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

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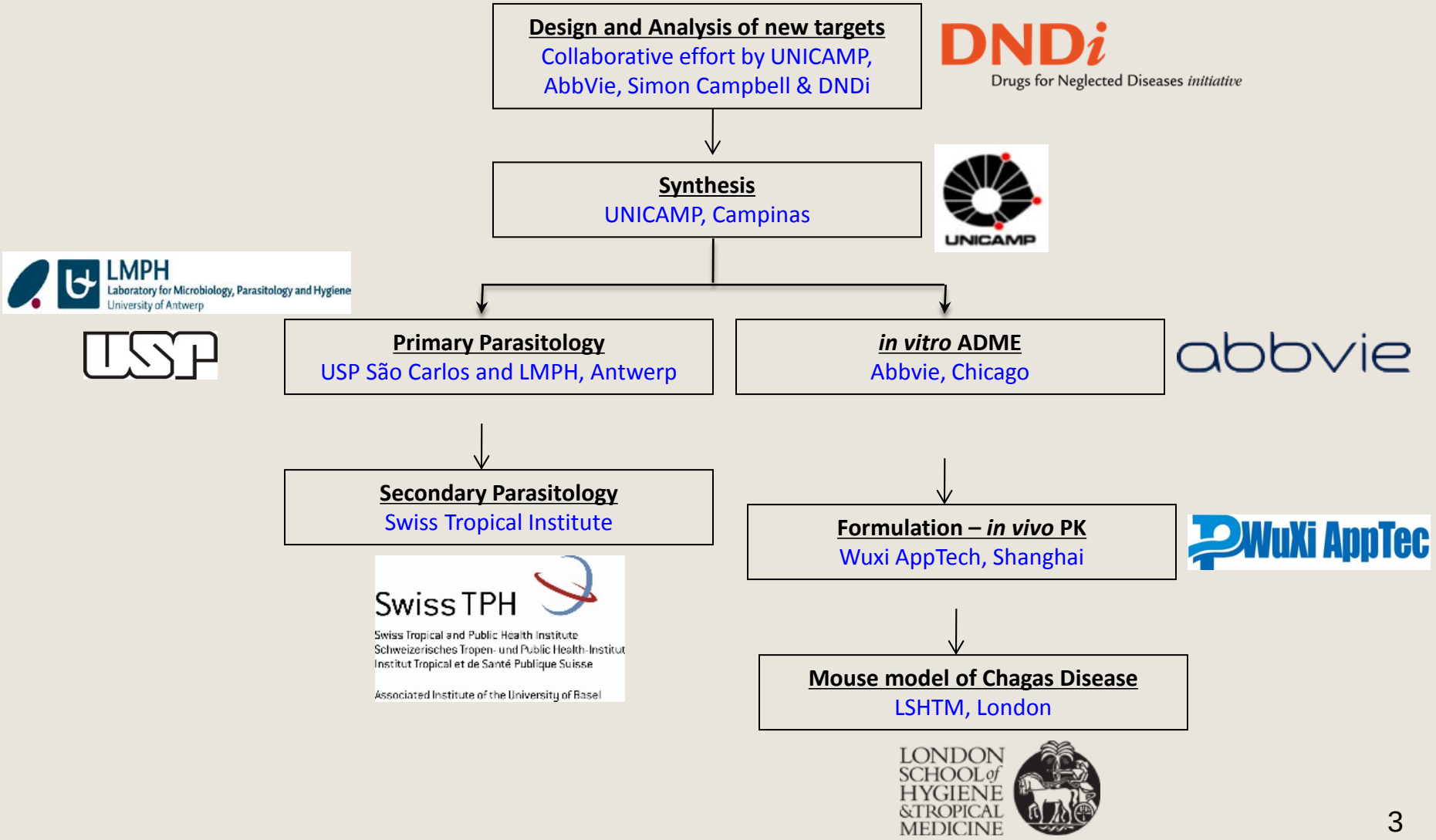
DNDi
Drugs for Neglected Diseases *initiative*

Building a DNDi LOLA consortium

Key component	Chagas	VL
Medicinal chemistry & DMPK leadership Data analysis, screen progression & compound design	UNICAMP & AbbVie & Simon Campbell	UNICAMP & AbbVie & Simon Campbell
Synthetic chemistry Route design, problem solving and synthesis	UNICAMP	UNICAMP
Biology *in vitro* *in vivo*	LMPH & USP, Sao Carlos TBA	LMPH & USP, Sao Carlos LMPH (temporary)
DMPK – in vitro & in vivo	AbbVie & Wuxi	AbbVie & Wuxi
Drug safety & toxicology	TBA	TBA
Formulations & solid form	Wuxi	Wuxi
Consortium coordination	Leandro Christmann	
Consortium leaders	Charlie Mowbray & Eric Chatelain	

- Other specialist services available via additional CROs

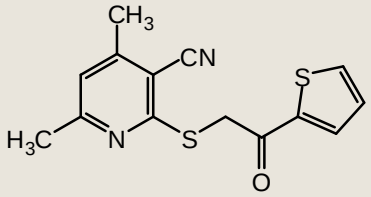
Early screening cascade



Origins of leads against *T. cruzi*

Early leads for new drugs for Chagas disease

- Monocyclic series

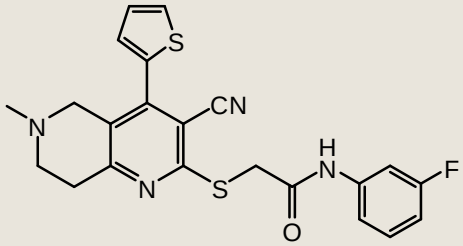


TDR30139

IC_{50} = 0.34 μM (*in vitro*)

