How to contribute

- Design and synthesis of compounds to achieve the objectives captured below (Objective section)
- Synthesis of compounds (see attached excel for the targets that are currently under synthesis and Medicinal Chemistry plans)
- Identification of putative metabolites for MMV693110 and/or MMV024408
- Carry out experimental in vitro Met ID for MMV693110 and/or MMV024408 in HLM and/or rat hepatocytes
- Screen front runners in lab derived strains other than 3D7; asexual intraerythrocytic blood stage assays, mechanism of action

You can confirm the activity to be undertaken either on Malaria Libre LinkedIn page (https://www.linkedin.com/groups/12435285/) or email to malaria.libre@mmv.org

Participants are requested to submit ideas in advance for discussion in the project meetings.

Please note that structures planned for synthesis must be shared in the form of SMILES.

Objectives:

- Improve asexual blood stage potency and understand parasite life cycle inhibition potential of representative compounds with central ring modifications
- Reduce log D ≤ 3
- Improve kinetic solubility (PBS, pH7.4 ≥ 50 µM)
- Improve high h microsomal clearance
- Reduce CYP inhibition potential (likely because of 4-Pyridyl group)

Plans:

- Generate in vitro Met ID for MMV693110 and/or MMV024408 (putative and experimental)
- MMV will screen representative compounds with central ring modifications in liver stage assays and DGFA
- Screen front runners in lab derived strains other than 3D7; asexual intraerythrocytic blood stage assays and determine mechanism of action
- Profile front runners in hERG assays

Medicinal Chemistry plans:

The aryl piperazine scaffold is further segregated into 3 subseries- series 1a, 1b, 1c based on the pharmacological and physicochemical profile of the molecules. Although only 3 compounds have been synthesised in series 1a the indications are that SAR may be different from the parent series (series 1c). Given that, MMV690872 has inherent low log D and has

potent liver stage activity, synthesis and screening of few analogues will help develop an understanding and further prioritisation of the optimum central ring.

Fig 1: Series description

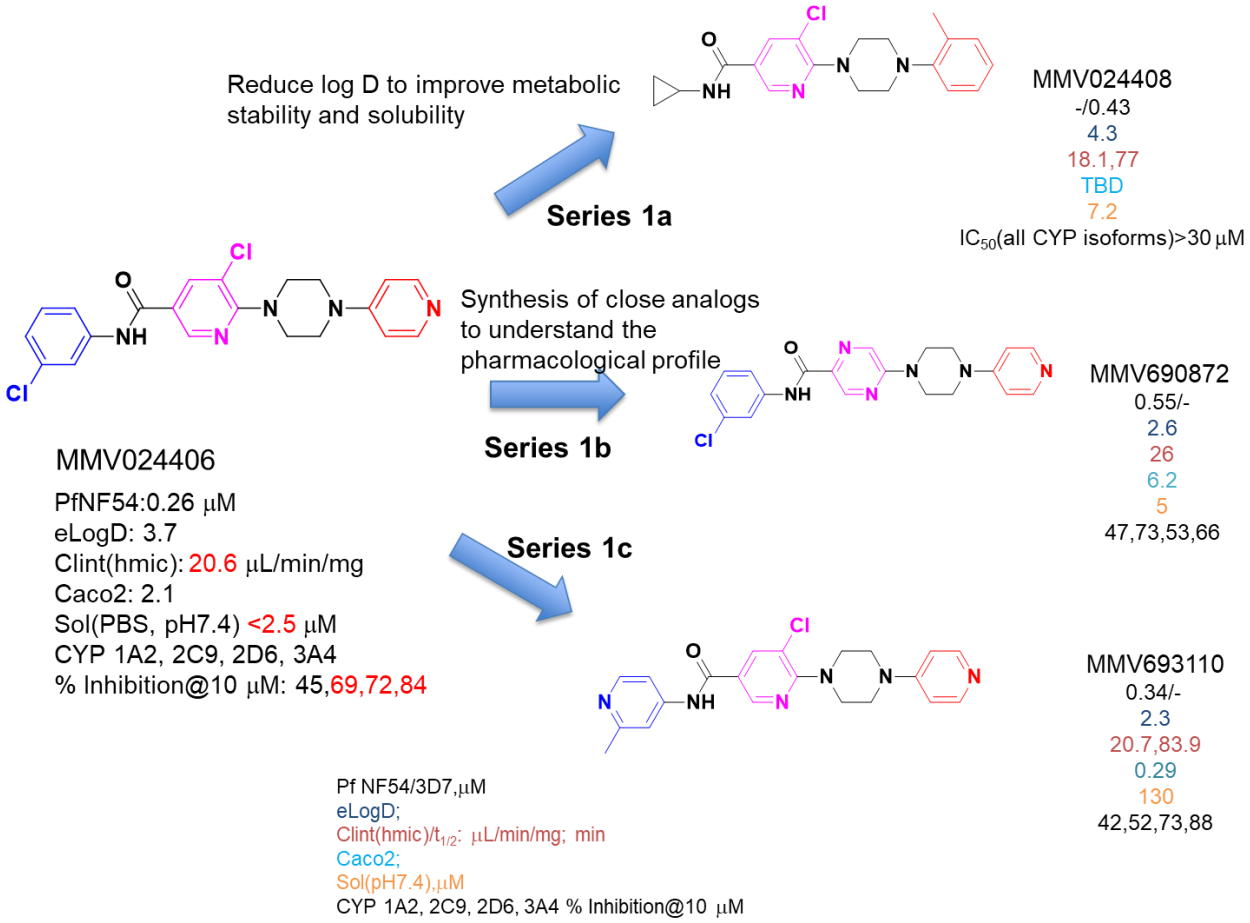

Fig 2: Planned Structural modifications (for specific plans see section Target molecules for synthesis)