Benzo[b]quinolizinium derivatives have a strong antimalarial activity and inhibit indoleamine dioxygenase

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 3433377
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Year 2015
Title Benzo[b]quinolizinium derivatives have a strong antimalarial activity and inhibit indoleamine dioxygenase
Journal Antimicrobial agents and chemotherapy
Volume 60
Number 1
Pages / **Article-Number** 115-25
The heme-containing enzymes indoleamine 2,3-dioxygenase-1 (IDO-1) and IDO-2 catalyze the conversion of the essential amino acid tryptophan into kynurenine. Metabolites of the kynurenine pathway and IDO itself are involved in immunity and the pathology of several diseases, having either immunoregulatory or antimicrobial effects. IDO-1 plays a central role in the pathogenesis of cerebral malaria, which is the most severe and often fatal neurological complication of infection with Plasmodium falciparum. Mouse models are usually used to study the underlying pathophysiology. In this study, we screened a natural compound library against mouse IDO-1 and identified 8-aminobenzo[b]quinolizinium (compound 2c) to be an inhibitor of IDO-1 with potency at nanomolar concentrations (50% inhibitory concentration, 164 nM). Twenty-one structurally modified derivatives of compound 2c were synthesized for structure-activity relationship analyses. The compounds were found to be selective for IDO-1 over IDO-2. We therefore compared the roles of prominent amino acids in the catalytic mechanisms of the two isoenzymes via homology modeling, site-directed mutagenesis, and kinetic analyses. Notably, methionine 385 of IDO-2 was identified to interfere with the entrance of l-tryptophan to the active site of the enzyme, which explains the selectivity of the inhibitors. Most interestingly, several benzo[b]quinolizinium derivatives (6 compounds with 50% effective concentration values between 2.1 and 6.7 nM) were found to be highly effective against P. falciparum 3D7 blood stages in cell culture with a mechanism independent of IDO-1 inhibition. We believe that the class of compounds presented here has unique characteristics; it combines the inhibition of mammalian IDO-1 with strong antiparasitic activity, two features that offer potential for drug development.
Publisher American Society for Microbiology
ISSN/ISBN 1098-6596
edoc-URL http://edoc.unibas.ch/41991/
Full Text on edoc No;
Digital Object Identifier DOI 10.1128/AAC.01066-15
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/26459907
Document type (ISI) Journal Article