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Chemical Matter - the Good, the Bad and the Ugly

Luiz Carlos Dias
Instituto de Química – UNICAMP
Campinas – SP, BRASIL

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Medicinal Chemistry and Organic Synthesis play a very important role in modern drug discovery

What is Medicinal Chemistry?

What is Organic Synthesis?

A Medicinal Chemist is not the same as a Synthetic Chemist

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- For a medicinal chemist, synthesis is a tool, not a goal
- A medicinal chemist integrates data from a variety of sources, and uses this information to design new generations of compounds
- Knowledge of synthetic chemistry comes in choosing these new targets, in designing and implementing the syntheses

Many disciplines play critical roles…

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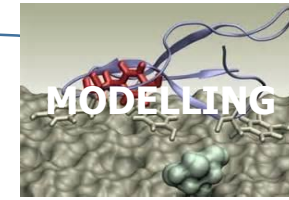
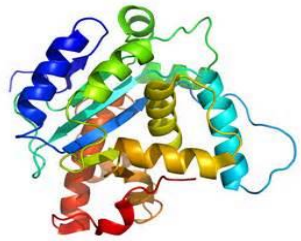
BIOLOGICAL SCREENING



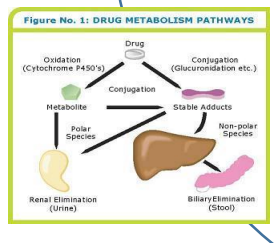
STRUCTURAL BIOLOGY



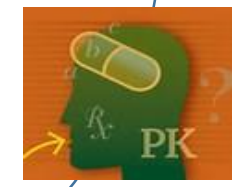
PHARMACOLOGY

MEDICINAL CHEMISTRY AND ORGANIC SYNTHESIS

DRUG METABOLISM

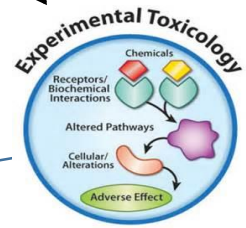


PHARMACO-KINETICS



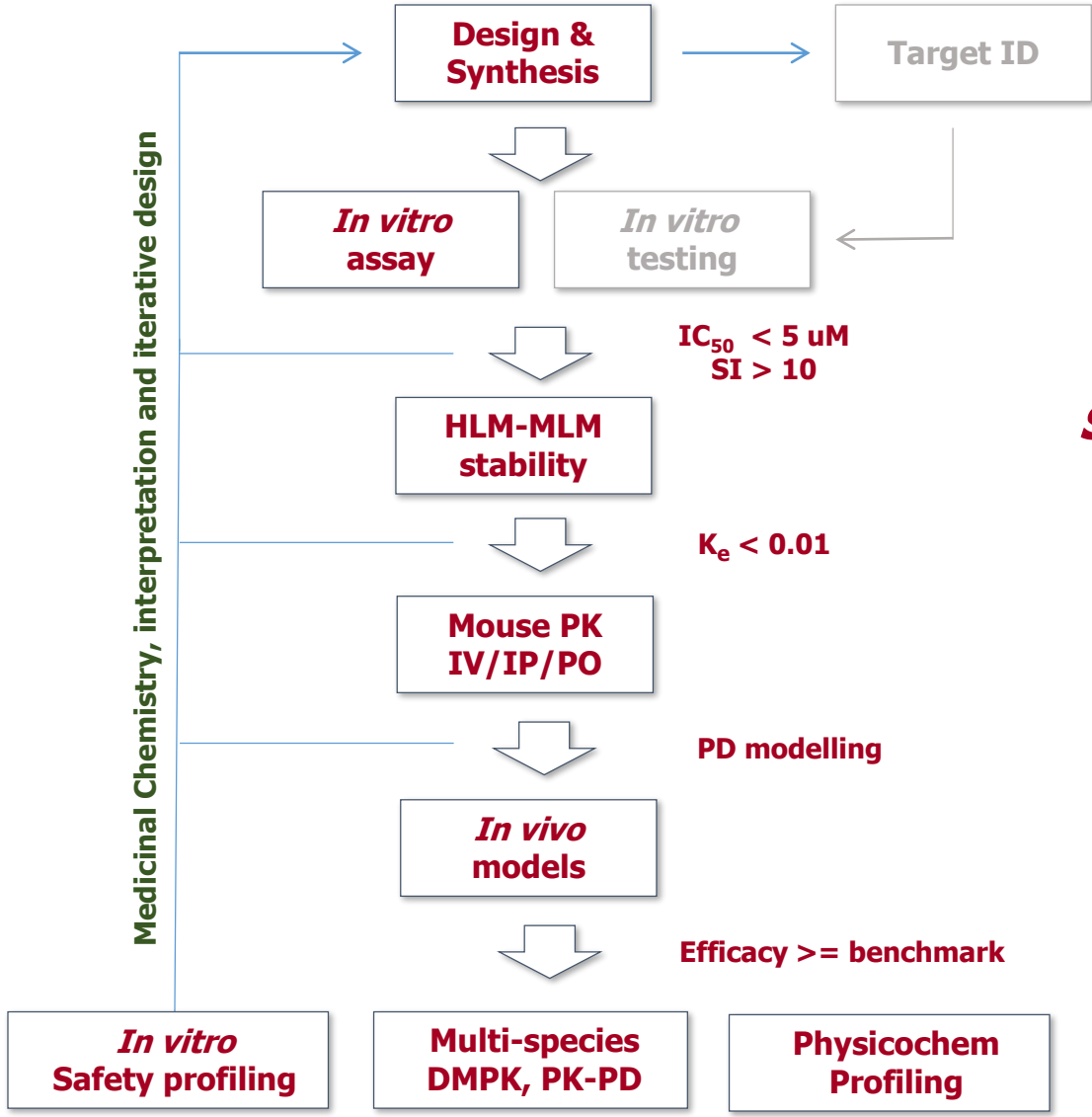
PHARMACEUTICS

TOXICOLOGY



… but chemistry is central

The role of the medicinal chemist is unique in the drug discovery process…



… because everything starts with the molecule; and with the iterative design process that optimizes the properties of the molecule

Your Partners Provide Key Data

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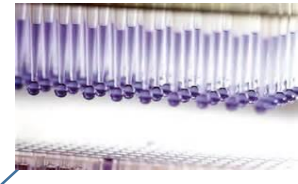
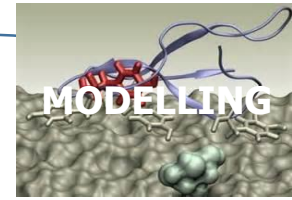
BIOLOGICAL SCREENING

Do my molecules interact with the desired targets?

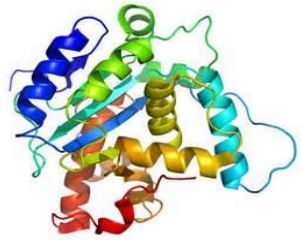




Hypothesis generation, selection/triage of new targets

STRUCTURAL BIOLOGY

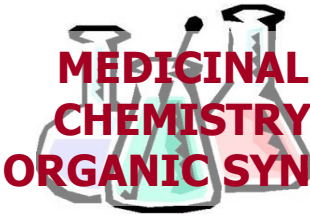
Identification of binding modes



PHARMACOLOGY

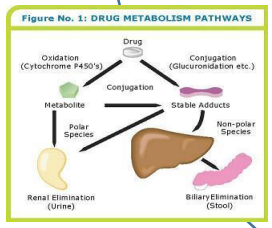
Do my molecules work in disease models?

MEDICINAL CHEMISTRY AND ORGANIC SYNTHESIS



DRUG METABOLISM

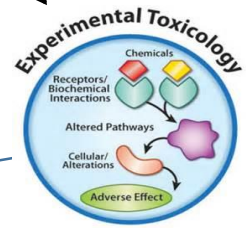
What removes my compound from the body?



What properties are impeding the ability of my drug to get where it needs to go, and to do its job once it's there?

PHARMACEUTICS

Are my molecules stable? soluble? crystalline?



TOXICOLOGY

What are the adverse interactions I need to avoid?

Responding to Structural Information

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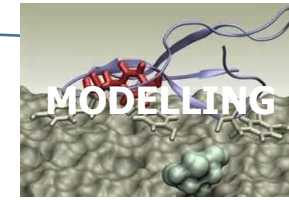
BIOLOGICAL SCREENING



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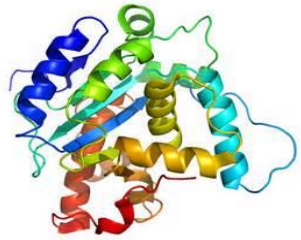

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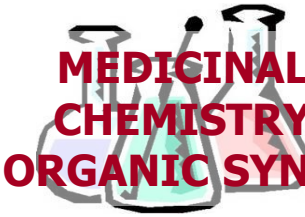

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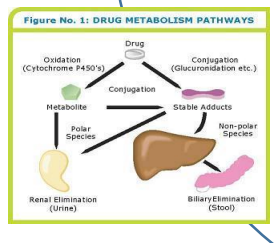
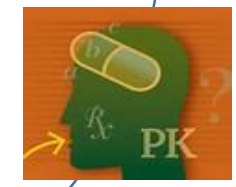


PHARMACO-KINETICS



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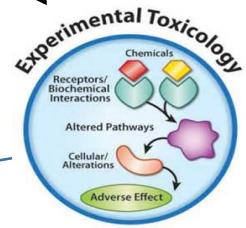
TOXICOLOGY



