INCT OF DRUGS AND MEDICINES

ANNUAL ACTIVITIES REPORT

2014

08 States

30 Research Groups

05 Associated Companies

79 Researchers

32 CNPq Researchers

04 International Institutions

71 Scholarship Researchers

15 Scientific Institutions

2014

INCT - INOFAR

ANNUAL ACTIVITIES REPORT

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A613a

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I. INCT-INOFAR

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www.inct-inofar.ccs.ufrj.br

SUPORT

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

ABOUT THE COVER

"The fear thou art in, Sancho," said Don Quixote, "prevents thee from seeing or hearing correctly, for one of the effects of fear is to derange the senses and make things appear different from what they are."

Miguel de Cervantes, Don Quixote

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Summary

"I invite you to check by reading this 2014 edition of Annual Activities Report (AAR-2014), the successes achieved in both aspects of innovation in drugs and medicines."

Eliezer J. Barreiro

2014

INCT-INOFAR | ANNUAL ACTIVITIES REPORT

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Editorial

The **National Institute of Science Technology on Drugs and Medicines (INCT-INOFAR)** observed significant results in the period of January to December 2014. Expected to be completed in December 2014, the original project was extended until December 2015, by approval of the Conselho Nacional de Pesquisa e Desenvolvimento (National Council of Research and Development - CNPq/BR). The quest for prolongation was a decision of the **INCT-INOFAR** Board of Governance and Monitoring (**CGA**) and was motivated on the uncertainty of the launch of new Notice by the Agency, which would allow new competition, that if successful allows the continuation of research efforts so far made. The continuity of the **INCT-INOFAR´s** subprojects is essential to this research network built around the innovation chain in drugs and medicines in Brazil and represents the greatest asset **INCT-INOFAR**. It is not up to this editorial adopt the colors of the "wailing wall", but it is undeniable that the eventual lack of continuity of the project has promoted a reduced the work momentum of all, especially of the researchers involved in the most advanced subprojects.

I invite you to check by reading this 2014 edition of **Annual Activities Report (AAR-2014)**, the successes achieved in both aspects of innovation in drugs and medicines. On the radical innovation by identifying new molecules as drug candidates of different possible therapeutic indications and on the incremental innovation by studying vertical, total and integrated synthetic routes to generic drugs as quetiapine, fluoxetine and valsartan, completed by **INCT-INOFAR** teams during 2014.

Reading the **Highlights** section of this **AAR-2014** you will see the most significant results that could be made public, obtained in some of the subprojects in study. The list of publications made by the team of **INCT- INOFAR** researchers allows the query to the set of results produced, giving the size of their research interests, in addition to the subprojects developed under **INCT-INOFAR**. Similarly, the consultation of dissertations and thesis completed successfully by numerous masters and doctoral students, under the guidance of researchers **INCT-INOFAR**, spread across various graduate programs throughout the country, will reveal their academic interests and the excellence of the work done.

Included in this **AAR-2014**, following all previous, the main activities of outreach carried out by the **INCT-INOFAR** in this the period.

This **AAR-2014** was constructed by the effort, dedication and hard work, of all staff members and researchers of the **INCT-INOFAR**, to whom I thank strongly. To all members of **INCT-INOFAR/CGA** my best acknowledgements for the excellent job done.

I wish great read at all.

Eliezer J. Barreiro
SCIENTIFIC COORDINATOR OF **INCT-INOFAR**

Rio de Janeiro, April 27, 2015.

2014

INCT-INOFAR
ANNUAL ACTIVITIES REPORT

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2014

INCT-INOFAR | ANNUAL ACTIVITIES REPORT

Presentation

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Presentation

National Institutes of Science and Technology Program (INCT)

In 2008, the Brazilian government published the announcement MCT/CNPq no014/2008 with a goal of recruiting scientists to work in networks, in research areas strategic for the sustainable development of the country. The public notice has been, so far, the one to most greatly support Science and Technology in Brazil.

At the time, part of the scientists associated with the Millennium Institute of Innovation and Development of Drugs and Medicines (IM-INOFAR) took on the challenge and submitted a new project to the public notice of the National Institutes of Science and Technology (INCTs). That is how the Drugs and Medicines INCT was established (**INCT-INOFAR**).

As in the case of **INCT-INOFAR**, 126 National Institutes of Science and Technology (INCTs) have been established. Articulating laboratories or associated research groups from different parts in the country, INCTs have the mission of acting in different areas of strategic importance for national sovereignty. **INCT-INOFAR** is in charge of health research aimed at the discovery of new drugs and medicines.

Drugs and Medicines INCT (INCT-INOFAR)

The National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) is a research network that brings together renowned scientists from different research institutions and universities in Brazil. Its mission is to act in the discovery of new drugs and medicines, as well as new synthesis routes for generic drugs, and also to work for the professional education of graduate and undergraduate students in Medicinal Chemistry and Pharmacology, key disciplines for the process of drug discovery.

Made up of nearly one hundred scientists from 30 research groups with efforts focused on radical pharmaceutical innovation and incremental innovation in generic drugs, **INCT-INOFAR** is present in 15 teaching and research institutions in 8 different Brazilian states.

With a task of qualifying personnel to work in important stages of the process of discovery/invention of new drugs – from the choice of therapeutic target to the conclusion of pre-clinical bioassays - **INCT-INOFAR** contributes to the identification and solving important bottlenecks in the chain of pharmaceutical innovation.

Parallel to the laboratory research, **INCT-INOFAR** also acts in society, promoting science and encouraging the rational and responsible use of drugs through health education actions. It also maintains the Drugs Portal, a website created to promote Pharmaceutical Sciences in the academic community and in society at large.

Mission

- To organize national scientific competencies in an effective and productive network of research in drugs and medicines;
- To support scientific research subprojects in the chain of innovation in drugs and medicines;
- To act in incremental innovation in drugs through generics;
- To study and develop new total synthesis routes for current and future generic drugs, advanced intermediates and strategic raw materials for the sector;
- To contribute for the scientific qualification of personnel in Medicinal Chemistry & Pharmacology;
- To promote scientific awareness related to the use of drugs and medicines, therefore contributing effectively for their rational and safe use.

INVESTING IN RADICAL AND INCREMENTAL PHARMACEUTICAL INNOVATION

With the contribution of its entire research network, **INCT-INOFAR** studies and develops several radical innovation subprojects and also acts in incremental innovation, studying new total synthesis routes for generic drugs.

In the field of radical innovation, the Institute aims to discover/invent original substances, active in *in vivo* widely validated pharmacological models able to originate new drug candidates in several pharmaceutical classes. The different research areas of interest to **INCT-INOFAR** are: inflammation, pulmonary diseases, pain, central nervous system, cardiovascular system and chemotherapy of cancer and of neglected diseases, particularly leishmaniasis.

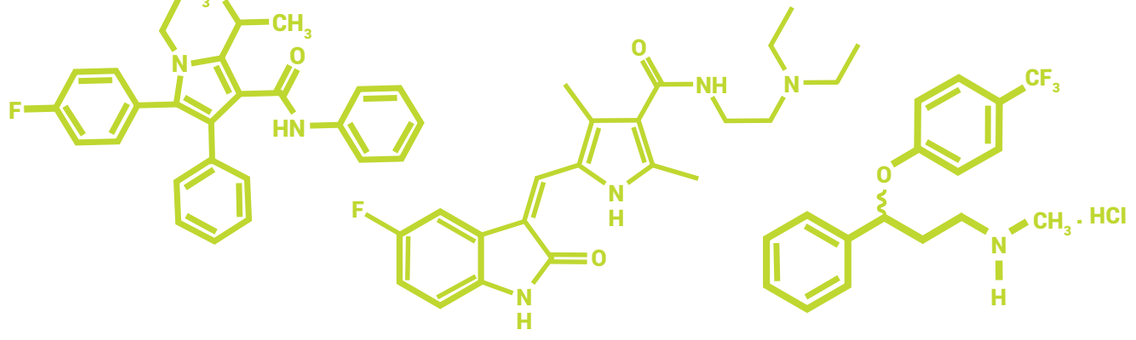
In the field of incremental innovation, **INCT-INOFAR** leads projects that are focused on the search for new synthetic routes, efficient and accessible, for generic drugs already in the market as well as for those about to have their patent protections expired, representing, by their market share, new business opportunities for the Brazilian pharmaceutical sector.

Innovation in new generic routes

In spite of advances after nearly 14 years of the Law of Generic Drugs (no 9.787/1999) in Brazil, unfortunately so far Brazilian pharmaceutical companies as a whole are limited to formulating and packaging active principles important from far away markets like China, India, and Korea. Working hard to try to reverse this "Indian Pathway" process, **INCT-INOFAR** makes efforts in the study and development of total synthesis routes for generic drugs with a goal of transferring the technology acquired to the local industry.

By studying and developing total synthesis routes of generic drugs, advanced intermediates and strategic raw materials for the sector, **INCT-INOFAR** researchers pave the way for the production of active principles of drugs that are important instruments for health care policies and for the population. Since its creation, in 2009, **INCT-INOFAR** has already developed new synthesis routes for the active principles of three drugs.

"INCT-INOFAR" Generic routes



ATORVASTATIN – In the same month when the patent for Lipitor™ /Pfizer expired in Brazil (December, 2010), **INCT-INOFAR** researchers announced the discovery of a new synthesis route for its active principle, atorvastatin. A continuous use drug for cholesterol reduction, Lipitor™ has been the best-selling drug in history. The synthesis route of atorvastatin has been patented, and represents an important technological asset for **INCT-INOFAR**, which has been trying to negotiate the production of this generic drug with a Brazilian pharmaceutical company ever since.

SUNITINIB – Recommended for certain types of stomach cancer, sunitinib is the active principle of Sutent™/Pfizer, a high cost drug, which is unfortunately not yet available in the Public Health Care System (SUS) and that is, therefore, the subject of several court cases, as it is the primary drug recommended for these cases. The sunitinib synthesis route was completed by **INCT-INOFAR** in September 2011. With the discovery, Brazil can prepare to produce the medication before the patent for the drug expires, reducing production cost.

FLUOXETINE - Antidepressant drug from the selective serotonin reuptake inhibitor class, fluoxetine was marketed by Eli Lilly under the name Prozac™, until its patent expired in Brazil, in 2001. Considered the controlled drug with the highest demand in the Public Health Care System, most fluoxetine consumed in Brazil is imported. Considering the social and market impacts of this drug, the technological know-how of the fluoxetine synthesis is an important **INCT-INOFAR** achievement.

MULTIDISCIPLINARY RESEARCH NETWORK

The process of innovation in drugs has clear interdisciplinary and multidisciplinary characteristics, demanding competencies in distinctive areas of Health Sciences.

INCT-INOFAR brings together, in a network, research groups of academic-scientific excellence, in different areas, covering all stages of the process of invention of new drugs, ranging from the election of the therapeutic target to the conclusion of pre-clinical stage bioassays, quantitative and qualitative analytical methods, as well as clinical pharmacology.

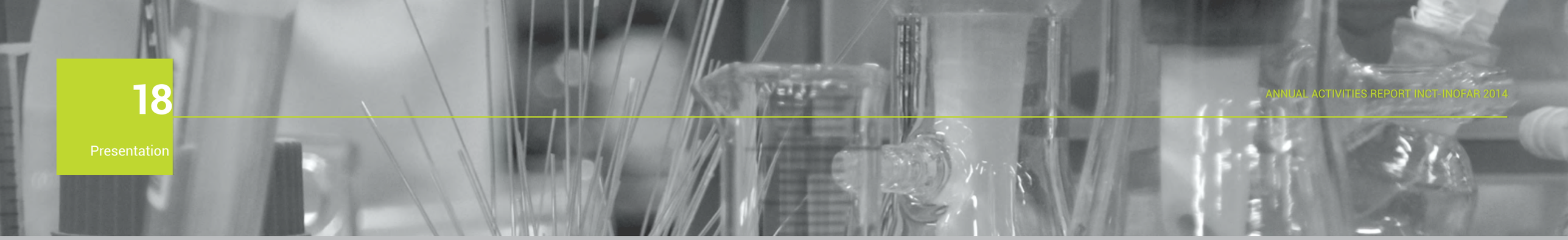
The **INCT-INOFAR** multidisciplinary team is made up of experts in different subjects, like Medicinal Chemistry, Pharmacology, Organic Chemistry, Toxicology, Organic Synthesis, Biochemistry, Computational Chemistry, Structural Biology, Spectroscopy, and Chemistry of Natural Products, among other related areas.

Scientific Exchange

Present in 15 teaching and research institutions, in eight different Brazilian states, **INCT-INOFAR** has actively contributed to diminish the regional scientific imbalance in Brazil, as well as to increase national expertise in a sector strategic to the country.

By making it possible for researchers from different institutions, in different geographical areas, to work together, **INCT-INOFAR** establishes an exchange between large centers and emerging research groups.

Cooperation is a way for **INCT-INOFAR** to contribute toward the increasing of scientific and technological production in emerging centers, especially in the Northeast and Midwest regions, benefitting the formation of undergraduate and graduate students in the field. Throughout the past 5 years, the scientific advancement of these emerging groups was notable.



INCT-INOFAR
LABORATORIES AND PERSONNEL IN CHARGE

Research Groups

NETWORK COORDINATOR:
Prof. Eliezer J. Barreiro (LASSBIO/UFRJ) Cv-Lattes

RIO DE JANEIRO

1. FIOCRUZ
Laboratory of Inflammation (IOC)
Marco Aurélio Martins CV-Lattes

Laboratory of Environmental Toxicology (ENSP)
Francisco José Roma Paumgartten CV-Lattes

2. UERJ
Department of Pharmacology (IBRAG)
Theresa Christina Barja-Fidalgo CV-Lattes

3. UFRJ
Laboratory of Evaluation and Synthesis of Bioactive Substances LASSBio (ICB)
Carlos Alberto Manssour Fraga CV-Lattes
Lidia Moreira Lima CV-Lattes

System of Information on the Chemical Industry – SIQUIM (EQ)
Adelaide Maria de Souza Antunes CV-Lattes

Laboratory of Pulmonary Investigation (IBCCF)
Patrícia Rieken Macedo Rocco CV-Lattes

Laboratory of Biochemical and Molecular Pharmacology (ICB)
François Germain Noel CV-Lattes

Laboratory of Cardiovascular Pharmacology (ICB)
Gisele Zapata Sudo CV-Lattes

Laboratory of Muscular Excitation-Contraction Coupling (ICB)
Roberto Takashi Sudo CV-Lattes

Laboratory of Natural Products and Chemical Transformations (IQ)
Angelo da Cunha Pinto CV-Lattes

Laboratory of Support to Technological Development (IQ)
Francisco Radler de Aquino Neto CV-Lattes

Laboratory of Pharmacology of Pain and Inflammation (ICB)
Patricia Dias Fernandes CV-Lattes

4. UFRRJ
Institute of Exact Sciences (IQ)
Carlos Maurício Rabello de Sant´Anna CV-Lattes

5. LNCC-MCTI
Group of Molecular Modelling of Biological Systems (Department of Computational Mechanics)
Laurent Emmanuel Dardenne CV-Lattes

SÃO PAULO

6. USP
Laboratory of Pain and Inflammation (Faculty of Medicine - Ribeirao Preto)
Fernando de Queiroz Cunha CV-Lattes

Laboratory of Design and Synthesis of Chemotherapeuticals Potentially Active on Neglected Diseases (Faculty of Pharmaceutical Sciences - Sao Paulo)
Elizabeth Igne Ferreira CV-Lattes

7. UNICAMP
Laboratory of Synthetic Organic Chemistry (IQ)
Luiz Carlos Dias CV-Lattes

MINAS GERAIS

8. UFMG
Group of Innovation in Organic and Inorganic Compounds with Pharmacological Activity (Department of Chemistry)
Heloísa de Oliveira Beraldo CV-Lattes

Laboratory of Experimental Toxicology (*in vitro* and *in vivo*)
Carlos Alberto Tagliati CV-Lattes

9. UNIFAL
Laboratory of Phytochemistry and Medicinal Chemistry (Faculty of Pharmacy)
Cláudio Viegas Junior CV-Lattes

Agency of Innovation and Entrepreneurship (Dean of Graduate School and Research)
Marcia Paranho Veloso CV-Lattes

RIO GRANDE DE SUL

10. UFRGS
Laboratory of Experimental Psychopharmacology (Faculty of Pharmacy)
Stela Maris Kuze Rates CV-Lattes

11. UNIPAMPA
Laboratory of Pharmacology – LABFAR (Faculty of Pharmacy)
Sandra Elisa Haas CV-Lattes

GOIÁS

12. UFG
Laboratory of Bioconversion (Faculty of Pharmacy)
Valeria de Oliveira CV-Lattes

Laboratory of Medicinal Pharmaceutical Chemistry (Faculty of Pharmacy)
Ricardo Menegatti CV-Lattes

ALAGOAS

13. UFAL
Laboratory of Pharmacology and Immunity (Institute of Biological and Health Sciences)
Magna Suzana Alexandre Moreira CV-Lattes

CEARÁ

14. UFC
Unit of Clinical Pharmacology (Faculty of Medicine)
Manoel Odorico de Moraes CV-Lattes

Laboratory of Pharmacology of Inflammation and Cancer (Faculty of Medicine)
Ronaldo de Albuquerque Ribeiro CV-Lattes

Department of Physiology and Pharmacology (Faculty of Medicine)
Claudia do Ó Pessoa CV-Lattes

PARAÍBA

15. UFPB
Laboratory of Toxicological Assays – LABETOX (Department of Pharmaceutical Sciences)
Margareth de Fátima Formiga Melo Diniz CV-Lattes

MAP OF RESEARCH NETWORK

1. UFC | BioTechCell
2. UFPB
3. UFAL
4. UFG
5. UFMG | UNIFAL | In Vitro Cells
6. UNICAMP | USP
   Cristália | Ciallyx
7. UFRJ | UERJ | UFRRJ | FIOCRUZ
   Nortec Química | LNCC
8. UNIPAMPA | UFRGS

08 | STATES
15 | INSTITUTIONS
30 | RESEARCH GROUPS
32 | CNPq RESEARCHERS
05 | ASSOCIATED COMPANIES
04 | INTERNATIONAL INSTITUTIONS

QUALIFICATION OF PERSONNEL

Collaborating to the enhancement of Brazilian expertise in the discovery/invention of new drugs and medicines, **INCT-INOFAR** works strongly in the qualification of personnel in the several research centers associated with it.

At **INCT-INOFAR**, scientific qualification is improved at different academic levels: undergraduate, Master's Degree, Doctorate, and Post-Doctorate. As part of this qualification, graduate students connected to the projects under study are encouraged to take part in scientific exchange with participating laboratories with specific expertise, so as to meet the agreed goals in adequate time.

Through scientific exchange promoted and encouraged by **INCT-INOFAR**, the Institute contributes not only for the qualification of new researchers, but also to the continuing education and updating of senior researchers. Keeping talented professionals in the country is also an **INCT-INOFAR** goal.

Training of personnel

Academic-scientific exchange

Continuing education and updating of senior researchers

Keeping talent researchers in the country

Cooperating to improve Graduate education in the country

INCT-INOFAR researchers actively take part in personnel qualification activities, through membership in 35 prestigious Graduate Programs, throughout the country, most of them offered at both the Master's and Doctorate levels. Over half of the Graduate Programs with the participation of **INCT-INOFAR** researchers are classified at excellence grades 6 and 7 (out of a maximum 7) by the Commission for the Improvement of Higher Education Personnel (CAPES).

CAPES is an agency of the Ministry of Education responsible for ranking and evaluation *Stricto Sensu* Graduate Programs (Academic Master's Degree, Professional Master's Degree, and Doctorate) in the country.

The process of evaluation of Graduate Programs conducted by CAPES is continuous. The course must be evaluated every three years (triennial evaluations) to assess if the goals proposed in the initial project were fully achieved within the Program, earning the corresponding grades ranging from 2 to 7.

Capes Grades

GRADUATE PROGRAMS INVOLVING INCT-INOFAR RESEARCHERS

7

Graduate Program in Cellular and Molecular Biology (FIOCRUZ) M/D Levels

Graduate Program in Pharmaceutical Sciences (UFRGS) M/D Levels

Graduate Program in Pharmacology (USP/RP) M/D Levels

Graduate Program in Chemistry (UFMG) - M/D Levels

Graduate Program in Chemistry (UFRJ) - M/D Levels

Graduate Program in Chemistry (UNICAMP) - M/D Levels

6

Graduate Program in Pharmacology (UFC) - M/D Levels

Graduate Program in Computational Modelling (LNCC) M/D Levels

Graduate Program in Public Health (FIOCRUZ) - M/D Levels

5

Graduate Program in Animal Sciences (UFG) - M/D Levels

Graduate Program in Pharmaceutical Sciences (UFMG) M/D Levels

Graduate Program in Pharmacology and Medicinal Chemistry (UFRJ) - M/D Levels

Graduate Program in Neurosciences (UFRGS) - M/D Levels

Graduate Program – Northeast Network in Biotechnology (RENORBIO) - D Level

Graduate Program in Biopharmaceutical Innovation (UFMG) - F Level

4

Graduate Program in Clinical and Toxicological Analyses (UFMG) M/D Levels

Graduate Program in Computational Biology and Systems - (FIOCRUZ) M/D Levels

Graduate Program in Biotechnology (UFC) - M Level

Graduate Program in Cardiology (UFRJ) - M/D Levels

Graduate Program in Surgical Sciences (UFRJ) - M/D Levels

Graduate Program in Health Sciences (UFAL) - M/D Levels

Graduate Program in Pharmaceutical Sciences (UFG) M Level

Graduate Program in Pharmaceutical Sciences (UNIFAL) M/D Levels

Graduate Program in Pharmacology and Therapeutic (UFRGS) - M/D Level

Graduate Program in Drugs and Medicines (USP) - M/D Levels

3

Graduate Program in Physics (UFG) M/D Levels

Graduate Program in Pharmaceutical Innovation (UFG) D Level

Graduate Program in Mathematical and Computational Modelling (UFRRJ) - M Level

Graduate Program in Nanosciences and Advanced Materials (UFABC) - M/D Level

Graduate Program in Chemistry (IME) - M/D Levels

Graduate Program in Chemistry (UFRRJ) - M/D Levels

Graduate Program in Chemistry (UNIFAL) - M/D Levels

Graduate Program in Intellectual Property and Innovation (INPI) F Level

Graduate Program in Pharmaceutical Sciences (UNIPAMPA) M Level

Graduate Program in Pharmaceutical Sciences (UFAL) M Level

Source: Triennial Evaluation Report 2013 – Reference 2010-2013, CAPES.

*See full list of master's degree and doctoral theses advised by **INCT-INOFAR** researchers completed in 2014 on chapter 5 of this publication.*

ORGANIZATIONAL STRUCTURE

The organizational structure of **INCT-INOFAR** is made up of a Coordinator, a Vice-Coordinator, and the Monitoring and Follow-Up Committee (CGA). The CGA is a consulting and deliberative collegiate, which acts in the strategic planning of **INCT-INOFAR** activities.

The Scientific Superintendence supports the Coordination, acting both in the technical scientific evaluation of projects under study, and on the meeting of previously established deadlines for the goals.

INCT-INOFAR also has the participation, under confidentiality, of expert consultants who provide scientific assistance in the evaluation of projects under study, to optimize research activities. In a few projects, consultants suggest possible route changes needed to fulfill the ultimate goal of the Institute: contributing toward the discovery of new Brazilian drugs.

The **INCT-INOFAR** scientific competences network is made up of 30 different research groups located in 15 institutions in 8 different Brazilian states. Each **INCT-INOFAR** associate research group is led by an expert, responsible for the scientific interaction of his or her team and with the other teams of the Institute.

Secretaries of Finances, Communication, and Outreach Activities, as well as Executive Secretary support the full development of the research and education activities of **INCT-INOFAR**, and are physically located at the Center for Health Sciences (CCS) of UFRJ, the administrative headquarters of the Institute.

With a goal of establishing strong cooperation in the areas of management, research, and scientific awareness, **INCT-INOFAR** periodically meets with other National Institutes of Science and Technology (INCTs).

The coordinators forum, called I5 + (due to the fact that it was organized by five INCTs that initially got together in late 2009 to start discussions), creates documents who are sent to CNPq with concrete proposals to solve operational, bureaucratic, and funding issues, referring to the Institutes funded by the INCTs program.

INCT-INOFAR ORGANIZATION CHART

MONITORING AND FOLLOW-UP COMMITTEE (CGA)
- Prof. Dr. Angelo C. Pinto (UFRJ)
- Prof. Dr. Elizabeth Igne Ferreira (USP-SP)
- Prof. Dr. Heloísa Beraldo (UFMG)
- Prof. Dr. Luiz Carlos Dias (UNICAMP)
- Prof. Dr. Marco Aurélio Martins (FIOCRUZ)

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

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

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

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

ASSOCIATED RESEARCH GROUPS
- 08 States
- 15 Institutions
- 30 Research Groups
- 32 CNPq Researchers
- 05 Associated Companies
- 04 International Institutions

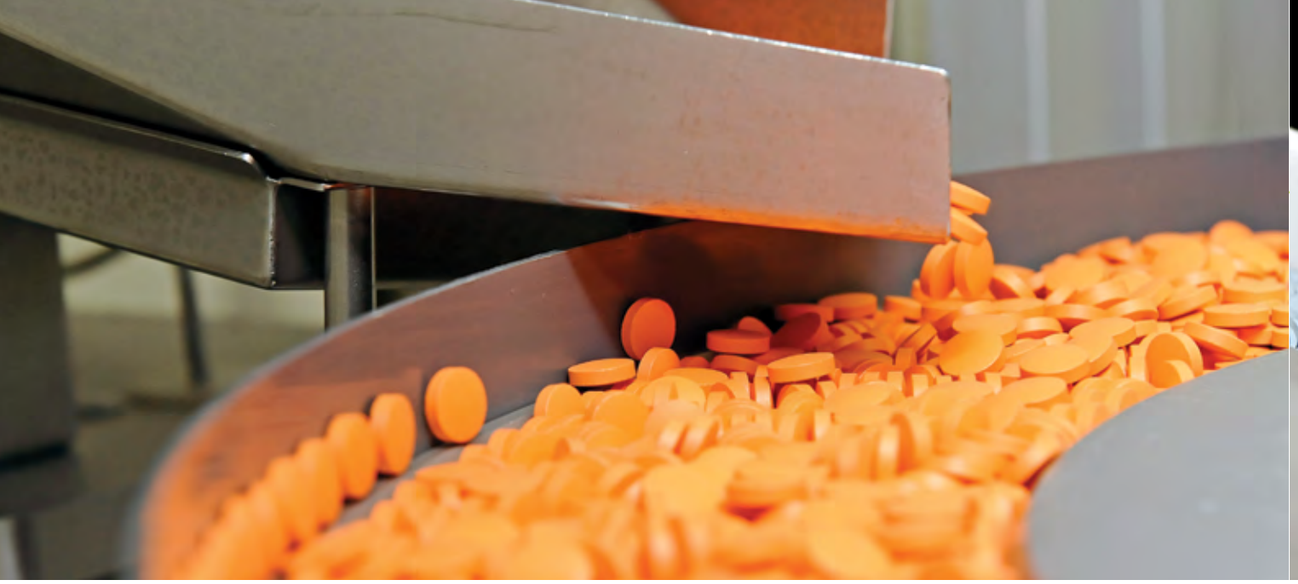
FINANCIAL SECRETARY

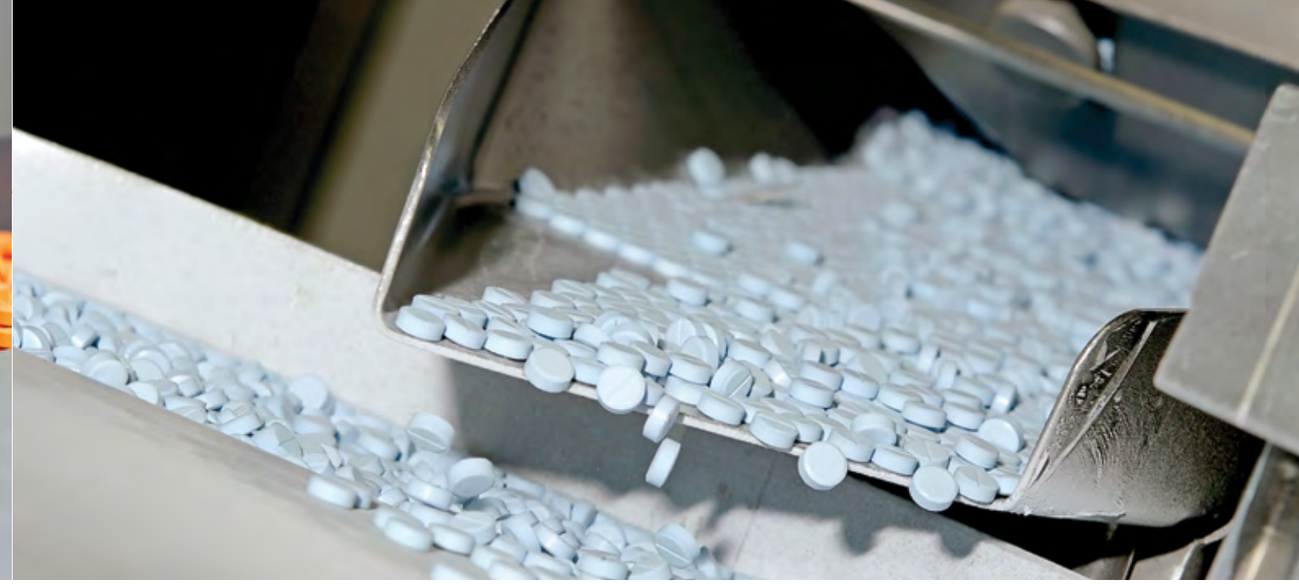
SECRETARY OF COMMUNICATION

SECRETARIES

EXECUTIVE SECRETARY

OUTREACH ACTIVITIES SECRETARY





ASSOCIATED COMPANIES

INCT-INOFAR has the support, even if informal, of pharmaceutical and related companies, like *In Vitro* Cells -Toxicological Research PLC, Cristalia Chemical and Pharmaceutical Products Ltd., Ciallyx Laboratories & Consulting Ltd., BiotechCell, and Nortec Chemistry.

