

Novel Compounds for the Treatment of Chagas Disease

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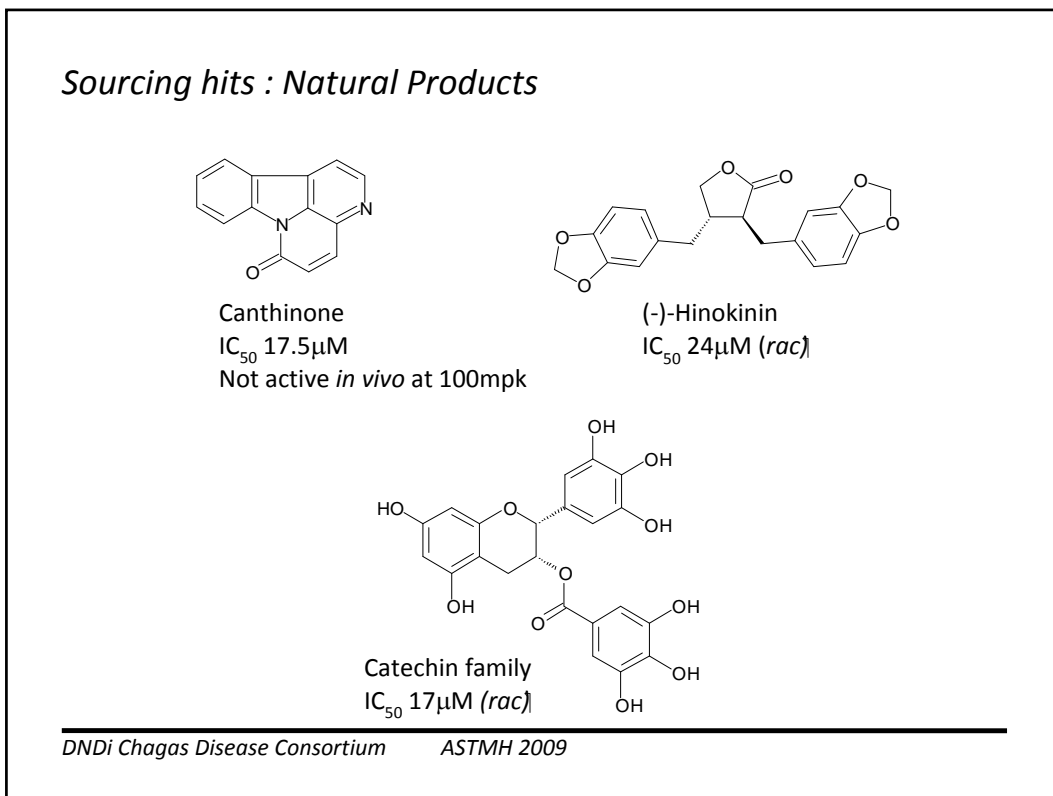
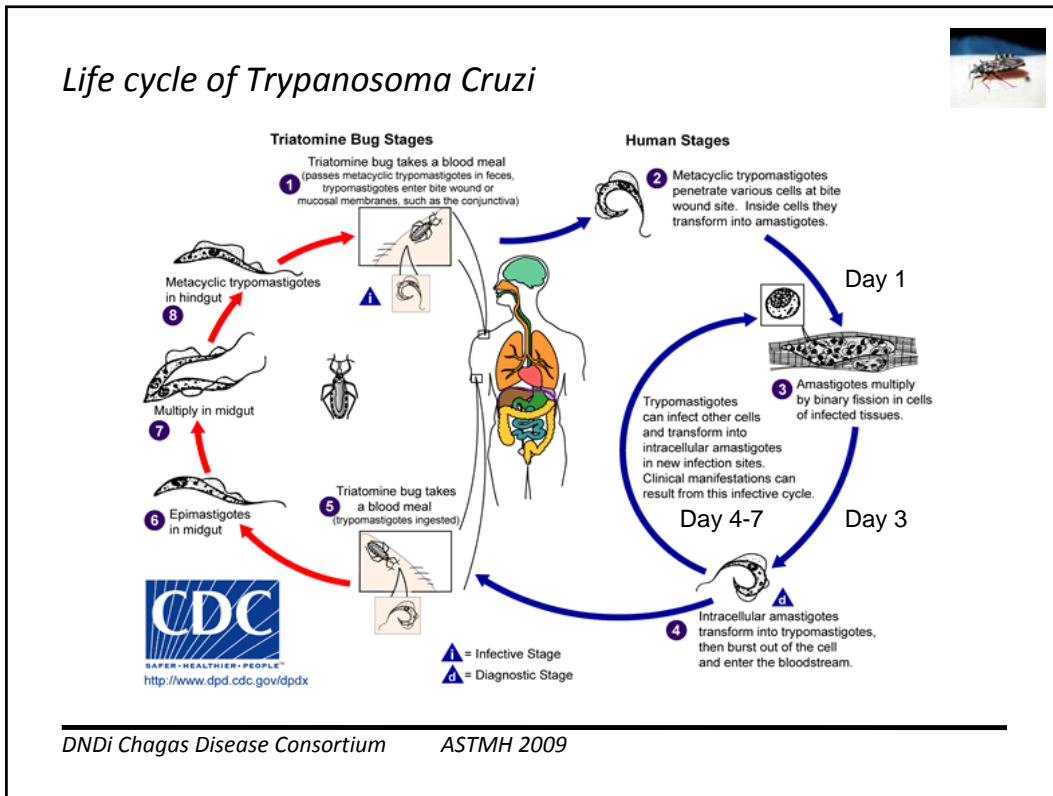
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Acknowledgements

