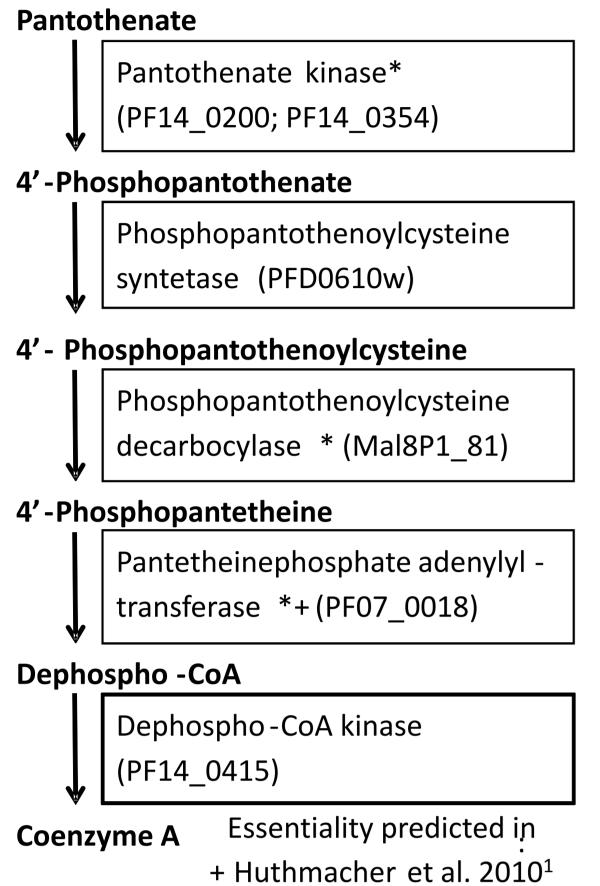


Discovery of chemically diverse compounds targeting the Plasmodium falciparum coenzyme A pathway

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1) Coenzyme A synthesis pathway



Plata et al. 2010²

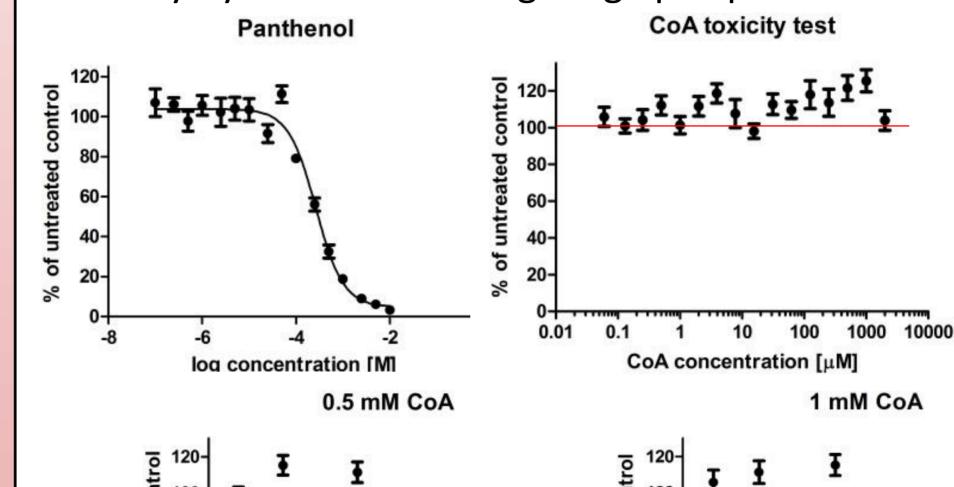
The five enzymatic steps of CoA synthesis highly conserved.

However, the amino acid sequences of the enzymes catalysing the reactions show low conservation between species¹.

could allow This specifically target the Plasmodium falciparum enzymes without affecting the human host.

2) Chemical rescue of growth inhibition

The principal idea of the chemical rescue approach is that supplementation of an unbranched pathway's end product - in this case CoA - should negate, or at least alleviate, negative growth effects of compounds inhibiting any step in this pathway. (Adapted from a study by Yeh et al investigating apicoplast function³).

