Supporting Information

Development of new deoxycytidine kinase inhibitors and non-invasive *in vivo* evaluation using Positron Emission Tomography

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For a general method for the synthesis of compounds 8 - 14 follow the procedure for the synthesis of 15a with one modification to step 3: a mixture of thioamide and 1,3-dichloroacetone (2 equiv.) in ethanol was stirred under refluxing conditions for 2.5 h. The resulting mixture was cooled and concentrated *in vacuo* to remove residual solvent. The crude residue was purified by flash column chromatography over silica gel.

2-(((2-(4-(2-fluoroethoxy)-3-methoxyphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (8a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.52 (s, 1H), 7.42 – 7.38 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.13 (brs, 4H), 5.11 (s, 1H), 4.72 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.32 (s, 2H), 4.24 (dt, *J* = 30.5, 4.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.0, 166.9, 163.9 (2), 154.5, 149.8, 149.6, 126.9, 119.6, 116.6, 113.7, 109.5, 83.2 (d, J_{CF} = 165.8 Hz), 79.5, 68.4 (d, J_{CF} = 18.9 Hz), 56.1, 29.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5O_2S_2$ H, 408.0964; found 408.0978.

6-(((2-(4-(2-fluoroethoxy)-3-methoxyphenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (8b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.56 (s, 1H), 7.42 – 7.39 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.76 (brs, 2H), 6.70 (brs, 2H), 4.72 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.34 (s, 2H), 4.24 (dt, *J* = 30.5, 4.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.3, 167.2, 166.1 (2), 153.8, 149.9, 149.6, 126.9, 119.7, 116.9, 113.7, 109.5, 83.2 (d, J_{CF} = 165.8 Hz), 68.4 (d, J_{CF} = 18.9 Hz), 56.1, 29.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{17}FN_6O_2S_2$ H, 409.0917; found 409.0934.

2-(((2-(3-(2-fluoroethoxy)-4-methoxyphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-

diamine (9a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.53 (s, 1H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.14 (brs, 4H), 5.13 (s, 1H), 4.75 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.33 (s, 2H), 4.29 (dt, *J* = 30.5, 4.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.1, 166.9, 163.9 (2), 154.5, 151.2, 148.3, 126.4, 120.3, 116.5, 112.7, 110.9, 83.3 (d, J_{CF} = 166.0 Hz), 79.5, 68.5 (d, J_{CF} = 18.9 Hz), 56.1, 29.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5O_2S_2$ H, 408.0964; found 408.0928.

6-(((2-(3-(2-fluoroethoxy)-4-methoxyphenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (9b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.57 (s, 1H); 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.78 (brs, 2H), 6.73 (brs, 2H), 4.75 (dt, *J* = 47.5, 4.0 Hz, 2H), 4.36 (s, 2H), 4.29 (dt, *J* = 30.0, 4.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.3, 167.2, 166.1 (2), 153.8, 151.3, 148.3, 126.4, 120.3, 116.9, 112.7, 110.9, 83.3 (d, J_{CF} = 166.0 Hz), 68.5 (d, J_{CF} = 18.8 Hz), 56.1, 29.2; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{17}FN_6O_2S_2$ H, 409.0917; found 409.0934.

2-(((2-(4-ethoxy-3-(2-fluoroethoxy)phenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (10a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.50 (s, 1H), 7.43 – 7.41 (m, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.12 (brs, 4H), 5.11 (s, 1H), 4.72 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.31 (s, 2H), 4.27 (dt, *J* = 30.5, 4.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.1, 166.9, 163.9 (2), 154.5, 150.6, 148.4, 126.4, 120.4, 116.5, 113.9, 111.5, 83.3 (d, J_{CF} = 166.0 Hz), 79.5, 68.7 (d, J_{CF} = 18.8 Hz), 64.4, 29.9, 15.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{20}FN_5O_2S_2$ H, 422.1121; found 422.1105.

6-(((2-(4-ethoxy-3-(2-fluoroethoxy)phenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (10b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.54 (s, 1H), 7.43 – 7.42 (m, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.76 (brs, 2H), 6.70 (brs, 2H), 4.72 (dt, *J* = 48.0, 3.0 Hz, 2H), 4.34 (s, 2H), 4.27 (dt, *J* = 30.5, 3.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.3, 167.2, 166.1 (2), 153.8, 150.6, 148.4, 126.3, 120.5, 116.9, 113.9, 111.5, 83.3 (d, J_{CF} = 165.9 Hz), 68.7 (d, J_{CF} = 18.9 Hz), 64.4, 29.2, 15.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{19}FN_6O_2S_2$ H, 423.1073; found 423.1082.

