

Next-Generation Antimalarial Drugs: Hybrid Molecules as a New Strategy in Drug Design

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ABSTRACT Malaria is a disease that affects nearly 40% of the global population, and chemotherapy remains the mainstay of its control strategy. The global malaria situation is increasingly being exacerbated by the emergence of drug resistance to most of the available antimalarials, necessitating search for novel drugs. A recent rational approach of antimalarial drug design characterized as “covalent bitherapy” involves linking two molecules with individual intrinsic activity into a single agent, thus packaging dual-activity into a single hybrid molecule. Current research in this field seems to endorse hybrid molecules as the next-generation antimalarial drugs. If the selective toxicity of hybrid prodrugs can be demonstrated in vivo with good bioavailability at the target site in the parasite, it would offer various advantages including dosage compliance, minimized toxicity, ability to design better drug combinations, and cheaper preclinical evaluation while achieving the ultimate object of delaying or circumventing the development of resistance. This review is focused on several hybrid molecules that have been developed, with particular emphasis on those deemed to have high potential for development for clinical use. *Drug Dev Res* 71:20–32, 2010. © 2009 Wiley-Liss, Inc.

Key words: malarial conjugates; trioxaquinines and trioxolaquinines; aminoquinolines; antimalarial resistance; malarial chemotherapy

INTRODUCTION

Chloroquine (CQ), a 4-aminoquinoline, has been the mainstay of malarial chemotherapy for much of the past five decades. The drug has several advantages including limited host toxicity, ease of use, low cost, and effective synthesis. However, the use of CQ been eroded by development of resistance [Vangapandu et al., 2003; Kouznetsov and Gómez-Barrio, 2009]. Unfortunately, most AQ drugs are structurally related, and show cross-resistance [Foley and Tilley, 1998; Bloland, 2001]. Currently, artemisinin-based combination therapy (ACT) is the World Health Organization (WHO) golden standard against *Plasmodium falciparum* malaria, in which the regimen uses a double- or

triple-combination therapy geared towards delay of resistance, or circumvents it altogether [Capela et al., 2009; Araújo et al., 2009; Maude et al., 2010]. Although no clinical resistance has been registered against artemisinins, recent reports from south-east Asia are

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