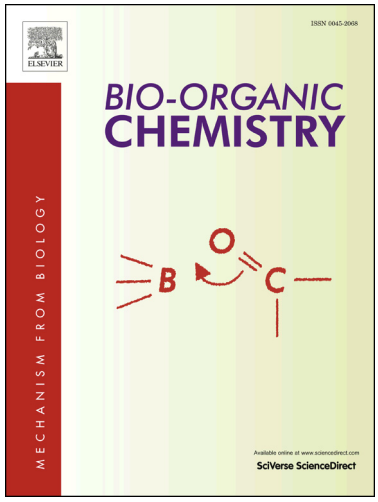

Aryl- or heteroaryl-based hydrazinylphthalazine derivatives as new potential antitrypanosomal agents

Angel H. Romero, Jonathan Rodríguez, Yael García, Jacques Leañez, Xenón Serrano-Martín, Simón E. López

PII: S0045-2068(16)30433-3
DOI: http://dx.doi.org/10.1016/j.bioorg.2017.03.008
Reference: YBIOO 2035

To appear in: *Bioorganic Chemistry*

Received Date: 7 January 2017
Revised Date: 14 February 2017
Accepted Date: 13 March 2017

Please cite this article as: A.H. Romero, J. Rodríguez, Y. García, J. Leañez, X. Serrano-Martín, S.E. López, Aryl- or heteroaryl-based hydrazinylphthalazine derivatives as new potential antitrypanosomal agents, *Bioorganic Chemistry* (2017), doi: http://dx.doi.org/10.1016/j.bioorg.2017.03.008

Aryl- or heteroaryl-based hydrazinylphthalazine derivatives as new potential antitrypanosomal agents

Angel H. Romero[a*], Jonathan Rodríguez[b], Yael García[b], Jacques Leañez,[b] Xenón Serrano-Martín[b], Simón E. López[a*]

[a]*Laboratorio de Química Medicinal y Heterociclos, Departamento de Química, Universidad Simón Bolívar, Valle de Sartenejas, Baruta, Caracas 1080-A, Venezuela.*

[b]*Laboratorio de Biología y Quimioterapia de Parasitosis Tropicales, Área de Salud, Instituto de Estudios Avanzados (IDEA), Caracas, Venezuela.*

[a]***Corresponding authors e-mail:** angel.romero12@ucv.ve, slopez@usb.ve

---

ABSTRACT: A series of twenty phthalazinyl-hydrazones were synthesized and tested as potential anti-*Trypanosoma cruzi* agents. The phthalazines containing 5-nitroheteroaryl moiety **3l** and **3m** displayed an excellent *in vitro* antitrypanosomal profile, exhibiting low micromolar EC_{50} values against proliferative epimastigote of *T. cruzi* and minimal toxicity toward Vero cells. These derivatives were more potent than the reference drug benznidazole against the epimastigote stage of the parasite. Structure-property analysis indicates that the highly conjugated 5-nitroheteroaryl moiety connected to the phthalazin scaffold play an important role in the antichagasic activity of these phthalazines. The decrease on the mitochondrial dehydrogenase activity and significant ROS production found for the parasites treated with **3l** and **3m** suggest that both nitro-derivatives can act through an oxidative stress mechanism.

Keywords: *Trypanosoma cruzi*, phthalazine, nitroheterocycle, mitochondrial dehydrogenase, epimastigotes.
