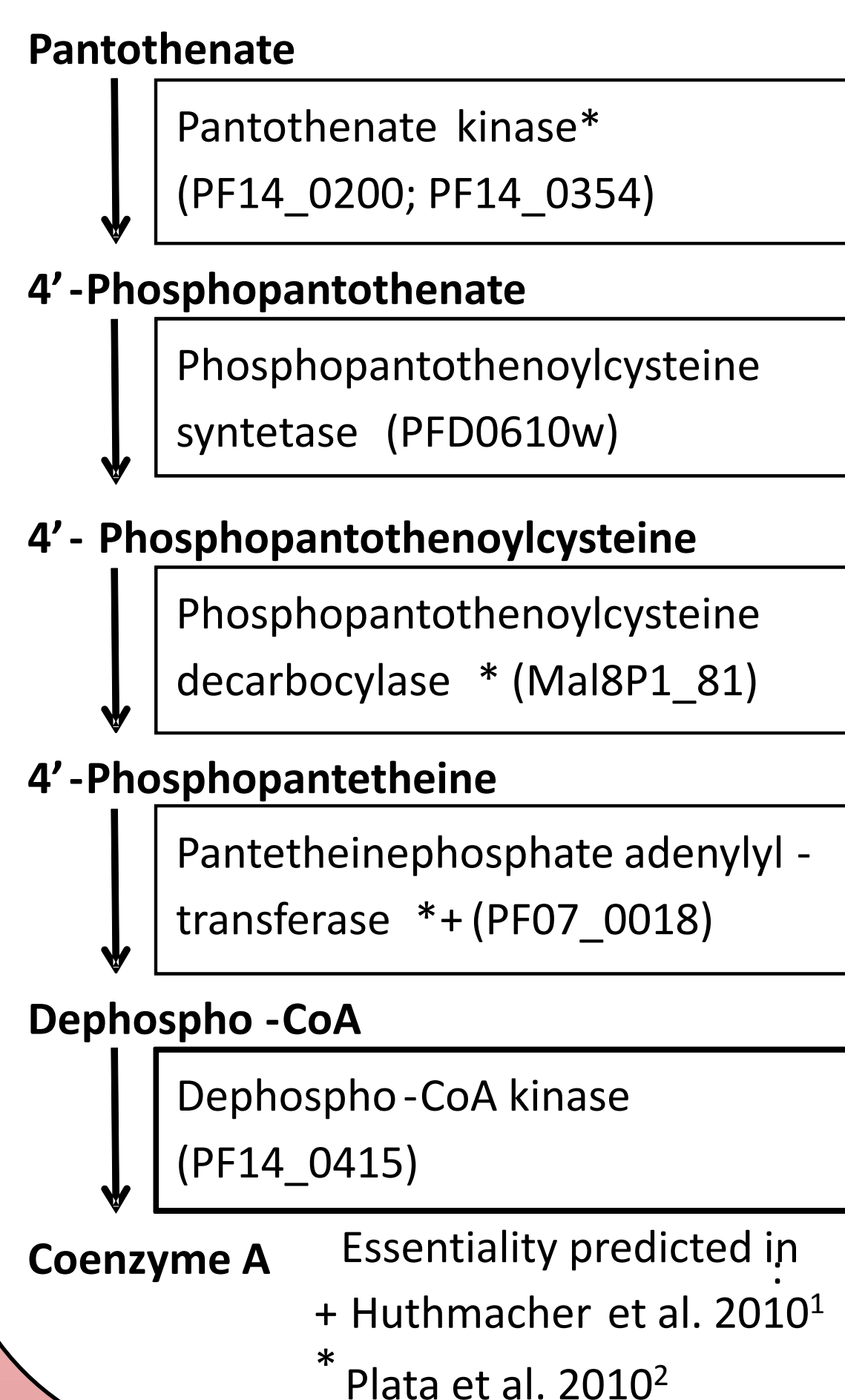


# Discovery of chemically diverse compounds targeting the *Plasmodium falciparum* coenzyme A pathway

S Fletcher and VM Avery

ESKITIS Institute for Drug Discovery, Griffith University, Brisbane, QLD AUSTRALIA

