Supporting Information

Diego González Cabrera,[a] Frederic Douelle,[a] Yassir Younis,[a] Tzu-Shean Feng,[a] Claire Le Manach,[a] Aloysius T. Nchinda,[a] Leslie J. Street,[a] Christian Scheurer,[b,f] Jolanda Kamber,[b,f] Karen L. White,[c] Oliver D. Montagnat,[c] Eileen Ryan,[c] Kasiram Katneni,[c] K. Mohammed Zabiulla,[d] Jayan T. Joseph,[d] Sridevi Bashyam,[d] David Waterson,[e] Michael J. Witty,[e] Susan A. Charman,[c] Sergio Wittlin,[b,f] and Kelly Chibale* [a,g]

[a]Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa; [b]Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland; [c]Centre for Drug Candidate Optimisation, Monash University (Parkville campus), 381 Royal Parade, Parkville, VIC 3052, Australia; [d]Syngene International Ltd., Biocon Park, Plot No. 2 & 3. Bommasandra IV Phase, Jigani Link Road, Bangalore 560099, India; [e]Medicines for Malaria Venture, ICC, Route de Pré-Bois 20, PO Box 1826, 1215 Geneva, Switzerland; [f]University of Basel, 4002 Basel, Switzerland; [g]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa.

Contents:

A. Additional Spectroscopic Data.

LC purity traces were performed using one of these methods:

Method 1:

- Method 1A: Using a water Xbridge C18 column, 20 µL injection volume, flow 1.2 mL/min; gradient: 10 – 100% B in 9 min (hold 3 min), 100 – 10% in 1 min (hold 8 min) (Mobile phase A: 10 mM ammonium formate in H_2O and Mobile phase B: 10 mM ammonium formate in Methanol) with a 2998 photodiode array detector.
- Method 1B: Using a Phenomenex-Luna 3u C18(2) 100A column, 10 µL injection volume, flow 1 mL/min; gradient: 5 – 95% B in 7 min (hold 3 min), 95 – 5% in 3 min (hold 5 min) (Mobile phase A: H_2O and Mobile phase B: 0.1% acetic acid in Acetonitrile) with a Spectra Series UV100 detector set at 254 nm.

Method 2:

- Method 2A: Using a Hypersil BDS C18 column, 1 µL injection volume, flow 0.7 mL/min; gradient: 10 – 70% B in 20 min, 70 – 100% B in 10 min (hold 5 min), 100 – 10% in 3 min (hold 7 min) (Mobile phase A: 0.1% TFA in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).

- Method 2B: Using a Symmetry C18 column, 1 µL injection volume, flow 1 mL/min; gradient: 30 – 100% B in 15 min (hold 5 min), 100 – 30% in 3 min (hold 5 min) (Mobile phase A: 10 mM Ammonium Acetate in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).
- Method 2C: Using a Kromosil BDS C18 column, 3 µL injection volume, flow 1 mL/min; gradient: 30 – 100% B in 15 min (hold 8 min), 100 – 30% in 5 min (hold 4 min) (Mobile phase A: 10 mM Ammonium Acetate in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).
- Method 2D: Using a Hypersil BDS C18 column, 1.5 µL injection volume, flow 1 mL/min; gradient: 30 – 100% B in 15 min (hold 5 min), 100 – 30% in 3 min (hold 5 min) (Mobile phase A: 0.1% TFA in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).
- Method 2E: Using an Atlantis d C18 column, 2 µL injection volume, flow 1.2 mL/min; gradient: 10 – 95% B in 4 min (hold 1 min), 95 – 10% in 0.5 min (hold 1.5 min) (Mobile phase A: 0.1% Acetic Acid in H_2O and Mobile phase B: Methanol) with PDA – maximum chromatogram (210 – 400 nm).
- Method 2F: Using a Phenomenox Luna C18, 5 µL injection volume, flow 1 mL/min; gradient: 30 – 100% B in 15 min (hold 5 min), 100 – 30% in 5 min (hold 4 min) (Mobile phase A: 10 mM Ammonium Acetate in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).
- Method 2G: Using BDS C18 column, 5 µL injection volume, flow 0.7 mL/min; gradient: 30 – 100% B in 15 min (hold 5 min), 100 – 30% in 3 min (hold 5 min) (Mobile phase A: 0.1% TFA in H_2O and Mobile phase B: Acetonitrile) with PDA – maximum chromatogram (210 – 400 nm).

3-(6-methoxypyridin-3-yl)-5-(3-*N*,*N*-(dimethylsulfonamide)phenyl)pyridin-2-amine **3**. According to GP1: Yield 0.14 g, 68%; mp 137-139 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.39 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.82 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.72-7.70 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.99 (br s, 2H), 3.88 (s, 3H), 2.60 (s, 6H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 163.4, 157.8, 147.1, 146.4, 142.7, 140.1, 136.6, 132.9, 128.7, 127.4, 126.5, 123.6, 1117.8, 111.1, 53.7, 38.1; Anal. RP-HPLC $\mathbf{t}_R$ = 12.85 min (method 1A, purity 99.70%); LRMS (APCI): *m/z* = 384.1 [M$^+$] (anal. calcd for $C_{19}H_{20}N_4O_3S^+$: *m/z* = 384.13).

