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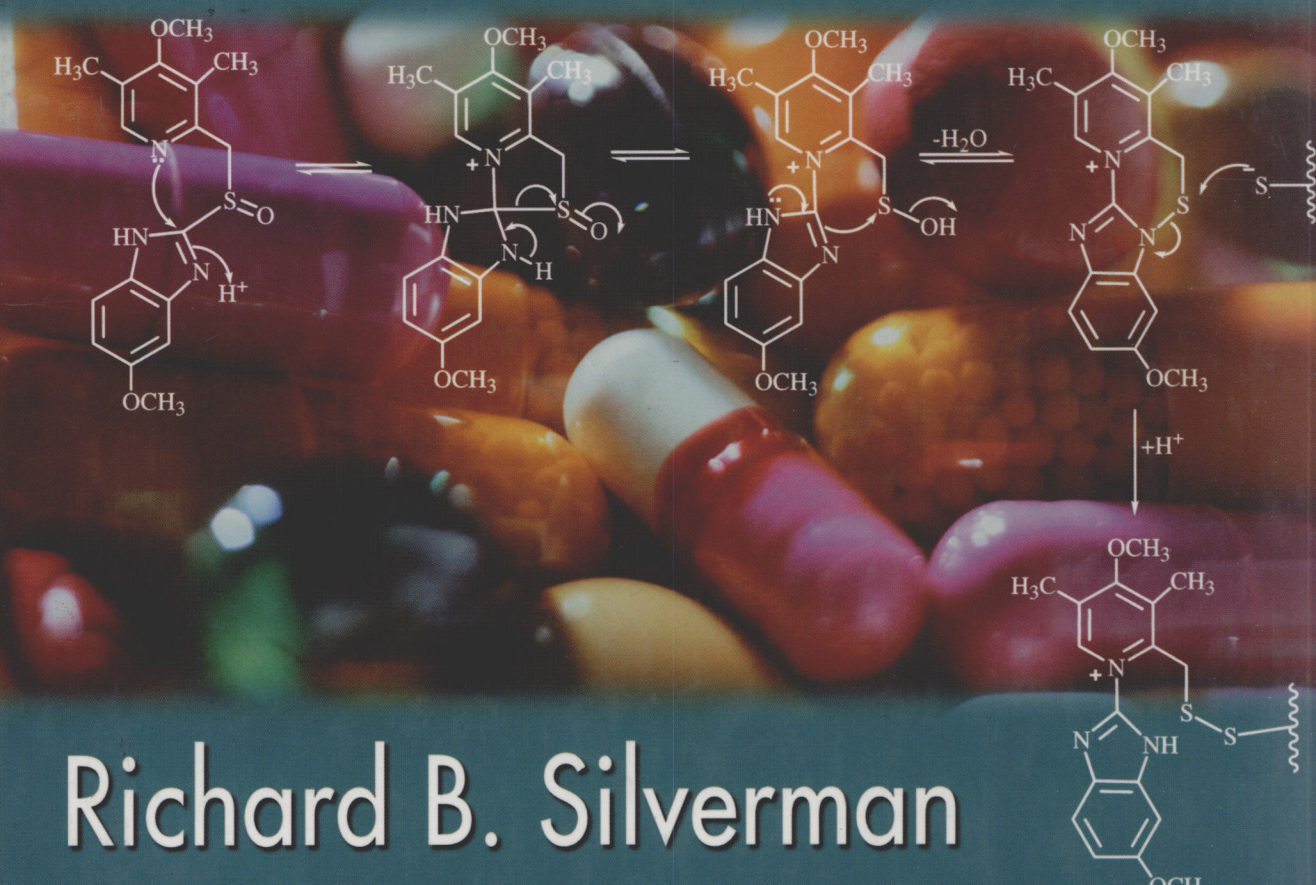
The ORGANIC CHEMISTRY of DRUG DESIGN and DRUG ACTION

Second Edition



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Second Edition

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To Mom and the memory of Dad, for their love, their humor, their ethics, their inspiration, but also for their genes

