

MEDICINAL CHEMISTRY

Fulvio Gualtieri

Department of Pharmaceutical Sciences, University of Florence, Italy

Keywords: Drugs, medicinal chemistry, drug design, drug synthesis, drug development, pharmacokinetics, toxicology, lead identification, lead optimization

Contents

1. Introduction
 - 1.1. Definition of a Drug
 - 1.2. Classification of Drugs
 - 1.3. Definition of Medicinal Chemistry
 2. From Bioactive Molecules to Drugs
 - 2.1. Pharmacokinetics: Absorption, Distribution, Metabolism, Excretion (ADME)
 - 2.2. Toxicity (T)
 - 2.3. Impact of Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) on Drug Design and Development
 3. The Basis for Drug Action
 - 3.1 Mechanism of Action of Drugs
 - 3.2. Drug Targets
 - 3.3. Preclinical Evaluation of Drug Activity
 4. Drug Discovery and Development
 - 4.1. Drug Design and Development: *in Silico* Studies
 - 4.2. Drug Design: Lead Identification
 - 4.2.1. Existing Drugs
 - 4.2.2. Natural Compounds
 - 4.2.3. Serendipity
 - 4.2.4. Systematic Screening
 - 4.2.5. Combinatorial Chemistry
 - 4.2.6. Rational Design
 - 4.3. Drug Development: Lead Optimization
 - 4.3.1. Isosteric Replacement
 - 4.3.2. Molecular Simplification
 - 4.3.3. Molecular Complication
 - 4.3.4. Electronic Modulation
 - 4.3.5. Steric Modulation
 - 4.3.6. Derivatization (Prodrugs)
 5. Clinical Evaluation
 6. Industrial Drug Development
 7. Conclusions
- Glossary
Bibliography
Biographical Sketch

Summary

Drug discovery is an iterative process which uses a variety of strategies but essentially comprises a few discrete stages: target identification and validation; pharmacological screening; hits and lead identification; lead optimization; preclinical and clinical evaluation; industrial development. Medicinal chemistry plays its role essentially in the phases of hits and lead discovery and lead optimization, building structure-activity relationships (SAR) and identifying drug candidates. Toward this end, understanding the nature and structure of drug targets as well as knowledge of the mechanism of action and of the pharmacokinetic and toxicological behavior of putative drugs is of utmost importance.

1. Introduction

1.1. Definition of a Drug

A drug can be defined as a chemical that interacts with a biological system and produces a biological response. This definition covers the medicines that we take when we are ill but can be extended to several other substances that are consumed with food and beverages and to the mineral, vegetal and animal xenobiotics with which one may come in contact during a lifetime. The effect of a drug depends on the dose: given at the proper dose, a deadly poison like curare may be extremely useful in surgery, while a drug like insulin, which is essential for life, in high doses is dangerous and may cause death. Drugs are characterized by their *efficacy* to treat a given disease, by the *dose* necessary for therapeutic action and by the unwanted effects that they might cause at active doses (*side effects*). The *therapeutic index* is a measure of drug safety: for a given drug, it is the ratio between the dose that gives toxic effects in 50% of the patients treated and the dose that cures 50% of them. The drugs (*active principles*) are identified by a common or generic name (*nonproprietary name*) and may be administered alone or in association with other drugs. In both cases, the active principle is associated with some inert ingredients (*excipients*) that are used to vehicle the drug, or other minor ingredients to preserve it. Finished pharmaceutical products in a definite composition, form, dosage and formulation are identified by brand names; accordingly, it may happen that pharmaceutical preparations containing the same active principle are sold with different brand names.

A new active principle that has received marketing authorization is usually protected by a patent and can be marketed only by the company owning the patent or by licensed companies. However, when the patent expires, the drug assumes the status of generic drug and, under some given rules, can be produced and marketed by any other company.

1.2. Classification of Drugs

So far, the complex nature of medicines has escaped a unique, generally accepted drug classification system. The origin of the drugs (natural or synthetic), their chemical structure (betalactams, steroids...), the mode of action (enzyme inhibitors, antihistaminics...) or the nature of the disease (anticancer drugs, antihypertensive

drugs...) has been at the base of some classifications systems. In 1968 the World Health Organization (WHO) proposed a physiologically-based system whereby drugs are classified by the body structure on which they act, for instance the digestive system or the circulatory system. However, quite often a combination of all these systems is used. The simpler classification system, that for this very reason is fairly popular, divides drugs into the four major classes reported and defined in Table 1. The WHO has also elaborated a list of essential active principles that are defined as "those that satisfy the primary health care needs of the population" The most recent version of the list (the 14th) can be found at the following WHO Internet address: <http://www.who.int/medicines/organization/par/edl/eml.shtml> .

