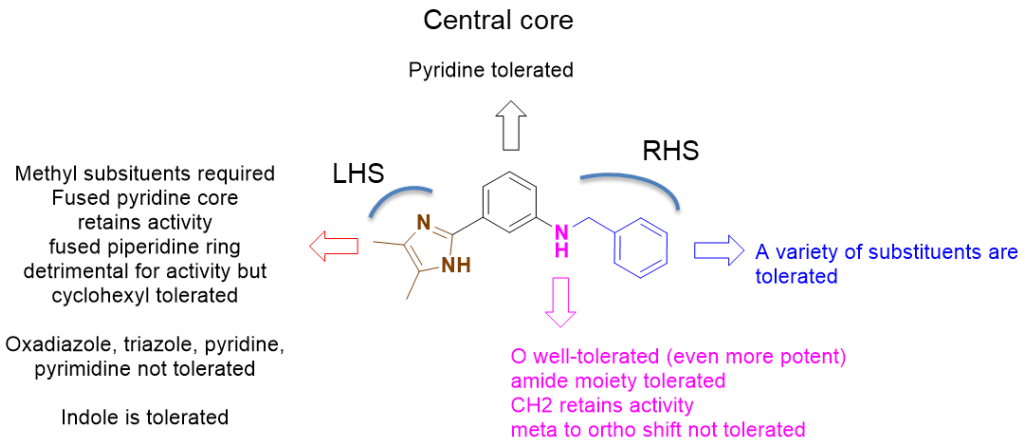
Aryl imidazole (MMV023227) scaffold

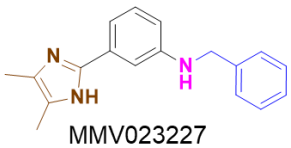
This template was identified from HTS phenotypic screening by GSK (TCMDC-133419) and subsequently included in the Pathogen box. Around 60 analogs were synthesised to validate the hit and draw a preliminary structure activity relationship (Pf ABS assay). Representative compounds were profiled across the plasmodium lifecycle - There is some evidence of activity against stage V gametocytes and Pb liver schizonts but this wil need to be confirmed on more potent analogues in MMV`s DGFA and Pf liver schizont assays.

Fig 1: Snap shot of SAR



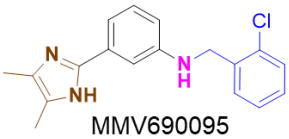
4 regions of modifications have been broadly explored to understand the SAR and impact of these modifications on physicochemical and drug metabolism properties. MMV023227 is active in Pb liver stage assays and a stage V gametocyte assay but is associated with high lipophilicity (e logD:3.5), moderate kinetic solubility (PBS buffer 60 µM at pH7.4) and high human microsomal clearance (175 µL/min/mg). It showed no cross resistance when screened in resistant cell lines and fast rate of killing in *in vitro* assays. Ether and corresponding phenethyl derivative retain potency indicating the potential to move away from the hidden aniline. MMV884798, an amide derivative, retains potency but the corresponding o-chloro derivative shows a loss in potency so both the compounds will be rescreened to confirm their potency.

Fig 2: Representative modifications on RHS and LHS region

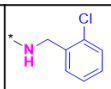
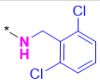
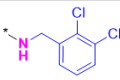
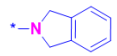
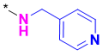
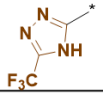
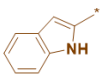


MMV023227

Pf 3D7: 0.46 µM
Pb liver: 0.56 µM
HepG2: 10.5 µM
Gam stage V: 1.9 µM



MMV690095

					
MMVID	690095	693100	692842	1794346	690907
Pf NF54/Pf 3D7 (µM)	-/0.23	0.52/-	0.20/0.34	-/0.35	4.6/-
Pb liver(µM)	0.25	0.66	0.76	ND	ND
HepG2 (µM)	2.47	1.95	6.23	ND	ND
Gam stage V (µM)	0.032	40	0.90	ND	ND
					
MMVID	690144	691975	689990	692597	692594
Pf NF54/Pf 3D7 (µM)	>10/-	>10/-	>10/-	0.71/0.58	2.5/>1

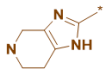
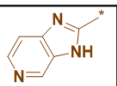
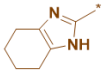
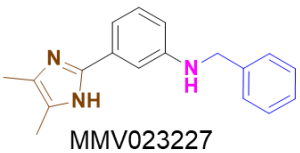
			
