DND*i* Australian Discovery Consortium

Early medicinal chemistry to identify new candidate drugs

ICTMM 2012 September 2012
Rio de Janeiro

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DNDi Drugs for Neglected Diseases *initiative*

epichem molecules made to order

MURDOCH UNIVERSITY PERTH, WESTERN AUSTRALIA

cdco CENTRE FOR DRUG CANDIDATE OPTIMISATION

Early medicinal chemistry to identify new candidate drugs

- Aim of the discovery effort
- Hit identification
- Profiling and early optimisation
- Flow scheme and assay correlation
- Further optimisation
- Are we there yet?

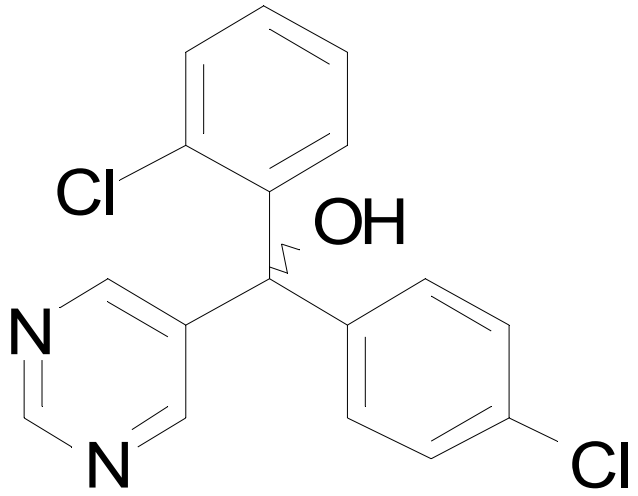
Aims

- To develop a drug that kills *Trypanosoma cruzi* a kinetoplastid parasite and causative agent of Chagas Disease in humans
- The target product profile:
  - Orally available
  - Cheap
  - Efficacy non-inferior to standard treatment
  - Better tolerated than standard treatment
  - Efficacious against chronic infections, multiple strains
  - No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs

Hit Identification

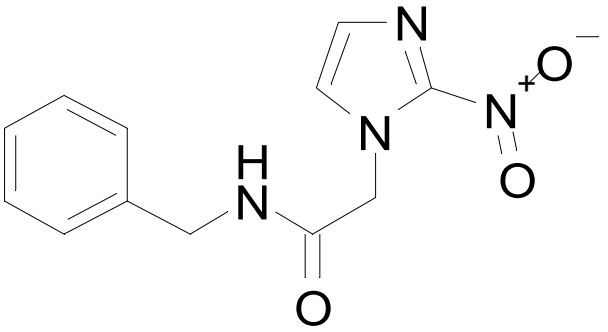
- *In vitro* screen: whole parasite assay targeting intracellular amastigote *T. cruzi* forms
- Where to find hits?
  - High-throughput screening (HTS)
  - Compound libraries – (non)-targeted
  - Existing drugs or published compounds
  - Rational design
  - Natural products