Responding to metabolism data

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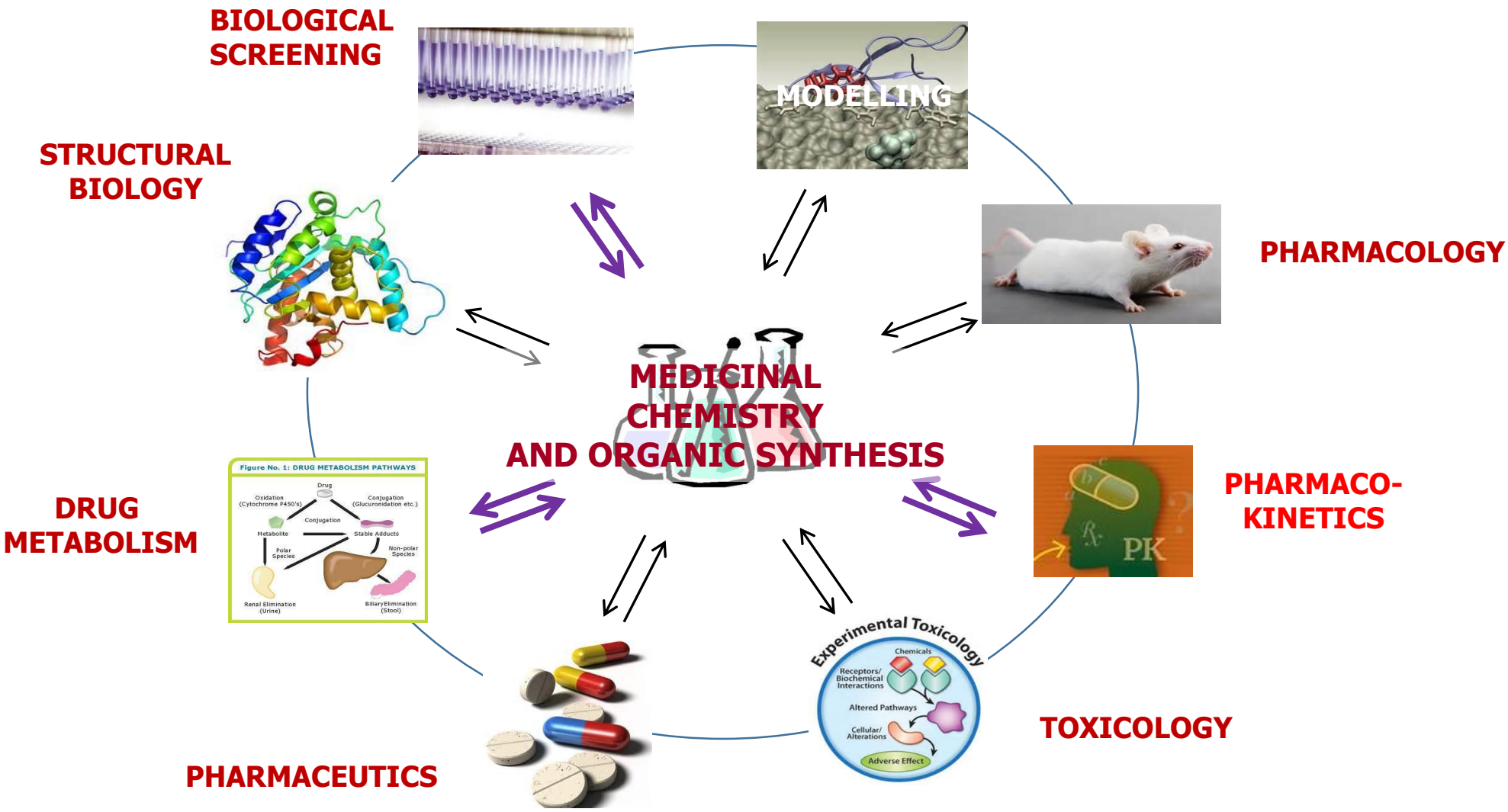

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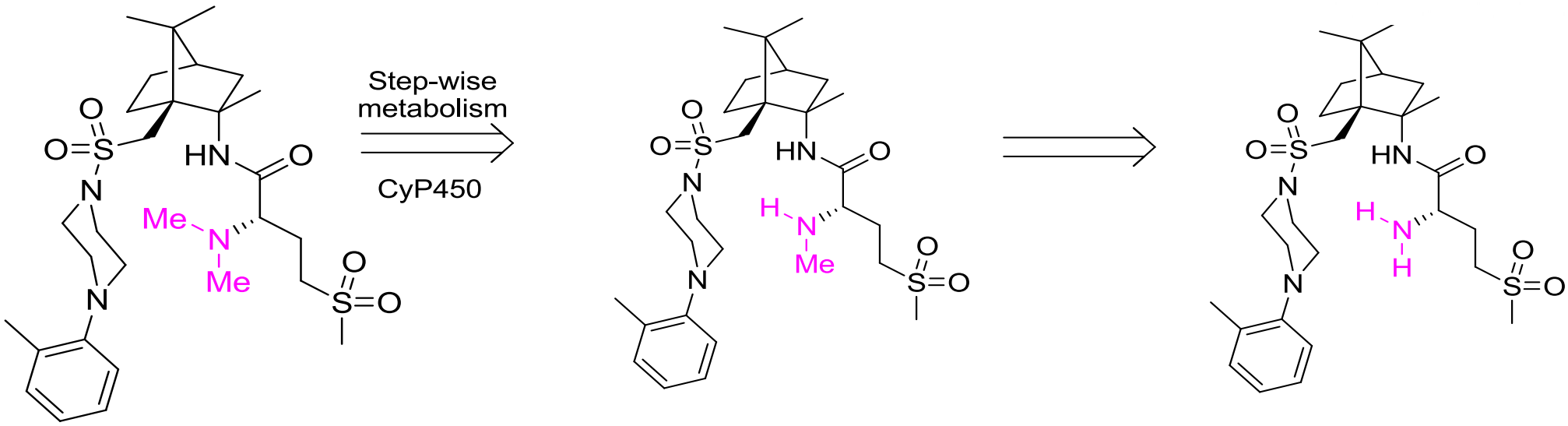

Active OT receptor antagonist
Rapidly metabolized
Low bioavailability

Both metabolites are
active OT antagonists;
the N-Me is also metabolized
rapidly, but the -NH_2 analog
is stable, with improved bioavailability

2000

Plasma drug, ng/mL

Responding to safety data

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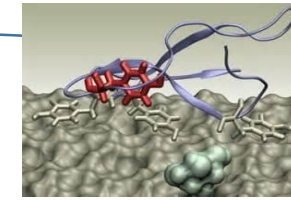
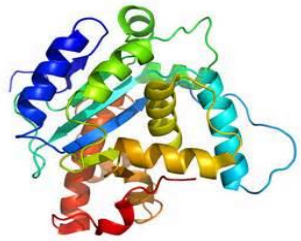
BIOLOGICAL SCREENING

MODELLING

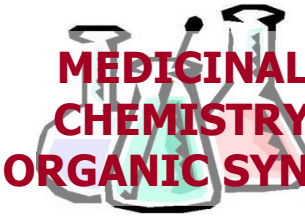


STRUCTURAL BIOLOGY



PHARMACOLOGY

MEDICINAL CHEMISTRY AND ORGANIC SYNTHESIS



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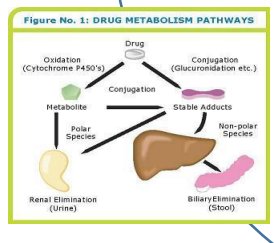

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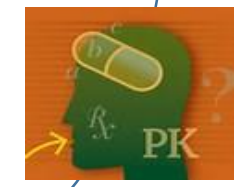
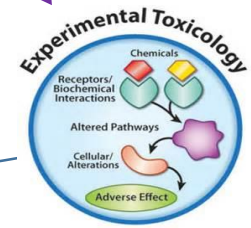
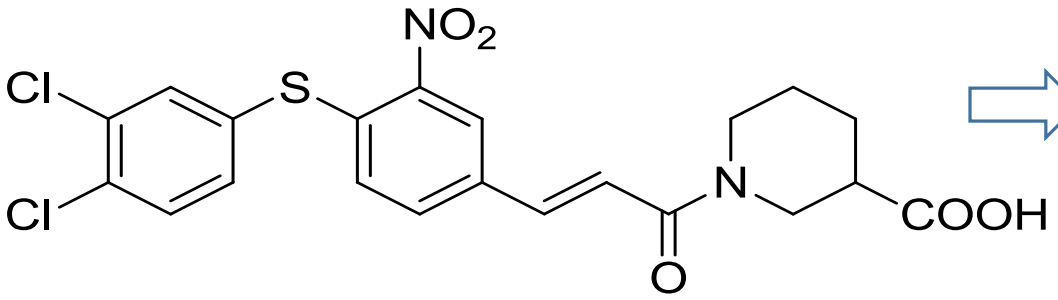


PHARMACEUTICS

TOXICOLOGY



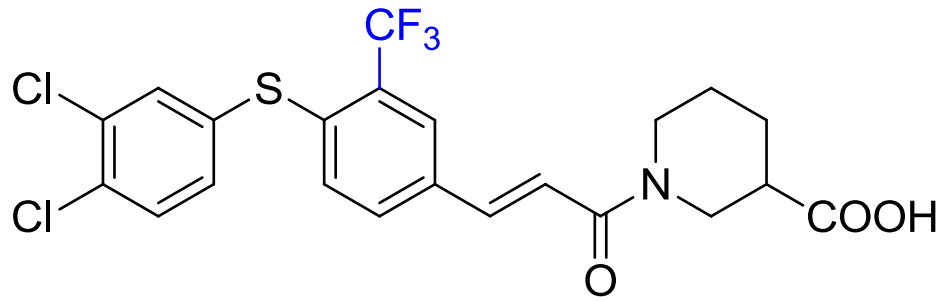
Responding to safety data



Inhibitor of cell adhesion

Potent, good PK profile
Ames positive

From DEREK analysis :
Aryl-NO_2 can be genotoxic



Potent, good PK profile
Ames negative

The Ames test is a widely employed method that uses bacteria to testwhether a given chemical can cause mutations in the DNA of the test organism.

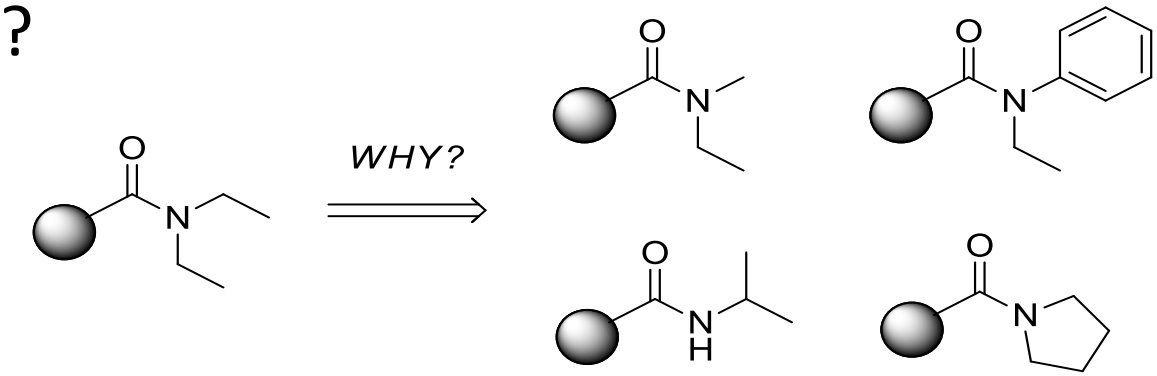
Is is a biological assay to assess the mutagenic potential of chemical compounds

The Complex Reality

- If you want to make a drug, you have to solve all of these challenges simultaneously, in one molecule
- It isn't sufficient to take them on one at a time; it doesn't help to make 500 analogs of a lead structure…
  - if they all have the same metabolism problem…
  - or the same safety issue…
  - or they are all highly bound to plasma proteins…
  - or none of them can cross membranes to get to the target
- You (with your partners) need to identify critical issues ASAP, and focus your attention on addressing these
  - Your testing strategy needs to adjust so that you can get rapid feedback on key challenges
  - *Be aware, that solutions to one problem, can introduce another*!