3-(6-methoxypyridin-3-yl)-5-(4-*N*-(methylsulfonamide)phenyl)pyridin-2-amine **4**. According to GP1: Yield 0.11 g, 54%; mp 95-97 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.41 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 0.8 Hz, 2.4 Hz, 1H), 7.93-7.87 (m, 2H), 7.85 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.79-7.75 (m, 2H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.40 (br s, 2H), 3.91 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8, 157.1, 146.5, 145.7, 141.5, 139.5, 136.9, 136.0,127.2, 126.9, 125.8, 123.3, 117.1, 110.5, 53.1, 28.6; Anal. RP-HPLC $\mathbf{t}_R$ = 11.88 min (method 1A, purity 99.35%); LRMS (APCI): *m/z* = 370.0 [M$^+$] (anal. calcd for $C_{18}H_{18}N_4O_3S^+$: *m/z* = 370.11).

3-(6-methoxypyridin-3-yl)-5-(4-(sulfonamide)phenyl)pyridin-2-amine **5**. According to GP1: Yield 0.13 g, 50%; mp 190-192 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.20 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.76 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.65-7.53 (m, 5H), 7.30 (br s, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.53 (br s, 2H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 163.2, 157.4, 147.7, 146.8, 139.8, 138.1, 133.8, 132.5, 132.0, 129.2, 127.8, 117.6, 113.5, 111.0, 53.6; Anal. RP-HPLC $\mathbf{t}_R$ =

10.95 min (method 1A, purity 99.63%); LRMS (APCI): *m/z* = 356.1 [M^+] (anal. calcd for $C_{17}H_{16}N_4O_3S^+$: *m/z* = 356.09).

3-(6-methoxypyridin-3-yl)-5-(4-*N*-(cyclopropylsulfonamide)phenyl)pyridin-2-amine 6. According to GP1: Yield 0.18 g, 63%; mp 101-103 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.41 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.91-7.89 (m, 3H), 7.85 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.05 (s, 2H), 3.90 (s, 3H), 2.11-2.08 (m, 1H), 0.47 (q, *J* = 4.2 Hz, 2H), 0.40 (q, *J* = 4.2 Hz, 2H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 162.8, 157.1, 146.5, 145.7, 141.5, 139.5, 137.9, 136.0, 127.3, 126.9, 125.7, 123.2, 117.2, 110.5, 53.1, 24.1, 5.1; Anal. RP-HPLC t_R = 8.85 min (method 2C, purity 94.11%); LRMS (APCI): *m/z* = 397.0 [$(M+H)^+$] (anal. calcd for $C_{20}H_{20}N_4O_3S^+$: *m/z* = 396.13).

3-(6-methoxypyridin-3-yl)-5-(4-(morpholinylsulfonyl)phenyl)pyridin-2-amine 7. According to GP1: Yield 0.15 mg, 67%; mp 184-186 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.44 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.85 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.75-7.72 (m, 3H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.05 (br s, 2H), 3.91 (s, 3H), 3.64 (t, *J* = 4.4 Hz, 4H), 2.90 (t, *J* = 4.4 Hz, 4H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 162.9, 157.3, 146.5, 145.9, 142.4, 139.5, 136.1, 131.9, 128.2, 126.8, 126.0, 123.0, 117.2, 110.5, 65.2, 53.1, 45.8; Anal. RP-HPLC t_R = 12.91 min (method 1A, purity 97.85%); LRMS (APCI): *m/z* = 426.1 [M^+] (anal. calcd for $C_{21}H_{22}N_4O_4S^+$: *m/z* = 426.14).

3-(6-methoxypyridin-3-yl)-5-[4-(4-methyl-1-piperazinyl)sulfonyl]phenyl)pyridin-2-amine 8. According to GP1: Yield 0.15 mg, 62%; mp 208-210 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.43 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 0.8 Hz, 2.4 Hz, 1H), 7.95-

7.92 (m, 2H), 7.85 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.74-7.71 (m, 3H), 6.92 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 6.03 (br s, 2H), 3.91 (s, 3H), 2.91 (t, *J* = 4.4 Hz, 4H), 2.36 (t, *J* = 4.4 Hz, 4H), 2.14 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8, 157.2, 146.5, 145.9, 142.3, 139.5, 136.1, 132.4, 128.1, 126.9, 125.9, 123.0, 117.2, 110.5, 53.5, 53.1, 45.7, 45.2; Anal. RP-HPLC $\mathbf{t}_R$ = 11.54 min (method 1A, purity 94.59%); LRMS (APCI): *m/z* = 439.1 [M$^+$] (anal. calcd for $C_{22}H_{25}N_5O_3S^+$: *m/z* = 439.17).

3-(6-methoxypyridin-3-yl)-5-(4-methylsulfonamide)phenyl)pyridin-2-amine **9**. According to GP1: Yield 0.20 g, 51%; mp 124-126 ^{o}C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 9.74 (s, 1H), 8.28-8.26 (m, 2H), 7.84 (d, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.82 (br s, 2H), 3.90 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 164.0, 155.3, 146.8, 144.4, 138.9, 137.0, 136.2, 134.7, 127.4, 126.9, 125.9, 121.5, 119.0, 111.6, 53.7, 39.5; Anal. RP-HPLC t_R = 8.40 min (method 2B, purity 99.33%); LRMS (APCI): m/z = 371.0 [(M+H)$^+$] (anal. calcd for $C_{18}H_{18}N_4O_3S^+$: m/z = 370.11).

