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SUPPLEMENTARY MATERIAL TO

New 4-aminoquinolines as moderate inhibitors of *P. falciparum* malaria

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EXPERIMENTAL DETAILS

Melting points were determined on a Boetius PMHK apparatus and were not corrected. IR spectra were recorded on a Thermo-Scientific Nicolet 6700 FT-IR Diamond Crystal. NMR: ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 and 50 MHz, respectively) and/or a Bruker Ultrashield Advance III spectrometer (at 500 and 125 MHz, respectively) in the indicated solvent using TMS as the internal standard. Chemical shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. The elemental analysis was performed on the Vario EL III – C, H, N, S/O elemental analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). ESI MS spectra of the synthesized compounds were recorded on an Agilent Technologies 6210 Time-of-Flight LC/MS instrument in positive ion mode using CH_3CN/H_2O = 1/1 with 0.2 % HCOOH as the carrying solvent solution. The samples were dissolved in pure acetonitrile (HPLC grade). The selected values were as follows: capillary voltage = 4 kV; gas temperature = 350 °C; drying gas = 12.l min^{-1}; nebulizer pressure = 45 psig; fragmentor voltage =70 V. Compounds were analyzed for purity using Waters 1525 HPLC dual pump system equipped with an Alltech Select degasser system, and a dual λ 2487 UV-VIS detector, and Agilent 1200 HPLC system equipped with Quat Pump (G1311B), Injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+(G1315C). All analyzed compounds were >95 % pure. HPLC analysis was performed in two diverse systems for each analyzed compound. Compounds were dissolved in methanol, final concentrations were ~ 1 mg/mL. Applied HPLC methods were as follows:

Method A: Zorbax Eclipse Plus C18 2.1 × 100 mm, 1.8µ, S.N.USUXU04444 was used as the stationary phase. Eluent was made of the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analysis were performed at 330 nm for compounds **14** and **17**, and at 320 nm for compounds **15** and **16**. Flow rate was 0.5 mL/min.

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Compounds **14-17** were eluted using gradient protocol: 0–1 min 95 % A, 1–2 min 95 % A → 5 % A, 2–10 min 5 % A, 10–11 min 5 % A → 95 % A, 11–13 min 95 % A.

Method B: Zorbax Eclipse Plus C18 2.1 × 100 mm, 1.8µ, S.N.USUXU04444 was used as the stationary phase. Eluent was made of the following solvents: 0.2 % formic acid in water (A) and methanol (B). The analysis were performed at 330 nm for compounds **14** and **17**, and at 320 nm for compounds **15** and **16**. Flow rate was 0.2 mL/min.

Compounds **14-17** were eluted using gradient protocol: 0–1 min 95 % A, 1–2 min 95 % A → 5 % A, 2–10 min 5 % A, 10–11 min 5 % A → 95 % A, 11–13 min 95 % A.

General procedure

3-Bromobenzaldehyde (200 mg, 1.08 mmol) and **ACQ2 (**359 mg, 1.62 mmol) were dissolved in dry CH_2Cl_2/MeOH mixture (18 mL, 1:2 v/v), anh. AcOH (93 µL, 1.62 mmol) was added and mixture was stirred under Ar atmosphere at room temperature. After 2 h, $NaBH_4$ (245 mg, 6.48 mmol) was added and stirring at r.t. was continued for another 18 h. Solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (40 mL). The organic layer was washed with 2M NH_4OH (15 mL). The layers were separated, and water layer was extracted with CH_2Cl_2 (2×15 mL). Combined organic layers were washed with brine and dried over anh. Na_2SO_4. Finally, the solvent was removed under reduced pressure and crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH).

N-*(3-Bromobenzyl)*-N'-*(7-chloroquinolin-4-yl)ethane-1,2-diamine (**4**)*

The crude product was purified using dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). Yield: 380 mg (90 %). Pale yellow amorphous powder. m.p. 137-138 °C; IR (ATR, cm^{-1}): 3314*w*, 3184*w*, 3032*w*, 2953*s*, 2896*m*, 2843*m*, 1606*w*, 1581*s*, 1540*m*, 1450*m*, 1390*w*, 1364*m*, 1331*w*, 1279*w*, 1230*w*, 1200*w*, 1170*w*, 1141*w*, 1107*w*, 1080*w*, 1045*w*, 1009*w*, 928*w*, 891*w*, 831*w*; ^{1}H-NMR (200 MHz, $CDCl_3$, *δ* / ppm): 8.53-8.48 (1H, *m*), 7.96-7.92 (1H, *m*), 7.73-7.65 (1H, *m*), 7.52 (1H, *s*), 7.43-7.33 (2H, *m*), 7.26-7.13 (2H, *m*), 6.37-6.31 (1H, *m*), 5.84 (1H, *m*, -NH), 3.81 (2H, *s*), 3.36-3.24 (*m*, $CH_2NHCH_2C\underline{H}_2NHAr$), 3.08-2.96 (*m*, $CH_2NHC\underline{H}_2CH_2NHAr$), 1.82 (1H, *m*, -NH); ^{13}C-NMR (50 MHz, $CDCl_3$, *δ* / ppm): 152.01, 149.78, 149.05, 142.36, 134.81, 131.02, 130.29, 130.07, 128.64, 126.63, 125.32, 122.68, 121.22, 117.31, 99.16, 52.60, 46.70, 41.95; (+)ESI-HRMS (*m/z*): $[M + H]^+$ 390.03666 (error -0.15 ppm); Anal. Calcd. for $C_{18}H_{17}BrClN_3 \times 0.5H_2O$: C, 54.09; H, 4.54; N, 10.51 %. Found: C, 54.00; H, 4.34; N, 10.62 %.

N-*(3-Bromobenzyl)*-N'-*(7-chloroquinolin-4-yl)propane-1,3-diamine (**5**)*

3-Bromobenzaldehyde (200 mg, 1.08 mmol) and **ACQ3 (**381 mg, 1.62 mmol) were coupled to afford **5** (340 mg, 78 %) using AcOH (93 µL, 1.62 mmol) and $NaBH_4$ (245 mg, 6.48 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **5**: Pale yellow amorphous powder; m.p. 70-72 °C; IR (ATR, cm^{-1}): 3285*s*, 3070*m*, 2944*m*, 2848*m*, 1691*w*, 1609*w*, 1579*s*, 1539*m*, 1483*w*, 1450*m*, 1364*m*, 1329*m*, 1284*w*, 1248*w*, 1195*w*, 1139*w*, 1112*w*, 1076*w*, 988*w*, 903*w*, 857*m*, 823*w*; ^{1}H-NMR (200 MHz, $CDCl_3$, *δ* / ppm): 8.46 (1H, *d*, *J* = 5.4 Hz), 7.93-7.89 (1H, *m*), 7.55-7.31 (4H, *m*), 7.30-7.17 (3H, *m*), 6.29 (1H, *d*, *J* = 5.4 Hz), 3.80 (2H, *s*), 3.44-3.32 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2NHAr$), 2.99-2.90 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2NHAr$), 2.11 (1H, *m*, -NH), 2.01-1.87 (*m*, $CH_2NHCH_2C\underline{H}_2CH_2NHAr$); ^{13}C-NMR (50 MHz, $CDCl_3$, *δ* / ppm): 151.83, 150.43, 148.81, 141.78, 134.70, 131.28, 130.50, 130.22, 128.20, 126.94, 125.07, 122.70, 121.88, 117.38, 98.28, 53.68, 49.11, 43.74, 27.31; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ 202.52934 (error -2.36 ppm), $[M + H]^+$ 404.05203 (error -0.83 ppm); Anal. Calcd. for $4C_{19}H_{19}BrClN_3 \times 5H_2O$: C, 53.41; H, 5.07; N, 9.84 %. Found: C, 53.38; H, 4.73; N, 9.94 %.

