Supplementary Material

Farnesyl Diphosphate Synthase Inhibitors With Unique Ligand-Binding Geometries

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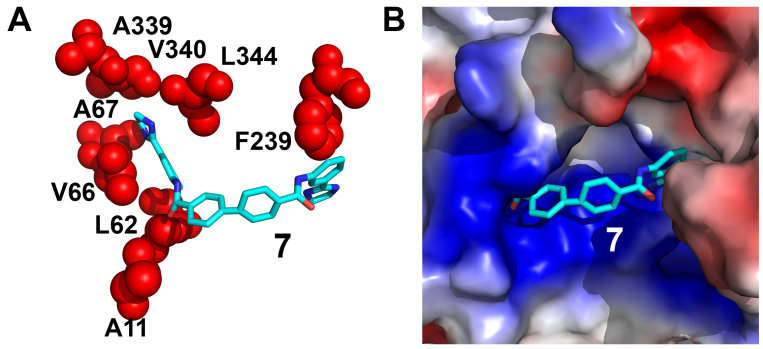
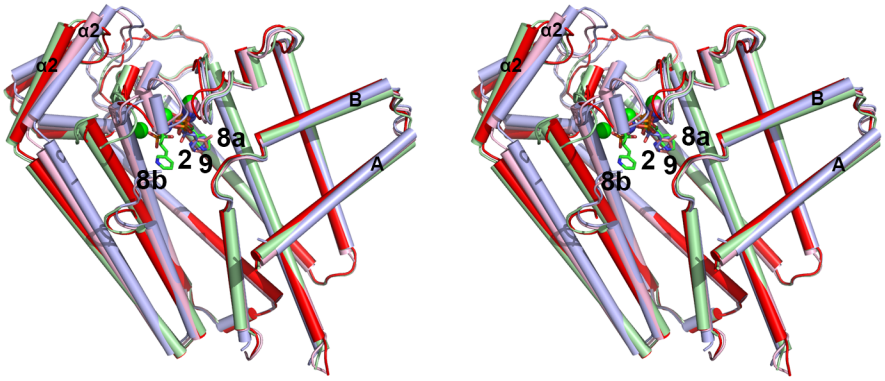
Contents

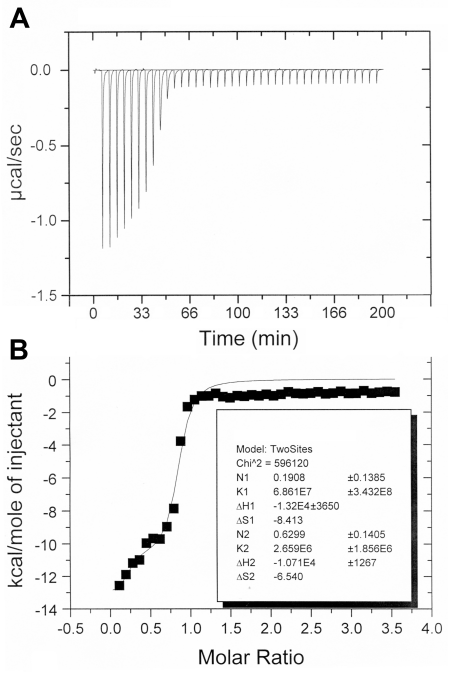
1. **Figure S1: Structural representation of diamidine inhibitor 7 bound to HsFPPS.** (A) Hydrophobic residues close to **7**. (B) Electrostatic surface plot showing solvent exposure of the biphenyl group in **7**.



2. **Figure S2: X-ray structures of TbFPPS.** The color codes are as follows: apo-TbFPPS (PDB ID Code 4RYP) in red; TbFPPS•**8** (PDB ID Code 4RXC) in green; TbFPPS•**2** (PDB ID Code 4RXD) in purple; TbFPPS•**9** (PDB ID Code 4RXE) in pink.



3. **Figure S3:** (A) ITC data for **8** binding to TbFPPS. (B) Fitting curve for **8** binding to TbFPPS.



4. **Expression, purification and crystallization of human and *T. brucei* FPPS**

Expression and purification of human and *T. brucei* FPPS were carried out as described previously.[1, 2] Crystallization of human FPPS with diamidine **7** was performed by adding 3 mg of **7** to 1 mg/mL purified human FPPS. After incubating for 2 days, the mixture was concentrated to 20 mg/mL by using a 30 kDa Amicon. The final co-crystallization was carried out by mixing 2 µL of the concentrated human FPPS/**7** mixture with 2 µL of precipitant (1.2 M Na/K phosphate buffer, pH 5.6 and 25% glycerol) in the presence of 1 mM geranyl diphosphate. Crystals appeared within 2 days and grew to full size within a week at 20°C. Crystals were collected, mounted and stored in liquid nitrogen. Crystallization of *T. brucei* FPPS with compounds **2, 8, 9** was carried out as described previously.[3]

5. Data collection and refinement

Diffraction data were collected at the Life Science Collaborative Team (LS-CAT) beamline 21-ID at the Advanced Photon Source, Argonne National Laboratory. Complete crystallographic results are shown in Table 1. Data were processed by using HKL3000[4] (human FPPS) or HKL2000[5] (TbFPPS). For human FPPS, phases were obtained by using molecular replacement with a human FPPS structure (PDB ID code 2F8Z). The solution was found and the subsequent refinement was carried out in CCP4[6] and Coot[7]. For *T. brucei* FPPS, final phase solutions were obtained by searching against a reported *T. brucei* FPPS structure (PDB ID code 2OGD). These modeled structures were then refined by using CCP4,[6] CNS[8, 9] and Coot.[7] Structural Figures were generated by using PyMOL.[10]

6. Chemicals

Inhibitors were from the batches whose synthesis and characterization were reported earlier and were ≥95% pure as determined by HPLC/MS or microchemical analysis.

7. References

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