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# Redox Polypharmacology as an Emerging Strategy to Combat Malarial Parasites

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## Abstract

© 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. 3-Benzylmenadiones are potent antimalarial agents that are thought to act through their 3-benzoylmenadione metabolites as redox cyclers of two essential targets: the NADPH-dependent glutathione reductases (GRs) of Plasmodium-parasitized erythrocytes and methemoglobin. Their physicochemical properties were characterized in a coupled assay using both targets and modeled with QSPR predictive tools built in house. The substitution pattern of the west/east aromatic parts that controls the oxidant character of the electrophore was highlighted and accurately predicted by QSPR models. The effects centered on the benz(o)yl chain, induced by drug bioactivation, markedly influenced the oxidant character of the reduced species through a large anodic shift of the redox potentials that correlated with the redox cycling of both targets in the coupled assay. Our approach demonstrates that the antimalarial activity of 3-benz(o)ylmenadiones results from a subtle interplay between bioactivation, fine-tuned redox properties, and interactions with crucial targets of *P.falciparum*. Plasmodione and its analogues give emphasis to redox polypharmacology, which constitutes an innovative approach to antimalarial therapy.

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## Keywords

Cheminformatics, Menadione, Multitarget drugs, QSPR, Redox potential