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Editorial

Peptide Chemistry

Introduction. Since its early origins in endogenous natural hormone synthesis, innovation in peptide science continues to shape the practice of synthetic and analytical chemistry, due to inherent challenges to assemble these polyfunctional molecules and their abundant applications in various fields including medicine, materials science, catalysis, and nanotechnology. Peptide chemistry encompasses a broad variety of subjects as was evidenced by the >750 references featuring the subject during the period analyzed (January 2011 to mid-June 2012) for this joint virtual issue of articles originally published in *The Journal of Organic Chemistry*, *Organic Letters*, and *The Journal of the American Chemical Society*. Apologies are made, because this survey has by necessity been limited and subjective and no doubt misses relevant research that merits equal time in the spotlight. In the hope of providing the readership with a greater appreciation of the growing impact of the field and the players of peptide chemistry, this cross-section has been made to highlight modern trends, rising stars and novel innovations. Publications have been broadly organized into methods, targets, and applications research, although the reader may quickly recognize considerable overlap in these categories.

Methods. Among the important advances in modern peptide chemistry, the advent of native chemical ligation (NCL) has greatly impacted on the size and molecular diversity of targets and has brought into being the field of protein total synthesis.[1−9] Key for NCL is the reaction of peptide thioesters with thiol-containing (e.g., cysteinyl) peptides involving thiol−thioester exchange followed by acyl migration from sulfur to nitrogen to form a native peptide bond. Multiple innovations to enhance this method and uses of NCL to attack more challenging targets have been recently reported in *The Journal of Organic Chemistry*, *Organic Letters*, and *The Journal of the American Chemical Society*. In particular, recent efforts have focused on new methods for preparing thioester electrophiles,[1−5] thiol nucleophiles (as well as their selenol counterparts),[6−9] and more complex peptide and protein targets.

Key for successful NCL, the reactivity of peptide thioesters has also hamstringed their synthesis by conventional solid-phase Fmoc-based methods because of their susceptibility to cleavage during deprotection using nucleophilic bases like piperidine. Three strategies have been recently employed to surmount the issues of solid-phase peptide thioester synthesis by an Fmoc-based strategy. Several reports have taken advantage of pH control to affect N- (or O-) to S-acyl migration, such that a peptide amide (ester) is first prepared on resin and subsequently converted to the thioester by rearrangement.[1−5] For example, the Melnyk laboratory has explored solid-phase protocols for the synthesis of bis(2-sulfanylethyl)amido peptides using Fmoc-protection.[1] After cleavage, the amides are equilibrated in aqueous solution to the corresponding *S*-2-(2-mercaptoethylamino)ethyl thioester peptides by way of an N- to S-acyl shift mechanism. Subsequent exchange with 3-mercaptopropionic acid under mild acid conditions

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(4) Sharma, I.; Crich, D. Direct Fmoc-Chemistry-Based Solid-Phase Synthesis of Peptidyl Thioesters. *J. Org. Chem.* **2011**, *76*, 6518–6524.

(5) Raz, R.; Rademann, J. Fmoc-Based Synthesis of Peptide Thioesters for Native Chemical Ligation Employing a *tert*-Butyl Thiol Linker. *Org. Lett.* **2011**, *13*, 1606–1609.

(6) Siman, P.; Karthikeyan, S. V.; Brik, A. Native Chemical Ligation at Glutamine. *Org. Lett.* **2012**, *14*, 1520–1523.

(7) Malins, L. R.; Payne, R. J. Synthesis and Utility of β-Selenol–Phenylalanine for Native Chemical Ligation–Deselenization Chemistry. *Org. Lett.* **2012**, *14*, 3142–3145.

(8) Ding, H.; Shigenaga, A.; Sato, K.; Morishita, K.; Otaka, A. Dual Kinetically Controlled Native Chemical Ligation Using a Combination of Sulfanylproline and Sulfanylethylanilide Peptide. *Org. Lett.* **2011**, *13*, 5588–5591.

