

# Preface

Peptide mimicry may be broadly defined as an approach for conceiving molecular structures that can replicate the molecular recognition elements that contribute to the activity of natural peptides [1–3]. The term peptide mimic (peptidomimetic) is used to describe such compounds. Peptidomimetics arise from the combination of chemical synthesis and employment of techniques from various other sciences which are necessary for ascertaining the potential of peptide surrogates. The pursuit of peptidomimetics is propelled by the desire to preserve the remarkable attributes, such as high potency and low toxicity, while simultaneously removing liabilities of the natural parent peptide structures, such as their rapid metabolism, lack of receptor selectivity, and poor bioavailability.

Heterocycles serve fundamental roles in the folding and function of natural peptides. For example, proline drives turn and helical structures by constraining the peptide backbone to a limited set of dihedral angles. Peptide macrocycles adopt commonly well-defined conformations responsible for their activity. The imidazole and indole heterocycle side chains of the amino acids histidine and tryptophan play vital roles for the recognition of various biologically relevant peptides. The various heterocycles used in natural peptides inspire the design of peptidomimetic counterparts.

The application of heterocycle chemistry in peptide mimicry has been paramount to successful designs of peptidomimetics. In addition to adding rigidity to stabilize active conformations and serving as side chain substitutions to improve recognition by targeted receptors, heterocycles have been employed in peptidomimetics to enhance metabolic stability. For example, replacement of amide and disulfide bonds by heterocycles has improved respectively stability against proteolytic cleavage and disulfide bond reduction.

The emphasis of this two-volume set is to illustrate contemporary applications of heterocycles in peptide mimicry. A bias towards the applications of the resulting peptidomimetics in chemical biology and medicinal chemistry is present likely due to the important history of peptides as drugs [4] as well as the boom of investment into peptide-based medicine [5, 6]. Concurrent growth of interest in peptidomimetic science has taken place with the rising employment of peptides in the

pharmaceutical industry, because of two primary goals: to provide probes to gain insight into the biologically active conformation of the native peptide and to furnish prototypes to improve pharmacokinetic properties for drug development. Aspects of heterocycle chemistry in peptide mimicry for other applications such as materials science and catalysis are specifically covered in particular chapters.

Reflecting on advances in peptide mimicry through the employment of heterocycles, different themes emerge from examination of their structural motifs and methods of synthesis. Heterocycles have been typically employed within single amino acid residues and dipeptides, as well as units that nucleate folding to replicate entire secondary structures, such as turns, helices, and sheets [7]. Applications of heterocycles within discrete units that fold into ordered conformations when placed into oligomers, so-called foldamers [8], have been restricted herein to examples that mimic natural peptide geometry, and for more information on alternative non-natural motifs, the interested reader is asked to consult a recent comprehensive review [9]. Similarly, the reader is directed elsewhere for information on heterocyclic frameworks that mimic peptide ligands for diverse receptors, so-called privileged structures [10–14], albeit the potential for diaze- and triazepinones to mimic  $\gamma$ - and  $\beta$ -turn conformations has recently been supported by crystallographic evidence [15, 16 and references therein], and certain heterocycle motifs have served in the *de novo* design of peptide mimics [17, 18]. Methods for making heterocycles and for employing their reactions to prepare constrained peptidomimetics are covered with particular focus on contemporary protocols that exhibit high tolerance for the various functional groups found in natural peptide structures.

The concept of peptide mimicry is broadly applied in this treatise. For example, peptides possessing a single non-natural alteration featuring a heterocycle are included as peptidomimetics in spite of their appearance as selectively modified variants of the natural structure. Similarly, natural products containing non-proteinogenic heterocycles are presented in certain chapters illustrating that nature too makes peptidomimetics. For example, the natural antibiotic penicillin, which inhibits transpeptidase and carboxypeptidase enzymes involved in the construction of the bacterial cell wall material peptidoglycan, functions by mimicking the D-alanine-D-alanine motif of the peptide component [19]. Modified peptide macrocycles are also considered as heterocycles. Finally, some chapters may mention heterocyclic peptidomimetics for which relationships to natural peptide structure and activity have yet to be established. In such cases, the purist is asked to be forgiving of the looseness of the definition and reminded that the goal of the work is to give a contemporary perspective, which aims to inspire future research in a growing field.

