DESIGN OF TRYPANOCIDAL DRUGS INTERFERING WITH THE TRYPANOTHIONE SYSTEM.

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In trypanosomatids trypanothione substitutes for the mammalian redox mediator glutathione in the detoxification of hydroperoxides, heavy metals, drugs and hydroxyaldehydes[1]. For hydroperoxide detoxification, trypanothione reduces tryparedoxins, which in turn reduce peroxiredoxin-type and GPx-type peroxidases[2]. Tryparedoxins are also essential for nucleic acid synthesis[1]. Several, though not all, components of the system proved to be pivotal to viability and virulence of trypanosomatids[3]. Suppression of trypanothione synthetase (TryS) by dsRNA interference impairs viability in unstressed *T. brucei* and rapidly kills the parasites under mild oxidative stress[4]. Further aspects supporting the use of TryS as drug target are low abundance and uniqueness of sequence[5]. TryS inhibition is therefore considered to be a particularly attractive strategy to fight infections with African trypanosomes and likely those caused by *Trypanosoma* and *Leishmania* species in general. A series of N^5-substituted paullones inhibits TryS at nM concentrations, decrease trypanothione in *T.cruzi* and *T. brucei*, impair viability and, thus, is considered to provide leads for the development of trypanocidal drugs.

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