2-(((2-(3-(2-fluoroethoxy)-4-methylphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (11a). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.53 (brs, 1H), 7.45 (s, 1H), 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 5.65 (brs, 4H), 5.37 (s, 1H), 4.81 (dt, *J* = 47.5, 4.0 Hz, 2H), 4.42 (s, 2H), 4.37 (dt, *J* = 29.0, 4.0 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 168.8, 167.0, 164.1 (2), 157.2, 155.1, 132.8, 131.1, 129.0, 118.9, 115.5, 108.7, 82.8 (d, J_{CF} = 167.4 Hz), 79.6, 67.8 (d, J_{CF} = 19.5 Hz), 29.8, 15.4; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5OS_2$ H, 392.1015; found 392.1029.

6-(((2-(3-(2-fluoroethoxy)-4-methylphenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (11b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.61 (s, 1H), 7.38 (s, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.75 (brs, 2H), 6.70 (brs, 2H), 4.75 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.35 (s, 2H), 4.30 (dt, *J* = 30.0, 4.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.3, 167.3, 166.1 (2), 157.2, 154.0, 132.5, 131.7, 129.1, 119.3, 117.5, 109.0, 83.4 (d, J_{CF} = 165.9 Hz), 68.1 (d, J_{CF} = 19.0 Hz), 29.1, 16.4; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{17}FN_6OS_2$ H, 393.0968; found 393.0970.

2-(((2-(3-(3-fluoropropoxy)-4-methoxyphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (12a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.53 (s, 1H), 7.45 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44 (s, 1H), 7.04 (d, *J* = 9.0 Hz, 1H), 6.16 (brs, 4H), 5.14 (s, 1H), 4.61 (dt, *J* = 47.5, 6.0 Hz, 2H), 4.34 (s, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 2.12 (dtt, *J* = 25.5, 6.0, 6.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.0, 167.0, 163.9 (2), 154.4, 151.3, 148.6, 126.5, 120.1, 116.4, 112.7, 110.7, 81.9 (d, J_{CF} = 160.6 Hz), 79.5, 65.0 (d, J_{CF} = 5.9 Hz), 56.2, 30.4 (d, J_{CF} = 19.5 Hz), 29.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{20}FN_5O_2S_2$ H, 422.1121; found 422.1116.

6-(((2-(3-(3-fluoropropoxy)-4-methoxyphenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (12b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.55 (s, 1H), 7.50 – 7.41 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.76 (brs, 2H), 6.69 (brs, 2H), 4.58 (dt, *J* = 47.5, 6.0 Hz, 2H), 4.34 (s, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 2.10 (dtt, *J* = 25.0, 6.0, 6.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.3, 167.2, 166.1 (2), 153.8, 151.3, 148.6, 126.4, 120.1, 116.9, 112.7, 110.7, 81.9 (d, J_{CF} = 160.5 Hz), 65.0 (d, J_{CF} = 6.0 Hz), 56.2, 30.4 (d, J_{CF} = 19.6 Hz), 29.2; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{19}FN_6O_2S_2$ H, 423.1073; found 423.1076.

2-(((2-(5-(2-fluoroethoxy)-2-methoxyphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (13a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.75 (d, *J* = 3.5 Hz, 1H), 7.60 (s, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.04 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.12 (brs, 4H), 5.12 (s, 1H), 4.71 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.36 (s, 2H), 4.21 (dt, *J* = 30.0, 4.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.2, 163.9 (2), 160.7, 152.9, 152.6, 151.2, 122.4, 118.4, 118.1, 114.4, 112.8, 83.4 (d, J_{CF} = 165.8 Hz), 79.5, 68.3 (d, J_{CF} = 18.8 Hz), 56.8, 29.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd

for $C_{17}H_{18}FN_5O_2S_2$ H, 408.0964; found 408.0982.