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N-*(2-Bromobenzyl)*-N'-*(7-chloroquinolin-4-yl)propane-1,3-diamine (**6**)*

2-Bromobenzaldehyde (100 mg, 0.54 mmol) and **ACQ3** (191 mg, 0.81 mmol) were coupled to afford **6** (187 mg, 85 %) using AcOH (46 μL, 0.81 mmol) and $NaBH_4$ (123 mg, 3.24 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **6**: Yellow amorphous powder; m.p. 110-112 °C; IR (ATR, cm^{-1}): 3426*m*, 3219*m*, 3064*w*, 3009*w*, 2923*w*, 2850*w*, 1676*w*, 1610*m*, 1582*s*, 1463*m*, 1436*m*, 1383*w*, 1365*w*, 1331*w*, 1308*w*, 1280*w*, 1254*w*, 1230*w*, 1200*w*, 1167*w*, 1137*w*, 1110*w*, 1080*w*, 1023*w*, 896*w*, 852*w*, 825*w*, 802*w*; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 8.49-8.43 (1H, *m*), 7.91-7.88 (1H, *m*), 7.71 (1H, *m*, -NH), 7.64-7.57 (1H, *m*), 7.47-7.32 (3H, *m*), 7.31-7.17 (1H, *m*), 7.08-7.00 (1H, *m*), 6.31-6.25 (1H, m), 3.92 (2H, *s*), 3.45-3.34 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2NHAr$), 3.02-2.93 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2NHAr$), 2.26 (1H, *m*, -NH), 2.03-1.88 (*m*, $CH_2NHCH_2C\underline{H}_2CH_2NHAr$); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 151.83, 150.52, 148.81, 138.47, 134.55, 133.10, 130.68, 129.20, 128.14, 127.69, 124.72, 124.19, 122.21, 117.40, 98.14, 54.06, 49.12, 43.99, 27.13; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ 202.52993 (error +0.53 ppm), $[M + H]^+$ 404.05151 (error -2.12 ppm); Anal. Calcd. for $C_{19}H_{19}BrClN_3 \times 0.5H_2O$: C, 55.16; H, 4.87; N, 10.16 %. Found: C, 54.97; H, 4.53; N, 10.23 %

N-*(7-Chloroquinolin-4-yl)*-N'-*(3,4-dibromobenzyl)ethane-1,2-diamine (**7**)*

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **ACQ2** (126 mg, 0.56 mmol) were coupled to afford **7** (139 mg, 78 %) using AcOH (36 μL, 0.62 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **7**: Yellow amorphous powder; m.p. 136-139 °C; IR (ATR, cm^{-1}): 3748*w*, 3302*w*, 3074*w*, 2931*w*, 2848*w*, 2359*w*, 1611*m*, 1583*s*, 1534*w*, 1457*w*, 1371*w*, 1332*w*, 1277*w*, 810*w*; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 8.51 (1H, *d*, *J* = 5.4 Hz), 7.94 (1H, *d*, *J* = 2.0 Hz), 7.67 (1H, *d*, *J* = 9.0 Hz), 7.63 (1H, *d*, *J* = 1.9 Hz), 7.54 (1H, *d*, *J* = 8.1 Hz), 7.37 (1H, *dd*, *J* = 9.0 Hz, *J* = 2.0 Hz), 7.12 (1H, *dd*, *J* = 8.1 Hz, *J* = 1.9 Hz), 6.35 (1H, *d*, *J* = 5.4 Hz), 5.78 (1H, *m*, -NH), 3.78 (2H, *s*), 3.35-3.30 (*m*, $CH_2NHCH_2C\underline{H}_2NHAr$), 3.04-3.00 (*m*, $CH_2NHC\underline{H}_2CH_2NHAr$); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 151.92, 149.74, 148.97, 141.06, 134.89, 133.63, 133.09, 128.65, 128.17, 125.40, 124.94, 123.21, 121.09, 117.27, 99.19, 52.08, 46.83, 42.06; (+)ESI-HRMS (*m/z*): $[M + H]^+$ = 467.94639 (error -1.78 ppm); Anal. Calcd. for $C_{18}H_{16}Br_2ClN_3 \times H_2O$: C, 44.34; H, 3.72; N, 8.62 %. Found: C, 44.55; H, 3.56; N, 8.77 %.

N-*(7-Chloroquinolin-4-yl)*-N'-*(3,4-dibromobenzyl)propane-1,3-diamine (**8**)*

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **ACQ3** (134 mg, 0.57 mmol) were coupled to afford **8** (115 mg, 63 %) using AcOH (36 μL, 0.62 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **8**: Yellow amorphous powder; m.p. 111-113 °C; IR (ATR, cm^{-1}): 3269*m*, 2930*w*, 2846*w*, 1986*w*, 1610*m*, 1584*s*, 1539*w*, 1457*w*, 1369*w*, 1332*w*, 1140*w*, 809*w*; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 8.50 (1H, *d*, *J* = 5.4 Hz), 7.93 (1H, *d*, *J* = 2.1 Hz), 7.61 (1H, *d*, *J* =2.1 Hz), 7.57 (1H, *d*, *J* = 8.1 Hz), 7.51 (1H, *d*, *J* = 8.8 Hz), 7.23 (1H, *dd*, *J* = 8.8 Hz, *J* = 2.1 Hz), 7.12 (1H, *dd*, *J* = 8.1 Hz, *J* = 2.1 Hz), 7.06 (1H, *m*, -*N*H), 6.33 (1H, *d*, *J* = 5.4 Hz), 3.78 (2H, *s*), 3.42-3.38 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2NHAr$), 2.94-2.90 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2NHAr$), 1.98-1.91 (*m*, $CH_2NHCH_2C\underline{H}_2CH_2NHAr$), 1.78 (1H, *m*, -NH); ^{13}C-NMR (125 MHz, $CDCl_3$, δ / ppm): 152.00, 150.23, 149.02, 140.63, 134.74, 133.77, 133.33, 128.57, 128.44, 125.14, 125.03, 123.46, 121.54, 117.39, 98.48, 53.10, 48.91, 43.61, 27.61; (+)ESI-HRMS (*m/z*): $[M + H]^+$ = 481.96289 (error +0.02 ppm); Anal. Calcd. for $C_{19}H_{18}Br_2ClN_3$: C, 47.19; H, 3.75; N, 8.69 %. Found: C, 47.19; H, 3.80; N, 8.74 %.

