2C), 120.76, 123.21, 123.65, 124.66, 125.42, 125.61, 126.56, 126.66, 127.85, 128.27, 128.64 (2C), 128.81, 129.84, 133.86, 134.55, 139.15, 141.05, 142.32, 156.25, 159.30, 162.10, 166.99; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_5O_3S$ [M + H]+, 538.1913, found, 538.1906. HPLC purity: 96.05%.

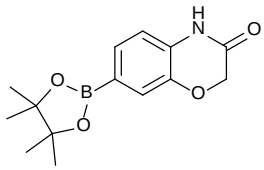


2-Amino-5-bromophenol (17). To a solution of 5-bromo-2-nitrophenol (**16**, 5 g, 22.94 mmol) in 200 mL of EtOH was added a solution of ammonium chloride (12.3 g, 224.8 mmol) dissolved in 100 mL of water. The mixture was heated to 50 °C before ion powder (6.42 g, 114.68 mmol) was added and then heated at 70 °C for 30 min. The mixture was cooled to room temperature, filtered and concentrated. To the residue was added ethyl acetate (200 mL) and saturated aqueous $NaHCO_3$ (200 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide the title compound (3 g, 70%) as a brown solid; mp 138-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):

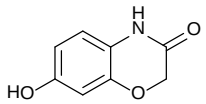
4.67 (s, 2H), 6.51 (s, 1H), 6.57-6.75 (m, 2H), 9.48 (s, 1H); MS (ESI) *m*/*z* 188.0 $[M + H]^+$.



7-Bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (18). To a stirred solution of 2-amino-5-bromophenol (**17**, 3 g, 15.96 mmol) in acetonitrile (180 mL) was added chloroacetylchloride (1.4 mL, 17.55 mmol) dropwise followed by portionwise addition of cesium carbonate (15.6 g, 47.87 mmol). The mixture was stirred at room temperature overnight and then concentrated. To the residue was added CH_2Cl_2 (200 mL) and water (200 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide the title compound (3 g, 82%) as a yellow solid; mp 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.59 (s, 2H), 6.83 (d,*J* = 8.1 Hz, 1H), 7.11-7.16 (m, 2H), 10.83 (s, 1H); MS (ESI) *m*/*z* 228.0 $[M + H]^+$.

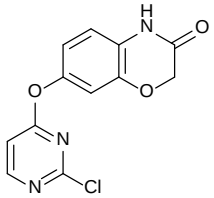


7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (19). A mixture of 7-bromo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**18**, 1 g, 4.39 mmol), bis(pinacolato)-diboron (1.34 g, 5.26 mmol), Pd(dppf)Cl_2 (321 mg, 0.44 mmol), and potassium acetate (1.43 g, 13.16 mmol) in dioxane (30 mL) was purged with bubbling argon for 3 min and then heated at 100 °C for 1 h. After cooling to room temperature, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography eluting with 20% ethyl acetate in petroleum ether to provide the title compound (1.07 g, 88%) as a yellow solid; mp 202-204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.27 (s, 12H), 4.55 (s, 2H), 6.89 (d, *J* = 7.2 Hz, 1H), 7.13 (s, 1H), 7.26 (dd, *J* = 7.5, 1.2 Hz, 1H), 10.85 (s, 1H); MS (EI) *m*/*z* 275 $[M]^+$.

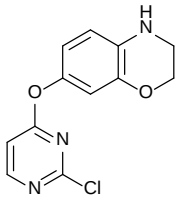


7-Hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (20). To a stirred solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**19**, 542 mg, 1.97 mmol) in acetic acid (8 mL) was added aqueous hydrogen peroxide (0.67 mL, 30%, 5.91 mmol) dropwise. The mixture was stirred at room temperature for 5 h, diluted with water (50 mL), extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography

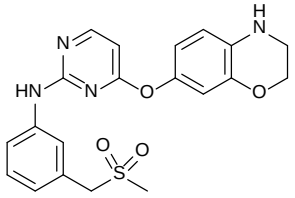
eluting with 3% MeOH in CH_2Cl_2 to provide the title compound (289 mg, 89%) as a pink solid; mp 220-222 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.47 (s, 2H), 6.33-6.37 (m, 2H), 6.65-6.70 (m, 1H), 9.27 (s, 1H), 10.42 (s, 1H); MS (ESI) *m*/*z* 164.2 $[M-H]^-$.



