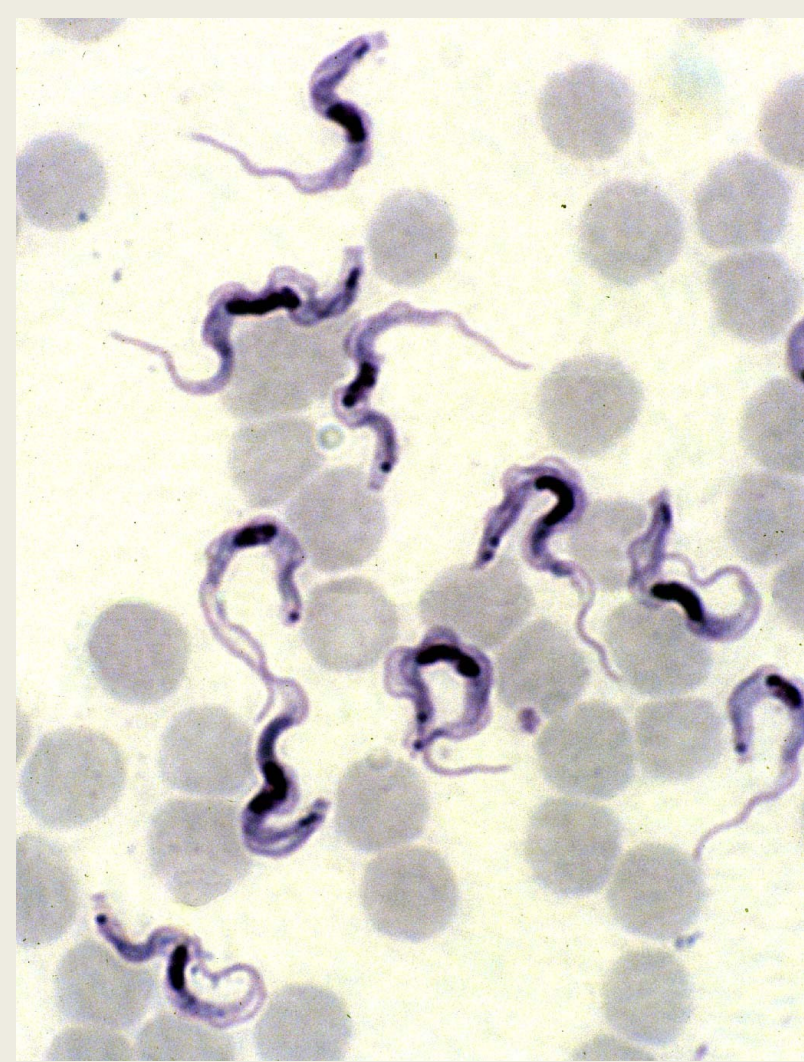


# Collaborative drug discovery for neglected diseases: Novel compounds for the treatment of Chagas disease

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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 (DNDi)** 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 **DNDi** 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.