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N-*(7-Chloroquinolin-4-yl)*-N'-*(3,4-dibromobenzyl)butane-1,4-diamine (**9**)*

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **ACQ4** (142 mg, 0.57 mmol) were coupled to afford **9** (130 mg, 69 %) using AcOH (36 μL, 0.62 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **9**: Pale yellow amorphous powder; m.p. 121-122 °C; IR (ATR, cm^{-1}): 3232*w*, 3114*w*, 3063*w*, 3012*w*, 2958*w*, 2874*w*, 2816*w*, 1612*w*, 1581*s*, 1550*w*, 1456*m*, 1430*w*, 1368*w*, 1341*w*, 1320*w*, 1279*w*, 1249*w*, 1147*w*, 1014*w*, 896*w*, 871*w*, 850*w*, 815*m*; ^{1}H-NMR (500 MHz, MeOD, δ / ppm): 8.32 (1H, *d*, *J* = 5.7 Hz), 8.05 (1H, *d*, *J* = 9.0 Hz), 7.75 (1H, *d*, *J* = 2.1 Hz), 7.65 (1H, *d*, *J* =2.0 Hz), 7.56 (1H, *d*, *J* = 8.2 Hz), 7.35 (1H, *dd*, *J* = 9.0 Hz, *J* = 2.1 Hz), 7.17 (1H, *dd*, *J* = 8.2 Hz, *J* = 2.0 Hz), 6.46 (1H, *d*, *J* = 5.7 Hz), 3.68 (2H, *s*), 3.36-3.30 (*m*, $CH_2NHCH_2CH_2CH_2C\underline{H}_2NHAr$), 2.63-2.58 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2CH_2NHAr$), 1.80-1.72 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2CH_2NHAr$), 1.69-1.62 (*m*, $CH_2NHCH_2C\underline{H}_2CH_2CH_2NHAr$); ^{13}C-NMR (125 MHz, MeOD, δ / ppm): 152.83, 152.49, 149.75, 142.56, 136.42, 134.88, 134.84, 130.22, 127.70, 126.05, 125.63, 124.43, 123.99, 118.89, 99.76, 53.26, 43.94, 28.14, 27.26; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ 248.49354 (error +2.55 ppm), $[M + H]^+$ 495.97832 (error -0.43 ppm); Anal. Calcd. for $C_{20}H_{20}Br_2ClN_3$: C, 48.27; H, 4.05; N, 8.44 %. Found: C, 47.94; H, 4.06; N, 8.35 %.

N-*(7-Chloroquinolin-4-yl)*-N'-*(3,4-dibromobenzyl)hexane-1,6-diamine (**10**)*

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **ACQ6** (158 mg, 0.57 mmol) were coupled to afford **10** (122 mg, 61 %) using AcOH (36 μL, 0.62 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **10**: Pale yellow amorphous powder; m.p. 105-106 °C; IR (ATR, cm^{-1}): 3211*m*, 3108*m*, 3062*m*, 2933*m*, 2848*m*, 1583*s*, 1546*m*, 1490*w*, 1451*s*, 1366*m*, 1328*w*, 1279*w*, 1256*w*, 1220*w*, 1200*w*, 1140*w*, 1113*w*, 1079*w*, 1010*w*, 900*w*, 884*w*, 850*w*, 832*w*, 811*m*; ^{1}H-NMR (500 MHz, MeOD, δ / ppm): 8.32 (1H, *d*, *J* =5.7 Hz), 8.07 (1H, *d*, *J* = 9.0 Hz), 7.75 (1H, *d*, *J* = 2.2 Hz), 7.65 (1H, *d*, *J* = 2.0 Hz), 7.57 (1H, *d*, *J* = 8.2 Hz), 7.36 (1H, *dd*, *J* = 9.0 Hz, *J* = 2.2 Hz), 7.17 (1H, *dd*, *J* = 8.2 Hz, *J* = 2.0 Hz), 6.46 (1H, *d*, *J* = 5.7 Hz) 3.65 (2H, *s*), 3.38-3.29 (*m*, $CH_2NH(CH_2)_5C\underline{H}_2NHAr$), 2.55-2.51 (*m*, $CH_2NHC\underline{H}_2(CH_2)_5NHAr$) 1.77-1.69 (*m*, $CH_2NH(CH_2)_4C\underline{H}_2CH_2NHAr$), 1.57-1.50 (*m*, $CH_2NHCH_2C\underline{H}_2(CH_2)_4NHAr$), 1.47-1.36 (*m*, $CH_2NH(CH_2)_2C\underline{H}_2C\underline{H}_2(CH_2)_2NHAr$); ^{13}C-NMR (125 MHz, MeOD, δ / ppm): 152.85, 152.51, 149.81, 142.58, 136.39, 134.89, 134.83, 130.23, 127.72, 126.02, 125.61, 124.43, 123.97, 118.89, 99.72, 53.29, 49.96, 44.08, 30.47, 29.44, 28.27, 28.21; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ 262.50876 (error +0.79 ppm), $[M + H]^+$ 524.00906 (error -1.46 ppm); Anal. Calcd. for $C_{22}H_{24}Br_2ClN_3$: C, 50.26; H, 4.60; N, 7.99 %. Found: C, 50.07; H, 4.66; N, 8.05 %.

N-*(3,4-Dibromobenzyl)*-N'-*quinolin-4-ylethane-1,2-diamine (**11**)*

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **DCACQ2** (106 mg, 0.57 mmol) were coupled to afford **11** (120 mg, 73 %) using AcOH (112 μL, 1.94 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 9/1). **11**: Yellow oil; IR (ATR, cm^{-1}): 3257*m*, 3065*m*, 2907*m*, 2840*m*, 1581*s*, 1539*m*, 1457*m*, 1391*w*, 1336*m*, 1252*w*, 1129*w*, 1112*w*, 1013*w*, 809*m*; ^{1}H-NMR (500 MHz, $CDCl_3$, δ / ppm): 8.56-8.54 (1H, *m*), 7.99-7.97 (1H, *m*), 7.78-7.76 (1H, *m*), 7.66-7.62 (2H, *m*), 7.57-7.53 (1H, *m*), 7.48-7.43 (1H, *m*), 7.15-7.11 (1H, *m*), 6.41-6.39 (1H, *m*), 5.76 (1H, *m*, -NH), 3.79 (2H, *s*), 3.39-3.34 (*m*, $CH_2NHCH_2C\underline{H}_2NHAr$), 3.05-3.01 (*m*, $CH_2NHC\underline{H}_2CH_2NHAr$), 1.85 (1H, *m*, -NH); ^{13}C NMR (125 MHz, $CDCl_3$, δ / ppm): 150.89, 149.76, 148.24, 141.14, 133.63, 133.13, 129.75, 129.08, 128.19, 124.92, 124.77, 123.17,

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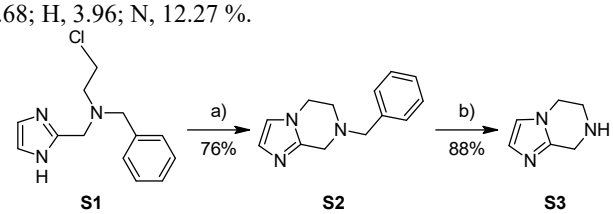
119.45, 118.86, 98.91, 52.13, 46.98, 42.15; (+)ESI-HRMS (*m/z*): $[M + H]^+$ 433.98624 (error +0.10 ppm); Anal. Calcd. for $C_{18}H_{17}Br_2N_3$: C, 49.68; H, 3.94; N, 9.66 %. Found: C, 49.29; H, 4.00; N, 9.46 %.

