

FAPESP-RSC-MMV-DNDi workshop

Frontiers in Science on Neglected Diseases



Recent collaborations with *Drugs for Neglected Diseases initiative-DNDi* and with *Medicines for Malaria Venture-MMV* in the area of neglected diseases

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The *Lead Optimization Latin America (LOLA)* consortium: collaborative drug discovery for Neglected Tropical Diseases (NTDs)

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DNDi

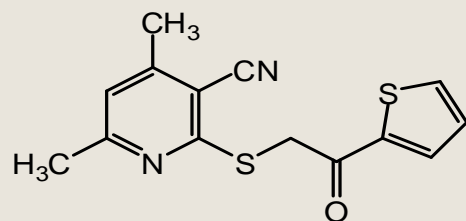
Drugs for Neglected Diseases *initiative*

Lead Optimization Latin America (LOLA)

Origins of leads against *T. cruzi*

Early leads for new drugs for Chagas disease

Monocyclic series

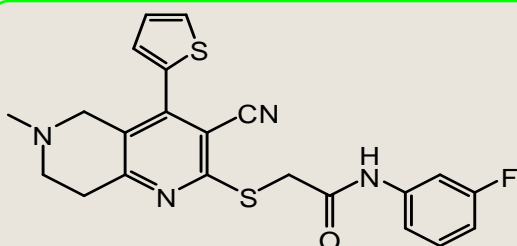


TDR30139

$IC_{50} = 0.34 \mu\text{M}$ (*in vitro*)

- TDR screening campaign
- TDR optimisation project

Bicyclic series



LOLA4

$IC_{50} = 0.03 \mu\text{M}$ (*in vitro*)

- NIH funded screen of the Broad Institute compound collection



Medicinal Chemistry Centre for Chagas Disease in Brazil

World Health Organization

New Medicinal Chemistry Centers to Join Drug Discovery Networks
T24/181/136 ID No. A80141

The Special Program for Research and Training in Tropical Diseases
TDR/UNICEF/UNDP/WB/WHO

PRINCIPAL INVESTIGATORS



ADRIANO D. ANDRICOPULO
University of Sao Paulo

MEDICINAL CHEMISTRY
AND DRUG DESIGN



GLAUCIUS OLIVA
University of Sao Paulo

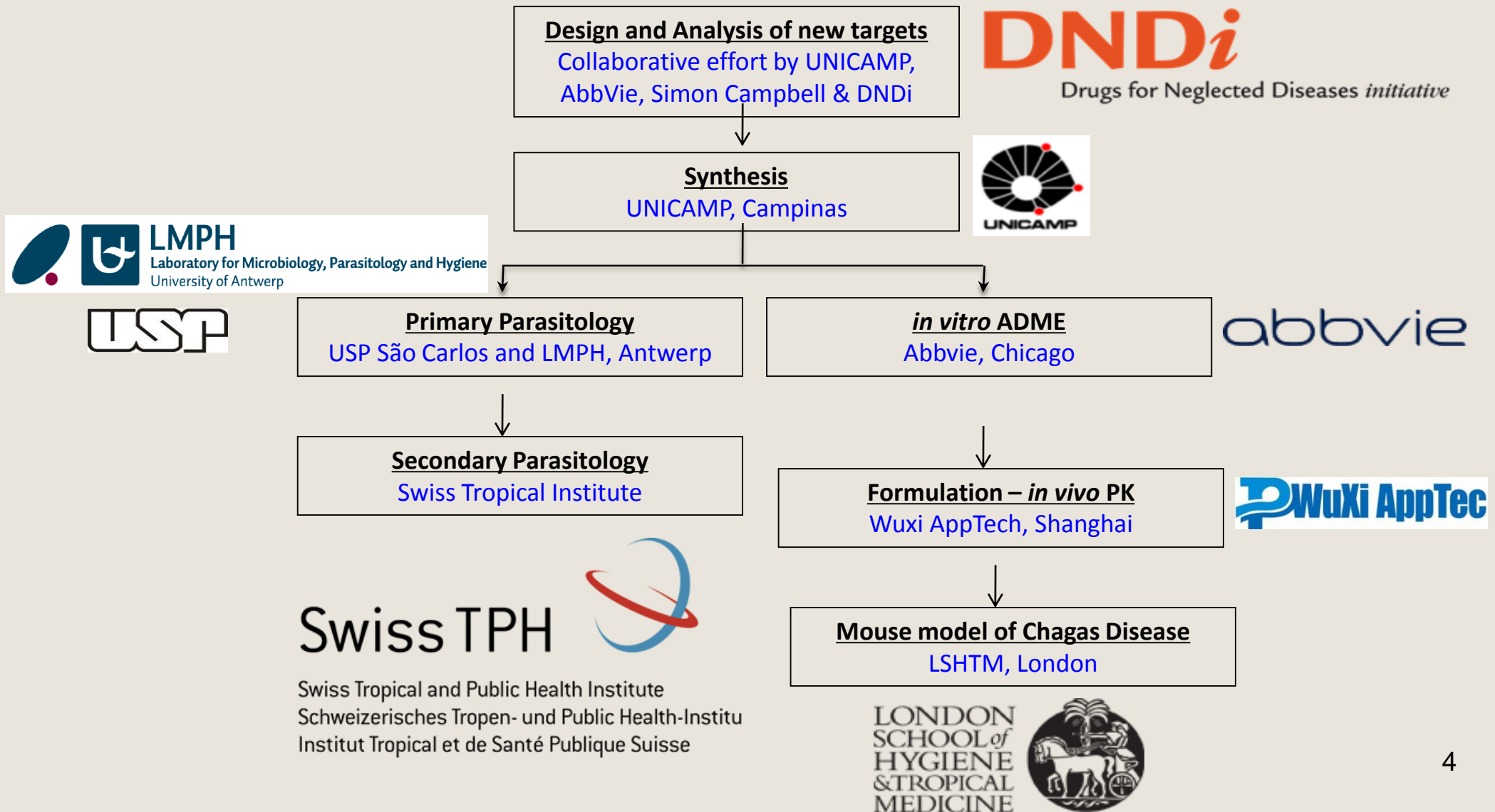
STRUCTURAL BIOLOGY
AND STRATEGIC PLANNING