Preface to the First Edition

From 1985 to 1989 I taught a one-semester course in medicinal chemistry to senior undergraduates and first-year graduate students majoring in chemistry or biochemistry. Unlike standard medicinal chemistry courses that are generally organized by classes of drugs, giving descriptions of their biological and pharmacological effects, I thought there was a need to teach a course based on the organic chemical aspects of medicinal chemistry. It was apparent then, and still is the case now, that there is no text that concentrates exclusively on the organic chemistry of drug design, drug development, and drug action. This book has evolved to fill that important gap. Consequently, if the reader is interested in learning about a specific class of drugs, its biochemistry, pharmacology, and physiology, he or she is advised to look elsewhere for that information. Organic chemical principles and reactions vital to drug design and drug action are the emphasis of this text with the use of clinically important drugs as examples. Usually only one or just a few representative examples of drugs that exemplify the particular principle are given; no attempt has been made to be comprehensive in any area. When more than one example is given, it generally is to demonstrate different chemistry. It is assumed that the reader has taken a one-year course in organic chemistry that included amino acids, proteins, and carbohydrates and is familiar with organic structures and basic organic reaction mechanisms. Only the chemistry and biochemistry background information pertinent to the understanding of the material in this text is discussed. Related, but irrelevant, background topics are briefly discussed or are referenced in the general readings section at the end of each chapter. Depending on the degree of in-depthness that is desired, this text could be used for a one-semester or a full-year course. The references cited can be ignored in a shorter course or can be assigned for more detailed discussion in an intense or full-year course. Also, not all sections need to be covered, particularly when multiple examples of a particular principle are described. The instructor can select those examples that may be of most interest to the class. It was the intent in writing this book that the reader, whether a student or a scientist interested in entering the field of medicinal chemistry, would learn to take a rational physical organic chemical approach to drug design and drug development and to appreciate the chemistry of drug action. This knowledge is of utmost importance for the understanding of how drugs function at the molecular level. The principles are the same regardless of the particular receptor or enzyme involved. Once the fundamentals of drug design and drug action are understood, these concepts can be applied to the understanding of the many classes of drugs that are described in classical medicinal chemistry texts. This basic understanding can be the foundation for the future elucidation of drug action or the rational discovery of new drugs that utilize organic chemical phenomena.

Richard B. Silverman
Evanston, Illinois
April 1991

Preface to the Second Edition

In the 12 years since the first edition was written, certain new approaches in medicinal chemistry have appeared or have become commonly utilized. The basic philosophy of this textbook has not changed, that is, to emphasize general principles of drug design and drug action from an organic chemical perspective rather than from the perspective of specific classes of drugs. Several new sections were added (in addition to numerous new approaches, methodologies, and updates of examples and references), especially in the areas of lead discovery and modification (Chapter 2). New screening approaches, including high-throughput screening, are discussed as are the concepts of privileged structures and drug-likeness. Combinatorial chemistry, which was in its infancy during the writing of the first edition, evolved, became a separate branch of medicinal chemistry, then started to wane in importance during the 21st century. Combinatorial chemistry groups, prevalent in almost all pharmaceutical industry at the end of the 20th century, began to be dissolved, and a gradual return to traditional medicinal chemistry has been seen. Nonetheless, combinatorial chemistry journals have sprung up to serve as the conduit for dissemination of new approaches in this area, and this along with parallel synthesis are important approaches that have been added to this edition. New sections on SAR by NMR and SAR by MS have also been added. Peptidomimetic approaches are discussed in detail. The principles of structure modification to increase oral bioavailability and effects on pharmacokinetics are presented, including log P software and "rule of five" and related ideas in drug discovery. The fundamentals of molecular modeling and 3D-QSAR also are expanded. The concepts of inverse agonism, inverse antagonism, racemic switches, and the two-state model of receptor activation are introduced in Chapter 3. In Chapter 5 efflux pumps, COX-2 inhibitors, and dual-acting drugs are discussed; a case history of the discovery of the AIDS drug ritonavir is used to exemplify the concepts of drug discovery of reversible enzyme inhibitors. Discussions of DNA structure and function, topoisomerases, and additional examples of DNA-interactive agents, including metabolically activated agents, are new or revised sections in Chapter 6. The newer emphasis on the use of HPLC/MS/MS in drug metabolism is discussed in Chapter 7 along with the concepts of fatty acid and cholesterol conjugation and antedrugs. In Chapter 8 a section on enzyme-prodrug therapies (ADEPT, GDEPT, VDEPT) has been added as well as a case history of the discovery of omeprazole. Other changes include the use of both generic names and trade names, with generic names given with their chemical structure, and the inclusion of problem sets and solutions for each chapter.