N-*(3,4-Dibromobenzyl)*-N'-*quinolin-4-ylbutane-1,4-diamine* ***(12)***

3,4-Dibromobenzaldehyde (100 mg, 0.38 mmol) and **DCACQ4** (123 mg, 0.57 mmol) were coupled to afford **12** (109 mg, 63 %) using AcOH (112 μL, 1.94 mmol) and $NaBH_4$ (84 mg, 2.22 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 9/1). **12**: Yellow oil; IR (ATR, cm^{-1}): 3278*m*, 3072*m*, 2928*m*, 2856*m*, 2361*w*, 1618*w*, 1581*s*, 1542*m*, 1457*m*, 1376*w*, 1341*m*, 1258*w*, 1129*w*, 1013*w*, 866*w*, 810*m*; ^{1}H NMR (500 MHz, $CDCl_3$, δ / ppm): 8.54-8.52 (1H, *m*), 7.99-7.95 (1H, *m*), 7.74-7.71 (1H, *m*), 7.62-7.58 (2H, *m*), 7.55-7.52 (1H, *m*), 7.38-7.35 (1H, *m*), 7.12-7.10 (1H, *m*), 6.40-6.38 (1H, *m*), 5.54 (1H, *m*, -NH), 3.73 (2H, *s*), 3.35-3.29 (*m*, $CH_2NHCH_2CH_2CH_2C\underline{H}_2NHAr$), 2.72-2.66 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2CH_2NHAr$), 1.88-1.80 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2CH_2NHAr$), 1.71-1.64 (m, $CH_2NHCH_2C\underline{H}_2CH_2CH_2NHAr$); ^{13}C NMR (125 MHz, $CDCl_3$, δ / ppm): 150.82, 149.82, 148.18, 141.34, 133.53, 133.11, 129.69, 128.99, 128.18, 124.76, 124.50, 122.92, 119.41, 118.70, 98.63, 52.70, 48.63, 43.10, 27.65, 26.41; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ = 231.51308 (error +3.00 ppm) $[M + H]^+$ = 462.01695 (error -1.19 ppm); Anal. Calcd. for $C_{20}H_{21}Br_2N_3$: C, 51.86; H, 4.57; N, 9.07 %. Found: C, 52.49; H, 4.83; N, 8.73 %.

N-*(3-Bromo-4-nitrobenzyl)*-N'-*(7-chloroquinolin-4-yl)propane-1,3-diamine* ***(13)***

3-Bromo-4-nitrobenzaldehyde (100 mg, 0.43 mmol) and **ACQ3** (153 mg, 0.64 mmol) were coupled to afford **13** (127 mg, 65 %) using AcOH (37 μL, 0.65 mmol) and $NaBH_4$ (99 mg, 2.62 mmol). The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH = 95/5). **13**: Yellow oil; IR (ATR, cm^{-1}): 3431*m*, 2924*m*, 2851*m*, 1581*s*, 1524*s*, 1449*m*, 1333*s*, 1280*m*, 1240*m*, 1201*w*, 1135*m*, 1078*w*, 1037*w*, 877*w*, 849*w*, 806*m*; ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 8.51-8.45 (1H, *m*), 7.92 (1H, *d*, *J* = 2.2 Hz), 7.81 (1H, *d*, *J* = 8.4 Hz), 7.72 (1H, *d*, *J* = 1.6 Hz), 7.55 (1H, *d*, *J* = 9.0 Hz), 7.39 (1H, *dd*, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.24 (1H, *dd*, *J* = 9.0 Hz, *J* = 2.2 Hz), 6.76 (1H, *m*, -NH), 6.37-6.31 (1H, *m*), 3.89 (2H, *s*), 3.47-3.35 (*m*, $CH_2NHCH_2CH_2C\underline{H}_2NHAr$), 2.96-2.86 (*m*, $CH_2NHC\underline{H}_2CH_2CH_2NHAr$), 2.15 (1H, *m*, -NH), 2.05-1.90 (*m*, $CH_2NHCH_2C\underline{H}_2CH_2NHAr$); ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 151.80, 150.19, 148.77, 148.56, 146.15, 134.86, 134.37, 128.38, 127.71, 125.87, 125.18, 121.37, 117.26, 114.84, 98.59, 52.84, 48.58, 43.13, 27.80; (+)ESI-HRMS (*m/z*): $[M + 2H]^{2+}$ 225.02285 (error +2.18 ppm), $[M + H]^+$ 449.03705 (error -0.88 ppm); Anal. Calcd. for $C_{19}H_{18}BrClN_4O_2 \times 0.5H_2O$: C, 49.75; H, 4.17; N, 12.21 %. Found: C, 49.68; H, 3.96; N, 12.27 %.



Scheme S-1.

The synthesis of **S1** has been previously reported.[1]

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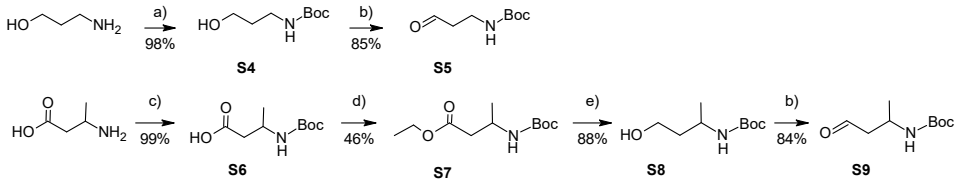
*7-Benzyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine (**S2**)*

To a suspension of NaH (673 mg, 0.017 mol, 60 % dispersion in mineral oil) in dry DMF (20 mL) was added solution of **S1** (3.82 g, 0.015 mol) in DMF (39 mL), and the mixture was stirred under Ar atmosphere at 100 °C. After 24 h, water was added and solvent was removed under reduced pressure, and crude product was purified using dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH). Yield 2.47 g (76 %), brown oil. IR (ATR): 3352*s*, 3196*s*, 2929*w*, 2816*w*, 1666*s*, 1501*m*, 1450*m*, 1391*m*, 1348*m*, 1279*w*, 1188*w*, 1132*w*, 1106*w*, 1067*w*, 1001*w*, 865*w*, 742*m*, 700*m*, 675*m*, 571*m*, 460*w*, cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 7.40-7.27 (m, 5H), 7.10–7.02 (m, 1H), 6.90–6.85 (m, 1H), 4.01 (t, J = 5.5 Hz, 2H), 3.87 (s, 2H), 3.74 (s, 2H), 2.97–2.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.52; 136.30; 128.94; 128.61; 127.83; 122.87; 118.58; 61.47; 49.91; 48.14; 44.95. GC/MS (m/z (%)): 213.1 ([M^+], 50); 122.0 (100); 91.0 (90).