## Volume I

Peptide backbone geometry is defined by the  $\phi$ ,  $\psi$ , and  $\omega$  dihedral angle values of the respective amino acids in the sequence [20]. Local constraints that restrict such dihedral angles about these bonds in a single amino acid or between two amino

acids in a dipeptide can have significant consequences on the global conformation of the entire peptide. For example, a proline residue can favor turn geometry and align the amide bonds of distant amino acid residues in the peptide chain to form ordered hairpin and  $\beta$ -sheet conformations [21]. In longer peptides, such local restrictions combine with hydrophobic effects, van der Waals interactions, and hydrogen bonds to overcome peptide solvation and give rise to relatively stable folded protein three-dimensional structures [22]. Shorter peptides (i.e., <10 residues) may however exist in a dynamic balance of equilibrating conformations. Considering that the entropy penalty for folding into a conformation pre-organized for receptor affinity may be paid by electronic and structural constraints that offset the dynamic equilibrium, heterocycles have been employed strategically to place restrictions on particular dihedral angles with consequences on global geometry.

In Volume I of this treatise, the application of heterocycles that restrain single amino acid and dipeptide conformation are discussed in detail. The importance of the natural amino acid proline has led to various analogs possessing ring substituents to alter ring puckering, as well as to modify the  $\psi$  and  $\omega$  dihedral angles by way of steric and electronic interactions [23–25]. In light of their importance to contemporary research on peptides in chemical biology, medicine, materials science, and catalysis, three chapters of this volume are dedicated to such modified prolines. Illustrating the consequence of a single atom replacement on the global geometry of peptides and entire proteins, Newberry and Raines present the synthesis and conformational analysis of analogs bearing 4-fluoroproline. Substitution of fluorine for hydrogen at the 4-position of proline causes significant inductive effects that influence the ring pucker, as well as the amide bond isomer equilibrium and rate of isomerization of its N-terminal amino acid residue. The consequences of such changes on peptide and protein structures are reviewed in detail with special attention to collagen stabilization. The replacement of the 4-position methylene by a dimethylsilyl group has been explored by Rémond, Martin, Martinez, and Cavalier, who discuss the influence of silaproline on heightening lipophilicity and improving resistance to biodegradation in a variety of peptide targets relevant to medicine and biomaterials science. Finally, the impact of an additional bridging methylene on the conformation of proline is described by Vilchis-Reyes and Hanessian, who detail the challenges in synthesizing such methanoproline and their various applications including serving as a component in the antidiabetic drug Onglyza as well as acting as organocatalysts. Expanding on the theme of proline-like heterocyclic amino acids, the chapter by Handy and Sello presents a review of research on the synthesis and applications of piperazic acid. This 6-aza-variant of pipercolic acid, a proline homologue, exhibits influence on N-terminal amide geometry and local peptide conformation as a component of many natural products with anti-tumor, anti-HIV, antifungal, and antibacterial activities.

The pyrrolidine and piperidine amino acids, proline and pipercolate, feature a bridge between their nitrogen and  $\alpha$ -carbon. By moving the bridge from the N- to the C-terminal amino group in a peptide, a lactam ring is created which joins two amino acids ensemble. Such  $\alpha$ -amino lactam dipeptide surrogates, so-called

Freidinger-Weber lactams, have been used to explore the conformation of a variety of biologically relevant peptides, since the Merck laboratory employed this heterocycle system to constrain the Gly-Leu fragment of luteinizing hormone-releasing hormone and received an agonist with nearly tenfold greater potency to that of the native hormone for release of luteinizing hormone in a pituitary cell culture system [26]. In two chapters, contemporary advances are featured in the synthesis and application of Freidinger-Weber lactam analogs. Reviewing recent literature on the synthesis of biologically active peptides bearing ring substituted  $\alpha$ -amino  $\gamma$ -lactams, St-Cyr, Garcia-Ramos, Doan, and Lubell present recent developments of lactams and their elaboration into aza-variants in *N*-amino-imidazolone and *N*-amino-imidazolidinone dipeptides with particular attention to the influence of a second nitrogen on the conformation of these  $\beta$ -turn mimic analogs. The corresponding seven member  $\alpha$ -amino  $\epsilon$ -lactams are highlighted by Ballet, Guillemyn, Van der Poorten, Schurgers, Verniest, and Tourwé, who examine various synthetic methods for introducing such azepinone amino acids into medicinally relevant peptides with emphasis on elucidating biologically active conformations.

