Supporting Information

Chemical interrogation of malarial host and parasite kinomes

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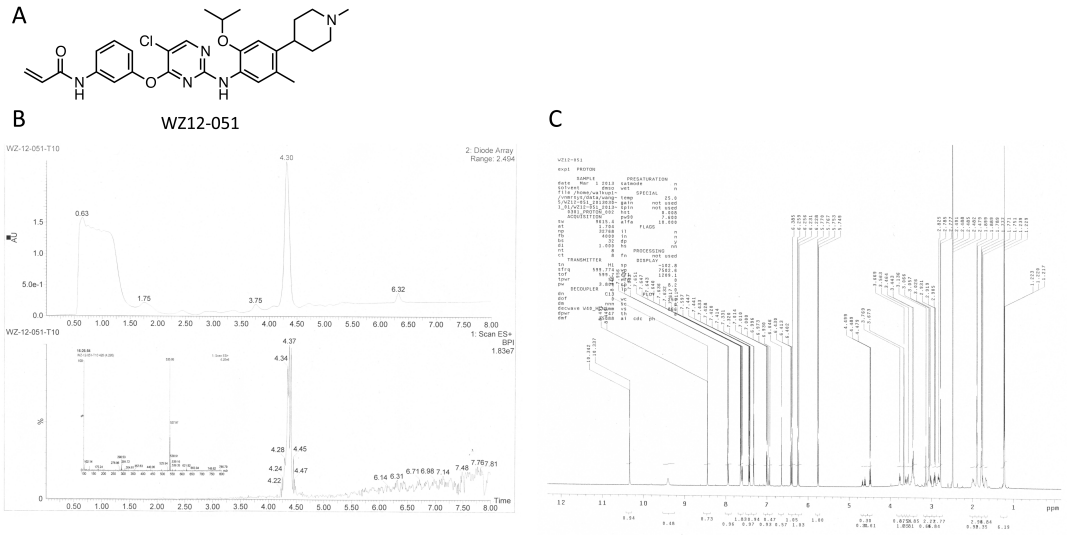

Figure S1. (A) Structure of WZ12-051. (B) Characterization of WZ12-051 by LC-MS. (C) ^{1}H nuclear magnetic resonance spectrum of WZ12-051.

