

TABLE S3. Hemoglobin, free heme and hemozoin levels in drug-treated *pfcr*-modified Dd2 parasites.

| PPQ drug treatment | Dd2 ^{Dd2} | | | PPQ drug treatment | Dd2 ^{Dd2+C101F} | | |
|----------------------------------|--------------------------------|-------------------------------|------------------------------|----------------------------------|--------------------------------|-------------------------------|------------------------------|
| | Amount of hemoglobin (fg/cell) | Amount of free heme (fg/cell) | Amount of hemozoin (fg/cell) | | Amount of hemoglobin (fg/cell) | Amount of free heme (fg/cell) | Amount of hemozoin (fg/cell) |
| No drug control | 3.2 ± 1.1 | 6.4 ± 1.5 | 66.8 ± 3.6 | No drug control | 2.3 ± 0.4 | 5.2 ± 0.5 | 62.7 ± 3.5 |
| -- | -- | -- | -- | 0.1x LD ₅₀ (16.2 nM) | 2.5 ± 0.1 | 5.7 ± 0.4 | 44.6 ± 1.4*** |
| -- | -- | -- | -- | 0.25x LD ₅₀ (40.6 nM) | 2.6 ± 0.2 | 7.1 ± 0.4** | 43.7 ± 2.7** |
| 0.5x IC ₅₀ (22.2 nM) | 3.2 ± 0.6 | 12.8 ± 1.9** | 52.4 ± 2.7* | 0.5x LD ₅₀ (81.2 nM) | 4.2 ± 0.5* | 16.4 ± 2.3*** | 38.5 ± 2.2*** |
| 1.0x IC ₅₀ (44.5 nM) | 4.7 ± 0.4 | 15.9 ± 0.8** | 46.2 ± 4.5** | 1.0x LD ₅₀ (162.5 nM) | 5.4 ± 0.8** | 28.2 ± 2.9*** | 30.9 ± 1.7*** |
| 2.0x IC ₅₀ (89.0 nM) | 5.7 ± 0.4 | 24.7 ± 0.8*** | 32.5 ± 3.4*** | 2.0x LD ₅₀ (325.0 nM) | 10.5 ± 1.1** | 45.0 ± 0.9** | 16.1 ± 2.3** |
| 2.5x IC ₅₀ (111.2 nM) | 7.0 ± 0.7* | 28.0 ± 1.1*** | 30.9 ± 1.2*** | 2.5x LD ₅₀ (406.2 nM) | 13.5 ± 1.2** | 46.7 ± 1.5** | 14.0 ± 2.4*** |
| 3.0x IC ₅₀ (133.5 nM) | 7.5 ± 0.6** | 32.1 ± 1.1*** | 24.4 ± 3.2*** | -- | -- | -- | -- |

| CQ drug treatment | Dd2 ^{Dd2} | | | CQ drug treatment | Dd2 ^{Dd2+C101F} | | |
|-----------------------------------|--------------------------------|-------------------------------|------------------------------|----------------------------------|--------------------------------|-------------------------------|------------------------------|
| | Amount of hemoglobin (fg/cell) | Amount of free heme (fg/cell) | Amount of hemozoin (fg/cell) | | Amount of hemoglobin (fg/cell) | Amount of free heme (fg/cell) | Amount of hemozoin (fg/cell) |
| No drug control | 2.4 ± 0.2 | 6.5 ± 0.7 | 67.3 ± 4.9 | No drug control | 2.7 ± 0.5 | 4.2 ± 0.2 | 59.1 ± 0.5 |
| 0.5x IC ₅₀ (183.3 nM) | 4.0 ± 0.2*** | 8.9 ± 0.7 | 63.9 ± 4.3 | 0.5x IC ₅₀ (36.3 nM) | 3.1 ± 0.6 | 4.5 ± 0.6 | 55.4 ± 2.4 |
| 1.0x IC ₅₀ (366.7 nM) | 6.6 ± 0.6*** | 10.0 ± 1.3* | 40.5 ± 1.6*** | 1.0x IC ₅₀ (72.7 nM) | 4.9 ± 1.0* | 6.9 ± 1.0** | 44.7 ± 1.8*** |
| 2.0x IC ₅₀ (733.4 nM) | 8.2 ± 0.3*** | 10.5 ± 1.3* | 21.5 ± 2.8*** | 2.0x IC ₅₀ (145.4 nM) | 9.4 ± 0.6*** | 9.2 ± 0.5*** | 27.7 ± 1.9*** |
| 2.5x IC ₅₀ (916.7 nM) | 10.2 ± 0.3*** | 11.5 ± 0.7*** | 16.1 ± 0.8*** | 2.5x IC ₅₀ (181.7 nM) | 9.5 ± 0.7*** | 10.7 ± 0.6*** | 22.6 ± 1.3*** |
| 3.0x IC ₅₀ (1100.1 nM) | 10.9 ± 1.2*** | 14.8 ± 1.0*** | 18.9 ± 1.4*** | 3.0x IC ₅₀ (218.1 nM) | 14.0 ± 1.4** | 15.2 ± 1.4** | 21.4 ± 0.6** |

Mean±SEM amount of hemoglobin, free heme and hemozoin are represented as fg/cell. The amounts of heme in different parasite lines were determined by the heme fractionation assay (see methods). Parasites were treated with increasing concentrations of PPQ or CQ (at different multiples of their IC₅₀ or LD₅₀ values) and hemoglobin, free heme and hemozoin amounts were measured 32 h later. Data were calculated from 6–8 values per concentration. Statistical comparisons of the drug-treated lines to their untreated controls were performed using two-tailed Mann-Whitney *U* tests. **p*<0.05; ***p*<0.01; ****p*<0.001.