LUIZ CARLOS DIAS
UNICAMP

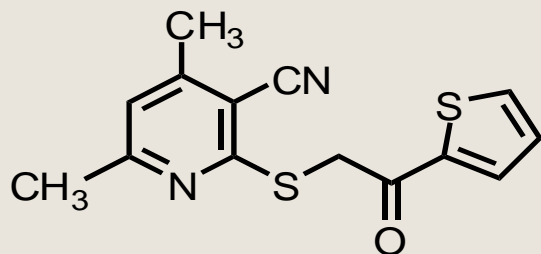
ORGANIC SYNTHESIS

Early screening cascade & partners



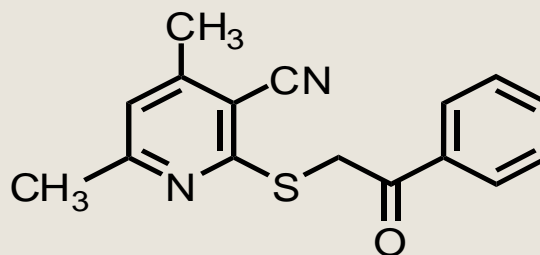
MOA is not CYP51 inhibition

- **TDR30139 & TDR91219** have promising *in vitro* activity against *T. cruzi*
- Hit to lead chemistry in progress at University of Campinas
- Check for CYP51 inhibition before investing too much effort:



TDR30139

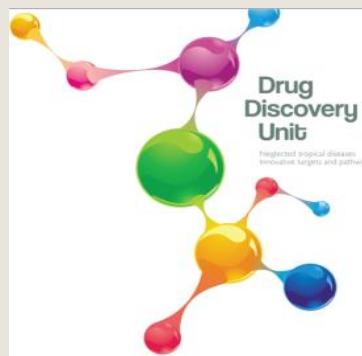
T. cruzi IC₅₀ = 0.34 μM
CYP51 IC₅₀ > 10 μM



TDR91219

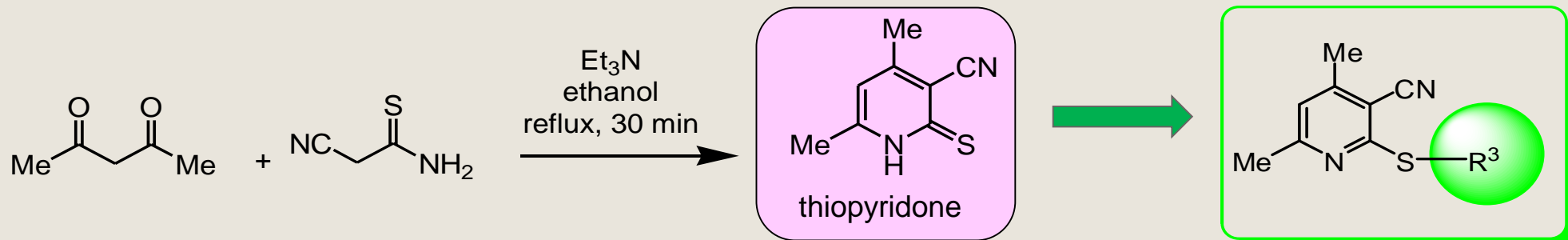
T. cruzi IC₅₀ = 0.7 μM
CYP51 IC₅₀ > 10 μM

- Experiment kindly carried out by collaborators at GSK, Tres Cantos, and Dundee Drug Discovery Unit