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afforded thioesters suitable for NCL. Peptide thioesters have also been prepared by application of a thioamide linker to the resin during solid-phase synthesis, followed by S-alkylation and solvolysis of the resulting thioimidate.[4] Finally, the exceptional stability of *tert*-butyl thioesters against nucleophilic bases and strong acids, and their reactivity to thiolates, was employed by Raz and Rademann, who developed the 4-mercapto-4-methylpentanol linker, which allowed standard Fmoc-solid phase synthesis followed by cleavage with 3-mercaptopropionic acid methyl ester in the presence of sodium thiophenolate to give peptide thioesters in high purity (>90%) and good yield (65−90%).[5]

Cysteine served as an initial thiol nucleophile in NCL to link unprotected peptide segments and assemble larger peptides and protein structures, which folded into their natural states. Although cysteine is common in peptides, many targets lack this residue, requiring innovation of alternative thiols and selective chemical methods for removing the thiol after ligation.[6−9] Inspired by the reductive cleavage of the carbon−sulfur bond of cysteine to provide an alanine residue, new strategies have involved synthesis of thiol- and selenol-bearing phenylalanine and proline analogues for ligation at these residues.[7−9] Such methods entail elegant synthetic methodology to prepare the modified amino acid in a form suitable for incorporation into the peptide and chemoselective methods for removing the sulfur (selenium) appendage after NCL. Illustrating such challenges, a method for NCL at glutamine (Gln) residues has been developed by the laboratory of Brik.[6] Ligation at Gln is of interest due to its high abundance in protein sequences. Through preparation and application of protected γ-mercaptoglutamine, several ligations were performed, including the synthesis of a WW-domain, by NCL followed by desulfurization using nickel boride. The method offers potential for preparing poly-Gln repeats in proteins, which are involved in neurodegenerative disorders, such as Huntington's disease.

Although peptide synthesis with common proteinogenic amino acids can be performed effectively using contemporary coupling agents, sterically hindered residues such *N*-methyl and Cα-methyl amino acids represent challenging building blocks to introduce into linear sequences. Collaboration between Albericio, Kaminski, and co-workers has produced 4-(4,6-di[2,2,2-trifluoroethoxy]-1,3,5-triazin-2-yl)-4-methylomorpholinium tetrafluoroborate (DFET), a novel coupling agent for assembly of challenging sterically hindered sequences.[10] In comparative solid-phase syntheses of Leu-enkephalin analogues in which the Gly-Gly fragment of the pentapeptide was replaced by Aib-Aib (Aib: α-aminoisobutyric acid), *N*-methylvaline-*N*-methylvaline, and *N*-methylleucine-*N*-methylleucine sequences, the triazine reagent outperformed the commonly used aminium salt 2-(1*H*-benzotriazole-1- yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), providing product of greater purity and higher yield.

Two chemical reactions, ring-closing metathesis (RCM)[11−13] and copper-catalyzed azide−alkyne cycloaddition (CuAAC),[14−19] have become mainstays in peptide science with abundant applications in the reviewed literature, particularly for the preparation of macrocycles and peptidomimetics. For example, Kong, Chen, and co-workers have developed a practical RCM protocol for the preparation of Vaniprevir, a potent NS3/4a protease inhibitor under late stage clinical evaluation for the treatment of hepatitis C virus.[13] The 20-membered macrocycle of the inhibitor was constructed by RCM employing slow catalyst addition, low catalyst loading, and relatively high concentrations to achieve high yield for a scalable, cost-effective synthesis of Vaniprevir. For the synthesis of templates to nucleate turn and β-hairpin structures, Zhao, Li and co-workers have employed the CuAAC reaction to prepare 1,4-dialkoxyphenyl-1,2,3-triazoles, which were shown by X-ray crystallography to adopt a planar geometry featuring two intramolecular six-membered ring C5−H···O hydrogen bonds.[18] Additional investigation using NMR spectroscopy in chloroform demonstrated that the U-shaped conformation adopted by the 1,4-diaryltriazole mediated intramolecular N−H···O hydrogen-bonding in the shortest of β-sheet structures. Moreover, a thermal Huisgen azide−alkyne cycloaddition was employed by Ballet and coworkers for the preparation of a constrained histidine dipeptide mimic, which was used to replace the His-Pro dipeptide segment in angiotensin IV (Val-Tyr-Ile-His-Pro-Phe-OH) to provide an inhibitor of insulin regulated aminopeptidase and aminopeptidase-N with equal potency to the native peptide.[19]

