

Supplementary Information

Inhibition of trypanothione reductase and glutathione reductase by ferrocenic 4-aminoquinoline ureas

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In honour of Prof Torbjorn Norin on the occasion of his 75th anniversary

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***N*-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N''*,*N''*-dimethylaminomethyl)ferrocenylmethyl]-propane-1,3-diamine, (3b).** Red glassy solid; Yield: 1.204g (61%); mp: 108-110°C; R_f (silica/CH₂Cl₂: MeOH: Et₃N = 80:20:1) 0.2; δ_H (400 MHz; CDCl₃) 8.44 (1H, d, ³ J_{HH} = 6), 7.86 (1H, d, ⁴ J_{HH} = 2), 7.50 (1H, d, ³ J_{HH} = 9), 7.11 (1H, dd, ⁴ J_{HH} = 2 and ³ J_{HH} = 9), 6.22 (1H, d, ³ J_{HH} = 6), 4.19-4.15 (2H, m), 4.12 (1H, t, ³ J_{HHH} = 2), 4.05 (5H, s), 3.79 (1H, d, ² J_{HH} = 12), 3.74 (1H, d, ² J_{HH} = 12), 3.42 (1H, d, ² J_{HH} = 12), 3.36-3.31 (2H, m), 2.99-2.92 (2H, m), 2.79 (1H, d, ² J_{HH} = 12), 2.11 (6H, s) and 1.94-1.72 (2H, m); $\delta_{C\{H\}}$ (100.6 MHz; CDCl₃) 152.1, 150.7 (¹³C), 149.1 (¹³C), 134.4 (¹³C), 128.2, 124.8, 122.9, 117.7 (¹³C), 97.9, 85.9 (¹³C), 84.1 (¹³C), 71.2, 70.3, 68.0 (5C), 65.8, 58.3, 49.3, 48.3, 44.9 (2C), 44.3, 26.9; IR (KBr) ν_{max} 3249br w, 1610s, 1586vs, 1544s, 1457s, 1329m, 1104m 999m, 856s, 819m, 489m; HRMS (EI) m/z 490.15824 [M^+ , C₂₆H₃₁N₄³⁵ClFe requires 490.11590], 445.1, 380.0, 255.1, 241.1, 227.0, 213.0, 191.0, 154.0, 134.0, 121.0, 91.0, 58.1, 55.9; Found: C, 63.89; H, 6.39; N, 11.15. Calc. for C₂₆H₃₁N₄ClFe: C, 63.62; H, 6.37; N, 11.41%.

***N*-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N''*,*N''*-dimethyl-aminomethyl)ferrocenylmethyl]-butane-1,4-diamine, (3c).** Red glassy solid; Yield: 1.337g (65%); mp: 103-104°C; R_f (silica/CH₂Cl₂: MeOH: Et₃N = 80:20:1) 0.17; δ_H (400 MHz; CDCl₃) 8.44 (1H, d, ³ J_{HH} = 6), 8.14

(1H, d, $^3J_{\text{HH}} = 9$), 7.88 (1H, d, $^4J_{\text{HH}} = 2$), 7.31 (1H, dd, $^4J_{\text{HH}} = 2$ and $^3J_{\text{HH}} = 9$), 6.29 (1H, d, $^3J_{\text{HH}} = 6$), 4.20-4.07 (3H, m), 4.06 (5H, s), 3.77 (1H, d, $^2J_{\text{HH}} = 13$), 3.53 (1H, d, $^2J_{\text{HH}} = 13$), 3.33-3.29 (3H, m), 2.83 (1H, d, $^2J_{\text{HH}} = 13$), 2.69-2.66 (2H, m), 2.10 (6H, s), 1.85-1.80 (2H, m), 1.75-1.70 (2H, m); $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz; CDCl_3) 151.8, 150.4 (^{13}C), 149.2 (^{13}C), 134.7 (^{13}C), 128.2, 125.0, 123.0, 117.7 (^{13}C), 98.5 (^{13}C), 83.7 (^{13}C), 71.6, 71.0, 69.4 (5C), 66.6, 57.9, 47.0, 46.0, 44.4 (2C), 42.3, 25.4, 25.3; IR (KBr) ν_{max} 3285br s, 1610m, 1581vs, 1540m, 1451m, 1105m, 1000m, 851m, 809m, 489w; HRMS (EI) m/z 504.1746 [M^+ , $\text{C}_{27}\text{H}_{33}\text{N}_4^{35}\text{ClFe}$ requires 504.1427], 460.1, 394.1, 255.1, 240.0, 213.0, 134.0, 121.0, 91.0, 58.1, 55.9; Found: C, 64.01; H, 6.60; N, 11.15. Calc. for $\text{C}_{27}\text{H}_{33}\text{N}_4\text{ClFe}$: C, 64.20; H, 6.58; N, 11.14%.