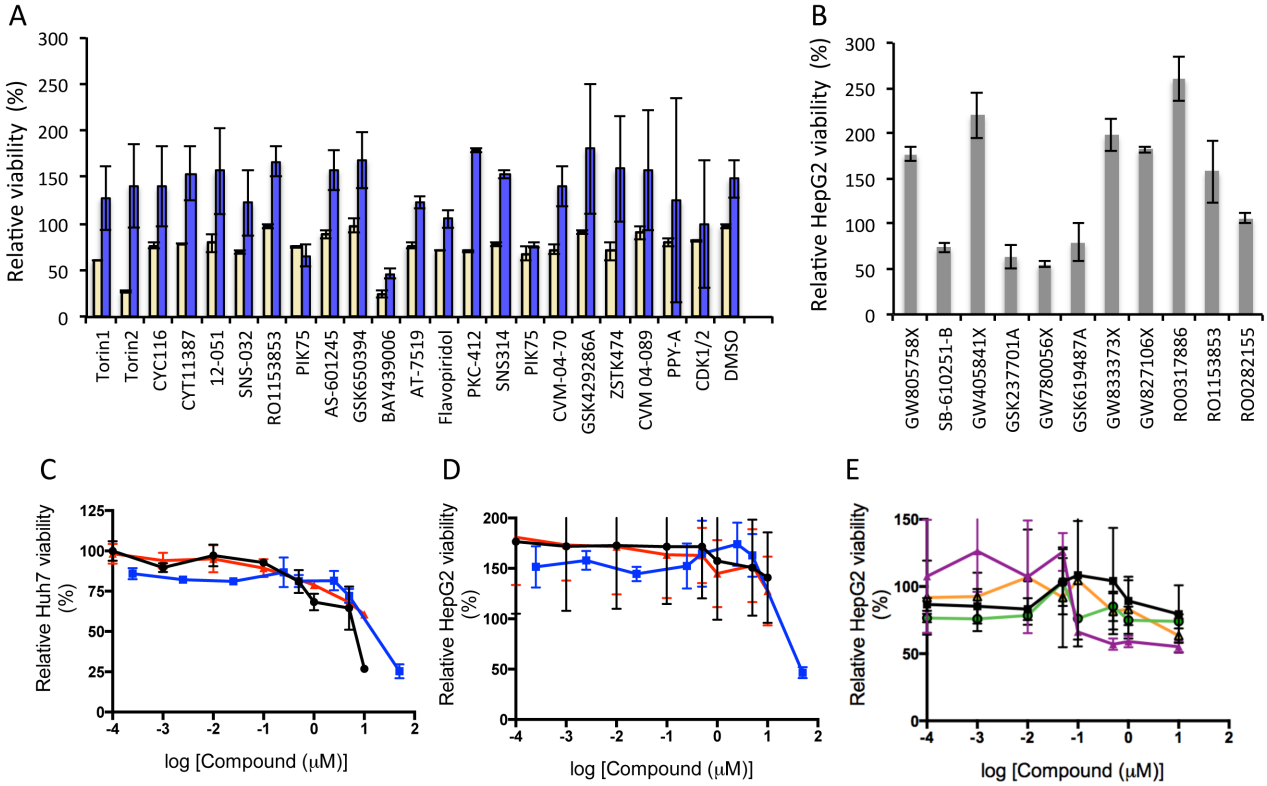

Figure S2. HepG2 and Huh7 viability in the presence of kinase inhibitors. (A) Commercially available kinase inhibitors were tested for toxicity to Huh7 (yellow) and HepG2 (blue) cells using CellTiter-Glo (Promega). All compounds were at 10 μM except BAY439006, which was at 40 μM. (B) Screening hits from the Roche and GSK PKIS libraries were tested for toxicity to HepG2 cells at 10 μM using CellTiter-Fluor (Promega). Due to the limited availability of kinase inhibitors from these libraries they were not tested for toxicity to Huh7 cells. Dose-response curves were generated for every inhibitor, but only compounds that had reduced viability in panels A and B are shown. Dose-response curves for Torin2 (black circles), Torin1 (red triangles) and BAY439006 (blue squares) toxicity to Huh7 and HepG2 cells, (C) and (D), respectively. (E) Dose-response curves for GSK619487A (black circles), GW780056X (purple triangles), GSK237701A (orange squares) and SB-610251-B (green triangles) toxicity to Huh7 cells are shown. Data points in (C), (D), and (E) are connected with lines. All IC_{50} values are above 10 μM except for Torin2 inhibition of Huh7 cells (IC_{50} ~ 3 μM).

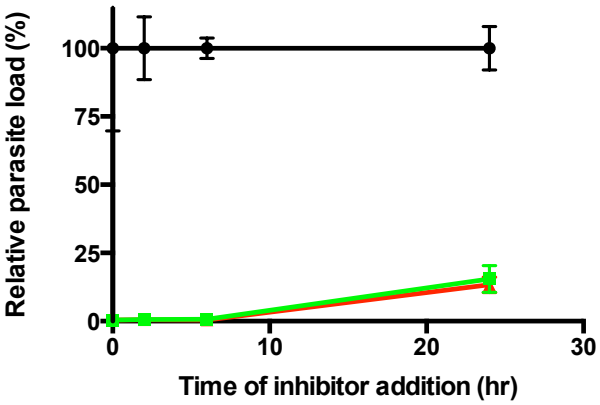

Figure S3. Timecourse of Torin1 and ZSTK474 inhibition of liver stage malaria. A DMSO control (black), Torin1 (green), or ZSTK474 (red) was added -1, 3, 8, and 24 hours after HepG2 infection with *P. berghei* parasites. Compounds were at 10 μM. All parasite levels were measured 48 hours post-infection. Inhibitors have targets that are essential for both early and late stages of parasite development in liver cells.

