

# Supporting Information

## The Application of Flow Microreactors to the Preparation of a Family of Casein Kinase I Inhibitors

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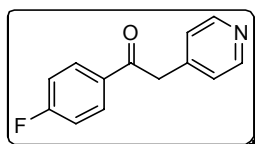
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## General experimental details:

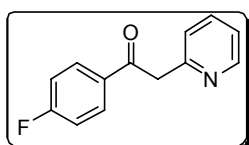
All solvents were distilled prior to use and stored under argon.  $^1\text{H}$  NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with residual solvent as the internal reference.  $^{13}\text{C}$  NMR spectra were also recorded on the same spectrometer with the central peak of the residual solvent as the internal reference using the deuterated solvent signal as the internal lock. IR spectra were recorded on a Perkin–Elmer SpectrumOne FT-IR spectrometer neat. Letters in the parentheses in the IR refer to relative absorbency of the peak: w, weak, <40% of the main peak; m, medium, 41–74% of the main peak; s, strong, >74% of the main peak. LC/MS analysis was performed on an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HPLC/MSD mass spectrometer. Elution was carried out using a reversed-phase gradient of MeCN/water with both solvents containing 0.1% formic acid. For HRMS an LCT Premier Micromass spectrometer was used.

### *1-(4-fluorophenyl)-2-pyridin-4-ylethanone (6a)*<sup>1</sup>:



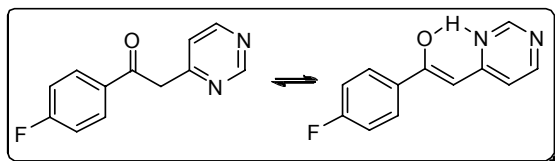
was obtained in 94% isolated yield as yellow solid.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.25 (s, 2H), 7.14 (t, 2H,  $J = 8.5$  Hz), 7.18 (psd, 2H), 8.01 (dd, 2H,  $J_1 = 5.0$  Hz,  $J_2 = 9$ Hz), 8.56 (psd, 2H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 45.0, 116.3, 116.5, 125.2, 131.5, 131.6, 142.6, 150.4, 165.2, 167.7, 194.7; HRMS (+ES) calculated for  $\text{C}_{13}\text{H}_{11}\text{FNO}$  216.0825, found 216.0830; LC-MS Rt = 2.48 min,  $\text{M}^+\text{H}$   $m/z$  = 216.11; IR (thin film)  $\nu$  1685.4(w), 1593.8(w), 1505.9(w), 1416.5(w), 1330.9(w), 1228.9(w), 1203.5(w), 1160.3(w), 999.9(w), 849.1(w), 834.6(w), 803.1(w), 767.3(w), 726.6(w)  $\text{cm}^{-1}$ .

### *1-(4-fluorophenyl)-2-pyridin-2-ylethanone (6b)*<sup>2</sup>:



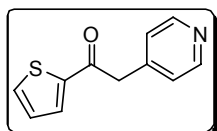
was obtained in 65% isolated yield as yellow solid and was consistent with previous literature data.

### *1-(4-fluorophenyl)-2-pyrimidin-4-ylethanone (6c)*<sup>3</sup>:



was obtained in 90% isolated yield as 1:2 mixture of two tautomers.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.41 (s, 2H), 7.14 (t, 2H,  $J = 8.5$  Hz), 7.34 (dd, 1H,  $J_1 = 1.0$  Hz,  $J_2 = 5.0$  Hz), 8.06 (dd, 2H,  $J_1 = 5.0$  Hz,  $J_2 = 8.5$  Hz), 8.66 (d, 1H  $J = 5$ ), 9.15 (s, 1H); Tautomer  $\delta$ : 5.94 (s, 2H), 6.90 (d, 1H,  $J = 5.5$  Hz), 7.09 (t, 2H,  $J = 9.0$  Hz), 7.83 (dd, 2H,  $J_1 = 5.05$  Hz,  $J_2 = 9$  Hz), 8.40 (d, 1H,  $J = 5.5$ ), 8.80 (s, 1H), 15.04 (br, 1H); HRMS (+ES) calculated for  $\text{C}_{12}\text{H}_{10}\text{FN}_2\text{O}$  217.0777, found 217.0784; LC-MS Rt = 3.85 min,  $\text{M}^+\text{H}$   $m/z$  = 217.06

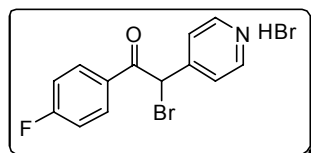
### *1-(thien-2-yl)-2-pyridin-4-ylethanone (6d)*:



was obtained in 79% isolated yield as yellow solid.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.15 (s, 2H), 7.10 (t, 2H,  $J = 5.0$  Hz), 7.19 (d, 2H,  $J = 6.0$  Hz), 7.64 (d, 1H,  $J = 6$  Hz), 7.73 (dd, 1H  $J_1 = 1.0$  Hz,  $J_2 = 4.0$  Hz), 8.51 (d, 2H,  $J = 6.0$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 45.1, 126.6, 128.3, 132.7, 134.6, 143.0, 143.3, 149.8, 188.5; HRMS (+ES) calculated for  $\text{C}_{11}\text{H}_{10}\text{NOS}$  204.0483, found 204.0491; LC-MS Rt = 0.99 min,  $\text{M}^+\text{H}$   $m/z$  = 204.16; IR (thin film)  $\nu$  3045.5(w), 1660.8(m), 1601.8(w), 1559.5(w), 1519.3(w),

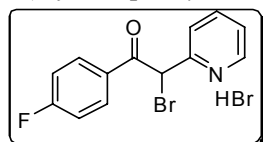
1416.1(w), 1404.7(w), 1353.7(w), 1323.8(w), 1230.5(w), 1200.7(w), 1090.9(w), 1070.1(w), 1060.2(w), 990.6(w), 937.7(w), 849.7(w), 805.9(w), 751.4(m), 719.7(w)  $\text{cm}^{-1}$ .

*1-(4-fluorophenyl)-2-bromo-2-pyridin-4-ylethanone (7a)<sup>4</sup>:*



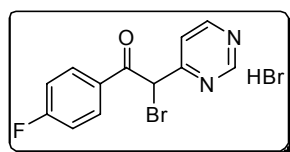
was obtained in quantitative yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz, MeOD)  $\delta$ : 7.16 (s, 1H), 7.32 (t, 2H,  $J=8.5$  Hz), 8.27 (dd, 2H,  $J_1=5.5$  Hz,  $J_2=9$ Hz), 8.40 (d, 2H,  $J=6.5$  Hz), 8.96 (d, 2H,  $J=6.5$  Hz);  $^{13}\text{C-NMR}$  (100 MHz, MeOD)  $\delta$ : 44.2, 117.3, 117.25, 129.9, 131.4, 133.61, 133.7, 142.8, 158.0, 166.5, 169.1, 190.0; HRMS (+ES) calculated for  $\text{C}_{13}\text{H}_{10}\text{NOFBr}$  293.9930, found 293.9927; LC-MS Rt = 4.12 min,  $\text{M}^+\text{H}$   $m/z$  = 295.95; IR (thin film)  $\nu$  3394.0(w), 3332.2(w), 3280.1(w), 3198.1(w), 3101.2(w), 3059.3(w), 2988.2(w), 2920.5(w), 2575.8(w), 2360.7(w), 2257.3(w), 2182.8(w), 2059.2(w), 2030.1(w), 2022.1(w), 2004.6(w), 1988.8(w), 1915.5(w), 1678.6(s), 1631.0(m), 1590.1(s), 1504.8(s), 1456.8(m), 1452.1(m), 1408.7(m), 1340.4(m), 1312.6(w), 1302.6(w), 1289.9(m), 1270.8(m), 1228.6(s), 1220.6(s), 1190.9(m), 1155.3(s), 1100.0(m), 1060.9(m), 991.1(m), 979.5(m), 965.0(m), 953.6(m), 927.5(m), 851.7(s), 841.9(m), 806.4(m), 777.7(s), 766.0(s), 755.8(s), 712.1(m), 696.7(m), 680.3(m), 666.5(m)  $\text{cm}^{-1}$ .

