SUPPORTING INFORMATION

Development of dual casein kinase 1δ/1ε (CK1δ/ε) inhibitors for treatment of breast cancer

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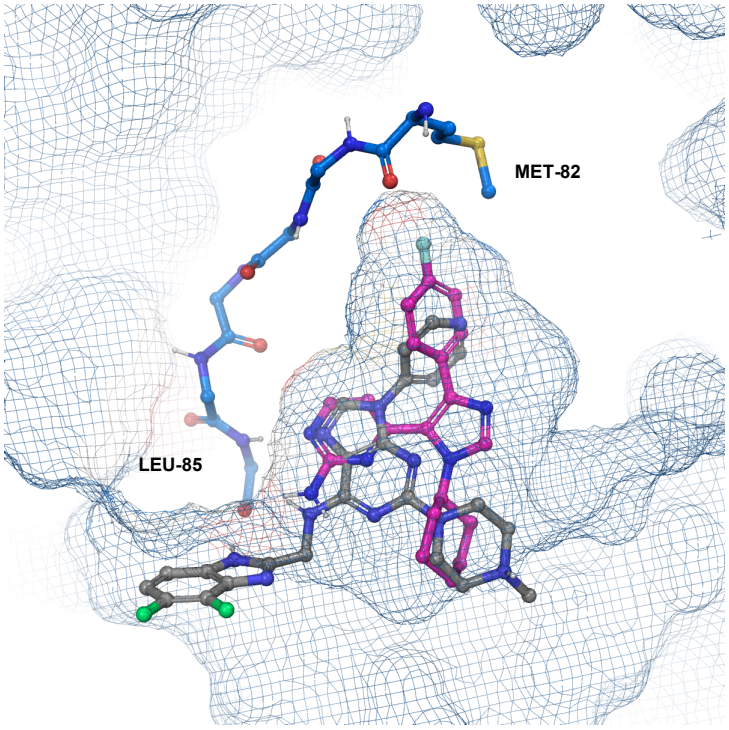
PDB coordinates of CK1δ (PDB: 3UYT) with 17 and 28 can be found in the supporting information section.



SI-1. A, docking pose of 28 (grey) and PF670462 (pink) in the CK1δ active site (mesh representation)

Compounds characterization

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-methyl-2-morpholino-9H-purin-6-amine (11). Compound **11** was prepared using general procedure in 40% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.04 (s, 1H), 7.79 (s, 1H), 7.23 – 7.10 (m, 2H), 4.81 (s, 2H), 3.58 (s, 3H), 3.50 (d, *J* = 30.5 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.3, 156.2, 153.9, 151.5, 144.8 (dd, *J* = 9.8, 233.3 Hz), 140.0 (dd, *J* = 14.7, 250.3 Hz), 138.9, 133.1 (d, *J* = 7.6 Hz), 132.4 (d, *J* = 12.0 Hz), 113.5, 110.6 (d, *J* = 21.2 Hz), 106.7, 66.0, 44.6, 38.6, 28.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, *J* = 21.3 Hz), -155.8 (d, *J* = 21.6 Hz). HRMS(ESI-TOF): calcd for $C_{18}H_{18}F_2N_8O$ $(M+H)^+$ 401.1644, found 401.1658.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-ethyl-2-morpholino-9H-purin-6-amine (12). Compound **12** was prepared using general procedure in 53% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.51 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.31 – 6.99 (m, 2H), 4.80 (s, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.49 (d, *J* = 21.5 Hz, 8H), 1.35 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.2, 156.1, 154.0, 151.0, 144.9 (d, *J* = 229.0 Hz), 140.0 (d, *J* = 246.0 Hz), 138.0, 133.1, 132.4, 113.8, 110.6, 106.7, 65.9, 44.6, 38.6, 37.5, 15.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, *J* = 21.0 Hz), -155.8 (d, *J* = 21.4 Hz). HRMS(ESI-TOF): calcd for $C_{19}H_{20}F_2N_8O$ $(M+H)^+$ 415.1801, found 415.1795.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-2-morpholino-9H-purin-6-amine (SR-3029, 13). Compound **13** was prepared using general procedure in 52% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.41 (s, 1H), 8.29 (s, 1H), 7.90 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.86 (dt, *J* = 1.3, 8.1 Hz, 1H), 7.60 (td, *J* = 6.6, 8.3 Hz, 1H), 7.33 – 7.06 (m, 3H), 4.83 (s, 2H), 3.50 (d, *J* = 14.8 Hz, 8H).^{13}C NMR (176 MHz, DMSO-d_6) δ 162.3 (d, *J* = 243.9 Hz), 158.6, 156.0, 154.3, 150.6, 144.9 (dd, *J* = 9.8, 233.4 Hz), 140.0 (dd, *J* = 14.4, 250.5 Hz), 137.2 (d, *J* = 10.6 Hz), 136.6, 133.1 (d, *J* = 7.6 Hz), 132.4 (d, *J* = 11.4 Hz), 131.2 (d, *J* = 9.0 Hz), 117.5, 114.2, 113.3 (d, *J* = 21.0 Hz), 110.7 (d, *J* = 21.3 Hz), 108.9 (d, *J* = 25.8 Hz), 106.8 (d, *J* = 5.7 Hz), 65.9, 44.5, 38.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.4 (d, *J* = 21.3 Hz), -155.8 (d, *J* = 21.5 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{19}F_3N_8O$ $(M+H)^+$ 481.1707, found 481.1714.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(4-fluorophenyl)-2-morpholino-9H-purin-6-amine (14). Compound **14** was prepared using general procedure in 28% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.46 – 8.23 (m, 2H), 8.09 – 7.75 (m, 2H), 7.41 (dd, *J* = 7.8, 9.8 Hz, 2H), 7.29 – 7.10 (m, 2H), 4.83 (s, 2H), 3.49 (d, *J* = 12.7 Hz, 8H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -115.3, -150.5 (d, *J* = 21.4 Hz), -155.8 (d, *J* = 21.3 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{19}F_3N_8O$ $(M+H)^+$ 481.1707, found 481.1717.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3,4-difluorophenyl)-2-morpholino-9H-purin-6-amine (15). Compound **15** was prepared using general procedure in 16% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.37 (s, 1H), 8.29 (s, 1H), 8.11 (ddd, *J* = 2.5, 7.1, 12.1 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 1H),

7.72 – 7.58 (m, 1H), 7.26 – 7.11 (m, 2H), 4.82 (s, 2H), 3.50 (d, *J* = 28.3 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.6, 155.9, 154.3, 150.5, 149.3 (dd, *J* = 13.3, 245.7 Hz), 147.8 (dd, *J* = 12.8, 245.6 Hz), 144.8 (dd, *J* = 12.0, 231.8 Hz), 140.0 (dd, *J* = 12.8, 250.6 Hz), 136.6, 133.1, 132.4, 132.4, 118.6, 118.2 (d, *J* = 18.2 Hz), 114.0, 111.5 (d, *J* = 20.7 Hz), 110.6, 106.8, 65.9, 44.5, 38.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -136.0 (d, *J* = 22.6 Hz), -140.7 (d, *J* = 23.2 Hz), -150.4 (d, *J* = 21.9 Hz), -155.8. HRMS(ESI-TOF): calcd for $C_{23}H_{18}F_4N_8O$ $(M+H)^+$ 499.1613, found 499.1620.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2,3-difluorophenyl)-2-morpholino-9H-purin-6-amine (16). Compound **16** was prepared using general procedure in 34% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.33 (s, 1H), 8.18 – 8.09 (m, 1H), 7.67 – 7.53 (m, 2H), 7.42 (tdd, *J* = 1.8, 5.5, 7.6 Hz, 1H), 7.27 – 7.12 (m, 2H), 4.83 (s, 2H), 3.44 (s, 8H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -136.8 (d, *J* = 22.1 Hz), -146.5 (d, *J* = 22.2 Hz), -150.5 (d, *J* = 21.5 Hz), -155.8 (d, *J* = 21.4 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{18}F_4N_8O$ $(M+H)^+$ 499.1613, found 499.1618.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3,5-difluorophenyl)-2-morpholino-9H-purin-6-amine (17). Compound **17** was prepared using general procedure in 15% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.48 (s, 1H), 8.33 (s, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.22 – 7.06 (m, 2H), 4.83 (s, 2H), 3.51 (d, *J* = 26.4 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.6 (dd, *J* = 15.1, 244.9 Hz), 158.6, 155.9, 154.3, 150.6, 144.9 (dd, *J* = 8.3, 236.2 Hz), 140.0 (dd, *J* = 14.7, 250.0 Hz), 138.0, 136.4, 133.1 (d, *J* = 7.7 Hz), 132.4 (d, *J* = 9.8 Hz), 114.2, 110.7 (d, *J* = 20.0 Hz), 106.8 (d, *J* = 9.2 Hz), 105.1 – 104.5 (m), 101.8 (t, *J* = 26.2 Hz), 65.8, 44.5, 38.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -107.8, -150.4 (d, *J* = 23.6 Hz), -155.8 (d, *J* = 19.9 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{18}F_4N_8O$ $(M+H)^+$ 499.1613, found 499.1632.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2,5-difluorophenyl)-2-morpholino-9H-purin-6-amine (18). Compound **18** was prepared using general procedure in 33% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.71 (ddd, *J* = 3.2, 5.9, 9.0 Hz, 1H), 7.59 (td, *J* = 4.9, 9.6 Hz, 1H), 7.41 (ddt, *J* = 3.4, 8.0, 9.3 Hz, 1H), 7.27 – 7.10 (m, 1H), 4.82 (s, 2H), 3.45 (s, 8H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -116.8 (d, *J* = 17.0 Hz), -127.2 (d, *J* = 16.7 Hz), -150.4 (d, *J* = 21.3 Hz), -155.8 (d, *J* = 21.6 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{18}F_4N_8O$ $(M+H)^+$ 499.1613, found 499.1632.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2,4-difluorophenyl)-2-morpholino-9H-purin-6-amine (19, TFA salt). Compound **19** was prepared using general procedure in 29% yield over two steps as a white solid (required reversed-phase HPLC for purification). ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.07 (s, 1H), 7.76 (td, *J* = 5.9, 8.8 Hz, 1H), 7.60 (ddd, *J* = 2.8, 9.2, 11.2 Hz, 1H), 7.31 (td, *J* = 2.7, 8.7 Hz, 1H), 7.26 (dd, *J* = 3.7, 8.9 Hz, 1H), 7.20 (dt, *J* = 7.9, 11.4 Hz, 1H), 5.10 – 4.51 (m, 2H), 3.42 (s, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 161.5 (dd, *J* = 11.4, 248.3 Hz), 158.7, 156.2 (dd, *J* = 13.1, 252.3 Hz), 156.0, 154.2, 151.5, 145.1 (dd, *J* = 9.7, 234.2 Hz), 139.1 (d, *J* = 245.5 Hz), 138.0, 133.9, 131.9, 129.6 (d, *J* = 10.3 Hz), 119.3 (d, *J* = 12.2 Hz), 113.0, 112.2 (dd, *J* = 3.6, 22.6 Hz), 111.1 (d, *J* = 21.0 Hz), 108.1, 105.3 (dd, *J* = 23.9, 27.2 Hz),

