Supporting Information

Expanding the Diversity of Allosteric Bcr-Abl Inhibitors

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Contents

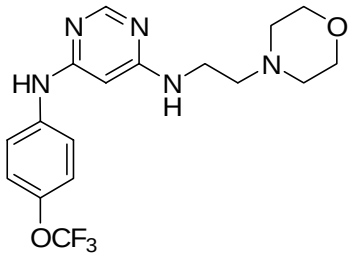
1. Chemistry. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on 400 MHz (Bruker XWIN-NMR) or 600 MHz (Varian AS600), and chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Spin multiplicities are described as s (singlet), brs (broad singlet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a Waters Micromass ZQ instrument. Preparative HPLC was performed on a Waters Symmetry C18 column (19 x 50 mm, 5μM) using a gradient of 5-95% acetonitrile in water containing 0.05% trifluoacetic acid (TFA) over 8 min (10 min run time) at a flow rate of 30 mL/min.

2. Spectral data of 4a, 4c-4e, 5a-5k, 6a-6f, 7a-7d, 8a-8g, 9a-9l, 12, 14b-14g, 16b-16d, 20b, 21b-21f, 21h-21l and 22.

Table 1.

Compounds **4a** and **4c-4f** were prepared using similar synthetic procedure of **4b**.

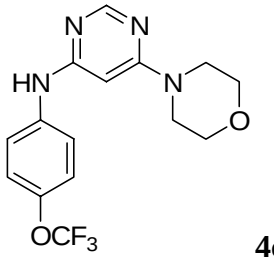
***N*^{4}-(2-morpholinoethyl)-*N*^{6}-(4-(trifluoromethoxy)phenyl)pyrimidine-4,6-diamine**



4a

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.76 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.89 (s, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 2.27(d, *J* = 4.3 Hz, 2H), 2.58 (t, *J* = 5.2 Hz, 2H), 2.45 (t, *J* = 5.3 Hz, 4H). MS (ESI) *m/z* 384 (M+1)

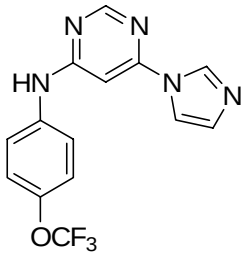
6-morpholino-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



4c, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.24 (s, 1H), 7.48 (d, *J* = 6.6 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 5.99 (s, 1H), 3.75 (t, *J* = 4.8 Hz, 4 H), 3.69 (t, *J* = 4.8 Hz, 4H). MS (ESI) *m/z* 341 $(M+H)^+$.

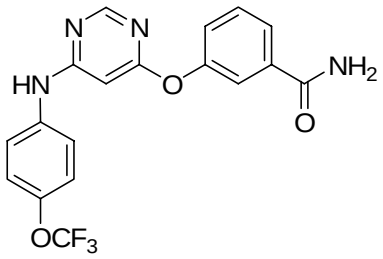
6-(1H-imidazol-1-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



4d

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.67 (s, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.51 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.05 (s, 1H). MS (ESI) *m/z* 322 $(M+H)^+$.

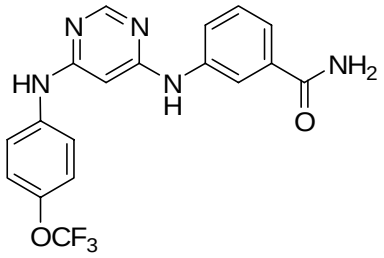
3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yloxy)benzamide



4e, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.32 (d, *J* = 0.6 Hz, 1H), 7.80 (ddd, *J* = 0.6, 1.2, 8.4 Hz, 1H), 7.69 (t, *J* = 1.8 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 7.56 (t, *J* = 8.4 Hz, 1H), 7.36 (ddd, *J* = 0.6, 2.4, 10.8 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.11 (d, *J* = 0.6 Hz, 1H). MS (ESI) *m/z* 391 $(M+H)^+$.

3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-ylamino)benzamide

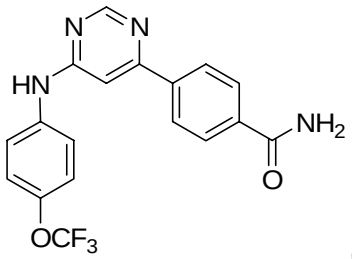


4f, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.31 (s, 1H), 7.93 (t, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.54-7.51 (m, 3H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.14 (s, 1H). MS (ESI) *m/z* 390 $(M+H)^+$, HRMS (ESI) calcd for $C_{18}H_{14}F_3N_5O_2$ 389.1100, found 390.1178 $(M+H)^+$.

Compounds **5a-5h** were prepared using similar synthetic procedure of **1**[1].

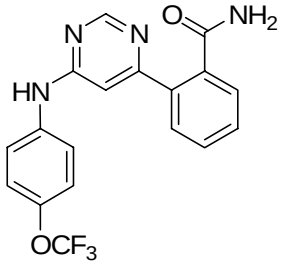
4-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzamide



5a, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.81 (d, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 0.6 Hz, 1H). MS (ESI) *m/z* 375 $(M+H)^+$.

2-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzamide

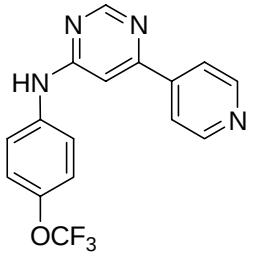


5b, TFA salt

[1] Adrian, F. J.; Ding, Q.; Sim, T.; Velentza, A.; Sloan, C.; Liu, Y.; Zhang, G.; Hur, W.; Ding, S.; Manley, P.; Mestan, J.; Fabbro, D.; Gray, N. S. Allosteric inhibitors of Bcr-abl-dependent cell proliferation. *Nat. Chem. Biol.* **2006**, *2*, 95-102.

^{1}H NMR (600 MHz, CD_3OD) δ 8.79 (s, 1H), 8.21 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.80-7.77 (m, 3H), 7.74 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.59 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.93 (s, 1H). MS (ESI) *m/z* 375 $(M+H)^+$.

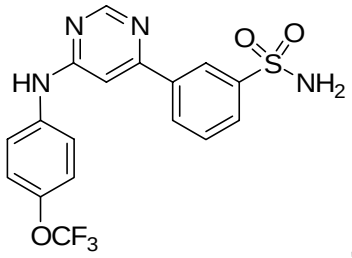
6-(pyridin-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



5c

^{1}H NMR (400 MHz, $CDCl_3$), δ 8.83 (s, 1H), 8.79 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 1H). MS (ESI) *m/z* 333 $(M+H)^+$.

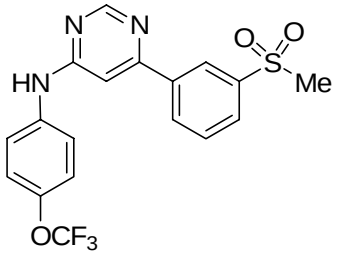
3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzenesulfonamide



5d

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.53 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 5.1 Hz, 1H), 7.85 (d, *J* = 6.9 Hz, 2H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.48 (s, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.33 (s, 1H). MS (ESI) *m/z* 411 $(M+H)^+$.

