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

Sailu Sarvagalla Pondicherry University, India

Mohane Selvaraj Coumar Pondicherry University, India

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.

DOI: 10.4018/978-1-5225-1762-7.ch043

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 Mg²⁺ 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

27 more pages are available in the full version of this document, which may be purchased using the "Add to Cart" button on the publisher's webpage:

www.igi-global.com/chapter/protein-protein-interactions-ppis-as-analternative-to-targeting-the-atp-binding-site-of-kinase/174163

Related Content

QSAR-Based Studies of Nanomaterials in the Environment

Valeria V. Kleandrova, Feng Luan, Alejandro Speck-Plancheand M. Natália D. S. Cordeiro (2015). *Quantitative Structure-Activity Relationships in Drug Design, Predictive Toxicology, and Risk Assessment* (*pp. 506-534*).

www.irma-international.org/chapter/qsar-based-studies-of-nanomaterials-in-the-environment/124478

Functional and Antioxidant Properties of Protein Hydrolysates From Ricinodendron Heudelotii(Bail.) Flours From Cameroon

Ngangoum Eric Serge, Mezajoug Kenfack Laurette Blandine, Sanjit Kumar, Mookambeswaran Vijayalakshmiand Tchiégang Clergé (2018). *Research Advancements in Pharmaceutical, Nutritional, and Industrial Enzymology (pp. 326-340).*

www.irma-international.org/chapter/functional-and-antioxidant-properties-of-protein-hydrolysates-from-ricinodendronheudelotiibail-flours-from-cameroon/203821

QSPR/QSAR Analyses by Means of the CORAL Software: Results, Challenges, Perspectives

Andrey A. Toropov, Alla P. Toropova, Emilio Benfenati, Orazio Nicolotti, Angelo Carotti, Karel Nesmerak, Aleksandar M. Veselinovi, Jovana B. Veselinovi, Pablo R. Duchowicz, Daniel Bacelo, Eduardo A. Castro, Bakhtiyor F. Rasulev, Danuta Leszczynskaand Jerzy Leszczynski (2017). *Pharmaceutical Sciences: Breakthroughs in Research and Practice (pp. 929-955).*

www.irma-international.org/chapter/qsprqsar-analyses-by-means-of-the-coral-software/174156

Roles of Phytochemical Agents in the Prevention of Primary Cancer

Ayodeji Ojo Oteyola, Raffaele Pilla, Folasade Adesola Ola-Oladimeji, Omotayo Fagbuaro, Daiana Silva de Avila, Chibuisi Gideon Alimba, Erika Cristina Jorgeand Fernanda R. C. L. de Almeida (2023). *Natural Products as Cancer Therapeutics (pp. 230-253).*

www.irma-international.org/chapter/roles-of-phytochemical-agents-in-the-prevention-of-primary-cancer/329161

Cancer Drug Delivery: Pharmacogenetics, Biomarkers, and Targeted Therapies

Jai N. Pateland Jeryl Villadolid (2017). *Pharmaceutical Sciences: Breakthroughs in Research and Practice* (pp. 185-228).

www.irma-international.org/chapter/cancer-drug-delivery/174126