2009

ANNUAL ACTIVITIES REPORT

INCT OF DRUGS AND MEDICINES

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

SUPORT

FAPERJ DECIT CNPq inct institutos nacionais de ciência e tecnologia

MEDICINES = QUALITY OF LIFE

2009

ANNUAL ACTIVITIES REPORT

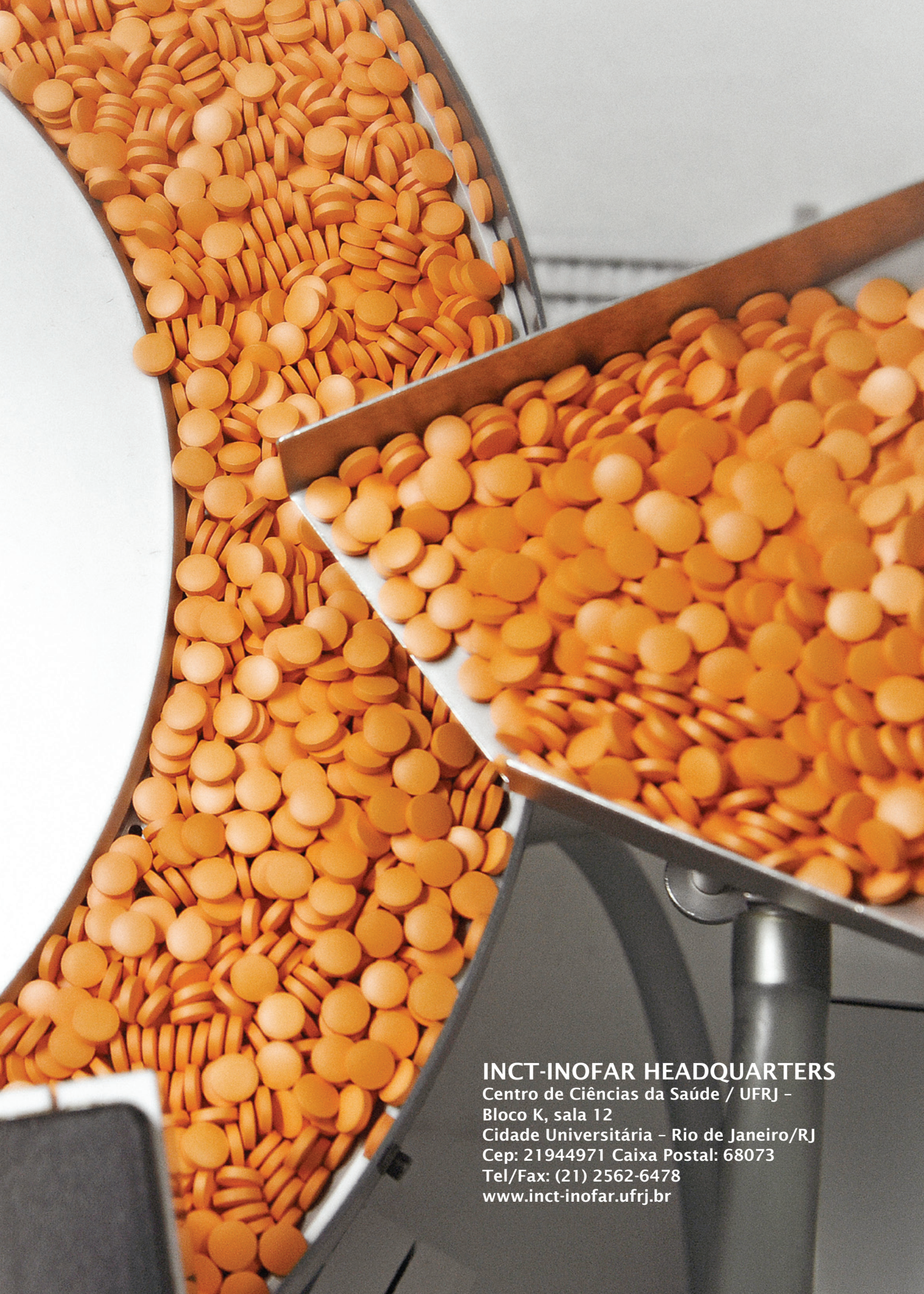
INCT OF DRUGS AND MEDICINES

INCT OF DRUGS AND MEDICINES

ANNUAL ACTIVITIES REPORT | 2009
Text: **Lúcia Beatriz Torres**
Photos: **Lúcia Beatriz Torres and Laboratório Cristália**
Cooperation: **Jéssica Senna and Natália Medeiros**
Design: **Claudio Ventura Comunicação** www.claudioventura.com.br

The allegory created by Miguel de Cervantes in Don Quixote expresses the human search for knowledge and truth. The image on the cover shows the pilgrimage of the character of Sancho Panza, Don Quixote's squire, gazing upon a constellation of chemical structures, which are the object of study at INCT-INOFAR, not passively, but trying to uncover the truths it contains.

DR. ANGELO DA CUNHA PINTO



INCT-INOFAR HEADQUARTERS

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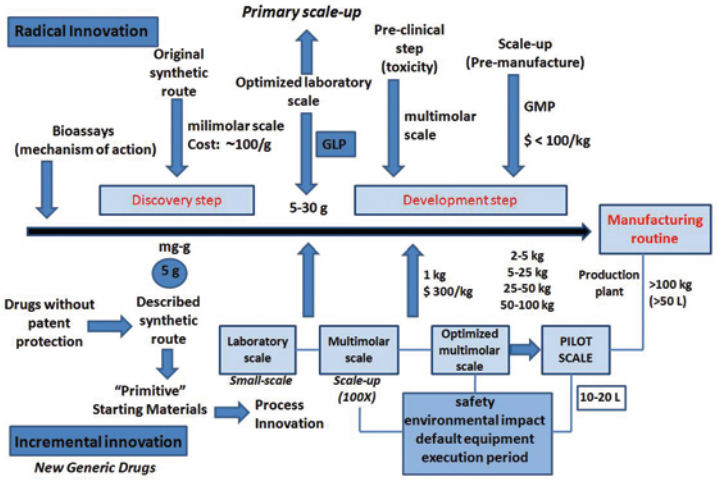
Message from the Coordinator of the National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR)

Prof. Eliezer J. Barreiro
Coordinator of INCT-INOFAR

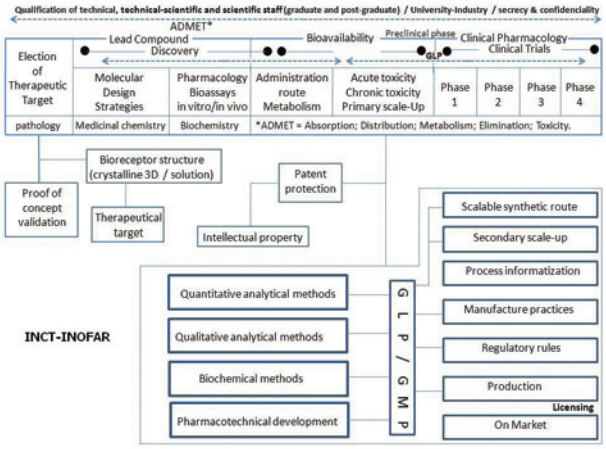
Pharmaceuticals are the active principles of medications. They can have several distinct pharmaceutical forms, due to the technological component used in their production, observing a rigorous quality criteria defined by the currently effective regulations. Medications are, therefore, industrialized products essential to the recovery, maintenance, preservation, and promotion of Health, and they represent indispensable tools in public health policies. Pharmaceuticals and medications are directly involved in the continuous increase of life expectancy for men and women, providing them a higher quality of life as well as more social welfare.

The world pharmaceutical market reached, in 2009, US$ 785 billion. Brazil represented around 10% of that market, reaching R$ 19 billion in the same year. This number is made up of brand name pharmaceuticals, as well as generic medications – those without patent protection – with the latter representing 22% of medication sales in Brazil. This important industrial sector, which is one of the five most important worldwide, has as one of its main characteristics its strong dependence on scientific research and innovation, especially breakthrough innovation, but also, on a smaller scale, on the so called incremental innovation. It is not sheer coincidence or chance that the main pharmaceutical companies that invent/discover innovative medications do so in the countries where they are headquartered, for the most part, or in their research centers located in countries with a strong scientific tradition. A few cooperation contracts and specialized technical-scientific services are established between Big Pharmas and smaller technological based companies, representing outsourcing that already happens as part of the strategies adopted by this sector.



Brazil has an excellent postgraduate education system, which is responsible for awarding ca. 10,000 doctoral titles and 30,000 master's degrees. Many of these masters and doctors are involved in multidisciplinary projects in the search for new pharmaceuticals and medications, especially in the areas of Health, Biological, and Exact Sciences. In these areas there are strategic fields for the sector, like Pharmacy, Pharmacology, and Chemistry, with several specialties such as Medicinal Pharmaceutical Chemistry, Organic Chemistry, and Synthesis Chemistry. Brazil is responsible for ca. 2.6% of the production of new scientific knowledge worldwide, with over 32,000 publishings in 2009. This powerful reality of scientific ability has not yet translated itself into scientific knowledge capable of producing our own pharmaceuticals, ones that "speak our own language", needed in the pharmaceutical care of our population, which is our biggest asset. Unfortunately, our medications in Brazil "speak" all the other languages, except our own!

The goal of the National Institute of Science and Technology of Drugs and Medicines - INCT-INOFAR – is to contribute to revert this situation in the country, aiming to bring together and organize existing national competencies in several scientific specialties that are part of the chain of innovation in pharmaceuticals and medications, distributed in several universities and/or research institutes, most of them part of the public system of higher education in Brazil, articulating them around research projects in pharmaceutical and medications sciences, with goals of inventing new pharmaceuticals that represent radical innovations. Another goal of the INCT-INOFAR is to articulate efforts for the development of routes of synthesis for generic pharmaceuticals that are part

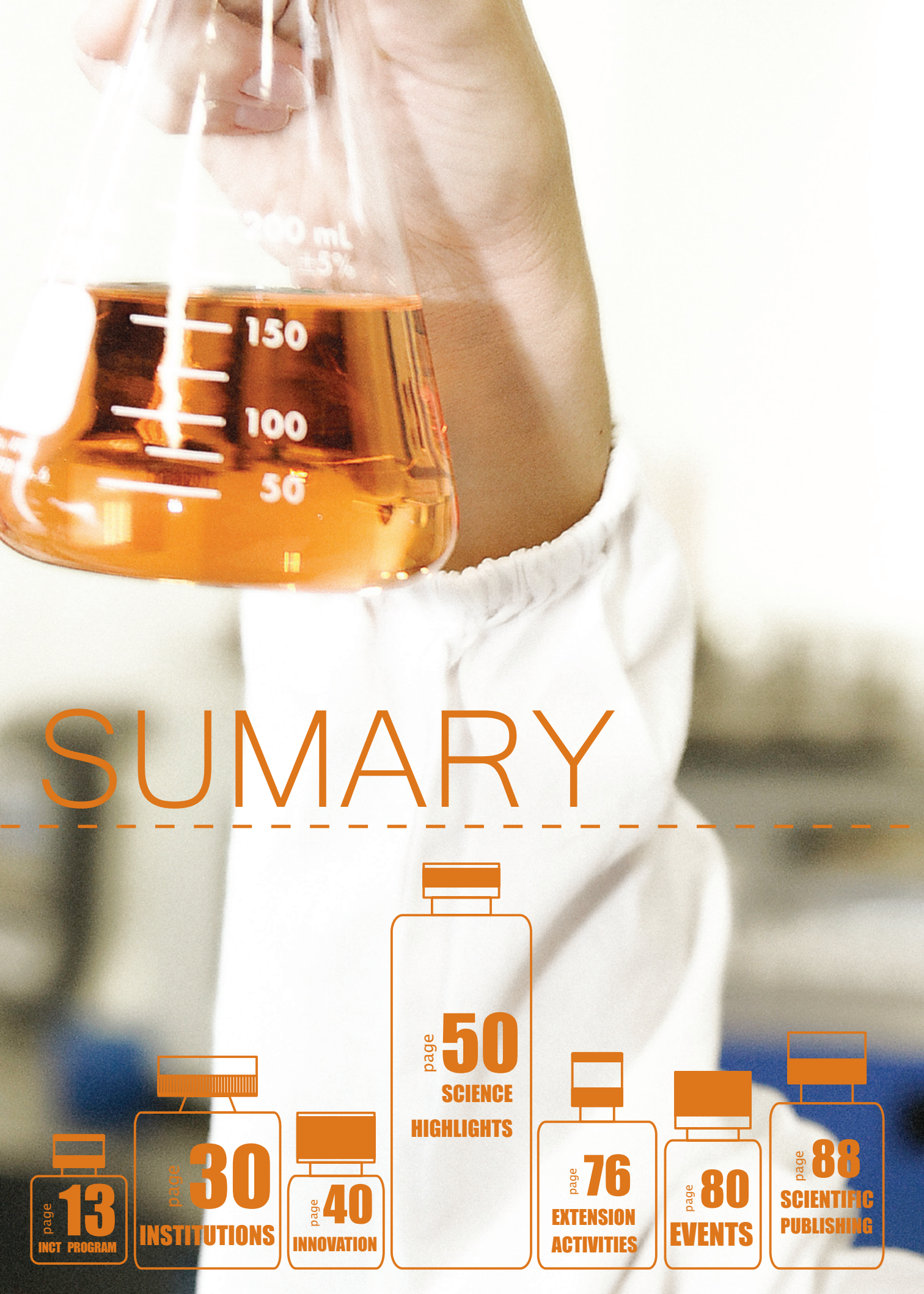


of the national list of essential medications for the public health system, representing significant expense of resources due to the volumes imported, as well as for new generic pharmaceuticals, represented by those that will soon have expired patents.

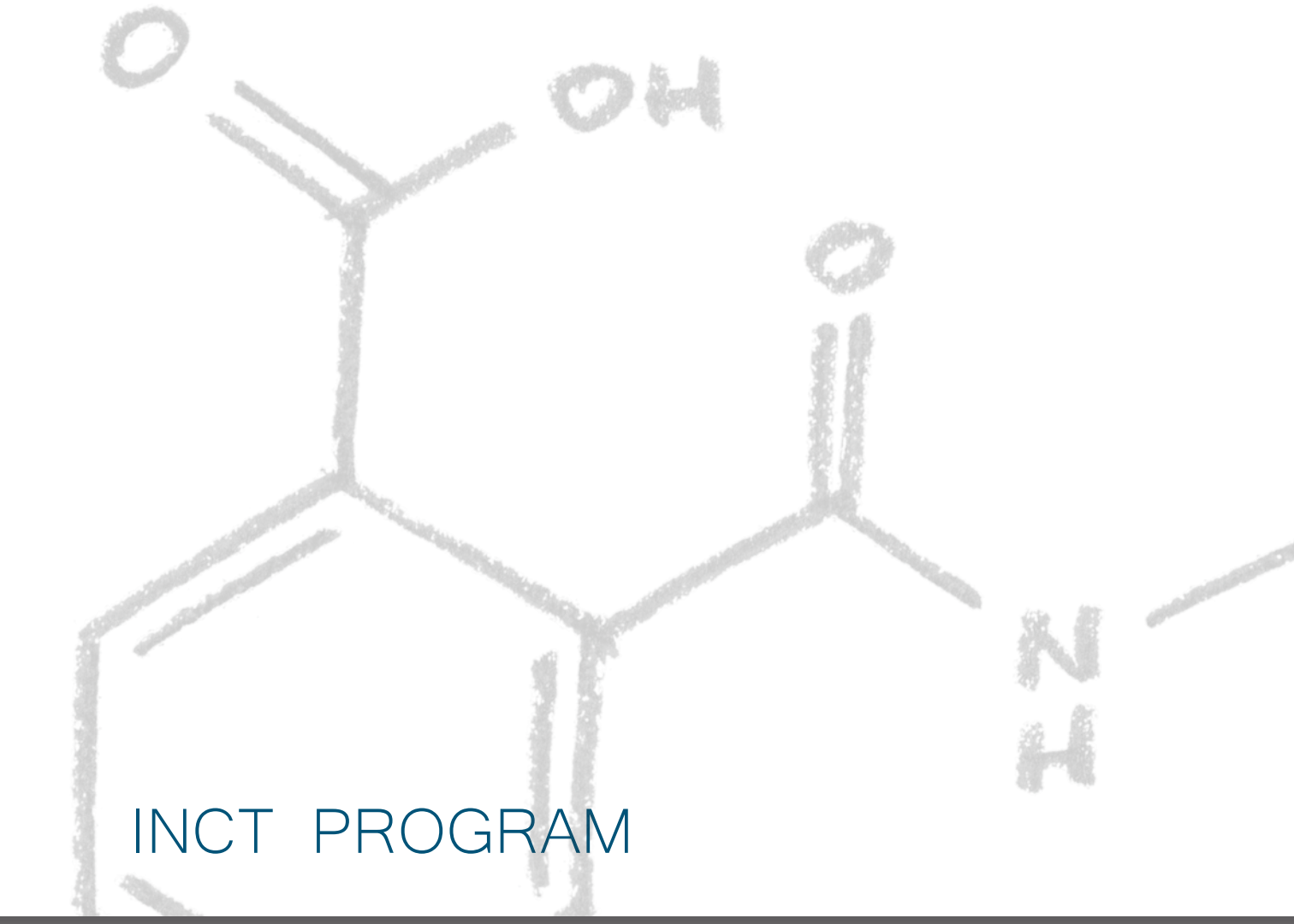
INCT-INOFAR also has a mission of fostering an environment favorable to the transfer of technologies discovered or created in these platforms to the productive pharmaceutical business sector, both public and private. As part of this path, new possible weak spots in this chain of innovation may be detected and identified, such as the one already recorded in the extreme lack of scaling laboratories, which seriously reduces the inventive capabilities of this sector. This search for technological qualification also allows for the proposal of new solutions to live up to our technological potential in this important sector of the health industrial complex: pharmaceuticals and medications.

To complement the INCT-INOFAR mission statements, there are also personnel qualification actions on all levels, among which we must emphasize postgraduate education in Medicinal Chemistry, Pharmacology, and Toxicology, the promotion of qualification courses in aspects of intellectual property, as well as other initiatives, carried out jointly with other INCTs or otherwise, and the publicizing and popularizing of Pharmaceuticals and Medications Sciences. INCT-INOFAR maintains a website – Pharmaceuticals Portal (www.portaldosfarmacos.ccs.ufrj.br) – to promote and increase awareness in the safe and rational use of medications.

ELIEZER J. BARREIRO
Professor – UFRJ
Coordinator of INCT-INOFAR

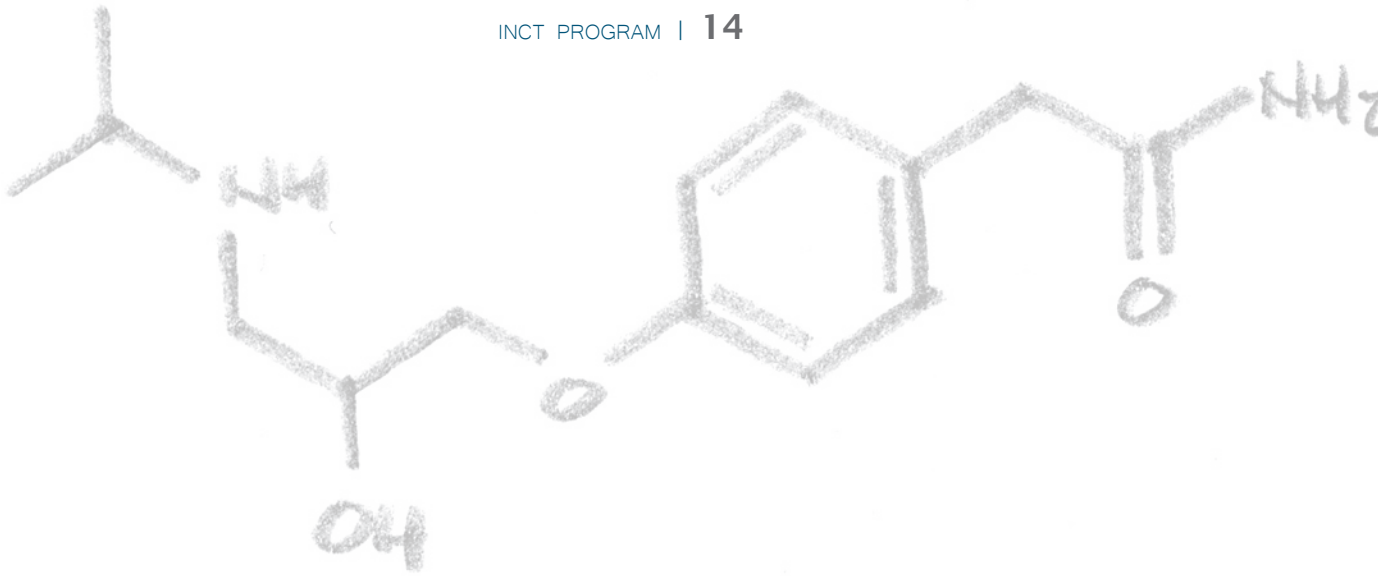


SUMARY



INCT PROGRAM

The program entitled National Institutes for Science and Technology (INCT) has a goal of promoting the creation of research networks in strategic areas for the sustainable development of the country. Under the coordination of a host institution, characterized by the excellence of its scientific and technological production, the National Institutes work in a multicentric way, articulating sets of laboratories or associated research groups to act in a well-defined area or theme. With 122 approved projects so far, INCTs have been the largest Science and Technology incentive program in Brazil since 2009.