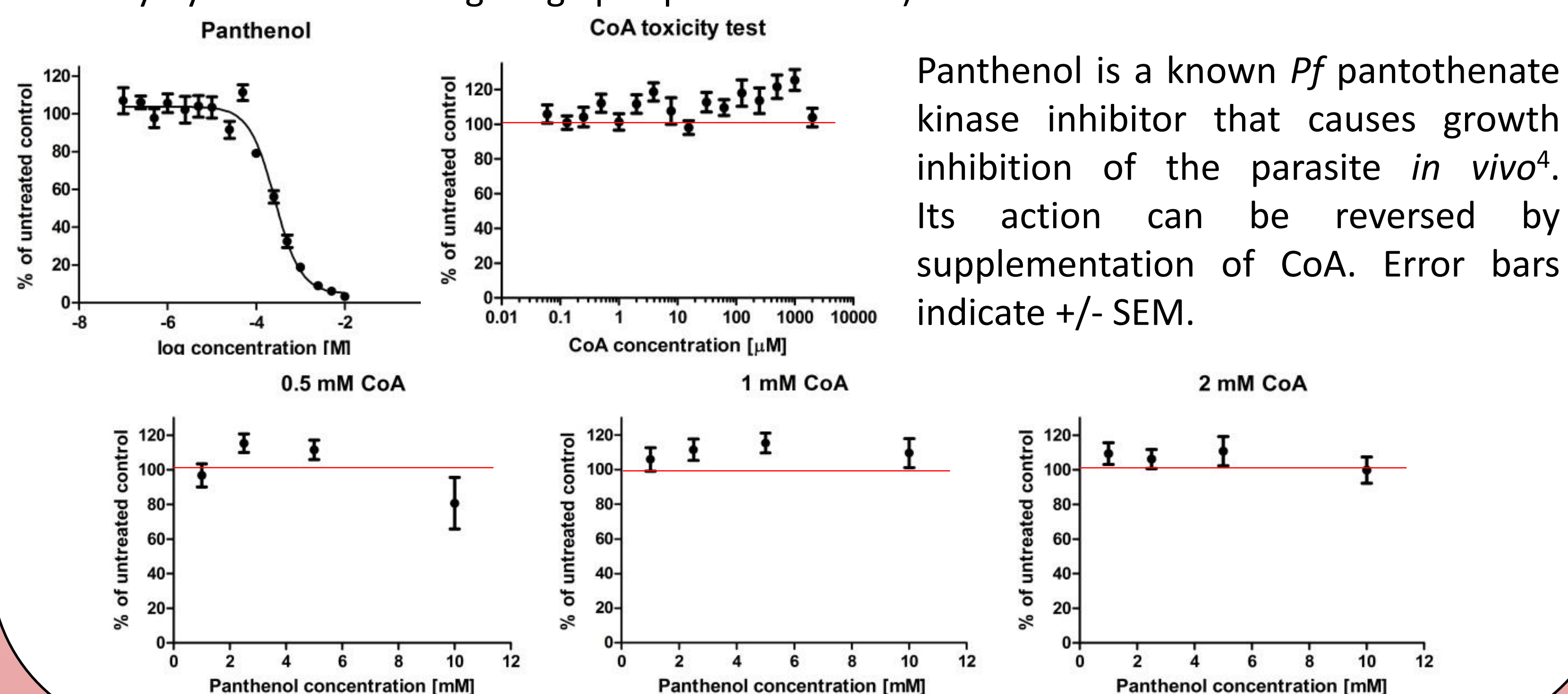
## 1) Coenzyme A synthesis pathway



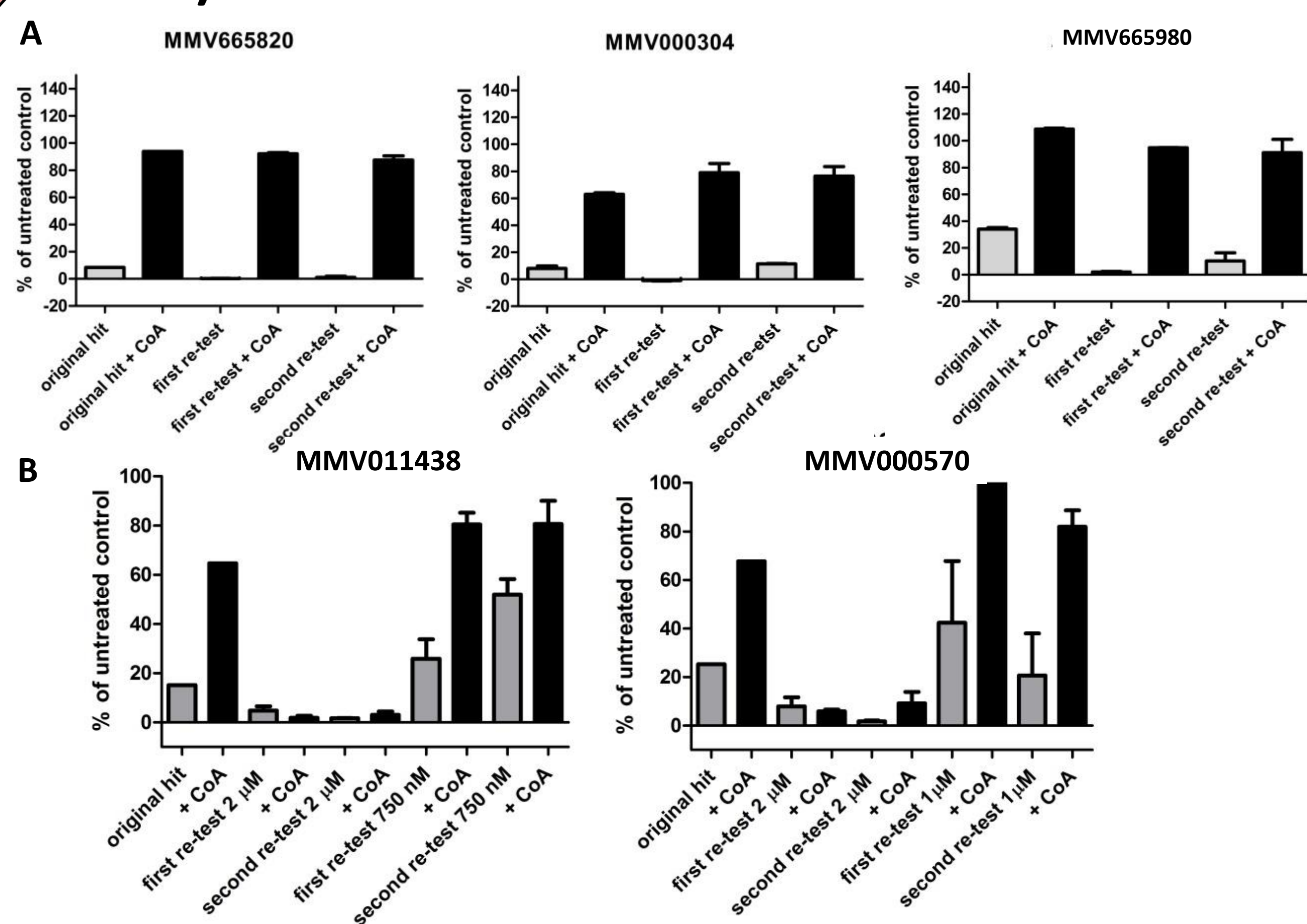
The five enzymatic steps of CoA synthesis are highly conserved. However, the amino acid sequences of the enzymes catalysing the reactions show low conservation between species<sup>1</sup>. This could allow to specifically target the *Plasmodium falciparum* enzymes without affecting the human host.

