CHAPTER 1

Introduction to Kinase Drug Discovery – Modern Approaches

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1.1 Kinase Drug Discovery

Kinases are a large family of over 500 enzymes that catalyse the transfer of a phosphate from a donor molecule such as ATP (adenosine triphosphate) to their substrates. A growing number of kinases are, or have been, targets of drug discovery efforts over the last couple of decades and undoubtedly more of these will become targets for similar efforts over the coming years as our understanding of their often complex biology develops. At the time of writing of the first edition (in 2011[1]) there were just 13 FDA approved small molecule kinase inhibitors along with a handful of biological therapeutics, but at the time of writing of this book, just 7 years later, there are 40 approved small molecules (most of which are shown in Figure 1.1), and the frequency of new approvals is increasing.

Many of the approved molecules have delivered significant benefits to patients, such as improvements to quality of life and/or life expectancy. Although potent against their target(s), many of the early reported kinase inhibitors were relatively promiscuous, which often led to toxicity. Such toxicity not only impacts on the quality of life of a patient, but may

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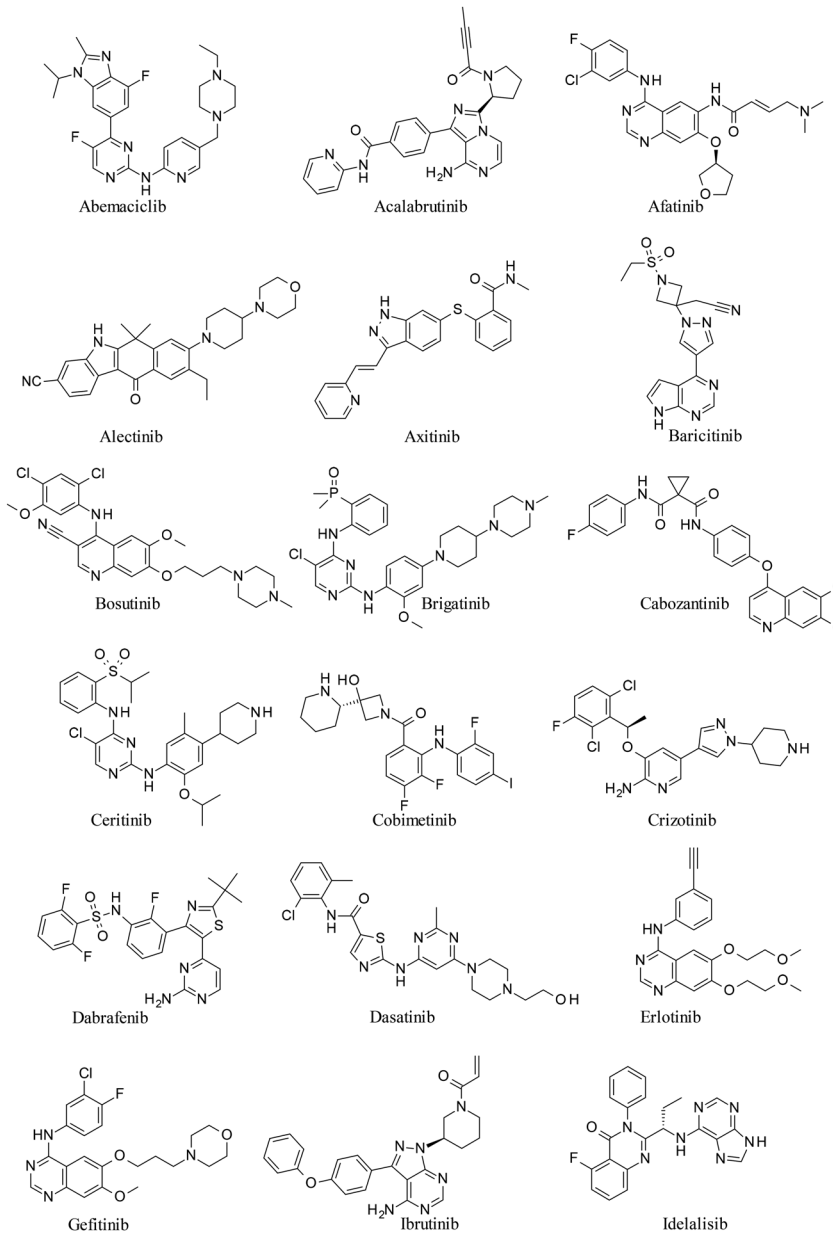
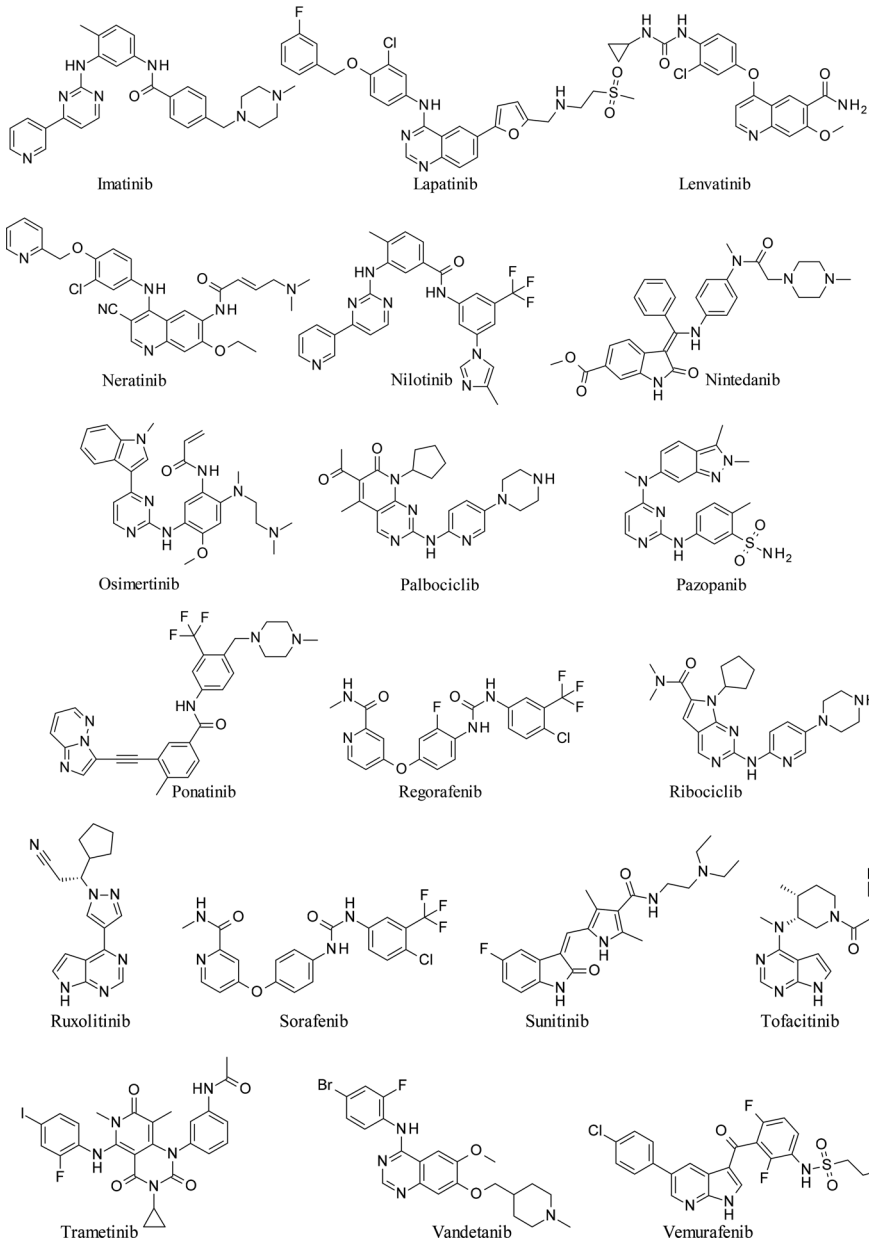


