SUPPORTING INFORMATION

Development of Novel ACK1 Inhibitors Using a Fragment Based Approach

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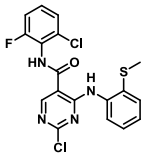
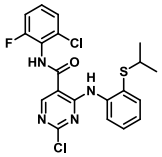
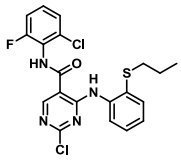


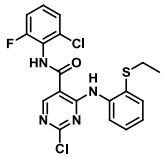
2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(methylthio)phenylamino)pyrimidine-5-carboxamide (10a): A solution of **7c** (1.000 g, 3.125 mmol), 2-(methylthio)aniline (0.522 g, 3.750 mmol) and DIPEA (0.652 mL, 3.750 mmol) in THF (5 mL) was heated in microwave reactor at 120 ºC for 1 h. The solvent was removed under reduce pressure and the crude material was purified using silica gel flash chromatography (20 g silica gel, 0-40% gradient EtOAc in Hexane) to give the title compound as a white solid (1.202 g, 91%), mp: 204-206 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 10.66 (s, 1H), 8.99 (s, 1H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78 – 7.34 (m, 4H), 7.27 (td, *J* = 7.6, 1.6 Hz, 1H), 7.21 (td, *J* = 7.6, 1.6 Hz, 1H), 2.39 (s, 3H); LC-MS (ESI+) *m/z* 423.03 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{18}H_{14}Cl_2FN_4OS$ $(M+H)^+$ 423.0244, found 423.0241.



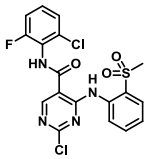
2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylthio)phenylamino)pyrimidine-5-carboxamide (10b): A solution of **7c** (1.000 g, 3.125 mmol), 2-thioisopropyl aniline hydrochloride (0.770 g, 3.750 mmol) and DIPEA (1.30 mL, 7.500 mmol) in THF (5 mL) was heated in microwave reactor at 120 ºC for 1 h. The reaction mixture was evaporated to dryness and water (20 mL) was added and sonicated for 10 min. The resulting precipitate was isolated by filtration and washed with water (20 mL). Then the yellow solid was sonicated in DCM (10 mL), filtered and washed with DCM (2 mL), dried under vacuum to afford the title compound as a white solid (1.187 g, 84%). mp: 202-205 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 1H), 10.66 (s, 1H), 8.98 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.38 (m, 4H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.23-3.14 (m, 1H), 1.11 (d, *J* = 6.4 Hz, 6H),); LC-MS (ESI+) *m/z* 451.06 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{20}H_{18}Cl_2FN_4OS$ $(M+H)^+$ 451.0557, found 451.0552.



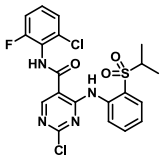
2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(propylthio)phenylamino)pyrimidine-5-carboxamide (10c): A solution of **7c** (1.000 g, 3.125 mmol), 2-(propylthio)aniline hydrochloride (0.700 g, 3.438 mmol) and DIPEA (1.195 mL, 6.875 mmol) in THF (5 mL) was heated in microwave reactor at 120 ºC for 1 h. The reaction mixture was evaporated to dryness, added water (20 mL) and sonicated for 10 min. The resulting precipitate was filtered and washed with water (20 mL). The yellow solid was sonicated in DCM:Hexane (1:2, 6 mL), filtered and dried under vacuum to afford the title compound as a white solid (1.080 g, 77%), mp: 197-200 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 10.66 (s, 1H), 8.99 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.38 (m, 4H), 7.34 (appt, *J* = 7.4 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.49-1.40 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); LC-MS (ESI+) *m/z* 451.05 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{20}H_{18}Cl_2FN_4OS$ $(M+H)^+$ 451.0557, found 451.0551.



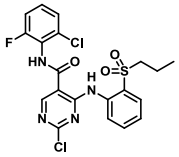
2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylthio)phenylamino)pyrimidine-5-carboxamide (10d): A solution of **7c** (1.000 g, 3.125 mmol), 2-(ethylthio)aniline (0.526 g, 3.438 mmol) and DIPEA (0.652 mL, 3.75 mmol) in THF (5 mL) was heated in microwave reactor at 120 ºC for 1 h. The reaction mixture was evaporated to dryness, added water (20 mL) and sonicated for 10 min. The resulting precipitate was filtered and washed with water (10 mL). The light yellow solid was sonicated in DCM:Hexane (10 mL, 1:1), filtered and quickly washed with DCM (2 mL), dried under high vacuum to afford the title compound as a white solid (1.35 g, 99%), mp: 205-208 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 10.67 (s, 1H), 8.99 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.38 (m, 4H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 2.83 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); LC-MS (ESI+) *m/z* 437.04 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{19}H_{16}Cl_2FN_4OS$ $(M+H)^+$ 437.0400, found 437.0390.



2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(methylsulfonyl)phenylamino)pyrimidine-5-carboxamide (11a): To a suspension of **10a** (0.634 g, 1.500 mmol) in EtOAc (40 mL), was added *m*-CPBA (77% max, 1.014 g, 4.500 mmol) at 0 ºC. The mixture was warmed up to r.t. and stirred for 2 h. The reaction was diluted with EtOAc (20 mL) and washed with sat. $Na_2S_2O_3$/$NaHCO_3$ (1:1 ratio, 20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL) sequentially. The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The solid was slurried with DCM/Hexane (1:5 ratio, 5 mL), filtered and dried under high vacuum to afford the title compound as a beige color solid (0.657 g, 96%), mp: 211-214 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (s, 1H), 10.63 (s, 1H), 9.03 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.90 (dd, J = 8.0, 1.6 Hz, 1H), 7.79–7.71 (m, 1H), 7.55–7.33 (m, 4H), 3.16 (s, 3H); LC-MS (ESI+) *m/z* 455.02 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{18}H_{14}Cl_2FN_4O_3S$ $(M+H)^+$ 455.0142, found 455.0134.

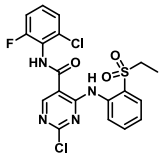


2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylsulfonyl)phenylamino)pyrimidine-5-carboxamide (11b): This compound was synthesized using the procedure described for **11a** except using **10b** (0.676 g, 1.500 mmol) and *m*-CPBA (77% max, 1.014 g, 4.500 mmol) to obtain the title compound as a white solid (0.657 g, 91%), mp: 225-227 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.14 (s, 1H), 10.62 (s, 1H), 9.01 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 7.6, 1.6 Hz, 1H), 7.78 (appt, J = 8.4 Hz, 1H), 7.50-7.37 (m, 4H), 1.09 (d, J = 6.8 Hz, 6H); LC-MS (ESI+) *m/z* 483.04 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{20}H_{18}Cl_2FN_4O_3S$ $(M+H)^+$ 483.0455, found 483.0458.