65.8, 44.4, 38.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.3 (TFA), -109.0 (d, J = 7.3 Hz), -117.5 (d, J = 5.4 Hz), -149.9, -155.6 (d, J = 22.0 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{18}F_4N_8O$ $(M+H)^+$ 499.1613, found 499.1632.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(o-tolyl)-9H-purin-6-amine (20). Compound **20** was prepared using general procedure in 56% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.47 – 7.39 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.25 – 7.13 (m, 2H), 4.84 (s, 2H), 3.41 (s, 8H), 2.13 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.6, 156.1, 154.2, 151.6, 144.9 (d, J = 234.4 Hz), 140.0 (d, J = 248.2 Hz), 138.3, 134.7, 134.0, 133.1 (d, J = 7.0 Hz), 132.5, 131.0, 128.8, 127.5, 126.8, 113.3, 110.7 (d, J = 21.0 Hz), 106.8, 65.8, 44.5, 38.7, 17.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.4 (d, J = 21.3 Hz), -155.8 (d, J = 21.6 Hz). HRMS(ESI-TOF): calcd for $C_{24}H_{22}F_2N_8O$ $(M+H)^+$ 477.1957, found 477.1965.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(2-(trifluoromethyl)phenyl)-9H-purin-6-amine (21). Compound **21** was prepared using general procedure in 55% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.26 (s, 1H), 8.02 – 7.94 (m, 2H), 7.88 (td, J = 1.4, 7.7 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.22 (dd, J = 3.7, 8.8 Hz, 1H), 7.17 (ddd, J = 7.1, 8.7, 11.4 Hz, 1H), 4.83 (s, 2H), 3.47 – 3.35 (m, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 156.1, 154.1, 153.0, 144.9 (dd, J = 9.6, 233.5 Hz), 140.0 (dd, J = 14.6, 250.3 Hz), 138.5, 138.4, 133.8, 133.1 (d, J = 7.5 Hz), 132.4, 131.2, 130.1, 127.3 (d, J = 5.1 Hz), 126.5 (q, J = 30.3 Hz), 123.0 (q, J = 273.8 Hz), 112.6, 110.7 (d, J = 21.0 Hz), 106.8, 65.8, 44.4, 38.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -58.4, -150.4 (d, J = 21.4 Hz), -155.8 (d, J = 21.3 Hz). HRMS(ESI-TOF): calcd for $C_{24}H_{19}F_5N_8O$ $(M+H)^+$ 531.1675, found 531.1690.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(thiophen-3-yl)-9H-purin-6-amine (22). Compound **22** was prepared using general procedure in 43% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 8.10 (d, J = 3.2 Hz, 1H), 7.79 (d, J = 5.3 Hz, 1H), 7.74 (dd, J = 3.2, 5.2 Hz, 1H), 7.26 – 7.09 (m, 2H), 4.82 (s, 2H), 3.67 (s, 4H), 2.49 – 2.23 (m, 7H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.9, 156.4, 154.7, 150.6, 145.3 (dd, J = 9.8, 232.7 Hz), 140.4 (dd, J = 14.7, 250.6 Hz), 137.0, 134.2, 133.5 (d, J = 7.5 Hz), 132.9 (d, J = 12.4 Hz), 127.4, 121.6, 114.2, 113.5, 111.1 (d, J = 20.9 Hz), 107.2, 53.9, 45.0, 43.4, 39.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, J = 21.5 Hz), -155.8 (d, J = 21.3 Hz). HRMS(ESI-TOF): calcd for $C_{22}H_{21}F_2N_9S$ $(M+H)^+$ 482.1681, found 482.1694.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(thiophen-3-yl)-9H-purin-6-amine (23). Compound **23** was prepared using general procedure in 42% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 8.10 (dd, J = 1.4, 3.3 Hz, 1H), 7.80 (d, J = 5.2 Hz, 1H), 7.74 (dd, J = 3.2, 5.2 Hz, 1H), 7.23 – 7.11 (m, 2H), 4.83 (s, 2H), 3.52 (d, J = 39.1 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 156.0, 154.2, 150.2, 144.8 (dd, J = 9.8, 232.9 Hz), 140.0 (dd, J = 14.3, 250.5 Hz), 136.4, 133.8, 133.1 (d, J = 7.8 Hz), 132.4 (d, J = 12.4 Hz), 126.9, 121.2, 113.8, 113.0, 110.7 (d, J = 21.2 Hz), 106.7, 65.9, 44.6, 38.7. ^{19}F NMR

(376 MHz, DMSO-d_6) δ -150.4 (d, J = 21.6 Hz), -155.8 (d, J = 21.5 Hz). HRMS(ESI-TOF): calcd for $C_{21}H_{18}F_2N_8OS$ $(M+H)^+$ 469.1365, found 469.1367.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (24). Compound **24** was prepared using general procedure in 68% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.59 (s, 1H), 9.15 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 8.33 (dt, J = 1.7, 8.4 Hz, 1H), 8.28 (s, 1H), 7.61 (dd, J = 4.7, 8.3 Hz, 1H), 7.16 (tt, J = 8.6, 15.9 Hz, 2H), 4.83 (s, 2H), 3.54 (s, 4H), 2.17 (s, 4H), 2.11 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 159.0, 156.4, 154.7, 151.2, 148.0, 145.3 (d, J = 232.8 Hz), 143.5, 140.4 (d, J = 253.1 Hz), 136.8, 133.5, 132.9, 132.9, 129.9, 124.7, 114.2, 111.1 (d, J = 20.6 Hz), 107.2, 54.6, 46.1, 44.2, 39.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, J = 21.4 Hz), -155.8 (d, J = 21.5 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{22}F_2N_{10}$ $(M+H)^+$ 477.2070, found 477.2078

N-((6,7-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (25). Compound **25** was prepared using general procedure in 81% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.15 (d, J = 2.6 Hz, 1H), 8.59 (dd, J = 1.5, 4.7 Hz, 1H), 8.42 (s, 1H), 8.35 (ddd, J = 1.5, 2.7, 8.3 Hz, 2H), 7.61 (ddd, J = 0.8, 4.7, 8.3 Hz, 1H), 7.28 – 7.10 (m, 2H), 4.83 (s, 2H), 3.49 (d, J = 16.0 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.6, 156.0, 154.2, 150.7, 147.0, 145.3 (dd, J = 9.5, 235.3 Hz), 142.4, 138.8 (dd, J = 15.3, 251.0 Hz), 136.5, 133.4, 132.6, 130.1, 128.7, 124.6, 113.8, 111.7 (d, J = 21.1 Hz), 108.4, 65.9, 44.5, 38.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.4 (d, J = 21.6 Hz), -155.8 (d, J = 21.1 Hz). HRMS(ESI-TOF): calcd for $C_{22}H_{19}F_2N_9O$ $(M+H)^+$ 464.1753, found 464.1764.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-2-yl)-9H-purin-6-amine (26). Compound **26** was prepared using general procedure in 67% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.61 (s, 1H), 8.56 – 8.47 (m, 2H), 8.29 (s, 1H), 8.14 – 7.88 (m, 1H), 7.40 (ddd, J = 1.1, 4.7, 7.5 Hz, 1H), 7.22 – 7.10 (m, 2H), 4.82 (s, 2H), 3.59 (s, 4H), 2.19 (s, 4H), 2.12 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, J = 21.5 Hz), -155.8 (d, J = 21.4 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{22}F_2N_{10}$ $(M+H)^+$ 477.2070, found 477.2082.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-2-yl)-9H-purin-6-amine (27). Compound **27** was prepared using general procedure in 67% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.63 (s, 1H), 8.57 – 8.51 (m, 2H), 8.33 (s, 1H), 8.11 – 8.02 (m, 1H), 7.40 (ddd, J = 0.9, 4.9, 7.5 Hz, 1H), 7.25 – 7.07 (m, 2H), 4.84 (s, 2H), 3.54 (d, J = 24.4 Hz, 8H).^{19}F NMR (376 MHz, DMSO-d_6) δ -150.4 (d, J = 21.3 Hz), -155.8 (d, J = 21.4 Hz). HRMS(ESI-TOF): calcd for $C_{22}H_{19}F_2N_9O$ $(M+H)^+$ 464.1753, found 464.1775.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-4-yl)-9H-purin-6-amine (28). Compound **28** was prepared using general procedure in 21% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.76 – 8.67 (m, 2H), 8.58 (s, 1H), 8.32 (s, 1H), 8.20 – 8.12 (m, 2H), 7.30 – 7.08 (m, 2H), 4.82 (s, 2H), 3.58 (s, 4H), 2.16 (s, 4H), 2.11 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.6, 155.9, 154.3, 151.1, 150.9, 144.9 (dd, J = 9.7, 233.2 Hz), 142.6,

140.0 (dd, *J* = 14.4, 250.8 Hz), 135.7, 133.1 (d, *J* = 7.3 Hz), 132.4 (d, *J* = 12.0 Hz), 114.7, 114.2, 110.6 (d, *J* = 21.3 Hz), 106.7, 54.3, 45.8, 43.9, 38.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.5 (d, *J* = 20.9 Hz), -155.8 (d, *J* = 21.7 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{22}F_2N_{10}$ $(M+H)^+$ 477.2070, found 477.2078.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-4-yl)-9H-purin-6-amine (29). Compound **29** was prepared using general procedure in 53% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.76 – 8.69 (m, 2H), 8.60 (s, 1H), 8.36 (s, 1H), 8.20 – 8.13 (m, 2H), 7.27 – 7.10 (m, 2H), 4.83 (s, 2H), 3.53 (d, *J* = 23.6 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 155.9, 154.3, 151.1, 150.8, 144.9 (d, *J* = 235.5 Hz), 142.6, 139.9 (d, *J* = 260.8 Hz), 135.9, 133.1, 132.4, 114.7, 114.4, 110.7, 106.8, 65.9, 44.5, 38.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -150.4 (d, *J* = 21.5 Hz), -155.8 (d, *J* = 21.6 Hz). HRMS(ESI-TOF): calcd for $C_{22}H_{19}F_2N_9O$ $(M+H)^+$ 464.1753, found 464.1753.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2-fluoropyridin-4-yl)-2-(4-methylpiperazin-1-yl)-9H-purin-6-amine (30). Compound **30** was prepared using general procedure in 46% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.62 (s, 1H), 8.38 (d, *J* = 5.7 Hz, 1H), 8.33 (s, 1H), 8.21 (d, *J* = 5.7 Hz, 1H), 7.98 (s, 1H), 7.24 – 7.06 (m, 2H), 4.98 – 4.68 (m, 2H), 3.57 (s, 4H), 2.17 (s, 4H), 2.10 (s, 3H).^{13}C NMR (176 MHz, DMSO-d_6) δ 163.9 (d, *J* = 232.7 Hz), 158.6, 155.8, 154.3, 150.9, 149.0 (d, *J* = 17.2 Hz), 147.0 (d, *J* = 11.1 Hz), 144.9 (d, *J* = 237.2 Hz), 140.0 (d, *J* = 258.1 Hz), 135.7, 133.1, 132.4, 114.1, 112.9, 110.6 (d, *J* = 21.2 Hz), 106.7, 99.8 (d, *J* = 43.7 Hz), 54.2, 45.7, 43.8, 38.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -66.2, -150.5 (d, *J* = 21.0 Hz), -155.8 (d, *J* = 21.5 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{21}F_3N_{10}$ $(M+H)^+$ 495.1976, found 495.1971.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2-fluoropyridin-4-yl)-2-morpholino-9H-purin-6-amine (31). Compound **31** was prepared using general procedure in 46% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.66 (s, 1H), 8.39 (d, *J* = 5.7 Hz, 2H), 8.24 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.32 – 7.05 (m, 2H), 4.83 (s, 2H), 3.53 (d, *J* = 22.0 Hz, 8H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -66.2, -150.4, -155.7. HRMS(ESI-TOF): calcd for $C_{22}H_{18}F_3N_9O$ $(M+H)^+$ 482.1659, found 482.1664.

9-(6-chloropyridin-3-yl)-N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9H-purin-6-amine (32). Compound **32** was prepared using general procedure in 27% yield over two steps as a white solid (required reversed-phase HPLC for purification). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.04 (d, *J* = 2.8 Hz, 1H), 8.50 – 8.38 (m, 2H), 8.30 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.11 (m, 2H), 4.81 (s, 2H), 3.53 (s, 4H), 2.13 (s, 4H), 2.09 (s, 3H). HRMS(ESI-TOF): calcd for $C_{23}H_{21}ClF_2N_{10}$ $(M+H)^+$ 511.1680, found 511.1688.