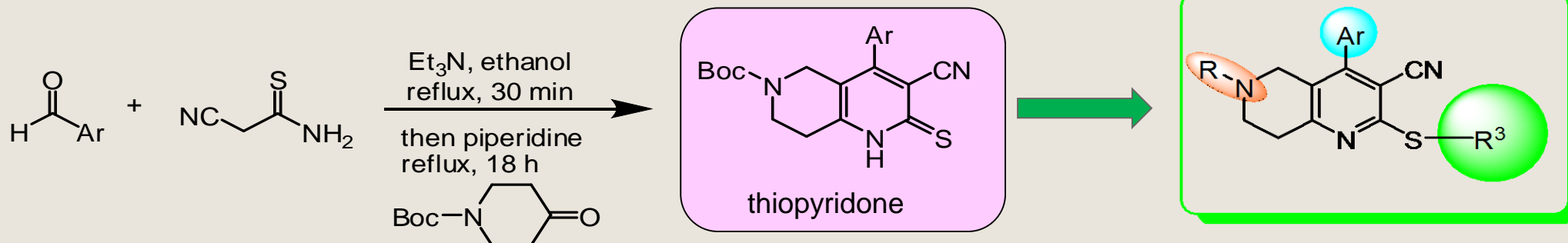
General Synthesis

monocyclic cyanopyridines



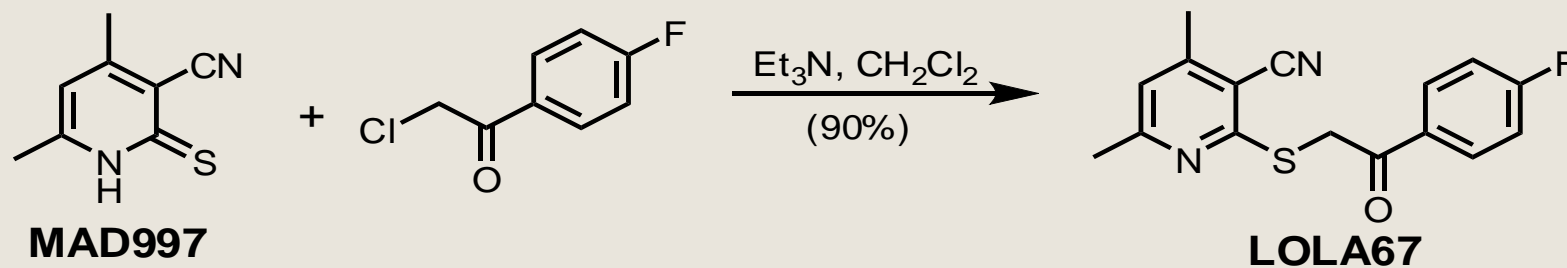
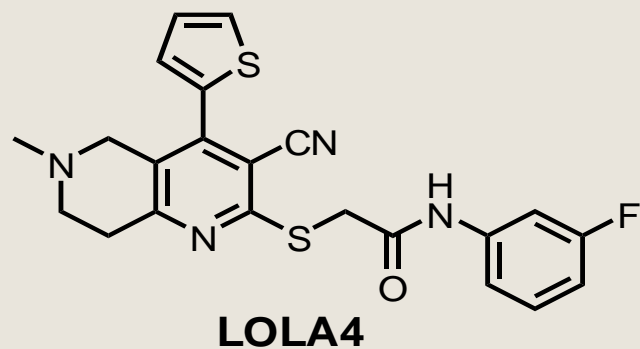
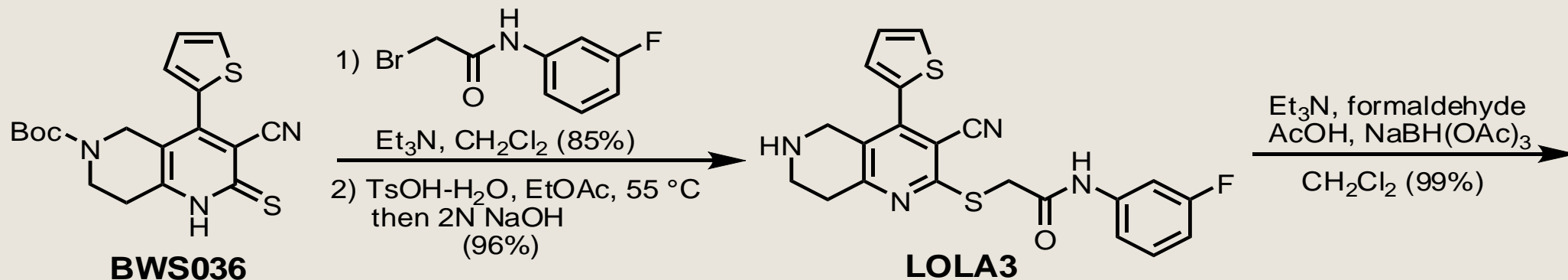
Schmidt, U.; Kubitzek, H. *Chem. Ber.* **1960**, 93, 1559-1565.

bicyclic cyanopyridines

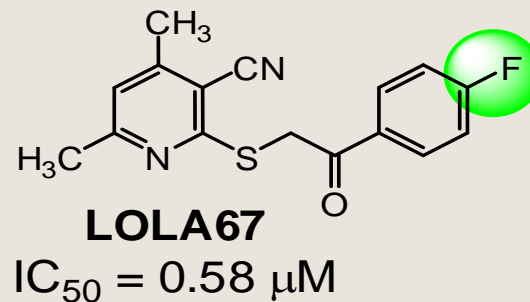