  - TDR screening campaign
  - TDR optimisation project

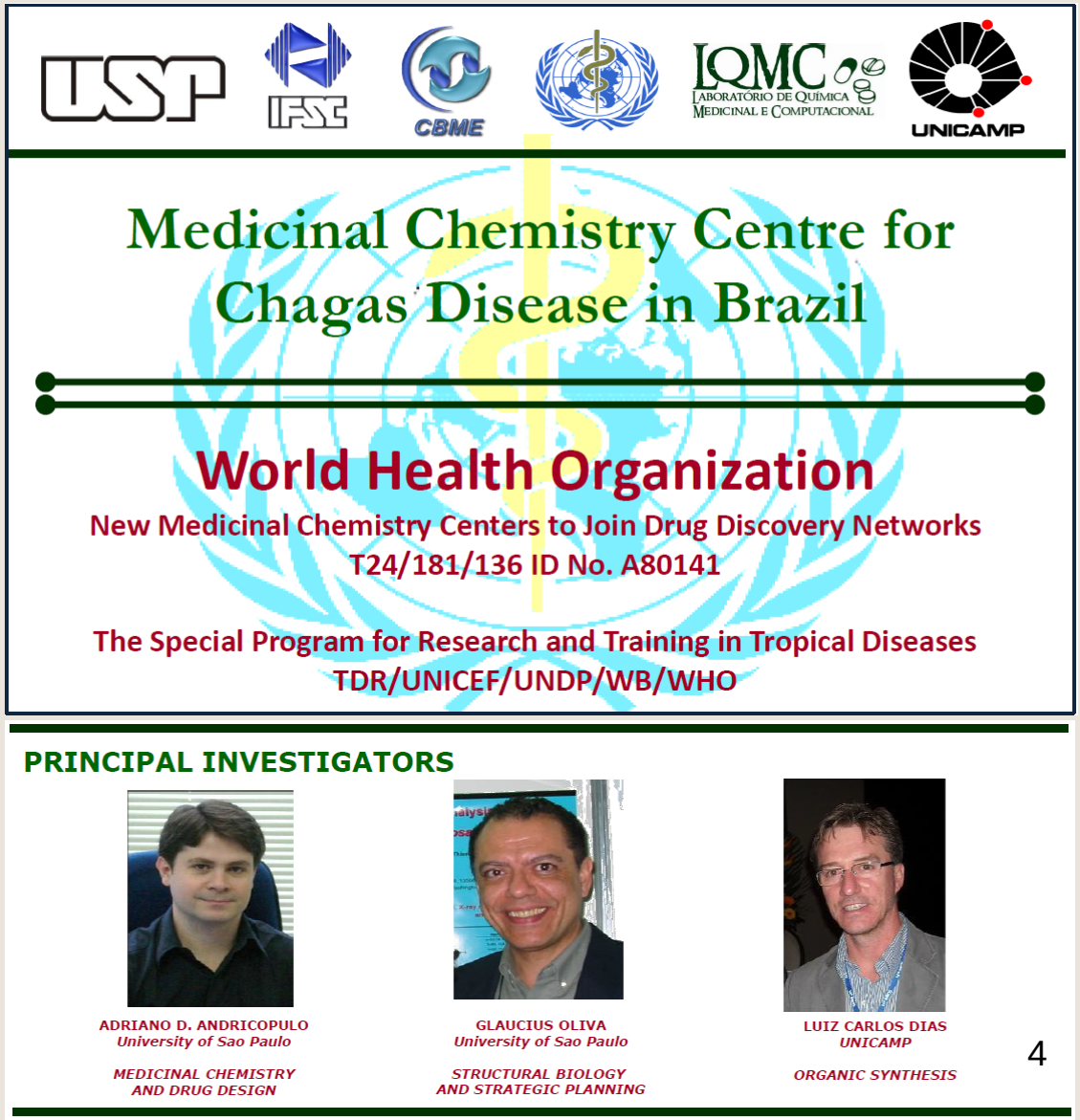
- Bicyclic series



LOLA4

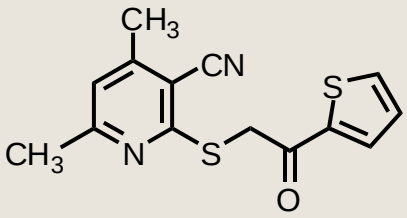
IC_{50} = 0.03 μM (*in vitro*)

  - NIH funded screen of the Broad Institute compound collection

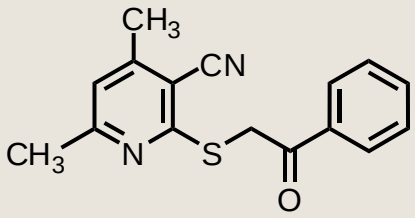


MOA is not CYP51 inhibition

- **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:

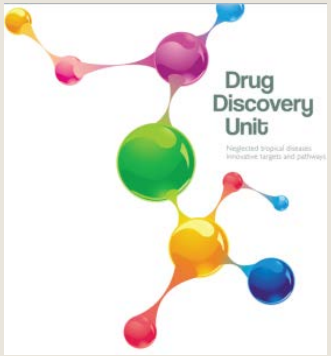


TDR30139
T. cruzi IC_{50} = 0.34 µM
CYP51 IC_{50} > 10 µM



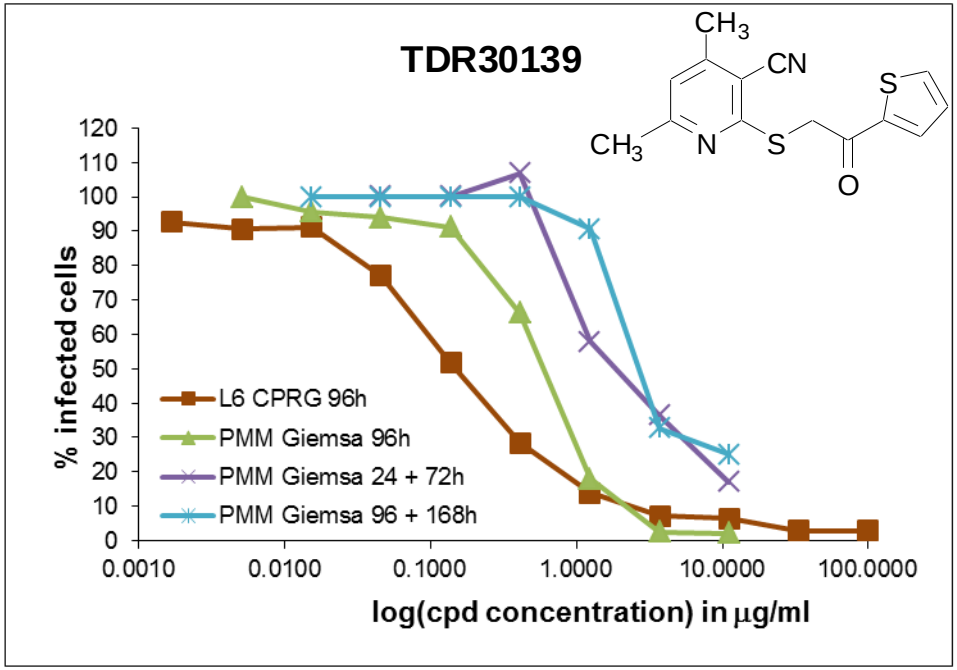
TDR91219
T. cruzi IC_{50} = 0.7 µM
CYP51 IC_{50} > 10µM

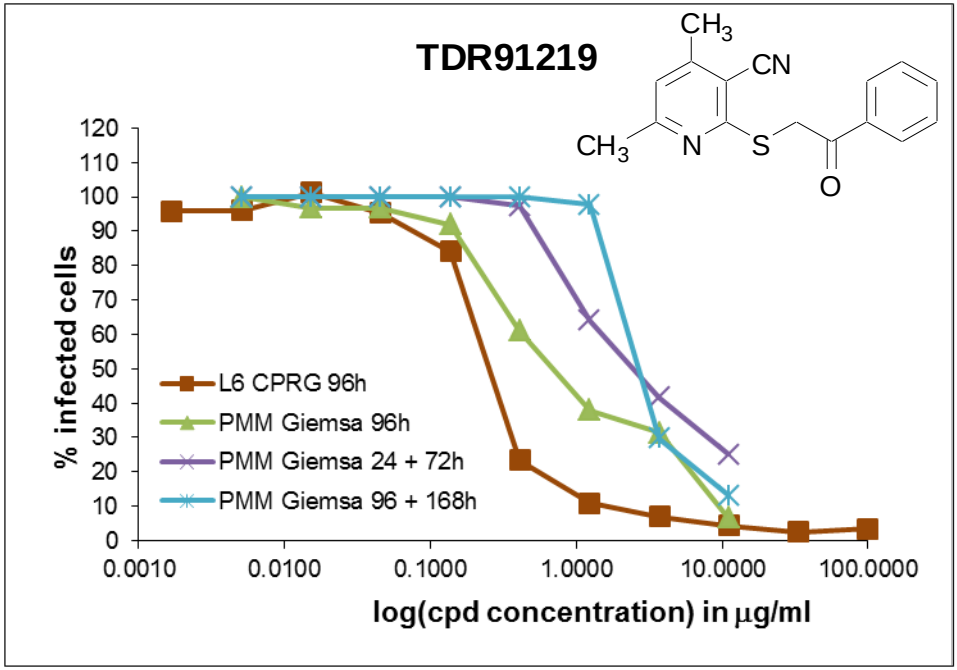
- Experiment kindly carried out by collaborators at GSK, Tres Cantos, and Dundee Drug Discovery Unit