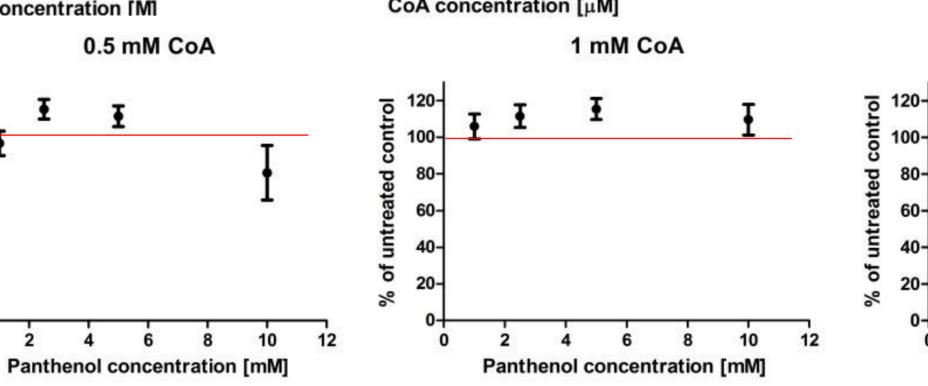


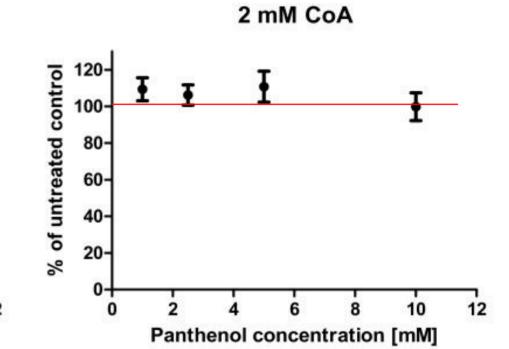
MMV011438 (3D7; HEK293)

MMV665820 (3D7; HEK293)

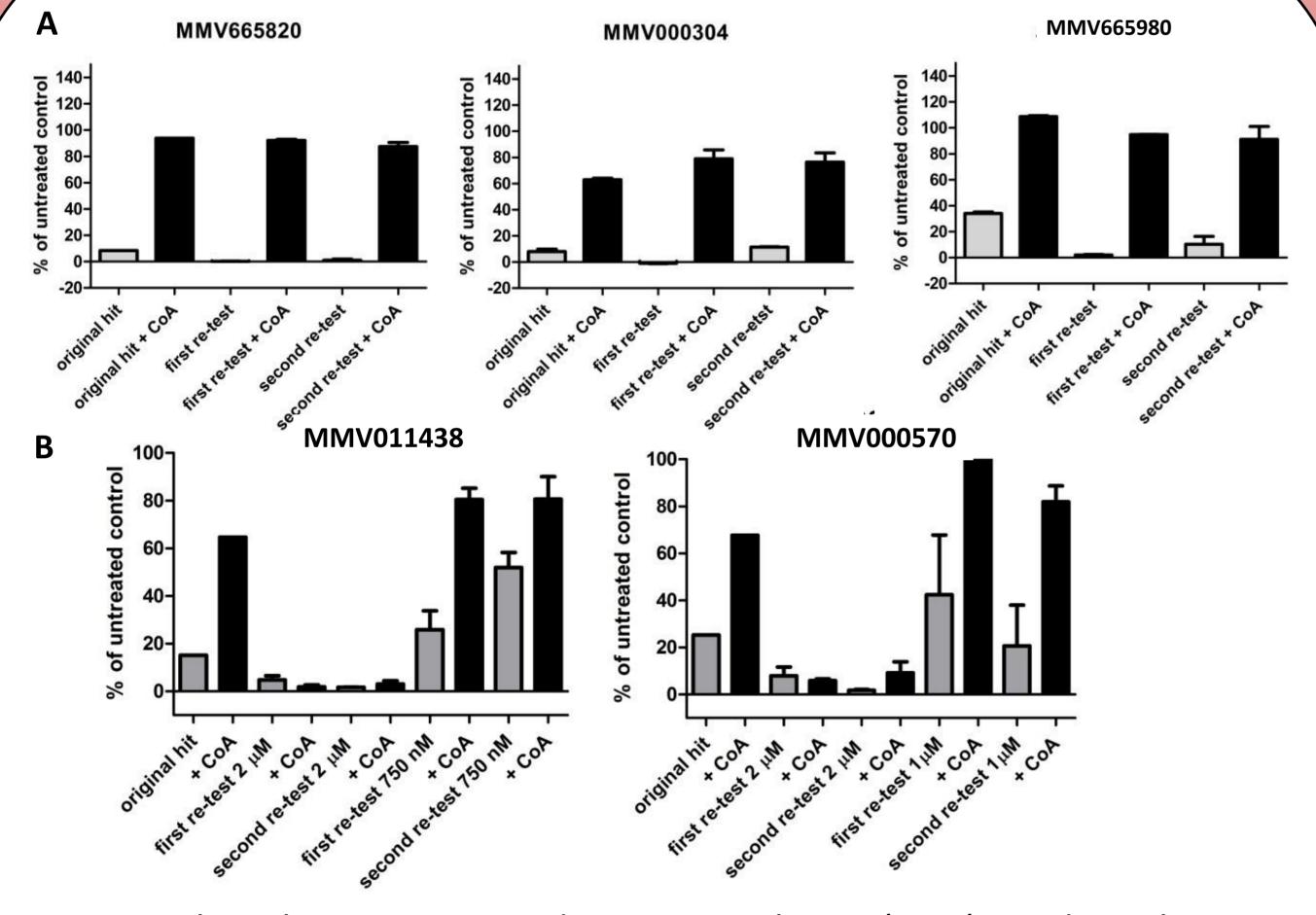
Amb4317088 (3D7; HEK293)

