Antitrypanosomal activity of 1,2-dihydroquinolin-6-ols and their ester derivatives

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Author(s) Fotie, J.; Kaiser, M.; Delfin, D. A.; Manley, J.; Reid, C. S.; Paris, J. M.; Wenzler, T.; Maes, L.; Mahasenan, K. V.; Li, C.; Werbovetz, K. A.
Author(s) at UniBasel Kaiser, Marcel ;
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The current chemotherapy for second stage human African trypanosomiasis is unsatisfactory. A synthetic optimization study based on the lead antitrypanosomal compound 1,2-dihydro-2,2,4-trimethylquinolin-6-yl 3,5-dimethoxybenzoate (TDR20364, 1a) was undertaken in an attempt to discover new trypanocides with potent in vivo activity. While 6-ether derivatives were less active than the lead compound, several N1-substituted derivatives displayed nanomolar IC(50) values against T. b. rhodesiense STIB900 in vitro, with selectivity indexes up to <18000. 1-Benzyl-1,2-dihydro-2,2,4-trimethylquinolin-6-yl acetate (10a) displayed an IC(50) value of 0.014 muM against these parasites and a selectivity index of 1700. Intraperitoneal administration of 10a at 50 (mg/kg)/day for 4 days caused a promising prolongation of lifespan in T. b. brucei STIB795-infected mice (<14 days vs 7.75 days for untreated controls). Reactive oxygen species were produced when T. b. brucei were exposed to 10a in vitro, implicating oxidative stress in the trypanocidal mode of action of these 1,2-dihydroquinoline derivatives

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