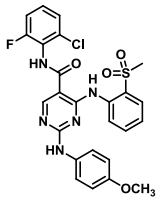


2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(propylsulfonyl)phenylamino)pyrimidine-5-carboxamide (11c): To a suspension of **10c** (0.676 g, 1.500 mmol) in EtOAc (40 mL) was added *m*-CPBA (77% max, 1.014 g, 4.500 mmol) at 0 ºC. The mixture was warmed up to r.t. and stirred for 2 h. The resulting precipitate was filtered and washed with EtOAc

(5 mL × 2) to afford the title compound (0.510 g). The filtrate was concentrated to dryness and slurried with EtOAc (5 mL), filtered and washed with EtOAc (3 mL) to afford the second crop of pure product, which was combined with the first crop of solid to afford the title compound as a white solid (0.629 g, 87%), mp: 226-229 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (s, 1H), 10.63 (s, 1H), 9.03 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.88 (dd, J = 7.6, 1.6 Hz, 1H), 7.78 (appt, J = 7.2 HZ, 1H), 7.50-7.40 (m, 4H), 3.20 (t, J = 7.6 Hz, 2H), 1.55-1.46 (m, 2H), 0.81 (t, J = 7.6 Hz, 3H); LC-MS (ESI+) *m/z* 483.04 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{20}H_{18}Cl_2FN_4O_3S$ $(M+H)^+$ 483.0455, found 483.0449.

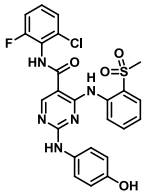


2-Chloro-*N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylsulfonyl)phenylamino)pyrimidine-5-carboxamide (11d): To a suspension of **10d** (0.740 g, 1.695 mmol) in EtOAc (40 mL) was added *m*-CPBA (77% max, 1.146 g, 5.086 mmol) at 0 ºC. The mixture was warmed to r.t. and stirred for 2 h. The resulting precipitate was filtered and washed with EtOAc (10 mL × 2) to afford the pure compound as a white solid (0.183 g). The filtrate was washed with sat. $Na_2S_2O_3$/$NaHCO_3$ (30 mL, 1:1), then washed with sat. $NaHCO_3$ (25 mL), brine (25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to dryness to afford a light brown solid. The solid was sonicated with DCM (5 mL), filtered and washed with DCM (3 mL) to afford the second crop of pure product, which was combined with the first crop of solid to afford the title compound as a white solid (0.555 g, 70%), mp: 230-233 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H), 10.63 (s, 1H), 9.02 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (appt, J = 6.8 Hz, 1H), 7.50-7.40 (m, 4H), 3.23 (q, J = 7.2 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H); LC-MS (ESI+) *m/z* 469.03 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{19}H_{16}Cl_2FN_4O_3S$ $(M+H)^+$ 469.0299, found 469.0295.

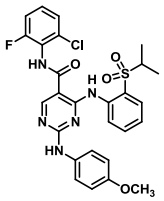


***N*-(2-chloro-6-fluorophenyl)-2-(4-methoxyphenylamino)-4-(2-(methylsulfonyl)phenylamino)pyrimidine-5-carboxamide (12a)**: A mixture of **11a** (0.050 g, 0.110 mmol), 4-methoxyaniline (0.016 g, 0.132 mmol), 4 M HCl in dioxane (0.033 mL, 0.132 mmol) in dioxane (1 mL) was heated in microwave reactor at 180 ºC for 30 min. The mixture

was evaporated to dryness. EtOAc (5 mL) was added and sonicated. The suspension was filtered and washed with sat. $NaHCO_3$ (5 mL × 2), then water (5 mL × 2) and dried under high vacuum to afford the title compound as a beige color solid (0.058 g, 97%), mp: 267 ºC (decomposed). HPLC 98.8% [t_R = 10.18 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H disappeared on D_2O shake), 10.09 (s, 1H disappeared on D_2O shake), 9.79 (brs, 1H disappeared on D_2O shake), 8.94 (s, 1H), 8.12 (brs, 1H), 7.87 (dd, J = 7.6, 1.2 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.46 – 7.33 (m, 6H), 6.75 (brs, 2H), 3.68 (s, 3H), 3.01 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.91- -115.95 (m); LC-MS (ESI+) *m/z* 542.10 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{25}H_{22}ClFN_5O_4S$ $(M+H)^+$ 542.1060, found 542.1062.

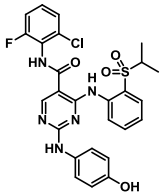


***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(methylsulfonyl)phenylamino)pyrimidine-5-carboxamide (12b)**: This compound was synthesized using the procedure described for **12a** using **11a** (0.050 g, 0.110 mmol), and 4-aminophenol (0.014 g, 0.132 mmol) to obtain the title compound as a light brown solid (0.056 g, 97%), mp: 238 ºC (decomposed). HPLC 96.7% [t_R = 7.34 min, 50% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (s, 1H disappeared on D_2O shake), 10.09 (s, 1H disappeared on D_2O shake), 9.72 (brs, 1H disappeared on D_2O shake), 9.15 (brs, 1H disappeared on D_2O shake), 8.92 (s, 1H), 8.12 (brs, 1H), 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.52 – 7.23 (m, 6H), 6.58 (brs, 2H), 3.11 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.99- -116.03 (m); LC-MS (ESI+) *m/z* 528.09 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{24}H_{20}ClFN_5O_4S$ $(M+H)^+$ 528.0903, found 528.0899.

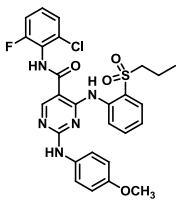


***N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylsulfonyl)phenylamino)-2-(4-methoxyphenylamino)pyrimidine-5-carboxamide (12c)**: This compound was synthesized using the procedure described for **12a** except using **11b** (0.054 g,

0.111 mmol), 4-methoxyaniline (0.016 g, 0.133 mmol) to obtain the title compound as a white solid (0.058 g, 91%), mp: 246 ºC (decomposed). HPLC 99.5% [t_R = 5.49 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.13 (s, 1H disappeared on D_2O shake), 10.15 (s, 1H disappeared on D_2O shake), 9.91 (brs, 1H disappeared on D_2O shake), 8.92 (s, 1H), 8.06 (brs, 1H), 8.05 (brs, 1H), 7.83 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.70 (appt, *J* = 8.8 Hz, 1H), 7.47 – 7.34 (m, 6H), 6.74 (brs, 2H), 3.69 (s, 3H), 3.30-3.25 (m, 1H), 1.06 (d, *J* = 6.8 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.13- -116.16 (m); LC-MS (ESI+) *m/z* 570.14 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{27}H_{26}ClFN_5O_4S$ $(M+H)^+$ 570.1373, found 570.1372.

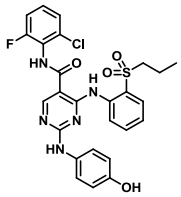


***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(isopropylsulfonyl)phenylamino)pyrimidine-5-carboxamide: (12d)**: This compound was synthesized using the procedure described for **12a** except using **11b** (0.054 g, 0.111 mmol), 4-aminophenol (0.015 g, 0.133 mmol) to obtain the title compound as a brown solid (0.045 g, 73%), mp: 168 ºC (decomposed). HPLC 95.7% [t_R = 3.10 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (s, 1H), 10.06 (s, 1H), 9.72 (brs, 1H), 9.11 (brs, 1H), 8.90 (s, 1H), 8.05 (brs, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.46 – 7.30 (m, 6H), 6.54 (brs, 2H), 1.06 (d, *J* = 6.8 Hz, 2H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.12- -116.16 (m); LC-MS (ESI+) *m/z* 556.12 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_4S$ $(M+H)^+$ 556.1216, found 556.1216.

