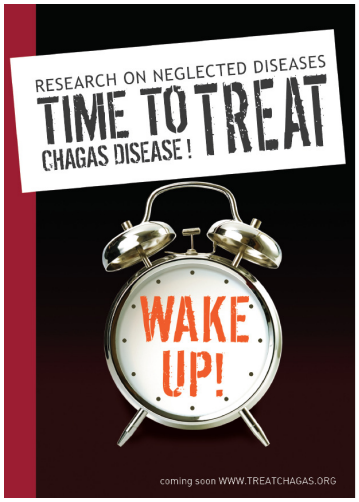
Compostos Azólicos na Doença de Chagas: situação atual

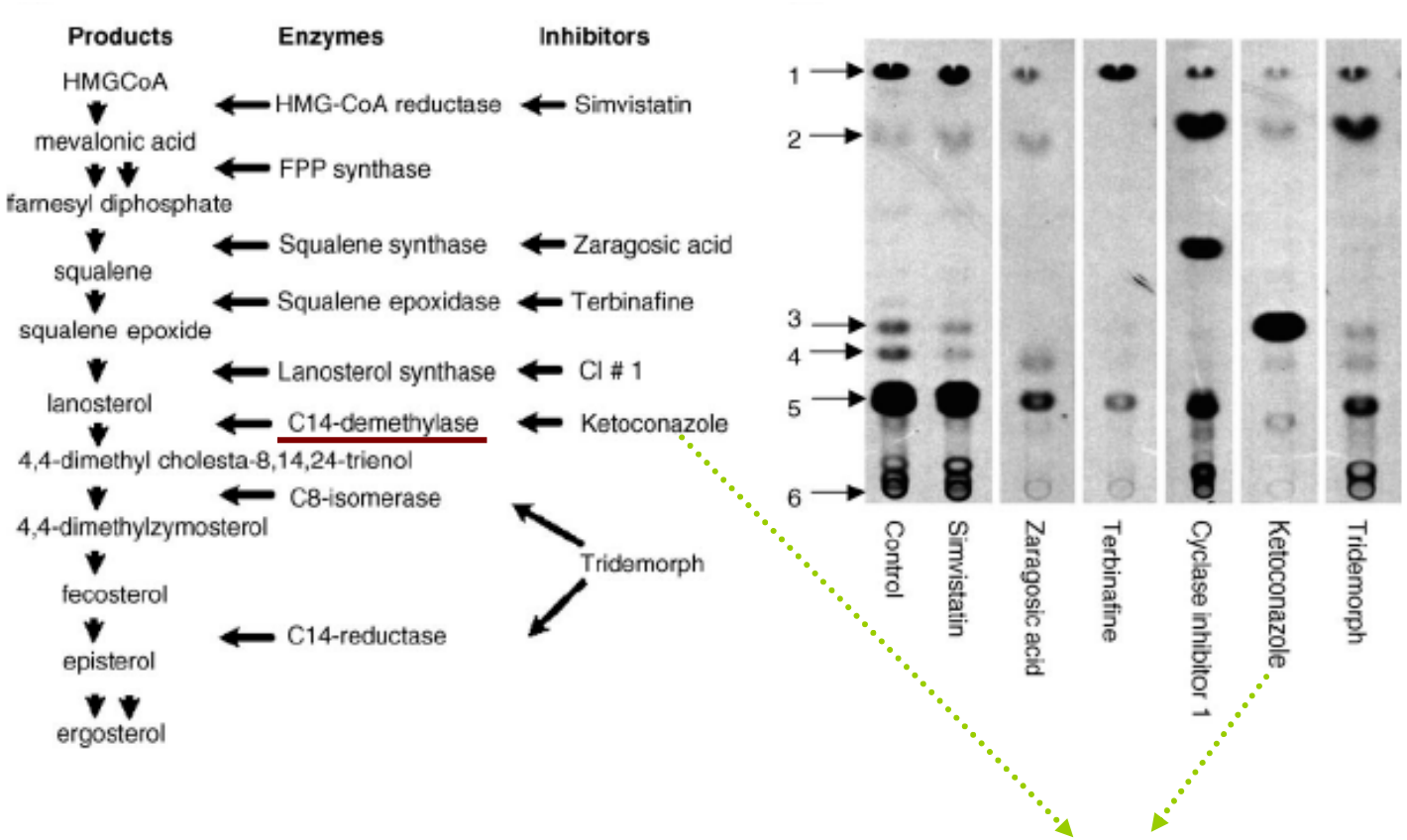


Isabela Ribeiro
Senior Project Manager, DNDi

Med Trop 2010

DNDi
Drugs for Neglected Diseases *initiative*

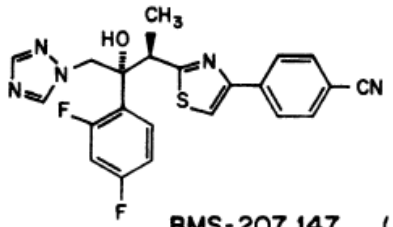
Trypanosoma cruzi
Biosíntese do Ergosterol



