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Novel inhibitors of *Plasmodium falciparum* based on 2,5-disubstituted furans

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TITLE: Novel Inhibitors of Plasmodium Falciparum based on 2,5-disubstituted Furans.

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ABSTRACT.

Phenotypic HTS campaigns with a blood stage malaria assay have been used to discover novel chemotypes for malaria treatment with potential alternative mechanisms of action compared to existing agents. N^1-(5-(3-Chloro-4-fluorophenyl)furan-2-yl)-N^3,N^3-dimethylpropane-1,3-diamine, **1** was identified as a modest inhibitor of *P.falciparum* NF54 (IC_{50} = 875nM) with an apparent long plasma half-life after high dose oral administration to mice, although the compound later showed poor metabolic stability in liver microsomes through ring- and side chain-oxidation and *N*-dealkylation. We describe here the synthesis of derivatives of **1**, exploring the influence of substitution patterns around the aromatic ring, variations on the alkyl chain and modifications in the core heterocycle, in order to probe potency and metabolic stability, where **4k** showed a long half-life in rats.

GRAPHICAL ABSTRACT.