INCT

National Institute of Science and Technology of Drugs and Medicines

INOFAR

ANNUAL ACTIVITIES REPORT

2015

INOFAR

INCT

National Institute of Science and Technology of Drugs and Medicines

INCT OF DRUGS AND MEDICINES

INCT-INOFAR (The National Institute of Science and Technology in Drugs and Medicines) is a wide research network, which brings together renowned scientists from several higher education institutions both national and international.

ANNUAL ACTIVITIES REPORT

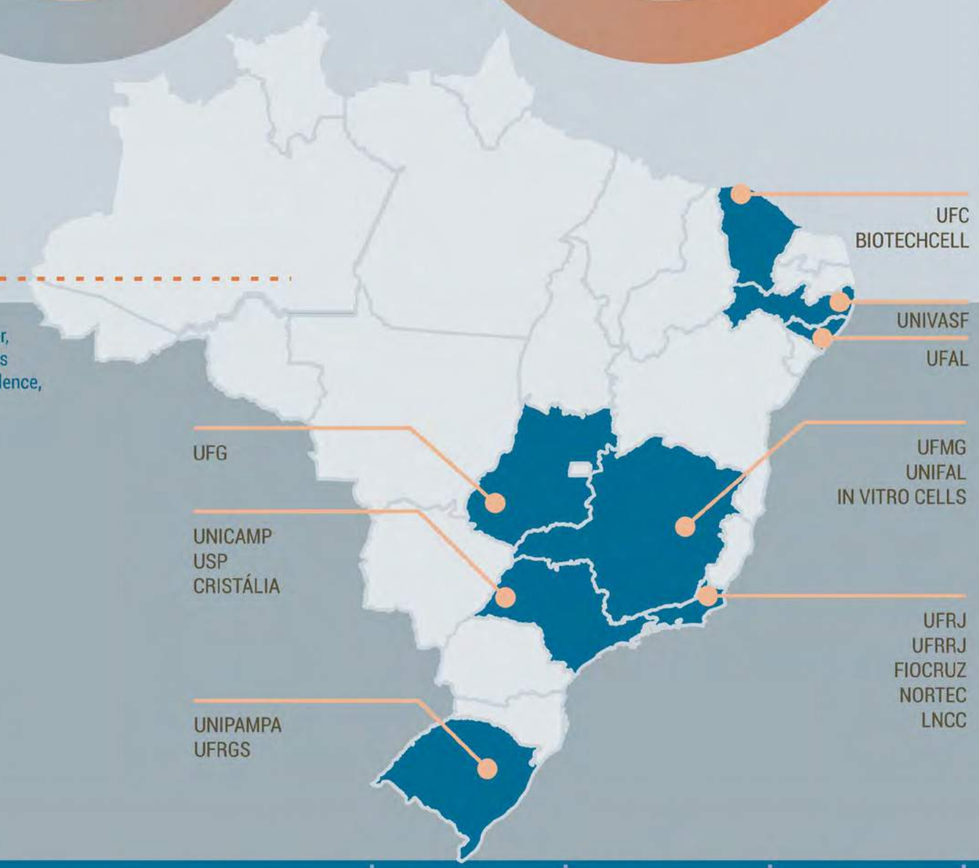
2015

INCT-INOFAR studies, researches, and develops several subprojects for the discovery of new drugs and medicines (radical innovation), new synthetic routes for generic drugs (incremental innovation)...

...and works in the professional qualification of undergraduate and graduate students in Medicinal Chemistry and Pharmacology, which are central disciplines in the complex process of drug discovery and development.

MAP OF RESEARCH NETWORK

INCT-INOFAR brings together, in a network, research groups of academic-scientific excellence, in different areas



PHARMACEUTICAL INNOVATION

In the field of radical innovation, **INCT-INOFAR** aims to discover/invent original substances, active in pharmacological models *in vivo* and *in vitro*, widely validated, capable of originating new drug candidates in different therapeutic classes.

The main research areas of interest to **INCT-INOFAR** are: inflammation, pulmonary diseases, pain, central nervous system, cardiovascular system, and chemotherapy of cancer and of neglected diseases, in particular leishmaniasis.

GENERIC ROUTES

In incremental innovation, **INCT-INOFAR** leads projects focused on the discovery of new synthetic routes, efficient and accessible, both for generic drugs already in the market, as well as for those drugs, which are about to have their patent protections expire.

03	08	04	14	23	26
INTERNATIONAL INSTITUTIONS	BRAZILIAN STATES	ASSOCIATED COMPANIES	RESEARCH INSTITUTES	RESEARCH GROUPS	CNPq SCHOLARS

inct inofar

National Institute of Science and Technology of Drugs and Medicines

ACTIVITIES

REPORT 2015

INCT-INOFAR makes efforts towards the study and development of generic drugs with the goal of transferring the technology acquired to local industry.

By studying and developing total synthetic routes of generic drugs, advanced intermediates and strategic raw materials for the pharmaceutical sector, the research conducted by **INCT-INOFAR** paves the way, in Brazil, for the production of drugs that represent important instruments for public health policies and for the pharmaceutical care of the population.

GENERIC ROUTES

In the past few years, INCT-INOFAR researchers finished the synthesis of five important generic drugs: Atorvastatin, Sunitinib, Fluoxetine, Valsartan and Dasatinib.

1. Widely used statin for cholesterol reduction, it is one of the best-selling drugs in the world.
2. Important therapeutic alternative used in the treatment of kidney and gastrointestinal cancers.
3. Antidepressant used in the control of several Central Nervous System disorders.
4. Drug widely used in the treatment of arterial hypertension.
5. Anticancer drug used in the treatment of chronic myeloid leukemia and acute lymphoblastic leukemia.

ATORVAS TATIN

SUNITINIB

FLUOXE TINE

VALSAR TAN

DASATINIB

353.998
A613a

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inct inofar instituto nacional de ciência e tecnologia de Fármacos e Medicamentos
www.inct-inofar.ccs.ufrj.br

CNPq 60 ANOS · DECIT · FAPERJ · inct institutos nacionais de ciência e tecnologia

ANNUAL ACTIVITIES REPORT **2015**

INCT of drugs and medicines

INCT-INOFAR HEADQUARTERS

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EDITORIAL AAR 2015

DEAR COLLEAGUES,

This is the seventh edition of the Annual Activities Reports (AAR) of National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) describing all activities performed in 2015. There is a decent chance that this is the last edition of the **INCT-INOFAR** project, started in 2009. CNPq approved this scientific project from a selection after a notice for INCT, replacing the former Millennium Institutes. From then on, our **INCT-INOFAR** community, including all scientific and support workers, lived a very friendly and productive time, working on distinct scientific projects on drug discovery (**DD**)developed in different laboratories from different Institutions.

A brief retrospective look indicates that our project, *i.e.***INCT-INOFAR**, is a truly success case, not only in the sense of a new drug discover approach, but also in the perspective of being a real and active **DD** network. An outlook of the Brazilian scientific experience in **DD** easily indicates that **INCT-INOFAR** is a unique experience and in my opinion,it represents one of our principal achievements. Obviously, all scientific results obtained from the running projects are very important indeed and have generated an amazing scientific production -more than one thousand and thirty publications in peer-reviewed scientific journals, during this period. This is an impressive result, of course! Other great achievement of **INCT-INOFAR** is the formation of human resources: the number of MSc and PhD thesis concluded in this period by young researchers comprehendeda total of 166 MSc dissertations and 209 PhD thesis! These young scientists represent the next generation of Brazilian drug discovers.

Seven editions-from the 16th (2010) to the 22th (2016) - of the Summer School on Medicinal Chemistry were sponsored by LASSBio/ICB-UFRJ with partial support of **INCT-INOFAR**, and this also represents an important activity of personal formation dedicated to innovation in **DD** process. In fact, many others important achievements could be described here, all of them with enormous impact on the Brazilian scientific capacity to work on innovation on drugs and medicines. I will not mention more for not discouraging you to read this **AAR-2015**. As you will see, in this 2015-edition a different format from the formers was adopted, putting together some of the featured activities of each year from 2009 to 2014. This edition of **AAR** is being disclosed during the 10th Follow-up Meeting of **INCT-INOFAR**, with less than six months from the end of the project and it is time to acknowledge all collaborators for the excellent work performed during this way. I want to express a special acknowledgment to the members of the Scientific Advisory Committee (**CGA**), including all support staff, for the impressive job done, making my own a very simple task!

Nowadays, the Brazilian economic situation promotes severe constraints in the policy to Science, Technology and Innovation, rendering almost impossible to preview the continuity of INCT Program. Due to this uncertain situation, it could not be impossible to find me around here on a next **AAR** editorial, in the case of an INCT new edition approval!

Eliezer J. Barreiro
(for one last time (?), Editor, **INCT-INOFAR/AAR**´s)

SUMMARY

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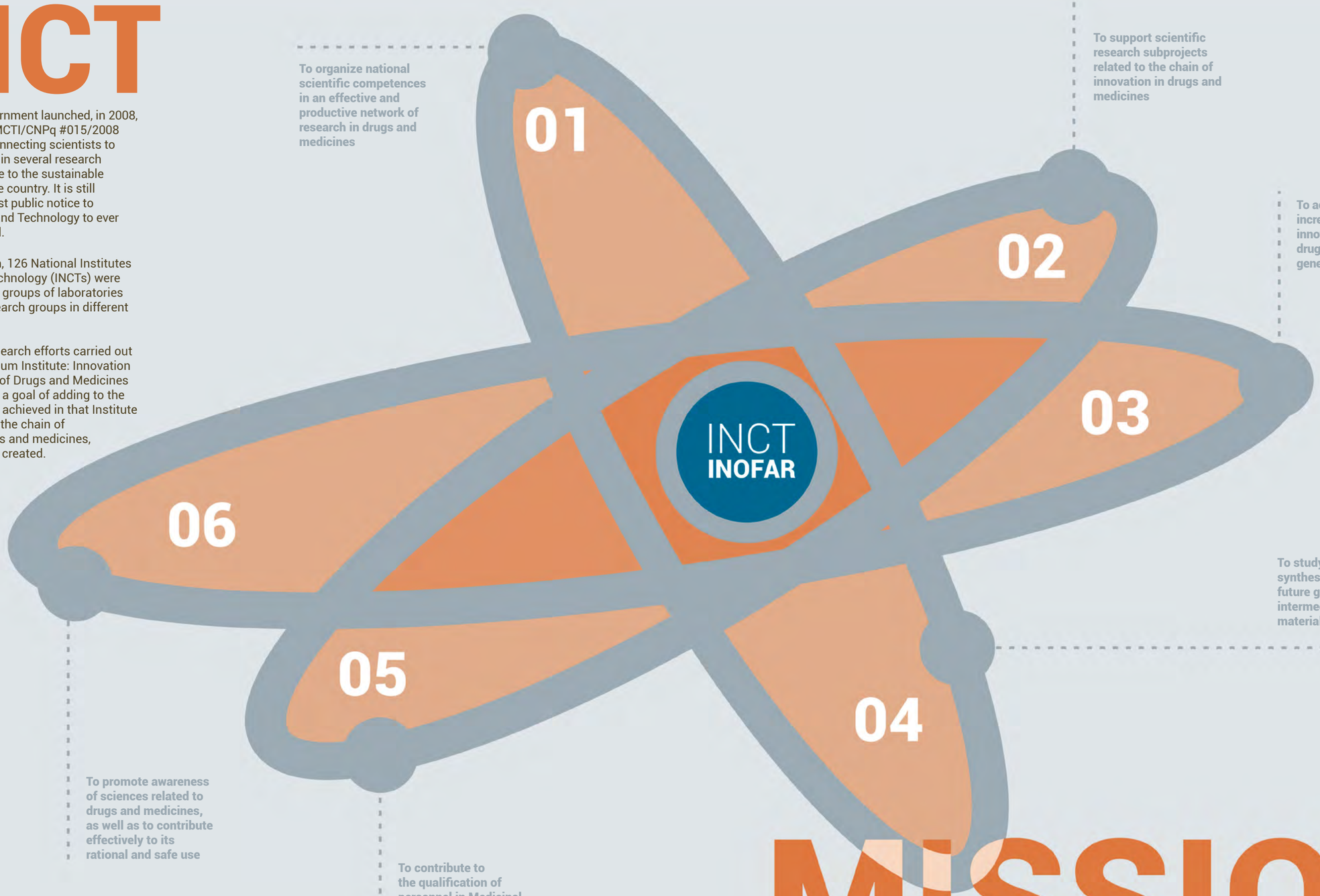
INCT

The Brazilian government launched, in 2008, the public notice MCTI/CNPq #015/2008 with the goal of connecting scientists to work in a network, in several research areas, to contribute to the sustainable development of the country. It is still currently the largest public notice to promote Science and Technology to ever take place in Brazil.

From that point on, 126 National Institutes of Science and Technology (INCTs) were created, gathering groups of laboratories or associated research groups in different parts of Brazil.

Continuing the research efforts carried out within the Millennium Institute: Innovation and Development of Drugs and Medicines (IM-INOFAR), with a goal of adding to the expressive results achieved in that Institute and to advance in the chain of innovation in drugs and medicines, **INCT-INOFAR** was created.



MISSION

INCT-INOFAR RESEARCH GROUPS

LABORATORIES AND CHIEF RESEARCHERS

NETWORK COORDINATOR

Prof. Eliezer J. Barreiro (LASSBio/UFRJ)

RIO DE JANEIRO

FIOCRUZ
1

Oswaldo Cruz Institute
Laboratory of Inflammation
Marco Aurelio Martins
Patricia Machado Rodrigues e Silva Martins

LNCC
3

National Laboratory of Scientific Computing
Molecular Modeling of Biological Systems Group
Laurent Emannuel Dardenne

UFRJ
4

Institute of Biomedical Sciences - ICB
Laboratory of Evaluation and Synthesis of Bioactive Substances - LASSBio
Carlos Alberto Manssour Fraga
Lidia Moreira Lima

5

Laboratory of Biochemical and Molecular Pharmacology
Francois Germain Noel

6

Laboratory of Cardiovascular Pharmacology
Gisele Zapata Sudo

7

Laboratory of Muscular Excitation-Contraction Coupling
Roberto Takashi Sudo

8

Laboratory of Pharmacology of Pain and Inflammation
Patricia Dias Fernandes

9

School of Chemistry - EQ
Information System on the Chemical Industry
Adelaide Maria de Souza Antunes

UFRRJ
10

Department of Chemistry
Institute of Exact Sciences
Carlos Mauricio Rabello de Sant'Anna

SÃO PAULO

USP
11

Laboratory of Design and Synthesis of Chemotherapeuticals Potentially Active in Neglected Diseases (LAPEN)
Elizabeth Igne Ferreira

12

Ribeirão Preto Campus
Faculty of Medicine
Laboratory of Pain and Inflammation
Fernando de Queiroz Cunha

UNICAMP
13

Institute of Chemistry
Laboratory of Synthetic Organic Chemistry
Luiz Carlos Dias

MINAS GERAIS

UFMG
14

Department of Chemistry - Icex
Laboratory of Inorganic Medicinal Chemistry (LABQUIM)
Heloisa de Oliveira Beraldo

UNIFAL
15

Institute of Chemistry
Laboratory of Phytochemistry and Medicinal Chemistry
Claudio Viegas Junior

16

Innovation and Entrepreneurship Agency (I9)
Marcia Paranho Veloso

RIO GRANDE DO SUL

UFRGS
17

Faculty of Pharmacy
Laboratory of Experimental Psychopharmacology
Stela Maris Kuze Rates

UNIPAMPA
18

Uruguaiana Campus - RS
Laboratory of Pharmacology (LABFAR)
Sandra Elisa Haas

GOIÁS

UFG
19

Faculty of Pharmacy
Laboratory of Bioconversion
Valeria de Oliveira

20

School of Veterinary and Animal Husbandry
Laboratory of Veterinary Cardiology
Rosangela de Oliveira Alves Carvalho

ALAGOAS

UFAL
21

Institute of Biological and Health Sciences - ICBS
Laboratory of Pharmacology and Immunity
Magna Suzana Alexandre Moreira

CEARÁ

UFC
22

Department of Physiology and Pharmacology
Laboratory of Experimental Oncology
Claudia do Ó Pessoa

PERNAMBUCO

UNIVASF
23

Nucleus of Studies and Research in Medicinal Plants (NEPLAME)
Jackson Roberto Guedes da Silva Almeida

2015 ORGANIZATION CHART

COORDINATOR
Prof. Dr. Eliezer J. Barreiro
(UFRJ)

VICE-COORDINATOR
Prof. Dr. Fernando de Q. Cunha
(USP-Ribeirão Preto)

MONITORING AND FOLLOW-UP COMMITTEE (CGA)
Prof. Dr. Elizabeth Igne Ferreira (USP)
Prof. Dr. Heloisa de Oliveira Beraldo (UFMG)
Prof. Dr. Luiz Carlos Dias (UNICAMP)
Prof. Dr. Marco Aurélio Martins
(FIOCRUZ-RJ)

SCIENTIFIC CONSULTING
Prof. Dr. Simon Campbell (UK)
Prof. Dr. Timothy Williams (UK)
Prof. Dr. Stefan A. Laufer (Germany)
Prof. Dr. Julio Urbina (USA)

SECRETARY OF COMMUNICATION

FINANCIAL SECRETARY

EXECUTIVE SECRETARY

SECRETARIES

OUTREACH ACTIVITIES SECRETARY

ASSOCIATED RESEARCH GROUPS
08 Brazilian States
14 Research Institutes
23 Research Groups
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03 International Institutions

SECRETARY OF INTERNATIONAL AFFAIRS
Prof. Dr. Carlos Alberto Manssour Fraga (UFRJ)

SCIENTIFIC SUPERINTENDENT
Prof. Dr. Lídia Moreira Lima
(UFRJ)

ASSOCIATED COMPANIES

***INCT-INOFAR** counts on the support of four pharmaceutical industries: In Vitro Cells Toxicology Research PLC, BiotechCell, Cristália Chemical Pharmaceutical Properties Ltd., and Nortec Chemistry PLC.*

IN VITRO CELLS
Toxicological Research PLC

With its technological base at the Biominas Foundation in Belo Horizonte, MG, the company helps **INCT-INOFAR** in the process of *in vitro* bioassays of evaluation of safety and efficacy of new drug candidates developed by the Institute.

CRISTÁLIA
Chemical Pharmaceutical Products Ltd.

Located in São Paulo, the company supports eventual pharmaceutics stages of development of new prototype compounds that reach this advanced stage in the chain of innovation in drugs and medicines.

BIOTECHCELL

Biotechnology company located in the Northeast region, acting in research and services of pre-clinical pharmacology, human biomonitoring, toxicogenetics and applied toxicology.

NORTEC
Chemistry

Located in Rio de Janeiro, the 100% Brazilian Pharmachemical Company is fully interested in partnering with **INCT-INOFAR** in the production of active pharmaceutical principles, and has already received the Award of Excellence in the Supply of Raw Materials, from the Pharmaceutical Industries Union of São Paulo (SINDUSFARMA).

INTERNATIONAL AGREEMENTS

*Through the signing of international cooperation agreements, **INCT-INOFAR** makes efforts to internationalize its research network with the goal of development projects in partnership with researchers from different countries, promote the exchange of professionals, organize international academic and scientific activities, and increase visibility for science, technology, and innovation actions in Brazil.*

Through this internationalization, important cooperation networks are built, offering training and qualification opportunity abroad for graduate and undergraduate students, as well as the exchange of materials and publications relevant in the field of Medicinal Chemistry.

INCT-INOFAR INTERNATIONAL COOPERATION NETWORK

The internationalization actions follow the recommendations provided by the National Council for Scientific and Technological Development (CNPq) and fall in line with the philosophy adopted by the Science without Borders program.

*Currently, **INCT-INOFAR** collaborates with three international Educational and Research Institutions, conducting exchange of its researchers with experts in Germany, Italy, and Uruguay.*

GERMANY

Interdisciplinary Center for Pharmacogenomics and Pharma Research (ICEPHA)

University of Tübingen, Germany.

Chief Researcher: Professor Stefan Laufer

ITALY

Department of Pharmaceutical Sciences

University of Ferrara, Italy.

Chief Researcher: Professor Píer G. Baraldi

URUGUAY

Department of Organic Chemistry National University of La Republica, Uruguay

Chief Researchers: Professors Hugo Cerecetto and Mercedes González

INCT INOFAR SCHOLARS

OSWALDO CRUZ FOUNDATION
FIOCRUZ/RJ

1) Bianca Torres Ciambarella CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: July 2013 to January 2014
Project: *"Studies of potential cellular targets and action mode of LASSBio-897 compound in control of experimental silicosis."*
Advisor: Prof. Dr. Patricia Machado Rodrigues e Silva Martins
FIOCRUZ/RJ

2) Julio Beltrame Daleprane CV-Lattes
CNPq Technological Development Scholarship – DTI-1
Time: December 2011 to February 2012
Project: *"Study of the potential anti-inflammatory effect of compound LASSBio 897, in models of silicosis and asthma."*
Advisor: Prof. Dr. Marco Aurelio Martins
FIOCRUZ/RJ

3) Vinicius Frias de Carvalho CV-Lattes
CAPES Post-doctoral Scholarship
Time: March 2010 to February 2012
Project: *"Study of pharmacological interaction of LASSBio-897 and LASSBio-294 with adenosine receptors in living cells."*
Advisor: Prof. Dr. Marco Aurelio Martins
FIOCRUZ/RJ

FEDERAL UNIVERSITY OF ALFENAS
UNIFAL

4) André Victor Pereira CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: June 2012 to May 2013, September 2013 to June 2014, August 2014 to December 2014, January 2015 to June 2015
Project: *"Technological foresight of intermediaries and synthetic chemical entities of interest in the scope of the **INCT-INOFAR**."*
Advisor: Prof. Dr. Marcia Paranho Veloso

STATE UNIVERSITY OF CAMPINAS
UNICAMP

5) Adriano Siqueira Vieira CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: August 2009 to June 2011
CNPq Technological Development Scholarship – DTI-1
Time: July 2011 to March 2012
Project: *"Synthesis of Atorvastatin"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

6) Elsa Moreno de Viguri CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: April 2013 to March 2014
Project: *"New quinic acid derivatives as Trypanosoma cruzi trans-sialidase inhibitors"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

7) Ellen Christine Polo CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: June 2015 to November 2015
Project: *"Synthesis of Dasatinib drug"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

8) Javier Ceras Arrese CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: April 2013 to March 2014
Project: *"Synthesis of Valsartan"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

9) Leila de Souza Conegero CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: July 2010 to January 2011
Project: *"Synthesis of Fluoxetine"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

10) Maitia Labora Poggi CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: March 2014 to October 2014
Project: *"Development of new anti-Chagas trans-sialidase inhibitor prototypes"*
Advisor: Prof. Dr. Luiz Carlos Dias
Institute of Chemistry

FEDERAL UNIVERSITY OF CEARÁ
UFC

11) Bruno Coêlho Cavalcanti CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: May 2010 to December 2010
Project: *"In vitro evaluation of cytotoxic, genotoxic and mutagenic potential of samples provided by **INCT-INOFAR**."*
Advisor: Prof. Dr. Leticia Veras Costa Lotufo
Unity of Clinical Pharmacology

FEDERAL UNIVERSITY OF GOIÁS
UFG

12) Ana Maria Calçado dos Santos CV-Lattes
CNPq Technical Support Scholarship – AT NM
Time: July 2010 to June 2011
Project: *"In silico prediction and in vitro production of pharmaceutical prototype candidates through bioconversion of human metabolites"*
Advisor: Prof. Dr. Valeria de Oliveira
Faculty of Pharmacy

13) Geovana Bárbara Ferreira Mendes CV-Lattes
CNPq Technical Support Scholarship – AT NM
Time: March 2013 to January 2014
Project: *"In silico prediction and in vitro production of pharmaceutical prototype candidates through bioconversion of human metabolites"*
Advisor: Prof. Dr. Valeria de Oliveira
Faculty of Pharmacy

14) Sarah da Silva Nunes CV-Lattes
CNPq Technical Support Scholarship – AT NM
Time: July 2011 to December 2011, February 2012 to July 2012 and September 2012 to February 2013
Project: *"In silico prediction and in vitro production of pharmaceutical prototype candidates through bioconversion of human metabolites"*
Advisor: Prof. Dr. Valeria de Oliveira
Faculty of Pharmacy

FEDERAL UNIVERSITY OF MINAS GERAIS - UFMG

15) Carolina Neris Cardoso CV-Lattes
CNPq Technological Initiation – ITI A
Time: September 2011 to January 2012
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

16) Carolina Maldonado Galassi CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: October 2009 to March 2013
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

17) Gabrielle Luck de Araujo CV Lattes
CNPq Junior Post-Doctorate Scholarship – PDJ
Time: July to December 2011
Project: *"Benzaldehyde Semicarbazone (BS): toxicological aspects"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

18) Isabella Pires Ferreira CV Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: June to November 2014
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Heloisa de Oliveira Beraldo
Institute of Exact Sciences

19) Manuela de Lima Toccafondo Vieira CV Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: May to October 2013
Project: *"PBPK Modelling and Simulation of LASSBIO-596 Compound"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

20) Marcus Vinícius dos Santos CV-Lattes
CNPq Technological Initiation – ITI A
October 2009 to March 2010
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

21) Nathalia Freitas Emiliano CV-Lattes
CNPq Technological Initiation – ITI A
Time: September 2011 to January 2012
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

22) Samira de Sá e Souza CV-Lattes
CNPq Technological Initiation – ITI A
Time: September 2011 to January 2012
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Carlos Alberto Tagliatti
Faculty of Pharmacy

23) Wallace Carvalho Ferreira CV-Lattes
CNPQ Technical Support Grant– AT NM
Time: August 2009 to January 2010
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Professor Dr. Marcio de Matos Coelho
Faculty of Pharmacy

FEDERAL UNIVERSITY OF RIO GRANDE DO SUL - UFRGS

24) Moacir Kaiser CV-Lattes
CNPQ Technological Development Grant– DTI-3
Time: July 2009 to March 2010
Project: *"Evaluation of pharmacokinetic profile of LASSBio-468."*
Advisor: Prof. Stella Maris Kuze Rates

FEDERAL UNIVERSITY OF RIO DE JANEIRO - UFRJ

25) Allan Kardec Nogueira de Alencar CV-Lattes
CNPQ Technical Support Grant– AT NM
Time: April to August 2010
Project: *"Development of new substances for the reduction of ventricular dysfunction, caused by arterial and pulmonary hypertension."*
Advisor: Prof. Roberto Takashi Sudo
Institute of Biological Sciences (ICB)

26) Alan Rodrigues de Sousa CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: February 2012 to June 2014
CNPq Technological Support Scholarship – AT NM
Time: August to 2012 to August 2013
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

27) Alexandra Basílio Lopes CV-Lattes
CNPQ Technological Development Grant– DTI-3
Time: June to September 2010
Project: *"Synthesis and evaluation of antinociceptive and anti-inflammatory activities of phenyl-pyridine-N-acylhydrazone compounds planned from imidazo [1,2-a] pyridine-N-acylhydrazone derivatives."*
Advisor: Prof. Eliezer J. Barreiro
LASSBio

28) Ana Carla dos Santos CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: July 2009 to June 2010
CNPq Technological Development Scholarship – DTI-2
Time: July to 2010 to June 2011
CNPq Technological Development Scholarship – DTI-1
Time: July 2011 to March 2012
CNPq Technical Support Scholarship – AT NS
Time: April 2012 to August 2012
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

29) Ana Cristina da Mata Silva CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: April 2012 to May 2013
CNPq Technological Development Scholarship – DTI-2
Time: June 2013 to August 2014
CNPq Technological Development Scholarship – DTI-1
Time: September 2014 to March 2015
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

30) Ana Gabriela de Almeida Silva CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: March 2013 to August 2013
Project: *"Implementation and validation of pre-clinical trial model for the evaluation of the teratogenic effect of bioactive substances: evaluation of the LASSBio 468 and LASSBio 596 prototypes"*
Advisor: Prof. Dr. Aloa Machado de Souza
LASSBio

31) Arthur Eugen Kümmerle CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
September 2009 to March 2010
Project: *"Study of the Inclusion of LASSBio-579 in cyclodextrin."*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

32) Arthur Henrique Freitas do Prado CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: May 2011 to February 2012
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

33) Bárbara Assis Novak CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: September 2012 to February 2013
Project: *"Implementation and validation of pre-clinical trial model for the evaluation of the teratogenic effect of bioactive substances: evaluation of the LASSBio 468 and LASSBio 596 prototypes"*
Advisor: Prof. Dr. Aloa Machado de Souza
LASSBio

34) Camila Ruis Frutuoso Gomes CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: June 2015 to July 2016
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

35) Carlos Eduardo da Silva Monteiro CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: May 2010 to February 2011
Project: *"Multitarget activation: strategy for symptomatic treatment of neuropathic pain."*
Advisor: Prof. Dr. Roberto Takashi Sudo
Institute of Biological Sciences (ICB)

36) Clemilson Berto Junior CV-Lattes
CAPES Master Scholarship
Time: October 2011 to March 2012
Project: *"Evaluation of teratogenic potential of LASSBio 596 and LASSBio 468 prototypes, antiasthmatic pharmaceutical candidates"*
Advisor: Prof. Dr. Aloa Machado
LASSBio

37) Daniel Nascimento do Amaral CV-Lattes
CAPES Master Scholarship
Time: March 2010 to February 2012
Project: *"Design, synthesis and pharmacological evaluation of new antitumor ß –tubulin inhibitor prototypes"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

38) Douglas Rodrigues Outeiro de Oliveira CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: September 2013 to November 2014
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

39) Edna Maria de Oliveira Ferreira CV-Lattes
CNPq Technological Development Scholarship – DTI-1
Time: September 2014 to November 2015
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

40) Fabricio Maia da Silva Salvador CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: October 2012 to July 2013
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

41) Fanny Nascimento Costa CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: July 2013 to December 2013
Project: *"The use of polycrystalline X-ray diffraction in the structural determination of new drug candidate N-acylhydrazone derivatives."*
Advisor: Prof. Eliezer J. Barreiro
LASSBio

42) Givanildo Santos da Silva CV-Lattes
CAPES Doctoral Grant
October 2009 to August 2010
Project: *"Studies for the discovery of new anti-influenza, neuraminidase inhibitor prototypes."*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

43) Hannah Carolina Tavares Domingos CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: September 2011 to February 2012
Project: *"Qnint"*
Advisor: Prof. Dr. Claudia Rezende
Institute of Chemistry

44) Jean Marcell Marcelino Pena CV-Lattes
CNPQ Technical Support Grant– AT NM
From November 2013 to June 2014 and September to December 2014
Project: *"Development of a new synthetic route for preparation of generic drugs clozapine and quetiapine"*
Advisor: Prof. Dr. Angelo da Cunha Pinto
Institute of Chemistry

45) Jéssica Silva dos Santos CV-Lattes
CNPQ Technical Support Grant– AT NM
From October to December 2010
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

46) Juliana Fátima Vilachã Madeira Rodrigues dos Santos CV Lattes
CNPq Technical Support Scholarship – IC
Time: March 2012 to Mar 2013, November 2015 to July 2016
Project: *"Planning, synthesis, and pharmacological evaluation of 1,2,3,4-tetrahydroacridine derivatives, acetylcholinesterase inhibitor prototypes."*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

47) Leandro Louback da Silva CV-Lattes
CAPES Doctoral Grant
Time: October 2009 to August 2010
Project: *"Study of the effects of different N-acylhydrazone derivatives on the cell-to-cell interaction mechanisms and inflammatory mediators that are part of the atherosclerotic process."*
Advisor: Prof. Dr. Ana Luisa Palhares de Miranda
LASSBio

48) Leonardo Ferreira de Oliveira CV-Lattes
CNPQ Technical Support Grant– AT NM
From December 2014 to July 2016
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

49) Lethycia Machado Tannuri CV-Lattes
CNPq Technological Development Scholarship – DTI-1
Time: November 2014 to July 2016
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