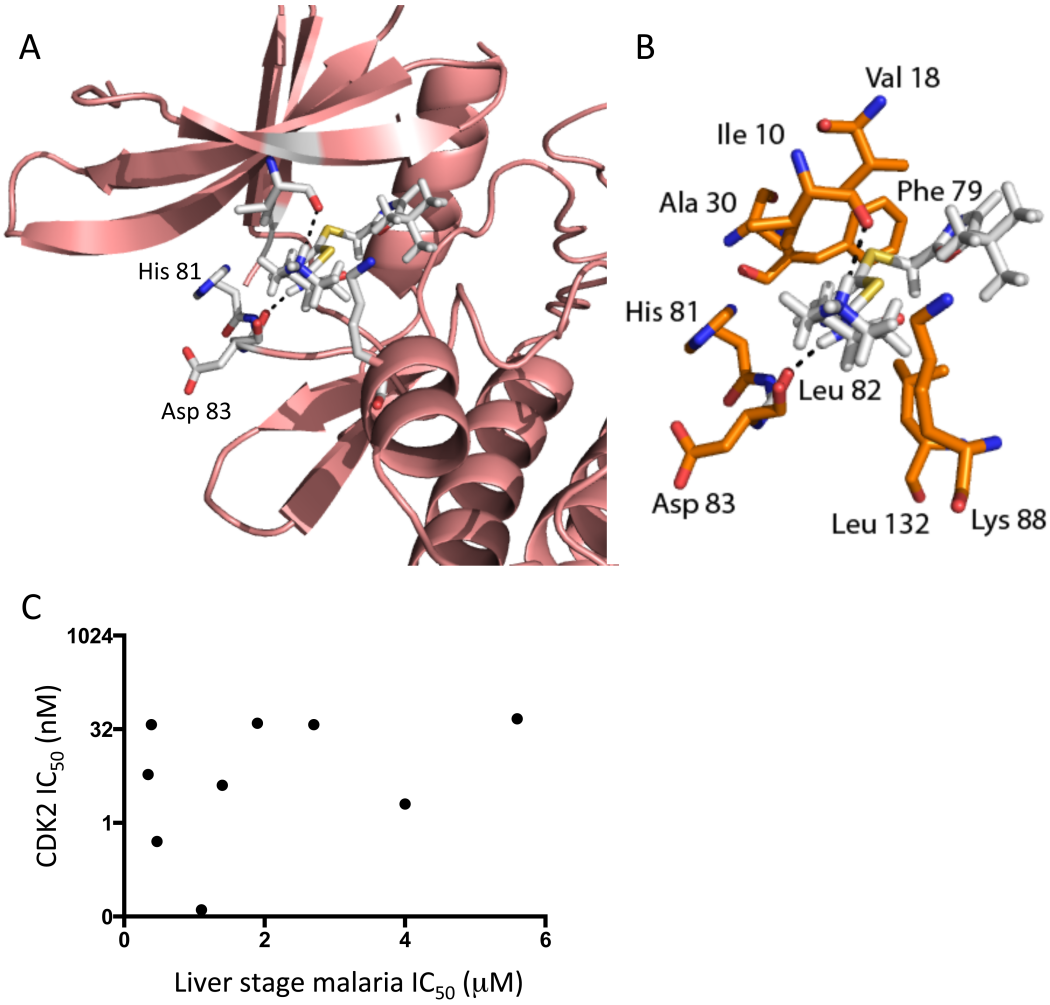

Figure S4. Structure of SNS-032 docked onto the *Pf*PK5 crystal structure (pdb 1V0O). (A) The protein kinase (pink) and SNS-032 carbon (grey), hydrogen (grey), nitrogen (blue), sulfur (yellow) and oxygen (red) atoms are shown. Hydrogen bonds are predicted to form (black dotted lines) between the protonated piperidine nitrogen of SNS-032 and Ile 10, and between the exocyclic amide proton of SNS-032 and Leu 82 (bond lengths < 2.5 Å). His81 and Asp83 are also shown. (B) SNS-032 (grey) is shown with residues in the active site (Ile10, Val18, Ala30, Phe79, and Leu132). Carbon atoms of *Pf*PK5 are in orange. (C) Evaluation of human CDK2 inhibitory activity of nine screening hits as a function of liver stage malaria activity. IC_{50} values for inhibition of human CDK2 are reported based on the product description on the manufacturer's websites and were assessed in a cell-based assay. Note the change in units (nM to μM) for activity against human CDK2 and liver stage malaria. The lack of a correlation between inhibition of CDK2 and inhibition of liver stage *P. berghei* suggests an alternative target is responsible for the observed phenotype.