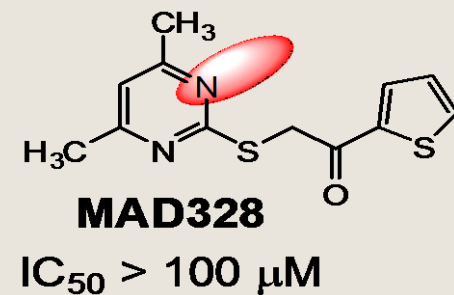
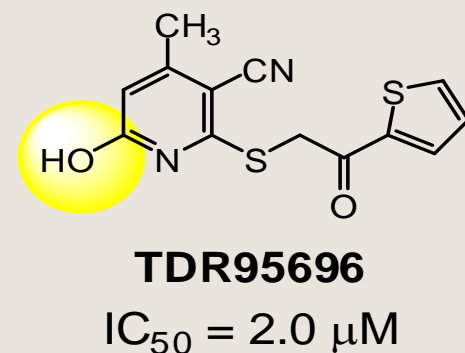
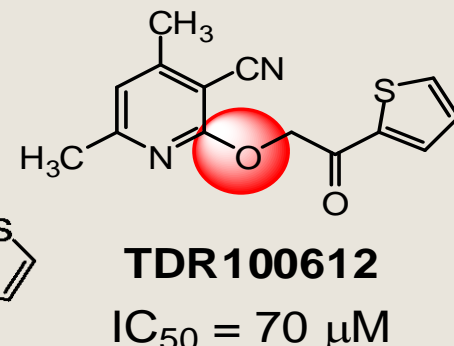
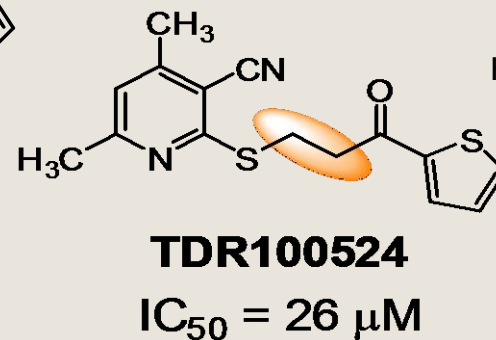
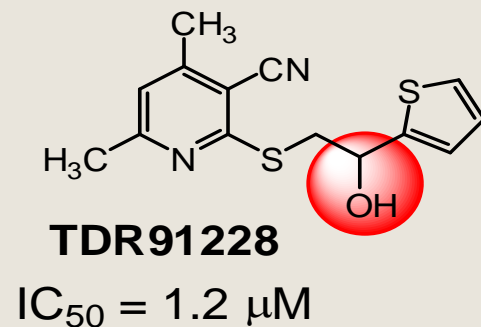
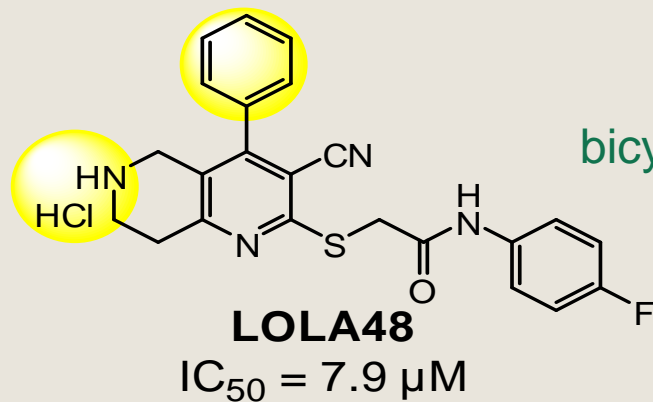
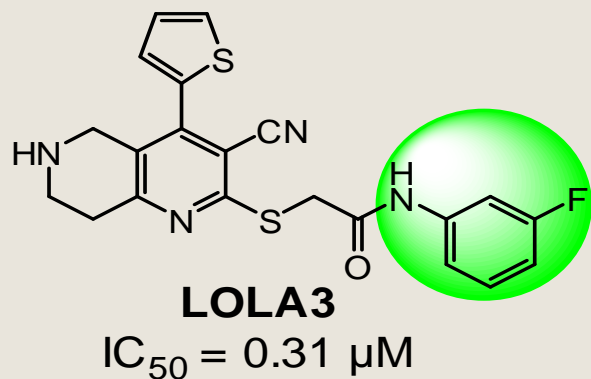
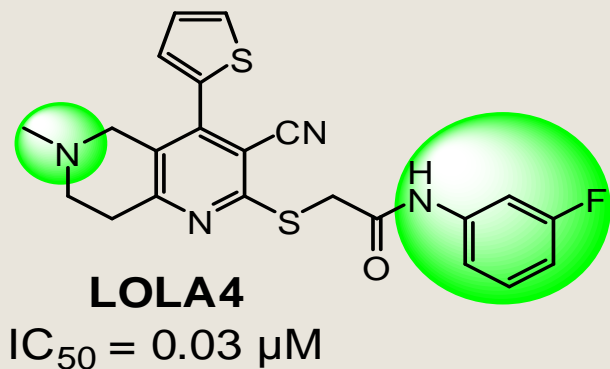