Designing New Targets

- It's not enough to make new compounds because they look like your current leads
- At the *beginning* of a program, you need to be thinking about the *end* of the program
  - What is the target profile (TPP) for your ideal compound?
  - How does your current lead fall short of this target?
  - What hypotheses do you have, for how to address these shortcomings?
  - What compounds can you design (and make) to test these hypotheses?



An Evolving Role

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- Medicinal chemists have a role in
  - Hit-To-Lead (HTL) Evaluation
    - Structure alerts
      - Toxicity "flags"
      - False hits, PAINS
    - Homology searching to probe SAR
  - Lead Optimization (LO)
    - Multi-property optimization through SAR studies
  - Candidate selection
    - "Tight SAR" for final optimization of properties
    - Early scale-up to support advanced characterization

…but…I'm a *REAL* chemist…

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- there's a very important role for a Chemist in pharma
  …in process research

- In process chemistry, you have a single synthetic target (the drug candidate)

  - Scale up (mg -> g -> kg and beyond)
  - Synthetic efficiency
  - Minimizing waste
  - Co$t

How med-chemists make Emend®

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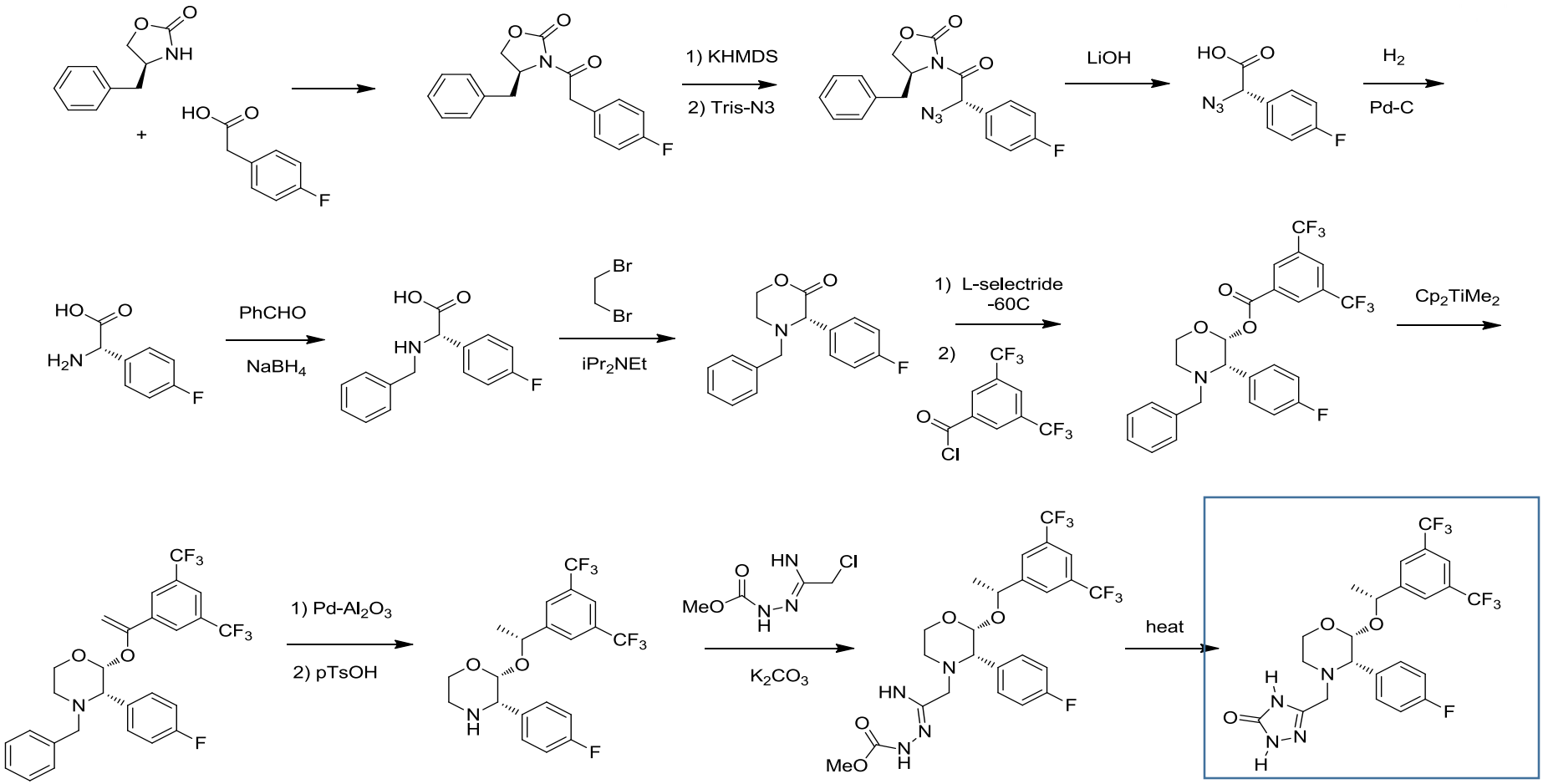
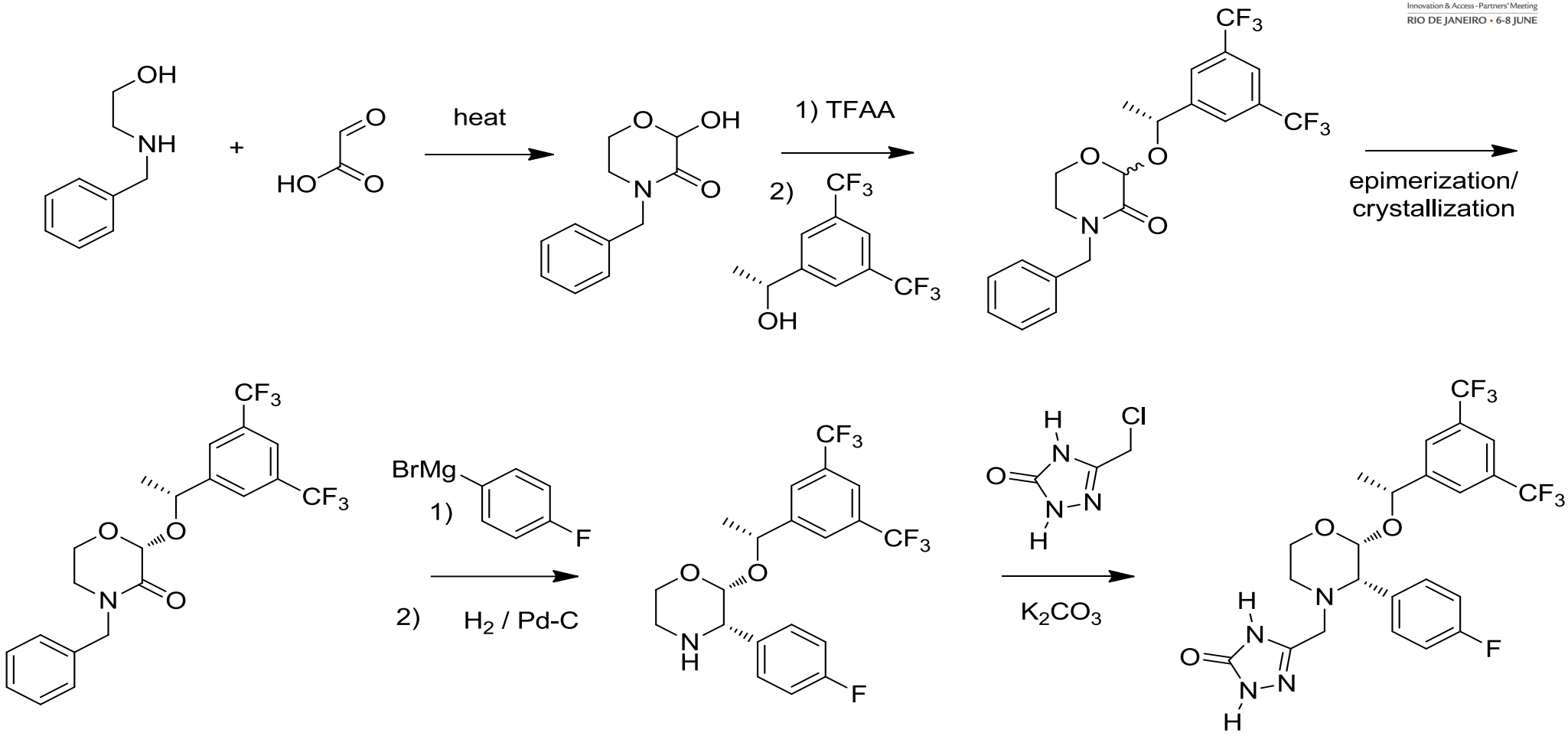


Anti-emetic
Merck

11 steps, < 20% overall yield
Toxic/reactive reagents
Low temperatures/inert atmosphere

The commercial process



- **6 STEPS, 55% OVERALL YIELD**
- **Total production waste reduced by 85%**

The Top Pharmaceuticals That Changed The World

Chemical and Engineering News Vol. 83, Issue 25 (**6/20/2005**)

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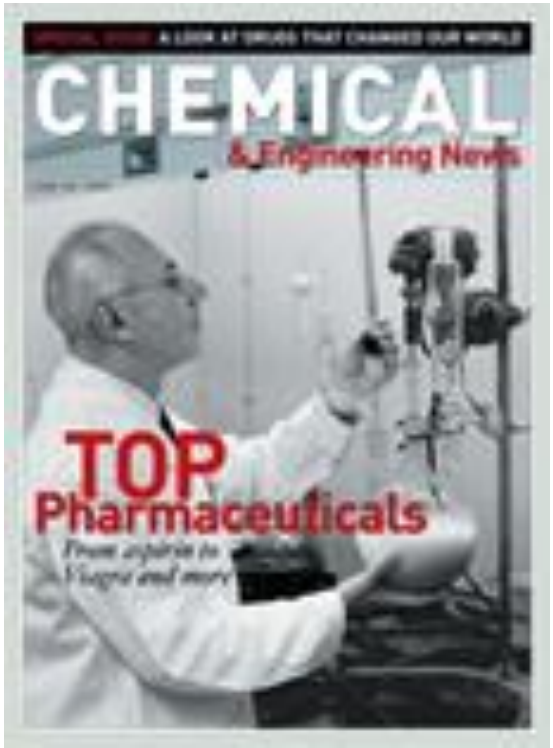
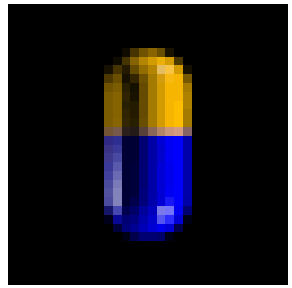
C&EN Special Issue