*5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrazine (**S3**)*

In a Parr reaction bottle, **S2** (2.12 g, 9.94 mmol) was dissolved in deoxygenated methanol (150 mL) and Pd/C (2.12 g, 10 mol% Pd) was added. The reactor was pressurized with 30 psi H_2 and the closed system was stirred at room temperature for 5 h. The reaction mixture was filtered through a pad of Celite. The solvents were removed under the reduced pressure, and crude product was purified using dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH/NH_3). Yield 1.07 g (88 %), brown oil. IR (ATR): 3296s, 2959s, 1660m, 1532m, 1502s,1448m, 1369m, 1325m, 1301m, 1274m, 1199w, 1178m, 1118m, 1082m, 996w, 961m, 936m, 896m, 853m, 741m, 693m, 671m, 528m, 467w cm^{-1}. ^1H NMR (500 MHz, $(CD_3)_2SO$, δ): 7.10 (s,1H), 6.89 (s, 1H), 4.10–3.90 (m, 4H), 3.30–3.10 (m, 2H). ^{13}C NMR (125 MHz, CD_3OD, δ): 142.44; 126.08; 118.30; 44.19; 43.13; 42.11. GC/MS (m/z (%)): 123.1 ([M^+], 70); 122.1 (100).



a) Boc_2O, CH_2Cl_2, 0 °C - r.t.; b) PCC, CH_2Cl_2, r.t.; c) 1. Boc_2O, NaOH (1M), $NaHCO_3$, H_2O, dioxane, 0 °C - r.t. 2. $KHSO_4$, 0 °C; d) $ClCO_2Et$, Et_3N, CH_2Cl_2, r.t.; e) $LiAlH_4$, THF, 0 °C - r.t.

Scheme S-2.

tert-*Butyl (3-hydroxypropyl)carbamate (**S4**)*[2]

To a solution of 3-aminopropan-1-ol (400 mg, 5.32 mmol) in CH_2Cl_2 (18 mL) di-*tert*-butyl dicarbonate (1.22 g, 5.59 mmol) was added at 0 °C. The reaction was stirred at r.t. for 2.5 h. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the crude residue was purified by dry-flash chromatography (SiO_2: hexane/EtOAc and EtOAc/MeOH) to yield **S4** (913 mg, 98 %) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.85 (bs, 1H), 3.85–3.50 (m, 2H), 3.40–3.20 (m, 2H), 1.75–1.62 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.16; 79.58; 59.19; 36.86; 32.84; 28.32.

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tert-*Butyl (3-oxopropyl)carbamate (**S5**)*

Alcohol **S4** (1.18 g, 6.73 mmol) was dissolved in CH_2Cl_2 (36 mL) followed by the addition of pyridinium chlorochromate (3.19 g, 14.8 mmol). After 2 h the mixture was transferred to a silica gel column and eluted with hexane/EtOAc to afford **S5** (989 mg, 85 %) as a colorless oil.

*3-[(*tert-*Butoxycarbonyl)amino]butanoic acid (**S6**)*[3]

To a solution of 3-aminobutanoic acid (755 mg, 7.32 mmol) in dioxane/water (2:1, v/v, 22.5 mL), 1M NaOH (aq) (3.8 mL) was added. The reaction mixture was cooled in an ice-bath, and di-*tert*-butyl dicarbonate (2.396 g, 10.98 mmol) and $NaHCO_3$ (615 mg, 7.32 mmol) were added. The reaction mixture was stirred for 16 h at r.t. and was then evaporated to half the initial volume. The residue was diluted with EtOAc, cooled in an ice-bath and acidified to pH 2–3 with 1M $KHSO_4$ (aq). The layers were separated and water layer was extracted with EtOAc. Combined organic layers were washed with brine and dried over anh. Na_2SO_4. Finally, the solvent was removed under reduced pressure, and crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH) to yield **S6** (1.47 g, 99 %) as colorless oil. IR (ATR): 3330m, 2980s, 2936m, 1809m, 1715s, 1516m, 1456m, 1398m, 1370s, 1303m, 1251m, 1213m, 1169s, 1120s, 1068m, 952w, 847m, 779w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.95 (bs, H-N), 4.05 (bs, 1H), 2.80–2.40 (m,2H), 1.44 (s, 9H), 1.24 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 176.37; 155.30; 79.58; 43.32; 40.74; 28.35; 20.44.

*Ethyl 3-[(tert-butoxycarbonyl)amino]butanoate (**S7**)*

To a solution of **S6** (1.47 g, 7.23 mmol) in dry CH_2Cl_2 (40 mL) Et_3N (2.0 mL, 14.4 mmol), and $ClCO_2Et$ (1.4 mL, 14.4 mL) were added. The reaction mixture was stirred for 18 h at r.t. and was then evaporated to dryness. The crude product was purified by dry-flash chromatography (SiO_2: CH_2Cl_2/MeOH) to yield **S7** (772 mg, 46 %). IR (ATR): 3365m, 2978s, 2934m, 1714s, 1517s, 1456m, 1369s, 1299m, 1249s, 1171s, 1094m, 1058m, 1030m, 887w, 851w, 783w, 593w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.94 (bs, H-N); 4.15 (q, J = 7.0 Hz, 2H); 4.04 (bs, 1H); 2.60–2.30 (m, 2H); 1.44 (s, 9H); 1.26 (t, J = 7.2 Hz, 3H); 1.21 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 171.73; 155.31; 79.47; 60.69; 43.68; 41.04; 28.58; 20.67; 14.38.

tert-*Butyl (4-hydroxybutan-2-yl)carbamate (**S8**)*

To a suspension of $LiAlH_4$ (122.7 mg, 3.235 mmol) in dry THF (3 mL) solution of **S7** (299 mg, 1.29 mmol) in dry THF (3 mL) was added at 0 °C, and the mixture was stirred for 1 h under Ar atmosphere. The reaction mixture was diluted with THF/H_2O (8 mL, 3 : 1, v/v), filtrated, and solvent was removed under reduced pressure. The crude product was purified using dry-flash chromatography (SiO_2: hexane/EtOAc) to yield **S8** (214 mg, 88 %) as colorless oil. IR (ATR): 3334m, 2974s, 2934m,1686s, 1530s, 1454m, 1390m, 1366m, 1276m, 1250m, 1173s, 1077m, 1052m, 987w, 967w, 853w, 782w, 751w, 648w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 4.57 (bs, H-N), 3.88 (bs, 1H), 3.70–3.56 (m, 2H), 1.90–1.72 (m, 1H), 1.45 (s, 9H), 1.40–1.30 (m, 1H), 1.19 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 156.71; 79.66; 58.85; 43.01; 40.61; 28.28; 21.39.

