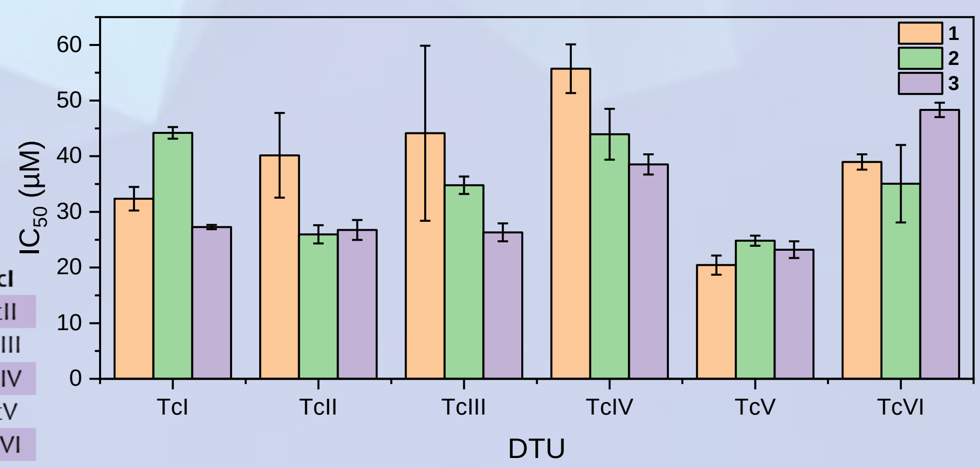
Proline transport inhibitors trigger differential responses in *Trypanosoma cruzi* growth inhibition

María Sol Ballari,* Lucia Fargnoli, Lucas Pagura, Julia A. Cricco, Ariel M. Silber and Guillermo R. Labadie

Proline has proved to be a fundamental amino acid for *Trypanosoma cruzi*, the etiological agent of Chagas disease. Proline is mainly incorporated by the parasite from the extracellular medium by amino acid transport systems, which are poorly studied as drug target. Decyl and farnesyl-substituted proline analogues proved to interact with the proline permease TcAAAP069 and, in consequence, inhibit the proline transport and uptake by *T. cruzi*. In this study, we deepened on the determination of proline transport-related mode of action.

Proline analogues are active against all *T. cruzi* DTUs

Sylvio	TcI
Y	TcII
M6241	TcIII
Can III	TcIV
92:80	TcV
CL14	TcVI



NBD-tagged decyl analogue is internalized into *T. cruzi* epimastigotes

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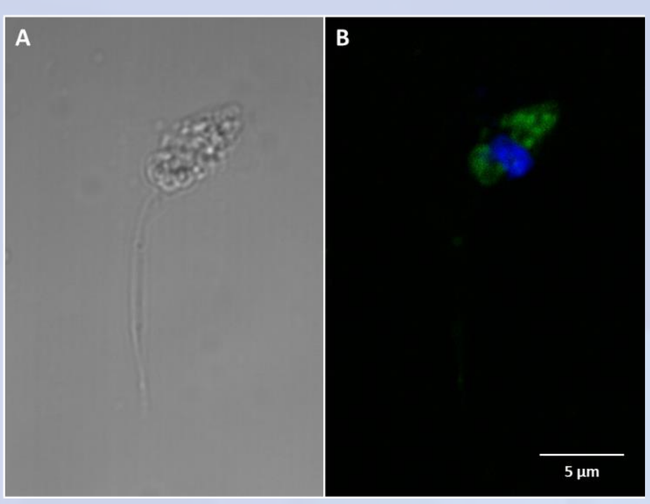
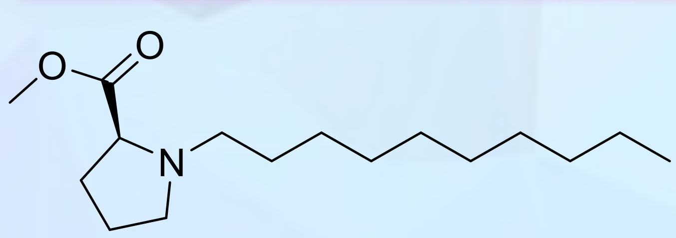
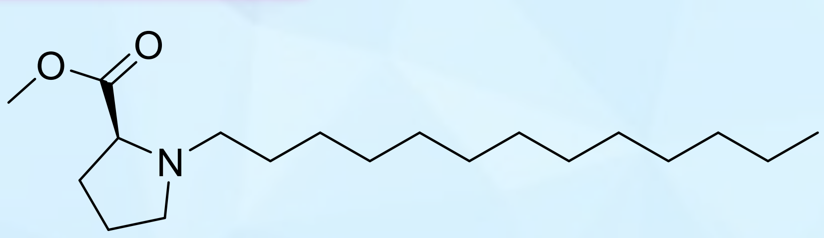


