Curvicollide D Isolated from the Fungus *Amesia* sp. Kills African Trypanosomes by Inhibiting Transcription

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Abstract

Sleeping sickness or African trypanosomiasis is a serious health concern with an added socio-economic impact in sub-Saharan Africa due to direct infection in both humans and their domestic livestock. There is no vaccine available against African trypanosomes and its treatment relies only on chemotherapy. Although the current drugs are effective, most of them are far from the modern concept of a drug in terms of toxicity, specificity and therapeutic regime. In a search for new molecules with trypanocidal activity, a high throughput screening of 2000 microbial extracts was performed. Fractionation of one of these extracts, belonging to a culture of the fungus *Amesia* sp., yielded a new member of the curvicollide family that has been designated as curvicollide D. The new compound showed an inhibitory concentration 50 (IC_{50}) 16-fold lower in *Trypanosoma brucei* than in human cells. Moreover, it induced cell cycle arrest, causing an accumulation of cells in the G2/M phase and disruption of the nucleolar structure. An analysis of nucleolus function revealed that RNA polymerase I transcription was inhibited at the ribosomal locus, but also at the locus where the variant surface glycoprotein is expressed. Treatment with curvicollide D also caused RNA Pol II transcription inhibition. Finally, we showed that curvicollide D binds to DNA and inhibits transcription in African trypanosomes, resulting in cell death. These results constitute the first report on the activity and mode of action of a member of the curvicollide family in *T. brucei.*