# THE ORIGIN OF PHARMACEUTICALS

**Eliezer J. Barreiro, Carlos Alberto M. Fraga** and **Lidia M. Lima**
*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®) Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CCS, Cidade Universitária, ZIP 21944-910 Rio de Janeiro, RJ, Brazil*

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## Contents



## Summary

The importance of natural products in therapeutics has been generally recognized from immemorial time. The Amerindians' knowledge of hallucinogenic plants used for their religious rituals, as well as the aphrodisiac properties of several potions prepared from several plant species, have accompanied man for millennia. Throughout the ages, the search for the well-being and for the pleasure has always stimulated man to approach nature, teaching him to make good use of plants and their components. Although plants and microorganisms remain a major source of new drugs, natural products from marine sources have been actively investigated in recent decades. In fact, the possibility of finding new medicines from natural sources is one of the more old man's activities and represents one of the most mentioned reasons for preserving biodiversity. The use of natural products as drug found several examples in therapeutics, as well as their use as an important template for molecular modification, being a crucial source of new original structural patterns that represents an authentic "molecular inspiration" for the design of new drugs. This chapter will cover the main natural products from plants, microorganisms and from marine sources that were developed to medicines and those that historically contributed as lead-compound for designing and discovery of more active and safer drug candidates.

## 1. Medicinal Chemistry Definition and the Role of the Lead-Compound in Drug Discovery

The Committee of the International Union of Pure and Applied Chemistry (IUPAC), recently, defined Medicinal Chemistry as: "*a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active*

*compounds, the interpretation of their mode of interaction at the molecular level, the construction of their structure-activity relationships, and the study of their metabolism*".

The interdisciplinarity between Chemistry and Biology, essential for medicinal chemistry, was brilliantly recognized by Arthur Kornberg, Nobel Laureate in Physiology and Medicine in 1959, when he said in the Congress of the American Association for the Advance of Science, in 1987: "*We have the paradox of the two cultures, chemistry and biology, growing further apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex*". By harmonizing these two "science", seemingly distinct conditions necessary and essential to the interaction of medicinal chemists, pharmacologists, toxicologists, biochemists, and so on, lead to the discovery or designing new molecular patterns, which under particular conditions could be considered as a lead-compound or a drug candidate.

A lead-compound is considered to be the prototype identified with equilibrium between the pharmacodynamic and pharmacokinetics properties, in order to assure it pharmacological activity in animal models (*in vivo*). Later, it needs to pass by several toxicological studies aiming to determine its therapeutic index, cellular and tissue damages, carcinogenic and teratogenic profiles. Finalized this toxicological step, the best lead-compound can be now considered a drug candidate.

Not rare, the identified lead-compound (LC) needs a step of optimization in order to adjust or improve some particular characteristics of the LC in the pharmacodynamic (PD) and/or pharmacokinetic (PK) phases. The optimization step consists in the rational design of specific molecular modifications to be introduced in the structure of the lead-compound, which often are performed by applying classic medicinal chemistry strategies, like bioisosterism and molecular simplification, and can be aided by the use of molecular modeling. The Figure 1 illustrated the LC approach of the rational drug design process.