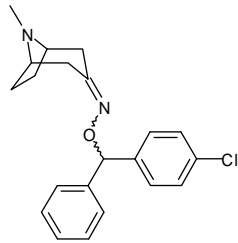
<i>Chemistry</i>	<i>Biology</i>	<i>DMPK</i>	<i>DNDi</i>
Mike Abbott	Tanya Armstrong	Karen White	Rob Don
Paul Alexander	Maria Kerfoot	David Shackleford	Ivan Scandale
Brad Bervan	Andrea Khong	<i>Susan Charman</i>	Tom von Geldern
Jason Chaplin	Andrea Botero		<i>Eric Chatelain</i>
Hugo Diao	<i>Andy Thompson</i>		
Joshua McManus			
Zhisen Wang			
<i>Wayne Best</i>			



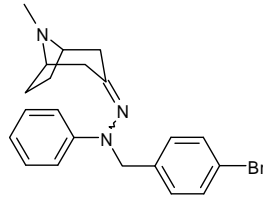
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Sourcing hits



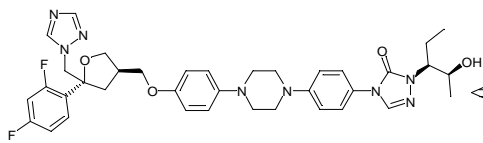
WEHI-100156
 IC_{50} 0.29 μ M (rac)



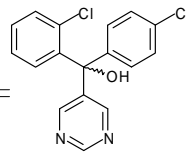
BS212
 IC_{50} 0.03 μ M (rac.HCl)

Not tolerated in mice at 100mpk

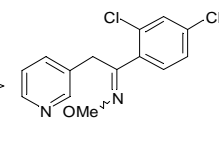
Sourcing hits : Agrochemicals



Posaconazole
 IC_{50} 0.0007 μ M

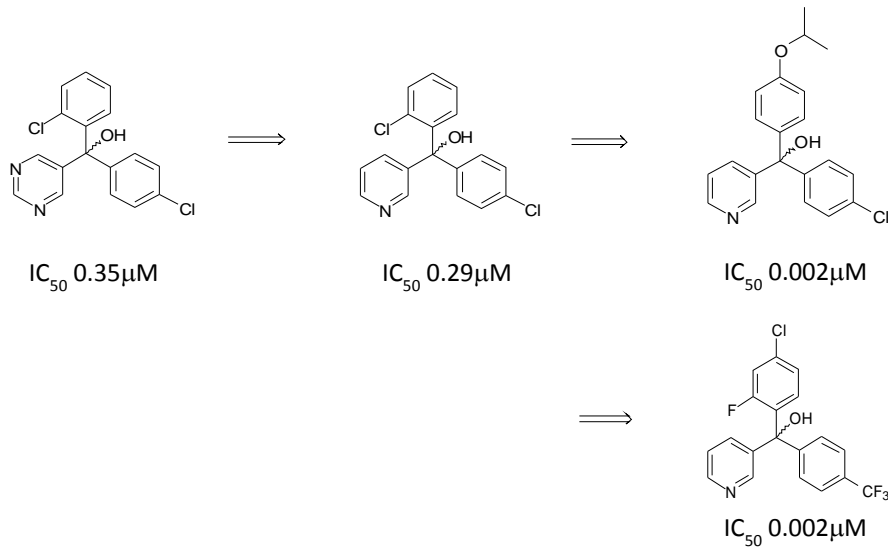


Fenarimol
 IC_{50} 0.35 μ M (rac)