6-(((2-(5-(2-fluoroethoxy)-2-methoxyphenyl)thiazol-4-yl)methyl)thio)-1,3,5-triazine-2,4-diamine (13b). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 3.5 Hz, 1H), 7.64 (s, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 7.05 (dd, *J* = 9.0, 3.5 Hz, 1H), 6.75 (brs, 2H), 6.70 (brs, 2H), 4.71 (dt, *J* = 48.0, 4.0 Hz, 2H), 4.38 (s, 2H), 4.21 (dt, *J* = 30.0, 4.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 178.4, 166.1 (2), 160.9, 152.6, 152.2, 151.2, 122.3, 118.8, 118.2, 114.4, 112.8, 83.4 (d, J_{CF} = 165.8 Hz), 68.3 (d, J_{CF} = 18.8 Hz), 56.9, 29.2; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{17}FN_6O_2S_2$ H, 409.0917; found 409.0924.

2-(((2-(4-(2-fluoroethoxy)-2-methoxyphenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (14a). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.12 (d, *J* = 8.5 Hz, 1H), 7.47 (s, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.11 (brs, 4H), 5.11 (s, 1H), 4.73 (dt, *J* = 47.5, 4.0 Hz, 2H), 4.33 (s, 2H), 4.30 (dt, *J* = 30.0, 4.0 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.2, 163.9 (2), 161.3, 161.0, 157.8, 152.4, 129.3, 116.6, 115.4, 107.3, 99.6, 83.2 (d, J_{CF} = 165.6 Hz), 79.5, 67.9 (d, J_{CF} = 18.9 Hz), 56.5, 30.0; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5O_2S_2$ H, 408.0964; found 408.0956.

2-(((2-(3,5-difluorophenyl)-5-methylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (16a). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.47 – 7.45 (m, 2H), 7.05 (tt, *J* = 9.0, 2.3 Hz, 1H), 5.71 (brs, 4H), 5.38 (s, 1H), 4.43 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 168.8, 164.2, 163.9 (2), 162.2 (d, J_{CF} = 239.6 Hz, 2C), 150.5, 136.8 (t, J_{CF} = 10.0 Hz), 131.3, 108.4 (dd, J_{CF} = 20.8, 6.7 Hz, 2C), 104.4 (t, J_{CF} = 25.9 Hz), 79.5, 27.7, 10.8; HRMS-ESI (*m/z*) $[M + H]^+$ calcd

for $C_{15}H_{13}F_2N_5S_2$ H, 366.0659; found 366.0660.

2-(((2-(3,5-difluorophenyl)-5-ethylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (16b). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.51 – 7.48 (m, 2H), 7.06 (tt, *J* = 9.0, 2.2 Hz, 1H), 5.72 (brs, 4H), 5.38 (s, 1H), 4.45 (s, 2H), 3.01 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 168.8, 164.2, 163.9 (2), 162.2 (d, J_{CF} = 227.4 Hz, 2C), 149.5, 139.1, 136.9 (t, J_{CF} = 10.0 Hz), 108.5 (dd, J_{CF} = 20.7, 6.8 Hz, 2C), 104.2 (t, J_{CF} = 25.8 Hz), 79.5, 27.7, 19.7, 15.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{15}F_2N_5S_2$ H, 380.0815; found 380.0827.

2-(((2-(3,5-difluorophenyl)-5-propylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (16c). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.51 – 7.47 (m, 2H), 7.07 (tt, *J* = 9.0, 2.3 Hz, 1H), 5.72 (brs, 4H), 5.39 (s, 1H), 4.48 (s, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.67 (qt, *J* = 7.4, 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 168.8, 164.2, 163.9 (2), 162.2 (d, J_{CF} = 205.0 Hz, 2C), 150.0, 137.3, 136.8 (t, J_{CF} = 10.1 Hz), 108.5 (dd, J_{CF} = 20.8, 6.8 Hz, 2C), 104.3 (t, J_{CF} = 25.9 Hz), 79.5, 28.0, 27.8, 25.0, 12.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{17}F_2N_5S_2$ H, 394.0972; found 394.0963.

2-(((2-(4-fluorophenyl)-5-methylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (17a). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.93 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.22 (dd, *J* = 8.8, 8.8 Hz, 2H), 5.62 (brs, 4H), 5.37 (s, 1H), 4.43 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.3, 164.4, 163.9 (2), 162.4, 162.2, 150.1, 130.2 (d, J_{CF} = 4.1 Hz, 2C), 128.5 (d, J_{CF} = 8.5 Hz, 2C), 116.7 (d, J_{CF} = 22.0 Hz), 79.6, 27.9, 11.8; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{14}FN_5S_2$ H, 348.0753; found 348.0757.