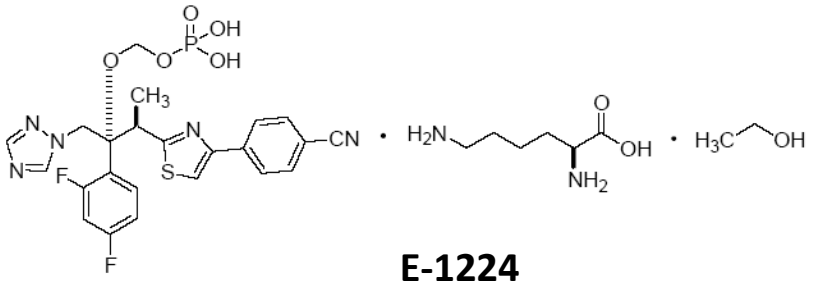
Compostos Azólicos: Ravuconazol, E1224, TK187, Posaconazol, Voriconazol

E.G. Hankins et al. / Molecular & Biochemical Parasitology 144 (2005) 68–75

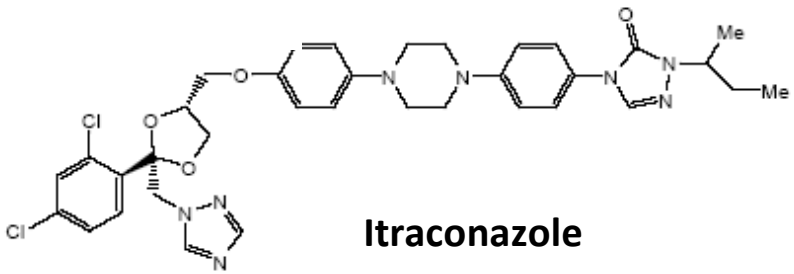
Compostos Azólicos – Estrutura Química



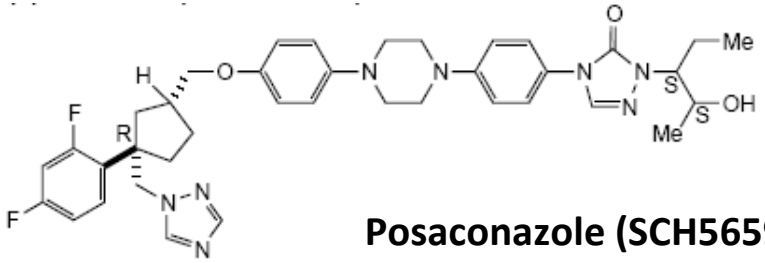
BMS-207,147 (RAVUCONAZOLE)



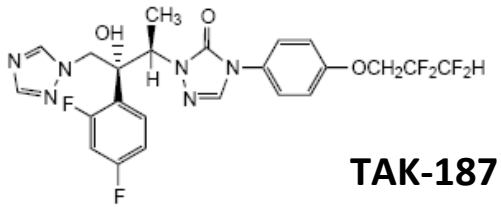
E-1224



Itraconazole



Posaconazole (SCH56592)