IN VITRO CELLS TOXICOLOGICAL RESEARCH PLC.

In Vitro Cells - Toxicological Research PLC Is a technology company located at Biominas Foundation (Belo Horizonte, MG). The founders are Professors at the Federal University of Minas Gerais (UFMG) in the fields of Toxicology and Biochemistry. The company is an **INCT-INOFAR** partner to conduct *in vitro* bioassays to evaluate the safety and efficacy of new drug candidates developed by the Institute.

CRISTALIA CHEMICAL PHARMACEUTICAL PRODUCTS LTD.

Cristalia Chemical Pharmaceutical Products Ltd. is a pharmaceutical company associated to **INCT-INOFAR**, qualified to support possible future stages of pharmaceutics development of new compound-prototypes that reach this advanced stage in the chain of innovation in drugs and medicines. Under non-disclosure and confidentiality agreements, Cristalia will benefit, if there is interest, of information on the projects under study, by expressing it during the appropriate timelines in internalizing the technologies developed by **INCT-INOFAR**. For technology transferring, the UFRJ Agency of Innovation and its equivalent in another research institution connected to **INCT-INOFAR** and to a specific project will negotiate directly with the interested parties, including the funders.

CIALLYX LABORATORIES & CONSULTING LTD.

Ciallyx Laboratories & Consulting Ltd. is a company housed at CIETEC (Center for Incubation of Technological Companies), which carries out efficacy studies (proofs of concept) and safety studies (toxicological studies and assays) for new molecules, drugs, and formulations. Ciallyx generates results according to national and international protocols under strict quality parameters, using, as a guide, the international norms of Good Laboratory Practices – GLP. The company is an **INCT-INOFAR** partner to conduct *in vivo* bioassays of safety and efficacy of new drug candidates developed by the Institute.

BIOTECHCELL

The term Biotechnology refers to a wide set of enabling and potentializing technologies that involve the use, controlled alteration and optimization of living organisms or their derivates, like cells and molecules, for the generation of processes and services. BiotechCellR is a biotechnology entrepreneurial company in the Northeast, born out of the scientific community from the ideal of a pair of young researchers who intended to align their vast academic experience to the management of technological innovation and services. It is an **INCT-INOFAR** partner that acts in research and pre-clinical pharmacological services, human biomonitoring, toxicogenetics, and applied toxicology.

NORTEC CHEMISTRY

In the process of pharmaceutical innovation, the active principle is fundamental for the construction of new synthesis routes. Nortec Chemistry is a 100% Brazilian pharmachemical company, with a stated intent of acting in partnership with **INCT-INOFAR** in the production of pharmaceutical active principles. Nortec Chemistry, established in the 1980s, is headquartered in Rio de Janeiro (RJ) and has, for several years in a row, received the Prize of Excellence in Supplying Raw Materials, awarded by SINDUSFARMA – Union of the Pharmaceutical Industries of Sao Paulo.

INTERNATIONAL AGREEMENTS

Among the main goals of international agreements are the development of joint research projects, organization of academic and scientific activities, exchange of researchers and/or students, as well as exchange of materials and publications relevant to the area.

INCT-INOFAR has directed efforts toward making its research network international, through signing cooperation agreements with international institutions. This is in accordance to the recommendations of the National Council for Scientific and Technological Development (CNPq) and the philosophy of the Science Without Borders program, supported by this financial agency.

The goal is to establish international visibility to Science, Technology, and Innovation activities in Brazil, and, most of all, allowing new cooperation networks is built, and that those may offer training opportunities for undergraduate and graduate students abroad. Currently, **INCT-INOFAR** has cooperation agreements with four Teaching and Research Institutes abroad, allowing for the exchange of its researchers with experts in Germany, Portugal, Italy, and Uruguay.

INCT-INOFAR International Cooperation Network

GERMANY

Interdisciplinary Center of Pharmacogenomics and Pharmaceutical Research (ICEPHA)

University of Tübingen, Germany.
Researcher in Charge: Professor Stefan Laufer

PORTUGAL

Department of Chemistry
University of Aveiro, Portugal.
Researcher in Charge: Professor Jose A. F. Cavalheiro

ITALY

Department of Pharmaceutical Sciences
University of Ferrara, Italy.
Researcher in Charge: Professor Pier G. Baraldi

URUGUAY

Department of Organic Chemistry
National University of the Republic, Uruguay.
Researchers in Charge: Professors Hugo Cerecetto and Mercedes Gonzalez

Annual “Germany + Brazil” Symposium for individualized medicine

In the year when Brazil and Germany straightened their links through the “Brazil + Germany 2013-2014” Year, comprising several events in Brazil, **INCT-INOFAR** was part of the workshop on “Individualized Medicine” in drug research.

Individualized or personalized therapy oppose the classic drug development and therefore are not dominant in the pharmaceutical industry. However, they have been strongly investigated by academic workgroups, among them the Interdepartmental Center for Pharmacogenomics and Drug Research (ICEPHA), of the University of Tübingen.

The event, which took place in the Brazilian Academy of Sciences (ABC), on March 28th, 2014, had the participation of Brazilian and German researchers, with the goal of effectively developing projects in a network.

The Workshop organized by Professor Dr. Stefan Laufer, of ICEPHA/University of Tübingen, is one of the fruits of the cooperation covenant that was signed in 2011 between the German research institute and **INCT-INOFAR**, with the approval of Prime Minister Winfried Kretschmann and of Minister Theresia Bauer (Minister of Science, Research, and Art, Baden-Württemberg).

Other international actions

Parallel to international agreements, **INCT-INOFAR** makes efforts to establish eventual collaborations between its researchers and renowned foreign scientists. Under confidentiality, **INCT-INOFAR** has the participation of international consultants who provide scientific assistance in the evaluation of projects under study. Currently, the Institute has three international consultants.

INCT-INOFAR International Scientific Consultants

Sir Simon Campbell
(Pfizer, *Royal Academy of Science*/England)

Professor Antonio Monge
(University of Navarra, Spain)

Dr. Camille G. Wermuth
(Prestwick Chemical, France)

Radical Innovation

INCT-INOFAR SUBPROJECTS UNDER STUDY

INFLAMMATION
(Pulmonary Disease)

1. Study of the potential anti-inflammatory effect of LASSBio 897 compound, in silicosis and asthma models:

- Professor Patricia Machado Rodrigues e Silva Martins (FIOCRUZ – RJ) CV-Lattes
- Professor Marco Aurelio Martins (FIOCRUZ – RJ) CV-Lattes

2. Study for the identification of new sulfonamide compounds effective in the control of pulmonary inflammation caused by silica in mice:

- Professor Patricia Machado Rodrigues e Silva Martins (FIOCRUZ-RJ) CV-Lattes

3. Development of new antiasthmatic drug prototypes (LASSBio-596):

- Professor Patricia Rieken Macedo Rocco (UFRJ) CV-Lattes
- Professor Lidia Moreira Lima (UFRJ) CV-Lattes

4. Impact of therapy with nanoparticles of the thymuline gene in chronic allergic asthma model:

- Professor Patricia Rieken Macedo Rocco (UFRJ) CV-Lattes

INFLAMMATION AND PAIN

5.New 5-aryl-2-furfuril-*N*-acylhydrazone functionalized derivatives with powerful anti-inflammatory and analgesic action: LASSBio-1609 and LASSBio-1636

- Professor Carlos Alberto Manssour Fraga (UFRJ) CV-Lattes

6. Development of new anti-arthritis drug candidates, MAPK p-38 modulators

- Professor Lidia Moreira Lima (UFRJ) CV-Lattes

7. Design, synthesis, structural characterization and pharmacological evaluation of new anti-inflammatory, anti-infection, and neuroactive drug candidates

- Professor Claudio Viegas Junior (UNIFAL) CV-Lattes

8. Development of new anti-inflammatory and analgesic drug candidates from safrole

- Professor Lidia Moreira Lima (UFRJ) CV-Lattes

9. Design of structural changes aimed at optimizing the affinity of the selective IKK2 enzyme inhibitor LASSBio-1524

- Professor Laurent Emmanuel Dardenne (LNCC) CV-Lattes

10. Benzaldehyde semicarbazone (BS)

- Professor Heloisa de Oliveira Beraldo (UFMG) CV-Lattes

CHEMOTHERAPY

11. Evaluation of antiparasitic activity of a series of semicarbazone and hydrazine-*N*-acylhydrazone derivatives (Leishmanicidal)

- Professor Magna Suzana Alexandre Moreira (UFAL) CV-Lattes

12. Discovery of new antitumoral drug candidate analogs to combrestatin A4 (Antineoplastic)

- Professor Lidia Moreira Lima (UFRJ) CV-Lattes

13. Theoretical investigation of action of dialkylphosphorilhydrazones as ribose 5-phosphate isomerase enzyme of *Trypanosoma cruzi* and *Plasmodium falciparum* (Trypanomicidal and antimalarial)

- Professor Carlos Mauricio R. de Sant'Anna (UFRRJ) CV-Lattes

CENTRAL NERVOUS SYSTEM

14. Study of *N*-phenylpiperazine functionalized derivatives as prototypes for the development of new atypical antipsychotics (antipsychotics)

- Professor Stela Maris Kuze Rates (UFRGS) CV-Lattes
- Professor Carlos Alberto Manssour Fraga (UFRJ) CV-Lattes

15. Pharmacological evaluation of new Zolpidem neuroactive derivatives (neuropathic pain)

- Professor Roberto Takashi Sudo (UFRJ) CV-Lattes

16. Design, synthesis and pharmacological evaluation of vectorized and self-organized neuroactive drug prototypes

- Professor Ricardo Menegatti (UFG) CV-Lattes

CASDIOVASCULAR SYSTEM

17. Therapeutic potential of new vasodilator (LASSBio 1289) in arterial and pulmonary hypertension

- Professor Gisele Zapata Sudo (UFRJ) CV-Lattes

18. Pharmacological and toxicological evaluation of new drug candidates for the prevention and treatment of miocardiopathy and neuropathy caused by diabetes mellitus

- Professor Gisele Zapata Sudo (UFRJ) CV-Lattes

Incremental Innovation

GENERICS

19. Synthesis of Quetiapine

- Professor Eliezer J. Barreiro (UFRJ) CV-Lattes
- Professor Angelo da Cunha Pinto (UFRJ) CV-Lattes

20. Synthesis of Fluoxetine

- Professor Eliezer J. Barreiro (UFRJ) CV-Lattes
- Professor Luiz Carlos Dias (UNICAMP) CV-Lattes
- Dr. Adriano V. Siqueira (UNICAMP) CV-Lattes

21. Synthesis of Valsartan

- Professor Eliezer J. Barreiro (UFRJ) CV-Lattes
- Professor Luiz Carlos Dias (UNICAMP) CV-Lattes

INCT-INOFAR helps increase female recognition in Science

INCT-INOFAR Researcher takes seat on Brazilian Academy of Sciences

Adding to the female presence in the Brazilian Academy of Sciences (ABC), Professor Heloisa de Oliveira Beraldo, of the Federal University of Minas Gerais (UFMG), took seat on May 06 as a full member in the field of Chemistry. Professor Heloisa, who is an **INCT-INOFAR** associate researcher and also a member of its Managing Committee, was one of four women to join the ranks of the nearly century-old Academy in 2014.

Professor Dr. Heloisa de Oliveira Beraldo has made important contributions to Inorganic Medicinal Chemistry, with studies of drug candidates and metallodrug candidates, among them antitumor, antimicrobial, and antiparasitic. The Professor was also responsible for the evaluation of pharmacological profiles of different compounds and investigated the action and interaction mechanism between organic compounds and metallic complexes with target biomolecules, such as DNA and enzymes/metalloenzymes.

Professor Heloisa Beraldo receives title of full member of the Brazilian Academy of Sciences from the Minister of Science, Technology, and Innovation

Working hard to break the historical paradigm of the male hegemony at the Brazilian Academy of Sciences (ABC), **INCT-INOFAR** is responsible for increasing, yearly, the number of female scientists as full members, especially in the field of Chemical Sciences. In 2012, **INCT-INOFAR** associate researcher Professor Vanderlan da Silva Bolzani, from State University of Sao Paulo (UNESP-Araraquara), also became a member of the Academy.

Young INCT-INOFAR researcher receives "For Women in Science" Award

Young **INCT-INOFAR** researcher Professor Dr. Carolina Horta Andrade, from the Federal University of Goias (UFG), was the 2014 winner of the "For Women in Science" Award in Chemistry. The research was on new multitarget drug candidates and metallodrug candidates for Leishmaniasis, and was awarded a prize of 20 thousand dollars.

Carolina Andrade was the first researcher from Goias to receive the "For Women in Science" Award

Youngest of a family of five women, Carolina was born in Formosa, in the state of Goias, and dedicated herself to studying from an early age. The passion for Medicinal Chemistry happened soon after graduating from the Federal University of Goias (UFG), where she was advised by Professor Dr. Valeria de Oliveira (UFG), an **INCT-INOFAR** associate researcher. After graduating, she decided to get her Master's Degree at the University of Sao Paulo (USP) with Professor Dr. Elizabeth Igne Ferreira, member of the **INCT-INOFAR** Managing Committee. An expert in the field, Professor Elizabeth Ferreira noticed Carolina Horta's excellent performance, and nominated her for a doctorate consecutively, before she had even finished her Master's Degree.

Currently at 31 years old, Carolina has a vast academic background, including an exchange doctoral program at the University of New Mexico, in Albuquerque, USA. To her, the award is an incentive to young women to choose careers in science. "The award encourages not only local scientific production, but also young female doctors who are beginning their careers in Brazilian research institutions", she stated.

Unicamp Researcher Dr. Luiz Carlos Dias has merit in Chemistry acknowledged

UNICAMP RESEARCHER HAS MERIT IN CHEMISTRY ACKNOWLEDGED

Coordinator of the **INCT-INOFAR** scientist group who developed a cheaper process for the production of atorvastatin, the active principle of Lipitor™, continuous use drug for the control of cholesterol best sold in the world, Professor Dr. Luiz Carlos Dias, from the Department of Organic Chemistry from the State University of Campinas (UNICAMP), was the winner of the 2014 edition of the Walter Borzani Award.

Promoted by the Regional Council of Chemistry (CRQ-IV), the contest intends to acknowledge professionals who made significant contributions to their areas and to the development of Chemistry.

The ceremony for the Walter Borzani Award took place on June 7, at the Council headquarters, during a celebration of Chemists Day.

Born in Balneario Camboriu (SC) and with an undergraduate degree in Chemistry Education from the Federal University of that state, Dias has a Doctorate in Chemistry (UNICAMP) and a Post-Doctorate (Harvard University/EUA, 1994-1995). He is a full professor of the Institute of Chemistry at UNICAMP and a CNPq researcher, a full member of the Brazilian Academy of Sciences and a Commander of the National Order of Scientific Merit. In 2008, his laboratory was accredited by the World Health Organization (WHO) as a World Reference Center for the synthesis of compounds for the treatment of Chagas disease.

As acknowledgment of his professional history, Professor Dr. Luiz Carlos Dias was asked to deliver the commencement speech for the 38th Meeting of the Brazilian Society of Chemistry (RASBQ), which will take place in May 2015, at Aguas de Lindoia – SP.

Aside from the Walter Borzani Award, Professor Luiz Carlos Dias was awarded the Santander Universities Award – 2014 Edition, Science and Innovation, in Health, with the project “Optimization of lead compounds for the treatment of tropical parasite diseases”, in cooperation with Drugs for Neglected Diseases Initiative (DNDi) and Medicines for Malaria Venture (MMV).

The award ceremony took place on November 05, 2015, at the Hotel Grand Hyatt, in Sao Paulo, with the presence of the President of Santander Bank Brazil, Jesus Zabalza, and of the governor of Sao Paulo, Geraldo Alckmin, among other authorities. The 2014 edition of “Santander Universities” awarded the scientist with a prize in the value of R$ 100 thousand Brazilian Reais.

Highlights 2014

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Highlights 2014

Docking, synthesis and antiproliferative activity of *N*-acylhydrazone derivatives designed as combretastatin A4 analogues

PLoS ONE 9 (2014) e85380 [doi: 10.1371/journal.pone.0085380]

Daniel Nascimento do Amaral, Bruno C. Cavalcanti, Daniel P. Bezerra, Paulo Michel P. Ferreira, Rosane de Paula Castro, José Ricardo Sabino, Camila Maria Longo Machado, Roger Chammas, Claudia Pessoa, Carlos M. R. Sant'Anna, Eliezer J. Barreiro, Lídia Moreira Lima

Cancer is the second cause of death in USA. Among the known classes of anticancer agents the microtubule-targeted antimitotic drugs are considered one of the most important. They are usually classified into two main groups. One group, known as the microtubule-destabilizing agents, which inhibits microtubule polymerization, such as the *Vinca* alkaloids, vincristine (1) and vinblastine (2) – the first anti-microtubule agents approved to treat cancer disease. The second group is known as the microtubule-stabilizing agents that stimulate microtubule polymerization such as paclitaxel, used to treat breast and ovarian cancer, non-small-cell lung cancer and Kaposi's sarcoma.

In attempts to develop orally available anti-microtubule agents that may overcome the neurotoxicity and the advance of resistance commonly described for *Vinca* alkaloids, paclitaxel and analogues; the combretastatin A4 (CA-4) is being considered a promise lead-compound. This natural stilbene isolated from *Combretum caffrum* binds to the colchicine domain on β-tubulin and exhibits low toxicity profile. However, CA-4 (4) failed to exhibit anticancer efficacy in animal models due to its low solubility in water, lack of oral bioavailability, short half-life and the in vivo isomerization of double bound that implies in loss affinity for tubulin and consequently loss of cytotoxic activity.

This paper the docking study, synthesis and antiproliferative activity of *N*-acylhydrazone derivatives (**5a-r**) designed as CA4 analogues are reported.

The genesis conception of *N*-acylhydrazone derivatives (**5a-r**) is depicted in Figure 1. The main structural modifications was based on the replacement of ethylene linker between the aromatic subunits A and B by a more stable scaffold represented by the *N*-acylhydrazone (NAH) moiety, originating compound **5a**. In order to design a congeneric series (**5b-r**) several modifications were introduced in the nature of aromatic subunit B based on docking studies with colchicine binding site of β-tubulin protein (Figure 2).

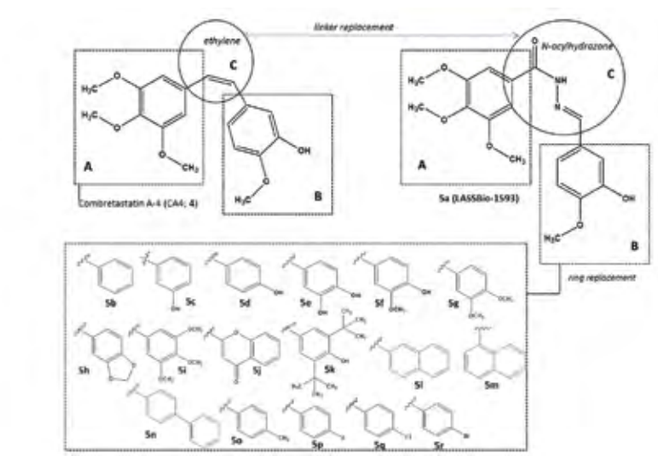

Figure 1. Initial conception and molecular design of *N*-acylhydrazone derivatives **5a-r**

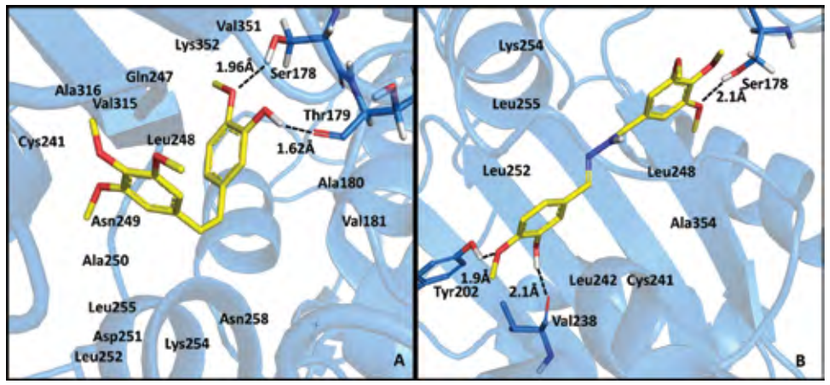

Figure 2. Polar interactions between CA-4 (**A**) or LASSBio-1593 (**B**) with the colchicine binding site of β-tubulin (PDB code: 1sa0).

Compounds **5a-r** were easily synthetized and the characterization of imine double bond (N=CH) was performed unequivocally using X-ray diffraction studies, as exemplified for compound **5b** (Figure 3).

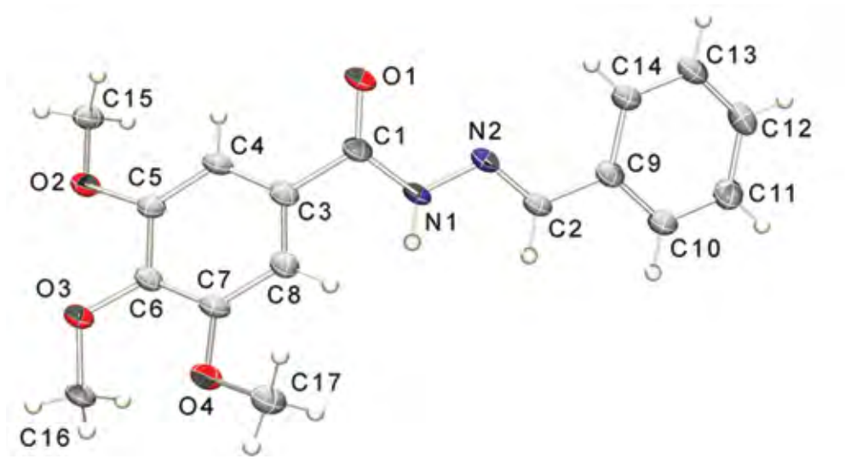

Figure 3. ORTEP view of compound **5b** with the atom displacement ellipsoids drawn at a 50% probability level.

The antiproliferative activity of compounds **5a-r** was determined based on an MTT assay, using CA-4 as standard, against the tumor cell lines: HL-60 (human leukemia), SF-295 (human glioblastoma), MDA-MB435 (melanoma), PC3M (prostate cancer), OVCAR-8 (ovaries adenocarcinoma), NCI-H258M (pulmonary bronchio-alveolar carcinoma) and HCT-8 (adenocarcinoma ileocecal). To determine the selectivity index of compounds **5a-r**, their antiproliferative profile was also evaluated toward human lymphocytes (Table 1).

Table 1: *In vitro* antiproliferative potency (IC_{50}-μM) of compounds **5a-r** and the standard CA-4 against tumor cell lines and human lymphocytes.

Compounds	HL-60	SF295	HCT-8	MDA-MB435	PC3M	OVCAR-8	NCI-H358M	Lympho-cytes
5a	4.72	1.55	2.08	0.39	2.22	1.44	1.58	2.58
5b	0.29	0.26	0.45	0.064	0.8	0.29	0.35	1.34
5c	1.63	13.05	4.3	0.12	7.51	5.78	9.5	4.48
5d	2.63	15.95	6.54	0.88	4.57	6.18	11.75	13.38
5e	9.3	> 25	> 25	11.78	24.4	> 25	> 25	7.36
5f	9.85	13.57	9.27	6.52	16.96	14.6	11.85	36.51
5g	4.43	18.08	7.05	2.11	12.55	7.11	10.18	17.98
5h	3.07	0.86	55.81	0.11	1.14	1.09	2.15	1.31
5i	>25	> 25	> 25	> 25	> 25	> 25	> 25	> 61.82
5j	>25	> 25	23.35	> 25	> 25	> 25	> 25	> 65.38
5k	>25	> 25	> 25	> 25	> 25	> 25	> 25	> 56.49
5l	0.015	0.057	0.011	0.004	0.008	0.0054	0.079	0.010
5m	0.018	0.085	0.050	0.043	0.027	0.026	0.63	0.010
5n	>25	> 25	> 25	> 25	> 25	> 25	> 25	> 64.07
5o	0.0048	0.093	0.046	0.035	0.0127	0.0082	0.891	0.0073
5p	1.27	2.69	2.02	1.58	4.48	0.96	2.16	3.82
5q	0.036	0.072	0.046	0.018	0.0275	0.024	1.055	0.060
5r	0.0109	0.059	0.022	0.0183	0.0127	0.0073	0.167	0.0314
CA-4	0.0021	0.0062	0.0053	0.0079	0.0047	0.00037	0.008	0.0032

Considering the IC_{50} (≤0.8 M and ≥0.064 M) and the SI values, LASSBio-1586 (**5b**) was selected as the most promising compound, and its ability to inhibit tubulin polymerization was investigated. The tubulin polymerization assay was performed by CEREP employing a single concentration of **5b** (C = 30 μM), using vinblastine as positive control. In this assay, LASSBio-1586 (**5b**) inhibited 91% of the tubulin polymerization, validating the rational design employed in the molecular design of the derivatives **5a-r**. Further, the antitumor activity of LASSBio-1586 was investigated using the Hollow Fiber Assay in BALB/c nude mice. As shown in Table 2, LASSBio-1586 (**5b**; dosages = 25 and 50 mg/kg/day) reduced the proliferation of both SF-295 (61.89 and 82.89%) and HCT-116 (72.68 and 80.76%) cell lines after 4 days of administration ($P < 0.05$), demonstrating its antiproliferative effect *in vivo*.

Taken together, LASSBio-1586 (**5b**) emerged as a simple antitumor drug candidate and was capable of inhibiting microtubule polymerization.

Table 2. *In vivo* antiproliferative activity of **5b** and 5-fluorouracil (5-FU) against tumor cells as evaluated by the in Hollow Fiber Assay (HFA).

Groups[1]	Dose (mg/kg/day)	Survival	Proliferation (OD595nm)		Inhibition (%)	
			SF-295	HCT-116	SF-295	HCT-116
Control[2]	-	6/6	1.50 ± 0.21	1.55 ± 0.18	-	-
5-FU[3]	25	7/7	0.52 ± 0.08*	0.59 ± 0.10*	65.40	62.08
5b	25	7/7	0.57 ± 0.05*	0.26 ± 0.04*	61.89	82.89
	50	6/6	0.41 ± 0.06*	0.29 ± 0.05*	72.68	80.76

[1]The data are reported as the mean ± S.E.M., n=6-7 animals/group, which were treated for 4 days intraperitoneally. [2]The negative control group received 5% DMSO. [3]5-Fluorouracil (5-FU) was used as the positive control.* $P < 0.05$ compared to the control by ANOVA, followed by Newman-Keuls test.