2-(((5-ethyl-2-(4-fluorophenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (17b). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.96 – 7.93 (m, 2H), 7.22 (dd, *J* = 8.8, 8.8 Hz, 2H), 5.65 (brs, 4H), 5.38 (s, 1H), 4.44 (s, 2H), 3.0 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 168.9, 164.4, 163.9 (2), 162.4, 162.1, 148.9, 130.3 (d, J_{CF} = 3.3 Hz, 2C), 127.9 (d, J_{CF} = 8.5 Hz, 2C), 115.8 (d, J_{CF} = 22.0 Hz), 79.4, 27.8, 19.6, 16.0; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{16}FN_5S_2$ H, 362.0909; found 362.0908.

2-(((2-(4-fluorophenyl)-5-propylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (17c). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.95 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.23 (dd, *J* = 8.9, 8.9 Hz, 2H), 5.62 (brs, 4H), 5.38 (s, 1H), 4.46 (s, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.68 (qt, *J* = 7.3, 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.2, 164.4, 163.9 (2), 162.5, 162.3, 149.7, 130.2 (d, J_{CF} = 2.9 Hz, 2C), 128.5 (d, J_{CF} = 8.6 Hz, 2C), 116.7 (d, J_{CF} = 21.9 Hz), 79.6, 28.2, 27.9, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5S_2$ H, 376.1066; found 376.1068.

2-(((2-(3-fluorophenyl)-5-methylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (18a). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.18 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 1H), 5.63 (brs, 4H), 5.38 (s, 1H), 4.44 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.1, 164.0 (2), 162.1, 161.6, 150.4, 136.0 (d, J_{CF} = 8.1 Hz), 131.0 (d, J_{CF} = 8.4 Hz), 130.4, 121.9 (d, J_{CF} = 2.8 Hz), 116.3 (d, J_{CF} = 21.4 Hz), 112.2 (d, J_{CF} = 23.5 Hz), 79.6 (d, J_{CF} = 4.9 Hz), 28.8, 10.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{14}FN_5S_2$ H, 348.0753; found 348.0757.

2-(((5-ethyl-2-(3-fluorophenyl)thiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (18b). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.72 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.67 (d, *J* = 10.0 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.20 (dd, *J* = 12.0, 5.0 Hz, 1H), 5.67 (brs, 4H), 5.39 (s, 1H), 4.47 (s, 2H), 3.03 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.1, 164.0 (2), 162.1, 161.8, 149.4 (d, J_{CF} = 4.7 Hz), 138.3, 136.1 (d, J_{CF} = 8.0 Hz), 131.0 (d, J_{CF} = 8.4 Hz), 121.9 (d, J_{CF} = 2.8 Hz), 116.3 (d, J_{CF} = 21.4 Hz), 112.2 (d, J_{CF} = 23.5 Hz), 79.6, 27.9, 19.8, 16.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{16}FN_5S_2$ H, 362.0909; found 362.0894.

2-(((2-(3-fluorophenyl)-5-propylthiazol-4-yl)methyl)thio)pyrimidine-4,6-diamine (18c). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.71 (d, *J* = 8.0 Hz, 1H), 7.66 (ddd, *J* = 10.0, 2.5, 2.5 Hz, 1H), 7.49 (ddd, *J* = 8.0, 8.0, 6.0 Hz, 1H), 7.19 (ddd, *J* = 8.5, 8.5, 2.0 Hz, 1H), 5.63 (brs, 4H), 5.38 (s, 1H), 4.47 (s, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 1.68 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.1, 164.0 (2), 162.1, 161.9, 149.9, 136.4, 136.1 (d, J_{CF} = 8.1 Hz), 131.0 (d, J_{CF} = 8.4 Hz), 121.9 (d, J_{CF} = 2.8 Hz), 116.3 (d, J_{CF} = 21.5 Hz), 112.2 (d, J_{CF} = 23.5 Hz), 79.6 (d, J_{CF} = 4.9 Hz), 27.7, 27.4, 25.2, 13.0; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{18}FN_5S_2$ H, 376.1066; found 376.1067.

