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Zinc(II)-Sterol hydrazine complex as Possible Anti-Trypanosomatidae Drug

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Trypanosomatids are mainly responsible for leishmaniasis, sleeping sickness, and Chagas disease, which are the most challenging among the neglected tropical diseases due to growing issues with drug resistance. The available therapy often consists of prolonged treatments with broad-spectrum drugs that produce severe side effects and have limited efficacy. Therefore, there is a clinical unmet need for new chemotherapeutic agents. Trypanosomatid parasites are characterized by C-24-alkyl sterols (ergostane-base sterols) as a structural component in their cell membranes, rather than cholesterol found in mammalian host membranes. Several drugs interfere with sterol biosynthesis, these are used to treat fungal infections. Some have been proposed as potential treatments for the Trypanosomatid parasite. 22-hydrazone-imidazoline-2-yl-col-5-ene-3β-ol (H3) is a well-known, bioactive molecule that functions as an inhibitor of ergosterol biosynthesis. This was coordinated to Zn(II) ion using the strategy of metal-drug synergism. Here, we present the *in vitro* activities of H3 and its $ZnCl_2(H3)_2$ complex on *Trypanosoma cruzi* and *Leishmania amazonensis*. The free ligand H3 and its zinc complex showed significant inhibition of the growth of promastigotes and intracellular amastigotes of *L. amazonensi*, as well as, epimastogotes and amastigotes of *T. cruzi*. The IC_{50} values for H3 and $ZnCl_2(H3)_2$ were under 10 µM for epimastigotes and promastigotes of both parasites. However, for intracellular amastigotes of parasites $ZnCl_2(H3)_2$ exhibited $IC_{50} < 35$ nM, more potent than the free ligand H3 against this clinically relevant stage. Cytotoxicity assays and determination of selectivity index (SI) revealed that $ZnCl_2(H3)_2$ is more selective than H3 in *L. amazonensis* (CC_{50} = 5 µM and 10 µM, SI = 156 and 20, respectively) and also in *T. cruzi* (CC_{50} = 35,3 and 34,7 µM, SI = 13952 and 2743, respectively). The coordination of the ergosterol inhibitor (H3) to Zn(II) ion improved its potency and selectivity. This is another example that metal-drug synergism is an excellent strategy for developing new chemotherapeutic treatments against parasite diseases.

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References

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