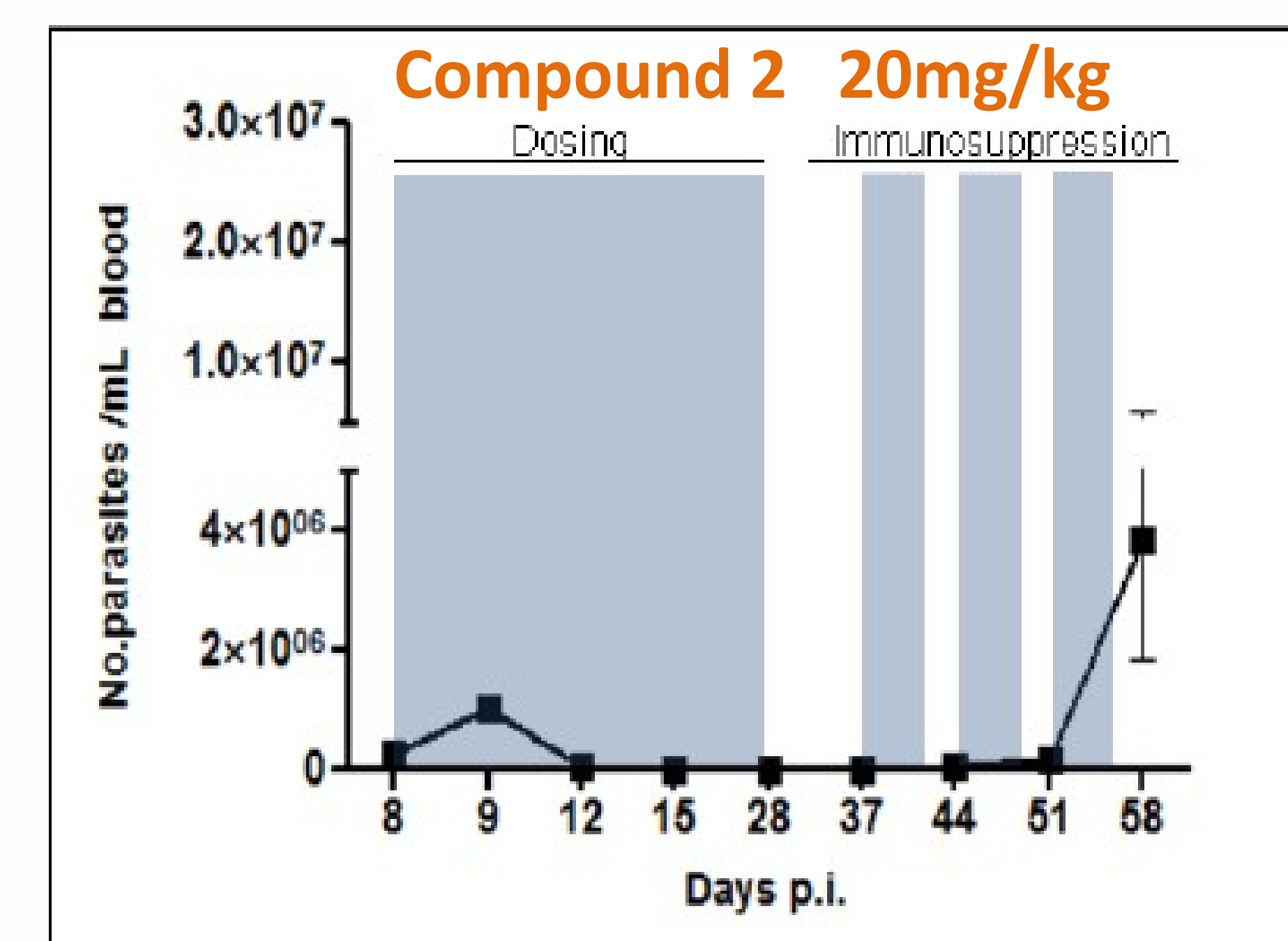