COMMENTS FROM AUTHOR

A new series of synthetic CA-4 analogues was designed based on docking studies with β-tubulin (PDB code: 1sa0). Compounds were easily synthetized and among them **5b** (LASSBio-1586) stood out showing cytotoxic potency varying between IC_{50}= 0.8 M to 64 nM, against different tumor cells. This compound showed better aqueous solubility than the natural prototype (CA-4) and possessed better selectivity index than CA-4. The minimum structural requirements essential for the anti-tubulin activity of LASSBio-1586 was proposed and its antiproliferative activity, *in vivo*, was demonstrated using Hollow Fiber Assay in BALB/c nude mice.

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Highlights 2014

Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Eur. J. Med. Chem. 71 (2014) 1-14.
[doi:10.1016/j.ejmech.2013.10.058]

Maria Letícia de Castro Barbosa, Lídia Moreira Lima, Roberta Tesch, Carlos Mauricio R. Sant'Anna, Frank Totzke, Michael H. G. Kubbutat, Christoph Schächtele, Stefan A. Laufer, Eliezer J. Barreiro

Protein kinases play important roles in the regulation of numerous cellular processes, including proliferation, differentiation and survival. In particular, the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor 2 (VEGFR-2) play key roles in tumor growth and angiogenesis. EGFR and VEGFR-2 are closely linked transmembrane receptor tyrosine kinases, sharing common downstream signal transduction pathways. Their functional relationship in cancer therapy is well known, *i.e.* inhibition of VEGFR-2 signaling pathway contributes to the antitumoral effect of EGFR inhibitors; whereas activation of VEGF expression independent of EGFR signaling is thought to be one of the resistance mechanisms to anti-EGFR therapy. The tyrosine kinases EGFR and VEGFR-2 are validated targets in cancer therapy and several inhibitors have been approved by the FDA for clinical use in EGFR and/or VEGFR-2 overexpressing solid tumors, including the ATP-mimetic tyrosine kinase inhibitors (TKIs) gefitinib (**1**) for EGFR and sorafenib (**4**) for VEGFR-2 (Figure 1).

Secondary resistance following the initial benefits of treatment with approved EGFR inhibitors remains a challenge in cancer therapy and demonstrates the need for the development of novel therapeutic alternatives. In this context, dual inhibition of EGFR and VEGFR-2 represents a promising approach for cancer treatment. Considering the great interest in associating EGFR and VEGFR-2 inhibition, we have performed the design of novel dual inhibitors of the tyrosine kinases EGFR and VEGFR-2, which are structurally and clinically related (Figure 1).

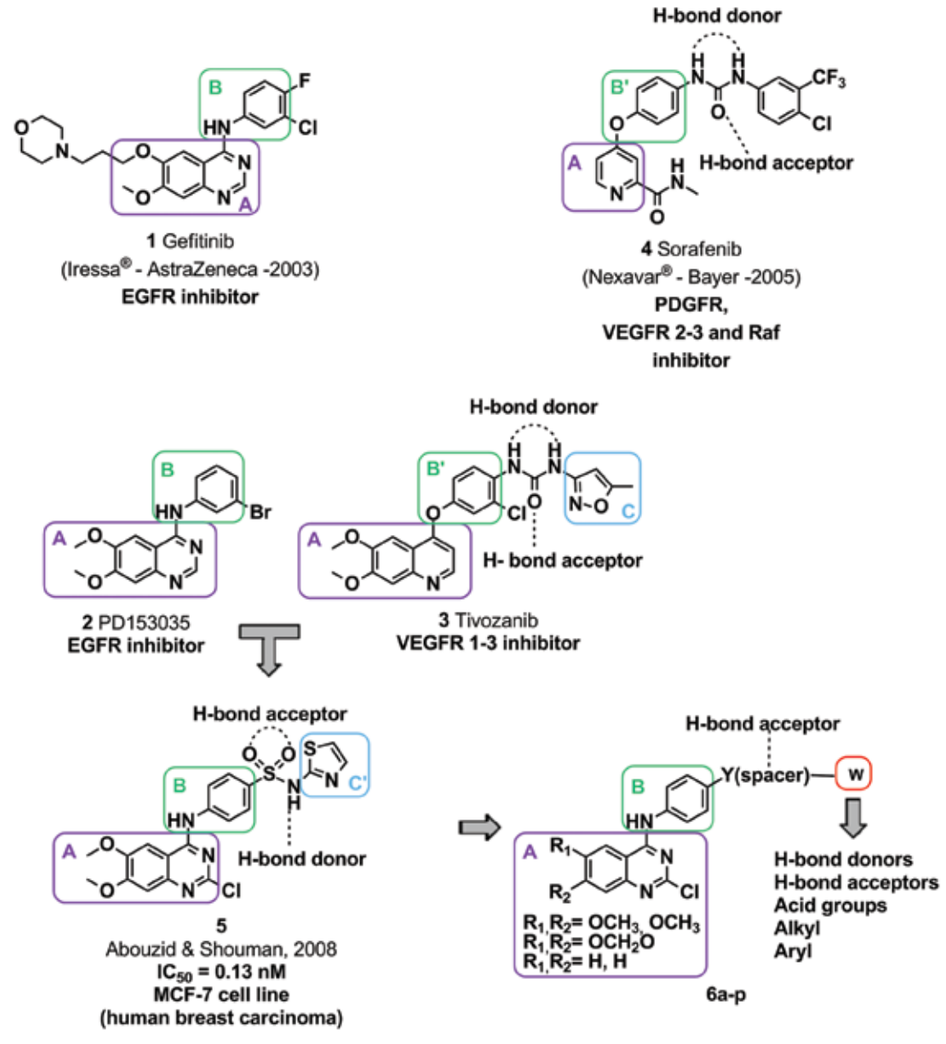
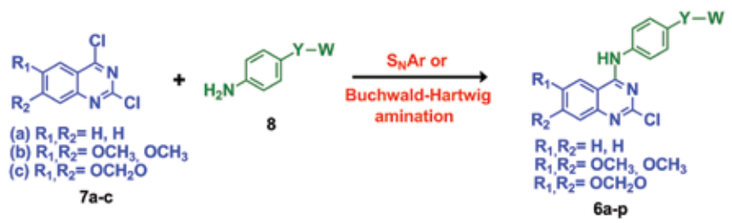


Figure 1. Structural design of the target 2-chloro-4-anilino-quinazoline derivatives (**6a-p**), planned as EGFR and VEGFR-2 dual inhibitors, starting from the prototypes **1-5**. Prototype **5** was previously described by Abouzid & Shouman, *Bioorganic & Medicinal Chemistry* **2008,** 16, 7543-7551.

The designed 4-anilino-quinazoline compounds (**6a-p**) were synthesized by a key condensation step between the 2,4-dichloro-quinazoline intermediates and the corresponding aniline derivatives through either a nucleophilic aromatic substitution or a Buchwald-Hartwig amination (Scheme 1) and their inhibitory activity was evaluated employing a radiometric protein kinase assay (^{33}PanQinase Activity Assay) (Table 1).



Scheme 1: General synthesis of the designed 2-chloro-4-anilino-quinazoline compounds **6a-p**. a) DIPEA, dioxane, 80°C, 12 h, 60-66%; b) isopropyl alcohol, 82°C, 24 h, 67-72%; c) ethanol, 78°C, 24 h, 64-73%; d) Pd(oAc)2, XPhos, tBuONa, tBuOH, toluene, 90°C, 1 h, 45-55%.

Table 1: EGFRwt and VEGFR-2 inhibition by the 2-chloro-4-anilino-quinazoline derivatives.

Compound	R_1, R_2	Y	W	EGFRwt[a,b] IC_{50} (μM)	VEGFR-2[a,b] IC_{50} (μM)
5[c]	OCH_3, OCH_3	SO_2		9.70	7.79
6a - LASSBio-1800	OCH_2O	SO_2		> 100	> 100
6b - LASSBio-1808	OCH_3, OCH_3	SO_2	$N(CH_3)_2$	67.2	43.3
6c - LASSBio-1807	OCH_2O	SO_2	$N(CH_3)_2$	18.3	23.4
6d - LASSBio-1809	H, H	SO_2	$N(CH_3)_2$	> 100	> 100
6e - LASSBio-1810	OCH_3, OCH_3	SO_2	CH_3	61.5	> 100
6f - LASSBio-1811	OCH_2O	SO_2	CH_3	> 100	> 100
6g - LASSBio-1814	OCH_3, OCH_3	SO_2	NH_2	2.37	1.02
6h - LASSBio-1815	OCH_2O	SO_2	NH_2	34.6	26.9
6i - LASSBio-1812	OCH_3, OCH_3	-	$N(CH_3)_2$	36.0	39.3
6j - LASSBio-1813	OCH_2O	-	$N(CH_3)_2$	> 100	> 100
6k - LASSBio-1816	OCH_3, OCH_3	SO_2	$NHCH_3$	1.63	0.85
6l - LASSBio-1821	OCH_3, OCH_3	-	OH	4.30	2.10
6m - LASSBio-1817	OCH_3, OCH_3	SO_2	OH	> 100	> 100
6n - LASSBio-1818[c]	OCH_3, OCH_3	C=O	OH	> 100	> 100
6o - LASSBio-1819	OCH_3, OCH_3	C=O	NH_2	0.90	1.17
6p - LASSBio-1820	OCH_3, OCH_3	-	$NHCOCH_3$	37.6	1.99

[a]A radiometric protein kinase assay (^{33}PanQinase Activity Assay) was used to measure the kinase activity of the protein kinases EGFRwt and VEGFR-2.[b] The IC_{50} values were calculated using Quattro Workflow V3.1.0 (Quattro Research GmbH, Munich, Germany; www.quattroresearch.com) and are in μM. [c]Previously described by Abouzid & Shouman, *Bioorganic & Medicinal Chemistry* **2008,** 16, 7543-7551.

As shown in Table 1, those derivatives containing a hydrogen bond donor at the *para* position of the aniline moiety presented lower IC_{50} values, highlighting compounds **6g** (LASSBio-1814; IC_{50} = 2.37 μM for EGFRwt and 1.02 μM for VEGFR-2), **6k** (LASSBio-1816; IC_{50} = 1.63 μM for EGFRwt and 0.85 μM for VEGFR-2) and **6o** (LASSBio-1819; IC_{50} = 0.90 μM for EGFRwt and 1.17 μM for VEGFR-2) as dual inhibitors of both the EGFR and VEGFR-2 tyrosine kinases.

Therefore, the biological data have demonstrated the relevance of a hydrogen bond donating substituent at the *para* position of the aniline (Figure 2) for interaction with the EGFR and VEGFR-2 tyrosine kinase domain binding sites.

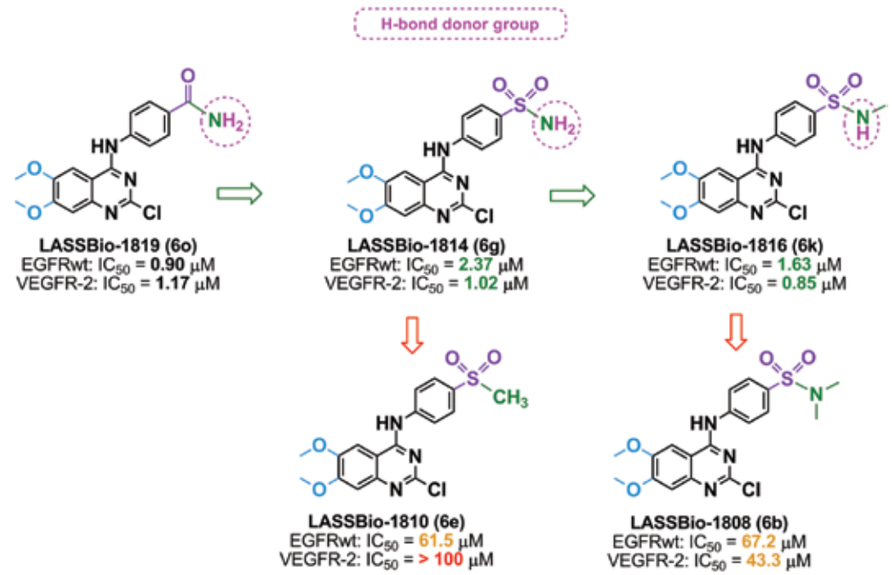


Figure 2: The relevance of a hydrogen bond donating substituent at the *para* position of the aniline (Table 1) for interaction with the EGFR and VEGFR-2 tyrosine kinase domain binding sites.

A docking study of this new class of ligands with the tyrosine kinase domains of EGFRwt and VEGFR-2 was performed to elucidate the molecular reasons behind the observed inhibition profile, as illustrated in the Figure 3 for compounds **6k** and **6o**.

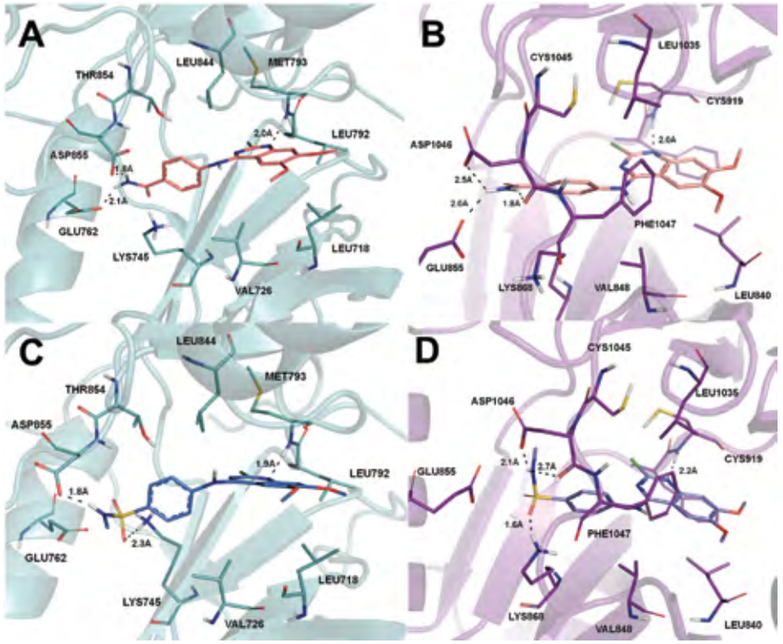


Figure 3: (A) Binding interactions of LASSBio-1819 (**6o**) with EGFRwt; (B) Binding interactions of LASSBio-1819 (**6o**) with VEGFR-2; (C) Binding interactions of LASSBio-1816 (**6k**) with EGFRwt; (D) Binding interactions of LASSBio-1816 (**6k**) with VEGFR-2. Docking studies were performed with the GOLD 5.1 program. Apolar hydrogen atoms were omitted to improve clarity. The images were generated with PyMol software.

In conclusion, this study has described the synthesis and biological testing of a novel series of 2-chloro-4-anilino-quinazoline EGFR and VEGFR-2 dual inhibitors. The associated modulation of these two tyrosine kinases represents a promising therapeutic approach to overcome and prevent resistance in cancer therapy due to a synergistic effect. Moreover, this study identified pharmacophoric groups for binding to the selected therapeutic targets and demonstrated the importance of a hydrogen bond donor at the *para* position of the aniline moiety for interaction with the conserved **Glu** and **Asp** amino acids in the EGFR and VEGFR-2 binding sites, which promotes a significant increase in potency (Figure 4).

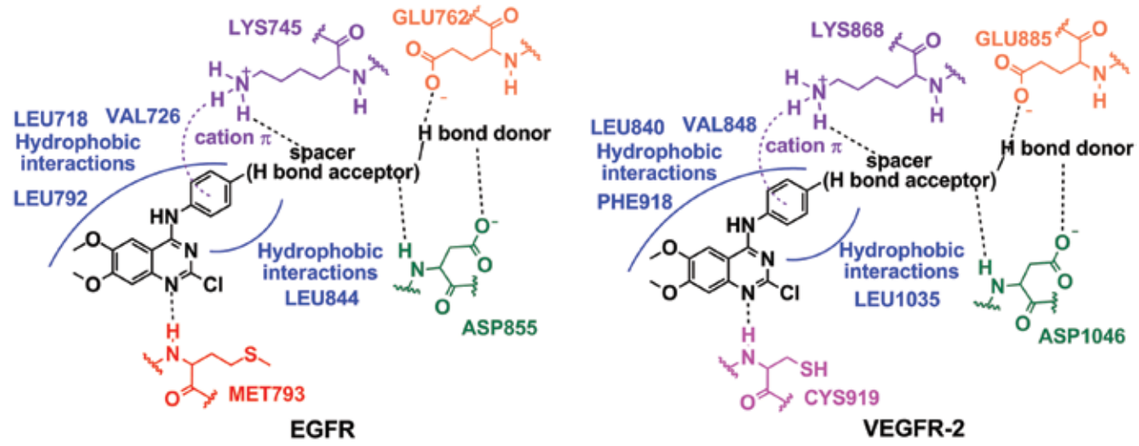


Figure 4: Pharmacophoric model for the interaction of the 2-chloro-4-anilino-quinazoline derivatives with the corresponding amino acid residues in the binding sites of the selected therapeutic targets, EGFR and VEGFR-2.

COMMENTS FROM AUTHOR

Novel 2-chloro-4-anilino-quinazoline derivatives were designed, synthesized and evaluated as EGFR and VEGFR-2 dual inhibitors, standing out compounds **6g** (LASSBio-1814), **6k** (LASSBio-1816) and **6o** (LASSBio-1819) as the most potent inhibitors. Moreover, the SAR and docking studies allowed the identification of pharmacophoric groups for both kinases and demonstrated the importance of a hydrogen bond donor at the *para* position of the aniline moiety for interaction with conserved Glu and Asp amino acids in EGFR and VEGFR-2 binding sites. These compounds present a great potential for future investigation as antitumor drug candidates, because EGFR and VEGFR-2 are validated targets in cancer therapy and the combined inhibition is considered to be synergistic for both antitumor activity and resistance prevention.

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Metal complexes with 2-acetylpyridine-N(4)-ortho-chloro-phenylthiosemicarbazone: cytotoxicity and effect on the enzymatic activity of thioredoxin reductase and glutathione reductase

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Highlights 2014

Cisplatin and the second generation complexes carboplatin and oxaliplatin are antitumor agents widely used in the treatment of a variety of solid tumors. Despite the clinical success of cisplatin, side effects, drug resistance and treatment failure still pose great challenges in chemotherapy with platinum complexes. Since DNA is the primary cellular target of platinum complexes, there is an increasing demand for novel metal-based-pharmaceuticals with a mode of action differing from that of the platinum generation of anticancer drugs.

Numerous metal complexes present cytotoxic or antitumor activities, such as gallium(III), gold(I,III), antimony(III), bismuth(III) and ruthenium(II) complexes. Much effort is presently directed to the search for the mechanism of action of these non-platinum compounds and of their preferential protein targets.

Thioredoxin reductase (TrxR) is a homodimeric selenoenzyme, which is responsible for the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of its substrate thioredoxin (Trx) in the thioredoxin system and for the reduction of many other oxidized cell constituents. It is involved in several metabolic pathways and pathophysiological conditions (cancer, infectious diseases, rheumatoid arthritis, etc). Cancer cells often overexpress both Trx and TrxR indicating that the thioredoxin system may have a crucial role in tumor progression. Hence, both Trx and TrxR might be considered as emerging targets for the development of new anticancer drug candidates.

It has been shown that the anti-rheumatic gold(I) complex auranofin presents antitumor activity and inhibits TrxR with great selectivity (approximately 1000-fold) compared to the related enzymes glutathione reductase (GR) and glutathione peroxidase (GP). In addition, it has been proposed that the relevant cytotoxic actions exhibited by a variety of gold(I) and gold(III) compounds are mainly the result of potent TrxR inhibition, suggesting that the main target of gold complexes is TrxR. Moreover, TrxR inhibition has also been observed with metal complexes different from gold.

Thiosemicarbazones have shown significant antineoplastic activity against a large number of human tumor cell lineages. α(*N*)-heterocyclic thiosemicarbazones have been extensively investigated for their anticancer activity, which has been attributed to the inhibition of ribonucleoside diphosphate reductase (RDR), an essential enzyme involved in the conversion of ribonucleotides into deoxyribonucleotides during DNA synthesis. We demonstrated that gallium(III), platinum(II), palladium(II), gold(I), antimony(III), and tin(IV) complexes with thiosemicarbazones show cytotoxic activity against human tumor cells. The mode of action of the gallium(III) complexes might involve inhibition of RDR while the palladium(II) and platinum(II) complexes probably bind to DNA and the gold(I) complexes act as TrxR inhibitors *in vitro*.

In previous works we reported that 2-acetylpyridine *N*(4)-*ortho*-, *N*(4)-*meta* and *N*(4)-*para*-chlorophenyl thiosemicarbazone were cytotoxic at nanomolar doses against glioma cells and were able to induce cell death by apoptosis induction. In addition, the thiosemicarbazones also proved to be cytotoxic at nanomolar doses against MCF-7 breast adenocarcinoma cells, the *ortho*-chloro derivative being particularly effective.

We now prepared gold(III), platinum(II), palladium(II), bismuth(III), tin(IV), antimony(III) and gallium(III) complexes with *N*(4)-*ortho*-chlorophenyl-2-acetylpyridine thiosemicarbazone (H2Ac4*o*ClPh) (Fig. 1) and assayed the compounds for their cytotoxic activity against MCF-7 breast adenocarcinoma and HT-29 colon carcinoma cells. The ability of the compounds to act as inhibitors of the enzymatic activities of TrxR and GR was investigated.

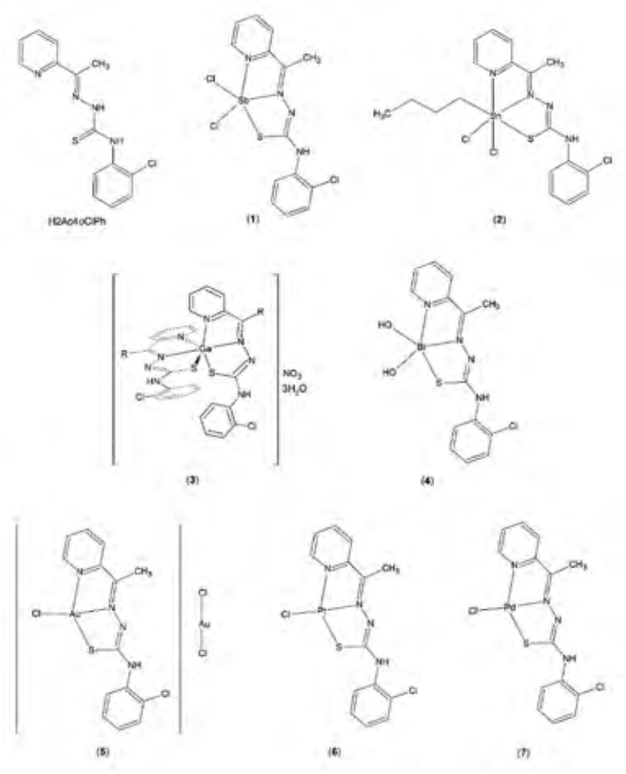


Fig. 1 Structures of 2-acetylpyridine-*N*(4)-*ortho*chlorophenyl thiosemicarbazone (H2Ac4*o*ClPh) and its complexes [Sb(2Ac4*o*ClPh)Cl_2] (**1**), [(*n*-Bu)Sn(2Ac4*o*ClPh)Cl_2] (**2**), [Ga(2Ac4*o*ClPh)$_2$]NO_3·3H_2O (**3**), [Bi(2Ac4*o*ClPh)$(OH)_2$] (**4**), [Au(2Ac4*o*ClPh)Cl]$AuCl_2$ (**5**), [Pt(2Ac4*o*ClPh)Cl] (**6**) and [Pd(2Ac4*o*ClPh)Cl] (**7**).

H2Ac4*o*ClPh and its antimony(III) (Figure 2), tin(IV), gallium(III), bismuth(III) and gold(III) complexes proved to be highly cytotoxic to MCF-7 and HT29 cells whereas the palladium(II) and platinum(II) complexes were not as effective (Table 1). Most of the compounds under study were less cytotoxic to non-malignant Vero cells than to the assayed tumor cell lineages.

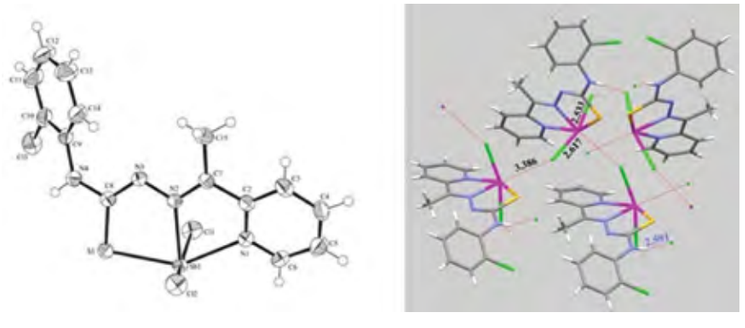


Fig. 2 Ortep drawing and molecular packing of [Sb(2Ac4*o*ClPh)Cl_2] (**1**).

H2Ac4*o*ClPh and its gallium(III) and tin(IV) complexes did not show any inhibitory activity against TrxR and GR. The palladium(II), platinum(II) and bismuth(III) complexes inhibited TrxR at micromolar concentrations but not GR. The antimony(III) (**1**) and gold(III) (**5**) complexes strongly inhibited TrxR at submicromolar doses with GR inhibition at higher concentrations (Table 1, Figure 3). The selectivity of these complexes for TrxR suggests metal binding to a selenol residue in the active site of the enzyme. TrxR inhibition is likely a contributing factor to the mode of action of the gold and antimony derivatives.

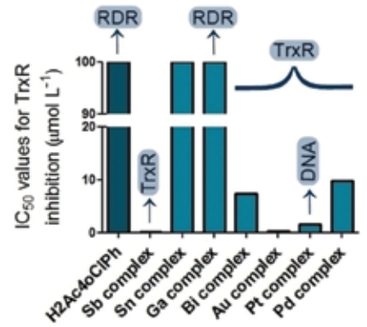


Fig. 3 IC_{50} values for TrxR inhibition by H2Ac4*o*ClPh and its metal complexes.

RDR is believed to be the main target of the thiosemicarbazone and of its gallium(III) complexes. Since gallium(III) and iron(III) show very similar charge-to-radius ratio, the chemical behavior of gallium(III) closely resembles that of iron(III). Due to competitive binding of gallium(III) and iron(III), gallium interacts directly with RDR, displacing iron from the enzyme. Although it has been suggested that the antiproliferative effects of organotin(IV) compounds are related to metal binding to thiol groups of proteins, the mode of cytotoxic action of these compounds remains largely unknown. In the present work [(*n*-Bu)Sn(2Ac4*o*ClPh)Cl_2] (**2**) was unable to inhibit both TrxR and GR enzymatic activities under the experimental conditions.