*1-(4-fluorophenyl)-2-bromo-2-pyridin-2-ylethanone (7b):*



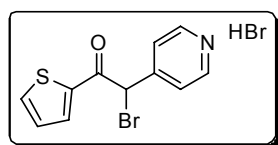
was obtained in quantitative yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.44 (s, 1H), 6.98 (t, 2H,  $J=8.0$  Hz), 7.03 (m, 1H), 7.61 (m, 2 Hz), 7.98 (dd, 2H,  $J_1=5.0$  Hz,  $J_2=9$  Hz), 8.39 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 51.5, 115.5, 115.7, 123.2, 124.2, 130.1, 131.7, 131.8, 137.0, 148.8, 155.3, 164.3, 166.8, 189.0; HRMS (+ES) calculated for  $\text{C}_{13}\text{H}_{10}\text{NOFBr}$  293.9918, found 293.9928; LC-MS Rt = 4.45 min,  $\text{M}^+\text{H}$   $m/z$  = 296.02; IR (thin film)  $\nu$  3043.8(w), 2614.0(w), 1683.9(w), 1596.3(w), 1531.6(w), 1508.7(w), 1465.0(w), 1411.9(w), 1359.7(w), 1299.9(w), 1234.2(w), 1160.3(w), 1099.5(w), 1044.7(w), 994.4(w), 854.7(w), 778.6(w), 757.2(w), 733.2(w), 696.9(w)  $\text{cm}^{-1}$ ; X-ray crystallography CCDC 756496. Formula:  $\text{C}_{13}\text{H}_{10}\text{Br}_2\text{F}_1\text{N}_1\text{O}_1$ ; Unit cell parameters: a 7.8896(2) b 8.2318(2) c 12.0308(3); alpha 83.177(1) beta 85.689(1) gamma 61.994(1); space group P-1.

*1-(4-fluorophenyl)-2-bromo-2-pyrimidin-4-ylethanone (7c):*



was obtained in quantitative yield as a mixture of tautomers and bromohydrates. HRMS (+ES) calculated for  $\text{C}_{12}\text{H}_9\text{N}_2\text{OFBr}$  294.9882, found 294.9886.

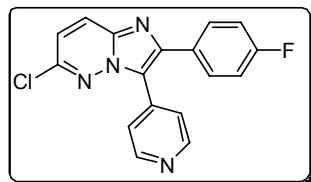
*1-(thien-2-yl)-2-bromo-2-pyridin-4-ylethanone (7d):*



was obtained in quantitative yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz, MeOD)  $\delta$ : 6.95 (s, 1H), 7.30 (dd, 1H,  $J_1=3.5$  Hz,  $J_2=4.5$  Hz), 8.02 (d, 1H,  $J=5.0$  Hz), 8.21 (m, 1H), 8.34 (psd, 1H), 8.90 (d, 2H,  $J=6.5$  Hz);  $^{13}\text{C-NMR}$  (100 MHz, DMSO)  $\delta$ : 44.8, 105.3, 127.1, 129.3, 136.1, 138.2, 139.9, 143.3, 183.5; HRMS (+ES) calculated for  $\text{C}_{11}\text{H}_9\text{NOSBr}$  281.9588, found 281.9596; LC-MS Rt = 3.82 min,  $\text{M}^+\text{H}$   $m/z$  = 284.10; IR (thin film)  $\nu$  2786.0(w), 1667.1(m), 1636.3(w), 1598.8(w), 1504.8(w),

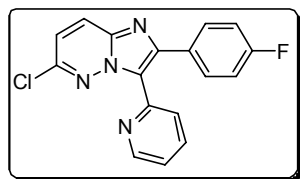
1457.9(w), 1405.9(w), 1349.3(w), 1325.9(w), 1291.7(w), 1246.8(w), 1224.2(w), 1194.3(w), 1136.0(w), 1089.6(w), 1057.9(w), 938.1(w), 852.2(w), 811.2(w), 775.9(m), 738.4(m), 661.0(w)  $\text{cm}^{-1}$ .

*6-chloro-2-(4-fluorophenyl)-3-(pyridin-4-yl)imidazo[1,2-b]pyridazine (9a):*



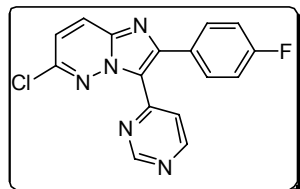
was obtained in 52% isolated yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.05 (t, 2H,  $J = 9.0$  Hz), 7.13 (d, 1H,  $J = 9.5$  Hz), 7.52 (d, 2H,  $J = 5.5$  Hz), 7.58 (dd, 2H,  $J_1 = 5.5$  Hz,  $J_2 = 8.5$  Hz), 7.94 (d, 1H,  $J = 9.5$  Hz), 8.70 (d, 2H,  $J = 5.1$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 116.2, 116.4, 120.4, 123.0, 124.5, 127.3, 129.6, 129.6, 130.9, 136.2, 138.5, 145.1, 147.4, 150.7, 162.3, 164.8; HRMS (+ES) calculated for  $\text{C}_{17}\text{H}_{11}\text{ClFN}_4$  325.0656, found 325.0654; LC-MS Rt = 4.15 min,  $\text{M}^+\text{H}$   $m/z = 325.04$ ; IR (thin film) 3062.5(w), 3036.8(w), 3000.0(w), 1672.4(w), 1606.6(m), 1554.5(w), 1541.9(w), 1518.8(m), 1511.9(m), 1481.8(w), 1471.1(w), 1454.9(w), 1422.9(w), 1410.2(m), 1370.7(w), 1348.6(m), 1299.0(m), 1215.2(m), 1153.6(m), 1141.4(w), 1123.9(w), 1103.9(s), 1071.9(w), 1012.9(w), 989.6(w), 971.2(w), 958.6(w), 950.0(w), 942.3(w), 896.7(w), 852.8(m), 840.9(s), 816.3(s), 806.7(m), 798.1(m), 759.8(w), 745.8(m), 734.9(m), 703.2(w), 681.7(m), 666.0(w)  $\text{cm}^{-1}$ .

*6-chloro-2-(4-fluorophenyl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine (9b):*



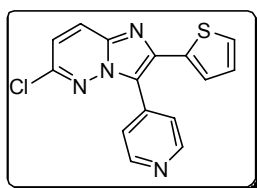
was obtained in 67% isolated yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.00 (t, 2H,  $J = 8.8$  Hz), 7.09 (d, 1H,  $J = 9.5$  Hz), 7.34 (1H, ddd,  $J_1 = 7.7$  Hz,  $J_2 = 4.9$  Hz,  $J_3 = 1.0$  Hz), 7.57 (m, 3H), 7.83 (dt, 1H,  $J_d = 1.5$  Hz,  $J_t = 8.0$  Hz), 7.93 (d, 1H,  $J = 9.0$  Hz), 8.75 (m, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 115.2, 115.4, 119.5, 123.5, 124.8, 126.0, 126.6, 129.5, 129.5, 130.3, 130.4, 136.6, 137.3, 144.5, 146.7, 148.0, 150.2, 161.7, 164.1; HRMS (+ES) calculated for  $\text{C}_{17}\text{H}_{11}\text{ClFN}_4$  325.0656, found 325.0672; LC-MS Rt = 4.02 min,  $\text{M}^+\text{H}$   $m/z = 324.86$ ; IR (thin film) 3034.9(w), 1586.1(m), 1515.1(m), 1466.3(m), 1425.8(m), 1342.7(m), 1301.4(m), 1214.7(m), 1139.7(m), 1093.7(s), 1003.4(m), 951.8(m), 838.4(s), 804.1(s), 777.5(s), 737.8(s), 693.1(m)  $\text{cm}^{-1}$ ; X-ray crystallography CCDC 756495. Formula:  $\text{C}_{17}\text{H}_{10}\text{ClF}_1\text{N}_4$ ; Unit cell parameters: a 11.6203(2) b 7.1518(2) c 17.4558(4) beta 99.360(1); space group P21/n.