9-(6-chloropyridin-3-yl)-N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9H-purin-6-amine (33). Compound **33** was prepared using general procedure in 41% yield over two steps as a white solid (required reversed-phase HPLC for purification). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 9.04 (d, *J* = 2.8 Hz, 1H),

8.53 – 8.42 (m, 2H), 8.36 (s, 1H), 7.75 (dd, *J* = 0.6, 8.7 Hz, 1H), 7.27 – 7.08 (m, 2H), 4.82 (s, 2H), 3.50 (d, *J* = 17.8 Hz, 8H). HRMS(ESI-TOF): calcd for $C_{22}H_{18}ClF_2N_9O$ $(M+H)^+$ 498.1364, found 498.1355.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(2-methylpyridin-4-yl)-9H-purin-6-amine (34). Compound **34** was prepared using general procedure in 51% yield over two steps as a white solid (required reversed-phase HPLC for purification). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.60 – 8.50 (m, 2H), 8.30 (s, 1H), 8.00 (dd, *J* = 3.4, 8.9 Hz, 2H), 7.28 – 7.09 (m, 2H), 4.81 (s, 2H), 3.56 (s, 5H), 2.54 (s, 3H), 2.15 (s, 4H), 2.09 (s, 3H). HRMS(ESI-TOF): calcd for $C_{24}H_{24}F_2N_{10}$ $(M+H)^+$ 491.2226, found 491.2245.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(2-methylpyridin-4-yl)-2-morpholino-9H-purin-6-amine (35). Compound **35** was prepared using general procedure in 52% yield over two steps as a white solid (required reversed-phase HPLC for purification). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 8.61 – 8.49 (m, 2H), 8.33 (s, 1H), 8.06 – 7.88 (m, 2H), 7.27 – 7.09 (m, 2H), 4.83 (s, 2H), 3.52 (d, *J* = 20.7 Hz, 8H), 2.54 (s, 3H). HRMS(ESI-TOF): calcd for $C_{23}H_{21}F_2N_9O$ $(M+H)^+$ 478.1910, found 478.1912.

N-((1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (36). Compound **36** was prepared using general procedure in 67% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.16 (d, *J* = 2.6 Hz, 1H), 8.58 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.39 (s, 1H), 8.34 (dt, *J* = 1.9, 8.5 Hz, 1H), 8.19 (s, 1H), 7.61 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.46 (d, *J* = 30.9 Hz, 2H), 7.11 (dt, *J* = 3.6, 6.0 Hz, 2H), 4.86 (s, 2H), 3.57 (s, 4H), 2.17 (s, 4H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.7, 154.4, 153.3, 150.7, 147.6, 143.0, 136.2, 134.3, 132.5, 129.4, 124.2, 121.4, 121.0, 118.2, 113.8, 111.1, 54.3, 45.8, 43.8, 38.7. HRMS(ESI-TOF): calcd for $C_{23}H_{24}N_{10}$ $(M+H)^+$ 441.2258, found 441.2265.

N-((1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (37). Compound **37** was prepared using general procedure in 76% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.16 (d, *J* = 2.7 Hz, 1H), 8.58 (dd, *J* = 1.4, 4.7 Hz, 1H), 8.41 (s, 1H), 8.35 (dt, *J* = 1.9, 8.5 Hz, 1H), 8.23 (s, 1H), 7.60 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.46 (s, 2H), 7.12 – 7.06 (m, 2H), 4.86 (s, 2H), 3.51 (d, *J* = 40.3 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.8, 154.4, 153.2, 150.6, 147.6, 143.0, 136.3, 132.5, 129.4, 124.2, 121.2, 114.0, 65.9, 44.5, 38.6. HRMS(ESI-TOF): calcd for $C_{22}H_{21}N_9O$ $(M+H)^+$ 428.1942, found 428.1961.

N-((1H-benzo[d]imidazol-2-yl)methyl)-2-(piperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (38, TFA salt). Compound **38** was prepared using general procedure in 78% yield over three steps (including Boc deprotection) as a yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.29 (s, 1H), 9.14 (s, 1H), 8.83 (s, 1H), 8.71 (s, 1H), 8.62 (d, *J* = 4.7 Hz, 1H), 8.50 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 7.75 (dt, *J* = 3.4, 6.1 Hz, 2H), 7.62 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.49 (dt, *J* = 3.0, 6.1 Hz, 2H), 5.07 (d, *J* = 5.4 Hz, 2H), 3.67 (s, 4H), 2.92 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 157.8, 154.1, 153.4, 150.8, 147.9, 143.2,

137.5, 132.2, 131.6, 131.4, 129.9, 125.3, 124.3, 113.9, 42.2, 40.8, 37.2. HRMS(ESI-TOF): calcd for $C_{22}H_{22}N_{10}$ $(M+H)^+$ 427.2102, found 427.2095.

N-((5-chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (39). Compound **39** was prepared using general procedure in 52% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.35 (s, 0.6H), 12.28 (s, 0.4H), 9.15 (d, *J* = 2.5 Hz, 1H), 8.59 (d, *J* = 4.7 Hz, 1H), 8.39 (s, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.22 (s, 1H), 7.61 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.46 – 7.38 (m, 1H), 7.13 (dd, *J* = 8.7, 11.6 Hz, 1H), 4.82 (s, 2H), 3.54 (s, 4H), 2.15 (s, 4H), 2.10 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 155.2, 154.7, 154.3, 150.7, 147.6, 144.2, 143.0, 142.0, 136.3, 135.1, 133.1, 132.5, 129.4, 125.8, 125.3, 124.2, 121.5, 121.2, 119.4, 117.6, 113.8, 112.3, 110.9, 54.3, 45.8, 43.8, 38.7 (as a mixture of 5-chloro and 6-chlorobenzimidazole tautomers, 0.6:0.4). HRMS(ESI-TOF): calcd for $C_{23}H_{23}ClN_{10}$ $(M+H)^+$ 475.1868, found 475.1867.

N-((5-chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (40). Compound **40** was prepared using general procedure in 53% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 0.6H), 12.29 (s, 0.4H), 9.15 (d, *J* = 2.6 Hz, 1H), 8.59 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.41 (s, 1H), 8.35 (ddd, *J* = 1.5, 2.6, 8.3 Hz, 1H), 8.28 (s, 1H), 7.61 (ddd, *J* = 0.8, 4.7, 8.4 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.47 – 7.39 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 4.83 (s, 2H), 3.50 (d, *J* = 15.8 Hz, 8H). HRMS(ESI-TOF): calcd for $C_{22}H_{20}ClN_9O$ $(M+H)^+$ 462.1552, found 462.1544.

N-((5-chloro-1H-benzo[d]imidazol-2-yl)methyl)-2-(piperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (41, TFA salt). Compound **41** was prepared using general procedure in 61% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.14 (d, *J* = 2.6 Hz, 1H), 8.87 (s, 1H), 8.65 – 8.58 (m, 2H), 8.48 (s, 1H), 8.34 (d, *J* = 8.2 Hz, 2H), 7.75 – 7.71 (m, 1H), 7.68 – 7.60 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 4.99 – 4.94 (m, 2H), 3.71 (s, 4H), 2.94 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 157.8, 154.9, 154.2, 150.7, 147.8, 143.1, 137.3, 135.5, 133.1, 132.3, 129.9, 128.0, 124.4, 124.0, 115.6, 114.3, 114.1, 42.2, 40.9, 37.9. HRMS(ESI-TOF): calcd for $C_{22}H_{21}ClN_{10}$ $(M+H)^+$ 461.1712, found 461.1702.

N-((5,6-dichloro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (42). Compound **42** was prepared using general procedure in 40% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.47 (s, 1H), 9.15 (s, 1H), 8.59 (d, *J* = 4.8 Hz, 1H), 8.39 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.66 – 7.59 (m, 2H), 4.82 (s, 2H), 3.62 – 3.45 (m, 4H), 2.17 (s, 4H), 2.12 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.6, 156.5, 154.3, 150.7, 147.6, 143.1, 143.0, 136.3, 133.9, 132.4, 129.4, 124.2, 123.8, 123.4, 119.4, 113.8, 112.5, 54.2, 45.6, 43.7, 38.7. HRMS(ESI-TOF): calcd for $C_{23}H_{22}Cl_2N_{10}$ $(M+H)^+$ 509.1479, found 509.1461.

N-((5,6-dichloro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (43). Compound **43** was prepared using general procedure in 51% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 9.15 (d, *J* = 2.6 Hz, 1H), 8.59 (dd, *J* = 1.5, 4.7 Hz, 1H), 8.41 (s, 1H), 8.37 – 8.27 (m, 2H), 7.72

(d, *J* = 38.5 Hz, 2H), 7.61 (ddd, *J* = 0.8, 4.8, 8.3 Hz, 1H), 4.83 (s, 2H), 3.49 (d, *J* = 9.8 Hz, 8H). HRMS(ESI-TOF): calcd for $C_{22}H_{19}Cl_2N_9O$ $(M+H)^+$ 496.1162, found 496.1170.

N-((5,6-dichloro-1H-benzo[d]imidazol-2-yl)methyl)-2-(piperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (44, TFA salt). Compound **44** was prepared using general procedure in 60% yield over three steps (including Boc deprotection) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (d, *J* = 2.5 Hz, 1H), 8.66 – 8.61 (m, 3H), 8.51 (s, 1H), 8.48 – 8.30 (m, 2H), 7.77 (s, 2H), 7.63 (ddd, *J* = 0.8, 4.7, 8.4 Hz, 1H), 4.84 (d, *J* = 5.4 Hz, 2H), 3.73 (s, 4H), 2.96 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 157.9, 156.4, 154.3, 150.6, 147.6, 143.0, 137.1, 136.6, 132.3, 130.0, 124.8, 124.4, 120.6, 115.9, 114.2, 42.3, 40.9, 38.5. HRMS(ESI-TOF): calcd for $C_{22}H_{20}Cl_2N_{10}$ $(M+H)^+$ 495.1322, found 495.1318.

N-((6-methoxy-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (45). Compound **45** was prepared using general procedure in 61% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 11.95 (s, 1H), 9.16 (d, *J* = 2.6 Hz, 1H), 8.59 (dd, *J* = 1.4, 4.7 Hz, 1H), 8.39 (s, 1H), 8.34 (dt, *J* = 1.9, 8.4 Hz, 1H), 8.13 (s, 1H), 7.62 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.34 (d, *J* = 66.2 Hz, 1H), 6.98 (d, *J* = 90.7 Hz, 1H), 6.77 – 6.72 (m, 1H), 4.80 (s, 2H), 3.74 (s, 3H), 3.63 – 3.55 (m, 4H), 2.26 – 2.19 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 154.4, 150.7, 147.6, 143.0, 137.6, 136.2, 134.9, 132.5, 129.4, 124.2, 119.5, 118.6, 113.8, 110.0, 101.1, 94.6, 55.4, 54.3, 45.7, 43.8, 38.6. HRMS(ESI-TOF): calcd for $C_{24}H_{26}N_{10}O$ $(M+H)^+$ 471.2364, found 471.2379.

N-((6-methoxy-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (46). Compound **46** was prepared using general procedure in 62% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 0.4H), 11.94 (s, 0.6H), 9.16 (d, *J* = 2.5 Hz, 1H), 8.59 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.41 (s, 1H), 8.38 – 8.32 (m, 1H), 8.19 (s, 1H), 7.61 (ddd, *J* = 0.8, 4.7, 8.3 Hz, 1H), 7.33 (dd, *J* = 8.7, 47.2 Hz, 1H), 6.98 (dd, *J* = 2.4, 58.6 Hz, 1H), 6.74 (td, *J* = 2.4, 8.7 Hz, 1H), 4.80 (s, 2H), 3.74 (s, 3H), 3.53 (d, *J* = 18.6 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.8, 154.4, 150.6, 147.6, 143.0, 137.5, 136.3, 134.9, 132.5, 129.4, 124.2, 118.6, 114.0, 111.3, 110.0, 101.1, 94.6, 65.9, 55.4, 44.5, 38.6. HRMS(ESI-TOF): calcd for $C_{23}H_{23}N_9O_2$ $(M+H)^+$ 458.2048, found 458.2060.