Deeper characterisation of *in vitro* activity

Recovery of T.cruzi amastigotes: Standard assay *vs.* wash-out



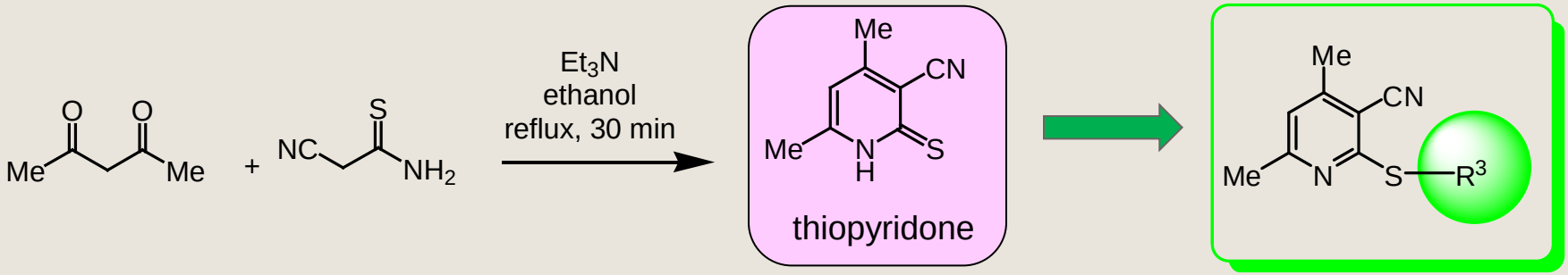


in µg/ml	L6 96h CPRG		PMM 96h Giemsa		PMM 24h + 72h Giemsa		PMM 96h +168h Giemsa	
	IC50	IC90	IC50	IC90	IC50	IC90	IC50	IC90
TDR91219	0.166	3.23	0.536	1.97	1.66	na	2.40	na
TDR30139	0.263	2.65	0.624	8.61	2.21	na	2.40	na

- Further confirmation of good *in vitro* activity
- Aim to test relevance of residual parasites in an *in vivo* assay

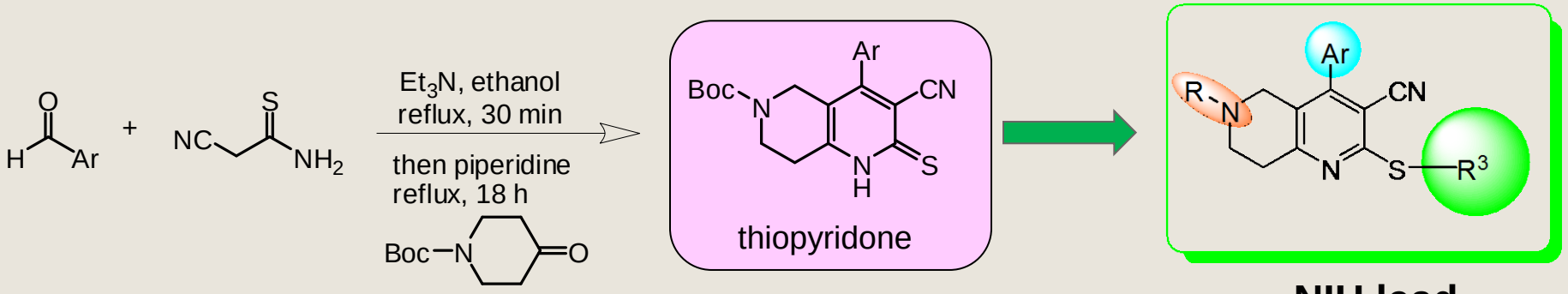
General Synthesis

monocyclic cyanopyridines



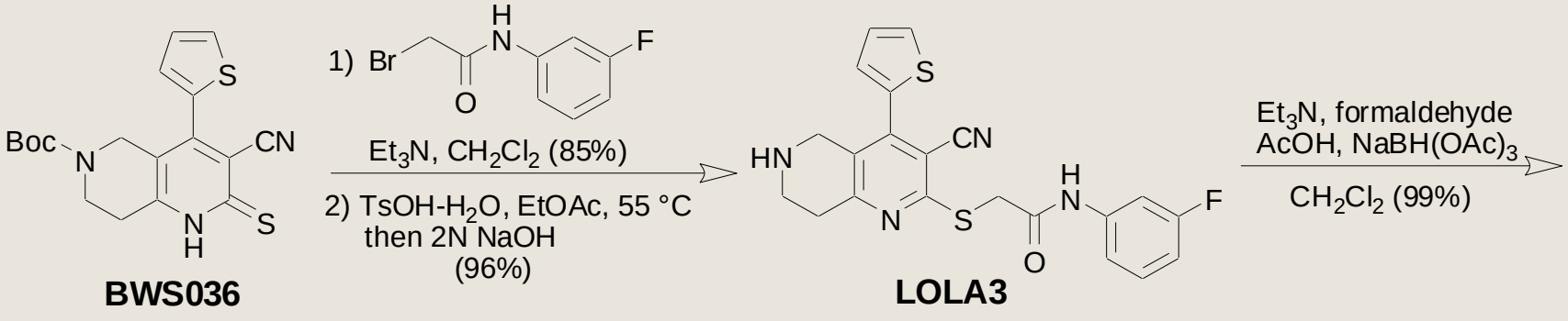
Schmidt, U.; Kubitzek, H. *Chem. Ber.* **1960**, *93*, 1559-1565.