Abdel-Wadood, F. K.; Abdel-Monem, M. I.; Fahmy, A. M.; Geies, A. A. *J. Chem. Res.* **2008**, 89-94.

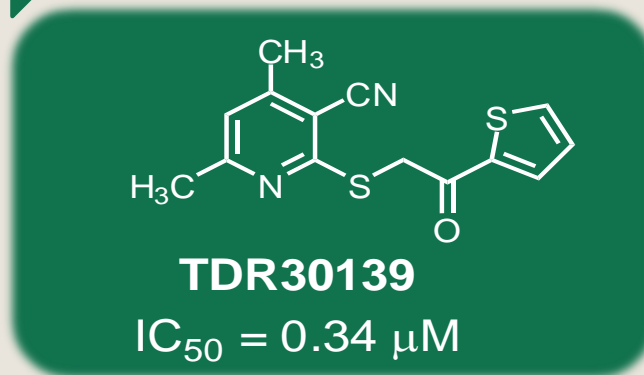
Scaleup



Synthesis of TDR30139 derivatives





monocyclic



bicyclic

Summary

- **Cyanopyridine series**
 - ▣ Synthetic chemistry is the key to progress
 - ▣ Encouraging *in vitro* profiles of lead compounds
 - ▣ Leads scaled up for formulation and *in vivo* studies
 - ▣ Mouse pk carried out
 - ▣ Applying metabolite ID to guide design
 - ▣ Aim to test leads in a mouse model of Chagas disease soon

- **Apply medicinal chemistry & drug discovery principles to other new chemical series from Pfizer and AbbVie**
 

- **Extend the LOLA consortium**
 - ▣ DMPK, *in vivo* models, more chemistry, safety/toxicology,...
 - ▣ Maintain the excellent, close teamwork

A young child with short dark hair is shown in profile, looking out of a window. The window has a view of trees and foliage, with warm, golden light filtering through. The child is wearing a light-colored t-shirt. The background is slightly blurred, focusing attention on the child and the window view.

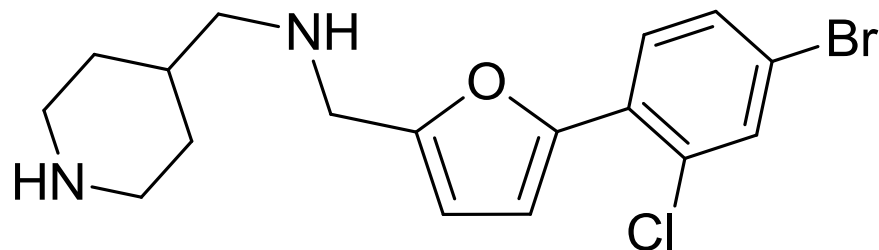
Unicamp/MMV
Anti-malarial drug
discovery Project