50) Lidilhone Hamerski Carbonezi CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: August 2010 to January 2011
Project: *"Synthesis of Sunitinib"*
Advisor: Prof. Dr. Angelo da Cunha Pinto
Institute of Chemistry (IQ)

51) Lucas Silva Franco CV-Lattes
CNPq Technical Support Scholarship – IC
Time: November 2015 to July 2016
Project: *"Planning, synthesis, and pharmacological evaluation of 1,2,3,4-tetrahydroacridine derivatives, acetylcholinesterase inhibitor prototypes."*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

52) Lúcia Beatriz Torres CV-Lattes
CNPq Technological Development Scholarship – DTI-2
Time: October 2010 to September 2011
CNPq Technological Development Scholarship – DTI-1
Time: October 2011 to July 2012 and July 2013 to February 2014
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

53) Luciana Almeida Piovesan CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: February 2009 to August 2009
Project: *"Design, Synthesis and Pharmacological Evaluation of Novel Anti-Cancer Drug-Candidate Prototypes"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

54) Luciano da Silva Santos CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: August 2011
CNPq Technical Support Scholarship – AT NS
Time: September 2011 to February 2012
Project: *"Synthesis and pharmacological activity of new ferrocene-N-acylhydrazone derivatives"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

55) Luis Eduardo Reina Gamba CV-Lattes
CAPES Doctoral Grant
Time: March 2014 to December 2014
Project: *"Design and Synthesis of New DPP4 Inhibitor Hypoglycemiant Drugs."*
Advisor: Prof. Dr. Ana Luisa Palhares de Miranda
LASSBio

56) Luis Gabriel Valdivieso Gelves CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: September 2015 to July 2017
Project: *"New 5-aryl-2-furfuryl-N-acylhydrazone derivatives functionalized with powerful anti-inflammatory and analgesic activity: LASSBio-1609, LASSBio-1636 and LASSBio-1825"*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio/UFRJ

57) Maria de Fatima do Nascimento Alfredo CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: January 2012 to September 2013
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

58) Mariana Trad Rosner da Motta CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: August 2011 to June 2012
Project: *"In vitro metabolism of new leishmanicidal and trypanomicidal pharmaceutical prototypes"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

59) Marlon Daniel Lima Tonin CV-Lattes
CNPq Technical Support Scholarship – DTI-3
Time: April to July 2012
Project: *"Novel 5-aryl-2-furfuryl-N-acylhydrazone derivatives with potent anti-inflammatory and analgesic activity: LASSBio-1609 and LASSBio-1636"*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio

60) Nailton Monteiro Nascimento Júnior CV-Lattes
CAPES Exchange Doctorate Scholarship (Dsw)
Time: March to August 2012
Project: *"Virtual screening, synthesis, and pharmacological evaluation of GPCRs ligands"*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio

61) Natalia Lacerda Alencar Peixoto CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: December 2014 to December 2015
Project: *"Synthesis of cyclodextrin complexes of LASSBio-596 salts"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

62) Natália Medeiros de Lima CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: August 2010 to July 2011
CNPq Technical Support Scholarship – DTI-2
Time: July 2013 to July 2016
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

63) Pedro Gabriel Dias Lobato Pereira CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: August to October 2011 and January 2012 to June 2012
Project: *"Synthesis of cyclodextrin complexes of LASSBio-596 salts"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

64) Priscila de Paula Cabral CV-Lattes
CNPq Technological Development Scholarship – DTI-3
Time: May 2012 to June 2012
Project: *"Scientific awareness and health education at **INCT-INOFAR**"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

65) Raquel de Oliveira Lopes CV-Lattes
CNPq Technical Support Scholarship – DTI-3
Time: October 2010 to December 2010
Project: *"Metabolic studies of LASSBio-596"*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

66) Roberta Tesch CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: June 2010 to July 2010
CAPES Master Scholarship
Time: March to April 2011
Project: *"Studies of molecular modeling and structural planning of new ligands to adenosine receptors"*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio

67) Rodolfo do Couto Maia CV-Lattes
CAPES Exchange Doctorate Scholarship (Dsw)
Time: February to July 2011
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: April 2012 to May 2012
Project: *"Synthesis and evaluation of antitumoral activity of a new family of pyrazole-pyridone compounds"*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio

68) Sabrina Teixeira Martinez CV-Lattes
CNPq Technical Support Scholarship – DTI-1
Time: September 2013 to January 2014
Project: *"Bibliographical review of methodologies of synthesis of clozapine and quetiapine"*
Advisor: Prof. Dr. Angelo da Cunha Pinto
Institute of Chemistry

69) Taís Rubia dos Santos CV-Lattes
CNPq Scientific Initiation Scholarship - IC
Time: September to November 2011, January to June 2012 and September 2012 to February 2013
Project: *"Planning, synthesis and pharmacological evaluation of new leflunomide analogs"*
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

70) Thais Emanoelle Tavares Pompeu CV-Lattes
CAPES Doctoral Grant
Time: June 2012 to August 2012
Project: *"New approaches for the in vitro study of new N-phenylpiperazines candidates for atypical antipsychotic drugs."*
Advisor: Prof. Dr. François Germain Noël
LASSBio

71) Thiago Stevanatto Sampaio CV-Lattes
CNPQ Technical Support Grant– AT NM
April 2009 to March 2010
Project: *"Design, synthesis and evaluation of cytotoxic properties of new TK inhibitor pharmaceutical candidate prototypes."*
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

FEDERAL UNIVERSITY OF THE SÃO FRANCISCO VALLEY - UNIVASF/PE

72) Juliane Cabral Silva CV-Lattes
CNPq Technical Support Scholarship – DTI-1
Time: September 2014 to December 2014
Project: *"Bibliographical review of methodologies of synthesis of clozapine and quetiapine"*
Advisor: Prof. Dr. Jackson Roberto da Silva Guedes
Center for Studies and Research of Medicinal Plants

UNIVERSITY OF SÃO PAULO
USP- RIBEIRÃO PRETO

73) Ana Kátia dos Santos CV-Lattes
CNPq Technical Support Scholarship – AT NM
Time: January to June 2012, August 2012 to June 2014 and August to December 2014
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Fernando de Queiroz Cunha
Faculty of Medicine of Ribeirão Preto

74) Danilo Roman Campos CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: February 2013 to December 2013
Project: *"Determination of the selectivity of compounds LASSBio-1609 and LASSBio-1825 on the blockage and biophysical properties of sodium channels Nav 1.8 and 1.9."*
Advisor: Prof. Dr. Carlos Alberto Manssour Fraga
LASSBio/UFRJ

75) Giuliana Bertozi Francisco CV-Lattes
CNPq Technical Support Scholarship – AT NM
Time: September 2010 to December 2011
Project: *"Benzaldehyde Semicarbazone (BS)"*
Advisor: Prof. Dr. Fernando de Queiroz Cunha
Faculty of Medicine of Ribeirão Preto

76) Jaqueline Raymondi Silva CV-Lattes
CNPq Junior Post-Doctorate Scholarship - PDJ
Time: October 2015 to July 2016
Project: *"Determination of the selectivity of compounds LASSBio-1609 and LASSBio-1825 on the blockage and biophysical properties of sodium channels Nav 1.8 and 1.9."*
Advisor: Prof. Dr. Fernando de Queiroz Cunha
Faculty of Medicine of Ribeirão Preto

STATISTICS BY TYPE OF SCHOLARSHIP

CNPq
JUNIOR POST-DOCTORATE (PDJ) – 19
INDUSTRIAL TECHNOLOGICAL DEVELOPMENT (DTI-1) – 9
INDUSTRIAL TECHNOLOGICAL DEVELOPMENT (DTI-2) – 4
INDUSTRIAL TECHNOLOGICAL DEVELOPMENT (DTI-3) – 12
TECHNOLOGICAL AND INDUSTRIAL INITIATION (ITI) – 4
MEDIUM LEVEL TECHNICAL SUPPORT (ATNM) – 12
HIGHER LEVEL TECHNICAL SUPPORT (ATNS) – 7
SCIENTIFIC INITIATION (IC) – 11

Total number of CNPq scholarships – 78

CAPES

MASTER – 3
DOCTORATE – 4
EXCHANGE DOCTORATE – 2
POST-DOCTORATE ABROAD – 1
Total number of CAPES scholarships – 10

INCT INOFAR

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69. Yolanda Karla Cupertino da Silva (UFAL) CV-Lattes

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71. Sarah da Silva Nunes (UFG) CV-Lattes
72. Taís Rúbia dos Santos (UFRJ) CV-Lattes
73. Thais Emmanoelle Tavares Pompeu CV-Lattes
74. Thiago Stevanatto Sampaio (UFRJ) CV-Lattes
75. Vinicius de Frias Carvalho (FIOCRUZ/RJ) CV-Lattes
76. Wallace Carvalho Ferreira (UFMG) CV-Lattes

INCT-INOFAR MEDIA

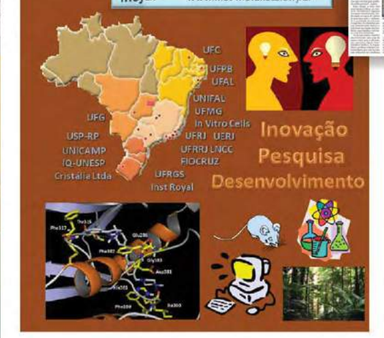
2014

2013

2012

2011

2010



2009

DRUGS PORTAL

www.portaldosfarmacos.ccs.ufrj.br

To promote and publicize Pharmaceutical Sciences, **INCT-INOFAR** maintains the **Drugs Portal** – a website where its research activities are publicized, alongside curious facts about the scientific world, in a simple and easy to understand language for web users. **INCT-INOFAR** also uses the site to make available, for general use, its own Health Education materials.

FACEBOOK

Since the creation of **INCT-INOFAR** in 2009, there have been over one hundred articles, news and never before published interviews published. All of these pertain to the pharmaceutical area. In 2014, the Facebook page for the Drugs Portal was created, to widen its social networking presence.

LINK:
https://www.facebook.com/PortalDosFarmacos

VIDEO ARCHIVE

INCT-INOFAR also maintains a series of videos, available at the **Drugs Portal**, of its activities throughout the years. As an example, we have the National Science and Technology Week. In 2013, **INCT-INOFAR** was present in six *Knowledge* Vessels, located in the neighborhoods of Irajá, Penha, Madureira, Vila Aliança, Padre Miguel and Santa Cruz, in Rio Janeiro city, to develop its health awareness and science publicity activities, focused on the theme "*The safe and correct use of drugs*", raising awareness on the risks of their indiscriminate use. The **INCT-INOFAR** also promoted the I National Science and Technology week in the city of Sao Francisco de Itabapoana, in the northern part of the Rio de Janeiro state, in 2014, having returned to the city in 2015.

LINK:
http://www.portaldosfarmacos.ccs.ufrj.br/videos.html

COMICS ARCHIVE

The Drugs Portal produces comics that make critical allusions to the irrational use of drugs, while proposing conscious alternatives for their consumption. Pharmacist and comic artist Natália Medeiros de Lima makes, in her drawings, criticism to the health situation in the country, promotes awareness on the use of condoms, and makes special drawings for holidays such as National Health Day, for example.

LINK:
http://www.portaldosfarmacos.ccs.ufrj.br/charges.html

WHAT YOU WILL FIND IN THE DRUGS PORTAL

In the Drugs Portal it is possible to access a calendar and media coverage of the main scientific events in the area, as well as to download educational booklets, written by the INCT-INOFAR team, dealing with the theme "The Rational Use of Drugs".

THE CORRECT USE OF ANTIBIOTICS

Written by scientists Angelo da Cunha Pinto and Lidia Moreira Lima, the booklet "Joey's Crew in: The Correct Use of Antibiotics", has an easy to understand approach for children on this topic. Through the story of the disease of the boy Joey, **INCT-INOFAR** explains how and why bacteria become resistant to antibiotics. It also warns of the importance of consulting a doctor and following the treatment as prescribed. The material is endorsed by the National Agency of Health Surveillance (ANVISA).

THE COMMANDMENTS OF THE CORRECT USE OF DRUGS

Co-written by **INCT-INOFAR** coordinator, Eliezer J. Barreiro, with pharmacist Natália Medeiros de Lima, the booklet "The Commandments of the Correct Use of Drugs" has received an animated version. The publication has colorful illustrations and simple language, providing guidelines about the different categories of drugs (prescription and over-the-counter) as well as explaining where and how to store drugs at home, and mentioning the risks of taking drugs without a doctor's prescription.

THE CORRECT USE OF ANTI-INFLAMMATORIES

Co-written by **INCT-INOFAR** Scientific Superintendent, Lidia Moreira Lima and educator Ana Cristina da Mata Silva, the third educational booklet by the Institute has, once again, the characters of Joey's Crew, this time to talk about the correct use of anti-inflammatories. In the end of the publication there are activities to help learn the contents of the booklet, making it easier for children to understand what they are reading with their parents.

DOWNLOAD - BOOKLETS IN BOOTH PRINT AND ANIMATION VERSIONS
http://www.portaldosfarmacos.ccs.ufrj.br/cartilhas.html

RESEARCH SUBPROJECTS

RADICAL INNOVATION (PERIOD 2009-2015)

2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

INFLAMMATION

STUDY OF POTENTIAL ANTI-INFLAMMATORY EFFECT OF LASSBIO 897 COMPOUNDS, ON SILICOSIS AND ASTHMA COMPOUNDS
Prof. Patricia Machado Rodrigues e Silva/ Prof.Marco Aurélio Martins - FIOCRUZ - RJ

DEVELOPMENT OF NEW ANTIAASHTMATIC DRUG PROTOTYPES (LASSBIO-596)
Prof. Patricia Rieken Macêdo Rocco (UFRJ)/Prof. Lidia Moreira Lima (UFRJ)

STUDY FOR THE IDENTIFICATION OF NEW SULFONAMIDE COMPOUNDS EFFECTIVE IN THE CONTRO OF PULMONARY INFLAMMATION CAUSED BY SILICA IN MICE
Prof. Patricia Machado Rodrigues e Silva Martins (FIOCRUZ)

IMPACT OF NANOPARTICLE THERAPY WITH THYMULIN GENE IN CHRONIC ALLERGIC ASTHMA MODEL
Prof. Patricia Rieken Macêdo Rocco (UFRJ)

INFLAMMATION AND PAIN

PLANNING, SYNTHESIS, STRUCTURAL CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF NEW ANTI-INFLAMMATORY, ANTI-INFECTIVE AND NEUROACTIVE DRUG CANDIDATES
Prof. Claudio Viegas Junior - Universidade de Alfenas

BENZALDEHYDE SEMICARBAZONE (BS)
Prof. Heloisa de Oliveira Beraldo (UFMG)

DEVELOPMENT OF NEW MAPK P-38 MODULATOR ANTI-ARTHRITIC DRUG CANDIDATES
Prof. Lidia Moreira Lima (UFRJ)

NEW 5-ARYL-2-FURFURIL-N-ACYLHYDRAZONE DERIVATIVES FUNCTIONALIZED WITH POWERFUL ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIY: LASSBIO-1609 AND LASSBIO-1636
Prof. Carlos Alberto Manssour Fraga (UFRJ)

RESEARCH SUBPROJECTS

RADICAL INNOVATION (PERIOD 2009-2015)

2009 2010 2011 2012 2013 2014 2015

INFLAMMATION AND PAIN

PLANNING OF STRUCTURAL CHANGES AIMED AT THE OPTIMIZATION OF THE AFFINITY OF THE SELECTIVE IKK2 ENZYME SELECTOR, LASSBIO-1524

Prof. Laurent Emmanuel Dardenne (LNCC)/Prof. Carlos Alberto Manssour Fraga (UFRJ)

DEVELOPMENT OF NEW ANTI-INFLAMMATORY AND ANALGESIC A12:G27DRUG CANDIDATES FROM SAFROLE

Prof. Lidia Moreira Lima (UFRJ)

CHEMOTHERAPEUTICALS

EVALUATION OF ANTIPARASITE ACTIVITY OF A SERIES OF SEMICARBAZONE AND HYDRAZINE-N-ACYLHYDRAZONE DERIVATIVES

Prof. Magna Suzana Alexandre Moreira (UFAL)/
Prof. Lidia M. Lima (UFRJ) /
Prof. Sandra Haas (UNIPAMPA)

THEORETICAL EVALUATION OF THE ACTION MECHANISM OF DIALKYLPHOSPHORYLHYDRAZENES AS RIBOSE-5-PHOSPHATE ISOMERASE ENZYME INBITITORS OF TRYPANOSOMA CRUZI AJD PLASMODIUM FALCIPARUM

Prof. Carlos Mauricio R. de Sant´Anna (UFRRJ)

EVALUATION OF ANTITUMORAL ACTIVITY OF NEW STRUCTURED MOLECULES PLANNED FROM IMATINIB PROTOTYPE

Prof. Patricia Dias Fernandes (UFRJ)

DISCOVERY OF NEW ANTITUMORAL DRUG CANDIDATES ANALOGUE TO COMBRETASTATIN A4

Prof. Lidia Moreira Lima (UFRJ)/ Prof Claudia Pessoa (UFC)

RESEARCH SUBPROJECTS

RADICAL INNOVATION (PERIOD 2009-2015)

2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

CENTRAL NERVOUS SYSTEM

STUDY OF N-PHENYLPIPERAZINE FUNCTIONALIZED AS PROTOTYPES FOR THE DEVELOPMENT OF NEW ATYPICAL ANTIPSYCHOTICS

Prof. Stela Maris Kuze Rates (UFRGS)/ Prof. C.A.M.Fraga (UFRJ)/ Prof. François Noel (UFRJ)

PLANNING, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF VECTORIZED AND SELF-ORGANIZED NEUROACTIVE DRUG PROTOTYPES.

Prof. Ricardo Menegatti (UFG)

PHARMACOLOGICAL EVALUATION OF NEW ZOLPIDEM NEUROACTIVE DERIVATIVES

Prof. Roberto Takashi Sudo (UFRJ)

CARDIOVASCULAR SYSTEM & DIABETES

THERAPEUTIC POTENTIAL OF NEW VASODILATOR (LASSBIO 1289) IN ARTERIAL AND PULMONARY HYPERTENSION

Prof.Gisele Zapata Sudo (UFRJ)

PHARMACOLOGICAL AND TOXICOLOGICAL EVALUATION OF NEW DRUG CANDIDATES FOR THE PREVENTION AND TREATMENT OF MIOCARDIOPATY AND NEUROPATHY CAUSED BY DIABETES MELLITUS

Prof.Gisele Zapata Sudo (UFRJ)

DESIGN & SYNTHESIS OF NEW DPP4 INHIBITOR HYPOGLYCEMIANTS

Prof. Lidia Moreira Lima (UFRJ)

RESEARCH SUBPROJECTS

INCREMENTAL INNOVATION (PERIOD 2009-2015)

2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

GENERICS

SYNTHESIS OF ATORVASTATIN
Prof. Luiz Carlos Dias (UNICAMP)

SYNTHESIS OF SUNITINIB
† Prof. Angelo da Cunha Pinto (UFRJ)

SYNTHESIS OF FLUOXETINE
Luiz Carlos Dias (UNICAMP)

SYNTHESIS OF VALSARTAN
Prof. Luiz Carlos Dias

SYNTHESIS OF DASATINIB
Luiz Carlos Dias (UNICAMP)

OTHERS

"IN SILICO" PREDICTION AND "IN VITRO" PRODUCTION THROUGH BIOCONVERSION OF HUMAN METABOLYTES OF DRUG PROTOTYPE CANDIDATES
Prof. Valeria de Oliveira (UFG)

TRIAGE OF NEW REPLICATION INHIBITORS FOR THE HUMAN IMMUNODEFICIENCY VIRUS OF TYPE 1 (HIV-1) FROM THE LASSBIO CHEMICAL LIBRARY
Prof. Luciana Jesus da Costa (UFRJ)

PROSPECTION OF OPPORTUNITY IN NEW GENERICS AND ORIGINAL GENERICS
Prof. Adelaide Mª de Souza Antunes (UFRJ)

IMPLEMENTATION AND VALIDATION OF PRE-CLINICAL MODEL FOR THE EVALUATION OF TERATOGENIC EFFECT OF BIOACTIVE SUBSTANCES: EVALUATION OF LASSBIO 468 AND LASSBIO 596 PROTOTYPES
Prof. Aloa Machado de Souza (UFRJ)

RESEARCH SUBPROJECTS

RADICAL INNOVATION (PERIOD 2009-2015)

2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

DISCOVERY OF NEW NEURAMINIDASE INHIBITORS OF THE INFLUENZA VIRUS

Prof. José Nelson dos Santos Silva Couceiro (UFRJ)

TECHNOLOGICAL PROSPECTION OF INTERMEDIATES AND SYNTHETIC CHEMICAL ENTITIES OF INTEREST TO INCT-INOFAR

Prof. Marcia Paranho Veloso (UNIFAL)

OTHERS

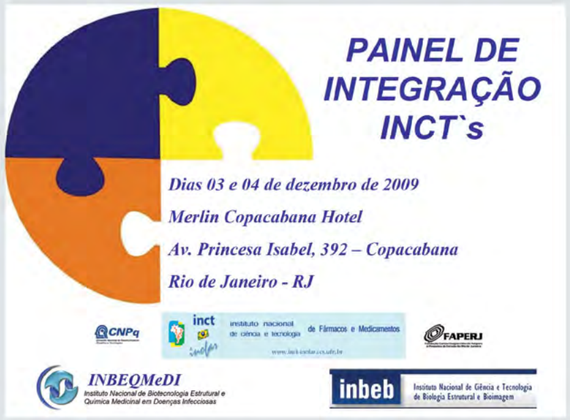
RATIONAL DESIGN OF DRUGS BASED ON STRUCTURES: APPLICATIONS AND DEVELOPMENT OF METHODS AND PROGRAMS

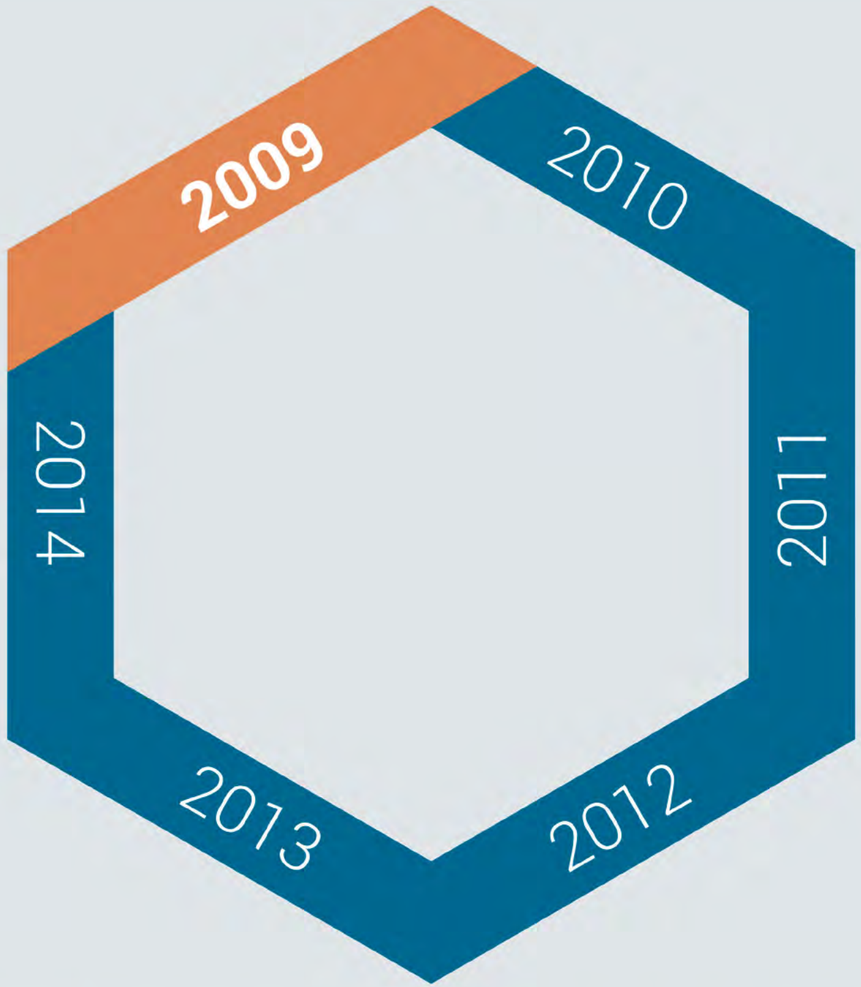
Prof. Laurent Emmanuel Dardenne (LNCC)

EVALUATION OF THERAPEUTIC POTENTIAL OF MEDICINAL PLANTS AND BIOACTIVE SYNTHETIC PRODUCTS WITH MYOCARDIUM CYTOPROTECTIVE ACTIVITY

Prof. Joao Xavier de Araujo Jr. – UFAL

INTEGRATION WITH OTHER INCTs



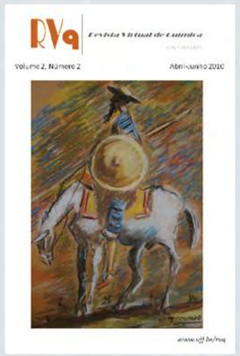


In December 2009, an Integration Panel took place in Rio de Janeiro. **INCT-INOFAR** was present, gathered with the Structural Biology and Bioimage INCT (INBEB) and the Structural Biology and Medicinal Chemistry in Infectious Diseases INCT (INBEQMed) to present their research projects, to identify academic-scientific meeting points for future partnerships.

The National Institute of Science and Technology in Drugs and Medicines joined I5+ in 2010. I5+is a group formed by **INCT-INOFAR** and another four National Institutes of Science and Technology: INCT of Complex and Functional Materials (INCT-INOMAT), INCT of Transfer of Materials Continent-Ocean (INCT-TMCOcean), INCT of Science and Technology of the Biorational Control of Insects and Pests (INCT-CBIP), and INCT of Energy and Environment (INCT-E&A).

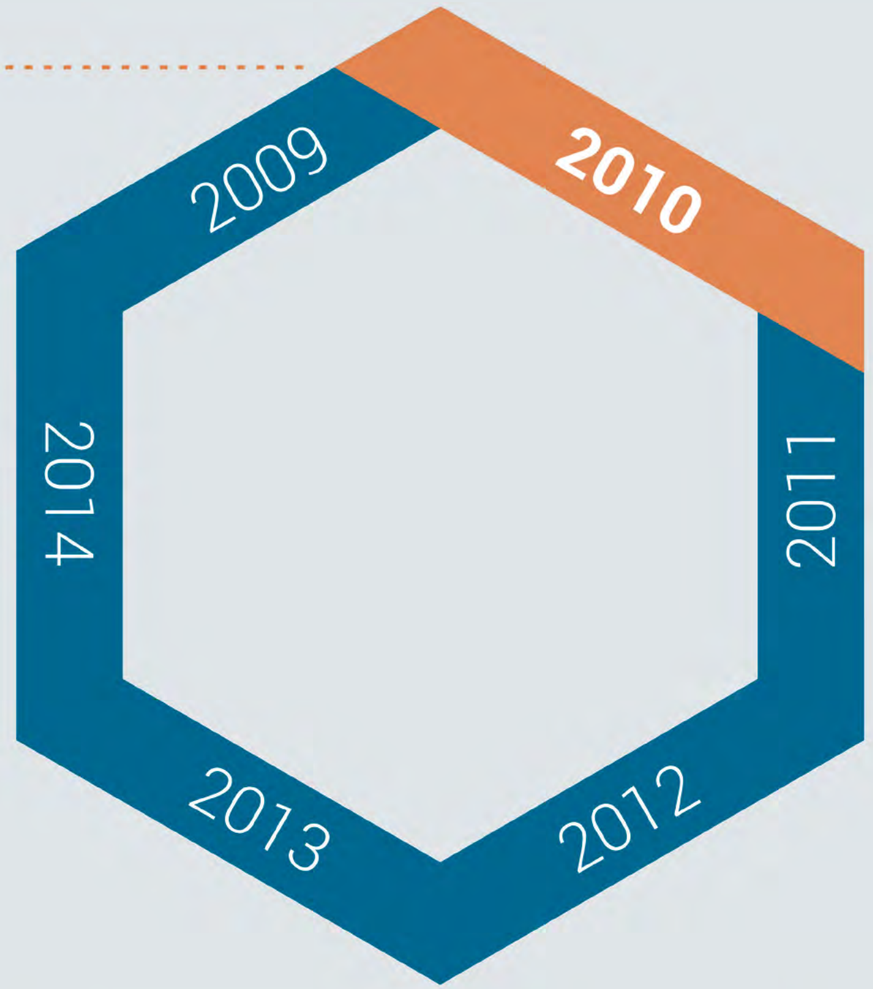
The goal of this integration is to discover INCT governance and to strengthen the bonds of scientific cooperation in the areas of research, training of personnel, and scientific publicity.

HIGHLIGHTS



http://www.uff.br/RVQ/index.php/rvq/issue/view/11

SPECIAL EDITION OF THE VIRTUAL CHEMISTRY MAGAZINE HAS **INCT-INOFAR** IN SPECIAL EDITION



In September 2010, the Virtual Chemistry Magazine published a *special issue* dedicated to research that **INCT-INOFAR** (National Institute of Science and Technology of Drugs and Medicines) conducted during the year. The Scientific Superintendent of the Institute, Lidia Moreira Lima, was in charge of the exclusive edition.

The issue had six articles on radical innovation and presented the most relevant results achieved by the research groups that make up **INCT-INOFAR**, showing that specialists in several areas can get together with the goal of working for the improvement of the chain of innovation in drugs and medicines in the country, as well as proving the qualifications of Brazilian researchers in the area of Science and Medicinal Chemistry.

Virtual Chemistry Magazine (RVq) is a quarterly publication by the Regional Secretary of the Brazilian Society of Chemistry in Rio de Janeiro (SBQ-Rio), freely accessible online, created to be a source of reference and publicity for articles on Chemistry and related areas.

HIGHLIGHTS

5th ENIFARMED HAS **INCT-INOFAR** PARTICIPATION

2009

2010

2011

2012

2013

2014

The National Institute for Science and Technology of Drugs and Medicines **(INCT-INOFAR)** was present at the 5th National Meeting for Innovation in Drugs and Medicines (ENIFarMed), in the city of São Paulo. The event, which discussed a common agenda for the advancement of technological innovation in drugs and medicines in Brazil, dealt with the topic: "The Health Industrial Complex: Strategic in the Access to Drugs".

INCT-INOFAR set up a stand in the 3rd EXPOFARMED – a business exposition connected to the 5th ENIFarMed – with a goal of publicizing projects studied in its network of research in drugs and medicines and of growing closer to the productive sector.

DEBATES

INCT-INOFAR coordinator, Eliezer J. Barreiro, was invited to be part of panel: "New Perspectives for Intellectual Property in the Pharmaceutical Sector", talking about pharmaceutical patents and the several barriers that Brazil has to overcome to innovate in the field of drugs and medicines.