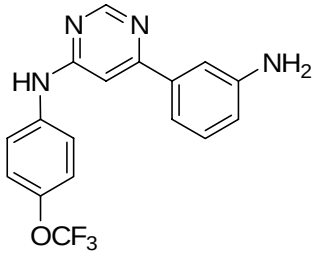
6-(3-(methylsulfonyl)phenyl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



5e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.55-8.54 (m, 1H), 8.30-8.28 (m, 1H), 8.10-8.03 (m, 1H), 7.71-7.68 (m, 1H), 7.55-7.53 (m, 2H), 7.28-7.27 (m, 1H), 7.10-7.09 (m, 2H), 3.11 (s, 3H). MS (ESI) *m/z* 410 $(M+H)^+$.

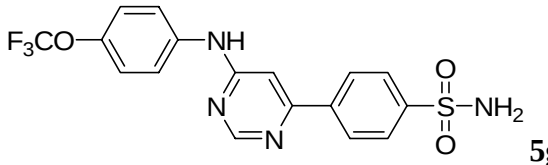
6-(3-aminophenyl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



5f, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.80 (s, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.46-7.42 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (s, 1H). MS (ESI) *m/z* 347 $(M+H)^+$.

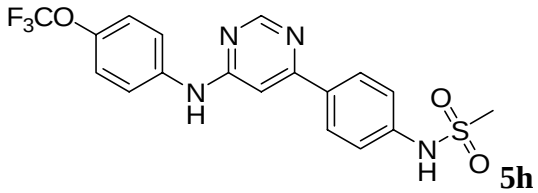
4-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzenesulfonamide



5g

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.97 (brs, 1H), 8.76 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.44 (brs, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 1H). MS (ESI) *m/z* 411 $(M + H)^+$.

N-(4-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)phenyl)methane-sulfonamide

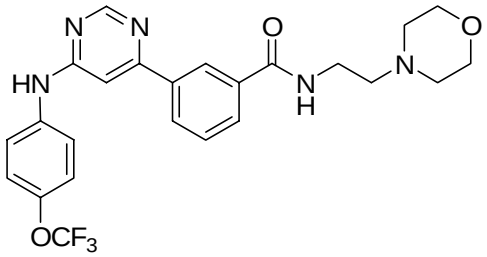


5h

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.80 (s, 1H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 0.8 Hz, 1H), 2.47 (d, *J* = 4.8 Hz, 3H). MS (ESI) *m/z* 425 $(M + H)^+$.

Compounds **5i-5k** were prepared using similar synthetic procedure of **2**.

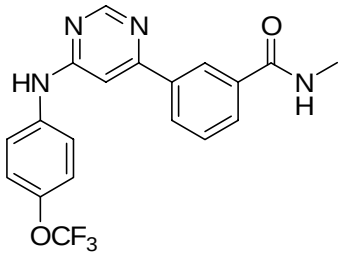
N-(2-morpholinoethyl)-3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzamide



5i

^{1}H NMR (600 MHz, CD_3OD) δ 8.69 (d, *J* = 1.2 Hz, 1H), 8.45 (t, *J* = 1.8 Hz, 1H), 8.13 (ddd, *J* = 1.2, 1.8, 7.8 Hz, 1H), 7.94 (ddd, *J* = 1.2, 1.8, 7.8 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 0.6, 9.0 Hz, 2H), 7.20 (d, *J* = 1.2 Hz, 1H), 3.71 (t, *J* = 4.8 Hz, 4H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 6.6 Hz, 2H), 2.56 (s, br, 4H). MS (ESI) *m/z* 488 $(M+H)^+$.

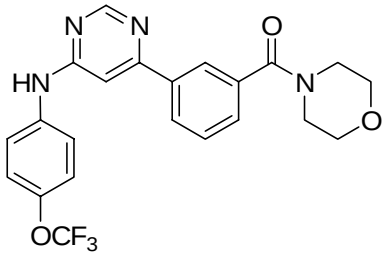
N-methyl-3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)benzamide



5j, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.83 (s, 1H), 8.33 (t, *J* = 1.8 Hz, 1H), 8.07-8.05 (m, 1H), 8.03-8.01 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.26 (s, 1H), 2.96 (s, 3H). MS (ESI) *m/z* 389 $(M+H)^+$.

Morpholino(3-(6-(4-(trifluoromethoxy)phenylamino)pyrimidin-4-yl)phenyl)methanone

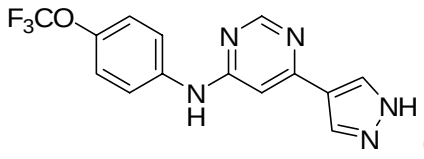


5k, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.85 (s, 1H), 7.98-7.97 (m, 1H), 7.92 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.76-7.71 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (s, 1H), 3.78 (brs, 4H), 3.65 (brs, 2H), 3.48 (brs, 2H). MS (ESI) *m/z* 445 $(M+H)^+$.

Compounds **6a-6f** were prepared using similar synthetic procedure to that of **1**, and corresponding substituted pyrazoleboronic acids were used.

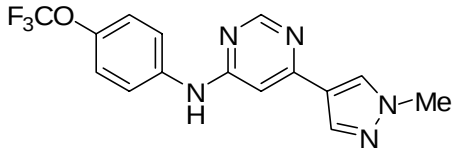
6-(1H-pyrazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



6a

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.84 (s, 1H), 8.42 (s, 2H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 2H), 7.14 (s, 1H). MS (ESI) *m/z* 322 $(M + H)^+$. HRMS (ESI) calcd for $C_{14}H_{10}F_3N_5O$ 321.0837, found 322.0910 $(M+H)^+$.

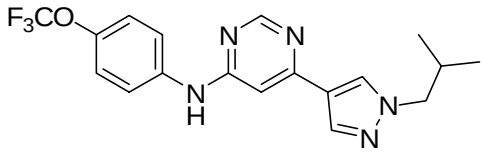
6-(1-methyl-1H-pyrazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



6b

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.58 (s, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H), 3.91 (s, 3H); MS (ESI) *m/z* 336 $(M + H)^+$.

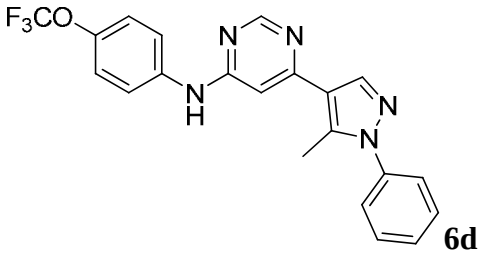
6-(1-isobutyl-1H-pyrazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



6c

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.71 (s, 1H), 8.44 (s, 1H), 8.09 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.00 (brs, 1H), 4.01 (d, J = 7.2 Hz, 2H), 2.19-2.12 (m, 1H), 0.87 (d, J = 4.0 Hz, 6H). MS (ESI) *m/z* 378 $(M + H)^+$.

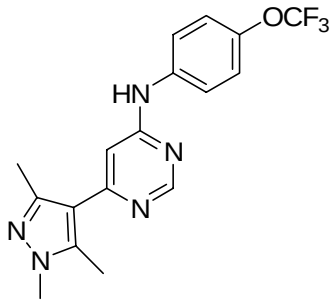
6-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



6d

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.77 (s, 1H), 8.19 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.64-7.63 (m, 3H), 7.55-7.51 (m, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.05 (s, 1H), 2.69 (s, 3H). MS (ESI) *m/z* 412 $(M + H)^+$.