Panthenol is a known *Pf* pantothenate kinase inhibitor that causes growth inhibition of the parasite in vivo⁴. action can be reversed by supplementation of CoA. Error bars indicate +/- SEM.



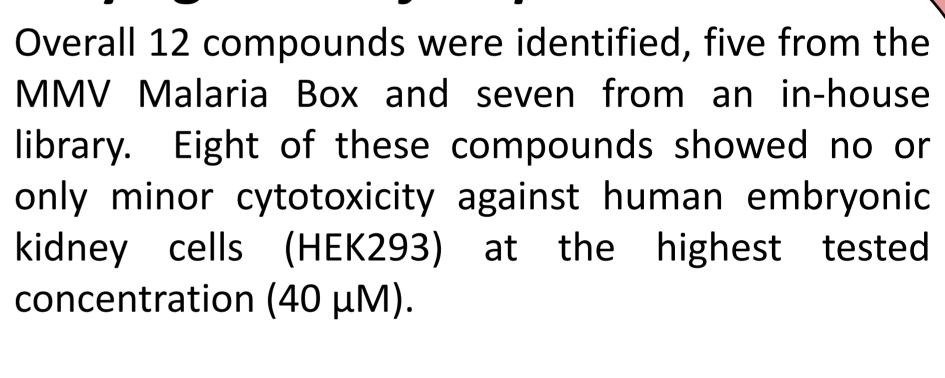


3) MMV Malaria Box - confirmed hits



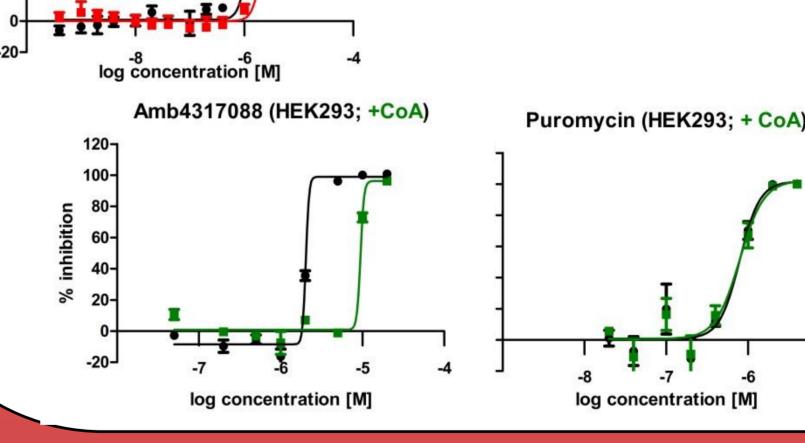
graphs show compound activity alone (grey) and with CoA substitution (black). A Original hit and two re-tests from solids at 2 μM compound concentration; **B** Original hit, two re-tests from solid at 2 µM concentration and two re-tests near the individual compound IC_{80} . Error bars indicate +/- SEM.