N-((6-methoxy-1H-benzo[d]imidazol-2-yl)methyl)-2-(piperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (47, TFA salt). Compound **47** was prepared using general procedure in 71% yield over three steps (including Boc deprotection) as a yellow solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.35 (s, 1H), 9.14 (d, *J* = 2.6 Hz, 1H), 8.89 (s, 1H), 8.69 (s, 1H), 8.62 (d, *J* = 4.7 Hz, 1H), 8.50 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 2.3, 9.0 Hz, 1H), 5.04 (d, *J* = 5.1 Hz, 2H), 3.83 (s, 3H), 3.68 (s, 4H), 2.93 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 157.8, 157.6, 154.1, 152.6, 150.8, 147.9, 143.2, 137.5, 132.3, 132.2, 129.9, 125.5, 124.3, 115.0, 114.7, 114.2, 96.4, 55.8, 42.2, 40.8, 37.1. HRMS(ESI-TOF): calcd for $C_{23}H_{24}N_{10}O$ $(M+H)^+$ 457.2207, found 457.2219

N-((5,6-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-methylpiperazin-1-yl)-9-(pyridin-3-yl)-9H-purin-6-amine (48). Compound **48** was prepared using general

procedure in 50% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.37 (s, 1H), 9.15 (s, 1H), 8.58 (d, *J* = 4.8 Hz, 1H), 8.38 (s, 1H), 8.36 – 8.31 (m, 1H), 8.21 (s, 1H), 7.61 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.55 (t, *J* = 9.0 Hz, 1H), 7.46 – 7.38 (m, 1H), 4.87 – 4.67 (m, 2H), 3.54 (s, 4H), 2.15 (s, 4H), 2.10 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 155.5, 154.3, 150.7, 147.6, 146.2 (d, *J* = 233.7 Hz, broad), 143.0, 138.5, 136.3, 132.5, 129.6, 129.4, 124.2, 113.8, 105.5, 99.1, 54.3, 45.8, 43.8, 38.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -145.1 (d, *J* = 22.6 Hz), -146.5 (d, *J* = 22.2 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{22}F_2N_{10}$ $(M+H)^+$ 477.2070, found 477.2090.

N-((5,6-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-morpholino-9-(pyridin-3-yl)-9H-purin-6-amine (49). Compound **49** was prepared using general procedure in 50% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.37 (s, 1H), 9.15 (s, 1H), 8.59 (d, *J* = 4.6 Hz, 1H), 8.41 (s, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 8.25 (s, 1H), 7.61 (dd, *J* = 4.7, 8.3 Hz, 1H), 7.50 (s, 2H), 4.82 (s, 2H), 3.50 (d, *J* = 25.2 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 158.7, 155.5, 154.3, 150.7, 147.6, 146.2 (dd, *J* = 14.5, 236.3 Hz), 143.1, 138.5, 136.4, 132.4, 129.6, 129.5, 124.2, 114.0, 105.5, 99.3, 65.9, 44.5, 38.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -144.9, -146.3. HRMS(ESI-TOF): calcd for $C_{22}H_{19}F_2N_9O$ $(M+H)^+$ 464.1753, found 464.1752

N-(benzo[d]oxazol-2-ylmethyl)-9-(3-fluorophenyl)-2-(tetrahydro-2H-pyran-4-yl)-9H-purin-6-amine (50). Compound **50** was prepared using general procedure in 41% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.41 (s, 1H), 7.93 – 7.80 (m, 2H), 7.71 – 7.62 (m, 2H), 7.59 (td, *J* = 6.6, 8.2 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.22 (tdd, *J* = 0.9, 2.6, 8.5 Hz, 1H), 4.85 (s, 2H), 3.52 – 3.38 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.9, 162.2 (d, *J* = 243.8 Hz), 158.5, 154.1, 150.7, 150.1, 140.8, 137.1 (d, *J* = 10.9 Hz), 136.8, 131.2 (d, *J* = 9.3 Hz), 124.8, 124.3, 119.3, 117.6 (d, *J* = 2.9 Hz), 114.0, 113.4 (d, *J* = 21.0 Hz), 110.7, 109.1 (d, *J* = 26.0 Hz), 65.8, 44.4, 38.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. LCMS(ESI): calcd for $C_{24}H_{21}FN_6O_2$ $(M+H)^+$ 445.2, found 445.2

N-(benzo[d]thiazol-2-ylmethyl)-9-(3-fluorophenyl)-2-morpholino-9H-purin-6-amine (51). Compound **51** was prepared using general procedure in 40% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.41 (s, 1H), 8.00 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.94 (dd, *J* = 1.1, 8.1 Hz, 1H), 7.93 – 7.83 (m, 2H), 7.60 (td, *J* = 6.6, 8.3 Hz, 1H), 7.48 (ddd, *J* = 1.3, 7.2, 8.4 Hz, 1H), 7.38 (ddd, *J* = 1.2, 7.2, 8.3 Hz, 1H), 7.28 – 7.18 (m, 1H), 5.01 (s, 2H), 3.62 – 3.51 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 162.2 (d, *J* = 243.6 Hz), 158.6, 154.0, 152.6, 150.8, 137.1 (d, *J* = 10.7 Hz), 136.9, 134.6, 131.2 (d, *J* = 9.2 Hz), 126.0, 124.8, 122.2, 122.2, 117.7, 114.0, 113.4 (d, *J* = 21.0 Hz), 109.1 (d, *J* = 26.1 Hz), 65.9, 44.5, 42.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{23}H_{20}FN_7OS$ $(M+H)^+$ 462.1507, found 462.1528.

9-(3-fluorophenyl)-2-morpholino-N-((4-phenyl-1H-imidazol-2-yl)methyl)-9H-purin-6-amine (522). Compound **52** was prepared using general procedure in 38% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.39 (s, 1H), 8.04 (s, 1H), 7.89 (dd, *J* = 9.5, 19.7 Hz, 2H), 7.73 (s, 2H), 7.60 (q, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.32 (s, 2H), 7.26 – 7.19 (m, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 4.68 (s, 2H), 3.61 (dd, *J* = 5.0, 13.4 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.1 Hz),

158.8, 154.3, 150.5, 146.4, 139.3, 137.3, 136.4, 134.9, 131.2 (d, *J* = 9.3 Hz), 128.4, 125.8, 124.0, 117.5, 114.1, 113.3 (d, *J* = 20.8 Hz), 112.4, 108.9 (d, *J* = 26.0 Hz), 66.0, 44.7, 38.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{25}H_{23}FN_8O$ $(M+H)^+$ 471.2052, found 471.2059.

9-(3-fluorophenyl)-2-morpholino-N-((4-phenyloxazol-2-yl)methyl)-9H-purin-6-amine (53). Compound **53** was prepared using general procedure in 31% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.40 (d, *J* = 10.5 Hz, 2H), 7.89 (d, *J* = 10.6 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.58 (q, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.21 (td, *J* = 2.5, 8.5 Hz, 1H), 4.72 (s, 2H), 3.62 – 3.45 (m, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.6, 162.2 (d, *J* = 243.5 Hz), 158.6, 154.1, 150.6, 139.6, 137.2 (d, *J* = 10.7 Hz), 136.7, 134.7, 131.2 (d, *J* = 9.3 Hz), 131.0, 128.7, 127.8, 125.0, 117.6, 114.0, 113.3 (d, *J* = 20.9 Hz), 109.0 (d, *J* = 25.7 Hz), 65.9, 44.5, 37.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{25}H_{22}FN_7O_2$ $(M+H)^+$ 472.1892, found 472.1891.

9-(3-fluorophenyl)-2-morpholino-N-((4-phenylthiazol-2-yl)methyl)-9H-purin-6-amine (54). Compound **54** was prepared using general procedure in 53% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.40 (s, 1H), 7.98 – 7.88 (m, 4H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.58 (q, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 8.6 Hz, 1H), 5.01 – 4.86 (m, 2H), 3.66 – 3.54 (m, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 170.7, 162.2 (d, *J* = 243.8 Hz), 158.6, 154.0, 153.3, 150.7, 137.1 (d, *J* = 10.6 Hz), 136.8, 134.2, 131.2 (d, *J* = 9.3 Hz), 128.7, 127.9, 125.9, 117.6, 114.1, 114.0, 113.3 (d, *J* = 21.1 Hz), 109.0 (d, *J* = 25.8 Hz), 66.0, 44.6, 42.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.9. HRMS(ESI-TOF): calcd for $C_{25}H_{22}FN_7OS$ $(M+H)^+$ 488.1663, found 488.1671.

9-(3-fluorophenyl)-N-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)methyl)-2-morpholino-9H-purin-6-amine (55). Compound **55** was prepared using general procedure in 29% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.19 (d, *J* = 2.7 Hz, 1H), 8.10 (s, 1H), 7.91 (d, *J* = 10.7 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.29 (dd, *J* = 2.9, 8.7 Hz, 1H), 7.22 (td, *J* = 2.4, 8.7 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 4.63 (s, 2H), 3.59 (s, 8H), 3.16 – 3.09 (m, 4H), 2.47 – 2.41 (m, 4H), 2.21 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.8 Hz), 158.8, 154.3, 150.4, 149.3, 145.2, 137.3, 136.6, 136.4, 131.2 (d, *J* = 9.1 Hz), 122.9, 121.0, 117.5, 114.0, 113.2 (d, *J* = 21.0 Hz), 108.9 (d, *J* = 25.9 Hz), 66.0, 54.0, 47.4, 45.2, 44.6, 42.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{26}H_{30}FN_9O$ $(M+H)^+$ 504.263, found 504.2632.

9-(3-fluorophenyl)-N-(4-(4-methylpiperazin-1-yl)benzyl)-2-morpholino-9H-purin-6-amine (56). Compound **56** was prepared using general procedure in 35% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.14 (s, 1H), 7.94 – 7.82 (m, 2H), 7.59 (td, *J* = 6.7, 8.3 Hz, 1H), 7.26 – 7.17 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.52 (s, 2H), 3.64 (s, 8H), 3.10 – 3.03 (m, 4H), 2.45 – 2.39 (m, 4H), 2.20 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.6 Hz), 158.9, 154.3, 150.3, 149.9, 137.3 (d, *J* = 10.4 Hz), 136.2, 131.2 (d, *J* = 9.1 Hz), 130.6, 128.4, 117.5, 115.2, 114.0, 113.2 (d, *J* = 20.9 Hz), 108.9 (d, *J* = 25.8 Hz), 66.0, 54.6, 48.3, 45.7, 44.6, 42.5. ^{19}F

NMR (376 MHz, DMSO-d_6) δ -111.0 HRMS(ESI-TOF): calcd for $C_{27}H_{31}FN_8O$ $(M+H)^+$ 503.2678, found 503.2705.

N-((1H-imidazol-2-yl)methyl)-9-(3-fluorophenyl)-2-morpholino-9H-purin-6-amine (57). Compound **57** was prepared using general procedure in 41% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 11.66 (s, 1H), 8.38 (s, 1H), 7.89 (dd, *J* = 9.6, 35.4 Hz, 3H), 7.60 (q, *J* = 7.7 Hz, 1H), 7.22 (td, *J* = 2.5, 8.4 Hz, 1H), 6.89 (s, 2H), 4.66 (s, 2H), 3.63 (s, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.8 Hz), 158.8, 154.4, 150.5, 145.6, 137.3, 137.2, 136.4, 131.2 (d, *J* = 9.2 Hz), 117.5, 114.1, 113.3 (d, *J* = 20.7 Hz), 108.9 (d, *J* = 26.6 Hz), 66.0, 44.6, 37.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{19}H_{19}FN_8O$ $(M+H)^+$ 395.1739, found 395.1753.

9-(3-fluorophenyl)-2-morpholino-N-(pyridin-2-ylmethyl)-9H-purin-6-amine (58, TFA salt). Compound **58** was prepared using general procedure in 40% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.69 (dd, *J* = 1.6, 5.4 Hz, 1H), 8.47 – 8.38 (m, 2H), 8.18 (s, 1H), 7.89 (dt, *J* = 2.3, 10.6 Hz, 1H), 7.84 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.23 (td, *J* = 2.5, 8.5 Hz, 1H), 4.94 – 4.79 (m, 2H), 3.51 (d, *J* = 38.8 Hz, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.5 Hz), 158.6, 155.6, 154.2, 150.6, 144.4, 142.1, 137.1, 136.9, 131.3, 123.8, 123.4, 117.7, 114.0, 113.4 (d, *J* = 21.5 Hz), 109.0 (d, *J* = 26.4 Hz), 65.9, 44.5, 43.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.6 (TFA), -111.0. HRMS(ESI-TOF): calcd for $C_{21}H_{20}FN_7O$ $(M+H)^+$ 406.1786, found 406.1797.