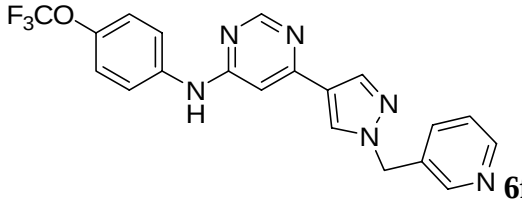
N-(4-(trifluoromethoxy)phenyl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyrimidin-4-amine



6e

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.65 (s, 1H), 7.82 (*d*, J = 9.2 Hz, 2H), 7.33 (*d*, J = 9.2 Hz, 2H), 6.82 (s, 1H), 3.72 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H); MS (ESI) *m/z* 364 $(M + H)^+$.

6-(1-(pyridin-3-ylmethyl)-1H-pyrazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)-pyrimidin-4-amine

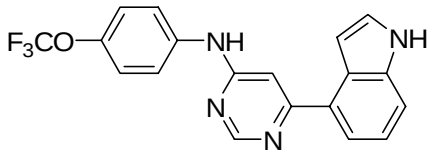


6f

^{1}H NMR (400 MHz, DMSO-d_6) 9.97 (s, 1H), 8.58 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.02 (brs, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.40-7.43 (m, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (s, 1H), 7.04 (s, 1H), 6.91 (m, 1H), 5.43 (s, 2H); MS (ESI) *m/z* 413 $(M + H)^+$.

Compounds **7a-7d** were prepared using similar synthetic procedure to that of **1**, and corresponding substituted heteroaromatic boronic acids were used.

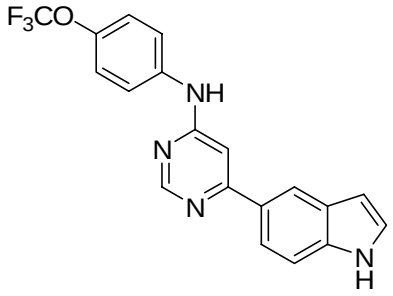
6-(1H-indol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



7a

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.86 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.63-7.58 (m, 2H), 7.42-7.39 (m, 3H), 7.27 (t, J = 3.2 Hz, 1H), 6.93 (brs, 1H); MS (ESI) *m/z* 371 $(M + H)^+$.

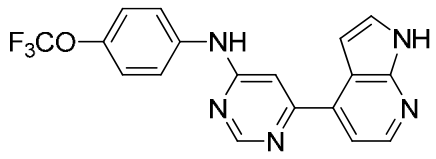
6-(1H-indol-5-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



7b

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 8.77 (s, 1H), 8.29 (s, 1H), 7.85 (d, J = 8.8 Hz, 1 H), 7.76 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 1H), 7.47 (t, J = 3.2 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.28 (s, 1H), 6.60 (brs, 1H); MS (ESI) *m/z* 371 $(M + H)^+$.

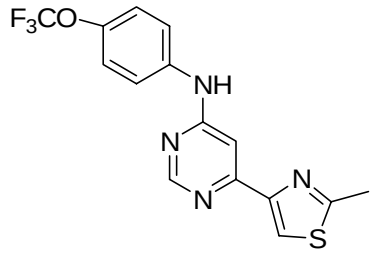
6-(1H-pyrrolo[2,3-b]pyridin-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



7c

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 10.21 (s, 1H), 8.88 (s, 1H), 8.40 (d, J = 4.8 Hz, 1 H), 7.88 (*d*, J = 8.4 Hz, 2H), 7.72 (t, J = 3.2 Hz, 1H), 7.65 (d, J = 5.2 Hz, 1H), 7.52 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 6.97 (*dd*, J = 2, 3.6 Hz, 1H); MS (ESI) *m/z* 372 (M + H)$^+$.

6-(2-methylthiazol-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



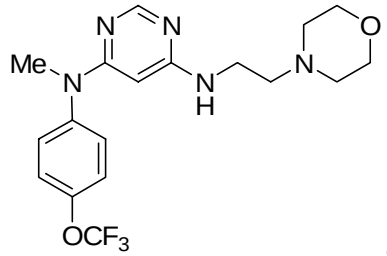
7d

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.67 (s, 1H), 8.24 (s, 1H), 7.84 (d, J = 9.2 Hz, 2H), 7.50 (d, J = 0.8 Hz, 1H), 7.35 (d, J = 9.2 Hz, 2H), 2.74 (s, 3H); MS (ESI) *m/z* 353 (M + H)$^+$.

Table 2.

Compounds **8a-8g** were prepared using the similar synthetic procedure to that of **4b**.

***N*^{4}-methyl-*N*^{6}-(2-morpholinoethyl)-*N*^{4}-(4-(trifluoromethoxy)phenyl)pyrimidine-4,6-diamine**

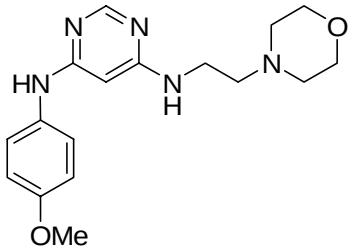


8a, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.22 (s, 1H), 7.49-7.45 (m, 4H), 5.68 (s, 1H), 3.92 (brs, 4H), 3.85 (t, J = 5.4 Hz, 2H), 3.47 (s, 3H), 3.41 (t, J = 6.0 Hz, 2H), 3.40-3.32 (m, 4H);

MS (ESI) *m/z* 398 $(M+H)^+$, HRMS (ESI) calcd for $C_{18}H_{22}F_3N_5O_2$ 397.1726, found 398.1791 $(M+H)^+$.

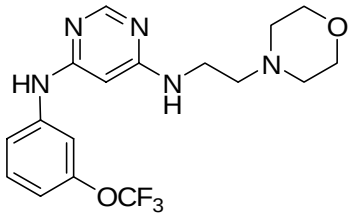
N^4-(4-methoxyphenyl)-N^6-(2-morpholinoethyl)pyrimidine-4,6-diamine



8b

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.33 (s, 1H), 8.08 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 5.74 (s, 1H), 3.78-3.86 (m, 4H), 3.76 (s, 3H), 3.65 (d, J = 5.6 Hz, 2H), 3.24-3.34 (m, 6H); MS (ESI) *m/z* 330 $M+H)^+$.

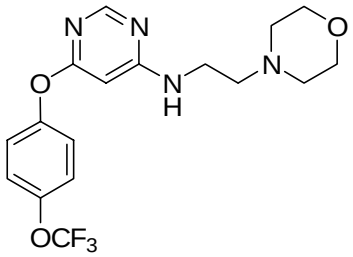
N^4-(2-morpholinoethyl)-N^6-(3-(trifluoromethoxy)phenyl)pyrimidine-4,6-diamine



8c

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 8.32 (s, 1H), 7.75 (s, 1H), 7.67 (s, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 5.93 (s, 1H), 3.80-3.88 (m, 4H), 3.65 (d, J = 5.6 Hz, 2H,), 3.26-3.36 (m, 6H); MS (ESI) *m/z* 384 $(M+H)^+$.

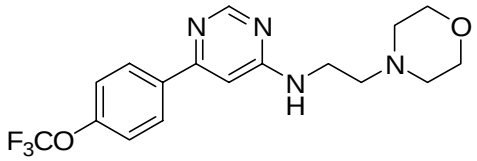
N-(2-morpholinoethyl)-6-(4-(trifluoromethoxy)phenoxy)pyrimidin-4-amine



8d

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.67 (s, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 3.86-3.94 (m, 4H), 3.66 (d, J = 5.6 Hz, 2H), 3.23-3.33 (m, 6H); MS (ESI) *m/z* 385 $(M+H)^+$.