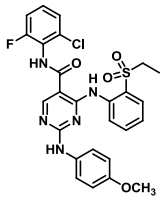


***N*-(2-chloro-6-fluorophenyl)-2-(4-methoxyphenylamino)-4-(2-(propylsulfonyl)phenylamino)pyrimidine-5-carboxamide (12e)**: This compound was synthesized using the procedure described for **12a** except using **11c** (0.054 g, 0.111 mmol), 4-methoxyaniline (0.016 g, 0.133 mmol) to obtain the title compound as a beige color solid (0.043 g, 68%), mp: 234-235 ºC. HPLC 99.2% [t_R = 5.79 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-

d_6): δ 11.01 (s, 1H), 10.09 (s, 1H), 9.80 (brs, 1H), 8.94 (s, 1H), 8.05 (brs, 1H), 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.47–7.34 (m, 6H), 6.71 (brs, 2H), 3.68 (s, 3H), 3.12 (brt, J = 6.8 Hz,2H), 1.47-1.42 (m, 2H), 0.69 (apps, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.07- -116.10 (m); LC-MS (ESI+) *m/z* 570.13 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{27}H_{26}ClFN_5O_4S$ $(M+H)^+$ 570.1373, found 570.1364.

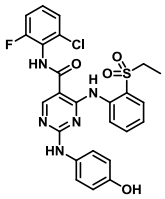


***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(propylsulfonyl)phenylamino)pyrimidine-5-carboxamide (12f)**: This compound was synthesized using the procedure described for **12a** except using **11c** (0.054 g, 0.111 mmol) and 4-aminophenol (0.015 g, 0.133 mmol) to obtain the title compound as a grey color solid (0.056 g, 90%), mp: 165 ºC (decomposed). HPLC 95.9% [t_R = 3.20 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 10.15 (s, 1H), 9.81 (brs, 1H), 8.93 (s, 1H), 8.01 (brs, 1H), 7.86 (dd, J = 8.0 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.47 – 7.27 (m, 6H), 6.53 (brs, 2H), 3.13 (brt, J = 7.2 Hz, 2H), 1.47-1.41 (m, 2H), 0.69 (brs, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.03- -116.07 (m); LC-MS (ESI+) *m/z* 556.11 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_4S$ $(M+H)^+$ 556.1216, found 556.1209.

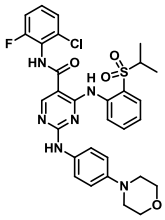


***N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylsulfonyl)phenylamino)-2-(4-methoxyphenylamino)pyrimidine-5-carboxamide (12g)**: This compound was synthesized using the procedure described for **12a** except using **11d** (0.055 g, 0.117 mmol), 4-methoxyaniline (0.017 g, 0.141 mmol) to obtain the title compound as a light brown color solid (0.045 g, 69%), mp: 263-265 ºC. HPLC 95.7% [t_R = 4.95 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (s, 1H), 10.08 (s, 1H), 9.78 (brs, 1H), 8.93 (s, 1H), 8.08 (brs, 1H), 7.85 (dd, J = 8.0, 1.2 Hz, 1H), 7.74 (dt, J = 7.4, 1.6 Hz, 1H), 7.47 – 7.34 (m, 6H), 6.74 (brs, 2H), 3.69 (s, 3H), 3.16 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz,

3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.00- -116.03 (m); LC-MS (ESI+) *m/z* 556.13 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_4S$ $(M+H)^+$ 556.1216, found 556.1199.

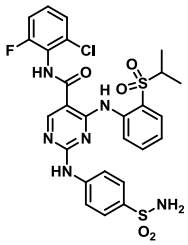


***N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylsulfonyl)phenylamino)-2-(4-hydroxyphenylamino)pyrimidine-5-carboxamide (12h)**: This compound was synthesized using the procedure described for **12a** except using **11d** (0.051 g, 0.117 mmol), 4-aminophenol (0.015 g, 0.141 mmol) to obtain the title compound as a beige color solid (0.043 g, 68%), mp: 201 ºC (decomposed). HPLC 96.1% [t_R = 5.53 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.16 (s, 1H), 10.25 (s, 1H), 9.96 (brs, 1H), 8.93 (s, 1H), 8.02 (brs, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.45–7.26 (m, 6H), 6.56 (brs, 2H), 3.13 (brq, 2H), 0.98 (brs, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -115.98 (brs); LC-MS (ESI+) *m/z* 542.11 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{25}H_{22}ClFN_5O_4S$ $(M+H)^+$ 542.1060, found 542.1052.

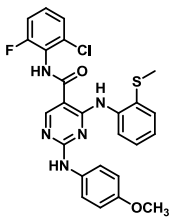


***N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylsulfonyl)phenylamino)-2-(4-morpholinophenylamino)pyrimidine-5-carboxamide (12i)**: A mixture of **11b** (0.054 g, 0.112 mmol), 4-morpholinoaniline (0.024 g, 0.134 mmol), 4 M HCl in dioxane (0.035 mL, 0.132 mmol) in dioxane (0.5 mL) was heated in microwave reactor at 180 ºC for 30 min. The solvent was removed, re-dissolved with DCM (15 mL) and washed with sat. $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude material was crystallized with EtOAC/Hex (5 mL, 1:1) to afford the title compound as a grey color solid (0.051 g, 73%), mp: 220 ºC (decomposed). HPLC 99.3% [t_R = 12.33 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 10.06 (s, 1H), 9.77 (brs, 1H), 8.91 (s, 1H), 8.09 (brs, 1H), 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.74 (appdt, *J* = 7.4, 1.2 Hz, 1H), 7.47–7.34 (m, 6H), 6.74 (brs, 2H), 3.71 (t, *J* = 4.4 Hz, 4H), 3.00 (brt, 4H), 1.07 (d, *J* = 6.4 Hz, 6 H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.13- -116.17

(m); LC-MS (ESI+) *m/z* 625.17 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{30}H_{31}ClFN_6O_4S$ $(M+H)^+$ 625.1795, found 625.1784.

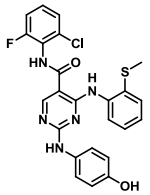


***N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylsulfonyl)phenylamino)-2-(4-sulfamoylphenylamino)pyrimidine-5-carboxamide (12j)**: A mixture of **11b** (0.054 g, 0.112 mmol), 4-aminobenzenesulfonamide (0.023 g, 0.134 mmol), 4 M HCl in dioxane (0.035 mL, 0.132 mmol) in dioxane (0.5 mL) was heated in microwave reactor at 180 ºC for 30 min. The solvent was removed and the mixture was re-dissolved with EtOAC (20 mL), washed with aq. HCl (1M, 15 mL) and sat. $NaHCO_3$ (15 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to dryness to afford the title compound as a creamy color solid (0.058 g, 84%), mp: 192 ºC (decomposed). HPLC 92.1% [t_R = 9.38 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H disappeared on D_2O shake), 10.29 (brs, 1H disappear on D_2O shake), 10.23 (s, 1H disappeared on D_2O shake), 9.02 (s, 1H), 8.07 (br d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.56–7.35 (m, 6H), 7.19 (brs, 2H disappeared on D_2O shake), 3.31-3.24 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 6 H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.09- -116.13 (m); LC-MS (ESI+) *m/z* 619.07 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{25}ClFN_6O_5S_2$ $(M+H)^+$ 619.0995, found 619.0988.

