A new nonpolar n-hydroxy imidazoline lead compound with improved activity in a murine model of late-stage Trypanosoma brucei brucei infection is not cross-resistant with diamidines

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Treatment of late-stage sleeping sickness requires drugs that can cross the blood-brain barrier (BBB) to reach the parasites located in the brain. We report here the synthesis and evaluation of four new N-hydroxy and 12 new N-alkoxy derivatives of bisimidazoline leads as potential agents for the treatment of late-stage sleeping sickness. These compounds, which have reduced basicity compared to the parent leads (i.e., are less ionized at physiological pH), were evaluated in vitro against Trypanosoma brucei rhodesiense and in vivo in murine models of first- and second-stage sleeping sickness. Resistance profile, physicochemical parameters, in vitro BBB permeability, and microsomal stability also were determined. The N-hydroxy imidazoline analogues were the most effective in vivo, with 4-((1-hydroxy-4,5-dihydro-1H-imidazol-2-yl)amino)-N-(4-((1-hydroxy-4,5-dihydro-1H-imidazol-2-yl)amino)phenyl)benzamide (14d) showing 100% cures in the first-stage disease, while 15d, 16d, and 17d appeared to slightly improve survival. In addition, 14d showed weak activity in the chronic model of central nervous system infection in mice. No evidence of reduction of this compound with hepatic microsomes and mitochondria was found in vitro, suggesting that N-hydroxy imidazolines are metabolically stable and have intrinsic activity against T. brucei. In contrast to its unsubstituted parent compound, the uptake of 14d in T. brucei was independent of known drug transporters (i.e., T. brucei AT1/P2 and HAPT), indicating a lower predisposition to cross-resistance with other diamidines and arsenical drugs. Hence, the N-hydroxy bisimidazolines (14d in particular) represent a new class of promising antitrypanosomal agents.

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