2-(3-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)phenoxy)ethanol (25). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.38 – 7.32 (m, 3H), 7.00 – 6.98 (m, 1H), 6.10 (brs, 4H), 5.13 (s, 1H), 4.84 (t, *J* = 5.5 Hz, 1H), 4.38 (s, 2H), 4.01 (t, *J* = 5.0 Hz, 2H), 3.69 (dt, *J* = 5.0, 5.0 Hz, 2H), 2.84 (t, *J* = 7.5 Hz, 2H), 1.56 (qt, *J* = 7.3, 7.3 Hz, 2H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.1, 163.8 (2), 163.3, 159.5, 149.5, 135.9, 134.7, 130.7, 118.5,

116.7, 111.4, 79.4, 70.1, 59.9, 28.0, 27.9, 25.2, 13.8; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{23}N_5O_2S_2$ H, 418.1371; found 418.1351.

2-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-fluorophenoxy)ethanol (26). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.55 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.29 (dd, *J* = 11.0, 8.5 Hz, 1H), 6.14 (brs, 4H), 5.15 (s, 1H), 4.93 (t, *J* = 5.0 Hz, 1H), 4.40 (s, 2H), 4.13 (t, *J* = 4.5 Hz, 2H), 3.73 (dt, *J* = 5.0, 5.0 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 1.57 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.2, 163.9 (2), 162.7, 154.1, 152.1, 149.6, 147.6 (d, J_{CF} = 11.0 Hz), 136.2, 130.5 (d, J_{CF} = 3.4 Hz), 119.2 (d, J_{CF} = 7.3 Hz), 117.3 (d, J_{CF} = 19.0 Hz), 112.1, 79.5, 71.3, 59.9, 28.2, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{22}FN_5O_2S_2$ H, 436.1277; found 436.1262.

2-(3-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-5-fluorophenoxy)ethanol (27). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.20 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 6.92 (ddd, *J* = 11.0, 2.0, 2.0 Hz, 1H), 6.14 (brs, 4H), 5.14 (s, 1H), 4.91 (t, *J* = 5.5 Hz, 1H), 4.40 (s, 2H), 4.05 (t, *J* = 5.0 Hz, 2H), 3.70 (dt, *J* = 5.0 , 5.0 Hz, 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 1.58 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.1, 164.7, 163.9 (2), 162.7, 162.1 (d, J_{CF} = 3.8 Hz), 161.1 (d, J_{CF} = 11.9 Hz), 149.9, 136.9, 135.9 (d, J_{CF} = 10.6 Hz), 108.5, 105.0 (d, J_{CF} = 23.9 Hz), 103.9 (d, J_{CF} = 25.0 Hz), 79.5, 70.8, 59.8, 28.2, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{22}FN_5O_2S_2$ H, 436.1277; found 436.1287.

N-(2-(3-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)phenoxy)ethyl)methanesulfonamide (28). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.51 – 7.50

(m, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.42 (brs, 1H), 5.64 (brs, 4H), 5.39 (s, 1H), 4.48 (s, 2H), 4.22 (t, *J* = 5.5 Hz, 2H), 3.56 (dt, *J* = 11.3, 5.5 Hz, 2H), 3.00 (s, 3H), 2.95 (t, *J* = 7.5 Hz, 2H), 1.69 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.1, 164.0 (2), 163.3, 159.1, 149.6, 135.7, 135.2, 130.2, 118.7, 115.9, 111.5, 79.6, 67.4, 42.4, 39.5, 28.1, 28.0, 25.2, 13.0; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{26}N_6O_3S_3$ H, 495.1307; found 495.1285.

N-(2-(3-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-5-fluorophenoxy)ethyl)methanesulfonamide (29). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.32 (s, 1H), 7.26 – 7.22 (m, 1H), 6.84 (dt, *J* = 10.6, 2.2 Hz, 1H), 6.43 (brs, 1H), 5.64 (s, 4H), 5.39 (s, 1H), 4.48 (s, 2H), 4.25 (t, *J* = 5.5 Hz, 2H), 3.56 (dt, *J* = 11.2, 5.5 Hz, 2H), 3.00 (s, 3H), 2.97 (t, *J* = 7.5 Hz, 2H), 1.69 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.0, 164.7, 163.9 (2), 162.7, 161.9 (d, J_{CF} = 3.8 Hz), 160.6 (d, J_{CF} = 11.7 Hz), 149.9, 136.4 (d, J_{CF} = 10.4 Hz), 108.1 (d, J_{CF} = 10.2 Hz), 105.1 (d, J_{CF} = 24.0 Hz), 103.1 (d, J_{CF} = 25.4 Hz), 79.6, 67.9, 42.3, 39.5, 29.7, 28.1, 25.2, 13.0; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{25}FN_6O_3S_3$ H, 513.1213; found 513.1203.

