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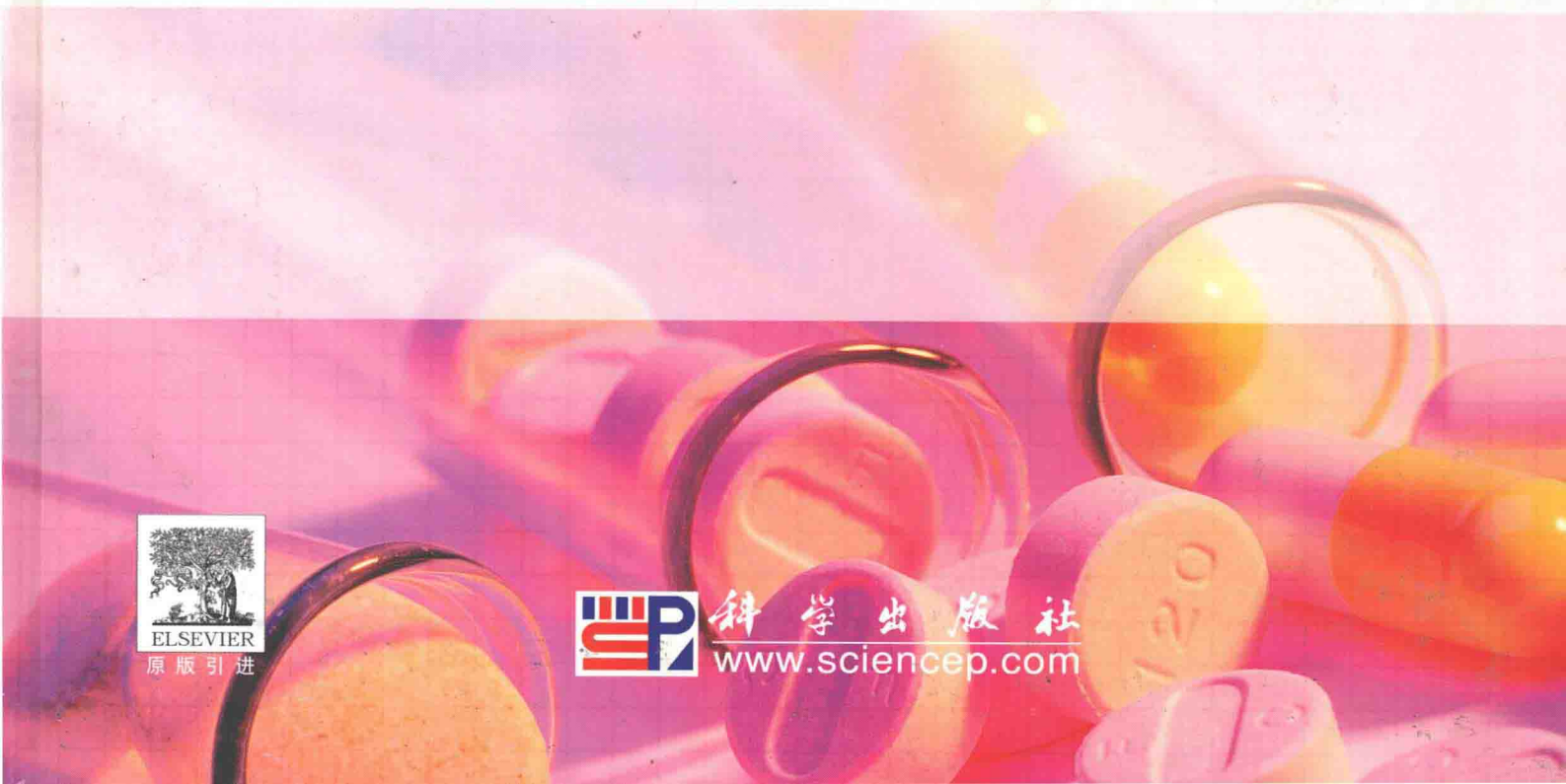
The Organic Chemistry of Drug Design and Drug Action

药物设计与药物行为的有机化学

(第二版)

