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Supplementary Materials for

The anticancer human mTOR inhibitor sapanisertib potently inhibits multiple *Plasmodium* kinases and life cycle stages

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The PDF file includes:

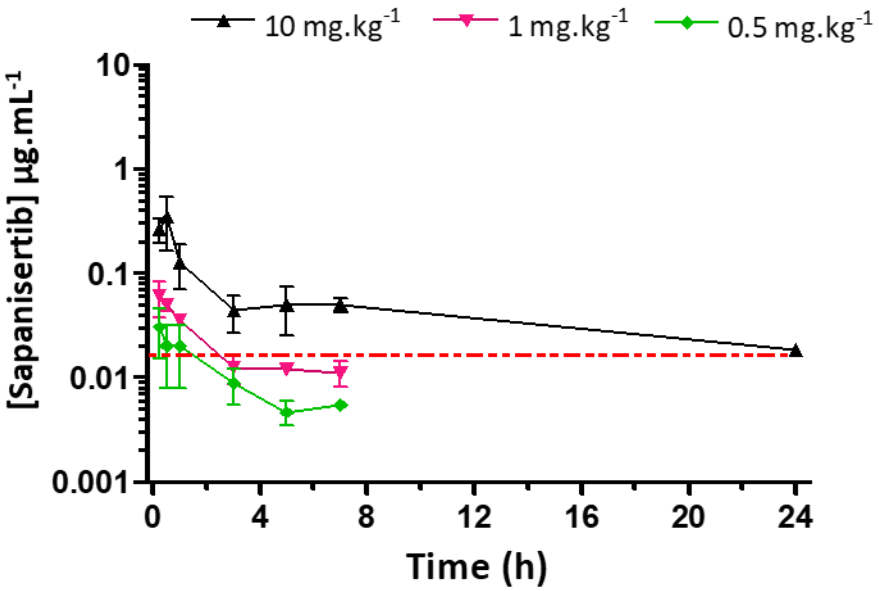
Figs. S1 to S3

Other Supplementary Material for this manuscript includes the following:

Data files S1 to S6
MDAR Reproducibility Checklist

Supplementary Figures

A



B

Parameter	10 mg.kg^{-1}	1 mg.kg^{-1}	0.5 mg.kg^{-1}
C_{max} (µg.mL^{-1})	0.43 (0.14)	0.07 (0.02)	0.03 (0.02)
$AUC_{(0\text{-}24h.)}$ (µg.h.mL^{-1})	0.84 (0.19)	0.14 (0.01)	0.07 (0.05)
T_{max} (h)	0.38 (0.18)	0.38 (0.18)	0.25 (0.00)

Fig. S1. Pharmacokinetic analysis of sapanisertib in a NSG mouse model of *P. falciparum* infection. (**A**) Mean whole blood concentration-time profile of sapanisertib following oral administration of the first dose on day 3 after infection (n=2 per dosing group). The red dashed line represents the in vitro IC_{50} of sapanisertib against *Pf* NF54 (0.058 µM/0.018 µg/mL). (**B**) Pharmacokinetic parameters of sapanisertib. $C_{max;}$ maximum whole blood concentration; AUC (area under the curve) $_{(0\text{-}24h.)}$, average daily exposure; T_{max}, time at which C_{max} is reached following dosing. AUC_{ED90} could not be determined due to the exposure levels of the 0.1 mg/kg and 0.05 mg/kg dosing groups being below the lowest limit of quantification (1 ng/mL).

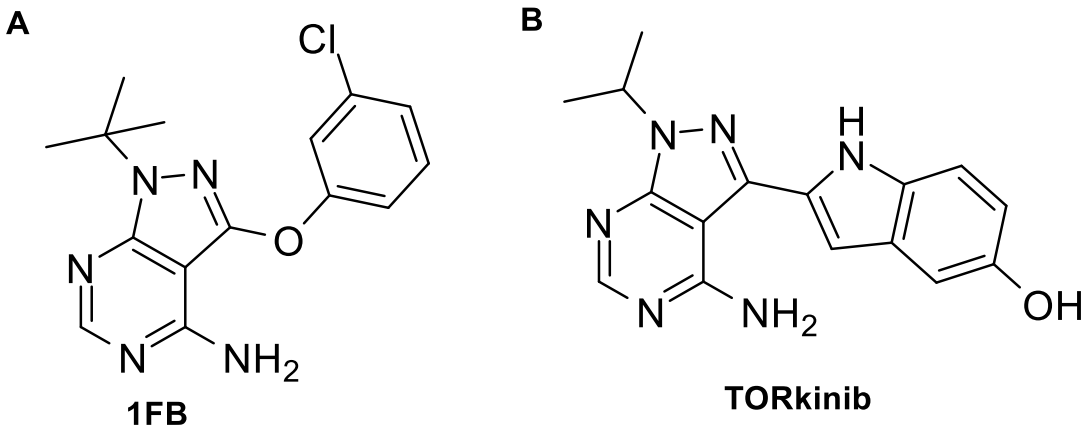


Fig. S2. Structures of inhibitors co-crystalised in kinase structures used for docking studies. (**A**) *Pv*PKG (PDB 5F0A) and (**B**) human mTOR (PDB 4JT5)