Fenarimol as an inhibitor of *T. cruzi*



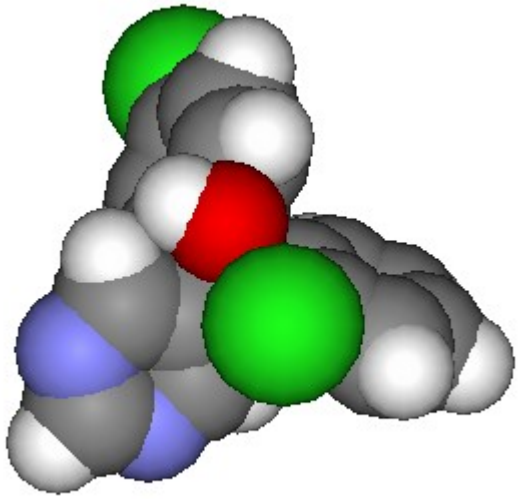
Fenarimol

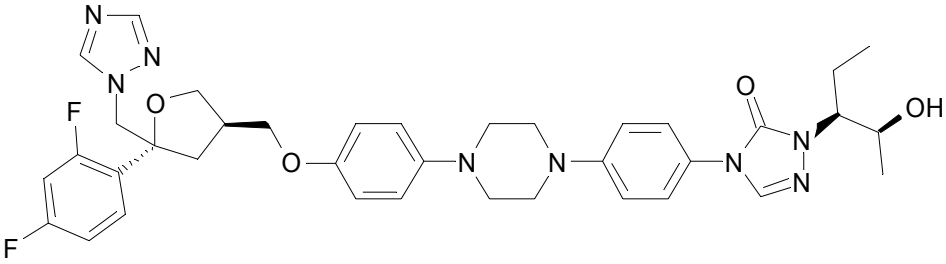
IC_{50} 350nM



Benznidazole

IC_{50} 1.15µM



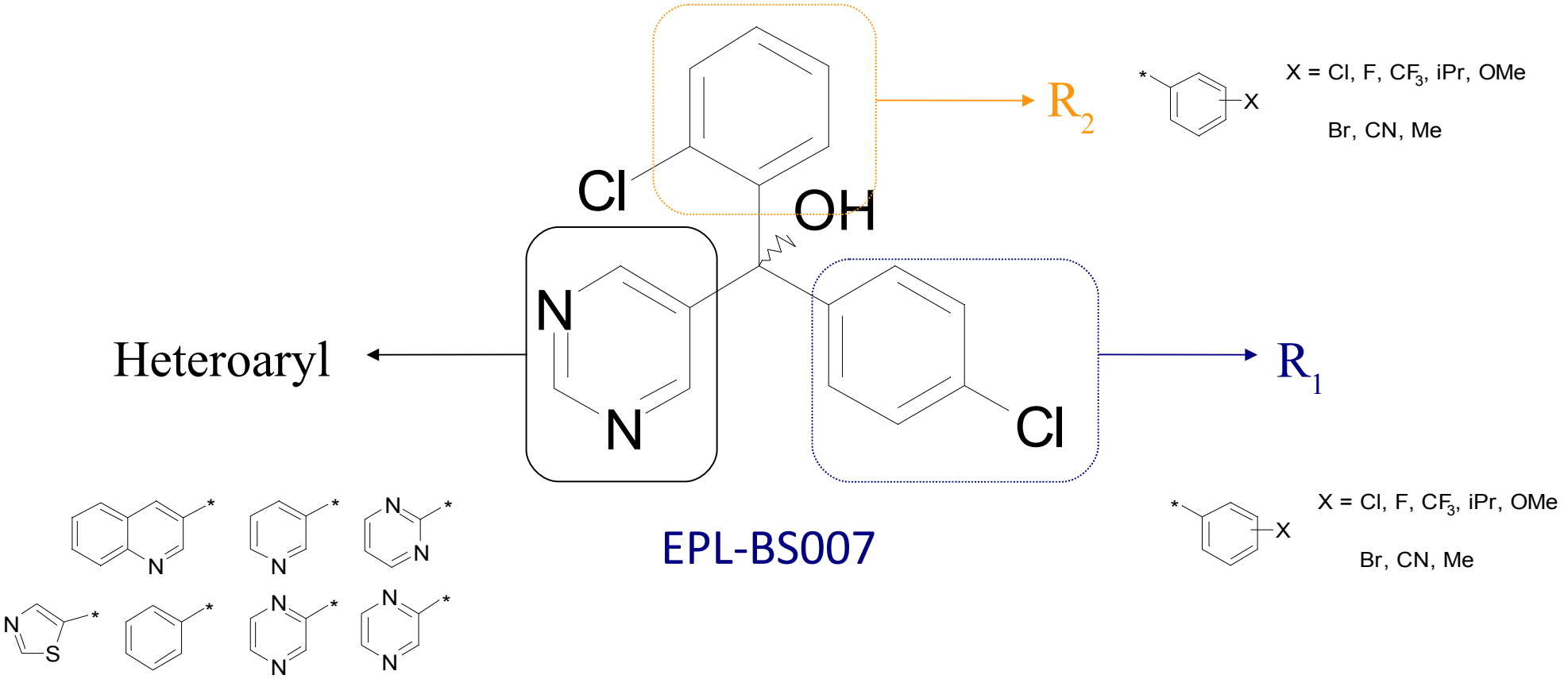


Posaconazole

IC_{50} 0.7nM

Profiling and early optimisation: *in vitro*

Design a strategy to define the Structure-Activity-Relationship (SAR)