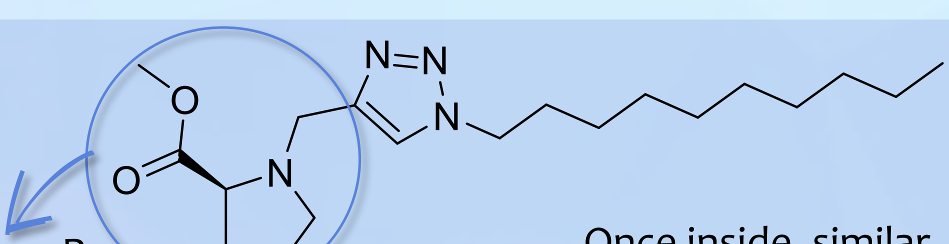
Triazole moiety is crucial for activity in decyl-substituted analogue



5 IC_{50} > 100 µM (CL14)



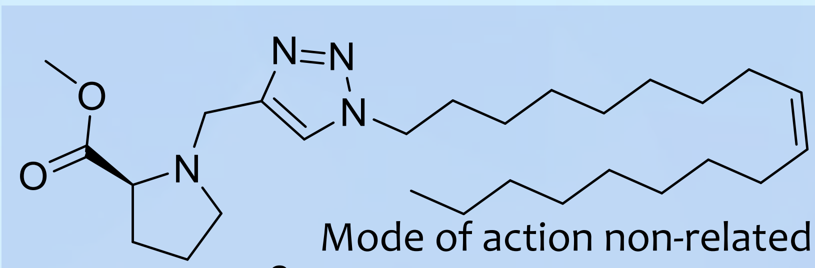
6 IC_{50} > 100 µM (CL14)



Transporter recognises Pro. Compound enters to the parasite

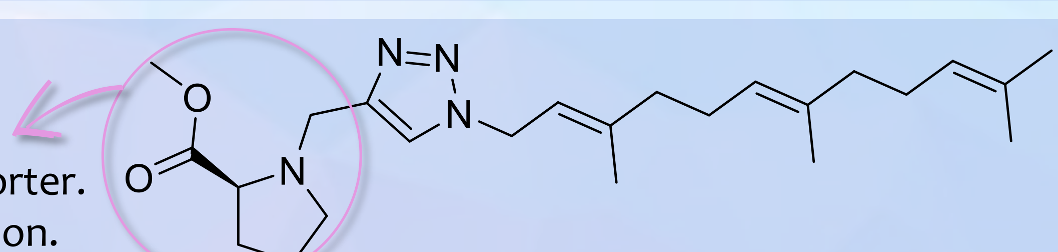
1

Once inside, similar behaviour than **2**



2

Mode of action non-related to Pro transport



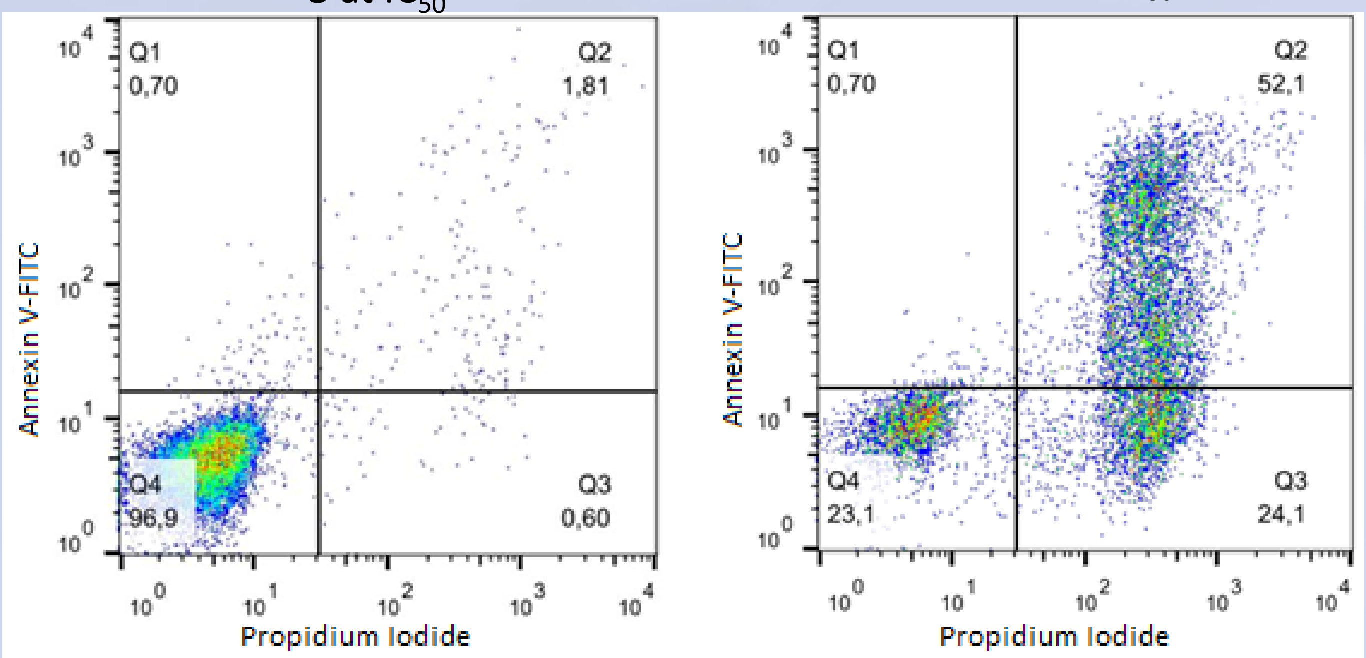
Blocks Pro transporter. Causes Pro depletion.