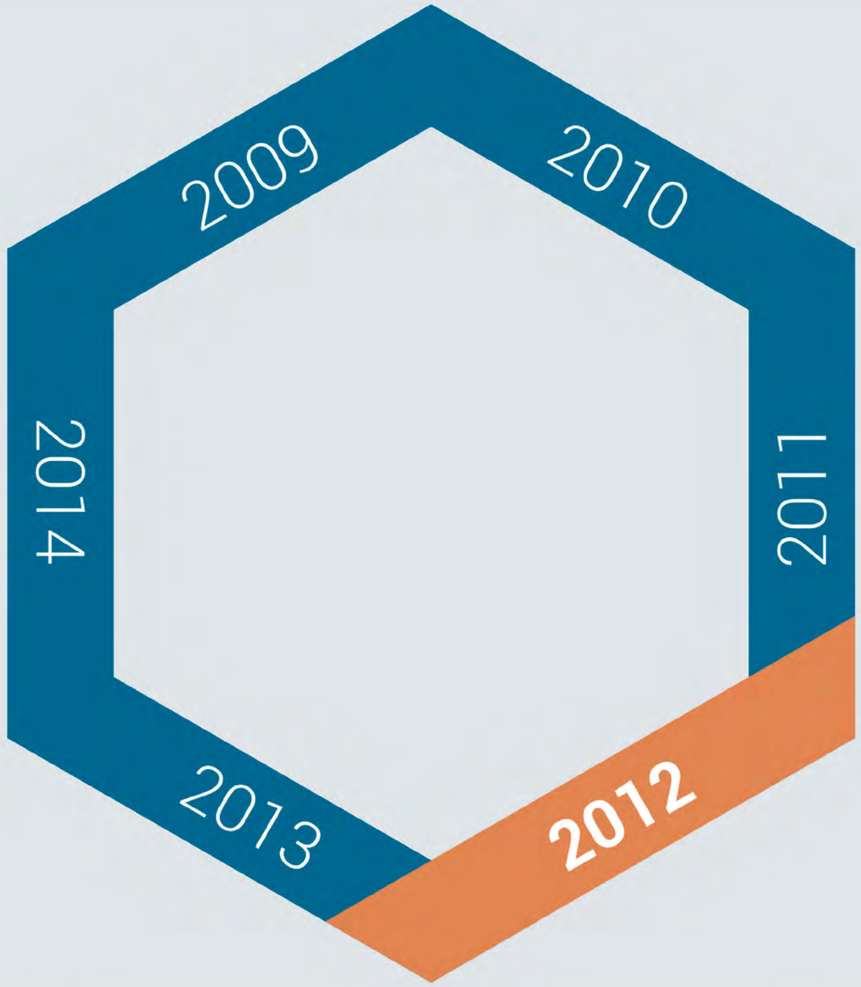
TECHNICAL ACKNOWLEDGEMENT AWARD

The panel "*Total Synthesis of Calcium Atorvastatin*", authored by Dr. Adriano Siqueira Vieira and Prof. Dr. Luiz Carlos Dias, **INCT-INOFAR** researchers connected to the Institute of Chemistry of UNICAMP/SP, received the Technical Acknowledgement Award.

The award acknowledged the efforts made by **INCT-INOFAR** in the discovery of a new synthetic route for Atorvastatin, the active principle in Lipitor®, which had its patent expired in November 2011. By reducing the stages of the total synthetic route, the UNICAMP/SP researchers have made it more efficient and cheaper in relation to the original route described in the Pfizer patent, with the advantage of presenting a few original intermediates, which are easily accessed synthetically and four folds overall yield.

HIGHLIGHTS

INCT-INOFAR ORGANIZES FOLLOW-UP AND EVALUATION MEETING



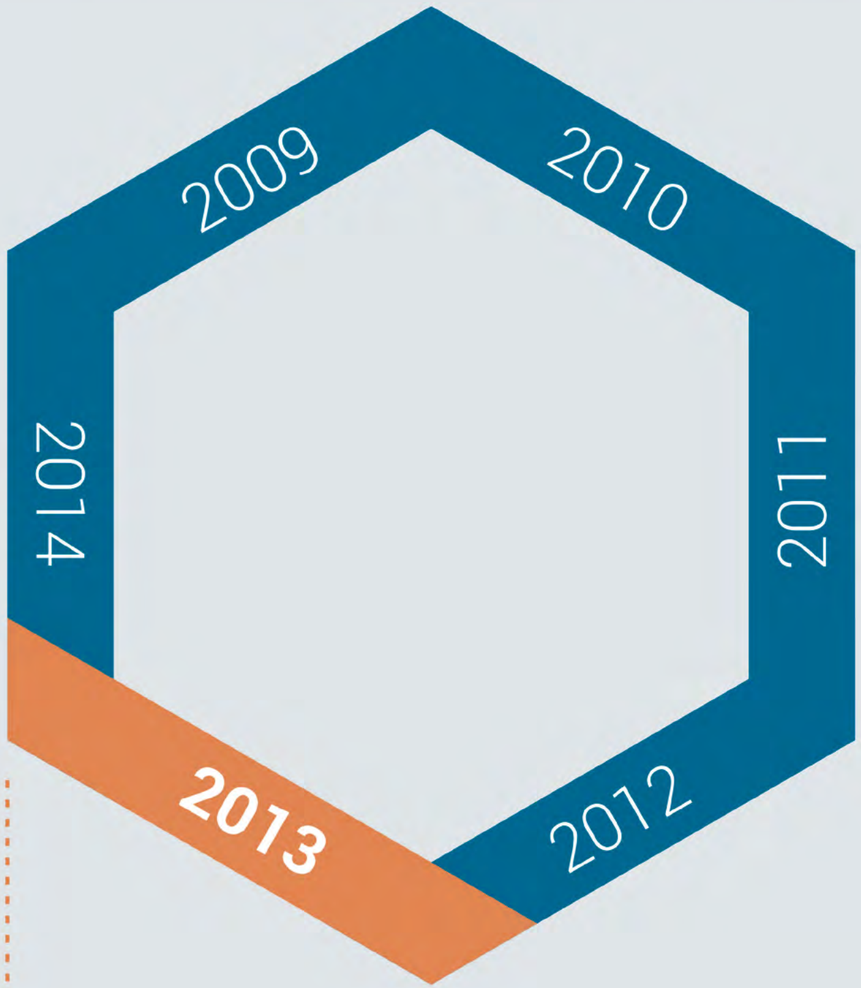
The VI Follow-Up and Evaluation Workshop promoted by **INCT-INOFAR** took place in May 2012, in Rio de Janeiro with a goal of strengthening scientific cooperation among its research network and discussing the results obtained so far in its subprojects.

Sir Simon Campbell, former Pfizer research senior director, responsible for the discovery of important drugs for Pfizer company, came to Brazil exclusively to take part in this 6th **INCT-INOFAR** Follow-Up and Evaluation Meeting.

At the event, as well as clearing doubts, such as on the choice of therapeutic targets, **INCT-INOFAR** researchers took part in conferences given by Sir Campbell on the discovery of two drugs in which he played an important part: antihypertensive Norvasc™ (Amlodipine) and Viagra™ (Sildenafil). Campbell also talked about his personal perspective on the future of the pharmaceutical industry, as well as complimented the multidisciplinary research network established by **INCT-INOFAR**.

HIGHLIGHTS

INCT-INOFAR AWARDED IN 7th ENIFARMED



INCT-INOFAR was present in the seventh edition of the National Meeting for Innovation in Drugs and Medicines (ENIFARMED), in August 2013, with the goal of publicizing projects under study in its network of research in drugs and medicines.

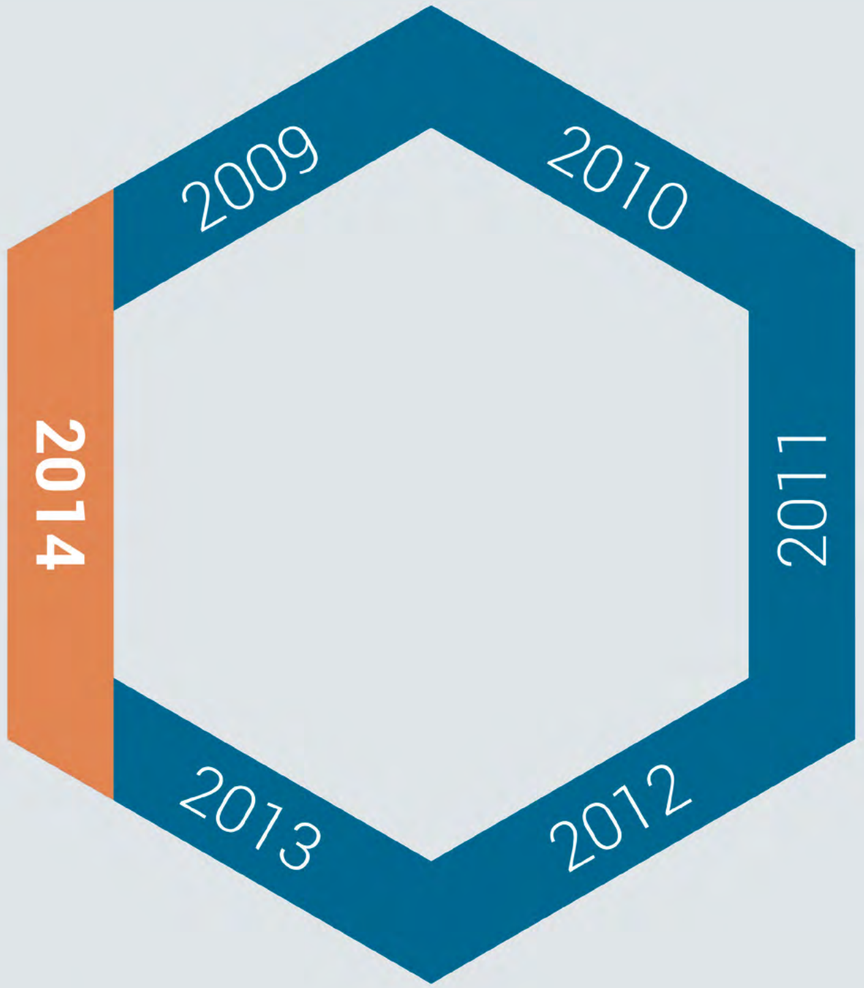
In its third participation, **INCT-INOFAR** was part of the 5th EXPOFARMED, the business exposition connected to the 7th ENIFARMED, with a booth that allowed approaching the productive sector as well as government agencies.

The National Meeting for Innovation in Drugs and Medicines gathered industry, academia, and representatives of government agencies to discuss a common agenda for the advancement of technological innovation in drugs and medicines in Brazil.

AWARDED RESEACHERS

Three **INCT-INOFAR** researchers received the Technical Acknowledgement Award, promoted by the event. The winners in first place, Dr. Barbara Vasconcellos da Silva, and fourth place, Dr. Isabelle Karine da Costa Nunes, presented the development of original synthesis routes for the production of generic versions of drugs that have a huge impact on the Public Health Care system (SUS). The research that awarded Dr. Adriano Siqueira Vieira with third place is on an innovative molecule for the treatment of severe asthma, chronic obstructive pulmonary disease, and silicosis.

BRAZIL AND GERMANY STRENGHTEN BONDS DURING INDIVIDUALIZED MEDICINE SYMPOSIUM



With a goal of celebrating the Year of Germany in Brazil 2013-2014, under the motto “When ideas meet”, the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) organized a Workshop on Individualized Medicine in Drug Research, in March 2014, at the Brazilian Academy of Science (ABC), in Rio de Janeiro city.

The Workshop is the result of a cooperation covenant that was signed in 2011 between German research institution ICEPHA and **INCT-INOFAR**, with the endorsement of German Prime Minister Winfried Kretschmann and of Madam Minister Theresia Bauer (Ministry for Science, Research, and Art, Baden-Württemberg).

Organized with the University of Tübingen, the event had a goal of developing concrete network projects and had the participation of Brazilian and German researchers.

The drugs that have a goal of providing individualized or personalized therapy are in opposition to classic drugs, which dominate the pharmaceutical industry. However, drugs focused on individualized medicine are very researched by academic teams, among them in the Interdepartmental Center for Pharmacogenomics and Pharma Research (ICEPHA) at the University of Tübingen.

ANNUAL ACTIVITIES REPORT 2015

*In the following pages the activities conducted by **INCT-INOFAR** during 2015 will be detailed, including its main research projects, the events it promoted and was part of, the health awareness and publicity activities and its publications (academic publishing and articles in journals).*

HIGH LIGHTS 2015

DESIGN, SYNTHESIS AND IN VITRO TRYPANOCIDAL AND LEISHMANICIDAL ACTIVITIES OF NOVEL SEMICARBAZONE DERIVATIVES

Eur. J. Med. Chem.100 (2015)24-33. [DOI]

Marina A. Alves, Aline C. de Queiroz, Magna Suzana Alexandre-Moreira, Javier Varela, Hugo Cerecetto, Mercedes González, Antonio C. Doriguetto, Iara M. Landre, Eliezer J. Barreiro, Lídia M. Lima

Neglected diseases (DN) represent a set of parasitic illnesses that primarily affect poor people in developing countries. Those caused by Trypanosomatidae protozoans include Chagas disease and sleeping sickness, produced by Trypanosoma species, and leishmaniasis, caused by different species belonging to the genus Leishmania [1]. Affording to World Health Organization (WHO), trypanosomiasis and leishmaniasis are the most challenging among the neglected tropical diseases [2]. A comparative genomics of trypanosomatid parasitic protozoa revealed a conserved core proteome of about 6200 genes among Leishmania major, Trypanosoma cruzi, and Trypanosoma brucei [3]. The highly syntenic genomes of the trypanosomatid species lead the assumption that they can encode similar proteins and drugs designed against conserved core processes should have the advantage of being potentially useful against all three protozoa. Among the possible drug targets in trypanosomatids, the peptidases or proteases have concerned attention due their many roles in highly specific functions to the parasites' life cycles [4-6]. Considering the ability of these enzymes to catalyze the hydrolysis of peptide bonds [7-9] compounds containing amide or amide-mimetic frameworks can be designed as proteolytic inhibitors with antitrypanosomatid activity.

In order to design new peptide mimetic derivatives enclosing frameworks able to be recognized by trypanosomatids proteases, a series of semicarbazone derivatives (6a-h and 7a-h) were planned by molecular modification on prototype 5 (LASSBio-1022) [14]. These modification were based on ring replacement between quinoxaline nucleus and 1,3-benzodioxole system (a, Chart 2); molecular simplification

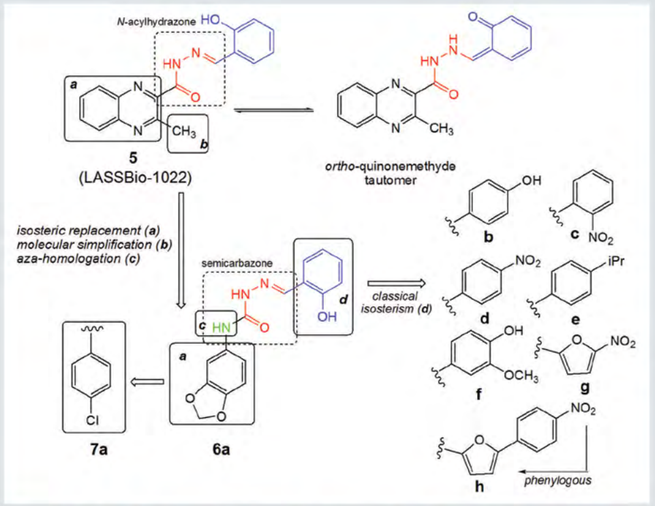


Chart 2: Design concept of semicarbazone derivatives (6a-h and 7a-h) from molecular modifications on prototype 5

represented by elimination of methyl group (b, Chart 2); followed by aza-homologation strategy (c, Chart 2), converting the N-acylhydrazone subunit in a semicarbazone framework. The congeners series was further designed by classical isosterism replacement on 2-hydroxyphenyl subunit, varying the electronic nature of the monovalent group (a-f) and by isosteric ring replacement of phenyl group by a substituted furan system (g) and its phenylogous analogue (h) (Chart 2) [15]. In this paper we described the synthesis of the designed compounds 6a-h and 7a-h and their trypanosomicidal and leishmanicidal activities.

Compounds 6a-h and 7a-h were synthetized in three linear steps from the amines 8 and 9, obtained commercially (Scheme 1). In the first step the amines were condensed with phenyl chloroformate in chloroform at room temperature in order to furnish the carbamates 10 and 11 [16-17]. These compounds were treated with hydrazine monohydrate in ethanol to provide the semicarbazide derivatives 12 and 13 [18]. These key-intermediates were finally condensed with appropriated aldehydes, selected based on the design concept depicted in Chart 2, to obtain the semicarbazones 6a-h and 7a-h in good overall yields.The unequivocal characterization of the relative configuration of imine double bond (E or Z) was performed using X-ray diffraction study (Figure 1).

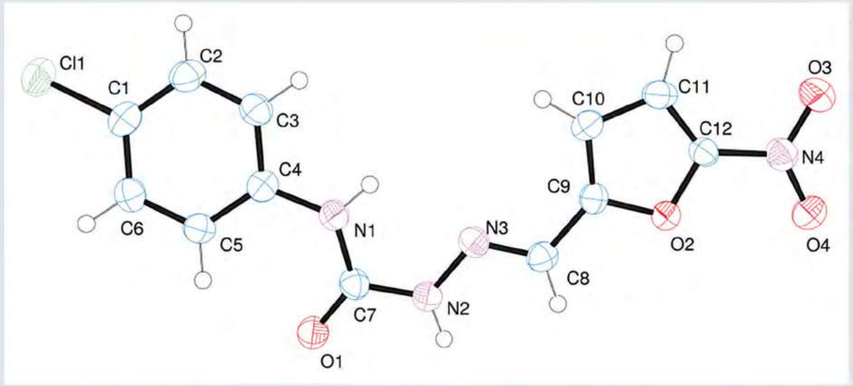


Figure 1: View of representative semicarbazone derivative 7g(LASSBio-1483)with ellipsoids represent 50%-probability level. H atoms are shown as small spheres of arbitrary radii.

Before starting the evaluation of the trypanosomicidal and leishmanicidal activities of semicarbazones 6a-h and 7a-h, the eventual cytotoxic profile of these compounds against mammalian cells was investigated by MTT assay [22]. Further, the semicarbazones 6a-h and 7a-h were evaluated in vitro against epimastigote forms of T. cruzi and against promastigotes and amastigotes forms of L. major.

The analysis of the obtained results allowed the selection of compound 7g (LASSBio-1483) as a dual trypanosomicidal and leishmanicidal agent. Therefore, the in silico prediction of physicochemical, ADME and toxicity properties of LASSBio-1483 (7g) were calculated and the results were compared to those obtained for nifurtimox and pentamidine.

Bearing in mind the possibility of the chemical instability of the imine function, present in the semicarbazone framework, the stability profile of compound 7g (LASSBio-1483) was investigated in buffer solution in pH = 2.0 and 7.4 (Figure 3). Moreover, in view of the peptide mimetic profile of semicarbazone scaffold, the plasma stability of LASSBio-1483 was also studied.

LASSBio-1483 showed high stability in buffer solution, either in pH value that simulate gastric juice (pH = 2) or either in pH value that mimic serum content (pH 7.4). In similar manner, this compound revealed great plasma stability.

In summary a series of semicarbazone derivatives (6a-h and 7a-h), containing structural modifications on the rings linked to the amine (NH) and imine (N=CH) groups, were designed and synthetized. From this series compound 7g (LASSBio-1483) highlighted, showing dual in vitro trypanosomicidal and leishmanicidal activities with potency similar to the standards drugs nifurtimox and pentamidine. This data, taken together with its good in silico druglikeness profile and its great chemical and plasma stabilities, make LASSBio-1483 (7g) a new antitrypanosomatid lead-candidate.

COMMENTS FROM AUTHOR

Trypanosomatids are protozoan parasites that cause various diseases in human, such as leishmaniasis, Chagas disease and sleeping sickness. The highly syntenic genomes of the trypanosomatid species lead the assumption that they can encode similar proteins, indicating the possibility to design new antitrypanosomatid drugs with dual trypanosomicidal and leishmanicidal activities. In this work a series of compounds (6a-h and 7a-h), containing a semicarbazone scaffold as a peptide mimetic framework, was designed and synthetized. From this series compound 7g (LASSBio-1483) highlighted, showing dual in vitro trypanosomicidal and leishmanicidal activities, with potency similar to the standard drugs nifurtimox and pentamidine. This data, taken together with its good in silico druglikeness profile and its great chemical and plasma stability, make LASSBio-1483 (7g) a new antitrypanosomatid lead-candidate.

JM25-1, A LIDOCAINE ANALOG COMBINING AIRWAY RELAXANT AND ANTI-INFLAMMATORY PROPERTIES: IMPLICATIONS FOR NEW BRONCHOSPASM THERAPY

Anesthesiology124 (2016) 109-120 [DOI]

Magda F. Serra, Josiane S. Neves, Gina C. Couto, Amanda C. Cotias, Camila R. Pão, Priscilla C. Olsen,Katharinne I. Moraes de Carvalho, Edna A. Anjos-Valotta, Robson X. Faria, Jorge C. S. Costa, Renato S. B. Cordeiro, Patricia M. R. Silva, Marco A. Martins.

Bronchospasm is a frequent life-threatening perioperative event during general anesthesia, which can be triggered by pharmacologic and mechanic factors, particularly in those pathological conditions where there is airway inflammation and hyper-reactivity. Lidocaine administered intravenously or via aerosol has been used to prevent irritant-induced bronchospasm during anesthesia in patients and animal models. However, in patients with reactive airway disease such as asthma, aerolized lidocaine can itself induce airway irritation and initial bronchoconstriction, indicating that caution in its use is required. When the airway effects of lidocaine and dyclonine (a lidocaine analogue displaying longer lasting and more intense local anesthetic activity) were compared in volunteers with bronchial hyper-reactivity, it became clear that attenuation of bronchospasm is independent of topical airway anesthesia, since only lidocaine inhibited histamine-induced bronchoconstriction, whereas dyclonine showed a more intense irritant response.

We previously demonstrated that aerolized JMF2-1, which is a fluorinated lidocaine analogue with reduced local anesthetic activity, prevented allergen-induced airway hyper-reactivity and inhibited lung eosinophilia, in a mechanism associated with down-regulation of Th2 cytokines and T cell function. Because fluorinated anilines have the potential to cause adverse side effects, such as hemolytic anemia and DNA damage, we questioned whether JM25-1(2-diethylamino-N-2,5-dimethylphenyl acetamide), a non-fluorinated lidocaine analogue with limited anesthetic activity, could inhibit bronchospasm and airway inflammation, and if so what might be the mechanism implicated.

In the current study, the effectiveness of JM25-1 was assessed in GH3 cells, rat tracheal rings and human eosinophil systems in vitro, assessing changes in Na+ current, contraction, proliferation, and survival, respectively. Lung function and inflammatory changes were studied in ovalbumin-sensitized A/J mice.We performed a patch-clamp analysis using the GH3 cell lineage as target in order to compare the effectiveness of lidocaine and JM25-1 (chemical structures shown in Fig. 1A) in blocking voltage-gated Na+ channels. As expected, a blockade of Na+ currents was observed following exposure to increasing concentrations of lidocainewith a 50% inhibitory concentration (IC50) of 0.2 mM. Higher concentrations of JM25-1 were required for blockade of Na+ currents in GH3 cells, resulting in a 758-fold higher IC50 value for the analogue (IC50 = 151.5 mM) (Fig. 1B).

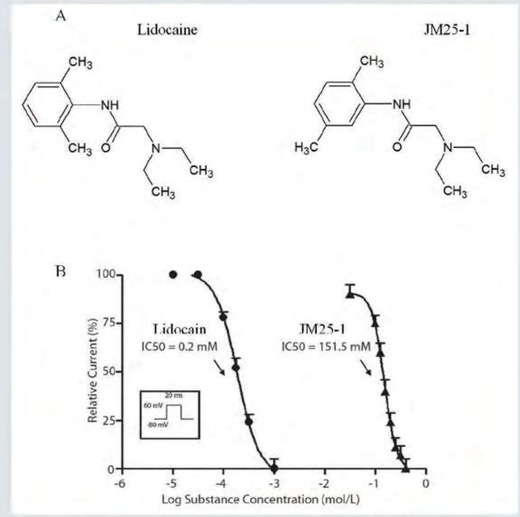


Fig. 1. (A) Chemical structures of lidocaine and JM25-1. (B) Concentration-dependent inhibition of Na+ currents in Gh3 cells by lidocaine (circles) and JM25-1 (triangles). Data are expressed as mean ± SD (n = 8 for JM25-1 and n = 5 for lidocaine); 50% inhibitory concentration (IC50) values were calculated by a fitting concentration–esponse relation to a sigmoidal model of theform log (inhibitor) versus response–variableslope.

Lidocaine and JM25-1 inhibited tracheal contraction triggered by cumulative addition of increasing concentrations of carbacholand also inhibited Ca2+-induced tracheal contraction. Pre-incubation of the adenylate cyclase inhibitor SQ22,536 did not alter carbachol-induced tracheal contraction, but attenuated the protective effect evidenced by 1 mM JM25-1 (Fig 2A, 2B). We then investigated a putative action of JM25-1 on intracellular levels of cAMP. As shown in Fig. 2C, JM25-1 concentration-dependently increased intracellular cAMP levels in cultured tracheal smooth muscle cells, achieving at the highest concentration values comparable to that of 0.1 mMforskolin, a known adenylyl cyclase activator. In addition, SQ22,536 inhibited the up-regulation of cAMP levels triggered by JM25-1(Fig. 2C).

Aerolized JM25-1 significantly inhibited the state of airway hyper-reactivity mainly concerning lung resistance changes. For lung compliance changes, statistically significant values were obtained only for the lowest concentration of methacholine, despite the tendency to return to baseline levels in all doses of methacholine (Fig. 3).

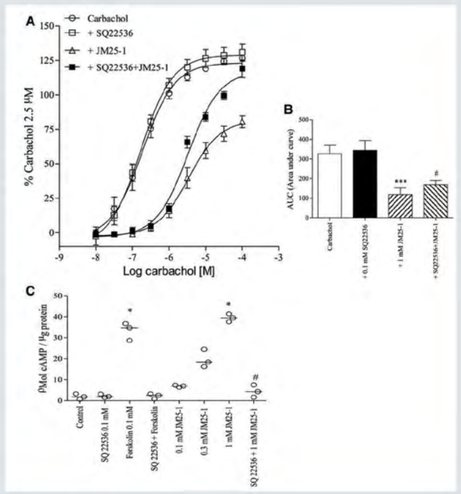


*Fig. 2. Effect of SQ22,536 on the tracheal smooth muscle relaxant and cyclic adenosine monophosphate (cAMP)–increasing properties presented by JM25-1. (A) Effect of 0.1 mM SQ22,536 on carbachol-induced tracheal contraction performed in the absence and presence of 1 mM JM25-1. Data are expressed as mean ± SD (n = 7 for all groups). Curves were fitted by using a sigmoidal model of the form log (agonist) versus response–variable slope. Differences among groups were analyzed as area under the curve (AUC) using one-way ANOVA followed by the Student–Newman–Keuls (B). ***P < 0.001 as compared with tracheal responses from untreated preparations (control), #P<0.05 when compared with JM25-1 group. (C) Effect of JM25-1 (0.1 to 1 mM) treatment on guinea pig tracheal smooth muscle cell cAMP intracellular levels. Data are expressed as median (n = 3). *P<0.05 versus untreated cells, #P<0.05 versus 1 mM JM25-1 group, Kruskal–Wallis test followed by Dunn multiple comparison test.*

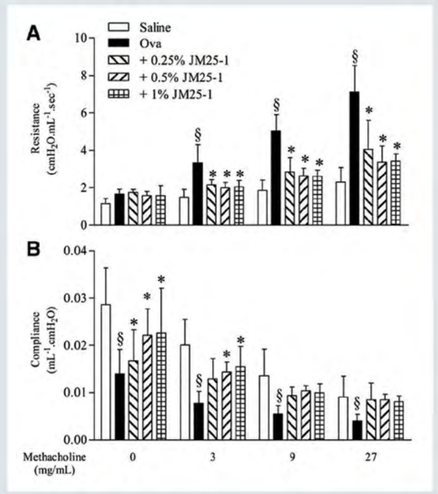


*Fig. 3. Effect of nebulized JM25-1 on methacholine-induced changes in transpulmonary resistance (A) and dynamic compliance (B) in A/J mice sensitized and challenged with ovalbumin (OVA). Ovalbumin-challenged mice were treated by exposure to an aerosol of JM25-1 (0.25 to 1%) or vehicle. Data are expressed as mean ± SD (n = 7 for all groups). §P < 0.05 versus saline group; *P < 0.05 versus ovalbumin-challenged group, two-way ANOVA followed by the Student–Newman– Keuls test.*

Next, to access the putative effect of aerolized JM25-1 on lung inflammatory changes triggered by allergen provocation, we have quantified peribronchiolar eosinophil and neutrophil numbers 24 h after the last provocation. The histologic analysis revealed that the JM25-1 inhibited peribronchiolar eosinophil and neutrophil infiltration in a dose-dependent manner (Fig. 4A-E). It also inhibited allergen-induced mucus exacerbation (Fig. 5A), and peribronchiolar collagen deposition (Fig. 5B). In another setting of experiments, we also demonstrated that aerolized JM25-1 also inhibited the increased levels of eotaxin-1), and the Th2 cytokines in lung tissue homogenates of ovalbumin-challenged mice (6A-D), in parallel with down-regulation of GATA-3 (Fig. 6E) and phosphorylated p38 expression (Fig. 6F).

