

Arylmethylamino steroids as antiparasitic agents.

Krieg R, Jortzik E, Goetz AA, Blandin S, Wittlin S, Elhabiri M, Rahbari M, Nuryyeva S, Voigt K, Dahse HM, Brakhage A, Beckmann S, Quack T, Grevelding CG, Pinkerton AB, Schönecker B, Burrows J, Davioud-Charvet E, Rahlfs S, Becker K (2017) Arylmethylamino steroids as antiparasitic agents. *Nat Commun* 8, 14478.

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Abstract

In search of antiparasitic agents, we here identify arylmethylamino steroids as potent compounds and characterize more than 60 derivatives. The lead compound **1o** is fast acting and highly active against intraerythrocytic stages of chloroquine-sensitive and resistant *Plasmodium falciparum* parasites (IC₅₀ 1-5 nM) as well as against gametocytes. In *P. berghei*-infected mice, oral administration of **1o** drastically reduces parasitaemia and cures the animals. Furthermore, **1o** efficiently blocks parasite transmission from mice to mosquitoes. The steroid compounds show low cytotoxicity in mammalian cells and do not induce acute toxicity symptoms in mice. Moreover, **1o** has a remarkable activity against the blood-feeding trematode parasite *Schistosoma mansoni*. The steroid and the hydroxyarylmethylamino moieties are essential for antimalarial activity supporting a chelate-based quinone methide mechanism involving metal or haem bioactivation. This study identifies chemical scaffolds that are rapidly internalized into blood-feeding parasites.

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