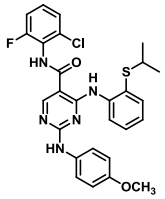


***N*-(2-chloro-6-fluorophenyl)-2-(4-methoxyphenylamino)-4-(2-(methylthio)phenylamino)pyrimidine-5-carboxamide (12k)**: This compound was synthesized using the procedure described for **12a** except using **10a** (0.050 g, 0.118 mmol), 4-methoxyaniline (0.018 g, 0.142 mmol) to obtain the title compound as a grey solid (0.056 g, 93%), mp: 261ºC (decomposed). HPLC 95.7% [t_R = 12.03 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H disappeared on D_2O shake), 10.10 (s, 1H disappeared on D_2O shake), 9.72 (brs, 1H disappeared on D_2O shake), 8.91 (s, 1H), 7.94 (brs, 1H), 7.50-7.35 (m, 6H), 7.23-7.14 (m, 2H), 6.78 (brs, 2H), 3.70 (s, 3H), 2.37 (s, 3H);

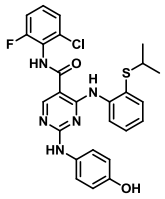
^{19}F NMR (376 MHz, DMSO-d_6): δ -116.18 to -116.21 (m); LC-MS (ESI+) *m/z* 510.12 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{25}H_{22}ClFN_5O_2S$ $(M+H)^+$ 510.1161, found 510.1151.



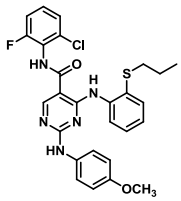
***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(methylthio)phenylamino)pyrimidine-5-carboxamide (12l)**: This compound was synthesized according to the procedure described for **12a** except using **10a** (0.050 g, 0.118 mmol), 4-aminophenol (0.016 g, 0.142 mmol) to obtain the title compound as a grey solid (0.055 g, 93%), mp: 246 ºC (decomposed). HPLC 99.3% [t_R = 9.81 min, 60% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s, 1H), 10.34 (s, 1H), 9.99 (s, 1H), 8.91 (s, 1H), 7.86 (brs, 1H), 7.48-7.18 (m, 8H), 6.63 (brs, 2H), 2.38 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.06 (s); LC-MS (ESI+) *m/z* 496.11 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{24}H_{20}ClFN_5O_2S$ $(M+H)^+$ 496.1005, found 496.0996.



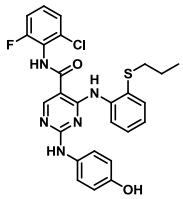
***N*-(2-chloro-6-fluorophenyl)-4-(2-(isopropylthio)phenylamino)-2-(4-methoxyphenylamino)pyrimidine-5-carboxamide (12m)**: This compound was synthesized using the procedure described for **12a** except using **10b** (0.050 g, 0.111 mmol), 4-methoxyaniline (0.016 g, 0.113 mmol) to obtain the title compound as a white solid (0.031 g, 52%), mp: 237-240 ºC. HPLC 99.7% [t_R = 7.03 min, 75% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H), 10.29 (s, 1H), 10.03 (brs, 1H), 8.88 (s, 1H), 8.16 (brs, 1H), 7.49-7.34 (m, 6H), 7.28 (brs, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 3.20 -3.13 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.19- -116.22 (m); LC-MS (ESI+) *m/z* 538.15 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{27}H_{26}ClFN_5O_2S$ $(M+H)^+$ 538.1474, found 538.1472.



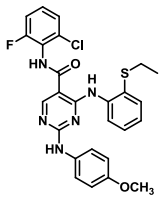
***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(isopropylthio)phenylamino)pyrimidine-5-carboxamide (12n)**: This compound was synthesized using the procedure described for **12a** except using **10b** (0.050 g, 0.111 mmol), 4-aminophenol (0.015 g, 0.113 mmol) to obtain the title compound as a beige color solid (0.057 g, 99%), mp: 232 ºC (decomposed). HPLC 99.3% [t_R = 12.68 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.29 (s, 1H), 10.10 (s, 1H), 9.68 (brs, 1H), 9.21 (brs, 1H), 8.85 (s, 1H), 8.19 (brs, 1H), 7.47-7.33 (m, 6H), 7.23 (brs, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 3.19 -3.12 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.19- -116.23 (m); LC-MS (ESI+) *m/z* 524.14 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_2S$ $(M+H)^+$ 524.1318, found 524.1310.



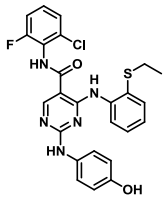
***N*-(2-chloro-6-fluorophenyl)-2-(4-methoxyphenylamino)-4-(2-(propylthio)phenylamino)pyrimidine-5-carboxamide (12o)**: This compound was synthesized using the procedure described for **12a** except using **10c** (0.050 g, 0.111 mmol) and 4-methoxyaniline (0.016 g, 0.133 mmol) to obtain the title compound as a beige color solid (0.040 g, 67%), mp: 248-249 ºC. HPLC 98.8% [t_R = 6.99 min, 75% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 10.07 (s, 1H), 9.69 (brs, 1H), 8.89 (s, 1H), 8.19 (brs, 1H), 8.09 (brs, 1H), 7.50-7.34 (m, 6H), 7.25 (appt, *J* = 6.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 6.4 Hz, 1H), 3.71 (s, 3H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.48-1.39 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.15- -116.18 (m); LC-MS (ESI+) *m/z* 538.14 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{27}H_{26}ClFN_5O_2S$ $(M+H)^+$ 538.1474, found 538.1464.



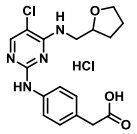
***N*-(2-chloro-6-fluorophenyl)-2-(4-hydroxyphenylamino)-4-(2-(propylthio)phenylamino)pyrimidine-5-carboxamide (12p)**: This compound was synthesized using the procedure described for **12a** except using **10c** (0.050 g, 0.111 mmol), 4-aminophenol (0.015 g, 0.133 mmol) to obtain the title compound as a beige color solid (0.047 g, 81%), mp: 208 ºC (decomposed). HPLC 99.1% [t_R = 12.16 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 10.15 (s, 1H), 9.73 (brs, 1H), 9.20 (brs, 1H), 8.87 (s, 1H), 8.04 (brs, 1H), 7.47-7.35 (m, 6H), 7.20 (brs, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.64 (brs, 1H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.48-1.39 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.13- -116.17 (m); LC-MS (ESI+) *m/z* 524.13 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_2S$ $(M+H)^+$ 524.1318, found 524.1307.



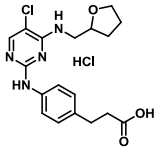
***N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylthio)phenylamino)-2-(4-methoxyphenylamino)pyrimidine-5-carboxamide (12q)**: This compound was synthesized using the procedure described for **12a** except using **10d** (0.051 g, 0.117 mmol) and 4-methoxyaniline (0.017 g, 0.141 mmol) to obtain the title compound as a beige color solid (0.043 g, 70%), mp: 250 ºC (decomposed). HPLC 98.5% [t_R = 5.66 min, 75% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15 (s, 1H), 10.26 (s, 1H), 9.96 (brs, 1H), 8.90 (s, 1H), 8.02 (brs, 1H), 7.48-7.35 (m, 6H), 7.25 (brt, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.56 (appd, *J* = 5.6 Hz, 2H), 3.72 (s, 3H), 2.81 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.11—116.14 (m); LC-MS (ESI+) *m/z* 524.13 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{26}H_{24}ClFN_5O_2S$ $(M+H)^+$ 524.1318, found 524.1317.