Richard B. Silverman



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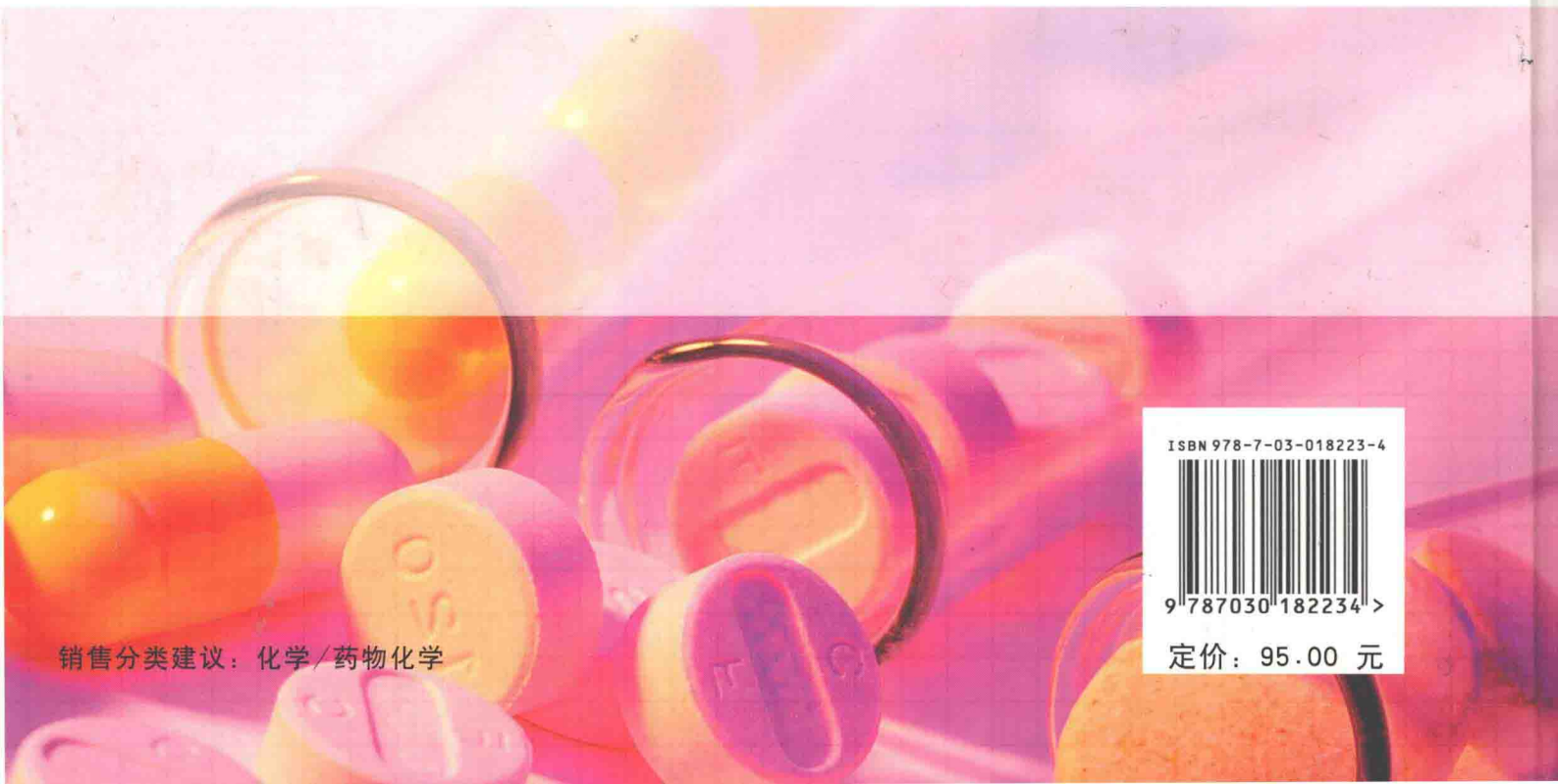
本书从有机化学的视角来讲述药物设计、药物作用，这实际上代表了现代药物研究的方向，即从小分子（配体）作用于大分子（受体）的分子水平来研究药物的作用，从揭示药物的作用出发来设计研究新药。第二版新增内容包括：药物发现、设计和开发的新方法，与受体、酶的抑制和失活、药物代谢、前药和药物传递系统、作用于DNA的药物等内容相关的新进展。

