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Some new leads for Human African Trypanosomiasis (African Sleeping Sickness)

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Background and Aims: Human African Trypanosomiasis (HAT) is a disease, which is caused by protozoan Trypanosoma brucei. There is an urgent need for alternative, less toxic treatments for HAT. A recent high-throughput screen of the 87,926-member WEHI (Walter and Eliza Hall Medical Institute, Melbourne) chemical library unearthed several leads with anti-trypanosomal activity, including the thiazole WEHI-1203394, and triazole WEHI-1203794. Initial targets were designed to test the influence of the fluorine and acyl substituents.
Methods: The amine precursor was prepared using a five steps procedure and coupled with different acid chlorides. The amides were initially tested against T. brucei brucei, using an Alamar Blue Viability Assay. Cells were grown in HMI-9 medium in a 384- well plate. Reference drugs were pentamidine, diminazene aceturate and puromycin. Also toxicity to a mammalian cell line was evaluated. A second series of 16 analogues were synthesised to examine stereoelectronic effects of the acyl substituent.
Results: The structure of synthesized compounds was confirmed by IR, 1HNMR, 13CNMR and Mass spectra. The benzamide derivative, MRK8, exhibits greater toxicity despite the absence of the fluoro substituent. Subsequently, MRK8 has been shown to posses more potent activity against the human pathogen T. brucei rhodesiense (EC50 = 78 nM), and is also toxic to T. cruzi (EC50 = 540 nM), a related parasite that causes the Chagas disease.
Conclusions: The MRK7potency is comparable to that of the lead thiazole, suggesting that the fluorine is not critical for activity. The toxicity of the MRK8 against T.brucei (EC50 = 0.25 μM), is higher than the lead thiazole (EC50 = 0.48 μM), and this compound can be considered as potential antitrypanosomiasis drug or a novel lead for developing new acive compounds. The testing of the series II analogues is currently underway and should provide valuable insight about the SAR of the amide substituent.

Keywords: African sleeping sickness; Trypanosomiasis; Thiazole