ACCOUNTS
of chemical research

GUEST EDITORIAL

Peptidomimetics

The rubric "peptidomimetics" covers a large and expanding field of research that has achieved profound successes and offers fascinating new challenges.[1] Biologically oriented chemists have been interested in peptidomimetic molecules for over a quarter century.[2] In a widely cited 1993 review,[3] Giannis and Kolter offered a purely functional definition: "a peptidomimetic is a compound that, as the ligand of a receptor, can imitate or block the biological effect of a peptide at the receptor level." Wiley and Rich[4] gave a related definition in the same year, "chemical structures designed to convert the information contained in peptides into small nonpeptide structures." In 1994, Gante[5] provided a definition that explicitly invokes both structure and function: "a peptidomimetic is... a substance having a secondary structure as well as other structural features analogous to that of the original peptide, which allows it to displace the original peptide from receptors or enzymes." Each of these definitions and virtually all of the early literature on this topic reflect the medicinal motivation for interest in peptide mimicry. Peptides display remarkable biological activities, but problems associated with proteolytic degradation and delivery hinder pharmaceutical application. Thus, the classical goal of peptidomimetic research has been to identify small, drug-like molecules that can mimic peptide function, as explicitly stated by Wiley and Rich.[4]

The evolution of the field now identified with the term "peptidomimetics" over the past decade is charted by the Accounts in this special issue. These Accounts can be loosely grouped into three sets. One set shows that classical medicinal goals remain subjects of avid pursuit and how the nature of these goals has diversified in recent years. The other two sets illustrate new goals that involve both structure and function. One set of Accounts highlights efforts to coax α-amino acid backbones to behave in new ways, and another set focuses on non-natural oligomeric backbones that display conformational behavior akin to that of peptides and proteins.

The vitality and breadth of medicinally oriented peptidomimetic research is illustrated in the Accounts of Tsantrizos, Chatterjee et al., Sun et al., Lai et al., and Hanessian and Auzzas. Tsantrizos provides a very accessible overview of efforts to develop therapeutically useful protease inhibitors, which has been a long-term goal in the field. Nonspecialist readers will value her concise summary of HIV protease development, since this story represents a fine contemporary example of chemistry improving the human condition. The discussion of hepatitis C virus NS3/4A protease inhibitor development nicely illustrates how challenging protease targets can be and how creatively medicinal chemists can respond to such challenges. Sun et al. highlight exciting recent progress in blocking protein−protein interactions; they show that a "classical" peptidomimetic approach is particularly well suited for inhibiting Smac−IAP interactions because binding is focused on a very short N-terminal segment of Smac. Lai et al. discuss larger peptide epitopes for mimicry, amphiphilic conformations adopted by antibacterial peptides. These workers describe the very imaginative use of the bile acid skeleton to achieve functional mimicry. Hanessian and Auzzas summarize the synthesis of cyclically constrained amino acids that can be used to construct unnatural peptides.

The Accounts of Chatterjee et al., Durani, Patgiri et al., Nowick, Robinson, and Takahashi and Mihara represent a departure from the focus on "translating" peptides into small, drug-like molecules. These Accounts deal with molecules that are largely or entirely comprised of α-amino acid residues. This aspect of modern peptidomimetic research reflects expansion beyond the very important practical goal of developing orally active pharmaceutical agents to

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include features of peptides that transcend the scope of small molecule chemistry. In some cases, the effort is very much in the original spirit of drug discovery, as nicely seen in the contribution of Chatterjee et al. These authors describe profound advantages that a seemingly simple modification, backbone amide N-methylation, can confer on biologically active cyclic peptides. The Account of Robinson, too, discusses cyclic peptides and interesting biological activities, including a remarkable example in which a β-hairpin (two-stranded β-sheet) conformation functionally mimics an α-helix. Stabilization of β-strand conformations and concomitant promotion of β-sheet formation can be achieved with carefully designed buttressing segments, as illustrated by Nowick. Patgiri et al. show how an α-helical conformation can be stabilized in relatively short peptides via carefully crafted cross-linking units. Durani highlights the profound conformational effects that can be achieved by using heterochiral peptides. Thoughtful design of both side chain and configuration sequences leads to remarkable folding patterns. Takahashi and Mihara describe the use of short peptides to control amyloid formation by larger peptides.

The remaining Accounts focus on oligomers constructed largely or entirely of subunits other than α-amino acid residues. These alternative building blocks are intended to lead to well-defined conformational propensities in the resulting oligomers, which have been dubbed "foldamers". Both editors of this issue have been engaged in this type of research for some time, and the Accounts in this area, collectively, can be seen as our effort to make the case that foldamer science is a logical outgrowth of the original peptidomimetic concept.

Li et al. describe the study of aminoxy acid oligomers, one of the first examples of foldamers. These peptide-like molecules display distinctive conformational propensities, which have been used to engineer interesting functions. The interplay between structure and function is a recurring theme in the foldamer field. This interplay can be seen in the review of experimental β-peptide studies provided by Seebach and Gardiner, and the complementary review of computational β-peptide analysis contributed by Wu et al. Brown et al. share a very exciting story from the realm of "peptoids", oligomers of N-substituted glycines. These peptidic foldamers lack backbone H-bond donors but nevertheless fold in specific ways. Brown et al. have developed peptoids that mimic the function of vital natural proteins, those that make up the lung surfactant system. Gong describes imaginative foldamer designs that depart significantly from the peptide prototype: these backbones are rich in aromatic rings, which confer intrinsic rigidity. Li et al. extend this theme and show how the resulting foldamers can be used for molecular recognition. The theme of backbone rigidification can be taken even farther, by using two-point connections between adjacent subunits, as discussed by Schafmeister et al. Horne and Gellman outline a relatively new theme in foldamer science, the use of backbones that contain more than one type of subunit. The contribution from Sakai et al. shows how far the foldamer concept can be pushed by an imaginative mind. The functional goal, creation of artificial ion channels, is inherently complex, and the molecules that perform this task are complex as well, containing both peptide and nonpeptide elements. The Account from Sakai et al. and a few others introduce an emerging theme in the field, an expansion from peptidomimetics to molecules that mimic structure and function at levels typically manifested by full-fledged proteins.

Our collection of Accounts illustrates the enduring significance of the original peptidomimetic concept, and the versatility of this concept as it has grown to encompass science not explicitly considered by the early practitioners. Because peptides and proteins display such a vast array of interesting structures and functions, this broad area of research should remain vibrant indefinitely.

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Guest Editors

REFERENCES

1 Linguistically, the chemist's use of "peptidomimetic" as a noun is unfortunate, since "mimetic" is generally defined as an adjective. In retrospect, "peptide mimic" might have been a better term.

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