

Supporting Information

Discovery, Synthesis and Biological Evaluation of Thiazoloquin(az)olin(on)es as Potent CD38 Inhibitors.

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6-Bromo-N-(3-chloro-4-fluorophenyl)-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 11.9 (br. s., 1H), 9.32 (s, 1H), 9.00 (s, 1H), 8.25 (d, *J* = 8.78 Hz, 1H), 8.08 (dd, *J* = 1.95, 6.63 Hz, 1H), 7.96 (d, *J* = 8.78 Hz, 1H), 7.67-7.85 (m, 1H), 7.56 (t, *J* = 9.07 Hz, 1H). Low-resolution MS (ES+) *m/e* 352 & 354 (MH+).

N-(3-Chloro-4-fluorophenyl)-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3b). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.3 (br. s., 1H), 9.21 (s, 1H), 8.78 (s, 1H), 8.68 (s, 1H), 8.50 (s, 1H), 8.26 (d, *J* = 8.78 Hz, 1H), 8.14 (dd, *J* = 2.24, 6.73 Hz, 1H), 7.86 (d, *J* = 8.78 Hz, 1H), 7.77-7.83 (m, 1H), 7.50 (t, *J* = 9.07 Hz, 1H). HRMS: C₁₇H₁₀ClFN₄S requires M+H at *m/z* 357.0377; found, 357.0369. RP-HPLC, *t*R = 1.20 min, 94% purity.

6-Bromo-N-(4-chlorophenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 334 & 336 (MH+).

N-(4-Chlorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3c). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.0 (br. s., 1H), 9.20 (s, 1H), 8.81 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.23 (d, *J* = 8.53 Hz, 1H), 7.79-7.98 (m, 3H), 7.49 (d, *J* = 8.78 Hz, 2H). HRMS: C₁₇H₁₁ClN₄S requires M+H at *m/z* 339.0471; found, 339.0464. RP-HPLC, *t*R = 1.13 min, 100% purity.

6-Bromo-N-(3-chlorophenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 334 & 336 (MH+).

N-(3-Chlorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3d). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.0 (s, 1H), 9.21 (s, 1H), 8.82 (d, *J* = 1.3 Hz, 1H), 8.67 (s, 1H), 8.52 (s, 1H), 8.25 (dd, *J* = 8.8, 1.5 Hz, 1H), 8.08 (s, 1H), 7.76 - 7.95 (m, 3H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.22 (dd, *J* = 8.0, 1.3 Hz, 1H). HRMS: C₁₇H₁₁ClN₄S requires M+H at *m/z* 339.0471; found, 339.0466. RP-HPLC, *t*R = 1.17 min, 99% purity.

6-Bromo-N-(2-chlorophenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 334 & 336 (MH+).

N-(2-Chlorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3e). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.1 (br. s., 1H), 9.18 (s, 1H), 8.80 (br. s., 1H), 8.50 (s, 1H), 8.45 (br. s., 1H), 8.24 (d, *J* = 8.28 Hz, 1H), 7.84 (d, *J* = 8.53 Hz, 1H), 7.52-7.69 (m, 2H), 7.45 (t, *J* = 7.28 Hz, 1H), 7.39 (d, *J* = 7.28 Hz, 1H). HRMS: C₁₇H₁₁ClN₄S requires M+H at *m/z* 339.0471; found, 339.0466. RP-HPLC, *t*R = 0.95 min, 100% purity.

6-Bromo-N-tert-butylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 318 & 320 (MH+).

N-(4-Fluorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3f). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (METHANOL-d₄): 400 MHz δ 9.17 (br. s., 1H), 8.94 (d, *J* = 1.26 Hz, 1H), 8.76 (br. s., 1H), 8.49 (s, 1H), 8.41 (dd, *J* = 1.63, 8.66 Hz, 1H), 7.92 (d, *J* = 8.78 Hz, 1H), 7.71-7.83 (m, 2H), 7.26 (t, *J* = 8.78 Hz, 2H). HRMS: C₁₇H₁₁FN₄S requires M+H at *m/z* 323.0766; found, 323.0760. RP-HPLC, *t*R = 0.92 min, 100% purity.

6-Bromo-N-(3-fluorophenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 318 & 320 (MH+).

N-(3-Chlorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3g). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ: 10.1 (s, 1H), 9.21 (s, 1H), 8.82 (s, 1H), 8.67 (s, 1H), 8.52 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 11.8 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.46 (q, *J* = 7.9 Hz, 1H), 6.92 - 7.09 (m, 1H). HRMS: C₁₇H₁₁FN₄S requires M+H at *m/z* 323.0766; found, 323.0762. RP-HPLC, *t*R = 1.01 min, 100% purity.

6-Bromo-N-tert-butylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 318 & 320 (MH+).

N-(2-Fluorophenyl)-6-(thiazol-5-yl)quinazolin-4-amine (3h). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.0 (br. s., 1H), 9.18 (s, 1H), 8.79 (s, 1H), 8.49 (d, *J* = 5.67 Hz, 2H), 8.24 (d, *J* = 7.88 Hz, 1H), 7.85 (d, *J* = 8.83 Hz, 1H), 7.57 (t, *J* = 7.57 Hz, 1H), 7.34-7.38 (m, 2H), 7.30 (d, *J* = 7.88 Hz, 1H). HRMS: C₁₇H₁₁FN₄S requires M+H at *m/z* 323.0766; found, 323.0758. RP-HPLC, *t*R = 1.21 min, 97% purity.

6-Bromo-N-p-tolylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 314 & 316 (MH+).

6-(Thiazol-5-yl)-N-p-tolylquinazolin-4-amine (3i). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.92 (s, 1H), 9.19 (s, 1H), 8.82 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.20 (dd, *J* = 1.38, 8.66 Hz, 1H), 7.82 (d, *J* = 8.53 Hz, 1H), 7.69 (d, *J* = 8.28 Hz, 2H), 7.24 (d, *J* = 8.03 Hz, 2H), 2.33 (s, 3H). HRMS: C₁₈H₁₄N₄S requires M+H at *m/z* 319.1005; found, 319.1007. RP-HPLC, *t*R = 1.01 min, 100% purity.

6-Bromo-N-m-tolylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 314 & 316 (MH+).

6-(Thiazol-5-yl)-N-m-tolylquinazolin-4-amine (3j). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.90 (s, 1H), 9.17 (s, 1H), 8.80 (s, 1H), 8.56 (s, 1H), 8.49 (s, 1H), 8.18 (dd, *J* = 1.13, 8.66 Hz, 1H), 7.81 (d, *J* = 8.53 Hz, 1H), 7.57-7.69 (m, 2H), 7.29 (t, *J* = 7.78 Hz, 1H), 6.98 (d, *J* = 7.53 Hz, 1H), 2.34 (s, 3H). HRMS: C₁₈H₁₄N₄S requires M+H at *m/z* 319.1017; found, 319.1007. RP-HPLC, *t*R = 1.16 min, 97% purity.

6-Bromo-N-o-tolylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 314 & 316 (MH+).

6-(Thiazol-5-yl)-N-o-tolylquinazolin-4-amine (3k). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (MeOH-d₄): 400 MHz δ 9.07 (s, 1H), 8.75 (d, *J* = 1.76 Hz, 1H), 8.39 (s, 1H), 8.37 (s, 1H), 8.20 (dd, *J* = 1.88, 8.66 Hz, 1H), 7.85 (d, *J* = 8.78 Hz, 1H), 7.25-7.44 (m, 4H), 2.28 (s, 3H). HRMS: C₁₈H₁₄N₄S requires M+H at *m/z* 319.1017; found, 319.1008. RP-HPLC, *t*R = 0.87 min, 100% purity.

6-Bromo-N-(3-(trifluoromethyl)phenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 368 & 370 (MH+).

6-(Thiazol-5-yl)-N-(3-(trifluoromethyl)phenyl)quinazolin-4-amine (3l). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.24 (s, 1H), 8.90 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 8.37 (d, *J* = 8.78 Hz, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.03 Hz, 1H), 7.92 (d, *J* = 8.78 Hz, 1H), 7.73 (t, *J* = 8.03 Hz, 1H), 7.62 (d, *J* = 7.78 Hz, 1H). HRMS: C₁₈H₁₁F₃N₄S requires M+H at *m/z* 373.0735; found, 373.0729. RP-HPLC, *t*R = 1.33 min, 100% purity.

4-(6-Bromoquinazolin-4-ylamino)benzenesulfonamide. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 379 & 381 (MH+).

4-(6-(Thiazol-5-yl)quinazolin-4-ylamino)benzenesulfonamide (3m). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (MeOH-d₄): 400 MHz δ 9.18 (br. s., 1H), 8.96 (d, *J* = 1.3 Hz, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 8.43 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.73 - 7.86 (m, 2H), 7.28 (t, *J* = 8.8 Hz, 2H). HRMS: C₁₇H₁₃N₅O₂S₂ requires M+H at *m/z* 384.0589; found, 384.0576.

N-{4-[(6-Bromo-4-quinazolinyl)amino]phenyl}methanesulfonamide. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 11.5 (br. s., 1H), 9.95 (s, 1H), 9.17 (s, 1H), 8.91 (s, 1H), 8.23 (dd, *J* = 8.88, 1.85 Hz, 1H), 7.90 (d, *J* = 8.78 Hz, 1H), 7.70 (d, *J* = 8.78 Hz, 2H), 7.31 (d, *J* = 8.78 Hz, 2H), 3.05 (s, 3H). Low-resolution MS (ES+) *m/e* 393 & 395 (MH+).