9-(3-fluorophenyl)-2-morpholino-N-(pyridin-3-ylmethyl)-9H-purin-6-amine (59). Compound **59** was prepared using general procedure in 60% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.42 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.36 (s, 1H), 8.34 (s, 1H), 7.89 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.84 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.77 (dt, *J* = 2.0, 7.9 Hz, 1H), 7.59 (td, *J* = 6.6, 8.3 Hz, 1H), 7.33 (dd, *J* = 4.7, 7.8 Hz, 1H), 7.21 (td, *J* = 2.5, 8.5 Hz, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 3.62 (s, 8H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.7 Hz), 158.8, 154.2, 150.4, 149.0, 147.9, 137.2 (d, *J* = 10.7 Hz), 136.5, 135.8, 135.2, 131.2 (d, *J* = 9.1 Hz), 123.4, 117.6, 114.0, 113.3 (d, *J* = 20.8 Hz), 109.0 (d, *J* = 26.2 Hz), 66.0, 44.6, 40.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. LCMS(ESI): calcd for $C_{21}H_{20}FN_7O$ $(M+H)^+$ 406.2, found 406.2.

9-(3-fluorophenyl)-N-((5-methylpyridin-2-yl)methyl)-2-morpholino-9H-purin-6-amine (60). Compound **60** was prepared using general procedure in 40% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 8.17 (s, 1H), 7.91 (dt, *J* = 2.4, 10.7 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.59 (td, *J* = 6.6, 8.2 Hz, 1H), 7.53 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.22 (dd, *J* = 6.9, 8.4 Hz, 2H), 4.77 – 4.62 (m, 2H), 3.57 (s, 8H), 2.26 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.7 Hz), 158.8, 156.3, 154.3, 150.4, 148.8, 137.2 (d, *J* = 10.4 Hz), 136.9, 136.4, 131.2 (d, *J* = 9.3 Hz), 130.8, 120.5, 117.5, 114.0, 113.2 (d, *J* = 20.9 Hz), 108.9 (d, *J* = 25.8 Hz), 66.0, 44.9, 44.5, 17.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{22}H_{22}FN_7O$ $(M+H)^+$ 420.1943, found 420.1941.

9-(3-fluorophenyl)-N-((6-methylpyridin-2-yl)methyl)-2-morpholino-9H-purin-6-amine (61). Compound **61** was prepared using general procedure in 41% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.20 (s, 1H), 7.96 – 7.76 (m, 2H), 7.59 (tt, *J* = 3.9, 8.2 Hz, 2H), 7.22 (td, *J* = 2.5, 8.5 Hz, 1H), 7.10 (dd, *J* = 7.6, 10.4 Hz, 2H), 4.67 (s, 2H), 3.57 (s, 8H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.7 Hz), 158.8, 158.7, 156.9, 154.3, 150.4, 137.2 (d, *J* = 10.6 Hz), 136.8, 136.4, 131.2 (d, *J* = 9.2 Hz), 121.1, 117.9, 117.5, 114.0, 113.2 (d, *J* = 21.0 Hz), 108.9 (d, *J* = 25.9 Hz), 66.0, 45.3, 44.5, 24.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0. HRMS(ESI-TOF): calcd for $C_{22}H_{22}FN_7O$ $(M+H)^+$ 420.1943, found 420.1960.

N-(2-fluorobenzyl)-9-(3-fluorophenyl)-2-morpholino-9H-purin-6-amine (62). Compound **62** was prepared using general procedure in 45% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.26 (s, 1H), 7.99 – 7.78 (m, 2H), 7.59 (td, *J* = 6.6, 8.3 Hz, 1H), 7.41 (td, *J* = 1.8, 7.7 Hz, 1H), 7.32 – 7.04 (m, 4H), 4.69 (s, 2H), 3.60 (s, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.7 Hz), 160.1 (d, *J* = 244.2 Hz), 154.2, 150.4, 137.1 (d, *J* = 10.9 Hz), 136.5, 131.2 (d, *J* = 9.2 Hz), 129.5, 128.6 (d, *J* = 8.1 Hz), 126.9 (d, *J* = 14.5 Hz), 124.2 (d, *J* = 3.3 Hz), 117.7, 115.0 (d, *J* = 21.4 Hz), 113.5, 113.3, 109.1 (d, *J* = 25.9 Hz), 66.0, 44.6, 36.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -119.2. HRMS(ESI-TOF): calcd for $C_{22}H_{20}F_2N_6O$ $(M+H)^+$ 423.1739, found 423.1752.

N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-9H-purine-2,6-diamine (63). Compound **63** was prepared using general procedure in 33% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.38 (s, 1H), 7.81 (d, *J* = 48.8 Hz, 2H), 7.62 (td, *J* = 6.4, 8.2 Hz, 1H), 7.36 – 7.18 (m, 4H), 4.91 (s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -149.3, -155.2. HRMS(ESI-TOF): calcd for $C_{19}H_{13}F_3N_8$ $(M+H)^+$ 411.1288, found 411.1310.

2-((6-(((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)amino)-9-(3-fluorophenyl)-9H-purin-2-yl)amino)ethan-1-ol (64). Compound **64** was prepared using general procedure in 70% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H), 7.94 (d, *J* = 10.6 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.60 (td, *J* = 6.6, 8.3 Hz, 1H), 7.34 – 7.19 (m, 3H), 4.88 (s, 2H), 3.27 (s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -149.2, -155.2 (d, *J* = 21.8 Hz). HRMS(ESI-TOF): calcd for $C_{21}H_{17}F_3N_8O$ $(M+H)^+$ 455.1550, found 455.1564.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-2-thiomorpholino-9H-purin-6-amine (65). Compound **65** was prepared using general procedure in 63% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.40 (s, 1H), 8.32 (d, *J* = 6.4 Hz, 1H), 7.88 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.83 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.60 (td, *J* = 6.5, 8.3 Hz, 1H), 7.26 – 7.11 (m, 3H), 5.00 – 4.69 (m, 2H), 3.89 (s, 4H), 2.30 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.8 Hz), 157.9, 156.0, 154.4, 150.7, 144.8 (dd, *J* = 9.2, 233.6 Hz), 140.0 (dd, *J* = 14.5, 250.7 Hz), 137.2 (d, *J* = 10.8 Hz), 136.6, 133.1 (d, *J* = 7.5 Hz), 132.5 (d, *J* = 12.0 Hz), 131.2 (d, *J* = 9.3 Hz), 117.6, 113.9, 113.3 (d, *J* = 20.9 Hz), 110.7 (d, *J* = 20.9 Hz), 109.0 (d, *J* = 25.7 Hz), 106.7, 46.5, 38.9, 25.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.4 (d, *J* =

21.5 Hz), -155.8 (d, *J* = 21.5 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{19}F_3N_8S$ $(M+H)^+$ 497.1478, found 497.1474.

4-(6-(((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)amino)-9-(3-fluorophenyl)-9H-purin-2-yl)thiomorpholine 1,1-dioxide (66). Compound **66** was prepared using general procedure in 52% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.48 (s, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 10.5 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.60 (td, *J* = 4.4, 8.6 Hz, 1H), 7.30 – 7.04 (m, 3H), 4.93 – 4.76 (m, 2H), 4.05 (s, 4H), 2.84 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.9 Hz), 157.2, 155.9, 154.6, 150.5, 144.9 (dd, *J* = 9.7, 233.2 Hz), 140.0 (dd, *J* = 15.5, 251.0 Hz), 137.3, 136.9 (d, *J* = 10.7 Hz), 133.0 (d, *J* = 7.5 Hz), 132.4 (d, *J* = 11.5 Hz), 131.3 (d, *J* = 9.2 Hz), 118.0, 114.6, 113.6 (d, *J* = 21.1 Hz), 110.8 (d, *J* = 21.2 Hz), 109.4 (d, *J* = 25.9 Hz), 106.8, 50.3, 42.9, 38.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.9 (d, *J* = 5.7 Hz), -150.3 (d, *J* = 21.5 Hz), -155.6 (d, *J* = 21.6 Hz). HRMS(ESI-TOF): calcd for $C_{23}H_{19}F_3N_8O_2S$ $(M+H)^+$ 529.1377, found 529.1371.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-2-(4-methoxypiperidin-1-yl)-9H-purin-6-amine (67). Compound **67** was prepared using general procedure in 41% yield over two steps as a white solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.55 (s, 1H), 8.38 (s, 1H), 8.23 (s, 1H), 7.91 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.85 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.60 (td, *J* = 6.5, 8.3 Hz, 1H), 7.25 – 7.10 (m, 3H), 4.80 (s, 2H), 4.06 (s, 2H), 3.27 (s, 1H), 3.16 (s, 3H), 3.09 (s, 2H), 1.61 (d, *J* = 12.5 Hz, 2H), 1.07 (s, 2H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.6 Hz), 158.4, 156.1, 154.3, 150.8, 144.9 (d, *J* = 236.9 Hz), 140.0 (d, *J* = 245.4 Hz), 137.3 (d, *J* = 10.6 Hz), 136.3, 133.1, 132.5, 131.2 (d, *J* = 9.3 Hz), 117.4, 113.8, 113.2 (d, *J* = 21.0 Hz), 110.6, 108.9 (d, *J* = 26.4 Hz), 106.7, 75.8, 54.6, 41.6, 38.8, 30.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.6 (d, *J* = 20.9 Hz), -155.8 (d, *J* = 21.3 Hz). HRMS(ESI-TOF): calcd for $C_{25}H_{23}F_3N_8O$ $(M+H)^+$ 509.2020, found 509.2014.

(1-(6-(((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)amino)-9-(3-fluorophenyl)-9H-purin-2-yl)piperidin-4-yl)methanol (68). Compound **68** was prepared using general procedure in 14% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 7.93 (dt, *J* = 2.3, 10.8 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.60 (td, *J* = 6.6, 8.3 Hz, 1H), 7.27 – 7.08 (m, 3H), 4.81 (s, 2H), 4.49 (d, *J* = 12.8 Hz, 2H), 4.37 (s, 1H), 3.21 – 3.03 (m, 3H), 2.66 (t, *J* = 12.8 Hz, 2H), 1.51 (s, 2H), 0.83 (s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.6, -155.8. HRMS(ESI-TOF): calcd for $C_{25}H_{23}F_3N_8O$ $(M+H)^+$ 509.2020, found 509.2007.

N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-N2-((tetrahydro-2H-pyran-4-yl)methyl)-9H-purine-2,6-diamine (69). Compound **69** was prepared using general procedure in 33% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.34 (s, 1H), 8.06 (d, *J* = 41.8 Hz, 2H), 7.84 (s, 1H), 7.58 (td, *J* = 6.6, 8.3 Hz, 1H), 7.25 – 7.09 (m, 3H), 6.80 (s, 1H), 4.84 (s, 2H), 3.62 (s, 2H), 3.23 – 2.58 (m, 4H), 1.97 – 1.16 (m, 2H), 1.05 – 0.80 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.27, -150.57, -155.81. HRMS(ESI-TOF): calcd for $C_{25}H_{23}F_3N_8O$ $(M+H)^+$ 509.2020, found 509.2038.