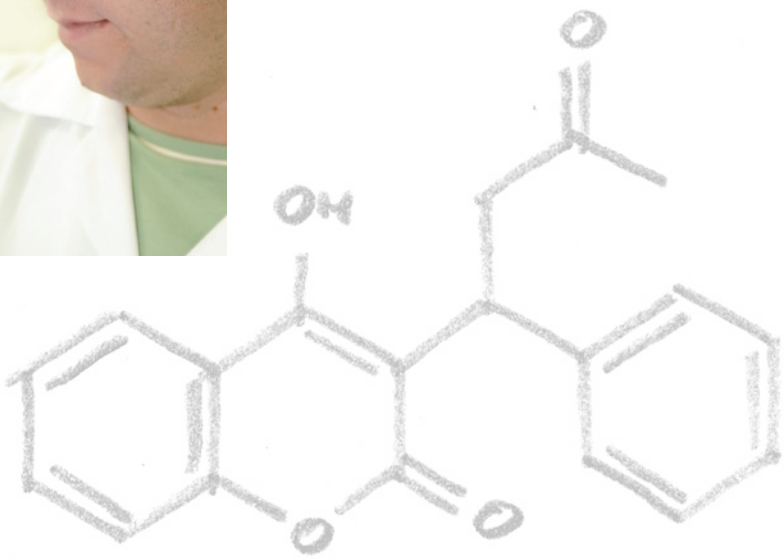


INCT of Drugs and Medicines (INCT-INOFAR)

The National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR) has a mission of articulating national scientific competences in a network, with a goal of discovering new compounds that are candidates for future medications.

Relying on the expertise of 33 research groups in 15 institutions located in 8 states in Brazil, INCT-INOFAR develops research projects in breakthrough pharmaceutical innovations, and in incremental pharmaceutics.

In the field of breakthrough innovation, the Institute aims to discover an original substance that will originate a completely new pharmaceutical. In the field of incremental innovation, it leads projects that aim to develop studies of new synthetic routes, both for generics already available in the market as well as for those that have patents about to expire.



MISSION

- To organize national scientific competencies in an effective pharmaceuticals and medications research network;

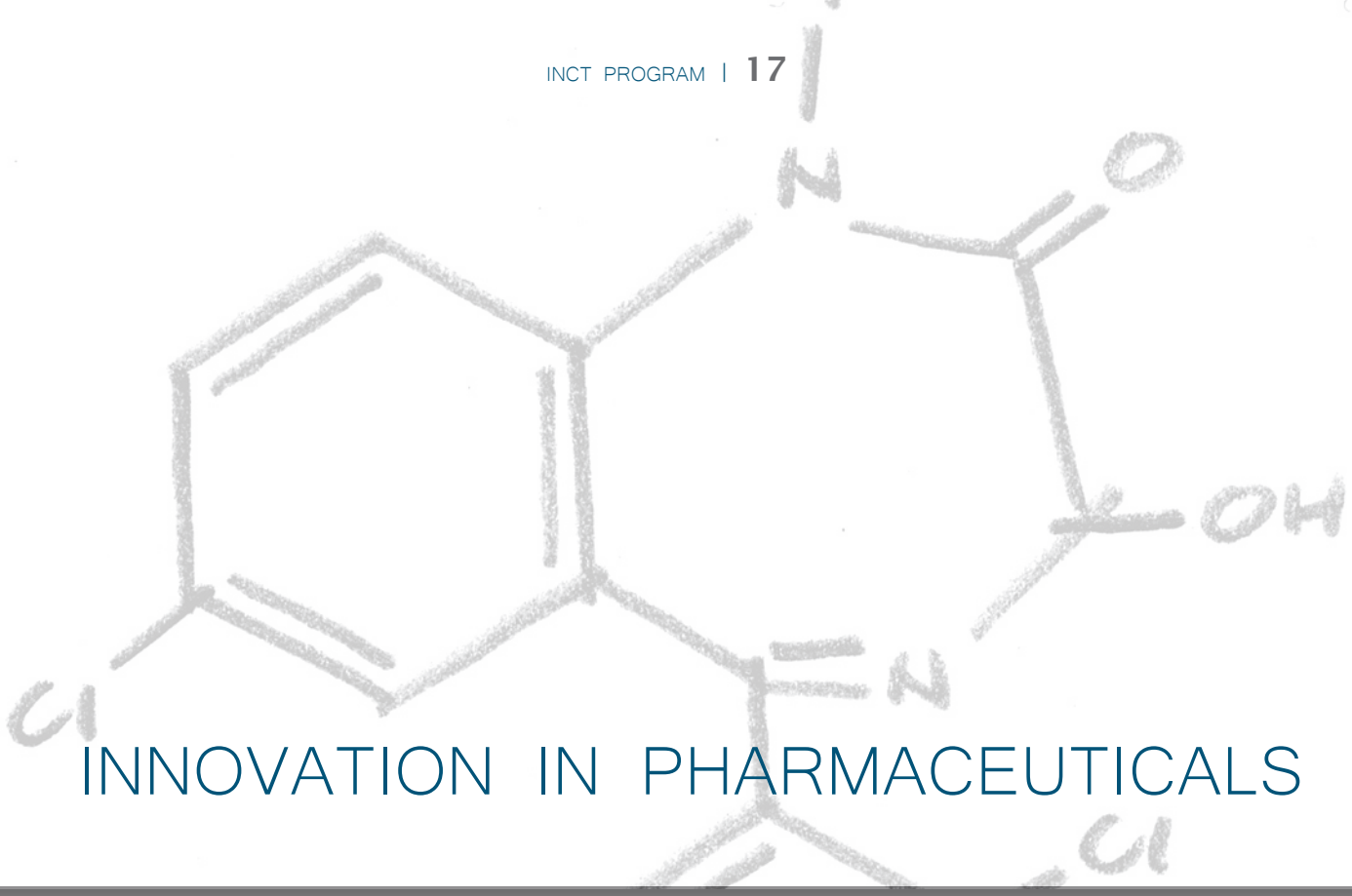
- To support multi-institution scientific research in the discovery of new pharmaceuticals;

- To contribute for incremental and radical innovation in new pharmaceuticals and generic drugs;

- To study and develop the total synthesis of generic drugs, advanced intermediates, and raw materials;

- To contribute to the scientific qualification of personnel in the fields of medicinal chemistry & pharmacology;

- To promote awareness of sciences related to pharmaceuticals and medications, as well as their rational and safe use.



INNOVATION IN PHARMACEUTICALS

The National Institute of Science and Technology of Drugs and Medicines* (INCT-INOFAR) was created in 2009, as the result of an initiative by the Ministry of Science and Technology (MCT), carried out by the National Council for Scientific and Technological Development (CNPq), with the support of the Foundation for Research Support of the State of Rio de Janeiro (Faperj), and of the Department of Science and Technology of the Ministry of Health (Decit/MS).

Formerly the Millennium Institute for Innovation and Development of Drugs and Medicines (IM-INOFAR), INCT-INOFAR articulates academic competences in teaching and research, through a national network, in the fields of breakthrough pharmaceutical innovation and the incremental development of generic pharmaceuticals.

The network of competences formed by INCT-INOFAR has the goal of carrying out the necessary studies for the fulfillment of the fundamental stages in the process of discovery of new pharmaceuticals – from the choice of a therapeutic target to the completion of pre-clinical assays. When combined, the scientific-academic competences are able to carry out all the actions in the complex chain of innovation in pharmaceuticals and medications in an optimal way, achieving promising results.

As it contributes to articulate the scientific knowledge between the 15 project member institutions, INCT-INOFAR creates favorable conditions for innovation in the pharmaceutical and pharmochemical sectors in the country, thus promoting the technical-scientific autonomy of Brazil in the field of pharmaceuticals – essential for the independency of this important sector.

*CNPq Process number 573.564/2008-6
FAPERJ Process number E-26/170.020/2008


INCT-INOFAR IS PRESENT IN 8 BRAZILIAN STATES

RESEARCH NETWORK PLURI-INSTITUTIONAL

INCT-INOFAR unifies the diverse Brazilian competences in the area of pharmaceuticals and medications, centralizing the knowledge produced in Universities and Institutes of Science and Technology (ICTs) along the country.

As it enables researchers of different institutions to work together, the Institute promotes the exchange between large centers and emerging research groups. It contributes, in this capacity, to reduce the regional imbalance in research activities, and to consolidate the Brazilian expertise in a strategic sector for health public policy.

The cooperative activity, through a network of institutions from different geographical regions, is a way to contribute to the increase of the scientific and technological production of emerging centers, mostly in the Midwest and Northeast regions, benefiting the qualification at undergraduate and graduate level.


UFG
USP
UNESP
UNICAMP
Cristália
Instituto Royal

RESEARCH NETWORK

UFC

UFPB

UFAL

UNIFAL

In Vitro Cells

UFMG

FIOCRUZ

UFRJ

UERJ

LNCC

UFFRJ

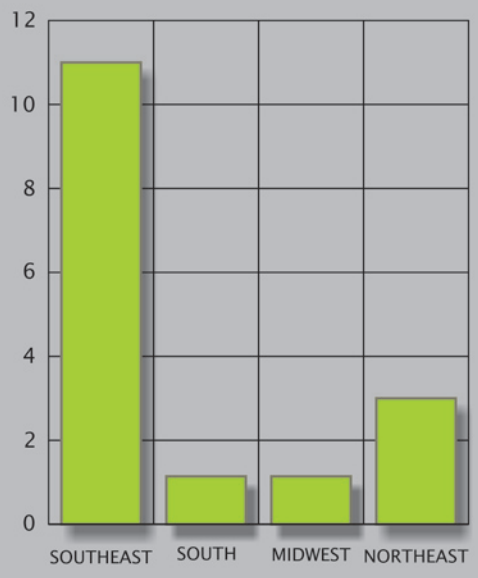
UFGRS

08 States

15 Institutions

33 Research Groups

25 CNPq Researchers

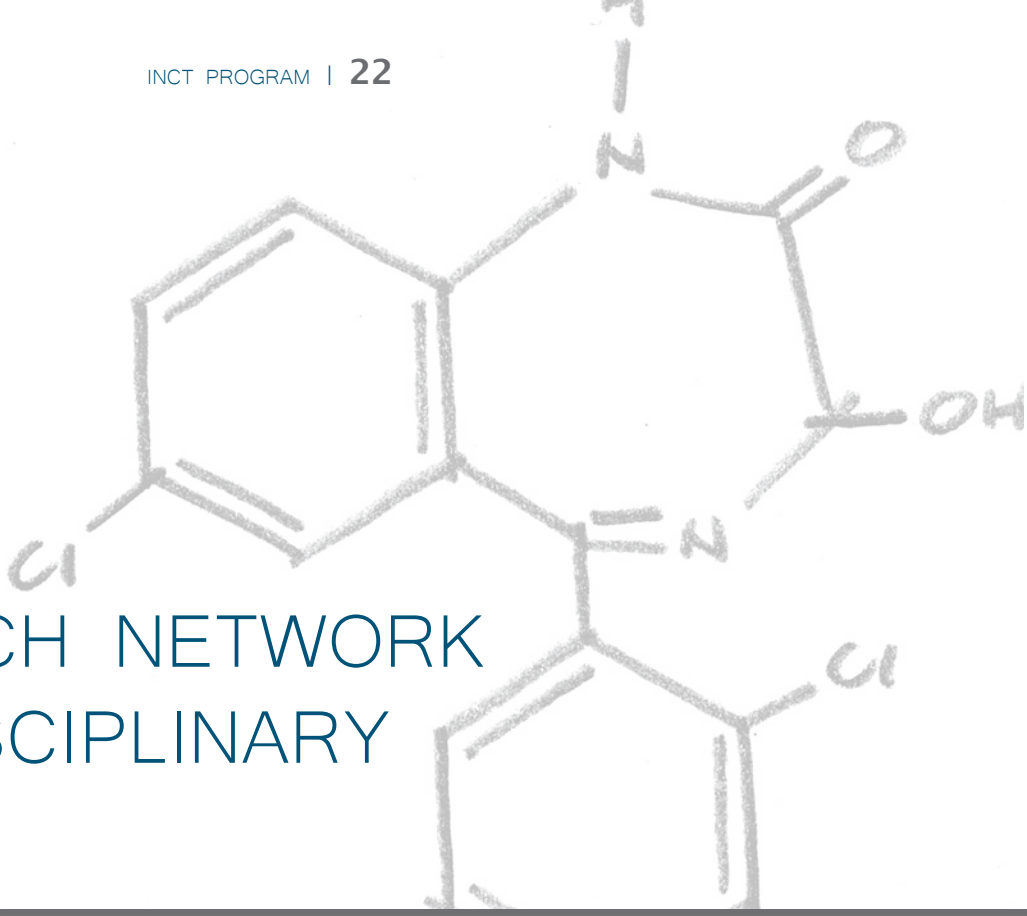


MIDWEST
Goiás

NORTHEAST
Ceará
Paraíba
Alagoas

SOUTHEAST
São Paulo
Minas Gerais
Rio de Janeiro

SOUTH
Rio Grande do Sul



RESEARCH NETWORK MULTIDISCIPLINARY

The innovation process in pharmaceuticals has multidisciplinary characteristics, which demands competences in several subfields in Health: Chemistry, Pharmacology, Pharmaceutical Technology, among other specific fields of science.

For that, INCT-INOFAR has a multidisciplinary and pluri-institutional team, with research groups of the highest academic excellence, qualified by their previous results and able to carry to term all the stages of the rational discovery of new pharmaceuticals successfully.

INCT-INOFAR is made up of specialists in the areas of Chemistry, Biology, and Health Sciences. Among these we highlight Pharmacology, Toxicology, X-Ray Crystallography, Molecular Modeling, Organic Chemistry, Medicinal Chemistry, Natural Products Chemistry, Computational Chemistry, and Organic Synthesis, among other related fields.

By promoting interdisciplinarity, INCT-INOFAR acts in the entire chain of innovation in pharmaceuticals and medications, making the current research projects advance through cooperation, aiming to achieve state of the art in pharmaceutical innovation.

HUMAN RESOURCES QUALIFICATION

So that a really innovative medication can be discovered, it is fundamental to have a diverse and extremely qualified workforce to carry out all the stages of the chain of innovation successfully.

With a goal of consolidating national competences in the discovery of new pharmaceutical and medications, INCT-INOFAR invests in the qualification of human resources in the different research centers associated to it.

Scientific qualification is enhanced in all the academic levels: undergraduate, graduate, Ph.D., and post-doctorate. Through the scientific exchange promoted, INCT-INOFAR contributes not only for the qualification of new researchers, but also for the recycling and new knowledge for senior researchers.

The maintenance of renowned talent professionals in the country is also one of the goals of INCT-INOFAR, avoiding the "Scientific Diaspora" that is so harmful for the development of Science, Technology, and Innovation in the country.

INCT-INOFAR researchers actively participate in qualification of human resources activities, through the connection to 19 Post-Graduate Programs of recognized academic merit. At the latest evaluation promoted by the Coordination of Personnel Qualification at College Level (CAPES), over half of these programs achieved the highest mark of 7 or the second highest of 6.

- Post-Graduate Program in Pharmacology (USP/RP) | **CAPES 7**
- Post-Graduate Program in Chemistry (UNICAMP) | **CAPES 7**
- Post-Graduate Program in Chemistry (UNESP) | **CAPES 7**
- Post-Graduate Program in Chemistry (UFRJ) | **CAPES 7**
- Post-Graduate Program in Biology (UERJ) | **CAPES 6**
- Post-Graduate Program in Pharmacology (UFC) | **CAPES 6**
- Post-Graduate Program in Natural Products and Bioactive Synthetics (UFPb) | **CAPES 6**
- Post-Graduate Program in Cellular and Molecular Biology (FIOCRUZ) | **CAPES 6**
- Post-Graduate Program in Chemistry (UFMG) | **CAPES 6**
- Post-Graduate Program in Pharmaceutical Sciences (UFRGS) | **CAPES 5**
- Post-Graduate Program in Pharmacology and Medicinal Chemistry (UFRJ) | **CAPES 4**
- Post-Graduate Program in Chemistry (UFRRJ) | **CAPES 4**
- Post-Graduate Program in Chemistry and Biotechnology (UFAL) | **CAPES 4**
- Post-Graduate Program in Applied Toxicology and Genetics (UFRGS) | **CAPES 4**
- Post-Graduate Program in Biological and Health Sciences (UFAL) | **CAPES 3**
- Post-Graduate Program in Pharmaceutical Sciences (UNIFAL) | **CAPES 3**
- Post-Graduate Program in Chemistry (UNIFAL) | **CAPES 3**
- Post-Graduate Program in Pharmaceutical Sciences (UFG) | **CAPES 3**

Under guidance of professors and researchers that are part of INCT-INOFAR, 18 Doctoral Theses and 39 Master Degree Dissertations have been completed. Additionally, 56 undergraduate students awarded Scientific Initiation grants were supervised, and 11 Post-Doctoral supervisions have been completed in the year that is the subject of this report.

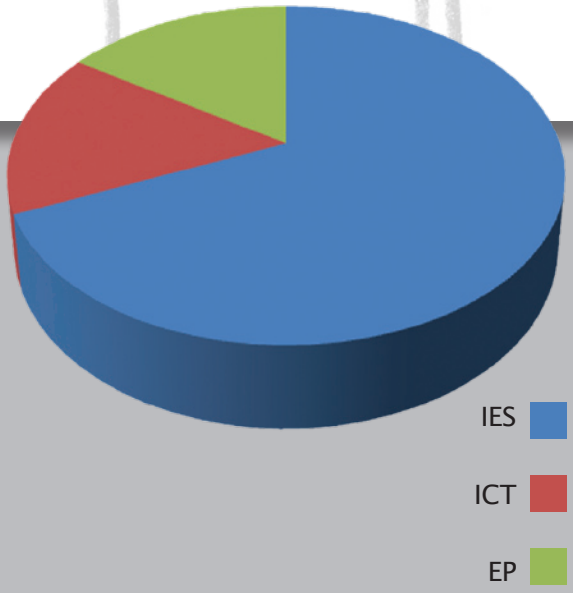
ORGANIZATIONAL STRUCTURE

INCT-INOFAR is made up of 33 research groups, in 15 educational and research institutions in Universities and Science and Technology Institutions – ICTs of 8 different Brazilian states: Rio de Janeiro, São Paulo, Minas Gerais, Rio Grande do Sul, Ceará, Paraíba, Alagoas, and Goiás. It has the support of associated companies: Cristalia Chemical Pharmaceutical Products Ltd., Royal Institute and In Vitro Cells Technology Research S.A. The administrative headquarters of the Institute is established in the Health Sciences Center of UFRJ.

INCT-INOFAR is coordinated by Eliezer J. Barreiro, Professor of Pharmacy of UFRJ and vice-coordinated by Prof. Fernando de Queiroz Cunha, Professor of USP Ribeirão Preto. It operates through its Governance and Follow-Up Committee (CGA) – consulting and deliberative agency that does the strategic planning for the Institute and approves the decisions of the coordination and vice-coordination.

CGA is made up of 5 researchers of the highest scientific level, aside from the coordinator and the vice-coordinator, with areas of expertise in different subfields of pharmaceuticals and medications: Prof. Vanderlan da Silva Bolzani (UNESP - Araraquara); Prof. Angelo da Cunha Pinto (UFRJ); Prof. Heloisa de Oliveira Beraldo (UFMG), Prof. Luiz Carlos Dias (Unicamp), and Prof. Marco Aurelio Martins (Fiocruz).

DISTRIBUTION TEAM



INCT-INOFAR Superintendency is responsible for the technical evaluation of all research projects developed by the Institute and it is led by Prof. Lidia Moreira Lima, of the Faculty of Pharmacy of UFRJ. Each research group has a lead researcher that mediates communication for scientific and financial matters between his or her laboratory and/or research group and the INCT-INOFAR coordination.

INCT-INOFAR has the participation, in confidential agreement, of specialist consultants in Brazil: Prof. Glaucius Oliva (USP), Prof. Francisco Silveira Guimaraes (USP), Prof. Vitor Francisco Ferreira (UFF), Manoel Barral Neto (Fiocruz/BA) and abroad: Prof. Antonio Monge, (Spain) and Prof. Camille Wermuth, (France), who are part of the continuous evaluation of the projects being carried out. In each specific stage of their development, they provide scientific support, producing reports with diagnoses that enable improvement of activities.