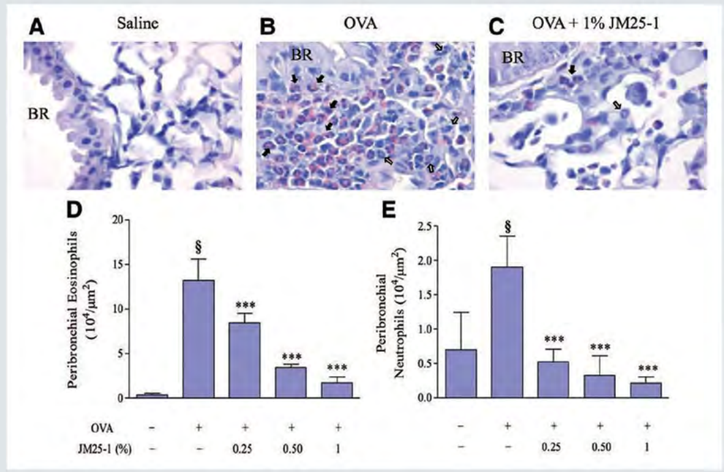


*Fig. 4. Nebulized JM25-1 reduces allergen-induced pulmonary inflammation in A/J mice sensitized and challenged with ovalbumin (OVA). (A–C) Photomicrographs of paraffin-embedded Sirius Red–stained lung sections from ovalbumin-sensi- tized mice challenged with saline, challenged with ovalbumin, and challenged with ovalbumin and treated with 1% JM25-1, respectively. The number of eosinophils (D) and neutrophils (E) in peribronchiolar regions was determined in lung sections by morphometric analyses. Black and white arrows indicate representative eosinophils and neutrophils, respectively. Ovalbumin- challenged mice were treated by exposure to an aerosol of JM25-1 (0.25 to 1%), and all samples for histologic examinations were undertaken 24 h after the last ovalbumin challenge. Data are expressed as mean±SD (n=7 for all groups). §P < 0.001 versus saline group, ***P < 0.001 versus ovalbumin-challenged group, one-way ANOVA followed by the Student–Newman– Keuls test. BR = bronchioles.*

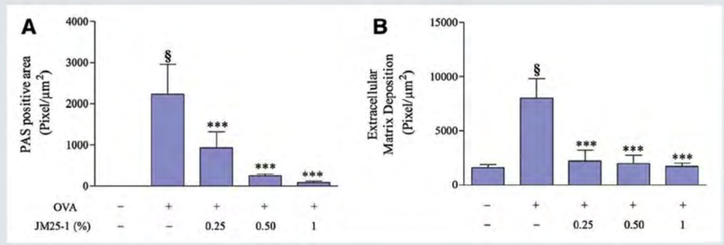
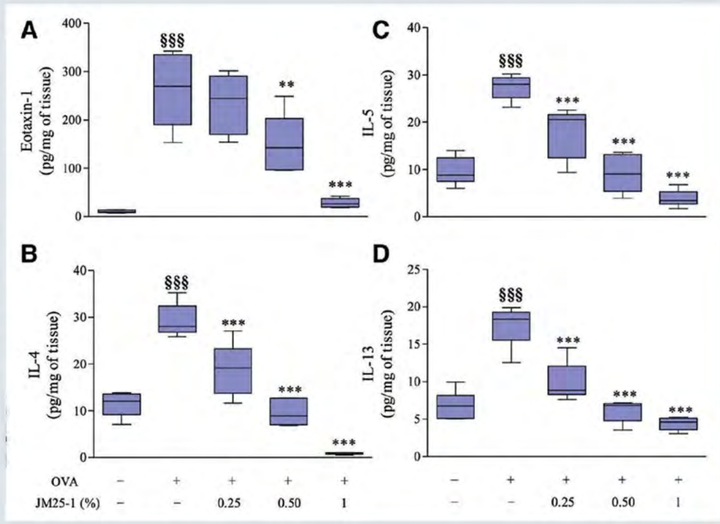
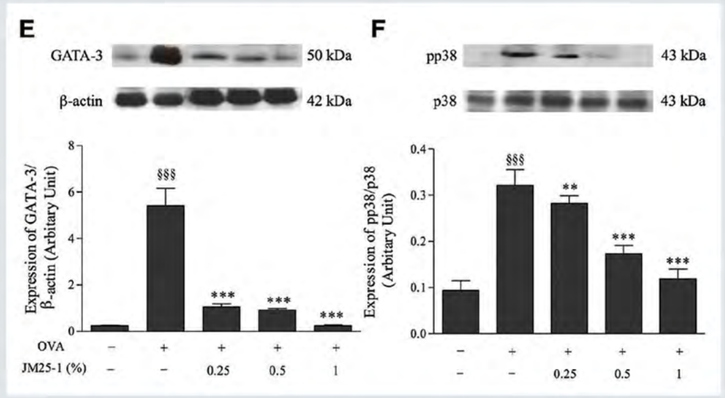


*Fig. 5. Nebulized JM25-1 reduces airway remodeling caused by allergen-induced lung inflammation in mice. Quantitative assessment of mucus production (A) and fibrotic changes (B) was carried out in lung sections by morphometric analyses. All his- tologic examinations were undertaken 24 h after the last ovalbumin (OVA) challenge. Ovalbumin-challenged mice were treated by exposure to an aerosol of JM25-1 (0.25 to 1%), and all samples for histologic examinations were obtained 24 h after the last ovalbumin challenge. Data are expressed as mean ± SD (n = 7 for all groups). §P< 0.001 versus saline group, ***P < 0.001 versus ovalbumin-challenged group, one-way ANOVA followed by the Student–Newman–Keuls test. PAS=periodicacid–Schiff.*

*Fig. 6. Nebulized JM25-1 reduces proinflammatory cytokine and chemokine levels and GATA-3 and phosphorylated p38 MAP kinase expression in lung tissue samples. Levels of eotaxin-1 (CCL11) (A), interleukin (IL)-4 (B), IL-5 (C), and IL-13 (D) were measured in lung homogenates by using enzyme-linked immunosorbent assay in ovalbumin (OVA)-challenged mice treated by exposure to an aerosol of JM25-1 (0.25 to 1%). n = 6 to 7 in each group. Whole-lung extract was analyzed by Western blotting for GATA-3 (E) and phosphorylated p38 MAP kinase expression (F). The membranes were reprobed with anti-actin or p38 as the loading controls, respectively (one of the three independent experiments with similar results is shown). Intensity of GATA-3 and phosphorylated p38 MAP kinase expression was quantified by densitometry and presented as relative intensity of GATA- 3 with respect to actin or relative intensity of phosphorylated p38 MAP kinase (pp38) with respect to total p38 MAP kinase (p38). Results are represented as whiskers: minimum to maximum (A–D) and mean ± SD (E–F). §§§P < 0.001 versus saline group; **P < 0.01 and ***P < 0.001 versus ovalbumin-challenged group, one-way ANOVA followed by the Student–Newman–Keuls test.*





Since eosinophils are leukocytes notable associated with bronchial reactive diseases, we next evaluated the effect of JM25-1 on isolated human eosinophils. By flow cytometry we found that JM25-1 concentration-dependently promoted eosinophil apoptosis (Fig. 7A). In contrast, the population of apoptic eosinophils following exposure to 1 mM lidocaine was lower than 20% (Fig. 7B).

Then, we performed another set of experiments evaluating the ability of JM25-1 in preventing eotaxin-induced eosinophil activation. By Western blotting we found that both JM25-1) and lidocaine inhibited the phosphorylation of p-38 MAP kinase after eotaxin stimulation at 1 mM concentration (Fig. 8).

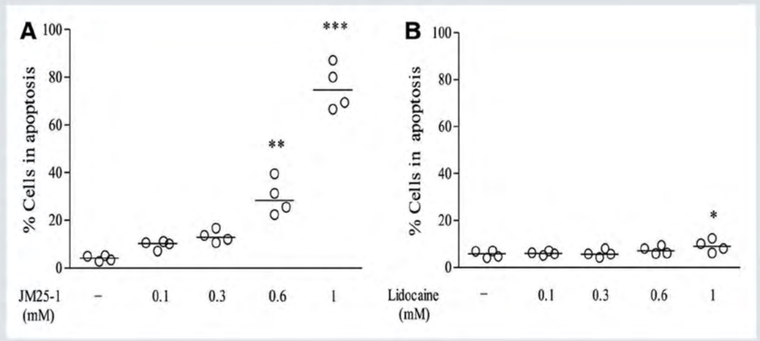


Fig. 7. JM25-1 induced apoptosis of isolated human peripheral eosinophils. Eosinophils were cultured in the presence of inter- leukin-5 (30 ng/ml) for 72 h in the absence or presence of lidocaine or JM25-1. Column scatter graphs represent the percentage of cells in apoptosis. Eosinophils were treated with JM25-1 at 0.1 to 1 mM (A) or lidocaine (B). Horizontal lines represent the mean value and the points represent the median (n = 4, four different eosinophil donors). Results were analyzed by Kruskal–Wallis test followed by the Dunn multiple comparison test. *P<0.05, **P<0.01, and ***P<0.001 versus untreated group.

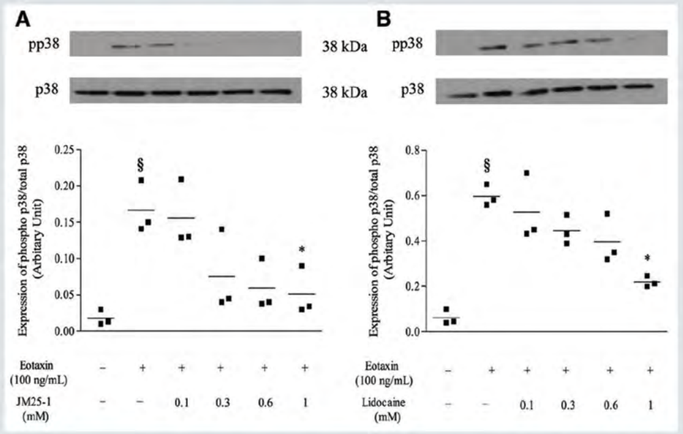


Fig. 8. JM25-1 prevented eotaxin-induced p38 MAPK phosphorylation in human eosinophils. Isolated human peripheral eo- sinophils were pretreated or not with JM25-1 (0.1 to 1 mM) (A) or lidocaine (0.1 to 1 mM) (B) for 15 min and stimulated with eotaxin (100 ng/ml, 1 min). Cell lysates were analyzed by Western blotting for phosphorylated p38 MAP kinase expression. The membrane was reprobed with anti-p38 as the loading control, respectively (the images represent one of the three independent experiments with similar results). Column scatter graphs represent the densitometry analysis of the bands presented as relative intensity of phosphorylated p38 MAP kinase (pp38) with respect to total p38 MAP kinase (p38). Horizontal lines represent the mean values (n = 3, three different eosinophil donors). Results were analyzed by Kruskal–Wallis test followed by the Dunn multiple comparison test. §P < 0.05 versus untreated group, *P < 0.05 versus eotaxin-stimulated group not treated with JM25-1 or lidocaine.

In conclusion, JM25-1, a lidocaine analogue with limited impact on Na+ channels and beneficial effects on airway smooth muscle and lung inflammation, holds promising perspectives as an alternative for treating life-threating conditions marked by airway hyper-reactivity and bronchoconstriction.

COMMENTS FROM AUTHOR

It is well accepted that drugs able to prevent bronchial spasm and inflammation may have therapeutic potential to control asthma symptoms. The local anesthetic lidocaine has received attention as a glucocorticoid mimetic agent in asthma therapy. It also prevents bronchospasm in response to airway instrumentation. However, aerolized lidocaine can also provoke bronchospasm by blocking sodium channels and attenuating bronchodilator neurogenic reflexes, indicating that caution in its use is required, particularly in patients with a reactive airway disease such as asthma. This paper capitalizes on the concept that the beneficial anti-inflammatory and antispasmodic properties of lidocaine are dissociated from the anesthetic one. JM25-1, a novel lidocaine analogue with limited sodium channel blockade activity, was more effective in reducing bronchial smooth muscle constriction, airway hyper-reactivity, lung inflammation, mucus exacerbation, and peribronchiolar fibrosis. Therefore, nebulized JM25-1 might be a means of achieving the antiasthmatic effects of lidocaine without the anesthetic effect.

BIOSYNTHESIS OF HUMAN DIAZEPAM AND CLONAZEPAM METABOLITES

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Núbia C. de Paula, Kelly C. F. A. Cordeiro, Paula L. de Melo Souza, Diogo F. Nogueira, Diego B. da Silva e Sousa, Maísa B. Costa, François Noel, Valéria de Oliveira

Since their discovery, benzodiazepines have become the most commonly prescribed drugs for the treatment of insomnia, anxiety and convulsions, and also as muscle relaxants and for anesthesia induction. They are currently the most frequently prescribed group of drugs for the control of anxiety worldwide. Recent studies have reported that compounds derived from 1,4-benzodiazepines have been found to exert an antiproliferative effect against cellular tumors. Benzodiazepines are extensively metabolized by cytochrome P-450 enzymes, particularly by CYP3A4 and CYP2C19; therefore, inhibitors of these enzymes may affect the metabolism of this class of drugs. The principal process of transformation is known to be demethylation in the liver. Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) is rapidly absorbed following oral administration, reaching maximum levels in 2 hours with a half-life of 20-50 hours. Its three main metabolites are N-desmethyldiazepam, oxazepam and temazepam, which are conjugated and excreted principally as a glucuronide in urine, N-desmethyldiazepam and oxazepam being metabolites common to other drugs of the same group. N-desmethyldiazepam is the principal pharmacologically active metabolite produced.

Hydroxylation at position 3 generates oxazepam (3-hydroxy-N-desmethyldiazepam), which is also active. Clonazepam (5-(2-chlorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one) is a partial benzodiazepine agonist with anticonvulsant, muscle-relaxant, and anxiolytic properties. The compound has a half-life of about 40 hours and time to maximum concentration in 2 hours. In humans, clonazepam is metabolized primarily to 7-AM by nitroreduction via hepatic cytochrome P450 and then N-acetylated to produce 7-ACT, which is excreted in the urine and feces following extensive biotransformation. Diazepam and clonazepam are biotransformed principally in the microsomal hepatic system by enzymes of the P450 cytochrome system subfamilies CYP1A2, 2C8, 2C19 and CYP3A4. For the benzodiazepines with substituents at the 1 or 2 position of the diazepam ring as shown in figure 1, the fastest metabolism involves the substitution and/or removal of the substituent.The majority undergoes microsomal oxidation, N-dealkylation and aliphatic hydroxylation, and in the phase II reactions the

metabolites are conjugated, forming glucuronide conjugates. Desmethyldiazepam has a half-life of more than 40 hours and is the active metabolite of chlordiazepoxide, diazepam, prazepam and clorazepate, being biotransformed into oxazepam. Clonazepam is a nitrobenzodiazepine metabolized by N-acetylation to 7-acetamido clonazepam (7-ACT) and to 7-aminoclonazepam (7-AM) by nitro reduction. Hydroxylation to 3-hidroxy clonazepam is also known. The extend of N-acetylation of this drug is under control of a polymorphic trait that determines the acetylator phenotype: rapid and slow acetylators. Slow acetylators excrete significantly less 7-ACT and more 7-AM than the rapid acetylators. The clonazepam benzophenone, a by-product of acid hydrolysis of clonazepam, can be useful at analysis and identification of presence of this benzodiazepine. Urine samples are usually hydrolysed with acid, the hydrolysis breaks down clonazepam and metabolites to benzophenones, yielding an increased sensitivity at analysis. The metabolites are useful in the clinical screening of the original drugs or as analytical reference standards. The determination and quantification of these drugs and their metabolites have numerous clinical, toxicological and forensic applications. In trials to evaluate the therapeutic efficacy of drugs both in the pharmaceutical equivalence and bioequivalence stages, the determination of metabolites is of key importance. Traditionally, in vivo studies of drug metabolism involve administering the drug to various species of laboratory animal (mice, dogs, cats, guinea pigs, rats, etc.), which are used as system models. The plasma and urine of these animals is subsequently analyzed. In vitro studies are used to complement the data obtained by perfusion in organs, tissues, cell cultures and microsomal preparations. These methods have various limitations, including cost, ethical controversies on the use of animals in research, and toxicity, which limits the amount of the drug that can be administered and, consequently, restricts the quantity of metabolites isolated. Identification of metabolites from animal sources and clinical samples may be further hampered by the reduced quantity of material produced (micrograms).The use of filamentous fungi for reactions catalyze is a promising strategy for the large scale production of metabolites from a variety of drugs (Fig.1). Production of milligrams of metabolites using whole microorganisms may be cheaper, faster and more cost-effective compared to the use of animals, cell culture or mammalian enzymatic systems. Filamentous fungi are able to metabolize polycyclic aromatic hydrocarbons through the cytochrome P450 monooxygenase and epoxide hydrolase enzymatic systems by a sequence of reactions similar to the process that occurs for these hydrocarbons in mammals.Since these active metabolites are broadly applicable and the process of their synthesis is very complex, the objective of this study was to produce compounds such as desmethyldiazepam, oxazepam, 7-acetamido clonazepam and 7-amino clonazepam for future pharmacological trials of new activities and to obtain standard chemical substances of metabolites on a laboratory scale.

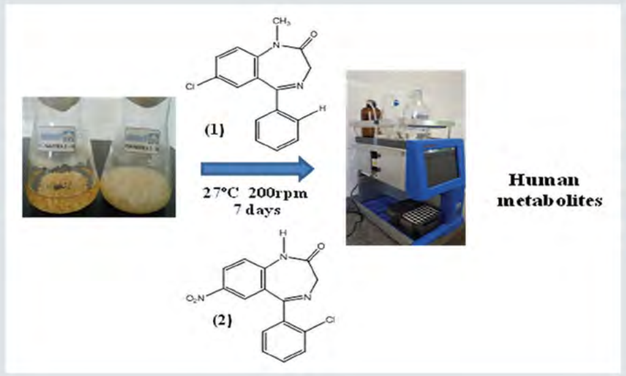

Fig.1 In vitro benzodiazepines (1) diazepam and (2) clonazepam metabolites production by filamentous fungi and their purification in preparative HPLC system.

The incubation with diazepam was demonstrate that Cunninghamella echinulata (ATCC 9244) produces only metabolite (1), Rhizopus arrhizus (ATCC 11145) metabolizes diazepam and produces three metabolites, 1, 2 and 3. Beauveria bassiana (ATCC 7159) produces one metabolite of clonazepam, metabolite 4. Chaetomium indicum LCP 984200 was able to form metabolites 4 and 5.

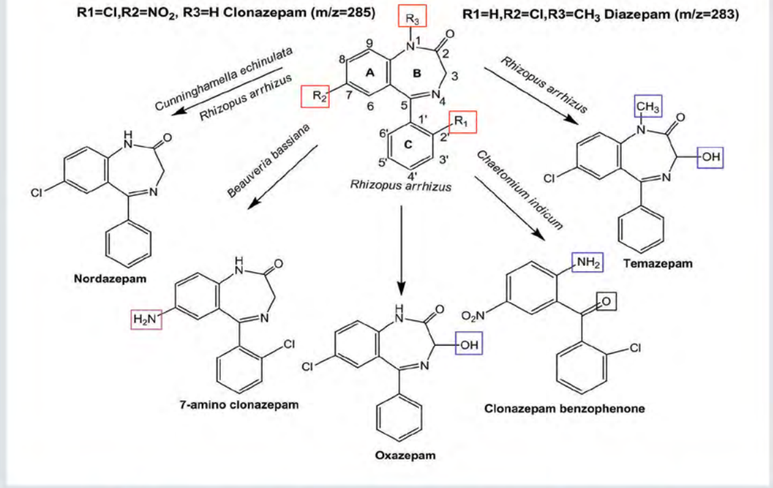

Fig.2 Benzodiazepines and its human metabolites produced by biosynthesis.

Diazepam and clonazepam metabolites were successfully identified by GC-MS and by comparison with chemical substances of reference. A selection carried out among nine strains frequently cited in the literature and used in our laboratory for the production of xenobiotic metabolites identified four strains capable of producing the desired products. Active metabolites of diazepam may be produced by biosynthesis using filamentous fungi to create nordazepam alone or in combination with oxazepam and temazepam, depending on the strain selected. All these features demonstrate the usefulness and versatility of biosynthesis catalyzed by fungi as a tool for production of active human metabolites. Scale up of the reactions can be done in bioreactors thereafter if necessary, adjusting the concentration of the compound, reaction time and aeration.

COMMENTS FROM AUTHOR

A screening of fungal and microbial strains allowed to select the best microorganisms to produce in high yields some of the human metabolites of two benzodiazepine drugs, diazepam and clonazepam, in order to study new pharmacological activities and for chemical standard proposes. Among the microorganisms tested, Cunninghamella echinulata ATCC 9244 and Rhizopus arrhizus ATCC 11145 strains, were the most active producers of the mains metabolites of diazepam which included demethylated, hydroxylated derivatives. Beauveria bassiana ATCC 7159 and Chaetomium indicum LCP 984200 produced the 7 amino-clonazepam metabolite and a product of acid hydrolysis of this benzodiazepine. Nowadays with all the difficulties of use of laboratory animals, the use of in vitro models for the study of drug metabolism which enables the achievement of satisfactory quantities of metabolites is presented as a very useful strategy.

NOVEL AGONIST OF ADENOSINE RECEPTOR INDUCES RELAXATION OF CORPUS CAVERNOSUM IN GUINEA PIGS: AN IN VITRO AND IN VIVO STUDY

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Erectile dysfunction (ED), a high worldwide prevalence disease, is defined as the inability to reach and/or maintain a penile erection sufficient for vaginal intercourse. Since discovery, PDE5 inhibitors have been used as a first-line therapy for ED, as recommended by the American Urological Association (AUA) and the European Association of Urology (EAU). However, up to 35% of patients with ED fail to respond to this treatment. Thus, a new pharmacological strategy based on interaction with an alternative target or simultaneously with the PDE5 molecule could be helpful for the treatment of non-responding patients. We thought that the highly distributed in the corpus cavernosum A2A receptor, which activation by adenosine increases cAMP and NO levels promoting smooth muscle relaxation and erection (Fig. 1), could be a relevant target for ED drug development.

Recently, a series of new N-acylhydrazone derivatives with vasodilator activities were synthesized from a Brazilian natural product, safrole, obtained from sassafras oil. The prototype compound for this series was LASSBio-294 (1), which has its structure based on the molecular simplification of pyridazinonephosphodiesterase inhibitors, promoted vasodilatation through the guanylate cyclase/cyclic guanylate monophosphate pathway in aortic rings. Preliminary studies performed in aortic rings from rats indicated that one of the analogues,(3,4-dimethoxyphenyl-N-methyl-benzoylhydrazide), named LASSBio-1359 (2), caused vascular relaxation similar to LASSBio-294. In addition, LASSBio-1359 reversed pulmonary arterial hypertension in rats through activation of the adenosinergic A2A receptor. Thus, according to these proven vasoactive effects of LASSBio-1359, we proposed that it could further induce CC relaxation by A2A receptor activation.

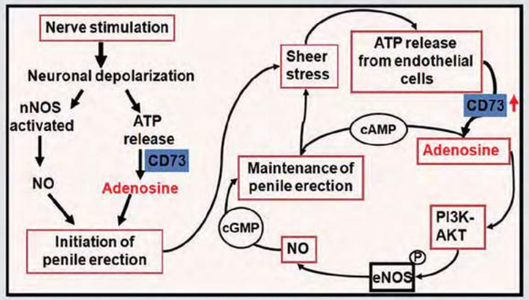
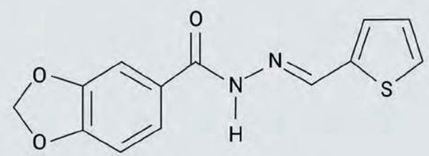
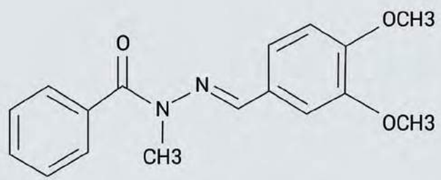


Fig. 1- Regulation of adenosine production and mechanism for initiating and maintenance of penile erection. Adenosine receptor A2A is distributed in both endothelial and smooth cells. The adenosine-induced corpus cavernosum relaxation followed by penile erection is not depend on inhibition of phosfodiesterase -5 (PDE5). Modified from Wen and Xia (ArterioscIerThrombVascBiol2012:32:845-850).



LASSBio-294
(1)



LASSBio-1359
(2)

In vitro experiments demonstrated that LASSBio-1359 caused relaxation on phenylephrine (Phe)-induced contractures of isolated CC from guinea pig in a dose-dependent manner (Fig. 2), which blockage by ZM241385 suggested interaction with A2A adenosine receptor.

Translational effects from in vitro to in vivo experiments demonstrated the potential value of LASSBio-1359 as a drug for the treatment of ED. Indeed, LASSBio-1359 was more effective to increase intra penile (IP) blood pressure in guinea pigs compared to sildenafil (Fig. 3). Interestingly, increased amplitude of IP pressure with oscillations, instead of sustained contracture, suggest less blood retention and risk of priapism due to production of IP blood clot.

Isobolographic analysis revealed a significant synergistic interaction between LASSBio-1359 and sildenafil (Fig. 4). This finding indicates that LASSBio-1359 may increase the responsiveness to the PDE5 inhibitors and as consequence reduces the dosage and side effects of this group of compounds. The action of LASSBio-1359 on adenosine A2a receptor located at vascular smooth muscle not dependent on integrity of endothelial cells represents a new approach for the treatment of ED. It is known that patients suffering of systemic vascular disease as hypertension and diabetic are part of PDE5 inhibitors-resistant ED.

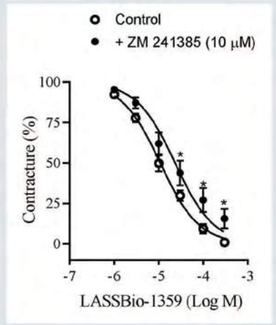


*Fig. 2-Relaxing effect of LASSBio-1359 on Phe-induced contracture of isolated corpus cavernosum of guinea pig in the absence (control) or presence of pre-treatment with the adenosine A2A receptor antagonist, ZM241385. Each point represents the average ± S.E.M. (n= 4-6). *P < 0.05 comparedtocontrol.*

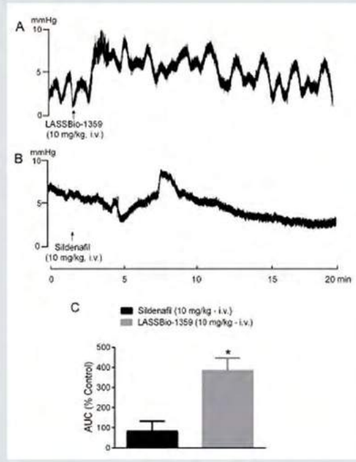


*Fig. 3- Typical tracing of intra penile blood pressure measurement ofguineapigin thecontrol and after administration of LASSBio-1359 (10 mgkg i.v.)(A) or sildenafil (10 mgkg i.v.) (B). Area under the curve (AUC) measured from the baseline was plotted (C). Note increase of amplitude of oscillation induced by LASSBio-1359. The data in C represents mean ± SEM (n=4).*P<0.05.*

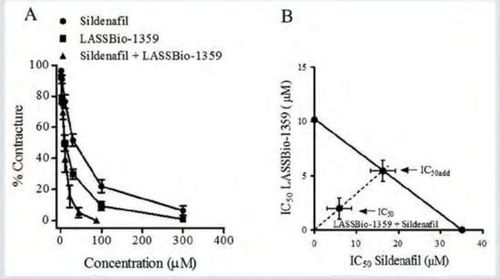


Fig. 4- Relaxing effect of sildenafil, LASSBio-1359 or mixture of sildenafil plus LASSBio-1359 on Phe-induced contracture of isolated corpus cavernosum of guineapig(A). Isobolograms showinginteractionofLASSBio-1359withsildenafil (B). The points of ordinate and abscissa represent the ED50 for LASSBio-1359 andsildenafil,respectively. Connectionofthesepointswasusedtoconstructthe additiveline. Notethattheexperimental ED50 wassignificantlylocatedattheleft andbelowthetheoretical ED50. Synergisticinteractionbetween LASSBio-1359 andsildenafilwasconfirmedusingstatisticalStudent'st-test.

COMMENTS FROM AUTHOR

The pharmacological treatment of erectile dysfunction (ED) is based on selective inhibition of phosphodiesterase type 5 enzyme (PDE5) located at endothelial cells/smooth muscle complex of corpus cavernosum(CC). Several tens of millions male individuals in the world have recognized the success of this treatment. However, approximately 35% of ED patients including those suffering of hypertension, atherosclerosis, diabetes and post-prostatectomy do not respond the PDE5i treatment. Finding new compounds interacting with alternative target beyond PDE5 was the main subject of this project. We thought that the highly distributed in the corpus cavernosum A2A receptor, which activation by adenosine increases cAMP and NO levels promoting smooth muscle relaxation and erection, could be a relevant target for ED drug development. Thus, this study characterized a new N-acylhydrazone derivative, 3,4-dimethoxyphenyl-N-methyl-benzoylhydrazide - LASSBio-1359, in which the CC relaxing activity measured in in vitro experiments was more potent than the PDE5 inhibitor sildenafil. Interestingly, the adenosine A2a receptor located both at endothelial and smooth muscle of corpus corpora in the penile was the target for the action of LASSBio-1359. Additionally, the isobolographic analysis revealed a significant synergistic interaction between LASSBio-1359 with sildenafil. This find suggested that single use of LASSBio-1359 or its combination with sildenafil could represent and advance for ED treatment. Translational effects from in vitro to in vivo experiments confirmed the potential value of LASSBio-1359 as a drug for the treatment of ED.

DYNAMIC WEIGHT BEARING (DWB) ISAN EFFICIENT AND PREDICTABLE METHOD FOR EVALUATION OFARTHRITIC NOCICEPTION AND ITS PATHOPHYSIOLOGICAL MECHANISMS INMICE

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Fernando Q. Cunha & Thiago M. Cunha

Arthritis is an inflammatory articular disorder involving one or more joints and characterized by pain, swelling, joint stiffness and disability. Pain is considered severe in 60% of patients and when combined with mechanical factors, including cartilage degradation and psychological aspects, causes moderate or severe disability in 70% of affected individuals. To better understand the pathophysiological mechanisms involved in arthritic pain, basic research studies are fundamental. However, the assessment of articular nociception in experimental animals is a challenge, especially because available methods present some limitations. For example, in almost all behavioral nociceptive tests, there is one direct investigator responsible for application of the nociceptive stimuli (mechanical, thermal) and/or visualization/quantification of the behavior/nociceptive end-point, which could be considered subjective analyses.

DWB is a device that measures the difference of weight exerted by each paw on a full-sensor floor, allowing to animals walk freely without experimenter interference. These characteristics make this method unique in evaluating the natural behavior of animals under nociceptive conditions. This was proven in models of inflammatory, neuropathic and cancer nociception in rat paws, and in CFA-induced paw inflammation in mice; however, no study until now has used DWB to evaluate joint nociception.

DWB with its components. A – sensor floor, B – acrylic cage, C – data transductor, D – software, E - camera

Using AIA (antigen induced arthritis), in both Balb/c and C57Bl/6 mice, we show that DWB is not only an effective and objective method for evaluation of articular nociception, is predictable for study of clinically-used drugs as well as the pathophysiological mechanisms involved in arthritic pain.

In our experiments, DWB detect dose- and time-dependent increase in joint nociception during AIA and is able to detect the dose-response effects of different classes of analgesics: non steroidal anti inflammatories: indomethacin and etoricoxib; corticosteroids: dexamethasone; immunobiologicals: infliximab and disease-modifying antirheumatic drugs (DMARDs): methotrexate. Using DWB, it wasalso possible to evaluate the participation of spinal glial cells (microglia and astrocytes) and cytokines (IL-1β and TNFα) for the genesis of joint nociception during AIA. Compared to other methods, DWB offersa major advantage by eliminating interference from the experimenter, making it a unique, objective anddifferential test in the study of articular nociception. Moreover, the longer observation time of animalsin DWB (5 minutes) compared to static weight bearing (5 to 10 seconds) is important for improvedand more reliable evaluation. Moreover, the freedom of movement by the animal reduces the possibilityof stress-induced analgesia. Furthermore, the possibility of mice to execute the exploratory behavior,specifically rearing behavior, improves the evaluation of joint nociception by requiring articular force,which is reduced during hyperalgesia.

In summary, our results indicate that DWB is an objective and sensitive method for assessingnociception in experimental models of arthritis. Furthermore, indicate that DWB can be usedto assess the efficacy of clinically used analgesic drugs for joint pain and may be of essential utility inthe preclinical development of novel analgesic drugs. Lastly, it is plausible to suggest that DWB is a usefultool for investigating the pathophysiological mechanisms involved in arthritic pain.

COMMENTS FROM AUTHOR

An experimental model of pathological pain relies on effective methods to evaluate its parameters. Until the moment, it is a challenge. It is hard to assess joint function when the responses exhibited by the animal are difficult to interpret and require extensive training for the experimenter. Furthermore, the correlation between behavioral responses observed in pre-clinical trials and clinical responses is unsatisfactory. Proof of this is that approximately 80% of prototype analgesic drugs tested in humans failed in phase III. Thus, establishing new criteria for animal tests is essential for the development of a novel pharmacological therapy to control pain. In this context, the standardization of DWB offers a unique possibility to improve the evaluation of articular nociception, with predictability to study of new analgesic drugs for arthritis treatment, as well as, pathophysiological mechanisms involved in chronic articular pain, thus contributing to therapeutic development of articular pain.

PARTIAL AGONISM AND FAST DISSOCIATION OF LASSBIO-579 AT DOPAMINE D2 RECEPTOR

Prog. Neuropsychopharmacol. Biol. Psychiatry 62 (2015) 1–6 [DOI]

Thais E.T. Pompeu, Fernando M. do Monte, Barbara Bosier, Carlos A.M. Fraga,
Eliezer J. Barreiro, Ricardo Menegatti, Emmanuel Hermans, François Noël

INTRODUCTION

Schizophrenia is a severe mental disorder characterized by positive and negative symptoms and cognitive dysfunction. The pharmacological treatment of schizophrenia essentially relies on drugs classified as typical (first generation) and atypical (second generation) antipsychotics. The mechanism supporting the atypical profile has not been unveiled, even for clozapine, and could have different backgrounds as suggested by several concepts that have been proposed such as dual antagonismat 5-HT2A and D2 receptors (Meltzer, 1989), selective blockade of D4 receptors (clozapine), partial agonism at 5-HT1A receptors(Newman-Tancredi & Kleven, 2011), rapid dissociation (Seeman, 2002)and/or partial agonism (Strange, 2008)at D2 receptors.The relative failure to treat all the symptoms of schizophrenia and the refractoriness of approximately 15% of patients to both typical and atypical antipsychotics (AAP) and the concern with the potential of AAP to cause severe metabolic side effects support the need for developing more effective and safer antipsychotics.

We previously described (Menegatti et al. 2003) the synthesis of LASSBio-579(1-[1-(4-chlorophenyl)-1H-4pyrazolylmethyl] phenylhexahydropiperazine), that has been elected as a new atypical antipsychotic lead compound based on in vitro and in vivo assays classically used in antipsychotic drug discovery programs. Our binding studies defined LASSBio-579 as a moderate affinity ligand of D2-like/D4/5-HT1Areceptors (Ki values around 0.2-0.4 μM) with low affinity for the 5-HT2A receptor (Ki around 7 μM) and other receptors putativelyinvolved in atypicality (Neves et al. 2010; Pompeu et al. 2013).We also identified and synthesized the main metabolite of LASSBio-579 in rats as its p-hydroxylated derivative (LQFM 037), and reported its binding to the D2 and D4 receptors at submicromolar concentrations, indicating that it could participate to the antipsychotic-like effects observed after administration of the parent compound(Gomes et al. 2013).antitrypanosomatid lead-candidate.