本书的内容系统、全面。全书由作者一人撰写，风格一致。 文字简洁，阅读轻松，概念清楚，实例丰富，内容从基础到前沿的都有介绍，是同类书中的佼佼者。它既可以用于入门的学习，也能成为药物研究工作者的案头书。本书讲授的知识对开发创新药物十分重要，相信会受到本行业的专业人士和准备进入本行业的本科生、研究生的欢迎。

特别应指出的是，本书中各章都附有相当数量的根据研究文献改编的问题和答案，这在同类书籍中少有见到。这些材料极有利于教师组织教学和读者自学。



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导　读

药物化学的教科书通常有两大类：一类为准备成为药师的药学生学习使用，另一类为研究开发药物的人员学习使用。前者通常是按药物的类型，介绍各个药物的化学和药理知识，后者主要介绍药物设计、药物研究及药物作用的内容，供化学、生物专业类的学生学习药物化学，进入药物研究行业使用。

本教科书属于后者，相当于国内的高等药物化学，药物化学概论或新药设计学一类的书籍。通常是药学及相关专业高年级本科生和药物化学研究生的课程。

本书从书名就可看出，作者是**从有机化学的视角来讲述药物设计、药物作用**的。这实际上代表了现代药物研究的方向，即从小分子（配体）作用于大分子（受体）的分子水平来研究药物的作用，从揭示药物作用出发来设计研究新药。读者一定要具备有机化学，包括糖、蛋白质等的基本知识。通过对本书的学习，学生可学到相关的生物、生理方面的知识和现代药物研究的种种方法，为在医药（含农药、兽药）的研究开发中就业作好知识准备。

本书共八章，各章内容简介如下：第一章介绍了药物化学的历史和现代药物研发的概况。第二章是本书比较重要的一章，主要以先导化合物为中心，讲授现代新药设计的两个步骤：先导化合物的发现，以现代新药设计的两个步骤先导化合物为中心，讲授先导化合物的发现，和如何从先导化合物进行结构修饰，得到新的药物。介绍了药物设计的相关的方法，包括近十年兴起和普遍应用的方法。第三章介绍了现代的受体理论和研究方法，并以 H_2 受体拮抗剂西米替丁的发现进行了案例分析。第四章介绍了特殊的受体-酶的理论。第五章介绍了酶抑制剂和失活剂，相当多的药物都是酶抑制剂，通过学习，可让读者了解酶抑制剂的作用机制和如何设计研究酶抑制剂类新药。第六章介绍作用于 DNA 的药物，主要是一些抗菌药和抗癌药的作用机制，书中介绍了 DNA 的基本理论，并介绍了各种作用于 DNA 的药物的作用机制和设计方法。第七章介绍药物的代谢，除了具有该类书籍的已有反应类型 I 相反应（官能团反应）和 II 相反应（结合反应），并分别介绍体内对药物发生的各种反应外，还介绍了对药物代谢研究的方法。第八章介绍**前药和生物传递系统。**导读者特别注意到其对前药的分类，很多国内的书籍都未详细地介绍。该书对载体前药（carrier prodrug）和生物前药（bioprecursor prodrug）分别进行了介绍，按照原药的官能团，给出了前药设计的思路和实例，而且实例非常丰富。

本书的内容系统、全面，可供开设一年的课程使用，如用于一学期可选用部分内容。此外本书由作者**一人撰写，全书风格一致。**文字简洁，阅读轻松，**概念清楚，实例丰富，**内容从基础到前沿都有介绍，是同类书中的佼佼者。特别应指出的是，本书中各章都**附有相当数量的根据研究文献改编的问题和答案，**这在同类书籍中少有见到，这些材料，极有利于教师组织教学和读者自学。

本书内容丰富，除了基本原理外，还“安排了许多较专业的，基本知识外的和可能更直接应用于制药工业的研发程序和方法相关的内容”。既可以用于入门的学习，也可如原书的推荐者所说，本书应成为药物研究工作者的案头书，在工作中参考。

