**Supplementary information**

**Evaluation of the antimalarial activity of SAM13-2HCl with morpholine amide (SKM13 derivative) against multiple antimalarial drug-resistant *Plasmodium* *falciparum* and *Plasmodium berghei* - infected ICR mice**

**Supplementary method**

NMR of each candidate compound

**Supplementary figures**

**Fig. S1. Raw data of IC50s**

**Fig. S2. Raw data of PK**

**Fig. S3. Adsorption data**

**Supplementary method**

All SAM series were prepared as HCl salts for further experiments and purified in MeOH and diethyl ether.

Synthesis of **SAM09-2HCl** and **SAM11-2HCl**

**SAM09** and **SAM11** were obtained by four steps: 1) a coupling reaction of Boc-Phe-OH and NHS by DCC, 2) an amide formation by reaction with a variety of amines, 3) Boc deprotection, and 4) a palladium coupling with 4,7-dichloroquinoline. **SAM09** 1H NMR (400 MHz, CDCl3) δ 2.19 (s, 6H), 2.22-2.40 (m, 2H), 3.17-3.36 (m, 4H), 4.39-4.44 (m, 1H), 6.44 (d, 1H, NH, *J* = 5.6 Hz), 7.12-7.32 (m, 7H), 7.44 (dd, 1H, *J* = 8.3, 1.5 Hz), 7.78 (d, 1H, *J* = 2.2 Hz), 8.15 (d, 1H, *J* = 9.0 Hz), 8.33 (d, 1H, NH, *J* = 5.6 Hz). **SAM11** 1H NMR (500 MHz, CDCl3) δ 1.04 (t, 6H, *J* = 7.0 Hz), 2.81 (q, 4H, *J* = 7.5 Hz), 2.84-3.01 (m, 2H), 3.27 (m, 2H), 3.45-3.64 (m, 2H), 4.31-4.39 (m, 1H), 6.34 (d, 1H, *J* = 5.5 Hz), 6.52 (brs, 1H, NH), 7.16-7.32 (m, 5H), 7.34 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.84 (d, 1H, *J* = 9.5 Hz), 7.86 (d, 1H, *J* = 1.5 Hz), 8.39 (d, 1H, *J* = 6.0 Hz), 8.83 (brs, 1H, NH).

Synthesis of **SAM10-2HCl** ~ **SAM17-HCl-TFA**

**SAM10**, **SAM12**, **SAM13** were obtained from 2-bromoethylamine hydrobromide, and **SAM14-17** obtained from Fmoc-Gly-OH, which is described in **Fig 1**. Most important step was Horner-Wadsworth-Emmons reaction with **15** using DBU and LiCl for a mild condition.

**SAM10-2HCl** 1H NMR (500 MHz, CD3OD) δ) 1.00 (t, 6H, *J* = 7.5 Hz), 2.50-2.57 (m, 6H), 3.11-3.15 (m, 2H), 3.26-3.31 (m, 2H), 4.58-4.65 (m, 1H), 5.99 (dd, 1H, *J* = 15.0 , 1.5 Hz), 6.41 (d, 1H, *J* = 5.5 Hz), 6.83 (dd, 1H, *J* = 15.5, 5.0 Hz), 7.09-7.33 (m, 5H), 7.40 (dd, 1H, *J* = 9.5, 2.5 Hz) ,7.75 (d, 1H, *J* = 2.0 Hz), 8.17 (d, 1H, *J* = 9.5 Hz), 8.27 (d, 1H, *J* = 5.5 Hz).

**SAM12-2HCl** 1H NMR (400 MHz, CD3OD) δ 1.69-2.05(m, 6H), 2.89-3.02 (m, 2H), 3.14-3.36 (m, 4H), 3.51-3.73 (m, 4H), 4.88-5.01 (m, 1H), 6.21 (d, 1H, *J* = 15.6 Hz), 6.80 (d, 1H, *J* = 6.8 Hz), 6.94 (dd, 1H, *J* = 15.2, 5.2 Hz), 7.09-7.38 (m, 5H), 7.71 (dd, 1H, *J* = 9.2, 1.6 Hz), 7.86 (d, 1H, *J* = 2.0 Hz), 8.31 (d, 1H, *J* = 6.8 Hz), 8.55(d, 1H, *J* = 9.2 Hz), 8.97 (d, 1H, NH, *J* = 7.6 Hz).

**SAM13-2HCl** 1H NMR (400 MHz, CD3OD) δ 3.08-3.19 (m, 2H), 3.23-3.32 (m, 4H), 3.51-3.69 (m, 4H), 3.82 (t, 2H, *J* = 9.6 Hz), 3.97-4.08 (m, 2H), 4.98-5.06 (m, 1H), 6.23 (d, 1H, *J* = 15.6 Hz), 6.80 (d, 1H, *J* = 7.2 Hz), 6.94 (dd, 1H, *J* = 15.6, 5.6 Hz), 7.15-7.36 (m, 5H), 7.70 (dd, 1H, *J* = 9.2, 1.6 Hz), 7.86 (d, 1H, *J* = 2.0 Hz), 8.31 (d, 1H, *J* = 6.8 Hz), 8.55(d, 1H, *J* = 9.2 Hz).