For peptide macrocycle synthesis, Londregan and coworkers have introduced a novel strategy for cyclization

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offering broad substrate scope.[20] Carboxylates bearing a pyridine-*N*-oxide were attached to the sequence *N*-terminal after iterative peptide synthesis. The pyridine-*N*-oxide was then activated using the phosphonium salt PyBroP (bromo-tris-pyrrolidinophosphonium hexafluorophosphate) to effect macrocyclization by nucleophilic attack of tethered natural amino acid side chains: phenol of tyrosine, alkylamine of lysine, and imidazole of histidine. Relative to their linear counterparts, the resulting 2-substituted pyridine macrocycles exhibited improved passive cellular membrane permeability and increased lipophilicity, favorable characteristics for improving peptide oral bioavailability.

For the study of structure–activity relationships, peptide mimicry, and enzyme inhibition, a variety of surrogates of the amino acid structure have been recently synthesized, including α-amino thioamides,[21] selenoamides,[22] and phosphinic acids,[23] as well as *N*-aminosulfamides.[24] The challenges of making such unnatural analogues and introducing them into peptide structures is illustrated by the synthesis of dialkylsilanediol dipeptide analogues reported by the Sieburth laboratory.[25] These tetrahedral mimics of hydrated carbonyls have served as hydrolytically stable protease inhibitors when embedded in peptide structures. Preparation of a silanediol precursor was accomplished by an intramolecular enantioselective hydrosilylation to set the β-silyl acid stereochemistry, a novel silyl ether reduction to afford an alkoxy silyl anion, and diastereoselective addition of the resulting dianion to a sulfinimine. Alcohol oxidation gave the fully functionalized dipeptide mimic with stereocontrol for subsequent introduction into peptide inhibitors.

Applications of two classes of amino acid analogues, β-amino acids[26−29] and *N*-substituted glycines, so-called peptoids,[30−33] have been significant in recent years due in part to the relative ease of synthesis of their oligomers, as well as their interesting structural and physical properties. For example, the DeGrado laboratory has demonstrated that peptides comprised exclusively of β-amino acid residues can switch between 12- and 14-helical structures in an environment- and sequence-dependent manner.[26] Employing a combination of synthesis, circular dichroism (CD) spectroscopic analysis, and computational modeling, 26-residue β-peptides were prepared, shown to adopt predominantly 14-helical conformations in trifluoroethanol, and contingent on sequence, were found to interconvert to a predominantly 12-helical conformation in dodecylphosphatidylcholine micelles. Understanding of the factors influencing such conformational dynamics is expected to have practical implications for the application of β-amino acids in molecular recognition. With respect to the latter topic, Murphy, Gellman, and coworkers developed a strategy for improving peptide stability to protease degradation featuring employment of β-amino acids to examine inhibitors of protein–protein recognition surfaces.[29] Antagonists of the interactions between vascular endothelial growth factor (VEGF) and its cell-surface receptor tyrosine kinases were targeted because they can inhibit angiogenesis and serve as therapeutics to treat cancer and wet macular degeneration. Commencing with a natural peptide lead inhibitor of VEGF-stimulated human umbilical vein endothelial cell proliferation, a systematic β-amino acid scan of the sequence was performed to identify positions at which the homologated residue was tolerated. Subsequently, VEGF signaling antagonists possessing around 30% β-amino acid were prepared exhibiting no toxicity and significantly decreased protease susceptibility.