OBJECTIVE

In an attempt to better understand the molecular mechanism of action ofLASSBio-579 and of LQFM 037, the aim of this work was to evaluate their intrinsic activity and binding kinetics at the dopamine D2 receptor.

RESULTS AND DISCUSSION

In transfected HEK cells expressing the D2L receptor under an inducible promoter, LASSBio-579 and LQFM 037, but not clozapine, behaved as weak partial agonists in [35S]-GTPγSbinding assays only when performed inoptimized conditions (i.e. high level of transfection and NMDG buffer instead of NaCl buffer; Fig.1) previously shown to be necessary for evidencing the partial agonist profile of aripiprazole. The effect of LASSBio-579 and LQFM 037 was a little bit smaller than that observed with aripiprazole (Emax = 36.4% and 32.6% of stimulation above the basal level, respectively, vs. 54% of stimulation for aripiprazole) and much smaller than observed with the full agonist dopamine (261%). On the other hand, domperidone and clozapine did not stimulate [35S]-GTPγS binding, neither in the NMDG buffer, as expected for (neutral) antagonists of the D2 receptor.

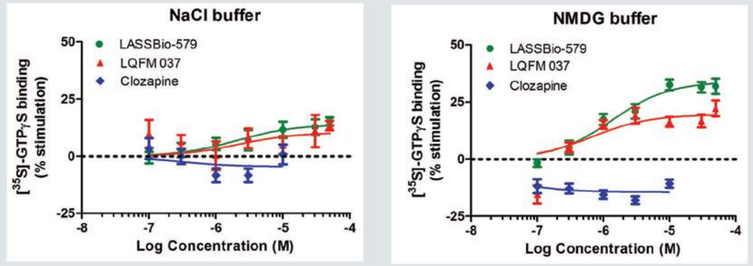

Figure 1: Effect of LASSBio-579, LQFM 037 and clozapine on [35S]-GTPγS binding in the NaCl and NMDG containing buffer. Data are expressed as the means from four independent experiments.

Based on the "fast-off" theory for explaining the atypicality of antipsychotic action (Kapur&Seeman, 2000), we decided to compare the kinetics of binding of our compounds withthose of haloperidol and clozapine, as controls for typical and atypical antipsychotics, respectively. As radiolabeled derivatives of LASSBio-579 and LQFM 037 are not available, we decided to adapt the competition association assay described originally by Motulsky and Mahan (1983) using [3H]-YM09151-2, a high-affinity and selective antagonist ligand for the dopamine D2 receptor. Thus, the kinetic of [3H]-YM09151-2 binding to rat striatal D2 receptors was determined in the absence and presence of a single concentration of the unlabeled competitors, chosen in order to achievesimilar inhibition at equilibrium. Usingthe kinetic rate indexbased on the strategy of the dual-point competition association assay validated by Guo et al. (2013) weshowedthat our compounds share a similar kinetic profile with clozapine, distinct from the typical antipsychotic haloperidol (Fig.2 and Table 1).

The kinetic rate index was obtained dividing the binding value calculated at 5 min (Bt1) by the value at 60 min (Bt2), as described in details in the Methods. Data are expressed as mean ± SEM from three to seven independent experiments. * vs control; # vs haloperidol; * or #; ** or ##; *** or ###: p< 0.05; 0.01; 0.001, One way ANOVA followed by Newman-Keuls post-hoc test.

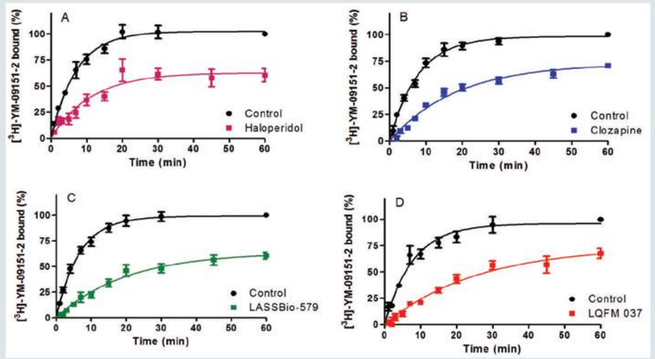

Figure 2.Kinetics of [3H]-YM09151-2 binding to rat striatal D2 receptors in the absence and presence of competitors. Data expressed as percent of the control at 60 min are the means from three to seven independent experiments. The curves were fitted according to the model of one phase exponentialassociation.

Compound (concentration)	% Inhibition (at equilibrium)	Half-life (min)	Kinetic rate index (Bt_1/Bt_2)
Control	-	5.10 ± 0.27	0.510 ± 0.020
Haloperidol(5 nM)	38.6 ± 6.4	7.70 ± 0.63	0.360 ± 0.024**
Clozapine(0.3 µM)	26.5 ± 2.3	12.6 ± 0.96***#	0.250 ± 0.015***#
LASSBio-579(0.3 µM)	33.2 ± 3.5	16.2 ± 2.3***##	0.230 ± 0.028***#
LQFM 037(0.3 µM)	22.3 ± 1.6	17.9 ± 1.8***##	0.190 ± 0.012***#

The kinetic rate index was obtained dividing the binding value calculated at 5 min (Bt_1) by the value at 60 min (Bt_2), as described in details in the Methods. Data are expressed as mean ± SEM from three to seven independent experiments. * *vs* control; # *vs* haloperidol; * or #; ** or ##; *** or ###: p< 0.05; 0.01; 0.001, One way ANOVA followed by Newman-Keuls *post-hoc* test.

Table 1. Kinetics parameters from the competition association assay: half-life time (t1/2) and kinetic rate index.

CONCLUSION

LASSBio-579 and its main metabolite (LQMF 037) share with aripiprazole, but not clozapine, the property to behave as weak partial agonists at the D2L receptor, at least in defined experimental conditions. Our compounds also have a binding kinetic profile similar to clozapinein vitro, indicating a rapid dissociation from the target(D2) receptor, at variance with haloperidol. These two characteristics could contribute tothe atypical-like profile observed after administration of LASSBio-579 to rodents, in different models of positive and negative symptoms.

COMMENTS FROM AUTHOR

In the scope of a program aiming to select drug candidates for the treatment of schizophrenia (Bioorg Med Chem 18 (2010) 1925-1935; Behav Brain Res 237 (2013) 86– 95; Eur J Med Chem 66 (2013) 122-134), we previously elected LASSBio-579 (1-[1-(4-chlorophenyl)-1H-4pyrazolylmethyl] phenylhexahydropiperazine) as a new atypical antipsychotic lead compound based on in vitro and in vivo assays classically used in antipsychotic drug discovery programs.

Here we report original data evaluating the intrinsic activity and binding kinetics of LASSBio-579, and its main metabolite LQFM 037, at the dopamine D2 receptor.

Our conclusion is that partial agonism similar to aripiprazole and fast dissociation at dopamine D2 receptor similar to clozapine, could explain the atypical-like profile observed after administration of LASSBio-579 to rodents, in models of positive and negative symptoms of schizophrenia.

TOTAL SYNTHESIS OF THE OXOPOLYENE MACROLIDE (−)-MARINISPOROLIDE C

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Luiz C. Dias, Emílio C. de Lucca Jr.

The oxopolyene macrolide (−)-marinisporolide Cwas isolated in 2009 from a saline culture of the marine actinomycete Marinispora, strain CNQ-140 (Figure 1).

Inspired by the challenge of forging a 34-membered macrolactone, containing 11 stereogenic centers, an internal spiroketal with one anomeric effect, a methyl group in α position of carbonyl, the C33 oxygen flanked by two tertiary carbons, and a conjugated pentaene system we decided to synthesize the marinisporolide C using several aldol reactions as key steps.

Due to its robustness and convergence, we were able to synthesize the C9–C35 fragment in gram scale.

After a number of coupling reactions and protecting group manipulations, the first total synthesis of marinisporolide C was concluded in 25 steps (longest linear sequence) with an overall yield of 1%, which corresponds to an average yield of 83% per step.

Synthetic and natural marinisporolide C were found to be identical by a variety of analytical methods (1H and 13C NMR, HRMS, UV/Vis, and circular dichroism) and this total synthesis confirms the relative and absolute stereochemical assignment by Fenical and co-workers.

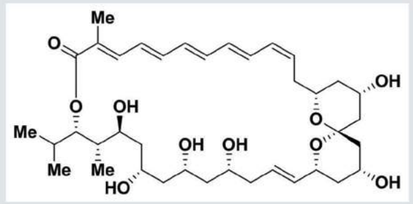

Figure 1: Marinisporolide C.

COMMENTS FROM AUTHOR

When we startedwork onthe total synthesisof(−)-marinisporolideC, our main objective was to demonstratethat thealdol reaction, studied byour groupfor more than10 years,is a robustandefficient strategyfor obtainingcomplex naturalproducts and we are very proud to show that the five pivotal aldol reactions, responsible for the constructionof 5C–C bonds and 6stereogeniccenters, provided a straightforward approach to the convergent synthesis of the marinisporolide C skeleton.

2015

EVENTS PROMOTED

The National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR), during the year, organizes and takes part of events with the goals of strengthening cooperation among its research groups, tightening the bonds between the National Institutes of Science and Technology (INCTs), as well as of establishing partnerships with companies and other Institutions to promote and publicize science through courses and lectures, taught by INCT-INOFAR, researchers at events, round tables, and science fairs, contributing, therefore, for scientific awareness in Brazil.

XXI SUMMER SCHOOL

IN MEDICINAL CHEMISTRY

The XXI Summer School in Medicinal Chemistry (SSMC), one of the most awaited events in the year for undergraduate and graduate students in Pharmaceutical Sciences, took place between the days of January 26 and 30, in the Center for Health Sciences (CCS) of the Federal University of Rio de Janeiro (UFRJ).

The SSMC has taken place since 1994, organized by the Laboratory of Evaluation and Analysis of Bioactive Substances (LASSBio/UFRJ - http://www.lassbio.icb.ufrj.br/). The 21st edition of SSMC gathered students from different parts of Brazil and other countries. The activities of the event were divided into five consecutive days. The Summer School programming had a round table, courses, and conferences taught by renowned Brazilian and foreign specialists. The course "Highlights in Medicinal Chemistry", which has now existed for a decade, was done in partnership with the International Union of Pure and Applied Chemistry (IUPAC), and had the participation of 11 important scientists in the field of Medicinal Chemistry, teaching both Highlights and the XXI SSMC conferences.

One of the highlights of the Summer School was the participation of Dr. Janos Fischer, director of the Sub-Committee on Drug Discovery and Development of IUPAC, who presented the conference "Serendipitous Target-based Drug Discoveries", mentioning examples of important drugs discovered "by chance" throughout the past 50 years.

Another highlight was the launch of the 3rd edition of the book "Medicinal Chemistry: molecular bases of the action of drugs", by authors Professors Eliezer J. Barreiro and Carlos Alberto Manssour Fraga. The fully updated version of the publication approaches the main advances and discoveries in the area of Pharmaceutical and Medicinal Chemistry. The participants of the XXI SSMC were also able to visit the facilities of the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**), closely seeing where countless research projects on drugs and medicines are developed.

The 21st edition of the Summer School in Medicinal and Pharmaceutical Chemistry went above expectations for most students due to the richness of the content provided to young students.

Students and speakers in the XXI Summer School in Medicinal and Pharmaceutical Chemistry

RESEARCHER OF THE YEAR AWARD

GOES TO UFRJ STUDENT

Allan Kardec with professors Eliezer J. Barreiro and Patricia Dias Fernandes

Allan Kardec Nogueira de Alencar, pharmacist and Master in Pharmacology and Medicinal Chemistry, a doctoral student in the Pharmacology and Medicinal Chemistry Program at the Institute of Biomedical Sciences of the Federal University of Rio de Janeiro (UFRJ) – the only course in Pharmacology and Medicinal Chemistry in Brazil (rated 5 by CAPES), under the guidance of Professors Eliezer J. Barreiro and Gisele Zapata-Sudo, was awarded Researcher of the Year (2014), in the Student Researcher category. The ceremony to hand in the award was held on June 1, in the Pharmacology Auditorium at UFRJ, by Professor Eliezer J. Barreiro. As well as the Student Researcher category, Professor Dr. Thiago Mattar Cunha, from the University of São Paulo (USP) **INCT-INOFAR**, was awarded as Full Researcher.

Created in 2012, the award is given by the biotechnology researchers network Biotech-Space. The choice of Researcher of the Year is made by a committee made up of respected researchers in bioscience to publicize innovative work done by professionals all over Brazil, to both the general public and professionals in the field. Due to the confinement caused by the improvement of their research, scientists tend to interact only with other experts. Therefore, their work is not well-known in society, remaining only within the confines of the scientific community.

With important contributions to scientific knowledge, Allan Kardec was part of projects in the Laboratory of Cardiovascular Pharmacology, located in the Institute of Biomedical Sciences of UFRJ. He has had 6 papers published in international journals (International Journal of Cardiology, British Journal of Pharmacology and Journal of Urology), has taken part in a some congresses – 5 local and 2 abroad – as well as has contributed to the work of colleagues in the laboratory that is part of the **INCT-INOFAR** network. During his doctorate, he was awarded a scholarship by the National Council for Scientific and Technological Development (CNPq), participating in research projects at Wake Forest University (USA).

"To speak of Allan is not hard work, due to his qualities and the countless research results he has achieved. This young man, who came from Paraiba 6 years ago, had a fast and positive development in the beginning of what is a promising career. I am honored to be able to contribute to his training and proud to know his work was recognized through this award by Biotech", says the student's advisor by email. The student, who came from the Federal University of Paraíba, was part of the research on understanding and treating cardiovascular disease, more specifically, Pulmonary Arterial Hypertension.

According to Professor Eliezer J. Barreiro, "the young man has a characteristic that sets him apart from other students: he has a thirst for knowledge that keeps him up at night if he has a question". The young man was also awarded as a rated 10 doctoral scholar by the Foundation for the Support of Research in the State of Rio de Janeiro (FAPERJ) and was awarded in biomedical congresses. The Researcher of the Year award, as well as acknowledging the work done by researchers, encourages them to continue becoming increasingly qualified. "The work was done with my advisors, and the result was this award", celebrates Allan.

NEGLECTED DISEASES

ARE THE TOPIC OF SEMINAR SPONSORED BY INCT-INOFAR

With the support of the National Institute for Science and Technology of Drugs and Medicines (**INCT-INOFAR**) and the Program for Research and Development of Drugs – of the Institute for Biomedical Sciences of UFRJ, took place in the Pharmacology auditorium (CCS/UFRJ), in June, the seminar "New arylamine derivatives as new potential antichagasic agents", taught by Dr. Silvia Perez Silanes, from the University of Navarra – Spain.

In her first visit to Brazil, the researcher spoke about her main area of research – Medicinal Chemistry, aimed at neglected diseases, especially Chagas disease, which was the topic of her presentation.

Her main line of work in Medicinal chemistry is the synthetic area. She is currently the director of the Master program in Investigation and Development and Innovation in Drugs at the University of Navarra.

Dr. Silva Perez Silanes

Professors Eliezer J. Barreiro and John A. Beutler

SEMINAR WITH EXPERT IN NATURAL PRODUCTS TAKES PLACE WITH **INCT-INOFAR** SUPPORT

With the support of the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) and from the Program of Research in Drug Development (PPDF) of UFRJ, an International Seminar on "Natural Products as Cancer Drug Leads" was taught by Professor John A. Beutler.

Dr. Beutler, who was invited by **INCT-INOFAR** coordinator Dr. Eliezer J. Barreiro, is a researcher at the National Cancer Institute – USA. He has already identified, extracted, isolated, and characterized several natural products with the potential to be new cancer-fighting drugs.

The scientist, alongside his team, advances in two natural product projects: englerines for kidney cancer and Ewing's sarcoma (a form of malignant bone tumor) and schweinfurthins for Central Nervous System (CNS) tumors.

In his speech he described the results achieved in the development of englerine A, a sesquiterpene derivative with important antiproliferative properties.

XXI SUMMER SCHOOL
IN MEDICINAL CHEMISTRY

2015

PRESENCE IN EVENTS

SANTANDER UNIVERSITY AWARD

Professor of the Institute of Chemistry of the University of Campinas (UNICAMP), Luiz Carlos Dias, member of the Committee of Governance and Follow-up (CGA) of the National Institute for Science and Technology of Drugs and Medicines (**INCT-INOFAR**), was one of the winners of the 10th edition of the Santander Universities Award, announced in November in the city of São Paulo.

Promoted by Santander Bank, through its Global Division Santander Universities, the award tries to support and encourage scientific production, focusing on innovative initiatives, the use of new technologies and the promotion of relationships between Universities and Industries. In the area of promotion of science and innovation, the Santander award was divided in six categories: Industry, Innovation, Communication, Education, Biotechnology, and Health. The winner in the Health category was scientist Luiz Carlos Dias, for his research titled "Optimization of Lead Compounds for the Treatment of Tropical Parasitic Diseases".

With an undergraduate degree in Chemistry from the Federal University of Santa Catarina (UFSC), Luiz Carlos Dias has a Doctorate in Chemistry from UNICAMP and a Post-Doctorate from Harvard University, USA. He is a full professor at the IQ/UNICAMP, where he has researched compounds for the treatment of tropical parasitic diseases and taught since June 1992.

INTERNATIONAL AWARD OF RECOGNITION OF WOMEN IN SCIENCE

Researcher from the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**), Carolina Horta Andrade, received the L'Oréal-UNESCO award for Women in Science from International Rising Talents, in March 2015, at the University of Sorbonne, in Paris.

Doctor in Drugs and Medicines from the Faculty of Pharmaceutical Sciences of the University of São Paulo (USP), Carolina was awarded for her discovery of a multifunctional drug for the treatment of Leishmaniasis, a disease affecting millions worldwide.

The researcher was one of the seven winners of the national edition of the Women in Science Award, 2014 edition, promoted by L'Oréal, by the United Nations Education, Science, and Culture Organization (UNESCO) and by the Brazilian Academy of Science (ABC).

Aside from being part of **INCT-INOFAR**, the scientist is an adjunct professor at the Faculty of Pharmacy at UFG and the chief researcher of a research group from the National Council for Scientific and Technological Development (CNPq/MCTI) at the Laboratory of Drug Design and Molecular Modeling.

38th ANNUAL MEETING OF THE BRAZILIAN SOCIETY OF CHEMISTRY

The National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) was represented in the 38th Annual Meeting of the Brazilian Society of Chemistry (SBQ), which took place in May 2015 in Águas de Lindóia, SP, through the participation of Professors Luiz Carlos Dias (IQ/UNICAMP), member of the Governance and Follow-Up Committee (CGA) of **INCT-INOFAR**, and Carlos Alberto Manssour Fraga (**LASSBio**/UFRJ).

Professor Dias presented the conference "A tribute to the wonderful and enchanting... Chemistry! From basic research to collaborations with MMV and DNDi in the area of neglected illnesses", during the opening ceremony of the event. He reported on how his work has been for over 20 years in the Institute of Chemistry at UNICAMP. The scientist also described the contributions by his research group in the total or formal synthesis of natural products such as: criptocanol A, pyronetine, basiliscamides A and B; crocacines C and D; callistatin A; goniotrionine; salinecetal; pteridic acids A and B; and more recently, nhatrangine and marinesporolide A.

Aside from that, the Professor presented the contribution of his research group in the synthesis of active principles for generic drugs, with incremental and occasionally radical innovation. The work done within **INCT-INOFAR** has presented results, such as the synthesis of antilipemic drug atorvastatin, with a synthetic route different from that of the original patent; antidepressant fluoxetine; and antihypertensive valsartan.

Finally, Professor Dias spoke about the collaboration of his research laboratory with the Drugs for Neglected Diseases Initiative (DNDi) and with Medicines for Malaria Venture (MMV), non-governmental research agencies, which attempt to optimize lead compounds for the treatment of tropical diseases such as Chagas and Malaria.

Professor Carlos Manssour Fraga presented the conference "Medicinal Chemistry in the XXI century and the invention of drug candidates for multifactorial chronic illnesses", showing the current scenario related to the development of multitarget drugs, in the context of both academia and pharmaceutical industries.

The scientist reported the contributions of the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**), in the development of multitarget drug candidates, highlighting compounds LASSBio-294 for treatment of congestive cardiac insufficiency, one of the main molecules planned in the laboratory; LASSBio-1135, for the treatment of neuropathic pain; and LASSBio-1359, for the treatment of pulmonary arterial hypertension.

INCT-INOFAR MEMBER ELECTED FULL MEMBER OF ACIESP

Professor Fernando de Queiroz Cunha, vice coordinator of the National Institute of Drugs and Medicines (**INCT-INOFAR**), was elected by the Academy of Sciences of the State of São Paulo (ACIESP) Full Member in the area of Biosciences.

Full Professor at the University of São Paulo (USP) and member of the Brazilian Academy of Sciences (ABC), Fernando Cunha is currently an ad doc consultant for the National Council of Scientific and Technological Development (CNPq). He also acts as a consultant for the Foundation for the Support of Research in the state of São Paulo (FAPESP).

The Academy of Sciences of the State of São Paulo (ACIESP) conducts meetings, symposiums, congresses and scientific conferences at state, national, and international levels. It organizes, supports, and follows projects of scientific investigation and promotion or of a cultural character, when of interest for the development of science. The elections, which take place every two or three years, had its results with the list new members publicized the ACIESP website.

Professor Fernando de Queiroz Cunha

SYMPOSIUM ON CHRONIC ILLNESSES

HAD THE PARTICIPATION OF INCT-INOFAR

The National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) was present at the course "New Aspects in the Treatment of Chronic Inflammation", which took place in Montevideo, Uruguay, from June 15 to 16, 2015

Conceived by the *Centro Argentino Brasileño de Biotecnología (CABBIO)*, a binational organization of Brazil and Argentina, comprehending a network of research groups in biotechnology, the event dealt with relevant themes like chronic illnesses and the therapeutic resources available to treat them.

Professors Eliezer J. Barreiro and Lidia Moreira Lima (**LASSBio**/UFRJ) were present during the event programming. Other experts in inflammatory diseases from different countries (Argentina, Brazil, Spain, and Uruguay) were part of the Symposium. The event had a total of twenty two graduate students, including Argentineans, Uruguayans, Colombians, Peruvians, and Brazilians. The students from Brazil were from the North, Midwest, and South regions of Brazil.

As **INCT-INOFAR** coordinator, Eliezer J. Barreiro explained to those present the role played by **INCT-INOFAR**, a Brazilian research network in the area of drugs. Accompanied by Professor Lidia Moreira Lima, they were part of a round table at the end of the Symposium. "People liked the way and the design of this research work in a network a lot, and they were positively surprised by the Brazilian initiative. It had a favorable repercussion", stated the scientist.

INFLAMMATION-DEPENDENT DISEASES

The acute inflammatory process is a defense mechanism of the body, which sets the stage for chronic degenerative diseases such as obesity, Type II Diabetes, and rheumatoid arthritis.

Happy with the result of the programming, the full professor at UFRJ speaks agreeably about how the activity went. "It was very positive to have this attendance. I was very impressed with the graduate students of all countries present. The initiative of these courses is positive in terms of cost-benefit ratio. For students who attend, it is of a practical nature". Personal enrichment, expenses that are accessible to most, knowledge and information are what professionals in the field seek.

67th ANUAL SBPC MEETING

The National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) was present at the 67th Annual Meeting of the Brazilian Society for the Progress of Science (SBPC), in July 12 to 18, in the Federal University of São Carlos, state of São Paulo.

Professors Eliezer J. Barreiro (**LASSBio**/UFRJ), Fernando de Queiroz Cunha (USP/RP) and Luiz Carlos Dias (UNICAMP), members of the Governance and Follow-Up Committee (CGA) of **INCT-INOFAR** were part of the round table on the 17th to debate the topic "The Importance of Integrating Research in Translational Medicine and Medicinal Chemistry for the Development of Drugs". During the programming, there were conferences, symposiums, and mini courses.

This is considered the largest scientific event in Latin America. The "Light, Science, Action" of 2015 makes reference to the International Year of Light and Light-Based Technologies, celebrated in 2015 by scientists all over the world and by the United Nations Education, Science, and Culture Organization (UNESCO).

The Meeting ends with the "Family in Science Day", with a goal of interacting with community and the activities that corroborate how science is part of daily life.

IV INTERNATIONAL SYMPOSIUM

ON DRUG DISCOVERY

Professor Eliezer J. Barreiro (**LASSBio**/UFRJ), coordinator of the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**), was honored during the IV International Symposium on Drug Discovery, from July 22 to 24 in the Faculty of Pharmaceutical Sciences of UNESP in Araraquara, SP, for his important role in encouraging students and professionals in the field of Pharmaceutical and Medicinal Chemistry in Brazil.

Under his coordination, the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) was created as a research network that connects scientists in different research institutions and Universities in Brazil. The Institute acts in the discovery of new drugs and medicines, and also contributes to the professional qualification of undergraduates and graduates in Medicinal Pharmaceutical Chemistry and Pharmacology. Alongside its laboratory research, **INCT-INOFAR** also carries out work in health awareness and science popularization, aimed at increasing awareness of the Correct and Safe Use of Drugs.

“When we started, we were a few of the pioneers in Medicinal Chemistry. It was very interesting to realize that in the Faculty of Pharmaceutical Sciences of UNESP in Araraquara, in this new generation of young researchers in the area, we are widely recognized. It was a very positive experience and I was very happy with the honor, because, in a way, the context was the acknowledgment of the effort made to promote Medicinal Chemistry in Brazil. Obviously this award, as I see, is not for only one person, but for a project that all in LASSBio have shared to strengthen Medicinal Chemistry in our country”, remarked the scientist.

NEW INVESTIGATOR TRAVEL AWARD

Doctoral student at the Laboratory of Cardiovascular Pharmacology of the Institute of Biomedical Sciences at UFR, connected to the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**), Jaqueline Soares da Silva, received the New Investigator Travel Award of research promotion for the cardiovascular evaluation of compound LASSBio-294 in diastolic dysfunction induced by hypertension associated with myocardial infarction.

Organized by the American Heart Association, the Basic Cardiovascular Sciences 2012 Scientific Sessions, in New Orleans, USA, from July 13 to 16, 2015, awarded 15 researchers. During the congress 432 papers were presented. “Three papers were developed in England, six in the United States, and only ours, developed in Brazil, was awarded. This shows the quality of our research”, says Dr. Zapata-Sudo.

Jaqueline is a student of Professor Gisele Zapata-Sudo (ICB/UFRJ), also a member of **INCT-INOFAR**, and talks about how this partnership has been. “I have been honored to work with Professor Zapata-Sudo from my first scholarship until currently, as a Post-Doctoral student advised by her. I have learned from her how research is conducted ethically, with responsibility and a lot of dedication”.

GERMAN DELEGATION

MEETS WITH **INCT-INOFAR** AND TOURS UFRJ FACILITIES

The National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) received, on July 30 and 31, a visit from a delegation of academic authorities and researchers from the Interfaculty Center for Pharmacogenomics and Pharma Research (**ICEPHA**), all from the University of Tubingen, Germany. Represented by the Dean, Dean of Research, and the Dean of International Relations of the same University, as well as by Professor Stefan Laufer, **INCT-INOFAR** collaborator, as an external international scientific consultant.

The agreement signed in 2012 between **INCT-INOFAR** and German educational Institution ICEPHA has produced significant results. During the time they were in Rio de Janeiro, Brazil, they visited the UFRJ Dean's Office meeting the current Dean, Professor Roberto Leher. They also visited the Technological Park of the Federal University of Rio de Janeiro (UFRJ) and were welcomed by the Scientific and Technological Directors of the Carlos Chagas Filho Foundation of Support to Research in the State of Rio de Janeiro (FAPERJ), where strategies to bring together research groups in the state of Rio de Janeiro and at the University of Tübingen were debated, to try to advance the chain of innovation in drugs.

*Members of the german delegation with the presence of Professors Eliezer J. Barreiro and Stefan Laufer (**INCT-INOFAR** external consultant)*

CPSA BRASIL 2015

The National Institute of Science and Technology in Drugs and Medicines **(INCT-INOFAR)** was present at the Clinical & Pharmaceutical Solutions through Analysis (CPSA) Brazil 2015, at the Transatlantic Club, in the city of São Paulo, from August 3 to 5.

The event had the presence of Scientific Superintendent of **INCT-INOFAR**, Professor Lidia Moreira Lima (**LASSBio**/ICB-UFRJ), during the Symposium: "Drug Discovery: Are We Prepared for That?", coordinated by Dr. Gabriela Barreiro (Eurofarma). Doctors Cristina Mendes and Cristia Ropke, representing INPI and Phytobios Northeast, respectively, were also present during the programming.

The presentations dealt with topics like information technology, Brazilian biodiversity as source of high aggregated value and the importance of academia in the discovery of drugs. **INCT-INOFAR** was presented as a national research source, gathering several researchers from Public Universities, Research Institutes and collaborators from the industrial sector, with the mission of researching and developing several subprojects for the discovery of new drugs and medicines (radical innovation), and new synthesis routes for generic drugs (incremental innovation) in the country.

CIFARP 2015

The National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** was part of the International Congress of Pharmaceutical Sciences (CIFARP), in its 10th edition, which took place in September 5 to 9, at the Convention Center in Ribeirão Preto (CCRP), SP. With approximately 550 enrolled people, there were five days where a lot was learned by attendees.

The event takes place every two years, with the support of the Federal University of São Paulo (USP), the Faculty of Pharmaceutical Sciences of Ribeirão Preto (USP) and of the Brazilian Society of Pharmaceutical Sciences (ABCF). It had a full schedule, with local and international lecturers sharing their professional experience with attendees. As well as its scheduled activities, CIFARP organized an exposition with booths for collaborators to publicize their work. The official opening of the congress had the participation of the Madrigal Revivis choir (USP/Ribeirão Preto), followed by conference Dr. David Newman, from the National Institutes of Health (NIH), USA.

The congress gathered several lecturers and students to share experiences

On the 6th, UFRJ Professor and **INCT-INOFAR** Scientific Superintendent, Lidia Moreira Lima delivered a lecture on the topic "The next generation of bioisosterism", speaking on the use of this strategy of molecular modification in Medicinal Chemistry and in the design of new drug candidates.

On the 7th, it was Professor Eliezer J. Barreiro (**LASSBio**/UFRJ), **INCT-INOFAR** coordinator, to lecture on the topic "New trends in anti-inflammatory drugs", speaking about the importance of Medicinal Chemistry and the drugs available to control and treat inflammatory acute and chronic illnesses. He also presented the results achieved by the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**), such as the derivative LASSBio-468, a dual agent for the control of asthma.

On the 8th, Professor Luiz Carlos Dias (IQ/UNICAMP), ,member of the Governance and Follow-Up Committee (CGA) of **INCT-INOFAR**, presented the topic: "Diseases Initiative (DNDi) and Medicines for Malaria Venture (MMV) in the area of Neglected Diseases", reporting how the research work with the "Drugs for Neglected Diseases Initiative" (DNDi), which works to raise awareness for neglected diseases and guarantee access to essential drugs for these diseases. The DNDi has headquarters in Brazil, located in the Jardim Botânico neighborhood, in the southern part of the city of Rio de Janeiro, and is partnered with the Institute of Chemistry of the State University of Campinas (USP), and with MMV, which is a non-profit organization created to discover, develop, and provide new drugs to prevent and fight malaria through public-private partnerships.

CONTACT WITH THE AUDIENCE (OUTREACH ACTIVITIES)

The **INCT-INOFAR** booth welcomed visitors from several educational institutions worldwide, with an approximate audience of 150 people. The Secretary of Extension and educator Ana Cristina da Mata Silva led the scientific publicity activities in the booth during the entire congress.