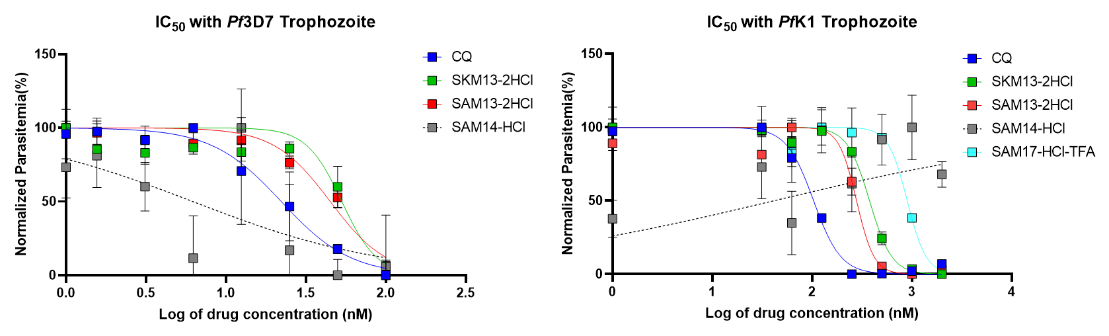
**SAM14-HCl** 1H NMR (400 MHz, CD3OD) δ 3.15-3.31 (m, 2H), 3.92 (ABq, 2H, *J* = 16.8 Hz), 4.33-4.37 (m, 2H), 4.95-5.06 (m, 1H), 6.20 (dd, 1H, *J* = 15.6, 1.2 Hz), 6.76 (d, 1H, *J* = 7.2 Hz), 6.89 (dd, 1H, *J* = 10.0, 5.6 Hz), 7.10-7.36 (m, 11H), 7.70 (dd, 1H, *J* = 9.2, 1.6 Hz), 7.84 (d, 1H, *J* = 1.6 Hz), 8.28 (d, 1H, *J* = 7.2 Hz), 8.42 (brs, 1H, NH), 8.49 (d, 1H, *J* = 6.8 Hz).

**SAM15-HCl** 1H NMR (400 MHz, CD3OD) δ 0.90 (t, 3H, *J* = 7.2 Hz), 1.26-1.38 (m, 2H), 1.40-1.50 (m, 2H), 3.12-3.32 (m, 4H), 3.92 (ABq, 2H, *J* = 16.8 Hz), 4.95-5.05 (m, 1H), 6.19 (dd, 1H, *J* = 15.6, 2.0 Hz), 6.77 (d, 1H, *J* = 7.2 Hz), 6.90 (dd, 1H, *J* = 15.6, 5.6 Hz), 7.10-7.36 (m, 5H), 7.72 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.84 (d, 1H, *J* = 2.0 Hz), 8.29 (d, 1H, *J* = 6.8 Hz), 8.47 (d, 1H, *J* = 7.6 Hz), 8.93 (d, 1H, NH, *J* = 8.0 Hz).

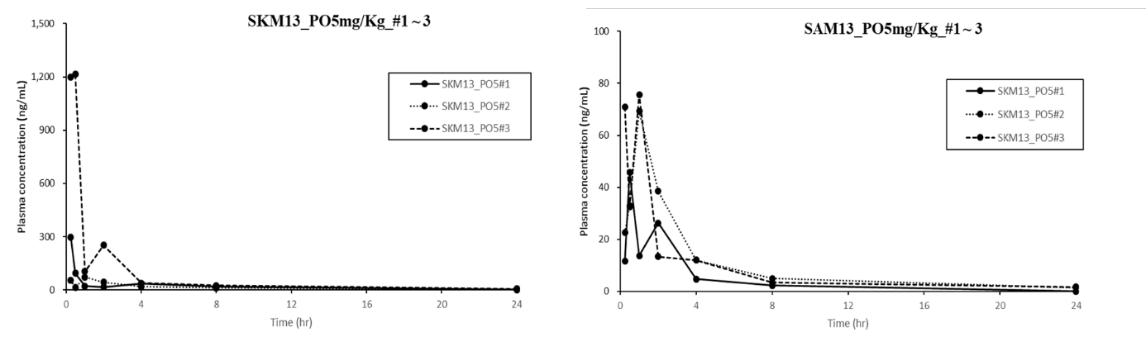
**SAM16-HCl** 1H NMR (400 MHz, CD3OD) δ 1.10 (d, 6H, *J* = 6.8 Hz), 3.16-3.26 (m, 2H), 3.83 (ABq, 2H, *J* = 18.0 Hz), 3.87-3.98 (m, 1H), 4.95-5.06 (m, 1H), 6.23 (d, 1H, *J* = 7.6 Hz), 6.78 (d, 1H, *J* = 6.8 Hz), 6.90 (dd, 1H, *J* = 15.6, 5.2 Hz), 7.08-7.36 (m, 5H), 7.70 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.85 (d, 1H, *J* = 2.0 Hz), 8.29 (d, 1H, *J* = 6.4 Hz), 8.51 (d, 1H, *J* = 9.2 Hz), 8.95 (d, 1H, NH, *J* = 7.6 Hz).