Among many innovative applications of peptoids,[30−33] the recent research of Zuckermann, DeYoreo, and coworkers has broad potential particularly in the fields of nanotechnology and materials science.[31] Two-dimensional sheet forming peptoid bilayers have been made using a versatile synthetic platform for adding multiple functions with precise order to the nanostructures.[30] Moreover, these non-natural biomimetic polymers have been shown to mimic peptides and proteins in the mineralization of $CaCO_3$.[31] Automated synthesis of a set of amphiphilic peptoids gave members exhibiting dramatic effects on calcite growth morphology, as well as an

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unprecedented 23-fold acceleration of growth at low concentration. Peptoids thus offer new potential for reducing greenhouse gases, because they can facilitate carbon dioxide sequestration.

Another class of amino acid surrogates growing in importance is the aza-analogue in which the CHα of a residue is replaced by nitrogen.[34−36] The resulting aza-peptide possesses a semicarbazide residue, which can induce conformational rigidity, increase potency, and improve favorable druglike properties. Employing an aza-scan of each residue of the sequence of a peptide inhibitor of the persistently activated protein kinase B, Gilon and co-workers demonstrated microwave irradiation as an effective means for significantly reducing reaction time to couple efficiently *N*-Fmoc-aza-amino acid chlorides.[36]

Peptide mimicry is used to create probes to explore folding, recognition, and fundamental properties in peptide chemistry as well as to make candidates for antagonizing protein−protein interactions in drug discovery.[37−46] The recently published literature in *The Journal of Organic Chemistry*, *Organic Letters*, and *The Journal of the American Chemical Society* features abundant examples of peptidomimetics, including mimics of disulfide bridges,[39] proline ring puckering,[40] secondary structures such as turns,[41,42] helices,[43,44] and sheets,[45,46] as well as larger protein surfaces. Mimics of the α-helix secondary structure are important targets because the motif is abundant in biologically active proteins and well suited for molecular recognition because of its outward projection of amino acid side chains in a regular pattern. Moreover, rigid helix mimics are needed because isolated peptides typically lack the ability to spontaneously adopt the helical conformation. Expanding on previous research employing bicyclic indane, terphenyl, and benzoylurea motifs as helix mimics, Adler and Hamilton prepared enaminone scaffolds by addition of anilines to ynones in order to improve solubility over earlier scaffolds.[44] Crystal structure analysis showed the size and shape of the enaminone scaffolds was viable for mimicry of the distances between side chains at the *i*, *i*+4, and *i*+7 residues of a helix and comparable to terphenyl counterparts. β-Sheets are found in natural antimicrobial macrocyclic peptides, such as gramicidin S. Macrocyclic peptide mimics adopting β-sheets have also been used as receptor ligands and enzyme inhibitors. Studying intermolecular β-sheet interactions to mimic protein quaternary structure, as well as to inhibit aggregation of amyloidogenic peptides,[45,46] Cheng and Nowick developed effective methodology for synthesizing 54-, 78-, and 102-membered-ring macrolactams by employing δ-linked ornithine β-turn mimics combined with the Hao tripeptide β-strand mimic.[45] The macrolactams were water-soluble, nonaggregating, and well-defined β-sheets, as observed by two-dimensional NMR spectroscopy in water.

Targets. Natural products containing peptide and modified peptide components are actively pursued for their challenging structures and intriguing activities, as illustrated by recent total and partial syntheses of largazole,[47,48] pacidamycin D,[49] petriellin A,[50] unguisin A,[51] complestatin A and B,[52] thiocillin I,[53] lysobactin,[54] cyclocinamide A,[55] sanguinamide B,[56] burkholdac B,[57]

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lucentamycin A,[58] microcin B17,[59] and their respective analogues. Illustrating the importance of synthetic chemistry for assignment of natural product structure as well as an elegant route to substituted proline analogues, Del Valle and co-workers report advances toward lucentamycin A.[58] Lucentamycins A−D comprise a novel family of nonribosomal tripeptides featuring an *N*-acylated homoarginine, a *C*-terminal leucine or tryptophan, and a central 4-ethylidene-3-methylproline residue, unprecedented in the natural product literature. Lucentamycin A has been claimed to inhibit in vitro growth of HCT-116 human colon carcinoma cells. Substituted alkylidene prolines were made by an ester enolate−Claisen rearrangement in which the chairlike transition state set both stereocenters and the pendant alkene geometry. Total synthesis of four lucentamycin A isomers revealed the natural product structure requires revision.