N-(4-{[6-(1,3-Thiazol-5-yl)-4-quinazolinyl]amino}phenyl)methanesulfonamide (3n). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.80 (br. s., 1H), 9.17 (s, 1H), 8.78 (s, 1H), 8.48 (s, 1H), 8.48 (s, 1H), 8.15 (d, *J* = 8.60 Hz, 1H), 7.77 (d, *J* = 8.60 Hz, 1H), 7.45 (d, *J* = 8.21 Hz, 2H), 6.98 (d, *J* = 8.21 Hz, 2H), 4.15 (br. s., 1H), 2.70 (s, 3H). HRMS: C₁₈H₁₅N₅O₂S₂ requires M+H at *m/z* 398.0745; found, 398.0734. RP-HPLC, *t*R = 0.78 min, 94% purity.

6-Bromo-N-[3-(methylsulfonyl)phenyl]-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 11.5 (br. s., 1H), 9.18 (d, *J* = 1.37 Hz, 1H), 8.99 (s, 1H), 8.37 (s, 1H), 8.24 (m, 1H), 8.22 (m, 1H), 7.92 (d, *J* = 8.79 Hz, 1H), 7.86 (m, 1H), 7.78 (m, 1H) 3.28 (s, 3H). Low-resolution MS (ES+) *m/e* 378 (MH+).

N-[3-(Methylsulfonyl)phenyl]-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3o). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.2 (br. s., 1H), 9.16 (s, 1H), 8.75 (s, 1H), 8.46 (s, 2H), 7.98 - 8.35 (m, 3H), 7.43 - 7.90 (m, 3H), 3.23 (s, 3H). HRMS: C₁₈H₁₄N₄O₂S₂ requires M+H at *m/z* 383.0636; found, 383.0629. RP-HPLC, *t*R = 0.94 min, 100% purity.

4-[(6-Bromo-4-quinazolinyl)amino]benzamide. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 11.6 (br. s., 1H), 9.24 (d, *J* = 1.4 Hz, 1H), 8.98 (s, 1H), 8.24 (dd, *J* = 9.0, 1.8 Hz, 1H), 8.04 (br. s., 1H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.43 (br. s., 1H). Low-resolution MS (ES+) *m/e* 343 & 345 (MH+).

4-[[6-(1,3-Thiazol-5-yl)-4-quinazolinyl]amino]benzamide (3p). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 10.2 (s, 1H), 8.87 (br. s., 1H), 8.60 (br. s., 1H), 8.26 (br. s., 1H), 7.95 (br. s., 8H), 7.32 (br. s., 1H). HRMS: C₁₈H₁₃N₅OS requires M+H at *m/z* 348.0919; found, 348.0910.

6-Bromo-N-[4-(1,3-oxazol-5-yl)phenyl]-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 11.6 (br. s., 1H), 9.22 (d, *J* = 1.76 Hz, 1H), 8.98 (s, 1H), 8.49 (s, 1H), 8.24 (dd, *J* = 8.88, 1.85 Hz, 1H), 7.92 (d, *J* = 8.78 Hz, 2H), 7.91 (s, 1H), 7.85 (d, *J* = 8.78 Hz, 2H), 7.74 (s, 1H). Low-resolution MS (ES+) *m/e* 367 & 369 (MH+).

N-[4-(1,3-Oxazol-5-yl)phenyl]-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3q). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆):

400 MHz δ 11.0 (br. s., 1H), 9.24 (s, 1H), 8.93 (s, 1H), 8.85 (s, 1H), 8.55 (s, 1H), 8.48 (s, 1H), 8.38 (d, J = 8.40 Hz, 1H), 7.92 (d, J = 8.00 Hz, 2H), 7.89 (s, 1H), 7.85 (d, J = 8.00 Hz, 2H), 7.72 (s, 1H). HRMS: $C_{20}H_{13}N_5OS$ requires M+H at m/z 372.0919; found, 372.0909. RP-HPLC, t_R = 0.97 min, 99% purity.

6-Bromo-N-[4-(1H-imidazol-1-yl)phenyl]-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 10.6 (br. s., 1H) 9.52 (s, 1H), 9.06 (d, J = 1.95 Hz, 1H), 8.74 (s, 1H), 8.23 (t, J = 1.46 Hz, 1H), 8.12 (d, J = 8.98 Hz, 2H), 8.07 (dd, J = 8.88, 2.05 Hz, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.81 (d, J = 8.98 Hz, 2H). Low-resolution MS (ES+) m/e 366 & 368 (MH+).

N-[4-(1H-Imidazol-1-yl)phenyl]-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3r). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 10.9 (br. s., 1 H), 9.63 (s, 1 H), 9.24 (s, 1 H), 8.92 (s, 1 H), 8.82 (s, 1 H), 8.55 (s, 1 H), 8.38 (d, J = 8.59 Hz, 1 H), 8.30 (s, 1 H), 8.05 (d, J = 8.59 Hz, 2 H), 7.84 - 7.98 (m, 4 H). HRMS: $C_{20}H_{14}N_6S$ requires M+H at m/z 371.1079; found, 371.1077. RP-HPLC, t_R = 0.54 min, 99% purity.

1-{4-[(6-Bromo-4-quinazolinyl)amino]phenyl}-2-pyrrolidinone. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 11.4 (br. s., 1H), 9.12 (d, J = 1.76 Hz, 1H), 8.91 (s, 1H), 8.22 (dd, J = 8.79, 1.95 Hz, 1H), 7.86 (d, J = 8.99 Hz, 1H), 7.67 - 7.81 (m, 4H, overlapping protons), 3.88 (t, J = 7.04 Hz, 2H), 2.49 - 2.58 (m, 2H, overlapping with solvent DMSO peaks), 2.09 (quin, J = 7.52 Hz, 2H). Low-resolution MS (ES+) m/e 383 & 385 (MH+).

1-(4-{[6-(1,3-Thiazol-5-yl)-4-quinazolinyl]amino}phenyl)-2-pyrrolidinone (3s). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 10.0 (br. s., 1H), 9.09 - 9.24 (m, 1H), 8.81 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.19 (d, J = 8.40 Hz, 1H), 7.75 - 7.87 (m, 3H), 7.66 - 7.74 (m, 2H), 3.87 (t, J = 6.93 Hz, 2H), 2.53 (m, 2H, partially covered by solvent peaks), 1.96 - 2.15 (m, 3H). HRMS: $C_{21}H_{17}N_5OS$ requires M+H at m/z 388.1232; found, 388.1228. RP-HPLC, t_R = 0.86 min, 94% purity.

6-Bromo-N-(pyridin-2-yl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 301 & 303 (MH+).

N-(Pyridin-2-yl)-6-(thiazol-5-yl)quinazolin-4-amine (3t). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.17 (s, 1H), 9.06 (br. s., 1H), 8.69 (br. s., 1H), 8.58 (s, 1H), 8.45 (d, J = 3.51 Hz, 2H), 8.22 (dd, J = 1.76, 8.78 Hz, 1H), 7.79-7.95 (m, 2H), 7.18 (dd, J = 5.27, 6.78 Hz, 1H). HRMS: $C_{16}H_{11}N_5S$ requires M+H at m/z 306.0813; found, 306.0808.

6-Bromo-N-(pyridin-3-yl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 301 & 303 (MH+).

N-(Pyridin-3-yl)-6-(thiazol-5-yl)quinazolin-4-amine (3u). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 10.1 (s, 1H), 9.20 (s, 1H), 8.99 (d, J = 2.26 Hz, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.51 (s, 1H), 8.33-8.41 (m, 1H), 8.19-8.31 (m, 2H), 7.87 (d, J = 8.78 Hz, 1H), 7.47 (dd, J = 4.64, 8.16 Hz, 1H). HRMS: $C_{16}H_{11}N_5S$ requires M+H at m/z 306.0813; found, 306.0808.

6-Bromo-N-(pyridin-4-yl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 301 & 303 (MH+).

N-(Pyridin-4-yl)-6-(thiazol-5-yl)quinazolin-4-amine (3v). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 10.0 (br. s., 1H),

9.08 (s, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 8.30 - 8.46 (m, 3H), 8.13 (d, $J = 8.8$ Hz, 1H), 7.86 (d, $J = 5.0$ Hz, 2H), 7.78 (d, $J = 8.8$ Hz, 1H). HRMS: $C_{16}H_{11}N_5S$ requires $M+H$ at m/z 306.0813; found, 306.0803. RP-HPLC, $t_R = 0.67$ min, 100% purity.

6-Bromo-N-cyclopropylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 264 & 266 (MH+).

N-Cyclopropyl-6-(thiazol-5-yl)quinazolin-4-amine (3w). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.15 (s, 1H), 8.53 (s, 2H), 8.45 (d, $J = 2.51$ Hz, 1H), 8.42 (s, 1H), 8.11 (dd, $J = 1.63, 8.66$ Hz, 1H), 7.74 (d, $J = 8.78$ Hz, 1H), 3.04 (dt, $J = 3.51, 7.03$ Hz, 1H), 0.85 (d, $J = 5.02$ Hz, 2H), 0.59-0.72 (m, 2H). HRMS: $C_{14}H_{12}N_4S$ requires $M+H$ at m/z 269.0861; found, 269.0856. RP-HPLC, $t_R = 0.64$ min, 99% purity.

6-Bromo-N-(2-chlorophenyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 278 & 280 (MH+).

N-Cyclobutyl-6-(thiazol-5-yl)quinazolin-4-amine (3x). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.17 (s, 1H), 8.60 (d, $J = 1.25$ Hz, 1H), 8.49 (d, $J = 6.78$ Hz, 1H), 8.45 (d, $J = 3.26$ Hz, 2H), 8.10 (dd, $J = 1.51, 8.53$ Hz, 1H), 7.72 (d, $J = 8.78$ Hz, 1H), 4.74 (m, 1H), 2.30-2.44 (m, 2H), 2.10-2.26 (m, 2H), 1.70-1.86 (m, 2H). HRMS: $C_{15}H_{14}N_4S$ requires $M+H$ at m/z 283.1017; found, 283.1007. RP-HPLC, $t_R = 0.80$ min, 100% purity.