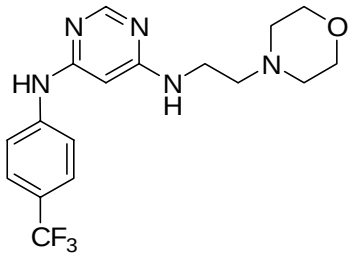
N-(2-morpholinoethyl)-6-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



8e

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.39 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.09 (s, 1H), 3.77-3.85 (m, 4H), 3.62 (d, J = 5.6 Hz, 2H), 3.32-3.42 (m, 6H); MS (ESI) *m/z* 369 $(M+H)^+$.

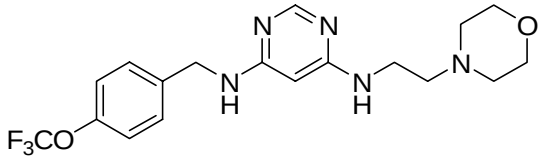
***N*^{4}-(2-morpholinoethyl)-*N*^{6}-(4-(trifluoromethyl)phenyl)pyrimidine-4,6-diamine**



8f

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.32 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 5.97 (s, 1H), 3.80-3.88 (m, 4H), 3.65 (d, J = 5.6 Hz, 2H), 3.26-3.36 (m, 6H); MS (ESI) *m/z* 368 $(M+H)^+$.

***N*^{4}-(4-(trifluoromethoxy)benzyl)-*N*^{6}-(2-morpholinoethyl)pyrimidine-4,6-diamine**



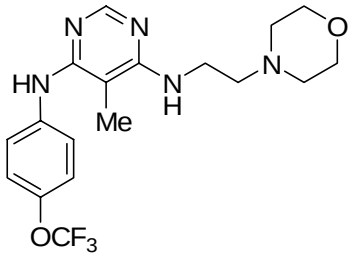
8g

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.57 (s, 1H), 4.47-4.51 (m, 2H), 3.76-3.84 (m, 4H), 3.58 (d, J = 5.6 Hz, 2H), 3.40-3.50 (m, 6H); MS (ESI) *m/z* 398 $(M+H)^+$.

Table 3.

Compounds **9a-9f** were prepared using the similar synthetic procedure to that of **4b**.

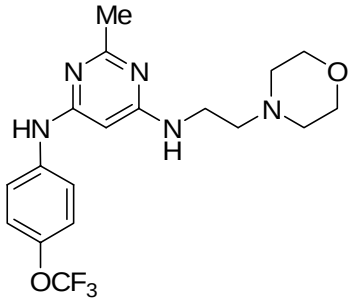
5-methyl-N^4-(2-morpholinoethyl)-N^6-(4-(trifluoromethoxy)phenyl)pyrimidine-4,6-diamine



9a, TFA salt

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.47-7.45 (m, 2H), 7.17 (d, J = 9.0 Hz, 2H), 6.18 (s, 1H), 5.50 (brs, 1H), 3.81 (brs, 4H), 3.68-3.62 (m, 2H), 2.76 (brs, 2H), 2.65 (s, br, 4H), 1.99 (s, 3H); MS (ESI) *m/z* 398 $(M+H)^+$.

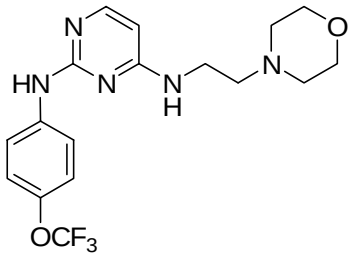
2-methyl-N^4-(2-morpholinoethyl)-N^6-(4-(trifluoromethoxy)phenyl)pyrimidine-4,6-diamine



9b, TFA salt

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.00 (brs, 1H), 5.57 (brs, 1H), 5.52 (s, 1H), 3.73-3.68 (m, 4H), 3.24 (brs, 2H), 2.58 (t, J = 6.0 Hz, 2H), 2.46 (brs, 4H), 2.41 (s, 3H); MS (ESI) *m/z* 398 $(M+H)^+$.

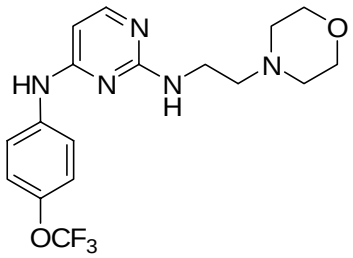
N^4-(2-morpholinoethyl)-N^2-(4-(trifluoromethoxy)phenyl)pyrimidine-2,4-diamine



9c

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.77 (s, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.22 (d, J = 6.0 Hz, 1H), 3.68-3.76 (m, 4H), 3.63 (d, J = 6.0 Hz, 2H), 3.26-3.36 (m, 6H); MS (ESI) *m/z* 384 $(M+H)^+$.

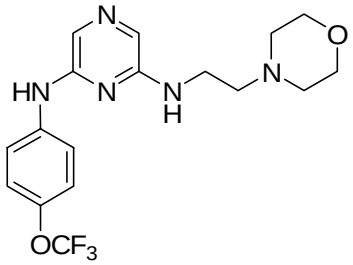
N^2-(2-morpholinoethyl)-N^4-(4-(trifluoromethoxy)phenyl)pyrimidine-2,4-diamine



9d

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.85 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.37 (d, J = 7.2 Hz, 1H), 3.71-3.78 (m, 4H), 3.60 (d, J = 6.0 Hz, 2H), 3.29-3.39 (m, 6H); MS (ESI) *m/z* 384 $(M+H)^+$.

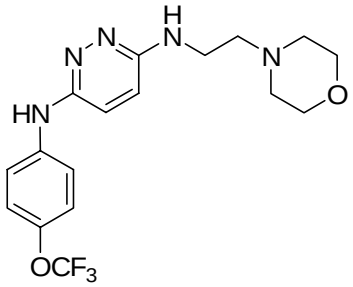
N^2-(2-morpholinoethyl)-N^6-(4-(trifluoromethoxy)phenyl)pyrazine-2,6-diamine



9e, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 7.66-7.63 (m, 2H), 7.34 (s, 1H), 7.30 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 3.92 (brs, 2H), 3.86 (t, J = 6.0 Hz, 2H), 3.75 (brs, 2H), 3.53 (brs, 2H), 3.41 (t, J = 6.0 Hz, 2H), 3.12 (brs, 2H); MS (ESI) *m/z* 384 $(M+H)^+$.

N^3-(2-morpholinoethyl)-N^6-(4-(trifluoromethoxy)phenyl)pyridazine-3,6-diamine

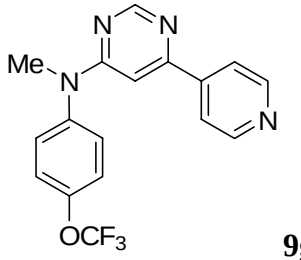


9f, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 7.65-7.63 (m, 2H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.42 (d, *J* = 10.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.94 (brs, 4H), 3.84 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 3.40 (brs, 4H); MS (ESI) *m/z* 384 $(M+H)^+$.

Compounds **9g-9k** were prepared using similar synthetic procedure to that of **1**.

