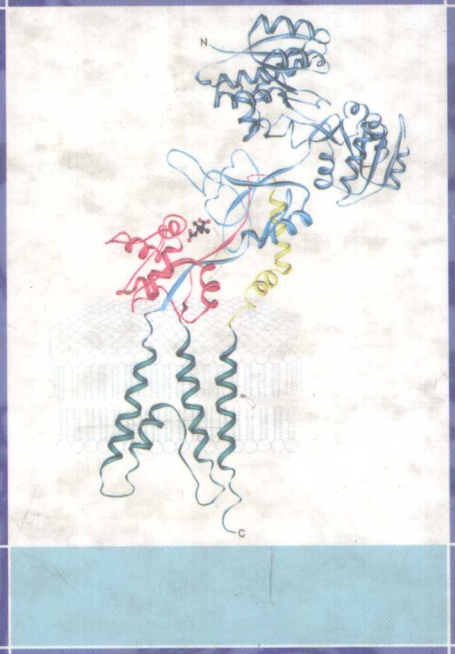
TEXTBOOK OF DRUG DESIGN AND DISCOVERY

THIRD EDITION



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Preface

The field of medicinal chemistry and drug design 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.

Where are the academic medicinal chemistry and drug design departments in this area of drug research, 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. 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, 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, 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 as well as a ligand-gated ion channel. 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 has been 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 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.

In this third edition of the textbook, all of these aspects of academic and industrial medicinal chemistry and drug design are dealt with in an educational context.

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