**16** 1H NMR (400 MHz, CD3OD) δ 1.47 (s, 9H), 3.18-3.32 (m, 2H), 3.35-3.56 (m, 8H), 3.78 (brs, 1H, NH), 4.12 (ABq, 2H, *J* = 17.2 Hz), 4.95-5.05 (m, 1H), 6.23 (dd, 1H, *J* = 15.2, 2.8 Hz), 6.77 (d, 1H, *J* = 7.2 Hz), 6.91 (dd, 1H, *J* = 15.6, 5.6 Hz), 7.12-7.35 (m, 5H), 7.72 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.85 (d, 1H, *J* = 2.0 Hz), 8.29 (d, 1H, *J* = 7.2 Hz), 8.48 (d, 1H, *J* = 5.6 Hz), 8.92 (d, 1H, NH, *J* = 7.6 Hz).

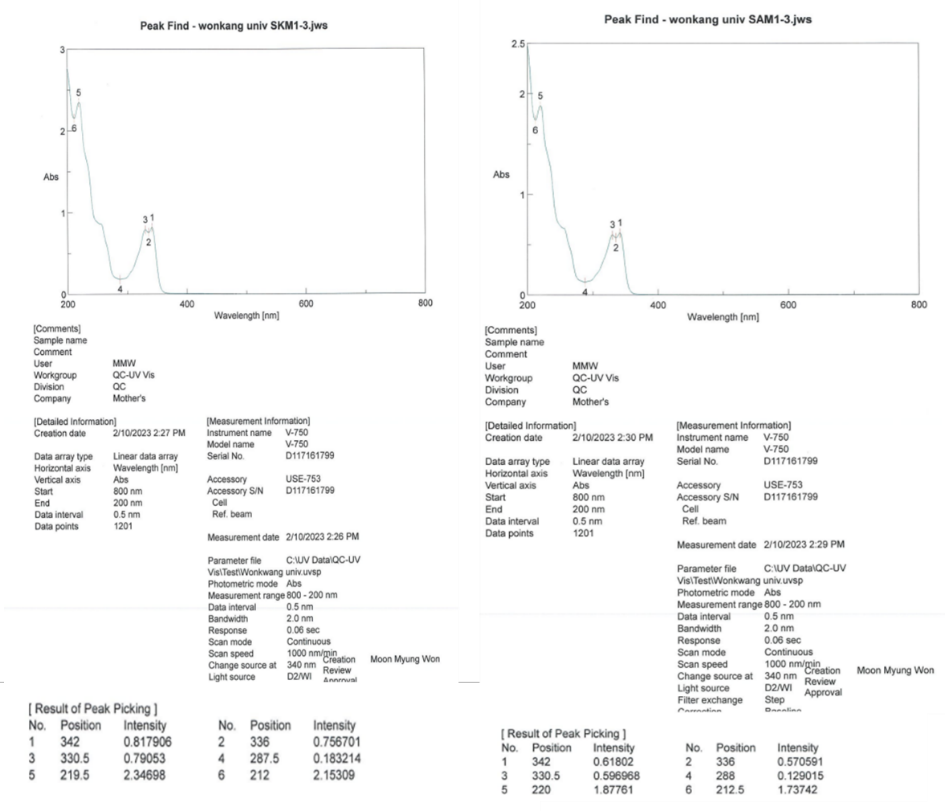
**SAM17-HCl-TFA** 1H NMR (400 MHz, CD3OD) δ 3.14-3.34 (m, 6H), 3.77 (s, 4H), 4.14 (ABq, 2H, *J* = 17.2 Hz), 4.96-5.05 (m, 1H), 6.24 (dd, 1H, *J* = 15.6, 1.6 Hz), 6.77 (d, 1H, *J* = 7.6 Hz), 6.92 (dd, 1H, *J* = 15.6, 5.6 Hz), 7.08-7.35 (m, 5H), 7.72 (dd, 1H, *J* = 9.2, 2.4 Hz), 7.85 (d, 1H, *J* = 1.6 Hz), 8.29 (d, 1H, *J* = 7.2 Hz), 8.47 (d, 1H, *J* = 5.2 Hz).



**Fig.S1. Raw data of IC50s**

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**Fig.S2. Raw data of PK**

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**Fig. S3. Adsorption data**