Preface

Cysteine proteases are known to mediate a broad range of biological processes across both plant and animal kingdoms. In this respect, they comprise one of the most ubiquitous enzyme classes in nature. The impact of genomics has served to further expand the recognized diversity of both structure and function of this enzyme class.

While there are many essential biological processes of low specificity, such as metabolism, which are mediated by cysteine proteases, they also mediate many aberrant endogenous processes as well processes essential to the proliferation of many exogenous pathogens. Thus, specific cysteine proteases can represent attractive targets for therapeutic intervention in a variety of disease states.

At the present time, therapeutic intervention with cysteine protease inhibitors has not shared in the clinical success realized by their aspartic and metalloprotease counterparts. This has been at least partially attributed to a paucity of inhibitors or inhibitor classes that demonstrate adequate pharmacokinetic and pharmacodynamic profiles. This was an early common problem also with the aspartic and metalloprotease inhibitors. It was only through focused and significant medicinal chemistry efforts that these problems were resolved to produce useful drugs. A surge of recent activity has occurred in the development of new classes of cysteine protease inhibitors for a variety of disease states including cancer, arthritis, osteoporosis, and viral and parasitic diseases. For the most part, the pharmacokinetic and pharmacodynamic issues remain. However, the continuously growing database of three-dimensional structural information available for many cysteine proteases or their homologues, and the evolution of combinatorial synthetic methods are working together to hasten the development of new and more specific inhibitors.

This Symposium-in Print is intended to be a forum for publication of recent work in the development and study of cysteine protease inhibitors and inhibitor classes. Just as there is a high level of diversity of structure and function of cysteine proteases, there is great diversity not only in the chemical structure and reactivity of inhibitors, but also in their mechanisms of inhibition. The articles that comprise this Symposium-in-Print highlight these observations. The organization of the articles begins with studies involving the development of new inhibitors, including the utilization of structure-based design and combinatorial synthesis methods, then proceeds to studies that probe the mechanism(s) of inhibition by a family of inhibitors, and concludes with articles which focus on the demonstration of therapeutic utility of cysteine protease inhibitors in the treatment of parasitic infections.

Collectively, the articles that embody this Symposium-in-Print should serve to accurately summarize some important current activity in the field of cysteine protease inhibitor design and development, to highlight the key issues, and provide a sound foundation for the future promise of cysteine proteases as targets for therapeutic intervention.

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