Top Pharmaceuticals

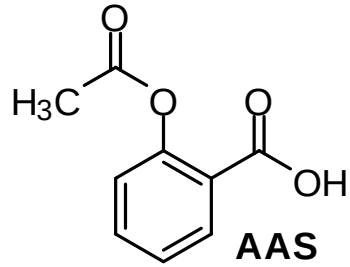
A Look At Drugs That Changed Our World



***Chemical & Engineering News* looks at 46 drugs that have had a major impact on human health and society**



Félix Hoffmann (1898)



AAS

ALPHABETICAL INDEX

- Allegra
- Aspirin
- AZT
- Botox
- Cisplatin
- Crixivan
- Cyclosporine
- Digoxin
- Erythropoietin
- Ether
- Fentanyl
- Fluoride
- Fosamax
- Hydrocortisone
- Insulin
- Isonizid
- Ivermectin
- Librium
- Lovastatin
- Medical marijuana
- 6-Mercaptopurine
- Methadone
- Morphine
- Oral contraceptives
- Oxytocin
- Penicillin
- Phenobarbital
- Premarin
- Prontosil
- Prozac
- Quinine
- Ritalin
- Rituxan
- RU-486
- Salbutamol
- Salvarsan
- Tagamet
- Taxol
- Thalidomide
- Thorazine
- Thyroxine
- Vaccines
- Viagra
- Vioxx
- Vitamins

Sir Simon Campbell

~80% synthetic compounds!!!

Source of new drugs

Until the beginning of twentieth century, the substances used for the treatment of diseases were obtained from natural sources.

Natural sources include plants, animals, and minerals.

Among the natural sources, plants were mainly used.

Sometimes minerals and occasionally animals were used for the same purpose.

Nowadays most of the drugs are manufactured in the laboratory, i.e. synthetic drugs.

Microorganisms also serve as a source of a large number of drugs.

Natural Products as Sources of New Drugs from 1981 to 2014
David J. Newman*† and Gordon M. Cragg‡
J. Nat. Prod., **2016**, *79* (3), pp 629–661
DOI: 10.1021/acs.jnatprod.5b01055

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The major categories used are as follows:

"B" Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.

"N" Natural product.

"NB" Natural product "Botanical" (in general these have been recently approved).

"ND" Derived from a natural product and is usually a semi-synthetic modification.

"S" Totally synthetic drug, often found by random screening/modification of an existing agent.

"S*" Made by total synthesis, but the pharmacophore is/was from a natural product.

"V" Vaccine.

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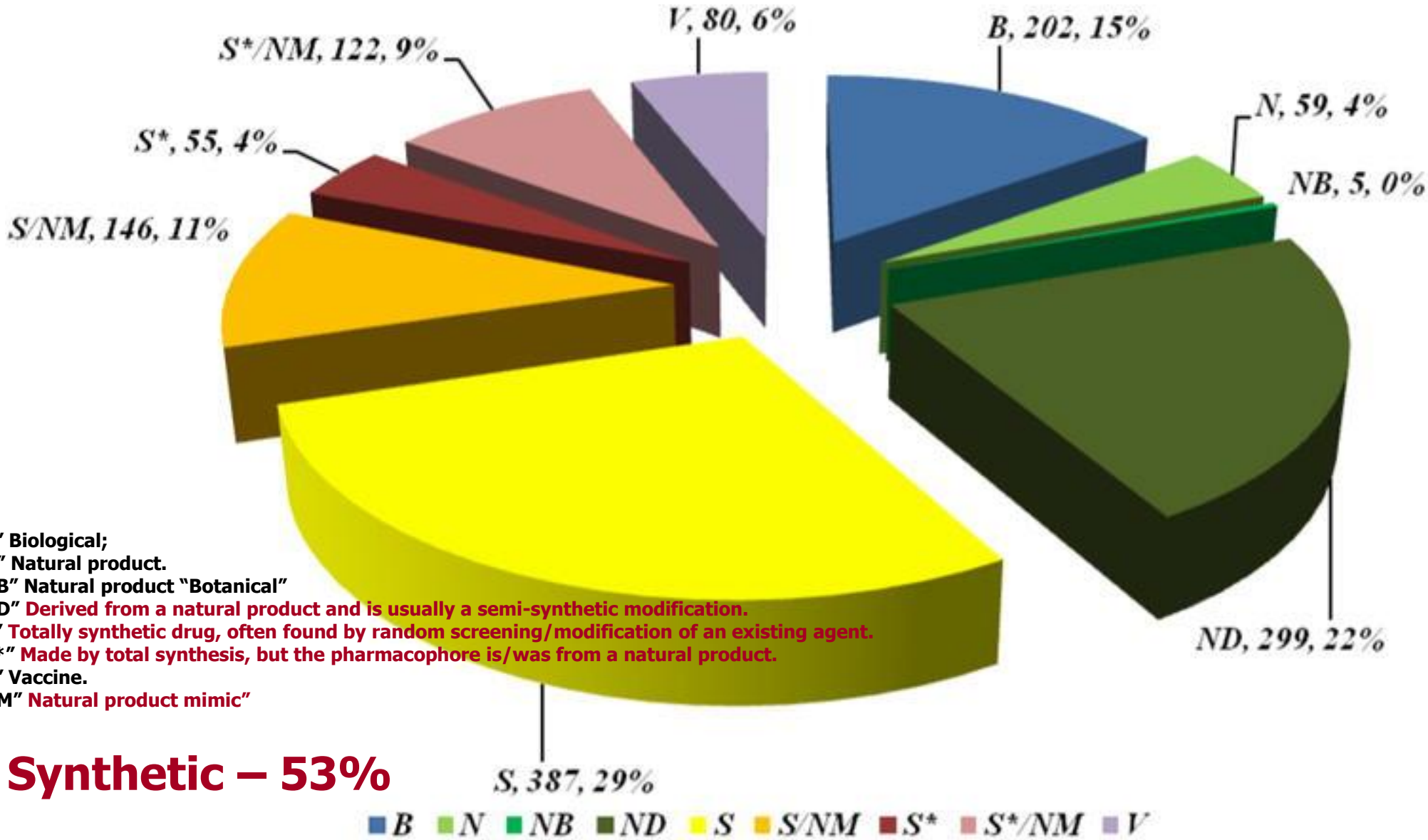
All New Approved Drugs; n = 1355



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"V" Vaccine.
"NM" Natural product mimic"

Synthetic – 53%

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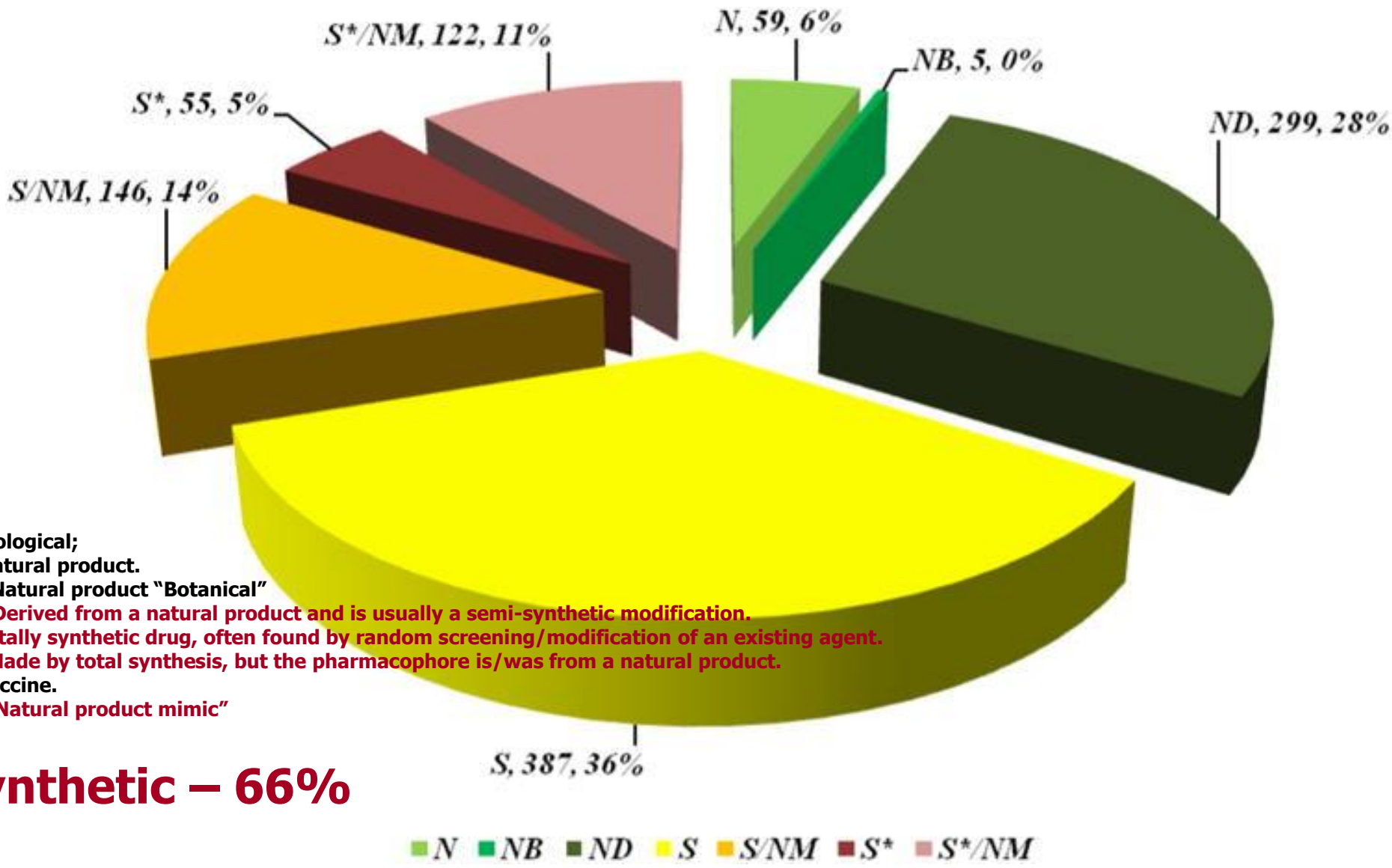
Source of Small Molecule Approved Drugs; n = 1073



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Synthetic – 66%

William C. Campbell, Satoshi Ōmura and Youyou Tu Win 2015 Nobel Prize for Physiology or Medicine