自我国开始加强保护知识产权以来，新药研究已成为我国制药界的热门话题。现在人们更多地谈到创新药物，得到自主知识产权的药物。许多大学、研究机构和企业都组织人力物力，进行创新药物

的研究工作。这是我国制药业的一个希望。**该书讲授的知识对开发创新药物十分重要。**科学出版社把这一本药物研究方法的力作引进到国内，使更多的同行可以阅读，相信会受到本行业的专业人士和准备进入该行业的学生、研究生的欢迎。

徐　正

2006 年 9 月于四川大学

第一版序言

1985 年到 1989 年期间，我为主修化学或生物化学的高年级大学生和一年级研究生开设了一门一学期的药物化学课程。与通常按药物的分类，描述各个药物的生物和药理作用的标准药物化学课程不同，我考虑需要讲授一门基于有机化学的药物化学课程。很明显到现在也没有一本教科书，专注于药物设计、药物开发和药物作用中的有机化学内容。本书填补了这一重要的空白。由此，如果读者对学习某些特定的药物类型、它的生物化学、药理学和病理学感兴趣，他可参考其它的信息源。对药物设计和药物作用必需的有机化学原理和反应，在本教科书给予特别的强调，并以这些原理在重要的临床药物中的应用为实例，加以阐明。书中通常用一个或少数的几个药物实例，简明地介绍给出特定的原理，并不打算对每个领域都作全面地介绍。当给出不止一个实例时，通常是为了证明不同的化学原理。作者假定本书的读者学过一年的有机化学课程，包括氨基酸、蛋白质和碳水化合物的化学，同时熟悉有机结构理论和基本的有机反应机理。本书只讨论为了理解书中的内容，所必要的有机化学和生物化学的背景知识，对相关但不够密切的知识，本书仅简要地叙及或请参见每章后附的相关读物。根据学习深度的需要，本教材可用于一学期或一年的课程。在短学期的课程中，可不用附上的参考文献，而在强化的或一年的课程中，可组织较深入地讨论。此外，并非所有的章节都需讲授，特别在描述的某些原理有多个实例的时候，教师可选用学生最有兴趣的实例来教学。编写本书的目的，就是想让读者，那些对药物化学领域感兴趣的学生或科学家，能够用一种理性的，自然的有机化学方法来设计药物和研究药物，并感受药物合成中化学的重要性。这些知识对理解药物在分子水平的作用至关重要。书中的原理是普遍适用的，并不仅涉及某一特定的受体或酶。一旦认识了药物设计或药物作用的基础，这些概念将用于理解经典的药物化学教科书上描述的很多类型的药物。这些基本的认识可能成为将来阐明药物作用机制，或使用有机化学现象来合理发现新药的基础。

Richard B Silverman

埃文斯通市　伊利诺斯州

1991 年 4 月

（徐正　译）

第二版序言

从第一版书到现在的12年间，一些新的药物化学方法被建立或得到普遍地应用。但本书的基本思想没有改变，这就是从有机化学的视角而不从特殊类型药物的角度，强调药物设计和药物作用的一般原理。这一版增加了几个新的小节（补充了许多新途径、方法；更新了实例和参考文献），在先导化合物的发现和修饰的领域中（第二章）增加较多。并讨论了新的筛选方法，包括高通量筛选，以及优势结构或药物类似物的概念。在第一版时刚问世的组合化学，后来发展成为药物化学的一个独立分支，但其重要性在21世纪已开始消退。组合化学的研究团队，在20世纪末几乎在所有的制药工业企业里盛行，现开始解散，人们看到逐渐回归到传统的药物化学的局面。然而，组合化学杂志作为该领域新方法的传播通道起了很大的促进作用，这与平行合成一起作为重要的新药研究方法，加进了本版。本版还增加了通过核磁共振谱和质谱研究构效关系的新的小节。拟肽化合物的讨论更为详尽。还讨论了为增加药物的口服活性和对药代动力学的影响的结构修饰原理，包括Log P的计算软件，生物利用度的“五数规则”（rule of five）和相关的药物发现的思想。对分子建模和3D-QSAR的基础内容也进行了扩充。在第三章中引入了反向激动（inverse agonism），反向拮抗，外消旋转换（racemic switches）和受体活化的两级模型的内容。第五章讨论了溢出泵、COX-2抑制剂、和双向作用药物（dual-acting drugs），用发现抗艾滋病药物利托那韦的案例，说明可逆性酶抑制剂药物发现的思想。在第六章新增的节和改写的节里，讨论了DNA的结构和功能，拓扑异构酶，并加入作用于DNA的药物实例，包括代谢活化药物。在第七章里新增了强调HPLC/MS/MS在药物代谢研究的应用的内容，和脂肪酸、胆固醇结合物和软药（antedrugs）的定义。在第八章增加了酶-前药复合物（enzyme-prodrug）治疗的一节，以及奥美拉唑发现的案例。本版的其它变化还有：同时使用药物的通用名和商品名，在给出的化学结构上附通用名，以及每章给出了练习题和答案。

