# Supplementary Information

## Isoxazolopyrimidine-based inhibitors of

## *Plasmodium falciparum* dihydroorotate dehydrogenase with antimalarial activity

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**Supplementary Table S1.** X-ray data collection and refinement statistics for compound **15**.

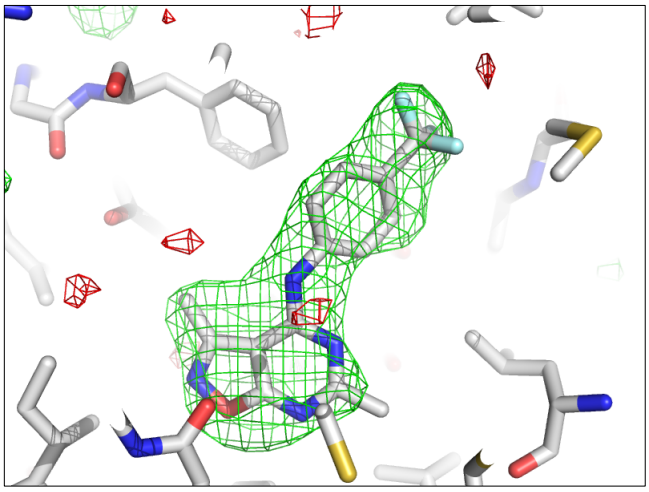
| Data collection | |
|---|---|
| Beam line/detector | ESRF ID23-1/ADSC Q315 |
| Resolution (Å) | 163-1.99 (2.29-1.99) |
| Observations | 137823 (6539) |
| Unique reflections | 35930 (1795) |
| Completeness (spherical) (%) | 46.8 (6.7) |
| Completeness (ellipsoidal) (%) | 90.2 (58.0) |
| Multiplicity | 3.8 (3.6) |
| Mean $I/\sigma I$ | 11.3 (2.0) |
| $R_{merge}$ | 0.088 (0.631) |
| $CC_{1/2}$ | 0.997 (0.709) |
| **Refinement** | |
| Resolution (Å) | 21.8-1.99 (2.05-1.99) |
| Reflections | 35879 (18) |
| $R_{work}/R_{free}$ | 0.163/0.206 (0.255/0.103) |
| Total number of atoms | 6488 |
| Protein atoms | 5891 |
| Ligand atoms | 128 |
| Waters | 469 |
| *Average B-factors (Å$^2$)* | |
| Protein (main chain/side chain) | 43.1/52.2 |
| Ligand atoms | 37.9 |
| Waters | 41.4 |
| *RMS deviations from ideal values* | |
| Bond lengths (Å) | 0.010 |
| Bond angles (°) | 1.18 |

Values for the highest resolution shell are given in parentheses

Preliminary structure refinement was carried out at 2.65 Å,
where data completeness was 98.5% overall (98.7% for 2.70-2.65 Å).

**Supplementary Figure S1. Electron density difference maps in the 15 binding sites.** Initial $F_o$-$F_c$ electron density maps contoured at 3σ (green) and -3σ (red) superposed on the refined protein-inhibitor complex structure. Maps calculated after preliminary refinement of an unliganded protein model against the structure factors of the protein-inhibitor complex. Maps are shown for both subunits A and B observed in the asymmetric unit.

A subunit



B subunit