Figure 1.1 Chemical structures and generic names of 37 FDA approved protein and lipid kinase inhibitors. For brevity, analogues of Staurosporine and Rapamycin have been omitted.



limit the dose and therefore ability of a drug to modulate its primary target(s). However, recent advances in kinase drug discovery have enabled the design of inhibitors with greater potency and selectivity, informed by the greater accessibility of kinase selectivity panels and appropriate experimental techniques. In addition, more recently kinase inhibitors with a greater variety of mechanisms of action have been developed to target kinases for which earlier approaches had not been successful, including a greater number of covalent inhibitors and also inhibitors targeting allosteric pockets. The ways in which the chemical leads (or start points) for these inhibitors have been identified has also evolved, whether they are from novel screening methods, structure-based design or knowledge-based approaches.

Drug discovery efforts against kinases remain far from complete. Mutations of a number of kinases have now been determined to drive various diseases and have also been observed as resistance mechanisms to early kinase targeting drug molecules. Therefore, for a number of therapeutically valuable kinases with well-established biology there have already been multiple "generations" of inhibitors reported to tackle these resistance mechanisms once observed. Recent years have also seen an explosion of interest in kinase drug discovery within academic institutions, some of which has been covered within this edition by our authors.

In this book, as with our previous edition, each chapter covers a different theme, rather than the more common approach of reviewing a particular kinase or kinase family, although the authors have used specific case studies to illustrate topics of interest. With this approach, we hope that the chapters will be readable guides to areas of interest. Also, by focusing on topics rather than targets, the chapters should remain relevant for longer as the general principles discussed should remain instructive as the field of kinase drug discovery matures. Although each of these chapters can be read as an individual standalone review of the topic, there are themes that are picked up in multiple chapters that allow the reader to review areas from the perspective of multiple authors. To supplement the information in these chapters, we have also included a list of internet websites that contain generally useful kinase information (Table 1.1) and assays to assess kinase activity (Table 1.2).

1.2 Preview of Topics Covered

In Chapter 2, Drewry and colleagues cover recent screening approaches that have been successfully utilised to find novel kinase lead series and assess selectivity. These include fragment screening, DNA encoded library technology, differential scanning fluorimetry (DSF), chemical proteomics and cellular screening.

To complement this chapter, Wu *et al.* report in Chapter 3 on the recent advances to identify inhibitors that bind to allosteric pockets (outside of the ATP-binding pocket) and the exciting opportunities that this approach offers

Table 1.1 Useful internet resources for general kinase information.

Information resource	Web link
Protein Data Bank	https://www.rcsb.org
Kinome	http://kinase.com/human/kinome
SGC kinase	http://www.thesgc.org/scientists/resources/kinases
Protein Kinase Resource	http://www0.nih.go.jp/mirror/Kinases
KinHub	http://www.kinhub.org
Chembl	https://www.ebi.ac.uk/chembl
Kinase SARfari	https://www.ebi.ac.uk/chembl/sarfari/kinasesarfari
DrugEBIlity	https://www.ebi.ac.uk/chembl/drugebility
Cysteinome	http://www.cysteinome.org
Approved KI drugs	http://www.brimr.org/PKI/PKIs.htm
Kinome scan and Kinativ data on selected KIs	http://lincs.hms.harvard.edu/kinomescan http://lincs.hms.harvard.edu/kinativ
Tool compounds	http://www.kinase-screen.mrc.ac.uk/kinase-inhibitors
Phosphorylation sites and other post-translation modifications	https://www.phosphosite.org
Catalogue of Somatic Mutations in Cancer	http://cancer.sanger.ac.uk/cosmic

Table 1.2 External sources for assays to assess kinase activity and selectivity, general profiling or elucidating mechanism of action (MOA).

Assay resource	Web link
Reaction Biology	http://www.reactionbiology.com/webapps/site/KinaseDetail.aspx
Thermofisher	https://www.thermofisher.com/uk/en/home/products-and-services/services/custom-services/screening-and-profiling-services/selectscreen-profiling-service/selectscreen-kinase-profiling-service.html
DiscoverX	https://www.discoverx.com/services/drug-discovery-development-services/kinase-profiling
Promega	https://www.promega.com/products/cell-signaling/kinase-assays-and-kinase-biology/kinase-selectivity-profiling-systems-general-panel
Eurofins	https://www.eurofinsdiscoveryservices.com/cms/cms-content/services/in-vitro-assays/kinases/screening-profiling-services
Proqinase	https://www.proqinase.com
SignalChem	https://www.signalchem.com/index.php
Kinativ	http://www.kinativ.com
Cell Signaling Technology	https://www.cellsignal.com/contents/science/protein-kinases-introduction/kinases
Residence Timer	https://www.ntrc.nl/services/residencetimer/
Carna Bioscience	https://www.carnabio.com/english/product/search.cgi?mode=profiling https://www.carnabio.com/english/product/live-cell.html https://www.carnabio.com/english/product/clari-cell.html
Luceome Biotechnologies	http://www.luceome.com/
AssayQuant	http://www.assayquant.com

to scientists, along with a practical discussion on screening and subsequent design of allosteric inhibitors.

Covalent kinase inhibitors have become a field of significant interest in recent years, leading to a number of approved drug molecules, as covered by de Bruin *et al.* in Chapter 4. This chapter discusses the disadvantages and advantages of a covalent mechanism and gives tips on how to successfully optimise such inhibitors in a general sense, along with a literature overview of advanced covalent inhibitors.

Structure-based design of kinase inhibitors is an area that has rapidly evolved, and a recurring theme in recent years has been the design and advantages of macrocyclic inhibitors. In Chapter 5 Poulsen and colleagues illustrate with case studies how such an approach can provide compounds with distinct profiles, also covering synthetic challenges and strategies to target this interesting class of compounds.