6-Bromo-N-cyclopentylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 292 & 294 (MH+).

N-Cyclopentyl-6-(thiazol-5-yl)quinazolin-4-amine (3y). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.16 (s, 1H), 8.61 (d, $J = 1.5$ Hz, 1H), 8.47 (s, 1H), 8.44 (s, 1H), 8.16 (d, $J = 6.8$ Hz, 1H), 8.08 (dd, $J = 8.8, 1.8$ Hz, 1H), 7.72 (d, $J = 8.8$ Hz, 1H), 4.49 - 4.71 (m, 1H), 1.95 - 2.20 (m, 2H), 1.78 (br. s., 2H), 1.55 - 1.71 (m, 4H). HRMS: $C_{16}H_{16}N_4S$ requires $M+H$ at m/z 297.1174; found, 297.1166. RP-HPLC, $t_R = 0.91$ min, 100% purity.

6-Bromo-N-cyclohexyl-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 8.63 (d, $J = 2.0$ Hz, 1H), 8.46 (s, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 7.86 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.59 (d, $J = 9.0$ Hz, 1H), 4.14 (dd, $J = 6.9, 3.4$ Hz, 1H), 1.93 (br. s., 2H), 1.77 (d, $J = 5.7$ Hz, 2H), 1.65 (d, $J = 12.3$ Hz, 1H), 1.24 - 1.50 (m, 4H), 1.08 - 1.26 (m, 1H). Low-resolution MS (ES+) m/e 306 & 308 (MH+).

N-Cyclohexyl-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3z). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.15 (s, 1H), 8.59 (s, 1H), 8.45 (br. s., 1H), 8.43 (s, 1H), 8.02 - 8.13 (m, 2H), 7.70 (d, $J = 8.8$ Hz, 1H), 4.21 (dd, $J = 6.9, 3.2$ Hz, 1H), 1.99 (d, $J = 9.6$ Hz, 2H), 1.80 (d, $J = 11.1$ Hz, 2H), 1.67 (d, $J = 12.3$ Hz, 1H), 1.30 - 1.50 (m, 4H), 1.10 - 1.27 (m, 1H). HRMS: $C_{17}H_{18}N_4S$ requires $M+H$ at m/z 311.1330; found, 311.1326. RP-HPLC, $t_R = 1.03$ min, 100% purity.

6-Bromo-N-(tetrahydro-3-furanyl)-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 294 & 296 (MH+).

N-(Tetrahydro-3-furanyl)-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3aa). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.16 (br. s., 1H), 8.65 (br. s., 1H), 8.41-8.54 (m, 2H), 8.37 (br. s., 1H), 8.10 (d, $J = 7.02$ Hz,

1H), 7.74 (d, $J = 7.02$ Hz, 1H), 4.81 (br. s., 1H), 3.96 (br. s., 2H), 3.76 (br. s., 2H), 2.29 (br. s., 1H), 2.06 (br. s., 1H). HRMS: $C_{15}H_{14}N_4OS$ requires $M+H$ at m/z 299.0966; found, 299.0956. RP-HPLC, $t_R = 0.60$ min, 100% purity.

6-Bromo-N-(tetrahydro-2H-pyran-4-yl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 308 & 310 (MH+).

N-(Tetrahydro-2H-pyran-4-yl)-6-(thiazol-5-yl)quinazolin-4-amine (3bb). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.16 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 8.44 (s, 1H), 8.17 (d, $J = 7.3$ Hz, 1H), 8.11 (d, $J = 8.5$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 4.45 (dd, $J = 11.2, 4.1$ Hz, 1H), 3.96 (dd, $J = 11.3, 2.8$ Hz, 2H), 3.45 - 3.51 (m, 2H), 1.94 (d, $J = 10.3$ Hz, 2H), 1.61 - 1.82 (m, 2H). HRMS: $C_{16}H_{16}N_4OS$ requires $M+H$ at m/z 313.1123; found, 313.112. RP-HPLC, $t_R = 0.65$ min, 100% purity.

6-Bromo-N-(tetrahydro-2H-pyran-3-yl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 8.66 (d, $J = 1.8$ Hz, 1H), 8.50 (s, 1H), 8.02 (d, $J = 7.4$ Hz, 1H), 7.90 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 4.22 - 4.42 (m, 1H), 3.94 (dd, $J = 10.5, 3.1$ Hz, 1H), 3.82 (d, $J = 11.3$ Hz, 1H), 3.30 - 3.42 (m, 1H), 3.22 (t, $J = 10.1$ Hz, 1H), 2.04 (d, $J = 10.9$ Hz, 1H), 1.54 - 1.88 (m, 3H). Low-resolution MS (ES+) m/e 307 & 309 (MH+).

N-(Tetrahydro-2H-pyran-3-yl)-6-(thiazol-5-yl)quinazolin-4-amine (3cc). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.17 (s, 1H), 8.60 (d, $J = 1.6$ Hz, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 8.11 (dd, $J = 8.6, 1.8$ Hz, 1H), 8.05 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 4.31 - 4.46 (m, 1H), 3.99 (dd, $J = 10.5, 3.1$ Hz, 1H), 3.84 (d, $J = 11.1$ Hz, 1H), 3.35 - 3.42 (m, 1H), 3.27 (t, $J = 10.1$ Hz, 1H), 2.00 - 2.15 (m, 1H), 1.55 - 1.89 (m, 3H). HRMS: $C_{16}H_{16}N_4OS$ requires $M+H$ at m/z 313.1123; found, 313.1119. RP-HPLC, $t_R = 0.69$ min, 98% purity.

1,1-Dimethylethyl 4-[(6-bromo-4-quinazolinyl)amino]-1-piperidinecarboxylate. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 10.3 (br. s., 1H), 9.21 (s, 1H), 8.78 (s, 1H), 8.68 (s, 1H), 8.50 (s, 1H), 8.26 (d, $J = 8.78$ Hz, 1H), 8.14 (dd, $J = 2.24, 6.73$ Hz, 1H), 7.86 (d, $J = 8.78$ Hz, 1H), 7.77-7.83 (m, 1H), 7.50 (t, $J = 9.07$ Hz, 1H). Low-resolution MS (ES+) m/e 407 & 409 (MH+).

1,1-Dimethylethyl 4-[[6-(1,3-thiazol-5-yl)-4-quinazolinyl]amino]-1-piperidinecarboxylate. The entitled compound was prepared in a similar manner as described for compound **3a** step 2. Low-resolution MS (ES+) m/e 412 (MH+).

N-4-Piperidinyl-6-(1,3-thiazol-5-yl)-4-quinazolinamine trifluoroacetate salt (3dd). A dioxane solution (20 mL) containing 1,1-dimethylethyl 4-[[6-(1,3-thiazol-5-yl)-4-quinazolinyl]amino]-1-piperidinecarboxylate (170 mg, 0.41 mmol) had 5 mL of a 4.0 M dioxane solution of HCl added to it. The resulting heterogeneous solution was stirred overnight at which time the bulk of the dioxane was removed in vacuo. The residue was triturated with Et_2O and the solid then taken up MeOH. It was then purified on the Agilent semi-prep HPLC yielding 84 mg (0.20 mmol) of N-4-piperidinyl-6-(1,3-thiazol-5-yl)-4-quinazolinamine trifluoroacetate salt as a white solid. 1H NMR (DMSO- d_6): 400 MHz δ 9.90 (d, $J = 6.63$ Hz, 1H), 9.24 (s, 1H), 8.92 (s, 1H), 8.83 (d, $J = 1.37$ Hz, 1H), 8.74 (d, $J = 9.37$ Hz, 1H), 8.50 (s, 1H), 8.38 (dd, $J = 1.37, 8.78$ Hz, 1H), 7.90 (d, $J = 8.78$ Hz, 1H), 4.56-4.79 (m, 1H), 3.45 (d, $J = 12.3$ Hz, 2H), 3.00-3.23 (m, 2H), 2.16 (d, $J = 12.5$ Hz, 2H), 1.82-2.04 (m, 2H). HRMS: $C_{16}H_{17}N_5S$ requires $M+H$ at m/z 312.1283; found, 312.1274. RP-HPLC, $t_R = 0.35$ min, 99% purity.

1,1-Dimethylethyl 4-[(6-bromo-4-quinazoliny)amino]-1-piperidinecarboxylate. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 407 & 409 (MH+).

1,1-Dimethylethyl 3-[[6-(1,3-thiazol-5-yl)-4-quinazoliny]amino]-1-piperidinecarboxylate. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 412 (MH+).

N-3-Piperidinyl-6-(1,3-thiazol-5-yl)-4-quinazolinamine trifluoroacetate salt (3ee). To CHCl₃ solution (40 mL) containing 1,1-dimethylethyl 3-[[6-(1,3-thiazol-5-yl)-4-quinazoliny]amino]-1-piperidinecarboxylate (866 mg, 2.10 mmol) was added 3.2 mL of TFA at rt. The resulting dark solution was stirred for 3 h at rt at which time the solution was concentrated. The remaining dark green oil was taken up in MeOH and purified on the Agilent semi-prep HPLC yielding 689 mg (1.62 mmol) of N-3-piperidinyl-6-(1,3-thiazol-5-yl)-4-quinazolinamine trifluoroacetate salt as a white solid. ¹H NMR (DMSO-d₆): 400 MHz δ 9.58 (d, *J* = 5.07 Hz, 1H), 9.23 (s, 1H), 9.12 (br. s., 1H), 8.81-9.02 (m, 2H), 8.74 (s, 1H), 8.50 (s, 1H), 8.35 (d, *J* = 7.80 Hz, 1H), 7.89 (d, *J* = 8.59 Hz, 1H), 4.56-4.89 (m, 1H), 3.50 (d, *J* = 10.7 Hz, 1H), 3.31 (d, *J* = 11.9 Hz, 1H), 3.03 (q, *J* = 10.5 Hz, 1H), 2.92 (d, *J* = 9.76 Hz, 1H), 2.07-2.18 (m, 1H), 1.94-2.06 (m, 1H), 1.68-1.91 (m, 2H). HRMS: C₁₆H₁₇N₅S requires M+H at *m/z* 312.1283; found, 312.1274.