4) Selectivity against P. falciparum



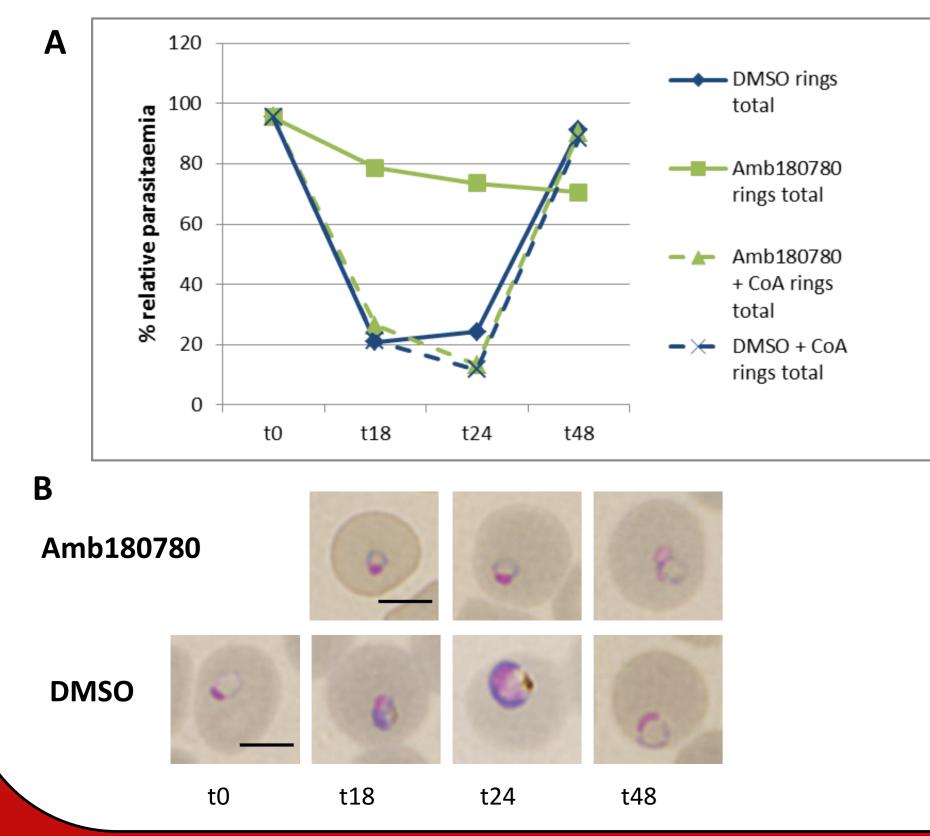
Five compounds had moderate selectivity indices (SI) between 5 and 18 times more effective on Pf compared to HEK293.

Only two compounds showed no parasite specificity and one compound was found to be of too low activity against *P. falciparum* to calculate a SI.



Compound cytotoxicity could be alleviated by CoA addition, whereas the toxicity of puromycin, a general protein synthesis inhibitor, was not affected.

5) Parasite stage of action and treatment phenotype



A Parasites treated with Amb180780 (solid green line) appear throughout the time course. CoA addition rescues the progression through the parasite stages (dashed green line)

B Representative Giemsa stained bright field microscopic images showing the predominant parasite phenotype at each time point for compound treatment (top panel) and DMSO control (bottom panel). Scale bar 5 µm.

Literature

- 1. Huthmacher et al, BMC Syst Biol 2010, **4:**120.
- 2. Plata et al, Mol Syst Biol 2010, **6:**408.
- 3. Yeh and DeRisi, *PLoS Biol* 2011, **9:**e1001138.
- 4. Saliba et al, Antimicrob Agents Chemother 2005, 49:632-637. **Read the complete article:** Fletcher and Avery, *Malar J.* 2014 Aug 31;13(1):343. [Epub ahead of print]

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