The emergence of brain tumours has been observed as a resistance mechanism to peripherally restricted kinase inhibitors. Consequently, targeting kinases in the brain is an area of increasing interest to oncology but also for the broader treatment of CNS-disorders. However, the properties of kinase inhibitors present some unique challenges for CNS design, as Skerratt and Storer cover in Chapter 6. The general medicinal chemistry principles and the challenges with designing brain-penetrant compounds are considered, along with a review of kinase case studies from oncology and other diseases pertinent to the CNS.

Computational approaches to kinase inhibitor design have benefitted from advances in structural biology. The increasing number and structural diversity of X-ray structures of kinases, along with continuing improvements in processor power have allowed computational chemists to tackle traditionally challenging areas such as estimating potency and ADME properties for novel compounds. Abel *et al.* give a general overview of this area in Chapter 7 and discuss the latest developments in this field.

Optimisation of physicochemical and pharmacokinetic properties is of central importance to medicinal chemistry, and in Chapter 8 Johnson and Hoffman discusses the specific challenges medicinal chemists face when designing kinase inhibitors. To illustrate this, comparisons have been made between kinase inhibitors and non-kinase drugs, as well as a discussion with case studies on how the challenges may differ depending on the nature of the binding pocket and inhibitor mechanism.

Chapter 9 explores the challenges of designing a kinase inhibitor with a suitable safety profile, written by Mogemark *et al.* Some of these themes continue from the previous chapter, although with kinase drug discovery there is a particular focus also on designing for selectivity within the kinome. Safety screening strategies are covered, as well as considerations for running safety studies and assessing kinase selectivity.

In recent years a growing number of kinases have been targeted by scientists although, as a discipline, we are still some way off being able to selectively target the whole kinome. Drewry *et al.* summarise the progress

towards drugging the kinome in Chapter 10, focusing on parts of the kinome that are covered by existing drugs and probes, the progress still to be made towards this goal, and how the drug discovery community can make further progress.

A hot topic in kinase drug discovery is the impact of kinase mutations on disease and inhibitor resistance, with the editors Ward and Goldberg covering the progress in Chapter 11. This field is particularly important to oncology, where targeting disease relevant mutations can in some cases lead to greater efficacy and tolerability. Chemists have the ability to target specific mutated forms of kinase targets, often in a rational way, particularly where crystal structures are available. This chapter discusses a number of such case studies that address kinase mutations.

Within oncology, one of the most exciting developments in recent years has been the impact of therapies that can enhance the immune response to cancer cells (or reduce immunosuppression), termed immuno-oncology (IO). Whilst this field initially concentrated on checkpoint inhibition with antibodies, many of the newer targets of interest for IO are kinases and inhibition can therefore be achieved with small molecules. The exciting opportunities that this presents are covered by Duffy and Parrish in Chapter 12.

The kinase drug discovery field thus far has focused on inhibiting the ATP-derived phosphate transfer catalysed by protein and lipid (functional) kinases. However, there is increasing awareness of a subset of the kinome that do not possess this catalytic activity, the pseudokinases, as well as an acknowledgement that functional kinases can also have important non-catalytic functions through, *e.g.*, protein–protein interactions. Targeting such pseudokinases (and non-catalytic function of conventional kinases) represents another exciting opportunity for medicinal chemists and will be covered in Chapter 13 by Lucet and Murphy.

Finally, to be consistent with the forward-looking focus of this book, Kurumbail *et al.* provide an opinion on the future of kinase inhibition in Chapter 14. Specifically, they focus on three exciting areas that they expect to impact the field over the next decade. First, they discuss kinase activation as an alternative paradigm to kinase inhibition. Secondly, they discuss protein degradation as an alternative way to inhibit a protein's function, with potentially differentiated profile particularly as regards the types of non-catalytic activity that were discussed in the previous chapter. Finally, they discuss the increasing impact expected from knowledge of drug resistance mechanisms in patients and the opportunities that presents, particularly within oncology.

1.3 Conclusions

By bringing together experts in these fields that represent many of the leading institutions in kinase drug discovery, both academic and industrial, to discuss a selection of interesting and emerging topics, we hope that the

reader will find this book an interesting resource, and that the individual chapters will serve as useful introductions to key topics that should impact this rapidly expanding field over the next decade.

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Reference

1. *Kinase Drug Discovery (RSC Drug Discovery Series)*, ed. R. A. Ward and F. Goldberg, Royal Society of Chemistry, December 2011.