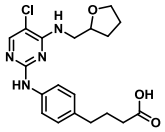
***N*-(2-chloro-6-fluorophenyl)-4-(2-(ethylthio)phenylamino)-2-(4-hydroxyphenylamino)pyrimidine-5-carboxamide (12r)**: This compound was synthesized using the procedure described for **12a** except using **10d** (0.051 g, 0.117 mmol) and 4-aminophenol (0.015 g, 0.141 mmol) to obtain the title compound as a light brown color solid (0.058 g, 97%), mp: 233 ºC (decomposed). HPLC 98.6% [t_R = 7.86 min, 65% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (s, 1H), 10.05 (s, 1H), 9.60 (brs, 1H), 9.14 (s, 1H), 8.88 (s, 1H), 8.08 (brs, 1H), 7.46-7.34 (m, 6H), 7.21 (brs, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.62 (appd, *J* = 6.8 Hz, 2H), 2.80 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.12- -116.16; MS (ESI+) *m/z* 510.13 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{25}H_{22}ClFN_5O_2S$ $(M+H)^+$ 510.1161, found 510.1154.



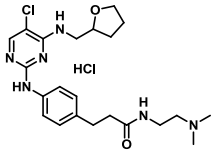
2-(4-((5-Chloro-4-(((tetrahydrofuran-2-yl)methyl)amino)pyrimidin-2-yl)amino)phenyl)acetic acid hydrochloride [(±)-23]: The **8a** (0.06 g, 0.242 mmol) and 4-aminophenylacetic acid (0.024 g, 0.161 mmol) were mixed in a microwave vial with acetonitrile (2 mL), added 2M HCl (3 drops) and the vial was sealed and heated at 150 °C for 2 h. Upon cooling, a precipitate formed. The reaction mixture was filtered, and the solid was purified by trituration with DCM to afford the title compound as a yellow solid (0.040 g, 69%), mp: 160 °C (decomposed). HPLC 91.9% [t_R = 9.40 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 4.19-4.13 (m, 1H), 3.84-3.79 (m, 1H), 3.75-3.70 (m, 1H), 3.64 (s, 2H), 3.60-3.58 (m, 2H), 2.03-1.88 (m, 3H), 1.66-1.58 (m, 1H); ^{13}C NMR (100 MHz, Methanol-d_4) δ 173.82, 159.25, 151.11, 138.86, 130.02, 123.14, 105.33, 76.75, 67.64, 45.33, 39.86, 28.53, 25.00; LC-MS (ESI+) *m/z* 363.12 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for C17H19ClN4O3 $(M+H)^+$ 363.1218, found 363.1226.



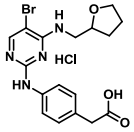
3-(4-((5-Chloro-4-(((tetrahydrofuran-2-yl)methyl)amino)pyrimidin-2-yl)amino)phenyl)propanoic acid hydrochloride [(±)**-24]**: The **8a** (0.024g, 0.966 mmol) and 3-(4-aminophenyl)propionic acid (0.106 g, 0.644 mmol) were mixed in a microwave vial with acetonitrile (8 mL), 2M aq. HCl (12 drops) was added and the vial was sealed and heated at 150 °C for 2 h. Upon cooling, a precipitate formed. The reaction mixture was filtered, and the solid was purified by trituration with DCM to afford the title compound as a light yellow solid (0.230 g, 95%), mp: 180 °C (decomposed). HPLC 95.9% [t_R = 9.787 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.19-4.13 (m, 1H), 3.84-3.79 (m, 1H), 3.75-3.70 (m, 1H), 3.63-3.56 (m, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.03-1.88 (m, 3H), 1.67-1.60 (m, 1H); ^{13}C NMR (100 MHz, Methanol-d_4) δ 173.47, 159.25, 138.73, 128.96, 123.31, 105.31, 76.72, 67.63, 45.29, 34.99, 29.90, 28.54, 25.01; LC-MS (ESI+) *m/z* 377.1390 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{18}H_{21}ClN_4O_3$ $(M+H)^+$ 377.14, found 377.1383.



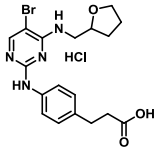
4-(4-(5-Chloro-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenyl)butanoic acid [(±)**-25**]: The **8a** (0.200 g, 0.806 mmol) and 4-(4-aminophenyl)-butyric acid (0.096 g, 0.537 mmol) were mixed in a microwave vial with acetonitrile (6 mL), 10 drops of 2M aq. HCl were added and the vial was sealed and heated at 150 °C for 2 h. Upon cooling, a precipitate formed. The reaction mixture was filtered, and the solid was purified by trituration with DCM to afford the title compound as a white solid (0.164 g, 78%), mp: 180 °C (decomposed). HPLC 94.1% [t_R = 10.34 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.19-4.12 (m, 1H), 3.84-3.79 (m, 1H), 3.75-3.70 (m, 1H), 3.60-3.58 (m, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.04-1.90 (m, 5H), 1.67-1.57 (m, 1H); ^{13}C NMR (100 MHz, Methanol-d_4) δ 175.77, 159.25, 138.71, 129.09, 123.45, 105.28, 76.72, 67.61, 45.27, 34.10, 32.68, 28.53, 26.45, 24.99; LC-MS (ESI+) *m/z* 391.15 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{19}H_{23}ClN_4O_3$ $(M+H)^+$ 391.1531, found 391.1541.



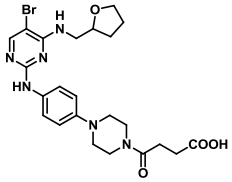
3-(4-(5-Chloro-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenyl)-*N*-(2-(dimethylamino)ethyl)propanamide [(±)-26]: The EDC-HCl (0.066 g, 0.346 mmol) was added to a solution of **24** (0.100 g, 0.266 mmol), *N*,*N*-dimethylethylenediamine (0.031 g, 0.346 mmol), HOBt (0.047 g, 0.346 mmol), and triethylamine (0.062 g, 0.612 mmol) in DMF (1 mL) and stirred under argon at room temperature for 18 hours. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate, and the solution was washed with sat. Na_2CO_3 solution. The organic phase was dried, filtered, and evaporated to afford the title compound as a light yellow powder (0.060 g, 51%), mp: 120 °C (decomposed). HPLC 92.0% [t_R = 7.79 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.80 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.20-4.14 (m, 1H), 3.91-3.86 (m, 1H), 3.78-3.73 (m, 1H), 3.61 (dd, J = 13.6, 4.8 Hz, 1H), 3.52 (dd, J = 13.6, 6.8 Hz, 1H), 3.27 (t, J = 6.8 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H), 2.45 (t, J = 7.6 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.25 (s, 6H), 2.08-1.86 (m, 3H), 1.73-1.63 (m, 1H); ^{13}C NMR (100 MHz, Methanol- d_4) δ 173.96, 158.17, 158.09, 152.26, 138.49, 134.17, 128.08, 119.36, 103.87, 77.46, 67.63, 57.67, 44.26, 43.93, 37.77, 36.39, 30.84, 28.46, 25.17; LC-MS (ESI+) *m/z* 447.23 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{22}H_{32}ClN_6O_2$ $(M+H)^+$ 447.2270, found 447.2270.