Antimicrobial peptides possess clinical interest because of their potency and potential to kill resistant strains of microorganisms.[60−64] Antimicrobial peptides, such as nisin A, merit interest in nutrition and agriculture because they are natural, toxicologically safe, antibacterial food preservatives. Mersacidin is a 20-residue polycyclic lantibiotic peptide that possesses promising antibacterial activity against problematic Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, which are resistant to common antibiotics. Pursuing the synthesis of mersacidin, Carrillo and VanNieuwenhze report the construction of the D-ring, which contains the unusual amino acid *S*-[(*Z*)-2-aminovinyl]-(3*S*)-3-methyl-D-cysteine, by a late-stage introduction of the enamide subunit, via oxidative decarbonylation promoted by diphenylphosphoryl azide or oxidative decarboxylation using $Pb(OAc)_4$.[60] Another peptide with broad spectrum bactericidal activity is sublancin 168, which contains 37 amino acids and a novel S-linked glycan. Employing an NCL-based strategy, Payne and co-workers prepared the native D-glucose containing glycopeptide, as well as two non-natural analogues bearing D-galactose and D-*N*-acetylgalactosamine at cysteine-22.[62] Insight to explain the similar antimicrobial activity observed for differentially *S*-glycosylated sublancin 168 analogues was obtained from NMR and CD spectroscopic studies, which showed the overall peptide conformation was unaffected by the identity or presence of a glycan moiety. To harness antimicrobial peptides exhibiting membrane-lytic activity for combating pathogens and cancerous tissues without side effects such as hemolytic activity, pH-sensitive membrane-active peptides have been designed to activate under acidic conditions that protonate Glu or Asp side chains. Employing L-tetrafluorotyrosine (L-f4Y), Gao and co-workers introduced pH sensitivity to milder acidic conditions into the membrane-lytic peptide magainin 2.[63] Protected L-f4Y was synthesized from commercially available L-pentafluorophenylalanine employing a regioselective nucleophilic addition−elimination of sodium allyloxide and used to replace the three phenylalanines of magainin 2. The resulting analogue lysed membranes at pH 5.0 but had no damaging activity under neutral pH at relatively high peptide concentration.

Cyclotides are plant-derived peptides that possess a knotted structure due to the combination of their head-to-tail cyclic backbone and three disulfide bonds. Possessing exceptional stability to heat and resistance to enzymatic degradation, cyclotides are natural plant defense agents that exhibit pesticide activity as well as druglike properties including uterotonic, anti-HIV, antitumor, and antimicrobial activity, albeit with undesirable toxicity, such as hemolytic and cardiotoxic effects. In a perspective written with Conibear, the 2012 Josef Rudinger Memorial Award recipient Craik presents a detailed overview of cyclotide chemistry, biology, and perspective applications, illustrating their novel structure and promising potential as sources of agricultural and medicinal products.[65]

Investigation of the assembly of peptide natural products has led to characterization of nonribosomal peptide synthetases (NRPS) with the goal of harnessing these biological factories for analogue synthesis. In this vein, Tang and co-workers have isolated from *Aspergillus terreus* NRPS325, which was employed in the synthesis of 63 different thiol-substituted pyrazines from combinations of two molecules of amino acid and one molecule of thiol.[66] The broad substrate specificity of NRPS325 was demonstrated by efficient incorporation of unnatural amino acids, such as trifluoroleucine and azidohomoalanine, into the pyrazine scaffolds.