N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-N2-(2-morpholinoethyl)-9H-purine-2,6-diamine (70). Compound **70** was prepared using general procedure in 30% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.51 (s, 1H), 8.34 (s, 1H), 8.12 (d, *J* = 23.4 Hz, 1H), 8.04 – 7.90 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.58 (td, *J* = 6.5, 8.2 Hz, 1H), 7.28 – 7.11 (m, 3H), 6.55 (s, 1H), 4.85 (s, 2H), 3.61 – 3.41 (m, 6H), 2.46 – 2.08 (m, 6H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.5 Hz), 161.1, 159.4, 155.9, 154.8, 144.9 (d, *J* = 228.4 Hz), 140.0 (d, *J* = 237.6 Hz), 137.3 (d, *J* = 10.7 Hz), 135.7, 133.1, 132.5, 131.1 (d, *J* = 9.3 Hz), 117.5, 114.1, 113.2 (d, *J* = 20.8 Hz), 110.7, 109.0, 106.8, 66.0, 57.4, 53.2, 38.0, 34.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.2, -150.4, -155.7. HRMS(ESI-TOF): calcd for $C_{25}H_{24}F_3N_9O$ $(M+H)^+$ 524.2129, found 524.2114.

N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-N2-(3-morpholinopropyl)-9H-purine-2,6-diamine (71). Compound **71** was prepared using general procedure in 60% yield over two steps as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 8.00 (s, 1H), 7.84 (s, 1H), 7.58 (q, *J* = 7.8 Hz, 1H), 7.26 – 7.11 (m, 3H), 6.73 (s, 1H), 4.85 (s, 2H), 3.67 – 3.09 (m, 6H), 2.45 – 2.03 (m, 6H), 1.69 (s, 2H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.5 Hz), 159.6, 155.9, 154.7, 150.9, 144.9 (d, *J* = 234.8 Hz), 140.0 (d, *J* = 250.1 Hz), 137.4 (d, *J* = 10.4 Hz), 135.7, 133.1, 132.5, 131.1 (d, *J* = 9.4 Hz), 117.5, 114.0, 113.2 (d, *J* = 20.9 Hz), 110.6, 109.0, 106.8, 65.9, 56.1, 53.0, 38.4, 25.7, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.1, -150.4, -155.7 (d, *J* = 21.0 Hz). HRMS(ESI-TOF): calcd for $C_{26}H_{26}F_3N_9O$ $(M+H)^+$ 538.2285, found 538.2274.

N2-butyl-N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-9H-purine-2,6-diamine (72). Compound **72** was prepared using general procedure in 48% yield over two steps as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 8.34 (s, 1H), 8.02 (s, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.58 (td, *J* = 6.6, 8.3 Hz, 1H), 7.26 – 7.10 (m, 3H), 6.67 (s, 1H), 4.85 (s, 2H), 3.14 (s, 2H), 1.63 – 1.03 (m, 4H), 0.76 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.2 (d, *J* = 243.4 Hz), 159.6, 156.0, 154.7, 151.1, 144.9 (dd, *J* = 9.2, 233.8 Hz), 140.0 (dd, *J* = 15.2, 250.9 Hz), 137.4 (d, *J* = 10.5 Hz), 135.6, 133.1, 132.6, 131.1 (d, *J* = 9.1 Hz), 117.4, 114.0, 113.1 (d, *J* = 20.9 Hz), 110.7, 108.8, 106.8, 40.7, 38.3, 31.3, 19.6, 13.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.2, -150.5, -155.8. HRMS(ESI-TOF): calcd for $C_{23}H_{21}F_3N_8$ $(M+H)^+$ 467.1914, found 467.1930.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-2-(4-(dimethylamino)piperidin-1-yl)-9-(3-fluorophenyl)-9H-purin-6-amine (73). Compound **73** was prepared using general procedure in 54% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 7.91 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.61 (td, *J* = 6.6, 8.3 Hz, 1H), 7.29 – 7.09 (m, 3H), 4.80 (s, 2H), 3.38 – 3.28 (m, 4H), 2.40 (s, 6H), 1.80 – 1.53 (m, 2H), 1.28 – 1.01 (m, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.5 (d, *J* = 21.5 Hz), -155.7 (d, *J* = 21.7 Hz). HRMS(ESI-TOF): calcd for $C_{26}H_{26}F_3N_9$ $(M+H)^+$ 522.2336, found 522.2328.

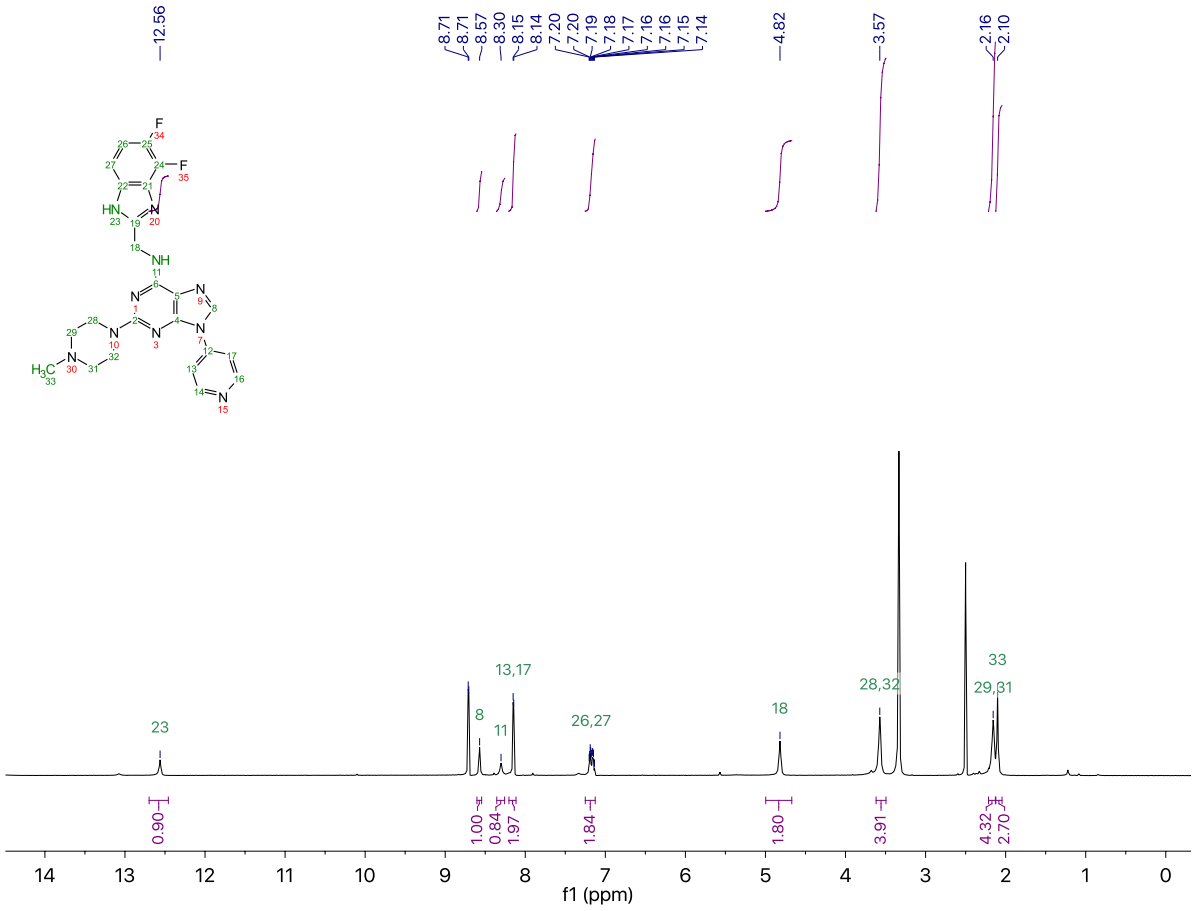
N6-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-N2-(1-methylpiperidin-4-yl)-9H-purine-2,6-diamine (74). Compound **74** was prepared using

general procedure in 45% yield over two steps as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.23 (s, 1H), 7.91 (dt, *J* = 2.3, 10.7 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.59 (dtd, *J* = 6.6, 8.3, 12.9 Hz, 1H), 7.28 – 7.08 (m, 4H), 4.81 (s, 2H), 4.51 – 4.27 (m, 2H), 2.99 – 2.69 (m, 3H), 1.72 – 1.57 (m, 2H), 1.31 – 1.18 (m, 3H), 1.11 – 0.99 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.2, -155.8 (d, *J* = 21.7 Hz). HRMS(ESI-TOF): calcd for $C_{25}H_{24}F_3N_9$ $(M+H)^+$ 508.2180, found 508.2166.

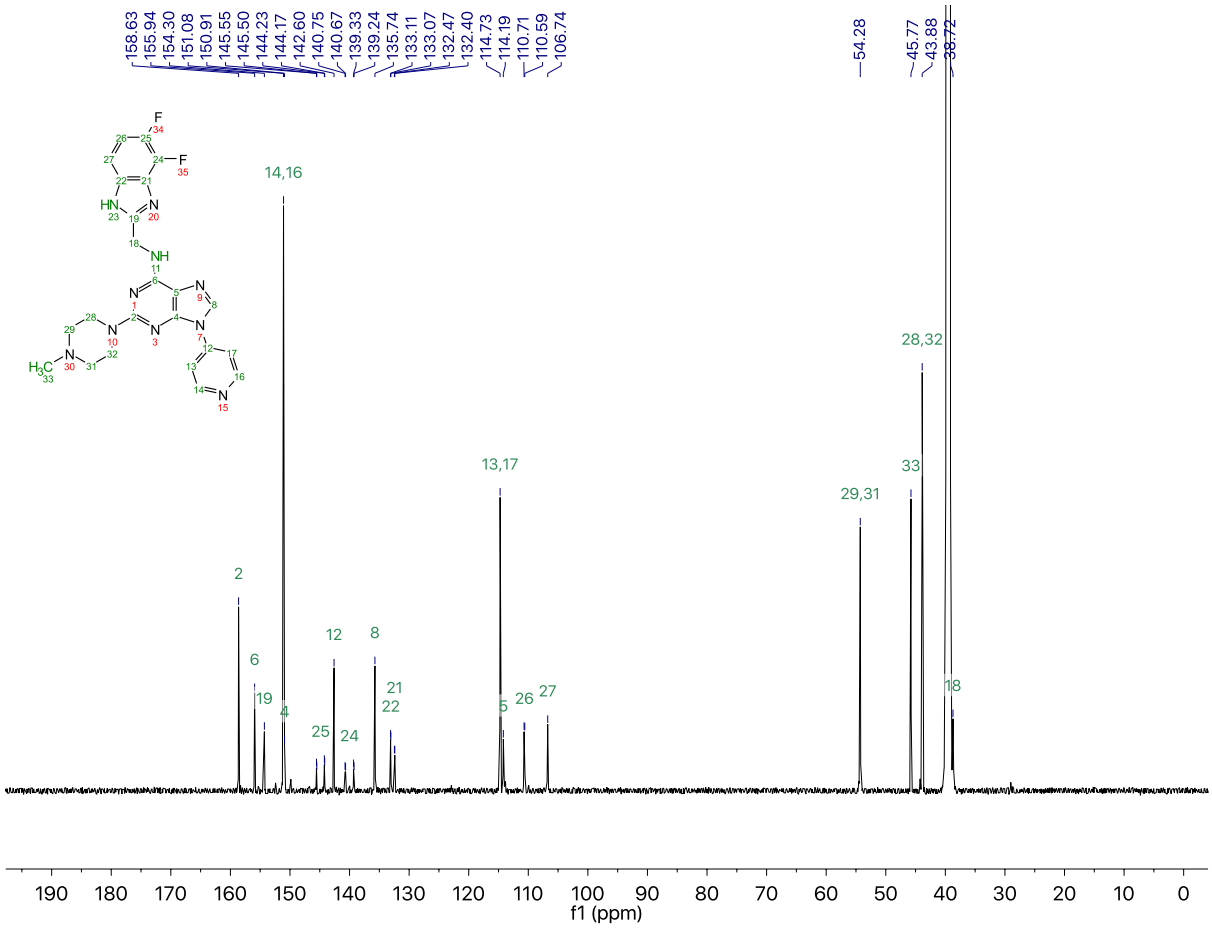
1-(6-(((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)amino)-9-(3-fluorophenyl)-9H-purin-2-yl)piperidin-4-one (75). Compound **75** was prepared using general procedure in 60% yield over three steps (including deprotection) as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.43 (s, 1H), 8.37 (s, 1H), 7.91 (dt, *J* = 2.3, 10.6 Hz, 1H), 7.86 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.61 (td, *J* = 6.5, 8.2 Hz, 1H), 7.23 (qd, *J* = 2.9, 9.0, 9.5 Hz, 2H), 7.16 (dt, *J* = 7.9, 11.5 Hz, 1H), 4.90 – 4.72 (m, 2H), 3.87 (t, *J* = 6.2 Hz, 4H), 2.10 (s, 4H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 208.0, 162.2 (d, *J* = 243.9 Hz), 158.0, 155.9, 154.6, 150.7, 144.9 (dd, *J* = 10.0, 233.4 Hz), 140.1 (d, *J* = 251.9 Hz), 137.1 (d, *J* = 11.2 Hz), 136.7, 133.2, 132.6, 131.3 (d, *J* = 9.1 Hz), 117.6, 114.3, 113.4 (d, *J* = 20.8 Hz), 110.6 (d, *J* = 22.0 Hz), 109.0 (d, *J* = 26.4 Hz), 107.0, 43.3, 40.2, 38.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -111.0, -150.2, -155.7 (d, *J* = 21.8 Hz).HRMS(ESI-TOF): calcd for $C_{24}H_{19}F_3N_8O$ $(M+H)^+$ 493.1707, found 493.1701.

