Preface

Scientific interest in peptidomimetic research continues to grow as efforts increase to understand and modulate the therapeutically important processes mediated by endogenous peptides. Many peptides are often intrinsically limited as drugs since they may exhibit poor solubility, stability, and/or bioavailability. Efforts to improve the metabolic stability, duration of action and bioavailability of such peptides has stimulated the search for new peptidomimetic drugs. Peptidomimetics represent peptide-like molecules which can mimic the binding of natural peptides at either their native receptor or enzyme targets. The ideal peptidomimetic will exhibit enhanced potency and selectivity for its biological target, while providing improved pharmacokinetic behavior. This collection of invited papers was assembled to convey the diversity and scope of the bioorganic and medicinal chemistry in this area.

The ultimate challenge and most time consuming aspect of many peptidomimetic research programs is to identify an orally active agent as a potential clinical candidate which retains all of the other desired pharmaceutical properties. A number of new programs are approaching clinical testing of orally active peptidomimetic drug candidates. The papers by Kempf *et al.* and Hungate *et al.* describe state of the art, complementary approaches to achieve oral bioavailability with new HIV-I protease inhibitors by modulating size, water solubility and hydrogen bonding potential. The following two papers summarize key aspects of current efforts to obtain orally active antiplatelet fibrinogen antagonists. The manuscript by Bovy *et al.* describes a novel ester pro-drug approach while that by Bondinell and co-workers presents an interesting application of template design based on cyclic peptides followed by secondary amide methylation. The three dimensional X-ray structure of a complex between human renin and an orally active truncated renin inhibitor is described by Hanson *et al.*, which provides new insight into the fundamental binding interactions available in this important enzyme.

Efforts continue to explore new approaches for obtaining potent peptidomimetic enzyme inhibitors. Aspartyl proteases continue to attract attention because of the interest in renin, HIV-I protease and other related proteases. The manuscript by Marshall and co-workers describes an interesting comparison of ketomethylene isosteres with their hydroxyethylene counterparts in renin and HIV-I protease inhibitors. Rosenberg and co-workers present a novel approach to simplified renin inhibitors using oxetanes as transition state mimics. The contributions by Wai *et al.* and Marsters *et al.* provide complementary approaches to new Ras farnesylation inhibitors which extends peptidomimetic chemistry into the cancer chemotherapy arena for the first time. The manuscript by Moss and co-workers describes an interesting potential entry to new antiviral herpes agents by providing an unusual approach to ribonucleotide reductase inhibitors. Unlike more traditional substrate-based inhibitors, these peptidomimetics act by disrupting subunit assembly in this system.

Similarly, efforts also continue to explore new approaches for obtaining potent peptidomimetic receptor antagonists. Here conformational constraint is often used to improve potency. The manuscript by Williams and co-workers provides new insight into the possible bioactive conformation of new oxytocin antagonists. The paper by Bock *et al.* extends the application of benzodiazepines to potent CCK receptor antagonists. Another strategy attempts to mimic key secondary structural elements in

therapeutically important peptides. The paper by Kelly *et al.* describes one such application to mimic the cyclic decapeptide, gramicidin S, with new acyclic, β-sheet peptidomimetics. The manuscript by Kahn *et al.* presents an interesting attempt to mimic the β-turn in CD4 as it binds to gp120.

Overall, these fourteen contributions reflect the broad diversity of peptidomimetic research. From enhancing bioavailability to defining the key molecular interactions with their biological targets, this area continues to provide new insight into fundamental biological processes and offers tremendous potential for further applications in new therapeutic areas.

James A. Sikorski
G. D. Searle R&D
700 Chesterfield Pkwy N.
St Louis, MO 63198
U.S.A.