Supporting Information

Lukens et al. 10.1073/pnas.1320886110

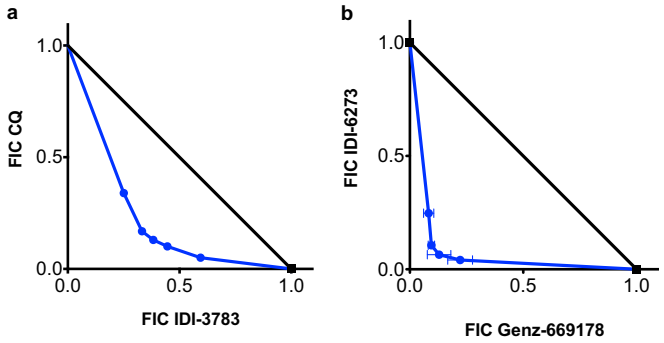
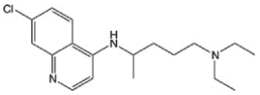
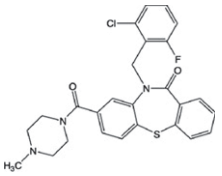
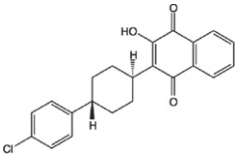
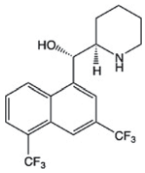


Fig. S1. (*A*) Synergy between paired inhibitors for both PfCRT and PfDHODH. CQ was tested in combination with IDI-3783 at multiple fixed volumetric ratios (10:0, 8:2, 6:4, 5:5, 4:6, 2:8, and 0:10). (*B*) Genz-669178 was tested in combination with IDI-6273 at multiple fixed volumetric ratios (15:0, 12:3, 9:6, 6:9, 3:12, and 0:15). Fractional inhibitory concentrations (FIC) for each drug were calculated and plotted. Synergy was defined as an FIC < 1.0, additivity as FIC = 1.0, and antagonism as FIC > 1.0 (1). Three biological replicates are shown.

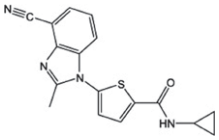
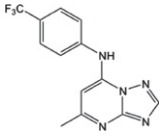
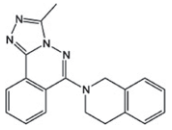
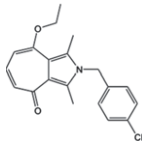
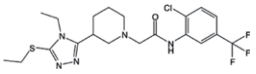
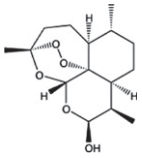
1. Fivelman QL, Adagu IS, Warhurst DC (2004) Modified fixed-ratio isobologram method for studying in vitro interactions between atovaquone and proguanil or dihydroartemisinin against drug-resistant strains of Plasmodium falciparum. *Antimicrob Agents Chemother* 48(11):4097–4102.

Table S1. EC_{50} values for CQ^S, CQ^r, and Dd2:Q352R parasites

Compound	Structure	SMILES	EC_{50} (nM) ± SD		
			Dd2	3D7	Dd2: Q352R
Chloroquine		CCN(CC)CCCC(C)NC1 = C2C = CC(Cl)=CC2 = NC = C1	100 ± 10	8.5 ± 1.3	14 ± 5.9
IDI-3783		CN1CCN(CC1)C(=O)C1 = CC = C2SC3 = CC = CC = C3C(=O)N(CC3 = C(F)C = CC = C3Cl)C2 = C1	3.7 ± 0.45	27,000 ± 15,000	4,400 ± 1900
Atovaquone		OC1 = C(C2CCC(CC2)C2 = CC = C(Cl)C = C2)C(=O)C(=O)C2 = CC = CC = C12	0.12 ± 0.025	0.15 ± 0.0098	0.16 ± 0.068
Mefloquine		O[C@H]([C@H]1CCCCN1)C1 = C2C = CC = C(C2 = NC(=C1)C(F)(F)F)C(F)(F)F	11 ± 0.82	14 ± 2.3	10 ± 0.77

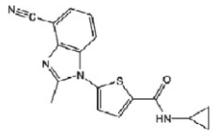
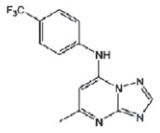
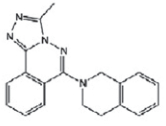
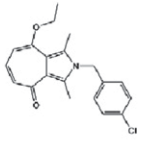
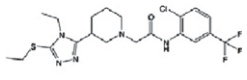
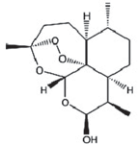
EC_{50} values are mean ± SD of three biological replicates, each with triplicate measurements.