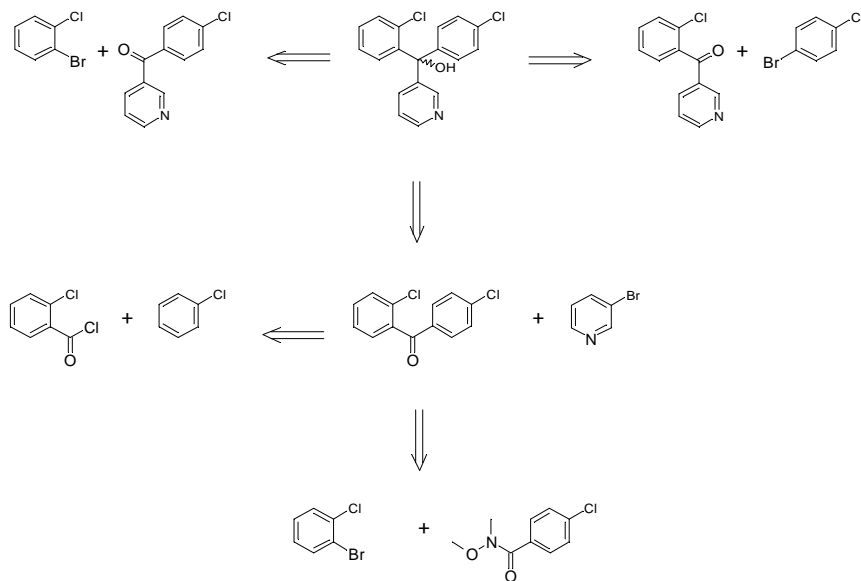
Pyrifenox
 IC_{50} 0.29 μ M

Fenarimol SAR



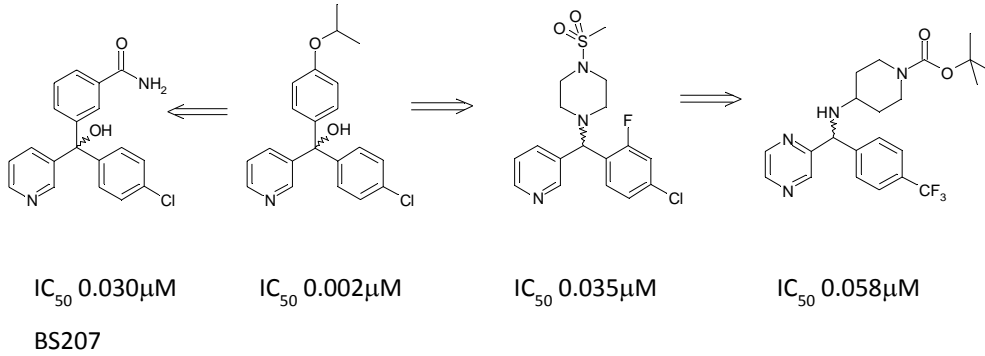
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Synthesis



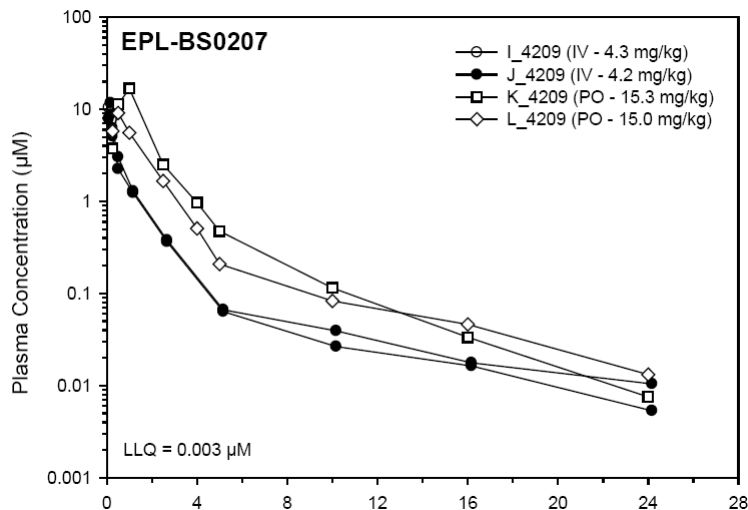
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Evolution of a series



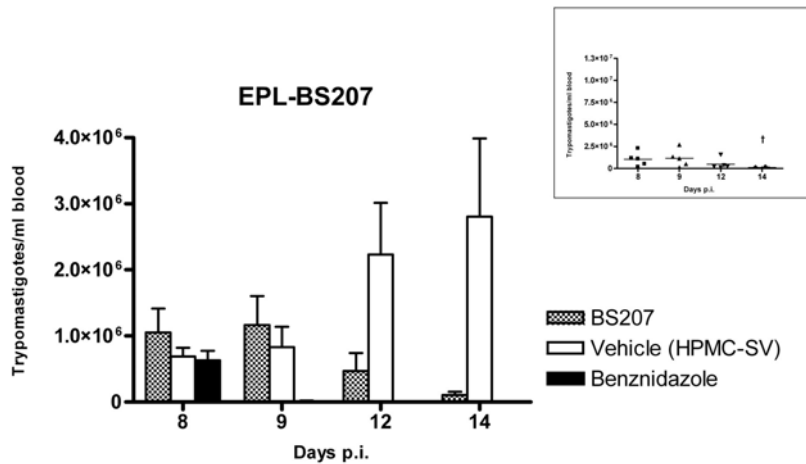
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Plasma concentrations of EPL-BS0207 following IV and oral administration to male Sprague Dawley rats.



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Activity of BS207 in mouse model of *T. cruzi* infection



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

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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

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