tert-*Butyl (4-oxobutan-2-yl)carbamate (**S9**)*

Alcohol **S8** (299 mg, 1.58 mmol) was dissolved in CH_2Cl_2 (10 mL) followed by the addition of pyridinium chlorochromate (749 g, 3.47 mmol). After stirring for 2 h at r.t. the mixture was transferred to a silica gel column and eluted with hexane/EtOAc to afford **S9** (232 mg, 84 %) as a colorless oil. IR (ATR): 3340m, 2977s, 2933m, 2731w, 1692s, 1522s,

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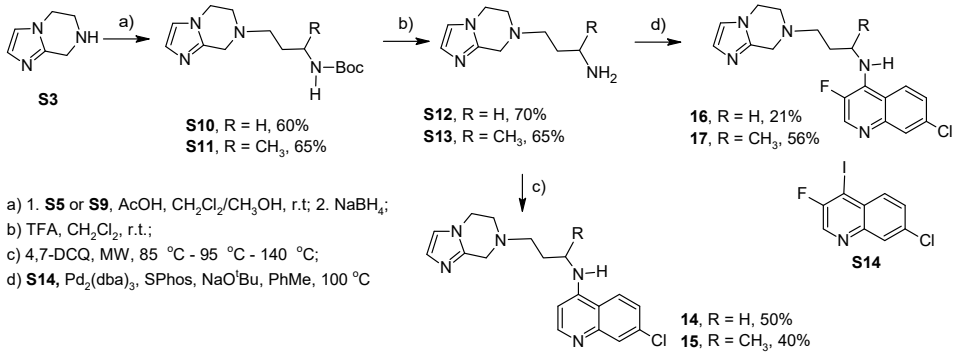
1455m, 1391m, 1368s, 1250s, 1172s, 1068m, 856w, 782w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 9.76 (s, 1H), 4.69 (bs, H-N), 4.20–4.10 (m, 1H), 2.80–2.40 (m, 2H), 1.43 (s, 9H), 1.30–1.20 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 200.86; 155.00; 79.69; 50.46; 42.26; 28.26; 20.87.



Scheme S-3.

The synthesis of **S14**[4] has been previously reported.

General procedure for reductive amination

tert-*Butyl [3-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)propyl]carbamate (**S10**)*

Aldehyde **S5** (343.2 mg, 1.981 mmol) and 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine **S3** (292.8 mg, 2.377 mmol) were dissolved in dry MeOH/CH_2Cl_2 mixture (24 mL, 2 : 1, v/v), anh. AcOH (143 μL, 2.377 mmol) was added, and the mixture was stirred under Ar atmosphere at rt. After 3 h, $NaBH_4$ (450 mg, 11.9 mmol) was added, and stirring was continued for another 18 h at rt. Solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with 2 M NH_4OH. The layers were separated and water layer was extracted with CH_2Cl_2. Combined organic layers were washed with brine and dried over anh. Na_2SO_4. Finally, the solvent was removed under reduced pressure, and crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc and CH_2Cl_2/MeOH). Yield 311.4 mg (60 %), colorless oil. IR (ATR): 3336w, 3112w, 3048w, 2973m, 2934m, 2873w, 2816w, 2772w, 1700s, 1528m, 1505m, 1452m, 1390w, 1366m, 1323w, 1275m, 1251m, 1172s, 1110m, 1077w, 994w, 943w, 858w, 734m, 698w, 676w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 6.99 (s, 1H), 6.81 (s, 1H), 5.00 (bs, H-N), 4.00 (t, J = 5,5 Hz, 2H), 3.70 (s, 2H), 3.30–3.15 (m, 2H), 2.87 (t, J = 5,3 Hz, 2H), 2.62 (t, J = 6,9 Hz, 2H), 1.85-1.65 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 157.55; 144.33; 129.78; 119.05; 80.66; 57.06; 53.55; 51.38; 45.55; 40.64; 29.97; 28.64.

tert-*Butyl [4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)butan-2-yl]carbamate (**S11**)*

Aldehyde **S9** (451.7 mg, 2.41 mmol) and 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine **S3** (386.2 mg, 3.133 mmol) were coupled to afford **S11** (406.2 mg, 65 %) using AcOH (188 μL, 3.133 mmol) and $NaBH_4$ (547 mg, 11.9 mmol). The crude product was purified by dry-flash chromatography (SiO_2: hexane/EtOAc and CH_2Cl_2/MeOH). Yield 406.2 mg (65 %), colorless oil. The product was used for the next reactions without further purification.

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*3-(5,6-Dihydroimidazo[1,2-*a*]pyrazin-7(8H)-yl)propan-1-amine (**S12**)*

To a solution of **S10** (311.4 mg, 1.112 mmol) in CH_2Cl_2 (7 mL, degassed) TFA (1.3 mL) was added. The reaction was stirred at r.t. for 3 h. The solvent was removed under reduced pressure, the reaction mixture was suspended in CH_2Cl_2/MeOH, and NaOH (aq) was added until pH 10. The organic layer was washed with brine, dried (anh. Na_2SO_4), filtered, and concentrated in vacuo. Yield 139.4 mg (70 %), brown oil. IR (ATR): 3361s, 2946s, 2821s, 1689m, 1572m, 1502s, 1469m, 1374m, 1324m, 1279m, 1199m, 1110m, 1077m, 994w, 939m, 824w, 741m, 676m cm^{-1}. ^1H NMR (500 MHz, CD_3OD, δ): 6.99 (s, 1H), 6.90 (s, 1H), 4.08-3.98 (m, 2H), 3.66 (s, 2H), 2.97-2.85 (m, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 1.85-1.70 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD, δ): 144.25; 129.27; 119.21; 57.02; 53.02; 51.42; 45.48; 41.42; 30.83. (+)ESI-HRMS (m/z): $[M + H]^+$ = 181.14477 (error +3.04 ppm).