2-(4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenyl)acetic acid [(±)-27]: The **8b** (0.100 g, 0.2418 mmol) and 4-aminophenylacetic acid (0.034 g, 0.228 mmol) were mixed in a microwave vial with acetonitrile (3 mL), 2M aq. HCl (5 drops) was added and the vial was sealed and heated at 150 °C for 2h. Upon cooling, a precipitate formed. The reaction mixture was filtered, and the solid was purified by trituration with DCM to afford the title compound as a light gray solid (0.070 g, 75.6%), mp: 120 °C (decomposed). HPLC 81.3% [t_R = 9.48 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, Methanol- d_4) δ 7.97 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.19-4.13 (m, 1H), 3.86-3.81 (m, 1H), 3.76-3.70 (m, 1H), 3.64-3.53 (m, 4H), 2.04-1.87 (m, 3H), 1.67-1.60 (m, 1H); LC-MS (ESI+) *m/z* 407.07 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{17}H_{19}BrN_4O_3$ $(M+H)^+$ 407.0713, found 407.0718.

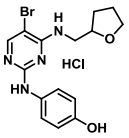


3-(4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenyl)propanoic acid [(±)-**28]**: The **8b** (0.100 g, 0.342 mmol) and 3-(4-aminophenyl)propionic acid (0.038 g, 0.228mmol) were mixed in a microwave vial with acetonitrile (3 mL), 5 drops of 2M aq. HCl were added and the vessel was sealed and heated at 150 °C for 2 h. Upon cooling, a precipitate formed. The reaction mixture was filtered, and the solid was purified by trituration with DCM to afford the title compound as a light gray solid (0.069 g, 73%), mp: 180 °C (decomposed). HPLC 81.0% [t_R = 9.85 min, 30% CH_3OH in 0.1% TFA water 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.46 (s, 1H), 8.25 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.07-4.04 (m, 1H), 3.72-3.67 (s, 1H), 3.61-3.55 (m, 1H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.50-2.30 (t, *J* = 7.2 Hz, 2H)), 1.90-1.77 (m, 3H), 1.59-1.53 (m, 1H). LC-MS (ESI+) *m/z* 421.09 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{17}H_{19}BrN_4O_3$ $(M+H)^+$ 421.0870, found 421.0878.

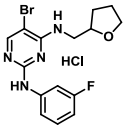


4-**(4-(4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenyl)piperazin-1-yl)-4-oxobutanoic acid** [(±)-**29**]: To a suspension of **9i** (0.129 g, 0.200 mmol) in chloroform (2 mL) under inert atmosphere was added DIPEA (0.259 g, 2.000 mmol). The mixture became a clear solution and cooled to 0 ºC. Succinic anhydride (0.020 g, 0.200 mmol) was added slowly. Then the reaction mixture was warmed up to r.t. and stirred for 1 h. The solvent was removed under reduced pressure. The residue was slurried with DCM/Hexane (1:1) and filtered to afford the title compound as a grey solid (0.095 g, 89%), mp: 177 ºC (decomposed). HPLC 98.5% [t_R = 3.20 min, 50% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 1H disappeared on D_2O shake), 9.00 (s, 1H disappeared on D_2O shake), 7.94 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 6.77 (appt, *J* = 5.2 Hz, 1H disappeared on D_2O shake), 4.10-4.04 (m, 1H), 3.78-3.73 (m, 1H), 3.63-3.56 (m, 5H), 3.42 (appt, 2H), 3.03 (appt, 2H), 2.96 (appt, 2H), 2.56 (t, *J* = 6.0 Hz, 2H),

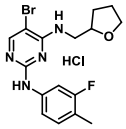
2.42 (t, *J* = 6.0 Hz, 2H), 1.92-1.77 (m, 3H), 1.62-1.54 (m, 1H); LC-MS (ESI+) *m/z* 533.16, 535.16 (Br isotope); $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{23}H_{30}BrN_6O_4$ $(M+H)^+$ 533.1506, found 533.1518.



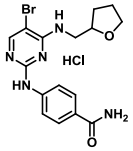
4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)phenol hydrochloride [(±)-30]: A suspension of **8b** (0.073 g, 0.250 mmol) and 4-aminophenol (0.027 g, 0.250 mmol) in EtOH (1 mL) was heated in a microwave reactor at 150 °C for 20 minutes. The mixture was evaporated and slurried with DCM/Hexane (3 mL) to afford the title compound as a white solid (0.078 g, 78%) mp: 206-207 ºC. HPLC 99.4% [t_R = 6.50 min, 35% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.89 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.18-4.13 (m, 1H), 3.86-3.81 (m, 1H), 3.77-3.71(m, 1H), 3.57 (appd, *J* = 4.8 Hz, 2H), 2.01-1.88 (m, 3H), 1.65-1.59 (m, 1H); LC-MS (ESI+) *m/z* 365.07 and 367.07 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{15}H_{18}BrN_4O_2$ $(M+H)^+$ 365.0608, found 365.0606.



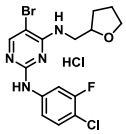
5-Bromo-*N*2-(3-fluorophenyl)-*N*4-((tetrahydrofuran-2-yl)methyl)pyrimidine-2,4-diamine hydrochloride [(±)-31]: This compound was synthesized using the procedure described for (±)-**30**, using **8b** (0.073 g, 0.250 mmol) and 3-fluoroaniline (0.028 g, 0.250 mmol) in EtOH (1 mL) and the product was recrystallized with DCM/Hexane (2/5) to afford the title compound as a white solid (0.080g, 79%). mp: 194-197 ºC; HPLC 98.4% [t_R = 15.31 min, 45% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.06 (s, 1H), 7.49-7.40 (m, 2H), 7.25 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 1H), 7.00 (tdd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 4.20-4.14 (m, 1H), 3.87-3.82 (m, 1H), 3.77-3.71 (m, 1H), 3.62 (d, *J* = 6.0 Hz, 2H), 2.07-1.99 (m, 1H), 1.96-1.87 (m, 2H), 1.67-1.59 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ -113.53; LC-MS (ESI+) *m/z* 367.05 and 369.05 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{15}H_{17}BrFN_4O$ $(M+H)^+$ 367.0564, found 367.0562.



5-Bromo-*N*2-(3-fluoro-4-methylphenyl)-*N*4-((tetrahydrofuran-2-yl)methyl)pyrimidine-2,4-diamine hydrochloride [(±)-32]: This compound was synthesized using the procedure described for (±)-**30,** except using 3-fluoro-4-methylaniline (0.031 g, 0.250 g) to afford the title compound as a white solid (0.090 g, 87%), mp: 189 ºC (decomposed). HPLC 98.2% [t_R = 8.67 min, 45% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.03 (s, 1H), 7.36 (d, *J* = 11.2 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.20-4.13 (m, 1H), 3.87-3.82 (m, 1H), 3.77-3.71 (m, 1H), 3.60 (d, *J* = 6.4 Hz, 2H), 2.27 (s, 3H), 2.06-1.98 (m, 1H), 1.96-1.87 (m, 2H), 1.67-1.58 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ -117.36; LC-MS (ESI+) *m/z* 381.08 and 383.08 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}BrFN_4O$ $(M+H)^+$ 381.0721, found 381.0720.

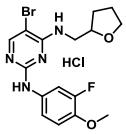


4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)benzamide hydrochloride [(±)-33]: This compound was synthesized using the procedure described for (±)-**30**, except using 4-aminobenzamide (0.034 g, 0.250 mmol) and re-crystalized with MeOH/DCM (1/2) to afford the title compound as a white solid (0.079g, 75%), mp: 251 ºC (decomposed). HPLC 98.8% [t_R = 7.44 min, 35% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.08 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 4.21-4.14 (m, 1H), 3.87-3.82 (m, 1H), 3.77-3.72 (m, 1H), 3.64-3.62 (m, 2H), 2.27, 2.07-1.99 (m, 1H), 1.96-1.90 (m, 2H), 1.70-1.62 (m, 1H); LC-MS (ESI+) *m/z* 392.07 and 394.07 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}BrN_5O_2$ $(M+H)^+$ 392.0717, found 392.0711.