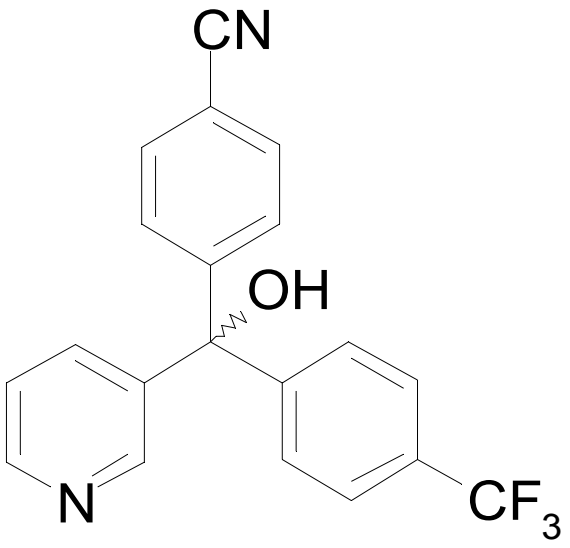


Profiling of additional *in vitro* properties

E_H(h) 0.82 : $Sol_{pH6.5}$ <25µg/ml : CYP3A4 IC_{50} 7µM

Profiling and early optimisation: *pharmacokinetics*

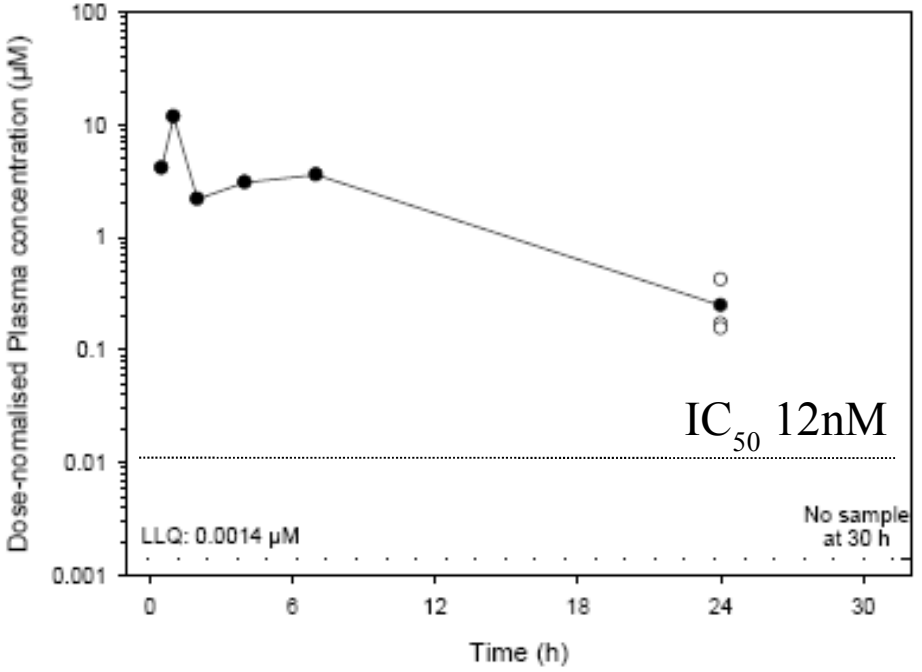
Oral exposure of compound in mouse plasma



EPL-BS0177

IC_{50} 12nM

EH(h) 0.5



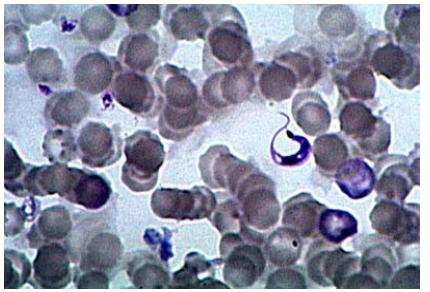
Compound Exposure in Mouse

[Compound] (µM) over Time (h)

