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# Optimization of compounds from the pyrazole series for malaria treatment

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Keywords: *Drug Discovery, Malaria, Organic Chemistry, Synthesis, SAR, Pyrazole.*

## Highlights

263 million malaria cases were reported in 2023; of those, 597,000 were fatal[1]. New efficient, oral, single-dose, long-duration antimalarial as an important tool to fight increasing resistance.

## Abstract

As malaria drug resistance spreads, emerges the urgent need for new therapeutic medicines to provide a safe and efficient treatment for those infected[1]. Unicamp and USP team joined forces with *MMV* (*Medicines for Malaria Venture*) to develop new chemical entities to treat the disease. The work with the pyrazole series started with a hit compound (*MMV2301*) being provided by *MMV* after phenotypic screening. A synthetic route has been developed to allow fast and efficient product synthesis such that modifications in various molecular sites can be achieved by minor changes, which is crucial to guarantee the speed of the drug discovery process. The series analogs are designed using the *SAR* (Structure-Activity Relationship) technique, whose accuracy is increased as more data is collected.

The *MMV2301* series has about 40 compounds synthesized, with modifications in both *RHS* (Right Hand Side), *LHS* (Left Hand Side), and central core, some illustrated, followed by its potency data in **Figure 1**. The most potent compounds – hundreds of nanomolar - have their pharmacokinetics data collected, providing information for further structure exploration. The analogs have no cross-resistance or cytotoxicity reported (HepG2 cells, hERG), and no further CYP inhibition was detected. In general, the series analogs have a high log D (greater than 4), resulting in poor solubility and a tendency to protein and membrane interactions[2]. A high lipophilicity is also associated with the selectivity of substrates for CYP450 enzymes, directly impacting clearance[3]. Therefore, the compounds show high clearance data.

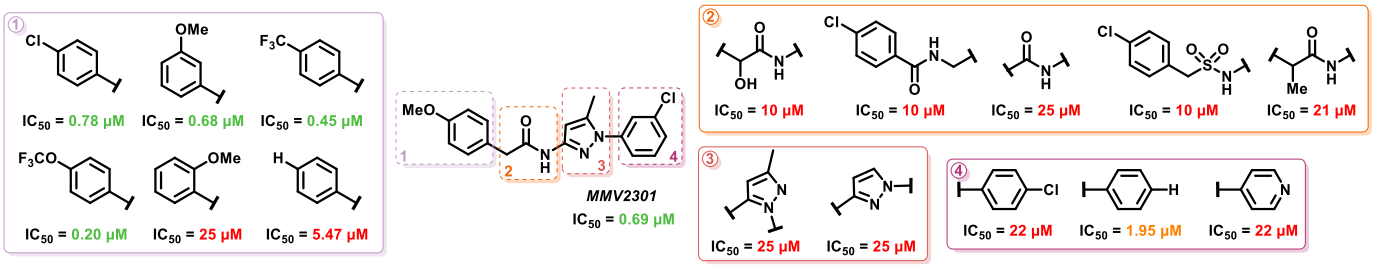


**Figure 1:** Main series analogs and its potency against *Plasmodium Pf*3D7.

The hit was submitted to a MetID study to provide deeper knowledge regarding the series clearance data. Results indicate molecular cleavage due to amide hydrolysis, a moiety already known for its instability in *in vivo* systems[4]. To address the metabolism issue, new analogs were designed aiming for amide moiety substitution or blockage[4].

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