Proteins and their Inhibitors

Inhibitors of Cyclin-dependent Kinases as Antitumor Agents

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This book reviews the discovery and development of small-molecule inhibitors of cyclin-dependent kinases (CDKs) as anticancer therapeutic agents. The CDK family of proteins has been of continuing interest as targets for the development of antiproliferative agents since their discovery in the mid-1980s. Based on their central role as "gatekeepers" of the cell cycle, and their marked dysregulation in many tumor cells, efforts to develop CDK inhibitors were initially, and have been most intensely, focused on their potential utility as anticancer therapeutics. Only recently have noncancer pathologies been active areas of research. Many notable reviews documenting progress in the oncology area of CDK research have appeared over the years. This book is distinguished from earlier reviews by its heavy weighting on medicinal chemistry aspects of the important CDK inhibitor chemotypes. The information in this book would be of high value to the medicinal chemist working in oncology, or other areas related to kinase inhibition. The chapters containing drug design rationale would also entertain the structural chemist. The book would be of lesser interest to scientists that are more centrally focused on CDK biology, clinical research, or the utility of CDK inhibitors in non-oncology areas.

The first part of this book is devoted to the background biology of CDKs. There are chapters in the early section on the biology of the cell cycle, the functional regulation of the cell cycle, and in vivo mouse models used to elucidate CDK function. There is also an anomalous chapter on CDKs and vascular disease; although interesting, the chapter seems quite misplaced in a book centered on antitumor agents. The second section includes chapters on evaluating CDK inhibitor selectivity and the use of structural chemistry for inhibitor development. Despite high-throughput screening playing a key role in the initial identification of inhibitor chemotypes, the early solution of inhibitor-bound protein structures contributed significantly to the understanding and refinement of protein binding and selectivity. It has provided a fertile and entertaining testing ground for rational drug design, as documented in this section and included in other chapters. The bulk of the book, however, is devoted to the discovery and development of ten CDK inhibitor chemotypes, including the clinically studied agents: flavopiridol, R-roscovitine and BMS-387032 (recently licensed by Bristol-Myers to Sunesis, and subsequently designated as SNS-032). A detailed chapter, oriented towards medicinal chemistry, is devoted to each chemotype with the exception of flavopiridol and UCN-01. These agents are presented from a more clinical perspective. Flavopiridol is the clinically most studied of these agents, and continues to provide some of the most interesting clinical results. Although it can be found elsewhere, it would have reinforced the focus of the book if there was additional medicinal chemistry detail devoted to these pioneering agents. It would have also enhanced the reader's experience if there was a short introductory chapter at the beginning of this section devoted to an overview of the different agents, which provided a perspective of their relative historical importance. This would have been an aid prior to reading the more detailed accounts, especially if written objectively by the editors. Finally, the last portion of the book is concerned with the clinical status and yet to be fully uncovered clinical utility of these agents. This section includes combination studies (preclinical and clinical) and a perspectives chapter for future directions for the development of CDK inhibitors. As a minor point, CGP60474 is incorrectly depicted with the Bristol–Myers pyazolopyridine ring system in this final chapter.

The overall organization of the book is readily discernible through the table of contents. A preface is provided that relates the thoughts of the editors on the book's organization. The preface is informative reading prior to delving into the individual chapters. The index is extensive, although it does not include company or author names. Finally, the book would have been more timely if there was an updated section, or editor's note, written closer to press time, which included some the latest preclinical and clinical studies with CDK inhibitors. The encouraging, emerging results in B-cell lymphomas, published recently, could have been included in this section. For these the reader will have to refer to the current literature.

Disclaimer: The views expressed in this book review are those of the author, and do not represent the views of, nor are they an endorsement by, the US Government or the National Institutes of Health.

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Telomerase Inhibition: Strategies and Protocols

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The telomeres of human cells protect chromosomal ends from fusion events.