*6-chloro-2-(4-fluorophenyl)-3-(pyrimidin-4-yl)imidazo[1,2-b]pyridazine (9c):*



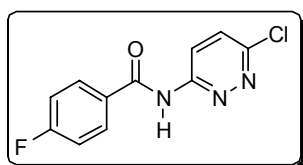
was obtained in 56% isolated yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.07 (t, 2H,  $J = 8.5$  Hz), 7.20 (d, 1H,  $J = 9.0$  Hz), 7.70 (dd, 2H,  $J_1 = 5.5$  Hz,  $J_2 = 9.0$  Hz), 7.94 (dd, 1H,  $J_1 = 1.5$  Hz,  $J_2 = 5.5$  Hz), 7.99 (d, 1H,  $J = 9.5$  Hz), 8.87 (d, 1H,  $J = 5.5$  Hz), 9.25 (d, 1H,  $J = 1.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 115.5, 120.6, 121.2, 127.0, 129.3, 129.3, 131.0, 131.1, 138.3, 140.2, 147.1, 155.0, 157.5, 159.0, 162.0, 164.5; HRMS (+ES) calculated for  $\text{C}_{16}\text{H}_{10}\text{ClFN}_5$  326.0609, found 326.0602; LC-MS Rt = 4.19 min,  $\text{M}^+\text{H}$   $m/z = 326.06$ ; IR (thin film)  $\nu$  3069.0(w), 1685.4(w), 1603.5(w), 1575.7(s), 1523.1(m), 1493.6(m), 1460.0(m), 1417.7(m), 1398.0(m), 1341.4(m), 1306.0(s), 1224.3(s), 1159.0(m), 1140.0(m), 1097.4(s), 1008.9(w), 987.4(w), 950.9(m), 843.8(m), 829.4(s), 807.2(s), 777.5(m), 750.7(m), 735.5(m), 702.2(m), 673.8(m)  $\text{cm}^{-1}$ .

**6-chloro-2-(thien-2-yl)-3-(pyridin-4-yl)imidazo[1,2-b]pyridazine (9c):**



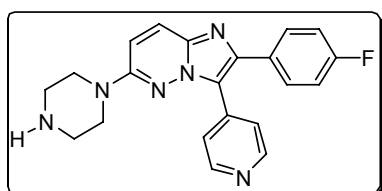
was obtained in 82% isolated yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.00 (dd, 1H,  $J_1 = 3.5$  Hz,  $J_2 = 5.0$ Hz) 7.12 (d, 1 H,  $J = 9.5$  Hz) 7.21 (dd, 1 H,  $J_1 = 1.0$  Hz,  $J_2 = 3.5$  Hz) 7.36 (dd,  $J_1 = 5.0$ ,  $J_2 = 1.0$  Hz, 1 H) 7.63 (m, 2 H) 7.93 (d, 1H,  $J = 9.5$  Hz) 8.77 (dd, 2H,  $J_1 = 1.5$  Hz,  $J_2 = 4.5$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 120.0, 124.5, 126.2, 126.5, 127.2, 127.9, 135.7, 135.9, 137.9, 139.9, 141.7, 147.0, 150.3; HRMS (+ES) calculated for  $\text{C}_{15}\text{H}_{10}\text{ClSN}_4$  313.0315, found 313.0312; LC-MS Rt = 4.02 min,  $\text{M}^+\text{H}$   $m/z = 313.21$ ; IR (thin film)  $\nu$  3166.6(w), 1690.3(w), 1644.4(w), 1596.6(w), 1570.1(w), 1494.5(w), 1453.8(w), 1410.7(w), 1354.7(w), 1329.3(w), 1254.1(w), 1199.8(w), 1141.4(w), 1098.0(w), 1059.3(w), 855.9(w), 838.0(w), 803.5(w), 713.1(m), 695.9(m)  $\text{cm}^{-1}$ .

**N-(6-chloropyridazin-3-yl)-4-fluorobenzamide (10):**



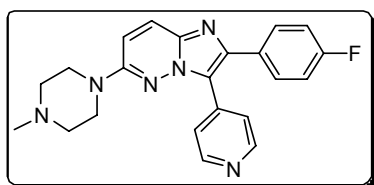
was isolated in 9% yield as white solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19 (t, 2H,  $J = 8.5$  Hz), 7.56 (d, 1H,  $J = 9.5$  Hz) 8.02 (dd, 2H  $J_1 = 5.0$  Hz,  $J_2 = 9.0$  Hz) 8.63 (d, 1H,  $J = 9.0$  Hz) 9.66 (br, 1H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 116.0, 116., 121.8, 130.1, 130.2, 130.3, 152.4, 154.8, 164.3, 165.3, 166.9; HRMS (+ES) calculated for  $\text{C}_{11}\text{H}_8\text{N}_3\text{ClF}$  252.0340, found 252.0344; LC-MS Rt = 4.03 min,  $\text{M}^+\text{H}$   $m/z = 252.02$ ; IR (thin film)  $\nu$  3359.7(w), 1669.9(m), 1599.6(m), 1570.0(w), 1518.9(w), 1488.8(s), 1411.3(w), 1398.7(m), 1340.4(m), 1307.2(w), 1261.6(w), 1226.8(s), 1161.7(m), 1148.5(s), 1117.0(m), 1096.8(m), 1064.9(m), 1036.5(w), 1015.2(m), 973.4(w), 948.0(w), 922.9(w), 894.9(m), 847.0(s), 827.5(m), 810.4(m), 758.4(s), 706.8(m), 672.8(m)  $\text{cm}^{-1}$ ; X-ray crystallography CCDC 756496. Formula:  $\text{C}_{11}\text{H}_7\text{ClF}\text{N}_3\text{O}$ ; Unit cell parameters: a 5.5835(3) b 8.4844(4) c 11.9337(7); alpha 105.020(3) beta 93.976(3) gamma 104.710(2); space group P-1.

**2-(4-fluorophenyl)-6-piperazin-1-yl-3-pyridin-4-ylimidazo[1,2-b]pyridazine (11):**



was obtained in 70% isolated yield as yellow solid.  $^1\text{H-NMR}$  (400 MHz, MeOD)  $\delta$ : 3.37 (m, 4H), 3.81 (m, 4H), 7.12 (t, 2H,  $J = 8.8$  Hz) 7.35 (d, 1H,  $J = 10.0$  Hz) 7.53 (dd, 2H,  $J_1 = 5.3$  Hz,  $J_2 = 8.8$  Hz) 7.63 (dd, 2H,  $J_1 = 1.5$  Hz,  $J_2 = 4.5$  Hz) 7.91 (d, 1H,  $J = 10.0$  Hz) 8.57 (dd, 2H  $J_1 = 1.5$  Hz,  $J_2 = 4.5$  Hz);  $^{13}\text{C-NMR}$  (100 MHz, MeOD)  $\delta$ : 44.1, 44.4, 113.9, 116.6, 116.8, 123.0, 125.7, 126.9, 131.1, 131.1, 131.7, 131.8, 138.4, 139.1, 143.7, 150.3, 155.9, 163.1, 165.6; HRMS (+ES) calculated for  $\text{C}_{21}\text{H}_{20}\text{FN}_6$  375.1733, found 375.1738; LC-MS Rt = 4.12 min,  $\text{M}^+\text{H}$   $m/z = 375.20$ ; IR (thin film)  $\nu$  3372.4(w), 2925.4(w), 2713.5(w), 2476.2(w), 1662.6(w), 1594.0(m), 1552.4(m), 1510.4(w), 1451.5(m), 1399.4(m), 1365.7(m), 1308.2(m), 1275.9(m), 1224.8(m), 1192.0(w), 1156.1(m), 1136.3(m), 1093.6(w), 1042.0(w), 1013.3(w), 991.5(w), 974.0(w), 913.9(m), 845.7(m), 821.4(m), 801.0(m), 754.0(m), 737.6(w), 715.0(w), 689.3(m)  $\text{cm}^{-1}$ .