Drugs acting on the central nervous system	Agents that act on the structures of the brain and on the spinal cord such as neuroleptic and antidepressive drugs
Pharmacodynamic drugs	Agents that affect the dynamic processes of the body such as cardiovascular and antiallergic drugs
Chemotherapeutic drugs	Agents that act on microorganisms and viruses. Include also anti tumor drugs
Drugs that effect metabolic and endocrine functions	Include a variety of agents such as antidiabetics, anti-inflammatory and steroidal hormones

Table 1: The simplest drug classification system

To explain the difficulties inherent in drug classification, it must be considered that a therapeutic effect (i.e. blood pressure reduction) can be obtained with different drugs acting with different mechanisms of action (diuretics, calcium antagonists, ACE inhibitors and so on) and that drugs very seldom present a single pharmacological action.

1.3. Definition of Medicinal Chemistry

Drug discovery is a complex process where chemistry and preclinical and clinical pharmacology have a prevalent role but it is also supported by the knowledge of several other life science disciplines such as genetics, physiology, pathology, microbiology, and molecular biology. Chemistry is involved in fundamental steps of a drug discovery process such as synthesis or extraction, drug analysis, formulation and pharmaceutical technology, but its main contribution is in drug design, discovery and development, that is, medicinal chemistry. In fact, medicinal chemistry relates to the design, study, development and production of drugs that can be used as medicines for disease treatment. In 1974 IUPAC (International Union of Pure and Applied Chemistry) gave the following definition of medicinal chemistry: "*Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemist is not restricted to drugs but include*

bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification and synthesis of the metabolic products of these drugs and related compounds”

After many centuries in which the search for therapeutic substances was based on the exploitation of natural resources, mainly plants whose therapeutic properties were discovered through an empirical approach, the advent of organic chemistry radically changed the perspective of drug discovery. In fact, progress in organic chemistry made purification and synthesis of sophisticated active principles possible, suggesting that new active drugs could be easily obtained by synthesis. At the same time, medicinal chemists realized that such molecules could be rationally designed, taking advantage of progress in physiology, molecular biology, pathology, microbiology, pharmacology, and eventually genetics. As a consequence, at present, the synthesis of active principles is largely guided by the study of the interactions between active substances and their molecular targets that have been disclosed by progress in genetics and molecular biology.

2. From Bioactive Molecules to Drugs

The number of chemicals that have some kind of action on biological organisms is huge, while only a few thousand molecules are actually used as drugs. This is due to the fact that, to exert its action, an active principle has to be put in the necessary conditions to reach its target. The identification of active principles and their transformation into useful medicines is one of the main goals of medicinal chemistry. To reach this goal, the pharmacokinetic properties of a candidate drug have to be evaluated and, if necessary, modulated during the development process. Since very seldom can it be applied directly to its site of action, the active molecule has to be absorbed, transported, and distributed to the target; it has to survive metabolism and elimination, to reach the target in suitable concentration and, last but not least, the drug should not damage the organism either directly or through its metabolites. These events control bioavailability and the hematic concentration of a drug that is directly related to its therapeutic effect. As a matter of fact, there is a mutual interaction between the drug and the living organism, as illustrated in Figure 1: the drug in some way modifies the biology of the organism (pharmacodynamic phase) and the organism, in turn, disposes of the drug (pharmacokinetic phase).

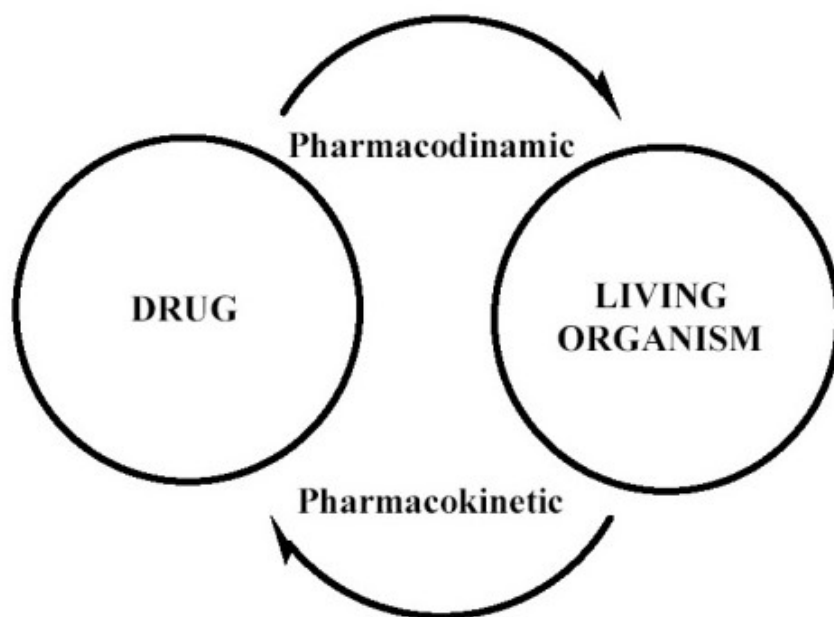


Figure 1: Mutual interactions between drugs and living organisms.