***N*-(7-Chloro-quinolin-4-yl)-*N'*-[2-(*N''*,*N''*-dimethyl-aminomethyl)ferrocenylmethyl]-hexane-1,6-diamine, (3d).** Red glassy solid; Yield: 1.729g (60%); mp: 92-95°C; R_f (silica/ CH_2Cl_2 : MeOH: $\text{Et}_3\text{N} = 80:20:1$) 0.07; δ_{H} (400 MHz; CDCl_3) 8.46 (1H, d, $^3J_{\text{HH}} = 6$), 8.16 (1H, d, $^3J_{\text{HH}} = 9$), 7.90 (1H, d, $^4J_{\text{HH}} = 2$), 7.24 (1H, dd, $^4J_{\text{HH}} = 2$ and $^3J_{\text{HH}} = 9$), 6.34 (1H, d, $^3J_{\text{HH}} = 6$), 4.28-4.15 (3H, m), 4.09 (5H, s), 3.81 (1H, d, $^2J_{\text{HH}} = 13$), 3.53 (1H, d, $^2J_{\text{HH}} = 13$), 3.55-3.50 (2H, m), 3.33 (1H, d, $^2J_{\text{HH}} = 13$), 2.86 (1H, d, $^2J_{\text{HH}} = 13$), 2.64 (2H, m), 2.14 (6H, s), 1.76-1.73 (2H, m), 1.60-1.54 (2H, m), 1.45-1.38 (4H, m); $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz, CDCl_3) 151.8, 150.3 (^{13}C), 149.2 (^{13}C), 134.7 (^{13}C), 128.3, 125.0, 122.6, 117.5 (^{13}C), 98.7, 83.8 (^{13}C), 71.6, 71.2, 69.5 (5C), 66.8, 57.8, 46.7, 45.5, 44.3 (2C), 42.5, 27.9, 27.0, 26.2, 25.9 (5' – 8'); IR (KBr) ν_{max} 3300br m, 1610s, 1580vs, 1540s, 1453s, 1331m, 1105m, 1000m, 850m, 810s, 489m, 424w; HRMS (EI) m/z 532.20585 [M^+ , $\text{C}_{29}\text{H}_{37}\text{N}_4^{35}\text{ClFe}$ requires 532.20561], 515.2, 487.1, 422.1, 255.1, 240.0, 213.0, 121.0, 91.0, 58.1, 55.9; Found: C, 65.40; H, 7.05; N, 10.64. Calc. for $\text{C}_{29}\text{H}_{37}\text{N}_4\text{ClFe}$: C, 65.33; H, 6.99; N, 10.55%.

3-Benzyl-1-[2-(7-chloro-quinolin-4-ylamino)-ethyl]-1-[2-(*N''*,*N''*-dimethylaminomethyl)-ferrocenylmethyl]urea (4a). Yellow crystalline solid; Yield: 345mg (90%); mp: 95-96°C; R_f (silica/ CH_2Cl_2 : MeOH = 80:20) 0.51; δ_{H} (400 MHz; CDCl_3) 8.45 (1H, d, $^3J_{\text{HH}} = 6$), 8.12 (1H, t, $^3J_{\text{HH}} = 6$), 7.96 (1H, d, $^4J_{\text{HH}} = 2$), 7.75 (1H, d, $^3J_{\text{HH}} = 9$), 7.15 (1H, dd, $^4J_{\text{HH}} = 2$ and $^3J_{\text{HH}} = 9$), 7.13-7.07 (5H, m), 6.32 (1H, d, $^3J_{\text{HH}} = 6$), 4.24-4.16 (7H, m), 4.08 (5H, s), 3.82 (1H, d, $^2J_{\text{HH}} = 13$), 3.73-3.68 (2H, m), 3.58-3.40 (2H, m), 2.82 (1H, d, $^2J_{\text{HH}} = 13$), 1.98 (6H, s); $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz; CDCl_3) 160.4 (^{13}C), 151.7 (^{13}C), 149.7, 146.7 (^{13}C), 140.2 (^{13}C), 135.7 (^{13}C), 128.2 (2C), 126.6, 126.5 (2C), 126.2, 125.7, 123.1, 116.9 (^{13}C), 97.5, 83.9 (^{13}C), 70.6, 69.5 (5C), 69.0, 67.7, 57.8, 47.0, 45.6, 44.6, 44.4 (2C), 43.7; IR (KBr) ν_{max} 3268br w 1611s, 1582vs, 1539s, 1452m, 1332m, 1105m, 1005m, 842m, 808m, 487m; HRMS (FAB) m/z 610.2030 [$\text{M}^+ + \text{H}$, $\text{C}_{33}\text{H}_{36}\text{N}_5\text{ClOFe} + \text{H}$ requires 610.2034], 565.1, 432.2, 409.1, 304.0, 255.1, 213.1, 191.0, 154.0, 134.1, 91.1; Found: C, 65.01; H, 5.83; N, 11.50. Calc. for $\text{C}_{33}\text{H}_{36}\text{N}_5\text{ClOFe}$: C, 64.98; H, 5.95; N, 11.48%.

