Novel Compounds for the Treatment of Chagas Disease

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**Life cycle of Trypanosoma Cruzi**

**Triatomine Bug Stages**
- Triatomine bug takes a blood meal.
- Metacyclic trypomastigotes enter the wound site.
- Inside cells, they transform into amastigotes.
- Amastigotes multiply intracellularly.
- In some host cells, amastigotes transform into trypomastigotes.
- Triatomine bug takes a blood meal (insect stage).

**Human Stages**
- Metacyclic trypomastigotes penetrate various sites at the wound site.
- Inside cells, they transform into amastigotes.

Day 1
- Infected Stage

Day 3
- Diagnostic Stage

Day 4-7
- Infective Stage

**Sourcing hits: Natural Products**

**Canthinone**
- IC$_{50}$ 17.5μM
- Not active in vivo at 100mpk

**(-)-Hinokinin**
- IC$_{50}$ 24μM (rac)

**Catechin family**
- IC$_{50}$ 17μM (rac)
**Sourcing hits**

WEHI-100156  
IC\textsubscript{50} 0.29\mu M (rac)  

BS212  
IC\textsubscript{50} 0.03\mu M (rac .HCl)  

*Not tolerated in mice at 100mpk*

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**Sourcing hits : Agrochemicals**

Posaconazole  
IC\textsubscript{50} 0.0007\mu M  

Fenarimol  
IC\textsubscript{50} 0.35\mu M (rac)  

Pyriflinox  
IC\textsubscript{50} 0.29\mu M  

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**Fenarimol SAR**

\[
\begin{align*}
\text{IC}_{50} & = 0.35 \mu M \\
\text{IC}_{50} & = 0.29 \mu M \\
\text{IC}_{50} & = 0.002 \mu M
\end{align*}
\]

**Synthesis**

\[
\begin{align*}
\text{Br} + \text{Cl} & \implies \text{Br} + \text{Cl} \\
\implies \text{Br} + \text{Cl} & \implies \text{Br} + \text{Cl}
\end{align*}
\]

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Evolution of a series

\[
\begin{align*}
&\text{BS207} \\
&\text{IC}_{50} \text{ 0.030}\mu\text{M} \\
&\text{IC}_{50} \text{ 0.002}\mu\text{M} \\
&\text{IC}_{50} \text{ 0.035}\mu\text{M} \\
&\text{IC}_{50} \text{ 0.058}\mu\text{M}
\end{align*}
\]

Plasma concentrations of EPL-BS0207 following IV and oral administration to male Sprague Dawley rats.
Activity of BS207 in mouse model of T. cruzi infection

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