The pharmacokinetic phase is usually identified with the acronym ADME (absorption, distribution, metabolism, elimination), while the safety of a drug is a matter of toxicology: both are crucial for a bioactive molecule to be used as a drug.

TO ACCESS ALL THE 42 PAGES OF THIS CHAPTER,
 Visit: <http://www.eolss.net/Eolss-sampleAllChapter.aspx>

Bibliography

Antonenko, V.V., Kulikov, N.V., Mortezaei, R. (2000). Combinatorial chemistry, in *New Trends in Synthetic Medicinal Chemistry* (ed. F. Gualtieri) pp 39-80. Weinheim: Wiley-VCH. [This book chapter gives an overview of the methods used in combinatorial chemistry.]

Erhardt, P.W. (2002). Medicinal chemistry in the new millennium. A glance into the future. *Pure Appl. Chem* **74**,703-785. [A documented and stimulating paper on the present and future of medicinal chemistry.]

Fernandes, P. B. (2001). Back to basic: from genes to medicines. *Medicinal Chemistry Research* **10**, 421-430. [A review on the influence of genetic in drug discovery.]

Gualtieri, F., Romanelli, M. N., Teodori, E. (1996). The frozen analog approach in medicinal chemistry, in *Progress in Medicinal Chemistry* (ed. M. I. Choudhary). Vol 1, pp. 271-318. The Netherlands: Harwood Academic Publishers. [This review approaches the problems of conformationally-restricted

molecules in drug research.]

Gubernator, K., Bohm, H. J. (1998). *Structure-Based Ligand Design*, pp. 153. Weinheim: Wiley-VCH. [The book describes the methods used for structure-based drug design.]

Kubinyi, H. (1993). *Hansch Analysis and Related Approaches*, pp. 240. Weinheim: Wiley-VCH. [A book on the principles and practice of quantitative structure-activity relationships.]

Leach, A.R. (2001). *Molecular Modelling: Principles and Applications*, 2nd ed, pp 744. Harlow: Pearson Education Ltd. [This book deals with the principles and practice of molecular modeling.]

Li, A. P. (2001). Screening for human ADME/Tox drug properties in drug discovery. *Drug Discovery Today* 6, pp. 357-366. [A review of the method used to evaluate pharmacokinetic and toxicity of drugs.]

O'Neil et al. (2001). An encyclopedia of chemicals, drugs, and biologicals, *The Merck Index* 13th ed. pp. 1818. Whitehouse Station: Merck & Co., Inc. [A fundamental reference book for chemical structures and pharmacological properties of biologically active compounds.]

Patani, G. A., Lavoie, E. J. (1996). Bio isosterism: a rational approach in drug design. *Chemical Reviews* 96, 3147-3176. [A review on the principles and methods of the isosteric-substitution approach.]

Patrick, G. L. (2005). *An Introduction to Medicinal Chemistry*, 3rd edition, pp. 770. Oxford University Press. [A text book introducing the principles of medicinal chemistry.]

Roberts, G. C. K. (2000) Applications of NMR in drug discovery. *Drug Discovery Today* 5, 230-240. [A review on the use of NMR technology in drug studies.]

Smith, D. A., Van De Waterbeemd, H., Walker, D.K. (2001). *Pharmacokinetics and Metabolism in Drug Design*, pp. 180. Weinheim: Wiley-VCH. [A book evidencing the impact of pharmacokinetics in drug discovery]

Walters, W.P., Stahl, M.T., Murcko M.A. (1998). Virtual screening- An overview. *Drug Discovery Today* 3, pp. 160-177. [A review on the theory and application of virtual screening]

Wermuth, C. G. (1996). *The Practice of Medicinal Chemistry*, pp 968. San Diego: Academic Press. [A precious text book in medicinal chemistry.]

Williams, D. A., Foye, W.O., Lemke, T. L. (2002). *Foye's Principles of Medicinal Chemistry*, 5th edition, pp. 1128. USA, Lippincot Williams & Wilkins. [A precious text book in medicinal chemistry.]

Biographical Sketch

Fulvio Gualtieri was born in Rome (1936) and graduated in Chemistry at the University of Rome (1960). He was postdoctoral fellow at the Stanford Research Institute of Palo Alto, California (1969-1970) and at the Chemistry Department of McGill University, Montreal (1972). After having been a teacher and researcher at Camerino and Palermo Universities, he is now Professor of Medicinal Chemistry in the Faculty of Pharmacy of the University of Florence, where he is the Director of the Department of Pharmaceutical Sciences. He has served as the Dean of the Faculty of Natural Sciences of Camerino University (1977-1980), Dean of the Faculty of Pharmacy of the University of Florence (1986-1995) and as President of the Medicinal Chemistry Division of the Italian Chemical Society (1991-1994). His main fields of interest are receptor ligands, calcium channel antagonists, multidrug resistance (MDR) modulators and related pathologies. On these subjects he is author or coauthor of some 200 papers, book chapters and books.