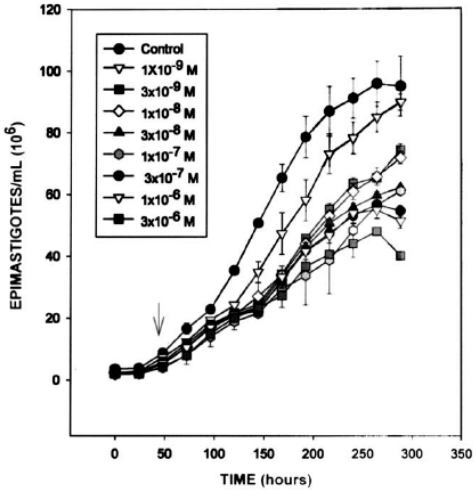
TAK-187

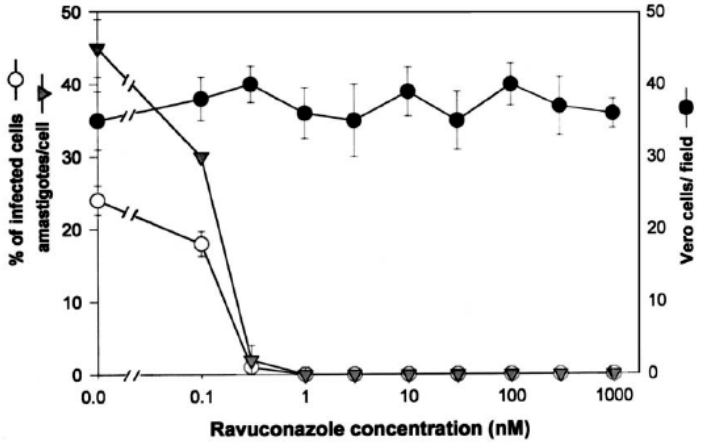
DNDi Drugs for Neglected Diseases initiative

Atividade Comparativa *In vitro*

- **Ravuconazol**
  - **MIC 300 nM (221 ng/ml) para formas epimastigotas**
  - **MIC 1 nM (7.4 ng/ml) and IC50 0.1 nM para formas amastigotas**

  - **Sem efeito em viabilidade celular e proliferação em concentrações >1000 MIC**
  - **Cepa não especificada (Cepas EP and Y mencionadas)**

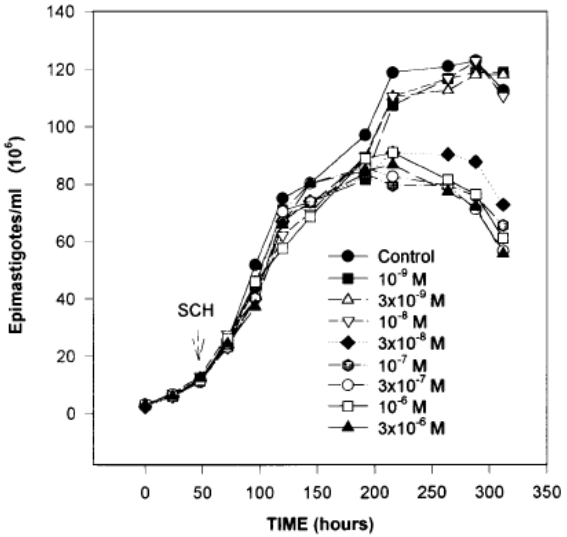


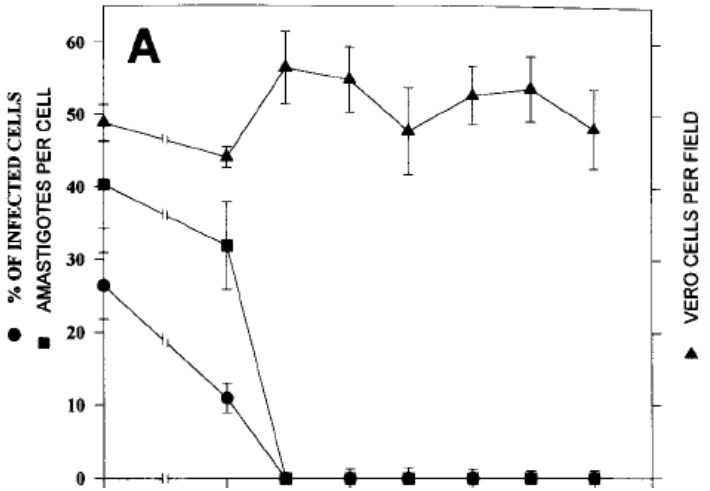


Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

Atividade Comparativa *In vitro*

- **Posaconazol**
  - **MIC 30 nM (21 ng/ml) para formas epimastigotas**
  - **MIC 0.3 nM (2.1 ng/ml) para formas amastigotas**
  - **Sem efeito na viabilidade celular e proliferação em concentrações >300X MIC (100 nM; 1uM data not shown)**
  - **Cepa não especificada (Cepas EP and Y mencionadas)**



