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Editorial

A Perspective on Protein Kinase Inhibitors

Signal transduction, the biochemical cascade by which extracellular signals are transmitted to the cell nucleus, is a key process in many biological events. Protein kinases and protein kinase-mediated phosphorylation play a fundamental role in many signal transduction pathways. Since protein kinases are involved in numerous biological events, such as cell growth, differentiation, apoptosis and metabolism, aberrant kinase activity is believed to contribute to numerous diseases such as cancer, diabetes, neurodegenerative and inflammatory disorders.

The protein kinases catalyze the transfer of a phosphate group from a molecule of ATP to a specific amino acid residue (Serine, Threonine, Tyrosine or Histidine) in a particular substrate. Although there are a number of mechanisms by which this can occur, they invariably involve the binding of the ATP molecule to a well-defined binding pocket in the kinase. The presence of this binding site has proven a double-edged sword for medicinal chemists. Through HTS and rational design, small molecules that mimic ATP and bind competitively at its binding site have been identified. However, historically there have been doubts about the level of selectivity that can be built into such inhibitors given the similarity of the binding pockets across the target class. Initially, many researchers believed that this issue was insurmountable and kinases were intractable as drug targets. More recently, very potent and selective inhibitors acting at the ATP site have been identified, and the first kinase inhibitors, Gleevec® and Iressa®, have entered the market. As a result, interest in kinases as potential drug targets remains high amongst pharma and biotech companies. For example, like many of its competitors, Aventis has recently moved to a target class approach to early drug discovery with kinases identified as one of the key areas.

This thematic issue is a collection of original articles from authors who have made major contributions to the methods, rational design and discovery of new kinase inhibitors. These manuscripts illustrate the current thinking on some of the challenges facing researchers investigating the chemical biology of kinases. It is my hope that this collection of articles from prominent researchers will inspire continued innovation toward drug design in this field of medicinal research. Finally, I would like to thank the authors for their contributions, their participation as reviewers and their patience in putting together this special issue on the recent advances in the design of kinase inhibitors as therapeutic agents.

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