# Book Reviews

**Burger's Medicinal Chemistry and Drug Discovery. Sixth Edition. Volumes 1−6.**. Edited by D. J. Abraham. Wiley-Interscience, Hoboken, NJ. 2003. 18 × 26 cm. Vol. 1: xv + 932 pp; ISBN 0-471-27090-3. Vol. 2: xv + 808 pp; ISBN 0-471-37028-2. Vol. 3: xv + 880 pp; ISBN 0- 471-37029-0. Vol. 4: xiv + 702 pp; ISBN 0-471-37030-4. Vol. 5: xv + 1084 pp; ISBN 0-471-37031-2. Vol. 6: xiv + 1084 pp; ISBN 0471-27401-1. $2100.00.

This treatise on rational drug design establishes a seamless integration between medicinal chemistry and molecular biology, a befitting memorial to Professor Alfred Burger (1905−2000). Each therapeutic class of agents is explored from the context of identifying tomorrow's best-in-class drug. Unlike previous editions, all volumes of the sixth edition were prepared for simultaneous release. This has permitted functional organization by scientific discipline or by the targeted disease state. Thorough groundwork ensured no omissions of major therapeutic classes. The new online version (www.mrw.interscience.wiley.com/bmcdd) will facilitate access and updating.

Volumes 1 and 2 are primarily devoted to a comprehensive consideration of advanced instrumental and computational technologies relevant to drug discovery in the genomic and proteomic era. Case studies therein demonstrate that the innovative application of bioinformatics can successfully exploit structural biology for tractable drug targets and lead compounds. Intelligent entry into this in silico universe can shorten the drug discovery life cycle by years. Prior to this edition of *Burger*, a full appreciation of the advantage that effective chemical information management offers in drug discovery had been largely limited to in-house corporate research.

The euphoric expectation that combinatorial chemistry would permit a duty-free bursting drug pipeline has given way to a more realistic outlook. Hits derived from high-throughput processes are seen to be more dependent on the intellectual framework, intuition, and art used in selecting the libraries screened than on playing the technology-driven and random numbers game. Even earlier in the drug discovery process, the human expert overrules therapeutic model predictions by flagging embedded toxicophores in candidate compounds.

The prominent role of X-ray crystallography in the structure-based discovery of potential therapeutic agents and the complements of NMR, mass spectroscopy, and electron cryomicroscopy are given due attention. Caveats include the moving target nature of receptors on conformationally dynamic proteins, the notoriously difficult characterization of target-rich membrane-bound proteins, the elusive goal of cocrystallizing a macromolecule with its bound ligand, and chirality as a confounder. Knowledge of enzyme mechanisms provides the conceptual scaffold for developing ultrahigh affinity transition-state inhibitors, e.g., pointing the direction for future "turbostatins". Atomic docking coordinates of native ligands direct the way to reverse small-molecule design when in concert with cloning, sequencing, and site-directed mutagenesis. Guidance is offered in the efficient search for privileged pharmacophores as an entreé into analogue design and optimization. Special focus is placed on secondary metabolites, endogenous peptides, oligonucleotides, and carbohydrates.

Other chapters in Volumes 1 and 2 cover general aspects of drug absorption and disposition, formulation development, prodrug design, toxicology, and retrometabolism as relates to hard and soft drugs. The interconnectiveness of pharmacokinetics with pharmacodynamics and the cruel restraints of ADME(Tox) are reconciled to favor successful commercialization of drug candidates.

A concise chronology of federalization in the drug industry is followed by current regulatory issues facing the industry, to balance safety with innovation. The closing chapter of Volume 2 enumerates the importance of protecting intellectual property (i.e., nonobvious and novel scientific enterprise) from free riders. The conflict between secrecy and scholarship/funding initiatives, as well as the uncomfortable coexistence of sunshine-type laws and trade secrets, dictates the need for experienced patent counsel.

Volumes 3−6 are organized by therapeutic class for drug discovery: Volume 3 (Cardiovascular Agents and Endocrines) visits the nuclear receptor superfamily; Volume 4 (Autocoids, Diagnostics, and Drugs from New Biology) delves into DNA microarrays as a revolutionary drug development tool; Volume 5 (Chemotherapeutic Agents) demonstrates that exploitation of monoclonal antibodies has advanced oncology research; Volume 6 (Nervous System Agents) describes how modulation of monoamines by neuropeptides may yield opportunities for use of peptidomimetic drugs. Many chapters in Volume 6 are updates from the previous edition or, on occasion, are limited to recent developments with reference to the fifth edition of *Burger* as background. However, over 30 completely new chapters grace the sixth edition to give a total of over 100 pioneering chapters. Each chapter stands on its own, with little or no cross-referencing within the edition. This leads to some overlap of content but contributes to the strength of each as an independent study.

Some additional consideration of the pharmacogenomic principles underlying the design and success of numerous new and emerging drugs would further distinguish this edition. The figures throughout make little attempt at artistry but are intended to be direct and to the point. The forthcoming textbook version of this monumental reference work would benefit from more visually engaging figures. Fine color plates included in each volume of the present edition, sparse as they may be, add elegance. References number in the thousands for such definitive chapters as those on steroids and analgesics. An extensive cumulative index supports individual volume indices. Contributing authors represent all academic, corporate, and governmental scientific/regulatory realms. Each author enjoyed considerable latitude in chapter style and format. However, the most striking constant found in this outstanding and peerless reference work is the high level of scientific scholarship and the state-of-the-art expertise brought to bear on "Things to Come".

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