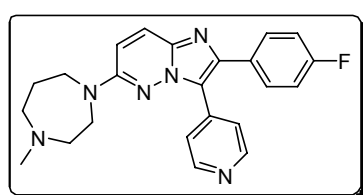
**2-(4-fluorophenyl)-6-(4-methylpiperazin-1-yl)-3-pyridin-4-ylimidazo[1,2-b]pyridazine (12):**



was obtained in 61% isolated yield as an off yellow solid.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.31 (s, 3H), 2.50 (m, 4H), 3.48 (m, 4H), 6.88 (d, 1H,  $J = 10.0$  Hz), 7.00 (t, 2H,  $J = 8.8$  Hz), 7.54 (m, 4H), 7.74 (d,

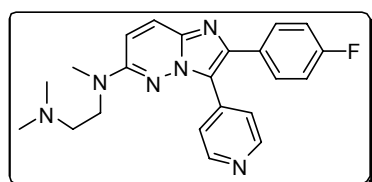
1H,  $J = 10.0$  Hz), 8.61 (dd, 2H,  $J_1 = 1.5$  Hz,  $J_2 = 6.0$  Hz).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 46.0, 46.1, 54.4, 110.7, 115.4, 115.6, 123.8, 125.8, 130.1, 130.2, 130.2, 130.3, 136.7, 137.1, 142.5, 149.7, 154.5, 161.4, 163.8; HRMS (+ES) calculated for  $\text{C}_{22}\text{H}_{22}\text{FN}_6$  389.1890, found 389.1906; LC-MS Rt = 3.87 min,  $\text{M}^+\text{H}$   $m/z$  = 389.17; IR (thin film)  $\nu$  3070.5(w), 3027.9(w), 2975.1(w), 2940.2(w), 2869.4(w), 2846.1(w), 2797.9(w), 2753.8(w), 2706.8(w), 1621.1(w), 1596.3(m), 1560.8(m), 1535.3(w), 1508.2(m), 1481.5(w), 1470.9(w), 1451.1(s), 1417.3(m), 1398.2(w), 1368.8(m), 1351.7(w), 1316.9(m), 1304.3(m), 1289.8(m), 1268.8(s), 1233.2(m), 1218.0(m), 1211.1(s), 1193.5(m), 1159.8(s), 1150.0(m), 1142.7(m), 1096.5(m), 1078.8(w), 1065.3(w), 1049.8(w), 1011.4(m), 1000.3(w), 992.2(m), 975.0(w), 959.1(w), 946.0(w), 912.9(m), 878.3(w), 839.9(s), 810.0(s), 788.5(m), 754.0(m), 742.4(m), 733.2(m), 709.9(m), 691.3(m), 665.4(w)  $\text{cm}^{-1}$ .

*2-(4-fluorophenyl)-6-(4-methyl-1,4-diazepan-1-yl)-3-pyridin-4-ylimidazo[1,2-b]pyridazine (13)*:



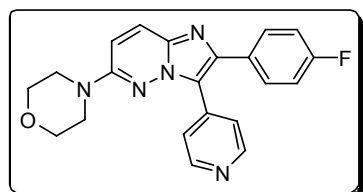
was obtained in 25% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz, MeOD)  $\delta$ : 2.32 (m, 2H), 2.94 (s, 3H), 3.48 (m, 4H), 3.78 (t, 2H,  $J = 6.3$  Hz), 4.01 (m, 2H), 7.11 (t, 2H,  $J = 8.8$  Hz), 7.23 (d, 1H,  $J = 10.0$  Hz), 7.51 (dd, 2H,  $J_1 = 5.5$  Hz,  $J_2 = 9.0$  Hz), 7.63 (d, 2H,  $J = 6$  Hz), 7.86 (d, 1H,  $J = 10.0$  Hz), 8.55 (d, 2H,  $J = 6$  Hz);  $^{13}\text{C}$ -NMR (100 MHz, MeOD)  $\delta$ : 25.8, 43.9, 45.0, 47.4, 57.2, 57.7, 112.5, 116.5, 116.8, 122.6, 125.6, 126.7, 131.2, 131.3, 131.7, 131.8, 138.1, 139.4, 143.3, 150.2, 155.0, 163.1, 165.5; HRMS (+ES) calculated for  $\text{C}_{22}\text{H}_{24}\text{FN}_6$  403.2046, found 403.2034; LC-MS Rt = 3.77 min,  $\text{M}^+\text{H}$   $m/z$  = 403.19; IR (thin film)  $\nu$  2431.8(w), 1590.8(m), 1558.1(m), 1471.7(m), 1420.6(m), 1398.7(m), 1372.1(m), 1317.6(m), 1225.5(s), 1179.1(m), 1159.9(m), 1136.9(m), 1089.3(m), 1010.5(m), 994.1(m), 950.3(m), 899.0(w), 843.5(s), 825.8(s), 800.3(s), 768.0(m), 730.7(s)  $\text{cm}^{-1}$ .

*N-[2-(4-fluorophenyl)-3-pyridin-4-ylimidazo[1,2-b]pyridazin-6-yl]-N,N',N'-trimethylethane-1,2-diamine (14)*:



was obtained in 59% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz, MeOD)  $\delta$ : 2.80 (s, 6H), 3.20 (s, 3H), 3.37 (t, 2H,  $J = 6.8$  Hz), 3.95 (t, 2H,  $J = 6.8$  Hz), 7.11 (t, 2H,  $J = 8.8$  Hz), 7.23 (d, 1H,  $J = 10.0$  Hz), 7.52 (dd, 2H,  $J_1 = 5.3$  Hz,  $J_2 = 8.8$  Hz), 7.66 (d, 2H,  $J = 6.0$  Hz), 7.88 (d, 1H,  $J = 10.0$  Hz), 8.61 (d, 2H,  $J = 6.0$  Hz);  $^{13}\text{C}$ -NMR (100 MHz, MeOD)  $\delta$ : 37.6, 43.9, 46.4, 55.5, 112.7, 116.5, 116.8, 122.4, 126.1, 126.7, 131.1, 131.1, 131.6, 131.6, 138.1, 139.8, 143.2, 150.4, 155.9, 163.1, 165.5; HRMS (+ES) calculated for  $\text{C}_{22}\text{H}_{24}\text{FN}_6$  391.2046, found 391.2063; LC-MS Rt = 3.76 min,  $\text{M}^+\text{H}$   $m/z$  = 320.14; IR (thin film)  $\nu$  2950.1(w), 2364.0(m), 1598.9(m), 1562.9(m), 1509.2(m), 1488.9(m), 1420.3(m), 1370.1(m), 1313.7(s), 1285.1(m), 1234.6(m), 1218.8(s), 1171.8(m), 1155.9(m), 1146.7(m), 1119.0(m), 1097.0(w), 994.6(m), 973.9(m), 935.8(m), 845.1(s), 817.7(s), 788.4(m), 763.3(m), 735.7(m), 708.9(m), 690.5(m)  $\text{cm}^{-1}$ .

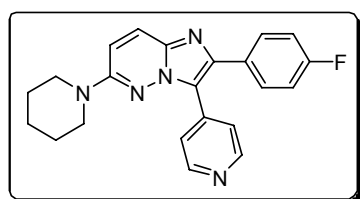
*2-(4-fluorophenyl)-6-morpholin-4-yl-3-pyridin-4-ylimidazo[1,2-b]pyridazine (15)*:



was obtained in 63% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz, MeOD)  $\delta$ : 3.44 (m, 4H), 3.77 (m, 4H), 7.08 (t, 2H,  $J = 8.8$  Hz), 7.20 (d, 1H,  $J = 10.0$  Hz), 7.47 (dd, 2H,  $J_1 = 5.0$  Hz,  $J_2 = 8.0$  Hz), 7.57 (d, 2H,  $J = 4.5$  Hz), 7.78 (d, 1H,  $J = 10.0$  Hz), 8.50 (d, 2H,  $J = 6$

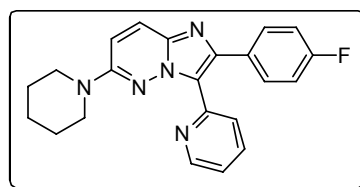
Hz);  $^{13}\text{C}$ -NMR (100 MHz, MeOD)  $\delta$ : 47.4, 67.4, 113.4, 116.5, 116.7, 122.7, 125.5, 126.3, 131.2, 131.3, 131.7, 131.8, 138.3, 139.1, 143.4, 150.2, 156.6, 163.0, 165.6; HRMS (+ES) calculated for  $\text{C}_{21}\text{H}_{19}\text{FN}_5\text{O}$  376.1574, found 376.1567; LC-MS Rt = 3.84 min,  $\text{M}^+\text{H}$   $m/z$  = 376.17; IR (thin film)  $\nu$  3068.8(w), 3030.5(w), 2967.0(w), 2854.0(w), 2164.0(w), 1926.3(w), 1621.4(w), 1598.5(m), 1561.1(m), 1536.6(m), 1508.4(m), 1468.8(m), 1449.7(m), 1419.4(m), 1364.2(m), 1311.8(m), 1262.9(s), 1232.4(m), 1212.0(s), 1191.1(m), 1157.1(s), 1123.6(s), 1114.3(s), 1096.1(m), 1057.9(m), 1010.6(w), 993.8(m), 975.2(m), 958.6(w), 931.9(m), 917.4(s), 865.5(w), 839.1(s), 809.3(s), 751.7(m), 742.9(m), 734.2(m), 706.3(m), 692.2(m), 657.5(m)  $\text{cm}^{-1}$ .