2,2'-((4-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-1,2-phenylene)bis(oxy))diethanol (30). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.38 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.12 (brs, 4H), 5.12 (s, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.83 (t, *J* = 5.5 Hz, 1H), 4.36 (s, 2H), 4.01 (dt, *J* = 5.5, 5.5 Hz, 4H), 3.69 (t, *J* = 5.0 Hz, 4H), 2.81 (t, *J* = 7.5 Hz, 2H), 1.55 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.3, 163.9 (2), 163.8, 150.6, 149.1, 149.0, 134.9, 126.6, 119.7,

114.1, 111.1, 79.5, 71.0, 70.8, 59.99, 59.93, 28.2, 28.1, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{27}N_5O_4S_2$ H, 478.1583; found 478.1595.

5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenol (31). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.36 (s, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.12 (brs, 4H), 5.14 (s, 1H), 4.36 (s, 2H), 3.79 (s, 3H), 2.82 (t, *J* = 7.5 Hz, 2H), 1.56 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.3, 163.9 (2), 163.8, 149.8, 149.0, 147.2, 134.6, 126.6, 117.8, 112.9, 112.7, 79.5, 56.1, 49.1, 28.2, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{21}N_5O_2S_2$ H, 404.1215; found 404.1198.

3-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)propan-1-ol (32). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.53 (d, *J* = 2.0 Hz, 1H), 7.42 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.64 (brs, 4H), 5.39 (s, 1H), 4.45 (s, 2H), 4.19 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.78 – 3.76 (m, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.03 (tt, *J* = 6.0, 6.0 Hz, 2H), 1.68 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.2, 164.0, 163.9 (2), 163.7, 151.2, 149.0, 134.5, 126.9, 119.0, 111.8, 110.2, 79.5, 66.1, 58.5, 55.3, 32.5, 29.7, 28.1, 25.2, 13.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{27}N_5O_3S_2$ H, 462.1634; found 462.1616.

2-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)ethanol (33). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.35 (s, 1H), 7.34 (d, *J* = 9.5 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.11 (brs, 4H), 5.12 (s, 1H), 4.84 (t, *J* = 5.5 Hz, 1H), 4.35 (s,

2H), 3.99 (t, *J* = 5.0 Hz, 2H), 3.77 (s, 3H), 3.69 (dt, *J* = 5.0, 5.0 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 1.54 (qt, *J* = 7.3, 7.3 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.3, 163.9 (2), 163.8, 151.1, 149.1, 148.8, 134.9, 126.5, 119.5, 112.6, 110.4, 79.5, 70.8, 59.9, 56.0, 28.2, 28.0, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{25}N_5O_3S_2$ H, 448.1477; found 448.1471.

2-(5-(4-(((4-aminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)ethanol (34). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.98 (d, *J* = 6.0 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.42 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.38 (brs, 2H), 6.27 (d, *J* = 5.5 Hz, 1H), 4.47 (s, 2H), 4.13 (t, *J* = 5.0 Hz, 2H), 3.90 (t, *J* = 5.0 Hz, 2H), 3.84 (s, 3H), 3.02 (brs, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.65 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 170.4, 163.8, 163.5, 155.3, 151.5, 148.9, 148.4, 134.7, 126.8, 119.4, 112.1, 111.1, 101.0, 70.9, 60.5, 55.3, 48.9, 28.0, 25.2, 13.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{24}N_4O_3S_2$ H, 433.1368; found 433.0613.

1-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)propan-2-ol (35). ^{1}H NMR (500 MHz, acetone-d_6) δ: 7.54 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.62 (brs, 4H), 5.39 (s, 1H), 4.45 (s, 2H), 4.13 (qt, *J* = 6.0, 6.0 Hz, 1H), 3.96 (d, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.69 (qt, *J* = 7.5, 7.5 Hz, 2H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.2, 164.0 (2), 163.6, 151.4, 149.0, 148.9, 134.5, 126.9, 119.4, 112.1, 111.3, 79.5, 74.9, 65.5, 55.4, 29.7, 28.1, 25.2, 19.3, 13.1; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{27}N_5O_3S_2$ H, 462.1634; found 462.1627.