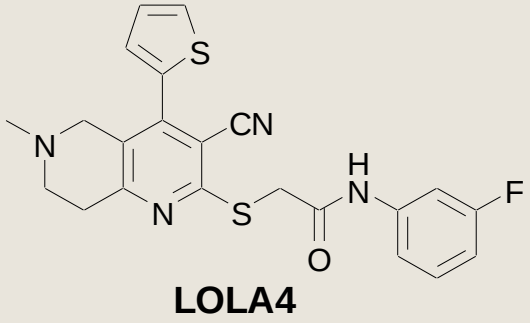
bicyclic cyanopyridines

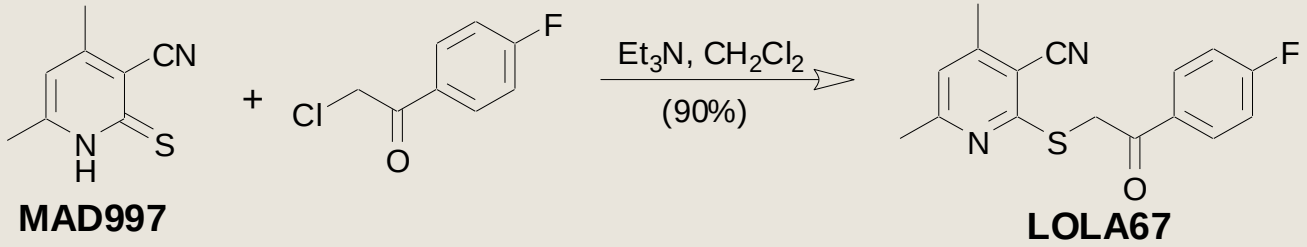


Abdel-Wadood, F. K.; Abdel-Monem, M. I.; Fahmy, A. M.; Geies, A. A. *J. Chem. Res.* **2008**, 89-94.

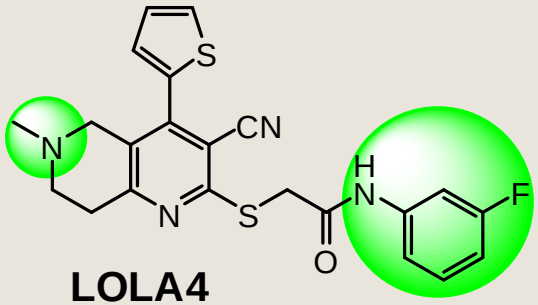
Scaleup


Boc
N
S
CN
N
H
S
BWS036
1) Br
H
N
O
F
Et3N, CH2Cl2 (85%)
2) TsOH-H2O, EtOAc, 55 °C
then 2N NaOH
(96%)
HN
S
CN
N
S
H
N
O
F
LOLA3
Et3N, formaldehyde
AcOH, NaBH(OAc)3
CH2Cl2 (99%)