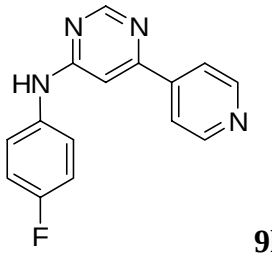
N-methyl-6-(pyridin-4-yl)-N-(4-(trifluoromethoxy)phenyl)pyrimidin-4-amine



9g, TFA salt

^{1}H NMR (600 MHz, CD_3OD) δ 8.85 (d, *J* = 4.8 Hz, 2H), 8.79 (s, 1H), 8.33 (d, *J* = 6.6 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.12 (s, 1H), 3.61 (s, 3H); MS (ESI) *m/z* 347 $(M+H)^+$, HRMS (ESI) calcd for $C_{17}H_{13}F_3N_4O$, found 347.1113 $(M+H)^+$.

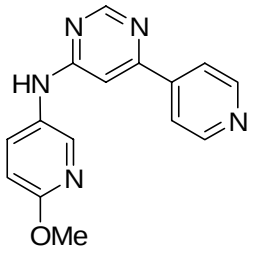
N-(4-fluorophenyl)-6-(pyridin-4-yl)pyrimidin-4-amine



9h

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.85 (d, J = 6.4 Hz, 2H), 8.78 (s, 1H), 8.14 (d, J = 6.4 Hz, 2H), 7.70-7.76 (m, 2H), 7.36 (s, 1H), 7.22 (t, J = 8.8 Hz, 2H); MS (ESI) *m/z* 267 $(M+H)^+$.

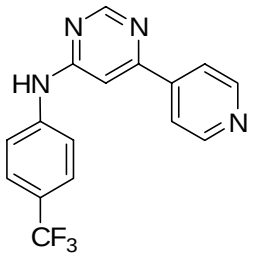
N-(4-methoxyphenyl)-6-(pyridin-4-yl)pyrimidin-4-amine



9i

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.86 (d, J = 6.4 Hz, 2H), 8.75 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 6.4 Hz, 2H), 8.02 (d, J = 8.8 Hz, 1H), 7.33 (s, 1H), 6.67 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H); MS (ESI) *m/z* 280 $(M+H)^+$.

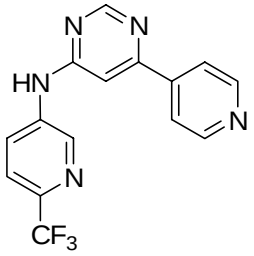
6-(pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyrimidin-4-amine



9j

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.89 (s, 1H), 8.85 (d, J = 6.4 Hz, 2H), 8.12 (d, J = 6.4 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.48 (s, 1H); MS (ESI) *m/z* 317 $(M+H)^+$.

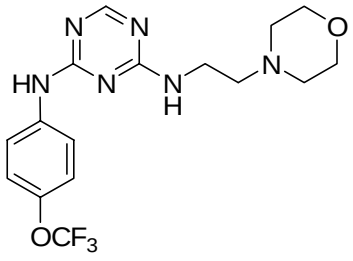
6-(pyridin-4-yl)-N-(6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-amine



9k

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.00 (d, J = 2.8 Hz, 1H), 8.93 (s, 1H), 8.87 (d, J = 4.8 Hz, 2H), 8.58 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 4.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H); MS (ESI) *m/z* 318 $(M+H)^+$.

Synthesis of N^2-(2-morpholinoethyl)-N^4-(4-(trifluoromethoxy)phenyl)-1,3,5-triazine-2,4-diamine

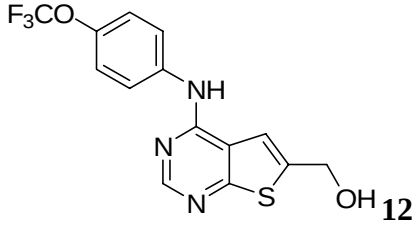


9l, TFA salt

To a stirred solution of 2,4-dichloro-1,3,5-triazine (30 mg, 0.2 mmol) in 1.0 mL of 2-PrOH was added 4-(trifluoromethoxy)benzenamine (27 μL, 0.2 mmol) and DIEA (52 μL, 0.3 mmol) at 0 ˚C. After 30 min, 2-morpholinoethanamine (45 μL, 0.35 mmol) was added at RT. After the reaction was complete as monitored by LC-MS, the solvent was removed and the title compound was purified by reverse-phase prep-HPLC using a water (0.05% TFA)/acetonitrile (0.05% TFA) gradient to afford the title compound **9l** as the TFA salt (78 mg, 78%). **9l** and its tautomer, ^{1}H NMR (600 MHz, CD_3OD) δ 8.43 (s, 0.2H), 8.38 (s, 0.8H), 7.74 (d, J = 8.4 Hz, 0.4H), 7.69 (d, J = 8.4 Hz, 1.6H), 7.36 (d, J = 8.4 Hz, 1.6 H), 7.26 (d, J = 8.4 Hz, 0.4H), 4.00-3.65 (m, 7.5 H), 3.60-3.40 (m, 4H), 3.20-3.00 (m, 0.5H); MS (ESI) *m/z* 385 $(M+H)^+$.

Table 4.

(4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]pyrimidin-6-yl)methanol

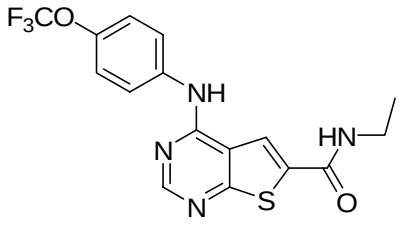


12

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.45 (s, 1H), 7.91 (d, J = 9.6 Hz, 2H), 7.21 (d, J = 9.6 Hz, 2H), 6.59 (s, 1H), 4.80 (s, 2H); MS (ESI) *m/z* 342 $(M + H)^+$.

Compounds **14b-4g** were prepared using synthetic procedure of **14a**, the corresponding amines were used.

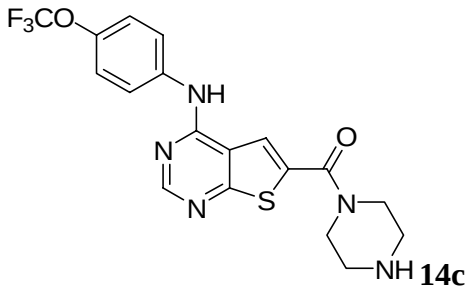
N-ethyl-4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]pyrimidine-6-carboxamide



14b

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.55 (s, 1H), 7.94 (d, J = 9.6 Hz, 2H), 7.31 (d, J = 9.6 Hz, 2H), 6.60 (s, 1H), 3.23 (q, J = 3.2 Hz, 2H), 1.78 (t, J = 3.3 Hz，3H); MS (ESI) *m/z* 383 $(M + H)^+$.

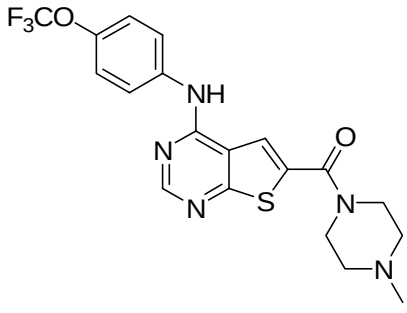
piperazin-1-yl(4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]pyrimidin-6-yl)methanone



14c

^{1}H NMR (600 MHz, CD_3OD) δ 8.53 (s, 1H), 8.18 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 4.08 (t, J = 5.4 Hz, 4H), 3.39 (t, J = 5.4 Hz, 4H); MS (ESI) *m/z* 424 $(M + H)^+$.