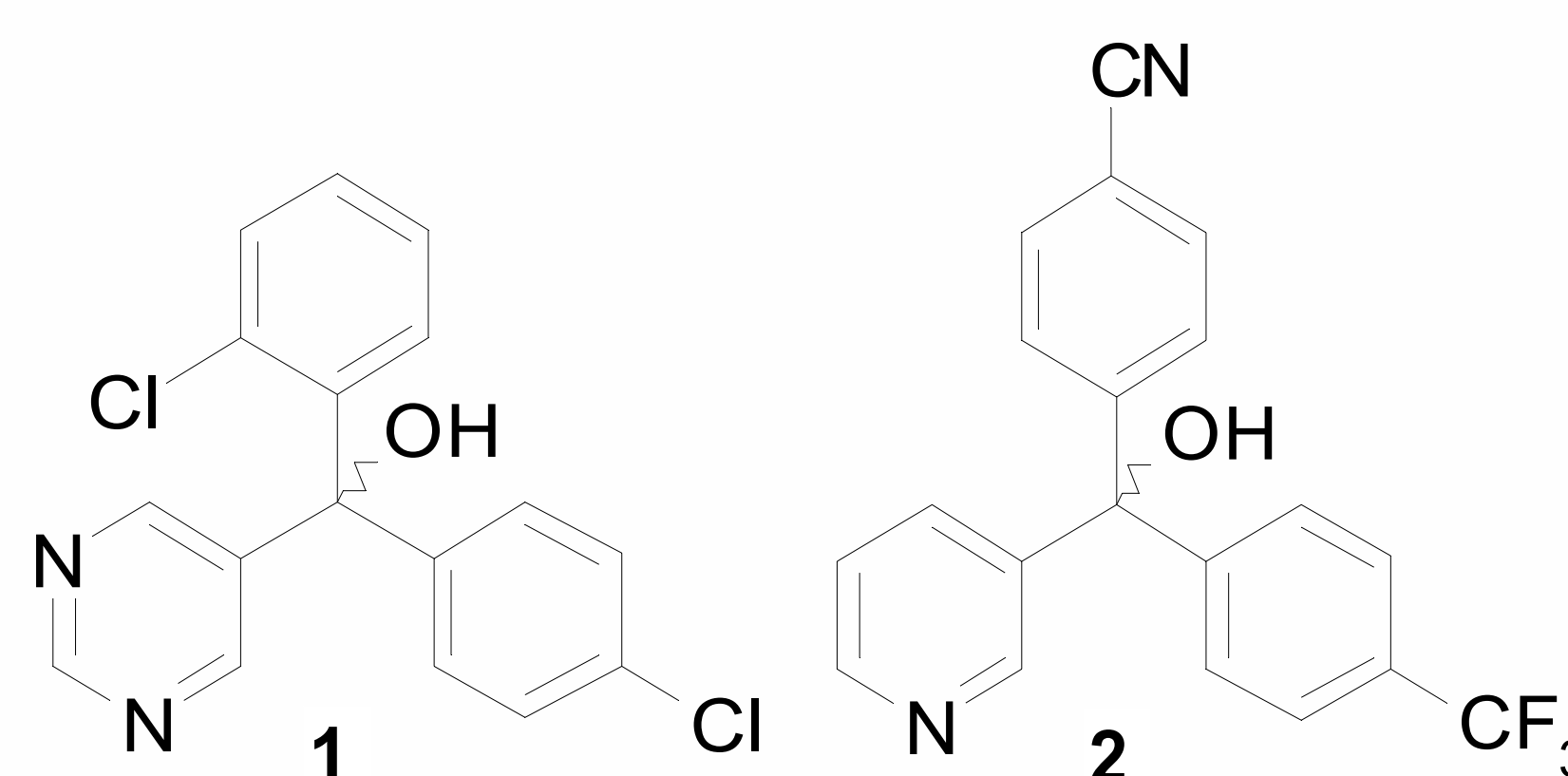
## Novel compounds active *in vivo*