Awards: Researchers' work led to drugs against roundworm diseases and malaria

Leading Edge

BenchMarks

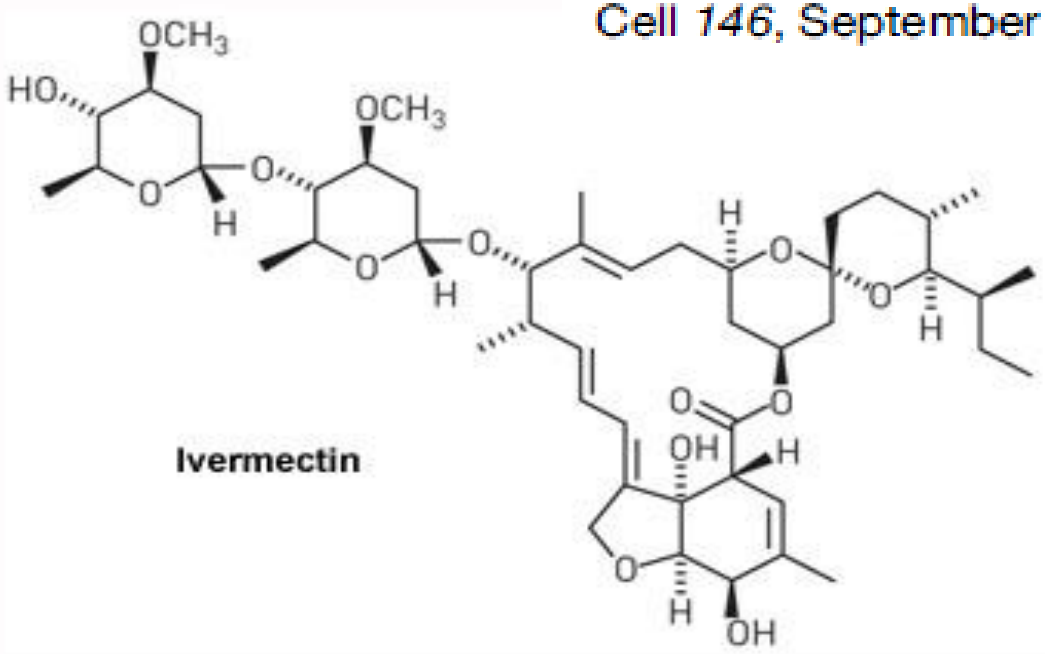
Cell

Artemisinin: Discovery from the Chinese Herbal Garden

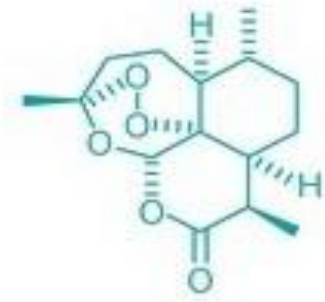
Louis H. Miller[1,*] and Xinzhuan Su[1]
[1]Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20852, USA
*Correspondence: lmiller@niaid.nih.gov
DOI 10.1016/j.cell.2011.08.024

This year's Lasker DeBakey Clinical Research Award goes to Youyou Tu for the discovery of artemisinin and its use in the treatment of malaria—a medical advance that has saved millions of lives across the globe, especially in the developing world.

Cell 146, September 16, 2011 ©2011 Elsevier Inc. 855



Ivermectin



(+)-Artemisinin

Ivermectin: C&EN's Top Pharmaceuticals That Changed the World:
http://pubs.acs.org/cen/coverstory/83/8325/8325ivermectin.html

DNDi 2016

Innovation & Access - Partners' Meeting

RIO DE JANEIRO • 6-8 JUNE

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

***Luiz Carlos Dias*[1], *Marco A. Dessoy*[1], *Brian W. Slafer*[1], *Adriano Andricopulo*[2], *Glaucius Oliva*[2], *Dale Kempf*[3], *Brian Brown*[3], *Mira Hinman*[3], *Yvonne C. Martin*[3], *Charles E.* Mowbray[4], Simon *F. Campbell*[5]**

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[2]Laboratorio de Química Medicinal e Computacional, Centro de Biotecnologia Molecular Estrutural– USP, São Paulo, Brazil

[3]AbbVie Inc., Chicago, USA

[4]Drugs for Neglected Diseases *initiative* (DND*i*), Geneva, Switzerland

[5]Independent consultant

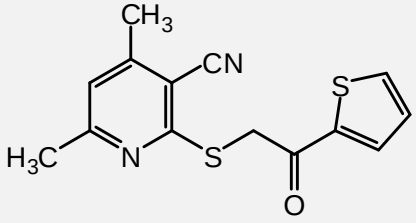
DNDi
Drugs for Neglected Diseases *initiative*

Lead Optimization Latin America (LOLA)

Origins of leads against *T. cruzi*

Early leads for new drugs for Chagas disease

☐Monocyclic series

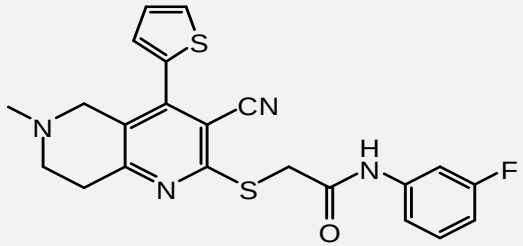


TDR30139

IC_{50} = 0.34 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

Early screening cascade & partners

Design and analysis of new targets
Collaborative effort by UNICAMP, USP Sao Carlos, AbbVie, Sir Simon Campbell & DNDi

Color coding:

Every compound

Few per series

Later stages

Synthesis
UNICAMP

Chagas, toxicity, and mode of action related testing

Primary Parasitology
USP Sao Carlos and LMPH, Antwerp

Secondary Parasitology
Swiss Tropical Institute

Mode of Action (CYP51) screen
GSK, Tres Cantos and University of Dundee – Drug Discovery Unit

DMPK

***in vitro* ADME** (LogD, Clint, Sol., Perm.)
AbbVie, Chicago

ADME predictions
AbbVie, Chicago

Metabolism (Met ID)
AbbVie, Chicago

Formulation – *in vivo* PK
Wuxi AppTech, Shanghai

Mouse model of Chagas Disease
LSHTM, London, USP-São Carlos

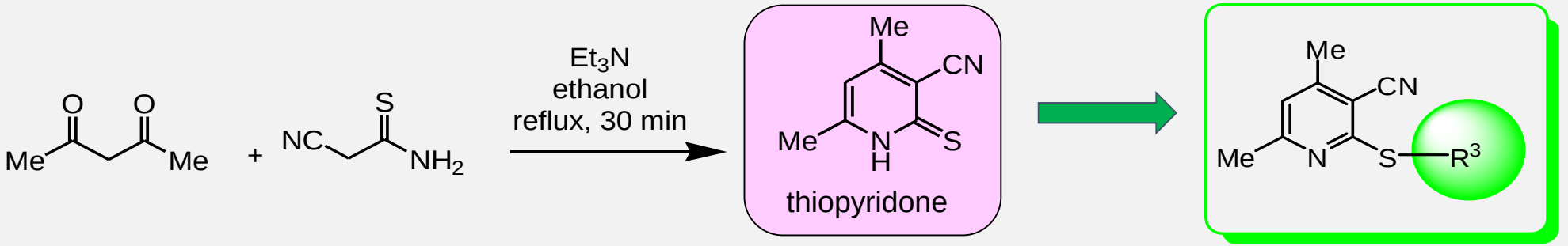
DNDi project collaborators in alphabetical order and their contribuitons

DNDi
Drugs for Neglected Diseases *initiative*

Antwerp University, Laboratory of Microbiology, Parasitology and Hygiene (LMPH, Belgium)	The LMPH (Laboratory of Microbiology, Parasitology and Hygiene) conduct *in vitro* testing of new compounds against *T. cruzi, L. infantum, T. brucei, T.b. rhodesiense* and parallel assessments of cytotoxicity against MRC-5 (human fibroblast) cells and PMMs (primary mouse macrophages). The same lab can test any active compounds in mouse and hamster animal models of VL.
GSK, Tres Cantos (Spain)	Test compounds for CYP51 inhibition to rule out this mode of action.
London School of Hygiene and Tropical Medicine (LSHTM)	World leading centre for research and education in public and global health. Providing testing for compounds in an acute mouse model of Chagas disease as a proof of concept.
Sandexis LLP (UK)	Provide expert medicinal and computational chemistry support to DND*i*, and have been supporting the optimization of the new series from the Pfizer collection.
Swiss Tropical and Public Health Institute (Switzerland)	Public organization which runs. *in vitro* drug action studies in *T. cruzi* on 2 leading compounds from the cyanopyridine series.
Unicamp (Campinas, Brazil)	Prof. L.C. Dias lab runs the project at UNICAMP. Selection of targets provided by DND*i*. Planning and synthesis of derivatives. Data evaluation and decision on course of the series.
University of Dundee – Drug Discovery Unit (UK)	Compounds tested in a CYP51 assay to evaluate the primary mechanism of action of the cyanopyridines against *T. cruzi*.
University of Sao Paulo at Sao Carlos, *Centre for Research and Innovation in Biodiversity and New Drugs*-CIBFAR, IFSC-USP	The LQMC (Laboratory of Medicinal and Computational Chemistry) conduct medicinal chemistry studies including *in vitro* testing of new compounds against *T. cruzi and L. donovani,* and parallel assessments of cytotoxicity against MRC-5 (human fibroblast) cells and PMMs (primary mouse macrophages). The same lab is establishing validated assays to test promising active compounds in animal models of VL and *T. cruzi*.
Wuxi AppTec (China)	CRO based in Shanghai, China, providing DMPK services to the project. This will mainly be *in vivo* rodent (mouse, hamster & rat) study to provide PK results for novel compounds. These results will be used to set appropriate dosing regimens for testing in subsequent animal models of Chagas and/or VL, and to understand general DMPK properties for further optimization.