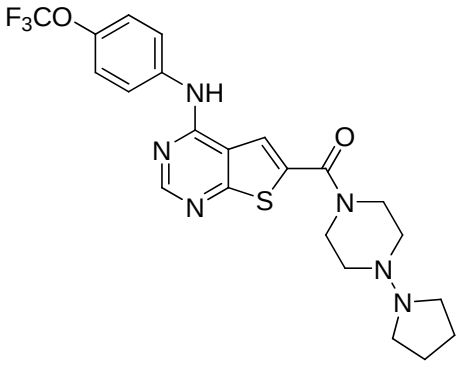
(4-methylpiperazin-1-yl)(4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]-pyrimidin-6-yl)methanone



14d

^{1}H NMR (600MHz, CD_3OD) δ 8.65 (s, 1H), 8.13 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 4.01 (brs, 4H), 2.83 (brs, 4H), 2.59 (s, 3H); MS (ESI) *m/z* 438 $(M + H)^+$.

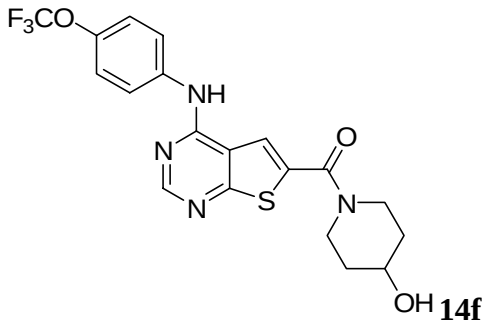
(4-(pyrrolidin-1-yl)piperazin-1-yl)(4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]pyrimidin-6-yl)methanone



14e

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.59 (s, 1H), 8.12 (s, 1H), 7.94 (d, *J* = 9.2 Hz, 2H), 7.42 (d, *J* = 9.2 Hz, 2H), 4.47-4.45 (m, 4H), 3.55-3.54 (*m*, 4H), 3.15-3.11 (m, 4H), 2.19-2.00 (m, 2H), 1.88-1.85 (m, 2H); MS (ESI) *m/z* 493 $(M + H)^+$.

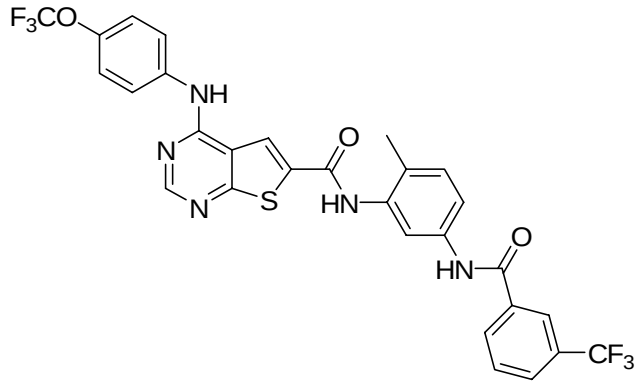
(4-hydroxypiperidin-1-yl)(4-(4-(trifluoromethoxy)phenylamino)thieno[2,3-*d*]-pyrimidin-6-yl)methanone



14f

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 9.32 (s, 1H), 8.86 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.69 (brs, 1H), 3.69-3.64 (m, 2H), 3.45-3.43 (m, 2H), 3.21-3.15 (m, 2H), 2.86-2.84 (m, 2H); MS (ESI) *m/z* 439 $(M + H)^+$.

N-(2-methyl-5-(3-(trifluoromethyl)benzamido)phenyl)-4-(4-(trifluoromethoxy)-phenylamino)-thieno[2,3-*d*]pyrimidine-6-carboxamide

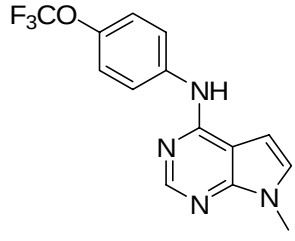


14g

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 10.35 (s, 1H), 10.15 (s, 1H) 8.61 (d, J = 4.4 Hz, 2H), 8.18 (s, 1H), 8.13 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 2 H), 7.89 (d, J = 2.4 Hz, 1H), 7.61 (dd, J = 8.4, 2.0 Hz, 1H) 7.43 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 1H), 2.50 (s, 3H); MS (ESI) *m/z* 632 $(M + H)^+$.

Table 5.

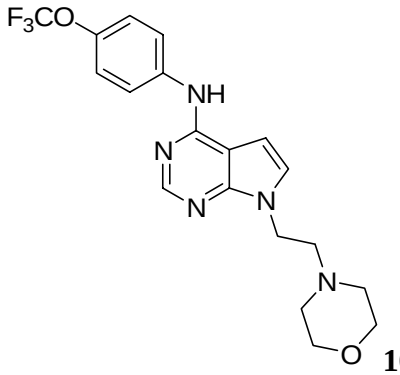
7-methyl-N-(4-(trifluoromethoxy)phenyl)-7H-pyrrolo-[2,3-*d*]pyrimidin-4-amine



16b

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.33 (s, 1H), 7.95 (d, J = 9.2 Hz, 2H), 7.39 (d, J = 9.2 Hz, 2H), 7.34 (d, J = 6.2 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H), 3.36 (s, 3H); MS *m/z* 309 $(M + H)^+$.

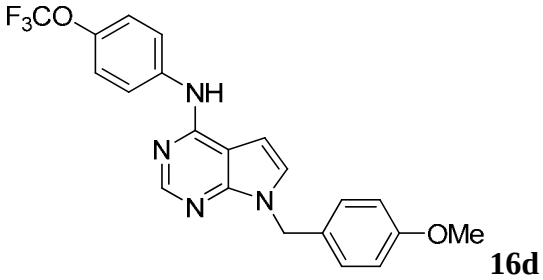
7-(2-morpholinoethyl)-N-(4-(trifluoromethoxy)phenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine



16c

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.80 (brs, 1H), 8.65 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 6.2 Hz, 1H), 7.17 (d, J = 6.0 Hz, 1H), 5.41-5.39 (m, 2H), 4.43-4.36 (m, 6H), 2.52-2.31 (m, 4H); MS m/z 408 $(M + H)^+$.

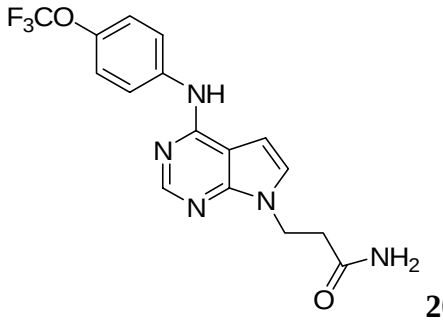
7-(4-methoxybenzyl)-N-(4-(trifluoromethoxy)phenyl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-amine



16d

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (brs, 1H), 8.36 (s, 1H), 7.98 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 6.2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 3.6 Hz, 1H), 5.33 (s, 2H), 3.78 (s, 3H); MS (ESI) m/z 415 $(M + H)^+$.

3-(4-(4-(trifluoromethoxy)phenylamino)-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-propanamide

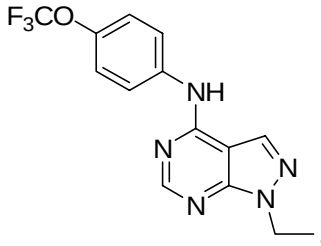


20b

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.22 (brs, 1H), 7.94 (d, J = 8.8 Hz, 2H,), 7.81 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 6.2 Hz, 1H), 7.18 (d, J = 6.0 Hz, 1H), 5.02 (t, J = 6.8 Hz, 2H), 3.25 (t, J = 6.8 Hz, 2H); MS (ESI) *m/z* 366 $(M + H)^+$.