4-((6-(Thiazol-5-yl)quinazolin-4-yl)amino)piperidine-1-carboxamide (3ff). To an iPrOH (2 mL) suspension of compound **3dd** (35 mg, 0.112 mmol), triethylamine (0.031 mL, 0.225 mmol), was added isocyanatotrimethylsilane (25.9 mg, 0.225 mmol). The reaction mixture was stirred at rt for 2 h. The mixture first turned clear and then cloudy again with white precipitate. The solid was filtered off and the filtrate was concentrated in vacuo. The resulting residue was loaded onto prep HPLC for purification affording 4-((6-(thiazol-5-yl)quinazolin-4-yl)amino)piperidine-1-carboxamide (27 mg, 0.076 mmol). ¹H NMR (DMSO-d₆): 400 MHz δ 9.36 (br. s., 1H), 9.20 (s, 1H), 8.80 (s, 1H), 8.73 (d, *J* = 1.56 Hz, 1H), 8.45 (s, 1H), 8.29 (d, *J* = 8.59 Hz, 1H), 7.84 (d, *J* = 8.79 Hz, 1H), 5.86 (br. s., 2H), 4.60 (m, 1H), 4.07 (d, *J* = 13.5 Hz, 2H), 2.78 - 2.93 (m, 2H), 1.94 (d, *J* = 9.96 Hz, 2H), 1.66 (qd, *J* = 12.0, 4.10 Hz, 2H). HRMS: C₁₇H₁₈N₆OS requires M+H at *m/z* 355.1341; found, 355.1327. RP-HPLC, *t*R = 0.54 min, 96% purity.

1,1-Dimethylethyl tetrahydro-2H-thiopyran-4-ylcarbamate. To a CH₂Cl₂ solution (150 mL) containing tetrahydro-2H-thiopyran-4-ylamine (4.87 g, 41.5 mmol) was added di-tert-butyl dicarbonate (9.07 g, 41.5 mmol) followed by triethylamine (4.20 g, 41.5 mmol) at rt. The resulting solution was stirred overnight at which time the solution was washed with dilute aqueous NaHSO₄ followed by drying over MgSO₄. The solvent was removed in vacuo and the residual white solid was purified on the Biotage (30-70% EtOAc/hexanes) affording 6.93 g (31.9 mmol) of 1,1-dimethylethyl tetrahydro-2H-thiopyran-4-ylcarbamate as a white solid. ¹H NMR (CDCl₃): 400 MHz δ 4.49 (br. s., 1H), 3.45 (d, *J* = 7.61 Hz, 1H), 2.53-2.81 (m, 4H), 2.22 (dd, *J* = 2.93, 13.1 Hz, 2H), 1.35-1.58 (m, 11H).

1,1-Dimethylethyl (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)carbamate. To a CH₂Cl₂ solution (130 mL) containing 1,1-dimethylethyl tetrahydro-2H-thiopyran-4-ylcarbamate (6.92 g, 31.8 mmol) and solid NaHCO₃ (5.35 g, 63.7 mmol) cooled to 0 °C was added mCPBA (15.0 g, 66.9 mmol, 77% by weight) portionwise. The solution was then slowly allowed to warm to rt overnight. The heterogeneous solution was filtered and the collected solid rinsed thoroughly with CH₂Cl₂. The filtrate was washed with saturated NaHSO₄ (2x), saturated NaHCO₃ (2x) and saturated NaCl followed by drying over MgSO₄. The solvent was removed in vacuo yielding 7.87 g (31.6 mmol) of 1,1-dimethylethyl (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)carbamate as a white solid. ¹H NMR (CDCl₃): 400 MHz δ 4.61 (br. s., 1H), 3.66-3.84 (m, 1H), 2.97-3.16 (m, 4H), 2.21-2.42 (m, 2H), 2.00-2.21 (m, 2H), 1.44 (s, 9H).

Tetrahydro-2H-thiopyran-4-amine 1,1-dioxide hydrochloride. To a flask containing 1,1-dimethylethyl (1,1-dioxidotetrahydro-2H-thiopyran-4-yl)carbamate (7.87 g, 31.6 mmol) in 100 mL of

dioxane was added 63 mL of a 4.0M dioxane (253 mmol) solution of HCl. The solution was stirred at rt overnight at which time the solution was concentrated. The residual solid was triterated with Et₂O and the solid collected via vacuum filtration yielding 5.63 g (30.3 mmol) of tetrahydro-2H-thiopyran-4-amine 1,1-dioxide as a white solid. ¹H NMR (DMSO-d₆): 400 MHz δ 8.50 (br. s., 3H), 3.39 (d, *J* = 4.69 Hz, 1H), 3.23-3.34 (m, 2H), 3.04-3.22 (m, 2H), 2.28 (d, *J* = 11.7 Hz, 2H), 2.04 (q, *J* = 11.3 Hz, 2H).

6-Bromo-N-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-d₆): 400 MHz δ 8.62 (d, *J* = 1.95 Hz, 1H), 8.52 (s, 1H), 8.15 (d, *J* = 7.61 Hz, 1H), 7.90 (dd, *J* = 2.05, 8.88 Hz, 1H), 7.63 (d, *J* = 8.78 Hz, 1H), 4.42 - 4.71 (m, 1H), 3.34 - 3.43 (m, 2H), 3.04-3.26 (m, 2H), 1.99 - 2.34 (m, 4H). Low-resolution MS (ES+) *m/e* 356 & 358 (MH+).

N-(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3gg). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.83 (d, *J* = 7.41 Hz, 1H), 9.26 (br. s., 1H), 8.96 (s, 1H), 8.77 (s, 1H), 8.51 (s, 1H), 8.41 (d, *J* = 7.80 Hz, 1H), 7.88 (d, *J* = 8.59 Hz, 1H), 4.74-4.93 (m, 1H), 3.35-3.62 (m, 2H), 3.21 (d, *J* = 12.3 Hz, 2H), 2.30 (br. s., 4H). HRMS: C₁₆H₁₆N₄O₂S₂ requires M+H at *m/z* 361.0793; found, 361.0784. RP-HPLC, *tR* = 0.57 min, 99% purity.

6-Bromo-N-(4-methylcyclohexyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 320 & 322 (MH+).

N-(4-Methylcyclohexyl)-6-(thiazol-5-yl)quinazolin-4-amine (3hh). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. The NMR showed ~ 70:30 mixture of diastereomers. ¹H NMR (CDCl₃): 400 MHz δ 8.77 (s, 1H), 8.75 (s, 1H, minor diastereomer), 8.59 (s, 1H), 8.58 (br. s., 1H, minor diastereomer), 8.11 (s, 1H), 8.10 (br. s., 1H, minor diastereomer), 7.79 - 7.90 (m, 3H), 7.74 (br. s., 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 5.64 (br. s., 1H, minor diastereomer), 4.34 - 4.45 (m, 1H), 4.10 - 4.25 (m, 1H, minor diastereomer), 2.15 (d, *J* = 10.0 Hz, 1H), 1.71 - 1.90 (m, 6H), 1.59 - 1.71 (m, 3H), 1.06 - 1.43 (m, 5H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H, minor diastereomer). HRMS: C₁₈H₂₀N₄S requires M+H at *m/z* 325.1487; found, 325.1486. RP-HPLC, *tR* = 1.15 min, 100% purity.

N-((1S, 2S)-2-Methylcyclohexyl)-6-(thiazol-5-yl)quinazolin-4-amine (3ii) & N-((1S, 2R)-2-methylcyclohexyl)-6-(thiazol-5-yl)quinazolin-4-amine (3jj). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. trans: ¹H NMR (DMSO-d₆): 400 MHz δ 9.18 (s, 1H), 8.64 (s, 1H), 8.46 (s, 1H), 8.44 (s, 1H), 8.03 - 8.20 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 4.08 (br. s., 1H), 1.63 - 2.02 (m, 5H), 1.05 - 1.47 (m, 4H), 0.92 (d, *J* = 6.3 Hz, 3H). HRMS: C₁₈H₂₀N₄S requires M+H at *m/z* 325.1487; found, 325.1482. RP-HPLC, *tR* = 1.12 min, 100% purity. cis: ¹H NMR (DMSO-d₆): δ: 9.18 (br. s., 1H), 8.73 (br. s., 1H), 8.48 (d, *J* = 3.5 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.87 (br. s., 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 4.46 (br. s., 1H), 2.31 (br. s., 1H), 1.15 - 1.94 (m, 8H), 0.95 (d, *J* = 6.3 Hz, 3H). HRMS: C₁₈H₂₀N₄S requires M+H at *m/z* 325.1487; found, 325.1481. RP-HPLC, *tR* = 0.99 min, 98% purity.