General Synthesis

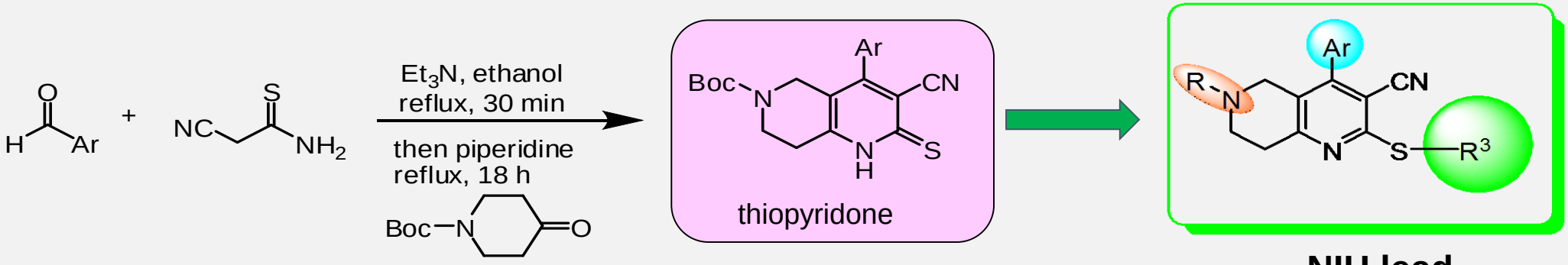
monocyclic cyanopyridines



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

TDR30139
analogues

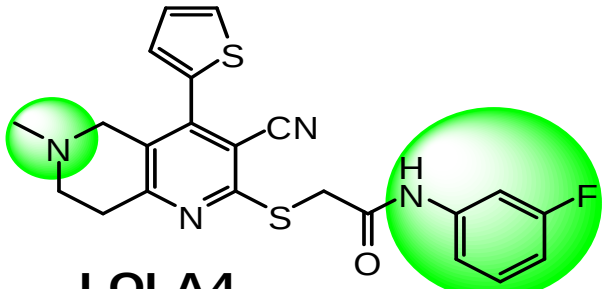
bicyclic cyanopyridines



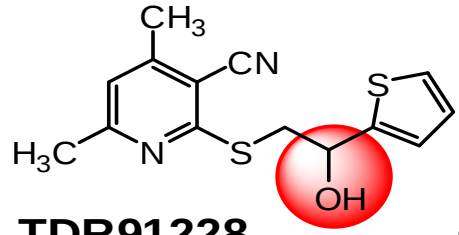
Abdel-Wadood, F. K.; Abdel-Monem, M. I.; Fahmy, A. M.; Geies, A. A. *J. Chem. Res.* **2008**, 89-94.

NIH lead
analogues

Synthesis of TDR30139 derivatives

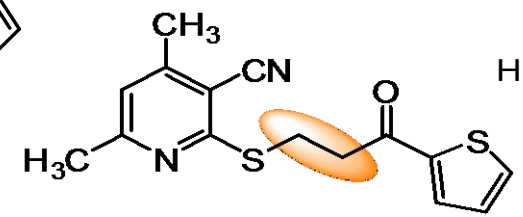


LOLA4
IC_{50} = 0.03 µM

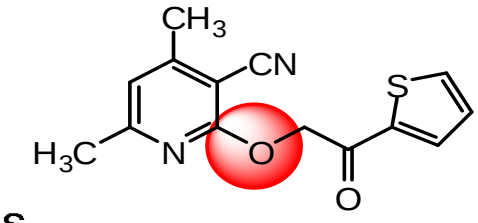


TDR91228
IC_{50} = 1.2 µM

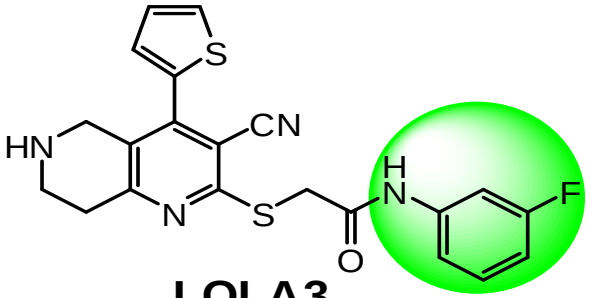
monocyclic



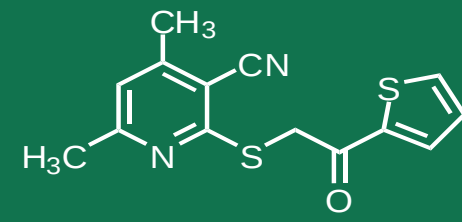
TDR100524
IC_{50} = 26 µM



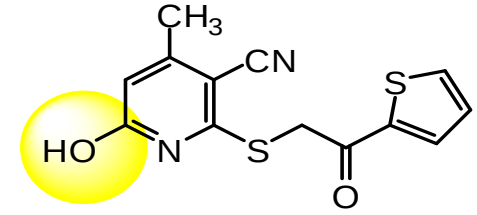
TDR100612
IC_{50} = 70 µM



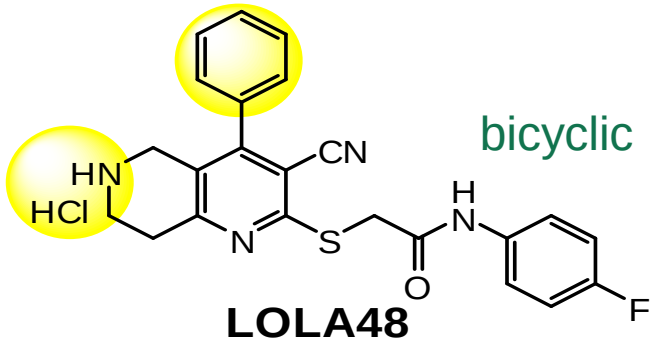
LOLA3
IC_{50} = 0.31 µM



TDR30139
IC_{50} = 0.34 µM

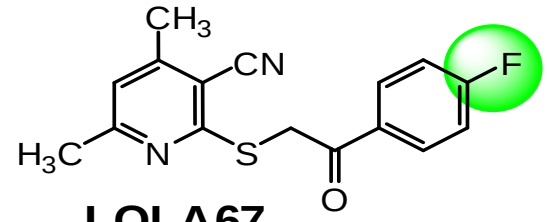


TDR95696
IC_{50} = 2.0 µM

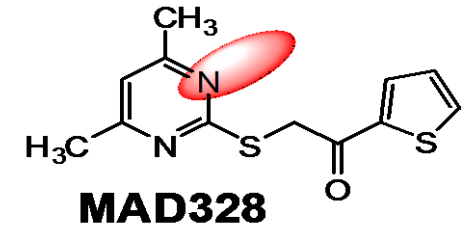


bicyclic

LOLA48
IC_{50} = 7.9 µM



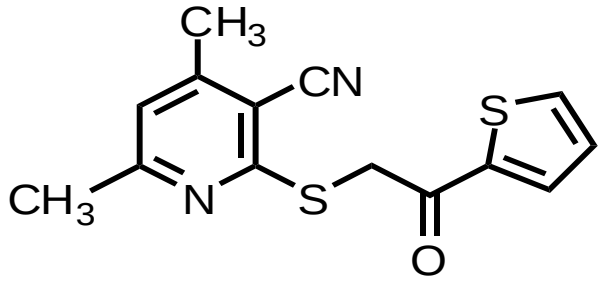
LOLA67
IC_{50} = 0.58 µM



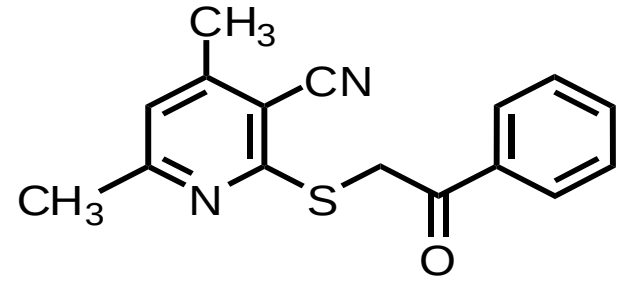
MAD328
IC_{50} > 100 µM

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

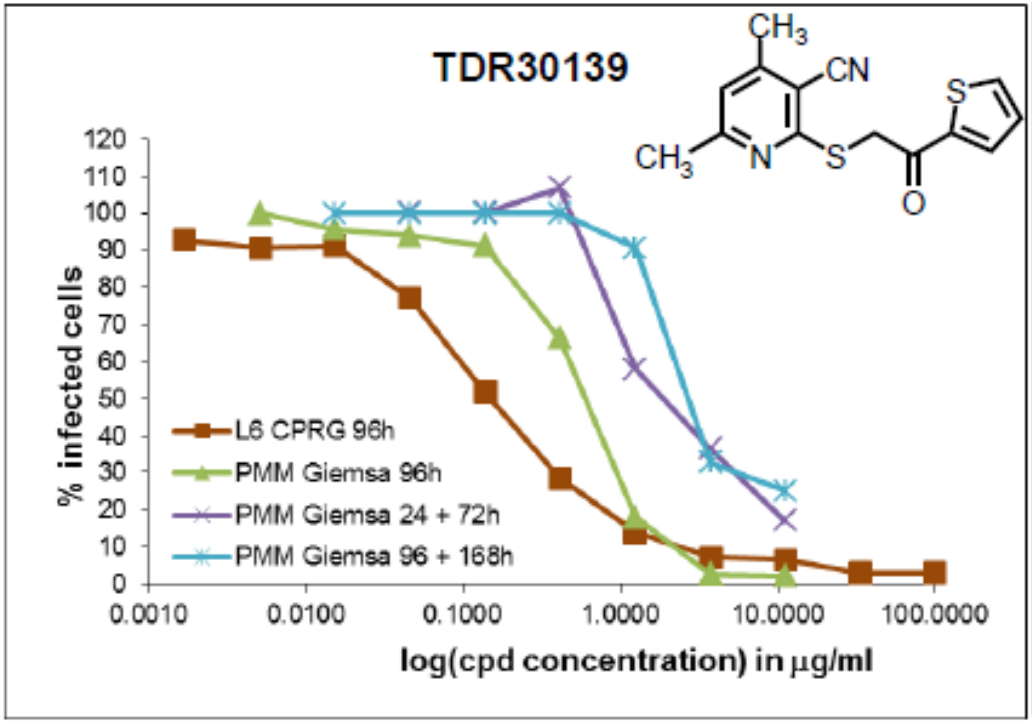
- Experiment kindly carried out by collaborators at GSK, Tres Cantos, and Dundee Drug Discovery Unit

