**Novel Compounds for the Treatment of Chagas Disease**

Martine Keenan  
Epichem Pty Ltd  
DNDi Chagas Disease Consortium

Presented at ASTMH 2009  
Washington DC, USA

---

**Acknowledgements**

**Chemistry**  
Mike Abbott  
Paul Alexander  
Brad Bervan  
Jason Chaplin  
Hugo Diao  
Joshua McManus  
Zhisen Wang  
Wayne Best

**Biology**  
Tanya Armstrong  
Maria Kerfoot  
Andrea Khong  
Andrea Botero  
**DMPK**  
Karen White  
David Shackleford  
Susan Charmain  
Andy Thompson

**DNDi**  
Rob Don  
Ivan Scandale  
Tom von Geldern  
**Eric Chatelain**

---

DNDi Chagas Disease Consortium  
ASTMH 2009
**Life cycle of Trypanosoma Cruzi**

**Triatomine Bug Stages**
1. *Trypanosoma* bug takes a blood meal from an infected mammal.
2. *Trypanosoma* replicate in the insect.
3. *Trypanosoma* exits in the insect’s feces.

**Human Stages**
1. Insect feces contaminate the human’s skin.
2. *Trypanosoma* enter the wound site and replicate in macrophages.
3. *Trypanosoma* replicate and enter the bloodstream.
4. *Trypanosoma* replicate in the heart and intestinal smooth muscle, causing heart failure and digestive problems.

**Sourcing hits: Natural Products**

- **Canthinone**
  - IC\textsubscript{50} 17.5μM
  - Not active in vivo at 100μM

- **(-)-Hinokinin**
  - IC\textsubscript{50} 24μM (rac)

- **Catechin family**
  - IC\textsubscript{50} 17μM (rac)
**Sourcing hits**

WEHI-100156  
IC$_{50}$ 0.29μM (rac)

BS212  
IC$_{50}$ 0.03μM (rac .HCl)

*Not tolerated in mice at 100mpk*

---

**Sourcing hits : Agrochemicals**

Posaconazole  
IC$_{50}$ 0.0007μM

Fenarimol  
IC$_{50}$ 0.35μM (rac)

Pyrifenox  
IC$_{50}$ 0.29μM
Fenarimol SAR

IC₅₀ 0.35 μM

IC₅₀ 0.29 μM

IC₅₀ 0.002 μM

Synthesis

Presented at ASTMH 2009
**Evolution of a series**

\[
\begin{align*}
\text{BS207} & \quad \text{IC}_{50} 0.030\mu\text{M} \\
\end{align*}
\]

**Plasma concentrations of EPL-BS0207 following IV and oral administration to male Sprague Dawley rats.**

DNDi Chagas Disease Consortium  ASTMH 2009
**Activity of BS207 in mouse model of T. cruzi infection**

![Graph showing activity of BS207 in mouse model of T. cruzi infection](image)

Mice inoculated with 25,000 T. cruzi Tulahuan
BS207 made up to 15mg/ml with HPMC-SV
Suspension was sonicated, vortexed and kept on ice when made and before each dose
100mpk (200µL) administered PO once daily for 5 days
Insert: individual mouse parasitaemia levels in BS207 treated group

---

**Summary**

- Several compound series with activity against *T. cruzi* were evaluated as hits
- A new lead series has been developed from the herbicide Fenarimol
  - Potent
  - Selective
  - No cytotoxicity
  - Easy to synthesise
- Lead compound BS207 has good oral bioavailability and is active in a mouse model of *T. cruzi* infection