7-(2-Chloropyrimidin-4-yloxy)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (21). To a stirred solution of 7-hydroxy-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**20**, 439 mg, 2.66 mmol) and 2,4-dichloropyrimidine (**5a**, 792 mg, 5.32 mmol) in 10 mL of DMSO was added DBU (1.2 mL, 7.98 mmol) dropwise. The mixture was stirred at room temperature for 1 h. The mixture was diluted with water (250 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over sodium sulfate, filtered, and concentrated to dryness. To the residue was added 15 mL of MeOH, and then subjected to sonication to provide a white suspension. The resulting precipitate was filtered and washed with minimal amount of MeOH, dried in vacuo to provide the title compound (660mg, 89%) as an off-white solid; mp 242-244 °C.^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.63 (s, 2H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.94-6.97 (m, 2H), 7.12 (d, *J* = 5.4 Hz, 1H), 8.60 (d, *J* = 5.7 Hz, 1H), 10.80 (s, 1H); MS (ESI) *m*/*z* 276.1 $[M-H]^-$.

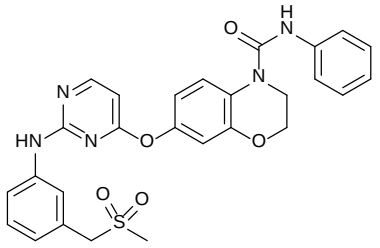


7-(2-Chloropyrimidin-4-yloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (22). To a stirred solution of 7-(2-chloropyrimidin-4-yloxy)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**21**, 532 mg, 1.92 mmol) in anhydrous THF (30 mL) under a argon atmosphere was added borane-THF complex (3.8 mL, 1 M solution in THF, 3.83 mmol). The mixture was heated to refluxed for 1 h, cooled to room temperature, quenched with MeOH, and concentrated. The residue was purified by silica gel chromatography eluting with 2% MeOH in CH_2Cl_2 to provide the title compound (279 mg, 55%) as a slight-brown oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.27 (m, 2H), 4.15 (t, *J* = 4.2 Hz, 2H), 5.87 (s, 1H), 6.52-6.62 (m, 3H), 6.98 (d, *J* = 5.4 Hz, 1H), 8.55 (d, *J* = 5.7 Hz, 1H).



4-(3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yloxy)-*N*-(3-((methylsulfonyl)methyl)phenyl)pyrimidin-2-amine (23). The title compound was prepared from 7-(2-chloropyrimidin-4-yloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (**22**, 233 mg,

0.88mmol) using a method analogous to the preparation of compound **13a**, as a white solid. (166 mg, 55%); mp 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.90 (s, 3H), 3.31 (m, 2H), 4.16 (t, J = 4.0 Hz, 2H), 4.31 (s, 2H), 5.80 (s, 1H), 6.33 (d, J = 5.6 Hz, 1H), 6.53-6.57 (m, 2H), 6.62 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.16-7.20 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 8.30 (d, J = 5.6 Hz, 1H), 9.67 (s, 1H); MS (ESI) m/z 413.1 $[M + H]^+$.



7-(2-((3-((Methylsulfonyl)methyl)phenyl)amino)pyrimidin-4-yloxy)-*N*-phenyl-2*H*-benzo[*b*][1,4]oxazine-4(3*H*)-carboxamide (24). To a solution of 4-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yloxy)-*N*-(3-((methylsulfonyl)methyl)phen yl)pyrimidin-2-amine (**29**, 20 mg, 0.049 mmol) and phenyl isocyanate (8 μL, 0.073 mmol) in 0.3 mL of DMF was added Et_3N (14 μL, 0.097 mmol). The mixture was heated at 70 °C for 3.5 h. The mixture was concentrated and purified by silica gel chromatography eluting with 60% ethyl acetate in petroleum ether to provide the title compound (16 mg, 62%) as a white solid; mp 100-102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.88 (s, 3H), 3.91 (t, J = 4.0 Hz, 2H), 4.29-4.32 (m, 4H), 6.43 (d, J = 5.6 Hz, 1H), 6.77 (dd, J = 9.2, 2.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.99-7.03 (m, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.28-7.32 (m, 2H), 7.49-7.52 (m, 2H), 7.58-7.64 (m, 3H), 8.35 (d, J = 5.6 Hz, 1H), 9.15 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 39.27, 42.87, 59.60, 65.46, 98.28, 110.11, 113.60, 118.84, 119.68 (2C), 121.02, 122.32, 123.66, 123.97, 124.17, 128.32, 128.37 (2C), 128.92, 139.62, 140.20, 146.22, 147.80, 153.34, 159.57, 159.79, 169.32. HRMS (ESI) m/z calcd for $C_{27}H_{25}N_5O_5NaS$ $[M + Na]^+$, 554.1474, found, 554.1470. HPLC purity: 99.35%.

Biological evaluation

Table S1 kinase Inhibition Profile of **3b**, **3c**, **3e** and **8h**[a]

compd	IC_{50} means (nM) ± SD				
	VEGFR-1	VEGFR-3	PDGFR-α	PDGFR-β	FGFR1
3b	1.9±0.4	12.0±0.4	27.6±6.2	10.2±0.6	>1000.0
3c	25.1±5.7	53.7±4.2	8.8±1.8	16.4±1.1	>1000.0
3e	6.8±0.4	17.9±6.2	43.9±20.8	11.0±0.6	>1000.0
8h	3.4±1.6	11.3±1.6	15.1±7.7	6.0±3.3	>1000.0
SU11248[b]	21.9±8.1	53.0±46.3	6.1±1.2	3.5±1.2	87.4±34.4

[a]All IC_{50} values were means of two independent experiments.