本教科书的第一版主要为药物设计和药物作用的相关领域有兴趣的高年级大学生和一年级研究生所写。在上个十年，很明显有更多的人群，特别是有机合成化学家，进入了制药工业。他们没有或仅有一点点药物化学知识，但希望通过学习将他们的技术运用于药物发现的研究。第一版为进入这一领域的学生和工作人员提供了一个概述，但后者对促进新药发现过程有更多的兴趣。对学生读者，以药物的发现的一般过程和作用机制为教学目的，第二版的内容已完全够用。在这些基本原理中，我分散安排了许多较专业的，基本知识外的和可能更直接应用于制药工业的研发程序和方法相关的内容。例如，在第二章，陈述了“Ajay和同事提出的药物类似物（drug-likeness）是某些分子的可能的固有性质”[1]，而这些性质可能决定某个分子可否用于药物筛选，在一些药物中可发现一些结构骨架而且可在最初的时候用于筛选，在此之后该陈述又作了增补：“在他们的计算中，使用一组一维和二维的参数，可以正确地判断全部药物化学（CMC）数据库中超过90%的化合物[2]。另外的一个可区分类似药物或非类似药物分子的计算机搜索程序已开发出来[3]，能在药物数据库Available Chemicals Directory (ACD)[4]中，以83%的正确率分辨药物类似物分子，在另一个数据库“药物索引（World Drug lndex, WDI)”[5]中正确率达77%，还建立了其它不同的方法来辨别药物特征分子[6]”。我认为学生读者群不需要在大脑里装满这些后来补充的专门资料，但应懂得基本的原理和方法。对盼望进入药物研究领域的学生，他们可以了解这些资料和查阅引用文献（课程的指导者如认为某些专题对学生有用，可指定阅读这些文献）。

对药物设计和药物作用的周边概念，我将只给出有关论题的综述文献，以满足读者的需要。如果指导者认为某个特定的概念在本书未得到详尽地讨论，可以在课堂上多花些时间，进一步的阅读资料

也列在书里。

为减少参考文献数字的差错，有些参考文献不止一次出现在不同的尾注。此外，虽然多个思路在某一篇文献中出现，该参考文献仅标注一次。如果你想知道书中某个讨论的源头，可看最近的一篇参考文献，或是前面，或是即将遇到的一篇。因为我的专长仅在与酶和酶抑制剂相关的领域，我想感谢阅读过本书的部分或全部章节，并反馈了修改意见的多位专家，他们包括（以字母排序）Shuet-Hing Lee Chiu，Young-Tae Chang，William A. Denny，Perry A. Frey，Richard Friary，Kent S. Gates，Laurence H. Hurley，Haitao Ji，Theodore R. Johnson，Yvonne C. Martin，Ashim K. Mitra，Shahriar Mobashery，Sidney D. Nelson，Daniel H. Rich，Philippa Solomon，Richard Wolfenden，和 Jian Yu。我非常感谢你们的投入。我也非常感谢在写本书时的我的两个主要的计算机助手：Andrea Massari 和 Clark Carruth，同样还感谢 Elsevier/ Acadmic 出版社的编辑（以 Jeremy Hayhurst 为首）。

Richard B. Silverman

埃文斯通市　伊利诺斯州

2003 年 5 月

（徐正　译）

The Organic Chemistry of Drug Design and Drug Action

Second Edition

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.