BRAZIL HETEROCYCLES

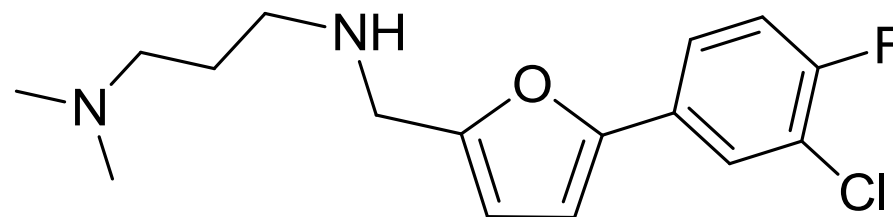
Defeating Malaria Together

MMV 
Medicines for Malaria Venture

Furan series: Hits from MMV Malaria Box



MMV019918



MMV020505

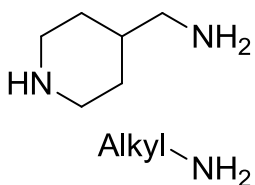
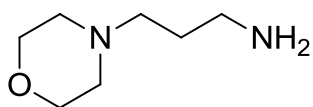
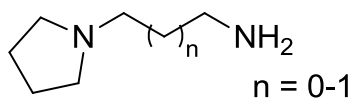
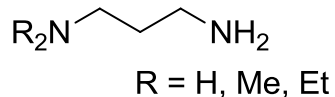
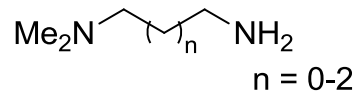
	In vitro					
	MWT	aLogP	EC50 Pf (nM)	Cytotoxicity EC50 MRC5 (μM)	Kinetic Solubility pH 7.4 (μM)	hERG % inh at 10 μM
MMV019918	384	3.9	800	3	4	83
MMV020505	311	3.4	875	17	44	48

Series found to have short duration of action in rodents

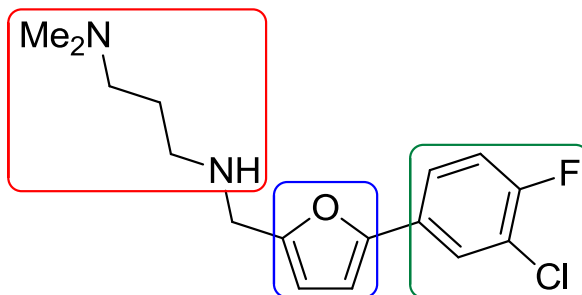
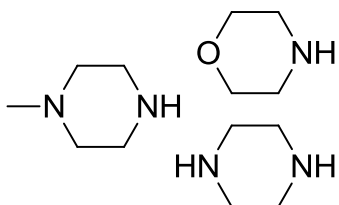
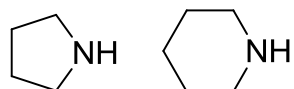
Sites of variation



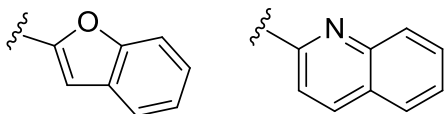
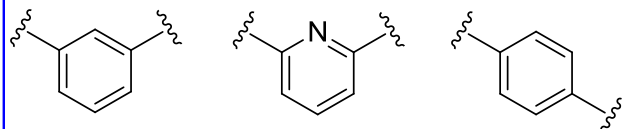
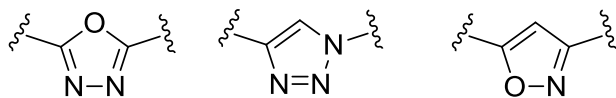
Primary amines:



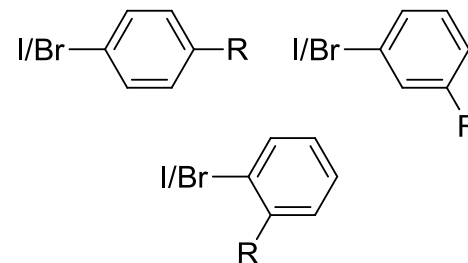
Secondary amines:



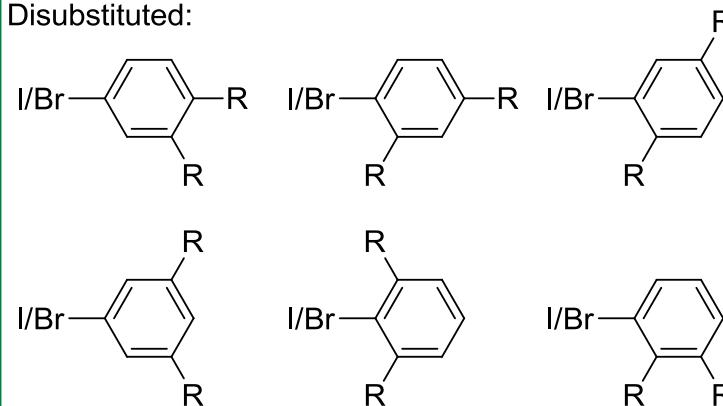
Furan replacements:



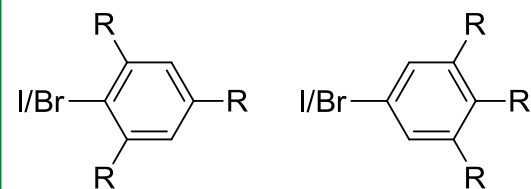
Monosubstituted:



Disubstituted:

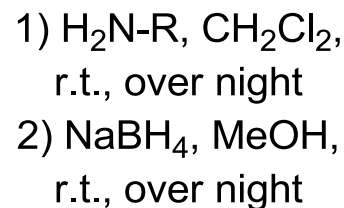
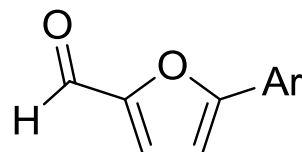
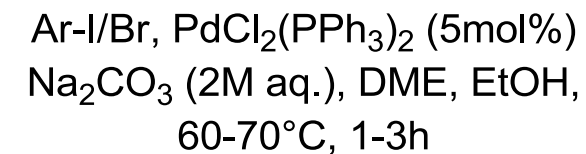
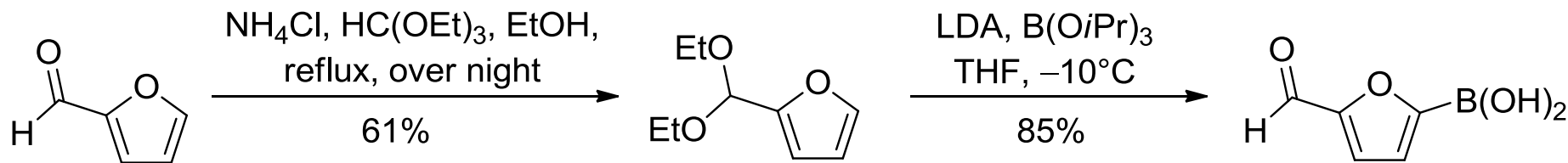