20mg/kg oral dose

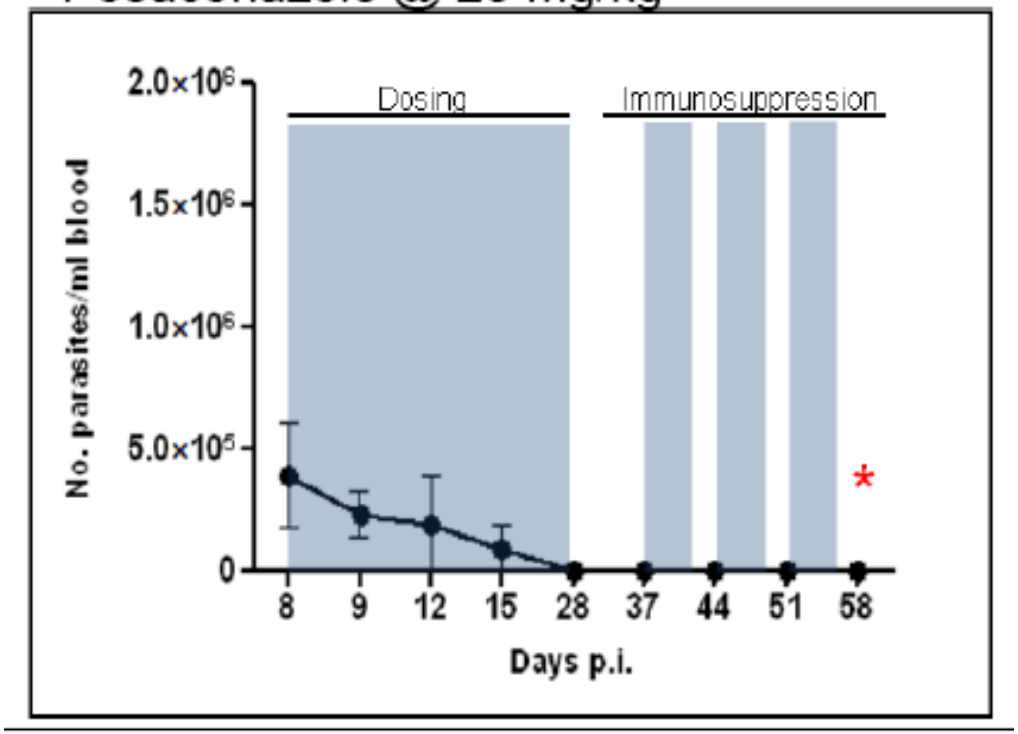
First connection between *in vitro* and *in vivo* assays

Profiling and early optimisation:
in vivo efficacy in a disease model
20-day mouse model of *T. cruzi* infection