MANAGING COMMITTEE

Dra. Vanderlan Bolzani (UNESP)
Dra. Heloisa Beraldo (UFMG)
Dr. Angelo C. Pinto (UFRJ)
Dr. Luiz Carlos Dias (UNICAMP)
Dr. Marco Aurélio Martins (FIOCRUZ)

COORDINATOR

Dr. Eliezer J. Barreiro (UFRJ)

VICE-COORDINATOR

Dr. Fernando de Q. Cunha (USP-RP)

SCIENTIFIC CONSULTING

Dr. Glaucius Oliva (USP-SC)
Dr. Francisco S. Guimarães (USP-SP)
Dr. Vitor F. Ferreira (UFF)
Dr. Manoel Barral (FIOCRUZ/BA)
Dr. Antonio Monge (Espanha)
Dr. Camile G. Wermuth (França)

Meeting of the Governance and Follow-Up Committee INCT-INOFAR at UFRJ

SCIENTIFIC SUPERINTENDENT

Dra. Lídia Moreira Lima (UFRJ)

ASSOCIATED RESEARCH GROUPS

13 IES & 3 ICT

INCT-INOFAR HEADQUARTERS
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Cidade Universitária, Ilha do Fundão – Rio de Janeiro/RJ
Cep: 21944971
Caixa Postal: 68073
Tel: (21) 2562-6478
www.inct-inofar.ufrj.br

ASSOCIATED COMPANIES

CRISTALIA PHARMACEUTICAL CHEMICAL PRODUCTS LABORATORIES

www.2cristalia.com.br

Cristalia, as a Pharmaceutical company associated with INCT-INOFAR, is responsible for the pharmacotechnical stages of development of eventual compound-prototypes that have reached this stage of the chain of innovation. Under terms of confidentiality, Cristalia will benefit from the privileged conception of projects, by always being the first company consulted for possible partnerships. In case Cristalia does not want to produce the molecule, the Institute is fully free to present it to another pharmaceutical industry.

ROYAL INSTITUTE

www.institutoroyal.org.br

Toxicology is a very delicate stage that can absolve or condemn a molecule. INCT-INOFAR prioritizes studies of genotoxicity and acute toxicology as early as possible in the chain of innovation in pharmaceuticals. To assure that all the stages of pre-clinical toxicology are accredited in Good Laboratory Practices (BPL), INCT-INOFAR has partnered with Royal Institute, the result of the merger between two toxicology laboratories incubated in different universities. Genotox-Royal Institute, in UFRGS, conducts the genetic toxicity studies, while Unitox-Royal, in University of Santo Amaro (Unisa-SP), is responsible for the animal toxicity tests.

IN VITRO CELLS

www.invitrocells.com.br

In Vitro Cells – Toxicology Research S.A. is a technology base company located in Biominas Foundation (Belo Horizonte, MG). Their founders are professors of the Federal University of Minas Gerais, in the areas of Toxicology and Biochemistry. The company is a INCT-INOFAR partner in the conduction of in vitro tests for the evaluation of the safety and efficacy of pharmaceutical candidates developed by the Institute.

INSTITUTIONS

RESEARCH GROUPS

RIO DE JANEIRO

RIO DE JANEIRO - RJ

UFRJ – FEDERAL UNIVERSITY OF RIO DE JANEIRO

INOFAR HEADQUARTERS

FACULTY OF PHARMACY
- Laboratory of Evaluation and Synthesis of Bioactive Substances – LASSBio

SCHOOL OF CHEMISTRY
- Chemical Industry Information System – SIQUIM
- Luiz Alberto Coimbra Institute of Graduate Studies and Research in Engineering – COPPE

CARLOS CHAGAS FILHO BIOPHYSICS INSTITUTE
- Pulmonary Investigation Laboratory
- Molecular Parasitology Laboratory

BIOMEDICAL SCIENCES INSTITUTE
- Laboratory of Biochemical and Molecular Pharmacology
- Laboratory of Cardiovascular Pharmacology
- Laboratory of Muscular Excitation-Contraction Coupling

PROFESSOR PAULO DE GOES INSTITUTE OF MICROBIOLOGY
- Laboratory of Molecular Virology I
- Laboratory of Genetics and Immunology of Viral Infections

INSTITUTE OF CHEMISTRY
- Laboratory of Natural Products and Chemical Transformations
- Laboratory of Support to Technology Development - LADETEC

SOUTHEAST REGION

UERJ - UNIVERSITY OF THE STATE OF RIO DE JANEIRO

ROBERTO ALCANTARA GOMES
INSTITUTE OF BIOLOGY
- Department of Pharmacology

FIOCRUZ – OSWALDO CRUZ FOUNDATION

OSWALDO CRUZ INSTITUTE
- Laboratory of Inflammation

NATIONAL SCHOOL OF PUBLIC HEALTH

SEROPÉDICA - RJ

UFRRJ – RURAL FEDERAL UNIVERSITY OF THE STATE OF RJ

INSTITUTE OF EXACT SCIENCES
- Department of Chemistry

PETRÓPOLIS - RJ

LNCC – NATIONAL LABORATORY OF SCIENTIFIC COMPUTATION

- Molecular Modeling of Biological Systems

MINAS GERAIS

BELO HORIZONTE – MG

UFMG – FEDERAL UNIVERSITY OF MINAS GERAIS

INSTITUTE OF EXACT SCIENCES,
DEPARTMENT OF CHEMISTRY
- Innovation in Organic and Inorganic Compounds with Pharmacological Activity Group

ALFENAS – MG

UNIFAL – FEDERAL UNIVERSITY OF ALFENASS

DEPARTMENT OF PHARMACY
- Laboratory of Phytochemistry and Medicinal Chemistry

SOUTHEAST REGION

SÃO PAULO

ARARAQUARA – SP

UNESP – STATE UNIVERSITY OF SÃO PAULO

ARAQUARA INSTITUTE OF CHEMISTRY

- Bioassays, Biosynthesis, and Ecophysiology of Natural Products Nucleus - NUBBe

CAMPINAS – SP

UNICAMP – STATE UNIVERSITY OF CAMPINAS

INSTITUTE OF CHEMISTRY

- Laboratory of Synthetic Organic Chemistry

RIBEIRÃO PRETO – SP

USP – UNIVERSITY OF SÃO PAULO

FACULTY OF MEDICINE OF RIBEIRÃO PRETO

- Laboratory of Pain and Inflammation

SOUTH REGION

RIO GRANDE DO SUL

PORTO ALEGRE - RS

UFRGS – FEDERAL UNIVERSITY OF RIO DE GRANDE DO SUL

FACULTY OF PHARMACY

- Laboratory of Experimental Psychopharmacology

CENTER OF BIOTECHNOLOGY – GENOTOX-ROYAL UNIT

LABORATORY OF GENOTOXICITY

ALAGOAS
MACEIÓ – AL

UFAL – FEDERAL UNIVERSITY OF ALAGOAS
INSTITUTE OF BIOLOGICAL SCIENCES AND HEALTH
- Laboratory of Pharmacology and Immunity

CEARÁ
FORTALEZA – CE

UFC – FEDERAL UNIVERSITY OF CEARÁS
DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY
- Clinical Pharmacology Unit
- Laboratory of Pharmacology of Inflammation and Cancer

PARAÍBA
JOÃO PESSOA – PB

UFPB – FEDERAL UNIVERSITY OF PARAÍBA
FACULTY OF PHARMACY
- Laboratory of Toxicology Assays

MIDWEST REGION

GOIÁS
GOIÂNIA - GO

UFG – FEDERAL UNIVERSITY OF GOIÁS
FACULTY OF PHARMACY
- Laboratory of Bioconversion
- Laboratory of Pharmacology and Cellular Toxicology
- Laboratory of Medicinal Pharmaceutical Chemistry
- Laboratory of Cardiovascular Pharmacology

SCIENTIFIC TEAM

LEADERS OF ASSOCIATED LABORATORIES

UFRJ

Adelaide Maria de Souza Antunes
Professor – CNPq 2

Angelo da Cunha Pinto
Professor – CNPq 1A

Carlos Alberto Manssour Fraga
Associate Professor – CNPq 1C

Eliezer J. Barreiro
Professor – CNPq 1A

Francisco Radler de Aquino Neto
Professor – CNPq 1A

François Germain Noel
Professor – CNPq 1C

Gisele Zapata Sudo
Associate Professor – CNPq 2

Jose Nelson dos Santos Silva Couceiro
Associate Professor – CNPq 1D

Lidia Moreira Lima
Professor – CNPq 2

Luciana Jesus da Costa
Professor

Patricia Dias Fernandes
Professor

Patricia Rieken Macedo Rocco
Associate Professor II – CNPq 1A

Ricardo de Andrade Medronho
Professor

Roberto Takashi Sudo
Professor – CNPq 2

UERJ

Thereza Christina Barja-Fidalgo
Professor – CNPq 1B

FIOCRUZ

Francisco Jose Roma Paumgartten
Researcher III – CNPq 2

Marco Aurelio Martins
Researcher – CNPq 1A

UFRRJ

Carlos Mauricio Rabello de Sant'Anna
Associate Professor II – CNPq 2

LNCC

Laurent Emmanuel Dardenne
Researcher

UFMG

Heloisa de Oliveira Beraldo
Professor – CNPq 1B

UNIFAL
Claudio Viegas Junior
Professor II

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INNOVATION

PHARMACEUTICAL INNOVATION

The National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR) integrates academic-scientific competences of different parts of the country, with a goal of carrying out the necessary studies to fulfill the necessary stages for the process of discovery of new pharmaceuticals.

Articulating different types of expertise capable of conducting, in an optimal manner, the main actions of the complex chain of innovation in pharmaceuticals, from the selection of a therapeutical target to the completion of pre-clinical assays, INCT-INOFAR develops research projects in breakthrough pharmaceutical innovation and incremental innovation in generic pharmaceuticals.

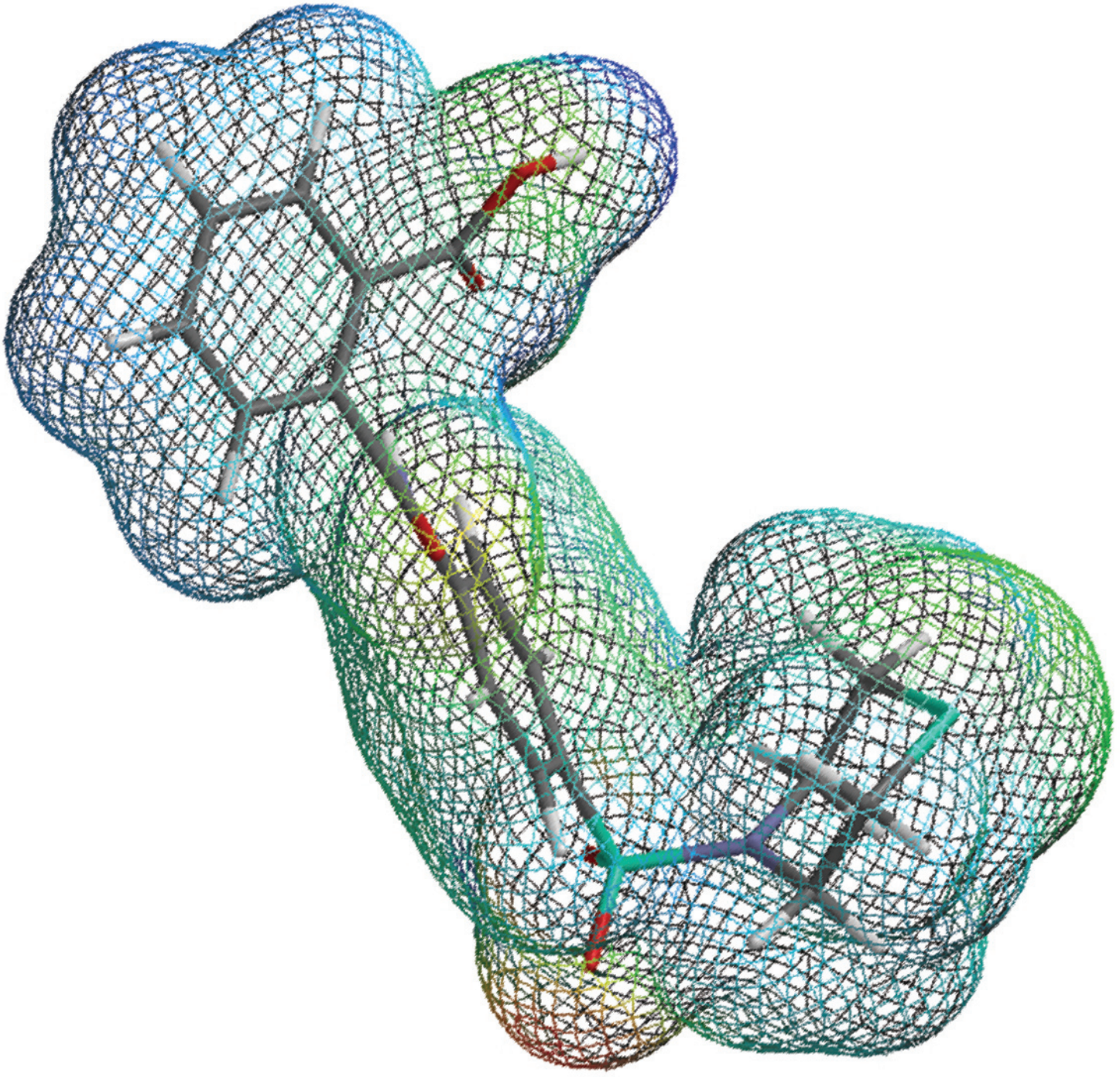
In the field of radical innovation, the Institute works on the discovery of substances with original structural patterns, capable of originating a totally new medication. As a substance is successful in the studies, the patent application* is filed.

INCT-INOFAR houses research projects that aim to find new compound-prototypes for anti-inflammatory drugs, analgesic drugs, and chemotherapeutical drugs for cancer and for neglected diseases, as well as pharmaceuticals that act on the central nervous system and the cardiovascular system.

A new bioactive molecule (LASSBio-596) capable of fighting asthma through an innovative action mechanism is one of the great promises of the Institute. With a patent request already filed, the substance – that can be much needed hope for patients who do not respond to the currently available therapies – is in the pre-clinical studies stage.

RESEARCH AREAS

- Inflammation;
- Asthma;
- Pain;
- Central Nervous System;
- Cardiovascular System;
- Chemotherapy: anticancer and antiparasitic.



** LASSBio-596: PI 0208767-7 (08/11/2002) PI 0401660-2 (27/04/2004); Study of functionalized n-fenilpiperazine derivates as prototypes for the development of new atypical antipsychotics: PI 0303465-8 (02/09/2003); Study of potential anti-inflammatory effect of LASSBio 897 compound, on silicosis and asthma models. PI0806985-9 (16/10/2008) PCT WO 2010/043010 A1 (22/04/2010);*

INCT-INOFAR IN THE ELECTRONIC JOURNAL OF CHEMISTRY

RVq Revista Virtual de Química
ISSN 1984-6835

Electronic Journal of Chemistry* (RVq) launched in 2009, joined the Drugs and Medicines research INCT (INCT-INOFAR), with a goal of being a tool in the human resources qualification in Medicinal Chemistry. As such, it will release a special six article issue of RVq, presenting some of the most relevant results achieved by the research groups of different Educational Institutions that are part of the Institute.

Fully dedicated to breakthrough innovation, the articles will narrate studies that go from the identification of genuine candidates for new anti-inflammatory, analgesic, and anti-asthma medications – acting through original pharmacological mechanisms – to the discovery of new structural patterns of synthetic and/or natural origin with properties on the Central Nervous System and as chemotherapeutic agents.

As requested by the Electronic Journal of Chemistry, Lidia Moreira Lima, Scientific Superintendent of the INCT of Drugs and Medicines, will be in charge of the special issue of RVq dedicated to INCT-INOFAR.

Illustrating different approaches used in the design/discovery of new bioactive prototypes, this theme issue of the Electronic Journal of Chemistry will display the Brazilian qualification in the area of Medicinal Chemistry. It will also show how bringing together research teams made up of specialists in different areas of knowledge can bring them together in a multidisciplinary and interdisciplinary way to work towards the chain of technological innovation in pharmaceuticals and medications.

**Electronic Journal of Chemistry is an initiative of the Regional Secretary of the Brazilian Chemistry Society (SBQ) in Rio de Janeiro. It is a quarterly electronic publication (www.uff.br/rqv) available freely online, to be a bibliographical and promotion source in Portuguese of articles related to Chemistry and related areas.*

THE SEARCH FOR THE 100% NATIONAL GENERIC PHARMACEUTICAL

In the area of incremental innovation, INCT-INOFAR leads projects that aim to develop new synthetic route studies for generics already available as well as for those that have patents about to expire.

So as to identify effective opportunities for the national production of generic medications, INCT-INOFAR uses research developed by the System of Chemical Industry Information (SIQUIM) by UFRJ. Based on virtual information systems, SIQUIM points out key molecules to INCT-INOFAR researchers, with strong market impact, which are currently not patented or that have patents about to expire.

Among these molecules, the Institute prioritizes developing research projects on the synthesis of generic pharmaceuticals of proven therapeutic interest, and that are widely used by the Unified Health System (SUS) in Brazil, in the medical care of the population, as well as future generic pharmaceuticals that present effective opportunities for the Brazilian pharmaceutical sector.

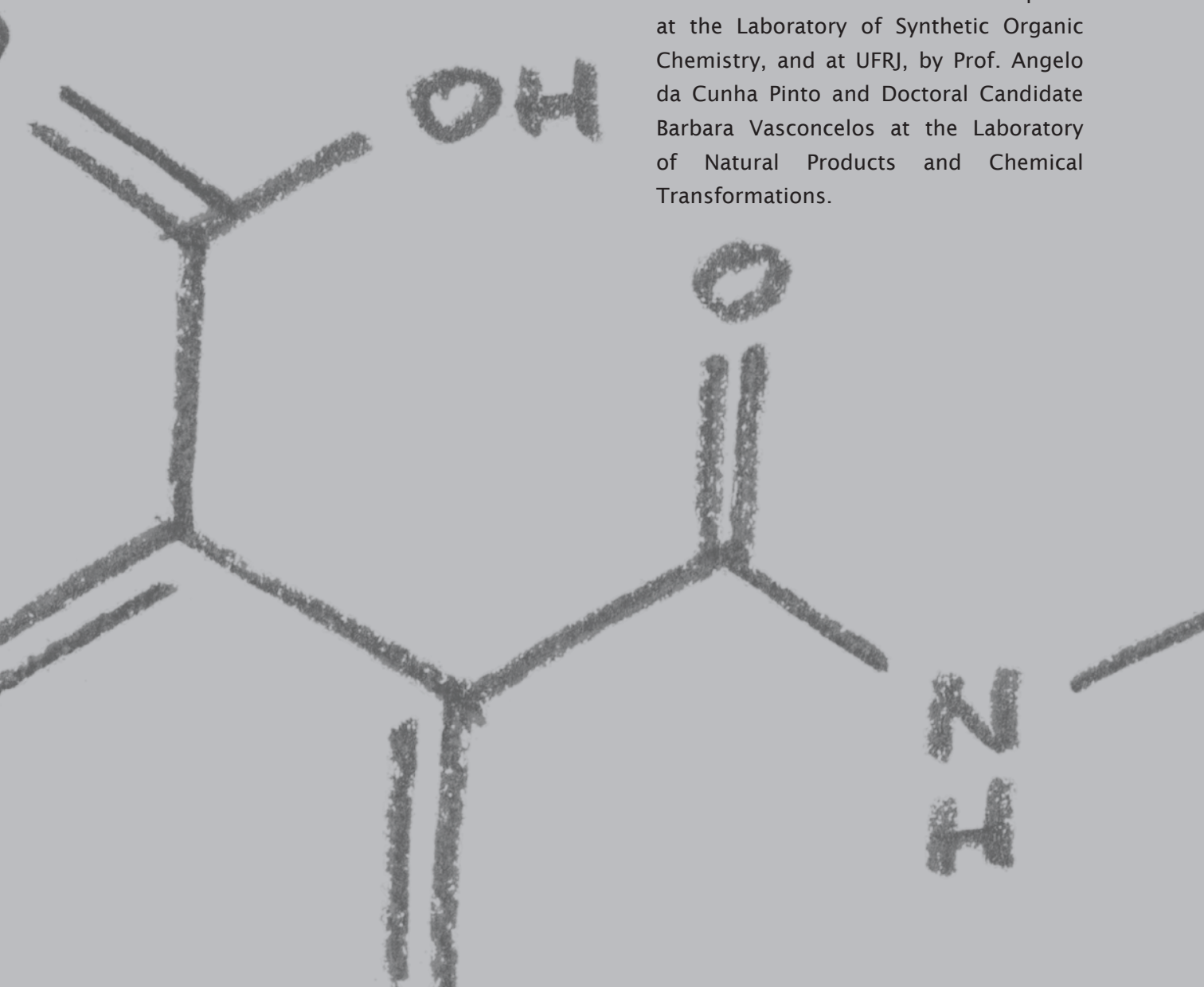
The market for generic pharmaceuticals is the highest growing market in the world, and it has represented 4.5 billion Reais in Brazil between 2006 and 2009. According to IMS Health, the company responsible for auditing Brazilian pharmaceutical companies, the expectation is that until 2011 generics will have a 25% market share.

Generic medications have been available in Brazil for over 10 years; however, few of these pharmaceuticals are produced with national technology. The Brazilian pharmaceutical industry is extremely dependent on imported raw materials from distant markets such as China and India, and as such is subject to whatever prices are practiced abroad.