Carolina Feres, a scientific initiation scholar from the Faculty of Pharmacy of the Federal University of Juíz de Fora (UFJF) – MG, was one of the students who visited the **INCT-INOFAR** booth and enjoyed knowing more about the work developed by the Institute. She was also interested in the XXII Summer School in Medicinal and Pharmaceutical Chemistry (SSMC), a continued education activity promoted by **LASSBio**/UFRJ with the support of **INCT-INOFAR**.

The student, who intends to continue an academic career with a focus on natural products, speaks of all she learned during the five days of the event. "I came to the congress for the view that is given to undergraduate students of Pharmacy, for the opportunity to be able to speak with scientists who are references and who we only know by name, and because they have met the professors at our University. It is also an opportunity to increase our professional contacts. For me, it was very valuable".

CABBIO COURSE IN BUENOS AIRES

The National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)**, represented by its coordinator, Professor Eliezer J. Barreiro was part of the *Entrepreneurship and Creation of Technology-based Companies* course, in Buenos Aires, from August 31 to September 04, by the Brazilian Center of Biotechnology(CABBIO), in the National University of San Martin (UNSAM).

The scientist taught the course "*La biología como fuente de productos y servicios biológicos y biotecnológicos*" ("Biology as a source of products and biological and biotechnological services"), for students from Argentina, Brazil, Uruguay, Paraguay, and a few other South American countries.

The Brazilian-Argentinean Center of Biotechnology (CABBIO) is a product of the cooperation between the Ministry of Science, Technology, and Productive Innovation of Argentina and of the Ministry of Science, Technology, and Innovation of Brazil. The goal of CABBIO is to promote the interaction between scientific centers and the productive sector, through two types of activities: the implementation of binational R & D projects and training of human resources at the graduate level, through courses taught by the Argentinean-Brazilian School of Biotechnology (EABBIO) professors.

47th SBFTE

Institute members present during four days of programming

The National Institute of Science and Technology in Drugs and Medicines **(INCT-INOFAR)** was part of the 47th Congress of the Brazilian Society of Pharmacology and Experimental Therapeutics (SBFTE), with a booth in the exposition area, with the goal of publicizing the work that it has been conducting over the years. The event took place from October 27th to November 1st, in Águas de Lindóia – São Paulo.

With 450 enrollments, from Brazil and other Latin American countries, the Congress, which takes place yearly, had 80 lecturers, 15 of them researchers from foreign Universities. The theme this year was "Emerging Challenges in the Discovery of Drugs and Therapies", and the president of SBFTE, Christina Avellar, in her first year of presidency at the time, mentioned during the opening ceremony the importance of the theme chosen. According to her focuses on the discussion among researchers worldwide the challenge is to find a way to keep the level of development of research during the current recession faced by most countries.

Vice-coordinator and member of the Governance and Follow-Up Committee (CGA) of **INCT-INOFAR**, Fernando de Queiroz Cunha (USP/Ribeirão Preto), together with other members of **INCT-INOFAR** such as Leticia Veras C. Lotufo (USP), Patricia Machado Rodrigues e Silva (IOC/FIOCRUZ) and François G. Noël (ICB/UFRJ), are some of the directors for the 2015-2017 term for the Brazilian Society of Pharmacology and Experimental Therapeutics (SBFTE) and were present during the four days of programming, going to the booths and taking part in the activities.

The booth received countless visits, among them from Professor Gerry Graham, from the University of Glasgow, Scotland, and Professor Graziano Pinna, from the Department of Psychiatry of the University of Illinois (UIC), in Chicago, USA.

The Institute of Biomedicine of the Brazilian Semiarid (INCT-IBISAB) took the opportunity to see the Scientific Publicity work done by **INCT-INOFAR**: "Advertising is crucial", said Geanne Matos de Andrade Cunha (UFC), who is part of INCT-IBISAB, after checking out the Annual Activities Report 2014 (AAR 2014).

SBFTE YOUTH

The initiative was from students who, because of their questions, had the desire to connect with professors participating in the event, sharing knowledge and solving their questions. In its second year, the group gathered for a talk. The professors were selected randomly, divided within the groups. The students had the opportunity to sign up for a talk with a specific expert. For one hour, the casual environment allowed for bonding not only between professors and students, but also among professors.

One of the participants of SBFTE Youth was Dr. Marco Aurelio Martins, a member of the **INCT-INOFAR CGA,** who is also the chief researcher at the Laboratory of Inflammation of Oswaldo Cruz Foundation (FIOCRUZ). At another moment, during the Congress, he was able to talk about the work done in the laboratory, with the topic "Novel local anesthetic analogues as candidates for asthma", as new therapeutic alternatives aimed at the treatment of asthma.

The **INCT-INOFAR** booth had over 100 visitors, who received the folder with the CD with the electronic version of AAR 2014. In general, the Congress fostered knowledge and allowed students to conduct workshops with the professionals present. SBFTE will now have its 48th edition in 2016 in Foz do Iguaçu.

ACADEMIC JOURNEY

IN CARDIOVASCULAR DISEASES

Full Professor Titular at UFRJ and coordinator of the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**), Eliezer J. Barreiro (**LASSBio**/UFRJ) took part in the III Annual Journey in Cardiovascular Sciences, on November 12, in the Biomedical Institute of the Federal University of the State of Rio de Janeiro (UFF), Niteroi, Rio de Janeiro. On his conference, the scientist dealt with the topic "Rational Planning of new drug candidates"

In its third edition, the event, promoted by the Graduate School in Cardiovascular Sciences at Universidade Federal Fluminense, Niterói city, RJ, on November 12 and 13, focused on the meeting ground for entrepreneurship, technology, and health. With the theme "New Technologies in Health", the Journey aimed to integrate the academic community with the professionals who work in innovation, through conferences, presentation of scientific papers, and case studies, while also promoting networking.

ABRAFARM CELEBRATIONS

Celebration of 30 years of the Brazilian Academy of Military Pharmacy organizes roundtable to receive new guests.

Coordinator of the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) and full member of the Brazilian Academy of Military Pharmacy, Prof. Eliezer J. Barreiro was invited by its President to be part of celebrations for the 30th ABRAFARM anniversary on November 13.

After taking place as Full Member of the Academy on 2011, the scientist sits on chair number 67, whose patron is Dr. Manoel Goncalves Paes Sobrinho, pharmacist who in 1916 was part of the committee who wrote the bylaws of the Brazilian Academy of Pharmacy (ABF).

Founded on July 16, 1985, the Brazilian Academy of Military Pharmacy has a goal of bringing together civilian and military pharmacists, as well as others interested in the health field. With the motto "Solidifying and Dignifying the Pharmaceutical Profession", the non-profit agency follows the laws and rules of public utility organization, and has worked for over 30 years for the improvement of Brazilian Pharmacy.

INCT-INOFAR AT USP EVENTS

***INCT-INOFAR** participated in two important events held in the University of São Paulo last November.*

Both were organized by Prof. Dr. Elizabeth Igne Ferreira, member of CGA of **INCT-INOFAR**, and her team, and involved many Brazilian and foreign researchers. The IV Symposium on Drug Design and Development for Neglected Diseases, held November 23 -25, has Prof. Dr. Eliezer J. Barreiro as chair in the session that discussed de contribution of the laboratories of universities from Brazil and abroad in the discovery and development of bioactive compounds for neglected diseases. Prof. Dr. Lidia Moreira Lima participated in the same session, talking about the contribution of **LASSBio**/UFRJ through a lecture about LASSBio-1636 as a new leishmanicidal drug candidate. In the XIII National Meeting of Medicinal Chemistry Professors, held November 25-27, the **INCT-INOFAR** coordinator gave a lecture about Medicinal Chemistry in Brazil: a brief view, and coordinated the round-table Medicinal Chemistry and R&D in Pharmaceutical Industries.

INNOVATION IN HEALTH AWARD

Winners will have opportunity to spend 15 days in the Research & Development department of Fleury Group

Allan Kardec Nogueira de Alencar received the I Innovation Award by the Fleury Group, on October 29, at the Jabaquara Headquarters of the Fleury Institute, São Paulo. Associated with the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**), the young scientist was part of the selection process with another 69 enrolled, with 18 of those being honored with oral presentations and 7 awarded with honorable mentions where the main prize was handed to the work by Allan Kardec de Alencar, titled "Development of new A_{2A} adenosine receptor agonists for the reversal of cardiac and vascular remodeling in rats with pulmonary arterial hypertension".

The goal of the award was to acknowledge promising and innovative scientific works focused on health, promoting future partnerships in the Research & Development team of the Fleury Group with future scientists and strengthening bonds with Universities. The first edition of the award included everything from basic research on molecular modeling to therapeutic treatments and technological innovations to create tools for the everyday lives of doctors.

MEETING THE WINNER

Pharmacist with an undergraduate degree from the Federal University of Paraíba, Allan Kardec Nogueira de Alencar, started working as a scientific initiation scholar in the Laboratory of Cardiovascular Pharmacology while still an undergraduate student. That time it was a great encouragement for the young man to decide to leave his hometown, his family, and friends to pursue his dream. He traveled to Rio Janeiro in 2010 to try to be admitted into the Graduate Program of Pharmacology and Medicinal Chemistry at UFRJ. After his arrival in the city, the student was welcomed by Professor Eliezer J. Barreiro and Professor Gisele Zapata-Sudo, who guided the scientist in his career. Currently a Master of Pharmacology and Medicinal Chemistry from the Federal University of Rio de Janeiro and a Doctoral student at the Graduate Program in Pharmacology and Medicinal Chemistry at the same University, Allan Kardec contributes very relevantly to the production of scientific knowledge.

During his Doctorate, he received a scholarship from the National Council for Scientific and Technological Development (CNPq), being part of research projects at Wake Forest University, USA.

In 2014, he received a Grade 10 Scholarship from the Carlos Chagas Filho Foundation of Support to Research in the State of Rio de Janeiro (FAPERJ). In June 2015, he received the Researcher of the Year Award, awarded by the network of Biotechnology researchers BiotechSpace. "The fruits of this project and of my effort, along with the contribution of my advisors and collaborators, have been recognized throughout my graduate education, which motivates me and is an example for students who want to work in research. Contributing to public health is the best legacy I will leave from my doctorate and I will continue working hard on this pursuit. I was able to dedicate myself exclusively to achieving results and learning countless laboratory techniques and physiopathological aspects of Pulmonary Arterial Hypertension, as well as specializing in Pharmacology and Medicinal Chemistry, by working with a team that is thought to be the best in the country in these two fields. I believe that, in spite of the current economic recession in our country, we have a vast potential in Science and Technology, and that awards of this type may help maintain and provide additional incentive to the investment in education by our government as well as by private companies", says the doctoral candidate.

PUBLICIZING AND PROMOTING SCIENCE

***INCT-INOFAR** researcher shares experiences and the importance of Science Publicity and Promotion*

The National Institute for Science and Technology of Drugs and Medicines **(INCT-INOFAR) coordinator, Professor** Eliezer J. Barreiro (**LASSBio**/UFRJ), was invited to lecture during the II Young Scientist Symposium of the IOC (Oswaldo Cruz Institute) on December 08, at the Oswaldo Cruz Foundation, in Manguinhos – RJ, on the importance of Scientific Publicity and Promotion. Aside from the lecture, the scientist was part of a round table where subjects such as phosphoethanolamine and the treatment of Zika virus were approached.

During his speech, the Professor spoke about **INCT-INOFAR and the work in Science Publicity and Promotion done by the Institute throughout the years, such as going to the city of São Francisco de Itabapoana, in the north of the state of Rio de Janeiro, to promote the National Science and Technology week, the action in the Knowledge Vessels in the city of Rio de Janeiro, among other activities. Under the responsibility of educator** Ana Cristina da Mata Silva, activities are carried in municipal public schools through **"INCT-INOFAR at Schools"**, as well as other similar initiatives, all of them focused on the theme "The Safe and Correct Use of Drugs".

The **INCT-INOFAR** team has developed animated booklets and printed booklets on the safe and correct use of drugs, including antibiotics and anti-inflammatories. The human board game called "Drugs are not toys" was also created, printed on fabric, where the path has instructions on the correct use of drugs. Through the Drugs Portal, pharmacist and cartoonist Natália Lima shares comics she draws, promoting health actions and increasing population awareness on the risks involved in the incorrect use of drugs.

The importance of Scientific Publicity has become increasingly more evident among research groups. Biologist Salvatore Siciliano, from the Oswaldo Cruz Foundation, also a visiting researcher at FAPERJ, is part of "Science Today Magazine for Children", spoke a little about his experience on Science Publicity and Promotion. According to him, the children who read the magazine sent handwritten letters, asking questions. "When we receive and read these letters, we feel very encouraged to continue our work", said the scientist.

Professor Eliezer J. Barreiro also mentioned the outreach activities promoted by **INCT-INOFAR** for the year 2015.

2015

OUTREACH ACTIVITIES

*Health education activities are the responsibility of the Secretary of Extension of **INCT-INOFAR**, headed by educator Ana Cristina da Mata Silva, carries out activities in public municipal schools aimed at increasing awareness in children as to how to use drugs correctly and safely. Folders with materials produced by the Institute are handed out, including booklets on the correct use of antibiotics and anti-inflammatories, puzzles, and interactive games, where youths can learn more about the topic and the world of science.*

AROUND
700 PEOPLE
VISITED

INCT-INOFAR
PROMOTES
ACTIVITIES DURING NATIONAL HEALTH WEEK 2015

Supporting the National Health Week, the National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** organized programming to promote outreach actions in the Science and Life Museum, in Duque de Caxias. The activities, which were conducted in April, went on for seven days. Around 700 people visited, from around 7 different cities in Rio de Janeiro. 15 schools visited, including public and private schools.

INCT-INOFAR members and Oswaldo Cruz Institute (IOC) researchers talked to the public on the correct ways to acquire, administer, store, and discard drugs, as well as informing the public on the creation and fight against "super bacteria", like on how to have an antibiogram laboratory exam, as well as on diseases of the respiratory tract like asthma, bronchitis, silicosis, and pulmonary emphysema. To better solve doubts, microscopes, bacterial slides, a replica of a human lung, as well as the Booklet "Joey's Crew on: The Correct Use of Antibiotics" were exhibited.

INCT-INOFAR, through its work, has provided guidance to the population and cleared questions on the use of preventive health measures, to engender healthy habits and the improvement of quality of life.

NATIONAL RATIONAL

USE OF DRUGS DAY

INCT-INOFAR chooses National Day for the Rational Use of Drugs as a way to celebrate Rio de Janeiro's 450th Anniversary

The Secretary Outreach Activities of the National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR),** responsible for the Science Publicity and Promotion activities, added the National Rational Use of Drugs Day to the official calendar of the celebrations for "450 Years of Rio", now celebrated on May 5.

On the topic of "The Safe and Correct Use of Drugs", **INCT-INOFAR** received the following schools: Tenente Antonio Joao, Pedro Lessa and Lavinia de Oliveira Escragnolle Doria, located in Cidade Universitária, Bonsucesso and Ilha do Governador, Rio de Janeiro city, respectively, in the Center for Health Sciences (CCS) facilities at the Federal University of Rio de Janeiro (UFRJ), to raise awareness among participants of the dangers of self-medication, and on the importance of being careful when acquiring, administering, and discarding drugs.

Pharmacist Thayssa Tavares (**LASSBio**/UFRJ) gave a lecture "The Rational Use of Drugs – do you know what that means?", piquing the students' curiosity, who then had the chance to ask several questions and have their questions answered. **INCT-INOFAR** and **LASSBio** coordinator, Professor Eliezer J. Barreiro, took the chance to chat with students, who were very excited to meet a real life scientist, as they had previously only seen scientists in movies.

The activities also contribute so that students can become familiar with the academic world. Elementary student Estephany Gonçalves Lopes Pereira, a 9th grader at Lavínia de Oliveira School, reported she had never before been to a University. Students were also able to see the facilities of the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**) where, with the help of graduate students Ciro Gonçalves, Isabelle Nunes, Thayssa Tavares, Julia Galvez and Thais Silva, they were able to see each stage of the work in synthesis, bioassays, and molecular modeling, in the incessant search for the discovery of a new drugs.

NATIONAL HEALTH DAY

AT INCT-INOFAR

The National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** was present at the Municipal School Capitão de Fragata Didier Barbosa Vianna, located in Ilha do Governador, on August 5, in celebration of National Health Day.

The activities were divided in two parts. The first part, in partnership with the Oswaldo Cruz Institute (IOC/FIOCRUZ) was the project "The Journey of Health". 5th and 6th graders were able to be part of a circuit where they learned about respiratory tract diseases and the development of bacteria. The students had access to microscopes, making it easier to have direct contact with the content taught.

The video version of the booklet "Joey's Crew in: The Correct Use of Antibiotics" was shown to around 70 students, and after the activities, **INCT-INOFAR** had a quiz in a dynamic and fun way: t-shirt painting, where students were able to paint what they had learned during the previous activities. Creativity was the strong point of the afternoon in the Municipal School, with very positive results.

During the second part, with evening students, Thayssa Tavares – **LASSBio**, researcher, spoke to the approximately 80 students present on the topic "Rational Use of Drugs – do you know what that means?". Her presentation was open to questions, and all of them were answered, raising awareness to the risks that the incorrect use of drugs might cause.

THE INITIATIVE

Teacher at the Program for the Education of Youths and Adults (EJA) at the Municipal School Capitão de Fragata Didier Barbosa Vianna, Bianca Guimarães Silva, in visit to the Faculty of Pharmacy of UFRJ during Worker Week, had the chance to watch the lecture on the correct use of drugs. After realizing how she had been using them incorrectly, she decided to contact the Secretary of Extension of **INCT-INOFAR**, and, with the help of educator Ana Cristina da Mata Silva, promote the same teachings at her school. "I believe we will have good results from now on. We intend to continue this change of behavior in our students, because education implies change, and this is what we want to see. We have many problems with self-medication and, through the dynamics and the interaction created by **INCT-INOFAR**, we can make a change", says Bianca, who was present for the activities of the National Day for the Rational Use of Drugs.

The **INCT-INOFAR** team once more successfully achieved the goals of outreach activities through awareness of the rational use and discarding of drugs.

RIO DE JANEIRO
STATE

Public schools have opportunity to tour the UFRJ facilities

INCT-INOFAR PROMOTES VISIT TO LASSBio FOR STUDENTS

Students of the José Veríssimo State School, located in the city of Magé, in Rio de Janeiro state, through a partnership established with the National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** and the Institute of Chemistry/UFRJ, had the opportunity to tour the facilities of the Laboratory of Evaluation and Synthesis of Bioactive Substances **(LASSBio)**, located in the Center for Health Sciences (CCS) at UFRJ in September.

From August 12 to 14, the V Chemistry Fair at the José Veríssimo State School took place. The students conducted several experiments, which were evaluated by the Chemistry teachers from their school. The best performing ones were awarded a "scientific tour" of the facilities of the Federal University of Rio de Janeiro (UFRJ) to see the work done by Professor Eliezer J. Barreiro. Three teachers were present, two of Chemistry and one of Biology, alongside around 40 students, all of them 10th, 11th, and 12th graders.

So that the work could be done, Professor Dr. Barbara Vasconcellos da Silva (IQ/UFRJ) coordinated the implementation of the "Double School" Program in the Public State School Jose Veríssimo: a successful school-university partnership, with the help of the Program for the Support to the Improvement of the Education in Public Schools Located in the State of Rio de Janeiro – Chemistry as vocation: all we need is improving it in High School, coordinated by Professor Dr. Angelo da Cunha Pinto, member of the Governance and Follow-Up Committee (CGA) of **INCT-INOFAR**, who organized the event.

The teenagers were welcomed by educator Ana Cristina da Mata Silva **(INCT-INOFAR)**, who spoke about the work done by **INCT-INOFAR,** showing the importance of the rational use of drugs and showing a presentation video for **LASSBio**, describing its actions. **INCT-INOFAR** Scientific Superintendent, Professor Lidia Moreira Lima (ICB/UFRJ) was also present, encouraging the group. The students were divided in teams so that they could visit all three **LASSBio** sectors: Synthesis, Bioassays, and Molecular Modeling. They were able to ask qualified professionals a lot of questions as well.

Biology teacher Eliane Lugão Monteiro talked about how the experience of providing the students with this visitation went. "Bringing my students here and being able to show that what I always tell them, which is to always seek more knowledge, was for me a wonderful experience and I saw that it was the same for my students. I hope a few of them can achieve their goals".

Lucas Antonio Correia, a 10th grader, was very happy to be able to ask questions and learn a bit more about the pharmaceutical field. "It is very interesting for us to see the discovery, each process done. I really enjoyed seeing the modeling, the equipment and the programs used".

May the project serve as inspiration to other schools and encourage students each time more, to clear the path they wish to take.

2015
NATIONAL SCIENCE AND TECHNOLOGY WEEK

*National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) successfully ends its participation in the II National Science and Technology Week of São Francisco de Itabapoana, RJ*

The Drugs and Medicines INCT **(INCT-INOFAR)** carried out activities of Science Publicity and Promotion during the 12th National Science and Technology Week (SNCT), from October 20 to 23, at the 2nd edition of the SNCT in São Francisco de Itabapoana in the North of the state Rio de Janeiro. **INCT-INOFAR** had approximately 1,200 visitors to its booth during the cultural fair, which took place in the Three Powers Square, in front of the City Hall. Several actions with the theme "The Rational Use of Drugs" were conducted with both the general population and the students of 18 Municipal Public Schools.

The year of 2015 was proclaimed the "International Year of Light" by the United Nations Organization (UNO) and with the theme "Light, science, and life", had as a goal celebrating light as a subject of science and technological development, as well as promoting the inclusion of Brazilian institutions in the celebrations throughout the Brazilian territory.

The work of Science Publicity is done by the **INCT-INOFAR** Secretary of Outreach Activities, headed by educator Ana Cristina da Mata Silva, who develops activities in a dynamic and objective way, using support materials developed by the qualified professionals who make up the Institute.

The theme for the São Francisco de Itabapoana SNCT this year was "Practicing science, changing lives", since the goal is to publicize and make science more popular, and there is no better way for students to learn other than by practicing. According to one of the organizers of the cultural fair, Amanda Passaline, "We want the student to know science up close. Maybe we have a lot of future scientists here that we are unaware of? We have to provide them with opportunities so that we can achieve results", says the coordinator of Science and Technology from the Municipal Secretary of Education and Culture.

INCT-INOFAR spoke to around 150 children by visiting Moranguinho and Macarino Rosa de Moraes Municipal Schools. The students watched a lecture and the video for "Joey's Crew in: The Correct Use of Antibiotics", and with the presence of pharmacists Thayssa Tavares and Ciro Gonçalves, they were able to ask questions on how to purchase, store, and discard drugs. They were very excited and most wanted to go home immediately to share what they had learned with their parents, since many of them were storing drugs incorrectly. They also received pedagogical games: "Joey's Crew" booklets and the puzzles developed by the **INCT-INOFAR** team.

In the cultural fair **INCT-INOFAR** had a booth to meet with young students who wished to ask questions and play the human board game “Drugs are not Toys" to learn the ways to administer drugs in their daily lives in a playful way, as well as how to store them correctly and what should not be done with drugs.

The Deputy Mayor Amaro Barros spoke during the opening ceremony of the importance of school for the personal and professional growth of young students, and also stated that teaching institutions are the place where everything is learned, from manners to a job, from teachers. “All students, make a difference. Never give up on your dreams and always look ahead", were the words of encouragement said by Amaro.

During the first day of activities the 2nd edition of the “Booklet o the Commandments of the Right Use of Drugs" was launched, and during the following days, health professionals, city authorities, event organizers and teachers came to get copies.

INCT-INOFAR, through a lecture delivered twice – for Elementary and High School students and for the Program of Young Adult Education (EJA) – by pharmacist Thayssa Tavares, on the topic “Rational Use of Drugs – do you know what that means?”, was able to share knowledge with approximately 400 people in the exposition pavilion. The children who were part of the discussion taught one another the difference between drug and medicine. The questions by adults were plentiful and one of the recurring questions, asked by the director of the Josefino Barros de Menezes Municipal School, Gilquelha Teixeira, was on the efficacy of generic drugs.

SPREADING SCIENCE THROUGH SOCIAL ACTION

Among the highlights of the week, the visit by the social inclusion group from the Association for Parents and Friends of Special Needs People (APAE) from São Francisco de Itabapoana was remarkable to the **INCT-INOFAR** team. They curiously approached the booth questioning how things worked in the pharmaceutical universe. They learned the commandments of the Safe and Correct Use of Drugs through the human board game. All participants had fun, and they even had fans cheering for them. The winner took home a personalized **INCT-INOFAR** backpack.

Something else that caught their eye was the “fun signs” to take photos with. Each sign had a different saying, like one of the commandments for the correct use of drugs and publicity for the Drugs and Medicines INCT websites (Drugs Portal and the **INCT-INOFAR** website).

KNOWLEDGE BEARS FRUIT

During SNCT-2104 in São Francisco de Itabapoana, **INCT-INOFAR** conducted Science Publicity and Promotion activities at the Herval Luiz dos Santos Batista Municipal School, encouraging young students to search for more science knowledge. This year, students presented their own projects, which were exposed in a booth in the culture fair for all to see. The **INCT-INOFAR** team was so happy to see the work done by the students and realize that the seed planted in the previous year was now bearing fruit.

Furthermore, teachers who were present in 2014 with their students returned to report how inspiring the work done in the I SNCT by **INCT-INOFAR** had been. The students learned and also shared the correct and safe methods for the use of drugs with all their friends and family.

Simone Ferreira Gomes is the principal of the Ernesto José Henrique Municipal School in the Rural Zone, and stated that the National Science and Technology Week is of great importance for all young students. “It is a different way to teach, and students get involved, building their own projects, learning more and presenting them to all. Possibly, a lot of them will discover the future job they want while in school”.

SOCIAL WORK DONE BY INCT-INOFAR IN THE CITY OF SÃO FRANCISCO DE ITABAPOANA

During the closing ceremony, Mayor Pedro Jorge Cherene Jr. went to the **INCT-INOFAR** booth to congratulate all on the work done. Pedrinho, as he is known around town, also requested a few copies of the “Booklet on the Correct Use of Medications" to be delivered to the Secretary of Health and later be made available to the Family Health Program (PSF) in the city. “Through this donation, we can bring knowledge to everyone", stated the Mayor.

Still during the presence of the local authority at the booth, there was a draw of two personalized backpacks with the **INCT-INOFAR** logo for EJA students.

The São Francisco de Itabapoana City Hall thanked the **INCT-INOFAR** team for their presence and handed a memento to educator Ana Cristina da Mata Silva, who was touched by this gesture and thanked them for their hospitality.

After being invited to return to the city next year, the National Institute of Science and Technology in Drugs and Medicines **(INCT-INOFAR)** said goodbye to the 2nd edition of the São Francisco de Itabapoana SNCT. With good results and fruits from the previous year, we are thankful to all who contributed to this project, and most of all to Professor Eliezer J. Barreiro (**LASSBio**/UFRJ), who coordinates **INCT-INOFAR**, supporting and encouraging the outreach work.

2015 PUBLICATIONS

ACADEMIC PRODUCTION

MASTER OF SCIENCE DISSERTATIONS 2015

1. Daniel Alencar Rodrigues. Identification of new histone deacetylase inhibitor antitumoral prototypes. Dissertation (Master's Degree in Chemistry) – Federal University of Rio de Janeiro, National Council for Scientific and Technological Development. Advisor: Carlos Alberto Manssour Fraga.

2. Thiago Peixoto. Technological Scenario for the field of education from Information extracted from patent literature. 2015. Dissertation (Professional Master's Degree in Industrial Property and Innovation) – National Institute of Industrial Property. Advisor: Adelaide Maria de Souza Antunes.

3. Natalia Lidmar Von Ranke. Base Integrity Technological Prospecting in Patent Documents in the Field of Biotechnology Focused on Cancer. 2015. Dissertation (Professional Master's Degree in Industrial Property and Innovation) – National Institute of Industrial Property of Portugal. Advisor: Adelaide Maria de Souza Antunes.

4. Andreisa Teixeira de Castro. Evaluation of Schistosomicidal Activity of Extract, fractions, and mixture of Major Alkaloids obtained from *Senna spectabilis* flowers (DC.). 2015. Dissertation (Master's Degree in Pharmaceutical Sciences) – Federal University of Alfenas, Coordination for the Improvement of Higher Education Personnel. Coadvisor: Claudio Viegas Junior.

5. Jessica Salvador Areias de Araujo. Evaluation of reproductive toxicity of glyphosate herbicide: a systematic review. 2015. Dissertation (Master's Degree in Health Surveillance) - Oswaldo Cruz Foundation. Coadvisor: Francisco Jose Roma Paumgartten.

6. Ana Paula Barbosa do Carmo. Study of the Pharmacokinetic Alterations of Primaquine during Pregnancy and in Malaria. 2015. Dissertation (Master's Degree in Public Health) – Oswaldo Cruz Foundation, Coadvisor: Francisco José Roma Paumgartten.

7. Natasha Paixao da Silva. New Digoxin Derivates: Effect on Na+/K+-ATPase and their Implications for the Viability of LLC-PK1 Cells. 2015. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Coadvisor: Francois Germain Noel.

8. Fernanda Granja da Silva Oliveira. Influence of extraction method on the production of phenol compounds in *Hymenaea martiana* (*Fabaceae*) and quality control in the vegetable drug. 2015. Dissertation (Master's Degree in Natural Resources of the Semiarid) – Federal University of the Sao Francisco Valley, Coordination for the Improvement of Higher Education Personnel. Advisor: Jackson Roberto Guedes da Silva Almeida.

9. Maria Thereza Nunes Morais da Silva. Study of the Evaluation of Prescription, Acceptance, and Use of Medicinal Plants and Phytotherapeutics by Doctors in Basic Health Units in the City of Petrolina-PE. 2015. Dissertation (Master's Degree in Health and Biological Sciences) – Federal University of the Sao Francisco Valley, Advisor: Jackson Roberto Guedes da Silva Almeida.

10. Carolina Carvalho Guilhon. Pharmacological and phytochemical analysis of the leaves of *Tibouchina granulosa*. 2015. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Dias Fernandes.

11. Gabriela dos Santos Marinho Figueiredo. Analysis of the acute anti-inflammatory profile of *Lippia origanoides*. 2015. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Dias Fernandes.

12. Larissa Jardim Ramalho Papa Raymundo. Anti-inflammatory potential of two new N-morpholine-3-hydroxy-2-oxyndole compounds, Convolutamydine A analogues. 2015. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal Universities of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Dias Fernandes.

13. Jorge Luis Amorim. Evaluation of the Resin-Oil of *Copaifera paupera* in the tissue repair of cutaneous lesions in diabetic mice. 2015. Dissertation (Master's Degree in Pharmaceutical Sciences) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Dias Fernandes.

PhD THESES 2015

1. Everton Tenorio de Souza. Study of anti-PDE4 sulfonamide and sulfonylhydrazone derivatives in murine silicosis model 2015. Thesis (Doctorate in Pharmacology and Medicinal Chemistry) – Federal University of Rio de Janeiro. Coadvisor: Lidia Moreira Lima.

2. Aline Cavalcanti de Queiroz. Study of Leishmanicidal activity of two series of derivatives (Semicarbazone and Hydrazine-N-Acylhydrazone): a proposal for new strategies in the treatment of Leishmaniasis. 2015. Thesis (Doctorate in Biotechnology - RENORBIO) – State University of Ceara, National Council for Scientific and Technological Development. Coadvisor: Lidia Moreira Lima.

3. Emilio Carlos de Lucca Junior. *Marinisporolideo* A: Synthetic strategy and structural conformation. 2015. Thesis (Doctorate in Chemistry) – State University of Campinas, Foundation for the Support of Research in the State of Sao Paulo. Advisor: Luiz Carlos Dias.

4. Ellen Christine Polo. Total Synthesis of the proposed structure for nhatrangin A and analogues. 2015. Thesis (Doctorate in Chemistry) - State University of Campinas, Foundation for the Support of Research in the State of Sao Paulo. Advisor: Luiz Carlos Dias.