S
CN
N
N
S
H
N
O
F
LOLA4

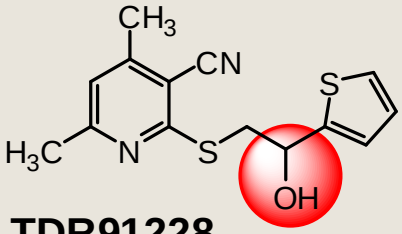

CN
N
H
S
MAD997
+
Cl
O
F
Et3N, CH2Cl2
(90%)
CN
N
S
O
F
LOLA67

Synthesis of TDR30139 derivatives



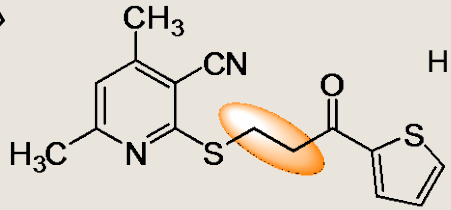
LOLA4

IC_{50} = 0.03 µM



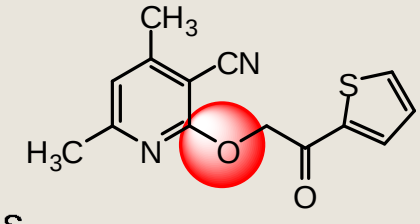
TDR91228

IC_{50} = 1.2 µM



TDR100524

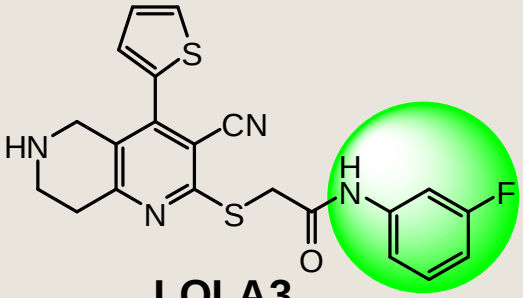
IC_{50} = 26 µM



TDR100612

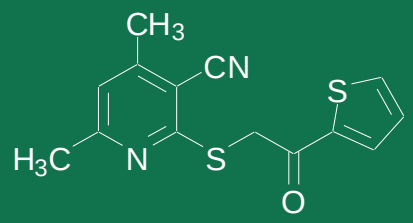
IC_{50} = 70 µM

monocyclic



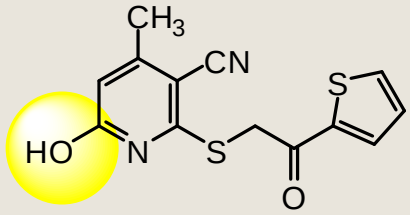
LOLA3

IC_{50} = 0.31 µM



TDR30139

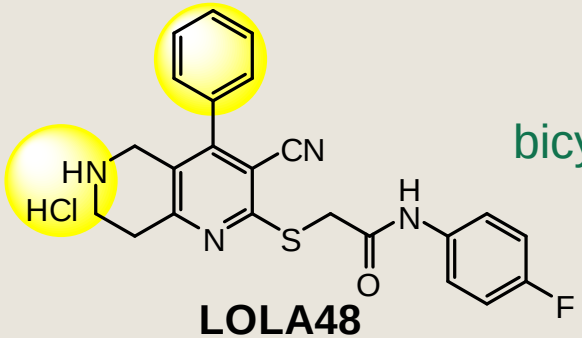
IC_{50} = 0.34 µM



TDR95696

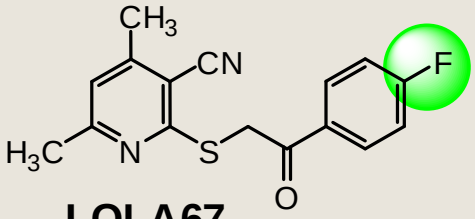
IC_{50} = 2.0 µM

bicyclic



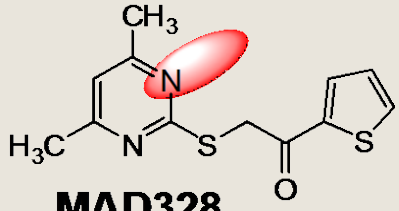
LOLA48

IC_{50} = 7.9 µM



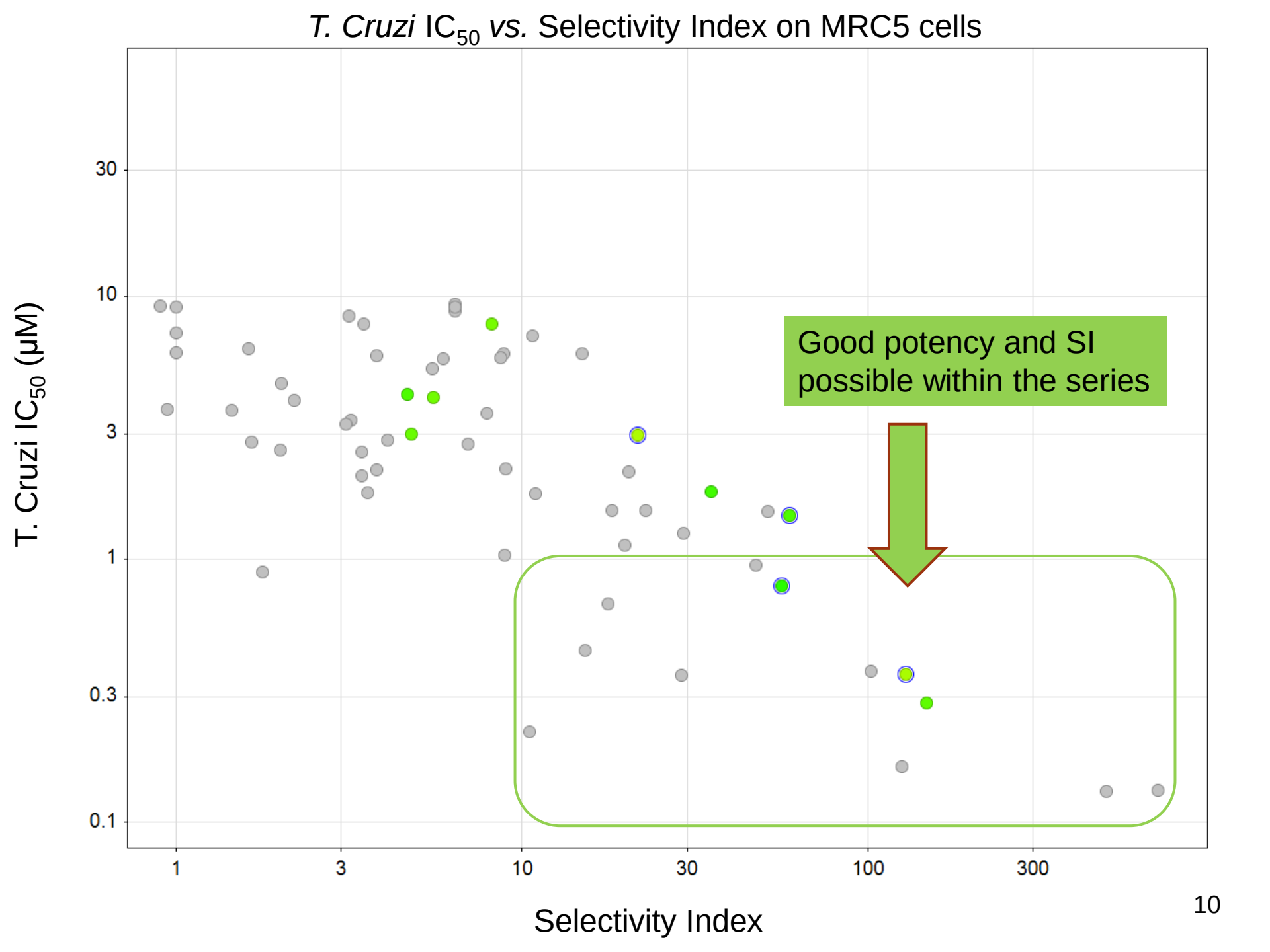
LOLA67

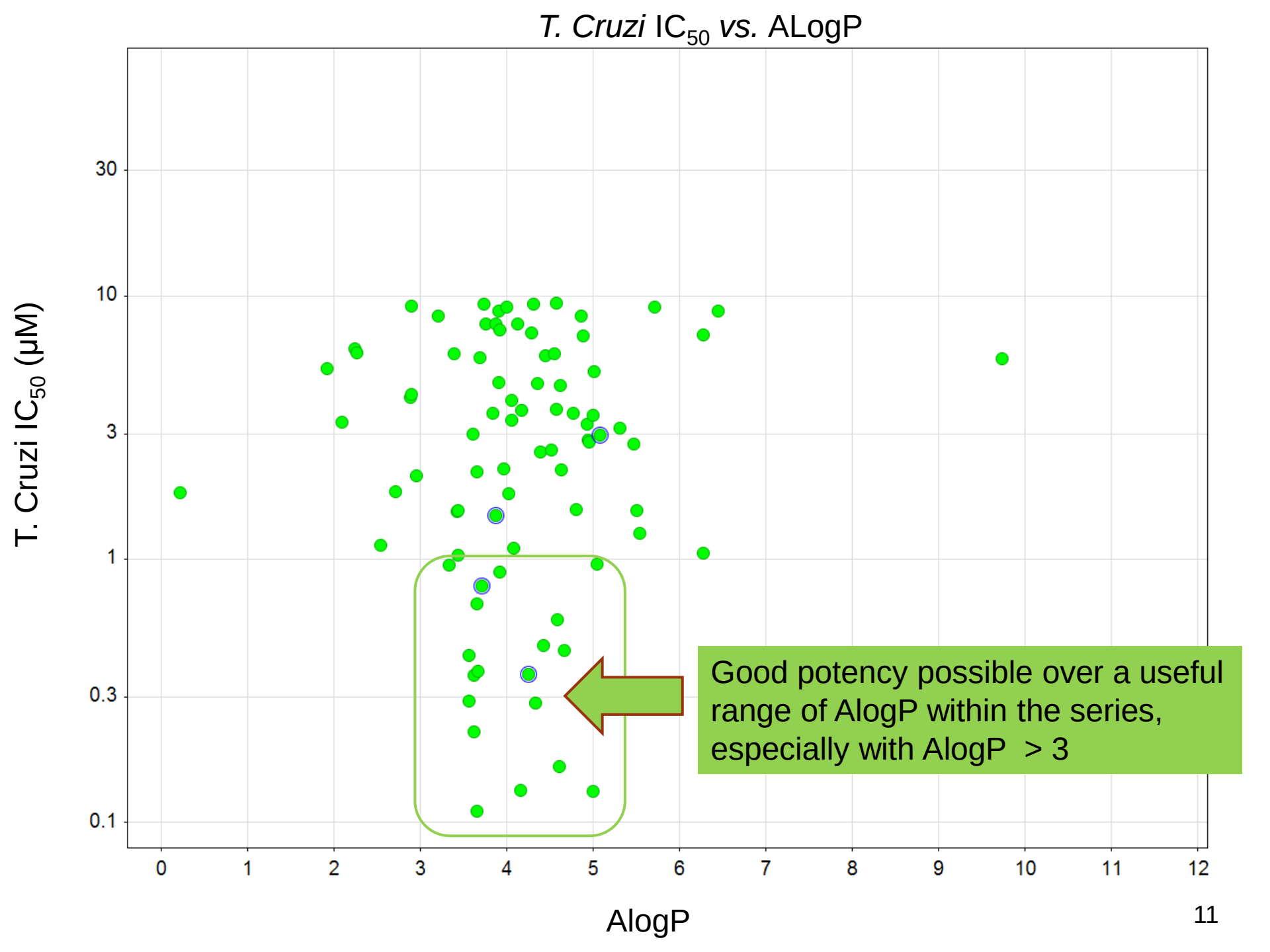
IC_{50} = 0.58 µM



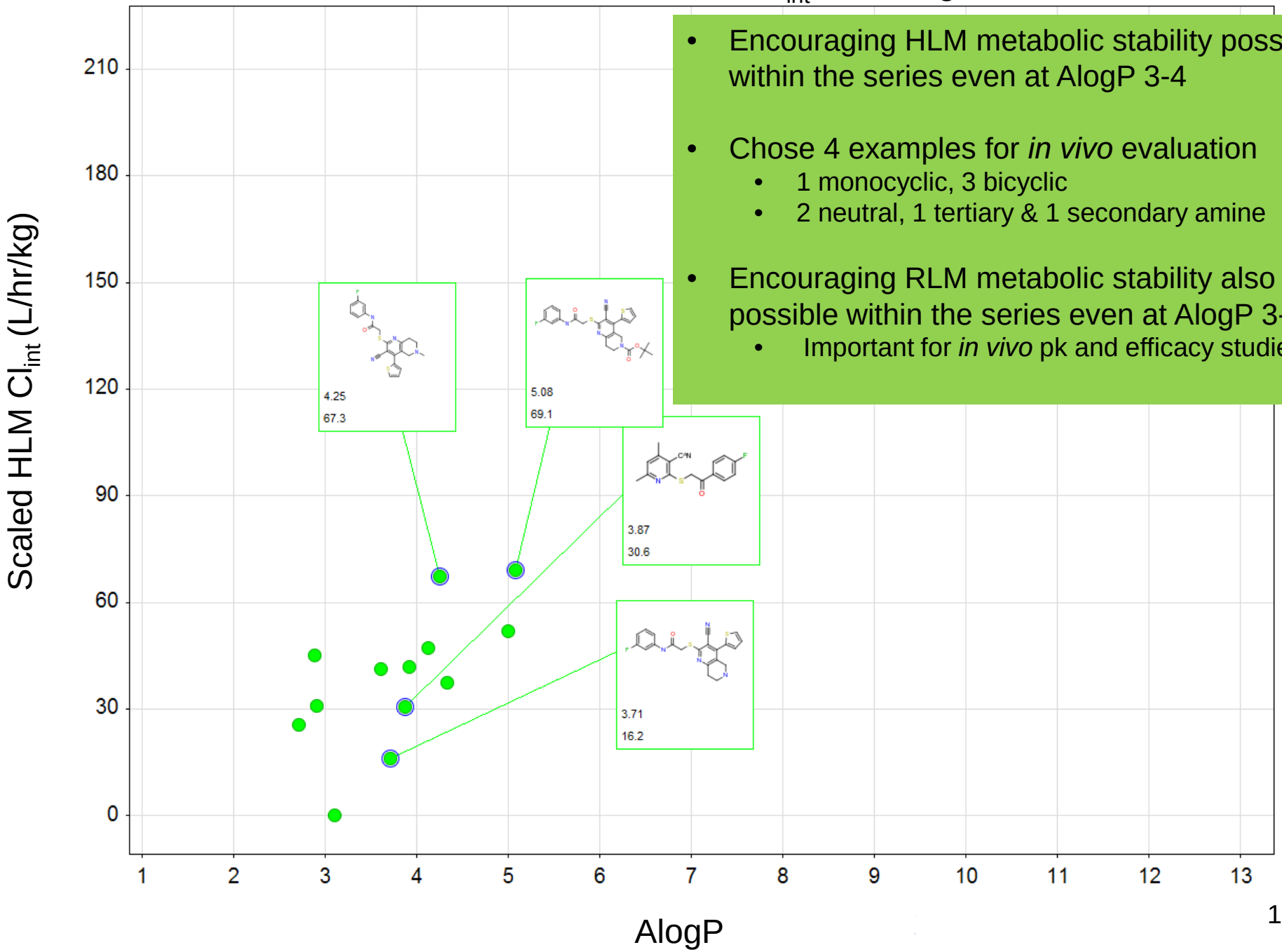
MAD328

IC_{50} > 100 µM


T. Cruzi IC_{50} *vs.* Selectivity Index on MRC5 cells
T. Cruzi IC_{50} (µM)
30
10
3
1
0.3
0.1
1
3
10
30
100
300
Selectivity Index
Good potency and SI possible within the series