## 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 function<sup>3</sup>).

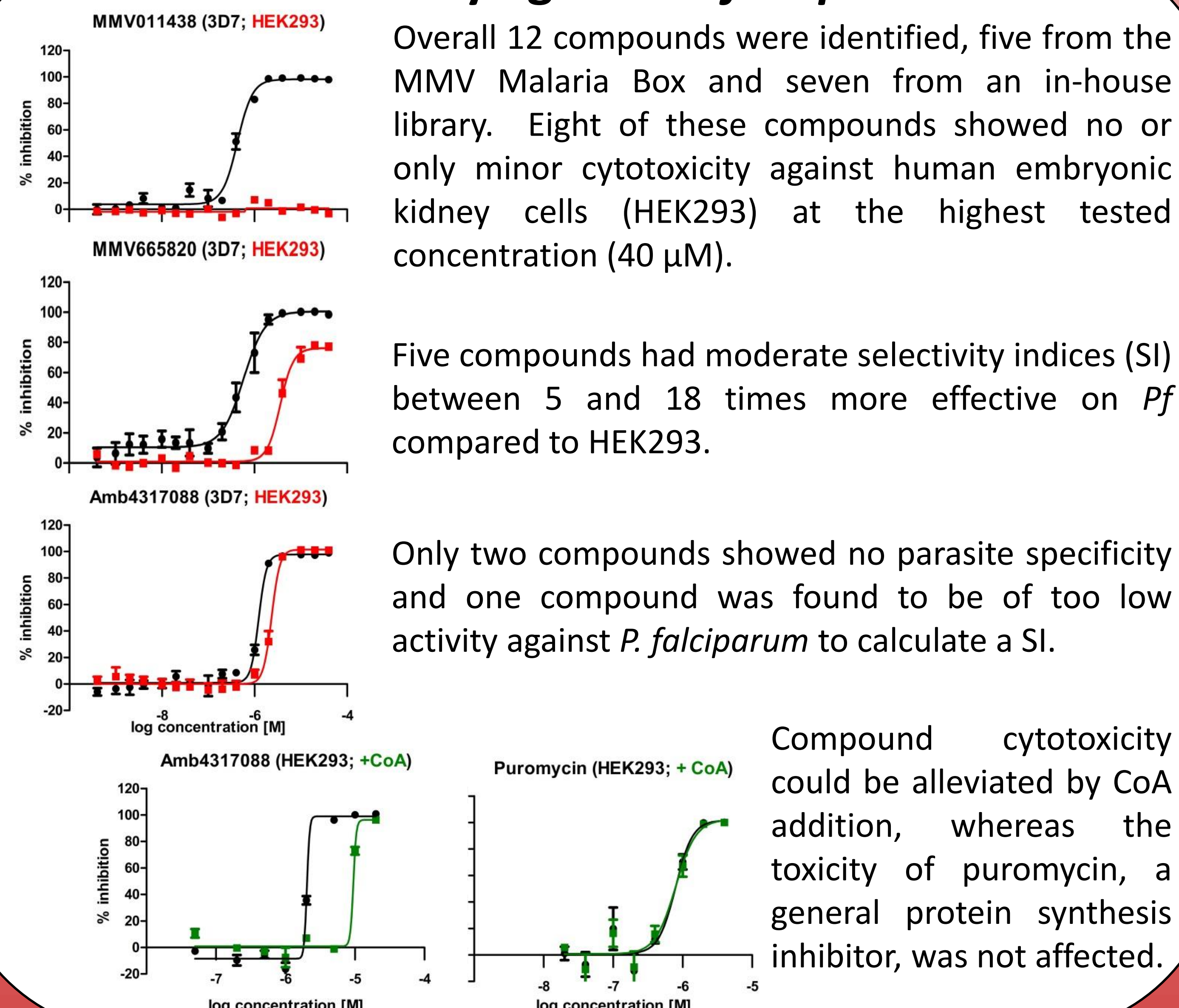


## 3) MMV Malaria Box - confirmed hits

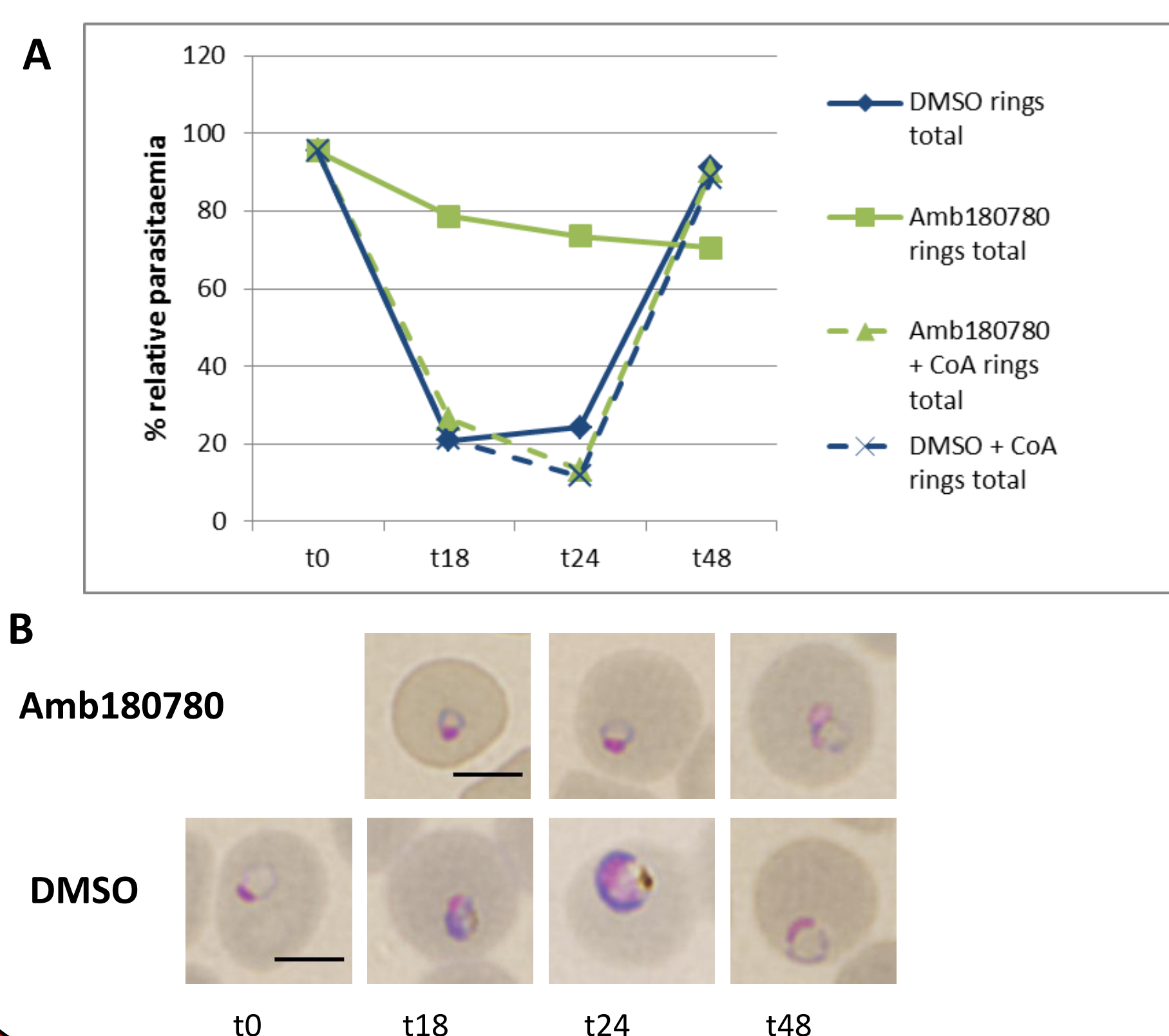


Bar graphs show compound activity alone (grey) and with CoA substitution (black). **A** Original hit and two re-tests from solids at 2 μM compound concentration; **B** Original hit, two re-tests from solid at 2 μM concentration and two re-tests near the individual compound IC<sub>80</sub>. Error bars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

## 4) Selectivity against *P. falciparum*



## 5) Parasite stage of action and treatment phenotype



**A** Parasites treated with Amb180780 (solid green line) appear to be arrested at the ring stage 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

- Huthmacher *et al*, *BMC Syst Biol* 2010, **4**:120.
  - Plata *et al*, *Mol Syst Biol* 2010, **6**:408.
  - Yeh and DeRisi, *PLoS Biol* 2011, **9**:e1001138.
  - 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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