5. Felipe Augusto Rocha Rodrigues. Toxicogenetic biomonitoring as health risk indicator for exposure to uranium from residents who inhabit the proximities of the largest uranium reserve in Brazil, in the city of Santa Quiteria, Ceara. 2015. Thesis (Doctorate in Pharmacology) – Federal University of Ceara, National Council for Scientific and Technological Development. Advisor: Claudia do O Pessoa.

6. Deise Riba Coelho. Non-clinical evaluation of the safety of meglumine antimoniate in rodents: toxicokinetics, toxicity for the development and effect on hepatic P450 cytochromes. 2015. Thesis (Doctorate in Public Health) – National School of Public Health FIOCRUZ, National Council for Scientific and Technological Development. Advisor: Francisco Jose Roma Paumgartten.

7. Jessica Barbosa do Nascimento Viana. LDT3 and LDT5, multitarget antagonists of α1A/1D adrenoceptors and 5-HT1A receptors inhibit the proliferation of human hyperplastic prostatic cells, prostatic contraction, and the increase of intraurethral pressure. 2015. Thesis (Doctorate in Biological Sciences (Pharmacology and Medicinal Chemistry)) - Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Coadvisor: Francois Germain Noel.

8. Alessandra Gomes Marques Pacheco. Chemical study and evaluation of pharmacological activity of *Hymenaea martiana* Hayne (*Fabaceae*). 2015. Thesis (Doctorate in Biotechnology) – Federal University of Feira de Santana, National Council for Scientific and Technological Development. Advisor: Jackson Roberto Guedes da Silva Almeida.

9. Thays de Lima Matos Freire Dias. Study of the Anti-neuroinflammatory Activity of Planned New *N*-acylhydrazone 1,2,3,4-tetrahydra-9-acrydine Derivates (Ia-I) for the Treatment of Alzheimer's Disease - EAANAH. 2015. Thesis (Doctorate in RENORBIO) – Federal University of Ceara, Advisor: Magna Suzana Alexandre Moreira.

10. Aline Cavalcanti de Queiroz. Study of Leishmanicidal activity of two series of derivatives (Semicarbazone and Hydrazine-*N*-Acylhydrazone): a proposal for new strategies in the treatment of Leishmaniasis. 2015. Thesis (Doctorate in RENORBIO) – Northeast Network of Biotechnology, National Council for Scientific and Technological Development. Advisor: Magna Suzana Alexandre Moreira.

11. Everton Tenorio de Souza. Study for the identification of new sulfonamide compounds able to control pulmonary inflammation caused by silica in mice. 2015. Thesis (Doctorate in Biological Sciences (Pharmacology and Medicinal Chemistry)) - Federal University of Rio de Janeiro, National Council for Scientific and Technological Development. Advisor: Patricia Machado Rodrigues e Silva Martins.

12. Carlos Eduardo da Silva Monteiro. Analgesic activity of the association of maprotiline to tramadol in neuropathic pain model. 2015. Thesis (Doctorate in Biological Sciences (Pharmacology and Medicinal Chemistry)) - Federal University of Rio de Janeiro, Coadvisor: Roberto Takashi Sudo.

SCIENTIFIC ARTICLES

NATIONAL

1. Paumgartten, Francisco Jose Roma; Epidemiology, toxicology and environmental causality of diseases. Vigilância Sanitária em Debate: Sociedade, Ciência & Tecnologia, v. 3, p. 3-8, 2015.
DOI: 10.3395/2317-269x.00585

2. Dias, K.S.T.; Paula, C. T.; Riquiel, M. M.; Lago, S. T. L.; Costa, K. C. M.; Vaz, S. M.; Machado, R. P.; Lima, L. M. S.; Viegas Jr., C.. Recent Applications of the Multi-Target Directed Ligands Approach for the Treatment of Alzheimer's Disease. Revista Virtual de Química, v. 7, p. 609-648, 2015.
doi: 10.2174/1570159X1203140511153200

3. Silva, J. I.; Nicastro, P.C.; Oliveira, P. C. M.; Fossaluzza, P. C.; Morais, É. P.; Dias, K.S.T.; Costa, R. S.; Castro, Newton G.; Cardoso, C. L.; Viegas Junior, C.. A Comparative Evaluation of Acetylcholinesterase Inhibition by AChE-ICER and *in vitro* Ellman's Modified Method of Simplified Analogs 3-O-Acetyl-*N*-Benzyl-Piperidine of Donepezil. Revista Virtual de Química, v. 07, p. 2334- 2346, 2015.
http://www.uff.br/RVQ/index.php/rvq/article/view/1141/685

4. Martins, Thiago Estevam Parente; Santos, Laísa Maria Freire dos; Oliveira, Ana Cecília Amado Xavier de; Torres, João Paulo de Machado; Araújo, Francisco Gerson; Delgado, Isabella Fernandes; Paumgartten, Francisco José Roma. The concentrations of heavy metals and the incidence of micronucleated erythrocytes and liver EROD activity in two edible fish from the Paraiba do Sul river basin in Brazil. Vigilância Sanitária em Debate: Sociedade, Ciência & Tecnologia, v. 3, p. 88-92, 2015.
DOI: 10.3395/2317-269x.00278

5. Ferreira, Carlos Gil Moreira; Silveira, Dâmaris; Hatsukami, Dorothy K.; Paumgartten, Francisco José Roma; Fong, Geoffrey T.; Glória, Maria Beatriz de Abreu; Toledo, Maria Cecília de Figueiredo; Talhout, Reinskje. The effect of tobacco additives on smoking initiation and maintenance. Cadernos de Saúde Pública (ENSP. Print), v. 31, p. 223-225, 2015.
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7. Lima, Lídia M.. Safrole and the Versatility of a Natural Biophore. Revista Virtual de Química, v. 7, p. 495-538, 2015.
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INTERNATIONAL

1. Lima Toccafondo Vieira, Manuela; Lidia Moreira Lima; Barreiro, Eliezer J.; Tagliati, Carlos Alberto. Investigation of Low Bioavailability Using Physiologically Based Pharmacokinetic Modeling: A Case Example (Lassbio-596). British Journal of Applied Science & Technology, v.5, p. 613-620, 2015.
DOI: 10.9734/BJAST/2015/13527

2. Ferreira, Andrea; Franca, Flavia Dayrell; Tagliati, Carlos Alberto; Chaves, Miriam Martins. Cyclic adenosine monophosphate protects renal cell lines against amphotericin B toxicity in a PKA-independent manner. Drug and Chemical Toxicology (New York, N.Y. 1978), p.1-7, 2015.
DOI: 10.3109/01480545.2015.1012210

3. Gontijo, V. S.; Januario, J. P.; Judice, W. A. S.; Antunes, A. A.; Cabral, I. S. R.; Assis, D. M.; Juliano, M. A.; Campos, I.; Marques, M.J.; Viegas Junior, C.; dos Santos, M. H.. Morelloflavone and its semisynthetic derivatives as potential novel inhibitors of cysteine and serine proteases. Journal of Medicinal Plant Research, v. 9, p. 426-434, 2015.
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DOI: 10.5897/JMPR2014.5641

4. Fernandes, I.A.; Almeida, L.; Ferreira, P. E.; Marques, M.J.; Rocha, R. P.; Leomil- Coelho, L. F.; Carvalho, D.T.; Viegas Jr., C.. Synthesis and biological evaluation of novel piperidine-benzodioxole derivatives designed as potential leishmanicidal drug candidates. Bioorganic & Medicinal Chemistry Letters (Print), v. 25, p. 3346-3349, 2015.
DOI: 10.1016/j.bmcl.2015.05.068

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DOI: 10.1016/j.biopha.2015.08.030

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8. Carvalho, K. M.; Winter, E.; Antunes, A. M. S.. Evaluation of the Development of R&D into Parkinson's Disease through Technology Monitoring Using Patent Documents and Scientific Articles. International Journal of Research in Pharmacy and Biosciences, v. 2, p. 17-24, 2015. http://www.ijrpb.org/pdf/v2-i3/4.pdf

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10. Rodrigues Cezário, Wendel; Maria de Souza Antunes, Adelaide; Fernando Leite, Luiz; Pio Borges de Menezes, Rodrigo. The energy revolution in the USA and the pre-salt reserves in Brazil: Risks and opportunities for the Brazilian petrochemical industry. Futures (London), v. 73, p. 1-11, 2015. DOI: 10.1016/j.futures.2015.07.013

11. Antunes, A. M. S.; Kropf F, M.. Technology Foresight of New Orthopedic Prostheses: Trends in Innovation and Development in Health. HNTMB, v. 2, p. 2-6, 2015. http://www.heraldopenaccess.us/fulltext/Nanotechnology-Nanomedicine-&-Nanobiotechnology/Technology-Foresight-of-New-Orthopedic-Prostheses-Trends-in-Innovation-and-Development-in-Health.pdf

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16. Paumgartten, Francisco José Roma; Commentary: Estrogenic and Anti-Androgenic Endocrine Disrupting Chemicals and Their Impact on the Male Reproductive System. Frontiers in Public Health, v. 3, p.165, 2015. DOI:10.3389/fpubh.2015.00165

17. Solecki, Roland; Rauch M; Gall, A.; Buschmann, J.; Clark, Ruth; Fuchs, A.; Kan, H.; Heinrich, Verena; Kellner, R.; Knudsen, Thomas B.; Li, W ; Makris, Susan; Ooshima, Y.; Paumgartten, F; Priesma, A. H.; Schoenfelder, Gilbert; Oelgeschlaeger, M.; Schaefer, C.; Shiota, Kohei; Ulbrich, B.; Ding, X.; Chahoud, I. Continuing harmonization of terminology and innovations for methodologies in developmental toxicology: Report of the 8th Berlin Workshop on Developmental Toxicity, 14-16 May 2014. Reproductive Toxicology (Elmsford, N.Y.), v. 57, p. 140-146, 2015. DOI: 10.1016/j.reprotox.2015.06.046

18. Paumgartten, Francisco José Roma; Letter to the Editor: DDT Exposure In Utero and Breast Cancer. The Journal of Clinical Endocrinology and Metabolism, v. 100, p. L104-L105, 2015. DOI: 10.1210/jc.2015-3243

19. Pinto, Flávia Cristina Morone; de-Oliveira, Ana Cecília A. X.; de-Carvalho, Rosangela R.; Gomes- Carneiro, Maria Regina; Coelho, Deise R; Lima, Salvador Vilar C.; Paumgartten, Francisco José R.; Aguiar, José Lamartine A.. Acute Toxicity, Cytotoxicity, Genotoxicity and Antigenotoxic Effects of a Cellulosic Exopolysaccharide Obtained From Sugarcane Molasses. Carbohydrate Polymers, vol. 137, p. 556–560, 2015. doi:10.1016/j.carbpol.2015.10.071

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INCT INOFAR 2014-2009

*In the following pages the main activities conducted by **INCT-INOFAR** in the years from 2009 to 2014 will be detailed, in reverse chronological order, highlight research activities, events promoted and health awareness and publicity activities of high importance in those years.*

ANNUAL ACTIVITIES REPORTS

2014 - http://www.inct-inofar.ccs.ufrj.br/download/aar/2014.pdf
2013 - http://www.inct-inofar.ccs.ufrj.br/download/aar/2013.pdf
2012 - http://www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf
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HIGH LIGHTS 2014

1 **DOCKING, SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY OF N-ACYLHYDRAZONE DERIVATIVES DESIGNED AS COMBRETASTATINA4 ANALOGUES**

Daniel Nascimento do Amaral, Bruno C. Cavalcanti, Daniel P. Bezerra, Paulo Michel P. Ferreira, Rosane de Paula Castro, José Ricardo Sabino, Camila Maria Longo Machado, Roger Chammas, Claudia Pessoa, Carlos M. R. Sant'Anna, Eliezer J. Barreiro, Lídia Moreira Lima. PLoS ONE 9 (2014) e85380 *Doi: 10.1371/journal.pone.0085380*

2 **NOVEL 2-CHLORO-4-ANILINO-QUINAZOLINE DERIVATIVES AS EGFR AND VEGFR-2 DUAL INHIBITORS**

Maria Letícia de Castro Barbosa, Lídia Moreira Lima, Roberta Tesch, Carlos Mauricio R. Sant'Anna, Frank Totzke, Michael H. G. Kubbutat, Christoph Schächtele, Stefan A. Laufer, Eliezer J. Barreiro. Eur. J. Med. Chem.71(2014) 1-14. *Doi:10.1016/j.ejmech.2013.10.058*

3 **METAL COMPLEXES WITH 2-ACETYLPYRIDINE-N(4)-ORTHO-CHLORO-PHENYLTHIOSEMICARBAZONE: CYTOTOXICITY AND EFFECT ON THE ENZYMATIC ACTIVITY OF THIOREDOXIN REDUCTASE AND GLUTATHIONE REDUCTASE**

Gabrieli L. Parrilha, Karina S.O. Ferraz, Josane A. Lessa, Kely N de Oliveira, Bernardo L. Rodrigues, Jonas P. Ramos, Elaine M. Souza-Fagundes, Ingo Ott*, Heloisa Beraldo*. Eur. J. Med. Chem. 84 (2014) 537-544 DOI:10.1016/j.ejmech.2014.07.055. *Doi:10.1016/j.ejmech.2014.07.055*

4 **N-ACYLHYDRAZONE DERIVATIVE AMELIORATES MONOCROTALINE-INDUCED PULMONARY HYPERTENSION THROUGH THE MODULATION OF ADENOSINE AA2R ACTIVITY**

Allan K.N. Alencar, Sharlene L. Pereira, Flavia E. da Silva, Luiza V.P. Mendes, Valéria do M.N. Cunha, Lidia M. Lima, Tadeu L. Montagnoli, Celso Caruso-Neves, Emanuelle B. Ferraz, Roberta Tesch, José H.M. Nascimento, Carlos M.R. Sant'Anna, Carlos A.M. Fraga, Eliezer J. Barreiro, Roberto T. Sudo, Gisele Zapata-Sudo. International J. Cardiol. 173(2014) 154-162. *Doi.org/10.1016/j.ijcard.2014.02.022*

5 **MYD88-, BUT NOT NOD1- AND/OR NOD2-DEFICIENT MICE, SHOW INCREASED SUSCEPTIBILITY TO POLYMICROBIAL SEPSIS DUE TO IMPAIRED LOCAL INFLAMMATORY RESPONSE**

Fabiane Sônego, Fernanda V. S. Castanheira, Paula G. Czaikoski, Alexandre Kanashiro, Fabricio O. Souto, Rafael O. França, Daniele C. Nascimento, Andressa Freitas, Fernando Spiller, Larissa D. Cunha, Dario S. Zamboni, José C. Alves-Filho, Fernando Q. Cunha. Plos One9(8): e103734(2014). *Doi 10.1371/journal.pone.0103734*

6 **LOCAL ADMINISTRATION OF GOLD NANOPARTICLES PREVENTS PIVOTAL PATHOLOGICAL CHANGES IN MURINE MODELS OF ATOPIC ASTHMA**

Emiliano Barreto;Magda Fraguas Serra; Rafael Vitaldos Santos; Cássio Eráclito Alvesdos Santos;Jandir Hickmann;Amanda Costa Cotias; Camila Ribeiro Rodrigues Pão; Suelen GaunaTrindade; Vanessa Schimidt; Cristiano Giacomelli; Vinicius Frias Carvalho; Patricia M. R. Silva; Renato Sérgio Balão Cordeiro; Marco Aurélio Martins. Journal of Biomedical Nanotechnology11 (2015)1038-1050. *doi.org/10.1166/jbn.2015.2024*

7 **ANTI-INFLAMMATORY PROPERTIES OF CONVOLUTAMYDINE A AND TWO STRUCTURAL ANALOGUES**

Patricia D. Fernandes, Renata S. Zardo, Gabriella S.M. Figueiredo, Bárbara V. Silva, Angelo C. Pintob. Life Sciences 116 (2014) 16–24. *http://dx.doi.org/10.1016/j.lfs.2014.08.019http://dx.doi.org/10.1016/j.lfs.2014.08.019*

8 **DONEPEZIL: AN IMPORTANT PROTOTYPE TO THE DESIGN OF NEW DRUG CANDIDATES FOR ALZHEIMER'S DISEASE**

Maria Cecília Rodrigues Simões, Flávia Pereira Dias Viegas, Marcella Soares Moreira, Matheus de Freitas Silva, Mariana Máximo Riquiel, Patrícia Mattos da Rosa, Maísa Rosa Castelli, Marcelo Henrique dos Santos, Marisi Gomes Soares and Claudio Viegas Jr. Mini-Reviews in Medicinal Chemistry, 2014, 14, 2-19. *DOI: 10.2174/1389557513666131119201353*

3

METAL COMPLEXES WITH 2-ACETYLPYRIDINE-N(4)-ORTHO-CHLOROPHENYLTHIOSEMICARBAZONE: CYTOTOXICITY AND EFFECT ON THE ENZYMATIC ACTIVITY OF THIOREDOXIN REDUCTASE AND GLUTATHIONE REDUCTASE

Parrilha, G. L.; Ferraz, K. S. O.; Lessa, J. A.; Oliveira, K. N.; Rodrigues, B. L.; Ramos, J. P.; Souza-Fagundes, E. M.; Ott, I.; Beraldo, H.

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY (2014) 84: 537-544.
DOI:10.1016/j.ejmech.2014.07.055

Metal complexes with 2-acetylpyridine-*N*(4)-orthochlorophenylthiosemicarbazone (H2Ac4oClPh) were assayed for their cytotoxicity against MCF-7 breast adenocarcinoma and HT-29 colon carcinoma cells. The thiosemicarbazone and most of the complexes were highly cytotoxic.

H2Ac4oClPh and its gallium(III) and tin(IV) complexes did not show any inhibitory activity against thioredoxin reductase (TrxR) and glutathione reductase (GR). The palladium(II), platinum(II) and bismuth(III) complexes inhibited TrxR at micromolar concentrations but not GR. The antimony(III) and gold(III) complexes strongly inhibited TrxR at submicromolar doses with GR inhibition at higher concentrations. The selectivity of these complexes for TrxR suggests metal binding to a selenol residue in the active site of the enzyme. TrxR inhibition is likely a contributing factor to the mode of action of the gold and antimony derivatives.

2014 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 **VIII ANNUAL INCT-INOFAR EVALUATION MEETING**

2 **CELEBRATION OF 20 YEARS OF LASSBIO/UFRJ**

3 **SYMPOSIUM "40 YEARS OF THE GRADUATE PROGRAM IN PHARMACOLOGY AND MEDICINAL CHEMISTRY"**

4 **20 YEARS**

OF THE SUMMER SCHOOL IN PHARMACEUTICAL AND MEDICINAL CHEMISTRY AND 2ª ESCUELA INTERNACIONAL DE QUÍMICA MEDICINAL Y FARMACOLOGIA

Organized by the Laboratory of Evaluation of Bioactive Substances (**LASSBio**), research group associated with the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**), the XX Summer School in Medicinal and Pharmaceutical Chemistry (SSMC), an event that has already become renowned in the field of Pharmaceutical Sciences, took place at the Federal University of Rio de Janeiro (UFRJ) facilities in January 2014.

Incorporated to **INCT-INOFAR** in 2009 as an extension activity, the twentieth SSMC took place alongside the *II Escuela Internacional de Química Medicinal y Farmacologia* (II International School of Medicinal Chemistry and Pharmacology), organized by Uruguayan Professors Hugo Cerecetto and Mercedez Gonzales, from the University of the Republic (UdelaR).

The Summer School has already become a tradition to undergraduate and graduate students from different Brazilian states and even from other countries. Students seek to enhance their academic and scientific knowledge in the field of Medicinal Chemistry, and give up vacation time to do so.

Six conferences were conducted, with several different topics, eight courses, and the participation of 15 professors. In celebration of its 20th anniversary, the SSMC created a commemorative publication, "Retrospective 1995-2014 Summer School: 20 years of contributions to Medicinal Pharmaceutical Chemistry.

THE WORLD CUP OF PHARMACY

In 2014, the 20th edition of the World Cup of Soccer took place in Brazil, and the SSMC was not left out. Following a suggestion from journalist Lucia Beatriz Torres, the "World Cup of Pharmaceutical Chemistry" was organized to tell, in a dynamic way, how the past 20 years of the Summer School in Pharmaceutical and Medicinal Chemistry had been.

The event takes place yearly, during summer vacation, and has hosted over 2,500 participants and offered over 100 different courses and 90 different conferences, with 36 of them being given by foreign professionals. At the XX SSMC, only foreign researchers were invited to be part of the Circle of Conferences.

OUTREACH ACTIVITIES

2014

1st EDITION SNCT IN *SÃO FRANCISCO DE ITABAPOANA*

INCT-INOFAR PROMOTES *NATIONAL SCIENCE AND TECHNOLOGY WEEK*

*In a brand new initiative, **INCT-INOFAR** held the 1st National Science and Technology Week (SNCT) of the city of São Francisco de Itabapoana, town located in the north of the state of Rio de Janeiro.*

The theme of this edition of the National Science and Technology Week was "Science and Technology for Social Development".

With the entire focus on social development, **INCT-INOFAR** conducted several activities raising awareness of the safe and correct use and discarding of drugs, aimed at a healthy life.

The Drugs and Medicines INCT team, under the command of educator Ana Cristina da Mata Silva, with the help of collaborator Raphael Segrini and of pharmacists Natália Lima and Thayssa Tavares, organized several activities on the publicity and promotion of science with students from the Elementary, High School, and the Program for the Education of Youths and Adults (EJA) levels, from the Municipal Schools Dirceu Dias da Silva and Herval Luiz dos Santos Batista. Among the actions undertaken, we would like to mention lectures, art workshops, and rounds of the human board game "Drugs are not toys ", movie sessions with the videos produced by the Institute, as well as participation in the Cultural Fair, which took place at the Three Powers Square, in front of the City Hall, where **INCT-INOFAR** had its booth to meet the population. In the occasion, over 500 people sought information and asked questions on how to safely acquire, administer, store, and discard drugs.

During activities, folders with a wide variety of informational materials on how to administer, use, and discard drugs correctly were distributed. Also included in the folders were the educational puzzles with the comics available at the Drugs Portal.

The work developed by the **INCT-INOFAR** team during the 1st National Science and Technology Week of São Francisco de Itabapoana was acknowledged by the City Hall, generating an interest in the Municipal Secretary of Education and Culture in establishing a partnership with **INCT-INOFAR**, which was made official through the Cooperation Agreement signed during this event.

HIGH LIGHTS 2013

9

BENEFICIAL EFFECTS OF A NOVEL AGONIST OF THE ADENOSINE A 2A RECEPTOR ON MONOCROTALINE-INDUCED PULMONARY HYPERTENSION IN RATS

Alencar, A. K. N.; Pereira, S. L.; Montagnoli, T. L ; Maia, R. C.; Kümmerle, A. E.; Landgraf, S. S.; Caruso-Neves, C.; Ferraz, E. B.; Tesch, R.; Nascimento, J. H. M.; Sant'Anna, C. M. R.; Fraga, C. A. M.; Barreiro, E. J.; Sudo, R. T.; Zapata-Sudo, G.

BRITISH JOURNAL OF PHARMACOLOGY (2013) 169: 953-962.
DOI:10.1111/bph.12193

A single i.p. injection of monocrotaline (MCT) in male Wistar rats induced changes in vascular and ventricular structure and function, characteristic of pulmonary arterial hypertension (PAH). 2 weeks later, oral LASSBio-1359 (50 mg/kg) or vehicle was given once daily for 14 days. This prototype reversed changes in vascular and ventricular structure and function and also reversed the endothelial dysfunction in pulmonary artery. In pulmonary artery rings from normal Wistar rats, LASSBio-1359 induced relaxation, which was decreased by the adenosine A2A receptor antagonist, ZM 241385.

In adenosine receptor binding studies, LASSBio-1359 showed most affinity for the A2A receptor that was also predicted by docking studies. In fact, LASSBio-1359 has similar binding model with A2A receptor than the agonist CGS21680. We can conclude that in rats with MCT-induced PAH, structural and functional changes in heart and pulmonary artery were reversed by treatment with oral LASSBio-1359, most probably through the activation of adenosine A2A receptors.

2013 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 II INCTS FOLLOW-UP AND EVALUATION SEMINAR

2 VII INCT-INOFAR FOLLOW-UP AND EVALUATION WORKSHOP & INCT-INOFAR STRATEGIC PLANNING MEETING

3 XIX SUMMER SCHOOL IN MEDICINAL PHARMACEUTICAL CHEMISTRY

VISIT: **PRESENCE IN EVENTS 2013**
http://www.inct-inofar.ccs.ufrj.br/english/participa_2013.html

4 DOCTOR SÉRGIO HENRIQUE FERREIRA AWARD FOR BEST THESIS

The National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) created the Doctor Sérgio Henrique Ferreira Award for best Doctoral Thesis in the Graduate Program in Pharmacology and Medicinal Chemistry (PGFQM/UFRJ), a new graduate course in Latin America, uniting Pharmacology and Medicinal Chemistry, created by the Institute of Biomedical Sciences (ICB), of the Federal University of Rio de Janeiro (UFRJ), with efforts from researchers associated with the Institute.

The Award was handed to Dr. Ariane Rennó Brogliato, for the thesis titled “Evaluation of the participation of the 5-LO pathway in the healing of wounds of its implications in oxidative stress”. Under the advice of Professor Claudia Farias Benjamim (ICB/UFRJ), the new doctor is experienced in experimental sepsis models and healing of cutaneous wounds in mice. The scientist is in the field of Immunopharmacology and develops research in projects that involve sepsis, inflammation, and tissue repair.

The ceremony for handing out the award took place on December 19, 2013 in the Pharmacology auditorium in the Center for Health Sciences (CCS) at UFRJ. Professor Angelo da Cunha Pinto (IQ/UFRJ), prior to announcing the awarded thesis, presented the lecture “The Brazil of travelers and the Chemistry of Brazilian Natural Products”. The Professor was part of the examining committee and also received an award for his scientific career.

1st

THESIS
“Evaluation of the participation of the 5-LO way in the healing of wounds and the implications for oxidative stress”

AUTHOR
Arianne Rennó Brogliato

ADVISOR
Prof. Claudia Farias Benjamim

INSTITUTION
Graduate Program in Pharmacology and Medicinal Chemistry (ICB/UFRJ)

OUTREACH ACTIVITIES

INCT-INOFAR ENCOURAGES SCIENCE AWARENESS IN RORAIMA

INCT-INOFAR *SCIENCE PROMOTION ACTIONS BOOK*

INCT-INOFAR IN SCHOOLS PROJECT

3RD FAPERJ FAIR

30 YEAR LIVE SCIENCE CELEBRATION

NATIONAL SCIENCE AND TECHNOLOGY WEEK

CIRCUIT OF VESSELS IS PROMOTED BY INCT-INOFAR

INCT-INOFAR was part of the 10th National Science and Technology Week (SNCT), which had the theme "Science, Health, and Sports". At the occasion, **INCT-INOFAR** promoted activities that support the interaction between sports, science, and health. The actions took place in the "Knowledge Vessels", spaces aimed at promoting digital inclusion for the population through access to information and technological advances, and located in the neighborhoods of Penha, Irajá, Madureira, Padre Miguel, Vila Aliança and Santa Cruz, Rio de Janeiro city. Over a thousand people visited.

On the first day of activities, **INCT-INOFAR** was enthusiastically welcomed by the population of Bangu, where the Knowledge Vessel Abadias do Nascimento is located, in the neighborhood of Vila Aliança. Among the many activities, one of the highest points of the event was the lecture by pharmacist Ciro Gonçalves, who spoke about the importance of vitamins and minerals in the lives of athletes.

On the second day, **INCT-INOFAR** held activities at the Knowledge Vessel Teacher Claudia Martins Augusto de Jesus, in Irajá. At the time, the lecturer was **INCT-INOFAR** Scientific Superintendent, Professor Lidia Moreira Lima, who organized a debate on self-medicating and the abusive use of drugs in sports. The controversial topic generated many questions in the young people present, and they were able to have their questions answered. Throughout the day, **INCT-INOFAR** members interacted with the Vessel team, helping them provide information and hand out visors and folders on fighting breast cancer, as part of the Pink October Movement.

Coordinated by educator and **INCT-INOFAR** Secretary of Extension Ana Cristina da Mata Silva, the Vessels Circuit led us to the Knowledge Vessel Journalist Joelmir Beting, in Penha. Aside from all activities, the event had the participation of Doctor in Vegetable Biotechnology Hélio Mattos Alves (UFRJ), who explained how drugs are made from the point of view of medicinal plants.

On the fourth day, the team set up at the Knowledge Vessel of Madureira, at the Madureira Park, and had the presence of the Municipal Secretary of Science and Technology Franklin Coelho and of **INCT-INOFAR** coordinator Eliezer J. Barreiro (UFRJ). The topic dealt with during this day was quality of life through the use of medication, in a lecture given by Doctor in Organic Chemistry Carlos A. Manssour Fraga.

Padre Miguel was the destination of **INCT-INOFAR** on the fifth day of the Vessels Circuit. The lecture given by pharmacist Daniel Nascimento do Amaral at the Knowledge Square Cinematographical Reporter Gelson Domingos, with the support of coworkers Roberta Tesch and Miguel Divino da Rocha, approached the topic "The Use of Anabolic Steroids and Doping in Sports – Danger to the Health of Athletes and Young People", and clarified organic changes both in and out of the sports world.

The last stop by the **INCT-INOFAR** team in the Knowledge Vessels circuit was in Santa Cruz, where the work focused on Science Publicity and Promotion. Educator Ana Cristina da Mata Silva and pharmacist Natália Lima presented the cartoon video for the "Commandments of the Correct Use of Drugs" booklet, and during this time, the Drugs and Medicines INCT launched its third booklet, called "Joey's Crew in: The Correct Use of Anti-inflammatories", as well as the "Drugs are not Toys" board game, in A3 size version. The children also played with the human board game of the same name, where, with the help of furry dice, children walk the course of the game while learning the Commandments of the Correct Use of Drugs.

HIGH LIGHTS 2012

1 **DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF N-ACYLHYDRAZONES AND NOVEL CONFORMATIONALLY CONSTRAINED COMPOUNDS AS SELECTIVE AND POTENT ORALLY ACTIVE PHOSPHODIESTERASE-4 INHIBITORS**

Arthur E. Kümmerle; Martine Schmitt; Suzana V. S. Cardozo; Claire Lugnier; Pascal Villa; Alexandra B. Lopes; Nelilma C. Romeiro; Helene Justiniano; Marco A. Martins; Carlos A. M. Fraga; Jean-Jacques Bourguignonand Eliezer J. Barreiro. Journal of Medicinal Chemistry 55 (2012) 7525-7545. DOI: 10.1021/jm300514y

2 **DISCOVERY OF NOVEL ORALLY ACTIVE ANTI-INFLAMMATORY N-PHENYLPYRAZOLYL-N-GLYCINYL-HYDRAZONE DERIVATIVES THAT INHIBIT TNF - α PRODUCTION**

Lacerda, R, B.; Silva, L. L.; Lima, C. K. F.; Miguez, E.; Miranda, A. L. P.; Laufer, S. A.; Barreiro, E. J.; Fraga, C. A. M. PLoS ONE 7 (2012) e46925. DOI: 10.1371/journal.pone.004692

3 **DOCKING, SYNTHESIS AND ANTI-DIABETIC ACTIVITY OF NOVEL SULFONYLHYDRAZONE DERIVATIVES DESIGNED AS PPAR-GAMMA AGONISTS**

Gisele Zapata-Sudo, Lídia M. Lima, Sharlene L. Pereira, Margarete M. Trachez, Filipe P. da Costa, Beatriz J. Souza, Carlos E. S. Monteiro, Nelilma C. Romeiro, Éverton D. D'Andréa, Roberto T. Sudoand Eliezer J. Barreiro. Current Topics Med. Chem. 12 (2012), 2037-2048.
DOI: 10.2174/1568026611212190002

4 **N4-PHENYL-SUBSTITUTED 2-ACETYLPYRIDINE THIOSEMICARBAZONES: CYTOTOXICITY AGAINST HUMAN TUMOR CELLS, STRUCTURE-ACTIVITY RELATIONSHIP STUDIES AND INVESTIGATION ON THE MECHANISM OF ACTION.**

Soares, M.A.; Lessa, J.A.; Mendes, I.C.; Da Silva, J.; Santos, R.G.; Salum, L.B.; Daghestani, H.; Andricopulo, A. D.; Day, B.W.; Vogt ,A.; Pesquero, J. L.; Rocha, W.; Beraldo, H. Bioorg. Med. Chem. 20 (2012) 3396-3409. DOI: 10.1016/j.bmc.2012.04.027

5 **INVESTIGATION OF TRYPANOTHIONE REDUCTASE INHIBITORY ACTIVITY BY 1,3,4-THIADIAZOLIUM-2-AMINIDE DERIVATIVES AND MOLECULAR DOCKING STUDIES.**

Raquel F. Rodrigues*, Denise Castro-Pinto, Aurea Echevarria, Camilla M. dos Reis, Catarina N. Del Cistia, Carlos Mauricio R. Sant'Anna, Filipa Teixeira, Helena Castro, Marilene Canto-Cavalheiro, Leonor L. Leon, Ana Tomás. Bioorganic & Medicinal Chemistry 20 (2012) 1760–1766. DOI:10.1016/j.bmc.2012.01.009

6 **TOLL-LIKE RECEPTOR 9 ACTIVATION IN NEUTROPHILS IMPAIRS CHEMOTAXISAND REDUCES SEPSIS OUTCOME**

Silvia C. Trevelin, José C. Alves Filho, Fabiane Sônego, Walter Turato, Daniele C. Nascimento, Fabricio O. Souto, Thiago M. Cunha, Ricardo T. Gazzinelli, Fernando Q. Cunha. Critical Care Medicine 40 (2012) 2631-7. DOI:10.1097/CCM.0b013e318258fb70.