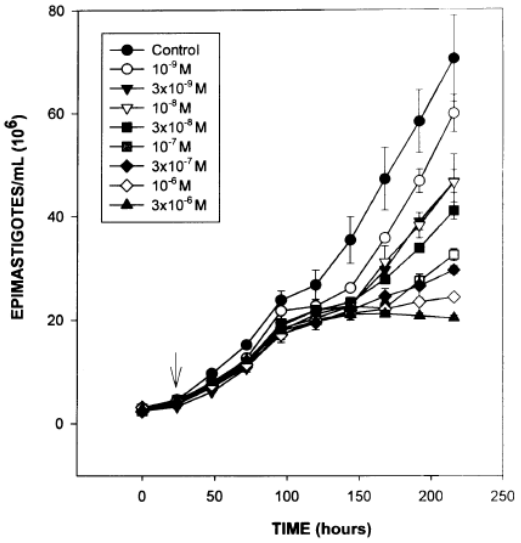


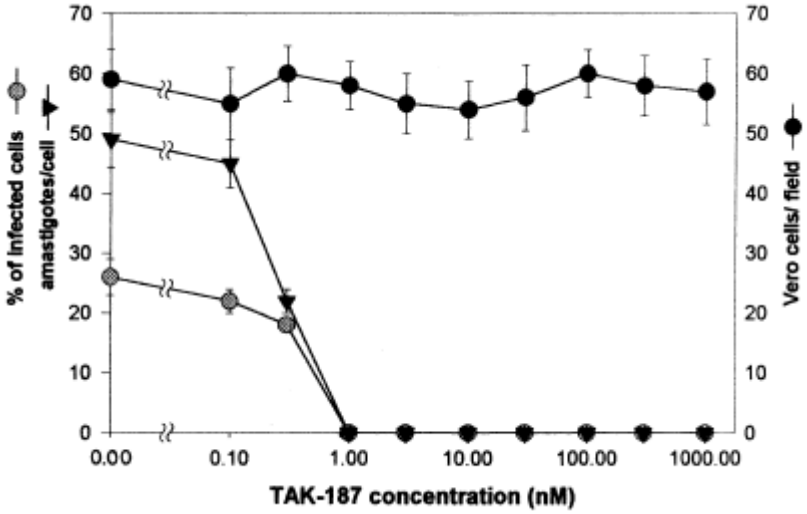
Urbina et al. Antimicrobial Agents and Chemotherapy July 1998, p. 1771–1777

Comparative *In vitro* Activity

- **TAK 187**
  - **MIC 0.3-1uM para epimastigotas**
  - **MIC 1 nM e IC50 0.3nM para amastigotas**

  - **Sem efeito em viabilidade celular e proliferação em concentrações >1000 MIC**
  - **Cepa não especificada (Cepas EP and Y mencionadas)**





J.A. Urbina et al. / International Journal of Antimicrobial Agents 21 (2003) 39 /48

Atividade Comparativa *In vivo* Modelo Murino Agudo

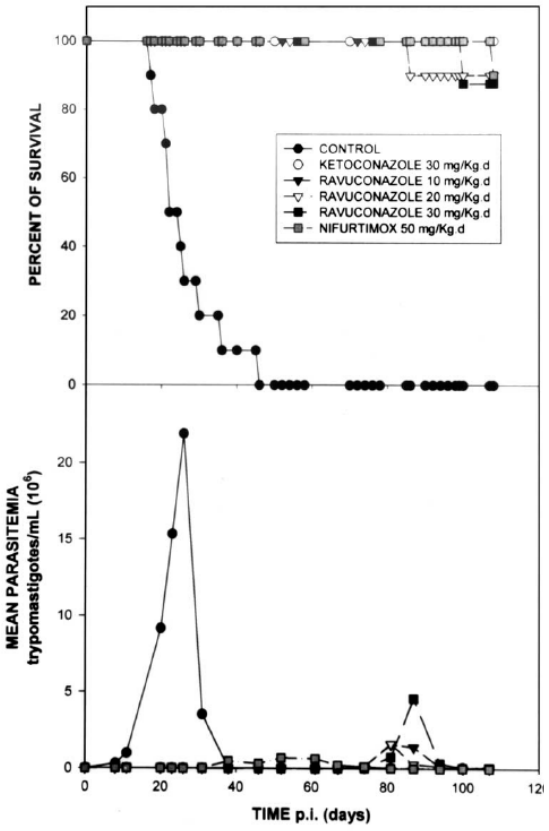
- **Cepa Y:**
  - **24h p.i. por 28 dias, 7 dias pausa, 15 dias adicionais de tratamento treatment**