3-Benzyl-1-[3-(7-chloro-quinolin-4-ylamino)-propyl]-1-[2-(*N''*,*N''*-dimethylaminomethyl)-ferrocenylmethyl]urea (4b). Yellow crystalline solid; Yield: 33mg (34%); mp: 88-89°C; R_f (silica/ CH_2Cl_2 : MeOH = 80:20) 0.46; δ_{H} (400 MHz; CDCl_3) 8.47 (1H, d, $^3J_{\text{HH}} = 6$), 8.05 (1H, d, $^3J_{\text{HH}} = 9$), 7.95 (1H, d, $^4J_{\text{HH}} = 2$), 7.30 (1H, dd, $^3J_{\text{HH}} = 2$ and $^4J_{\text{HH}} = 9$), 7.25-7.13 (5H, m), 6.39

(1H, d, $^3J_{\text{HH}} = 6$), 4.48 (1H, m), 4.39-4.38 (1H, m), 4.33 (1H, d, $^2J_{\text{HH}} = 16$), 4.26-4.21 (1H, m), 4.22 (1H, d, $^2J_{\text{HH}} = 16$), 4.14 (1H, t, $^3J_{\text{HHH}} = 3$), 4.03 (5H, s), 4.07 (2H, m), 3.91-3.82 (1H, m), 3.80 (1H, d, $^2J_{\text{HH}} = 13$), 3.48-3.43 (2H, m), 3.36-3.27 (2H, m), 2.77 (1H, d, $^2J_{\text{HH}} = 13$), 1.97 (6H, s) and 1.91-1.85 (2H, m); $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz; CDCl_3) 159.1 (^{13}C), 151.2 (^{13}C), 150.7, 140.7 (^{13}C), 135.8 (^{13}C), 128.2 (2C), 127.2, 126.7 (2C), 126.6, 125.4, 122.9, 117.6 (^{13}C), 97.8, 84.3 (^{13}C), 70.4, 69.5 (5C), 69.0, 67.4, 58.0, 45.4, 45.2, 44.7, 44.6 (2C), 39.4, 26.7; IR (KBr) ν_{max} 3437br s, 3322br s, 1611s, 1578vs, 1538s, 1455m, 1106w, 1005w, 850m, 809m; HRMS (FAB) m/z 624.1890 [$\text{M}^+ + \text{H}$, $\text{C}_{34}\text{H}_{38}\text{N}_5\text{ClOFe} + \text{H}$ requires 624.1908], 579.1, 446.1, 423.1, 318.0, 255.1, 213.1, 191.0, 154.0, 134.1 and 91.1; Found: C, 64.70; H, 6.23; N, 11.45. Calc. for $\text{C}_{34}\text{H}_{38}\text{N}_5\text{ClOFe}$: C, 64.41; H, 6.13; N, 11.27%.