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:

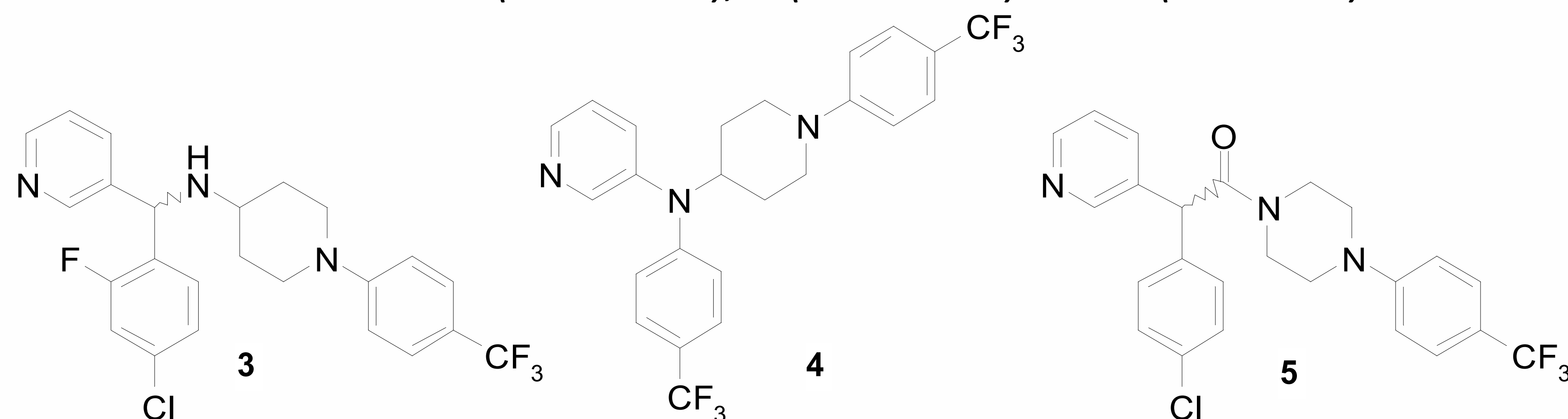
- mouse models simulating acute & chronic *T. cruzi* infection
- an understanding of the PK/PD relationship required for activity
- identified and progressed a suite of novel, orally available molecules active in the *in vivo* *T. cruzi* models at lower doses and shorter treatment times than standard 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), **4** ( $IC_{50}$  11nM) and **5** ( $IC_{50}$  7nM).



## Conclusion

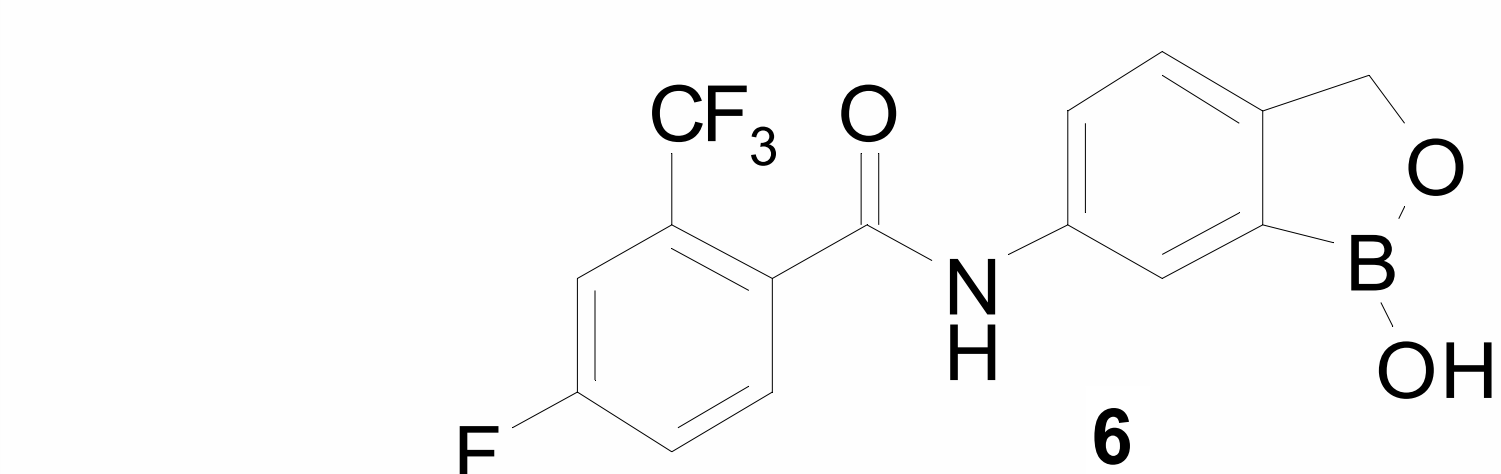
A collaborative drug discovery consortium established by **Drugs for Neglected Diseases initiative (DNDi)** has identified and developed **two novel compound series active against intracellular protozoan parasite *Trypanosoma cruzi* the causative agent of Chagas disease**.