*4-(5,6-Dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)butan-2-amine (**S13**)*

To a solution of **S11** (406.2 mg, 1.853 mmol) in CH_2Cl_2 (10 mL, degassed) and MeOH (0.5 mL), TFA (2 mL) was added. The reaction was stirred at r.t. for 3 h. The solvent was removed under reduced pressure, the reaction mixture was suspended in CH_2Cl_2/MeOH, and NaOH (aq) was added until pH 10. The organic layer was washed with brine, dried (anh. Na_2SO_4), filtered, and concentrated in vacuo. Yield 174 mg (65 %), pale-brown oil. IR (ATR): 3417w, 2972m, 2830m, 1677s, 1540w, 1506m, 1460w, 1424w, 1393w, 1327w, 1280w, 1201s, 1133s, 1034w, 942w, 834w, 801w, 743w, 723w, 676w cm^{-1}. ^1H NMR (500 MHz, $(CD_3)_2SO$, δ): 7.78 (bs, 2H, NH_2), 7.14 (s, 1H), 6.97 (s, 1H), 4.05–3.95 (m, 2H), 3.75–3.55 (m, 2H), 3.35–3.25 (m,1H), 2.90–2.75 (m, 2H), 2.70–2.55 (m, 2H), 1.90–1.55 (m, 2H), 1.19 (d, J = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, δ): 142.33; 126.10; 118.96; 53.07; 50.85; 49.24; 46.01; 43.99; 31.08; 18.62. (+)ESI-HRMS (m/z): $[M + H]^+$ = 195.16053 (error +2.26 ppm).

*7-Chloro-N-[3-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)propyl]quinolin-4-amine (**14**)*

A reaction vessel containing **S12** (19.1 mg, 0.105 mmol) and 4,7-dichloroquinoline (17.4 mg, 0.088 mmol) was stirred for 15 min at 80 °C, 30 min at 95 °C and 2 h at 140 °C in a MW reactor. The reaction mixture was suspended in CH_2Cl_2, transferred to a separation funnel, and washed well with 1M NaOH (aq). The organic layer was collected, dried with anh. Na_2SO_4, and filtered. Subsequently, the solvent was removed under reduced pressure and product **14** was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH). Yield 15.1 mg (50 %), pale-yellow amorphous powder, mp = 71 °C. IR (ATR): 3274m, 2925s, 2853m, 1673m, 1609m, 1582s, 1541m, 1502m, 1452m, 1370m, 1329m, 1281m, 1246w, 1202w, 1137m, 1111m, 1080w, 942w, 900w, 879w, 850w, 809w, 767w, 731w, 677w, 647w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.49 (d, J = 5.2 Hz, 1H), 7.90 (s, 1H), 7.22–7.07 (m, 2H), 7.05–6.92 (m, 2H), 6.33 (d, J = 5.2 Hz, 1H), 4.09 (t, J = 5.5 Hz, 2H), 3.88 (s, 2H), 3.50–3.42 (m, 2H), 3.01 (t, J = 5.7 Hz, 2H), 2.95–2.85 (m, 2H), 2.10–2.00 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 151.88; 150.24; 148.87; 142.23; 134.56; 128.97; 128.45; 125.10; 121.23; 117.75; 117.36; 98.44; 57.30; 51.81; 50.47; 44.01; 43.55; 24.22. (+)ESI-HRMS (m/z): $[M + H]^+$ = 342.14700 (error +4.53 ppm). HPLC purity, method A: t_R = 3.872, area 99.36 %. Method B: t_R = 4.504, area 99.20 %.

*7-Chloro-*N*-[(2*R*)-4-(5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)butan-2-yl]quinolin-4--amine (**15**)*

A reaction vessel containing **S13** (63.8 mg, 0.328 mmol) and 4,7-dichloroquinoline (32.5 mg, 0.164 mmol) was stirred for 15 min at 80 °C, 30 min at 95 °C and 2 h at 140 °C in a

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MW reactor. The reaction mixture was suspended in CH_2Cl_2, transferred to a separation funnel, and washed well with 1M NaOH (aq). The organic layer was collected, dried with anh. Na_2SO_4, and filtered. Subsequently, the solvent was removed under reduced pressure and product **15** was purified by dry-flash chromatography (SiO_2: EtOAc/MeOH and CH_2Cl_2/MeOH (NH_3)) and flash chromatography (Biotage SP, NH: hexane/EtOAc and EtOAc/MeOH). Yield 23.5 mg (40 %), pale-yellow oil. IR (ATR): 3269m, 2963m, 2818m, 1610m, 1578s, 1538m, 1501m, 1450m, 1374m, 1329m, 1277m, 1193w, 1153w, 1110w, 1078w, 933w, 880w, 850w, 810w, 734m, 699w, 678w, 648w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.47 (d, J = 5.5 Hz, 1H), 7.88 (d, J = 2.1 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.11 (s, 1H), 7.02–6.90 (m, 3H), 6,37 (d, J = 5.5 Hz, 1H), 4.10–3.98 (m, 2H), 3.95–3.78 (m, 3H), 3.05–2.85 (m, 3H), 2.78–2.69 (m, 1H), 2.12–2.00 (m, 1H), 1.86–1.75 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 151.88; 149.33; 149.23; 142.26; 134.53; 128.89; 128.61; 124.92; 121.26; 117.72; 117.49; 98.71; 54.38; 51.90; 50.38; 48.00; 43.93; 31.73; 19.28. (+)ESI-HRMS (m/z): $[M + H]^+$ = 356.16272 (error +4.15 ppm). HPLC purity, method A: t_R = 3.490, area 95.35 %. Method B: t_R = 7.515, area 97.30 %.

General procedure for Buchwald-Hartwig amination

7-Chloro-N-*[3-(5,6-dihydroimidazo[1,2*-a*]pyrazin-7(8*H*)-yl)propyl]-3-fluoroquinolin-4--amine (**16**)*

To a flame-dried reaction tube, $Pd_2(dba)_3$ (8 mg, 0.009 mmol, 5 mol% Pd), SPhos (7.2 mg, 0.017 mmol) and PhMe (1.5 mL) were added. The solution was stirred at r.t. under an inert atmosphere for 3 min, and was then added to a mixture of S**14** (53.7 mg, 0.175 mmol), **S12** (63 mg, 0.35 mmol), NaO*t*-Bu (47 mg, 0.49 mmol, 2.8 equiv) and PhMe (1.5 mL), the tube was sealed and the mixture was heated at 100 °C in an oil bath for 19 h. The crude product **16** was purified by dry-flash column chromatography (SiO_2: hexane/EtOAc and EtOAc/MeOH) and furthermore by flash column chromatography (Biotage SP, NH, hexane/EtOAc and EtOAc/MeOH). Yield 13.4 mg (21 %), pale-yellow oil. IR (ATR): 3270s, 2952s, 2822m, 1700m, 1597s, 1575s, 1539s, 1501s, 1455s, 1420s, 1372s, 1324m, 1298m, 1270m, 1191m, 1139m, 1110m, 1077m, 992w, 942m, 892w, 814m, 762m, 735m, 700w, 676w, 656w, 622w, 542w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + D_2O, δ): 8.45 (d, J = 5.8 Hz, 1H), 7.88 (s, 1H), 7.21 (d, J = 9.2 Hz, 1H), 7.15–7.12 (m, 1H), 6.97–6.91 (m, 2H), 4.07 (t, J = 5.5 Hz, 2H), 3.90–3.80 (m, 4H), 3.05–2.95 (m, 2H), 2.90–2.80 (m, 2H), 2.05–1.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 146.44; 143.58 (d, J = 238.3 Hz); 142.50 (d, J = 27.1 Hz); 142.88; 136.67 (d, J = 5.4 Hz); 133.80; 129.05; 128.85; 125.90; 121.74 (d, J = 5.4 Hz); 119.15 (d, J = 5.4 Hz); 117.85; 57.61; 52.13; 50.49; 46.59; 44.01; 25.52. (+)ESI-HRMS (m/z): $[M + H]^+$ = 360.13767 (error +4.04 ppm). HPLC purity, method A: t_R = 3.471, area 95.05 %. Method B: t_R = 7.381, area 97.14 %.

