State of the Art

The Art of Drug Synthesis

Edited by *Douglas S. Johnson* and *Jie Jack Li*.

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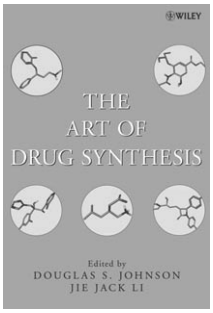

Whereas the art of natural product synthesis is extensively described by several experts in the field, the same is not true for its counterpart, the synthesis of drugs in the pharmaceutical industry. This comes as a surprise, as chemists at pharmaceutical companies make enormous efforts to find the best synthesis for a drug. This excellent book, edited by the same two chemists from Pfizer who co-authored *Contemporary Drug Synthesis* several years ago, helps to fill this gap and brings the work of many chemists working in drug synthesis to the limelight. The other strengths of this second volume are the descriptions of the therapeutic drug classes and their mode of action as well as the insight into how a first generation of drugs is refined by the application of medicinal chemistry for the discovery of superior later drug generations.

Fifteen important therapeutic drug classes with a total of 50 drugs are described in this book which, despite 16 different authors from various companies, is pleasantly uniform in its structure. These classes include: aromatase inhibitors (Aromasin, Arimidex and Femara), quinolone antibiotics (Levaquin, Avelox, Factive and Geninax), triazole antifungals (Sporanox, Diflucan, Vfend and Prodif), non-nucleoside HIV reverse transcriptase inhibitors (Viramune, Sustiva and Rescriptor), neuraminidase inhibitors (Tamiflu and Relenza), PPAR agonists (Avandia, Actos and Pargluva), AT1 antagonists (Cozaar, Diovan, Avapro, Atacand and Benicar), ACE inhibitors (Vasotec, Zestril, Accupril, Lotensin, Altace and Monopril), dihydropyridine calcium blockers (Adalat, Plendil, Norvasc and Calblock), second-generation HMG-CoA reductase inhibitors (Lescol, Crestor and Livalo), a cholesterol absorption inhibitor (Zetia), dual selective serotonin and norepinephrine reuptake inhibitors (Effexor, Ixel and Cymbalta), $GABA_A$ receptor agonists (Ambien, Sonata, Lunesta and Indiplon), $\alpha 2\delta$ ligands (Neurontin and Lyrica), and treatments for attention deficit hyperactivity disorder (Adderall, Ritalin and Straterra). For all drugs, both brand names and generic names are given together with the year of launch and the company by which the drug was developed.

Each chapter concisely discusses the science and history that led to the drug class and explains its mode of action. An aspect the reviewers found very educational is the description of the DMPK properties of the individual drugs and their implications for formulation and therapeutic use. This is nicely demonstrated, for example, in Chapter 17 on drugs for the treatment of attention deficit hyperactivity disorder, for which formulations were extensively used to improve the inherently poor PK profile of the drugs. The description of the synthetic routes typically starts with the original research synthesis followed by additional routes and procedures, and provides specific details of interest for the synthetic chemist. In some chapters, such as Chapter 7 on Tamiflu and Relenza, the authors do an excellent job in describing the difficulties in scaling up to ton quantities and explaining how process chemists solved these problems by changing routes as well as reaction and workup conditions. However, in several chapters it is unclear which routes are used for scale-up and manufacturing, and the authors miss out on the opportunity to compare the early discovery routes with later routes chosen for scale-up; they also fail to comment on the improvements made by process chemists.

Two introductory chapters precede the 15 synthesis chapters: 'The Role of Medicinal Chemistry in Drug Discovery' by John A. Lowe points out the hurdles in drug discovery and effectively describes the tools available in medicinal chemistry. This description is very beneficial for the non-medicinal chemist reader and even could have been supplemented by an additional chapter on DMPK parameters and their relevance in drug discovery. The second chapter by Neal G. Anderson is an excellent description of the challenges and requirements faced by process chemists in scaling up drug substances. However, as mentioned above, several of the following chapters do not make sufficient use of the foundations laid in this chapter.

In summary, this book is a very entertaining read for medicinal chemists as well as process chemists, and it is highly recommended for graduate students who want to learn about applied synthesis beyond the total synthesis of complex natural products in academia.

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