T. Cruzi IC50 vs. ALogP
T. Cruzi IC50 (µM)
30
10
3
1
0.3
0.1
0
1
2
3
4
5
6
7
8
9
10
11
12
AlogP
Good potency possible over a useful range of AlogP within the series, especially with AlogP > 3

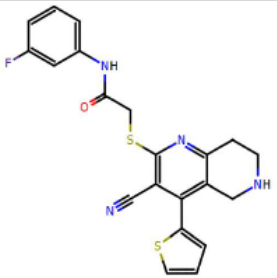
Scaled HLM Cl_{int} *vs.* ALogP



- Encouraging HLM metabolic stability possible within the series even at AlogP 3-4
- Chose 4 examples for *in vivo* evaluation
  - 1 monocyclic, 3 bicyclic
  - 2 neutral, 1 tertiary & 1 secondary amine
- Encouraging RLM metabolic stability also possible within the series even at AlogP 3-4
  - Important for *in vivo* pk and efficacy studies

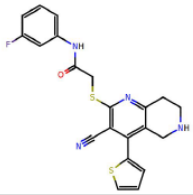
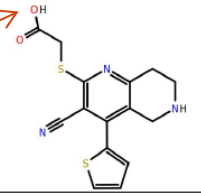
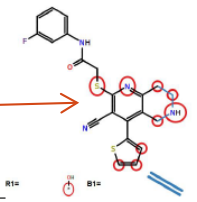
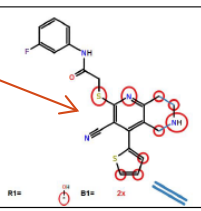
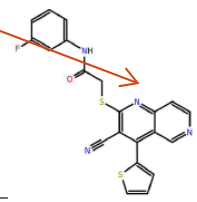
Metabolite identification for LOLA3

Metabolite ID report Metabolic soft spot ID	
property	value
Matrix	Liver Microsome
Species	Human, Rat
Incubation Time	60Min
Concentration	10µM
Project	NTD
Incubation Date	20140428



Substrate Name	A-1600908 = LOLA3

Major metabolites