5-(3-fluoro-4-(methylsulfonyl)phenyl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine **10**. According to GP1: Yield 0.13 g, 64%; mp 203-205 ^{o}C; ^{1}H NMR (400.0 MHz, CDCl$_3$): δ = 8.44 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.87-7.82 (m, 1H), 7.81 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.79-7.73 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.11 (br s, 2H), 3.88 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 163.5, 161.1, 158.6, 158.3, 147.2, 146.8, 140.1, 136.7, 130.0, 127.2, 126.0, 122.3, 121.9, 117.7, 114.0, 111.1, 53.7, 44.4; Anal. RP-HPLC t_R = 12.37 min (method 1A, purity 99.49%); LRMS (APCI): m/z = 373.1 [M$^+$] (anal. calcd for $C_{18}H_{16}FN_3O_3S^+$: m/z = 373.09).

5-(2-(trifluoromethyl)-4-(methylsulfonyl)phenyl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine 11. According to GP1: Yield 0.29 g, 63%; mp 166-168 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.24 (m, 1H), 8.25 (s, 1H), 8.20-816 (m, 2H), 7.94-7.87 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.01 (br s, 2H), 3.87 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 163.5, 157.7, 147.1, 146.9, 143.7, 140.6, 139.9, 138.2, 134.6, 131.3, 128.6, 127.1, 125.7, 123.1, 122.6, 116.7, 111.2, 53.8, 43.8; Anal. RP-HPLC t_R = 6.75 min (method 2D, purity 98.01%); LRMS (APCI): m/z = 424.10 [(M+H)$^+$] (anal. calcd for $C_{19}H_{16}F_3N_3O_3S^+$: m/z = 423.09).

3-(6-methoxypyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)pyridin-2-amine 12. According to GP1: Yield 0.13 g, 65%; mp 129-131 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.32 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, J = 0.8 Hz, 2.4 Hz, 1H), 7.85 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 7.79-7.75 (m, 2H), 7.65 (d, *J* = 2.4 Hz, 2H), 7.39-7.37 (m, 2H), 6.91 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 5.88 (br s, 2H), 3.91 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8, 156.7, 147.1, 146.5, 145.3, 139.5, 137.1, 135.9, 127.3, 127.0, 123.7, 121.3, 117.1, 110.5, 53.1; Anal. RP-HPLC t_R = 16.00 min (method 1A, purity 99.12%); LRMS (APCI): m/z = 361.1 [M$^+$] (anal. calcd for $C_{18}H_{14}F_3N_3O_2^+$: m/z = 361.10).

5-(4-(trifluoromethyl)phenyl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine 13. According to GP1: Yield 0.12 g, 62%; mp 138-140 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.40 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, J = 0.8 Hz, 2.4 Hz, 1H), 7.90-7.88 (m, 2H), 7.85 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.75-7.71 (m, 3H), 6.92 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 5.98 (br s, 2H), 3.91 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 162.8, 157.1, 146.5, 145.7, 141.7, 139.5, 136.0, 126.9, 126.0, 125.6 (x2), 123.3, 117.2, 110.5, 53.1;

Anal. RP-HPLC t_R = 15.90 min (method 1A, purity 98.94%); LRMS (APCI): m/z = 345.1 [M^+] (anal. calcd for $C_{18}H_{14}F_3N_3O^+$: m/z = 345.11).

3,5-bis(6-methoxypyridin-3-yl)pyridin-2-amine 14. According to GP1: Yield 0.14 g, 64%; mp 133-135 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.40 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 8.24 (d, *J* = 2.4 Hz, 1H), 7.95 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.81 (dd, *J* = 2.5 Hz, 8.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.76 (br s, 2H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 163.4, 163.1, 156.9, 147.1, 145.4, 144.1, 140.0, 137.3, 136.1, 127.6, 122.8, 117.8, 111.0, 53.7; Anal. RP-HPLC t_R = 13.23 min (method 1A, purity 98.55%); LRMS (APCI): m/z = 309.3 [$(M+H)^+$] (anal. calcd for $C_{17}H_{16}N_4O_2^+$: m/z = 308.13).

5-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine 15. According to GP1: Yield 31 mg, 28%; mp 210-212 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 9.29 (s, 1H), 8.37 (s, 1H), 8.29 (d, *J* = 2.4 Hz, 1H), 8.21-8.17 (m, 1H), 7.89-7.84 (m, 5H), 7.69 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.86 (br s, 2H), 3.89(s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 163.4, 157.2, 152.9, 147.1, 145.8, 142.7, 140.1, 137.7, 136.4, 135.8, 127.6, 127.2, 124.5, 120.3, 117.7, 111.1, 53.7; Anal. RP-HPLC t_R = 5.31 min (method 2D, purity 99.45%); LRMS (APCI): m/z = 345.0 [$(M+H)^+$] (anal. calcd for $C_{19}H_{16}N_6O^+$: m/z = 344.14).