3 Extracellular mode of action

Farnesyl analogue promotes necrosis at high concentration

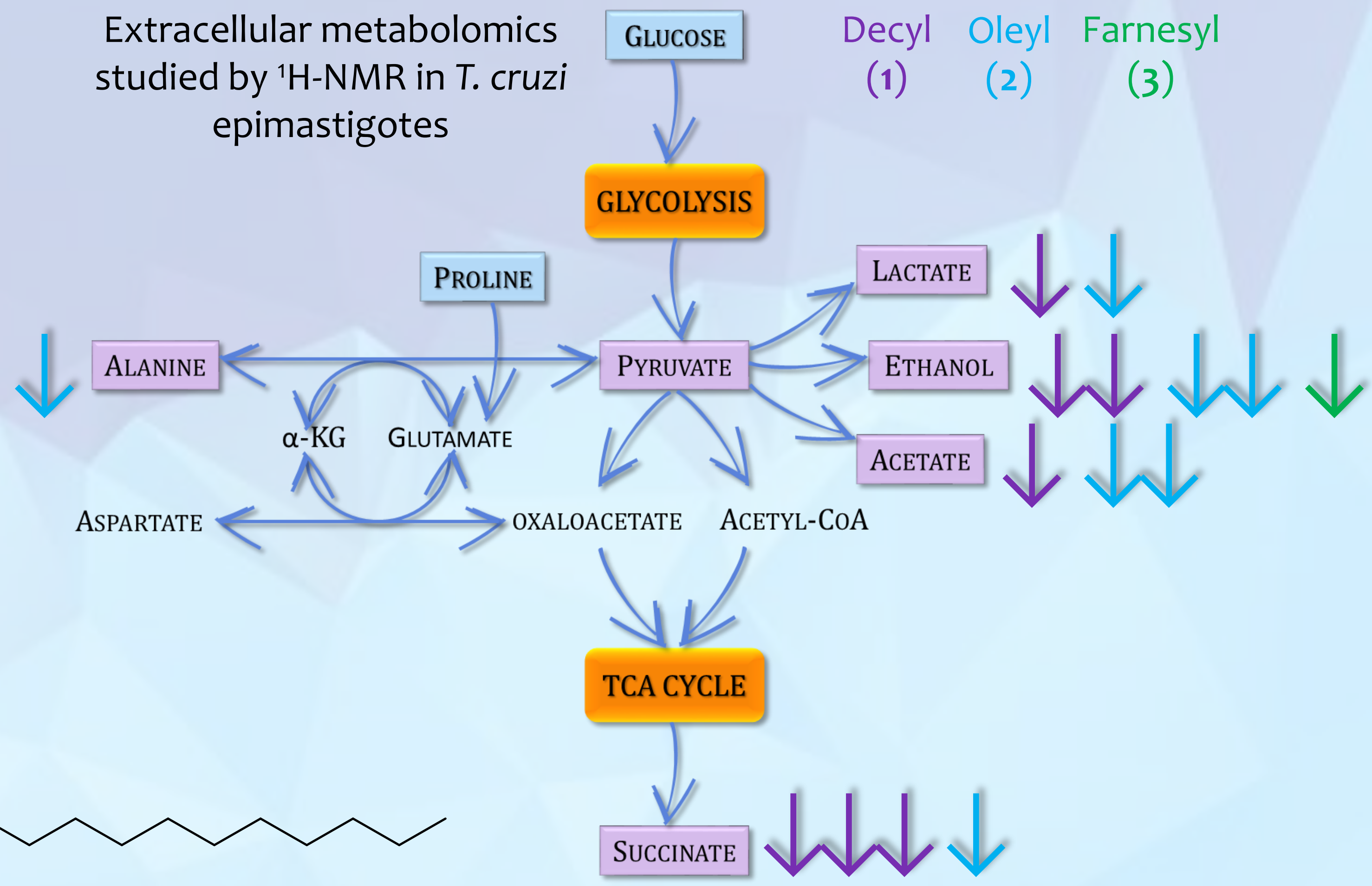
1 and **2** at IC_{50} and IC_{80}
3 at IC_{50}

3 at IC_{80}



Farnesyl analogue does not induce significant changes in energetic metabolism

Extracellular metabolomics studied by [1]H-NMR in *T. cruzi* epimastigotes



References: https://doi.org/10.3389/fchem.2020.00696
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*IQUIR-CONICET, Fac. Cs. Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Argentina.
e-mail: ballari@iquir-conicet.gov.ar

IQUIR CONICET