25
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Antibacterials

Volume I

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Preface

An essential – that is to say, life-saving – component of modern medicine is the reliable ability to suppress bacterial infection. The chemical entities entrusted with this responsibility correspond to exceeding structural diversity, mostly of natural product origin but increasingly as well of synthetic origin. They occupy a chemical space that is distinct in key respects as compared to the entities used in other therapeutic areas of medicinal chemistry [1–6]. This distinction when combined with the perpetual increase in bacterial resistance mechanisms [7–16], the seeming sparseness of valid antibacterial targets [17–23], and the belief that antibacterial discovery offers a poor return-on-investment [10, 24–36] support a widespread concern as to the future reliability of antibacterial chemotherapy [37–46]. While the assertion that the antibiotic apocalypse has yet to arrive is certainly correct [47] and while considerable reasons for optimism exist [47–49], we must be mindful both that the harbingers of possible apocalypse will arrive first elsewhere (in the third world) [50] and that successful drug discovery and development is emphatically noninstantaneous [51]. The fourteen chapters of these two volumes on antibacterial drug discovery capture this urgency, and add to its dimension the challenge, perspicacity, and ingenuity of contemporary antibacterial discovery. The compounds represented within these chapters include the antibacterials of Nature (the antibiotics) – both as starting material and as inspiration – and de novo structures. The chapters emphasize antibacterial target selection, emerging concepts for antibacterial discovery and structure-activity refinement, and antibacterial clinical development and utility.

All medicinal chemistry efforts begin with a hypothesis as to an intimate interconnection among a structure, a target, and a disease. While one does not need to have at the outset both the structure and target, a recurring discussion point in antibacterial discovery is whether the universe of antibacterial targets extends beyond those targets already known. In the opening chapter of the first volume, Sutterlin et al. [52] address antibacterial target selection from the vantage of screening methodology and the relationship between conditional essentiality and synthetic lethality among intersecting bacterial pathways. A complementary

perspective on targets – especially with respect to the different resistance mechanisms used by the Gram-positive and Gram-negative bacteria, and including both multitargeting and antibacterial combinations – is provided by Silver [53]. Bush critically assesses the possibility of synergistic antibiotic combinations to address the clinical emergence of multidrug-resistant bacteria [54]. Melander and Melander [55] extend the concept of mechanistic synergy by judicious selection of structural pairs as antibacterial adjuvants. Given the proven value of allosteric modulation in other therapeutic areas of medicinal chemistry, Meisel et al. [56] address allosteric modulation of bacterial targets as a new antibacterial strategy. In addition to standards for efficacy, all drugs must meet rigorous standards of safety. The unique challenges presented by the antibacterials with respect to clinical evaluation for safety and efficacy are discussed by Shlaes [57]. In the last chapter of the first volume, Basarab [58] summarizes the diversity of the exploratory structural classes that act against a classic antibacterial target, the topoisomerases.

The second of these two volumes on antibacterial drug discovery gives further exemplification of the astonishing diversity of antibacterial structure. Bugg provides a perspective on the structure-activity relationships of the nucleoside antibiotics that target the MraY translocase catalyst of cell wall biosynthesis, a class that represents a possible solution to the pressing need for efficacious Gram-negative antibacterials [59]. Kleijn and Martin review our current understanding of the structurally complex, and mechanistically enigmatic, cyclic lipopeptide antibiotics [60]. The bacterial ribosome is the target of numerous antibacterial structural classes. Sun and Ciao [61] demonstrate the power of synthetic chemistry, as inspired by the tetracycline structures of Nature, to secure even more powerful and selective antibacterial structures. The oxazolidinone class of synthetic structures (also targeting the ribosome) have transformed the treatment of recalcitrant Gram-positive-caused infection in the twenty-first century and, as described by Barbachyn [62], are poised to continue in this capacity with new structures having improved safety and efficacy. The opportunities for both empirical and rational drug design, at the interface between natural and synthetic structures, are explored for the antifolates by Scocchera and Wright [63]. They remind us of the important historical role of the antifolates in antibacterial chemotherapy and the value of contemporary structure-based design to the preservation of this importance.

The two final chapters of the second volume address emerging strategies in antibacterial drug discovery. Bacteria have a rapacious need for iron and have devised extraordinary pathways for its sequestration and importation. Wencewicz and Miller [64] explore the exciting potential of incorporating siderophore (iron-chelating) structures into antibacterial design, as an enabling strategy for antibacterial delivery. The virtue of attenuating bacterial virulence as a means of control of bacterial infection is discussed by Kamal et al. [65], using the example of "pathoblocker" interference with the quorum sensing mechanisms of the notorious Gram-negative pathogen, *Pseudomonas aeruginosa*.

The collective value of these perspectives, as inspirational studies in antibacterial discovery, is the accomplishment of the authors of these chapters.

We thank them for their willingness to share not just with us, but with you as the readers of this volume, their reflections and guidance for advancing this most demanding, and most critical, realm of medicinal chemistry.

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Contents