Thiadiazole derived Compounds As New Plasmodium falciparum Inhibitors: Synthesis and Structure–Activity Relationships

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Abstract

Since its foundation in 1999, MMV has been devoted to reduce the burden of malaria in endemic countries. As part of its efforts to provide a SERCaP for malaria, MMV173, containing thiadiazole scaffold, was identified as a hit compound. This compound possesses micromolar potency against blood stage malaria infection (Pf3D7- IC50) and bear no toxicity problem. This series has no cross-resistance issue, and it has novel mode of action. It also has good solubility and moderate rate of killing profile. The issues associated with this series is high metabolism in rat and human and high hERG channel activity. A series of analogues were designed and synthesized to increase potency and address the metabolic and high hERG channel activity. So far, we have synthesized 40 analogues via structural modification of MMV173. Our SAR campaign delivered analogues with two to three-fold increase in potency compared to MMV173 however high metabolism issue persist.

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Keywords

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