Trisubstituted:

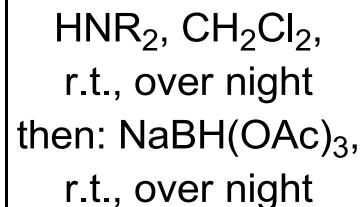
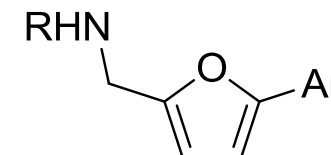


$\text{R} = \text{F}, \text{Cl}, \text{Br}, \text{Me}, \text{OMe}$

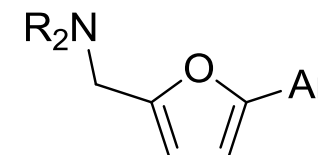
Synthetic Pathway



24-96%



83-94%



Key Partners for screening



In vitro DMPK
In silico modelling

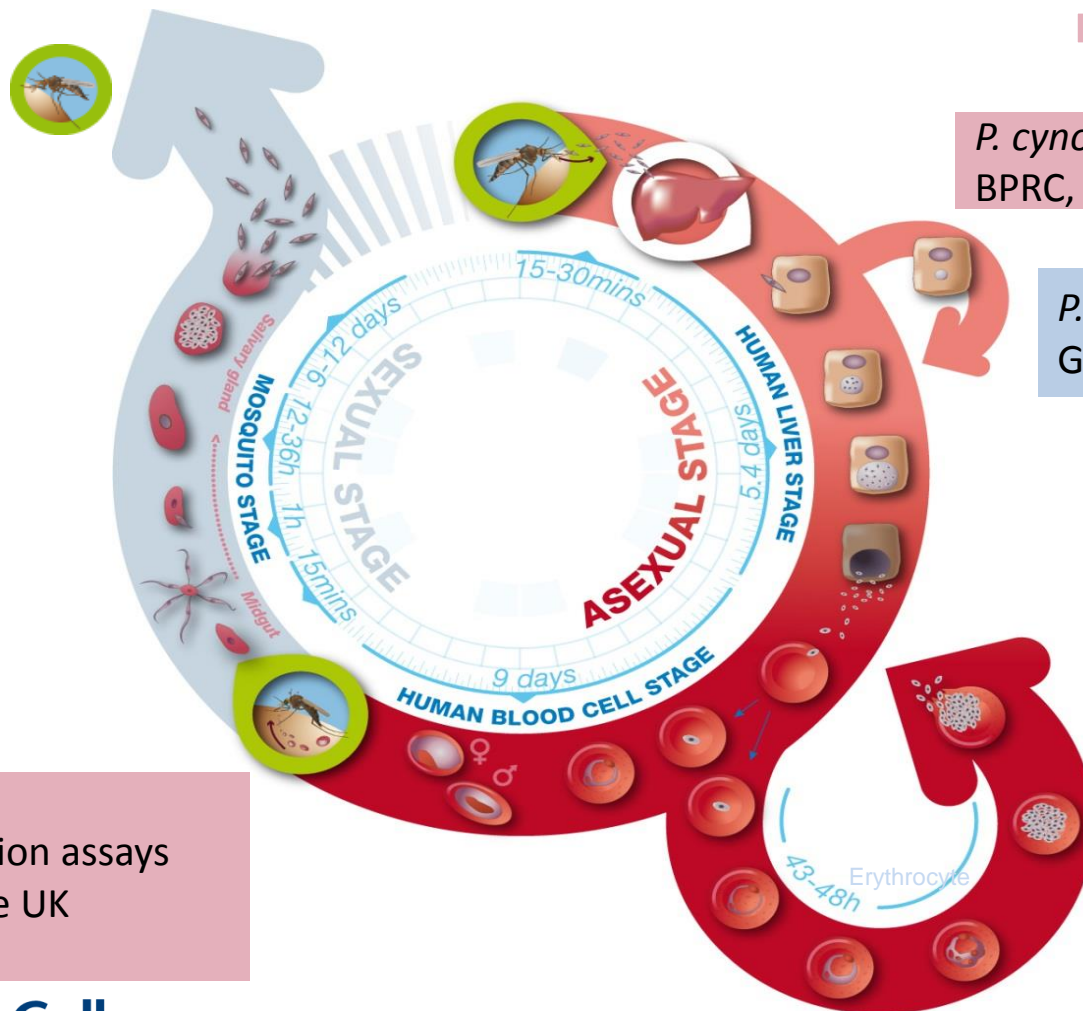


In vitro DMPK
In vivo DMPK
Phys Chem
measurements

Gamete formation assays
Imperial College UK



Resistance risk assessment
Columbia University, USA



Academia Industry

P. cynomolgi hypnozoite assay
BPRC, Netherlands

P. berghei liver stage assay
GNF Novartis/ UCSD, USA

In vitro blood stage activity
Swiss TPH, Switzerland

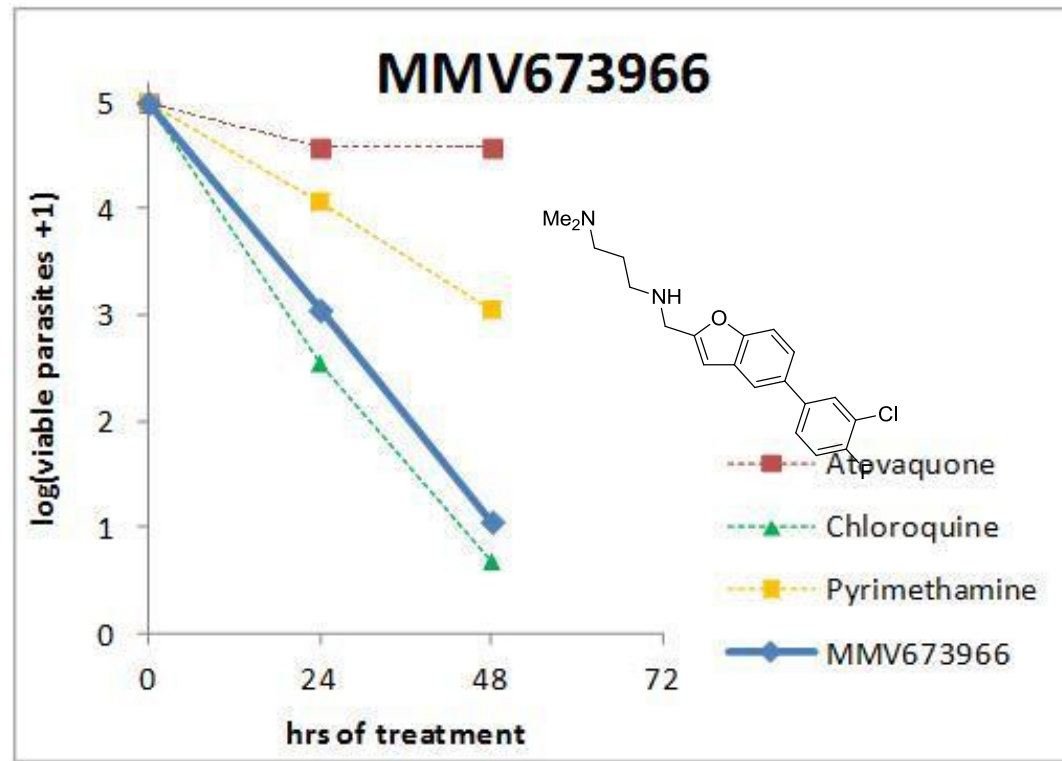
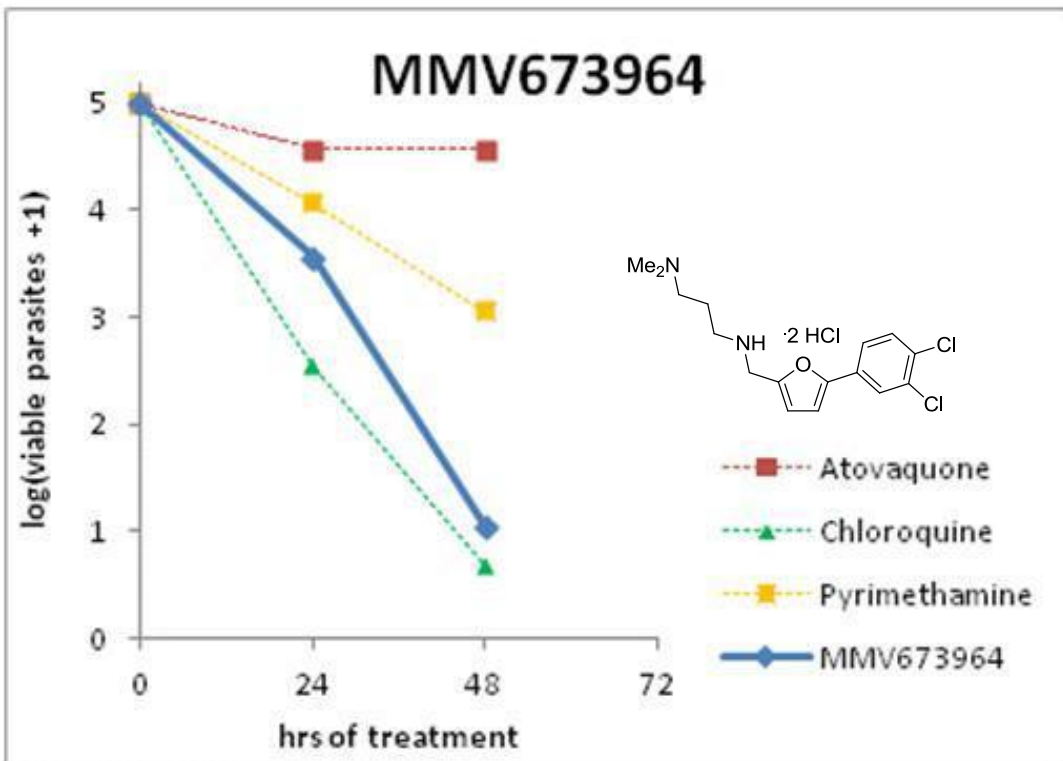