5-(4-(1H-pyrazol-1-yl)phenyl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine 16. According to GP1: Yield 76 mg, 31%; mp 194-196 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.54 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.88-7.84 (m, 3H), 7.79-7.74 (m, 3H), 7.68 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.55 (t, *J* = 2.0 Hz, 1H), 5.88 (br s, 2H), 3.90 (s, 3H); ^{13}C NMR (100.6 MHz,

[D_6]DMSO): δ = 162.8, 156.4, 146.5, 145.0, 140.8, 139.5, 138.2, 135.7, 135.4, 127.5, 127.1, 126.4, 124.2, 118.7, 117.1, 110.5, 107.7, 53.1; Anal. RP-HPLC t_R = 10.08 min (method 2C, purity 97.58%); LRMS (APCI): m/z = 344.2 [$(M+H)^+$] (anal. calcd for $C_{20}H_{17}N_5O^+$: m/z = 343.14).

3-(6-methoxypyridin-3-yl)-5-(4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)pyridin-2-amine 17. According to GP1: Yield 0.11 g, 42%; mp 215-217 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.43 (s, 1H), 8.31 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.88-7.85 (m, 3H), 7.74 (s, 1H), 6.93 (s, 1H), 6.04 (br s, 2H), 3.91 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 163.6, 163.4, 162.8, 156.7, 146.3, 145.3, 140.5, 139.2, 135.6, 126.6, 125.9, 123.6, 121.3, 117.1, 110.2, 52.9, 10.2; Anal. RP-HPLC t_R = 5.72 min (method 2D, purity 97.76%); LRMS (APCI): m/z = 360.2 [$(M+H)^+$] (anal. calcd for $C_{20}H_{17}N_5O_2^+$: m/z = 359.14).

5-(H-imidazo[1,2-a]pyridin-6-yl)-3-(6-methoxypyridin-3-yl)pyridin-2-amine 18. According to GP1: Yield 0.20 g, 59%; mp 202-204 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.89 (s, 1H), 8.32 (dd, *J* = 2.4 Hz, 8.4 Hz, 2H), 7.88-7.84 (m, 2H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.59-7.56 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.92 (br s, 2H), 3.90 (s, 3H); Anal. RP-HPLC t_R = 7.37 min (method 2F, purity 95.49%); LRMS (APCI): m/z = 318.0 [$(M+H)^+$] (anal. calcd for $C_{18}H_{15}N_5O^+$: m/z = 317.1277).

3-(6-methoxypyridin-3-yl)-5-(1-methyl-1H-indazol-6-yl)pyridin-2-amine 19. According to GP1: Yield 0.13 g, 53%; mp 194-196 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.44 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.88 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.78-7.76 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.60 (s, 2H), 4.08 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100.6 MHz,

[D_6]DMSO): δ = 162.8, 156.4, 146.6, 145.6, 140.4, 139.5, 136.3, 135.7, 132.1, 127.1, 125.4, 122.2, 121.0, 119.1, 117.1, 110.5, 105.9, 53.1, 35.3; Anal. RP-HPLC t_R = 10.04 min (method 2F, purity 95.25%); LRMS (APCI): m/z = 332.2 [$(M+H)^+$] (anal. calcd for $C_{19}H_{17}N_5O^+$: m/z = 331.14).

3-(6-methoxypyridin-3-yl)-5-(quinolin-6-yl)pyridin-2-amine 20. According to GP1: Yield 0.14 g, 47%; mp 225-227 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.86-8.85 (m, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.37-8.33 (m, 2H), 8.28 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.89 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.99 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 162.7, 156.4, 149.7, 146.6, 146.3, 145.4, 139.2, 135.9, 135.5, 135.3, 129.1, 128.1, 127.6, 126.8, 124.2, 123.3, 121.4, 117.2, 110.2, 52.9; Anal. RP-HPLC t_R = 13.15 min (method 2B, purity 97.63%); LRMS (APCI): m/z = 329.2 [$(M+H)^+$] (anal. calcd for $C_{20}H_{16}N_4O^+$: m/z = 328.13).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)benzoic acid 21. According to GP1: Yield 0.16 g, 45%; mp 197-199 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.34 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.80 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.87 (br s, 2H), 3.87 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 168.9, 163.3, 157.4, 147.0, 146.0, 141.5, 140.0, 136.4, 131.3, 127.5, 125.6, 125.6, 124.6, 117.7, 111.0, 53.7; Anal. RP-HPLC t_R = 13.31 min (method 2A, purity 96.91%); LRMS (APCI): m/z = 322.0 [$(M+H)^+$] (anal. calcd for $C_{18}H_{15}N_3O_3^+$: m/z = 321.11).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)benzamide 22. According to GP1: Yield 0.10 g, 45%; mp 203-205 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.39 (s,

1H), 8.31 (s, 1H), 8.00 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.34 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.97 (br s, 2H), 3.91 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 167.5, 162.8, 156.8, 145.5 (x2), 140.3, 139.5, 135.9, 132.0, 128.1, 127.0, 125.0, 124.1, 117.1, 110.5, 53.16; Anal. RP-HPLC t_R = 11.13 min (method 1A, purity 99.41%); LRMS (APCI): *m/z* = 321.2 [(M+H)$^+$] (anal. calcd for $C_{18}H_{16}N_4O_2^+$: *m/z* = 320.13).