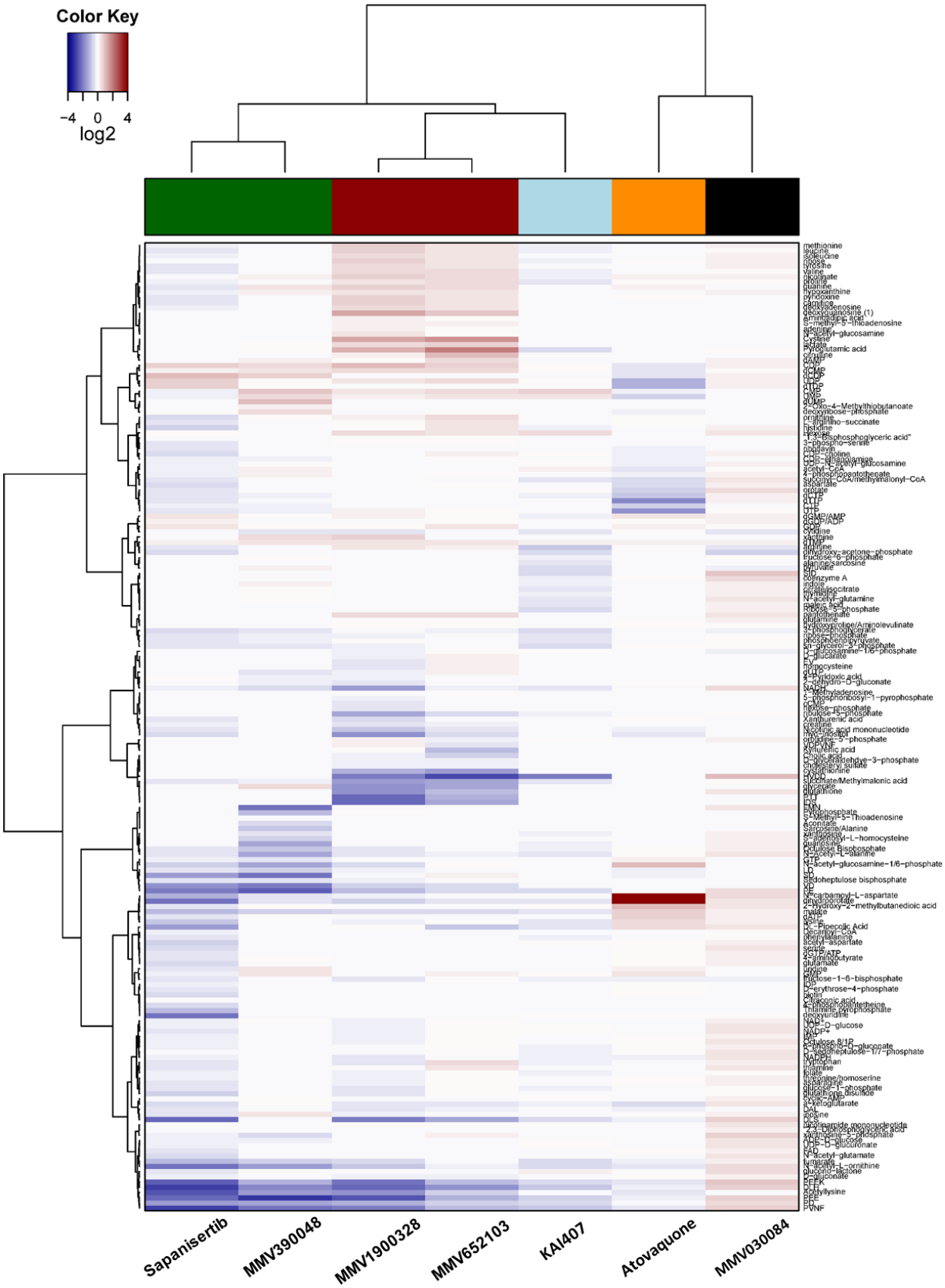


Fig. S3. Metabolite perturbations following treatment of *P. falciparum* trophozoites with kinase inhibitors. Heat map illustrates the Log_2 fold change values of 113 metabolites relative to a no-drug control for each inhibitor tested (Data File S6). Atovaquone was included as a control. The Pearson-Ward method was used for distance clustering.