Collaborative drug discovery for neglected diseases: Novel compounds for the treatment of Chagas disease

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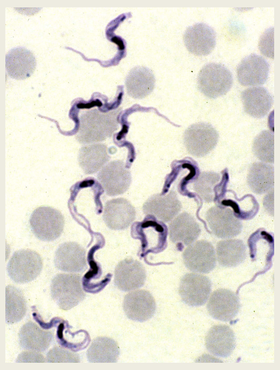


Essential medicines to treat diseases that affect the world's poor are too expensive, no longer produced, highly toxic, or ineffective. Drugs for Neglected Diseases *initiative* (DND*i*) is a collaborative, patients' needs-driven, non-profit R&D organisation developing new treatments for malaria, visceral leishmaniasis, sleeping sickness, and **Chagas disease.**

Working in partnership with industry & academia DND*i* has built the largest ever R&D portfolio for the kinetoplastid diseases.

Chagas disease, caused by the parasite *Trypanosoma cruzi,* is a major neglected parasitic disease endemic in South and Central America**.**

Aim: to discover a new oral therapy for Chagas disease non-inferior to existing treatment Benznidazole, with improved safety profile, shorter treatment time, active against the chronic form of the disease, inexpensive and easy to manufacture.

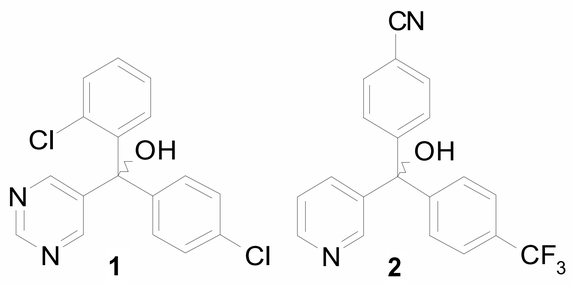
Novel compounds active *in vivo*

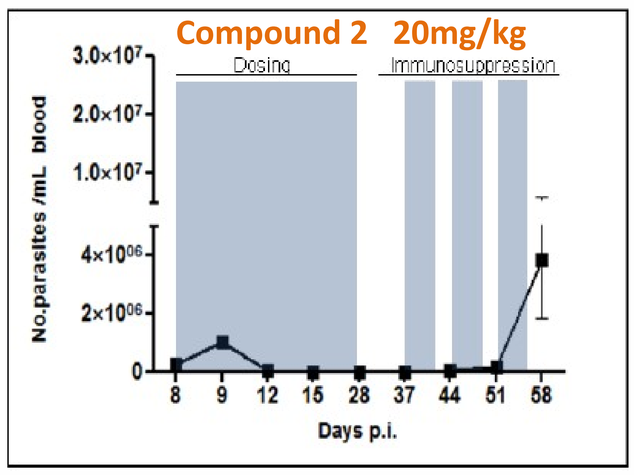
In 2008, DNDi brought together Epichem (Medicinal Chemistry), Murdoch University Parasitology group (Biology) and The Centre for Drug Candidate Optimisation (DMPK) to form the ***Chagas Disease Drug Discovery Consortium****.*

The team has developed:

i) mouse models simulating acute & chronic T. cruzi infection[6]
ii) an understanding of the PK/PD relationship required for activity
iii) identified and progressed a suite of novel, orally available molecules active in the in vivo T. cruzi models at lower doses and shorter treatment times than standard of care Benznidazole.

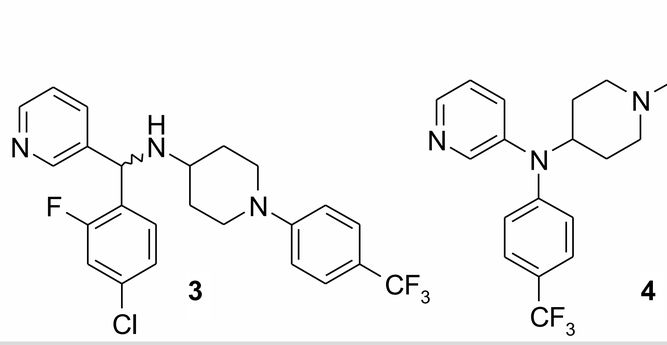
Plant fungicide ***fenarimol (1)*** *was identified as an inhibitor of T. cruzi (IC_{50} 350nM) following a targeted screening campaign. SAR investigations led to* ***2*** *a potent (IC_{50} 12 nM), easy to synthesise compound, efficacious in vivo suppressing parasitemia to negligible levels after a daily oral dose of 20 mg/kg for 20-days. Parasite rebound occurred after 2-rounds of immunosuppression.*