N-((4,5-difluoro-1H-benzo[d]imidazol-2-yl)methyl)-9-(3-fluorophenyl)-2-(4-(methylamino)piperidin-1-yl)-9H-purin-6-amine (76, TFA salt). Compound **76** was prepared using general procedure in 74% yield over three steps (including Boc deprotection) as a beige solid. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.36 (s, 1H), 7.90 (dt, *J* = 2.3, 10.6 Hz, 1H), 7.84 (dd, *J* = 2.0, 8.1 Hz, 1H), 7.61 (td, *J* = 6.6, 8.2 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.19 (qd, *J* = 4.3, 8.2, 9.0 Hz, 1H), 4.83 (s, 2H), 4.61 – 4.47 (m, 2H), 3.14 (s, 1H), 2.79 – 2.69 (m, 2H), 2.48 – 2.45 (m, 3H), 1.87 – 1.70 (m, 2H), 1.21 – 1.01 (m, 2H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 162.3 (d, *J* = 243.9 Hz), 158.1, 156.0, 154.3, 150.7, 145.1 (d, *J* = 234.9 Hz), 139.1 (d, *J* = 233.8 Hz), 137.1 (d, *J* = 11.0 Hz), 136.7, 134.1, 133.3, 131.3 (d, *J* = 9.3 Hz), 117.6, 114.0, 113.4 (d, *J* = 20.7 Hz), 111.0, 109.0 (d, *J* = 25.8 Hz), 108.1, 55.4, 42.2, 38.7, 29.1, 27.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ -74.4 (TFA), -111.0, -149.5, -155.3 (d, *J* = 23.7 Hz). HRMS(ESI-TOF): calcd for $C_{25}H_{24}F_3N_9$ $(M+H)^+$ 508.2180, found 508.2167.

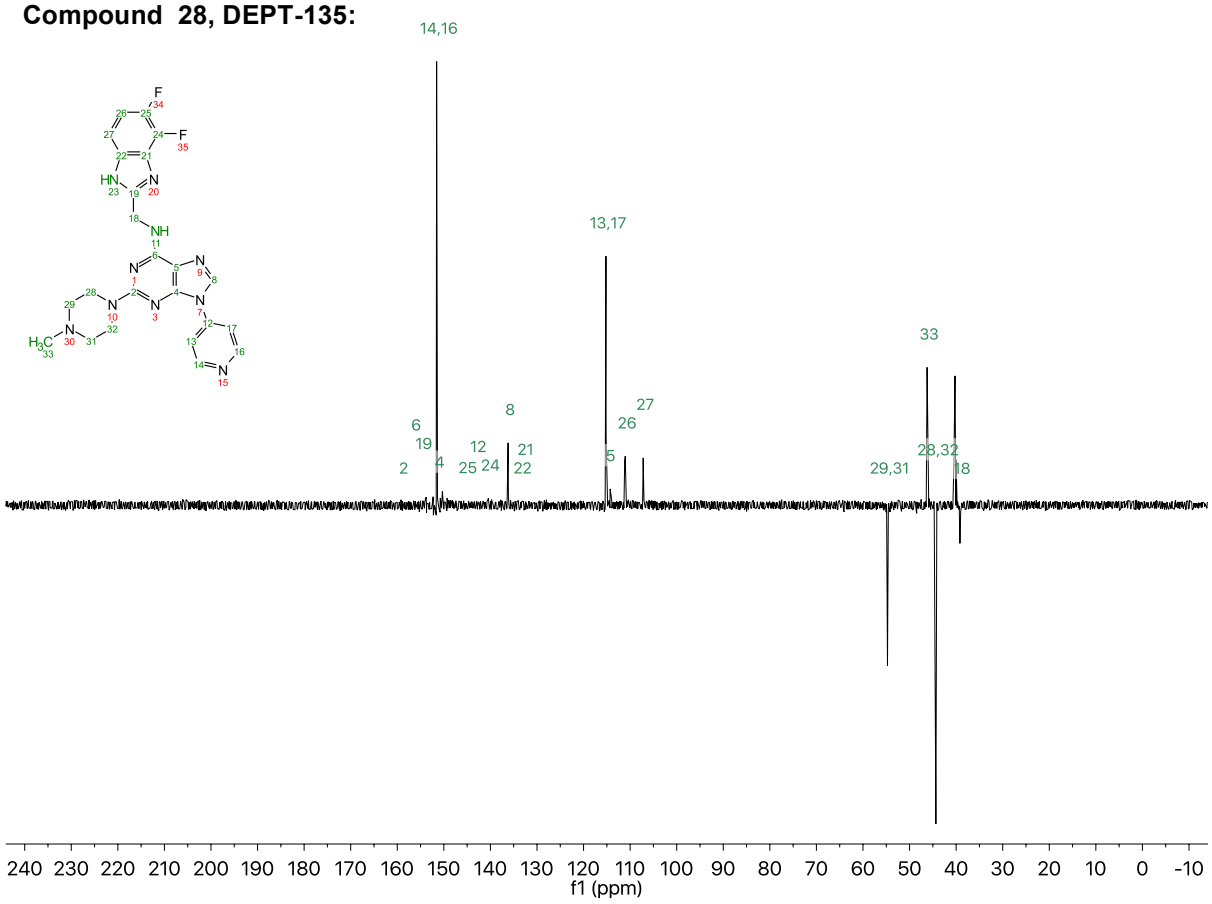
Compound 28, ^{1}H NMR:



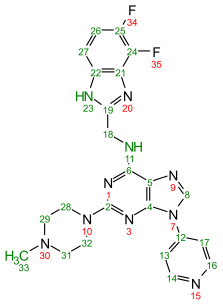
Compound 28, ^{13}C NMR:



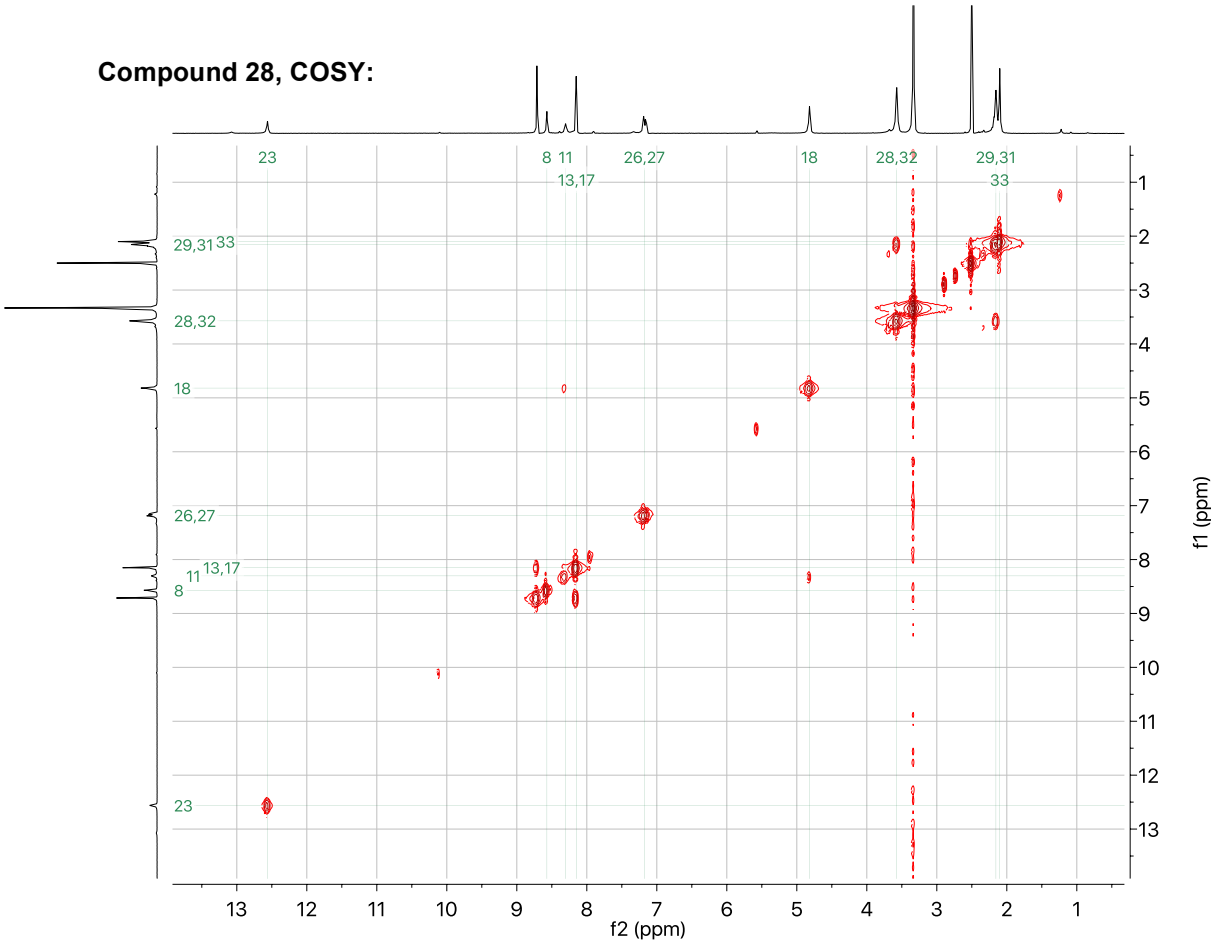
Compound 28, DEPT-135:



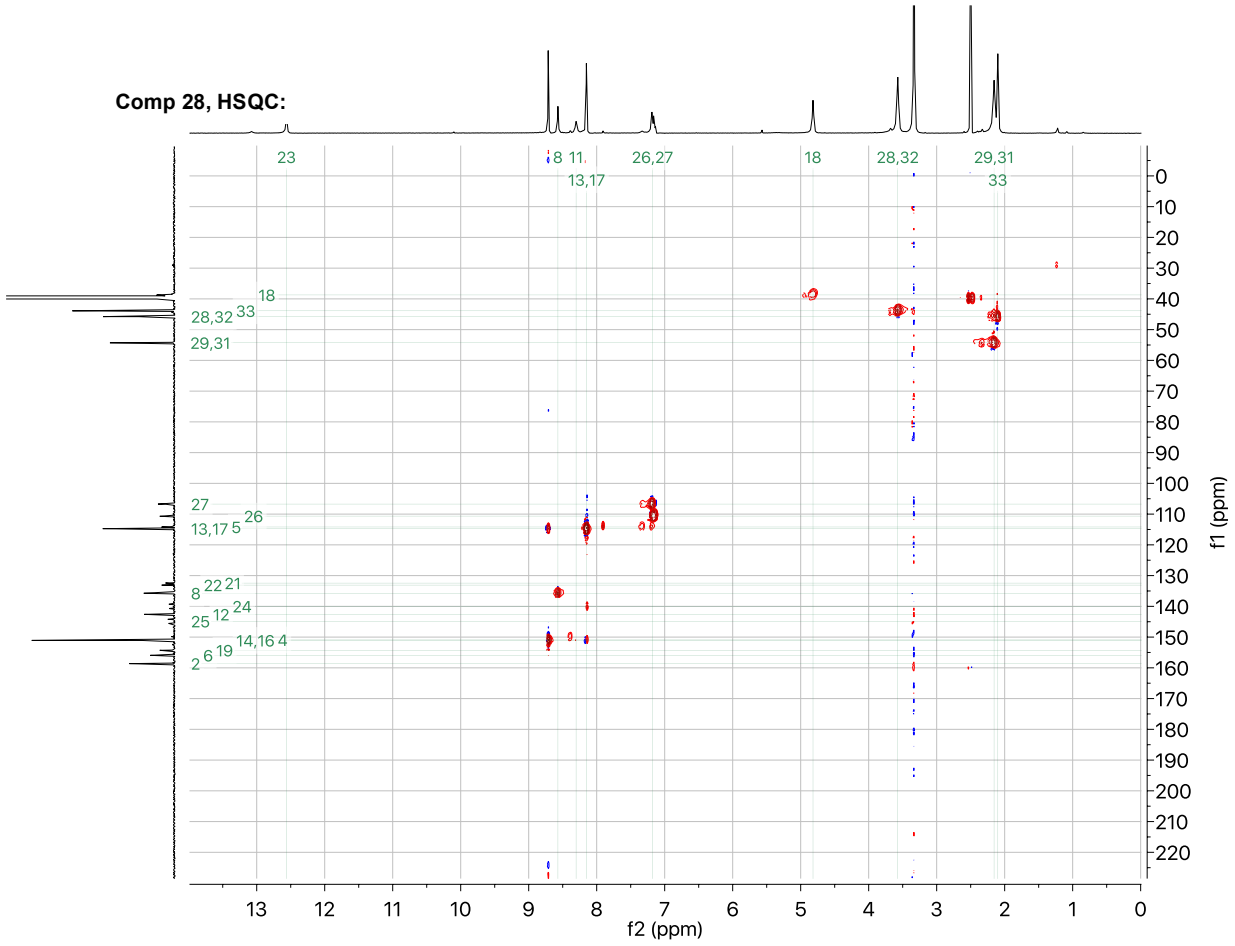
Compound 28, ^{19}F NMR:



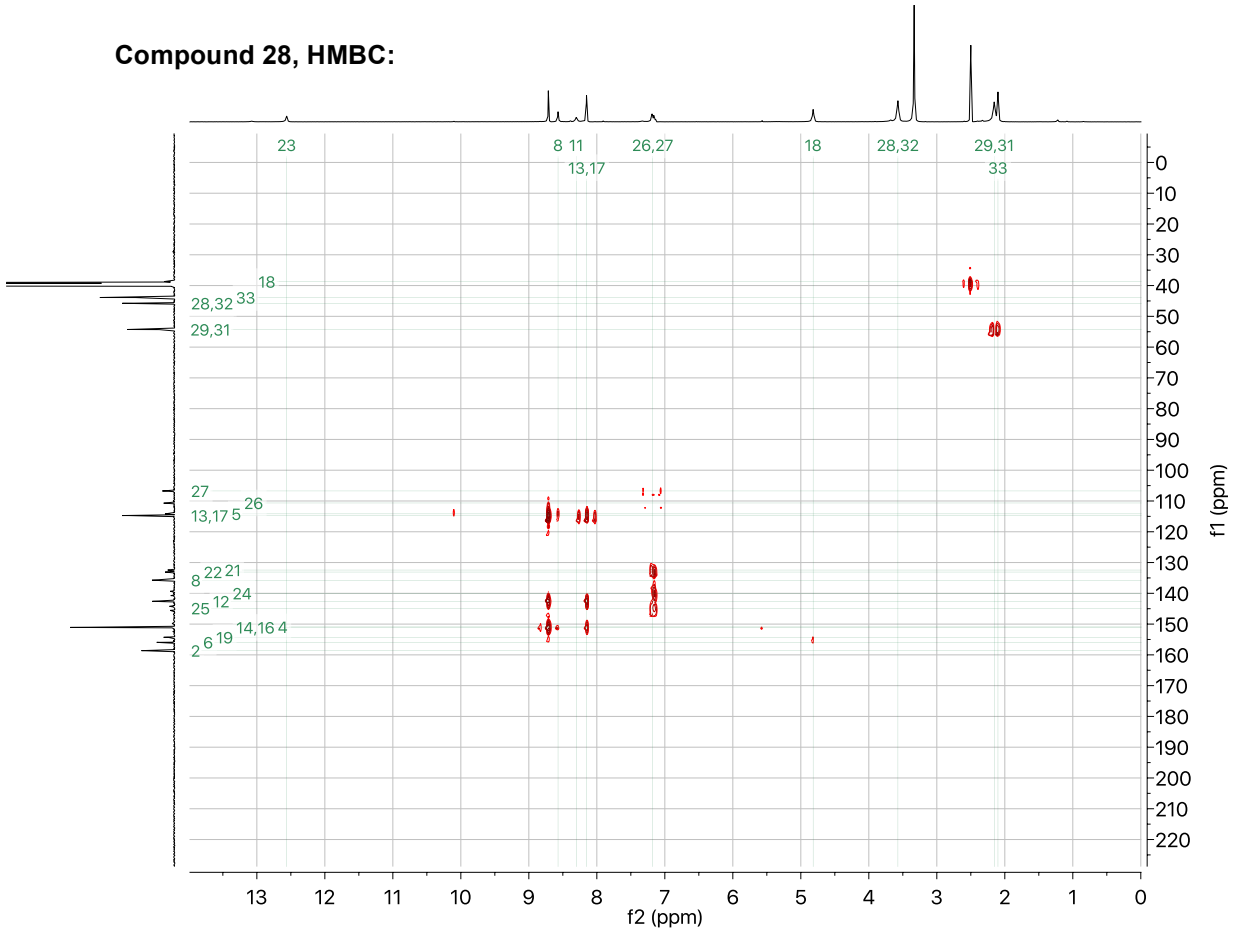
Compound 28, COSY:



Comp 28, HSQC:


23
8 11
13,17
26,27
18
28,32
29,31
33
18
28,32 33
29,31
27
13,17 5 26
8 22 21
25 12 24
2 6 19 14,16 4
f2 (ppm)
f1 (ppm)

Compound 28, HMBC:



Cmpd	CK1δ IC_{50} (nM)	CK1ε IC_{50} (nM)	MDA-MB-231 EC_{50} (nM)	PAMPA $P_{app} \cdot 10^{-6}$	Solubility (μM)	Microsome stability, min (H/M/R)	CYP % inhibition 1A2	2C9	2D6	3A4
11	> 10000	> 10000								
12	4010	6560				16 / 3 / 5	40	49	14	76
13	44	260	26		0.1	18 / 5 / 17	12	62	-3	37
14	535	395								
15	4520	990								
16	48	80	101		0.4	17 / 5 / 10	23	89	47	72
17	53	145	68		0.1	26 / 5 / 27	-48	42	-2	38
18	10	16	38		0.3	12 /3 /6	-41	73	8	64
19	525	250								
20	110	135	6280							
21	230	175	9790							
22	47	125	75			13 / 2 / 4	46	41	47	34
23	54	105	43			15 / 2 / 6	91	84	53	62
24	700	1145								
25	335	500			0.1	25 / 5 / 9	96	95	67	86
26	260	860								
27	440	1905								
28	175	315	28		28	36 / 4 / 11	-1	21	47	44
29	260	385			0.4	20 / 5 / 9	61	53	50	74
30	295	660								
31	145	245	8		0.1	32 / 12 / 9	-9	31	10	18
32	1120	860								
33	> 9900	1195								
34	295	385								
35	1195	245								
36	1565	2955								
37	1155	2095								
38	825	1840								
39	335	630								
40	520	715				9 /3/ 10	97	96	79	86
41	430	915								
42	100	320	< 1		1.6	5 /1 / 4	30	44	67	60
43	50	105	4			55 / 16 /26	90	91	80	88
44	80	255	6		2.8	19 / 5 / 18				
45	610	335								
46	520	975								
47	625	1765								
48	200	660	1040							

Cmpd	CK1δ IC_{50} (nM)	CK1ε IC_{50} (nM)	MDA-MB-231 EC_{50} (nM)	PAMPA $P_{app} \cdot 10^{-6}$	Solubility (μM)	Microsome stability, min (H/M/R)	CYP % inhibition 1A2	2C9	2D6	3A4
49	175	340	60		1.1	22 / 7 / 9	91	92	62	85
50	42	150	> 10000	< 0.1	0.1	16 / 3 / -	59	61	31	-38
51	9	115	> 10000	< 0.1	0.1	30 / 9 / -	66	52	42	-12
52	215	280	1400	< 0.1						
53	> 10000	> 10000		< 0.1						
54	> 10000	> 10000		< 0.1						
55	245	380	1850	0.3						
56	50	54	7160	7.1						
57	180	205	> 10000	0.1						
58	85		> 10000	6.8			68	31	1	-17
59	98		> 10000				74	74	18	74
60	80		6460							
61	37		> 10000			6 / 2 / .	37	35	-12	-31
62	89		> 10000	< 0.1		15 / 6 / -	85	67	38	-51
63	55	170	580							
64	76	205	185							
65	185	310	130							
66	175	370	145							
67	230	205	190							
68	69	50	130							
69	320	375	1290							
70	830	1230	-							
71	915	1310	-							
72	1030	2010	-							
73	1180	1200	625							
74	160	305	175							
75	150	265	390							
76	620	655	195							

Matrix of Compound Screen for compound 17

Gene Symbol	%Ctrl @ 10000nM
ABL1(E255K)-phosphorylated	93
ABL1(T315I)-phosphorylated	92
ABL1-nonphosphorylated	97
ABL1-phosphorylated	83
ACVR1B	86
ADCK3	87
AKT1	92
AKT2	91
ALK	95
AURKA	100
AURKB	91
AXL	82
BMPR2	99
BRAF	100
BRAF(V600E)	100
BTK	100
CDK11	69
CDK2	97
CDK3	100
CDK7	46
CDK9	78
CHEK1	100
CSF1R	98
CSNK1D	5.2
CSNK1G2	95
DCAMKL1	100
DYRK1B	51
EGFR	95
EGFR(L858R)	99
EPHA2	98
ERBB2	86
ERBB4	87
ERK1	100
FAK	85
FGFR2	90
FGFR3	85
FLT3	17
GSK3B	79
IGF1R	97
IKK-alpha	100
IKK-beta	94
INSR	93
JAK2(JH1domain-catalytic)	91
JAK3(JH1domain-catalytic)	100
JNK1	91
JNK2	83
JNK3	93
KIT	70

Gene Symbol	%Ctrl @ 10000nM
KIT(D816V)	100
KIT(V559D,T670I)	98
LKB1	93
MAP3K4	62
MAPKAPK2	85
MARK3	81
MEK1	79
MEK2	91
MET	99
MKNK1	100
MKNK2	90
MLK1	98
p38-alpha	91
p38-beta	96
PAK1	81
PAK2	66
PAK4	96
PCTK1	59
PDGFRA	99
PDGFRB	56
PDPK1	71
PIK3C2B	100
PIK3CA	99
PIK3CG	100
PIM1	89
PIM2	94
PIM3	87
PKAC-alpha	85
PLK1	100
PLK3	95
PLK4	91
PRKCE	100
RAF1	99
RET	96
RIOK2	84
ROCK2	84
RSK2(Kin.Dom.1-N-terminal)	75
SNARK	93
SRC	78
SRPK3	80
TGFBR1	100
TIE2	73
TRKA	74
TSSK1B	66
TYK2(JH1domain-catalytic)	98
ULK2	90
VEGFR2	99
YANK3	88
ZAP70	100

%Ctrl Legend

0≤x<.1	.1≤x<1	1≤x<10	10≤x<35	x≥35