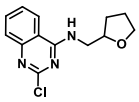


5-Bromo-*N*2-(4-chloro-3-fluorophenyl)-*N*4-((tetrahydrofuran-2-yl)methyl)pyrimidine-2,4-diamine hydrochloride [(±)-34]: This compound was synthesized using the procedure described for (±)-**30**, except using 4-chloro-3-fluoroaniline (0.035 g, 0.250 mmol) to afford the title compound as a white solid (0.076 g, 70%), mp: 172 ºC (decomposed). HPLC 98.5% [t_R = 14.23 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.07 (s, 1H), 7.68 (dd,

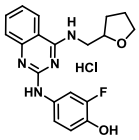
J = 11.2, 2.4 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.26 (ddd, *J* = 8.8, 2.4, 1.2 Hz, 1H), 4.19-4.13 (m, 1H), 3.86-3.83 (m, 1H), 3.77-3.72 (m, 1H), 3.61 (d, *J* = 6.0 Hz, 2H), 2.07-1.99 (m, 1H), 1.97-1.89 (m, 2H), 1.68-1.60 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ -115.76; LC-MS (ESI+) *m/z* 401.03 and 403.01 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{15}H_{16}BrClFN_4O$ $(M+H)^+$ 401.0175, found 401.0175.



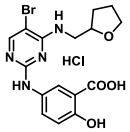
5-Bromo-*N*2-(3-fluoro-4-methoxyphenyl)-*N*4-((tetrahydrofuran-2-yl)methyl)pyrimidine-2,4-diamine hydrochloride [(±)-35]: This compound was synthesized using the procedure described for (±)-**30,** except using 3-fluoro-4-methoxyaniline (0.035 g, 0.250 mmol) to afford the title compound as a purple color solid (0.070 g, 65%), mp: 169 ºC (decomposed). HPLC 97.4% [t_R = 4.21 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (s, 1H), 7.38 (d, *J* = 12.8 Hz, 1H), 7.18-7.13 (m, 2H), 4.18-4.12 (m, 1H), 3.87-3.81 (m, 1H), 3.77-3.71 (m, 1H), 3.58 (d, *J* = 6.0 Hz, 2H), 2.05-1.96 (m, 1H), 1.90-1.89 (m, 2H), 1.66-1.57 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ -134.79; LC-MS (ESI+) *m/z* 397.07 and 399.07 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{16}H_{19}BrFN_4O_2$ $(M+H)^+$ 397.0670, found 397.0667.



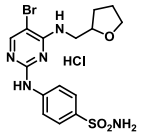
2-Chloro-*N*-((tetrahydrofuran-2-yl)methyl)quinazolin-4-amine [(±)-36]: To a solution of (tetrahydrofuran-2-yl)methanamine (0.620 mL, 6.000 mmol) in MeOH (10 mL) was added triethylamine (0.836 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 10 minutes. 2,4-Dichloroquinazoline (1.000 g, 5.000 mmol) in DCM (5 mL) was added dropwise at 0 °C. After the addition, the reaction mixture was warmed up to r.t. and stirred for 30 minutes. The solvent was removed and water (30 mL) was added to the residue. The suspension was sonicated, filtered and washed with water (10 mL × 2), dried under high vacuum to afford the title compound as a white solid (1.309 g, 99%), mp: 132-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.71 (m, 3H), 7.45 (td, *J* = 8.0, 1.6 Hz, 1H), 6.46 (brs, 1H), 4.18 (ddd, *J* = 16.0, 7.6, 3.6 Hz, 1H), 4.05 (ddd, *J* = 13.6, 6.4, 3.2 Hz, 1H), 3.97-3.91 (m, 1H), 3.86-3.80 (m, 1H), 2.15-2.07 (m, 1H), 2.00-1.93 (m, 2H), 1.71-1.62 (m, 1H); HPLC-MS (ESI+) *m/z* 264.2 $(M+H)^+$.



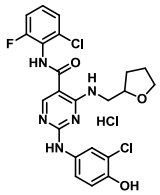
2-Fluoro-4-(4-((tetrahydrofuran-2-yl)methylamino)quinazolin-2-ylamino)phenol hydrochloride [(±)-**37]**: This compound was synthesized using the procedure described for (±)-**30,** except using (±)-**36** (0.066 g, 0.250 mmol) and 4-amino-2-fluorophenol (0.032 g, 0.250 mmol) and re-crystalized with MeOH/DCM/Hexane (5 mL, 1:4:5) to afford the title compound as a grey colored solid (0.077 g, 79%), mp: 144 ºC (decomposed). HPLC 98.6% [t_R = 9.31 min, 45% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.47 (td, *J* = 7.6, 0.8 Hz, 1H), 7.32 (d, *J* = 12.4 Hz, 1H), 7.07 (ddd, *J* = 8.4, 2.4, .1.2 Hz, 1H), 7.00 (t, *J* = 8.4 Hz, 1H), 4.27-4.21 (m, 1H), 3.90-3.84 (m, 1H), 3.79-3.74 (m, 2H), 3.67-3.63 (m, 1H), 2.08-2.00 (m, 1H), 1.97-1.87 (m, 2H), 1.69-1.61 (m, 1H); LC-MS (ESI+) *m/z* 355.15 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{19}H_{20}FN_4O_2$ $(M+H)^+$ 355.1565, found 355.1564.



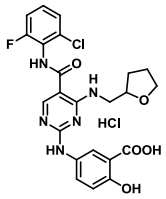
5-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)-2-hydroxybenzoic acid hydrochloride [(±)-**38]**: This compound was synthesized using the procedure described for (±)-**30,** except using **8b** (0.073 g, 0.250 mmol) and 5-amino-2-hydroxybenzoic acid (0.038 g, 0.250 mmol). The compound was then slurried with MeOH/DCM (4 mL, 1:1) and sonicated. The mixture was filtered, and the resulting solid was dried to afford the title compound as a grey solid (0.068 g, 61%), mp: 211 ºC (decomposed). HPLC 98.4% [t_R = 6.77 min, 45% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.09 (brs, 1H disappeared on D_2O shake), 9.98 (s, 1H disappeared on D_2O shake), 8.15 (s, 1H disappeared on D_2O shake), 8.07 (s, 1H overlapping with brs), 8.03 (brs, 1H overlapping with singlet, disappeared on D_2O shake), 7.58 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.06-4.00 (m, 1H), 3.70-3.65 (m, 2H overlapping with water peak), 1.83-1.73 (m, 3H), 1.54-1.48 (m, 1H); LC-MS (ESI+) *m/z* 409.05 and 411.05 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{16}H_{18}BrN_4O_4$ $(M+H)^+$ 409.0506, found 409.0509.