*2-(4-fluorophenyl)-6-piperidin-1-yl-3-pyridin-4-ylimidazo[1,2-b]pyridazine (16):*



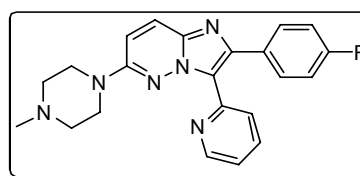
was obtained in 63% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.64 (m, 6H), 3.44 (m, 4H), 6.90 (d, 1H,  $J=10.0$  Hz), 7.01 (t, 2H,  $J=8.8$  Hz), 7.56 (m, 4H), 7.70 (d, 1H,  $J=10.0$  Hz), 8.60 (d, 2H,  $J=6.0$  Hz).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.3, 25.2, 47.3, 111.3, 115.3, 115.6, 121.6, 123.8, 125.5, 130.1, 130.2, 130.4, 130.4, 136.6, 137.3, 142.3, 149.7, 154.7, 161.3, 163.8; HRMS (+ES) calculated for  $\text{C}_{22}\text{H}_{21}\text{FN}_5$  374.1718, found 374.1795; LC-MS Rt = 4.46 min,  $\text{M}^+\text{H}$   $m/z$  = 374.14; IR (thin film)  $\nu$  2931.8(w), 2733.0(w), 2527.1(w), 2357.2(w), 1598.1(w), 1558.5(w), 1508.5(w), 1458.5(w), 1448.8(w), 1366.9(w), 1312.6(w), 1276.3(w), 1257.0(w), 1230.9(w), 1212.4(w), 1190.9(w), 1157.0(w), 1128.2(w), 1095.0(w), 1031.9(w), 991.1(w), 911.8(w), 839.9(w), 809.3(w), 747.6(w), 690.6(w)  $\text{cm}^{-1}$ .

*2-(4-fluorophenyl)-6-(piperidin-1-yl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine (17):*



was obtained in 72% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.63 (m, 6H), 3.41 (m, 4H), 6.89 (d, 1H,  $J=10.0$  Hz), 6.98 (t, 2H,  $J=9.0$  Hz), 7.27 (t, 1H,  $J=4.3$  Hz), 7.64 (m, 2H), 7.73 (d, 1H,  $J=9.5$  Hz), 7.78 (m, 2H,  $J=3.5$  Hz), 8.68 (dt, 1H,  $J_t=1.5$  Hz  $J_d=5.0$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 24.4, 25.3, 47.3, 111.0, 114.9, 115.1, 121.2, 122.5, 125.2, 125.4, 125.6, 130.0, 130.1, 130.7, 135.6, 135.9, 142.1, 149.4, 149.7, 154.8, 161.2, 163.7; HRMS (+ES) calculated for  $\text{C}_{22}\text{H}_{21}\text{FN}_5$  374.1781, found 374.1781; LC-MS Rt = 4.18 min,  $\text{M}^+\text{H}$   $m/z$  = 373.96; IR (thin film)  $\nu$  3021.7 (w), 2940.9 (w), 2853.7 (w), 2821.2 (w), 1610.1 (w), 1586.4 (m), 1541.6 (s), 1503.7 (s), 1459.6 (s), 1449.4 (s), 1422.5 (s), 1364.8 (m), 1314.6 (s), 1272.2 (m), 1256.2 (s), 1197.0 (s), 1157.7 (s), 1126.3 (s), 1090.9 (w), 1050.7 (w), 1029.7 (w), 1016.6 (w), 915.5 (m), 854.3 (w), 834.8 (s), 800.5 (s), 782.6 (s), 744.0 (s), 697.8 (w), 666.4 (w)  $\text{cm}^{-1}$ ; X-ray crystallography CCDC 756494. Formula:  $\text{C}_{22}\text{H}_{20}\text{F}_1\text{N}_5$ ; Unit cell parameters: a 6.0627(4) b 10.2605(6) c 15.1321(11); alpha 101.825(3) beta 97.542(3) gamma 98.935(4); space group P-1.

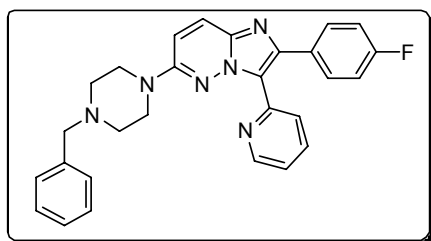
*2-(4-fluorophenyl)-6-(4-methylpiperazin-1-yl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine (18):*



was obtained in 75% isolated yield as an off yellow solid.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.28 (s, 3H), 2.46 (m, 4H), 3.42 (m, 4H), 6.82 (d, 1H,  $J = 10.0$  Hz), 6.94 (t, 2H,  $J = 9.0$  Hz), 7.23 (m, 1H), 7.60 (dd, 2H,  $J_1=5.8$  Hz,  $J_2 = 8.3$  Hz), 7.72 (m, 3H), 8.65 (d, 1H,  $J = 4.5$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 45.9, 46.1, 54.5, 110.3, 114.9, 115.1, 122.6, 124.1, 125.7, 130.0, 130.1, 130.6, 130.6, 136.0, 141.2, 142.4, 149.3, 149.7, 154.5,

161.2, 163.7; HRMS (+ES) calculated for  $C_{22}H_{22}FN_6$  389.1890, found 389.1897; LC-MS Rt = 3.87 min,  $M^+H$   $m/z$  = 389.20; IR (thin film)  $\nu$  3336.8(w), 3058.2(w), 2939.2(w), 2884.8(w), 2843.0(w), 2797.9(w), 2181.8(w), 1664.8(w), 1616.5(m), 1588.0(m), 1567.2(w), 1543.2(m), 1504.7(s), 1453.7(s), 1416.8(s), 1364.7(s), 1313.7(m), 1288.6(m), 1264.5(s), 1216.8(s), 1196.8(s), 1159.9(s), 1146.4(s), 1137.3(s), 1122.7(m), 1097.9(m), 1078.4(m), 1063.9(w), 1051.7(w), 1006.3(m), 990.7(m), 976.3(m), 955.0(w), 930.9(w), 915.2(m), 896.8(w), 837.4(s), 793.3(s), 776.7(s), 756.4(m), 743.0(s), 725.6(s), 712.3(m), 668.8(m)  $cm^{-1}$ .

