Pentavalent organoantimony and organobismuth complexes: evidence of interaction with DNA, membrane permeability and activity against leishmania strains resistant to inorganic antimony

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Abstract (300 word limit)

In an effort to further investigate the potential of organoantimony(V) and organobismuth(V) complexes as antileishmanial agents, we report here new complexes with benzoic acid derivatives, their interaction with DNA, cytotoxicity and activities against amastigotes and Sb-sensitive and -resistant promastigotes from different Leishmania species. Four complexes of the $Ph_3M(L)_2$ type were synthesized and characterized, where M= Sb(V) or Bi(V) and L= deprotonated ligand of sodium salt of 3-(dimethylamino)benzoic acid (HL1) or 2-acetylbenzoic acid (HL2). The crystal and molecular structures of the complexes with L1 were determined by single crystal X-ray diffraction. An interaction was demonstrated between pX145 plasmid DNA and both organoantimony(V) and organobismuth(V), their complexes and the inorganic Sb(III). $Ph_3Sb(L1)_2$ and $Ph_3Sb(L2)_2$ were active against *L. amazonensis* and *L. infantum* promastigotes and intramacrophagic amastigotes in the range of 3.6-18 μM and showed selectivity index in the range of 2.1-3.9. $Ph_3Bi(L1)_2$ was more active against promastigotes (1.2-2.5 μM) than intramacrophagic amastigotes (3.8-11 μM), whereas $Ph_3Bi(L2)_2$ was inactive against the amastigote form. $Ph_3Sb(L1)_2$ and $Ph_3Bi(L1)_2$ showed no cross-resistance with inorganic Sb(III) in resistant MRPA-overexpressing *L. amazonensis* and AQP1-mutated *L. guyanensis* lines. Cytometric analysis using propidium iodide exhibited that $Ph_3Sb(L1)_2$ and $Ph_3Bi(L1)_2$ were able to permeate the cellular membrane. Our data taken altogether support the model of different mechanism of action and uptake pathway in *Leishmania* for these organometallic complexes, when compared to the conventional inorganic antimonial drugs.

Image

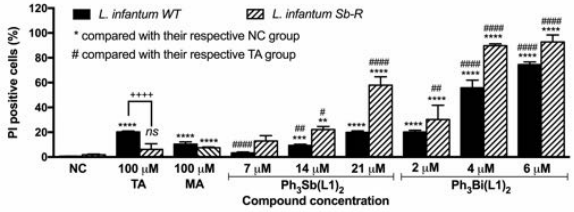


Fig 1. *L. infantum* membrane integrity. Promastigotes of *L. infantum* (WT or Sb-R) were exposed to TA 100 μM, MA 100 μM, $Ph_3Sb(L1)_2$ and $Ph_3Bi(L1)_2$ for 48h at 25 °C. Then, PI 5 μg/mL were added to cell culture and its intensity evaluated by flow cytometry. Percentage of PI stained cells. ANOVA, Bonferroni post-test compared to respective Negative control (NC) group (***p<0.01; ***p<0.001; ****p<0.0001), TA (#p<0.05; ##p<0.01; ####p<0.0001) or between strains ($^{++++}$p<0.0001).

Recent Publications (minimum 5)

1. Kelly C. Kato, Eliane de Morais-Teixeira, **Arshad Islam**, M. Fatima Leite, Cynthia Demicheli, Whocely V. de Castro, José D. Corrêa-Junior, Ana Rabello, Frédéric Frézard. Efficacy of Meglumine Antimoniate under Low Polymerization State Orally Administrated in Murine Model of Visceral Leishmaniasis. Accepted in "Antimicrobial agents and chemotherapy" on April 28, 2018.

2. Nazif Ullah, Akhtar Nadhman, Shaila Mehwish, Sumaira Siddiq, **Arshad Islam**, Laila Jafri, Muhammad Hamayun. (2016). Plants as Anti-leishmanial Agents: Current Scenario. Phytotherapy Research. DOI: 10.1002/ptr.5710. http://onlinelibrary.wiley.com/doi/10.1002/ptr.5710/full.

3. **Arshad Islam**, B.L. Rodrigues, I.M. Marzano, E.C. Perreira-Maia, D. Dittz, M.T. Paz Lopes, M. Ishfaq, F. Frézard, C. Demicheli. (2016). Cytotoxicity and Apoptotic Activity of Novel Organobismuth(V) and Organoantimony(V) Complexes in different Cancer Cell Lines. European Journal of Medicinal Chemistry 109: 254-267. doi:10.1016/j.ejmech.2016.01.003.

4. **Arshad Islam**, Jeferson Gomes Da Silva, Filipe Moan Berbet, Sydnei Magno da Silva, Bernardo Lages Rodrigues, Heloisa Beraldo, Maria Norma Melo, Frédéric Frézard and Cynthia Demicheli. (2014). Novel Triphenylantimony(V) and Triphenylbismuth(V) Complexes with Benzoic Acid Derivatives: Structural Characterization, In Vitro Antileishmanial and Antibacterial Activities and Cytotoxicity against Macrophages. Molecules 19(5): 6009-6030. doi:10.3390/molecules19056009.

5. Weverson A. Ferreira‡, **Arshad Islam**‡, Aretha Priscilla S. Andrade, Flaviana R. Fernandes, Frédéric Frézard and Cynthia Demicheli. (2014). Mixed Antimony(V) Complexes with Different Sugars to Modulate the Oral Bioavailability of Pentavalent Antimonial Drugs. Molecules 19(5): 5478-5489. doi:10.3390/molecules19055478.



Dr. Arshad Islam, currently a postdoctoral research fellow at Universidade Federal de Minas Gerais – Brazil, has experience in inorganic chemistry, biological chemistry, medicinal chemistry, nano-biotechnology and molecular biology. He has been working on various research projects including synthesis and characterization of organometallic complexes, nanosystems, metal nanoparticles and their evaluation in *in vitro* and *in vivo* experimental models of leishmaniasis, cancer, bacterial infection and Chagas disease and also their interaction with various biomolecules involved in different metabolic pathways. He has published 7 scientific articles in international scientific journals of high impact and a book chapter. Dr. Islam has presented his research in several national and international conferences.

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