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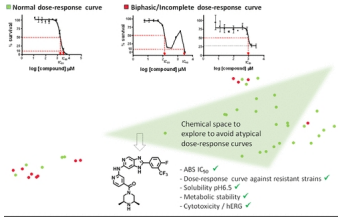
Abstract

A lead-optimization program around a 2,6-imidazopyridine scaffold was initiated based on the two early lead compounds, 1 and 2, that were shown to be efficacious in an *in vivo* humanized *Plasmodium falciparum*
NODscidIL2Rγnull mouse malaria infection model. The observation of atypical dose–response curves when some compounds were tested against multidrug resistant malaria parasite strains guided the optimization process to define a chemical space that led to typical sigmoidal dose–response and complete kill of multidrug resistant parasites. After a structure and property analysis identified such a chemical space, compounds were prepared that displayed suitable activity, ADME, and safety profiles with respect to cytotoxicity and hERG inhibition.



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