Chapter 43
Protein–Protein Interactions (PPIs) as an Alternative to Targeting the ATP Binding Site of Kinase:
In Silico Approach to Identify PPI Inhibitors

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ABSTRACT

Most of the developed kinase inhibitor drugs are ATP competitive and suffer from drawbacks such as off-target kinase activity, development of resistance due to mutation in the ATP binding pocket and unfavorable intellectual property situations. Besides the ATP binding pocket, protein kinases have binding sites that are involved in Protein-Protein Interactions (PPIs); these PPIs directly or indirectly regulate the protein kinase activity. Of recent, small molecule inhibitors of PPIs are emerging as an alternative to ATP competitive agents. Rational design of inhibitors for kinase PPIs could be carried out using molecular modeling techniques. In silico tools available for the prediction of hot spot residues and cavities at the PPI sites and the means to utilize this information for the identification of inhibitors are discussed. Moreover, in silico studies to target the Aurora B-INCENP PPI sites are discussed in context. Overall, this chapter provides detailed in silico strategies that are available to the researchers for carrying out structure-based drug design of PPI inhibitors.

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INTRODUCTION

Protein kinase enzymes, also known as phosphotransferases, are the most extensively pursued class of drug targets in current pharmaceutical research. Several kinase inhibitors are registered for pre-clinical & clinical trial evaluation for different ailments, including cancer (O'Brien & Fallah Moghaddam, 2013; Rask-Andersen, Zhang, Fabbro, & Schioth, 2014; J. Zhang, Yang, & Gray, 2009). These enzymes transfers ATP terminal phosphate group to the substrate protein, and thereby regulate various activities including cell proliferation, differentiation, survival, transcription, apoptosis, metabolism, and a wide array of other signal transduction process (Adams, 2001; P. Wu, Nielsen, & Clausen, 2015). The involvement of kinases in various pathological conditions, makes them an attractive drug target for therapeutic intervention in diseases such as cancer (Fabbro, Cowan-Jacob, Mobitz, & Martiny-Baron, 2012), vascular (Abeyrathna & Su, 2015; Kikuchi et al., 2014) & central nervous system (CNS) disorders (Chico, Van Eldik, & Watterson, 2009), inflammatory disease conditions (Barnes, 2013; Rommel, 2010), and diabetes (Banks et al., 2015; Y. Wu & Chakrabarti, 2015). Consequently, for the past one and half decades, pharmaceutical companies and academic researchers are mounting intense efforts to develop small molecule kinase inhibitors. As a result of this, the first successful kinase inhibitor imatinib was approved in 2001 by FDA for the treatment of chronic myeloid leukemia (Gambacorti-Passerini & Piazza, 2015; Wisniewski et al., 2002). Since then, understanding of kinase structural and functional mechanism and their involvement in pathological conditions has significantly improved by the advancement of cell and molecular biology, structural biology, genetics, and associated fields. Concomitantly, the kinase inhibitors approval has also increased, and presently around 28 small molecule kinase inhibitors are approved by the US FDA for therapeutic usage in various cancers (Fabbro, 2015; P. Wu et al., 2015; Z. Zhao et al., 2014). The structures of approved kinase inhibitor drugs are represented in Figure 1.

The entire human genome encodes approximately 518 protein kinases (Manning, Whyte, Martinez, Hunter, & Sudarsanam, 2002), and have conserved kinase domain fold. The 3D structure of kinase contains a helix-dominated conserved C-terminal region, and a β sheet-dominated N-terminal region, which varies in sequence length and amino acid composition. A flexible hinge region connects the N- and C-terminal lobes, and in between these two lobes there exist a conserved ATP binding cleft. Glycine rich loop contains a conserved GXGXXG motif, and acts like a clamp to stabilize the binding of ATP at this cleft. Binding of ATP to the active site is controlled by the activation loop N-terminal starting residues Asp-Phe-Gly, also called DFG motif which adapts "DFG-in" and "DFG-out" conformation according to protein active and inactive state, respectively. The DFG motif residue Asp together with metal ion Mg^{2+} regulates kinase transactivation mechanism during phosphorylation process (Eswaran & Knapp, 2010; Thaimattam, Banerjee, Miglani, & Iqbal, 2007).

KINASE INHIBITORS, THEIR BINDING MECHANISM AND DRAWBACKS

The small molecule kinase inhibitors are useful as therapeutic agents, as well as to understand various cellular functions in normal and disease conditions. To date, most of the discovered kinases inhibitors are ATP competitive in nature; the heterocyclic core group in the inhibitor forms one to three hydrogen bond interactions with the conserved hinge region residues of the kinase (Garuti, Roberti, & Bottegoni, 2010; J. Zhang et al., 2009). Thus, they mimic the typical hydrogen bond interactions of adenine ring of ATP with the kinase. Based on the inhibition mechanism, kinase inhibitors are classified as either reversible

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