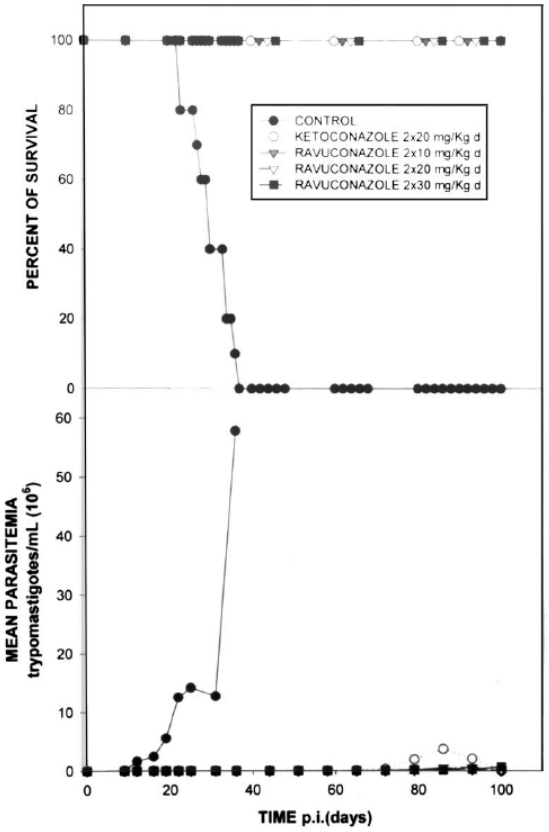
- **Ravuconazol**
  - **Comparação com cetoconazol ou nifurtimox**
  - **Tratamento com Ravuconazole levou a altos níveis de cura parasitológica, mas apenas quando administrado duas vezes ao dia (b.i.d.): 100% sobrevida, 70% negativização de parasitemia**

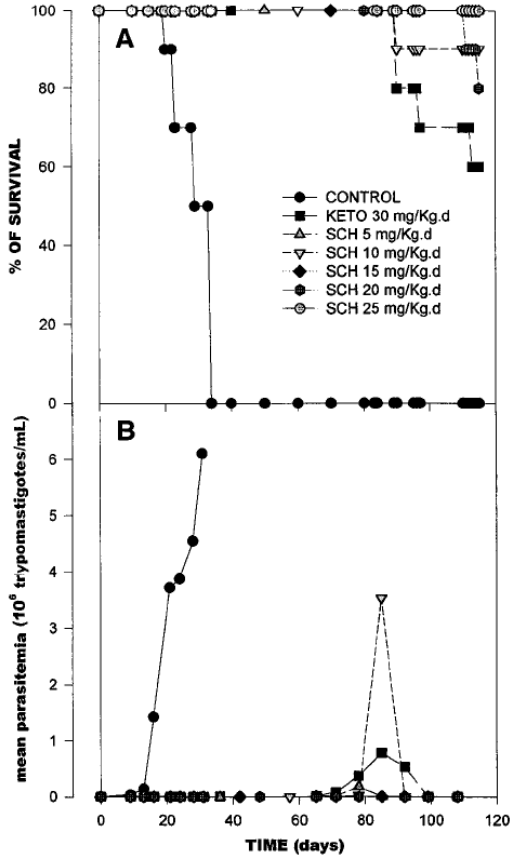
- **Posaconazol**
  - **Comparação com cetoconazol ou benznidazol**
  - **Altos níveis de cura parasitológica com dose única diária: 100% sobrevida, >75% negativização de parasitemia (até 100% com 25 mg/kg)**

Urbina et al. Antimicrobial Agents and Chemotherapy July 1998, p. 1771–1777
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

Atividade Comparativa *In vivo*
Modelo Murino Agudo







Urbina et al. Antimicrobial Agents and Chemotherapy July 1998, p. 1771–1777
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

Atividade Comparativa *In vivo* Modelo Murino Agudo

- **Cepas CL, Colombiana, SC-28 e VL-10**
  - **4 dias p.i. por 28 dias, 7 dias pausa, 15 dias adicionais de tratamento**

- **Posaconazol**
  - **Comparação com benznidazol**
  - **90 a 100% cura com cepas CL and Y e 50% cepa Colombiana**

TABLE 2. Effects of SCH 56592 and benznidazole in a murine model of acute Chagas' disease with different strains of *T. cruzi*

Strain	No. of survivors/total no. receiving[a]:				
	No drug (control)	Benznidazole, 100 mg/kg/day	SCH 56592, 5 mg/kg/day	SCH 56592, 10 mg/kg/day	SCH 56592, 20 mg/kg/day
CL	0/10	9/10	6/10	9/10	9/10
Y	0/10	8/10	9/10	10/10	9/10
Colombiana	0/10	6/10	9/10	9/10	8/10
SC-28	0/10	7/10	9/10	9/10	10/10
VL-10	0/10	7/10	4/10	10/10	9/10