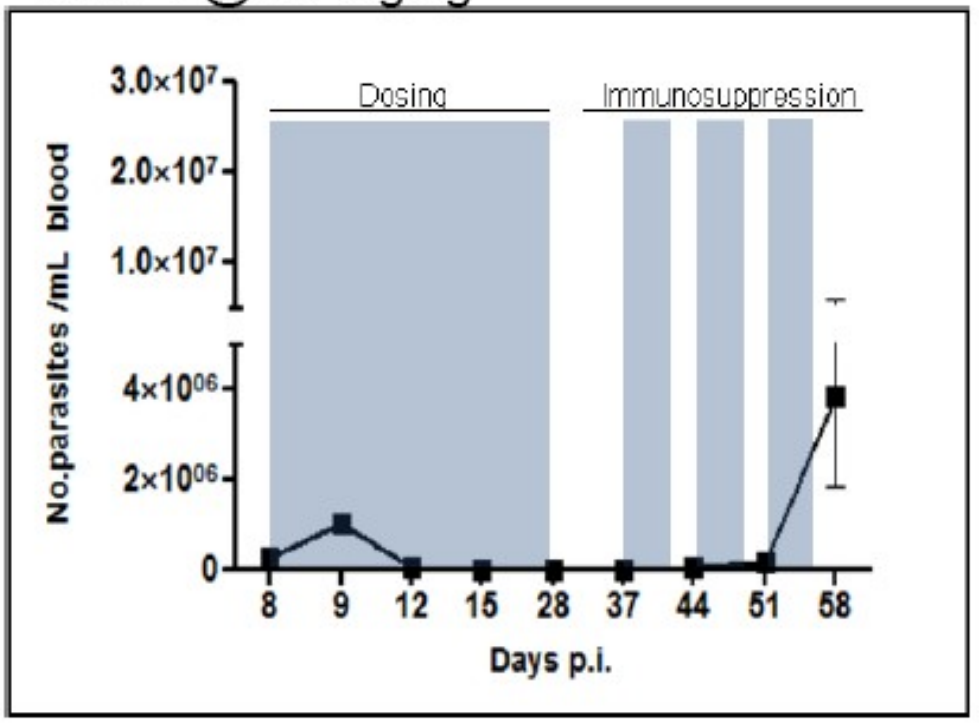
Control drug

Posaconazole @ 20 mg/kg

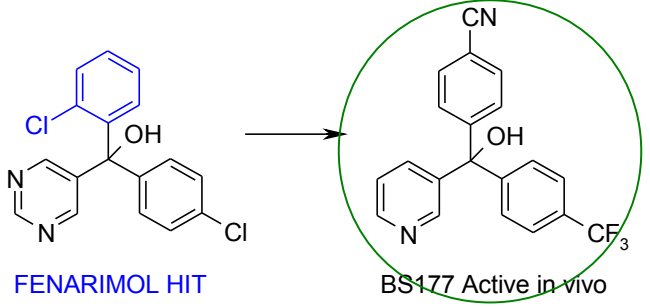


Our Drug

BS177 @ 20 mg/kg

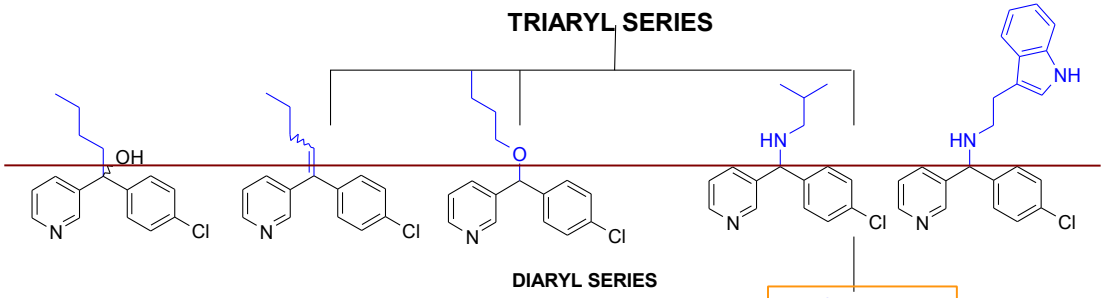


It works !

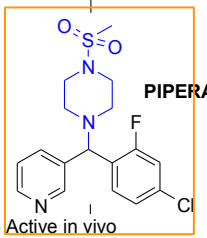


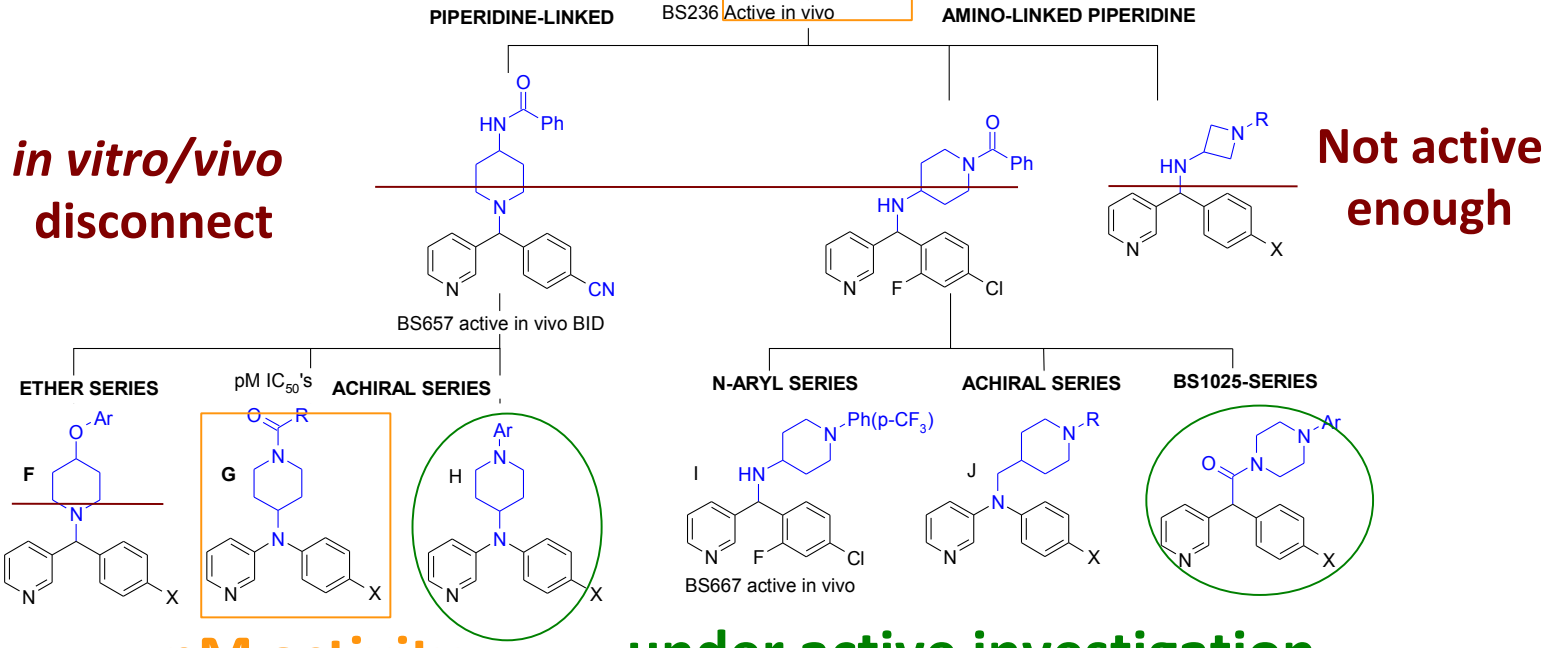
EPL-BS177 efficacious in *T. cruzi* infection model