3-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)benzamide **22a**. According to GP1: Yield 52 mg, 45%; mp 214-216 ^{o}C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.38 (s, 1H), 8.31 (s, 1H), 8.12 (s, 1H), 8.07 (s, 1H), 7.87-7.77 (m, 3H), 7.73 (s, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.92 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 167.8, 162.8, 156.6, 146.5, 145.3, 139.5, 137.6, 135.9, 134.8, 128.8, 128.1, 127.1, 125.1, 124.5, 124.3, 117.1, 110.5, 53.2; Anal. RP-HPLC t_R = 5.85 min (method 2C, purity 95.76%); LRMS (APCI): *m/z* = 321.0 [(M+H)$^+$] (anal. calcd for $C_{18}H_{16}N_4O_2^+$: *m/z* = 320.13).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)-N,N-dimethylbenzamide **23**. According to GP1: Yield 0.12 g, 65%; mp 158-160 ^{o}C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 2.4 Hz, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.88 (br s, 2H), 3.98 (s, 3H), 3.09 (br s, 3H), 3.04 (br s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 169.9, 162.8, 156.7, 146.5, 145.3, 139.5, 138.6, 135.8, 134.3, 127.7, 127.0, 125.2, 124.3, 117.1, 110.5, 53.1, 33.7; Anal. RP-HPLC t_R = 12.02 min (method 1A, purity 94.87%); LR-MS (APCI): m/z = 349.1 [(M+H)$^+$] (anal. calcd for $C_{20}H_{20}N_4O_2^+$: m/z = 348.16).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)-N-methylbenzamide 24. According to GP1: Yield 0.10 g, 56%; mp 157-159 °C; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 0.8 Hz, 2.4 Hz, 1H), 8.18 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.39-7.35 (m, 2H), 6.90 (dd, *J* = 0.8 Hz, 8.4 Hz, 1H), 6.61-6.57 (m, 2H), 5.63 (q, 5.2 Hz, 1H), 5.55 (br s, 2H), 3.91 (s, 3H), 2.70 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 166.2, 162.8, 156.8, 146.6, 145.4, 140.1, 139.5, 135.9, 132.3, 127.6, 127.0, 125.1, 124.1, 117.1, 110.5, 53.2, 26.2; Anal. RP-HPLC t_R = 14.28 min (method 1A, purity 99.82%); LR-MS (APCI): m/z = 334.12 [$(M+H)^+$] (anal. calcd for $C_{19}H_{18}N_4O_2^+$: m/z = 334.14).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)-N-(3-hydroxypropyl)benzamide 25. According to GP1: Yield 0.25 g, 61%; mp 105-107 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.45 (s, 1H), 8.38 (s, 1H), 8.30 (s, 1H), 7.88-7.84 (m, 3H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.96 (s, 2H), 4.48 (t, *J* = 5.2 Hz, 1H), 3.90 (s, 3H), 3.46 (q, *J* = 5.2 Hz, 2H), 3.31 (s, 2H), 1.68 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 165.9, 162.9, 156.8, 146.6, 145.5, 140.1, 139.5, 135.9, 132.4, 127.7,126.4, 125.1, 124.1, 117.2, 110.5, 58.6, 53.2, 36.6, 32.4; Anal. RP-HPLC t_R = 6.40 min (method 2F, purity 98.78%); LR-MS (APCI): m/z = 379.0 [$(M+H)^+$] (anal. calcd for $C_{21}H_{22}N_4O_3^+$: m/z = 378.17).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)-N-(2-morpholinoethyl)benzamide 26. According to GP1: Yield 0.15 g, 66%; mp 94-96 °C; ^{1}H NMR (400.0 MHz, [D_6]DMSO): δ = 8.44-8.39 (m, 2H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.89-7.84 (m, 3H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.97 (s, 2H), 3.91 (s, 3H), 3.57 (s, 4H), 3.40-3.38 (m, 2H), 2.49-2.42 (m, 6H); ^{13}C

NMR (100.6 MHz, [D_6]DMSO): δ = 165.7, 162.8, 156.8, 146.5, 145.4, 140.2, 139.5, 135.9, 132.3, 127.7, 126.6, 125.1, 124.0, 117.1, 110.5, 66.2, 57.3, 53.3, 53.1, 36.5; Anal. RP-HPLC t_R = 5.89 min (method 2C, purity 95.29%); LR-MS (APCI): m/z = 434.0 [$(M+H)^+$] (anal. calcd for $C_{24}H_{27}N_5O_3^+$: m/z = 433.21).

