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TRENDS IN DRUG RESEARCH III

Proceedings of the 13th Noordwijkerhout-Camerino Symposium

EDITED BY

Henk van der Goot

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PREFACE

Trends in Drug Research
followers or setters

This volume of Pharmacochemistry Library comprises the text of invited lecturers presented at the Noordwijkerhout-Camerino Symposium *Trends in Drug Research*, held in Noordwijkerhout, The Netherlands, from 6-11 May 2001.
During the 13th symposium in the series the question was asked whether medicinal chemists are following trends or perhaps trendsetters. The answer was clear: trendsetters. Through the years of the series - the first one dates back to 1974 - topics of the programme have been developing into almost routine aspects of medicinal chemistry; QSAR, modelling, receptor models.

The 13th symposium fitted perfectly well in this tradition. On the programme were sessions on chemical and biological diversity, on new paradigms in drug action, on new insights in receptor mechanisms. A session which got much attention - and which brought new insights - was on green chemistry, the interface between organic synthesis and biosynthesis.
A special symposium was devoted to the growing problem of resistant micro-organisms and the possibilities to identify new - and better - antibiotics.
In a final session on very recent developments the new finding of small molecules with insulin sensitizing properties received much attention. Would an insulin-mimetic, a small molecule, be possible?

The organizers of the Noordwijkerhout-Camerino Symposia express their sincere thanks to those who supported the 2001 symposium financially: Astra Zeneca, Byk Nederland, DSM, Glaxo Wellcome, Janssen Research Foundation, Lundbeck A/S, E. Merck, Organon Research, Pfizer (Parke Davis), UCB, Yamanouchi Europe.

H.Timmerman,
Chairman Organizing Committee

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H. van der Goot (Editor)
Trends in Drug Research III

Towards Rational Design of AMPA Receptor Ligands: An Integrated Medicinal, Computational, Biostructural and Molecular Pharmacological Approach

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1. Medicinal Chemistry, a Science Undergoing Rapid Transformations

The field of medicinal chemistry is in a state of swift development and is at present undergoing major restructuring. The molecular biological revolution and the progressing mapping of the human genome have created a new biochemical and biostructural "world order". These developments have provided new challenges and opportunities for drug research in general and for drug design in particular. The major objectives of the medicinal chemists are transformation of pathobiochemical and - physiological data into a "chemical language" with the aim of designing molecules interacting specifically with the derailed or degenerating processes in the diseased organism.

Potential therapeutic targets are being disclosed with increasing frequency, and this exponential growth will continue during the next decades. In this situation, there is a need for rapid and effective target validation and for accelerated lead discovery procedures. Consequently, most industrial medicinal chemistry laboratories have built up new technologies in order to meet these demands. Key words in this regard are construction of compound libraries, high or ultrahigh throughput screening, accelerated ADME and toxicity tests, and automatized cellular assay systems.

In parallel with this development, biostructure-based drug design and intelligent molecular mimicry or bioisosterism are areas of growing importance in the medicinal chemistry "playing field". Structural biology is becoming an increasingly important part of molecular biology and biochemistry, and, furthermore, organic chemists are increasingly directing their attention towards synthetic aspects of biomolecules and biologically active compounds biosynthesized by plants and animals. Thus the borderland between biology, biochemistry, and chemistry is rapidly broadening and is becoming the most fruitful working field for innovative and intuitive drug design scientists.

2. Industrial Drug Discovery - Academic Drug Design

Where are the academic medicinal chemistry departments in this area of drug research, which is now undergoing profound changes, and which is moving towards an increasing degree of integration of scientific disciplines? Furthermore, how should medicinal chemistry teaching programmes be organized and taught in this highly dynamic research area? These burning questions need to be effectively addressed, and if the responsible academics fail to meet these challenges, academic medicinal chemistry will degenerate into traditional organic synthesis, from where it originates, or into trivial service functions in relation to industrial drug design and development programmes.