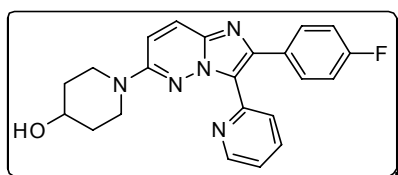
*6-(4-benzylpiperazin-1-yl)-2-(4-fluorophenyl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine (19):*



was obtained in 63% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 2.53 (m, 4H), 3.44 (m, 4H), 6.85 (d, 1H,  $J=10.0$  Hz), 6.98 (t, 2H,  $J=8.8$  Hz), 7.25 (m, 2H), 7.31 (m, 4H), 7.64 (dd, 2H,  $J_1=5.5$  Hz,  $J_2=8.8$  Hz), 7.75 (m, 3H), 8.67 (m, 1H);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 46.1, 52.5, 62.9, 110.4, 114.9, 115.1, 122.5, 124.1, 125.5, 125.6, 127.2, 128.2, 129.1, 130.0, 130.1, 130.6, 130.6, 135.9, 136.0, 137.8, 142.3,

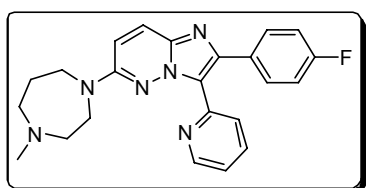
149.3, 149.3, 149.7, 154.6, 161.2, 163.7; HRMS (+ES) calculated for  $C_{28}H_{26}FN_6$  465.2203, found 465.2215; LC-MS LC-MS Rt = 3.94 min,  $M^+H$   $m/z$  = 465.26; IR (thin film)  $\nu$  3060.5(w), 2817.3(w), 1614.9(w), 1588.1(m), 1543.5(m), 1505.3(m), 1452.3(s), 1416.2(m), 1364.6(m), 1312.3(m), 1258.9(m), 1215.7(m), 1197.0(m), 1148.6(m), 1124.0(m), 1096.2(m), 1066.7(w), 1029.1(w), 1006.4(m), 987.3(m), 974.6(m), 915.6(m), 839.0(s), 800.3(s), 779.5(m), 756.5(m), 731.7(s), 712.9(m), 696.5(s), 671.1(m)  $cm^{-1}$ .

*1-(2-(4-fluorophenyl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazin-6-yl)piperidin-4-ol (20):*



was obtained in 61% isolated yield as yellowish solid.  $^1H$ -NMR (400 MHz, MeOD)  $\delta$ : 1.53 (m, 2H), 1.89 (m, 2H), 3.13 (m, 2H), 3.82 (m, 1H), 3.91 (m, 2H), 7.03 (t, 2H  $J=9.0$  Hz), 7.24 (d, 1H,  $J=10.0$  Hz), 7.42 (dd, 1H,  $J_1=6.0$  Hz,  $J_2=7.5$  Hz), 7.52 (dd, 1H,  $J_1=2.0$  Hz,  $J_2=5.3$  Hz), 7.79 (m, 2H), 7.96 (dt, 1H,  $J_f=1.5$  Hz,  $J_d=7.5$  Hz), 8.61 (m, 1H);  $^{13}C$ -NMR (100 MHz, MeOD):  $\delta$ : 33.5, 43.9, 67.2, 112.6, 114.9, 115.2, 123.8, 123.9, 124.9, 126.9, 130.0, 130.2, 130.5, 132.1, 137.6, 141.5, 149.0, 149.5, 155.2, 161.8, 164.2; HRMS (+ES) calculated for  $C_{22}H_{21}FN_5O$  390.1730, found 390.1742; LC-MS LC-MS Rt = 3.77 min,  $M^+H$   $m/z$  = 390.28; IR (thin film)  $\nu$  3259.0(w), 2931.0(w), 2848.7(w), 2177.3(w), 1617.5(m), 1588.2(m), 1551.1(m), 1504.9(m), 1456.4(s), 1423.8(m), 1364.6(m), 1313.8(m), 1218.4(s), 1190.7(m), 1157.0(m), 1113.3(m), 1086.8(s), 1049.0(m), 1011.7(m), 981.8(m), 912.1(m), 837.3(s), 801.6(s), 782.3(s), 742.1(s), 668.9(m)  $cm^{-1}$ .

*2-(4-fluorophenyl)-6-(4-methyl-1,4-diazepan-1-yl)-3-(pyridin-2-yl)imidazo[1,2-b]pyridazine (21):*

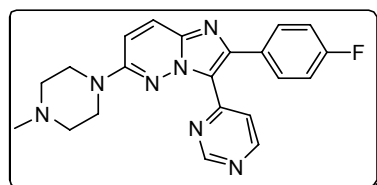


was obtained in 52% isolated yield as yellowish solid.  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 1.96 (m, 2H), 3.35 (s, 3H), 2.54 (dd, 2H,  $J_1=5.5$  Hz,  $J_2=5.6$  Hz), 2.66 (dd, 2H,  $J_1=5.0$  Hz,  $J_2=5.1$  Hz), 3.60 (dt, 2H,  $J=6.3$  Hz), 3.68 (m, 2H), 6.76 (d, 1H,  $J=10.0$  Hz), 6.97 (t, 2H,  $J=9.0$  Hz), 7.26 (dt, 1H,  $J_d=2.0$  Hz,  $J_t=5.0$  Hz), 7.64 (dd, 2H  $J_1=5.3$  Hz,  $J_2=9.0$  Hz), 7.73 (d, 1H  $J=9.5$  Hz), 7.78 (m, 2H), 8.67 (dt, 1H,  $J_t=1.5$  Hz  $J_d=5.0$  Hz);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ ):  $\delta$ /ppm 27.4, 46.7, 47.2, 47.5, 57.0, 57.8, 109.1, 114.8, 115.0, 119.6, 122.4,



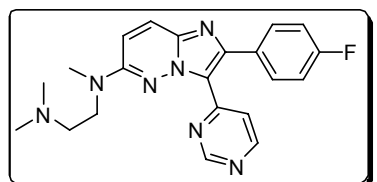
123.9, 125.5, 125.6, 129.9, 130.0, 130.8, 130.8, 131.6, 135.8, 141.9, 149.7, 153.3, 161.6, 163.6; HRMS (+ES) calculated for  $C_{23}H_{24}FN_6$  403.2046, found 403.2052; LC-MS LC-MS Rt = 3.59 min,  $M^+H$   $m/z$  = 403.23; IR (thin film)  $\nu$  2918.8(w), 2849.6(w), 2796.2(w), 1667.3(w), 1619.5(m), 1586.3(m), 1556.9(s), 1502.1(m), 1456.3(s), 1423.1(s), 1368.5(m), 1318.9(s), 1293.1(m), 1219.0(s), 1194.2(m), 1156.0(m), 1126.2(m), 1092.9(m), 1044.6(m), 1015.2(m), 1003.2(m), 986.4(m), 961.9(w), 945.0(w), 894.8(m), 839.2(s), 802.5(s), 784.9(s), 763.2(m), 743.5(m), 697.6(w)  $cm^{-1}$ .

*2-(4-fluorophenyl)-6-(4-methylpiperazin-1-yl)-3-pyrimidin-4-ylimidazo[1,2-b]pyridazine (22):*



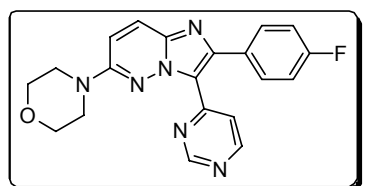
was obtained in 85% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 2.34 (s, 3H), 2.56 (m, 4H), 3.56 (m, 4H), 7.08 (t, 2H,  $J$  = 6.5 Hz), 7.25 (d, 1H,  $J$  = 10.0 Hz), 7.61 (m, 2H), 7.79 (d, 1H,  $J$  = 10.0 Hz), 8.16 (m, 1H), 8.82 (m, 1H), 9.02 (m, 1H);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 45.2, 45.7, 54.4, 113.2, 114.8, 115.0, 121.4, 125.3, 130.6, 130.7, 131.2, 131.3, 136.7, 137.6, 145.0, 155.6, 156.4, 157.1, 158.2, 162.1, 164.5; HRMS (+ES) calculated for  $C_{21}H_{21}FN_7$  390.1842, found 390.1846. LC-MS Rt = 3.91 min,  $M^+H$   $m/z$  = 390.34; IR (thin film)  $\nu$  3391.5(w), 2939.4(w), 2846.3(w), 2793.2(w), 1657.0(w), 1610.9(w), 1579.7(m), 1547.1(w), 1523.1(w), 1499.2(w), 1450.0(m), 1418.2(m), 1388.2(w), 1366.4(m), 1314.0(m), 1288.0(m), 1262.6(m), 1218.7(m), 1157.6(m), 1136.1(m), 1096.5(w), 1077.7(w), 1006.9(w), 977.8(w), 956.6(w), 913.4(m), 841.8(m), 803.8(m), 781.4(w), 759.6(m), 736.7(w), 718.7(w), 700.6(w), 676.1(w), 660.6(w)  $cm^{-1}$ .