4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide 27. According to GP1: Yield 0.15 g, 68%; mp 164-166 °C;1H NMR (400.0 MHz, [D_6]DMSO): δ = 13.14 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 2H), 8.14 (s, 1H), 7.91-7.85 (m, 3H), 7.66 (s, 1H), 7.56-7.54 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.94 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 165.7, 162.8, 156.8, 146.5, 145.4, 140.1, 139.5, 135.9, 132.3, 127.7, 127.0, 125.0, 124.0, 117.1, 110.5, 54.9, 53.6, 53.1, 38.6, 23.1; Anal. RP-HPLC t_R = 11.79 min (method 2A, purity 96.19%); LR-MS (APCI): m/z = 322.0 [$(M+H)^+$] (anal. calcd for $C_{24}H_{27}N_5O_3^+$: m/z = 321.11).

(4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)phenyl)(4-methylpiperazin-1-yl)methanone 28. According to GP1: Yield 0.10 g, 44%; mp 88-90 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.61-7.39 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.69 (br s, 2H), 3.97 (s, 3H), 3.89-3.37 (m, 4H), 2.42 (br s, 4H), 2.31 (s, 3H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 168.8, 162.8, 156.7, 146.5, 145.3, 139.5, 138.8, 135.9, 133.8, 127.6, 127.0, 125.4, 124.2, 117.1, 110.5, 54.5, 53.2, 45.5, 39.5; Anal. RP-HPLC t_R = 9.56 min (method 1A, purity 99.17%); LR-MS (APCI): m/z = 404.2 [$(M+H)^+$] (anal. calcd for $C_{23}H_{25}N_5O_2^+$: m/z = 403.20).

(4-(6-amino-5-(6-methoxypyridin-3-yl)pyridin-3-yl)phenyl)(morpholino)methanone 29. According to GP1: Yield 0.17 g, 60%; mp 164-

166 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.35 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.86 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.89 (br s, 1H), 3.92 (s, 3H), 3.68-3.42 (m, 8H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 168.9, 162.8, 156.7, 146.5, 145.3, 139.5, 138.9, 135.8, 133.4, 127.8, 127.0, 125.4, 124.2, 117.1, 110.5, 66.1, 53.2, 47.6; Anal. RP-HPLC t_R = 11.89 min (method 1A, purity 94.00%); LR-MS (APCI): m/z = 391.2 [(M+H)$^+$] (anal. calcd for $C_{22}H_{22}N_4O_3^+$: m/z = 390.17).

5-bromo-3-(6-methoxypyridin-3-yl)pyridin-2-amine 30. To a solution of 5-bromo-3-iodopyridin-2-amine[5] (10.00 g, 33.4 mmol) in 1,4-dioxane (100 mL), 6-methoxypyridin-3-yl-3-boronic acid (5.62 g, 36.8 mmol) was added. The mixture was thoroughly degassed with nitrogen for 15 min, at which time $Pd(PPh_3)_2Cl_2$ (1.64 g, 2.30 mmol) was added under an atmosphere of nitrogen, followed by (1M) aqueous K_2CO_3 (34.01 mL, 34.01 mmol). The reaction mixture was stirred at 90 °C for 14 h, poured into H_2O (150 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The remaining residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate in a 8:2 v/v ratio as eluent to furnish **30** as a white solid (6.7 g, 72%); mp 97-99 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.65 (dd, *J* = 2.4 Hz, 8.6 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.57 (s, 2H), 3.99 (s, 3H); LR-MS (APCI): *m/z* = 280.2 [(M+H)$^+$] (anal. calcd for $C_{11}H_{10}BrN_3O^+$: *m/z* = 279.00).

(4-(6-amino-5-bromopyridin-3-yl)phenyl)(morpholino)methanone 32. To a solution of 3-bromo-5-iodopyridin-2-amine[5] (0.9 g, 3.01 mmol) in 1,4-dioxane (10 mL),

4-(morpholine-4-carbonyl)phenylboronic acid (0.83 g, 3.55 mmol) was added. The mixture was thoroughly degassed with nitrogen for 15 min, at which time $Pd(PPh_3)_2Cl_2$ (0.15 g, 0.21 mmol) was added under an atmosphere of nitrogen, followed by aqueous K_2CO_3 (3.61 mL, 3.61 mmol). The reaction mixture was stirred at 90 ^oC for 14 h and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol in a 9.7:0.3 v/v ratio as eluent to furnish **32** as a white solid. Yield 0.69 g, 71%; mp 228-230 ^oC; ^1H NMR (300.1 MHz, [D_6]DMSO): δ = 8.33 (d, *J* = 1.9 Hz, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.43 (s, 2H), 3.58 (s, 8H); LR-MS (APCI): m/z = 362.1 [$(M+H)^+$] (anal. calcd for $C_{16}H_{16}BrN_3O_2^+$: m/z = 361.04).

(4-(6-amino-5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)(morpholino)methanone 33a. Compound **33a** was obtained by the same procedure using 4-(trifluoromethyl)phenylboronic acid as reagent. Yield 0.23 g, 76%; mp 103-105 ^oC; ^1H NMR (400.0 MHz, [D_6]DMSO): δ = 8.40 (d, *J* = 2.4 Hz, 1H), 7.84-7.71 (m, 7H), 7.47-7.43 (m, 2H), 5.87 (br s, 2H), 3.63-3.60 (m, 4H), 3.52 (br s, 4H); ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 168.8, 155.8, 145.7, 142.0, 138.6, 135.7, 133.5, 129.2, 127.5, 125.4, 125.2, 124.4, 122.7, 118.8, 65.9, 44.8; Anal. RP-HPLC t_R = 14.41 min (method 1A, purity 98.34%); LR-MS (APCI): m/z = 428.1 [$(M+H)^+$] (anal. calcd for $C_{23}H_{20}F_3N_3O_2^+$: m/z = 427.15).