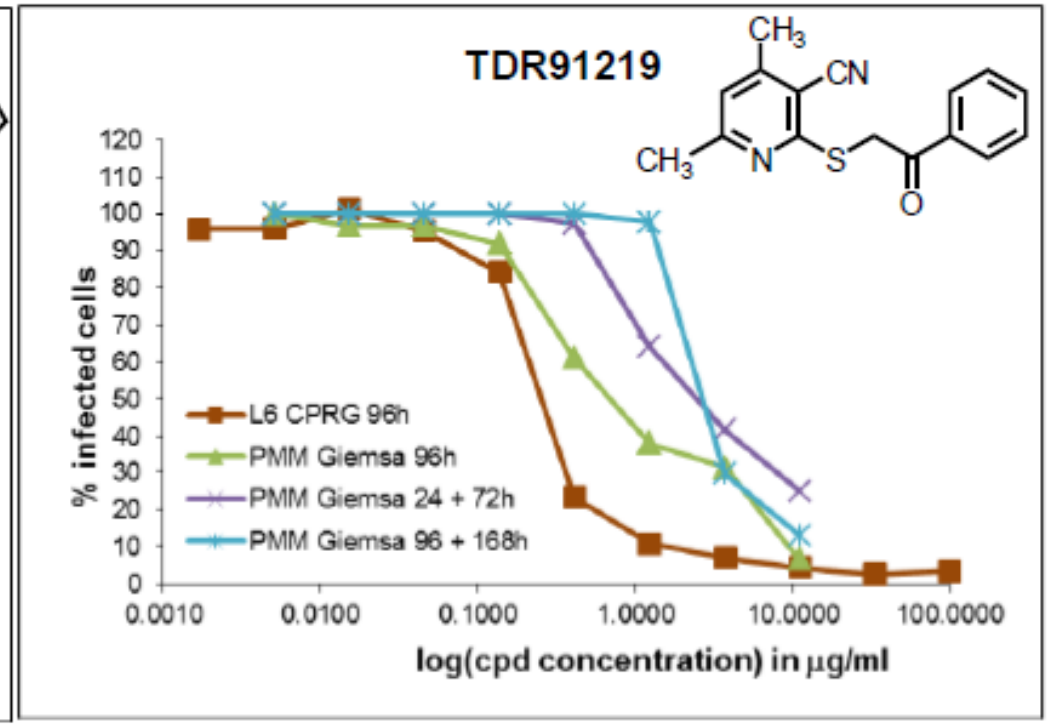
gsk
do more
feel better
live longer

Deeper characterisation of *in vitro* activity

SwissTPH

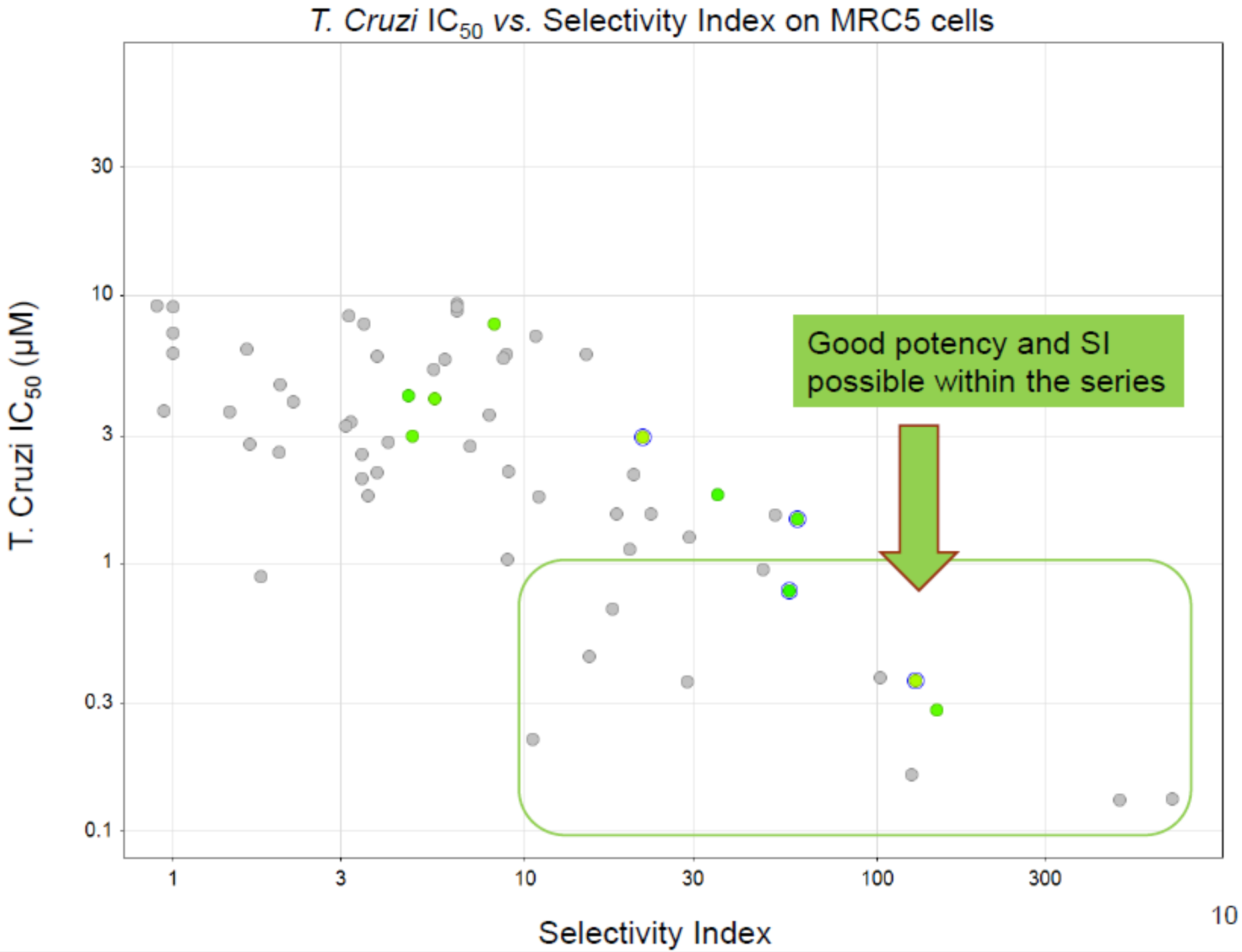
Recovery of T.cruzi amastigotes: Standard assay *vs.* wash-out



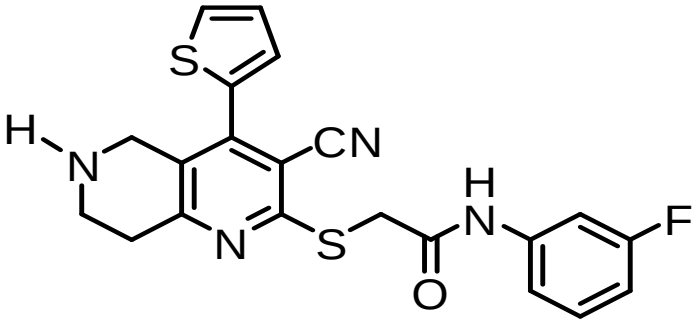


in µg/ml	L6 96h CPRG		PMM 96h Giemsa		PMM 24h + 72h Giemsa		PMM 96h +168h Giemsa	
	IC50	IC90	IC50	IC90	IC50	IC90	IC50	IC90
TDR91219	0.166	3.23	0.536	1.97	1.66	na	2.40	na
TDR30139	0.263	2.65	0.624	8.61	2.21	na	2.40	na

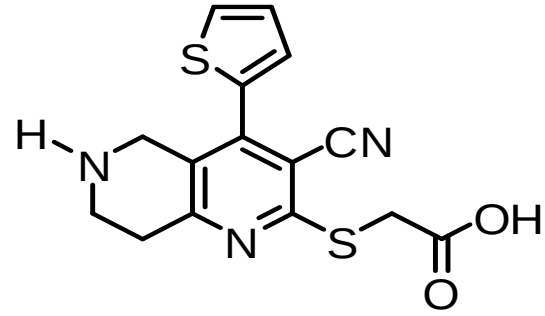
- Further confirmation of good *in vitro* activity
- Aim to test relevance of residual parasites in an *in vivo* assay


T. Cruzi IC50 vs. Selectivity Index on MRC5 cells
T. Cruzi IC50 (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

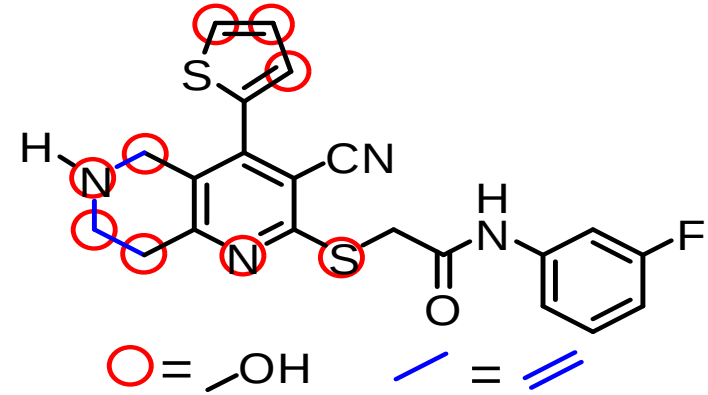
Metabolic Stability



LOLA3 (parent M = 425)
human - 96.31%
rat - 94.30%

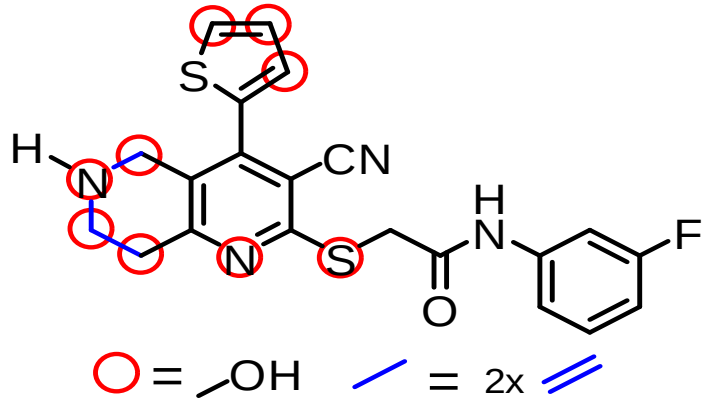


(M - 93)
rat - 5.35%



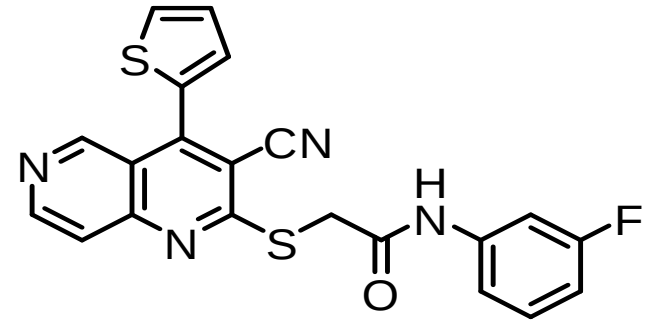
O = OH / = =

(M + 14)
human - 1.65%



O = OH / = 2x

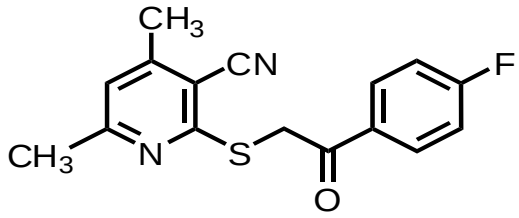
(M + 12)
human - 0.35%
rat - 1.05%



(M - 4)
human - 0.99%

- Incubation in human and rat liver microsomes (60 min, 10 µM) (AbbVie).
- However, 0% remaining in female mouse plasma at rt after 0.5 h (Wuxi).
- Amide likely unstable.