Table 6.

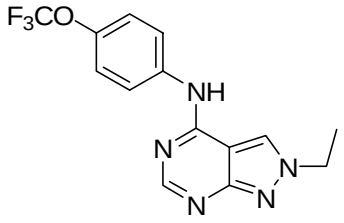
1-ethyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21b-I,

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.45 (s, 1H), 8.34 (s, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 324 $(M + H)^+$.

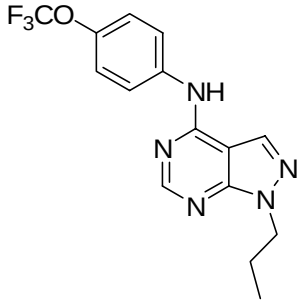
2-ethyl-N-(4-(trifluoromethoxy)phenyl)-2H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21b-II

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.64 (s, 1H), 8.56 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 324 $(M + H)^+$.

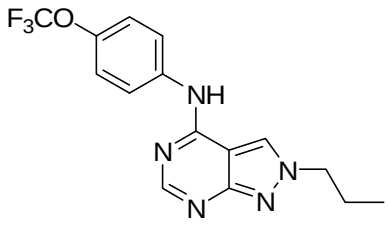
1-propyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21c-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.45 (s, 1H), 8.33 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 4.32 (t, J = 7.2 Hz, 2H), 1.86 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 338 $(M + H)^+$.

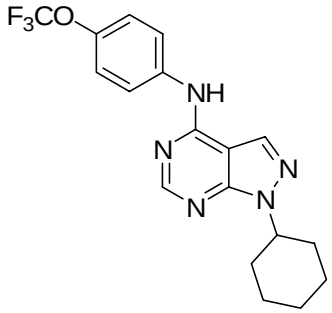
2-propyl-N-(4-(trifluoromethoxy)phenyl)-2H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21c-II

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 4.35 (t, J = 7.2 Hz, 2H), 1.85 (m, 2H), 0.80 (t, J = 7.6 Hz, 3H); MS (ESI) *m/z* 338 $(M + H)^+$.

1-cyclohexyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine

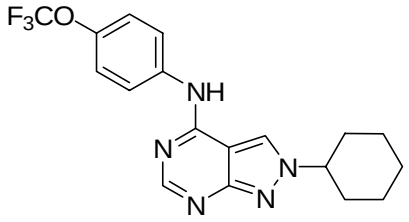


21d-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.36 (s, 1H), 8.25 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 4.63-4.56 (m, 1H), 1.88-1.77 (m, 8H), 1.42-1.37

(m, 2H); MS (ESI) *m/z* 378 $(M + H)^+$, HRMS (ESI) calcd for $C_{18}H_{18}F_3N_5O$ 377.1463, found 378.1534 $(M+H)^+$.

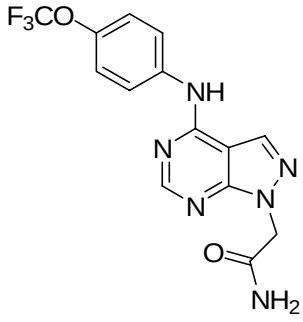
2-cyclohexyl-N-(4-(trifluoromethoxy)phenyl)-2H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21d-II

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 8.86 (s, 1H), 8.42 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 4.51-4.45 (m, 1H), 1.88-1.72 (m, 8H), 1.40-1.32 (m, 2H); MS (ESI) *m/z* 378 $(M + H)^+$.

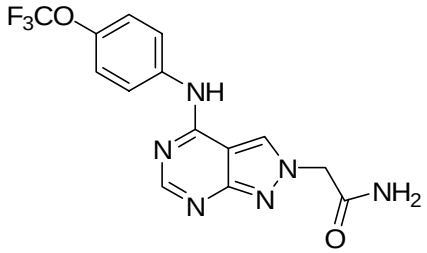
2-(4-(4-(trifluoromethoxy)phenylamino)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-acetamide



21e-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.44 (s, 1H), 8.32 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.60 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 1H), 4.9 (s, 2H); MS (ESI) *m/z* 353 $(M + H)^+$.

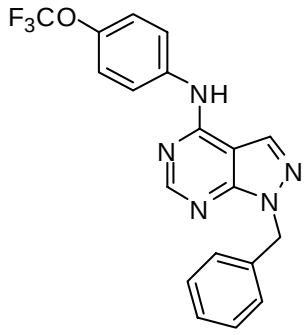
2-(4-(4-(trifluoromethoxy)phenylamino)-2H-pyrazolo[3,4-*d*]pyrimidin-2-yl)-acetamide



21e-II

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.78 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.30 (s, 1H), 5.17 (s, 2H); MS (ESI) *m/z* 353 $(M + H)^+$.

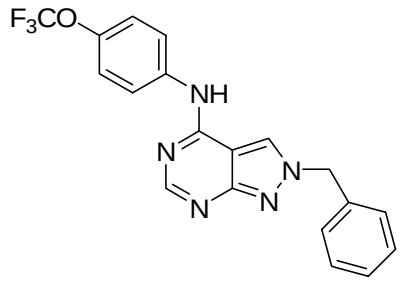
1-benzyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21f-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 8.48 (s, 1H), 8.36 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.30-733 (m, 2H), 7.28-7.24 (m, 3H), 5.57 (s, 2H); MS (ESI) *m/z* 386 $(M + H)^+$.

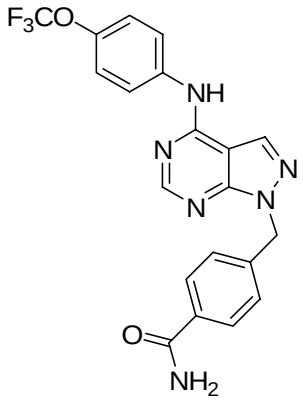
2-benzyl-N-(4-(trifluoromethoxy)phenyl)-2H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21f-II

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.37-735 (m, 2H), 7.29-7.26 (m, 3H), 5.66 (s, 2H); MS (ESI) *m/z* 386 $(M + H)^+$.

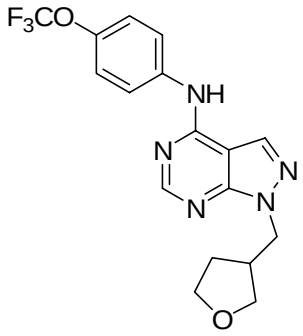
4-((4-(4-(trifluoromethoxy)phenylamino)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-methyl)benzamide



21h-I

^{1}H NMR (600 MHz, CD_3OD) δ 8.42 (s, 1H), 8.18 (brs, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 4H), 5.68 (s, 2H); MS (ESI) *m/z* 429 $(M + H)^+$.

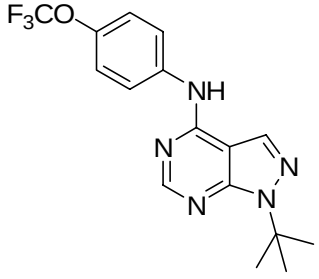
1-((tetrahydrofuran-3-yl)methyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21i-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.44 (s, 1H), 8.33 (s, 1H), 7.99 (d, *J* = 9.2 Hz, 2H), 7.41 (d, *J* = 9.2 Hz, 2H), 4.58-4.47 (m, 2H), 4.29-4.26 (m, 2H), 3.79-3.76 (m, 2H), 2.09-2.00 (m, 1H), 1.86-1.79 (m, 1H), 1.69-1.61 (m, 1H); MS (ESI) *m/z* 380 $(M + H)^+$.