*N-[2-(4-fluorophenyl)-3-pyrimidin-4-ylimidazo[1,2-b]pyridazin-6-yl]-N,N',N'-trimethylethane-1,2-diamine (23):*



was obtained in 74% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz, MeOD)  $\delta$ : 2.85 (s, 6H), 3.21 (s, 3H), 3.40 (t, 2H,  $J$  = 6.5 Hz), 3.95 (t, 2H,  $J$  = 6.8 Hz), 7.11 (t, 2H,  $J$  = 8.8 Hz), 7.27 (d, 1H,  $J$  = 10.0 Hz), 7.60 (dd, 2H,  $J_1$  = 5.5 Hz,  $J_2$  = 9 Hz), 7.91 (d, 1H,  $J$  = 10.0 Hz), 7.98 (dd, 1H,  $J_1$  = 1.5 Hz,  $J_2$  = 5.0 Hz), 8.84 (d, 1H,  $J$  = 5.5 Hz), 9.16 (d, 1H,  $J$  = 1.0 Hz);  $^{13}C$ -NMR (100 MHz, MeOD)  $\delta$ : 37.7, 44.2, 46.7, 55.7, 113.3, 116.1, 116.3, 121.0, 125.8, 130.2, 130.3, 132.0, 132.0, 137.2, 145.3, 146.3, 154.8, 156.1, 156.0, 158.5, 163.8, 165.7; HRMS (+ES) calculated for  $C_{21}H_{23}FN_7$  392.1999, found 392.1999; LC-MS Rt = 4.01 min,  $M^+H$   $m/z$  = 392.36; IR (thin film)  $\nu$  2951.6(w), 2405.6(w), 1614.9(w), 1593.8(w), 1577.9(s), 1563.6(s), 1520.5(m), 1496.9(m), 1459.7(m), 1419.1(m), 1381.8(m), 1315.2(s), 1287.4(m), 1218.8(s), 1173.3(w), 1147.3(m), 1127.0(w), 1012.8(w), 980.9(m), 936.0(m), 843.9(s), 815.6(m), 789.0(m), 767.1(m), 738.0(w), 717.8(m), 673.9(m)  $cm^{-1}$ .

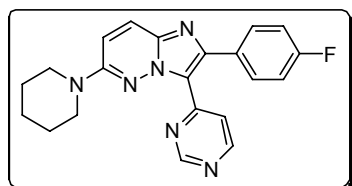
*2-(4-fluorophenyl)-6-morpholin-4-yl-3-pyrimidin-4-ylimidazo[1,2-b]pyridazine (24):*



was obtained in 58% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 3.47 (m, 4H), 3.84 (m, 4H), 6.93 (d, 1H,  $J$  = 10.0 Hz), 7.06 (t, 2H,  $J$  = 8.8 Hz), 7.67 (dd, 2H,  $J_1$  = 5.5 Hz,  $J_2$  = 9.0 Hz), 7.83 (d, 1H,  $J$  = 10.0 Hz), 7.96 (dd, 1H,  $J_1$  = 1.3 Hz,  $J_2$  = 5.3 Hz), 8.80 (d, 1H,  $J$  = 5.5 Hz), 9.18 (d, 1H,  $J$  = 1.0 Hz);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 46.4, 66.3, 111.0, 115.0, 115.2, 120.7, 126.1, 130.2, 130.3, 130.7, 130.8, 137.2, 145.3, 146.3, 154.8, 156.1, 156.8, 158.8, 161.6, 164.0; HRMS (+ES) calculated for  $C_{20}H_{18}FN_6O$

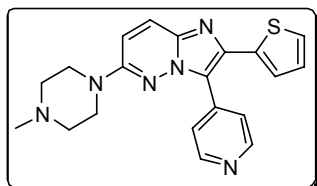
377.1526, found 376.1519; LC-MS Rt = 4.19 min,  $M^+H$   $m/z$  = 377.31; IR (thin film)  $\nu$  2854.9(w), 1614.5(w), 1574.2(s), 1520.5(m), 1448.9(s), 1415.8(m), 1385.7(m), 1364.5(m), 1313.4(m), 1259.9(s), 1219.6(s), 1157.5(m), 1114.4(s), 1056.4(m), 977.6(m), 918.9(s), 839.6(s), 801.9(s), 781.0(m), 758.5(m), 737.2(m), 717.4(m), 673.9(m), 658.4(m)  $cm^{-1}$ .

*2-(4-fluorophenyl)-6-piperidin-1-yl-3-pyrimidin-4-ylimidazo[1,2-b]pyridazine (25):*



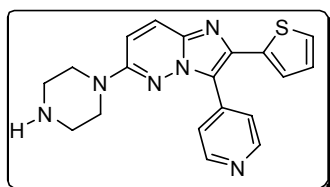
was obtained in 52% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 1.68 (m, 6H) 3.50 (m, 4H), 6.97 (d, 1H,  $J$  = 10.0 Hz), 7.03 (t, 2H,  $J$  = 8.8 Hz), 7.70 (dd, 2H,  $J_1$  = 5.5 Hz,  $J_2$  = 9.0 Hz), 7.76 (d, 1H,  $J$  = 10.0 Hz), 8.1 (d, 1H,  $J$  = 5.5 Hz), 9.16 (s, 1H);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 24.3, 25.3, 47.4, 112.0, 115.0, 115.2, 119.6, 120.5, 125.7, 130.2, 130.3, 130.7, 130.8, 137.2, 145.3, 146.3, 154.8, 156.1, 156.8, 158.8, q 161.6, 164.0; HRMS (+ES) calculated for  $C_{21}H_{20}FN_6$  375.1733, found 374.1728; LC-MS Rt = 4.66 min,  $M^+H$   $m/z$  = 375.33; IR (thin film)  $\nu$  2935.4(w), 1610.6(w), 1579.3(s), 1545.1(m), 1520.9(m), 1496.6(w), 1448.6(m), 1418.4(m), 1385.7(m), 1366.4(m), 1313.1(m), 1294.4(m), 1274.3(m), 1256.9(m), 1218.8(s), 1157.0(m), 1125.8(m), 1029.5(w), 984.3(w), 910.1(w), 842.9(s), 800.8(m), 782.0(m), 755.3(m), 737.1(m), 713.9(w), 673.7(w)  $cm^{-1}$ .

*6-(4-methylpiperazin-1-yl)-3-pyridin-4-yl-2-(2-thienyl)imidazo[1,2-b]pyridazine (26):*



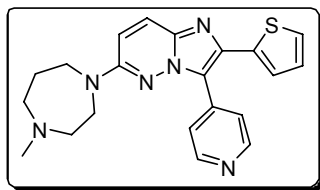
was obtained in 77% isolated yield as yellowish solid.  $^1H$ -NMR (400 MHz, MeOD)  $\delta$ : 2.52 (s, 3H), 2.81 (m, 4H), 3.62 (m, 4H), 7.04 (dd, 1H,  $J_1$  = 3.7 Hz,  $J_2$  = 5.1 Hz), 7.18 (dd, 2H,  $J_1$  = 1.5 Hz,  $J_2$  = 4.0 Hz), 7.29 (d, 1H,  $J$  = 10.0 Hz), 7.45 (dd, 1H,  $J_1$  = 1.3 Hz,  $J_2$  = 5.0 Hz), 7.75 (d, 2H,  $J$  = 6.5 Hz), 7.83 (d, 1H,  $J$  = 10.0 Hz), 8.62 (d, 2H,  $J$  = 6.5 Hz);  $^{13}C$ -NMR (100 MHz, DMSO)  $\delta$ : 35.9, 36.5, 45.5, 104.2, 113.1, 116.6, 116.7, 117.8, 118.1, 119.1, 127.6, 128.7, 128.9, 129.6, 140.8, 146.7; HRMS (+ES) calculated for  $C_{20}H_{21}N_6S$  377.1548, found 377.1545; LC-MS Rt = 3.79 min,  $M^+H$   $m/z$  = 377.31; IR (thin film)  $\nu$  3390.2(m), 1599.9(s), 1556.2(s), 1452.0(s), 1370.1(m), 1338.4(w), 1266.8(m), 1141.1(w), 1005.5(w), 909.5(w), 827.3(w), 700.6(w)  $cm^{-1}$ .