The first edition of this text was written primarily for upperclass undergraduate and first-year graduate students interested in the general field of drug design and drug action. During the last decade it has become quite evident that there is a large population, particularly of synthetic organic chemists, who enter the pharmaceutical industry with little or no knowledge of medicinal chemistry and who want to learn the application of their skills to the

process of drug discovery. The first edition of this text provided an introduction to the field for both students and practitioners, but the latter group has more specific interests in how to accelerate the drug discovery process. For the student readers, the basic principles described in the second edition are sufficient for the purpose of teaching the general process of how drugs are discovered and how they function. Among the basic principles, however, I have now interspersed many more specifics that go beyond the basics and may be more directly related to procedures and applications useful to those in the pharmaceutical industry. For example, in Chapter 2 it is stated that "Ajay and coworkers proposed that *drug-likeness* is a possible inherent property of some molecules,[1] and this property could determine which molecules should be selected for screening." The basic principle is that some molecules seem to have scaffolds found in many drugs and should be initially selected for testing. But following that inital statement is added more specifics: "They used a set of one- and two-dimensional parameters in their computation and were able to predict correctly over 90% of the compounds in the Comprehensive Medicinal Chemistry (CMC) database.[2] Another computational approach to differentiate drug-like and nondrug-like molecules using a scoring scheme was developed,[3] which was able to classify correctly 83% of the compounds in the Available Chemicals Directory (ACD)[4] and 77% of the compounds in the World Drug Index (WDI).[5] A variety of other approaches have been taken to identify drug-like molecules."[6] I believe that the student readership does not need to clutter its collective brain with these latter specifics, but should understand the basic principles and approaches; however, for those who aspire to become part of the pharmaceutical research field, they might want to be aware of these specifics and possibly look up the references that are cited (the instructor for a course who believes certain specifics are important may assign the references as readings).

For concepts peripheral to drug design and drug action, I will give only a reference to a review of that topic in case the reader wants to learn more about it. If the instructor believes that a particular concept that is not discussed in detail should have more exposure to the class, further reading can be assigned.

To minimize errors in reference numbers, several references are cited more than once under different endnote numbers. Also, although multiple ideas may come from a single reference, the reference is only cited once; if you want to know the origin of discussions in the text, look in the closest reference, either the one preceding the discussion or just following it. Because my expertise extends only in the areas related to enzymes and the design of enzyme inhibitors,

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[1] Ajay; Walters, W. P.; Murcko, M. A. *J. Med. Chem.* **1998**, *41*, 3314.

[2] This is an electronic database of Volume 6 of *Comprehensive Medicinal Chemistry* (Pergamon Press) available from MDL Information systems, Inc., San Leandro, CA 94577.

[3] Sadowski, J.; Kubinyi, H. *J. Med. Chem.* **1998**, *41*, 3325.

[4] The ACD is available from MDL Information systems, Inc., San Leandro, CA, and contains specialty and bulk commercially available chemicals.

[5] The WDI is from Derwent Information.

[6] (a) Walters, W. P.; Stahl, M. T.; Murcko, M. A. *Drug Discovery Today* **1998**, *3*, 160. (b) Walters, W. P.; Ajay; Murcko, M. A. *Curr. Opin. Chem. Biol.* **1999**, *3*, 384. (c) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3743. (d) Oprea, T. I. J. *Comput.-Aided Mol. Des.* **2000**, *14*, 251. (e) Gillet, V. J.; Willett, P. L.; Bradshaw, J. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 165. (f) Wagener, M.; vanGeerestein, V. J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 280. (g) Ghose, A. K.; Viswanadhan, V.N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (h) Xu, J.; Stevenson, J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177. (i) Muegge, I.; Heald, S. L.; Brittelli, D. *J. Med. Chem.* **2001**, *44*, 1841. (j) Anzali, S.; Barnickel, G.; Cezanne, B.; Krug, M.; Filimonov, D.; Poroikiv, V. *J. Med. Chem.* **2001**, *44*, 2432. (k) Brstle, M.; Beck, B.; Schindler, T.; King, W.; Mitchell, T.; Clark, T. *J. Med. Chem.* **2002**, *45*, 3345.

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still in Evanston, Illinois
May 2003

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