Acaricidal activity against *Rhipicephalus microplus* by triosephosphate isomerase inhibitors

Luiz Saramago[1], Helga Gomes[1], Elena Alguilera[2], Hugo Cerecetto[2], Mercedes González[2], Mauricio Cabrera[3], Itabajara da Silva Vaz[4], Beatriz Aguirre-López5, Nallely Cabrera[5], Ruy Pérez-Montfort[5], Alicia Merlino[6], Guzmán Alvarez[3]* and Jorge Moraes[1]

[1] Laboratório Integrado de Bioquímica Hatisaburo Masuda- NUPEM and Instituto de Bioquímica Médica Leopoldo de Meis, UFRJ, RJ, Brazil; [2] Facultad de Ciencias, UDELAR, Montevideo, Uruguay; [3] Laboratorio de Moléculas Bioactivas – CENUR, UDELAR, Paysandú, Uruguay; [4] CBIOT and Faculdade de Veterinária, UFRGS, Porto Alegre, Brazil; [5] Instituto de Fisiología Celular, UNAM, México; [6] Laboratorio de Química Teórica y Computacional, Facultad de Ciencias, Facultad de Ciencias, UDELAR, Montevideo, Uruguay.

Introduction: The cattle tick *Rhipicephalus microplus* is one of the most important ectoparasites worldwide causing economic losses. The most commonly strategy to control ticks is the application of acaricides that lead the generation of resistant strains of *R. microplus.* In this context, the exploration of new molecules with acaricidal activity becomes necessary. The glycolytic enzyme Triosephosphate isomerase could be a druggable target for the development of new acaricidal agents for R. microplus. **Material and Methods:** TIM activity was determined by measuring the amount of D-glyceraldehyde 3-phosphate conversion to dihydroxyacetone phosphate. Docking calculations were carried out with Autodock 4.2 using the the Lamarckian Genetic Algorithm. The addition of compounds to BME26 cell cultures was evaluated by MTT assays and also by Fluorescentmicroscopy. Administration of RmTIM compound 14 was realized by *in vivo* artificial feeding. **Objectives**: Two hundred and twenty seven compounds were screened to find new inhibitors of RmTIM. **Results and Discussion**: Four compounds from our in-house chemo-library showed inhibition of this enzyme with IC50 values between 25 and 50 μM. In addition, ligand-protein molecular docking was performed to study enzyme-ligand interactions. The best result was observed with compound 14 that binds to the dimer interface of protein, interacting with residues on loop 3 (Glu70, Gln71, Ser79, Met82) and on alpha helix 1 (Gly16 and Ser17). This compound establishes two strong hydrogen bonds with Gln71 from chain A and with Gly16 from chain B (2.8 Å and 2.9 Å, respectively). Furthermore, compound 14 shows an in vitroand in vivo acaricidal activity in *R. microplus* models at micromolar levels. **Conclusion:** We describe the first selective inhibitor of this enzyme, compound 14, which also has an *in vitro* activity against BME26 cells from *R. microplus*. The proof of concept *in vivo* was satisfactory, determining a new potential acaricidal with simple and cheap production, potentially applicable to agriculture.

Word keys: Ticks, *Rhipicephalus microplus,*Triosephosphate isomerase.
Supported by: FAPERJ, CNPq, CAPES