TABLE 3. Effects of SCH 56592 and benznidazole in a murine model of acute Chagas' disease with different strains of *T. cruzi*

Strain	No. of negative mice/no. tested[c]				
	Control (untreated)	Benznidazole, 100 mg/kg/day	SCH 56592, 5 mg/kg/day	SCH 56592, 10 mg/kg/day	SCH 56592, 20 mg/kg/day
CL	0/10	9/9	6/6	9/9	9/9
Y	0/10	4/8	5/9	6/10	7/9
Colombiana	0/10	3/6	5/9	4/9	6/8
SC-28	0/10	2/7	5/9	6/9	8/8
VL-10	0/10	1/7	2/4	3/10	5/9

Molina et al. Antimicrobial Agents and Chemotherapy, Jan. 2000, p. 150–155

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Atividade Comparativa *In vivo*
Modelo Murino Agudo

- **Y strain:**
  - **20 dias de tratamento, 4 dpi**

- **Ravuconazol**
  - **Comparação com benznidazole**
  - **100% sobrevida, 58% negativização de parasitemia**

- **Posaconazol**
  - **Comparação com benznidazole**
  - **100% sobrevida, 89% negativização de parasitemia**

Molina et al. Antimicrobial Agents and Chemotherapy, Jan. 2000, p. 150–155
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

DNDi Drugs for Neglected Diseases initiative

Comparative *In vivo* Activity
Acute Murine Model

- **Colombiana strain:**
  - **20 day treatment protocol, 4 dpi**

- **Ravuconazole**
  - **Comparison with benznidazole**
  - **100% survival, 0% parasite negative (bid dosing) (bz 100% survival, 33% cure)**

- **Posaconazole**
  - **Comparison with benznidazole**
  - **100% survival, 44% parasite negative (bz 9% cure; 60% cumulative survival)**

Molina et al. Antimicrobial Agents and Chemotherapy, Jan. 2000, p. 150–155
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

DNDi Drugs for Neglected Diseases initiative

Atividade Comparative *In vivo*
Modelo Murino Crônico

- **Cepa Bertoldo:**
  - **20 dias de tratament, 4 dpi**

- **Ravuconazol**
  - **Comparação com benznidazol**
  - **100% sobrevida, 0% cura parasitológica (dose bid) (bz 100% survival, 33% cure), avaliado 202 dias pós-infecção**

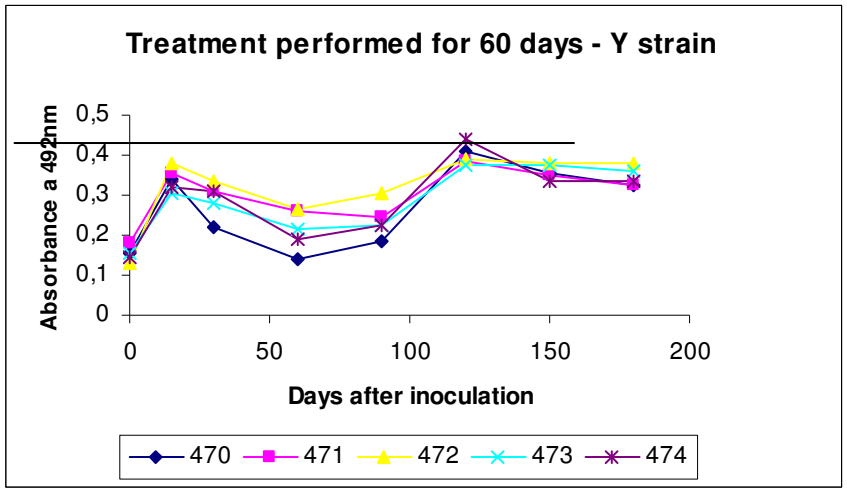
- **Posaconazol**
  - **Comparação com benznidazol**
  - **100% sobrevida, 44% cura parasitológica (Bz 9% cura; 60% sobrevida cumulativa), avaliados 114 dias pós-infeccção**