MMVID	1795562	884792	1794344
Pf NF54/Pf 3D7 (µM)	-/8.34	1.55/1.16	-/1.01

Fig 3: Modifications around the core and linker region



MMV023227

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HepG2: 10.5 µM
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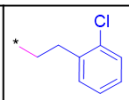
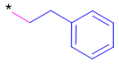
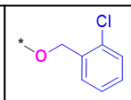
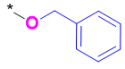
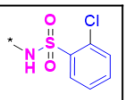
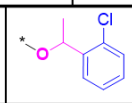
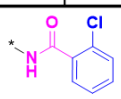
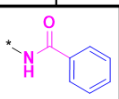
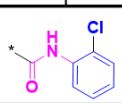
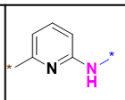
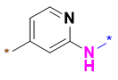
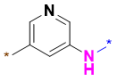
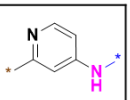
					
MMVID	1794035	1794345	1794348	693239	1804169
Pf NF54/Pf 3D7 (µM)	-/0.18	-/0.72	0.20/0.34	-/0.08	4.6/3.83
Pb liver(µM)	0.25	ND	ND	0.43	ND
HepG2 (µM)	8.93	ND	ND	14.5	ND

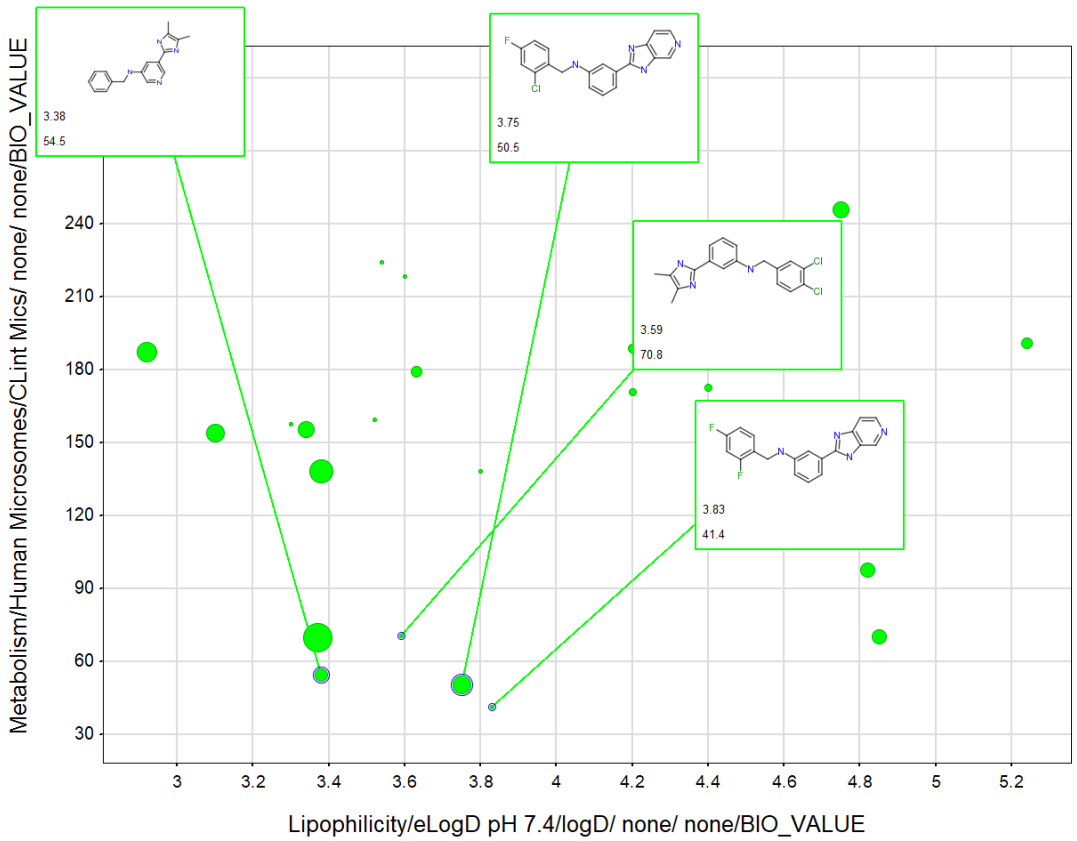
				
MMVID	1804207	1804111	884798	1803991
Pf 3D7 (µM)	0.32	10.15	1.27	2.72

				
MMVID	892878	892879	892881	892883
Pf 3D7 (µM)	7.45	2.55	0.72	0.88

ND: Not done

In the given set of compounds, no correlation between microsomal stability (mouse) and log D is observed (log D is >3 for all compounds except one). Replacement of imidazole with deazapurine improved human microsomal clearance (numerically) indicating that methyl groups at imidazole may be one of the sites prone to metabolism.

Fig 4: Correlation between log D and Human Microsomes (Clint)



Size of dot is indicative of Pf 3D7 potency- smaller dot indicates higher potency

Challenges:

Improve metabolic stability of compounds while retaining/improving activity