Table S2. EC_{50} values for 3D7, 3D7 E182D, and 3D7 E182D: D182E parasites

Compound	Structure	SMILES	EC_{50} (nM) ± SD		
			3D7	3D7 E182D	3D7 E182D: D182E
Genz-669178		CC1 = NC2 = C(C = CC = C2N1C1 = CC = C(S1)C(=O)NC1CC1)C#N	13 ± 2.3	73 ± 0.63	22 ± 2.9
DSM74		FC(F)(F)C1 = CC = C(NC2 = CC(C)=NC3 = NC = NN32)C = C1	130 ± 25	710 ± 130	190 ± 20
IDI-6253		CC1 = NN = C2C3 = C(C = CC = C3)C(N4CCC5 = C(C = CC = C5)C4)=NN21	12,000 ± 1,400	11,000 ± 700	17,000 ± 2,000
IDI-6273		CCOC1 = CC = CC(=O)C2 = C(C)N(CC3 = CC = C(Cl)C = C3)C(C)=C12	2,300 ± 202	210 ± 21	4,000 ± 410
GSK-3		CCSC1 = NN = C(N1CC)C2CCCN(C2)CC(NC3 = C(Cl)C = CC(C(F)(F)F)=C3)=O	320 ± 34	1,800 ± 260	480 ± 47
Dihydro-artemisinin		C[C@]1(O2)CC[C@@]3([H])[C@H](C)CC[C@@]4([H])[C@@H](C)[C@@H](O)O[C@@]2([H])[C@]43OO1	2.7 ± 0.079	1.8 ± 0.071	2.9 ± 1.1

EC_{50} values are mean ± SD of three biological replicates, each with triplicate measurements. SMILES, simplified molecular-input line-entry system.

Table S3. EC_{50} values for Dd2 parasites selected with a combination of PfDHODH inhibitors (Genz-669178 and IDI-6273)

Compound	Structure	SMILES	Dd2	Selection 1	Selection 2	Selection 3	Selection 4
Genz-669178		CC1 = NC2 = C(C = CC = C2N1C1 = CC = C(S1)C(=O) NC1CC1)C#N	3.5 ± 0.36	3.8 ± 1.8	3.6 ± 1.4	3.8 ± 0.65	3.4 ± 0.85
DSM74		FC(F)(F)C1 = CC = C(NC2 = CC(C)=NC3 = NC = NN32)C = C1	1,200 ± 150	1,700 ± 1,080	1,300 ± 510	1,100 ± 430	1,300 ± 4,500
IDI-6253		CC1 = NN = C2C3 = C(C = CC = C3)C(N4CCC5 = C(C = CC = C5)C4)=NN21	70 ± 22	67 ± 15	59 ± 12	72 ± 26	73 ± 36
IDI-6273		CCOC1 = CC = CC(=O)C2 = C(C)N(CC3 = CC = C(Cl)C = C3)C(C)=C12	54 ± 22	82 ± 43	79 ± 41	49 ± 13	52 ± 10
GSK-3		CCSC1 = NN = C(N1CC) C2CCCN(C2)CC(NC3 = C(Cl)C = CC(C(F)(F)F)=C3)=O	1,800 ± 240	1,900 ± 450	1,900 ± 290	1,900 ± 330	2,000 ± 380
Dihydro-artemisinin		C[C@]1(O2)CC[C@@] 3([H])[C@H](C)CC[C@@] 4([H])[C@@H](C)[C@@H](O) O[C@@]2([H])[C@]43OO1	3.8 ± 1.0	3.4 ± 0.43	3.1 ± 0.051	3.9 ± 1.9	4.3 ± 1.5

EC_{50} values are mean ± SD of three biological replicates, each with triplicate measurements.

Table S4. Purchased compound sources

Source	Catalog	SMILES	IDI number
Sigma-Aldrich	C6628	CCN(CC)CCCC(C)NC1 = C2C = CC(Cl)=CC2 = NC = C1	Chloroquine
USP	1044651	OC1 = C(C2CCC(CC2)C2 = CC = C(Cl)C = C2)C(=O)C(=O)C2 = CC = CC = C12	Atovaquone
Sigma-Aldrich	M2319	O[C@H]([C@H]1CCCCN1)C1 = C2C = CC = C(C2 = NC(=C1)C(F)(F)F)C(F)(F)F	Mefloquine
ChemDiv	C380-0605	CN1CCN(CC1)C(=O)C1 = CC = C2SC3 = CC = CC = C3C(=O)N(CC3 = C(F)C = CC = C3Cl)C2 = C1	IDI-3783
ChemDiv	4861–0080	CCOC1 = CC = CC(=O)C2 = C(C)N(CC3 = CC = C(Cl)C = C3)C(C)=C12	IDI-6273
Asinex	ASN10333790	CCSC1 = NN = C(C2CCCN(CC(=O)NC3 = CC(=CC = C3Cl)C(F)(F)F)C2)N1CC	GSK-756619