Medicamento
Genérico

In the search for the 100% national generic, scientists from INCT-INOFAR have been developing new synthetic routes for medications that have expired patents or patents close to expiration. With a goal of being independent from imported raw materials, researchers are investigating new ways to develop the synthetic route of each intermediate involved in the process. As such, they use incremental innovation to propose a more efficient synthetic route so that the pharmaceutical can be prepared in larger quantities, in a quicker, more practical, and cheaper way.

INCT-INOFAR is currently developing two research projects in generic pharmaceuticals. At Unicamp, the challenge is undertaken by Prof. Luiz Carlos Dias and Dr. Adriano Siqueira at the Laboratory of Synthetic Organic Chemistry, and at UFRJ, by Prof. Angelo da Cunha Pinto and Doctoral Candidate Barbara Vasconcelos at the Laboratory of Natural Products and Chemical Transformations.



INCT – INOFAR RESEARCH SUBPROJECTS

Development of new anti-asthmatic pharmaceutical prototypes (LASSBio-596)
Prof. Patricia Rieken Macedo Rocco /
Prof. Lidia Moreira Lima – UFRJ

Study of functionalized *N*-phenylpiperazine derivatives as prototypes for the development of new atypical antipsychotic drugs
Prof. Stela Maris Kuze Rates – UFRS

Study of potential anti-inflammatory effect of LASSBio-897 compound, in silicosis and asthma models
Prof. Patricia Machado Rodrigues e Silva /
Prof. Marco Aurelio Martins – FIOCRUZ

Semicarbazone Benzaldehyde (BS)
Prof. Heloisa de Oliveira Beraldo – UFMG

Therapeutic potential of new vasodilator (LASSBio-1289) on pulmonary and arterial hypertension
Prof. Gisele Zapata Sudo – UFRJ

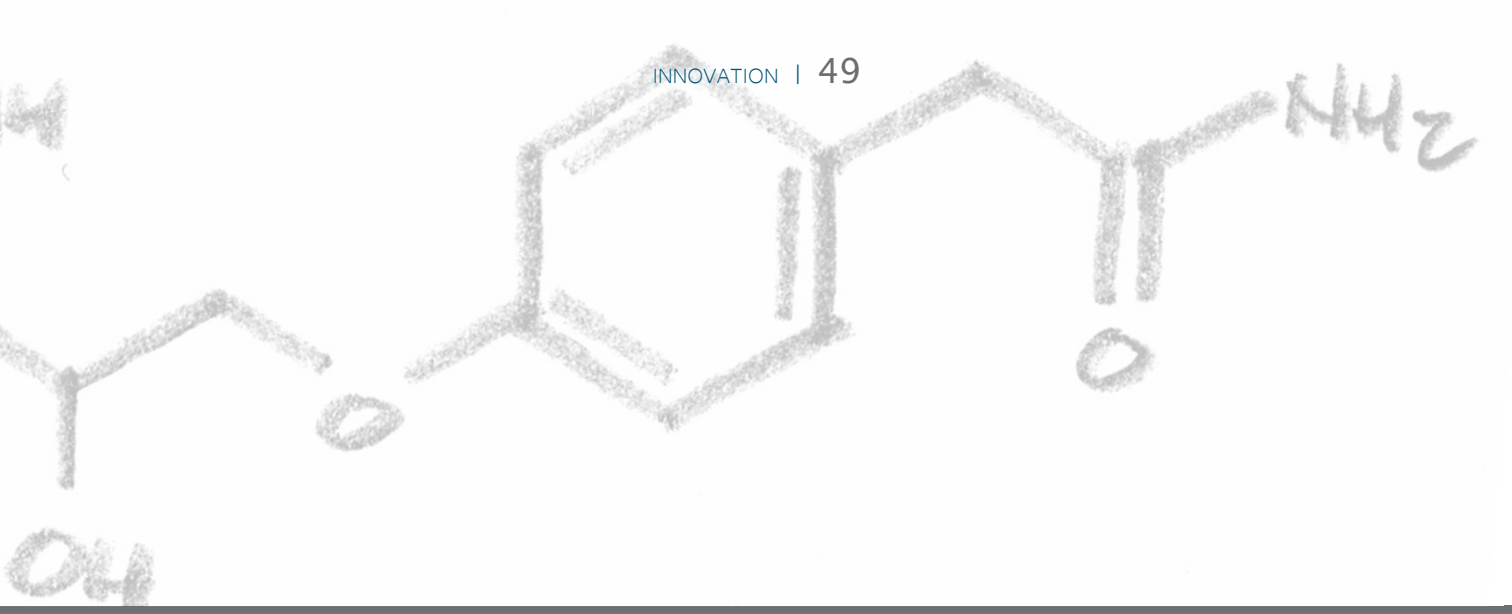
Pharmacological evaluation of new zolpidem neuroactive derivates
Prof. Roberto Takashi Sudo – UFRJ

***In silico* planning and *in vitro* production through bioconversion of human metabolites of pharmaceutical prototype candidates**
Prof. Valeria de Oliveira – UFG

Planning, synthesis, and pharmacological evaluation of vectorized and self-organized neuroactive pharmaceutical prototypes
Prof. Ricardo Menegatti – UFG

Planning, synthesis, structural characterization and pharmacological evaluation of new anti-inflammatory, anti-infectious, and neuroactive pharmaceutical candidates
Prof. Claudio Viegas Junior –UNIFAL

Evaluation of antiparasitic action of a series of semicarbazone and hydrazine-*N*-acylhydrazone candidates
Prof. Magna Suzana Alexandre Moreira – UFAL



Evaluation of mutagenic profile of bioactive substances that are pharmaceutical prototype candidates: a contribution to the chain of innovation in pharmaceuticals and medications
Prof. Ana Luisa P. Miranda – UFRJ

Theoretical investigation of the dialkylphosphorylidrazones action mechanism as ribose 5-phosphate isomerase enzyme inhibitor in *Trypanosoma cruzi* and *Plasmodium falciparum*
Prof. Carlos Mauricio R. de Sant'Anna – UFRRJ

Triage of new replication inhibitors in the human immune deficiency virus of the type 1 (HIV-1) from the LASSBio chemical library
Prof. Luciana Jesus da Costa – UFRJ

Evaluation of antitumor activity of new molecules structurally planned from tinib prototype
Prof. Patricia Dias Fernandes – UFRJ

Discovery of new neuramidase inhibitors of the influenza virus
Prof. Jose Nelson dos Santos Silva Couceiro – UFRJ

Evaluation of therapeutic potential of medicinal plants and bioactive synthetic products with myocardium cytoprotective activity
Prof. Joao Xavier de Araujo Jr. – UFAL

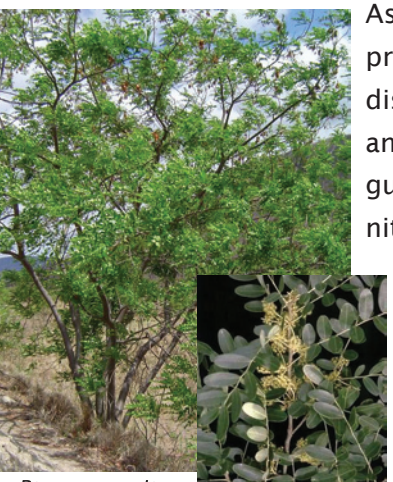
Rational design of pharmaceuticals based in structures: applications and development of methods and programs
Prof. Laurent Emmanuel Dardenne - LNCC

Prospection of opportunities in new generics and new forms of generics
Prof. Adelaide Maria de Souza Antunes – UFRJ

Studies in the synthesis of new generic drugs
Prof. Luiz Carlos Dias – UNICAMP /
Prof. Angelo da Cunha Pinto – UFRJ

CYTOTOXIC GUANIDINE ALKALOIDS FROM PTEROGYNE NITENS

Regasini, L. O.; Castro-Gamboa, I.; Silva, D. H. S.; Furlan, M.; Barreiro, E. J.; Ferreira, P. M. P.; Pessoa, C.; Lotufo, L. V. C.; Moraes, M. O.; Young, M. C. M.; Bolzani, V. S. *J. Nat. Prod.*, (**2009**) 72, 473-476. **DOI**: 10.1021/np800612x



Pterogyne nitens

As part of a bioprospecting program aimed at the discovery of potential anticancer drugs, two new guanidine-type alkaloids, nitensidines D and E (**1**, **2**), and the known pterogynine (**3**), pterogynidine (**4**), and galegine (**5**), were isolated from the leaves of Pterogyne nitens.

The structures of 1 and 2 were established on the basis of spectroscopic data interpretation. These compounds were tested against a small panel of human cancer cell lines. Compound 2 exhibited cytotoxicity for HL-60 (human myeloblastic leukemia) and SF-245 (human glioblastoma) cells.

The structure of nitensidine E (2) constitutes the first report of the alkaloids, and has been reported only within a limited number of plant genera. Furthermore, terpenoid-like alkaloids may have some taxonomic significance for Fabaceae and Euphorbiaceae, since their occurrence is most common among these taxa.

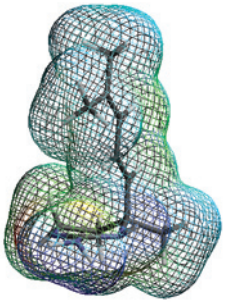


Table 2. Cytotoxic Activity of Compounds 1-5 Isolated from Pterogyne nitens against Human Tumor Cell Lines[a,b]

compound	cell line			
	HL-60 (leukemia)	HCT-8 (colon)	MDA-MB-435 (melanoma)	SF-295 (glioblastoma)
2	3.6	> 5	> 5	4.9
doxorubicin	0.02	0.04	0.47	0.25

[a] Data are presented as IC50 values given in µg/mL obtained by nonlinear regression.

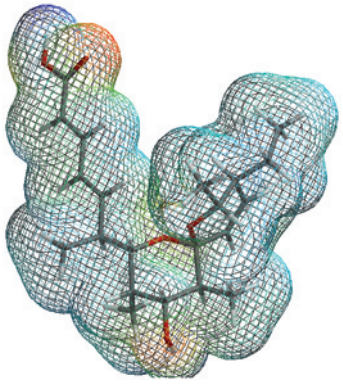
[b] Compounds **1**, and **3** - **5** were inactive (IC50 > 5µg/mL) for all cell lines used.

TOTAL SYNTHESIS OF PTERIDIC ACIDS A AND B

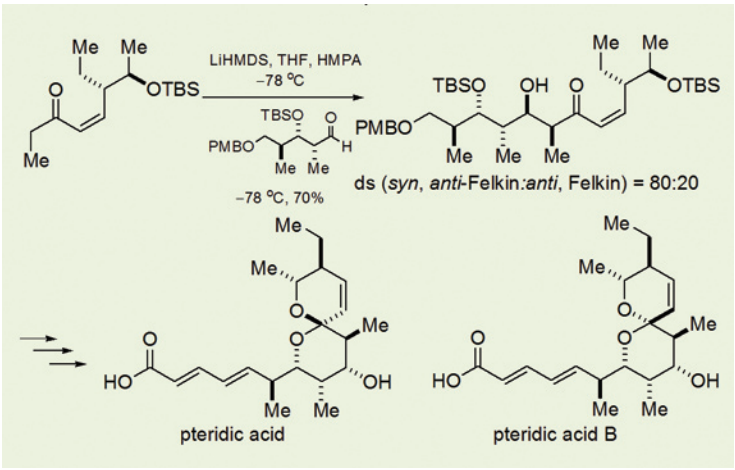
Dias, L. C. ; Salles Jr., A, G *The Journal of Organic Chemistry* (**2009**) 74, 5584-5589 **DOI**:10.1021/jo9010365

As limited amounts of pteridic acids A and B are available from nature, we initiated a project directed toward their total synthesis. In addition, attracted by their promising anticancer activities, we intend to provide material for more extensive biological studies, along with access to novel analogues.

Pteridium aquilinum: Natural source of pteridic acid



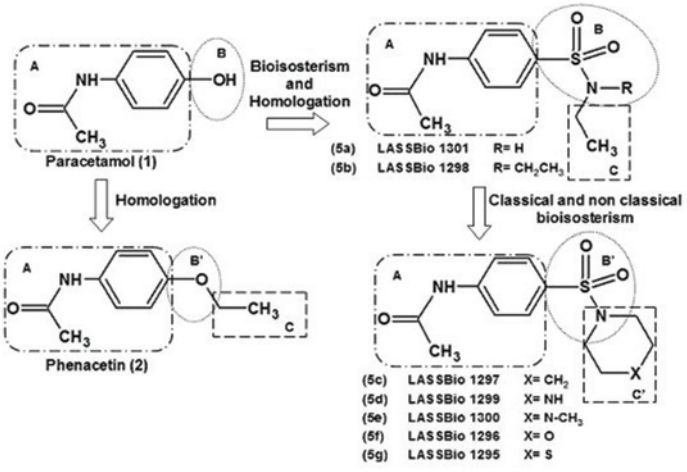
We have achieved the total synthesis of pteridic acids A and B. Notable features of this approach include convergence, a lithium enolate-mediated aldol reaction to set up the desired C9 and C10 stereocenters and a spiroketalization reaction, providing pteridic acids A and B in 2.9% and 2.8% overall yield, respectively. This approach is readily applicable for the preparation of additional novel structural analogues.



SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF *N*-PHENYL-ACETAMIDE SULFONAMIDES DESIGNED AS NOVEL NON-HEPATOTOXIC ANALGESIC CANDIDATES

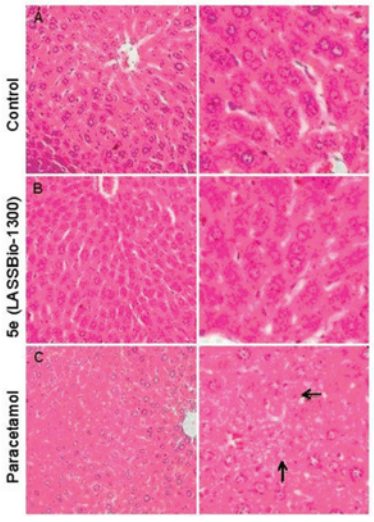
Barbosa, M. L. C.; Albuquerque-Melo, G. M.; Silva, Y. K. C.; Lopes, R. O.; Souza, E. T.; Queiroz, A. C.; Smaniotto, S.; Alexandre-Moreira, M. S.; Barreiro, E. J.; Lima, L. M. *Eur. J. Med. Chem.* (**2009**) 44, 3612-3620. **DOI**:10.1016/j.ejmech.2009.02.026

In a continuing effort to develop new analgesic drug candidates, we report in this paper the design, synthesis and pharmacological evaluation of *N*-phenyl-acetamide sulfonamide derivatives (5a-g), planned by structural modification on the prototype paracetamol (1). The design concept considered the need to carry out structural modifications in the toxicophoric unit of paracetamol (1), avoiding its biotransformation to the reactive metabolite NAPQI.

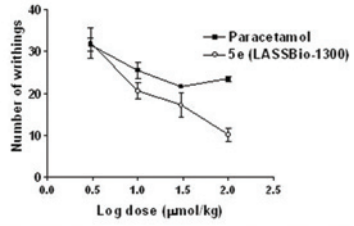


The synthesis of these new series was undertaken using a classical methodology, based on several functional group interconversions.

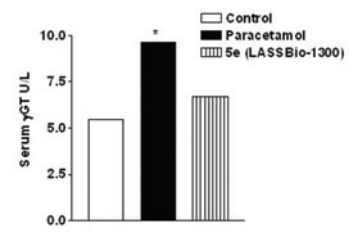
All *N*-phenyl-acetamide sulfonamide derivatives (5a-g) produced marked inhibition of acetic acid-induced writhing response (dose = 100 μmol/kg, p.o.), being compounds 5d and 5e significantly more active than the standard paracetamol.



The comparative hepatotoxicity of paracetamol (1) and its *N*-phenyl-acetamide sulfonamide analogues (5a–g) was investigated. The microscopic liver analysis of animals treated with saline (control group) and with LASSBio-1300 (5e) demonstrated a regular morphology of the liver parenchyma, with well-designed and evident hepatic cells and sinusoids. On the other hand, the liver of animals treated with paracetamol (1) showed histological changes in the micro architecture of the liver lobule and degenerated hepatocytes, showing perinuclear vacuolization in most areas.



Otherwise, mice treated with paracetamol (1) showed a significant increase in serum gamma-glutamyl transferase (gGT), while no significant effect was observed for LASSBio-1300.

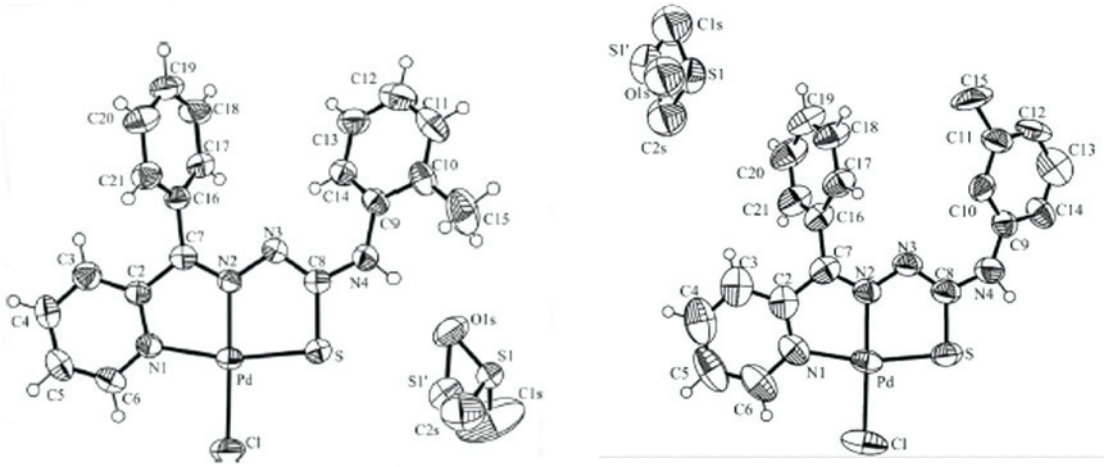


In conclusion, a new series of analgesic drug candidates were identified, stands out compound LASSBio-1300 as a new non-hepatotoxic drug candidate, more potent than the standard 1 and presenting a better hypothermic profile.

2-BENZOYLPYRIDINE-*N*(4)-TOLYL THIOSEMICARBAZONES AND THEIR PALLADIUM(II) COMPLEXES: CYTOTOXICITY AGAINST LEUKEMIA CELLS

Ferraz, K. S. O.; Fernandes, L.; Carrilho, D.;. Pinto, M. C. X.; Leite, M. F.; Souza-Fagundes, E. M.;. Speziali, N. L.; Mendes, I. C.; Beraldo, H. *Bioorg. Med. Chem.* (**2009**) 17, 7138-7144. **DOI**:10.1016/j.bmc.2009.08.063

Today platinum drugs are among the most active and widely used clinical agents for the treatment of advanced cancer. Thiosemicarbazones and their metal complexes present a wide range of pharmacological applications. In many circumstances the activity increases upon coordination to metal ions. It has been shown that palladium(II) and platinum(II) complexes with thiosemicarbazones are active against cisplatin-resistant human tumor cell lines, probably because their mode of action involves inter-strand crosslinks with DNA, instead of intra-strand crosslinks, which is the major coordination mode of cisplatin.