6-Bromo-N-(3-methylcyclohexyl)-4-quinazolinamine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. The product is a 1:0.8 ratio of a cis/trans mixture by NMR. ¹H NMR (CDCl₃): 400 MHz δ 8.57 - 8.67 (2 sets of singlets, 1H) 7.84 - 7.98 (2 sets of doublets, 1H), 7.71 - 7.76 (2 sets of doublets, 1H), 7.64 - 7.70 (2 sets of doublets, 1H), 5.92-6.02 (2 sets of broad singlet, 1H), 4.18 - 4.64 (2 sets of multiplet, 1H), 1.07 - 2.20 (m, 8H), 0.90 - 1.01 (2 sets of triplet, 3H), 0.74 - 0.89 (m, 1H). Low-resolution MS (ES+) *m/e* 320 & 322 (MH+).

N-(3-Methylcyclohexyl)-6-(1,3-thiazol-5-yl)-4-quinazolinamine (3kk). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.15 (s, 1H), 8.60 (dd, *J* = 15.8, 1.56 Hz, 1H), 8.45 (dd, *J* = 6.55, 5.18 Hz, 2H), 8.01 - 8.13 (m, 2H), 7.71

(dd, $J = 8.60, 2.54$ Hz, 1H), 4.15 - 4.62 (m, 1H, 2 sets of multiplets making 1 proton), 1.89 - 2.16 (m, 2H, 2 sets of multiplets making 2 protons), 1.19 - 1.87 (m, 6H), 0.90 - 1.04 (m, 3H, 2 sets of doublets making 3H from Me), 0.75 - 1.25 (m, 1 H). HRMS: $C_{18}H_{20}N_4S$ requires $M+H$ at m/z 325.1487; found, 325.1472. RP-HPLC, $t_R = 1.17$ min, 100% purity.

4-(6-Bromoquinazolin-4-ylamino)cyclohexanol. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) m/e 323 & 325 (MH+).

4-(6-(Thiazol-5-yl)quinazolin-4-ylamino)cyclohexanol (3II). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.16 (s, 1H), 8.57 (d, $J = 1.3$ Hz, 1H), 8.46 (s, 1H), 8.43 (s, 1H), 8.01 - 8.13 (m, 2H), 7.71 (d, $J = 8.8$ Hz, 1H), 4.07 - 4.28 (m, 1H), 3.46 - 3.53 (m, 2H), 1.83 - 2.05 (m, 4H), 1.40 - 1.60 (m, 2H), 1.21 - 1.40 (m, 2H). HRMS: $C_{17}H_{18}N_4OS$ requires $M+H$ at m/z 327.1279; found, 327.1268. RP-HPLC, $t_R = 0.62$ min, 100% purity.

1,1-Dimethylethyl [trans-4-(aminocarbonyl)cyclohexyl]carbamate. To an acetonitrile (10 mL) solution of trans-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (500 mg, 2.06 mmol), pyridine (0.183 mL, 2.26 mmol) was added BOC₂O (0.716 mL, 3.08 mmol). The mixture was stirred at rt for 1 h then solid ammonium bicarbonate (244 mg, 3.08 mmol) was added. The resulting mixture was stirred at rt overnight at which time the solvent was removed in vacuo and the residue was redissolved in DCM. This mixture was washed with 1:1 mixture of 1.0 M HCl and brine. The aqueous was extracted twice with DCM. The combined organics were washed with brine and dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified on the ISCO Combiflash eluting with 30-80% EtOAc/hexanes to afford 1,1-dimethylethyl [trans-4-(aminocarbonyl)cyclohexyl]carbamate (470 mg, 1.94 mmol). 1H NMR (DMSO- d_6): 400 MHz δ 7.08 (br. s., 1 H), 6.70 (br. s., 1H), 6.66 (br. s., 1H), 3.62 (m, 1H), 2.40 (m, 1H), 1.33 - 1.73 (m, 8H), 1.38 (s, 9H).

trans-4-Aminocyclohexanecarboxamide hydrochloride. HCl (15 mL, 60.0 mmol, 4.0 M in dioxane) was added to a suspension of 1,1-dimethylethyl [trans-4-(aminocarbonyl)cyclohexyl]carbamate (450 mg, 1.857 mmol) in 1,4-dioxane (5 mL). The mixture was stirred overnight at which time the solvent was removed in vacuo to afford trans-4-aminocyclohexanecarboxamide (270 mg, 1.51 mmol) as a white solid. 1H NMR (MeOH- d_4): 400 MHz δ 3.08 (m, 1H), 2.20 - 2.36 (m, 1H), 1.89 - 2.16 (m, 4H), 1.31 - 1.67 (m, 4H).

trans-4-[(6-Bromo-4-quinazolinyl)amino]cyclohexanecarboxamide and trans-4-[(6-bromo-4-quinazolinyl)amino]cyclohexanecarboxylic acid. A DMF (4 mL) solution of 6-bromo-4-chloroquinazoline (243 mg, 1 mmol) and trans-4-aminocyclohexanecarboxamide (179 mg, 1.00 mmol) with iPr_2NEt (0.524 mL, 3.00 mmol) was heated in a microwave reactor to 120 °C for 40 min at which time most of the solvent was removed in vacuo. The residue was filtered and loaded onto semi-prep HPLC for purification affording trans-4-[(6-bromo-4-quinazolinyl)amino]cyclohexanecarboxamide (150 mg, 0.430 mmol) as a pale yellow solid. 1H NMR (DMSO- d_6): 400 MHz δ 9.68 (br. s., 1H), 8.91 (s, 1H), 8.85 (d, $J = 1.76$ Hz, 1H), 8.16 (dd, $J = 8.89, 1.86$ Hz, 1H), 7.71 (d, $J = 8.98$ Hz, 1H), 7.27 (br. s., 1H), 6.78 (br. s., 1H), 4.31 (dd, $J = 7.23, 3.52$ Hz, 1H), 2.08 - 2.22 (m, 1H), 1.78 - 2.04 (m, 4H), 1.35 - 1.62 (m, 4H). Low-resolution MS (ES+) m/e 349 & 351 (MH+). Also isolated was trans-4-[(6-bromo-4-quinazolinyl)amino]cyclohexanecarboxylic acid (110 mg, 0.314 mmol), also a pale yellow solid, presumably from hydrolysis. 1H NMR (DMSO- d_6): 400 MHz δ 11.9 - 12.5 (br. s., 1H), 9.56 (br. s., 1H), 8.87 (s, 1H), 8.84 (d, $J = 1.76$ Hz, 1H), 8.14 (dd, $J = 8.89, 1.86$ Hz, 1H), 7.70 (d, $J = 8.79$ Hz, 1H), 4.30 (m, 1H), 2.27 (m, 1H), 2.01 (m, 4H), 1.36 - 1.61 (m, 4H). Low-resolution MS (ES+) m/e 350 & 352 (MH+).

trans-4-[[6-(1,3-Thiazol-5-yl)-4-quinazolinyl]amino]cyclohexanecarboxamide (3mm). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR

(DMSO- d_6): 400 MHz δ 9.88 (br. s., 1H), 9.24 (s, 1H), 8.92 (s, 1H), 8.79 (s, 1H), 8.50 (s, 1H), 8.38 (d, J = 8.20 Hz, 1H), 7.84 (d, J = 8.39 Hz, 1H), 7.29 (br. s., 1H), 6.78 (br. s., 1H), 4.40 (m, 1H), 2.16 (m, 1H), 1.78 - 2.08 (m, 4H), 1.36 - 1.71 (m, 4H). HRMS: $C_{18}H_{19}N_5OS$ requires M+H at m/z 354.1388; found, 354.1376. RP-HPLC, t_R = 0.63 min, 95% purity.

trans-1,1-Dimethylethyl -3-(aminocarbonyl)cyclohexyl]carbamate. This compound was prepared in a similar fashion as described for compound **3mm** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 7.08 (br. s., 1H), 6.61 - 6.77 (m, 2H), 3.62 (m, 1H), 2.40 (dd, J = 8.01, 3.91 Hz, 1H), 1.52 - 1.68 (m, 3H), 1.40 - 1.52 (m, 5H), 1.38 (s, 9H).

trans-3-Aminocyclohexanecarboxamide hydrochloride. This compound was prepared in a similar fashion as described for compound **3mm** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 8.08 (br. s., 3H), 6.33 - 6.76 (br. s., 2H), 3.39 (m, 1H), 2.59 (m, 1H), 1.98 (m, 1H), 1.65 - 1.86 (m, 2H), 1.29 - 1.63 (m, 5H).

trans-3-[(6-Bromo-4-quinazoliny]amino]cyclohexanecarboxamide. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 9.40 (d, J = 5.47 Hz, 1H, aniline NH proton), 8.92 (d, J = 1.95 Hz, 1H), 8.89 (s, 1H), 8.16 (dd, J = 8.79, 1.95 Hz, 1H), 7.71 (d, J = 8.99 Hz, 1H), 7.24 (br. s., 1H), 6.81 (br. s., 1H), 4.47 (m, 1H), 2.66 (m, 1H), 1.98 (m, 1H), 1.73 - 1.90 (m, 3H), 1.46 - 1.72 (m, 4H). Low-resolution MS (ES+) m/e 349 & 351 (MH+).

trans-3-[[6-(1,3-Thiazol-5-yl)-4-quinazoliny]amino]cyclohexanecarboxamide (3nn). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 9.67 (d, J = 7.23 Hz, 1H, NH proton), 9.24 (s, 1H), 8.91 (s, 1H), 8.84 (d, J = 1.37 Hz, 1H), 8.51 (s, 1H), 8.37 (dd, J = 8.79, 1.56 Hz, 1H), 7.84 (d, J = 8.79 Hz, 1H), 7.28 (br. s., 1H), 6.83 (br. s., 1H), 4.86 (m, 1H), 2.70 (m, 1H), 2.08 (m, 1H), 1.77 - 1.96 (m, 3H), 1.44 - 1.75 (m, 4H). HRMS: $C_{18}H_{19}N_5OS$ requires M+H at m/z 354.1388; found, 354.1375. RP-HPLC, t_R = 0.68 min, 97% purity.