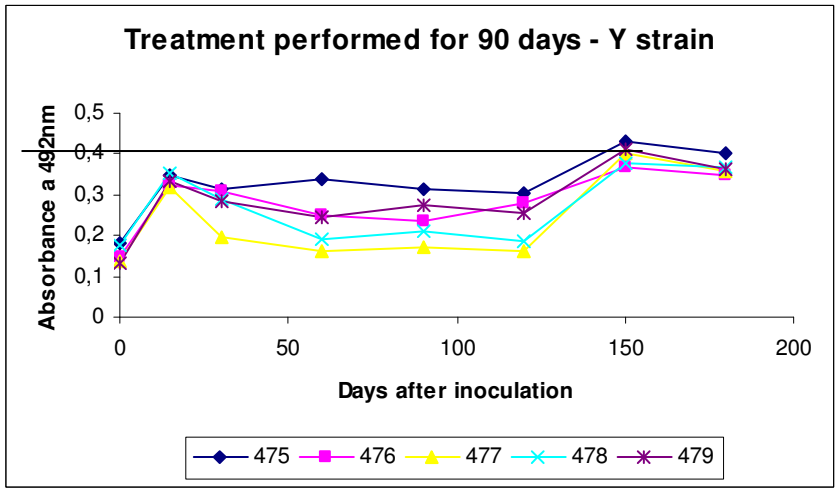
Molina et al. Antimicrobial Agents and Chemotherapy, Jan. 2000, p. 150–155
Urbina et al. International Journal of Antimicrobial Agents 21 (2003) 27/38

Resumo

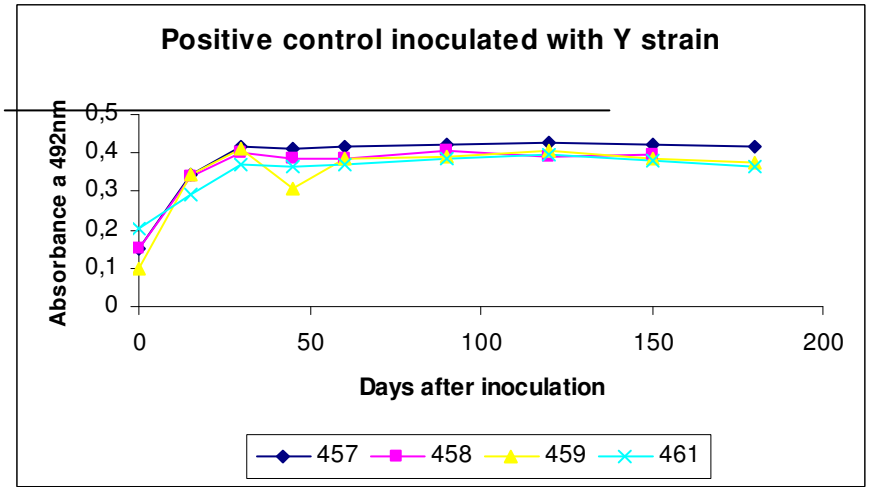
- **Sem comparações diretas em compostos azólicos (exceto com cetoconazol)**
- **Potência In vitro**
  - **Posaconazol>Ravuconazol>=TAK187**
- **Potência In vivo (modelo murine)**
  - **Posaconazole> TAK187 >=Ravuconazole bid**
  - **Cepas multi-resistentes: sem demonstração de cura com ravuconazol bid; Posaconazol> TAK187**
  - **Modelos Crônicos (cepa Bertoldo): cure limitada com ravuconazol bid; TAK187> Posaconazol**

Estudos em Cães – Cepa Y
Resultados de Sorologia





Limiar=0.269 a.u.



Dose 6 mg/kg bid

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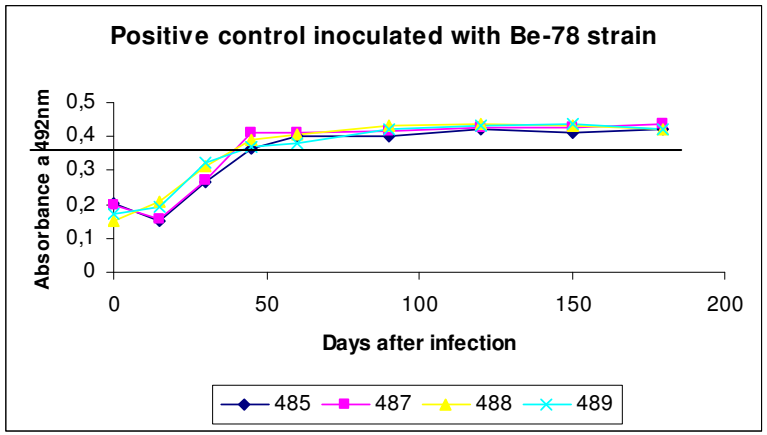
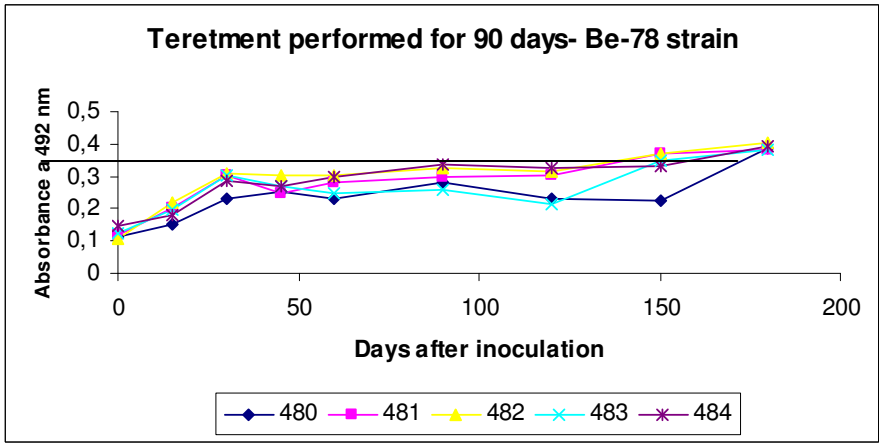
Estudos em Cães- Cepa Be-78
Resultados de Sorologia