In the present work 2-benzoylpyridine *N*(4)-*ortho*-tolyl, (H2Bz4oT, **1**), *N*(4)-*meta*-tolyl (H2Bz4mT, **2**), and *N*(4)-*para*-tolyl (H2Bz4pT, **3**) thiosemicarbazones and complexes [Pd(2Bz4oT)Cl] (**4**), [Pd(2Bz4mT)Cl] (**5**), and [Pd(2Bz4pT)Cl] (**6**) have been evaluated for their in vitro antiproliferative activity against HepG2 (human hepatoma), Jurkat (immortalized line of T lymphocyte), HL60 (human promyelocytic leukemia) and HL60.Bcl-X_L (human promyelocytic leukemia ectopically expressing the anti-apoptotic protein Bcl-X_L that confers resistance to cytotoxic stimulus) human cancer cell lines

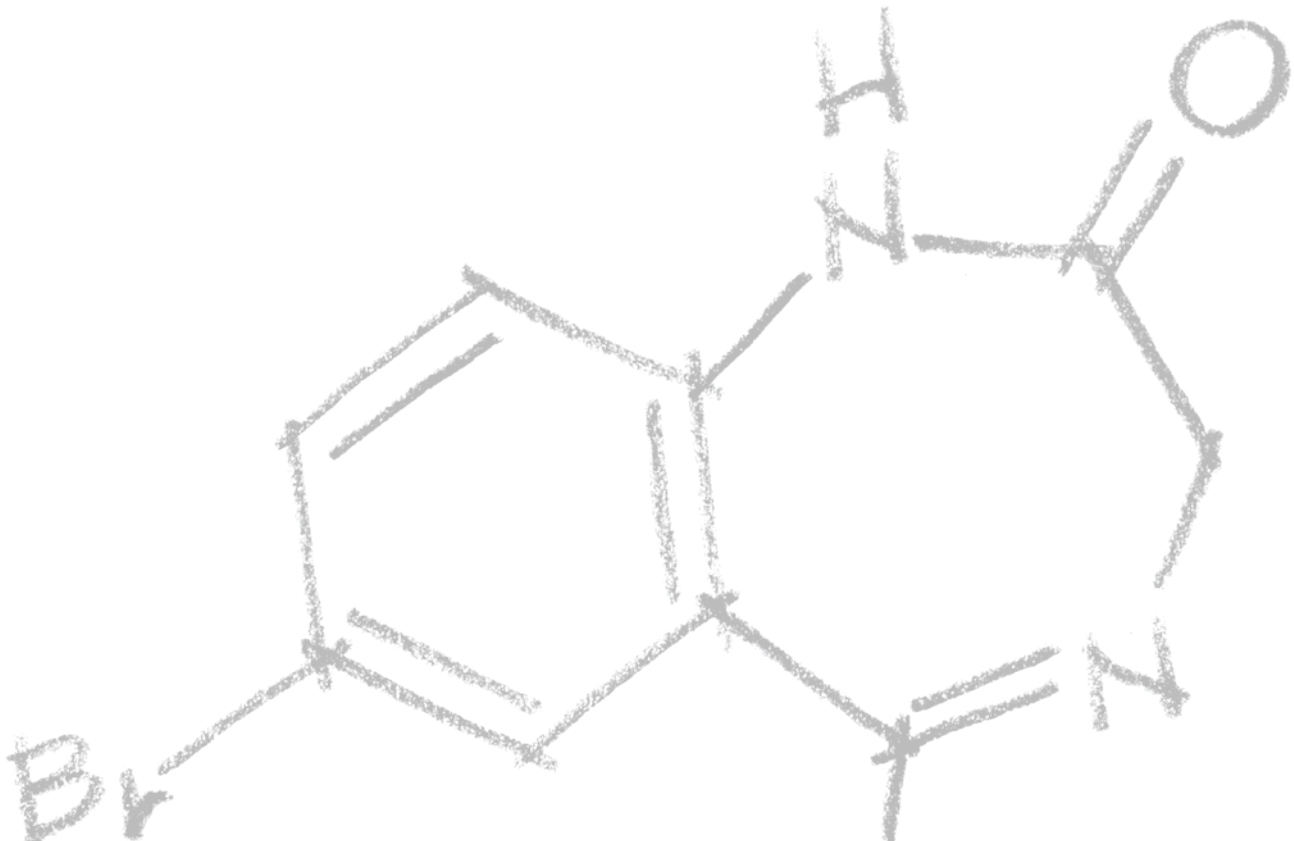
The best values of cytotoxic activities of the studied thiosemicarbazones against the three leukemia cell lines were at nanomolar level while their cytotoxic effects against HepG2 cells were observed at concentrations greater than 50 μM, comparable to that determined for cisplatin. The cytotoxicity of complexes **4–6** against HepG2 cells were also observed at concentrations greater than 50 μM.

Tab. 2. Inhibition of HL60, HL60.Bcl-XL and Jurkat cell proliferation by thiosemicarbazones (1–3) and their palladium(II) complexes (4–6)

Compound	IC_{50} (μM) ± SEM		
	Jurkat[a]	HL60[b]	HL60.Bcl-X_L[c]
H2Bz4oT (1)	0.015 ± 0.003	0.0095 ± 0.0010	0.019 ± 0.006
H2Bz4mT (2)	0.017 ± 0.001	0.0059 ± 0.0007	0.038 ± 0.002
H2Bz4pT (3)	0.034 ± 0.001	0.014 ± 0.001	0.028 ± 0.002
[Pd(2Bz4oT)Cl] (4)	3.43 ± 0.04	5.39 ± 0.32	ND
[Pd(2Bz4mT)Cl] (5)	48.1 ± 2.1	1.46 ± 0.24	6.79 ± 0.81
[Pd(2Bz4pT)Cl] (6)	ND	ND	ND
Cisplatin	1.26 ± 0.35	1.69 ± 0.44	7.65 ± 0.30

ND — not determined.
a Jurkat — immortalized line of T lymphocyte cells cell line.
b HL60 — acute myeloid leukemia cell line.
c HL60.Bcl-XL cell line — HL60 cells ectopically expressing the anti-apoptotic protein Bcl-XL. Representative data of at least three independent experiments performed in triplicate.

The observed cytotoxic effect of the thiosemicarbazones against leukemia cells at nanomolar doses, together with their lower toxicity against hepatoblastoma HepG2 cells indicate that it would be worth to carry on further investigation on this class of compounds.



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

Nelilma C. Romeiro, N. C.; Aguirre, G.; Hernández, P.; González, M.; Cerecetto, H. Aldana, I.; Pérez-Silanes, S.; Monge, A.; Barreiro, E. J.; Lima, L. M. *Bioorg. Med. Chem.* (**2009**) 17, 641-652. **DOI**:10.1016/j.bmc.2008.11.065

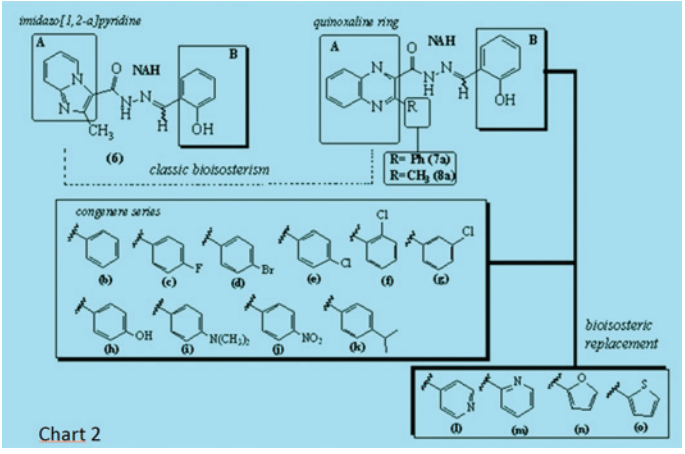
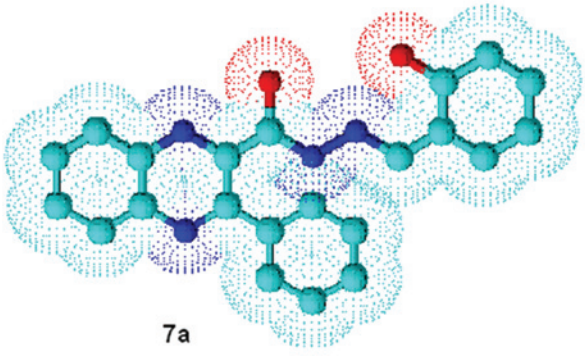
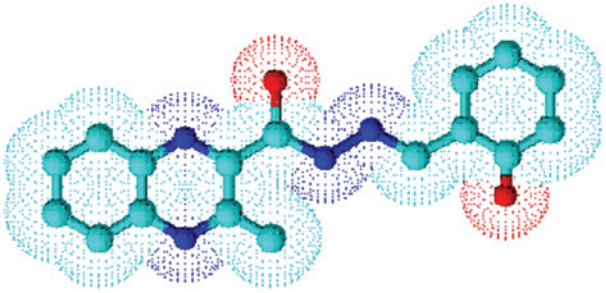


Chart 2

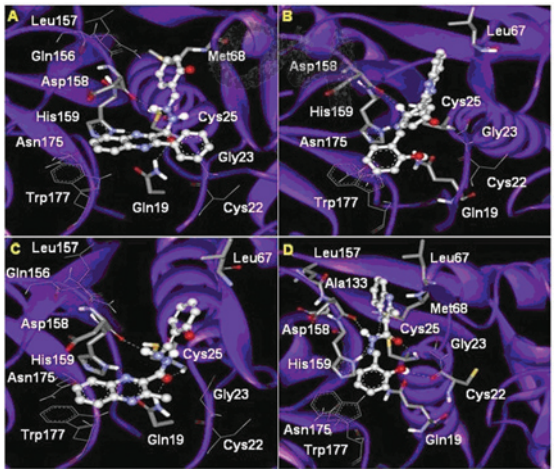
In this paper, are reported the design, synthesis, trypanocidal activity and docking studies of novel quinoxaline-*N*-acylhydrazone (NAH) derivatives (7a-o and 8a, Chart 2), planned as cruzain inhibitors candidates.

All compounds were tested (at 25 μM) in vitro against epimastigote forms of Trypanosoma cruzi, Tulahuen 2 strain. Seven, out of the sixteen evaluated compounds, presented percentage of growth inhibition superior to 30%, standing out the derivatives 7a and 8a with inhibitions of 96% and 81%, respectively. These compounds were selected and next the IC50 value determined. The quinoxaline *N*-acylhydrazones presented IC50 values of the same magnitude order than the standard drug Nfx. Also, unspecific cytotoxicity of the most active derivatives 7a and 8a and one inactive compound (7o) against mammalian cells was evaluated in vitro at 100, 200 and 400 μM, using J774 mice macrophages as the cellular model and

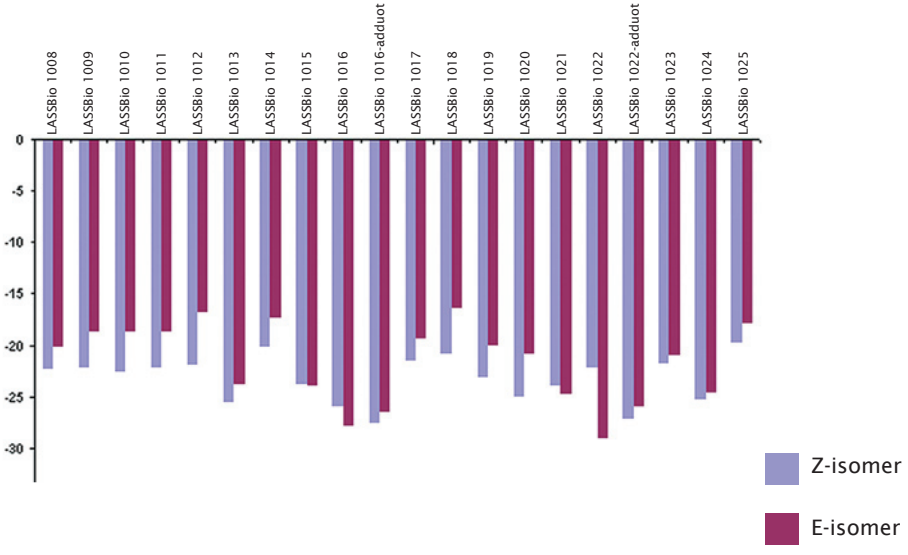

7a


8a

In an attempt to theoretically explain the difference found in the trypanocidal activity of the new quinoxaline NAH derivatives (7a-o, 8a), docking studies using the enzyme cruzain were performed.



From the docking experiments, the best complex of the quinone adduct of LASSBio-1016 with cruzain reveals that the carbon atom of the amide carbonyl group of LASSBio-1016 (7a) is within 2.69 Å of the sulfur atom of Cys25, the key nucleophilic amino acid residue in the active site of cruzain.



A new series of trypanocidal quinoxaline-*N*-acylhydrazone (NAH) derivatives were discovered, outstanding the salicylaldehyde *N*-acylhydrazones 7a and 8a with IC_{50} of the same magnitude order than the standard drug nifurtimox (Nfx). The docking studies have shown a reasonable correlation with the molecular design of the quinoxaline derivatives towards cruzain.

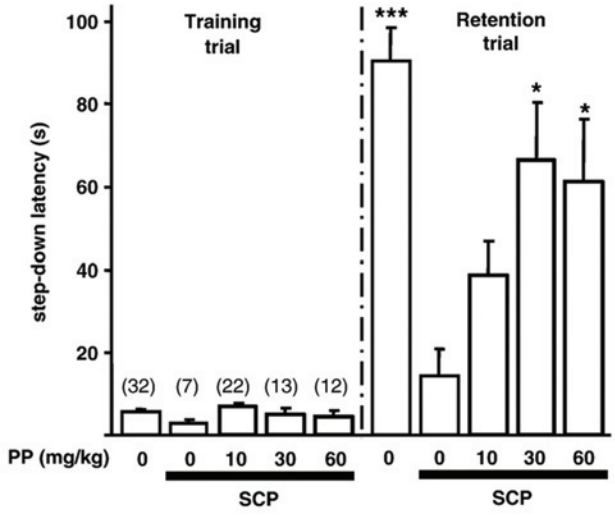
GEISSOSPERMUM VELLOSII STEMBARK: ANTICHOLINESTERASE ACTIVITY AND IMPROVEMENT OF SCOPOLAMINE-INDUCED MEMORY DEFICITS

Lima, J. A.; Costa, R. S.; Epifânio, R. A.; Castro, N. G.; Rocha, M. S.; Pinto, A. C. *Pharmacol Biochem Behav.* (**2009**), 92, 508-513. **DOI**: 10.1016/j.pbb.2009.01.024

Geissospermum vellosii

This study evaluated the cholinesterase inhibitory activity of an alkaloid-rich fraction of stem bark from *Geissospermum vellosii* (PP), and its effect on memory tests in mice. PP inhibited rat brain and electric eel acetylcholinesterase, as well as horse serum butyrylcholinesterase in a concentration-dependent manner with mean IC50 values of 39.3 µg/mL, 2.9 µg/mL, and 1.6 µg/mL, respectively.

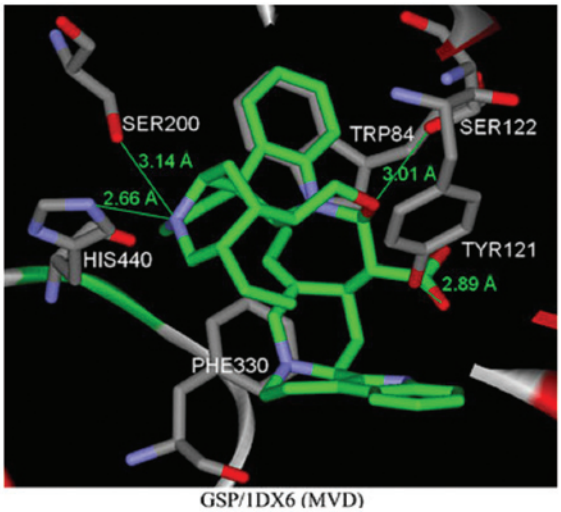
The main alkaloid with anticholinesterase activity in PP was isolated and identified as geissospermine. PP significantly reduced scopolamine-induced amnesia in the passive avoidance and Morris water maze tests, at 30 mg/kg i.p. (given 45 min before the test sessions). At the highest effective dose (60 mg/kg), administration of PP did not result in noticeable peripheral or central cholinergic side effects. Only after administration of 200 mg/kg, mice showed convulsions affecting the whole body followed by death. These results show that compounds present in G. *vellosii* stem bark have anticholinesterase activity, and that they can revert cognitive deficits in a model of cholinergic hypofunction.



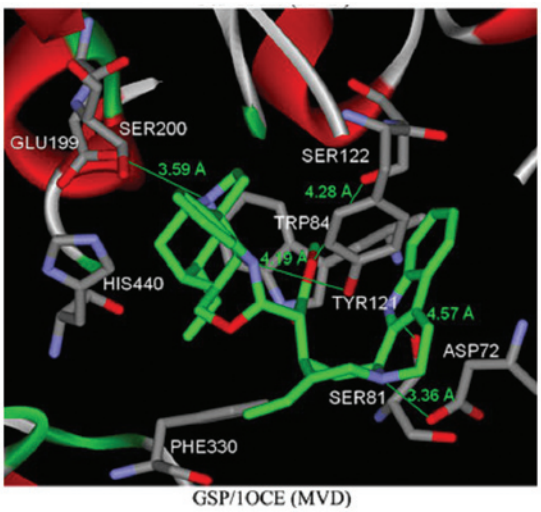
Effects of PP on scopolamine-induced amnesia in the step-down passive avoidance test in mice. In order to induce amnesia, mice were treated with scopolamine (SCP; 1 mg/kg, i.p.) 30 min prior to the training (left panel) and retention trial (rightpanel). Vehicle or PP (10, 30 or 60 mg/kg) was administered i.p. 15 min before scopolamine

However, the binding mode (i.e., conformation and orientation) of this indole-indoline alkaloid into the AChE active site is unknown. Therefore, in order to propose a plausible binding mode between GSP and AChE, which might explain the observed experimental inhibitory activity, we performed comparative automatic molecular docking simulations using the AutoDock and Molegro Virtual Docker (MVD) programs.

A sample of ten crystal structures of the Pacific electric ray (Torpedo californica) TcAChE, in complex with ten diverse active site ligands, was selected as a robust re-docking validation test, and also for GSP docking.



GSP/1DX6 (MVD)



GSP/1OCE (MVD)

The MVD results indicate a preferential binding mode between GSP and AChE, in which GSP functional groups may perform specific interactions with residues in the enzyme active site, according to the ligand-protein contacts detected by the LPC/CSU server. Four hydrogen bonds were detected between GSP and Tyr121, Ser122, Ser200, and His440, in which the last two residues belong to the catalytic triad (Ser200···His440···Glu327). Hydrophobic and π-π stacking interactions were also detected between GSP and Phe330 and Trp84, respectively; these are involved in substrate stabilization at the active site. This study provides the basis to propose structural changes to the GSP structure, such as molecular simplification and isosteric replacement, in order to aid the design of new potential AChE inhibitors that are relevant to the treatment of Alzheimer's disease

REGULATION OF CHEMOKINE RECEPTOR BY TLR2 IS CRITICAL TO NEUTROPHIL MIGRATION AND RESISTANCE TO POLYMICROBIAL SEPSIS

Alves-Filho, J. C.; Freitas, A.; Souto, F. O.; Spiller, F.; Paula-Neto, H.; Silva, J. S.; Gazzinelli, R. T.; Teixeira, M. M.; Ferreira, S. H.; Cunha, F. Q. *Proc. Natl. Acad. Sci. USA* (**2009**) 106, 4018-4023. **DOI**: 10.1073/pnas.0900196106

Patients with sepsis present a marked defect in neutrophil migration. Here we identify a key role of TLR2 in the regulation of neutrophil migration and resistance during polymicrobial sepsis. The expression of the chemokine receptor CXCR2 is dramatically down-regulated on circulating neutrophils from WT mice with severe sepsis, which correlates with reduced chemotaxis to CXCL2 *in vitro* and impaired migration into infectious focus *in vivo*. TLR2 deficiency prevented the down-regulation of CXCR2 and failure of neutrophil migration. Moreover, TLR2$^{-/-}$ mice presented higher bacterial clearance, lower serum inflammatory cytokines and improved survival rate during severe sepsis than WT mice (Fig. 1 and Fig. 2, not shown).

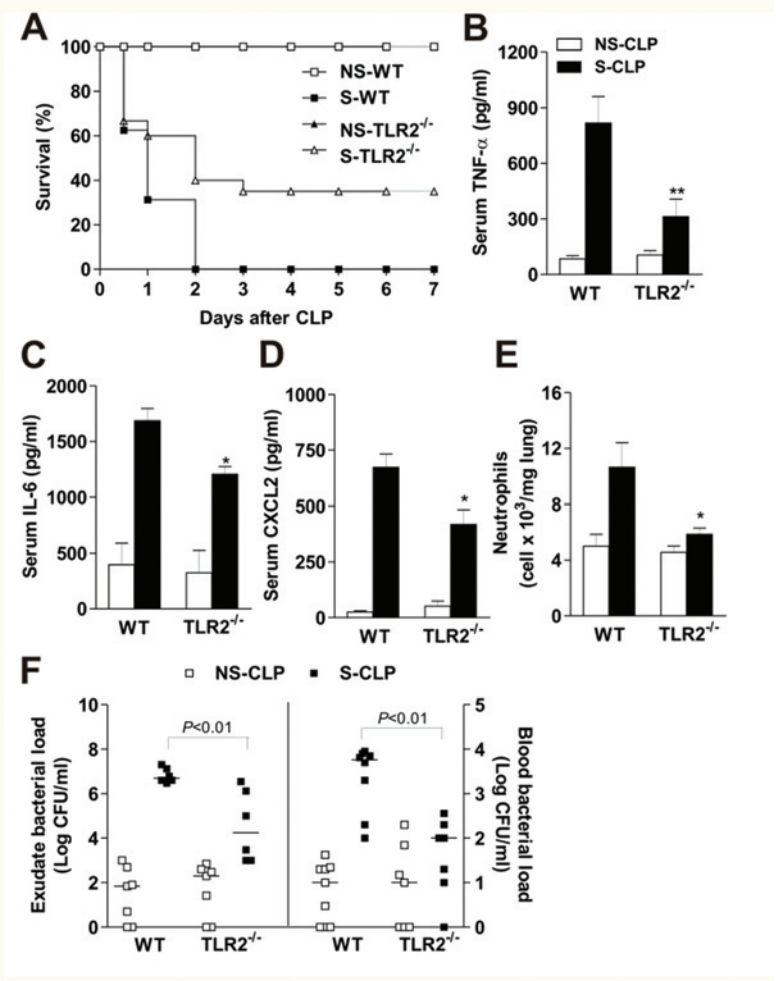


Fig. 1. TLR2 deficiency improves survival during septic peritonitis. (A) Survival rate after non-severe CLP (NS-CLP) or severe CLP (S-CLP) in WT or TLR2$^{-/-}$ mice (n = 20). Log-rank test ($P < 0.05$). (B-D) ELISA of TNF-α (B), IL-6 (C) and CXCL2 (D) in serum of WT (n = 10) and TLR2$^{-/-}$ (n = 10) mice 6 h after CLP. (E) Neutrophil sequestration in lung measured 6 h after CLP. Data are means ± SEM. * $P < 0.05$, ** $P < 0.01$, relative to S-CLP WT. (F) CFU in peritoneal exudate and blood 6 h after CLP. Horizontal bars represent median values and squares represent individual mice (n = 6-8 each).