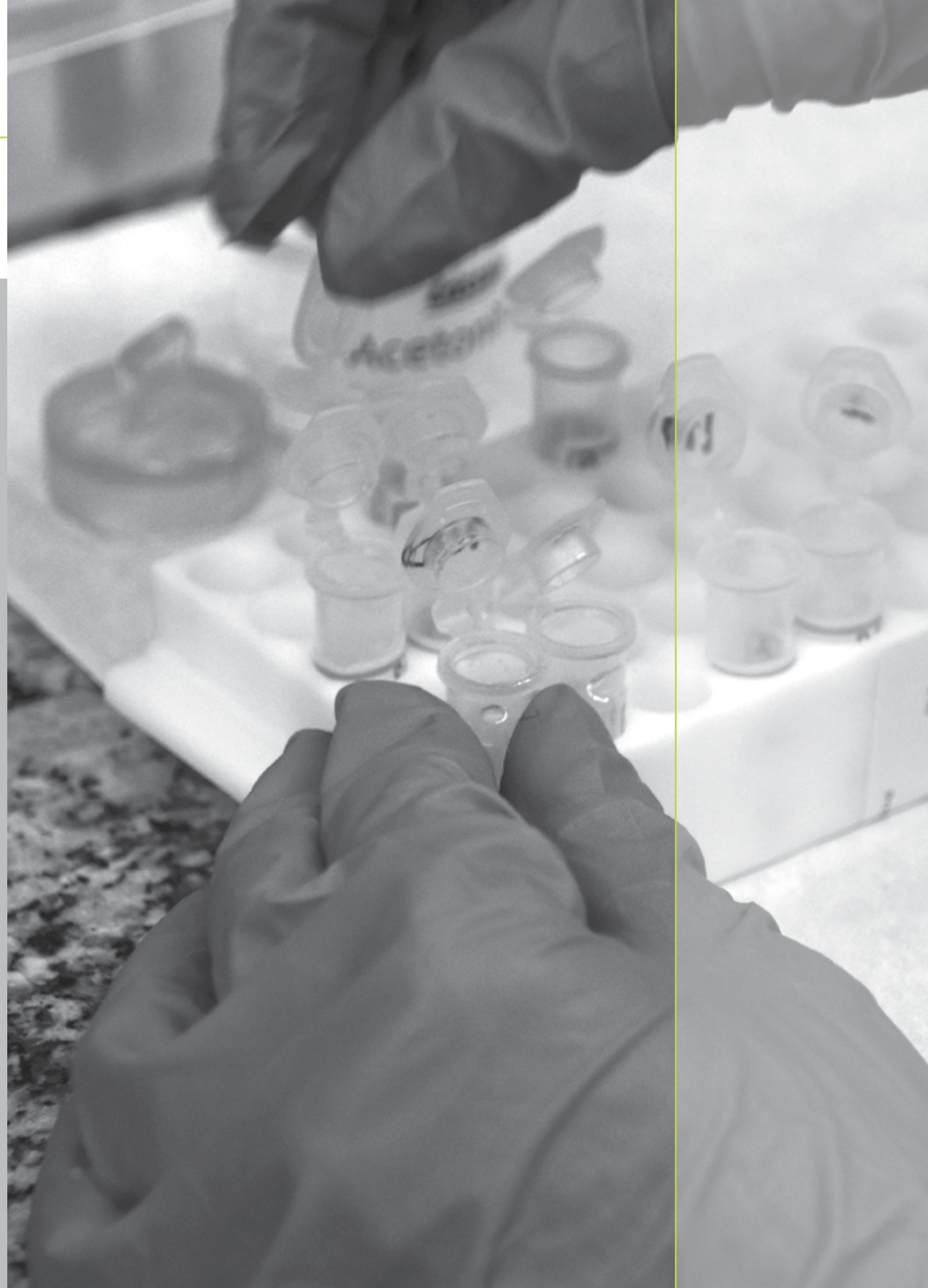
Table 1: IC_{50} values of compounds for TrxR and GR inhibition and cytotoxic activity against HT-29, MCF-7 and Vero cells

Compounds	Enzyme inhibition (IC_{50}, µmol L^{-1})		Cytotoxic effect (IC_{50}, µmol L^{-1})		
	TrxR	GR	MCF-7	HT-29	Vero
H2Ac4oClPh (HL)	>100	>100	7.02 ± 1.14 × 10^{-3}	6.96 ± 1.28 × 10^{-3}	0.02 ± 0.01
[Sb(L)Cl_2] (1)	0.16 ± 0.03	37.71 ± 5.11	3.55 ± 1.07 × 10^{-3}	4.75 ± 0.75 × 10^{-3}	0.13 ± 0.11
[(n-Bu)Sn(L)Cl_2] (2)	>100	>100	4.60 ± 0.64 × 10^{-3}	5.23 ± 0.43 × 10^{-3}	0.10 ± 0.04
[Ga(L)$_2$]NO_3 (3)	>100	>100	3.56 ± 0.44 × 10^{-3}	1.84 ± 0.37 × 10^{-3}	0.02 ± 0.01
[Bi(L)$(OH)_2$] (4)	7.35 ± 2.68	>100	4.30 ± 1.63 × 10^{-3}	6.16 ± 0.72 × 10^{-3}	0.02 ± 0.01
[Au(L)Cl][$AuCl_2$] (5)	0.23 ± 0.02	1.22 ± 0.09	10.20 ± 0.42 × 10^{-3}	35.89 ± 3.47 × 10^{-3}	0.09 ± 0.01
[Pt(L)Cl] (6)	1.57 ± 1.32	>100	8.16 ± 2.74	2.87 ± 2.32	14.44 ± 0.98
[Pd(L)Cl] (7)	9.73 ± 1.50	>100	1.38 ± 0.95	2.00 ± 0.93	2.84 ± 0.99

Overall the cytotoxic effect of the compounds is largely the result of the thiosemicarbazone ligand. However, selective inhibition of TrxR by complexes (**1**) and (**5**) adds another mechanism contributing to their pharmacological profile. The complexes might thus provide prototypes for multi-target anticancer metal-based drugs. Further structural optimization of the compounds and elucidation of relevant cellular pathways are surely of interest.

COMMENTS FROM AUTHOR

DNA is the primary cellular target of cisplatin and second generation platinum complexes. Current research aiming to overcome the problems associated with platinum anticancer drugs has focused on other metal-based therapeutics with different mechanisms of action. Gold complexes proved to have cytotoxic activity and are recognized as extremely potent inhibitors of thioredoxin reductase (TrxR), a large homodimeric selenoenzyme, which controls the redox state of thioredoxin (Trx) in the thioredoxin system. In previous works we demonstrated that 2-acetylpyridine-*N*(4)-*ortho*-chlorophenylthiosemicarbazone (H2Ac4*o*ClPh) presents cytotoxic effect at nanomolar doses against human tumor cell lineages. In the present study we showed that H2Ac4*o*ClPh and its gold(III), gallium(III), tin(IV), antimony(III), and bismuth(III) complexes are highly cytotoxic against MCF-7 breast adenocarcinoma and HT-29 colon carcinoma cells. The antimony(III) and gold(III) complexes strongly inhibited TrxR at submicromolar doses with GR inhibition at higher concentrations. The selectivity of these complexes for TrxR suggests metal binding to a selenol residue in the active site of the enzyme. Selective inhibition of TrxR by the antimony(III) and gold(III) complexes adds another mode of action contributing to their pharmacological profile. As we mentioned in the published article, the identification of TrxR as a target for gold(III) and antimony(III) complexes might hopefully lead to the discovery of more effective, "mechanism-oriented", anticancer metal-based drugs. In addition, to our knowledge this is the first report on inhibition of TrxR by an antimony(III) compound. This finding is important also due to the known anti-parasitic effects of antimonial drugs since TrxR could be an additional target for their pharmacological or toxic effects.



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Highlights 2014

N-acylhydrazone derivative ameliorates monocrotaline-induced pulmonary hypertension through the modulation of adenosine AA2R activity.

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Pulmonary arterial hypertension (PAH) is characterized by excessive pulmonary vasoconstriction and abnormal vascular remodeling processes that usually affect all vessel layers and result in severe loss of cross-sectional area and, therefore, increased right ventricular (RV) afterload. Although the pathogenesis of PAH is incompletely understood, evidence suggests that PAH is associated with activation of inflammatory processes, endothelial damage and dysfunction, and abnormal coagulation.

Adenosine is a potent modulator of cardiovascular function. Adenosine A_{2A}receptors ($A_{2A}R$) are located primarily in the vasculature where they mediate vasodilatation, and in the heart they promote cardioprotective effects. Current therapies for chronic PAH are designed to reduce pulmonary arterial resistance by inducing vasodilatation, but these therapies only provide symptomatic relief. Recently, we have shown that an N-acylhydrazone derivative from safrole, a substance present in sassafras oil, may contribute to the prevention of MCT-induced PAH by reversing pulmonary vascular remodeling, which in turn reduces RV hypertrophy.

In the present study, we investigated the efficacy and a possible molecular mechanism of (*E*)-*N*'-(3,4dimethoxybenzylidene)-4-methoxybenzohydrazide (LASSBio-1386), a new compound of the N-acylhydrazone class synthesized by our group (Fig. 1A), in MCT-induced PAH rats. The vasodilator activity of LASSBio-1386 was evaluated in pulmonary artery rings from normal Wistar rats. The compound induced relaxation of Phe-contracted vessels (10^{-5} M) in a concentrationdependent manner. The concentration of LASSBio-1386 that reduced 50% of the Phe-induced contraction (IC_{50}) was 6.8 ± 0.6 μM (Fig. 1B). The vasodilator effect of LASSBio-1386 was investigated in the presence of ZM 241385 (10^{-7} M), which is a selective antagonist of $A_{2A}R$. Pretreatment of pulmonary arteries with ZM 241385 induced a rightward shift of the concentration-response curve and reduced the maximal relaxation from 100% to 57.4% ± 1.8% (P b 0.05, Fig. 1B). The proposed molecular rationale for the activation of $A_{2A}R$ by LASSBio-1386 was determined observing the highest score pose obtained after a docking run into the binding site of $A_{2A}R$ (PDB ID 3EML). It can be observed that the methoxy group of the para-methoxyphenyl subunit of LASSBio-1386 makes a hydrogen bond with the peptidic NH group of this same residue, but this interaction is expected to be weaker than the hydrogen bond of ZM 241385 that involves the negatively charged carboxylate group of Glu169 (Fg.1C-D).

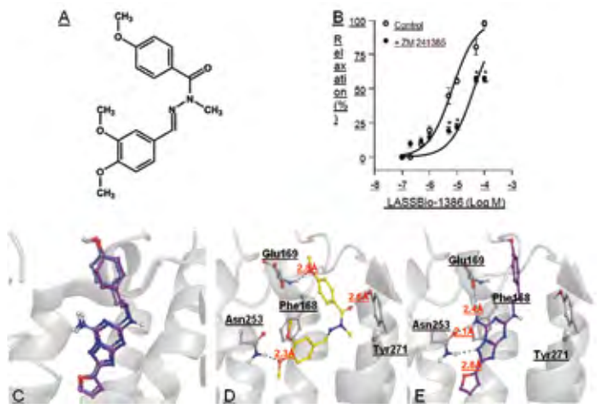

Fig. 1. (A) Chemical structure of (E)-N'-(3,4-dimethoxybenzylidene)-4-methoxybenzohydrazide (LASSBio-1386). (B) Concentration-response curves for LASSBio-1386 in pulmonary artery rings from normal Wistar rats, contracted with phenylephrine (10^{-5} mol/L), in the presence or absence of ZM 241385 (10^{-7} mol/L). Data are mean ± SEM (n = 5). ⁎P b 0.05 compared to control. (C) Superposition of ZM241385 conformation in the crystal structure of A_{2A} receptor (purple) and that obtained after re-docking (light purple) using the program GOLD 5.2. RMSD = 0.63 Å. (D) Binding mode predicted of LASSBio-1386 and its interactions in A_{2A} adenosine receptor. (E) Interactions of the co-crystallized antagonist ZM 241385 in the A_{2A} adenosine receptor (PDB ID: 3EML).

The animals were submitted to a treadmill test before, 14 days after, and 28 days after the MCT injection. The EC for control rats before the MCT injection was 1631.0 ± 67.5 m·kg, and for the MCT groups (MCT, MCT + vehicle, and MCT + LASSBio-1386) it was 1715.0 ± 52.7 m·kg, 1677.0 ± 78.5 m·kg, and 1812.0 ± 49.4 m·kg, respectively. Fourteen days after the MCT injection, the EC was significantly reduced from 1544.0 ± 109.1 m·kg in the control group to 871.7 ± 27.8 m·kg (MCT) and 760.9 ± 34.7 m·kg (MCT + vehicle). Fourteen days after MCT administration in animals that were treated with LASSBio-1386 (MCT + LASSBio-1386), the EC was further reduced to 630.1 ± 31.2 m·kg (P b 0.05 vs. control); while at 28 days after MCT injection, oral treatment with LASSBio-1386 significantly increased the EC to 1357.0 ± 87.8 m·kg (Fig. 2).

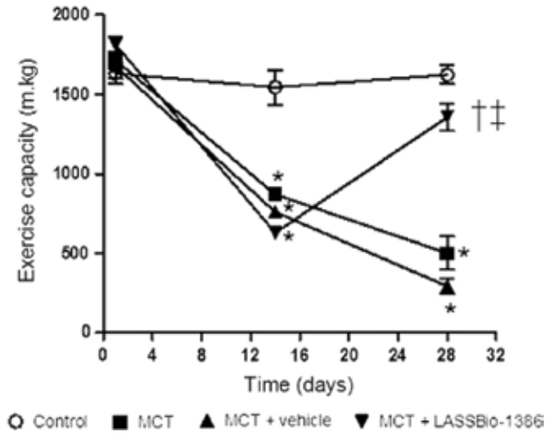

Fig. 2. Effects of the oral treatment with vehicle (DMSO) or LASSBio-1386 (50 mg/kg/day) of MCT-injected rats in exercise test protocol. Data are mean ± SEM (n =5-6). *P b 0.05 compared to control; †P b 0.05 compared to MCT; ‡P b 0.05 compared to MCT + vehicle. All groups were evaluated before MCT injection, 14 and 28 days after MCT injection. 14 days after MCT injection, MCT-injected rats received vehicle or LASSBio-1386 for 2 weeks.

Pulmonary hypertension and RV dysfunction were found in MCT-treated rats as indicated by a significant increase in RVSP values at day 28, compared with the control rats (49.60 ± 5.0 mm Hg vs. 27.28 ± 2.1 mm Hg, P b 0.05). However, RVSP was attenuated in rats treated with LASSBio-1386 at a dose of 50 mg/kg (27.03 ± 1.2 mm Hg) (Fig. 3).

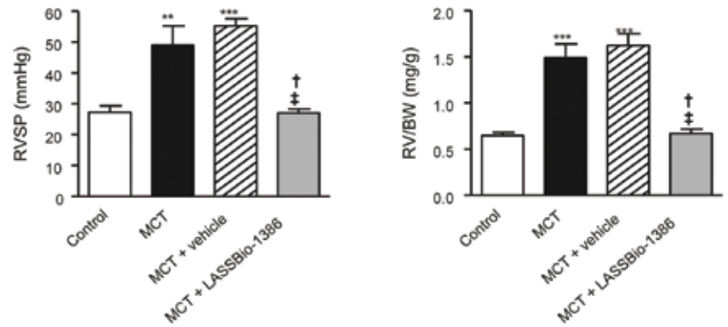

Fig. 3. Effects of the oral treatment with LASSBio-1386 (50 mg/kg/day) for 2 weeks on right ventricular systolic pressure (RVSP) and on right ventricular (RV) hypertrophy in MCT-injected rats. (A) Representative tracings of RVSP of control rats, monocrotaline (MCT), MCT + vehicle (DMSO), and MCT + LASSBio-1386, respectively. (B) Right ventricular systolic pressure (RVSP). Oral treatment with LASSBio-1386 recovered this parameter. (C) RV weight to body weight ratio [RV/BW]. Treatment with LASSBio-1386 decreased the RV hypertrophy. Each column represents the mean ± SEM (n = 6). **P b 0.01, ***P b 0.001 compared to control; †P b 0.05 compared to MCT; ‡P b 0.05 compared to MCT + vehicle.

Representative images of the pulmonary arterioles are shown in Fig. 4. The wall thickness of the pulmonary arterioles (b50 μm) was significantly increased from 64.7% ± 1.7% (control rats) to 77.2% ± 2.6% (MCT + vehicle rats). Oral treatment with LASSBio-1386 (50 mg/kg) reduced the wall thickness of these vessels to 69.1% ± 1.6% (P b 0.05 vs. MCT + vehicle; Fig. 4). In vessels with diameter ranging between 50 and 150 μm, the wall thickness was increased from 56.2% ± 2.3% (control rats) to 66.9% ± 2.3% (MCT + vehicle rats). The wall thickness of pulmonary arterioles of MCT-injected rats treated with LASSBio-1386 decreased to 57.9% ± 1.8% (P b 0.05 vs. MCT + vehicle; Fig. 4).Western blot analysis of RV tissue showed that PAH reduced $A_{2A}R$ expression (Fig. 5). LASSBio-1386 enhanced the levels of $A_{2A}R$ in the RV from MCT-induced pulmonary hypertensive rats. To determine which molecular pathways are involved in LASSBio1386 intervention in RV dysfunction, we investigated the effects of LASSBio-1386 on Ca^{2+} handling through SERCA2a and PLB expression. SERCA2a protein expression was downregulated, while PLB was overexpressed in PAH rats. After treatment with LASSBio-1386, SERCA2a protein expression was elevated, and a reduction in the PLB protein level was observed. PAH induced a reduction in Ca^{2+}-ATPase activity in RV tissues. However, LASSBio-1386 was found to reverse this reduction of Ca^{2+}-ATPase activity in MCT-treated rats.

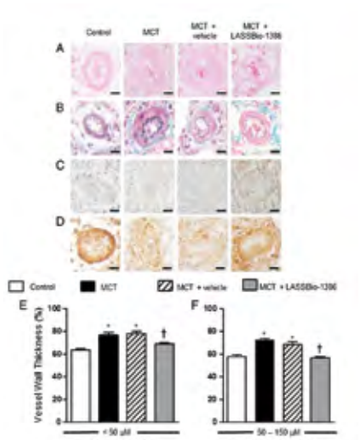

Fig. 4. Representative images of lung sections of control rats and MCT-injected rats treated orally with vehicle (DMSO) or LASSBio-1386 (50 mg/kg/day). Images show vessels at 40x magnification. Each bar represents 20 µm. (A) Hematoxylin and Eosin; (B) Gomori's trichrome; (C) Negative control and (D) Immunohistochemical staining for alpha-actin. (E) Wall thickness expressed as a percent of the total area of the vessel (b 50 µm). (F) Wall thickness of vessels ranging between 50 – 150 µm in external diameter. Each column represents the mean ± SEM.

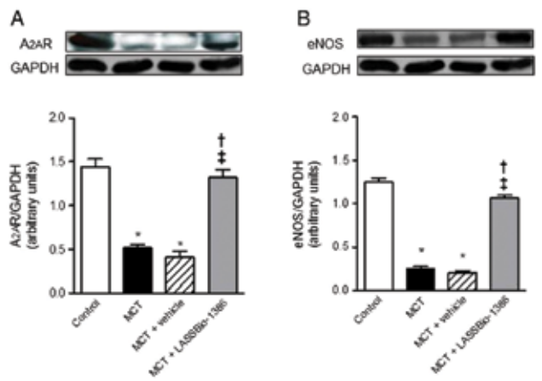

Fig. 5. Western blot analyses of (A) adenosine A_{2A} receptor ($A_{2A}R$) and (B) endothelial NO synthase (eNOS) expression in lungs from control, monocrotaline (MCT), MCT + vehicle (DMSO), and MCT + LASSBio-1386 groups, respectively. GAPDH was used for normalization. Graphs show protein quantification. Each column represents the mean ± SEM (n = 5-6).

The present study shows that LASSBio-1386 reduces pulmonary vascular remodeling, RV systolic pressure, and RV hypertrophy in rats with MCT-induced PAH. Moreover, we were able to demonstrate that these beneficial effects are accompanied by a significant improvement of exercise capacity. LASSBio-1386 administration decreased the presence of proliferative changes in the pulmonary arterioles and the pulmonary vascular remodeling as well as recovered endothelial dysfunction of pulmonary artery rings, as assessed by the normalized ACh-induced relaxation. This result probably occurs because $A_{2A}R$ activation represents an important regulatory mechanism to control the development of PAH and pulmonary vascular remodeling. Pretreatment of pulmonary artery rings with the $A_{2A}R$ antagonist ZM 241385 significantly decreased the vasodilator effect of LASSBio-1386. This finding suggests the involvement of $A_{2A}R$ in this process.

COMMENTS FROM AUTHOR

In this study, the orally administered LASSBio-1386 reduced the hypertrophic vascular and cardiac remodeling, which is observed in PAH. Our findings have important pharmacological and clinical implications, as some alterations of eNOS, A2AR, SERCA2a and PLB expression were restored after treatment with LASSBio-1386 suggesting a promise therapeutic approach for the disease.

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Highlights 2014

MyD88-, but Not Nod1- and/or Nod2-Deficient Mice, Show Increased Susceptibility to Polymicrobial Sepsis due to Impaired Local Inflammatory Response

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Sepsis is a complex syndrome caused by the inability of the host to control an infection, usually triggered by bacteria. Neutrophil recruitment to the infection site has been demonstrated to be essential for the bacterial clearance, preventing the spread of the infection. The recruitment of neutrophils is enabled by the establishment of inflammatory response after the pathogen detection by two main families of pattern recognition receptors in the host immune cell: Toll-like receptors (TLR) and Nucleotide-binding oligomerization domain (Nod)-like receptors (NLR). In this study, we investigated the role of Nod1, Nod2, and MyD88, the adaptor protein of the most of TLR in the chemokine production and neutrophil recruitment after caecal ligation and puncture (CLP) in C57Bl/6 mice.

Nod1 and Nod2 have been described to play role in the immune response to several bacterial infections. Moreover, Nod1 ligands have been show to induce production of chemokines and neutrophil recruitment *in vivo*. Unexpectedly, neutrophil recruitment and chemokines CXCL1 and CXCL2 levels were similar in WT, *Nod1*- and *Nod2*-deficient mice 6 and 24 h after CLP (Figure 1a, 1b, and 1c). Consequently, bacterial loads in the peritoneal cavity and the blood were also similar in all the groups tested (Figures 1d and 1e). In addition, we demonstrated that systemic parameters such as IL-6 and neutrophil sequestration at the lungs were not altered by the absence of Nod1 or Nod2 (Figure 1f and 1g). As expected, WT, *Nod1*- and *Nod2*-deficient mice showed similar survival rates in CLP-induced sepsis (Figure 1h). Reaffirming these results, double deficient mice for *Nod1* and *Nod2* (*Nod1/Nod2*) as well as mice lacking their downstream adaptor protein Rip2 also showed unaltered local and systemic responses to WT mice. Neutrophil recruitment, CXCL1, and CXCL2 local production, bacterial load in the peritoneal cavity and blood, IL-6 systemic production and neutrophil sequestration at the lung were similar to the ones in WT mice (Figure 2a-g). As consequence, the survival curve was also similar between Nod1/Nod2 and Rip2 and WT (Figure 2h and 2i).

On the other hand, our group has reported that TLR2, 4 and 9 play deleterious role in neutrophil recruitment and in the outcome to CLP-induced sepsis. It is believed that the activation of many TLRs during the polymicrobial challenge contributes to the overwhelming of inflammatory response observed in sepsis and may leads to high mortality rates. However, here we demonstrate that the abrogation of most TLR signalling, assessed by *MyD88*-deficient mice, leads to high susceptibility to sepsis because of the inability to establish a local inflammatory response. Neutrophil recruitment and CXCL1 and CXCL2 local levels were markedly reduced in *MyD88*- deficient mice (Figure 3a-c) leading to increase in bacterial load in the peritoneal cavity and in the blood (Figure 3d and 3e). The *MyD88*-deficient mice also showed a strong reduction in IL-6 levels (Figure 3f) in the peritoneal cavity. However, *MyD88*-deficient neutrophils are recruited in response to CXCL2 *in vitro* and *in vivo* in non-septic mice (Figures 4a e 4b), indicating that the reduction in the neutrophil recruitment in *MyD88*-deficient mice is not due to a reduction in the chemotactic ability of the neutrophils. Tracked neutrophils from WT and *MyD88*-deficient mice injected into WT mice 2 h before sepsis induction showed similar numbers of WT and *MyD88*-deficient neutrophils in the peritoneal lavage of WT mice after sepsis induction (Figure 4c). Moreover, the adoptive transfer of WT resident cells into MyD88-deficient mice before the induction of sepsis resulted in the increase of local levels of CXCL2 (Figure 4d). Additionally, there was an increase in neutrophil recruitment to the peritoneal cavity during CLP-induced sepsis (Figure 4e). As expected, we showed that *MyD88*-deficient mice were markedly susceptible to CLP-induced sepsis (Figure 4f).

In conclusion, our data indicate that Nod1 and Nod2 are not required for the development of the inflammatory response and the outcome of polymicrobial sepsis in our experimental conditions. Nonetheless, we demonstrated that MyD88-dependent signalling is crucial for sepsis because the removal of this molecule completely dampened the establishment of the local inflammatory response, culminating in a high susceptibility to CLP-induced sepsis.

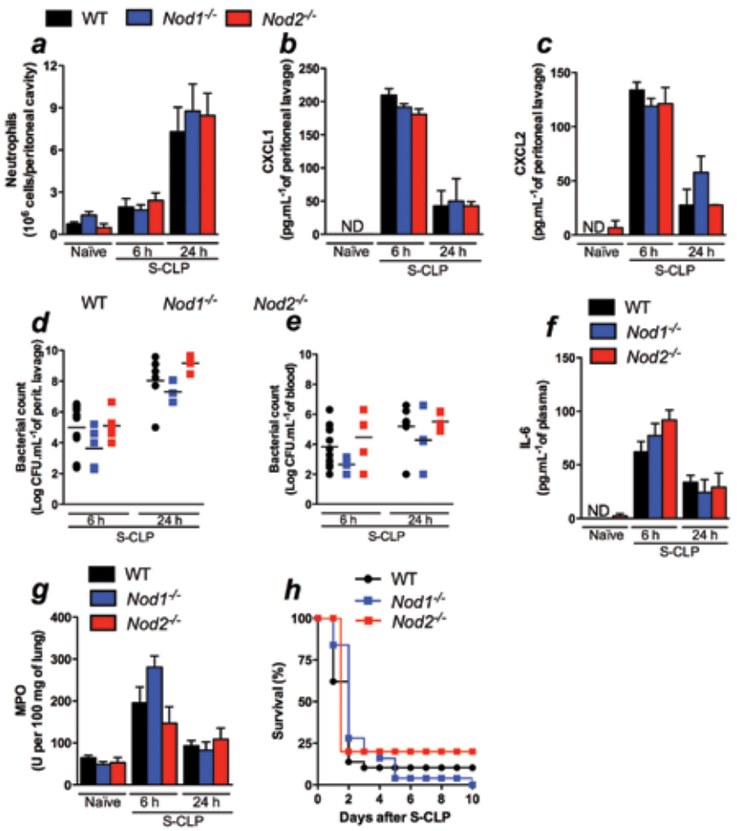

Figure 1. Nod1 and Nod2 are not crucial for the inflammatory response during severe polymicrobial sepsis. Six or 24h *Nod1*- and *Nod2*-deficient mice (WT, *Nod1*$^{-/-}$ and *Nod2*$^{-/-}$, respectively) underwent CLP-induced severe sepsis they were assessed for: a) neutrophil recruitment to the peritoneal cavity; b) CXCL1 and c) CXCL2 levels in the peritoneal lavage, as measured by ELISA; d) bacterial count in the peritoneal lavage and e) blood; f) IL-6 levels in plasma; g) lung MPO activity. The data were analysed by multifactorial ANOVA and are expressed as the mean ± SEM in a, b, c, f and g and as median in d and e. h) The survival curve was observed up to 10 days after the induction of severe sepsis (S). The results are expressed as percentage of survival and were analysed by the Mantel-Cox log-rank test. The graphs represent the mean of the results of two or three independent experiments. n = 3 to 6 per experiment; ND = not detected.