*6-piperazin-1-yl-3-pyridin-4-yl-2-(2-thienyl)imidazo[1,2-b]pyridazine (27):*



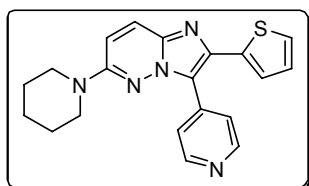
was obtained in 54% isolated yield as an off yellow solid.  $^1H$ -NMR (400 MHz, MeOD)  $\delta$ : 3.34 (m, 4H), 3.77 (m, 4H), 7.01 (dd, 1H,  $J_1$  = 3.7 Hz,  $J_2$  = 5.1 Hz), 7.15 (d, 1H,  $J$  = 3.5 Hz), 7.30 (d, 1H,  $J$  = 10.0 Hz), 7.44 (d, 1H,  $J$  = 5.0 Hz), 7.71 (d, 2H,  $J$  = 5.5 Hz), 7.85 (d, 1H,  $J$  = 10.0 Hz), 8.61 (d, 2H,  $J$  = 6 Hz);  $^{13}C$ -NMR (100 MHz, MeOD)  $\delta$ : 44.1, 44.3, 113.8, 122.5, 126.1, 126.6, 127.3, 127.7, 128.7, 137.0, 138.2, 138.6, 139.0, 150.4, 155.8; HRMS (+ES) calculated for  $C_{19}H_{19}N_6S$  363.1392, found 363.1393; LC-MS Rt = 3.66 min,  $M^+H$   $m/z$  = 363.15; IR (thin film)  $\nu$  3372.0(w), 3060.6(w), 2924.3(m), 2720.6(m), 2495.6(m), 1669.1(m), 1593.6(m), 1552.6(m), 1523.2(m), 1444.9(m), 1412.3(s), 1367.8(s), 1340.7(s), 1316.0(m), 1273.2(s), 1252.7(m), 1216.4(m), 1189.8(m), 1152.7(m), 1131.1(m), 1078.2(m), 1037.9(m), 1006.3(m), 992.0(m), 931.0(m), 909.6(m), 851.3(m), 826.0(m), 800.4(s), 726.3(s), 699.6(m)  $cm^{-1}$ .

*6-(4-methyl-1,4-diazepan-1-yl)-3-pyridin-4-yl-2-(2-thienyl)imidazo[1,2-b]pyridazine (28)*:



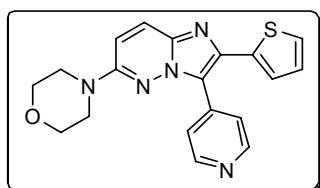
was obtained in 51% isolated yield as an off yellow solid. <sup>1</sup>H-NMR (400 MHz, MeOD) δ: 1.96 (m, 2H), 2.37 (s, 3H), 2.62 (m, 2H), 2.73 (m, 2H), 3.57 (t, 2H, *J* = 6.2 Hz), 3.66 (m, 2H), 6.98 (dd, 1H, *J*<sub>1</sub> = 3.7 Hz, *J*<sub>2</sub> = 5.1 Hz), 7.04 (d, 1H, *J* = 10.0 Hz), 7.10 (dd, 2H *J*<sub>1</sub> = 1.1 Hz, *J*<sub>2</sub> = 3.3 Hz), 7.64 (m, 3H), 8.52 (d, 2H *J* = 6 Hz); <sup>13</sup>C-NMR (100 MHz, MeOD) δ: 27.7, 46.5, 47.5, 48.0, 57.9, 58.4, 112.5, 122.0, 125.8, 125.8, 126.9, 127.3, 128.6, 137.4, 137.7, 137.7, 139.1, 150.1, 155.1; HRMS (+ES) calculated for C<sub>21</sub>H<sub>22</sub>N<sub>6</sub>S 391.1705, found 391.1708; LC-MS Rt = 3.69 min, M<sup>+</sup>H *m/z* = 391.31; IR (thin film) ν 3358.2(m), 2942.6(m), 1658.7(s), 1598.9(s), 1558.9(s), 1458.6(s), 1371.4(s), 1334.8(s), 1212.2(m), 1130.6(m), 991.1(m), 894.0(m), 852.4(m), 827.5(m), 804.2(m), 719.6(m) cm<sup>-1</sup>.

*6-piperidin-1-yl-3-pyridin-4-yl-2-(2-thienyl)imidazo[1,2-b]pyridazine (29)*:



was obtained in 90% isolated yield as an off yellow solid. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.61 (m, 6H) 3.4 (m, 4H), 6.86 (d, 1H, *J* = 10.0 Hz), 6.96 (dd, 1H, *J*<sub>1</sub> = 4.0 Hz, *J*<sub>2</sub> = 5.3 Hz), 7.14 (d, 1H, *J* = 3.0), 7.27 (d, 1H, *J* = 4.3 Hz), 7.67 (m, 3H), 8.66 (d, 2H, *J* = 6 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 24.3, 25.2, 47.2, 111.3, 121.0, 124.2, 124.8, 125.3, 125.6, 127.4, 136.4, 137.0, 137.2, 137.3, 149.7, 154.6; HRMS (+ES) calculated for C<sub>20</sub>H<sub>20</sub>N<sub>5</sub>S 362.1439, found 362.1439; LC-MS Rt = 4.54 min, M<sup>+</sup>H *m/z* = 362.28; IR (thin film) ν 3104.5(w), 3027.7(w), 2935.4(w), 2816.3(w), 1604.9(m), 1547.9(s), 1441.0(m), 1415.9(m), 1371.5(m), 1333.7(m), 1303.9(m), 1272.7(m), 1257.3(s), 1226.2(m), 1212.0(m), 1190.6(m), 1124.1(s), 1077.7(w), 1029.0(m), 990.3(m), 948.1(w), 907.5(m), 852.2(m), 840.8(m), 828.5(m), 804.7(s), 794.0(m), 749.9(m), 713.8(s), 693.8(s), 654.2(m) cm<sup>-1</sup>.

*6-morpholin-4-yl-3-pyridin-4-yl-2-(2-thienyl)imidazo[1,2-b]pyridazine (30)*:



was obtained in 88% isolated yield as yellowish solid. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.4 (m, 4H), 3.8 (m, 4H), 6.85 (d, 1H, *J* = 10.0 Hz), 6.96 (m, 1H), 7.15 (d, 1H, *J* = 3.0 Hz), 7.30 (d, 1H, *J* = 4.1 Hz), 7.65 (d, 2H, *J* = 4.5 Hz), 7.79 (d, 1H, *J* = 10.0 Hz), 8.69 (d, 2H, *J* = 3 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 46.2, 66.3, 110.4, 121.2, 124.3, 124.3, 125.1, 125.8, 125.9, 127.6, 136.6, 137.0, 137.7, 149.8, 154.6; HRMS (+ES) calculated for C<sub>19</sub>H<sub>18</sub>N<sub>5</sub>OS 364.1232, found 364.1230; LC-MS Rt = 3.96 min, M<sup>+</sup>H *m/z* = 364.29; IR (thin film) ν 3035.5(w), 2993.1(w), 2956.2(w), 2853.5(w), 1597.4(m), 1551.8(s), 1463.8(m), 1440.8(m), 1417.0(m), 1394.1(w), 1376.8(m), 1358.7(w), 1335.9(m), 1305.1(m), 1267.0(m), 1250.8(s), 1213.2(m), 1196.8(m), 1142.4(w), 1117.0(s), 1055.8(m), 1022.1(w), 990.2(m), 952.7(m), 926.0(w), 910.4(s), 873.0(w), 851.2(m), 825.3(s), 803.4(s), 750.8(m), 716.8(m), 700.4(s), 666.0(m), 654.2(m) cm<sup>-1</sup>.

## References

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