trans-N-Ethyl-4-[[6-(1,3-thiazol-5-yl)-4-quinazoliny]amino]cyclohexanecarboxamide (3oo). A DMF (4 mL) solution of trans-4-[[6-(1,3-thiazol-5-yl)-4-quinazoliny]amino]cyclohexanecarboxylic acid (70 mg, 0.198 mmol) (see compound **3mm** step 3) and HATU (90 mg, 0.237 mmol) had iPr_2NEt (0.069 mL, 0.395 mmol) added. The mixture was stirred for 20 min before ethylamine (10.7 mg, 0.237 mmol) was added. The resulting mixture was stirred overnight at which time the reaction mixture was loaded onto an Agilent semi-prep HPLC. The desired product was collected upon removing the solvent affording trans-N-ethyl-4-[[6-(1,3-thiazol-5-yl)-4-quinazoliny]amino]cyclohexanecarboxamide (65 mg, 0.131 mmol) as a light tan solid. 1H NMR (DMSO- d_6): 400 MHz δ 9.90 (br. s., 1H), 9.24 (s, 1H), 8.93 (s, 1H), 8.79 (s, 1H), 8.50 (s, 1H), 8.38 (d, J = 8.00 Hz, 1H), 7.83 (d, J = 8.58 Hz, 1H), 7.79 (br. s., 1H), 4.41 (m, 1H), 3.06 (m, 2H), 2.15 (m, 1H), 1.76 - 2.08 (m, 4H), 1.39 - 1.69 (m, 4H), 1.02 (t, J = 6.44 Hz, 3H). HRMS: $C_{20}H_{23}N_5OS$ requires M+H at m/z 382.1701; found, 382.1694. RP-HPLC, t_R = 0.76 min, 97% purity.

cis-4-((6-Bromoquinazolin-4-yl)amino)cyclohexanecarboxylic acid. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. 1H NMR (DMSO- d_6): 400 MHz δ 12.2 (br. s., 1H), 8.67 (br. s., 1H), 8.48 (s, 1H), 8.09 (d, J = 7.41 Hz, 1H), 7.87 (dd, J = 8.98, 1.95 Hz, 1H), 7.60 (d, J = 8.98 Hz, 1H), 4.23 (m, 1H), 2.56 (m, 1H), 1.99 - 2.15 (m, 2H), 1.72 - 1.82 (m, 2H), 1.49 - 1.69 (m, 4H). Low-resolution MS (ES+) m/e 350 & 352 (MH+).

cis-4-[[6-(1,3-Thiazol-5-yl)-4-quinazoliny]amino]cyclohexanecarboxylic acid (3pp). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. 1H NMR (DMSO- d_6): 400 MHz δ 12.4 (br. s., 1H), 9.69 (br. s., 1H), 9.24 (s, 1H), 8.88 (s, 1H), 8.79 (d, J = 1.56 Hz, 1H), 8.49 (s, 1H), 8.36 (dd, J = 8.60, 1.76 Hz, 1H), 7.83 (d, J = 8.60 Hz, 1H), 4.22 - 4.58 (m, 1H), 2.66 (d, J = 3.13 Hz, 1H), 2.16 (d, J = 12.1 Hz, 2H), 1.86 (d, J = 8.99 Hz, 2H), 1.57 - 1.79 (m, 4H).

HRMS: C₁₈H₁₈N₄O₂S requires M+H at *m/z* 355.1228; found, 355.1217. RP-HPLC, *t*R = 0.79 min, 94% purity.

trans-4-{{6-(1,3-Thiazol-5-yl)-4-quinazolinyl}amino}cyclohexanecarboxylic acid (3qq). For the preparation of the starting bromide see compound **3mm** step 3 (by-product). The entitled compound was prepared in a similar manner as described for compound **3a** step B. ¹H NMR (DMSO-*d*₆): 400 MHz δ 12.3 (br. s., 1H), 9.72 (br. s., 1H), 9.24 (s, 1H), 8.88 (s, 1H), 8.78 (d, *J* = 1.56 Hz, 1H), 8.50 (s, 1H), 8.36 (dd, *J* = 8.79, 1.76 Hz, 1H), 7.82 (d, *J* = 8.60 Hz, 1H), 4.40 (m, 1H), 2.29 (m, 1H), 2.06 (m, 4H), 1.37 - 1.69 (m, 4H). HRMS: C₁₈H₁₈N₄O₂S requires M+H at *m/z* 355.1228; found, 355.1219. RP-HPLC, *t*R = 0.71 min, 99% purity.

6-Bromo-N-(4-(methylsulfonyl)cyclohexyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. ¹H NMR (DMSO-*d*₆): 400 MHz δ 9.58 (d, *J* = 6.4 Hz, 1H), 9.01 (d, *J* = 1.8 Hz, 1H), 8.93 (s, 1H), 8.19 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 4.38 - 4.65 (m, 1H), 3.28 (t, *J* = 5.0 Hz, 1H), 3.03 (s, 3H), 2.05 - 2.37 (m, 4H), 1.95 (dt, *J* = 9.2, 4.6 Hz, 2H), 1.70 - 1.88 (m, 2H). Low-resolution MS (ES+) *m/e* 384 & 386 (MH⁺).

N-((1*r*,4*r*)-4-(Methylsulfonyl)cyclohexyl)-6-(thiazol-5-yl)quinazolin-4-amine (3rr). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-*d*₆): 400 MHz δ 9.17 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 8.45 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 4.34 (br. s., 1H), 3.25 (d, *J* = 4.7 Hz, 1H), 3.01 (s, 3H), 2.08 - 2.25 (m, 4H), 1.87 - 2.02 (m, 2H), 1.79 (dd, *J* = 8.6, 4.5 Hz, 2H). HRMS: C₁₈H₂₀N₄O₂S₂ requires M+H at *m/z* 389.1106; found, 389.1091. RP-HPLC, *t*R = 0.68 min, 98% purity.

1-(1,4-Dioxaspiro[4.5]decan-8-yl)pyrrolidin-2-one. To a CH₂Cl₂ solution (150 mL) containing 1,4-dioxaspiro[4.5]decan-8-one (5.0 g, 32.0 mmol), ethyl 4-aminobutanoate hydrochloride (5.37 g, 32.0 mmol) and triethylamine (3.24 g, 32.0 mmol) was added sodium triacetoxyborohydride (6.79 g, 32.0 mmol) at rt. The resulting solution was stirred at rt overnight at which time it was quenched with H₂O. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and the solvent removed in vacuo. The residual orange liquid was purified on the ISCO Combiflash (5-15% MeOH/CH₂Cl₂) yielding 1.67 g (7.41 mmol) of 1-(1,4-dioxaspiro[4.5]decan-8-yl)pyrrolidin-2-one as a brown oil which slowly solidified on standing. ¹H NMR (CDCl₃): 400 MHz δ 4.01-4.14 (m, 1H), 3.95 (s, 4H), 3.36 (t, *J* = 7.02 Hz, 2H), 2.40 (t, *J* = 8.10 Hz, 2H), 1.92-2.06 (m, 2H), 1.60-1.84 (m, 8H).

1-(4-Oxocyclohexyl)pyrrolidin-2-one. An acetone solution (50 mL) containing 1-(1,4-dioxaspiro[4.5]decan-8-yl)pyrrolidin-2-one (1.65 g, 7.32 mmol) had 10 mL of 2 M HCl added to it at rt. The resulting solution was stirred at rt overnight at which time the solution was concentrated. The residual aqueous solution was directly purified on the ISCO (5-15% MeOH/CH₂Cl₂) yielding 1.21 g (6.68 mmol) of 1-(4-oxocyclohexyl)pyrrolidin-2-one as an amber solid. ¹H NMR (CDCl₃): 400 MHz δ 4.48 (tt, *J* = 3.80, 12.1 Hz, 1H), 3.35 (t, *J* = 7.02 Hz, 2H), 2.33-2.63 (m, 6H), 1.96-2.12 (m, 4H), 1.79-1.96 (m, 2H).

1-(4-Aminocyclohexyl)pyrrolidin-2-one. A 2-neck flask containing 10% Pd/C (1.5 g) had a 7.0 M NH₃/MeOH solution (40 mL) containing 1-(4-oxocyclohexyl)pyrrolidin-2-one added to it under nitrogen. The flask was then evacuated 3x under vacuum followed each time with a hydrogen fill via a balloon. The flask was then stirred under the balloon of H₂ overnight. The catalyst was then removed via filtration through a bed of celite. The celite was rinsed thoroughly with CH₂Cl₂ and the solution concentrated yielding an amber foam. The NMR of this material still showed a small amount of SM. The material was directly taken into the next step.

1-(4-((6-Bromoquinazolin-4-yl)amino)cyclohexyl)pyrrolidin-2-one. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 388 & 391 (MH+).