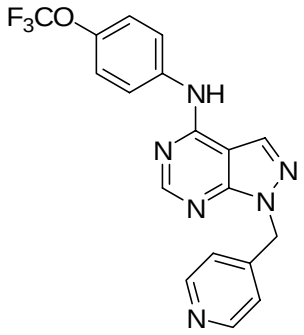
1-tert-butyl-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



21j-I

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.81 (s, 1H), 8.63 (s, 1H), 7.96 (d, J = 9.2 Hz, 2H), 7.47 (d, J = 9.2 Hz, 2H), 1.68 (s, 9H); MS (ESI) *m/z* 352 $(M + H)^+$.

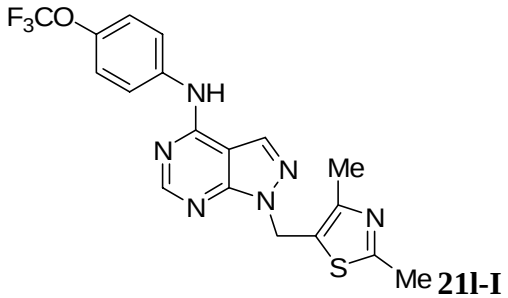
1-(pyridin-4-ylmethyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]-pyrimidin-4-amine



21k-I

^{1}H NMR (600 MHz, CD_3OD) δ 8.47 (d, J = 3.0 Hz, 2H), 8.43 (s, 1H), 8.24 (brs, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 6.0 Hz, 2H), 5.68 (s, 2H); MS (ESI) *m/z* 387 $(M + H)^+$.

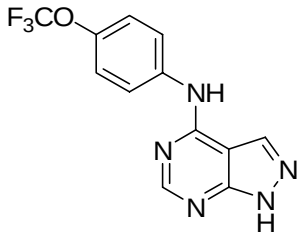
1-((2,4-dimethylthiazol-5-yl)methyl)-N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo-[3,4-*d*]pyrimidin-4-amine



21l-I

^{1}H NMR (600 MHz, CD_3OD) δ 8.41 (s, 1H), 8.13 (brs, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.62 (s, 2H), 2.52 (s, 3H), 2.47 (s, 3H); MS (ESI) *m/z* 421 $(M + H)^+$.

N-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine



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^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.90 (s, 1H), 8.52 (s, 1H), 7.79 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H), 7.16 (s, 1H); MS (ESI) *m/z* 296 $(M + H)^+$.

3. HPLC purity determination.

Instrument and column: Compound purities were determined using an Agilent 1200 series HPLC system using C8 column (Agilent ZORBAX Eclipse XDB-C8 5 μm, 4.6 × 50 mm).

Solvent system: Mobile phase A: Acetonitrile containing 0.1% formic acid; Mobile phase B: Water containing 0.1% formic acid. The flow-rate was 1.0 mL/min and the injection volume was 5 μL. The system was operated at 25 ˚C. Peaks were detected at 254 nm and 210 nm.

Elution condition:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0	10	90
0.1	10	90
4.0	90	10
4.3	100	0
7.6	100	0
8.0	10	90

4. Pharmacokinetic Parameters of compounds 5g, 6a, 14d, 21b-I (Table S1).

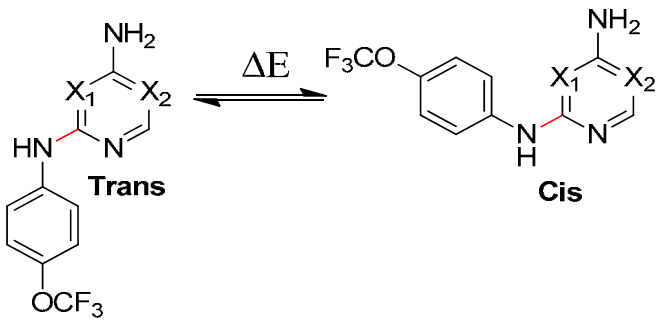
Snapshot PK study[2].

Five to six week old male Balb/c mice (20-25 g) were obtained from Jackson Laboratory (Bar Harbor, Maine, USA). The oral dose was prepared in a 3:1 formulation of PEG300 and D5W and administered at 20 mg/kg via oral gavage (n = 3). Five blood samples (50 µL) were serially drawn via retro orbital sinus within 5 hours after dosing. Plasma concentrations of compound were quantified utilizing a Liquid Chromatography/Mass Spectrometry (LC/MS/MS) assay. Pharmacokinetic parameters were calculated by non-compartmental regression analysis using Winnonlin 4.0 software (Pharsight, Mountain View, CA, USA). Pharmacokinetic parameters: AUC = area under the curve (measure of exposure), C_{max} = maximum plasma concentration, T_{max} = time of maximum plasma concentration.

Compound ID	Route	Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	AUC $_{0\text{-}5\ hours}$ (min*µg/mL)	Oral exposure
5g	PO	20	1.0	2001	563.15	high
6a	PO	20	3.0	3396	366.35	high
14d	PO	20	0.5	1090	144.35	moderate
21b-I	PO	20	0.5	262.75	12.05	low

Compounds **5g**, **6a** demonstrated high oral exposure with $AUC_{0\text{-}5\ hours}$/dose value > 10 (min*µg/mL)/(mg/kg); **14d** showed moderate oral exposure with $AUC_{0\text{-}5\ hours}$/dose value between 2 and 10; while **21b-I** showed low oral exposure with $AUC_{0\text{-}5\ hours}$/dose value < 2.

5. Calculations of relative transformed energy from trans to cis (Table S2).



[2] Liu, B.; Chang, J.; Gordon, W. P.; Isbell, J.; Zhou, Y.; Tuntland, T. Snapshot PK: a rapid rodent in vivo preclinical screening approach. *Drug Discovery Today*, **2008**, *13*, 360-367.

Table S2. Relative energy from trans to *cis* conformation for the above model molecules.

Cmpd	X_1	X_2	$\triangle E_{trans\text{-}cis}$ (Kcal/mol)	cis	trans
4a	CH	N	+1.89(+0.22)*	disfavored	favored
9a	CCH_3	N	+11.46(+4.94)*	disfavored	favored
9c	N	CH	+0.11	equal	equal
9l	N	N	-0.18	equal	equal

* The numbers in the parenthesis are for energy differences if rotation of the phenyl ring about amine bond is allowed. The twist of **4a** phenyl ring is 26.3 degrees. Compound **9a** twist angle is 37.2 degrees. Compound **9c** and **9l** cis conformations have stable planar configuration, therefore do not have corresponding numbers in parenthesis. Compound **9a** planar *cis* conformation is highly unstable, while twist cis is stable but higher in energy compared to trans. All compounds have planar trans conformation.

The calculations were performed by Jaguar quantum mechanical program in Schrodinger software suite [3] . Density functional theory was used with B3LYP functional and pseudospectral 6-31G** basis set. The calculations were done on fine grid with level of accuracy being "accurate"[3].

6. Fluorescence polarization assay results of selected compounds (**5g**, **7a**, **12**, **21a-I**) (Table S3).

Table S3.

Select analogs	Kd (μM)	Cellular EC50 (μM)
5g	0.091	0.12
7a	0.125	0.14
12	0.200	0.33
21a-I	0.219	0.25

[3] http://www.schrodinger.com