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Analogues of Marine Guanidine Alkaloids Are *in Vitro* Effective against *Trypanosoma cruzi* and Selectively Eliminate *Leishmania* (*L.*) *infantum* Intracellular Amastigotes

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Supporting Information

ABSTRACT: Synthetic analogues of marine sponge guanidine alkaloids showed *in vitro* antiparasitic activity against *Leishmania* (*L.*) *infantum* and *Trypanosoma cruzi*. Guanidines **10** and **11** presented the highest selectivity index when tested against *Leishmania*. The antiparasitic activity of **10** and **11** was investigated in host cells and in parasites. Both compounds induced depolarization of mitochondrial membrane potential, upregulation of reactive oxygen species levels, and increased plasma membrane permeability in *Leishmania* parasites. Immunomodulatory assays suggested an NO-independent effect of guanidines **10** and **11** on macrophages. The same compounds also promoted anti-inflammatory activity in *L.* (*L.*) *infantum*-infected macrophages cocultured with splenocytes, reducing the production of cytokines MCP-1 and IFN-γ. Guanidines **10** and **11** affect the bioenergetic metabolism of *Leishmania*, with selective elimination of parasites via a host-independent mechanism.

Considerable attention has been raised to address the effective cure of neglected tropical diseases (NTDs) in the past decade, which globally impact mainly economically disfavored nations. These infectious pathogenies, of which most have parasites as the causative agents, have spread and now affect populations in developed countries as well. Most drugs to treat NTDs were developed decades ago and show harmful, even deadly, adverse effects. Therefore, the search for new drugs or vaccines to treat human neglected diseases is a priority for the World Health Organization and other organizations.[1,2]

Two of the deadliest NTDs are leishmaniasis and Chagas disease. Leishmaniasis affects 12 million people in 98 countries mainly in Africa, Asia, and Latin America.[3,4] Two distinct human pathological conditions are observed for leishmaniasis, cutaneous and visceral. *Leishmania* (*L.*) *infantum* is the etiologic agent of visceral leishmaniasis (VL) in South America and southern Europe countries, while *Leishmania* (*L.*) *donovani* is in Asian and African countries. Visceral leishmaniasis promoted by *L.* (*L.*) *infantum* is fatal, with a mortality rate of 100% if untreated.[4] Leishmaniasis is included as a target disease by DNDi (Drugs for Neglected Diseases Initiative) and iOWH (Institute for One World Health).

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