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**.

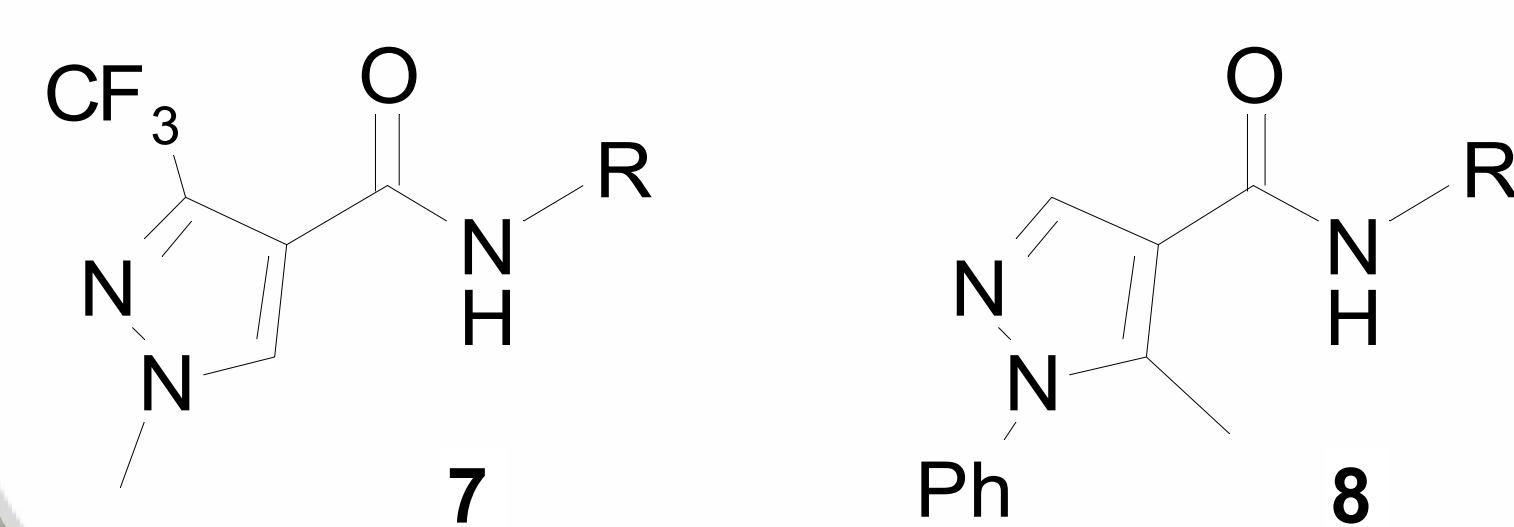
Studies continue to progress compounds to pre-clinical candidate status.