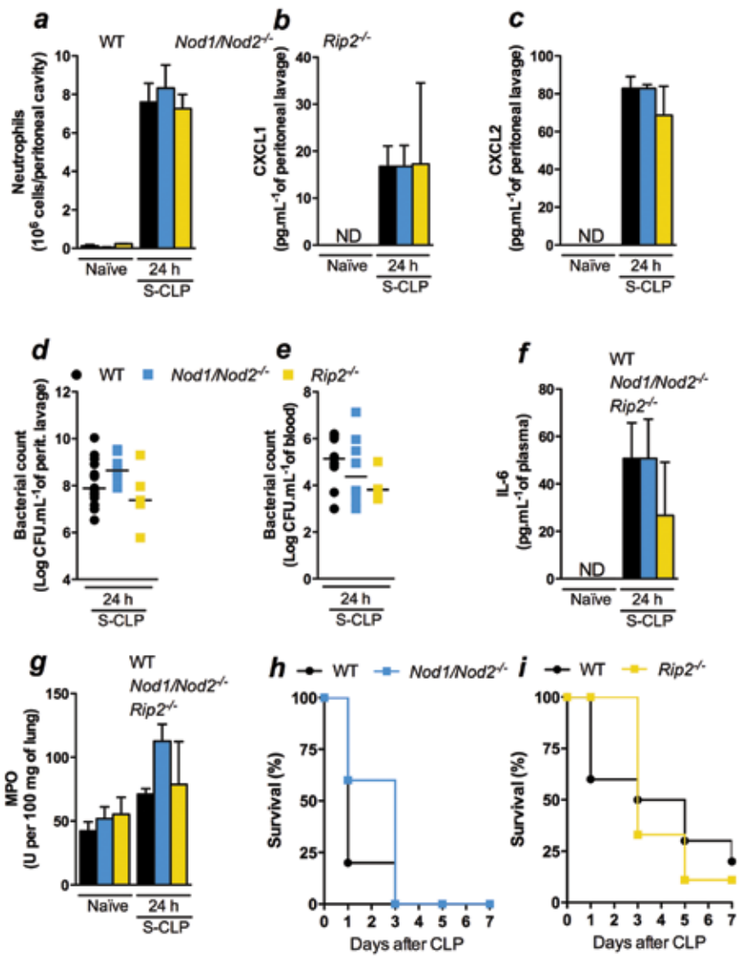

Figure 2. The additive response of Nod1 and Nod2 is not essential to the inflammatory response during severe polymicrobial sepsis. At 24h *Nod1/Nod2*- and *Rip2*-deficient mice (*Nod1/Nod2*$^{-/-}$ and *Rip2*$^{-/-}$, respectively) underwent CLP they were assessed for: a) neutrophil recruitment to the peritoneal cavity; b) CXCL1 and c) CXCL2 levels in the peritoneal lavage as measured by ELISA; d) bacterial count in peritoneal lavage and e) blood; f) IL-6 levels in plasma; g) lung MPO activity; h) survival of WT and *Nod1/Nod2*-deficient mice and i) *Rip2*-deficient mice post-CLP-induced severe sepsis. The data are expressed as the mean ± SEM in a, b, c, f and g; median in d and e; and as a percentage of survival in h and i. The data in a, b, c, d, e, f and g were analysed by multifactorial ANOVA and the data in h and i were analysed by Mantel-Cox log-rank test. The results are representative of at least two independent experiments. n = 5 to 8; ND = not detected.

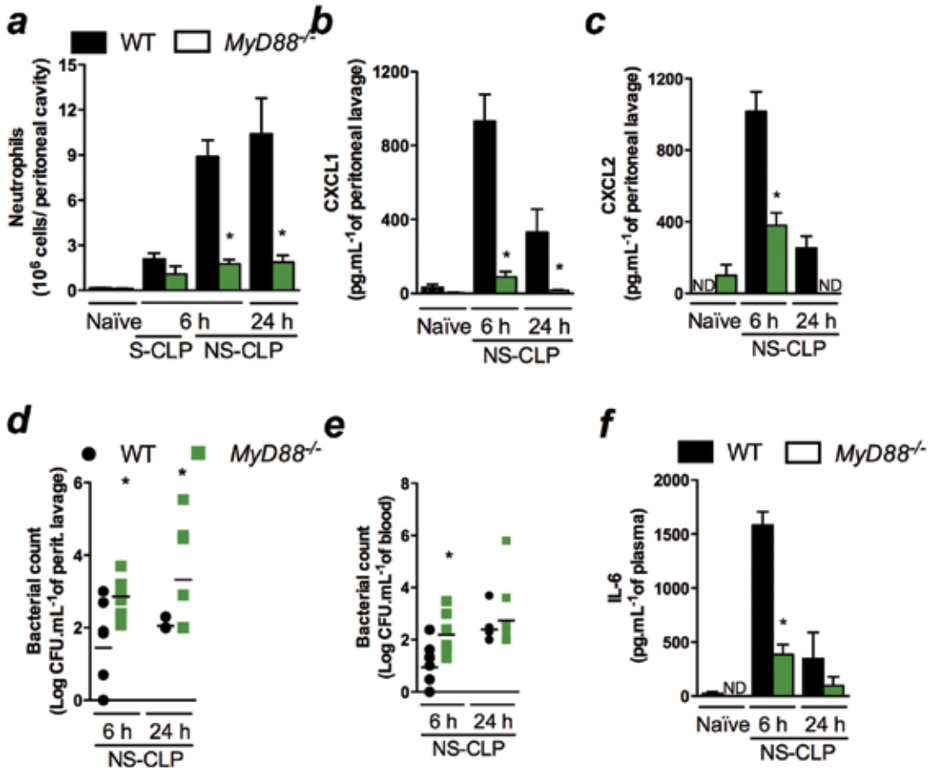

Figure 3. MyD88 is crucial for the resolution of non-severe sepsis. Non-severe (NS) and severe (S) sepsis were induced by CLP in WT and *MyD88*-deficient mice and 6 or 24 h after sepsis induction, the following were assessed: a) neutrophil recruitment to the peritoneal cavity; b) CXCL1 and c) CXCL2 levels in the peritoneal lavage determined by ELISA; d) bacterial count in the peritoneal lavage and e) blood; f) IL-6 levels in the plasma, as measured by ELISA. These data are expressed as the mean ± SEM in a, b, c, and f and median in d and e. The data were analysed by multifactorial ANOVA followed by unpaired t test. The graphs are representative of one to four independent experiments. n = 4 to 10; ND = not detected.*P<0.05.

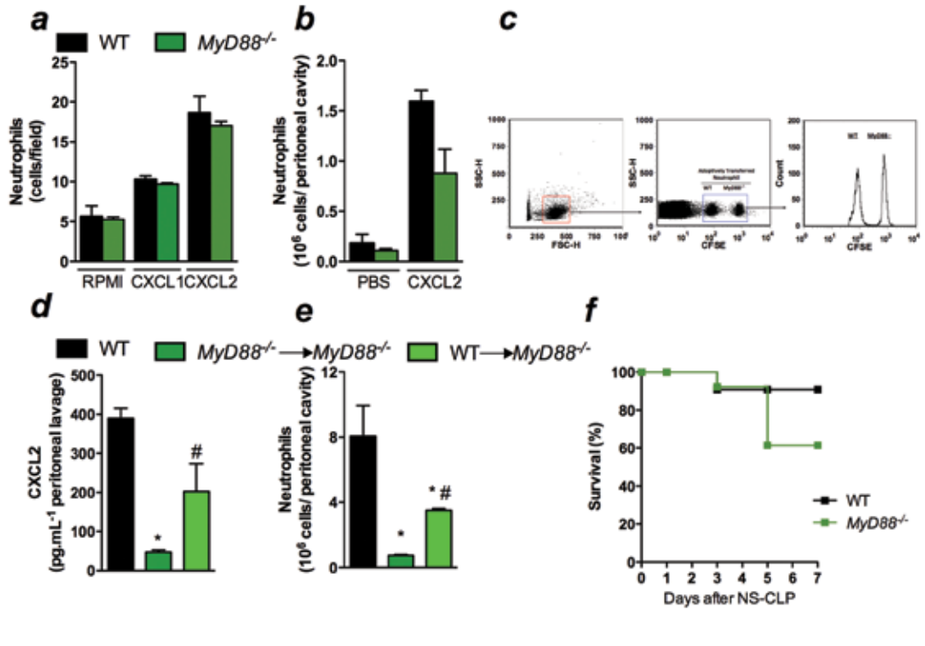

Figure 4. MyD88 is crucial for the establishment of the inflammatory response during polymicrobial sepsis. a) Bone marrow-isolated neutrophils (5×10^4/well) from WT or MyD88-deficient mice ($MyD88^{-/-}$) were stimulated by CXCL1 or CXCL2 (10 ng/mL) in a Boyden chamber to measure chemotaxis. b) Neutrophil recruitment to the peritoneal cavity 6 h after an i.p. injection of CXCL2 (30 ng/cavity). c) Neutrophils from the bone marrow of WT or MyD88-deficient mice were stained with different concentrations of CFSE and administered (5×10^6/mouse; i.v.) into WT mice 2 h before non-severe (NS) sepsis induction by CLP. Cells in the peritoneal lavage were harvested 6 h after CLP surgery and analysed by flow cytometry. For d–e, resident peritoneal cells from WT and *MyD88*-deficient mice were harvested and transferred (5×10^6/intraperitoneal cavity) to *MyD88*-deficient mice 30 minutes before CLP surgery. d) CXCL2 was measured by ELISA in the peritoneal lavage at 6 h after CLP surgery, as was the e) neutrophil recruitment to the peritoneal cavity. The data are expressed as the mean ± SEM and were analysed by unpaired t test. f) Sepsis was induced in WT and *MyD88*-deficient mice (WT, $MyD88^{-/-}$, respectively) using CLP model. The survival curve was observed up to 10 days after the induction of non-severe (NS) sepsis. The results are expressed as percentage of survival and were analysed by Mantel-Cox log-rank test. The graphs represent one of one to two independent experiments. *n = 5 to 6* per experiment. *$P<0.05$ compared to WT and #$P<0.05$ compared to $MyD88^{-/-}\rightarrow MyD88^{-/-}$.

COMMENTS FROM AUTHOR

The recognition of bacteria during an infection is crucial for the establishment of an immune response. During this process, neutrophils are recruited to the infection site to control bacterial growth. The impairment of the neutrophil recruitment has been strongly associated to a poor outcome to sepsis. The main families involved in the recognition of pathogens are Toll-like receptors (TLR) and Nod-like receptors (NLR). Nod1 and Nod2 have been previously shown to be involved in neutrophil recruitment during bacterial infections. However, here we clearly demonstrated that the absence of Nod1 and Nod2 are not indispensable for the establishment of a local inflammatory response, and neutrophil recruitment in sepsis. By contrast, we showed that MyD88-dependent TLR signalling plays a crucial role in the local production of inflammatory mediators and the consequent recruitment of neutrophils to the infection site, preventing mortality. Therefore, this study contributes to the further understanding of the sepsis physiopathology, by describing the differing involvement of the two main families of pattern recognition receptors during the establishment of the immune response.

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Highlights 2014

Local Administration of Gold Nanoparticles Prevents Pivotal Pathological Changes in Murine Models of Atopic Asthma

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Atopic asthma is a chronic inflammation of the lung airways triggered by environmental antigens in genetically predisposed individuals. The prevalence of asthma has increased over the last 50 years, impacting around 300 million individuals worldwide and causing 250,000 annual deaths globally. Asthma pathogenesis is accounted for by a complex interplay of numerous cell types and inflammatory mediators, leading to airway hyper-reactivity (AHR), lung tissue remodeling and airflow limitation. T cells and T-helper 2 (Th2) cytokines orchestrate this complex response in which infiltrating eosinophils, and in some occasions also neutrophils, are suggested to play a major effector role.

Nanoscale structures can exhibit widely different properties to bulk materials or small molecules, which renders them applicable in the fields of medical imaging and therapy.On the other hand, it is well established that gold compounds have a variety of biomedical applications due to its anti-inflammatory and anti-oxidant activity.Remarkably, administration of gold nanoparticles can lead to anti-inflammatory effects in different pathophysiological conditions. For instance, they cause inhibition of inflammatory cell accumulation and reduction in TNF-α and IL-1β generation in experimental arthritis.Also, they are known to down-regulate the TLR4–NF-kB pathway by reducing oxidative damage in experimental uveitis triggered by LPS.Moreover, gold nanoparticles possess anti-angiogenic properties, as attested by impairment of both VEGF-induced migration of vascular endothelial cells in vitro and angiogenesis in nude mouse ear and mouse ovarian tumor experiments in vivo.

In the current study, we have employed outbred and inbred mouse strains, namely Swiss-Webster and A/J mice, respectively, to investigate the effect of intranasal instillation of low amounts of gold nanoparticles on allergen-induced lung inflammation, mucus exacerbation, subepithelial fibrosis and airway hyper-reactivity.

We have used small angle X-ray scattering (SAXS) and zeta-potential measurements in order to determine shape, size, dispersity and average zeta-potential of citrate-stabilized gold nanoparticles used in this study. As shown in Figure 1, their characteristic SAXS intensity profile was typical of scattering objects consisting of widely separated homogenous hard-spheres.

Ovalbumin provocation of sensitized A/J mice caused significant airway hyper-reactivity, as demonstrated by increased lung resistance and elastance after methacholine provocation (Figure 2). As shown in the same figure, intranasal treatments with gold nanoparticles prevented allergen-induced airway hyper-reactivity.

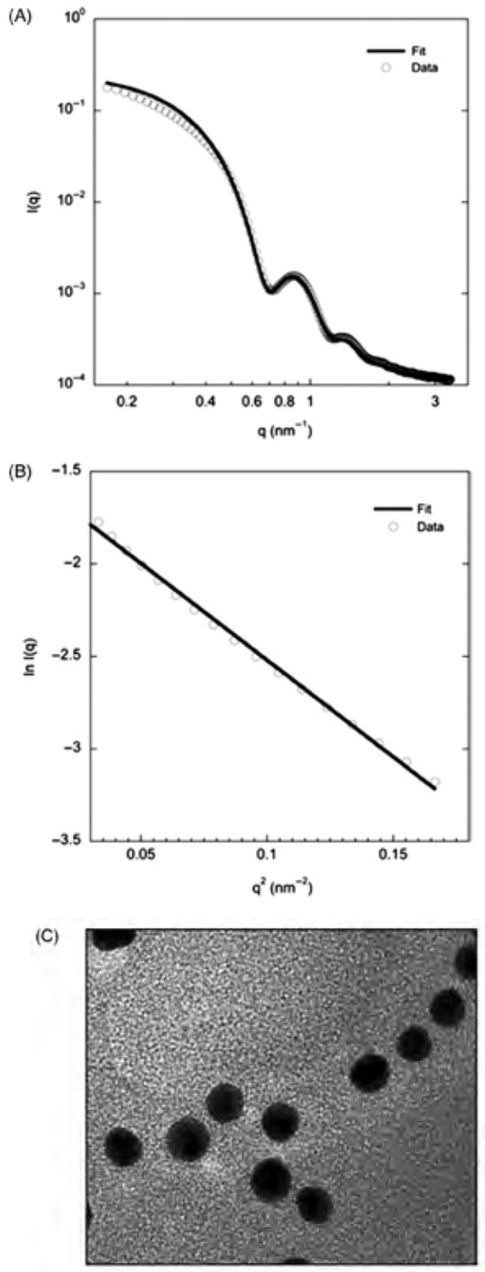

Figure 1. SAXS scattering profile with corresponding curve fitting (A) and Guinier plot (B) for 0.05 mg/mL AuNPs stabilized by 1.0 mM citrate species. Representative TEM micrographs of AuNP (C).

Next, we examined the anti-inflammatory and anti-remodelling effects of the nanoparticles. Lung tissue was collected 24 h after the last ovalbumin challenge in sen- sitized and challenged A/J mice. In ovalbumin-induced asthmatic mice, we observed an intense eosinophilic (cells stained in orange) leukocyte infiltration into the perivas- cular and peribronchiolar areas (Fig. 3B), as compared to the sham-challenged group (Fig. 3A). This inflammatory response was significantly inhibited in animals pretreated with gold nanoparticles (60 µg/kg) (Fig. 3C)), reaching a blockade of about 55% 24 h post-challenge (Fig. 3D).

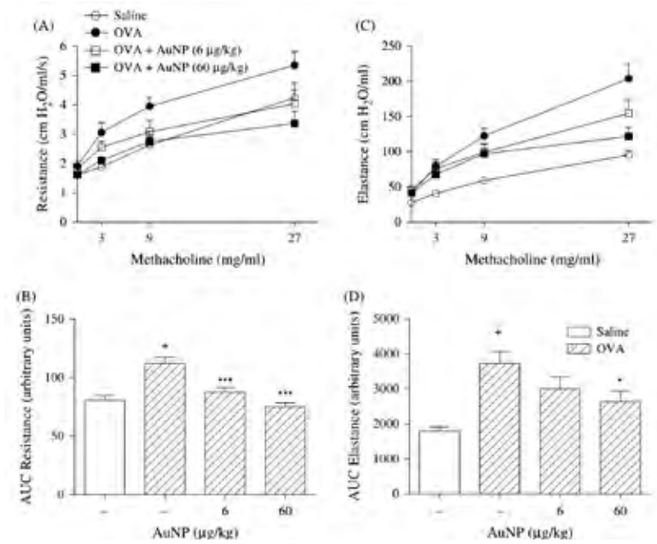

Figure 2. AuNP attenuates the ovalbumin-induced AHR caused by methacholine aerosolization of sensitized and challenged A/J mice. AHR was monitorized by assessing changes in airway resistance ((A), (B)) and elastance ((C), (D)) induced by increasing concentrations of methacholine 24h after the last ovalbumin or saline challenge. (B) and (D) represent area under the curve calculated from the dose-response curves of bronchoconstriction to methacholine. Data are expressed as mean ± S.E.M. of mice. $^{+}P < 0.001$ as compared to the sham-challenged group. $*P < 0.05$ and $***P < 0.001$ as compared to the ovalbumin-challenged group.

Our data further revealed that gold nanoparticles significantly reduces the mucus hyper-secretion(Fig. 4), as well adverse airway remodelling (Fig. 5), pointed out by over-deposition of extracellular matrix in the lung sub-epithelial area of allergen-challenged animals. In addition, the protective effects of gold nanoparticles administered locally correlated with the blockade of a range of Th2 pro-inflammatory cytokines and chemokines, also confirmed in an outbred strain of mice, named Swiss-Webster (data not shown).

Asthma pathological changes are associated with airway inflammation and oxidative stress in many ways. Remarkably, the treatment led to significant reduction in the generation of free radicals, including ROS and MDA. Allergen provocation led to a significant increase in the levels of lung tissue lipid peroxidation, which was quantified by MDA formation. MDA levels in these samples increased from 71.4 ± 2.4 (n = 6) to 100.5 ± 3.8 nmol/mg of protein (mean ± S.E.M.) (N = 6) ($p< 0.001$) in sham- and allergen-challenged mice, respectively. Upon gold nanoparticle treatment (60 µg/kg), a significant reduction in the levels of MDA was observed in the lung of allergen-challenged mice (84.8 ± 1.7 nmol/mg of protein; mean ± S.E.M.) (N = 6) ($p< 0.01$).

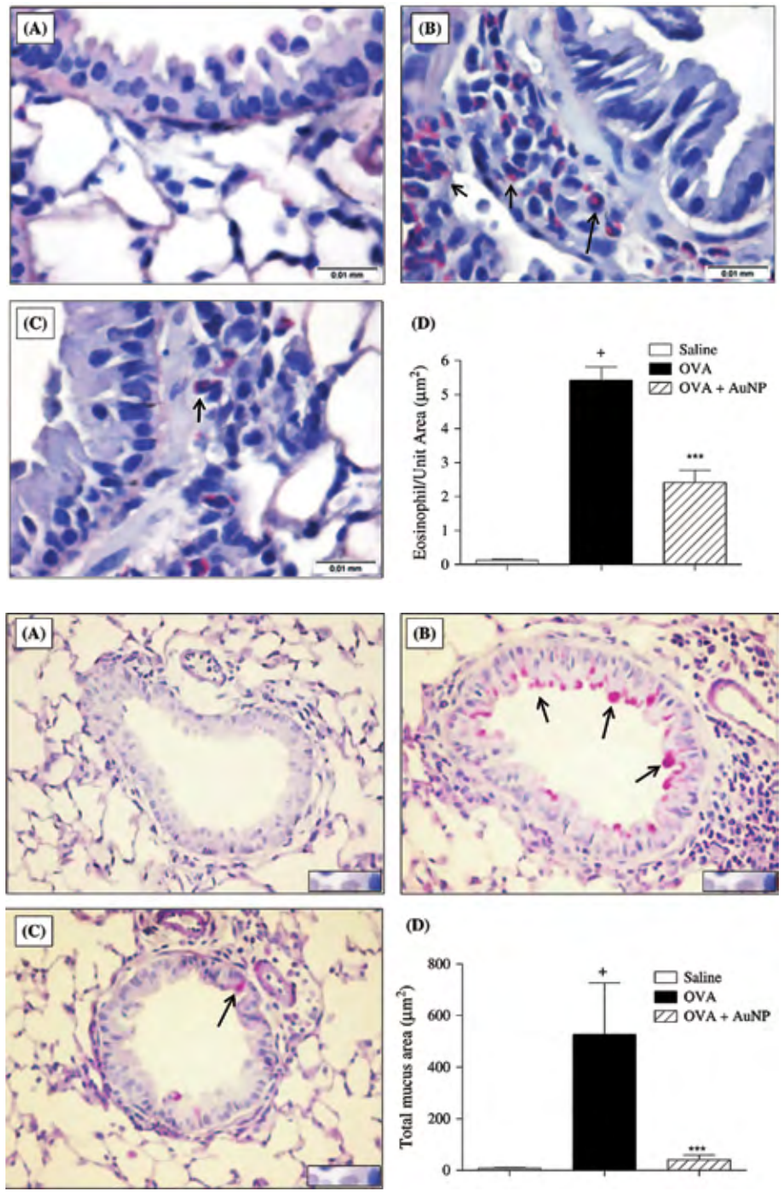

Figure 3. Effect of AuNPs on lung tissue inflammatory cell infiltration in A/J mice. Panels show photomicrographs of lung preparations stained with Llewellyn's Sirus Red from the sham-challenged (A), ovalbumin-challenged (B) and AuNP-treated (60 μg/kg) ovalbumin-challenged mice (C). Eosinophil numbers are shown in panel (D). Data are expressed as mean ± S.E.M. of 6 mice. $^{+}P < 0.001$ as compared to the sham-challenged group. $^{***}P < 0.001$ as compared to the ovalbumin-challenged group.

Figure 4. AuNPs reduced mucus production in allergen-challenged A/J mice. Panels show photomicrographs of lung preparations stained with Periodic Acid-Schiff (PAS), from sham-challenged (A), ovalbumin-challenged (B) and AuNP-treated (60 μg/kg) ovalbumin-challenged mice (C). Quantitative mucus production is seen in panel (D). Data are expressed as mean ± S.E.M. of 6 mice. $^{+}P < 0.001$ as compared to the sham-challenged group. $^{***}P < 0.001$ as compared to allergen-challenged group.

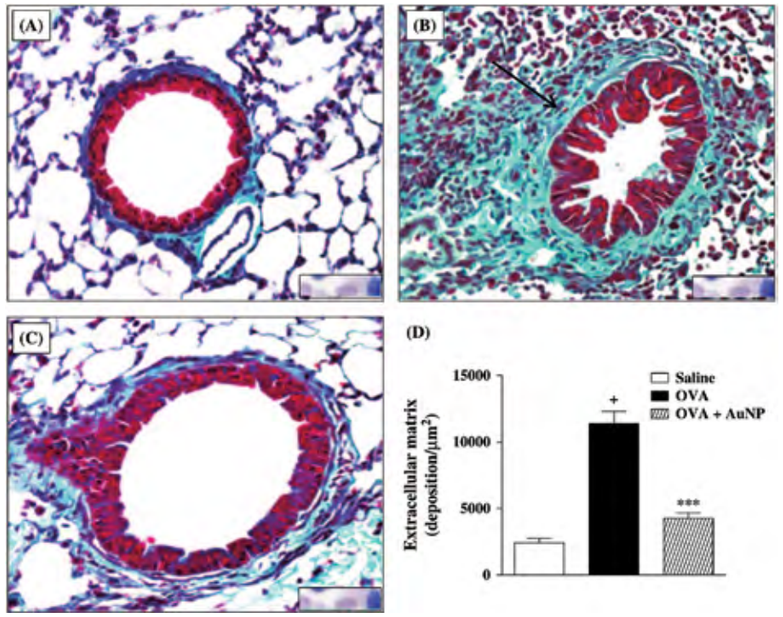

Figure 5. AuNP decreases airway extracellular matrix deposition triggered by allergen in A/J mice. Panels show photomicro-graphs of lung preparations stained qith Gomori trichrome from the saline-challenged (A), ovalbumin-challenged (B) and AuNP-treated (60 μg/kg) ovalbumin-challenged mice (C). Quantitative extracellular matrix deposition is panel (D). Data are expressed as mean ± S.E.M. of mice. $^{+}P < 0.001$ as compared to the sham-challenged group. $^{***}P < 0.001$as compared to the ovalbumin-challenged group.

Altogether, these results are in line with the interpretation that gold nanoparticles have indeed clinical potential as anti-asthma therapy. A possible antioxidant effect of gold nanoparticles may protect the lung tissue against the injurious oxidants agents induced after allergen challenge, and also may alter the inflammatory events, which have a central role in the pathogenesis of airway and lung diseases.

COMMENTS FROM AUTHOR

Inflammation is pivotal in lung chronic diseases, such as asthma, which have high socioeconomic impact worldwide and in Brazil, and can be fatal. Inhaled glucocorticoids are the most effective treatment to control asthma so far, but adverse effects and resistance to anti-inflammatory steroids limit their effectiveness.The use of metallic gold or its complexes for the treatment of different inflammatory conditions has several thousand years of history. Nanotechnology provides novel materials in the nanometer range with putative applications in clinical settings. Using distinct animal models of asthma, we provided evidence that gold nanoparticles have indeed marked antiasthma properties, clearly associated with their anti-inflammatory and antioxidant activities. Findings that intranasal administration of gold nanoparticles can robustly inhibit several pathological features of this disease, including pulmonary inflammation, airway hyper-reactivity, mucus exacerbation and lung remodeling are suggestive that this treatment can be beneficial for asthmatics. In addition, the unique properties of biocompatibility, high surface of reactivity and flexibility in functionalization may further support novel clinical applications for this millenary and precious material.

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Highlights 2014

Anti-inflammatory properties of convolutamydine A and two structural analogues

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Inflammation is a stereotyped response of living organisms to a possible harmful stimuli in vascular tissues. This physiologic event has a protective role aiming at the removal of the offending agent by activating a cascade of events and production of inflammatory mediators. The ultimate goal is the destruction of the offending agent and tissue restoration. The current pharmacological therapies for inflammation consist primarily of non-steroidal anti-inflammatory drugs (NSAIDs). This class has a long history of clinical use and major deficiencies, and many of the drug discovery efforts in the area of inflammation have focused on the incremental improvement of this class of compounds.

However, adverse side-effects (i.e., ulcers and bleeding) have limited their use. Many new molecules have been synthesized with the aim of seeking those with reduced side effects.

Amathia convoluta is a marine bryozoan species from which the oxindole alkaloid named Convolutamydine A was isolated. Because convolutamydine is only isolated from this Bryozoan in small amounts and due to its promising biological activities, it has been synthesized by several research groups. Garden et al. were the first group to propose the synthesis of a racemic mixture of convolutamydine A from isatin, a small, versatile, and widely applicable pharmacological molecule.

Convolutamydine A promoted alterations in HL-60 cell line. In addition to convolutamydine A, the literature includes reports of other 3-substituted-3-hydroxyindolin-2-ones with applications in medicinal chemistry, such as active potent growth hormone secretagogues, potassium channel openers, anticonvulsants and antinociceptives.

In our continuous search for bioactive substances, the purpose of the present work was to investigate the anti-inflammatory effects of convolutamydine A and its analogues in animal models of inflammation.

The pretreatment of mice with 0.01, 0.1 or 1 mg/kg of each compound demonstrated that convolutamydine A and ISA003 significantly reduced the licking response to formalin injection at all doses tested, whereas ISA147 did not affect the response (Figure 1).

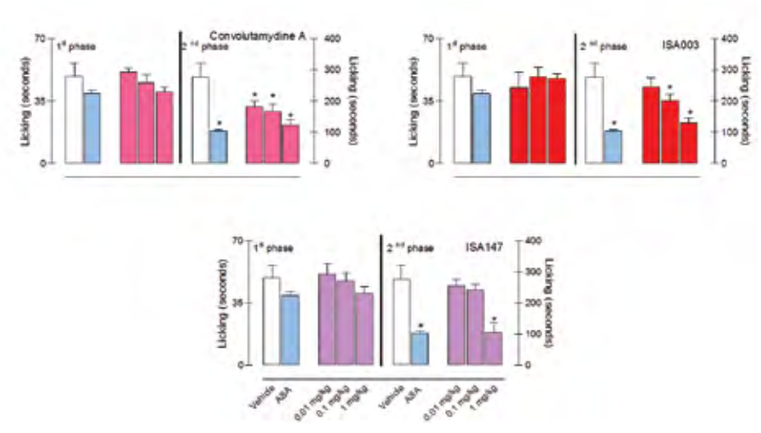


Figure 1 –The effects of Convolutamydine A, ISA003 and ISA147 on the formalin-induced licking response in mice. Convolutamydine A or analogues 0.01, 0.1 or 1 mg/kg), acetylsalicylic acid (ASA, 100 mg/kg) or vehicle were orally administered to mice. Values mean ± S.D. (n=6–10). *P<0.05 compared to vehicle-treated mice using ANOVA followed by Bonferroni's test.