Highly metabolised



Worked *in vivo* couldn't be optimised





***in vitro/vivo* disconnect**

Not active enough

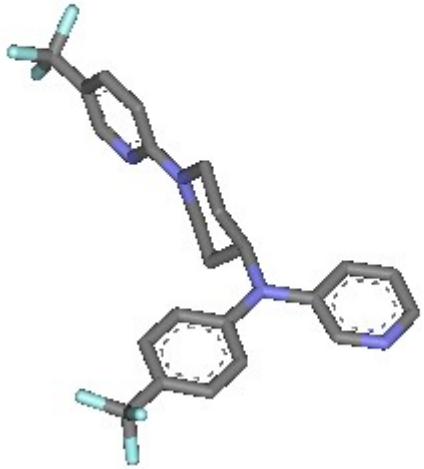
Not active enough

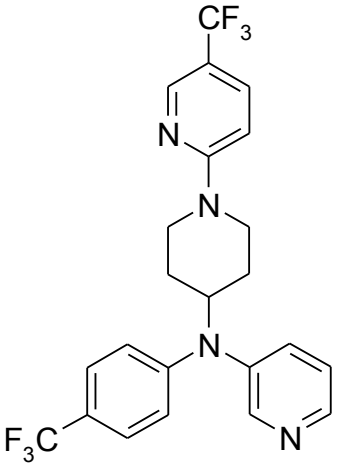
pM activity

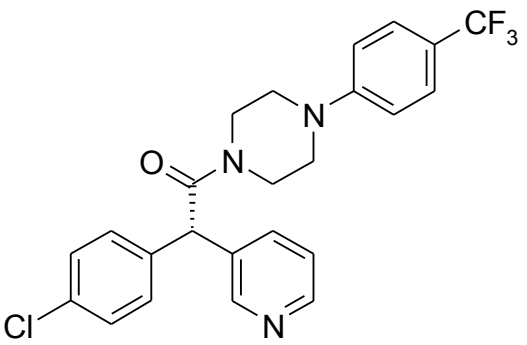
under active investigation

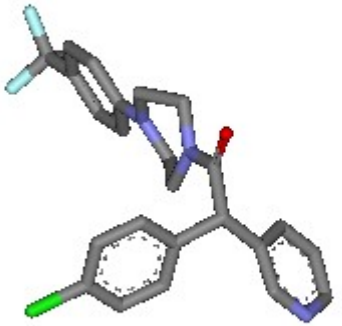
Pre-Clinical Candidates

EPL-BS0967 and **EPL-BS1246** both demonstrate 'cure' in the in the *T. cruzi in vivo* efficacy model in mice









Early phase discovery target product profile check-list

- ✔ Orally available and cheap
- ✔ Efficacy non-inferior to standard treatment
- ✔ Efficacious against chronic infection in a discovery model

Late phase discovery profiling ongoing

Acknowledgements

DNDi: Eric Chatelain, Delphine Launay, Ivan Scandale, Tom von Geldern.
Epichem: Paul Alexander, Jason Chaplin, Mike Abbott, Zhisen Wang, Josh McManus, Hugo Diao, Wayne Best, Martine Keenan.
Murdoch University Parasitology: Andrea Khong, Maria Kerfoot, Tanya Armstrong, Adriana Botero, Catherine Perez, Scott Cornwall, Andrew Thompson.
CDCO, Monash University: Karen White, David Shackleford, Sue Charman.
UFOP and IPK