In vitro, TLR2 agonist, lipoteichoic acid (LTA), down-regulated CXCR2 expression and markedly inhibited neutrophil chemotaxis and actin polymerization induced by CXCL2. Moreover, neutrophils activated ex vivo by LTA and adoptively transferred into naïve WT recipient mice displayed a significantly reduced competence to migrate toward thioglycolate-induced peritonitis. We also showed that LTA enhanced expression of G-protein-coupled receptor kinases-2 (GRK2) in neutrophils. Moreover, increased expression of GRK2 was observed in blood neutrophils from WT, but not TLR2$^{-/-}$ mice, with severe sepsis (Fig 3). Our findings identified an unexpected detrimental role of TLR2 in polymicrobial sepsis and suggest that inhibition of TLR2 signaling may improve survival from sepsis.

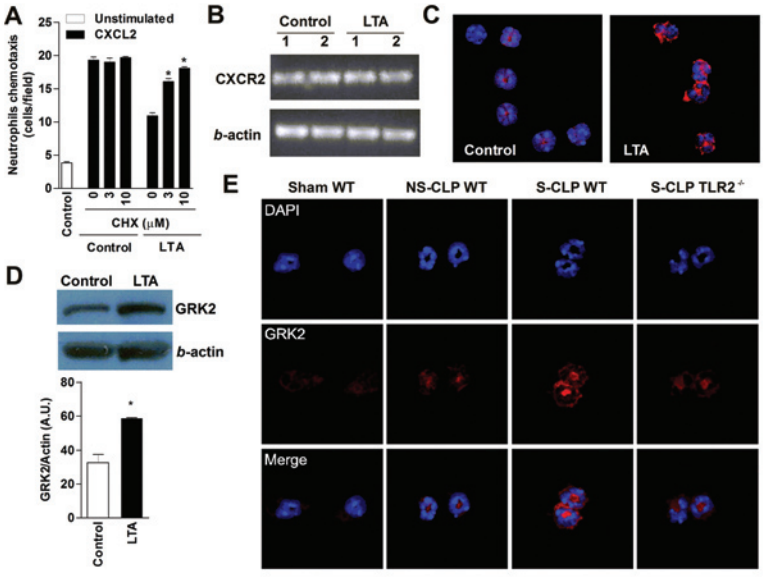
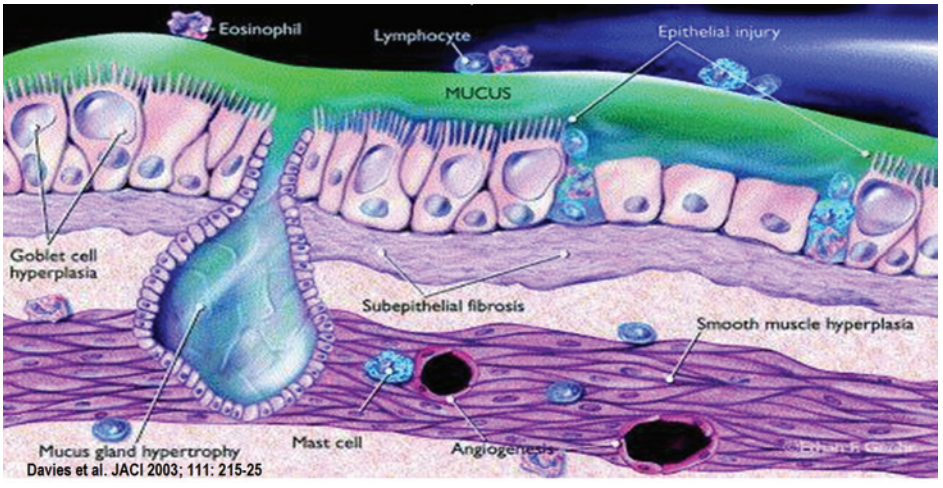


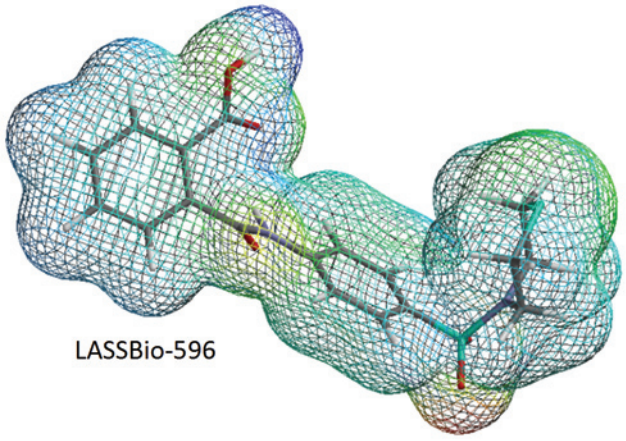
Fig. 3. TLR2 signaling up-regulates GRK2 expression in neutrophils. (**A**) CXCR2 and β-actin gene expression in LTA-treated neutrophils by RT-PCR. (**B**) Neutrophils chemotaxis to CXCL2 after treatment with cycloheximide (CHX), a protein synthesis inhibitor, for 30 min and later with LTA (10 μg/ml) for plus 1 h. Data are means ± SEM. **P* < 0.001, relative to WT control group plus CXCL2. (**C**) Representative fluorescence microscopy for GRK2 (red) in BM neutrophils after treatment with LTA (10 μg/ml) for 1 h. Nuclei were stained by DAPI (blue). (**D**) Representative immunoblot of GRK2 and β-actin in neutrophils lysates after treatment with LTA (10 μg/ml) for 1 h. Graph indicate data in arbitrary units (AU) of the density of GRK2 per β-actin band. **P* < 0.01. (E) Representative fluorescence microscopy for GRK2 (red) in blood neutrophils isolated from septic WT and TLR2$^{-/-}$ mice 2 h after CLP. Nuclei were stained by DAPI (blue).

THE IMPACT OF LASSBIO-596 ON LUNG MORPHOFUNCTION IN RESPIRATORY DISEASES

Research teams of LASSBio-596:
Principal researchers: Patrícia M. R. Rocco (UFRJ); Patrícia M. R. e Silva (Fiocruz); Marco Aurélio Martins (Fiocruz); Francisco J. R. Paumgartten (Fiocruz); Fernando Q. Cunha (USP-RP); Lídia M. Lima (UFRJ); Eliezer J. Barreiro (UFRJ).
Collaborators: Isac A. Medeiros (UFPb); Magareth de F. F. M. Diniz (UFPb); Manoel O. de Moraes (UFC); Letícia V. Costa-Lotufo (UFC), Claudia do Ó Pessoa (UFC); Teresa Dalla-Costa (UFRGS).

Asthma is an inflammatory disease that involves large and distal airways, as well as lung parenchyma (Xisto et al., 2005), and steroid treatment is the “gold” standard therapy for this condition. The long-term use of steroids, particularly in young children, have stimulated the discovery of novel anti-inflammatory molecules with high tolerability and clinical efficacy (Campos et al. 2006). Furthermore, since lung remodeling is associated with an accelerated rate of deterioration in respiratory function and with perpetuation of symptoms (Bousquet et al., 2000), a drug with the capacity to act not only in the inflammatory process but also by preventing airway remodeling would be useful in the treatment of asthma.





In this context, LASSBio-596, designed as a hybrid of thalidomide and aryl sulfonamide, is a new agent that exhibits potent anti-inflammatory and immunomodulatory properties (Lima et al., 2002; Rocco et al., 2003).

Asthma model was induced using an adjuvant-free protocol by the intraperitoneal (*ip*) injection of 10 µg ovalbumin (OVA) on 7 alternate days. Forty days after the beginning of sensitization, an intratracheal challenge was performed according to the following protocol. Mice were anesthetized with sevoflurane, a 0.5-cm long midline cervical incision was made to expose the trachea, and 20 µg OVA in 20 µL warm (37ºC) sterile saline (0.9% NaCl) was instilled. This procedure was performed three times at 3-day intervals. Animals were treated with dexamethasone (ip) and LASSBio596 (ip or oral route) for 8 consecutive days, starting 24 h before the first intratracheal challenge with OVA. Another group of animals received LASSBio596 (ip) after the last instillation during 8 days.

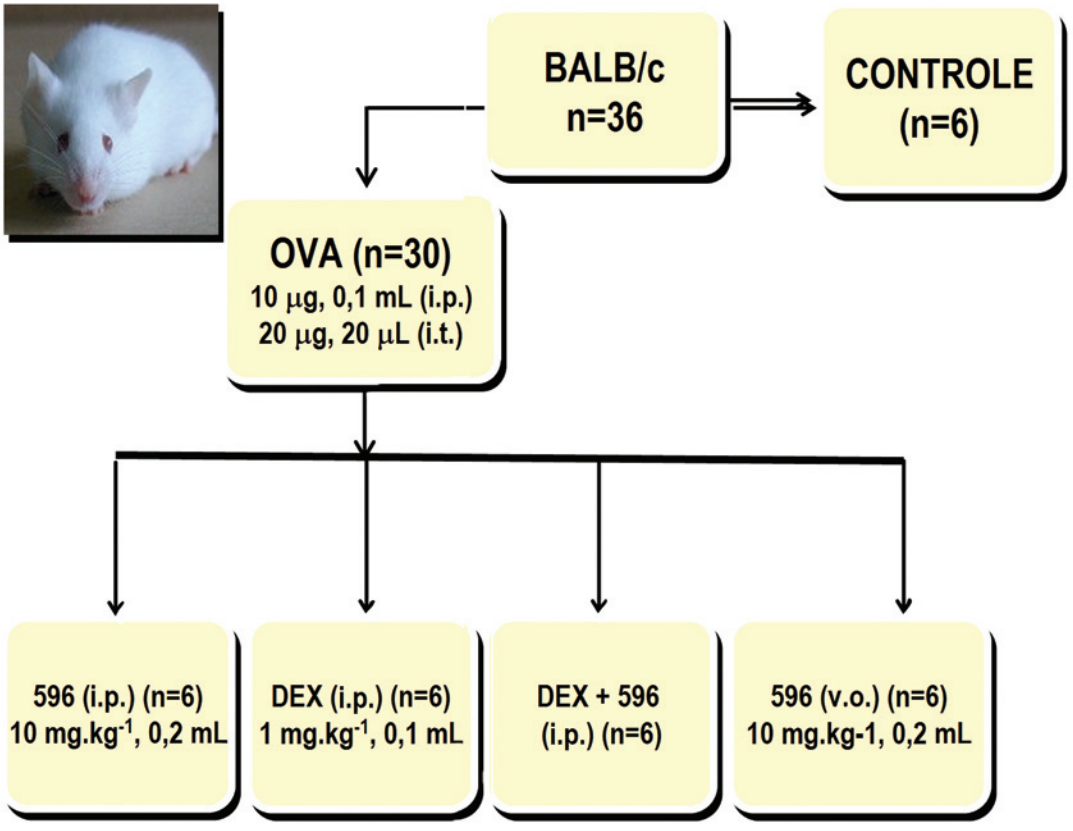


Figure 1 – Experimental design

Histological changes in the asthma group included alveolar collapse and narrower central airways, which were avoided by the administration of LASSBio596 independent of the route and moment of administration. Although dexamethasone inhibited the changes in central airways, lung parenchyma displayed areas of alveolar collapse. The collagen fiber content in the alveolar septa and airways was greater in the asthma group than in control animals. Both dexamethasone and LASSBio596 inhibited lung parenchyma and airway fibrosis. The present study provides evidence that LASSBio596 (oral route or *ip*) is as effective as dexamethasone in inhibiting inflammatory changes in the airways and preventing lung parenchyma and airway remodeling in a murine model of chronic asthma. Additionally, LASSBio596 prevented alveolar collapse to a greater extent than dexamethasone, although there were no functional differences between the LASSBio596 and dexamethasone groups. In a murine model of chronic asthma, LASSBio596 prevented mechanical and histological lung changes and inhibited collagen deposition when administered to sensitized animals before and after they were challenged with OVA (Figure 2). Furthermore, LASSBio596 reduced the expression of TNF-a, IL-4, and TGF-b in lung tissue.

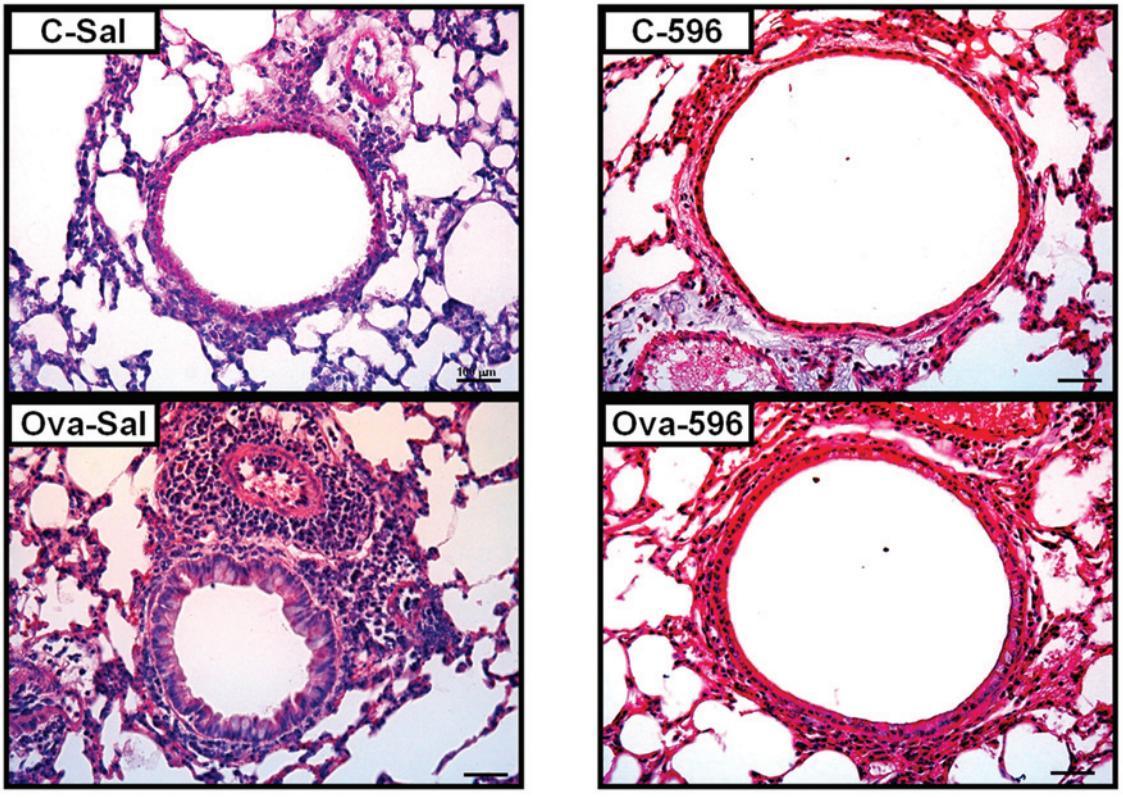


Figure 2 – Photomicrographs of airways stained with hematoxylin eosin. Bars= 100 mm. OVA- mice sensitized and challenged with ovalbumin. C – animals that received saline using the same protocol. 596 – animals treated with LASSBio596 1 h after the last challenge during 8 days

Because of LASSBio596 beneficial effects in asthma inhibiting the fibrotic process through TGF-b, another study was performed using LASSBio596 in an experimental model of silicosis. Silicosis is a pneumoconiosis that involves formation of nodules and destruction of large areas of the lung leading to impaired gas-exchange and pulmonary function, which may result in respiratory failure. Despite extensive efforts, no available therapy has been shown to halt or efficiently reverse this disorder (Maron-Gutierrez et al., 2010).

In order to develop experimental model of silicosis, mice received intratracheal (i.t.) injection of 20 mg of silica crystals (SiO_2, particle size: 80% between 1 and 5 µm; Sigma Chemical, St. Louis, MO) suspended in saline solution (total volume = 50 µl). One hour and 14 days after silica administration, LASSBio596 was intraperitonealy injected. LASSBio596 minimized functional and histological parameters independent of the moment of treatment through its action on fibrogenesis (Figure 3).

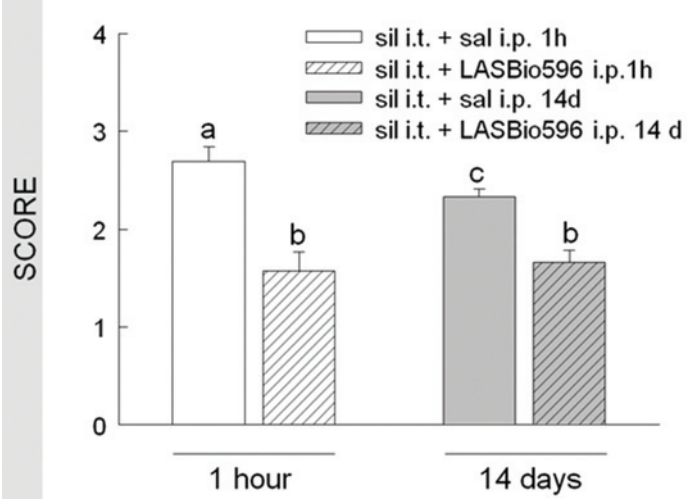


Figure 3. Score of granuloma. 0= no granuloma; 1= 1- 25%; 2= 26-50 %; 3= 51-75% and 4= 76-100% of the field occupied by granuloma. Different letters mean significant differences among the groups.

In summary, LASSBio596 due to its anti-inflammatory and anti-fibrogenic activity may be a useful therapy for patients with severe persistent asthma and those with silicosis.

Professor Rocco, P. M. R. team

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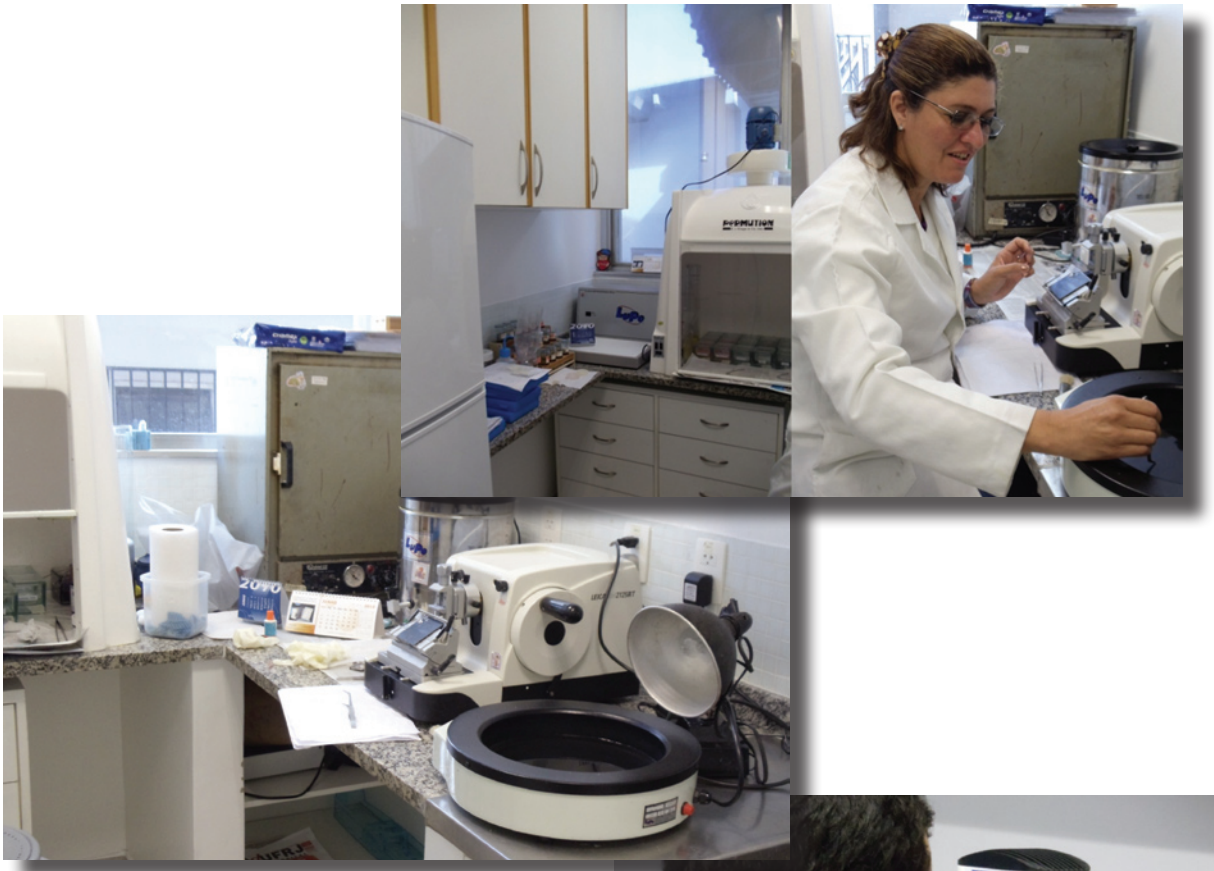
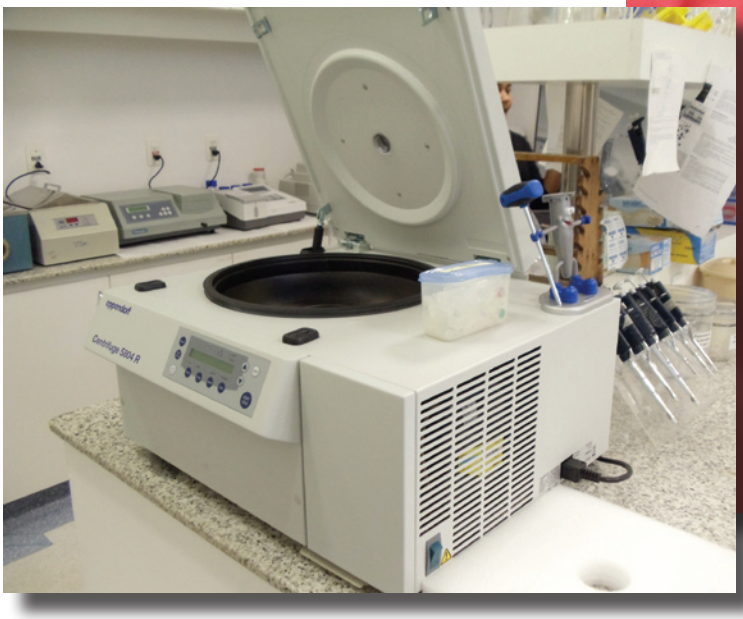
Barreiro, E. J.; Rocco, P. R. M.; Zin, W. A.; Lima, L. M.; Fraga, C. A. M.; Koatz, V. L. G. **Patent: PI0208767-7. BR**