The inhibitory effect observed for convolutamydine A and its analogues is indicative of a possible anti-inflammatory effect. Accordingly, we evaluated convolutamydine A, ISA003 and ISA147 in another model of inflammation, the subcutaneous air pouch (SAP) model. The injection of carrageenan (1%) into the SAP produced a marked increase in the exudate volume and leukocyte number in the pouch, accompanied by an increase in almost seven-fold above the level of the control group (PBS injected into the SAP). The pre-treatment of mice with convolutamydine A or its analogues (at doses of 0.1, 1 or 10 mg/kg) significantly suppressed the number of leukocytes in the exudates.

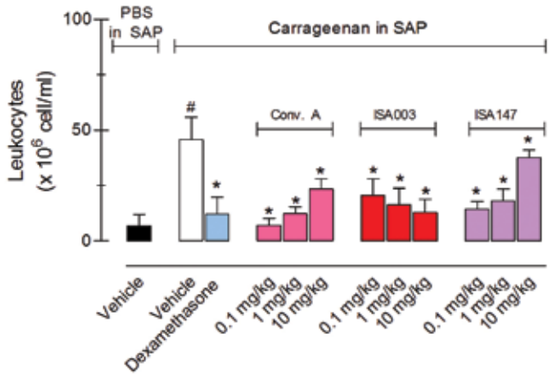


Figure 2 - Effects of convolutamydine A (Conv. A), ISA003 and ISA147 in leukocyte migration into the subcutaneous air pouch (SAP). The animals were pretreated with different doses of each substance, dexamethasone (5 mg/kg, i.p.) or vehicle 1 h before carrageenan (1%) injection into the SAP. Values mean ± S.D. (n=6–10). #*P*<0.05 compared to vehicle-treated mice receiving PBS in SAP and ⋆p<0.05 compared to vehicle-treated mice receiving carrageenan in SAP using ANOVA followed by Bonferroni's test.

Because convolutamydine A and its analogues significantly reduced cell migration into the SAP, we decided to further analyse other parameters that are present in carrageenan-induced inflammation. In this regard, we measured the amount of some cytokines (i.e., TNF-α and IL-6) in the exudates. Carrageenan induced 2.6- and 0.7-fold increases in the amount of TNF-α and IL-6, respectively. All tested doses of convolutamydine A and ISA147 (0.1, 1 and 10 mg/kg) reduced cytokine levels, whereas ISA003 only showed an effect at the 1 or 10 mg/kg doses (Figure 3).

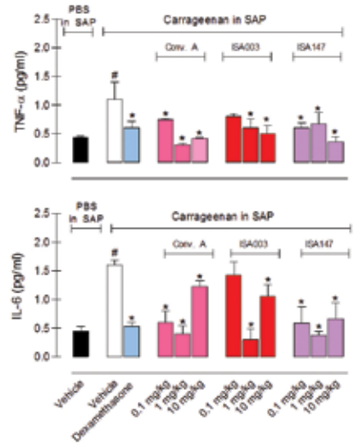


Figure 3 - Effect of convolutamydine A (Conv. A), ISA003 and ISA147on carrageenan-induced TNF-α, IL-6 and nitric oxide (NO) production in the subcutaneous air pouch (SAP). The animals were pretreated with different doses of each substance, dexamethasone (5 mg/kg, i.p.) or vehicle. The results are presented as the mean ± S.D. (n= 6-10). #*P*<0.05 compared to vehicle-treated mice receiving PBS in SAP and ⋆p<0.05 compared to vehicle-treated mice receiving carrageenan in SAP using ANOVA followed by Bonferroni's test.

Figure 4 shows that both convolutamydine A and its analogues significantly and dose-dependently reduced NO and PGE2 production by the leukocytes that migrated into the SAP after carrageenan injection.

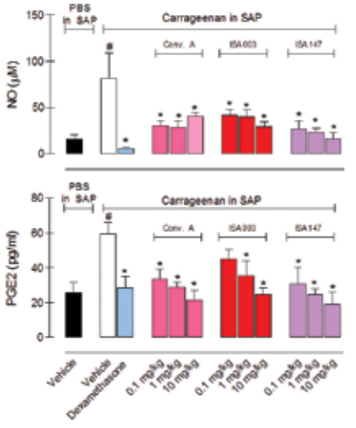


Figure 4 - The effect of convolutamydine A (Conv. A), ISA003 and ISA147on levels of nitric oxide (NO) and prostaglandin E2 (PGE2) accumulated in the subcutaneous air pouch (SAP). The animals were pretreated with different doses of each substance, dexamethasone (5 mg/kg, i.p.) or vehicle. The results are presented as the mean ± S.D. (n= 6-10). #*P*<0.05 compared to vehicle-treated mice receiving PBS in SAP and ⋆p<0.05 compared to vehicle-treated mice receiving carrageenan in SAP using ANOVA followed by Bonferroni's test.

To further evaluate the effect of convolutamydine A and its analogues and to eliminate the possibility that the reduction in cytokines, NO and PGE2*in vivo* could simply be the result of a reduction in the number of cells that migrated into the SAP, we decided to carry out *in vitro* assays. We first investigated a possible direct cytotoxic effect of convolutamydine A, ISA003 and ISA147on RAW 264.7 cells. Neither the compounds alone, at concentrations up to 100 μM, nor the compounds in the presence of LPS (1 μg/ml) affected cell viability (data not shown). To examine if the inhibitory effects of convolutamydine A, ISA003 and ISA147 occurred due to an

inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2) expression, the levels of each protein was determined by western blot analysis. As shown in Figure 7, the expression of the iNOS and COX-2 proteins was almost undetectable in unstimulated cells. However, upon LPS treatment, the iNOS and COX-2 proteins were markedly increased. Convolutamydine A, ISA003 and ISA147 significantly reduced the induction of iNOS and COX-2 protein expression (Figure 5).

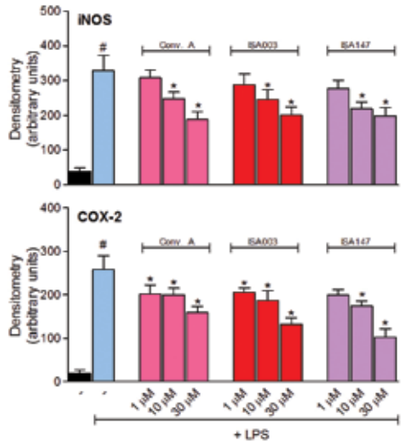
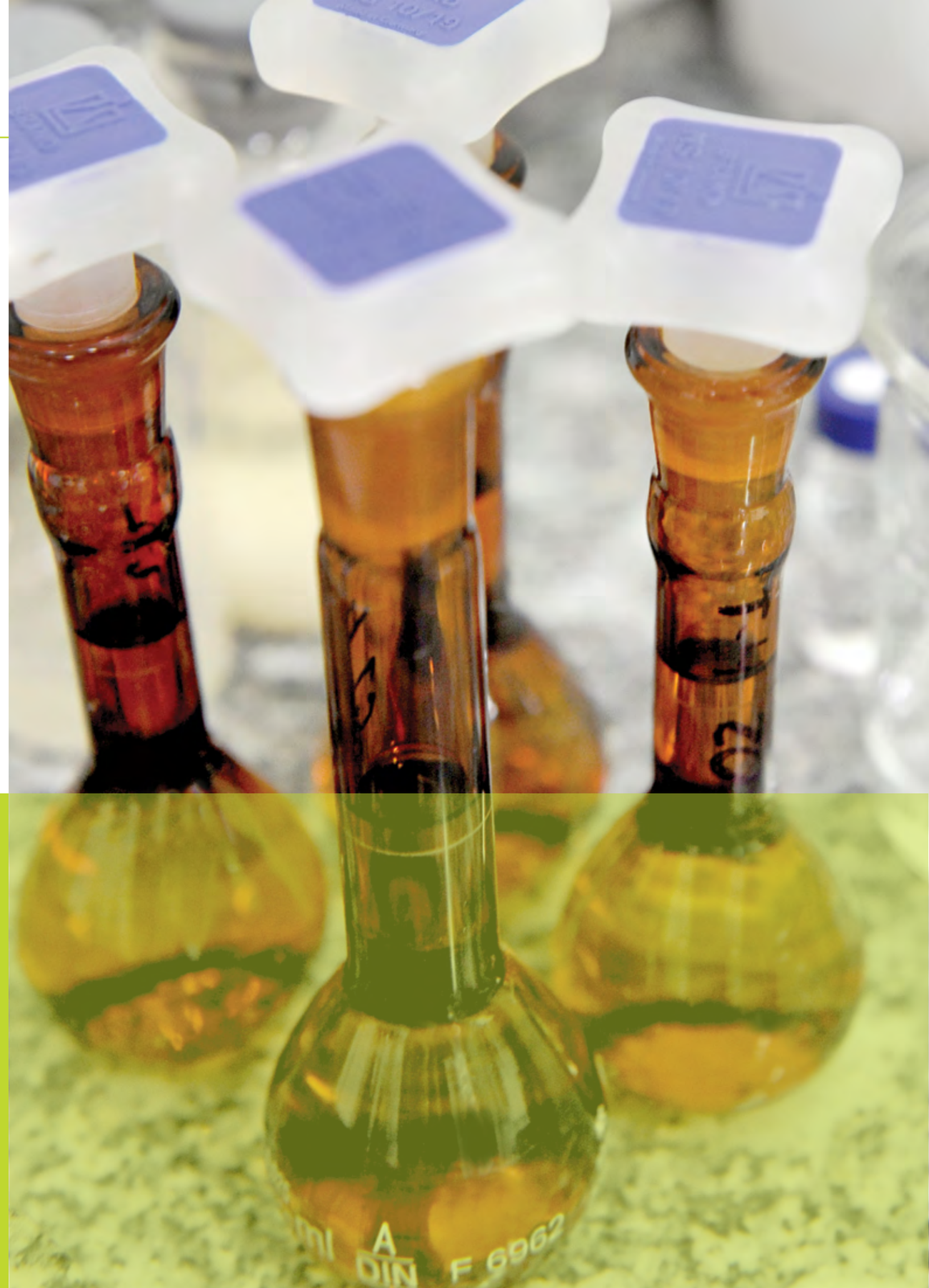


Figure 5 - The effects of convolutamydine A, ISA003 and ISA147 on iNOS or cyclooxygenase-2 (COX-2) enzyme expression in RAW 264.7 cells. RAW 264.7 cells were activated or not with LPS (1 µg/ml) and then incubated with the compounds (1, 10 or 30 µM). After 6 h of incubation, western blot analysis was performed to visualise iNOS and COX-2 levels. The results are presented as the mean ± S.D. (n=4). Statistical significance was calculated by ANOVA followed by Bonferroni's test. $^{\#}P<0.05$ when comparing LPS-activated with non-activated cells; $^{*}P<0.05$ when comparing the LPS-activated cells that were pre-incubated with compounds to the LPS-activated cells.

COMMENTS FROM AUTHOR

Two new analogs from Convolutamydine A, named ISA003 and ISA147, were evaluated in model of acute inflammation. The anti-inflammatory effects of convolutamydine A, ISA003 and ISA147 were investigated in a formalin-induced licking behavior model, where mice received an intraplantar injection of formalin and their licking behavior was evaluated for 30 min. Additionally, inflammatory parameters were evaluated in a subcutaneous air pouch (SAP) model of carrageenan-induced inflammation. Exudates were collected for leukocyte counts; measurement of protein, prostaglandin E2 (PGE2) and cytokines by ELISA; and analysis of nitric oxide (NO) using a nitrate conversion protocol. Cyclooxygenase-2 (COX2) and inducible nitric oxide synthase (iNOS) from RAW 264.7 cells were quantified by immunoblotting. Convolutamydine A and its two analogues inhibited the formalin-induced licking response at doses as low as 0.01 mg/kg. An inhibitory effect was also observed on leukocyte migration and the production of NO, PGE2 and cytokines (IL-6 and TNF-α). The reduction in inflammatory parameters did not appear to be correlated with a direct reduction in the number of cells in the SAP, because a reduction in NO and PGE2 production by cultured macrophages was observed in addition to the inhibition of iNOS and COX2 enzyme expression. These results indicate that convolutamydine A and its two analogues have significant anti-inflammatory effects. These substances can be improved to generate lead compounds for the synthesis of new anti-inflammatory drugs.



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Highlights 2014

Donepezil: An Important Prototype to the Design of New Drug Candidates for Alzheimer's Disease

Mini-Reviews in Medicinal Chemistry, 2014, 14, 2-19
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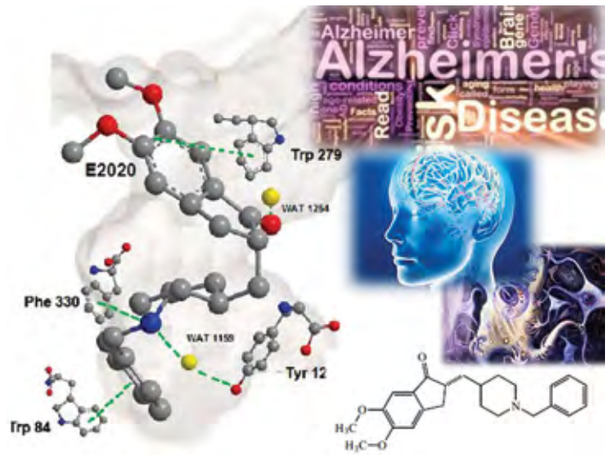
Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by an insidious onset and a complex chronic multi-factorial progress, affecting hippocampus and frontal cortex in brain. This devastating pathology manifests its symptoms as a severe loss in memory, language skills decline and other cognitive impairments, with dramatic behavioral changes that progress to depression and, eventually, death. Recent data points that AD is responsible for ca. 50-60% of all cases of dementia in people over age 65. It is estimated that more than 4.5 million people have AD in the US and 18 million worldwide. The etiology of AD remains unclear, however many pathophysiologic hallmarks of the disease have been disclosed and are currently well established. They involve a complex network of interconnected factors such as a rapid onset of cholinergic dysfunction, with remarkable depletion of acetylcholine (ACh), accomplished by aggregation and accumulation of extracellular β-amyloid (βA) peptide as senile neuritic plaques, and intracellular formation of neurofibrillary tangles (NFTs), composed by a hyperphosphorylated form of the microtubule-associated protein tau, oxidative stress, and neuronal loss. The Ca^{2+} ion plays an important role in the cerebral homeostasis, acting as a second messenger in the brain. The imbalance of Ca^{2+} is currently considered one of the main causes of neurodegeneration due to A_ effects on the capacity of membrane cells to regulate their permeability and internal concentration of ions Ca^{2+}. The Ca^{2+} -associated neurodegeneration begins when Aβ causes an increase in the ion influx as a result of the activation of the *N*-Methyl-Daspartate receptors by the neurotransmitter glutamate. Besides cognitive and motor changes, AD patients also present diverse behavioral alterations as irritability, anxiety, depression, disorientation and restlessness. To date, AD remains incurable and with few available therapeutic alternatives to ameliorate cognition and life quality of the patient, arousing special attention and efforts in the search for new effective drugs. All current drugs available for the treatment of AD are only symptomatic, acting mainly as acetylcholinesterase inhibitors (AChEIs) [3b]. Drugs from this therapeutic class are supported by the "Cholinergic Hypothesis" that points to restore the cholinergic deficit in central nervous system (CNS) by selective inhibition of AChE enzyme, and thus result in a delay of the cognitive decline and in the control of AD symptoms. During the last two decades, only few anticholinergic drugs have been launched in the market, and are mainly indicated for the treatment of mild and moderate stages of the disease, such as tacrine, donepezil, rivastigmine and galanthamine. Another drug recently approved by FDA is memantine, that acts as na antagonist of glutamate receptors, being indicated for the treatment of moderate and severe stages of AD.

However, due to a number of adverse peripheral effects arising from the excessive activation of cholinergic system, including confusion, hallucinations, behavioral abnormalities, nausea, gastric irritation and hepatotoxicity, these drugs have a quite limited clinical use. Besides the treatment with AChEIs and memantine, many other therapeutic approaches, such as the use of neurotrophic and anti-inflammatory drugs, antioxidant compounds and formulations, compounds that could interfere in Aβ-aggregation process have been exploited in the search for new effective therapeutic alternatives. In this context, the more recent approach that has emerged to support the design of more effective chemical entities have considered the multifactorial and complex interconnected and, in some cases parallel or simultaneous, biochemical pathways in AD. This strategy is called Multi-target directed ligands (MTDLs) or multifunctional ligands, that is based on the fact that using a one-target-direct drug, it is not Always likely that the therapeutical effect will be effective to block disease evolution. In the structure of donepezil, *N*-benzylpiperidine and indanone moieties were identified as important interaction binding sites with AChE, and are responsible for inhibitory selectivity. In spite of donepezil had been developed as a racemic mixture, with both enantiomers exhibiting the same

activity, the eutomer is the *R* isomer, which exhibited 5-fold more affinity for AChE (Ki = 3.35 nM) than the *S* isomer (Ki = 17.5 nM) [10]. Donepezil is recognized by AChE by interactions in the middle gorge of the active site of the enzyme, mainly by three subunits: the benzyl moiety, the nitrogen atom at the piperidine ring, and the dimethoxyindanone portion. These interactions involve direct contacts mediated by water molecules that seem to be crucial for binding and specificity. During the last two decades, Alzheimer's disease has been the focus of enormous scientific and medical efforts and investments around the world, in a run against the time for more effective and secure medicines and, the so waited, discovery for cure. This neuropathology has great social and economic impacts, due to the disastrous functional and behavioral impairments caused in patients, that usually have death as the end point, after 8-10 years after the first symptoms of AD are recognized. Since donepezil has been launched in the Market in 1996s, this drug has attracted special attention due to its AChE inhibitory potency, high selectivity, low toxicity and good bioavailability. Thus, donepezil has also been exploited as molecular scaffold for design and development of new AChE inhibitor drug candidates. Moreover, molecular hybridization has been the main approach for rational drug design of new ligands, capable to act as dual, multipotent and/or multi-target directed mechanisms of action.



COMMENTS FROM AUTHOR

After discovery of Donepezil and its approval for the treatment of Alzheimer disease, this drug has gained special importance due to its low side effects and much better effectiveness against AD. For this reason, structural features of donepezil have been exploited in the search of new anti-Alzheimer drug candidates trying to reproduce its AChE inhibitory properties and also introducing other structural attributes to ensure a multiple targets profile of action. This approach have been used in our group in the last decade, aiming to produce novel drug candidates prototypes planned by molecular hybridization with other antioxidant, anti-inflammatory, metal scavengers and neuroprotective natural and synthetic compounds. This strategy allowed us the discovery of few active molecules, with multi-target directed profiles that are under pre-clinical investigation for their effectiveness in AD treatment. In this context, we are searching for novel molecules with new mechanisms of action that could represent radical innovation on AD therapy.


Cáncer
El cáncer es un proceso en el que una célula, o un grupo de ellas, sufren cambios y adquieren capacidades especiales diferentes de las células normales. Dichos cambios provocan una alteración morfológica y funcional seguida de la proliferación descontrolada de las celulas de un tejido que invaden, desplazan y destruyen, localmente y posteriormente a distancia, otros tejidos sanos del organismo.

Events

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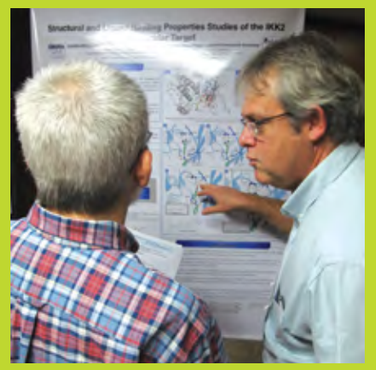
Promotion and participation in events

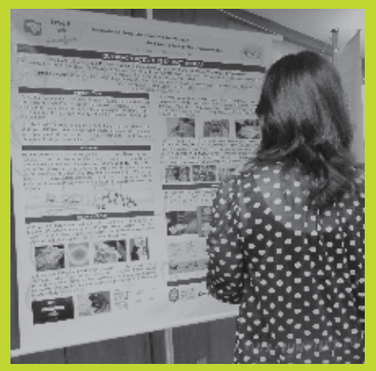
Since its creation, in 2009, the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) has periodically organized events that help evaluate and internally discuss its research projects and subprojects, as well as analyze recent advancements made by the Institute in the chain of innovation in drugs and medicines.

As part of its institutional routine, **INCT-INOFAR** researchers also take part in relevant events in their field, such as congresses, meetings, seminars, symposiums, and workshops, to actively contribute to the diffusion of knowledge within the academic and scientific communities.

In conjunction with these actions, **INCT-INOFAR** also promotes courses and conferences in Pharmaceutical Sciences, helping the qualification of human resources and the advancement of studies toward new drugs and medicines.

VIII Annual INCT-INOFAR Evaluation Meeting





Keeping the tradition of internally evaluating its academic-scientific performance, on May 15, 2014, the Brazilian Academy of Sciences (ABC) was the stage to the VIII Evaluation and Follow-Up Meeting of the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**). The event, which took place in Rio de Janeiro, brought together leaders of associated laboratories to present results of their main research projects. Representatives of different pharmaceutical companies were present at the meeting and were impressed by the evolution of projects during the past five years.

According to Research, Development & Industry manager of Cristalia Laboratories, Dr. Roberto Debom Menezes, who has been closely following the development of **INCT-INOFAR** projects since its creation, the research has matured greatly in the past few years, and have come to the point where they may be truly absorbed by industry, as they have become pharmaceutical candidates, and not just promising molecules.

"Research has evolved a lot, so much so that they are leaving the field of basic research and moving into applied research. This is very important to the Brazilian industry. I was very impressed with the presentations of this meeting, where I saw many molecules with defined targets and action mechanisms, as well as identified toxicities. It is at the right stage for industry development".

Roberto Debom
CRISTALIA LABORATORIES

With innovative dynamics that allowed for presenting 23 projects in a single day, the VIII **INCT-INOFAR** Evaluation and Follow-Up Meeting was considered a success by the researchers present. As well as following up and evaluating the projects in priority areas to **INCT-INOFAR** such as cancer, inflammation, neglected diseases, central nervous system, and cardiovascular system, synthesis of new routes and prospection of opportunities for generic drugs and intermediates, the Institute opened the floor for the Secretary of Outreach Activities to show works that has been developed with the community, concerning the correct use of drugs.

According to **INCT-INOFAR** coordinator, Professor Eliezer J. Barreiro (UFRJ), the actions in Scientific Awareness have garnered many compliments to the Institute, as was proven by the presentation "*Outreach Activities of **INCT-INOFAR***", which reported these activities in an international congress of Public Communication of Science, in Salvador, Bahia.

The event discussed proposals for a new INCT public announcement

The expectation around the new INCT public announcement set the tone to yearly evaluation meeting, generating a discussion of how an innovative proposal could be formulated, focused on drugs and medicines. The floor was also open to representatives from companies invited to the event. Under confidentiality and non-disclosure terms, Cristalia Laboratories, Sanofi-Aventis, BiotechCell, Biozeus, Libbs and *In Vitro* Cells were able to share opinions on the paths that the **INOFAR** research network should follow to participate in its new INCT edition.

VIII **INCT-INOFAR** Evaluation and Follow-Up Meeting, which took place in the Brazilian Academy of Science, and discussed proposals for the new INCT public announcement.

It was unanimous, among the researchers present, that **INCT-INOFAR** should adopt a "more aggressive" stance when it comes to industry, while still maintaining room for researcher creativity. At the same time it could develop researches toward industry interests, with room for research to order, **INCT-INOFAR** would also keep a number of projects in its portfolio with frontier research goals, like, for example, the identification of targets yet unknown to the pharmaceutical industry.

During the follow-up and evaluation event, which took place in the Brazilian Academy of Sciences, **INCT-INOFAR** coordination requested suggestions to its researchers to improve **INCT** operations, in terms of management and of continuous flow of information, as well as the identification of possible bottlenecks faced by the current Institute, which should be overcome in a proposal for the future public notice.

Among the items highlighted to improve knowledge management are the importance of developing tools to improve internal communication, so that the research network is connected in real time, and the conduction of more theme meetings. The suggestion of researchers to group according to therapeutical targets, as opposed to by molecules under study, was also presented in the meeting.

Overcoming bottlenecks in Brazilian Science

We have identified as bottlenecks, not only in **INCT-INOFAR**, but also in the entire field of research in new drugs and medicines in Brazil: toxicology, pharmacokinetics, and molecule scaling up.

In the field of pharmacokinetics, there is a current partnership between **INCT-INOFAR** and CEMSA, a company headquartered at USP, specialized in Applied Mass Spectrometry, which has already conducted the evaluation free of charge of a few compounds of the Institute. To conduct the bioavailability studies, Professor Sandra Elisa Haas, from the Federal University of the Pampa (UNIPAMPA), an expert on the subject, was asked to join **INCT-INOFAR**.

In what concerns the primary scaling up of molecules, **INCT-INOFAR** joined an initiative from Professor Wanderlei de Souza (UFRJ), one of the innovation directors at INMETRO. Ministry of Health has approved the project, which allows for the construction of a scaling lab and that has **INCT-INOFAR** as one of its users.

During the meeting, the director of Medical and Scientific Alliances of Sanofi Aventis, Dr. Jaderson Lima, highlighted the positive points of the research network in drugs and medicines created by **INCT-INOFAR**. According to the Sanofi director, the company has a current term of confidentiality with **INCT-INOFAR** and will soon sign cooperation agreements for specific mutually interesting projects, bringing together industry and academic knowledge.

"We believe that the INCT-INOFAR initiative is extremely relevant for new paths that Brazil is following in innovation, because the Institute brings together professionals of the highest caliber, renowned researchers, qualified in their field, in a very interesting multidisciplinary approach. We understand that this is how innovation is made, bringing together the thinkers, the knowledge, so that we can ask better questions and seek the most adequate answers"

Dr. Jaderson Lima
SANOFI AVENTIS

INCT-INOFAR increases the level of research in Brazil

At the end of the **INCT-INOFAR** VIII Evaluation and Follow-Up Meeting, Professor Laurent Emmanuel Dardenne, of the National Laboratory of Scientific Computation (LNCC/MCTI), highlighted the importance of connecting researchers with different expertise in the Institute. "*To me, one of the biggest values brought by INCT is diversity. I am a physicist, and I am here to create cooperation and interact, and this has made me a better researcher",* stated the Professor.

To him, who is responsible for the development of the **DockThor Portal <** http://dockthor.lncc.br/>, aimed at evaluating small ligand molecules, this has benefited the Brazilian research, even those outside of **INCT-INOFAR**.

The evolution of research has been considered a success

Pharmaceutical companies were present at the VIII Evaluation and Follow-Up Meeting

"The INCT-INOFAR success is unattainable! Even if in 5 years we do not have a drug, it is already a success, because we have generated quality in research and enhanced the studies in Brazilian Medicinal Chemistry, whether it was developed within INCT-INOFAR or not. The Institute will be fulfilling an extremely relevant role in society, regardless of its final product."

Prof. Laurent Dardenne
LNCC/MCTI

XX Summer School in Medicinal and Pharmaceutical Chemistry & II *Escuela Internacional de Química Medicinal y Farmacologia*

The Summer School in Medicinal and Pharmaceutical Chemistry (EVQFM) has reached its twentieth edition, becoming a celebrated event in the area of Pharmaceutical Sciences. Organized by the Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio/UFRJ), research group associated to **INCT-INOFAR**, the event was incorporated by the Institute in 2009 as an outreach activity.

Between January 27 and 31, 2014, the XX Summer School in Medicinal and Pharmaceutical Chemistry took place together with the *II Escuela Internacional de Química Medicinal y Farmacologia*, organized by Uruguayan Professors Hugo Cerecetto and Mercedes Gonzales from the Universidad de la Republica (UdelaR), at the Health Sciences Center (CCS) of the Federal University of Rio de Janeiro (UFRJ).

20 Years of Summer School Publication

To record its trajectory and bring back memories of these past 20 years, and pay tribute to those who helped its scientific success, the EVQFM created a publication called "1995-2014 Retrospective of the Summer School: 20 Years of Contributions to Medicinal Pharmaceutical Chemistry".

The tradition and quality of the Summer School attract students from different states in Brazil and from other countries. In the year it celebrates 20 consecutive editions, it was no different. Undergraduate and graduate students gave up part of their summer vacation and came to Rio de Janeiro to deepen their academic and scientific knowledge of Medicinal Pharmaceutical Chemistry.