Azabicyclo[X.Y.0]alkanone amino acids are heterocyclic systems in which the central amide nitrogen of a dipeptide is bridged to the  $\alpha$ -carbons of both its N- and C-terminal amino acid residues [27–29] [30 and references therein] [31, 32]. These bicyclic dipeptide mimics combine attributes of proline-like and  $\alpha$ -amino lactam structures described above. Since pioneering syntheses of the thia-indolizidinone [31] and thiapyrroloazepinone [32] constrained dipeptides, azabicycloalkanone amino acids have been employed to control peptide folding and to serve as rigid platforms for orienting pharmacophores in peptide science and medicinal chemistry. The development of synthetic methods to access these heterocycles has led to various studies of the influences of their ring sizes, stereochemistry, and ring substituents on peptide conformation. Exploring applications of carbohydrates as building blocks for the effective construction of azabicycloalkanone amino acids possessing polyhydroxylated frameworks, Wuttke and Geyer describe the propensity of such systems to favor turn and loop conformations. The utility of polyhydroxylated bicyclic dipeptides is contrasted with other sugar-amino acid hybrids [33] and highlighted for the ability to stabilize stand-alone peptide hairpins and to mediate protein–protein interactions.

Finally, Volume I concludes with two chapters on five-member heterocycles that have garnered significant use in peptide, protein, and peptidomimetic chemistry. Thiazoles have been employed as amide bond surrogates, pharmacophores, and directing groups in enzyme inhibitors, receptor agonists and antagonists, and mediators of protein–protein interactions. Examining physical properties, such as dipole movement and potential for hydrogen bonding, Mak, Xu, and Fairlie illustrate the utility of thiazoles in peptide mimicry with focus on their importance in natural products and broad applications in drug design in which they serve as the most common 5-membered heterocycle of contemporary pharmaceuticals. Triazoles are emerging rapidly as the most important heterocycle for peptide and protein science in great part because of their effective synthesis by contemporary methods such as copper-catalyzed and strain-promoted azide–alkyne

cycloadditions (CuAAC and SPAAC). Examining the development of triazole chemistry in the context of peptide mimicry, Diness, Schoffelen, and Meldal illustrate how modern synthetic methods have advanced applications of these heterocycles from amide bond isosteres, to disulfide bond mimics, to versatile linchpins for cross-linking various biomolecular entities to peptide structures. Conception of biocompatible approaches for their construction has liberated triazole synthesis from conventional organic methods to empower applications inside live cells to study dynamic biological phenomena.

## Volume II

In contrast to Volume I, which focuses predominantly on the local constraints of heterocyclic amino acids, dipeptides, and five-membered ring systems, and their consequences on the global geometry and biological activity of peptides and proteins, Volume II focuses on larger peptide structures. For example, the syntheses of mimics of helices, sheets, and larger folded motifs are discussed in chapters focusing on techniques for their stabilization using multiple heterocycle ring constraints, nucleating units that template hydrogen bonds, as well as cyclic peptides. Methods that assemble multiple rings from iminium ion intermediates are discussed in depth because of their power to add conformational constraint by a single step performed often on the peptide structure late in the synthesis. Peptide macrocycles are discussed within the context of their ability to adopt favored conformations, such as  $\beta$ -sheets. Novel methods for the effective synthesis of macrocycles are reviewed and focus is given to important biologically active macrocycle examples in medicinal chemistry oriented to deliver new antibiotics as well as therapeutics to treat maladies of misfolding, such as Alzheimer's and Parkinson's diseases. Finally, post-translational modification of peptides and proteins by heterocycle structures is discussed with specific focus on the heterocyclic disulfide lipoic acid.

## Brief Historical Perspective

The chemistry of peptide mimicry finds origins in pioneering research on heterocycles, amino acids, and peptides. Scholarly appreciation of contemporary research on peptidomimetics in synthetic laboratories around the world at the moment necessitates a knowledge of the relevance of seminal chemistry, much of which was developed over a hundred years ago, to the foundation of modern method discovery. In our age of search engines that tend to juxtapose information without concern for chronological order, the student engaged in the science of peptide mimicry may feel somewhat lost swimming in the sea of knowledge without historical perspective. In this light, the authors of individual chapters

have made important efforts to place research into context by summarizing key discoveries. For the interest of full pedagogic disclosure, some relevant background is now provided with citations to key publications and review articles that may offer a broader stage on which the interested student may build a core of knowledge regarding the origins of heterocycles in peptide mimicry.