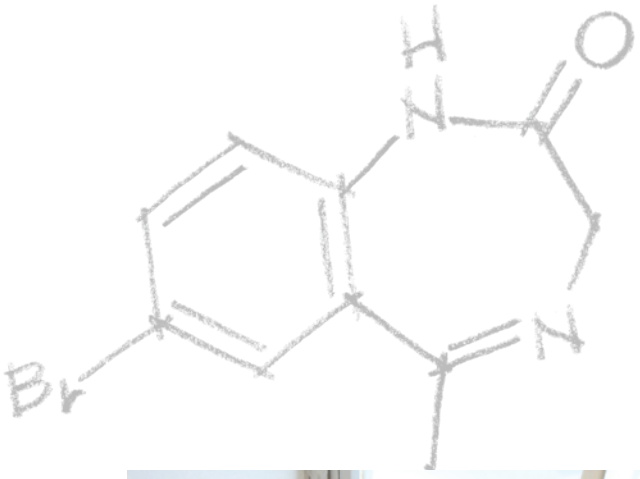


Equipments for preparation of tissue for histologic and morphometric study

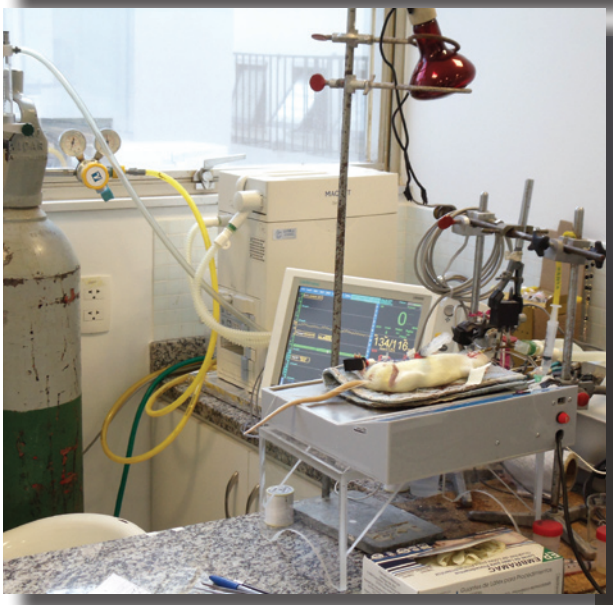
Equipment for analysis of lung histology and peripheral organs



Equipment for analysis of molecular biology



Equipment for analysis of respiratory mechanics in vitro



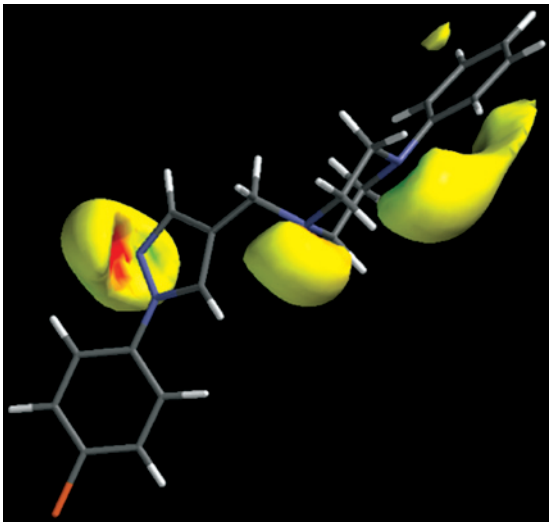
Equipment for analysis of respiratory mechanics in vivo

Equipment for analysis of diaphragmatic function

LASSBIO-579: A NEW *N*-PHENYLPIPERAZINE ANTIPSYCHOTIC LEAD COMPOUND

Research teams of LASSBio-579:
Principal researchers: Stela M. K. Rates (UFRGS); Carlos Alberto Manssour Fraga (UFRJ); Eliezer J. Barreiro (UFRJ); François G. Nöel (UFRJ); Ricardo Menegatti (UFG).
Collaborators: Manoel O. de Moraes (UFC); Letícia V. Costa-Lotufo (UFC), Claudia do Ó Pessoa (UFC); Teresa Dalla-Costa (UFRGS); Valéria Oliveira (UFC).

Considering that more effective and safer drugs to treat schizophrenia are still needed our team research has been working in a research program aiming the development of new atypical antipsychotic drugs.



Firstly we described the design and synthesis of three *N*-phenylpiperazine derivatives LASSBio-579 (1), LASSBio-580 (2) and LASSBio-581 (3) which differ by the isosteric replacement between pyrazole and 1,2,3-triazole heterocyclic rings. These compounds were originally proposed to be selective ligands for the D2 and/or D4 receptors as they resulted from hybridization of the lead compounds clozapine and L-741.

An initial pharmacological evaluation demonstrated that 1 and 3 act as agonists at pre-synaptic dopamine D2-like receptors while 2 acts as antagonist at the same receptor (Menegatti et al., 2003). We also showed that compound 1 (30 mg/kg ip) inhibits the induction of stereotyped behavior by amphetamine in rodents, an effect predictive of efficacy for treating the positive symptoms of schizophrenia (Neves et al., 2003).

These data generated Patent Request Nº PI PI04055418-0 filed on Septembre 05th, 2004, at the Instituto Nacional de Propriedade Intelectual (National Institute for Intellectual Property). BR

Subsequently, an independent research group (Löber et al., 2006) showed that compound 5 (Fig.1 and Neves et al., 2010) has a high affinity for the D4 receptor, presenting a Ki value of 9.9 nM and a selectivity ratio of 86–150 when compared to other D2-like receptors. However, by using in vivo studies we have demonstrated that 1 and 3 modify behaviors and pharmacological effects mediated by dopaminergic and serotoninergic neurotransmission in rodents, more specifically associated with D2-like, 5-HT1A, and 5-HT2A/C receptors (Neves et al., 2003; Neves et al., 2008) pointing to a pharmacological profile characterized by the involvement of multiple receptors as seen in atypical antipsychotic drugs.

Thus the molecular scaffold of compounds 1 and 3 was explored in the search of new antipsychotic lead-compounds with a multi-target profile. The molecular diversity of the compounds was achieved in three different subunits of the basic scaffold: (a) isosteric replacement of the heterocyclic ring at the biaryl motif generating pyrazole, 1,2,3-triazole and 2-methylimidazole[1,2-a] pyridine analogues, (b) addition of different substituents at the *para*-biaryl position (W), and (c) substitution at the *para*-phenylpiperazine position (Y) (Fig.1; Neves et al., 2010).

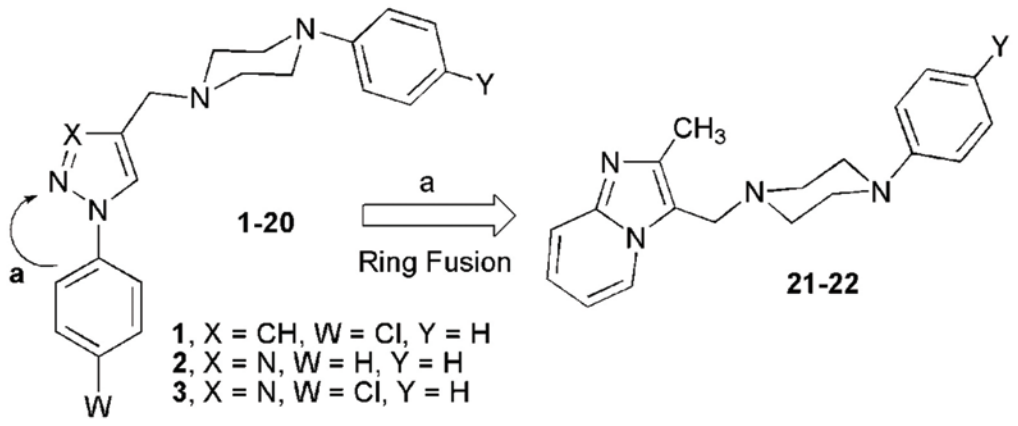


Fig. 1. Molecular diversity of functionalized N-phenylpyrazole, N-phenyl-1,2,3-triazole, and imidazo[1,2-a]pyridine N-phenylpiperazine derivatives (1–21).

Out of twenty one new derivatives, LASSBio-579 (1) and its 4-fluorophenyl analogue LASSBio-664 exhibited the highest affinity for D2-like (Ki around 100 nM) and 5-HT1A (Ki around 50-90 nM) receptors. In mice, these derivatives demonstrated a potential for treating positive symptoms of schizophrenia, since they inhibited apomorphine-induced climbing behavior (Fig. 2) at doses that they were devoid of cataleptogenic effects (Neves et al., 2010). Data from LASSBio-579 are showed in the Figures 3 and Table 1.

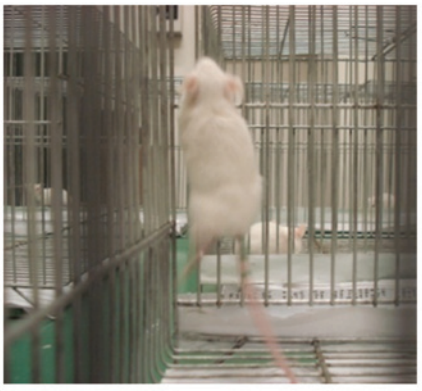


Fig.2. Mice climbing behavior

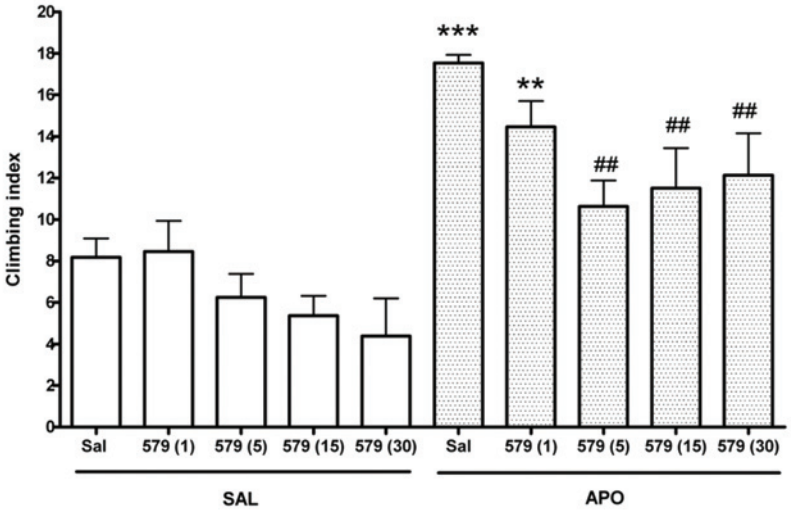


Fig.3. Dose-effect curve of LASSBio-579 (1, 5, 15 and 30 mg/kg p.o.) on apomorphine-induced climbing in mice. Results are expressed as means ± error. APO: apomorphine (1 mg/kg i.p.); SAL:saline

LASSBio-579 acute toxicity was evaluated by LD_{50} determination. In this procedure, the OECD and ICH recommendations for maximum dose administration were followed (OECD, 2001a; ICH, 2008). The most important alterations observed were palpebral ptosis and immobile behavior, signs commonly associated to antidopaminergic drugs. The calculated LD_{50} value was 1405 ± 173 mg/kg i.p. According to this result, LASSBio-579 can be classified as category 4 according to the Global Harmonized Classification System (LD_{50} between 300 and 2000 mg/kg) (OECD, 2001b). Comparing this value with data for haloperidol (mice LD_{50} = 60 mg/kg i.p.) and clozapine (mice LD_{50} = 61 mg/kg i.v. and 199 mg/kg p.o.) (Budavari, 1996) we can assume that LASSBio-579 has a minor acute toxicity.

Table 1. Effect of LASSBio-579in the catalepsy test

Treatment (oral route)		Catalepsy (s)		
		30 min	60 min	90 min
Vehicle		1.8 ± 1.1	2.7 ± 2.9	2.4 ± 2.6
LASSBio-579	30 mg/kg	3.9 ± 2.7	13.4 ± 19.2	10.5 ± 9.2
Clozapine	15 mg/kg	23.4 ± 36.5	12.0 ± 8.1	3.5 ± 8.7
Haloperidol	4 mg/kg	54.4 ± 68.2**	89.7 ± 79.1***	105.0 ± 75.9***

Data are expressed as mean ± S.D. Two-way repeated measure ANOVA (treatment factor $F_{8,269}$=11.620 P<0.001; time factor $F_{2,269}$=5.537 P=0.006; treatment x time interaction $F_{16,269}$=2.608 P=0.001): different from vehicle+vehicle group at the same time of measure in post-hoc test, **p<0.01 ***p<0.001.

Since clozapine-induced agranolucytosis is a main limitation for its clinical use, hematological parameters were evaluated after LASSBio-579 repeated doses administration to rats (30 mg/kg i.p. during 14 days). The values of hematocrit, hemoglobin and differential leukocyte count were in accordance with rat's normal range and there were no relevant difference between LASSBio-579 and vehicle treated animals. In addition, bone marrow histological analysis did not show any difference between treated and control animals. Rats body weight did not differ between treatment groups and signs of toxicity were not identified during the treatment. These data suggest that LASSBio-579 presents low toxicity (Neves, 2003).

Altogether these results so far characterize LASSBio-579 as an antipsychotic lead compound with a preclinical pharmacology predictive of efficacy for treating schizophrenia positive symptoms and with advantageous side effects profile, when compared to current therapeutic arsenal.

LASSBio-579 (hydrochloride) pharmacokinetic profile was determined in rats (Conrado et al., 2008). It showed a limited oral bioavailability and lower brain penetration suggesting that its Central Nervous System activity may be due to a specific distribution into brain structures or active metabolites. Identification of LASSBio-579 main metabolites and its pharmacological evaluation are in progress. Furthermore, considering that pharmacokinetic evaluation was performed in rats whereas pharmacodynamic studies were conducted in mice mainly, pharmacokinetic evaluation in mice is planned.

Looking ahead, we carried out a theoretical study to estimate the LASSBio-579 first doses in human for clinical trials. It was tentatively performed based on the minimal climbing effective dose (ED) and on the maximal dose that did not cause catalepsy in mice (assumed as NOAEL: no obseved adverse effect level). The projected doses ranged from 3 to 70 mg (Antonio et al., 2009).

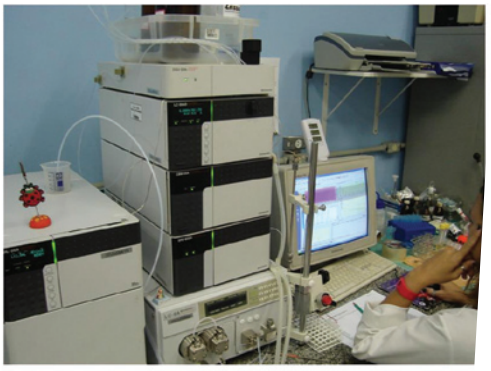
At this moment our project focuses on the investigation of the effect of LASSBio-579 on animal models of schizophrenia coginitive and negative symptoms as well as on the pharmaceutical strategies to improve its bioavailability. Besides we are evaluating new functionalized N-phenylpiperazine derivatives with potential antipsychotic activity in search of compounds with more favorable pharmacokinetic profile and innovative mode of action.

Professor Rates, S. M. K . team

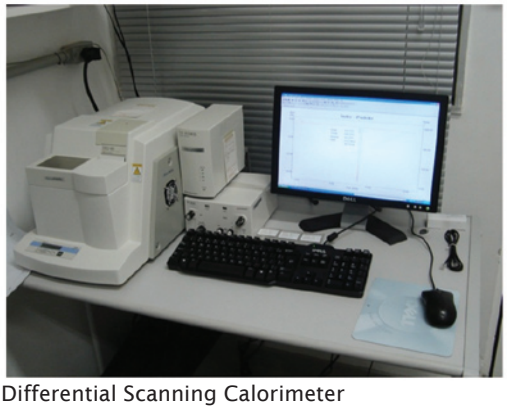
Professor Nöel F. G. team

LASSBio team

Laboratory of organic synthesis



HPLC



Differential Scanning Calorimeter

Elemental analysis equipment (CHN)

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Agilent

EXTENSION ACTIVITIES

SCIENTIFIC AWARENESS & HEALTH EDUCATION

The promotion and popularization of Science and Technology is a factor of evident importance in the construction of a critical awareness in the current globalized world, allowing, mostly among young populations, that new vocations be displayed, including those that are unrelated to their family environment.

Diverse actions that demystify Science within the community, highlighting its importance in our daily well-being, can represent a cultural broadening of horizons, while increasing citizenship.

The INCT of Drugs and Medicines (INCT-INOFAR) believes that it is just as important to build up critical awareness within the population as to the benefits and risks that the new discoveries of the pharmaceutical industry are, as it is to increase knowledge in the area of pharmaceutical and medication know-how. This is why it invests in scientific awareness and health education initiatives.

When it identifies the medication – an essential instrument in the preservation, maintenance, and promotion of Health – as a fruit of scientific knowledge, INCT-INOFAR promotes the understanding of what Science represents in the daily lives of the population, and it stimulates their interest in this subject.

PHARMACEUTICALS WEBSITE

www.portaldosfarmacos.ccs.ufrj.br

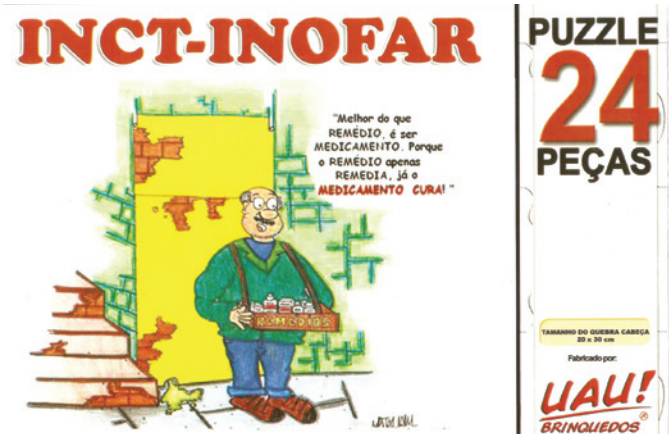
The Pharmaceuticals Website is the channel for scientific awareness and health education by INCT-INOFAR. The website acts as an observatory into the Institute's research projects, with the aim to make Pharmaceutical Sciences and related areas more popular and publicized, through the practice of scientific journalism. To enhance health education, the Pharmaceuticals Website develops educational tools, contributing to increasing critical awareness in the population about the correct use of medications.

In the Pharmaceuticals Website, the population can keep up with coverage of scientific events, as well as have access to never before released reports on up to date topics concerning innovation in pharmaceuticals and medication, as well as health in general. In 2009, the Pharmaceuticals Website produced 26 scientific journalism reports. Among these, 15 were coverage of scientific-academic events relevant to the area of pharmaceuticals and medications.

Among the topics dealt with in these reports, we wish to highlight: doping, neglected diseases, stem cell related therapies, HIV resistance, natural phytotherapeutic products, medicinal chemistry, pharmaceutical innovation, pre-clinical assays, scale transposition, advertisement for medications, and several reports on bioactive molecules discovered within university environments that represent potential candidates for the production of new medications.

With the goal of increasing scientific awareness, the Pharmaceuticals Website is a space where young researchers can write articles and reviews, in language specific for a layman public, about the important discoveries published in renowned scientific articles in the field of pharmaceuticals and medications. It functions as a way to encourage future scientists to create their own methodologies to create societal awareness of the knowledge acquired within university environments.

