7-N-substituted-3-oxadiazole quinolones with potent antimalarial activity target the cytochrome bc1 complex

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Author(s) Nguyen, W.; Dans, M. G.; Currie, I.; Awalt, J. K.; Bailey, B. L.; Lumb, C.; Ngo, A.; Favuzza, P.; Palandri, J.; Ramesh, S.; Penington, J.; Jarman, K. E.; Mukherjee, P.; Chakraborty, A.; Maier, A. G.; van Dooren, G. G.; Papenfuss, T.; Wittlin, S.; Churchyard, A.; Baum, J.; Winzeler, E. A.; Baud, D.; Brand, S.; Jackson, P. F.; Cowman, A. F.; Sleebs, B. E.
Author(s) at UniBasel Wittlin, Sergio ;
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The development of new antimalarials is required because of the threat of resistance to current antimalarial therapies. To discover new antimalarial chemotypes, we screened the Janssen Jumpstarter library against the P. falciparum asexual parasite and identified the 7-N-substituted-3-oxadiazole quinolone hit class. We established the structure-activity relationship and optimized the antimalarial potency. The optimized analog WJM228 (17) showed robust metabolic stability in vitro, although the aqueous solubility was limited. Forward genetic resistance studies uncovered that WJM228 targets the Q(o) site of cytochrome b (cyt b), an important component of the mitochondrial electron transport chain (ETC) that is essential for pyrimidine biosynthesis and an established antimalarial target. Profiling against drug-resistant parasites confirmed that WJM228 confers resistance to the Q(o) site but not Q(i) site mutations, and in a biosensor assay, it was shown to impact the ETC via inhibition of cyt b. Consistent with other cyt b targeted antimalarials, WJM228 prevented pre-erythrocytic parasite and male gamete development and reduced asexual parasitemia in a P. berghei mouse model of malaria. Correcting the limited aqueous solubility and the high susceptibility to cyt b Q(o) site resistant parasites found in the clinic will be major obstacles in the future development of the 3-oxadiazole quinolone antimalarial class.
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