Malaria eradication remains a challenge worldwide with the emergence of drug-resistant parasites rendering first-line antimalarials ineffective in endemic countries. Resistance against various chemical classes such as the aminoquinolines, artemisinins, as well as the sulfodrugs amongst others have been documented in the clinic. An important strategy in the fight against malaria is to develop new compounds that are unrelated to the currently used drugs and ideally target unexplored targets and biochemical pathways. This should minimize the risk of pre-existing cross-resistance in clinical isolates and reduce the development of new forms of resistance by selecting compounds with low frequency of mutagenesis. In an effort to identify unique and clinically-suitable chemical scaffolds which exert their activity on novel cellular pathways to combat drug-resistant parasites in the field we have recently established an integrated discovery pipeline for the rapid identification of new drug – target combinations. At this stage, we have already carried out a number of screens of novel compound libraries and identify new classes of chemical scaffolds with strong activity against the critical ring stage parasite. One of these compounds has now been further optimized for preclinical evaluation.