The equipment for automatized combinatorial chemistry and for high throughput screening procedures, now in operation in most industrial medicinal chemistry departments, is expensive, and purchase of such technical facilities is normally far beyond the financial capacity of academic departments. Furthermore, in terms of operation, these automatized procedures are predominantly technical, and although students should understand the prospects and limitations of such technologies, these aspects can only be limited parts of student courses in medicinal chemistry. The scientific challenges of the conversion of solution synthetic chemistry procedures into solid-phase synthetic methodologies are mainly of basic chemical nature, and the development of cell-based assay systems is predominantly a biochemical pharmacological task.

In order to attract the attention of intelligent students, the creative and fascinating nature of drug design must be the underlying theme of basic and advanced student courses in medicinal chemistry. In relation to industrial screening programmes and "hit-finding" procedures, students should be taught that the conversions of "hits" into lead structures and further into drug candidates require advanced synthetic chemistry supported by computational chemistry. Furthermore, these medicinal chemistry approaches should be integrated with molecular pharmacology studies using cloned target receptors, ion channels, or enzymes, expressed in appropriate model systems.

It is beyond doubt that a steadily increasing number of biomolecules will be subjected to X-ray crystallographic structural analysis. The number of enzymes with established three-dimensional structure is now increasing exponentially [1], and this growth will continue during the next decades. Even oligomeric membrane-bound receptors can now be crystallized and subjected to X-ray crystallographic analysis [2], but such analyses of mono- or oligomeric receptors are still hampered by major experimental difficulties. In recent years, however, biostructural scientists have succeeded in crystallizing recombinant versions of the binding domains of a G protein-coupled receptor [3] as well as a ligand-gated ion channel [4]. Structural analyses of these binding domains co-crystallized with agonist and antagonist ligands have already provided insight into the structural basis of receptor-ligand interactions and of receptor activation and blockade.

These breakthroughs in biostructural chemistry have opened up new avenues in drug design. Structural information derived from X-ray analyses of enzyme-inhibitor conglomerates has been and continues to be very valuable for the design of new types of inhibitors. Similar pieces of information derived from studies of receptor binding domains co-crystallized with different types of competitive or noncompetitive ligands undoubtedly will be of key importance in receptor ligand design projects. These approaches which are in the nature of drug design on a rational basis will become important parts of student teaching programmes in medicinal chemistry.

In academic research and teaching, biologically active natural products probably will play a progressively important role as lead structures. Not only do such compounds often possess novel structural characteristics, but they also frequently exhibit unique biological mechanisms of action, although naturally occurring "toxins" typically show nonselective pharmacological effects. By systematic structural modification, including molecular mimicry approaches, it may be possible to "tame" such "toxins" and convert them into leads with specific actions on biofunctions of key importance in diseases. Biologically active natural products undoubtedly will be continue to be important starting points for academic drug design projects, and such approaches will continue to be exciting case stories in student medicinal chemistry courses.

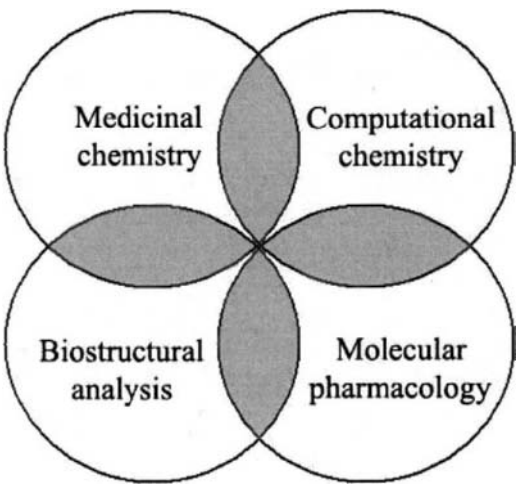

Figure 1. Leading academic medicinal chemistry departments or centres capable of establishing innovative collaborative projects with major industrial drug discovery units will optimally have the above "four-leaf clover" integrated composition of expertises.