1-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)-2-methylpropan-2-ol (36). ^{1}H NMR (500 MHz, MeOD) δ: 7.51 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 5.48 (s, 1H), 5.32 (s, 1H), 4.48 (s, 2H), 3.89 (s, 3H), 3.86 (s, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 1.67 (qt, *J* = 7.5, 7.5 Hz, 2H), 1.33 (s, 6H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, MeOD) δ: 168.8, 165.2, 163.8 (2), 151.2, 148.9, 148.0, 135.4, 126.4, 119.7, 111.8, 110.7, 79.2, 77.0, 69.6, 55.2, 48.4, 27.9, 27.8, 25.0, 24.9, 12.6; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{29}N_5O_3S_2$ H, 476.1790; found 476.1772.

N-(2-(5-(4-(((4,6-diaminopyrimidin-2-yl)thio)methyl)-5-propylthiazol-2-yl)-2-methoxyphenoxy)ethyl)methanesulfonamide (37). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.41 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.39 (s, 1H), 7.25 (t, *J* = 6.0 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.13 (brs, 4H), 5.15 (s, 1H), 4.39 (s, 2H), 4.07 (t, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.36 (dt, *J* = 5.5, 5.5 Hz, 2H), 3.15 (d, *J* = 5.5 Hz, 1H), 2.98 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 1.58 (qt, *J* = 7.5, 7.5 Hz, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 168.3, 163.9 (2), 163.7, 151.1,149.1, 148.3, 135.0, 126.5, 119.9, 112.7, 110.6, 79.5, 68.3, 60.2, 42.4, 31.2, 28.2, 28.0, 25.4, 13.9; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{28}N_6O_4S_3$ H, 525.1412; found 525.1404.

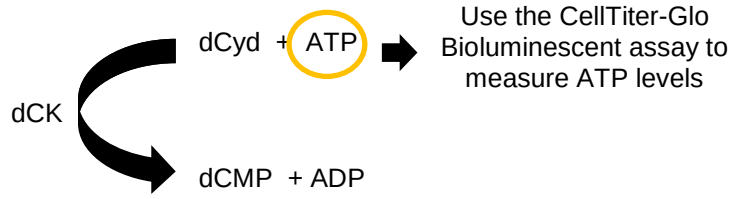
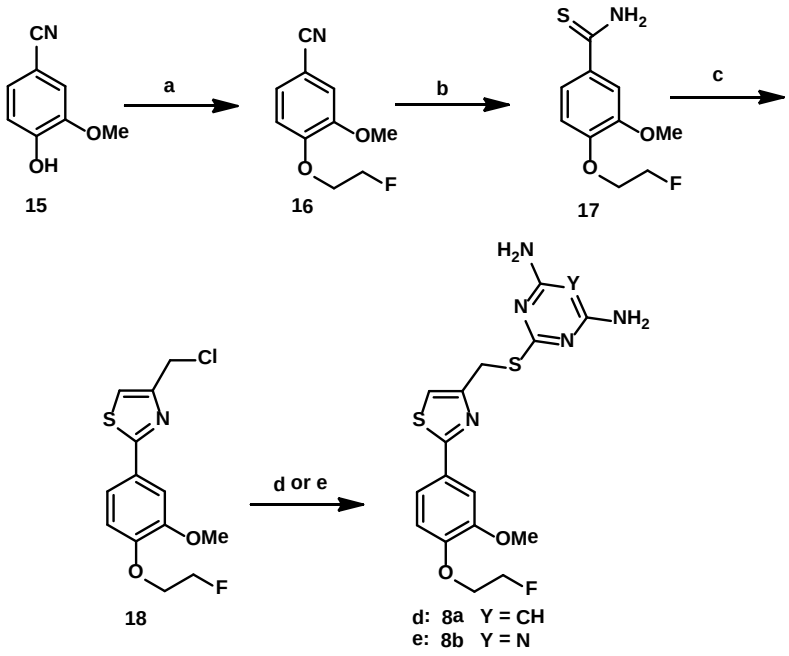


