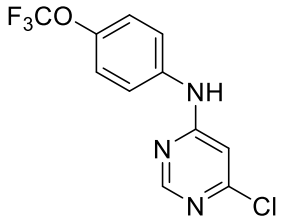
Synthesis of Allosteric BCR-ABL1 PROTAC and Diastereomer Control

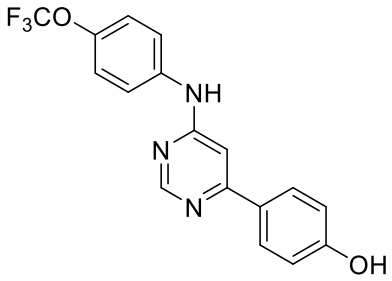
6-chloro-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



Following a literature procedure,[1] 4,6-dichloropyrimidine (1 g, 6.71 mmol) and 4-(trifluoromethoxy)aniline (1189 mg, 6.71 mmol) suspended in ethanol (30 ml) and triethylamine (0.93 ml, 6.71 mmol) added. Reaction heated to reflux overnight, allowed to cool to r.t. and concentrated *in vacuo*. Residue purified by column chromatography eluting with 0-6% methanol/DCM to yield the title compound as an off white solid (1.04 g, 54%).

Data matches literature reports.[1]

4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenol

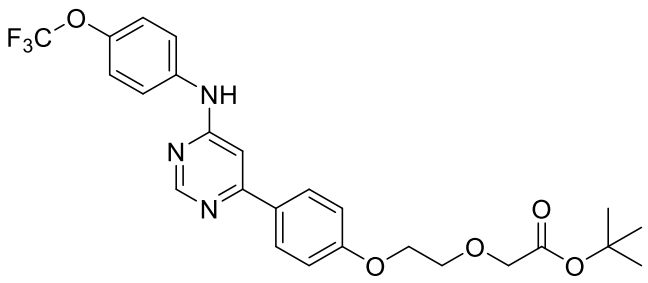


Following an adapted literature procedure,[1] 6-chloro-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine (300 mg, 1.04 mmol), (4-hydroxyphenyl)boronic acid (143 mg, 1.04 mmol), tetrakis(triphenylphosphine)palladium(0) (120 mg, 10 mol%) and sodium carbonate (439 mg, 4.14 mmol) were heated to reflux in a 1:1 mixtures of acetonitrile/water (20 ml) overnight. The resulting suspension was filtered hot, cooled to r.t., adjusted to pH 4 with conc. HCl. The resulting precipitate was collected by filtration, washed with water and dried *in vacuo* (345 mg, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 10.18 (s, 1H), 8.71 (s, 1H), 7.82 (dd, J = 17.2, 8.8 Hz, 4H), 7.35 (d, J = 8.6 Hz, 2H), 7.17 (s, 1H), 6.91 (d, J = 8.5 Hz, 2H).

LC-MS (ESI) m/z: 348

tert-butyl 2-(2-(4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenoxy)ethoxy)acetate



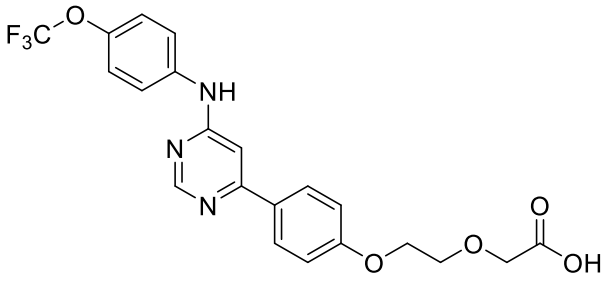
4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenol (100 mg, 0.288 mmol) was suspended in 1,4-dioxane (4 ml) and treated with tert-butyl 2-(2-iodoethoxy)acetate (82 mg, 0.288 mmol) and

caesium carbonate (113 mg, 0.346 mmol). The reaction mixture was heated to 120 °C under microwave conditions for 4 hours, cooled to r.t., filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0-30% ethyl acetate/hexane to yield the title compound (60 mg, 42%)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 1.1 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.27 – 7.20 (m, 4H), 6.97 (dd, *J* = 5.0, 3.8 Hz, 3H), 4.23 – 4.16 (m, 2H), 4.08 (s, 2H), 3.96 – 3.85 (m, 2H), 1.47 (s, 8H).

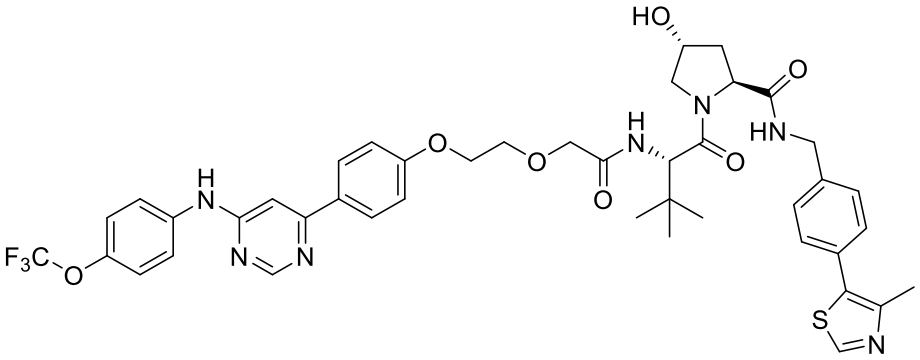
LC-MS (ESI) m/z: 506

2-(2-(4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenoxy)ethoxy)acetic acid



tert-butyl 2-(2-(4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenoxy)ethoxy)acetate (40 mg, 0.079 mmol) dissolved 20% TFA in DCM (10 ml) and stirred for 2 hours at r.t. Reaction concentrated *in vacuo* and used immediately in next step.