## Further collaborations

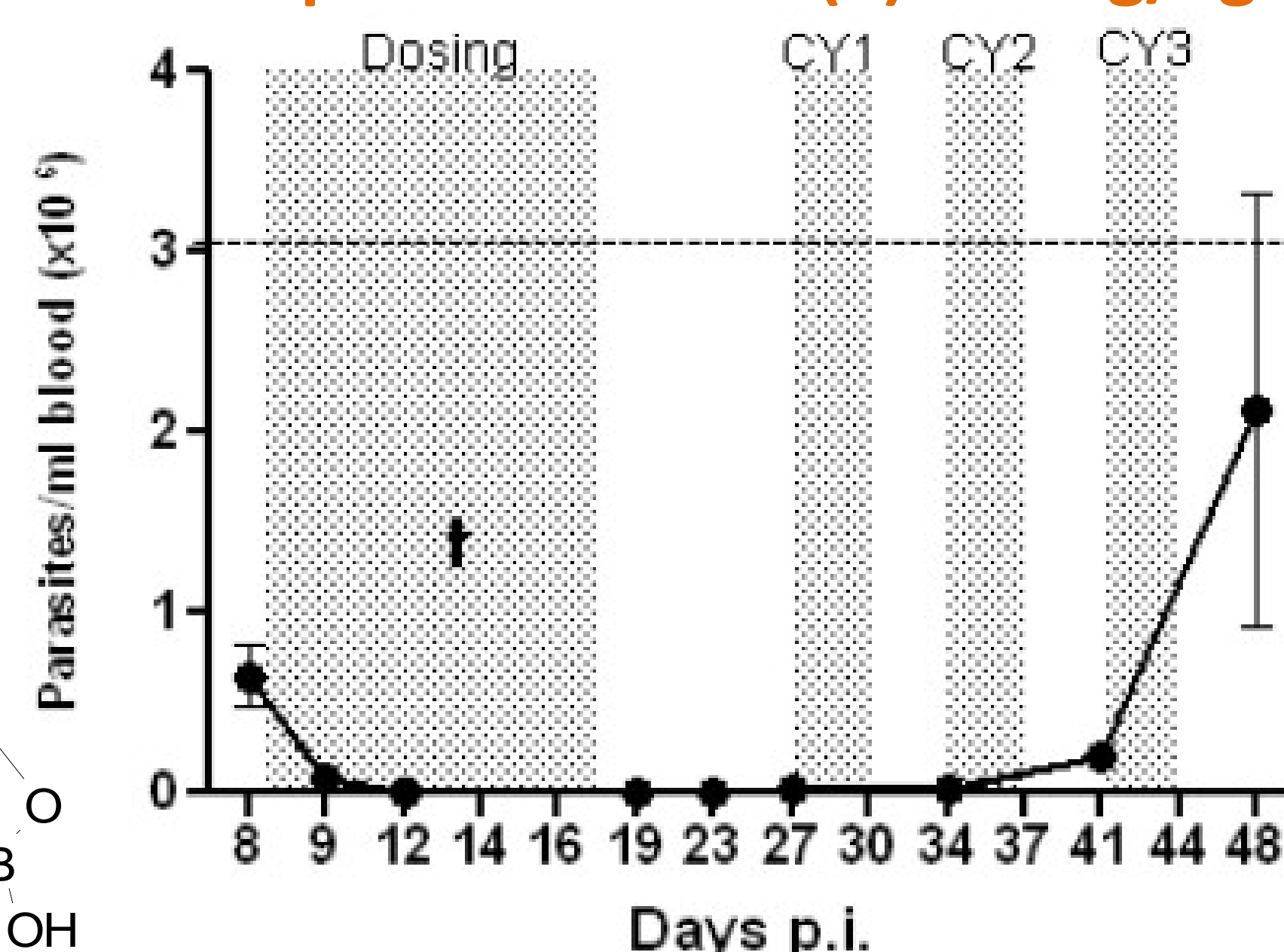
With **DNDi**, the **Chagas Consortium** has collaborated with **Anacor Pharmaceuticals** to profile novel benzoxaborole compounds active against *T. cruzi* *in vitro*. **AN4169 (6)** was active *in vivo* following oral treatment at 10mg/kg/day, with parasite rebound occurring after 2-rounds of immunosuppression.



SAR investigations have identified novel pyrazole analogues **7 & 8** also active *in vivo*.



**Compound AN4169 (6) 10mg/kg**



**<sup>6</sup>In vivo model: Acute phase.** Female Swiss mice (n=5/group) are infected with 25,000 bloodstream forms of *T. cruzi* (Tulahuen 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 parasitemia 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.