

**Methods in  
ENZYMOLOGY**

**Volume 493**

**Fragment-Based Drug Design:  
Tools, Practical Approaches,  
and Examples**

*Edited by*

**Lawrence C. Kuo**



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# METHODS IN ENZYMOLOGY

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## PREFACE

There has been a plethora of technological innovations since the late 1980s that have influenced the way research is pursued in the biotechnology and pharmaceutical arena. Investigators are now applying ever more elaborate methods to elucidate the molecular basis underlying the biology of human diseases and to tackle discovery of new medicine. A few of these new technologies have fundamentally altered the means by which we look for hits as well as the routes we use to evolve hits to leads. Notably, protein crystallography was applied in the early 1990s to provide a structure-based approach to optimize drug leads and at about the same time high-throughput automated screening was introduced to evaluate at an unprecedented speed the effect of compounds on protein targets. Both were adopted swiftly as standard operating procedures by the pharmaceutical industry. In contrast, the use of very low molecular weight compounds, known as fragments and introduced by Abbott Laboratories in the mid-1990s, has only gained widespread acceptance in recent years.

A typical screening exercise searches a compound library with the aim of finding inhibitors against a protein target. Traditional high-throughput screening does not always offer hits of sufficient quality to be progressed into a lead compound. Fragment-based approaches utilize low molecular weight compounds that are associated with favorable physicochemical and pharmacokinetic properties. Hits derived from low molecular weight compounds offer a viable and an orthogonal entry point to finding lead compounds that in principle and by design shun unappealing pharmacophores. The use of fragments is now accepted as a “legitimate” starting point in the discovery of new medical entities as therapeutics. There are numerous, excellent reviews on Fragment-Based Drug Design (FBDD). For those new to the field, there is a need for comprehensive walk-through protocols with which one can embark readily on this creative approach to complement traditional screening methodologies. This *Methods in Enzymology* volume offers tools, practical approaches, and hit-to-lead examples on how to conduct FBDD screens. The chapters in this volume are written by experts in the field to cover methods that have proven to be successful with a focus on how to mount a successful FBDD campaign. The chapters include computational techniques, nuclear magnetic resonance, surface plasma resonance, thermal shift and enzyme kinetic assays, protein crystallography, and medicinal chemistry. Emphasis is placed on practical aspects and effective progression of lead generation to include sample preparations

of fragments, proteins, protein crystals, and G-protein coupled receptors. Explicit examples are given on how to generate leads from low-affinity fragment hits.

I want to thank all the authors; it is solely their contributions that render this volume possible. I want to thank Paul Prasad Chandramohan and Zoe Kruze of Elsevier Publishing Company for their guidance and patience throughout all stages of putting this volume together. Thanks are also due to Drs. John Abelson and Melvin Simon for their support in selecting the timely topic. I am grateful to my wife and my children for their patience during my time spent on this volume.

LAWRENCE C. KUO

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