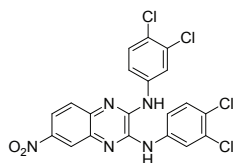
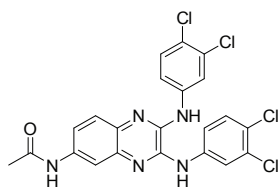


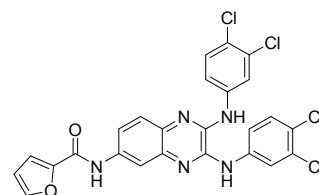
Compound 22



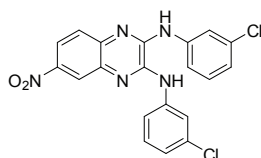
Compound 22c



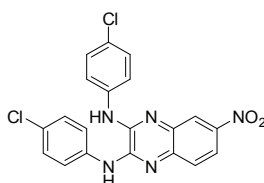
Compound 22f



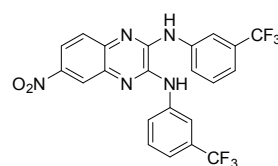
Compound 25



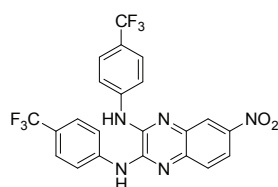
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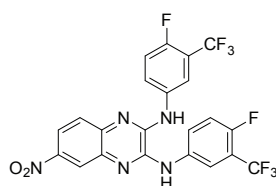
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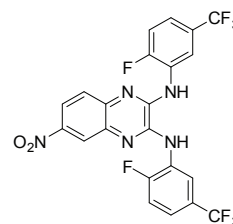
Compound 31



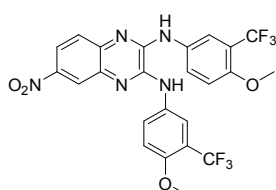
Compound 32



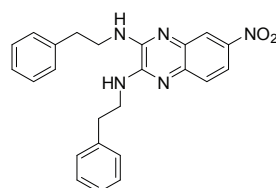
Compound 33



Compound 35



Compound 37



426

427 **Supplementary Figure 1: Structures of compounds**

428

429

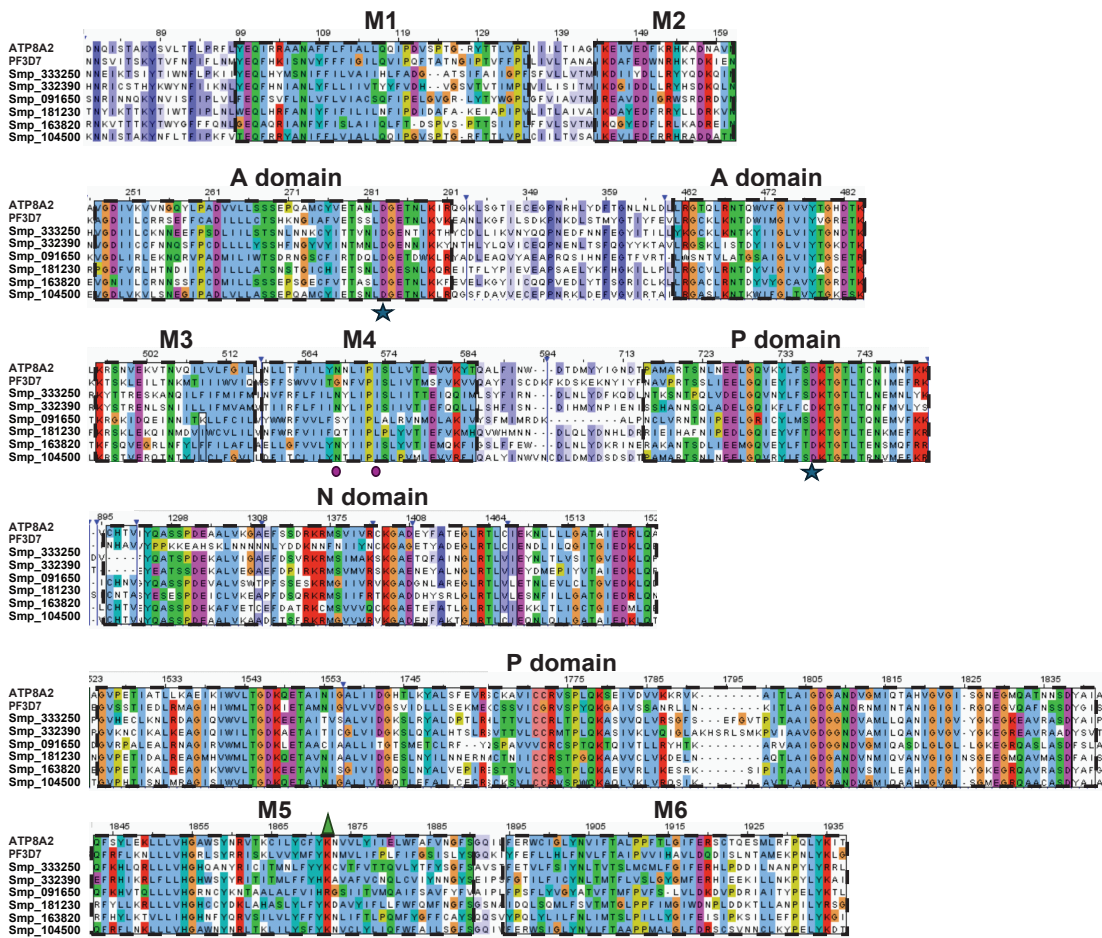
A

Organism	Gene ID	Gene name	Accession no.
Human	ATP8A2	ATP8A2	Q9NTI2
<i>P. falciparum</i>	PF3D7_1219600	ATP2	Q8I5L4
<i>S. mansoni</i>	Smp_091650	Smp_091650	A0A3Q0KJ05
<i>S. mansoni</i>	Smp_104500	Smp_104500	A0A5K4EK18
<i>S. mansoni</i>	Smp_163820	Smp_163820	A0A5K4EW97
<i>S. mansoni</i>	Smp_181230	Smp_181230	A0A3Q0KTZ9
<i>S. mansoni</i>	Smp_332390	Smp_332390	A0A5K4F868
<i>S. mansoni</i>	Smp_333250	Smp_333250	A0A5K4FA05

430

431

B



432

433

**Supplementary Figure 2: Sequence alignment of phospholipid flippases. A)** Lipid flippases used in the alignment. **B)** Sequence alignment of human ATP8A2, *P. falciparum* PfATP2, and six putative lipid-translocating ATPases from *S. mansoni*. The actuator (A), nucleotide binding (N), and phosphorylation (P) domains are shown, as well as the first six transmembrane segments (M1-6). Key conserved residues D (in A domain) and E (P domain) involved in the phosphorylation (DKTGT) and dephosphorylation (DGET) cycle are highlighted by a star. The purple circles highlight the conserved N and I residues located in M4 domain that are important for recognition and release of lipid, respectively. The green triangle indicates the K residues in the M5 domain required for the sensitivity to the lipid subtype [14, 28].

442

443 **List of Supplementary Tables**

444

445 **Supplementary Table 1:** Compound information.

446

447 **Supplementary Table 2:** Activity against *Plasmodium* asexual blood stages, *Schistosoma*  
448 schistosomula and HepG2 cells.

449

450 **Supplementary Table 3:** Single-nucleotide variants for compound **22**-selected clones.

451

452 **Supplementary Table 4:** Copy number variants from compound **22**-selected clones.

453