(4-(6-amino-5-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-yl)phenyl)(4-methylpiperazin-1-yl)methanone 34a. According to GP3: Yield 0.13 g, 42%; mp 70-72 ^oC; ^1H NMR (400.0 MHz, [D_6]DMSO): δ = 8.39 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz,

2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.74-7.72 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.03 (s, 2H), 3.60 (br s, 4H), 2.32 (br s, 4H), 2.19 (s, 3H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 168.8, 156.1, 145.9, 142.2, 138.7, 136.0, 133.9, 129.5, 127.6, 125.7, 125.4, 124.3, 123.0, 118.9, 54.5, 47.0, 45.5, 41.7; Anal. RP-HPLC t_R = 5.83 min (method 2D, purity 99.63%); LR-MS (APCI): m/z = 441.2 [(M+H)$^+$] (anal. calcd for $C_{24}H_{23}F_3N_4O^+$: m/z = 440.18).

(4-(6-amino-5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)(piperazin-1-yl)methanone 35a. According to GP4: Yield 0.15 g, 50%; mp 100-102 °C; ^{1}H NMR (400.0 MHz, [D$_6$]DMSO): δ = 8.40 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.72-7.74 (m, 3H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.03 (s, 2H), 3.62 (br s, 4H), 2.76 (br s, 4H); ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 168.8, 156.1, 145.9, 142.2, 138.6, 136.0, 134.0, 129.5, 127.6, 125.7, 125.4, 124.3, 122.9, 118.9, 47.7, 45.3, 42.7; Anal. RP-HPLC t_R = 14.63 min (method 2A, purity 96.80%); LR-MS (APCI): m/z = 427.2 [(M+H)$^+$] (anal. calcd for $C_{23}H_{21}F_3N_4O$: m/z = 426.17).

B. In vitro *P. falciparum* assay and in vivo antimalarial efficacy studies.

Compounds were screened against multidrug resistant (K1) and sensitive (NF54) strains of P. falciparum in vitro as described by Vennerstrom et al.[1] In vivo efficacy was conducted as previously described,[1] with the modification that mice (n = 5) were infected with a GFP-transfected P. berghei ANKA strain (donated by A. P. Waters and C. J. Janse, Leiden University, The Netherlands), and parasitemia determined using standard flow cytometry techniques. Compounds were dissolved or suspended in 70/30 Tween 80/ethanol and diluted 10× with water. With the single-dose regimen, blood was collected on day 3 (72 h after infection). Samples for the quadruple-dose regimens were collected on day 4 after infection.

C. Solubility estimates and logD measurements.

Compound in DMSO was spiked into either pH 6.5 phosphate buffer or 0.01M HCl (approx pH 2.0) with the final DMSO concentration being 1%. Samples were then analysed via Nephelometry to determine a solubility range as described by Bevan and Lloyd.[2]

Partition coefficient values (logD) of the test compounds were estimated by correlation of their chromatographic retention properties against the characteristics of a series of standard compounds with known partition coefficient values. The method employed is a gradient HPLC based derivation of the method developed by Lombardo et al.[3]

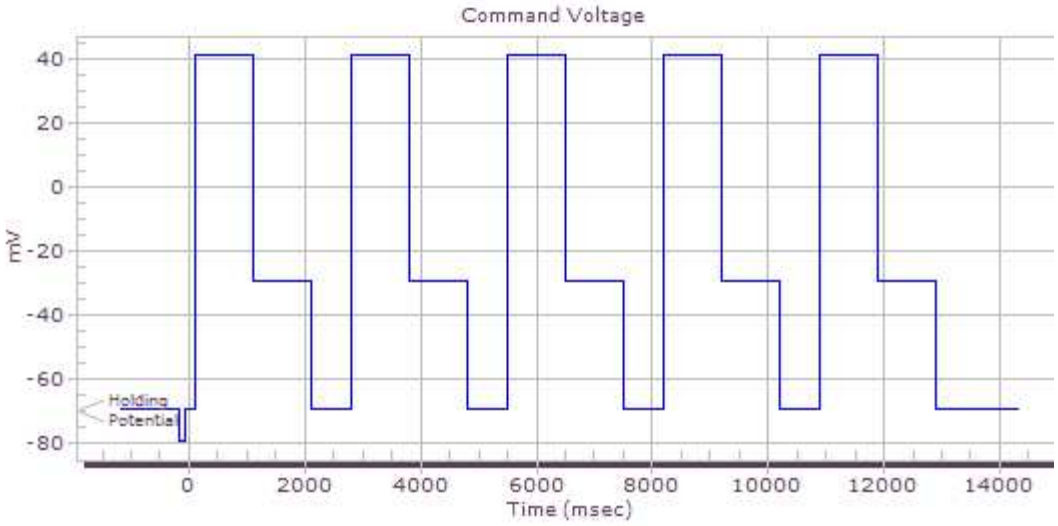
D. In vitro microsomal stability assay methods.