[b]SU11248 was used as the positive control.

Kinase inhibition assay

The inhibitory ability of the compounds on a panel of kinases was tested by enzyme linked immunosorbent assay (ELISA). The kinases domain of EGFR (WT), EGFR (T790M/L858R), ErbB2, IGF-1R, FGFR-1, VEGFR-2 were expressed using the Bac-to-Bac™ baculovirus expression system (Invitrogen, Carlsbad, CA, USA) and purified on Ni-NTA columns (QIAGEN Inc., Valencia, CA, USA). Recombinant ErbB4, RET, VEGFR-1, Flt-3, c-Src, ABl, EPH-A2, PDGFR-α, and PDGFR-β proteins were obtained from Upstate Biotechnology. The 96-well ELISA plates were coated with substrate which obtain 20 μg/mL Poly $(Glu, Tyr)_{4:1}$ (Sigma, St. Louis, MO). Each reaction contained 10 μmol/L ATP solution which was diluted in kinase reaction buffer (50 mM HEPES pH 7.4, 20 mM $MgCl_2$, 0.1 mM $MnCl_2$, 0.2 mM Na_3VO_4, 1 mM DTT). Compounds were dissolved in DMSO and added 1μL to each reaction. Appropriate tyrosine kinase diluted in kinase reaction buffer initiated reaction in 100 μL system. After incubation at 37 °C for 60 min, the wells were washed three times with phosphate buffered saline (PBS) containing 0.1% Tween 20(T-PBS). Next,100 μL anti-phosphotyrosine (PY99) antibody (1:1000, Santa Cruz Biotechnology, Santa Cruz, CA) diluted in T-PBS containing 5 mg/mL BSA was added and the plate was incubated at 37°C for 30 min. After the plate was washed three times, 100 μL horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000, Calbiochem, SanDiego, CA) diluted in T-PBS containing 5mg/mL BSA was added and the plate was incubated at 37 °C for 30 min. Washed the plate and then 100μL citrate buffer (0.1 M, pH 5.5) containing 0.03% H_2O_2 and 2 mg/mL *o*-phenylenediamine was added for color development. The reaction was terminated by adding 50 μL of 2M H_2SO_4, and the plate was read using a multi-well spectrophotometer (VERSAmax™, Molecular Devices, Sunnyvale, CA, USA) at 490 nm. The inhibitory rate (%) was calculated with the formula: $[1- (A_{490treated}/A_{490control})] \times 100\%$. IC_{50} values were calculated from the inhibitory curves.

Cell proliferation inhibition assay

The primary human umbilical vein endothelial cells (HUVEC) were obtained from PromoCell (Heidelberg, Germany) and cultured by Endothelial Cell Growth Medium 2 without VEGF (0.02 mL/mL Fetal Calf Serum, 5 ng/mL EGF, 10 ng/mL bFGF, 20 ng/mL long R3 IGF, 1 μg/mL Ascorbic Acid, 22.5 μg/mL Heparin and 0.2 μg/mL Hydrocortisone). HUVEC were plated into 96-well plates at 5500 per well and starved with Endothelial Cell Basal Medium which contains no serum and growth factors for 24 h. Different concentration of compounds were added 2 hours before 100 ng/mL recombinant human $VEGF_{165}$ (R&D Systems, Abingdon, UK) and then the cells were incubated at 37 °C CO_2 incubator for 48 h. The effects on proliferation were determined by Cell Counting Kit-8(CCK-8) assay (Dojindo Molecular

technologies Inc., Shanghai, China). Agent CCK-8 were added 10 μL per well, after incubated for 4 h at 37 ℃ CO_2 incubator, the amount of formazan dye generated by cellular dehydrogenase activity was measured by absorbance at 450 nm using a multi-well spectrophotometer (VERSAmax™, Molecular Devices, Sunnyvale, CA, USA). The inhibitory rate (%) of compounds was calculated with the formula: [1-($A_{450treated}$/$A_{450control}$)] × 100%. IC_{50} values were calculated from the inhibitory curves.

Tube formation assay

HUVEC were starved with Endothelial Cell Basal Medium for 24 h and then were placed at the density of 20000 per well on 96-well plates, which were pre-coated by Growth Factor Reduced (GFR)Standard BD Matrigel matrix (BD Biosciences, Billerica, USA) 60 μL per well. Different concentration of compounds and $VEGF_{165}$ (final, 100 ng/mL) were added simultaneously. Plates were incubated for 6 h at 37 °C CO_2 incubator until the tube network formed. Photographs were then taken through a stereoscope (OLYMPUS IX51) at a 4 magnification. Experiment was repeated three times.

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