7 **ULIGINOSIN B, A PHLOROGLUCINOL DERIVATIVE FROM HYPERICUM POLYANTHEMUM, PRODUCE ANTIDEPRESSANT-LIKE EFFECT IN MICE: A NEW MOLECULAR PATTERN PROMISING TO THE DEVELOPMENT OF ANTIDEPRESSANT DRUGS**

Ana C Stein, Alice F Viana, Liz G Müller, Jéssica M Nunes, Eveline D Stolz, Jean C Do Rego, Jean Constentin, Gilsane L von Poser, Stela Maris Kuze Rates. Behavior Brain Research 228 (2012) 66-73. DOI: 10.1016/j.bbr.2011.11.031

8 **PLANT DERIVED ALKALOID (-)-CASSINE INDUCES ANTI-INFLAMMATORY AND ANTI-HYPERALGESICS EFFECTS IN BOTH ACUTE AND CHRONIC INFLAMMATORY AND NEUROPATHIC PAIN MODELS**

Kathryn A.B.S. da Silva, Marianne Neves Manjavachi, Ana Flávia Paszcuk, Marcos Pivatto, Claudio Viegas Jr., Vanderlan S. Bolzani, João B. Calixto. Neuropharmacology 62 (2012) 967-977. DOI: doi:10.1016/j.neuropharm.2011.10.002

9 **BIOTRANSFORMATION OF LASSBIO-579 AND PHARMACOLOGICAL EVALUATION OF P-HYDROXYLATED METABOLITE A N-PHENYLPIPERAZINE ANTIPSYCHOTIC LEAD COMPOUND**

Tatiana. F. Gomes; Thais E. T. Pompeu; Daniel A. Rodrigues; François Noël; Ricardo Menegatti; Carolina H. Andrade; José R. Sabino; Eric S. Gil; Teresa Dalla Costa; Andresa H. Betti; Camila B. Antonio; Stela M. K. Rates; Carlos A. M. Fraga; Eliezer J. Barreiro;Valéria de Oliveira. European Journal of Medicinal Chemistry (2012), doi.org/10.1016/j.ejmech.2012.08. 011.V 62, April 2013, 214–221.

1

DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF N-ACYLHYDRAZONES AND NOVEL CONFORMATIONALLY CONSTRAINED COMPOUNDS AS SELECTIVE AND POTENT ORALLY ACTIVE PHOSPHODIESTERASE-4 INHIBITORS

Kümmerle, A. E.; Schmitt, M.; Cardozo, S. V. S.; Lugnier, C.; Villa, P.; Lopes, A. B.;. Romeiro, N. C.; Justiniano, H.; Martins, M. A.; Fraga, C. A. M.; Bourguignon, J.; Barreiro, E. J.

JOURNAL OF MEDICINAL CHEMISTRY (2012) 55: 7525-7545.
DOI: 10.1021/jm300514y

Among a small series of tested N-acylhydrazones (NAHs), the compound 8a was selected as a selective submicromolar phosphodiesterase-4 (PDE4) inhibitor associated with anti-TNF-α properties measured both in vitro and in vivo. The recognition pattern of compound 8a was elucidated through molecular modeling studies based on the knowledge of the 3D-structure of zardaverine, a PDE4 inhibitor resembling the structure of 8a, cocrystallized with the PDE4. Based on further conformational analysis dealing with N-methyl-NAHs, a quinazoline derivative (19) was designed as a conformationally constrained NAH analogue and showed similar in vitro pharmacological profile, compared with 8a. In addition 19 was found active when tested orally in LPS-evoked airway hyperreactivity and fully confirmed the working hypothesis supporting this work.

2012 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 VI INCT-INOFAR FOLLOW-UP AND EVALUATION WORKSHOP

2 18th EDITION OF SUMMER SCHOOL IN MEDICINAL AND PHARMACEUTICAL CHEMISTRY

In its eighteenth edition, the Summer School in Medicinal and Pharmaceutical Chemistry (SSMC), traditionally organized by the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**) and later incorporated to the Drugs and Medicines INCT **(INCT-INOFAR)** as an extension activity at UFRJ during the summer academic vacation, with five days of courses and conferences in January, with local and foreigner experts in the field of Medicinal Pharmaceutical Chemistry.

Created in 1995, the School has already gathered over 2,500 participants from several parts of Brazil and from other countries. It has had renowned scientists – such as scientists responsible for the development of innovative drugs – sharing their experiences in the pharmaceutical market with students. **INCT-INOFAR** has offered scholarships to students from Mercosur countries, supporting them during the XVIII SSMC. The event received researchers from Uruguay, graduate students of Biochemistry at the University of the Republic (Udelar).

In celebration of the 18 years of the Summer School, the Organizing Committee for the SSMC 2012 created the Camille-Georges Wermuth Medal of Honor in Medicinal Chemistry, to award a person who has had a noteworthy scientific career in Medicinal Chemistry. The winner of the metal in 2012 was Professor Carlos Alberto Manssour Fraga, **INCT-INOFAR** researcher and participant of one of the first Summer Schools, when he was still applying to be an adjunct professor at UFRJ. Currently Manssour is a Full Professor at the same Institution and works at **LASSBio**.

The XVIII Summer School in Medicinal and Pharmaceutical Chemistry had very interesting programming, dealing with topics like “Synthesis of Drugs” and courses on “Introduction to Medicinal Chemistry” and “Drug Metabolism and Drug Interaction". The world level conferences dealt with important topics in Medicinal Pharmaceutical Chemistry. The XVIII SSMC welcomed Professor. Holger Stark from *University Johann Wolfgang Goethe, Germany;* Professor Pier G. Baraldi from the University of Ferrara, Italy; and Professor Jose A. S. Cavaleiro from the University of Aveiro, Portugal.

OUTREACH ACTIVITIES

2012

ANIMATION
"JOEY'S CREW IN THE CORRECT USE OF ANTIBIOTICS"

BOOK
EXPERIMENTS IN ORGANIC CHEMISTRY

INCT-INOFAR
IN SCHOOLS

EXPOSITION HAS SUPPORT OF ***INCT-INOFAR***

"WHERE IS CHEMISTRY?"

In celebration of the International Year of Chemistry, the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) promoted a visit for all students of the Public Municipal School Edmundo Lins, Ramos to the House of Science (UFRJ) and, in partnership with the Brazilian Society of Chemistry, organized the exposition "Where is the Chemistry?" in order to show the chemical components present in our daily lives.

In the programming, the students from the 1st and 4th grade visited the exposition, which had four stages and took place on both April 26th and 27th and on May 3rd and 4th. During the circuit, students were able to find out how Chemistry relates to our daily lives. They were also part of the "Molecule Hunter" game, in which they were able to build molecules present in our lives such as water (H_2O) and carbon dioxide (CO_2).

The children also visited several sets that represented rooms in a house, which are familiar to them, like a living room, where they watched a cartoon about the history of Chemistry, wearing 3D glasses. They were able to visit the "master's bedroom" space, where they were invited to lie on the bed and understand how the chemistry of hormones in the human body works.

"Chemistry is present everywhere, from our clothing to the food we eat", said the coordinator of projects and vice-director of the House of Science (UFRJ), Isabela Cristina de Azevedo. According to her, the goal of the event was to make people realize that chemistry is part of our daily lives.

HIGH LIGHTS 2011

1 **THE METHYLATION EFFECT IN MEDICINAL CHEMISTRY**

The methylation effect in medicinal chemistry. Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M.; Chemical Reviews (2011) 111: 5215-5246. DOI: 10.1021/cr200060g

2 **DISCOVERY OF LASSBIO-772, A 1,3-BENZODIOXOLE N-PHENYLPIPERAZINE DERIVATIVE WITH POTENT ALPHA 1A/DADRENERGIC RECEPTOR BLOCKING PROPERTIES**

Romeiro, L. A. S.; Ferreira, M. S.; DaSilva, L. L.; Castro, H. C.; Miranda, A. L. P.; Silva, C. L. M.; Noel, F. G.; Nascimento, J. B.; Araujo, C. V.; Tibiriçá, E.; Barreiro, E. J.; Fraga, C. A. M. Eur. J. Med. Chem. 46 (2011) 3000-3012. DOI: 10.1016/j.ejmech.2011.04.032

3 **QUERCETIN REDUCES NEUTROPHIL RECRUITMENT INDUCED BY CXCL8, LTB4, AND FMLP. INHIBITION OF ACTIN POLYMERIZATION**

Souto, F.O.; Zarpelon, A. C.; Staurengo-Ferrari, L.; Fattori, V.; Casagrande, R.; Fonseca, M. J. V.; Cunha, T. M.; Ferreira, S. H.; Cunha, F. Q.; Verri Jr, W. A. J. Nat. Prod. 74 (2011) 113-118. DOI:10.1021/ np1003017

4 **TADALAFIL ANALGESIA IN EXPERIMENTAL ARTHRITIS INVOLVES SUPPRESSION OF INTRA-ARTICULAR TNF RELEASE**

F.A.C., Rocha; F.S., Silva Jr; A.C.R.M., Leite; A.K.R.M., Leite; V.C.C., Girão; R.R., Castro;F.Q., Cunha. Brit. J. Pharmacol. 164 (2011) 828–835. DOI: 10.1111/j.1476-5381.2011.01469.x

5 **PHARMACOLOGICAL ACTIVITY OF NOVEL 2-HYDROXYACETOPHENONE ISATIN DERIVATIVES ON CARDIAC AND VASCULAR SMOOTH MUSCLE IN RATS**

Daniele Gabriel; Luana Braga Pontes; Jaqueline Soares da Silva; Roberto TakashiSudo; Marilza Baptista Corrêa; Ângelo da Cunha Pinto; Simon John Garden; Gisele Zapata-Sudo. J. Cardiovasc. Pharmacol. 57 (2011) 20-27. DOI: 10.1097/FJC.0b013e3181fd341c

6 **GOLD(I) COMPLEXES WITH THIOSEMICARBAZONES: CYTOTOXICITY AGAINST HUMAN TUMOR CELL LINES AND INHIBITION OF THIOREDOXIN REDUCTASE ACTIVITY**

Josane A. Lessaa , Juliana C. Guerrab , Luana F. de Mirandab , Carla F. D. Romeirob , Jeferson G. Da Silvaa , Isolda M. C. Mendesc , Nivaldo L. Spezialid , Elaine M. Souza-Fagundesband Heloisa Beraldoa * J. Inorg. Biochem. 105 (2011) 1729-1739. DOI:10.1016/j.jinorgbio.2011.09.008

7 **DETERMINATION OF THE CARDIOACTIVE PROTOTYPE LASSBIO-294 AND ITS METABOLITES IN DOG PLASMA BY LC–MS/MS: APPLICATION FOR A PHARMACOKINETIC STUDY**

Rodolpho C. Braga, Andréa C.B. Tôrres, Camille B. Persiano, Rosângela O. Alves, Carlos A.M. Fraga, Eliezer J. Barreiro, Valéria de Oliveira. Journal of Pharmaceutical and Biomedical Analysis 55 (2011) 1024– 1030. DOI:10.1016/j.jpba.2011.02.031

8 **ANTICHOLINESTERASIC, NEMATOSTATIC AND ANTHELMINTIC ACTIVITIES OF PYRIDINIC AND PYRAZINIC COMPOUNDS**

Valli M.; DanuelloA.; Pivatto M.; Saldaña J.C.; Heinzen H.; Domínguez L.; Campos V.P.; Marqui S.R.; Young M.C.M.; Viegas Jr. C.; Silva D.H.S.; Bolzani V.S. Current Medicinal Chemistry. 18 (2011) 3423- 3430. DOI:10.2174/092986711796504718

1

THE METHYLATION EFFECT IN MEDICINAL CHEMISTRY

Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M.

CHEMICAL REVIEWS (2011) 111: 5215-5246.
DOI: 10.1021/cr200060g

The role of the simple methyl group as a very useful structural modification in the rational design of bioactive compounds and drugs is discussed. The methyl effect alters both biological phases of a drug, represented by its pharmacodynamic and pharmacokinetic profile, due to the modifications introduced in the stereoelectronic character of the final molecule. The methyl group is very important in the molecular recognition of endogenous and exogenous organic compounds by their specific bioreceptors. Although it only participates in London dispersion interactions, which are the weakest of all intermolecular interactions, methyl groups have stereoelectronic effects on micromolecules and biomacromolecules, thereby leading to diverse biological effects, including selectivity among bioreceptors, increased potency, and modulate metabolism stability. Several examples will be presented and discussed in this review.

2011 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 I 2011 EVALUATION AND FOLLOW-UP MEETING

2 II 2011 EVALUATION AND FOLLOW-UP MEETING

3 XVII SUMMER SCHOOL IN MEDICINAL CHEMISTRY

4 2008 NOBEL OF CHEMISTRY WINNER AT UFRJ

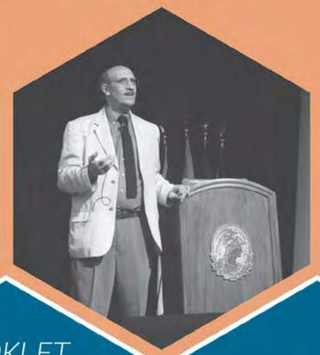
INCT-INOFAR supported the visit to Brazil from the winner of the Nobel of Chemistry Prize in 2008, Professor Martin Chalfie, to be part of the opening of the National Science and Technology Week 2011, which took place in October, in the Complexo do Alemao, in Rio de Janeiro.

Professor Chalfie gave a lecture before the official opening of the event with the topic “Fluorescent Proteins (GFP): Illuminating Life”, at the Graduate Program in Chemistry of UFRJ facilities. The scientist spoke about his career in science and in the field of GFP, the research area which lead to him winning the Nobel of Chemistry Prize in 2008, alongside researchers Osamo Shimomura e Roger Tsein. Martin Chalfie is a professor at the Department of Biological Sciences of the University of Columbia, in the USA

OUTREACH ACTIVITIES

2011

INCT-INOFAR *IN THE INTERNATIONAL YEAR OF CHEMISTRY*

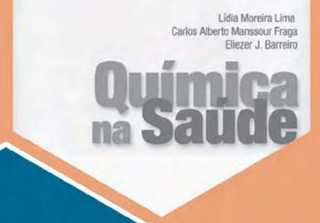


BOOKLET 2009-2011 SCIENTIFIC AWARENESS AND HEALTH EDUCATION

NOBEL PRIZE IN CHEMISTRY CONFERENCE AT UFRJ

INCT-INOFAR *"365 DAYS OF CHEMISTRY"*

E-BOOK "CHEMISTRY IN HEALTH"



AIQ *CONFERENCE CYCLE*

EDMUNDO LINS MUNICIPAL SCHOOL, RJ

INCT-INOFAR PROMOTES ***HEALTH EDUCATION***

As part of a new initiative, **INCT-INOFAR** conducted health education activities in Municipal School Edmundo Lins, in the Northern region of Rio de Janeiro city, dealing with the topic "The safe and correct use of drugs", so as to raise awareness among students on the dangers caused by their incorrect use.

INCT-INOFAR presented the Booklet "The Commandments of the Correct Use of Drugs" and had a questions and answers section, with the presence of pharmacists Roberta Tesch and Bruna de Lima, to answer any questions the students might have. The most participative students were rewarded with the puzzles created by **INCT-INOFAR,** which present how carefully one must be when taking drugs in a fun way.

After closing activities, many students approached the pair of pharmacists to ask questions, such as what the difference between a doctor and a pharmacist is. At the end of the event, each student was asked to write a report on what they had learned during the **INCT-INOFAR** visit and the best works were shown in the school bulletin board.

HIGH LIGHTS 2010

1 **IL-17 MEDIATES ARTICULAR HYPERNOCICEPTION IN ANTIGEN-INDUCED ARTHRITIS IN MICE**

L. G. Pinto, T. M. Cunha, S. M. Vieira, H. P. Lemos, W. A. Verri Jr, F.. Q. Cunha, S. H. Ferreira. Pain (2010) 148:247-56. DOI:10.1016/j.pain.2009.11.006

2 **LASSBIO-294, A COMPOUND WITH INOTROPIC AND LUSITROPIC ACTIVITY, DECREASES CARDIAC REMODELING AND IMPROVES CA2+ INFLUX INTO SARCOPLASMIC RETICULUM AFTER MYOCARDIAL INFARCTION**

D. G. Costa , J. C. Silva, A. E. Kummerle, R. T. Sudo, S. S. Landgraf, C. Caruso-Neves, C. A. M. Fraga, E. J. Barreiro, and G. Zapata-Sudo. Journal of Hypertension (2010) 23: 1220-1227. DOI:10.1038/ajh.2010.157

3 **BONE MARROW-DERIVED MONONUCLEAR CELL THERAPY IN EXPERIMENTAL PULMONARY AND EXTRAPULMONARY ACUTE LUNG INJURY**

I. M. Araújo, S. C. Abreu, T. Maron-Gutierrez, F. F. Cruz, L. Fujisaki, H. Carreira-Junior, F. Ornellas, D. S. Ornellas, A. Vieira-de-Abreu, H. C. C. Faria-Neto, A. Ab´Saber, W. R. Teodoro, DB. L. iaz, C. Peres da Costa, V. L. Capelozzi, P. Pelosi, M. M. Morales, P. R. M. Rocco. Crit. Care Med. (2010) 38: 1733-1741. DOI: 10.1097/CCM.0b013e3181e796d2

4 **2-ACETYLPYRIDINE THIOSEMICARBAZONES: CYTOTOXIC ACTIVITY IN NANOMOLAR DOSES AGAINST MALIGNANT GLIOMAS**

J.A. Lessa, I.C. Mendes, P. R.O. da Silva, M. A. Soares, R. G. dos Santos, N. L.. Speziali, N. C. Romeiro, E. J. Barreiro and H. Beraldo. European Journal of Medicinal Chemistry (2010) 45: 5671-5677. DOI:10.1016/j.ejmech.2010.09.021

5 **THE INFLUENCE OF B-SUBSTITUENTS IN ALDOL REACTIONS OF BORON ENOLATES OF B-ALKOXYMETHYLKETONES**

L. C. Dias, E. C. de Lucca, M. A. B. Ferreira, D. C.Garcia, C. F. Tormena. Organic Letters (2010) 12: 5056-5059. DOI:10.1021/ol102303p

6 **MICROWAVE-ASSISTED SYNTHESIS AND STRUCTURE–ACTIVITY RELATIONSHIPS OF NEUROACTIVE PYRAZOLO[3,4-B]PYRROLO[3,4-D] PYRIDINE DERIVATIVES**

N. M. Nascimento-Júnior, T. C.F. Mendes, D. M. Leal, C. M. N. Corrêa, R. T. Sudo, G. Zapata-Sudo, E. J. Barreiro and C. A. M. Fraga. Bioorganic & Medicinal Chemistry Letters (2010) 20: 74-77. DOI:10.1016/j.bmcl.2009.11.038

7 **DESIGN OF NEW DOPAMINE D2 RECEPTOR LIGANDS: BIOSYNTHESIS AND PHARMACOLOGICAL EVALUATION OF THE HYDROXYLATED METABOLITE OF LASSBIO-581**

F. Pazini, R. Menegatti, J. R. Sabino, C. H. Andrade, G. Neves, S. M. K. Rates, F. Noël, C. A. M. Fraga, E. J. Barreiro, V. de Oliveira. Bioorg. Med. Chem. Lett. (2010) 20: 2888-2891. DOI:10.1016/j.bmcl.2010.03.034

8 **CASEARIN X, ITS DEGRADATION PRODUCT AND OTHER CLERODANEDITERPENES FROM LEAVES OF CASEARIASYLVESTRIS: EVALUATION OF CYTOTOXICITY AGAINST NORMAL AND TUMOR HUMAN CELLS**

A. G.dos Santos, P. M. P. Ferreira, G. M. Vieira Jr, C. C. Perez, A. G. Tininis, G. H. Silva, V. da S. Bolzani, L. V. Costa-Lotufo, C. do Ó Pessoa, A. J. Cavalheiro
Chemistry & Biodiversity (2010) 7: 205-215
DOI: 10.1002/cbdv.200800342

9 **INTERLEUKIN-33 ATTENUATES SEPSIS BY ENHANCING NEUTROPHIL INFLUX TO THE SITE OF INFECTION**

A. G.dos Santos, P. M. P. Ferreira, G. M. Vieira Jr, C. C. Perez, A. G. Tininis, G. H. Silva, V. da S. Bolzani, L. V. Costa-Lotufo, C. do Ó Pessoa, A. J. Cavalheiro. Chemistry & Biodiversity (2010) 7: 205-215. DOI: 10.1038/nm.2156

9

INTERLEUKIN-33 ATTENUATES SEPSIS BY ENHANCING NEUTROPHIL INFLUX TO THE SITE OF INFECTION

Alves-Filho, J. C.; Sônego, F.; Souto, F. O.; Freitas, A.; Verri Jr, W. A.; Auxiliadora-Martins, M.; Basile-Filho, A.; McKenzie, A. N.; Xu, D.; Cunha, F. Q.; Liew, F. Y.

NATURE MEDICINE (2010) 16: 708–712.
DOI:10.1038/nm.2156

Sepsis is a systemic inflammatory condition following bacterial infection with a high mortality rate and limited therapeutic options. Here we show that interleukin-33 (IL-33) reduces mortality in mice with experimental sepsis from cecal ligation and puncture (CLP). IL-33–treated mice developed increased neutrophil influx into the peritoneal cavity and more efficient bacterial clearance than untreated mice. IL-33 reduced the systemic but not the local proinflammatory response, and it did not induce a T helper type 1 (TH1) to TH2 shift. The chemokine receptor CXCR2 is crucial for recruitment of neutrophils from the circulation to the site of infection. Activation of Toll-like receptors (TLRs) in neutrophils downregulates CXCR2 expression and impairs neutrophil migration. We show here that IL-33 prevents the downregulation of CXCR2 and inhibition of chemotaxis induced by the activation of TLR4 in mouse and human neutrophils. Furthermore, we show that IL-33 reverses the TLR4-induced reduction of CXCR2 expression in neutrophils via the inhibition of expression of G protein–coupled receptor kinase-2 (GRK2), a serine-threonine protein kinase that induces internalization of chemokine receptors. Finally, we find that individuals who did not recover from sepsis had significantly more soluble ST2 (sST2, the decoy receptor of IL-33) than those who did recover. Together, our results indicate a previously undescribed mechanism of action of IL-33 and suggest a therapeutic potential of IL-33 in sepsis.

2010 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 INCT-INOFAR FOLLOW-UP AND EVALUATION WORKSHOPS

2 INCT's FOLLOW-UP AND EVALUATION MEETING

3 XVI SUMMER SCHOOL IN MEDICINAL PHARMACEUTICAL CHEMISTRY

VISIT: **PRESENCE IN EVENTS 2010** - http://www.inct-inofar.ccs.ufrj.br/english/participa_2010.html

4 SYMPOSIUM ON MALIGNANT HYPERTHERMIA 200

With the support of the **National Institute of Science and Technology of Drugs and Medicines,** the Symposium "Hyperthermia 200" took place in the Center for Health Sciences (CCS) at UFRJ in October 2010, with the goal of presenting scientific efforts of the Malignant Hyperthermia Diagnostic Center of UFRJ, coordinated by Professor Roberto Takashi Sudo, researcher associated with **INCT-INOFAR**.

Malignant Hyperthermia is a rare genetic illness, unchained by the action of drugs used during general anesthesia. The Pharmaceutical Industry does not yet have drugs to cure the disease, but there is a single drug, Sodium Dantrolene, which is able to reverse the hypermetabolic syndrome caused by an adverse reaction to general anesthetics. To reduce mortality, it is important to have early detection of an individual's propensity towards the disease. This work has been developed in the Malignant Hyperthermia Diagnostic Center since 1993 by Professor Sudo.

Professor Carlos Alberto Manssour Fraga, of the Laboratory of Evaluation and Synthesis of Bioactive Substances (**LASSBio**/UFRJ), presented a few of the **INCT-INOFAR** strategies for the planning of new Dantrolene analogues. Through molecular modifications we have been able to achieve new prototypes of the substance, which are being evaluated for their potential for the relaxation of the skeletal musculature.

The event had the participation of researchers in the basic and clinical areas, as well as representatives of the pharmaceutical industry and of civil society groups. The first patient submitted to the biopsy was present, as well as her sister, who survived a Malignant Hyperthermia crisis in 1991.

OUTREACH ACTIVITIES

2010

SAQUAREMA, RJ

SCIENTIFIC PUBLICITY IS TOPIC OF I5+ MEETING

With a goal of exchanging experiences in the area of Science Publicity and Promotion, aimed at the development of future joint actions, the National Institute of Science and Technology in Drugs and Medicines **(INCT-INOFAR)** was present at the I Theme School for Scientific Promotion, in Saquarema, Rio de Janeiro.

The initiative came from the I5+, a group that was initially made up of five National Institutes of Science and Technology (INCTs): the Drugs and Medicines INCT, coordinated by Professor Eliezer J. Barreiro (**LASSBio**/UFRJ); the Functional Complex Materials INCT, coordinated by Professor Fernando Galembeck (UNICAMP); the Science and Technology of the Biorational Control of Insects and Plagues INCT, headed by coordinator Professor Maria Fátima das Graças Fernandes da Silva (UFSCAR); the Investigation in Immunology INCT, coordinated by Professor Jorge Kalil (INCOR); and the Energy and Environment INCT, coordinated by Professor Jailson Bittencourt de Andrade (UFBA).

In its first edition, the Theme School of Scientific Promotion happened right before the opening of the 7th edition of the National Science and Technology Week. Each representative spoke of activities carried out in his or her Institute. **INCT-INOFAR** coordinator, Eliezer J. Barreiro, spoke about the Scientific Promotion and Health Education activities, mentioning the media developed by the **INCT-INOFAR** team to publicize science and promote the correct use of drugs, through activities carried out in Public Municipal Schools in the state of Rio de Janeiro, where students learn, from a young age, to safely acquire, store, use, and discard drugs.

Presentations showed how hard the institutions have worked in developing science publicity and promotion activities. According to Medicinal Chemistry expert Eliezer J. Barreiro, the exchange of information and the inclusion of new partners were the great achievements of the meeting, making it very useful and positive.

HIGH LIGHTS 2009

5

SYNTHESIS, TRYPANOCIDAL ACTIVITY AND DOCKING STUDIES OF NOVEL QUINOXALINE-N -ACYLHYDRAZONES, DESIGNED AS CRUZAIN INHIBITORS CANDIDATES.

Romeiro, N. C.; Aguirre, G.; Hernández, P.; González, M.; Cerecetto, H.; Aldana, I.; Pérez-Silanes, S.; Monge, A.; Barreiro, E. J.; Lima, L. M.

BIOORGANIC MEDICINAL CHEMISTRY (2009) 17: 641-652.
DOI:10.1016/j.bmc.2008.11.065

The structural design, synthesis, trypanocidal activity and docking studies of novel quinoxaline-*N*-acylhydrazone (NAH) derivatives, planned as cruzain inhibitors candidates, a cysteine protease essential for the survival of Trypanosoma cruzi within the host cell, are described. The salicylaldehyde *N*-acylhydrazones 7a and 8a presented IC_{50} values of the same magnitude order than the standard drug nifurtimox (Nfx), when tested in vitro against epimastigote forms of *Trypanosoma cruzi* (Tulahuen 2 strain) and were non-toxic at the highest assayed doses rendering selectivity indexes higher than the standards drugs.

2009 EVENTS PROMOTED

As a part of it's institutional routine, INCT-INOFAR organizes promotes, supports and takes part in events in their research area dealing with innovation in drugs and medicines.

1 TRIAD PARTNERSHIP INCT's

2 COURSE "FROM GRAM TO KILOGRAM"

FORUM "CRACK - THE PROGRESSIVE DESTRUCTION OF SOCIETY: CAN ACADEMIA HELP?"

3 XV SUMMER SCHOOL IN MEDICINAL PHARMACEUTICAL CHEMISTRY

4 1st FOLLOW-UP AND EVALUATION WORKSHOP

IS ORGANIZED BY

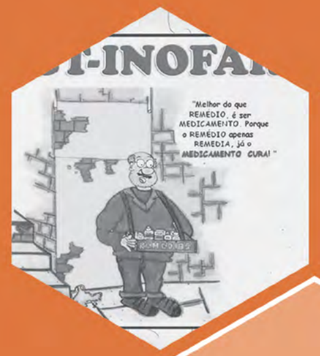
INCT-INOFAR

The National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** held its opening Workshop in March 2009 in Rio de Janeiro with the goal of presenting the directives of the Institute and discussing the main points with the associated researchers.

The Follow-Up and Evaluation Workshop for the **INCT-INOFAR** research projects had the presence of the presidents of CNPq, Professor Marco Antonio Zago, and of FAPERJ, Professor Ruy Garcia Marques.

OUTREACH ACTIVITIES

2009



GUIDEBOOK
COMMANDMENTS OF THE CORRECT USE OF MEDICATIONS

INCT-INOFAR
PUZZLES

VIDEO
"LASSBIO 596: FROM MOLECULE TO MEDICATION"

INCT-INOFAR
IN THE COMMUNITY

*HEALTH EDUCATION IS **INCT-INOFAR** PROPOSAL IN ITS FIRST YEAR OF ACTIVITIES*

16th EDITION
FIOCRUZ FOR YOU

The National Institute of Science and Technology in Drugs and Medicines **(INCT-INOFAR)** was part of the 16th edition of "FIOCRUZ for you", at the campus of the Oswaldo Cruz Foundation, in Manguinhos, RJ. The yearly event takes place during the first phase of the National Campaign of Vaccination against Poliomyelitis, which ensures protection against childhood paralysis in children under five years of age.

For the event, **INCT-INOFAR** created a project for health publicity and promotion in which activities were carried out in its booth to increase awareness on how to safely use and discard drugs.

Visitors were part of recreational and playful activities connected to the topic of science and the risks of self-medicating, cleared doubts and learned more on how to safely acquire, store, and administer drugs.

As well as making sure children got their two drops, the event offered families leisure, culture, education, and health and citizenship promotion activities. The reception had clowns, jugglers, and other artists on campus. Several times a day, there were air shows as well as the performance by "Clown", the scientist clown.

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ANNUAL ACTIVITIES REPORT

2015

INCT OF DRUGS AND MEDICINES

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