The World Cup of Medicinal Pharmaceutical Chemistry

In the year where soccer was the most talked about subject in Brazil, the moment of relaxation at the EVQFM was the **"World Cup of Medicinal Pharmaceutical Chemistry".** The metaphor was created by journalist Lucia Beatriz Torres to present, in a playful way, a Retrospective of the 20 years of the event.

During two decades, the EVQFM has already had over 2,500 participants and offered over 100 courses and 90 conferences, with 36 of them including foreign experts. During the event, internationally renowned researchers have given courses and conferences. To celebrate 20 years, the Summer School invited only foreign researchers for its Cycle of Conferences.

XX EVQFM Conferences

THE TEAM OF THE 20TH EDITION OF THE SUMMER SCHOOL, REPRESENTING SEVEN DIFFERENT COUNTRIES

The coverage of the 2014 edition, as well as daily reports, had special bilingual reports on the conferences. See all at http://www.evqfm.com.br/xx_evqfm/.

"New drugs for Chagas disease treatment: from basic Science to clinical trials"

Professor Dr. Julio Urbina, from the *Instituto Venezolano de Investigaciones Cientificas*, in Venezuela, presented the most promising approaches for the development of new drugs for Chagas disease, from basic science to clinical assays.

"Electron Spin Resonance as a Powerful Tool for Studying Antioxidants and Radicals involved in Parasitic diseases"

Professor Dr. Claudio Olea Azar, from the University of Chile, in Chile, presented the current available techniques associated with Electron Spin Resonance (ESR) for the study of antioxidants and the use of these techniques for the study of parasitic diseases.

"Publish or Perish: Scientific Publishing in Medicinal Chemistry"

Professor Dr. Stefan Laufer, from the University of Tübingen, in Germany, gave tips on how to prepare a good scientific article to be accepted by the top publications in the field, like the Journal of Medicinal Chemistry.

"Neurodegenerative diseases: an urgent challenge for drug discovery and development"

Professor Dr. Ana Martinez, from the *Consejo Superior de Investigaciones Científicas*, in Spain, presented the efforts of her research group to discovery a new drug for Alzheimer's Disease.

"Inducción Selectividad Antineoplásica em Nuevos Inhibidores de Polimerización de Tubulina"

Professor Dr. Arturo San Feliciano, from the University of Salamanca, in Spain, presented the search to reduce the toxicity of podophyllotoxin, a natural product with antitumoral activity through the inhibition of the polymerization of tubulins.

"New agonists with quinolonic structure of the CB2 cannabinoid receptor"

Professor Dr. Pier G. Baraldi, from the University of Ferrara, in Italy, demonstrated that the typical quinolonic structures, which are generally used as antibacterial agents, is also capable of interacting the CB2 cannabinoid receptor, and is useful for the development of new analgesic and anti-inflammatory agents.

STEFAN LAUFER (Alemanha)
MERCEDEZ GONZALEZ (Uruguai)
CARLOS MANSSOUR (LASSBio)
CARLOS M. SANTANNA (LASSBio)
PIER BARALDI (Italia)
JULIO URBINA (Venezuela)
ELIEZER J. BARREIRO (LASSBio)
ARTURO SAN FELICIANO (Espanha)
ANA MARTINEZ (Espanha)
CLAUDIO OLEA (Chile)
VIRGINIA LOPEZ (Uruguai)
WILLIAMS PORCAL (Uruguai)
HUGO CERCETTO (Uruguai)
MARCIO COELHO (UFMG)
LIDIA LIMA (LASSBio)

8th National Meeting of Innovation in Drugs and Medicines

8ºENIFarMed
ENCONTRO NACIONAL DE INOVAÇÃO EM FÁRMACOS E MEDICAMENTOS

The National Meeting of Innovation in Drugs and Medicines (ENIFarMed) is a consolidated forum to promote interaction between R, D & I professionals from companies in the productive chain of the pharmaceutical sector with INCT (National Institutes of Science and Technology) researchers. The event has, for eight years, brought together academia, industry, and government representatives to discuss a common agenda for the advancement of technological innovation in drugs and medicines in Brazil.

On September 08 and 09, 2014, at the Rebouças Convention Center in Sao Paulo, **INCT-INOFAR** was present on the 8th edition of ENIFarMed. During the event, Institute researchers gave significant contributions to the Meeting, mainly on discussions about the technological dependence faced by local pharmaceutical industry, considering that **INCT-INOFAR** has as one of its goals producing a genuinely Brazilian drug.

According to the Institute of Research and Development of Drugs and Pharmaceutical Products (IPD-Farma), the entity in charge of the event, it is possible to produce a technical report with a detailed analysis of the difficulties faced by the sector, and the main suggestions to solve it. The document, produced after each edition of the event, is always forwarded to the responsible agencies.

INCT-INOFAR is part of Business Fair

With a goal of publicizing the projects under study in its network of research in drugs and medicines, and coming closer to the productive sector and government agencies, **INCT-INOFAR** was part of the 6th ExpoFarMed, a business fair connected to the event. This was the fourth time that the Institute was part of the ExpoFarMed. Those who visited the **INCT-INOFAR** booth at the event were impressed by its updated layout and were able to see the research developed by the Institute, take home a copy of the Annual Activities Report, and have their questions answered by present **INCT-INOFAR** members.

INCT-INOFAR receives Technical Recognition Award

Completing the debate sessions and the Business Fair, the 8th ENIFarMed opened the floor for researchers to present, in poster format, innovative management and bench projects for a selected audience of Health industry entrepreneurs. Among the works with the most innovative content, market focus, and social relevance, six of them were awarded the Technical Recognition Award, which led to a speaking presentation during the event.

The work “Molecular Modeling Studies for the Identification of New Aldehyde Deshydrogenase 2 (ALDH-2) Selective Inhibitors”, developed by Master's Degree student from the Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio/UFRJ), Thayssa Tavares, **INCT-INOFAR** member, was awarded the 2nd place.

Thayssa Tavares (LASSBio/UFRJ), **INCT-INOFAR** researcher, was Runner Up in the Technical Recognition Award at the 8th ENIFarMed

Celebration of 20 years of LASSBio/UFRJ

A historical event for Brazilian Medicinal Chemistry was the 20th anniversary, in 2014, of the Laboratories of Evaluation and Synthesis of Bioactive Substances (LASSBio), of the Federal University of Rio de Janeiro (UFRJ). On April 19, 1994, LASSBio was formed and began its journey, from the creation of a small research group in Medicinal Chemistry in UFRJ, started by Professor Eliezer J. Barreiro, **INCT-INOFAR** coordinator.

In the past two decades, countless research projects were finished, and many of them were topics of Master's dissertations and Doctoral theses. LASSBio, in its 20 years, through several *Stricto sensu* Graduate programs, has reached the mark of over one hundred titles awarded.

Helping popularize Medicinal Chemistry in Brazil

LASSBio has been a pioneer in creating innovative knowledge in Medicinal Chemistry, in the state of Rio de Janeiro, which grants it an important position and a renowned excellence in the field in Brazil, as well as well-deserved international recognition.

Within its scope, LASSBio has developed and promoted countless national and international academic scientific events, to popularize Medicinal Chemistry. The Summer School is its most recognizable fruit, having reached, in 2014, its 20th anniversary of uninterrupted occurrences.

Countless internationally and nationally renowned researchers were present in the traditional LASSBio seminars, which habitually happen on Monday afternoons, giving lectures or teaching courses. Among them, we would like to highlight Professors Camille George Wermuth, from *Université Louis Pasteur*, in France, author of one of the main books on Medicinal Chemistry ever written, and Robin Ganellin, from the University of London, in England, who is one of the inventors of cimetidine.

Coordinated by Professor Dr. Eliezer J. Barreiro, LASSBio is responsible for filing 75 patent requests for new drugs since 1999, at the National Institute for Industrial Property (INPI). During the past 20 years, LASSBio has had a great number of citations in scientific papers produced by its members.

Former LASSBio students and important researchers in Brazilian Medicinal Chemistry gathered at UFRJ to celebrate the LASSBio 20th anniversary

The 20-year history portrayed in book, video, and comic book

To mark its 20th anniversary, LASSBio promoted, on September 24 and 25, at the Center for Health Sciences (CCS) of UFRJ, the Workshop "Two Decades of the Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio)". The celebration had the participation of former laboratory students and researchers who helped make LASSBio a reference in Brazilian Medicinal Chemistry.

With a goal of recording the legacy of its history for future LASSBio generations, journalist Edna Ferreira produced a publication with a retrospective of its 20-year trajectory in Medicinal Pharmaceutical Chemistry.

Furthermore, as part of the celebration of 20 years of the laboratory, a video documentary telling the history of LASSBio was produced, starting at its creation in 1994. In this video, professors and former students, who were part of the Laboratory, retell important and intriguing facts. The video "LASSBio and Medicinal Chemistry: 20 years of history", produced by journalist Lethycia Tanuri, is 30 minutes long, and is available on YouTube, at: https://www.youtube.com/watch?v=Va65wIYlwaQ&feature=youtu.be.

The celebratory cartoons were also a special touch in the LASSBio 20th anniversary. In a playful way, different themes in the development and technological innovation in the area of Medicinal Chemistry were approached by the pharmacist and cartoonist Natalia Medeiros de Lima.

Symposium “40 Years of the Graduate Program in Pharmacology and Medicinal Chemistry"

The Graduate Program in Pharmacology and Medicinal Chemistry (PPGFQM), which replaced the Program in Pharmacology and Experimental Therapeutics, celebrated 40 years in 2014. The Graduate Program was celebrated with this Symposium, which took place at Block N of the Center for Health Sciences (CCS/UFRJ), on November 17, 2014.

Responsible for the qualification and training of personnel in the field of research and development of new drugs and medicines, the Program has its research activities connected to the Laboratory of Synthesis and Evaluation of Bioactive Substances (LASSBio), of the Federal University of Rio de Janeiro (UFRJ). Through its bold mission and the activities developed, it is also now part of the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**).

The Symposium had the participation of international experts in the field of Medicinal Chemistry, like Professors David Thurston (King's College of London) and Rob Leurs (Vrije University Amsterdam), as well as important names in Brazilian Pharmacology, like Professors Fernando de Queiroz Cunha (USP-RP) and Roberto Soares de Moura (IBRAG, UERJ), the former having been the first PPGFQM coordinator.

The construction of PPGFQM

When one reminisces about the past of the Graduate Program in Pharmacology and Medicinal Chemistry (PPGFQM), it is important to remember the creation of the course, in 1974, which started it: the Master's Degree in Biological Sciences in Pharmacology and Experimental Therapeutics, of the Institute of Biomedical Sciences (ICB) of UFRJ. The implementation of the course was possible due to actions headed by Lauro Sollero, a Full Professor at the old Department of Basic and Clinical Pharmacology. It was the only Graduate course in Pharmacology in the state of Rio de Janeiro, and one of the first in Brazil, and it positively reflected in qualifying personnel associated with therapeutics.

Once again, a pioneer, the Program expanded to a Doctoral Program in 2000, becoming the only *Stricto sensu* Graduate Program in Latin America to integrate formally the subjects of Pharmacology and Medicinal Chemistry.
This new goal of the program, consolidated with a modification of the curriculum and the official change of its name from Biological Sciences in Pharmacology and Experimental Therapeutics to Pharmacology and Medicinal Chemistry, in 2009, were the results of a gradual overlapping with LASSBio, an important UFRJ research group in Medicinal Chemistry.

These actions culminated in the insertion of the Graduate Program in Pharmacology and Medicinal Chemistry (PPGFQM) in the National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**).

The Master's and Doctoral courses in Pharmacology and Medicinal Chemistry have graduated 204 Masters and 46 Doctors, dating from the beginning of their operation to October 2014. Recently, the courses were promoted to Grade 5 by the Coordination for the Improvement of Higher Education Personnel (CAPES).

In the context of celebrating four decades of the Graduate Program, we would like to acknowledge the people who have contributed, from the moment of its creation, to the strengthening and improving of the PPGFQM during its forty-year trajectory.

Events where INCT-INOFAR was represented

NOVEMBER 06, 2014
III Workshop of Projects and Dissertations of the Graduate Program in Pharmaceutical Sciences
Federal University of Piaui – PI
Lecture: *"Design and development of new drugs: first steps in Brazil"*

OCTOBER 27 TO 30, 2014
VII Iberoamerican Symposium of Medicinal Plants
II Iberoamerican Symposium of Cancer Investigation
Convention Center Hotel Praia do Sol - BA

OCTOBER 23, 2014
II FUNVIC Pharmaceutical Symposium
Faculty of Pindamonhangaba - SP
Mini-course: *" Medicinal Chemistry and Drug Innovation"*

OCTOBER 15, 2014
XXIV Chemistry Academic Week
Federal Fluminense University - RJ
Lecture: *"The Misadventures of Methyl in Medicinal Chemistry"*

OCTOBER 07, 2014
I Brazilian Symposium of Bioactive Compounds
University of Campinas – SP
Lecture: *"Development of Pharmaceutically Interesting Molecules"*

SEPTEMBER 07 TO 11, 2014
XXIII *International Symposium on Medicinal Chemistry*
***European Federation for Medicinal Chemistry* - Portugal**

AUGUST 16, 2014
61st UNESP / Araraquara Pharmaceutical Journey
State University of Sao Paulo – SP
Symposium: *"New Technologies in Cancer Treatment"*

JULY 21 AND 22, 2014
II UFU Chemistry Meeting
Federal University of Uberlandia - MG
Course: *"Drug Design"*
Lecture: *"Medicinal Chemistry in Drug Discovery"*

May 30 and 31, 2014
XXIX Annual Meeting of the Federation of Societies of Experimental Biology(FeSBE)
Convention Center – Tambau Hotel - PB
Lecture: *"The role of Natural Products in the Contemporary Therapeutic Arsenal"*
Lecture: *"Design and Rational Development of Drugs – the **INCT-INOFAR** Experience"*

MAY 26, 2014
37th Annual Meeting of the Brazilian Society of Chemistry
Natal Convention Center - RN
Workshop: *"New Challenges in Medicinal Chemistry"*

APRIL 09, 2014
Federal University of Piaui - PI
Inaugural Class "Chemical Medicine in Pharmaceutical Sciences"

APRIL 03, 2014
I Pharmaceutical Sciences Seminar
Federal University of Juiz de Fora - MG
Lecture: *"Pharmaceutical Sciences"*

JANUARY 08, 2014.
***Federal University of Ceara* - CE**
Lecture: "Opportunities for Drug Innovation – INCT-INOFAR"

*through the presence of its coordinator, Prof. Eliezer J. Barreiro (LASSBio/UFRJ).


EXERCÍCIO
TEMPERATURA

Outreach activities and popularizing science

The National Institute of Science and Technology of Drugs and Medicines (**INCT-INOFAR**) currently develops several research project for innovation in drugs and medicines. Aside from the research activities, **INCT-INOFAR** also invests in actions of Publicizing and Popularizing Science, Technology, and Innovation, understanding the importance of scientific awareness in building a more critical and thinking society.

For that, **INCT-INOFAR** promotes and coordinates activities of Scientific Awareness & Health Education. This way, it is able to generate interest in Science in children and teenagers, as well as having them as possible multipliers of knowledge among their family and friends. Through scientific promotion, the Institute helps and encourages new vocations among youths, especially those unconnected to family background.

To promote and publicize scientific knowledge in Pharmaceutical Sciences, as well as to effectively contribute to the rational and safe use of drugs, **INCT-INOFAR** periodically produces educational materials focused on the correct use of drugs, taking them to public schools to generate discussion on the topic, through its Health Education projects.

These activities have the support of the Secretary of Outreach Activities, which acts with three other Secretaries – Communication, Executive, and Finances – in the **Institute,** to widen the actions of promotion and popularization of Pharmaceutical Sciences within the community.

The permanent projects in Health Publicizing and Popularization conducted by **INCT-INOFAR** can be followed in the Drugs Portal at www.portaldosfarmacos.ccs.ufrj.br.

INCT-INOFAR promotes Science to 100 students of Municipal School Ruy Barbosa, who go up the FIOCRUZ hills to see its landmark Castle

Very interested, Taina recorded everything around her in video. On the back of her t-shirt, she drew the Fiocruz Castle

Scientific Awareness & Health Education

National Health Week: "Be Serious About Your Health"

Bringing scientific knowledge closer to 100 students from the Municipal School Ruy Barbosa in a playful way during the National Health Week, which took place at FIOCRUZ, was another challenging task that **INCT-INOFAR** took on as part of its Scientific Awareness & Health Education activities. Through a partnership established with the Oswaldo Cruz Institute (IOC), **INCT-INOFAR** has brought access to Science to children and teenagers present at the event. With ages ranging from 10 to 14, they were thirsty for knowledge and curious to see the landmark FIOCRUZ Castle, a century-old institution that works developing Science, Technology, and Health Innovation.

In awe with the interior of the famous FIOCRUZ "Castle", students kept on asking questions and recording, through photographs, every detail of what was explained to them.

Student Taina Alves da Silva was especially careful in recording almost all she was seeing, and said "I don't want to miss anything!", as she recorded the explanations given by the Museum guide.

In the official opening of the Event, in honor of the National Health Week, in Arthur Neiva Auditorium (FIOCRUZ), members of the Brazilian Scientific Community welcomed the children, who were able to experience a ceremony similar to an academic celebration.

Wilson Savino (IOC Director), Nisia Trindade Lima (Vice-President of Teaching, Information, and Communication at FIOCRUZ) and Eliezer J. Barreiro, (**INCT-INOFAR** Coordinator) were unanimous in highlighting the importance of each child, and how happy they were with their seeking for knowledge.

National Health Week took place between April 8 and 11, 2014. On the first day of the event, activities focused on the "Safe and Correct Use of Drugs", with lectures on the topic and the presentation of Videos of **INCT-INOFAR** booklets "Commandments of the Safe Use of Drugs" and "Joey's Crew in: The Correct Use of Antibiotics". The children were also able to learn a little more about the safe use of drugs with rounds of a human board game called "Drugs are Not Toys", developed by **INCT-INOFAR**.

Through programming created to fill the Week with playful and educational activities, all of them instructive and most of all, interactive, it was possible to make Science easily understood by children. Most students had never before crossed the walls of the Institution that is a landmark in Public Health in Brazil, and were very enthusiastic and inquisitive, making the initiative highly successful.

Researchers welcome the children

At the end of the first day, as a way to assess he results of the activities conducted, the students were given t-shirts by **INCT-INOFAR**, and instructed to picture what they learned during the day.

"These children were unaware of who Oswaldo Cruz was, and had no idea of his contribution, as well as of other important researchers mentioned during the visit, for the advancement of health in our country", said Professor Miriam dos Reis, in charge of class 1.601, who were themselves also many times surprised by the information relayed during the guided visit.

Another point that interested **INCT-INOFAR** as far as encouraging a new generation of researchers was the initiative from student Jefferson Oliveira de Souza, who volunteered to wear the laboratory coat and top hat worn by Oswaldo Cruz. This action showed the importance of the commitment undertaken by this Institute in making scientific knowledge accessible to underprivileged classes.

"Drugs are Not Toys" Game

"Never accept used drugs"

On the final day of the event, a visit to the interactive exposition, at the Museum of Life, helped create a critical conscience in students about health care. They had the opportunity to learn all about prevention and care for Dengue fever, a disease that sadly affects hundreds of people in the country yearly.

At the end of these activities, students were given a kit with educational and awareness material on preventing Dengue, authored by IOC and also by **INCT-INOFAR**, and they had learned a little more about the mosquito, through living and dead specimens, shown by Graduate students of Institute Oswaldo Cruz at the event.

Keeping an eye out for the Dengue mosquito: children observe mosquito larvae and their reproduction

According to **INCT-INOFAR** members, "*as the result of these activities, which were planned in accordance with the **INCT-INOFAR** goals of Scientific Promotion and Popularization, we were certain that we cannot break the barriers of lack of information, and lack of knowledge, without reaching out to the school environment, without scheduling activities that include students from early grades in the world of science, through actions that make possible to meet researchers and access scientific knowledge, proving to them that this a path they can walk*".

The IOC (Oswaldo Cruz Institute) has produced a video on the "Be Serious About Health" project: https://www.youtube.com/watch?v=xALO41EN4UE

INCT-INOFAR has published an album with photos from this activity during the National Health Week at FIOCRUZ: https://www.facebook.com/PortalDosFarmacos.

Joe the Drop (mascot of the Vaccination Campaign at Fiocruz) visited the INCT-INOFAR booth

INCT-INOFAR is part of the National Vaccination Campaign at "FIOCRUZ FOR YOU 2014"

People of all ages visited the **INCT-INOFAR** booth

As part of its Scientific Awareness & Health Education activities, the National Institute of Science and Technology in Drugs and Medicines (**INCT-INOFAR**) was part of the event "FIOCRUZ FOR YOU 2014", educating the population on the Rational Use of Drugs.

The event, which took place on November 08, 2014, was part of the 36th National Campaign of Vaccination against measles and polio, making this the 21st edition. With the participation of several scientific institutions, the Oswaldo Cruz Foundation has become the largest vaccination spot against poliomyelitis in Brazil. The intense fight against poliomyelitis in Brazil caused the complete eradication of the disease by 1990.

INCT-INOFAR, as it has done in earlier editions, was present once again, contributing to the success of the event. With a goal of increasing awareness in the Correct Use and Proper Discard of Drugs, **INCT-INOFAR** set up a booth where it was possible to broadcast information to all of those taking part in the National Vaccination Campaign at Fiocruz.

Videos for the Booklets "Commandments of the Correct Use of Drugs" and "Joey's Crew in: The Correct Use of Antibiotics", as well as the conduction of educational play like the human board game "Drugs are Not Toys".

The population also got their questions on purchasing, administering, storing, and discarding drugs answered. Each participant present in the booth got a personalized **INCT-INOFAR** folder, with informational material and educational games, as well as the printed booklet of the video shown during the event.

In a day of learning and fun, even favorite cartoon characters were sure to check the INCT-INOFAR tips and be present at the booth

INCT-INOFAR is part of 2014 National Science and Technology Week

In 2014, **INCT-INOFAR** set up a partnership with the Municipal Secretary of Education in the city of Sao Francisco de Itabapoana, in the state of Rio de Janeiro, and promoted its Scientific Awareness and Health Education activities during the 11th edition of the National Science and Technology Week (SNCT) in 2014.

Dealing with the topic *"Science and Technology for Social Development"*, the event took place during the week of October 13 to 19. 327 km away from the city of Rio de Janeiro, at the Northern part of the state, this was the first time in which the city of Sao Francisco de Itabapoana/ RJ was able to take part in an SNCT.

To **INCT-INOFAR**, the topic proposed by the SNCT was a great opportunity to join scientific production to the social challenges that the Brazilian society faces currently. The topic tries to stimulate institutions to approach Science & Technology in the social realm, as an instrument for inclusion, social change, and human development.

Always guided by the purpose of creating critical conscience in the population about the Safe Use and Discard of Drugs, **INCT-INOFAR** ratified the importance of the topic chosen for the 2014 edition, as it is also one of its missions, and planned several activities of Scientific Awareness and Health Education in the city of Sao Francisco de Itabapoana.

During the **I National Science and Technology Week of Sao Francisco de Itabapoana**, the community and students at local schools, ranging from grade school to the Education of Youths and Adults, had easier access to scientific knowledge, through scientific awareness and popularization of science activities promoted by **INCT-INOFAR**.

This action supported part of a population in a region where the Human Development Index (IDH) is under desired levels, and was a landmark moment for **INCT-INOFAR** in the North of the state. This city has, currently, one of the lowest IDH rankings in the state, at place 91 out of 92 in the state of Rio de Janeiro.

Sao Francisco do Itabapoana in the map of RJ

With very peculiar characteristics, simple habits, and a very welcoming and engaged population, the city of Sao Francisco de Itabapoana/RJ received, on October 16 and 17, 2014, **INCT-INOFAR**, present to promote its 1st National Science and Technology Week. This was the first time in which the small town in the North of the state had access to the event, which is already in its 11th edition in the rest of the country.

The event, renowned for its importance in academia, has presented different important themes in previous editions, and in 2014 was focused on social development, thus allowing **INCT-INOFAR** to contribute to the promotion of citizenship in a portion of the population that lives on the margins of public policy concerning Education and Health.

The **INCT-INOFAR** team traveled over 320 km from the Institute headquarters at UFRJ to the city of Sao Francisco de Itabapoana/RJ

Bringing **INCT-INOFAR** to remote locations, of difficult access and with deficient Health and Education programs has been a constant concern for coordinator Professor Eliezer J. Barreiro (LASSBio/UFRJ). According to him, engaging the population on the importance of know-how in Science & Technology for development is a mission that needs to be done, and needs to be done well.

The activities developed at **SNCT-2014,** in **Sao Francisco de Itabapoana,** were planned by the **INCT-INOFAR** Secretary of Outreach Activities, with a goal of reaching students from those in grade school to those enrolled in the Education of Youths and Adults (EJA), as well as the public in general.

This initiative has allowed for resent visits from the **INCT-INOFAR** team to Municipal Public Schools Dirceu Dias da Silva, in the Guaxindiba neighborhood (http://escoladirceudias.blogspot.com.br/), and Herval Luiz dos Santos Batista, a recently opened school downtown.
To support other Schools in the city, as well as the population in Sao Francisco do Itabapoana, **INCT-INOFAR** was part of the Cultural Fair in the I National Science and Technology Week, with a 36 m² booth. With a public ranging from six and seventy-four years old, the audience actively engaged in the activities promoted by the Institute. The **INCT-INOFAR** team, made up of Pharmacists Thayssa Tavares and Natalia Lima, Educator Ana Cristina da Mata Silva and Raphael Faria Segrini, was responsible for interacting with over 500 people.

Among the different activities developed by the outreach team in town were: lectures on the correct use of drugs and how to properly discard them, rounds of the Human Board Game "Drugs are not Toys", and movie sessions with the videos of the **Institute** cartoons. There was also the traditional distribution of the green-and-yellow portfolio folders, inspired by the Brazilian flag, containing the educational material produced by the **Institute.** This time, the kit had a new item: a theme puzzle with a popular version, with cartoons from the Drugs Portal www.portaldosfarmacos.ccs.ufrj.br.

The activities conducted in local schools included an Art Workshop, in which each student was given a plain white t-shirt to illustrate the guidelines received from **INCT-INOFAR** in it. The students wanted to record everything they had seen and heard, both in the t-shirts as well as on the blank banner, taken to be part of the collection maintained by the Institute. The Art Workshop was an important measuring tool for **INCT-INOFAR**, because it was possible to see how much the audience understood of the topics taught.

To promote digital inclusion, **INCT-INOFAR** had a draw with the prizes of a Tablet and several pen drives, as a means of **social contribution to the local population,** and the **Institute** also gave away personalized backpacks as prizes for the students.

All of the work done by **INCT-INOFAR** in the **I National Science and Technology Week of Sao Francisco de Itabapoana** was acknowledged and complimented by the local City Hall. The success of the partnership has piqued the interest of the Municipal Secretary of Education, Professor Katia Regina Martins dos Santos, in establishing a Cooperation Agreement with the Institute, which was signed during the event.

INCT-INOFAR in Sao Francisco de Itabapoana generated a photo magazine for the **I National Week of Science and Technology in the City:** http://www.inct-inofar.ccs.ufrj.br/download/snct2014_revista.pdf

Event Schedule

Cartoon Archive

Drugs Portal

The Drugs Portal www.portaldosfarmacos.ccs.ufrj.br is a website maintained by **INCT-INOFAR**, aimed at the diffusion and popularization of Pharmaceutical Sciences. Through this portal, **INCT-INOFAR** publicizes its research activities, in a language accessible to laymen, and makes its Health Education materials available.

- Publicizing **INCT-INOFAR** research activities in language accessible to laymen;
- Publishing new articles on current themes on innovation in drugs and medicines and health in general;
- Schedule and press coverage of the main scientific events in the area;
- *Download* of educational **INCT-INOFAR** booklets on the topic of the correct use of drugs.

In harmony with the new trends in scientific journalism, the Drugs Portal has a schedule and press coverage of relevant scientific events. Periodically, it publishes new articles and interviews on current topics in innovation in drugs & medicines and health in general. It also produces cartoons, which in a playful way, allude to the irrational use of drugs, proposing instead conscious alternatives for their consumption.

Over one hundred never previously published articles, reports, and interviews have been published in the Drugs Portal since the creation of **INCT-INOFAR**, in 2009. In 2014, the Institute invested in an update of its website and reinforced its social media presence, through the Drugs Portal Facebook page https://www.facebook.com/PortalDosFarmacos.