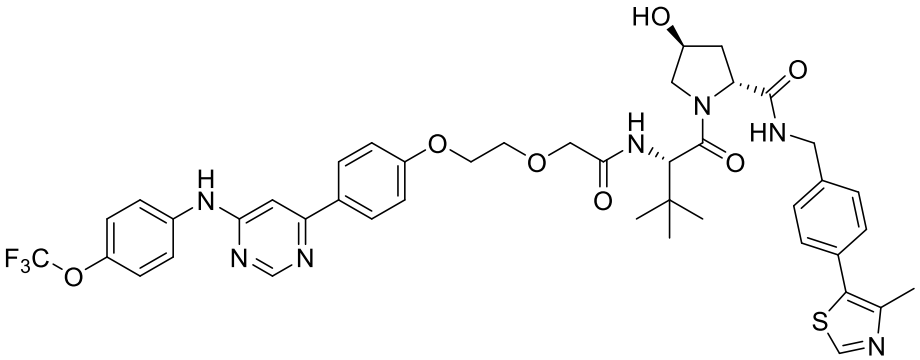
(2S,4R)-1-((S)-3,3-dimethyl-2-(2-(2-(4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenoxy)ethoxy)acetamido)butanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (GMB_475)



2-[2-[4-[6-[4-(trifluoromethoxy)anilino]pyrimidin-4-yl]phenoxy]ethoxy]acetic acid (35 mg, 0.079 mmol) was dissolved in DMF (10 ml) and treated with (2S,4R)-1-[(2S)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-N-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (34 mg, 0.079 mmol), HATU (36 mg, 0.095 mmol) and triethylamine (55 µl, 0.395 mmol). The reaction mixture was stirred overnight at r.t., diluted with ethyl acetate (30 ml) and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0-10% methanol/DCM.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 – 8.55 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.38 – 7.18 (m, 9H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 1.2 Hz, 1H), 4.65 – 4.44 (m, 4H), 4.18 (t, *J* = 4.3 Hz, 2H), 4.05 (d, *J* = 4.8 Hz, 2H), 3.88 (d, *J* = 4.2 Hz, 1H), 3.68 – 3.55 (m, 1H), 2.46 (s, 3H), 0.93 (s, 9H).
HRMS: calc. $[M+H]^+$ for $C_{43}H_{46}F_3N_7O_7S$ = 862.3165; found = 863.2714 $[M+H]^+$.

(2R,4S)-1-((S)-3,3-dimethyl-2-(2-(2-(4-(6-((4-(trifluoromethoxy)phenyl)amino)pyrimidin-4-yl)phenoxy)ethoxy)acetamido)butanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (GMB-651)



2-[2-[4-[6-[4-(trifluoromethoxy)anilino]pyrimidin-4-yl]phenoxy]ethoxy]acetic acid (16 mg, 0.036 mmol) was dissolved in DMF (10 ml) and treated with (2R,4S)-1-[(2S)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-N-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (15.5 mg, 0.036 mmol), HATU (17 mg, 0.043 mmol) and triethylamine (25 µl, 0.180 mmol). The reaction mixture was stirred overnight at r.t., diluted with ethyl acetate (30 ml) and washed with water (2 x 10 ml) and brine (10 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0-10% methanol/DCM.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (d, *J* = 1.1 Hz, 1H), 8.62 (s, 1H), 7.92 – 7.85 (m, 2H), 7.50 (td, *J* = 6.3, 5.7, 2.2 Hz, 3H), 7.34 – 7.29 (m, 3H), 7.24 – 7.20 (m, 1H), 7.17 (d, *J* = 6.9 Hz, 1H), 6.96 (s, 1H), 6.93 (d, *J* = 1.4 Hz, 2H), 4.74 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.64 – 4.49 (m, 2H), 4.31 (d, *J* = 7.0 Hz, 1H), 4.21 (dd, *J* = 15.5, 5.0 Hz, 1H), 4.12 – 4.05 (m, 3H), 3.91 (d, *J* = 15.7 Hz, 1H), 3.71 (dd, *J* = 5.9, 3.2 Hz, 2H), 3.63 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.51 (d, *J* = 15.7 Hz, 1H), 2.47 (s, 3H), 1.05 (s, 9H).

HRMS: calc. $[M+H]^+$ for $C_{43}H_{46}F_3N_7O_7S$ = 862.3165; found = 862.3298 $[M+H]^+$.

1. X. Deng, B. Okram, Q. Ding, J. Zhang, Y. Choi, F. J. Adrián, A. Wojciechowski, G. Zhang, J. Che, B. Bursulaya, S. W. Cowan-Jacob, G. Rummel, T. Sim and N. S. Gray, *Journal of Medicinal Chemistry*, 2010, 53, 6934-6946.