Compounds were incubated at 37°C at 1 μM concentration in human, rat or mouse liver microsomes (BD Gentest, Discovery Labware Inc., Woburn, MA) suspended in 0.1 M phosphate buffer (pH 7.4) at a final protein concentration of 0.4 mg per mL. Metabolic reactions were initiated by the addition of an NADPH-regenerating system (1 mg/mL NADP, 1 mg/mL glucose-6-phosphate, 1 U/mL glucose-6-phosphate dehydrogenase) and $MgCl_2$ (0.67 mg/mL) and were quenched at various time points up to 60 min by the addition of ice-cold acetonitrile. Quenched samples were centrifuged and the relative loss of parent compound over the course of the incubation was monitored by LC-MS using either a Micromass single quadrupole, triple quadrupole or TOF mass spectrometer (Waters Corporation, Milford, MA). Concentration versus time data for each compound were fitted to an exponential decay function to determine the first order rate constant for substrate depletion which was then used to calculate the degradation half-life, an *in vitro*

intrinsic clearance value and subsequently a predicted *in vivo* intrinsic clearance value according to the methods of Obach.[4] *In vivo* CL_{int} values were converted to a predicted *in vivo* hepatic extraction ratio (E_H) using the following equation: $E_H = CL_{int} / Q + CL_{int}$ where Q is liver blood flow which was assumed to be 20.7 mL/min/kg, 55.2 mL/min/kg and 90 mL/min/kg for humans, rats and mice, respectively.[5]

E. hERG method summary.

Electrophysiological recordings were made from a Chinese Hamster Lung cell line stably expressing the full length hERG channel. Single cell ionic currents were measured in the perforated patch clamp configuration (100 μg/mL amphoterocin) at room temperature (21 - 23°C) using an IonWorks Quattro instrument. The internal solution contained (mM): 140 KCl, 1 $MgCl_2$, 1 EGTA, 20 HEPES and was buffered to pH 7.3. The external solution contained (mM): 138 NaCl, 2.7 KCl, 0.9 $CaCl_2$, 0.5 $MgCl_2$, 8 Na_2HPO_4, 1.5 KH_2PO_4 also buffered to pH 7.3. Cells were clamped at a holding potential of -70mV for 30s and then stepped to +40mV for 1s. This was followed by a hyperpolarising step of 1s to -30mV to evoke the hERG tail current. This sequence was repeated 5 times at a frequency of 0.25Hz. Currents were measured from the tail step at the 5^{th} pulse, and referenced to the holding current. Compounds were then incubated for 6-7 minutes prior to a second measurement of the hERG signal using an identical pulse train.



F. Abbreviated Mouse Exposure Experiments.

Compounds were administered by oral gavage (0.2 mL/mouse) to 5-6 week old male Swiss outbred mice (n = 3 mice per compound). Two blood samples were collected from each mouse, the first via cheek-bleed (approximately 120 µL; conscious sampling), and the second via terminal cardiac puncture (0.6 mL; while mice were anaesthetized using inhaled Isofluorane). Sample times for each mouse were varied in order to obtain two plasma samples (from two different mice) at each of 0.5, 8 and 24 h post-dose. No urine samples were collected as mice were housed in bedded cages during the study. Blood was collected directly into polypropylene Eppendorf tubes containing heparin as anticoagulant and stabilisation cocktail (containing Complete® (a protease inhibitor cocktail), potassium fluoride and EDTA) to minimise potential for ex vivo degradation of test compounds any potential metabolites in blood/plasma samples. Once collected, blood samples were centrifuged immediately, supernatant plasma was removed, and plasma concentrations of test compounds were determined by LC-MS. Lower limits of quantitation (LLQ) ranged from 0.0012 µM to 0.0032 µM. No metabolite identification was conducted in this study.

G. Additional References.

(1) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Tomas, J. S.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S. and Charman, W. N. Identification of an antimalarial synthetic trioxolane drug development candidate, *Nature*, **2004**, *430*, 900-904.

(2) Bevan, C. D. and Lloyd, R. S. A High-Throughput Screening Method for the Determination of Aqueous Drug Solubility Using Laser Nephelometry in Microtiter Plates, *Anal. Chem*. **2000**, *72*, 1781-1787.

(3) Lombardo, F.; Shalaeva, M. Y.; Tupper, K. A. and Gao, F. ElogD$_{oct}$: A Tool for Lipophilicity Determination in Drug Discovery. 2. Basic and Neutral Compounds, *J. Med. Chem.* **2001**, *44*, 2490-2497.

(4) Obach, R. S. Prediction of Human Clearance of Twenty-Nine Drugs from Hepatic Microsomal Intrinsic Clearance Data: An Examination of In Vitro Half-Life Approach and Nonspecific Binding to Microsomes, *Drug Metab. Dispos.* **1999**, *27*, 1350-1359.

(5) Davies, B. and Morris, T. Physiological parameters in laboratory animals and humans, *Pharm. Res*. **1993**, *10*, 1093-1095.