3-Benzyl-1-[4-(7-chloro-quinolin-4-ylamino)-butyl]-1-[2-(N'' , N'' -dimethylaminomethyl)-ferrocenylmethyl]urea (4c). Yellow crystalline solid; Yield: 75mg (58%); mp: 84-86°C; R_f (silica/ CH_2Cl_2 : MeOH = 80:20) 0.4; δ_{H} (400 MHz; CDCl_3) 8.47 (1H, d, $^3J_{\text{HH}} = 5$), 8.07 (1H, d, $^3J_{\text{HH}} = 9$), 7.91 (1H, d, $^4J_{\text{HH}} = 2$), 7.38-7.09 (6H, m, ArC₆-H), 6.35 (1H, d, $^3J_{\text{HH}} = 6$), 4.42-4.09 (5H, m), 4.06 (5H, s), 4.05-4.04 (2H, m), 3.79 (1H, d, $^2J_{\text{HH}} = 13$), 3.43 (4H, m), 2.77 (1H, d, $^2J_{\text{HH}} = 13$), 1.96 (6H, s), 1.79-1.65 (4H, m); $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz; CDCl_3) 158.7 (^{13}C), 151.3 (^{13}C), 150.8, 144.2 (^{13}C), 140.8 (^{13}C), 134.9 (^{13}C), 128.2 (2C), 127.8, 126.6 (2C), 126.5, 125.1, 122.9, 117.6 (^{13}C), 98.5, 84.6 (^{13}C), 70.3, 69.4 (5C), 69.2, 67.3, 57.9, 47.8, 45.2, 44.7 (2C), 44.5, 43.1, 26.7, 24.3; IR (KBr) ν_{max} 3437br s, 3322br s, 1611s, 1578vs, 1538s, 1455m, 1106w, 1005w, 850m, 809m; HRMS (FAB) m/z 638.2333 [$\text{M}^+ + \text{H}$, $\text{C}_{35}\text{H}_{40}\text{N}_5\text{ClOFe} + \text{H}$ requires 638.2347], 593.0, 505.2, 460.0, 437.0, 255.1, 213.0, 191.0, 154.0, 134.1, 91.1; Found: C, 65.71; H, 6.17; N, 11.23. Calc. for $\text{C}_{35}\text{H}_{40}\text{N}_5\text{ClOFe}$: C, 65.85; H, 6.32; N, 10.97%.

3-Benzyl-1-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-1-[2-(N'' , N'' -dimethylaminomethyl)-ferrocenylmethyl]urea (4d). Yellow crystalline solid; Yield: 78mg (57%); mp: 85-87°C; R_f (silica/ CH_2Cl_2 : MeOH = 80:20) 0.46; δ_{H} (400 MHz; CDCl_3) 8.39 (1H, d, $^3J_{\text{HH}} = 6$), 8.14 (1H, d, $^3J_{\text{HH}} = 9$), 8.02 (1H, d, $^4J_{\text{HH}} = 2$), 7.16-7.12 (5H, m), 7.04 (1H, d, $^3J_{\text{HH}} = 9$), 6.32 (1H, d, $^3J_{\text{HH}} = 6$), 4.41-4.17 (4H, m), 4.16 (1H, t, $^3J_{\text{HHH}} = 3$), 4.09 (5H, s), 4.08-4.07 (2H, m), 3.77 (1H, m), 3.31-3.21 (2H, m), 3.19 (2H, m), 2.89 (1H, d, $^2J_{\text{HH}} = 13$), 2.05 (6H, s), 1.74-1.33; $\delta_{\text{C}\{\text{H}\}}$ (100.6 MHz; CDCl_3) 158.5 (^{13}C), 151.9 (^{13}C), 149.1, 140.7 (^{13}C), 135.6 (^{13}C), 128.2 (2C), 126.5 (2C), 126.5, 125.6, 123.0, 117.1 (^{13}C), 98.0, 84.7 (^{13}C), 70.4, 69.5 (5C), 69.4, 67.5, 57.8, 46.6, 44.6 (2C), 44.3, 41.6, 27.7, 27.6, 25.0, 24.6; IR (KBr) ν_{max} 3306br s (NH), 1612s, 1582vs, 1540s, 1457m, 1106w, 1005w, 852m, 813m, 490m; HRMS (FAB) m/z 666.2648 [$\text{M}^+ + \text{H}$, $\text{C}_{37}\text{H}_{44}\text{N}_5\text{ClOFe} + \text{H}$ requires 666.2660], 621.1, 547.4, 502.2, 488.0, 465.0, 422.1, 360.0, 304.0, 255.1, 213.1, 191.0, 154.0, 134.1, 91.1; Found: C, 66.70; H, 6.60; N, 10.76. Calc. for $\text{C}_{37}\text{H}_{44}\text{N}_5\text{ClOFe}$: C, 66.69; H, 6.65; N, 10.56%.