



Abstract

Novel Antimalarial Inhibitors That Specifically Target the Invasion Motor Protein Myosin A in Malaria Parasites [†]

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[†] Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 7 August 2019

Abstract: Malaria remains a devastating disease with nearly half a million deaths per year. The WHO reports a stagnating number of new infections every year without a significant decline, as a result of insufficient access to antimalarials in endemic regions as well as complex resistance mechanisms of the parasites against current treatments. Due to its critical role during the parasite's life cycle, the invasion motor myosin A is a promising target, which has not yet been considered in drug discovery. Myosins appeared to be undruggable since they are ubiquitously expressed and involved in a wide range of cellular processes. In total, the protein superfamily of myosins comprises 35 known subclasses. However, recent studies highlighted the possibility to modulate the myosin motor activity of specific myosin isoforms and classes using small allosteric effector molecules. Exploiting the concept of reversible covalent binding, we show the development of highly potent and specific inhibitors of the key motor myosin A of the glideosome—a sophisticated motor machinery involved in parasite motility and host cell invasion. Combining chemical synthesis with biophysical in vitro analysis confirmed the preferential inhibition of the target protein in the submicromolar range. The developed compounds show significant antiparasitic activities and block efficiently glideosome-associated processes, parasite proliferation, and parasitemia of the malaria parasites. Our findings demonstrate the high potential of our approach using reversible covalent binding to develop new allosteric inhibitors, targeting specifically the key invasion motor as a novel drug target to treat infections caused by malaria parasites.

Keywords: Myosin A; Antimalarials; Inhibitors; Drug design



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