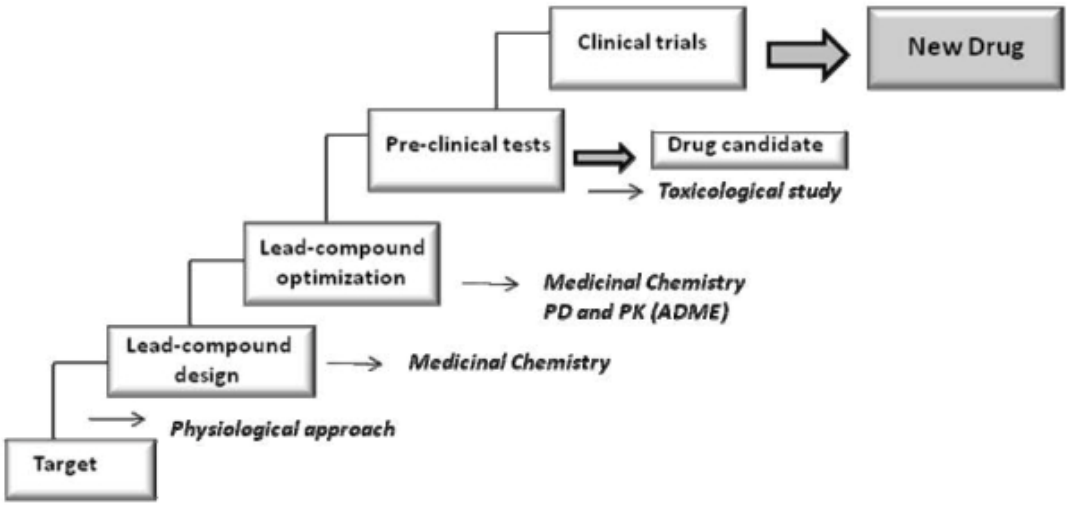


Figure 1. The lead-compound approach in the complex process of rational discovery of new drugs.

Each drug design (DD) program is unique and setbacks are not rare, making it difficult to predict accurately the duration or costs and it is now well accepted that predicted eventual toxicity in the very early stages seen to be important to identify the level of safety of this new drug candidate. Modern DD became a hybrid process, no more linear as some few years ago were considered, and efforts typically emerge in order to obtain new lead-compounds in a shorter time, with lower cost. In this process, different strategies can be employed, like the so called hyphen-strategies, resulting from the combination of two specific technologies (*e.g.* HTS-combinatorial chemistry), that are especially common in pharmaceutical industry laboratories or in high-tech small companies.

It is necessary to recognize that DD process represents an important example, maybe the most relevant, of the critical role of the basic science from different health disciplines to go gradually on a specific sequential of tasks to – if successfully – culminate in a new drug for the treatment of a human disease. This overall pathway is well-structured and start from the carefully selection of the drug target, applying the classical strategy of rational drug design named physiological approach. Besides, it can be initiated by bioprospecting natural products from different sources, leading to the identification of a new lead compound, that could be later modified in order to optimizing its structure, activity, selectivity, toxicity and so on, until it can be considered an authentic drug candidate for pre-clinical and clinical trials.

## 2. Natural Products as Medicines and Drugs Candidates

The importance of natural products in therapeutics has been generally recognized from immemorial time. The Amerindians' knowledge of hallucinogenic plants used for their religious rituals, as well as the aphrodisiac properties of several potions prepared from various plant species, have accompanied man for millennia.

Plants, fungi, insects, marine organisms and bacteria represent a rich sources of therapeutically useful compounds. Great part of the drugs in clinical use is of natural origin or was developed inspired on modification of a natural scaffold. A recent survey of all drugs approved worldwide between 1981 and 2006 pointed out that 34% of all small-molecule drugs are natural products or their direct semisynthetic derivatives. The impact of natural products is even more profound among drugs that are used to treat severe and/or life-threatening diseases such as cancer and infectious diseases. Among all approved small-molecule anticancer drugs (total 155), 47% are either natural products or direct semisynthetic derivatives. Similar dominance of natural products is observed among the anti-infective compounds, and amazingly >75% out of approved antibacterials are natural products or their semisynthetic derivatives (74 out of 98).

In spite of various strategies and methodologies currently available to design, synthesize and discover new medicines, natural products continues to represent an important and privileged starting material for drug discovery.

In general, one of the greatest challenges for natural product based drug discovery has been their structural complexity and low synthetic feasibility. Otherwise, they have quite distinct structural characteristics from synthetic molecules. For example, when

analyzed by either a size-independent 'chemistry space filter' or 'support-vector-machine' approach, natural products exhibit better scores of 'druglikeness' than synthetic compounds. Further, natural products contain on average twice as many oxygen atoms and three times fewer nitrogen atoms than synthetic drug molecules. They also contain a slightly higher number of hydrogen-bonding donors than do synthetic drugs. Natural products contain approximately four times more chiral centers and far fewer aromatic rings, a fact which may engender upon natural products better selectivity when binding to stereo-defined sites.