Applications. Peptide nucleic acids (PNAs) are nucleic acid mimics in which the naturally occurring sugar phosphodiester backbone is replaced with *N*-(2-aminoethyl)-glycine units. Exhibiting strong affinity and sequence

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selectivity toward DNA and RNA, as well as resistance to enzymatic degradation by proteases and nucleases, PNAs have served as regulators of gene expression, codes in drug discovery, amplifiers of genetic information, and organizers in self-assembly. Their utility has, however, been limited by poor water solubility and tendencies to aggregate and bind nonspecifically. Modifications to improve PNA solubility have often reduced binding affinity, decreased sequence specificity, and demanded tedious syntheses. Positioning diethylene glycol units onto the PNA backbone, Ly and co-workers have devised a practical solution for making water-soluble PNA.[67] Employing L-serine as the building block, enantiomerically pure PNAs were created bearing different levels of diethylene glycol, which improved aqueous solubility, enhanced ability to hybridize sequence selectively with DNA and RNA, as well as diminished tendencies for aggregation and nonspecific binding relative to the parent PNA.

Peptides can be tools for intracellular cargo delivery in applications, such as imaging, molecular biology, and gene therapy. For example, proline-rich collagen was found to transport plasmid DNA and siRNA into cells. Building on earlier studies on complexes between DNA and 4-aminoproline collagen mimics, Nanda and Ganesh developed 4-guanidinylproline collagen analogues, which were observed by CD spectroscopy to adopt single chain poly proline-II helices, instead of aggregated coiled-coils.[68] The 4-guanidinylproline peptides condensed DNA effectively and enhanced cellular transfection efficiency providing higher reporter gene expression in cells without apparent cytotoxicity compared to commercial agents.

For the creation of new catalysts, peptides are promising scaffolds because their structures can be readily modified to tune properties such as selectivity and turnover. Exploring enantioselective epoxidation, Romney and Miller embedded a trifluoromethyl ketone into a peptide turn motif to develop competent catalysts, which employ dioxirane intermediates.[69] Selectivity was amplified by varying the peptide sequence to provide proof-of-concept catalysts, which epoxidized a set of seven alkenes with high yield and enantioselectivity (up to 91:9 er).

Peptides are inspiring natural ligands and candidates of choice for probing biological receptors. For example, relaxin-3 is a two-chain disulfide-rich peptide, structurally related to insulin. Highly expressed in the mammalian brain together with its G protein-coupled receptor (RXFP3), relaxin-3 has suggested roles in sensory, emotional, and neuroendocrine processing, with links to controlling behavioral states, such as stress, metabolic regulation, circadian activity, and brain rhythms. The lack of selective antagonists has, however, impeded characterization of the neurological function of relaxin-3 and validation of RXFP3 as a pharmaceutical target, in part because the native peptide activates three different receptors (RXFP1, RXFP3, and RXFP4). Moreover, the complex two-chain structure of relaxin-3 requires tedious multistep strategies for analogue synthesis. Collaboration between Swedish and Australian laboratories led by Rosengren has prepared a readily synthesized single chain linear 23-amino acid peptide antagonist that exhibits receptor subtype selectivity and high-affinity for RXFP3.[70] This selective probe for exploring the role of the relaxin-3/RXFP3 interaction in neural signaling offers potential for developing pharmaceuticals to target RXFP3 for treatment of psychiatric diseases involving this receptor.

Through the development of innovative strategies for constructing structures of remarkable complexity and diversity, peptide chemistry has impacted heavily on the manner organic synthesis is performed and organic molecules are purified and characterized. Inspired by Nature, in which peptides perform abundant activities, peptide chemistry has been a fruitful source of innovation for various fields, including medicine, agriculture, materials science, and nanotechnology. The diverse methods, targets, and applications presented in this virtual issue demonstrate clearly the importance of peptide chemistry in contemporary research and future scientific exploration.

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