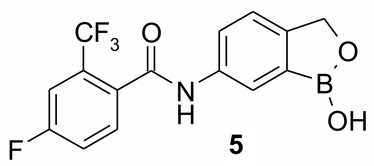
Structural diversity

Scaffold hopping has generated further compound series orally active in the chronic T. cruzi model: ***3*** *(IC_{50} 11nM) and* ***4*** *(IC_{50} 11nM).*

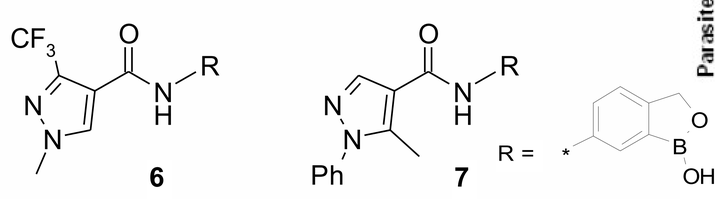


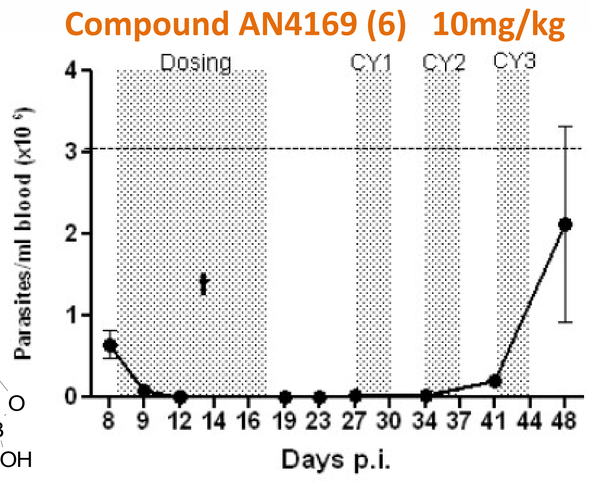
Further collaborations

With ***DNDi****,* ***the Chagas Consortium*** *has collaborated with Anacor Pharmaceuticals to profile novel benzoxaborole compounds active against T. cruzi in vitro.* ***AN4169*** *(****5****) was active in vivo following oral treatment at 10mg/kg/day, with parasite rebound occurring after 2-rounds of immunosuppression.*



SAR investigations have identified novel pyrazole analogues ***6*** *&* ***7*** *also active in vivo.*





Conclusion

A collaborative drug discovery consortium established by Drugs for Neglected Diseases *initiative* (DND*i*) has identified and developed **two novel compound series active against intracellular protozoan parasite *Trypanosoma cruzi* the causative agent of Chagas disease**.

Compounds suppress parasitemia to undetectable levels after once-a-day oral dosing in a mouse model of chronic *T. cruzi* infection. Compounds are non-cytotoxic and chemically tractable facilitating rapid optimisation of **target biology and drug characteristics**.

Studies continue to progress compounds to pre-clinical candidate status.

[6]*In vivo model:* ***Acute phase.*** Female Swiss mice (n=5/group) are infected with 25,000 bloodstream forms of *T.cruzi (*Tulahuén strain). Infection is non-lethal, parasites can be detected in a number of organs, and parasitemia levels peak in the blood on day 11 p.i. Mice are administered test compounds once daily for 20 consecutive days, starting day 8 p.i. A reduction in blood parasitemia over the course of treatment gives an indication of compound efficacy. Parasitemia is measured by taking 3µL of blood from the tail vein, diluting 1:10 with red blood cell lysis buffer, and counting live trypomastigotes using a neubauer haemocytometer. *Posaconazole and vehicle-only treated groups are included as controls*. ***Chronic phase.*** Animals showing significant reduction in parasitemia are immunosuppressed by three rounds of cyclophosphamide (4 days at 50 mg/kg per day followed by 3 days rest) to observe any rebound in parasitemia. If no rebound in blood parasitaemia is observed, PCR is used to confirm whether organs are cleared of parasites. *Benznidazole is active in the chronic model at 100 mg/kg, with parasite rebound after 2 rounds of immunosuppression.*