7-Chloro-N-*[4-(5,6-dihydroimidazo[1,2*-a*]pyrazin-7(8*H*)-yl)butan-2-yl]-3-fluoroquinolin-4--amine (**17**)*

Following the general procedure for Buchwald-Hartwig amination, compound **17** was obtained after dry-flash column chromatography (SiO_2: hexane/EtOAc and EtOAc/MeOH) as a pale-yellow oil (31.5 mg, 56 %) from **S13** (43.5 mg, 0.224 mmol) and **S14** (46 mg, 0.015 mmol) using $Pd_2(dba)_3$ (6.8 mg, 0.007 mmol), SPhos (6.1 mg, 0.015 mmol), NaO*t*-Bu (40.2 mg, 0.419 mmol) and PhMe (2 mL). IR (ATR): 3271s, 2966s, 2822m, 1596s, 1574s, 1540m, 1502m, 1449m, 1421m, 1380s, 1350m, 1298m, 1270m, 1192m, 1142m, 1112m, 1078m, 992w, 927w, 879w, 815w, 762w, 734m, 675w, 622w, 540w cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD, δ): 8.42 (d, J = 5.8 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.48 (d,

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J = 8.9 Hz, 1H), 7.10–7.00 (m, 2H), 6.93 (d, *J* = 1.2 Hz, 1H), 4.41–4.32 (m, 1H), 4.10–3.92 (m, 2H), 3.87–3.75 (m, 2H), 3.10–3.00 (m, 1H), 2.99–2.89 (m, 2H), 2.80–2.70 (m, 1H), 2.15-2.05 (m, 1H), 1.87–1.75 (m, 1H), 1.36 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD, *δ*): 146.15; 143.05 (d, *J* = 239.2 Hz); 142.43; 142.12 (d, *J* = 28.0 Hz); 136.38 (d, *J* = 4.5 Hz); 134.21; 128.26; 128.14; 125.94; 122.10 (d, *J* = 5.4 Hz); 119.33 (d, *J* = 4.5 Hz); 118.02; 54.23; 51.66; 50.37; 50.19; 44.05; 32.62; 21.63. (+)ESI-HRMS (m/z): $[M + H]^+$ = 374.15307 (error +4,56 ppm). HPLC purity, method A: t_R = 3.520, area 97.15 %. Method B: t_R = 7.549, area 98.21 %.

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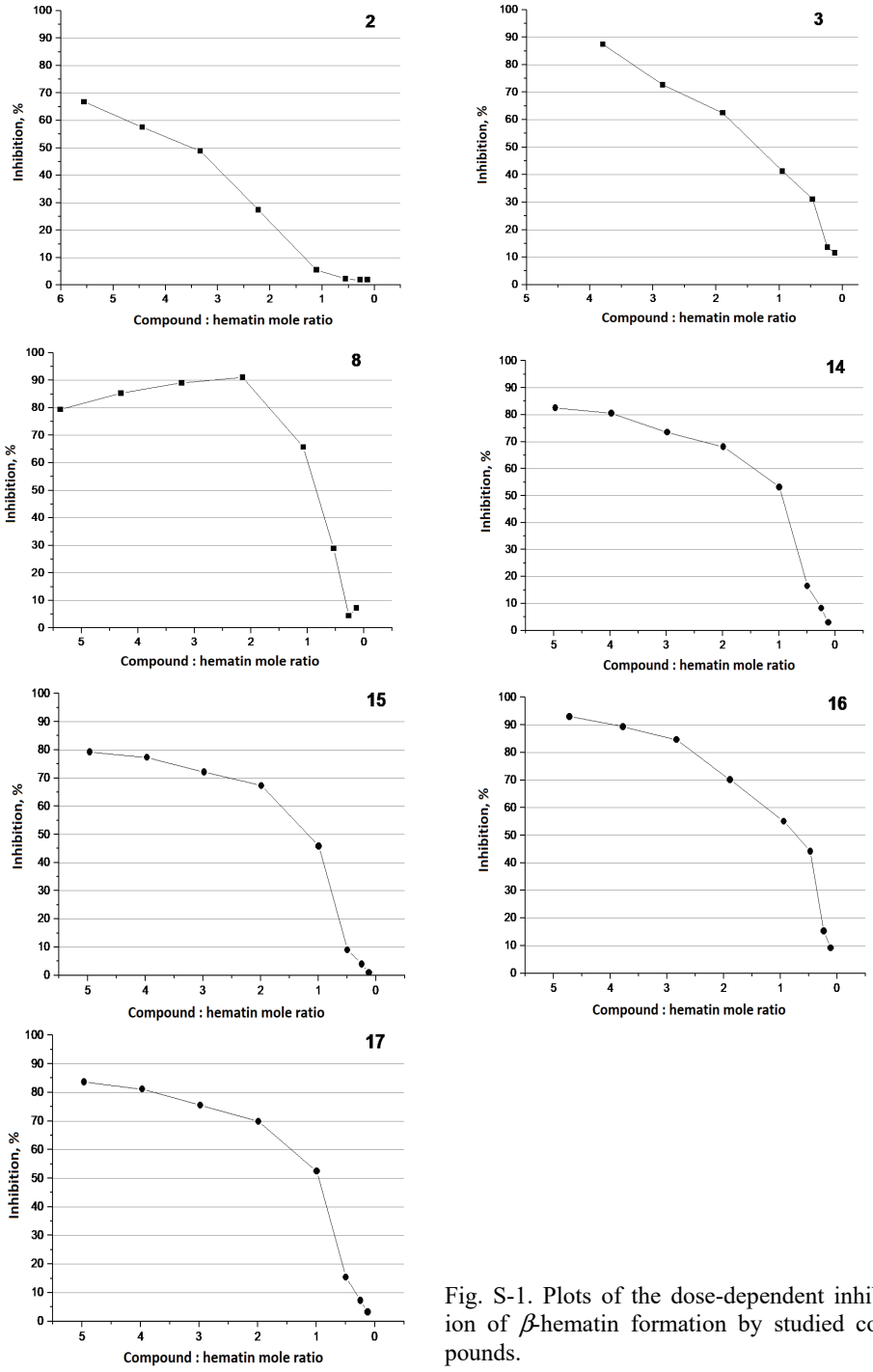

Fig. S-1. Plots of the dose-dependent inhibition of β-hematin formation by studied compounds.

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