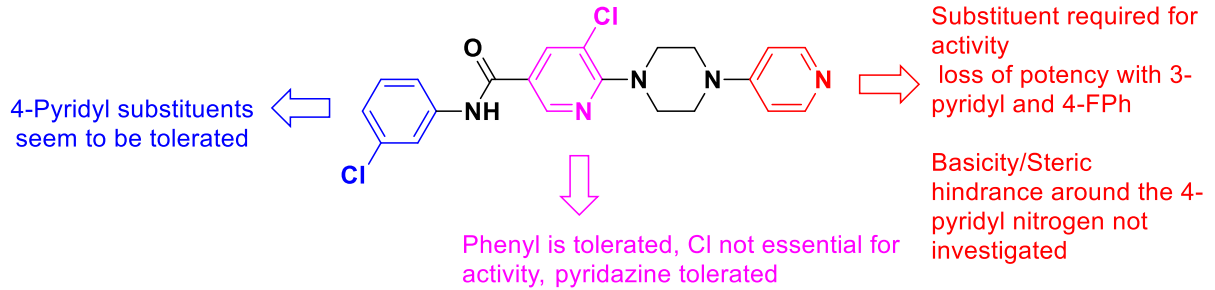
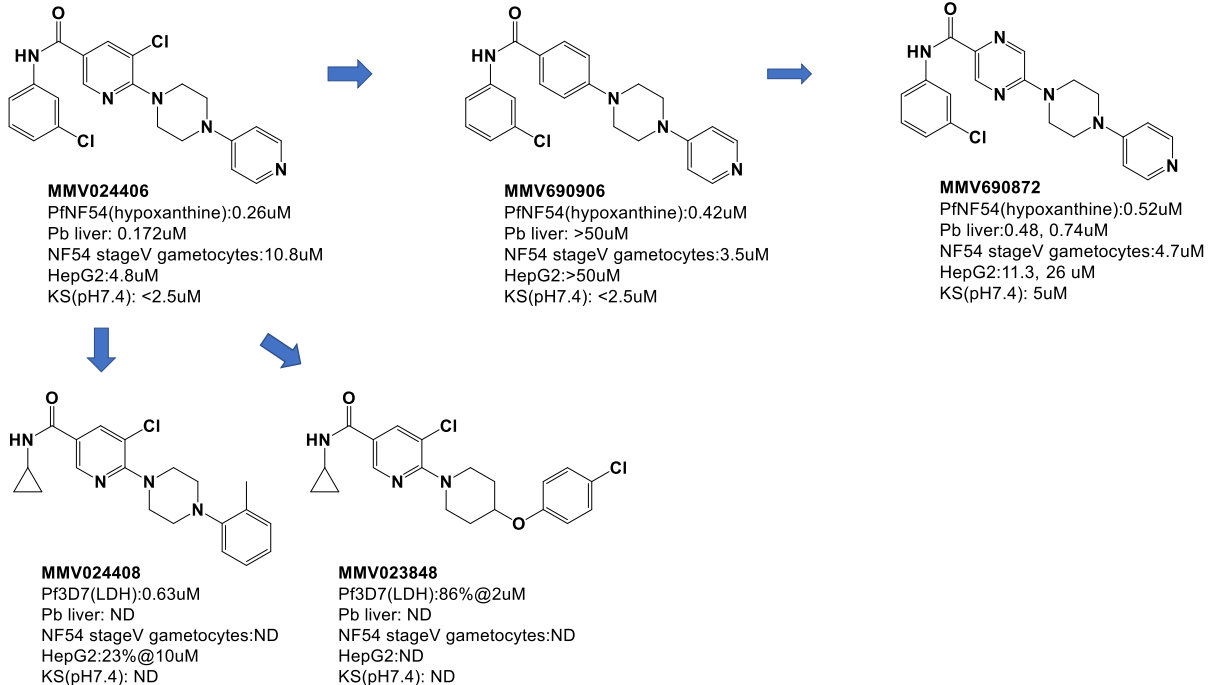


Aryl piperazine

MMV024406 analogs



Around 30 analogs have been synthesised till date around MMV024406, brief SAR explained above.



MMV024406 (logD:3.7) has Papp (PAMPA) of 0.0131 cm/s and Papp AB(Caco2) of 2.4×10^{-6} cm/s with ER(efflux ratio) of 4.3 indicating low to medium permeability and active efflux mechanisms involved. It also shows IC₅₀ of 0.124uM in hERG thallium binding assay and CYP inhibition as shown in the attached data sheet.

One of the reasons for poor kinetic solubility and CYP inhibition can be high lipophilicity – MMV 690906 and 690872 have log D of 2.9 and 2.6 respectively but no improvement in solubility or CYP profile is observed. Since MMV024408 and 023848 have reduced aromatic character, they can provide useful insights into Structure-Property relationship. Hidden aniline can be taken care of as is seen with these two compounds.

Next steps:

- Resynthesis of MMV024408 and 023848 – ongoing at TCGLS
 - profiling in LDH assays at TCGLS
 - Generate invitro ADME data - solubility, permeability, CYP inhibition
 - Pb liver stage and gametocyte stage V activity

Profile MMV024406, 690906, 690090 in 3D7LDH assays at TCGLS