Parasite Reduction Rate
in vivo hu-SCID model
GSK Tres Cantos, Spain





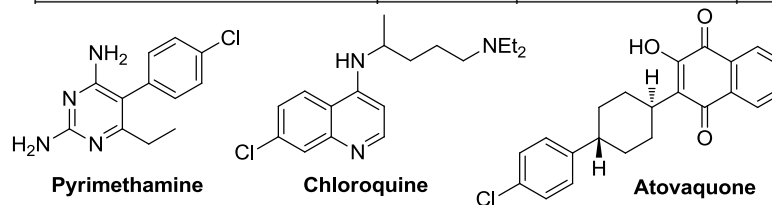
Rate of Killing assay - PRR

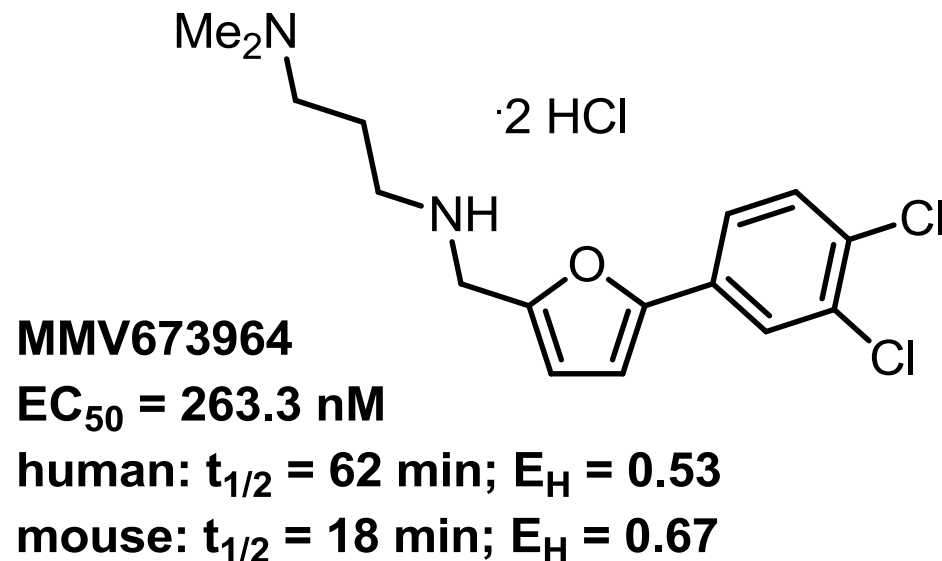
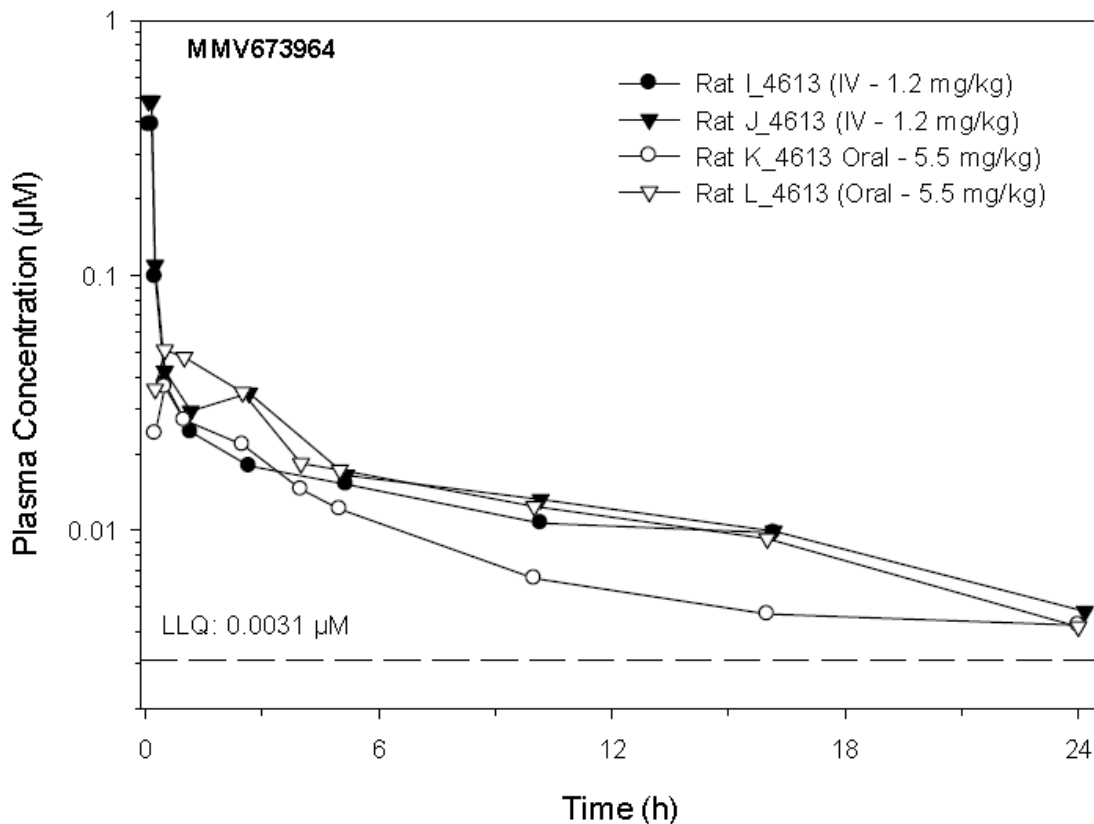


	log(viable parasites +1)		
	0	24 h treatment	48 h treatment
MMV673964 10x IC50	5	3.6	1.1
Chloroquine 10x IC50	5	2.5	0.7
Pyrimethamine 10x IC50	5	4.1	3.1
Atovaquone 10x IC50	5	4.6	4.6

	log(viable parasites +1)		
	0	24 h treatment	48 h treatment
MMV673966 10x IC50	5	3.1	1.1
Chloroquine 10x IC50	5	2.5	0.7
Pyrimethamine 10x IC50	5	4.1	3.1
Atovaquone 10x IC50	5	4.6	4.6

Compounds have a fast rate of killing (chloroquine like)





- **Total of 53 analogs synthesized**
- **Pharmacokinetic properties of series improved**
- **Series stopped due to tight SAR**
- **Novel MOA? Target identification with the Gates Target ID project**
- **Publication planned**

Acknowledgements



Prof. Luiz C. Dias, Marco Dessoy and Brian Slafer



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Laboratory for Microbiology, Parasitology and Hygiene
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abbvie

Brian Brown, Mira Hinman,
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Alan Brown

Swiss TPH



Marcel Kaiser

Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institu
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James Mills

DNDi

Drugs for Neglected Diseases *initiative*

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Leandro Christmann and
Simon Campbell



Wen Hua

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London



abbvie

Swiss TPH



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Institut Tropical et de Santé Publique Suisse

AstraZeneca



Mark Wenlock and
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Pharmacy and Pharmaceutical Sciences

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MMV
Medicines for Malaria Venture

gsk
GlaxoSmithKline

UC San Diego

Paul Willis, Coline Legrand
and Simon Campbell

Acknowledgments



DNDi

Drugs for Neglected Diseases *initiative*



SAVING LIVES!!!