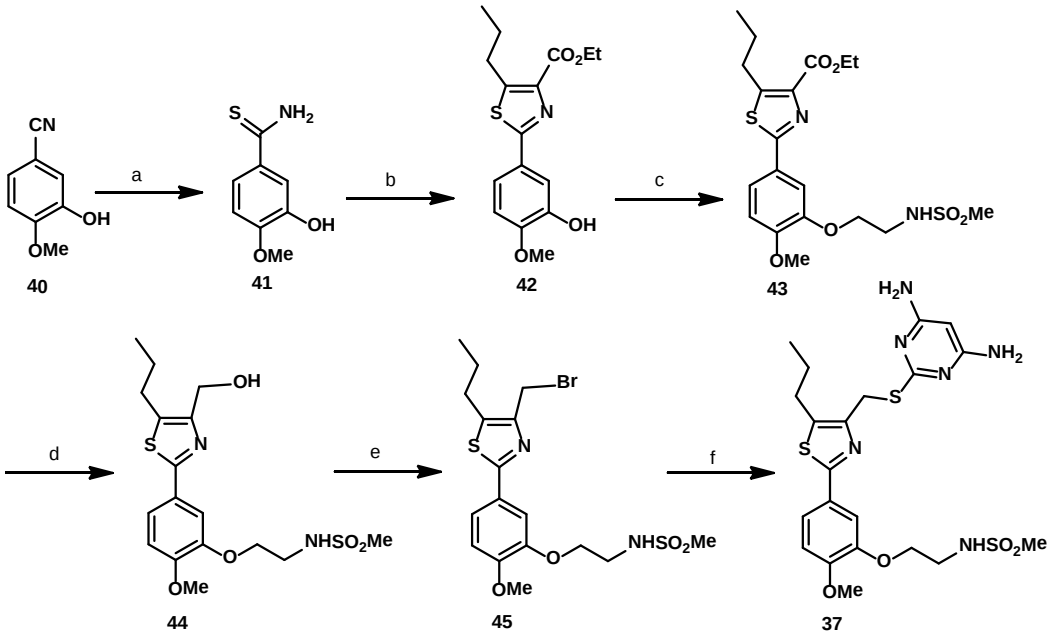
Figure S1. HTS Schematic

Scheme S2. Synthesis of Compounds **8a** and **8b**[a]



[a]Reagents and conditions: (a) 1-bromo-2-fluoroethane, Cs_2CO_3, DMF, 89%; (b) $(NH_4)_2S$ (20% in H_2O), pyridine, Et_3N, 87%; (c) 1,3-dichloroacetone, EtOH, 83%; (d) 4,6-diamino-2-mercaptopyrimidine, NaOH, EtOH, 75%; (e) 4,6-diamino-1,3,5-triazine-2(1H)-thione, NaOH, EtOH, 72%.

Scheme S3. Synthesis of Compound **37**[a]



[a]Reagents and conditions: (a) $(NH_4)_2S$ (20% in H_2O), pyridine, Et_3N, 90% ; (b) ethyl 3-bromo-2-oxohexanoate, EtOH, 60%; (c) *N*-(2-bromoethyl)methanesulfonamide, Cs_2CO_3, DMF, 78% (borsm); (d) DIBAL-H, CH_2Cl_2, 90%; (e) 1,1,1,3,3,3-hexabromoacetone, PPh_3, CH_3CN, 95%; (f) 4,6-diamino-2-mercaptopyrimidine, NaOH, EtOH, 92%.

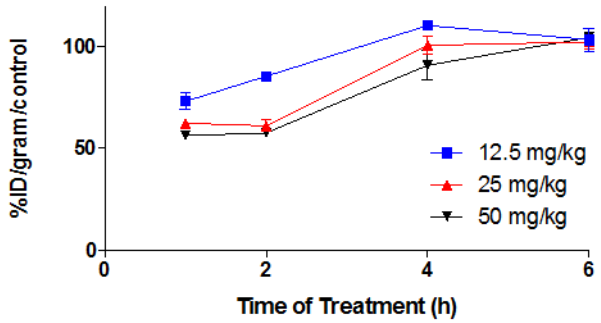


Figure S4. Dose escalation and time course for inhibition of ^{18}F-L-FAC uptake in the liver for compound 33, one of the compounds with the greatest inhibitory activity *in vitro*.