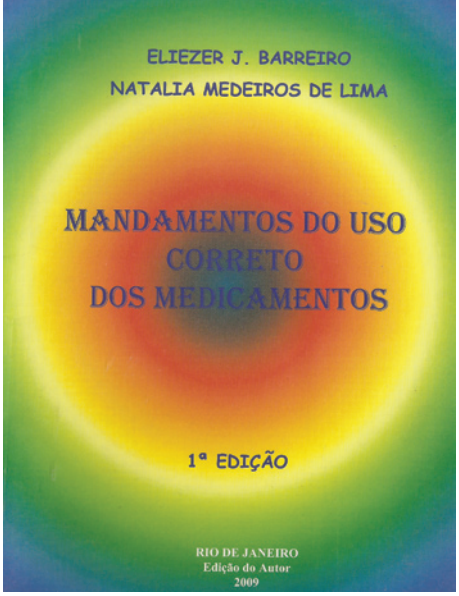
To provide useful information to the population on the adequate use of pharmaceutical products, the Pharmaceuticals Website publishes monthly cartoons that criticize the irrational use of medications, and that propose conscious alternatives for their consumption. On the site, it is also possible to download a guidebook on the correct use of medications that was produced by INCT-INOFAR.



PUZZLE

In an attempt to develop a teaching material that was also a game to increase awareness of the correct use of medications, INCT-INOFAR made the cartoons published in the Pharmaceuticals Portal and in their Guidebook into puzzles. A total of five versions of these theme games have already been produced.

Among the themes of the puzzles are the influence of pharmaceutical industry advertisement and the attention that must be paid to avoid purchasing counterfeit drugs.



ISBN: 978-85-910137-1-5

GUIDEBOOK

With colorful illustrations and simple and dynamic language, INCT-INOFAR produced, in October 2009, the guidebook "Guidelines on the Correct Use of Medications", to increase awareness of the risks associated with medications. In an educational way, the material provides guidance on different levels of prescriptions, talks about where and how to correctly store medications, and highlights possible abuse in advertisement perpetrated by the pharmaceutical industry.

At the end of the guidebook, children can enjoy a fun activity as they also learn the information presented through education games designed by pharmacists Natalia Medeiros, who authored the project. The goal is that the educational material can be enjoyed as a family, so that parents, children, and even neighbors and extended family may have access to information on the importance of the correct use of medications, and can therefore change their attitudes regarding irrational consumption of pharmaceutical products.

VIDEO

In March 2009, INCT-INOFAR produced the video "LASSBio 596: from molecule to medication".

At 13 minutes, the scientific promotion short film mixes fiction and science to tell the story of a substance developed by the Institute to fight asthma - LASSBio 596 – presenting all the research stages necessary for the medication to be available in drugstores.

In the script, the character Sonia – who became aware of the research work developed by Prof. Eliezer Barreiro, INCT-INOFAR coordinator, on a TV report – phones the scientist asking him if he cannot develop a better medication for her son's asthma, because the boy was not responding to any medication.

That is the hook for telling the story of LASSBio 596. In the video, all the required stages for the production of a medication are detailed. At each stage, a different INCT-INOFAR researcher describes the process.

* The video "LASSBio 596: from the molecule to the medication" is available on YouTube and on the INCT-INOFAR website at www.inct-inofar.ccs.ufrj.br.

INCT-INOFAR IN THE COMMUNITY

INCT-INOFAR always tries to be present in events to increase awareness of the benefits and risks involved in the use of medication.

On June 20, 2009, the day of the national vaccination against poliomyelitis campaign, the INCT-INOFAR/Pharmaceuticals Portal team took part in the "Fiocruz for you" event, carrying out educational playful activities with the children and their parents, to increase awareness of the proper usage of medication. Drawings and paintings depicting how children see medications were collected as a result of this action.

At the 3rd Brazilian Congress on the Rational Use of Medications, which took place in Fortaleza/CE in October 2009, INCT-INOFAR/Pharmaceuticals Portal released a guidebook "Rules of the correct use of Medications". What was supposed to be just a promotion of the INCT-INOFAR activities with academics and health professionals ended up attracting laypeople working in the event, such as the cleaning crew, kitchen workers, wait staff, loading workers, as well as actors dressed up as folk characters "Lampião" and "Maria Bonita" all visited the panel and took home a copy of the guidebook, with the promise to pass its knowledge on the basic use of medications along to family and friends

EVENTS

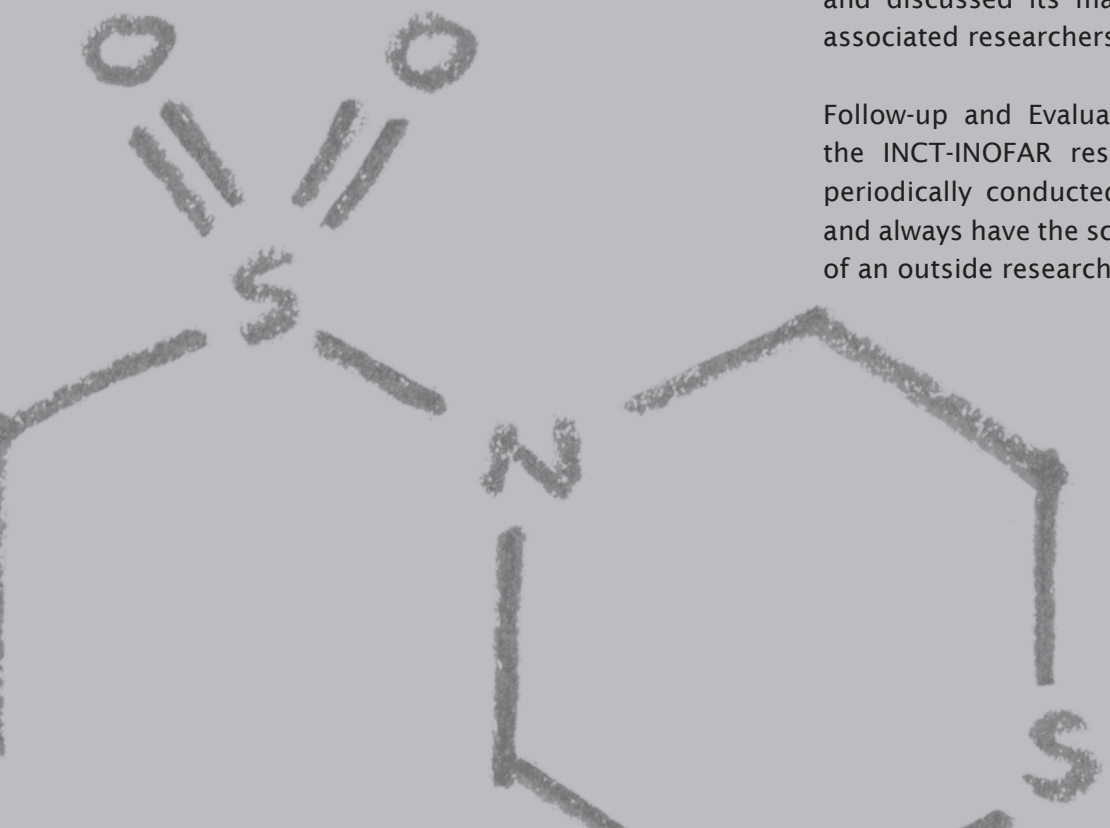
The National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR) periodically organizes events with a goal of strengthening cooperation between its research groups, stimulating integration with other INCTs, and attempting to establish partnerships with companies, NGOs, and institutions.

INCT-INOFAR researchers constantly take part in scientific events, teaching courses, giving lectures, taking part in workshops and round table discussions, and contributing for the promotion of scientific knowledge in person, as well as authoring papers. In parallel to these actions, the Institute supports courses and conferences, actively cooperating with the enhancement of human resources in Brazil and the advancement of research in new medications.

INOFAR WORKSHOPS

On March 06, 2009, INCT-INOFAR conducted its commencement workshop with the presence of the presidents of CNPq and FAPERJ, respectively Prof. Marco Antonio Zago, and Prof. Ruy Garcia Marques. At the event, the coordination and vice-coordination of INCT-INOFAR presented the directives for the Institute and discussed its main points with the associated researchers.

Follow-up and Evaluation Workshops of the INCT-INOFAR research projects are periodically conducted in Rio de Janeiro and always have the scientific consultancy of an outside researcher.



Marco Zago (President of CNPq), Fernando Cunha (Vice-Coordinator of INCT-INOFAR), Eliezer Barreiro (Coordinator of INCT-INOFAR) and Ruy Marques (President of FAPERJ)

Marco Zago (President of CNPq)

Commencement Workshop INCT-INOFAR

INCTS INTEGRATION WORKSHOP

I5+

With a goal of discussing governance in INCTs and fostering bonds of scientific and technological cooperation in research, human resources qualification, and scientific promotion, INCT-INOFAR became a member of the so-called I5+, made up of the Complex and Functional Materials INCT, the Continent-Ocean Transference of Materials INCT, the Science and Technology of the Biorational Control of Insects and Pest INCT, and the Energy and Environment INCT.

The first meeting of the I5+ took place in Bahia, in November 2009, and the second one, in Natal/RN, on July 27, 2009, during the 62nd Annual Meeting of the Brazilian Society for the Progress of Science (SBPC).

TRIAD PARTNERSHIP

On December 3 and 4, 2009, in Rio de Janeiro, an Integration Panel between the INCT (INOFAR) of Drugs and Medicines, the Structural Biology and Bioimaging INCT (INBEB) and the Structural Biology and Medicinal Chemistry in Infectious Diseases (INBEQMed) took place. At the event, scientists from the three INCTs presented research projects, trying to identify academic-scientific meeting points for the establishment of future partnerships.

SUPPORT TO EVENTS

SUMMER SCHOOL IN MEDICINAL AND PHARMACEUTICAL CHEMISTRY

Traditionally organized by the Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), the Summer School in Medicinal and Pharmaceutical Chemistry was incorporated by INCT-INOFAR as an extension and continuous education activity, for undergraduate as well as graduate students.

The event, which is always conducted during summer vacation, in the Health Sciences Center of UFRJ, offers 5 consecutive days of courses and conferences with renowned national and international specialists in the field of Medicinal Pharmaceutical Chemistry. Since its establishment in 1995, it has had over 2,000 participants and has received renowned scientists responsible for the development of innovative medications, such as Simon Campbell (sildenafil) and Robin Ganellin (cimetidine), who have related the stories of their discoveries in person.

COURSES OFFERED BY THE SUMMER SCHOOL 2009
- Introduction to Medicinal Pharmaceutical Chemistry
- Metabolism of Pharmaceuticals and Toxicity
- Planning of Pharmaceuticals for the Treatment of Neglected Diseases
- Computational Chemistry and Molecular Modeling
- Patents and Pharmaceutical Innovation
- Highlights in Medicinal Chemistry

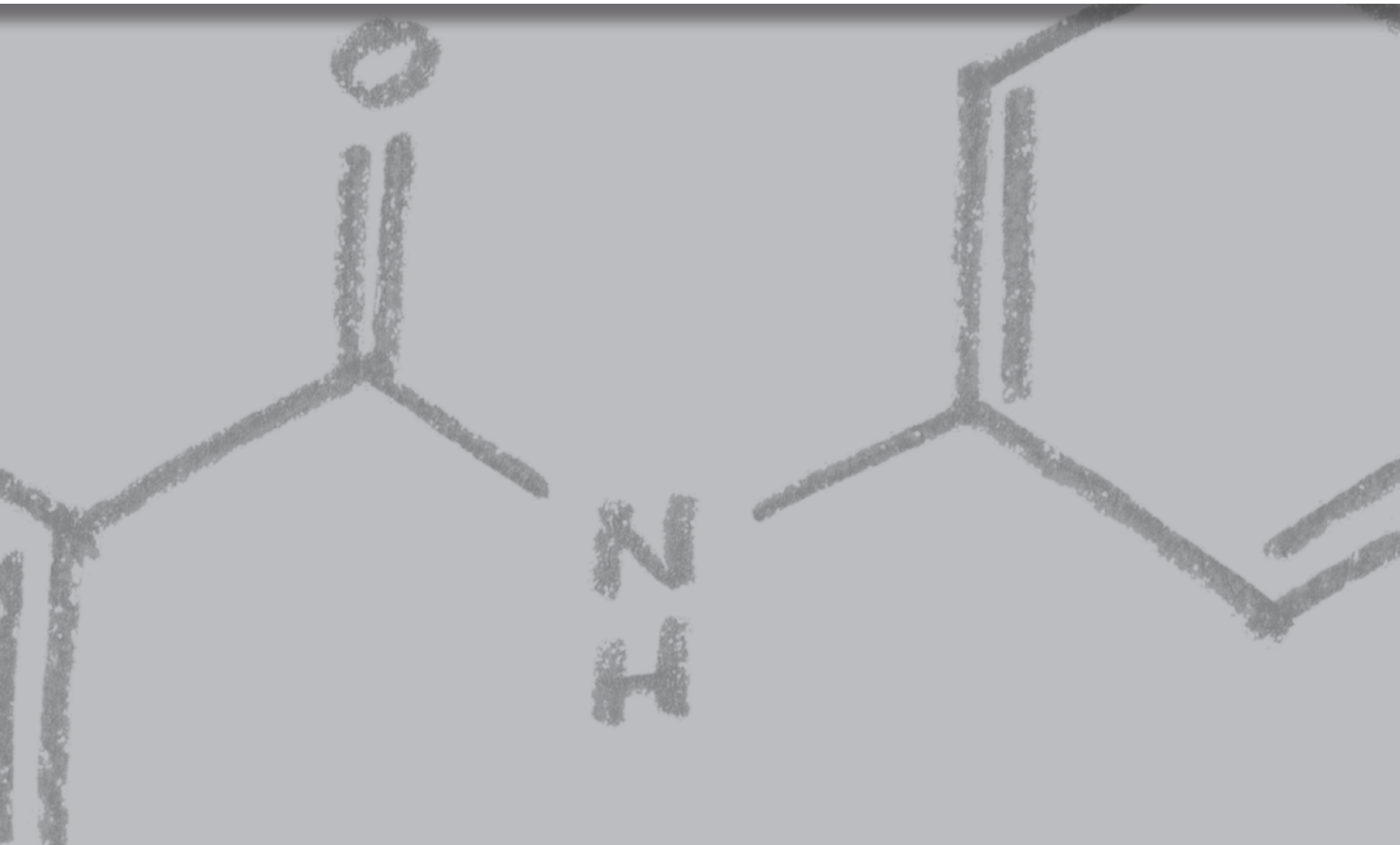
INTERNATIONAL CONFERENCES
- Stefan Laufer (University of Tubingen – Germany)
- Hugo Cerecetto (Universidad de La Republica – Uruguay)

COURSE "FROM GRAM TO KILOGRAM"

In December 2009, within the scope of the Regional Meetings of the Brazilian Society of Chemistry (SBQ), INCT-INOFAR sponsored the course "From Gram to Kilogram: the challenges of scale expansion" in the cities of Rio de Janeiro and Porto Alegre, taught by an expert in the field, Dr. Angelo Machado, who at the time was a member of the Pharmacochemical Division of Cristalia Laboratories.

CRACK FORUM

The Pharmaceuticals Development Program of the Institute of Biomedical Sciences of UFRJ conducted on December 07, 2009, with the support and participation of INCT-INOFAR researchers, the first meeting of the Forum titled "Crack – The Progressive Destruction of society: Can Academia help?". The event had the goal of making academic researchers more familiar with the various facets of this form of chemical dependence, to generate research projects aimed at developing possible antagonist pharmaceuticals to fight crack cocaine dependence.



Crack Forum

From Gram to Kilogram

SCIENCE PROMOTION

The promotion of activities in scientific journalism and health education are conducted by INCT-INOFAR in the academic-scientific community through the presentation of poster in events concerning the areas of Pharmacy and Scientific Promotion. In 2009, INCT-INOFAR presented their extension activities at:

XI REUNIÓN DE LA REDPOP

Network for the Popularization of Science and Technology in Latin America and the Caribbean
May 2009. Montevideo, Uruguay

3rd BRAZILIAN CONGRESS ON THE RATIONAL USE OF MEDICATIONS

October 2009. Fortaleza/ CE

INCT-INOFAR PRESENCE IN EVENTS

March 30 to April 4, 2009
Federal University of Ouro Preto
II Congress of Pharmaceutical Sciences of Ouro Preto (CONCIFOP)
Prof. Eliezer J. Barreiro

April 17, 2009
Federal University of São Carlos
Lecture: "The Discovery of New Prototypes for Symbiotic Pharmaceuticals"
Prof. Eliezer J. Barreiro

April 30, 2009
FIOCRUZ
SIBRATEC Meeting – Pharmaceuticals and Medications Network
Prof. Eliezer J. Barreiro

May 27, 2009
Federal University of Rio de Janeiro – Institute of Chemistry
Lecture: "This wonderful and exciting Organic… Chemistry"
Prof. Luiz Carlos Dias

June 15, 2009
Federal University of Sergipe
II Sergipe Meeting of Chemistry
Lecture: "This wonderful and exciting Organic… Chemistry"
Prof. Luiz Carlos Dias

July 02, 2009
University of Aveiro – Portugal
National Organic Chemistry Congress
Lecture: "Addition of boron enolates generated from methyl ketones to aldehydes. Recent progress towards the total synthesis of bioactive natural products"
Prof. Luiz Carlos Dias

July 07, 2009
University of Seville – Spain
Lecture: "Addition of boron enolates generated from methyl ketones to aldehydes. Recent progress towards the total synthesis of bioactive natural products"
Prof. Luiz Carlos Dias

July 10, 2009
University of Alicante – Spain
Lecture: "Addition of boron enolates generated from methyl ketones to aldehydes. Recent progress towards the total synthesis of bioactive natural products"
Prof. Luiz Carlos Dias

July 12 to July 17, 2009
Federal University of Amazonas
61st Meeting of the Brazilian Society for the Progress of Science – SBPC
Prof. Eliezer J. Barreiro

August 10, 2009
State University of São Paulo - UNESP – São Jose do Rio Preto
Commencement Speech of Graduate Program in Chemistry at UNESP
Lecture: "Graduate Education in Chemistry in Brazil and the CAPES Evaluation"
Prof. Luiz Carlos Dias

September 9, 2009
Secretary of Research and Development Policies and Development
Meeting of the SIBRATEC Headquarters of Pharmaceuticals and Medications Nucleus
Prof. Eliezer J. Barreiro

September 15, 2009
Reboucas Convention Center of the School of Medicine Foundation – São Paulo
2nd National Meeting of Innovation in Pharmaceuticals and Medications – ENIFarMed
Prof. Eliezer J. Barreiro

September 18, 2009
Federal University of the São Francisco Valley
II Symposium on Planning and Discovery of Pharmaceuticals
Prof. Eliezer J. Barreiro

September 22, 2009
Cristalia Chemical Pharmaceutical Products Ltd.
Opening Ceremony of the Research, Development, and Innovation Center
Prof. Eliezer J. Barreiro

September 25, 2009
University of São Paulo - USP
1st Symposium on Planning and Development of Pharmaceuticals for Neglected Diseases
Prof. Eliezer J. Barreiro

October 08 and 09, 2009
Institut Pasteur - France
DNDi Scientific Committee
Prof. Eliezer J. Barreiro

October 22 and 23, 2009
State University of São Paulo – UNESP - Araraquara
39th Chemistry Week
Prof. Eliezer J. Barreiro

November 09, 2009
INCA - National Cancer Institute
Lecture: "The National Institute of Science and Technology of Drugs and Medicines – INCT-INOFAR, its contribution to pharmaceutical innovation and multidisciplinary education"
Prof. Eliezer J. Barreiro

November 27, 2009
Federal University of Alagoas - UFAL - Maceió
1º Workshop em Educação e Ciências Farmacêuticas (1st Workshop in Education and Pharmaceutical Sciences)
Prof. Eliezer J. Barreiro

SCIENTIFIC PUBLISHING 2009

ARTICLES PUBLISHED IN JOURNALS

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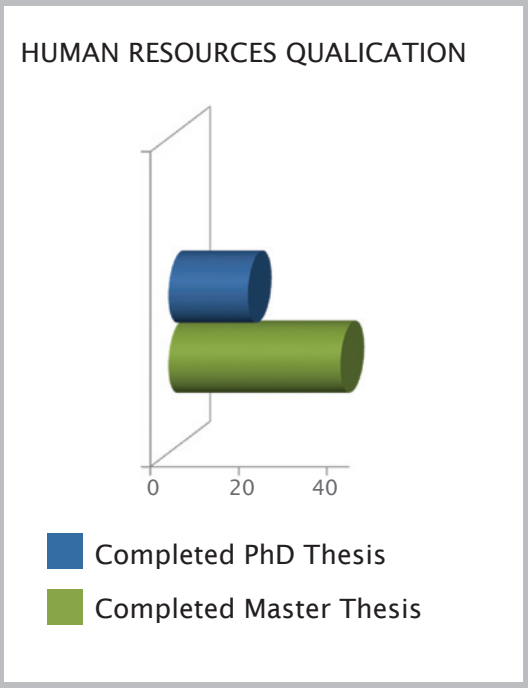

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