Publication

Aminoindoles, a novel scaffold with potent activity against Plasmodium falciparum

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 1027590
Author(s) Barker, R. H. Jr.; Urgaonkar, S.; Mazitschek, R.; Celatka, C.; Skerlj, R.; Cortese, J. F.; Tyndall, E.; Liu, H.; Cromwell, M.; Sidhu, A. B.; Guerrero-Bravo, J. E.; Crespo-Llado, K. N.; Serrano, A. E.; Lin, J. W.; Janse, C. J.; Khan, S. M.; Duraisingh, M.; Coleman, B. I.; Angulo-Barturen, I.; Jimenez-Diaz, M. B.; Magan, N.; Gomez, V.; Ferrer, S.; Martinez, M. S.; Wittlin, S.; Papastogiannidis, P.; O'Shea, T.; Klinger, J. D.; Bree, M.; Lee, E.; Levine, M.; Wiegand, R. C.; Munoz, B.; Wirth, D. F.; Clardy, J.; Bathurst, I.; Sybertz, E.
Author(s) at UniBasel Wittlin, Sergio ;
Year 2011
Title Aminoindoles, a novel scaffold with potent activity against Plasmodium falciparum
Journal Antimicrobial agents and chemotherapy
Volume 55
Number 6
Pages / **Article-Number** 2612-22
Keywords administration & dosage; Animals; antimalarials; Dogs; drug effects; Female; Humans; Indoles; Male; mice; pharmacokinetics; pharmacology; Plasmodium berghei; Plasmodium falciparum; Rats
This study characterizes aminoindole molecules that are analogs of Genz-644442. Genz-644442 was identified as a hit in a screen of 70,000 compounds in the Broad Institute's small-molecule library and the ICCB-L compound collection at Harvard Medical School. Genz-644442 is a potent inhibitor of Plasmodium falciparum in vitro (50% inhibitory concentrations [ICs], 200 to 285 nM) and inhibits P. berghei in vivo with an efficacy of >99% in an adapted version of Peters' 4-day suppressive test (W. Peters, Ann. Trop. Med. Parasitol. 69:155-171, 1975). Genz-644442 became the focus of medicinal chemistry optimization; 321 analogs were synthesized and were tested for in vitro potency against P. falciparum and for in vitro absorption, distribution, metabolism, and excretion (ADME) properties. This yielded compounds with ICs of approximately 30 nM. The lead compound, Genz-668764, has been characterized in more detail. It is a single enantiomer with ICs of 28 to 65 nM against P. falciparum in vitro. In the 4-day P. berghei model, when it was dosed at 100 mg/kg of body weight/day, no parasites were detected on day 4 postinfection. However, parasites recrudesced by day 9. Dosing at 200 mg/kg/day twice a day resulted in cures of 3/5 animals. The compound had comparable activity against P. falciparum blood stages in a human-engrafted NOD-scid mouse model. Genz-668764 had a terminal half-life of 2.8 h and plasma trough levels of 41 ng/ml when it was dosed twice a day orally at 55 mg/kg/day. Seven-day rat safety studies showed a no-observable-adverse-effect level (NOAEL) at 200 mg/kg/day; the compound was not mutagenic in Ames tests, did not inhibit the hERG channel, and did not have potent activity against a broad panel of receptors and enzymes. Employing allometric scaling and using in vitro ADME data, the predicted human minimum efficacious dose of Genz-668764 in a 3-day once-daily dosing regimen was 421 mg/day/70 kg, which would maintain plasma trough levels above the IC against P. falciparum for at least 96 h after the last dose. The predicted human therapeutic index was approximately 3, on the basis of the exposure in rats at the NOAEL. We were unable to select for parasites with >2-fold decreased sensitivity to the parent compound, Genz-644442, over 270 days of in vitro culture under drug pressure. These characteristics make Genz-668764 a good candidate for preclinical development

Publisher American Society for Microbiology
ISSN/ISBN 0066-4804
edoc-URL http://edoc.unibas.ch/47142/
Full Text on edoc No;
Digital Object Identifier DOI 10.1128/AAC.01714-10
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/21422215
ISI-Number WOS:000290713400018
Document type (ISI) Journal Article