Peak name	Structure proposal	m/z	ppm	Area %	Conditions	comments
Substrate -0		425.0888	2.8 3.0	96.31 94.30	Species=Human Species=Rat	
M1 -93 RT=8.59		332.0517	1.6	5.35	Species=Rat	
M3 +14 RT=11.19		439.0684	2.1	1.65	Species=Human	
M2 +12 RT=11.16		437.0526	2.4 2.3	0.35 1.05	Species=Rat Species=Human	
M4 -4 RT=12.35		421.0577	2.4	0.99	Species=Human	

Routes of metabolism observed:

- Amide hydrolysis
- Dehydrogenation
- Dehydrogenation & oxidation
- Aromatisation

Use this information to:

- Remove soft spots
- Block soft spots

Summary

- Cyanopyridine series
  - Encouraging *in vitro* profiles
  - Leads scaled up for formulation and *in vivo* studies
  - Mouse pk results awaited
  - Apply metabolite ID to guide design
  - Test leads in a mouse model of Chagas disease soon
- Apply medicinal chemistry & drug discovery principles to other new chemical series
- Extend the LOLA consortium
  - DMPK, *in vivo* models, chemistry, safety/toxicology,…

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Marcel Kaiser

Manu De Rycker

James Mills

Wen Hua

Charlie Mowbray, Eric Chatelain, Leandro Christmann and Simon Campbell