1-((1r,4r)-4-((6-(Thiazol-5-yl)quinazolin-4-yl)amino)cyclohexyl)pyrrolidin-2-one (3ss) and 1-((1s,4s)-4-((6-(thiazol-5-yl)quinazolin-4-yl)amino)cyclohexyl)pyrrolidin-2-one (3tt). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. trans isomer: ¹H NMR (DMSO-d₆): 400 MHz δ 9.17 (s, 1H), 8.70 (d, *J* = 1.17 Hz, 1H), 8.50 (s, 1H), 8.48 (s, 1H), 8.09 (dd, *J* = 1.66, 8.68 Hz, 1H), 7.70-7.80 (m, 2H), 4.36 (d, *J* = 3.51 Hz, 1H), 3.74-3.97 (m, 1H), 3.42 (t, *J* = 6.93 Hz, 2H), 2.18-2.28 (m, 2H), 2.14 (d, *J* = 10.9 Hz, 2H), 1.93 (quin, *J* = 7.56 Hz, 4H), 1.67-1.83 (m, 2H), 1.43-1.58 (m, 2H). HRMS: C₂₁H₂₃N₅OS requires M+H at *m/z* 394.1701; found, 394.1695. RP-HPLC, *t*R = 1.77 min, 99% purity. cis isomer: ¹H NMR (DMSO-d₆): 400 MHz δ 9.17 (s, 1H), 8.59 (d, *J* = 1.37 Hz, 1H), 8.47 (s, 1H), 8.45 (s, 1H), 8.16 (d, *J* = 7.61 Hz, 1H), 8.10 (dd, *J* = 1.66, 8.68 Hz, 1H), 7.72 (d, *J* = 8.58 Hz, 1H), 4.15-4.31 (m, 1H), 3.83 (quin, *J* = 7.71 Hz, 1H), 3.35 (s, 2H), 2.17-2.30 (m, 2H), 2.09 (d, *J* = 11.3 Hz, 2H), 1.92 (quin, *J* = 7.46 Hz, 2H), 1.48-1.73 (m, 6H). HRMS: C₂₁H₂₃N₅OS requires M+H at *m/z* 394.1701; found, 394.1696. RP-HPLC, *t*R = 0.90 min, 100% purity.

6-Bromo-N-ethylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 252 & 254 (MH+).

N-Ethyl-6-(thiazol-5-yl)quinazolin-4-amine (3uu). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.15 (s, 1H), 8.54 (d, *J* = 1.51 Hz, 1H), 8.45 (d, *J* = 13.8 Hz, 3H), 8.10 (dd, *J* = 1.63, 8.66 Hz, 1H), 7.72 (d, *J* = 8.53 Hz, 1H), 3.51-3.67 (m, 2H), 1.26 (t, *J* = 7.15 Hz, 3H). HRMS: C₁₃H₁₂N₄S requires M+H at *m/z* 257.0861; found, 257.0860. RP-HPLC, *t*R = 0.60 min, 100% purity.

6-Bromo-N-isopropylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 266 & 268 (MH+).

N-Isopropyl-6-(thiazol-5-yl)quinazolin-4-amine (3vv). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.16 (s, 1H), 8.59 (d, *J* = 1.26 Hz, 1H), 8.45 (d, *J* = 7.53 Hz, 2H), 8.00-8.19 (m, 2H), 7.71 (d, *J* = 8.78 Hz, 1H), 4.55 (qd, *J* = 6.63, 13.49 Hz, 1H), 1.30 (d, *J* = 6.53 Hz, 6H). HRMS: C₁₄H₁₄N₄S requires M+H at *m/z* 271.1017; found, 271.1006. RP-HPLC, *t*R = 0.71 min, 100% purity.

6-Bromo-N-tert-butylquinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 280 & 282 (MH+).

N-Tert-butyl-6-(thiazol-5-yl)quinazolin-4-amine (3ww). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.15 (s, 1H), 8.62 (d, *J* = 1.25 Hz, 1H), 8.48 (s, 1H), 8.47 (s, 1H), 8.05 (dd, *J* = 1.63, 8.66 Hz, 1H), 7.71 (d, *J* = 8.53 Hz, 1H), 7.52 (s, 1H), 1.58 (s, 9H). HRMS: C₁₅H₁₆N₄S requires M+H at *m/z* 285.1174; found, 285.1167. RP-HPLC, *t*R = 0.89 min, 100% purity.

2-(6-Bromoquinazolin-4-ylamino)ethanol. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 268 & 270 (MH+).

2-(6-(Thiazol-5-yl)quinazolin-4-ylamino)ethanol (3xx). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-d₆): 400 MHz δ 9.15 (s, 1H), 8.59 (d, *J* = 1.51 Hz, 1H), 8.53 (br. s., 1H), 8.45 (d, *J* = 6.27 Hz, 2H), 8.11 (dd, *J* = 1.76, 8.53 Hz, 1H), 7.72 (d, *J* = 8.53 Hz, 1H), 4.77-4.96 (m, 1H), 3.65 (br. s., 4H). HRMS: C₁₃H₁₂N₄OS requires M+H at *m/z* 273.0810; found, 273.0812.

6-Bromo-N-(2-methoxyethyl)quinazolin-4-amine. The entitled compound was prepared in a similar manner as described for compound **3a** step 1. Low-resolution MS (ES+) *m/e* 282 & 284 (MH+).

N-(2-Methoxyethyl)-6-(thiazol-5-yl)quinazolin-4-amine (3yy). The entitled compound was prepared in a similar manner as described for compound **3a** step 2. ¹H NMR (DMSO-*d*₆): 400 MHz δ 10.1 (br. s., 1H), 9.22 (s, 1H), 8.86 (s, 1H), 8.76 (s, 1H), 8.49 (s, 1H), 8.36 (dd, *J* = 1.13, 8.66 Hz, 1H), 7.83 (d, *J* = 8.78 Hz, 1H), 3.90 (q, *J* = 5.27 Hz, 2H), 3.64 (t, *J* = 5.40 Hz, 2H), 3.30 (s, 3H). HRMS: C₁₄H₁₄N₄OS requires M+H at *m/z* 287.0966; found, 287.0964.

Synthesis of 6-Bromo-4-chloroquinolin-2(1H)-one.

Methyl 3-((4-bromophenyl)amino)-3-oxopropanoate. A 2 L JLR (jacketed lab reactor) was charged with a solution of the 4-bromoaniline (90 g, 523 mmol) in ethyl acetate (1500 mL) along with TEA (95 mL, 680 mmol). The mixture was cooled to an internal temperature of 10 °C (jacket temp 10 °C) and the neat methyl 3-chloro-3-oxopropanoate (70.3 mL, 654 mmol) was added over 30 min maintaining the internal temperature below 17 °C. Following the addition, the mixture was stirred for 15 min. Water (1500 mL) was added and the mixture was stirred for 20 min. The layers were separated and the organics washed again with sat'd NaHCO₃ solution (1000 mL). The organics were then dried (MgSO₄), filtered and concentrated to half the volume and chased with heptane (500 mL) to give a nice slurry, which was cooled in an ice bath for 20 min and then filtered to give methyl 3-((4-bromophenyl)amino)-3-oxopropanoate as a white solid (122.75 g) which was air dried on the filter for 1 h. ¹H NMR (CDCl₃): 400 MHz δ 9.07 (br. s., 1H) 7.18 - 7.34 (m, 4H) 3.62 (s, 3H) 3.30 (s, 2H).

3-((4-Bromophenyl)amino)-3-oxopropanoic acid. A 2L JLR was charged with the methyl 3-((4-bromophenyl)amino)-3-oxopropanoate (113 g, 415 mmol), THF (1400 mL) and methanol (350 mL) and the solution was cooled to -5 °C. 2.0 N NaOH (350 mL) was added dropwise over 50 min maintaining an internal temperature of 5-7 °C. The reaction was stirred at 10 °C for 30 min and then cooled once again to -5 °C and 6.0 N HCl (125 mL) was added over 25 min. The reaction warmed to 20 °C and then the reaction mixture was concentrated under reduced pressure removing 1100 mL of solvent and chasing with water (500 mL). The resulting slurry was then filtered, washed with water twice and the resulting filter cake dried for 16 h to give a colorless solid (103.5 g). ¹H NMR (DMSO-*d*₆): 400 MHz δ 2.65 (br. s., 1H) 10.25 (s, 1H) 7.41 - 7.64 (m, 4H) 3.35 (s, 2H).

6-Bromoquinoline-2,4(1H, 3H)-dione. A 3 L 4-neck flask equipped with mechanical stirring was charged with the 3-((4-bromophenyl)amino)-3-oxopropanoic acid (103.5 g, 401 mmol) and methanesulfonic acid (520 mL, 8008 mmol) and the internal temperature was brought to 50 °C. In 5 portions of 20-25 g each phosphorus pentoxide (114 g, 802 mmol) was carefully added to the reaction mixture. The temperature was then brought to 70-72 °C and the mixture stirred for 120 min. until the HPLC showed complete reaction. Ice cold water was added slowly at 5 °C maintaining an internal temperature < 15 °C over the course of the addition - the first 125 mL was added over 15 min, the remaining 375 mL was added over another 15 min and the resulting mixture aged for another 20 min in an ice bath then filtered and washed once more with ice cold water and dried for 2 h. The solid was suspended in water on the funnel and the pH adjusted to 7-8 with the addition of 350 mL of 1.0 N NaOH. The filter cake was dried overnight to remove any excess water using a 65 °C vacuum oven with a nitrogen purge to give 6-bromoquinoline-2,4(1H, 3H)-dione as a colorless solid. (90 g). ¹H NMR (DMSO-*d*₆): 400 MHz δ 11.2 - 12.2 (m, 2H) 8.00 (d, *J* = 2.26 Hz, 1H) 7.77 (dd, *J* = 8.78, 2.26 Hz, 1H) 7.35 (d, *J* = 8.53 Hz, 1H) 5.90 (s, 1H).

6-Bromo-2,4-dichloroquinoline. A 1 L 4-neck flask equipped with overhead stirrer, and a 1.0 N NaOH scrubber, was charged with 6-bromoquinoline-2,4(1H,3H)-dione (90 g, 375 mmol) and phosphorus oxychloride (270 mL, 2897 mmol). The stirred mixture was heated to 100 °C internal temperature using a 130 °C sand bath during which the suspension never completely went into solution.

