Antimalarial N1,N3-dialkyldioxonaphthoimidazoliums: synthesis, biological activity, and structure-activity relationships

ID 4529703
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Year 2020
Title Antimalarial N1,N3-dialkyldioxonaphthoimidazoliums: synthesis, biological activity, and structure-activity relationships
Journal ACS medicinal chemistry letters
Volume 11
Pages 49-55
Here we report the nanomolar potencies of N (1),N (3)-dialkyldioxonaphthoimidazoliums against asexual forms of sensitive and resistant Plasmodium falciparum. Activity was dependent on the presence of the fused quinone-imidazolium entity and lipophilicity imparted by the N(1)/N(3) alkyl residues on the scaffold. Gametocytocidal activity was also detected, with most members active at IC50 < 1 muM. A representative analog with good solubility, limited PAMPA permeability, and microsomal stability demonstrated oral efficacy on a humanized mouse model of P. falciparum.
Publisher American Chemical Society
ISSN/ISBN 1948-5875
edoc-URL https://edoc.unibas.ch/75569/
Full Text on edoc No;
Digital Object Identifier DOI 10.1021/acsmedchemlett.9b00457
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/31938463