The age of the discovery and the characterization of twenty one of the amino acids from proteins started in 1820, when Braconnot isolated glycine from gelatin and continued steadily until the early 1920s when Mueller announced the discovery of methionine from casein [34]. Several milestones in amino acid and peptide science were accomplished during this time period. In particular, one of the first multicomponent reactions was developed by Strecker, who synthesized  $\alpha$ -amino nitriles in 1850 [35]. Soon thereafter, Limpricht used this process to synthesize racemic leucine from hydrolysis of the product from valeraldehyde, ammonia, and hydrocyanic acid [34]. Moreover, between 1881 and 1906, Curtius and Fischer employed respectively acid azides and acyl chlorides to make the amide bonds of the first synthetic peptides [36]. During the following hundred years, the science of peptide chemistry was transformed by synthetic methods. Heroic efforts to make important biologically relevant peptides led the way to modern technology for preparing libraries of peptide analogs and effective methods for the assembly of entire proteins from peptides fragments [37]. Key discoveries in the field during this transition included various protecting groups, coupling agents and solid supports [38], pioneering syntheses of oxytocin [39], insulin [40] and HIV protease [41], and revolutionizing technology such as peptide sequencing [42], Merrifield solid-phase synthesis [43], robotic synthesizers [44], and native-chemical ligation [45]. The advent of solid-phase synthesis ushered in the age of peptide analog synthesis, in which residues in the sequence were commonly replaced by other natural and later synthetic amino acids to gain insight into structure-activity relationships [46]. Scanning techniques began to be employed using systematic replacement of each residue of the sequence by a particular amino acid, such as alanine or proline, to gain respectively insight into the importance of side chains and conformation for biological activity [47]. To improve peptide metabolic stability, attention has been turned towards applications of amidation, acylation, *N*-methylation, and cyclization [48], as well as backbone modifications using amide isosteres [49], and replacement of the  $\alpha$ -carbons of amino acid residues with nitrogen in so-called azapeptides [50].

In the 1980s, perception in peptide science changed significantly as the application of heterocycle chemistry to control conformation took root. In 1980, Freidinger and Veber demonstrated the power of  $\alpha$ -amino lactams for controlling peptide conformation to identify a biologically active conformer and enhance biological activity [26, 51, 52]. Implementation of azabicyclo[X.Y.0]alkanone amino acids to control peptide folding and orient pharmacophores soon followed [27–32]. Industrial interest in harnessing peptides for applications in medicine drove the use of heterocycles to study peptide structures as conformational constraints of the parent sequence [26], in de novo designs of peptidomimetics [53, 54], and in privilege structures that interacted effectively with multiple receptors that bind endogenous peptide ligands [10–14]. Moreover, academic interest gave rise to several designs

of heterocycle templates that nucleated peptide secondary structures [7, 55, 56], such as  $\beta$ -turns [57],  $\beta$ -sheets [58], and  $\alpha$ -helices [59]. In addition, the concept of forming side chain to side chain bridges (commonly referred to as “stapled” peptides [47]) was formulated in the 1980s and applied to stabilize  $\alpha$ -helical conformations [60]. This decade was particularly rich with innovation for the synthesis of heterocyclic peptidomimetics and paved the way for many creative designs in the decades that followed.

The two treatises that follow provide background on the developments of the field of heterocycles in peptide and protein science since these pioneering discoveries highlight state-of-the-art achievements that define the future to come. In this light, the field of heterocyclic peptidomimetics has grown significantly from its roots in natural product isolation and medicinal chemistry. Analogous to the way methods for peptide synthesis provided impetus for the creation of novel reagents, reactions, and techniques that have advanced the field of organic chemistry in general, modern approaches for assembling heterocycles effectively in the presence of the diverse functional groups common in peptide structures are now influencing the exploration of various domains including chemical biology, materials science, catalysis, and nano-technology.

Montréal, QC, Canada

William D. Lubell

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Peptidomimetics I

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