Limiar = 0.269 a.u.

Tratamentos administrados entre 20-30 e 110-120 dias após a inoculação

Ravuconazol

- Falta de atividade curativa do Ravuconazol possivelmente relacionada às características farmacocinéticas do composto em animais

  – T½: camundongos (4.5h) → cães (8.8h) → homem (4.42-11.75 dias).

E1224

- Water-soluble prodrug monolysine form of ravuconazole, a sterol C14-demethylase inhibitor
- Completed general toxicology and safety pharmacology studies
- Completed 5 Phase I studies in the US: ascending, single and multiple loading and maintenance dose, bioavailability and food-effect study; ascending, multiple loading and maintenance dose study of E1224 administered intravenously over 14 days; effect of E1224 on CYP 450 enzymes; cardiac safety/QT study

- E1224 not specifically evaluated for CD in animals models BUT its PK characteristics show increased bioavailability, reliable oral absorption

- Weekly dosing after loading dose
- Indication of good stability and promising cost of goods

E1224

Drug Discovery News, November 2009 (vol. 5, No. 11)
(http://www.drugdiscoverynews.com/index.php?newsarticle=3352)

Bitten by the 'kissing bug'
(Drug Discovery News, November 2009)
By Lloyd Dunlap

GENEVA, Switzerland — **Eisai Co. Ltd.** and the **Drugs for Neglected Diseases initiative (DNDi)** have signed a collaboration and license agreement for the clinical development of a promising new drug for the treatment of Chagas disease, a fatal infectious disease that is endemic in 21 Latin American countries, where it causes about 14,000 deaths per year.

E1224 – Project Objectives

1. To evaluate the safety and efficacy of the azole compound E1224 for the treatment of patients with the chronic indeterminate form of Chagas Disease.
2. To establish manufacturing and industrial scale production of E1224 at the lowest possible cost, with 3-year shelf life in Climatic Zone IV, within international quality standards.
3. To evaluate the non-clinical safety and ADME of E1224 to support clinical trials and/or for registration.
4. To register E1224 for the therapeutic indication “chronic indeterminate Chagas Disease” in the endemic countries in Latin America.
5. To make E1224 treatment available and affordable for populations in need of Chagas Disease treatment.

DNDi Drugs for Neglected Diseases initiative

E1224 – Planned Phase II Clinical Trial

- Phase II multicenter, open label, randomized futility trial to evaluate the safety and efficacy of different regimens of E1224 for treatment of patients with chronic indeterminate form of Chagas disease (CD) with Bz calibration
- Target population: Adult patients (18-50y) with chronic indeterminate form of Chagas disease
- Study sites: Cochabamba, Bolivia (Stage I)
- Objective:
  - To evaluate the safety and efficacy of E1224 in individuals presenting chronic indeterminate form of CD, relative to a predetermined futility threshold (60%) and benznidazole calibration.
    - Efficacy endpoint: frequency of patients with negative PCR (3 samples) at the end of treatment

Secondary objectives:

- Efficacy (parasitological clearance) at 6 and 12 months
- Quantitative PCR at end of Rx, 6mo and 12 months
- Pop Pk of E1224 in adult patients with indeterminate CD
- Evaluate serological response at end of Rx, 6 and 12 months
- Other biological markers: ANP, BNP, prothrombotic markers
- Assess incidence of SAEs and AEs leading to discontinuation of study drugs

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