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**Biographical Sketches**

**Eliezer j. Barreiro** (born in 1947) is Pharmacist (1971) and MSc. in Chemistry of Natural Products (1973) from Federal University of Rio de Janeiro (Brazil). He is Docteur-Ès-Sciences d´État (1978) in Chimie Médicale from Université Scientifique et Médicale de Grenoble (France). Professor Barreiro is currently full professor of Medicinal Chemistry at Federal University of Rio de Janeiro since 1986. He published over 210 articles in specialized and indexed journals, including review articles (*e.g.* > 105 citations), has index *h* = 20 (Jan. 10, 2011). He is guest author of several chapters of books in Medicinal Chemistry, and author of 2 books in this field. He has 14 patent applications filed at INPI (BR) and a patent granted by the United States Patent and Trademark Office, number 7.091.238 of August 15, 2006. He is a mentor to more than 70 graduate students in the areas of Medicinal Chemistry, Pharmaceutical Chemistry, Pharmaceutical Sciences, Biochemistry and Pharmacology. He is scientific collaborator of over 350 scientists worldwide in joint research and scientific production. Prof. Barreiro received 7 scientific awards, including the Grand Master of the Order of National Scientific Merit of the Presidency of the Republic of Brazil (2010); the Order of National Scientific Merit of the Presidency of the Republic of Brazil (2004); the Rheinboldt-Hauptmann prize by the Institute of Chemistry of the University of São Paulo, SP (27/11/2002). He is member of the Brazilian Academy of Sciences since 2001. He is also fellow "Scientist of Rio de Janeiro State", FAPERJ. His research interests lie in the area of Medicinal Chemistry and Medicines or Pharmaceutical Chemistry. Currently, Prof. Barreiro is the scientific coordinator of the Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, www.farmacia.ufrj.br/lassbio; i.e. Laboratory of Evaluation and Synthesis of Bioactive Substances) at Federal University of Rio de Janeiro (UFRJ; Brazil), which was founded in 1994.

**Carlos Alberto Manssour Fraga** was born in Rio de Janeiro (Brazil) in 1964. He obtained a B.S. degree in Pharmacy in 1988 and his M.Sc. degree in Sciences (Medicinal Chemistry) from Federal University of Rio de Janeiro (UFRJ). After obtaining his PhD degrees from Chemistry Institute of UFRJ in 1994, working with the synthesis of novel stable prostacyclin mimetics under the supervision of Professor Eliezer J. Barreiro, Carlos Alberto Manssour Fraga joined the Faculty of Pharmacy of UFRJ (Rio de Janeiro) as Associate Professor in 1996 and was promoted to Professor in May 2006. He was Head of Drug Department of Faculty of Pharmacy (UFRJ) from 2008 to 2010 and currently he is Coordinator of the Post Graduate Program in Pharmacology and Medicinal Chemistry of Institute of Biomedical Sciences of UFRJ. Dr. Fraga is effective member of Brazilian Chemical Society since 1991, where he was Director of Medicinal Chemistry Division from 2002 to 2004. Apart from teaching, Professor Fraga develop his research activities in LASSBio® (*Laboratório de Avaliação e Síntese de Substâncias Bioativas*, UFRJ), focusing the design, synthesis and pharmacological evaluation of novel drug candidates able to act in multifactorial diseases, with particular emphasis in the use of *N*-acylhydrazone framework as privileged structure to discovery novel therapeutically valuable compounds.

**Lidia M. Lima** obtained her B.S. degree in Pharmacy from the Federal University of Rio de Janeiro (UFRJ, Brazil, 1994), MSc. in Organic Chemistry (UFRJ, BR, 1997), PhD in Medicinal Chemistry (UFRJ, BR, 2001) and a Post-Doctorate training in Medicinal Chemistry in the University of Navarra (UNAV, Pamplona, Spain). She is currently an Associate Professor at the Pharmacy College in the Federal University of Rio de Janeiro (UFRJ), teaching and supervising undergraduate and graduate students in the field of Medicinal Chemistry. Her research projects aim at contributing to the discovery of new drugs of various therapeutic classes, such as anti-inflammatory, anti-asthmatic, anti-cancer, antiviral and antiparasitic. She was granted a fellowship “Young Scientist of Rio de Janeiro State” (FAPERJ, BR) and a productivity grant from the National Council for Scientific and Technological Development (CNPq, BR). She is currently Secretary of the *Brazilian Chemical Society Regional Rio de Janeiro* (SBQ-Rio, 2010-2012).