4-(5-Bromo-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)benzenesulfonamide hydrochloride [(±)-39]: This compound was synthesized using the procedure described for (±)-**30,** except using **8b** (0.073 g, 0.250 mmol) and 4-aminobenzenesulfonamide (0.043 g, 0.250 mmol). The resulting precipitate was filtered upon cooling and washed with MeOH (1 mL × 2) to afford the title compound as a white solid (0.066 g, 57%), mp: 214 ºC (decomposed). HPLC 96.3% [t_R = 6.21 min, 35% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H disappeared on D_2O shake), 8.19 (s, 1H), 7.81 (d, J = 8.8 Hz, 3H overlapping with singlet), 7.73 (d, J = 8.8, 2H), 7.24 (brs, 2H disappeared on D_2O shake), 4.13-4.07 (m, 1H), 3.79-3.73 (m, 2H overlapping with water peak), 1.94-1.77 (m, 3H), 1.66-1.59 (m, 1H); LC-MS (ESI+) *m/z* 428.03 and 430.03 for Br-isotopes $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{15}H_{19}BrN_5O_3S$ $(M+H)^+$ 428.0387, found 428.0384.



2-(3-Chloro-4-hydroxyphenylamino)-*N*-(2-chloro-6-fluorophenyl)-4-((tetrahydrofuran-2-yl)methylamino)pyrimidine-5-carboxamide hydrochloride [(±)-40]: This compound was synthesized using the procedure described for (±)-**30,** except using **8c** (0.050 g, 0.130 mmol) and 4-amino-2-chlorophenol (0.019 g, 0.130 mmol). The resulting mixture was then concentrated and the resulting residue was re-crystalized with DCM/Hexane (1/2) to yield the title compound as a gray solid (0.053 g, 77%), mp: 158 ºC (decomposed). HPLC 97.5% [t_R = 9.27 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, CD_3OD): δ 8.53 (s, 1H), 7.60 (brs, 1H), 7.41-7.38 (m, 2H), 7.25-7.20 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 4.16-4.10 (m, 1H), 3.89-3.84 (m, 1H), 3.77-3.59 (m, 3H), 2.08-2.00 (m, 1H), 1.95-1.89 (m, 2H), 1.66-1.60 (m, 1H); ^{19}F NMR (376 MHz, CD_3OD): δ -118.23- -118.26 (m); LC-MS (ESI+) *m/z* 492.09 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{22}H_{21}Cl_2FN_5O_3$ $(M+H)^+$ 492.1000, found 492.0992.



5-(5-(2-Chloro-6-fluorophenylcarbamoyl)-4-((tetrahydrofuran-2-yl)methylamino)pyrimidin-2-ylamino)-2-hydroxybenzoic acid hydrochloride [(±)**-41]**: This compound was synthesized using the procedure described for (±)**-30,** except using **8c** (0.050 g, 0.130 mmol) and 5-amino-2-hydroxybenzoic acid (0.020 g, 0.130 mmol). The resulting precipitate was filtered upon cooling, and washed with MeOH (2 mL). The solid was dried under high vacuum to afford the title compound as a white solid (0.050 g, 71%), mp: 298 ºC (decomposed). HPLC 99.7% [t_R = 11.31 min, 55% CH_3OH in 0.1% TFA water, 20 min]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.99 (brs, 1H disappeared on D_2O shake), 9.91 (s, 1H disappeared on D_2O shake), 9.74 (brs, 1H disappeared on D_2O shake), 8.93 (s, 1H disappeared on D_2O shake), 8.76 (s, 1H), 8.57 (brs, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.42-7.33 (m, 3H), 6.90 (d, J = 8.8 Hz, 1H), 4.01-3.95 (m, 1H), 3.74-3.66 (m, 2H), 3.63-3.57 (m, 1H), 3.44-3.38 (m, 2H), 1.96-1.87 (m, 1H), 1.83-1.75 (m, 2H), 1.57-1.48 (m, 1H); ^{19}F NMR (376 MHz, DMSO-d_6): δ -116.22- -116.26 (m); LC-MS (ESI+) *m/z* 502.12 $(M+H)^+$; HRMS (ESI+) *m/z* calculated for $C_{23}H_{22}ClFN_5O_5$ $(M+H)^+$ 502.1288, found 502.1294.

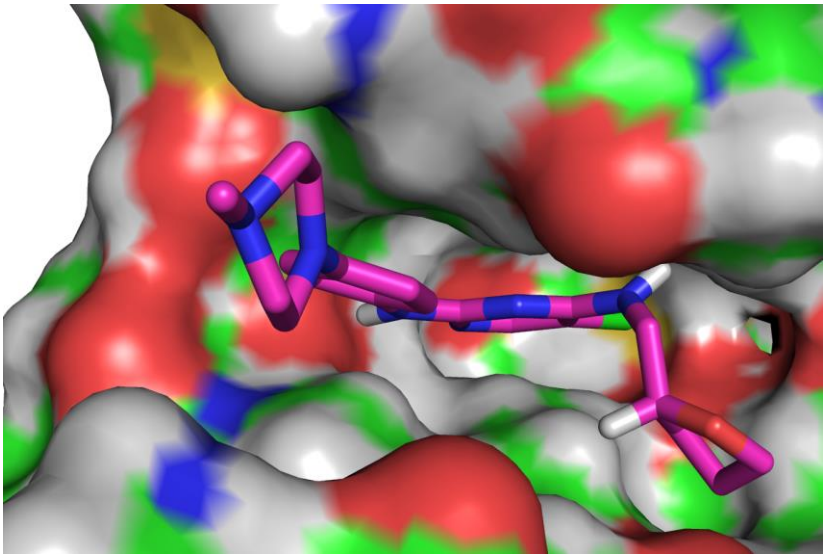


Figure S1. Compound (*R*)-**9b** (blue) (as docked in ACK1) superposed onto JAK2 (pdb 4JI9). The surface is colored according to atom type (carbon, green; hydrogen, gray; oxygen, red and nitrogen, blue). The image was rendered using Pymol.

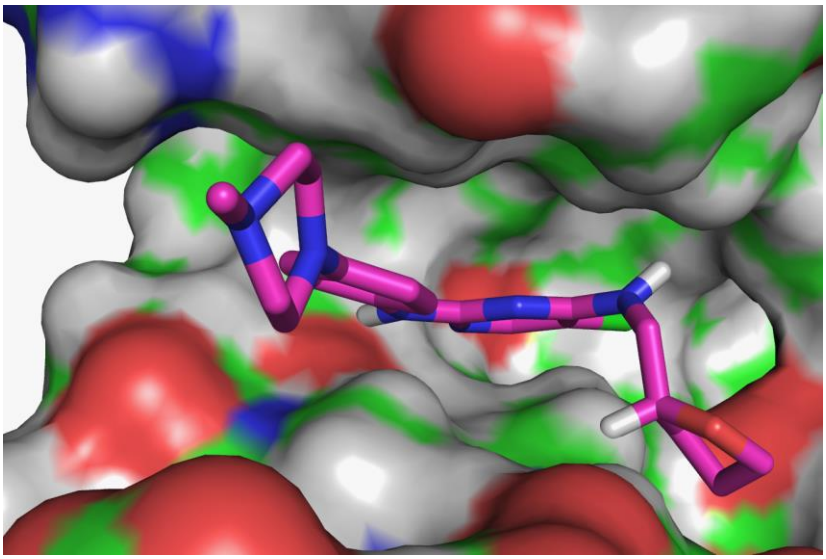


Figure S2. Compound (*R*)-**9b** (blue) (as docked in ACK1) superposed onto ALK (pdb 3AOX). The surface is colored according to atom type (carbon, green; hydrogen, gray; oxygen, red and nitrogen, blue). The image was rendered using Pymol.