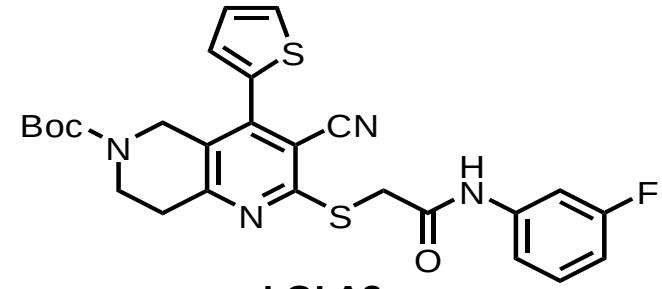
Kinetic Solubility Results



LOLA67

K.S. (pH 2.0) < 1 µM

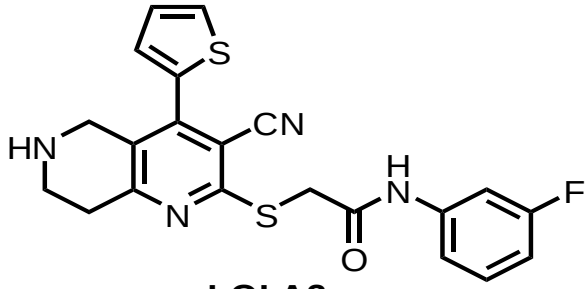
K.S. (pH 7.4) < 1 µM



LOLA2

K.S. (pH 2.0) < 1 µM

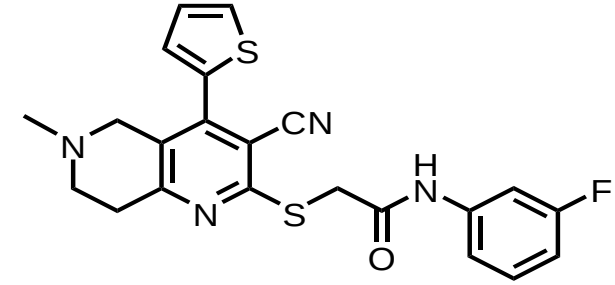
K.S. (pH 7.4) < 1 µM



LOLA3

K.S. (pH 2.0) > 200 µM

K.S. (pH 7.4) = 2.65 µM



LOLA4

K.S. (pH 2.0) > 200 µM

K.S. (pH 7.4) < 1 µM

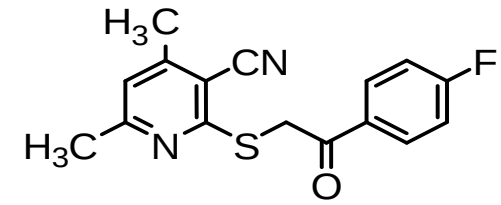
Theoretical concentration: 200 µM

K.S. Buffer: 50 µM phosphate buffer, pH 2.0 and 7.4

Formulation studies on LOLA67

In vivo (mouse) PK studies

Acute mouse model of Chagas Disease

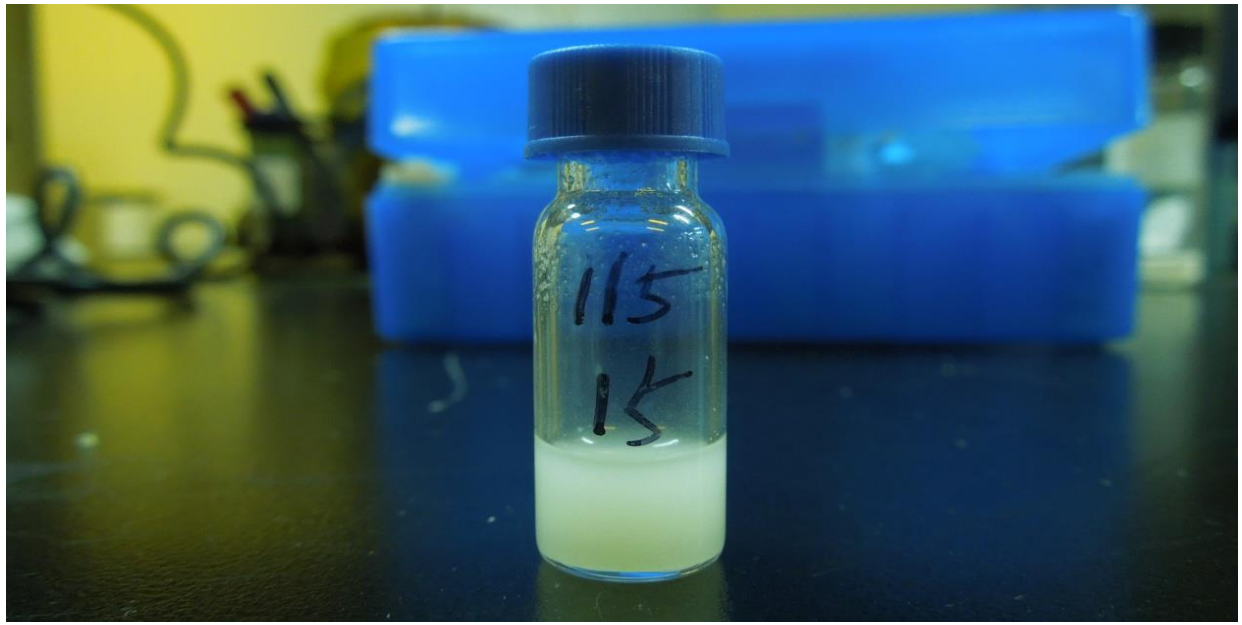


LOLA67

(MAD431)

IC_{50} = 0.58 μM

cLogP = 3.74 ± 0.53



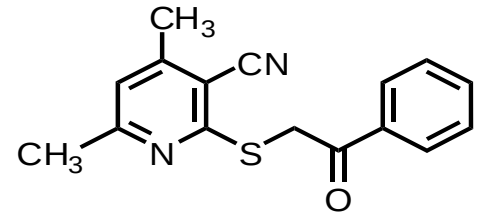
Poor plasma solubility

10 mg/mL

10% DMSO,
10% Cremophor EL,
40% PEG400,
40% Water; step by step

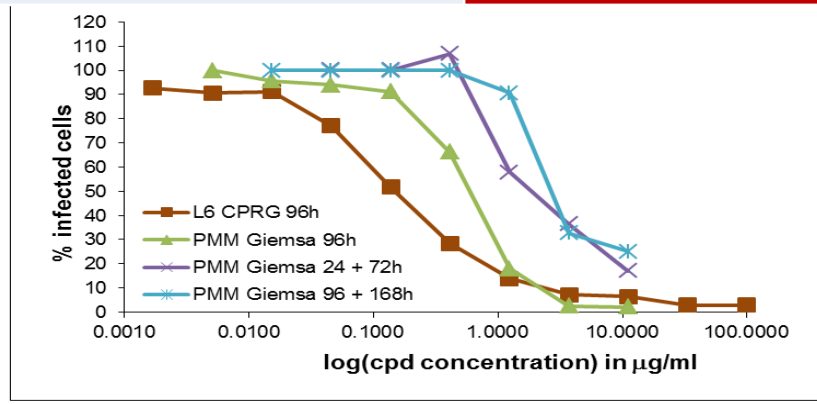
WuXi AppTec Shanghai, China

3-cyanopyridines



- Monocyclic and bicyclic subseries
- > 200 analogues synthesized for LOLA
- Sub-µM against *T. Cruzi* (*in vitro*)
- Potency not driven by CYP51 inhibition
- No cytotoxicity issues
- Good stability in human and rat liver microsomes
- Low clearance in human and rat
- *T. Cruzi* amastigote recovery <100% inhibition (limited by solubility)
- CN, C=O, Pyr, side chain, Me groups aryl ring very important
- **Increase solubility**

Property	Value
T. Cruzi	IC_{50} = 0.7 µM
CYP51	IC_{50} > 10 µM
Cytotox MRC-5 cells	IC_{50} > 64 µM
Cytotox PMM	IC_{50} > 64 µM
Cl_{int} (human mic.)	11.8 L/hr/kg
Cl_{int} (human hep.)	16 L/hr/kg
Cl_{int} (rat mic.)	42 L/hr/kg
Cl_{int} (rat hep.)	45.7 L/hr/kg
E_{max}	< 100% inhibition
solubility	poor

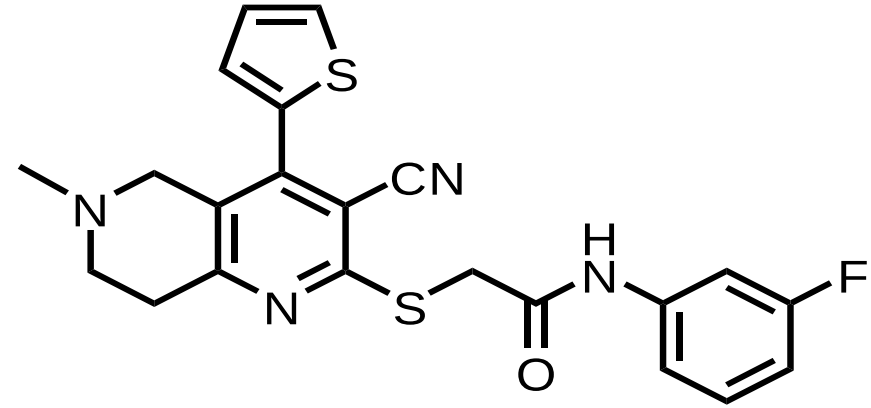


IV - Solution in 60% PEG400, 50 mM sodium citrate, pH 4.5.

PO- Solution in 25% hydroxypropyl-β-cyclodextrin, 50 mM sodium citrate, pH 3.3.

Bicyclic series - Issues

- > 40 analogues synthesized for LOLA
- Very variable *in vitro* results
- Low oral bioavailability from mouse PK
- Amides unstable in plasma
- More soluble analogues less active
- Challenging to achieve *in vivo* POC



Property	IC_{50} (µM)
T. Cruzi (LMPH)	54.86, 0.03, 0.03 >64 retest >64, 26.9 new batch
T. Cruzi (LMQC)	2.01 ± 0.37
Cytotox MRC-5 cells	>64, 52.9, 30 25.4, >64 retest >64, 34.3 new batch

Acknowledgements

Glaucius Oliva, Adriano Andricopulo, Marco Dessoy, Pablo Martinez and Celso Oliveira (+ Paul Koovits – 02-2016)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Yvonne C. Martin, and Dale Kempf

Alan Brown

Marcel Kaiser

Manu De Rycker

James Mills

Wen Hua

Charlie Mowbray and Simon Campbell

PREAC

Pró-Reitoria de Extensão e Assuntos Comunitários

Prof. Dr. João Frederico da Costa Azevedo Meyer
Vice-President for Extension and Outreach

INOVA UNICAMP

Innovation Agency

UNICAMP

ANO 50

IQ Instituto de Química