In silico* screening for β-haematin inhibitors active against *Plasmodium falciparum

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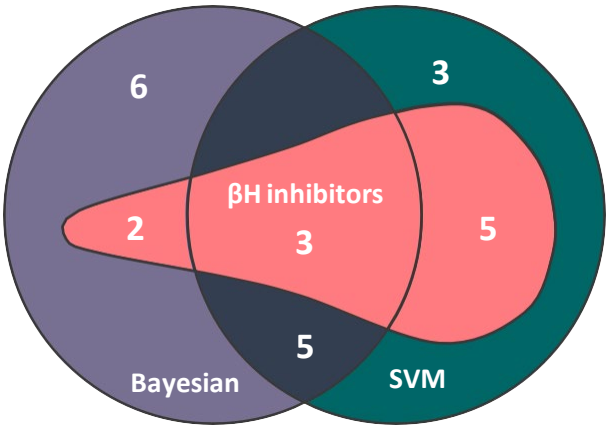

Figure 1. β-haematin inhibition activities of 24 purchased compounds predicted to be active against *Plasmodium falciparum* using a Bayesian classifier, support vector machine, or both.

The biomineral haemozoin has been the focus of several target-based screens for antiplasmodium activity. Together with the known β-haematin crystal structure, the availability of this screening data makes this target amenable to both structure- and ligand-based virtual screening. In this study, molecular docking and machine learning techniques were used in sequence to screen a commercial library for *in vitro* inhibitors of β-haematin with retained activity against cultures of *Plasmodium falciparum*. First, 25 000 drug-like, structurally diverse compounds from the ChemDiv 300k Representative Compounds Library were docked against the β-haematin crystal structure with AutoDock Vina. The top 1592 of these (Vina binding affinity ≤ 12 kcal/mol) were classified as hits, i.e., predicted β-haematin inhibitors. Antiplasmodium data for 1606 β- haematin inhibitors were then used to train Bayesian and Support Vector Machine (SVM) classifiers in the KNIME Analytics Platform. Both models were applied to the docking hits and a combined total of 404 compounds were predicted to be active against *P. falciparum*. Following similarity analysis and visual inspection of the docking poses, a selection of 32 prioritized compounds was purchased for experimental testing, 24 of which were predicted to be bioactive β-haematin inhibitors. The hit rate for β-haematin inhibition was found to be 43%, a major enrichment over random screening. In a preliminary screen for antiplasmodium activity, all ten β-haematin inhibitors resulted in <50% parasite survival at 5 μM.