The reaction was maintained at this temperature for 2 h until about 98% complete by HPLC. The sand bath was removed and once the temperature was 60 °C 600 mL of acetonitrile was added to maintain stirring overnight. The suspension was poured carefully over 2 L of crushed ice with stirring and then filtered to give 6-bromo-2,4-dichloroquinoline as a pale yellow solid. (96 g). ¹H NMR (DMSO-d₆): 400 MHz δ 8.34 (s, 1H) 8.02 - 8.13 (m, 2H) 7.99 (d, 1H).

6-Bromo-4-chloroquinolin-2(1H)-one. A 500 mL 3-neck flask equipped with mechanical stirrer, sand bath with internal and external probes (jacket control) was charged with 6-bromo-2,4-dichloroquinoline (10.33 g, 37.3 mmol), 6.0 N HCl (75 mL, 450 mmol), and 4.0 N HCl (85 mL, 340 mmol) in dioxane. The reaction mixture was heated to 90 °C (jacket 105 °C) and within 15 min was in solution, but was only 50% complete. The mixture became heterogeneous once again over the next 30 min and then continued heating for an hour over which point the HPLC showed no more starting material. There were another 2 impurity peaks (ca. 25%) corresponding to the dione and something else. The reaction was cooled and then aged in an ice bath for 30 min and filtered. The cake was washed with water and then cold Et₂O to give 6-bromo-4-chloroquinolin-2(1H)-one as an off white powder (7.45 g). ¹H NMR (DMSO-d₆): 400 MHz δ 12.1 (br. s., 1H) 7.93 (d, *J* = 2.26 Hz, 1H) 7.78 (dd, *J* = 8.78, 2.01 Hz, 1H) 7.32 (d, *J* = 8.78 Hz, 1H) 6.88 (s, 1H).

Synthesis of (1r,4r)-4-amino-N-methylcyclohexanecarboxamide.

Benzyl ((1r,4r)-4-(methylcarbamoyl)cyclohexyl)carbamate. To a DMF (30 mL) solution containing (1r,4r)-4-(((benzyloxy)carbonyl)amino)cyclohexanecarboxylic acid (3.0 g, 10.8 mmol) was added HATU (4.94 g, 13.0 mmol) and then iPr₂NEt (7.03 mL, 14.1 mmol). The reaction was stirred for 15 min before methanamine (0.672 g, 21.6 mmol) was added. A precipitate soon appeared and the reaction was stirred overnight. The solid was collected by filtration and washed with a small amount MeOH affording benzyl ((1r,4r)-4-(methylcarbamoyl)cyclohexyl)carbamate (2.95 g, 10.2 mmol). ¹H NMR (DMSO-d₆): 400 MHz δ 7.60 (d, *J* = 4.69 Hz, 1H), 7.22-7.41 (m, 5H), 7.15 (d, *J* = 8.01 Hz, 1H), 4.95 (s, 2H), 3.18 (m, 1H), 2.50 (d, *J* = 4.69 Hz, 3H), 1.87-2.04 (m, 1H), 1.58-1.83 (m, 4H), 0.97 - 1.42 (m, 4H). Low-resolution MS (ES⁺) *m/e* 291 (MH⁺).

(1r,4r)-4-Amino-N-methylcyclohexanecarboxamide. To a methanol (100 mL) suspension of benzyl ((1r,4r)-4-(methylcarbamoyl)cyclohexyl)carbamate (2.95 g, 10.2 mmol) was added 10% Pd/C (1.08 g, 1.02 mmol). The solution was degassed (3x) under H₂ and then stirred under H₂ balloon for 4 h. The reaction mixture was filtered through celite and concentrated in vacuo affording a yellow solid (1r,4r)-4-amino-N-methylcyclohexanecarboxamide (1.6 g, 10.2 mmol). ¹H NMR (DMSO-d₆): 400 MHz δ 2.49 (d, *J* = 4.69 Hz, 3H), 2.40 - 2.45 (m, 1H), 1.92 (tt, *J* = 12.1, 3.54 Hz, 1H), 1.52 - 1.80 (m, 4H), 0.82 - 1.41 (m, 4H).

Synthesis of trans-4-(2-methoxyethoxy)cyclohexanamine.

trans-4-(Dibenzylamino)cyclohexanol. Potassium carbonate (630 g, 4.56 mol) was added to a stirred solution of 175 g (1.52 mol) of trans-4-aminocyclohexanol in 6.0 L MeCN. The mixture was warmed to 30 °C, then 530 g (3.1 mol) benzylbromide was added over 30 min. After the addition, the mixture was warmed to 75 °C, and stirred at that temperature for 4 h. The reaction was cooled to 20 °C and then 8.0 L MTBE and 4.0 L water were added. The mixture was stirred for 15 min and the phases were separated. The organic phase was washed with water (4.0 L, twice) and the aqueous phase then was backwashed with 4.0 L MTBE. All organic phases were combined, dried with MgSO₄, filtered and concentrated. The MTBE was replaced with heptanes (3.0 L) and the product precipitated as a white solid. The product was filtered, washed with heptanes (1.0 L), and air-dried on the filter. The material was dried overnight in a vacuum oven at 40 °C to obtain 360 g (1.22 mol) of trans-4-(dibenzylamino)cyclohexanol. ¹H NMR (DMSO-d₆): 400 MHz δ 1.00 (m, 2H), 1.42 (m, 2H), 1.79 (m, 4H), 2.35 (m, 1H), 3.32 (m, 1H), 3.55 (s, 4H), 4.42 (d, *J* = 4.5 Hz, 1H), 7.17-7.34 (m, 10H).

trans-N,N-Dibenzyl-4-(2-methoxyethoxy)cyclohexanamine. trans-4-(Dibenzylamino)cyclohexanol (30 g, 102 mmol) dissolved in 100 mL DMPU had 1-bromo-2-methoxyethane (30 g, 216 mmol) added to it while stirring. Then 10 g (250 mmol) of NaH (60% dispersion in mineral oil) was added to the reaction portionwise over 2 h. The reaction was exothermic and some foaming was observed. The temperature was increased to 50 °C and the mixture was stirred for 1 h. An additional 30 g (216 mmol) of 1-bromo-2-methoxyethane and 10 g NaH (250 mmol) were added portionwise while the reaction temperature was increased to 60 °C. After stirring for an additional 2 h, 10 g (72 mmol) of 1-bromo-2-methoxyethane was added and stirring continued for an additional 6 h. HPLC indicated less than 1% remaining starting material. The mixture was cooled to 20 °C and poured slowly into 300 g of stirred ice-water. After the addition, 300 mL MTBE was added and the phases were separated. The organic phase was washed with water once, then the aqueous phase was backwashed once with MTBE. The combined organic phases dried with MgSO₄, filtered and concentrated to a pale yellow oil. The oil was dissolved in 100 mL dioxane, 40 mL hydrochloric acid solution (4.0 M in dioxane) added, the mixture stirred for 15 min and then concentrated to a white solid. Diethyl ether (150 mL) was added to the residue and the mixture stirred for 45 minutes followed by filtration. The cake was washed with 100 mL diethyl ether and dried to obtain 37.5 g (96 mmol) of the hydrochloride salt. ¹H NMR (DMSO-d₆): 400 MHz δ 0.98 (m, 2H), 1.71 (m, 2H), 2.08 (m, 2H), 2.25 (m, 2H), 3.03 (m, 1H), 3.22 (s, 3H), 3.23 (m, 1H), 3.38 (m, 2H), 3.50 (m, 2H), 4.14 (dd, *J* = 13.3, 6.0 Hz, 2H), 4.44 (dd, *J* = 13.3, 4.8 Hz, 2H), 7.41 (m, 6H), 7.59 (m, 4H), 10.7 (s (br), 1H). The hydrochloride salt was dissolved in 200 mL water. An aqueous NaOH solution (1.0 M, 150 mL) was added followed by 200 mL of MTBE. The mixture stirred for 15 min and the phases were separated. The aqueous phase was washed with MTBE twice. All organic phases were combined, dried with MgSO₄, filtered, and then concentrated to a colorless oil providing 34 g (96 mmol) of the desired free base. ¹H NMR (DMSO-d₆): 400 MHz δ 0.95 (m, 2H), 1.39 (m, 2H), 1.81 (m, 2H), 1.99 (m, 2H), 2.39 (m, 1H), 3.15 (m, 1H), 3.21 (s, 3H), 3.37 (m, 2H), 3.47 (m, 2H), 3.56 (s, 4H), 7.16-7.35 (m, 10H).

Trans-4-(2-methoxyethoxy)cyclohexanamine. trans-N,N-Dibenzyl-4-(2-methoxyethoxy)cyclohexanamine (51 g, 144 mmol) dissolved in 900 mL EtOH had the flask flushed with N₂ and then 12 g (17 mmol) of Pd(OH)₂ (20% on carbon) added. The flask was flushed with N₂ twice, and then vigorously stirred under H₂ blanket (20 °C, 1 atm) for 3 h. The flask was flushed with N₂ (3x) then the catalyst was filtered and washed with 100 mL EtOH. The filtrate was concentrated to a colorless oil to obtain 25 g (144 mmol) of trans-4-(2-methoxyethoxy)cyclohexanamine. ¹H NMR (DMSO-d₆): 400 MHz δ 1.00 (m, 2H), 1.11 (m, 2H), 1.53 (s (br), 2H), 1.71 (m, 2H), 2.50 (m, 1H), 3.15 (m, 1H), 3.23 (s, 3H), 3.39 (t, *J* = 4.5 Hz, 2H), 3.48 (t, *J* = 5.3 Hz, 2H).