What you may find in the Drugs Portal

As it is a portal with the mission of publicizing and popularizing Pharmaceutical Sciences, those who visit the Drugs Portal will find a lot of entertaining educational material, through which children, teenagers, and even adults can playfully learn about the importance of the rational and safe use of drugs and medicines.

Among the diverse range of products authored by **INCT-INOFAR** is the animated booklet on the "**Commandments of the Correct Use of Drugs**". With colorful illustrations and simple and dynamic language, the booklet educates on different drug prescription categories, where to safely store drugs at home, and warns of the risks of taking drugs without a doctor's prescription.

"Commandments of the Correct Use of Medications"
Link to download the booklet http://www.portaldosfarmacos.ccs.ufrj.br/download/cartilha_medicamento.pdf

Link to download the cartoon version (video): http://www.portaldosfarmacos.ccs.ufrj.br/cartilhas.html
Authors: Eliezer J. Barreiro and Natalia Medeiros de Lima

"Joey's Crew in: The Correct Use of Antibiotics"
Link to download the comic book http://www.portaldosfarmacos.ccs.ufrj.br/inct/cartilhas/cartilha_antibiotico.pdf

Link to watch the cartoon on YouTube: http://www.youtube.com/watch?v=GGIkKwcau-U
Authors: Lidia Moreira Lima and Angelo da Cunha Pinto

The booklet **"Joey's Crew in: The Correct Use of Antibiotics"** was initially published in comic book form, and then later turned into a cartoon. The publication has a goal of increasing awareness of the risk of incorrect use of antibiotics, emphasizing the importance of the rational use of drugs, and contributing to diminish harmful practices like self-medication.

In a playful and illustrated manner, through the illness suffered by the boy Joey, **INCT-INOFAR** explains in easily accessible scientific language how and why bacteria become resistant to antibiotics. It also highlights the importance of seeing a doctor, and most of all, rigorously following the treatment prescribed. The National Agency of Sanitation (ANVISA) has accredited the material.

"Joey's Crew in: The Correct Use of Anti-Inflammatories"
Link for *download* of the comic book

http://www.portaldosfarmacos.ccs.ufrj.br/inct/cartilhas/gibi_antibiotico.pdf
Authors: Lidia M. Lima and Ana Cristina da Mata Silva (collab.)

With the opportunity provided by the World Soccer Cup, and the interest of children and young people in social networking, **INCT-INOFAR** released the second edition of the educational booklet, which has the characters of Joey's Crew, to talk about the correct use of anti-inflammatories. At the end of the publication, there are activities for internalizing the content of the booklet, so that children can reflect on what they have learned from reading, together with their guardians.

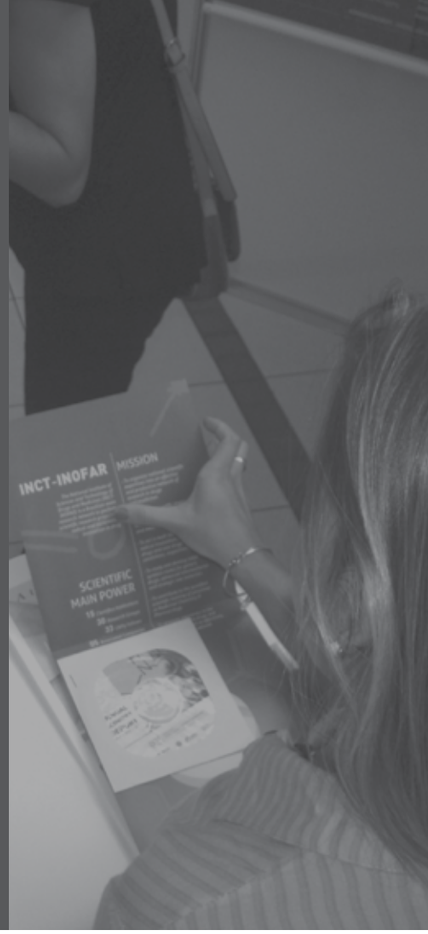
As well as producing booklets and educational games (not available online) in Health Education, **INCT-INOFAR** also invests in the production of videos to record its outreach activities and to encourage the scientific community to embrace this practice, so beneficial to the society.

In 2013, **INCT-INOFAR** produced a video documentary to portray its activities during the X National Science and Technology Week (SNCT). Created by the City Hall of Rio de Janeiro with a goal of bringing digital inclusion to in need-areas in the city, the Spaceships and the Knowledge Square are present in six different neighborhoods. During SNCT 2013, **INCT-INOFAR** was present, each day, in a different Spaceship, and at the Knowledge Square, conducting Health Education activities aimed at the safe and correct use of drugs.

"INCT-INOFAR in the Knowledge Spaceships Circuit"
Video (10 min) available at YouTube:
http://m.youtube.com/watch?v=L_C_ZGa4w3w

INCT-INOFAR is part of the 13th International Public Communication of Science and Technology Conference (PCST)

Natalia Lima, Pharmacist, and Ana Cristina da Mata Silva, Education specialist, responsible for the Secretary of Outreach Activities of **INCT-INOFAR**, presented the actions of the Institute for Scientific Awareness & Health Education at the 13th PCST



The conference was held between May 05 and 08, 2014, at the Hotel Pestana, in Salvador/BA.

The National Institute of Science and Technology of Drugs and Medicines **(INCT-INOFAR)** was present during the "*13th International Public Communication of Science and Technology Conference" **(PCST)***, organized by the International Network of Public Communication of Science and Technology (***PCST***).

Keeping its characteristic of innovating in all actions developed, **INOFAR** was the only INCT to be present at the event and to display the results of the work developed in Health Education and Scientific Awareness. In this edition, which was held in Latin America for the first time, and dealt with the topic "Public Communication of Science for Social Inclusion and Political Engagement", ***PCST*** received over 550 submissions, among which was the Poster ***"Outreach Activities of INCT-INOFAR"***, one of 50 works selected to be presented during the event.

The presentation of the poster at the event garnered compliments to the actions previously taken by **INCT-INOFAR**, and we were able to keep up with new trends in Scientific Publicizing in Brazil and in the world, as well as realizing that our own actions are not far from the minimum standards required internationally. However, **INCT-INOFAR** feels the need to act more and more to enhance and optimize its activities in this area.

During its participation in the **13th PCST, INCT-INOFAR** had direct contact with big names in world scientific publicizing, from nearly 50 countries represented. This dive into multiculturalism has created a need to think about scientific knowledge as something that needs to be widely publicized, increasing social inclusion – which was the theme of the **13th PCST.**

Although **INCT-INOFAR** already develops educational projects for science promotion and awareness, it has become apparent that we need to take on the role of multiplying agent in the process of contributing to ensure access to citizenship by all of the population.

As a way to promote self-evaluation and create new perspectives for the development of its Science Publicizing and Popularization activities, **INCT-INOFAR** members took part in sessions, panels, and discussions with topics related to scientific awareness.

Those who were part of the 13th International Conference on Public Communication of Science and Technology (PCST) were able to take photos, write small blurbs, comments, and publicize in their social media profiles (Instagram, Facebook, Twitter, Diaspora), using the hashtag **#PCST2014**, which gathered all the content related to the event. It was also possible to join the PCST community, in the Free Software platform, and post text and images. The initiative can serve as inspiration for future **INCT-INOFAR** events.

Press Clippings: INCT-INOFAR in the media

In 2014, **INCT-INOFAR** was highlighted in the media in several different occasions. The following are the interviews and reports of highest repercussion in the press.

Watch the full interview at:
https://www.youtube.com/watch?feature=share&v=IMuqVAn80BI&app=desktop.

INCT- INOFAR is present on Marcia Peltier Interview show

Approaching the importance of chemistry on quality of life, through the production of drugs, food, cosmetics, clothing, among others, **INCT-INOFAR** associated Professor Angelo da Cunha Pinto (UFRJ) was part of **Programa Marcia Peltier Entrevista**. On the interview, shown on CNT in August, Angelo talks of natural products that are being researched for the cure of several diseases, among them cancer, and also gives his opinion on what would be necessary for the better development of chemistry education and research in Brazil.


E6 | CORREIO POPULAR | DIA NACIONAL DOS MEDICAMENTOS GENÉRICOS

Pesquisador considera que o País poderia avançar mais na produção em larga escala pois ainda é muito dependente de mercados externos

Desafio é transformar Brasil em exportador

Read the full article at:
http://www.unicamp.br/unicamp/sites/default/files/clipping/Jornal%20Correio%20Popular%20pag%2050.pdf

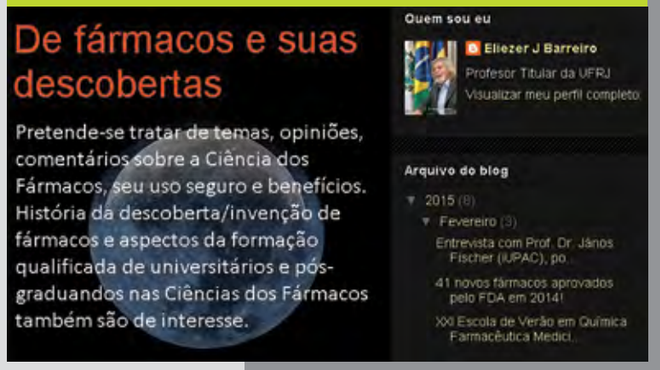

Portal dos Fármacos
22 de agosto de 2014
"História de vida acadêmica"
http://revistapesquisa.fapesp.br/.../vanderlan-da-silva-bolz.../
Vanderlan da Silva Bolzani: A química dos produtos naturais
Pesquisadora busca cooperação internacional e investiga moléculas
REVISTAPESQUISA.FAPESP.BR
Curtir · Comentar · Compartilhar · 2

http://revistapesquisa.fapesp.br/2014/08/21/vanderlan-da-silva-bolzani-quimica-dos-produtos-naturais/

INCT-INOFAR Researcher grants interview to *FAPESP Research* Magazine

The August edition of the FAPESP Research Magazine (issue 222) presented the scientific journey of **INCT-INOFAR** researcher Vanderlan da Silva Bolzani. Professor of the Institute of Chemistry of the State University of Sao Paulo (UNESP) in Araraquara, and internationally acknowledged researcher for her work in the field of Chemistry of Natural Products, Vanderlan Bolzani has received several awards, among them: *Distinguished Women in Science*, the Simao Mathias medal, and Capes-Elsevier.

Access the Blog at: http://ejb-eliezer.blogspot.com.br


De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

Quem sou eu
Eliezer J Barreiro
Profesor Titular da UFRJ
Visualizar meu perfil completo

Arquivo do blog
2015 (8)
Fevereiro (3)
Entrevista com Prof. Dr. János Fischer (IUPAC), po...
41 novos fármacos aprovados pelo FDA em 2014!
XXI Escola de Verão em Química Farmacêutica Medici...

INCT-INOFAR in the Correio Popular de Campinas newspaper

INCT-INOFAR was highlighted in the media with the article "Challenge is to make Brazil an exporter", on the occasion of the National Day for Generic Drugs. On the special report, published on May 20, 2014, in the Correio Popular newspaper, Professor Luiz Carlos Dias from the Institute of Chemistry of the State University of Campinas (UNICAMP), and member of the **INCT-INOFAR** Managing Committee, was interviewed. The researcher develops projects for the **Institute** searching for new synthesis routes for generics. In his interview, the researcher tackled the obstacles that Brazil must overcome to become more competitive in the production of drugs, and the main challenges in becoming a large scale exporter.

INCT-INOFAR Coordinator is Blog author on drug discovery

Another initiative from **INCT-INOFAR** is the Blog **"Of Drugs and their Discoveries"**, developed by Professor Eliezer J. Barreiro, Coordinator of the Institute. The Blog has as one of its main goals to approach themes, opinions, and commentary on the Science of Drugs, their safe use and benefits. The History of the discovery and invention of drugs, aspects of the qualification of college students at the graduate and undergraduate levels in Pharmaceutical Sciences are also part of the Blog.

Publications 2014

Scientific Articles

Brazilian Publications National Journals

1. Oliveira CA, Souza ACJ, Santos APB, Silva BV, Lachter ER, Pinto AC. Synthesis of Fruity Flavor Esters: An Experiment for Undergraduate Courses within one of the Principles of Green Chemistry. Revista Virtual de Química, v. 6, p. 152-167, 2014.[LINK]

2. Paumgartten FJR. Thalidomide and its analogues: comparative clinical efficacy and safety, and cost-effectiveness. Cadernos de Saúde Pública (ENSP. Impresso), v. 30, p. 684-686, 2014. [DOI]

3. França RRF, De Carvalho AS, Branco FSC, Pinto AC, Boechat N. Potent Inhibitors of the Enzyme Sterol 14α-demethylase Against*T. cruzi*.Revista Virtual de Química, v. 6, p. 1483-1516, 2014.

4. Pinto AC. Science City (Editorial).Revista Virtual de Química. v.6, p.168-168, 2014.

5. Pinto AC. Indicadores X qualidade: O dilema atual dos cientistas. Revista Virtual de Química. v. 6, p.833-833, 2014.

6. Britto ALS,Antunes AMS. A Regulação da Industria de Petróleo, gás Natural e Biocombustíveis e a sua contribuição para o sistema setorial de inovação. Cadernos de Prospecção, v. 7, p. 324-334, 2014.

7. Magalhães JL, Cartaxo RJA,Antunes AMS. Produção de Fármacos & Medicamentos no Brasil: uma proposta de metodologia para priorização da Lista Estratégica no Âmbito do SUS. RECIIS. Revista Eletrônica de Comunicação, Informação & Inovação em Saúde (Edição em Português. Online), v.8, p. 478-495, 2014.

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14. Paula Kishi Kuroishi. Total synthesis of (-)-Cryptocaryol A. 2014. Dissertation (Master's Degree in Chemistry) – State University of Campinas, Coordination for the Improvement of Higher Education Personnel. Advisor: Luiz Carlos Dias.

15. Maria Alice Pimentel Falcao. Evaluation of the anti-inflammatory and antinociceptive action mechanism of Caulerpa kempfii. 2014. Dissertation (Master's Degree in Health Sciences) – Federal University of Alagoas, Coordination for Improvement of Higher Education Personnel. Advisor: Magna Suzana Alexandre Moreira.

16. Francisco Stefanio Barreto. Study of cytotoxic activity of compounds obtained from the acetonic extract from the leaves of Annona muricata L. through bioacute fractioning. 2014. Dissertation (Master's Degree in Pharmacology) – Federal University of Ceara, National Council of Scientific and Technological Development. Advisor: Manoel Odorico de Moraes Filho.

17. Cristiano Walter Moraes Rola Junior. Profile of patients sent to admission at ICU through the Central of Regulation of beds in Fortaleza. 2014. Dissertation (Master's Degree in Pharmacology) – Federal University of Ceara. Advisor: Manoel Odorico de Moraes Filho.

18. Italo Savio Mendes Rodrigues. Biomonitoring of leather workers exposed at work to chemical mixtures containing chrome III through measuring of chrome in urine and from complete assay in Teresina-PI. 2014. Dissertation (Master's Degree in Graduate Program in Physiology and Pharmacology) – Federal University of Ceara. Advisor: Manoel Odorico de Moraes Filho.

19. Amanda da Costa Cotias. Effect of bupivacaine metabolite, pipecolic xylidine, in experimental asthma refractory to glucocorticoids. 2014. Dissertation (Master in Human and Experimental Biology) – State University of Rio de Janeiro, Carlos Chagas Filho Foundation of Support to Research in the State of RJ. Advisor: Marco Aurelio Martins.

20. Camila Ribeiro Rodrigues de Pao. Development and validation of an experimental model of asthma refractory to glucocorticoids. 2014. Dissertation (Master's Degree in Biological Science (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro. Advisor: Marco Aurelio Martins.

21. Thais Biondino Sardella. Isatin, n-methyl-isatin and n-methyl-3-(2-oxopropil)-3-hydroxy-2-oxindol: antinociceptive profile and action mechanism. 2014. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education People. Advisor: Patricia Dias Fernandes.

22. Natalia de Morais Sales. Evaluation of LASSBio-1524 and three new analogs in a new acute inflammation model. 2014. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Dias Fernandes.

23. Ananssa Maira dos Santos Silva. Effect of incorporation of dantrolene and azumolene in β-cyclodextrin in the regulation of muscular contractibility. 2014. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, National Council for Scientific and Technological Development. Advisor: Roberto Takashi Sudo.

24. Rachel do Amaral Ribeiro Araujo Vieiralves. New alfa-2 adrenergic agonist with analgesic efficacy on animal chronic pain model. 2014. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro, Advisor: Roberto Takashi Sudo.

25. Victor Jose Goncalves de Moura. New N-acylhydrazone derivate, LASSBio-1359, drug candidate for the treatment of erectile dysfunction. 2014. Dissertation (Master's Degree in Biological Sciences (Pharmacology and Medicinal Chemistry) – Federal University of Rio de Janeiro. Advisor: Roberto Takashi Sudo.

26. Renata Machado Brandao Costa. Impact of extracellular matrix derived from melanoma on the angiogenic profile of endothelial cells: Involvement of Integrin dependent pathways. 2014. Dissertation (Master's Degree in Biosciences) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Thereza Christina Barja Fidalgo.

Finished Doctoral Theses In 2014

1. Cristina d'Urso de Souza Mendes. Future vision for the production of antibiotics: research, development, and innovation trends. 2014. Thesis (Doctorate in Technology of Chemical and Biochemical Processes) – School of Chemistry – UFRJ. Advisor: Adelaide Maria de Souza Antunes.

2. Flavia Maria Lins Mendes. Methodology for the identification of key intermediates of synthetic active principles. Case Study: Antiretrovirals for the treatment of AIDS. 2014. Thesis (Doctorate in Technology of Chemical and Biochemical Processes) – School of Chemistry – UFRJ. Advisor: Adelaide Maria de Souza Antunes.

3. Viviane Masseran Antunes Parreiras. Proposal of trend observatory in a business R&D center – case of nanotechnology at CENPES. 2014. Thesis (Doctorate in Technology of Chemical and Biochemical Processes – School of Chemistry - UFRJ. Advisor: Adelaide Maria de Souza Antunes.

4. Sabrina Dias de Oliveira. Analysis of the Production of succinic acid from renewable sources: perspectives and challenges. 2014. Thesis (Doctorate in Technology of Chemical and Biochemical Processes) – School of Chemistry – UFRJ. Advisor: Adelaide Maria de Souza Antunes.

5. Fabio Teixeira da Silva. Ficus genus. Studies of historical and chemical aspects. 2014. Thesis. (Doctorate in Chemistry). Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Angelo da Cunha Pinto.

6. Daniel Rosa da Silva. Development of Empirical Models of Prediction of Activity of Acetylcholinesterase Enzyme of Torpedo californica and Aedes aegypti using the Semi-Empirical Method. 2014. Thesis (Doctorate in Chemistry) – Federal Rural University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Carlos Mauricio Rabello de Sant'Anna.

7. Lana Gabriela. Mapping and legal approaches of bioprospecting networks in Brazil. 2014. Thesis (Doctorate in Biotechnology - RENORBIO) – State University of Ceara, National Council for Scientific and Technological Development. Advisor: Claudia do Ó Pessoa.

8. Jose Rubens Costa Lima. Monitoring of venous hydration in the hemorrhagic fever in dengue and other pathologies. 2014. Thesis (Doctorate in Biotechnology - RENORBIO) – State University of Ceara. Advisor: Claudia do Ó Pessoa.

9. Paula Giselle Czaikoski. Role of NET in the evolution of sepsis. 2014. Thesis (Doctorate in Pharmacology) – Faculty of Medicine of Ribeirao Preto - USP, Foundation for the Support of Research in the State of Sao Paulo. Advisor: Fernando de Queiroz Cunha.

10. Gabriela Trentin Scortegagna. Physiopathological mechanisms involved in the susceptibility of NOD (non-obese diabetic) mice to sepsis, role of NETs (neutrophil extracellular traps), AGP (alfa-1 acid glycoprotein), and Histamine. 2014. Thesis (Doctorate in Basic and Clinical Immunology) – Faculty of Medicine of Ribeirao Preto – USP, Foundation for the Support of Research in the State of Sao Paulo. Advisor: Fernando de Queiroz Cunha.

11. Jaqueline Raymondi Silva. Neuro-immune interactions involved in the genesis and maintenance of nociceptive herpetic hypersensitivity and post-herpetic. 2014. Thesis (Doctorate in Immunology) – Faculty of Medicine of Ribeirao Preto – USP, Foundation for the Support to Research in the State of Sao Paulo. Advisor: Fernando de Queiroz Cunha

12. Guilherme Carneiro Montes. Investigation of the activity of N-methyl-Acylhydrazone derivates (LASSBio-1359 and LASSBio-1289) in central nervous system. 2013. Thesis (Doctorate in Biological Sciences (Pharmacology and Medicinal Chemistry)) – Federal University of Rio de Janeiro. Advisor: Gisele Zapata-Sudo.

13. Danilo Pereira de Sant'Ana. Synthesis of the C1-C9 fragment of (-)-dictyostatin and studies aimed at the total synthesis of (+)-tautomycetin. 2014. Thesis (Doctorate in Chemistry) – State University of Campinas, Foundation for Support of Research in the State of Sao Paulo. Advisor: Luiz Carlos Dias.

14. Yolanda Karla Cupertino da Silva. Evaluation of immune modulating activity of new N-acylhydrazone (NAH) pyrazine derivates: a proposal for the discovery of an antitumoral/ immunosuppresor drug. 2014. Thesis (Doctorate in RENORBIO) – Northeast Network of Biotechnology, Coordination for the Improvement of Higher Education Personnel. Advisor: Magna Suzana Alexandre Moreira.

15. Flavia Castelo Batista Magalhaes. From legal access and biological material to patenting of biotechnological product: Brazilian dimensions and challenges. 2014. Thesis (Doctorate in Biotechnology – RENORBIO) – State University of Ceara. Advisor: Manoel Odorico de Moraes Filho.

16. Francisco Jose Lopes Cajado. Use of liquid extract of the cactus pear, (Opunta ficus indica), as a diluting agent and criopreservative of the semen of fish cultivated in the Brazilian Northeast. 2014. Thesis (Doctorate in Biotechnology - RENORBIO) – State University of Ceara. Advisor: Manoel Odorico de Moraes Filho.

17. Diana Dalzy Viveiros. Effect of the N-acylhydrazone LASSBio-897 derivate on the inflammatory pulmonary response in experimental asthma and silicosis. 2014. Thesis (Doctorate in Cellular and Molecular Biology) – Oswaldo Cruz Foundation, Coordination for the Improvement of Higher Level Personnel. Advisor: Marco Aurelio Martins.

18. Suzana Vanessa Soares Cardoso. Triage and pharmacological evaluation of new PDE4 inhibitors, of N-methylacylhydrazones, for asthma control. 2014. Thesis (Doctorate in Cellular and Molecular Biology) – Oswaldo Cruz Foundation, Oswaldo Cruz Institute. Advisor: Marco Aurelio Martins.

19. Monica Lorena Dias Meireles. Clinical pharmacological Stage I and II assays with synthetic compound 5,7-Diacetox-4-Arylcromane, derivates of constituents of the Coutarea hexandra species in the treatment of herpes simplex. 2014. Thesis (Doctorate in Natural and Synthetic Bioactive Products) – Federal University of Paraiba. Advisor: Margareth de Fatima Formiga Melo Diniz.

20. Daiene Martins Lunguinho. Studies of Antitumoral and Toxicological Effects of the Essential Oil from the Leaves of Xylopia frutescens Aubl. (ANNONACEAE). 2014. Thesis (Doctorate in Natural and Synthetic Bioactive Products) – Federal University of Paraiba. Advisor: Margareth de Fátima Formiga Melo Diniz.

21. Heraldo Arcela de Carvalho Rocha. Clinical Assay with the Extract from the Roots of Panax Ginseng C. A. Meyer in the Treatment of Irritable Bowel Syndrome. 2014. Thesis (Doctorate in Natural And Synthetic Bioactive Products) – Federal University of Paraiba. Advisor: Margareth de Fatima Formiga Melo Diniz.

22. Cynthia Samary. Impact of transpulmonary pressures generated by the combination of different volumes and positive pressures at the end of expiration in an acute respiratory distress model. 2014. Thesis (Doctorate in Biological Sciences – Physiology) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Rieken Macedo Rocco.

23. Johnatas Dutra Silva. Effects of different mesenchymal cells in Acute Pulmonary Lesion model. 2014. Thesis (Doctorate in Biological Sciences – Physiology) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Patricia Rieken Macedo Rocco.

24. Milene Borsoi. Repeated forced swimming as a paradigm for the study of cognitive damage and synaptic plasticity changes related to neuropsychiatric illnesses. 2014. Thesis (Doctorate in Biological Sciences (Neuroscience)) – Federal University of Rio Grande do Sul, Coordination for the Improvement of Higher Education Personnel. Advisor: Stela Maris Kuze Rates.

25. Liz Girardi Müller. Study of the involvement of different biological targets in the mechanism of antidepressive action of a fraction enriched in dienic valepotriates obtained from Valeriana glechomifolia Meyer (Valerianaceae) of Valeriana glechomifolia Meyer (Valerianaceae). 2014. Thesis (Doctorate in Pharmaceutical Sciences) – Federal University of Rio Grande do Sul, Coordination for the Improvement of Higher Education Personnel. Advisor: Stela Maris Kuze Rates.

26. Antonio de Moraes Izquierdo. Expression of molecular markers of the process of radicular reabsorption induced by successive cycles of orthodontic movement. 2014. Thesis (Doctorate in Dentistry) – Federal University of Rio de Janeiro, Coordination for the Improvement of Higher Education Personnel. Advisor: Thereza Christina Barja Fidalgo.

INCT-INOFAR Scholarships

FIOCRUZ/RJ

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

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

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

UNIFAL

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

UNICAMP

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

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

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

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

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

UFC

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

UFG

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

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

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

UFMG

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

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

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

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

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

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

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

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

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

UFRGS

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

UFRJ

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

44) Juliana Fatima Vilacha Madeira Rodrigues dos Santos CV Lattes
CNPq Technical Support Scholarship – IC
Time: March 2012 to Mar 2013
Project: "Planning, synthesis, and pharmacological evaluation of 1,2,3,4-tetrahydroacridine derivates, acetylcholinesterase inhibitor prototypes."
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

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

46) Leonardo Ferreira de Oliveira CV-Lattes
CNPq Technical Support Grant– AT NM
From December 2014 to December 2015
Project: "Scientific awareness and health education at **INCT-INOFAR**"
Advisor: Prof. Dr. Lidia Moreira Lima
LASSBio

47) Lethycia Machado Tannuri CV-Lattes
CNPq Technological Development Scholarship – DTI-1
Time: November 2014 to November 2015
Project: "Scientific awareness and health education at **INCT-INOFAR**"
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

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

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

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

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

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

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

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

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

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

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

58) Natalia Medeiros de Lima CV-Lattes
CNPq Technical Support Scholarship – AT NS
Time: August 2010 to July 2011
CNPq Technical Support Scholarship – DTI-2
Time: July 2013 to December 2015
Project: "Scientific awareness and health education at **INCT-INOFAR**"
Advisor: Prof. Dr. Eliezer J. Barreiro
LASSBio

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

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

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

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

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

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

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

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

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

UNIVASF- PE

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

USP- RIBEIRAO PRETO

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

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

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

STATISTICS ACCORDING TO TYPE OF SCHOLARSHIP

CNPq

JUNIOR POST-DOCTORATE (PDJ) – 16

INDUSTRIAL TECHNOLOGICAL DEVELOPMENTL (DTI-1) – 9

INDUSTRIAL TECHNOLOGICAL DEVELOPMENT (DTI-2) – 4

INDUSTRIAL TECHNOLOGICAL DEVELOPMENT (DTI-3) – 12

INDUSTRIAL AND TECHNOLOGICAL INITIATION (ITI) - 4

MID-LEVEL TECHNICAL SUPPORT (ATNM) – 12

HIGHER LEVEL TECHNICAL SUPPORT (ATNS) - 6

SCIENTIFIC INITIATION (IC) - 10

Total CNPq Scholarships– 73

CAPES

MASTER DEGREE - 3

DOCTORATE - 4

PARTIAL FOREIGN EXCHANGE DOCTORATE - 2

POST-DOCTORATE ABROAD – 1

Total CAPES Scholarships– 10

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