

Designed molecules that fold to mimic protein secondary structures

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Molecules that fold to mimic protein secondary structures have emerged as important targets of bioorganic chemistry. Recently, a variety of compounds that mimic helices, turns, and sheets have been developed, with notable advances in the design of β -peptides that mimic each of these structures. These compounds hold promise as a step toward synthetic molecules with protein-like properties and as drugs that block protein–protein interactions.

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Introduction

Naturally occurring proteins are materials and molecular devices with properties that currently we can only dream of achieving in the laboratory. Spider silk is stronger than steel. Bacterial flagella are microscopic motors smaller than those fabricated by man. Enzymes catalyze reactions at fantastic rates and with great selectivity. Proteins achieve these functions by folding into compact, well-ordered structures. The formation of these tertiary and quaternary structures, in turn, depends on the formation of stable secondary structures. In proteins, common secondary structures consist of α -helices, turns, and β -sheets. Each of these structures plays a role in the various functions of proteins.

In the quest to understand, control, and mimic the actions of proteins, many chemists have first turned to the more basic idea of mimicking secondary structures. Abiotic oligomers that can fold into compact, well-ordered structures might allow chemists to not only duplicate nature by developing functional macromolecules, but also to transcend nature by developing molecules with superior properties. These compounds can offer novel structures, improved bio-availability, and greater thermodynamic stability. In this review, we describe synthetic compounds that mimic natural protein secondary structures and focus on work published during the past two years. The reader is directed to three prior reviews for coverage of earlier work [1,2,3••].

Helices

α -Helices are ubiquitous secondary structural elements that participate in protein–protein and protein–nucleic-acid recognition. Compounds that mimic α -helices are important targets in drug discovery because they can serve either as scaffolds that present protein-like functionality in

an organized fashion or as antagonists that block protein–protein interactions. During the past two years, fervent research efforts have focused upon the creation of β -peptides, γ -peptides, and δ -peptides and related compounds that adopt structures reminiscent of α -helices. A variety of other oligomers that fold into helical structures have also been reported.

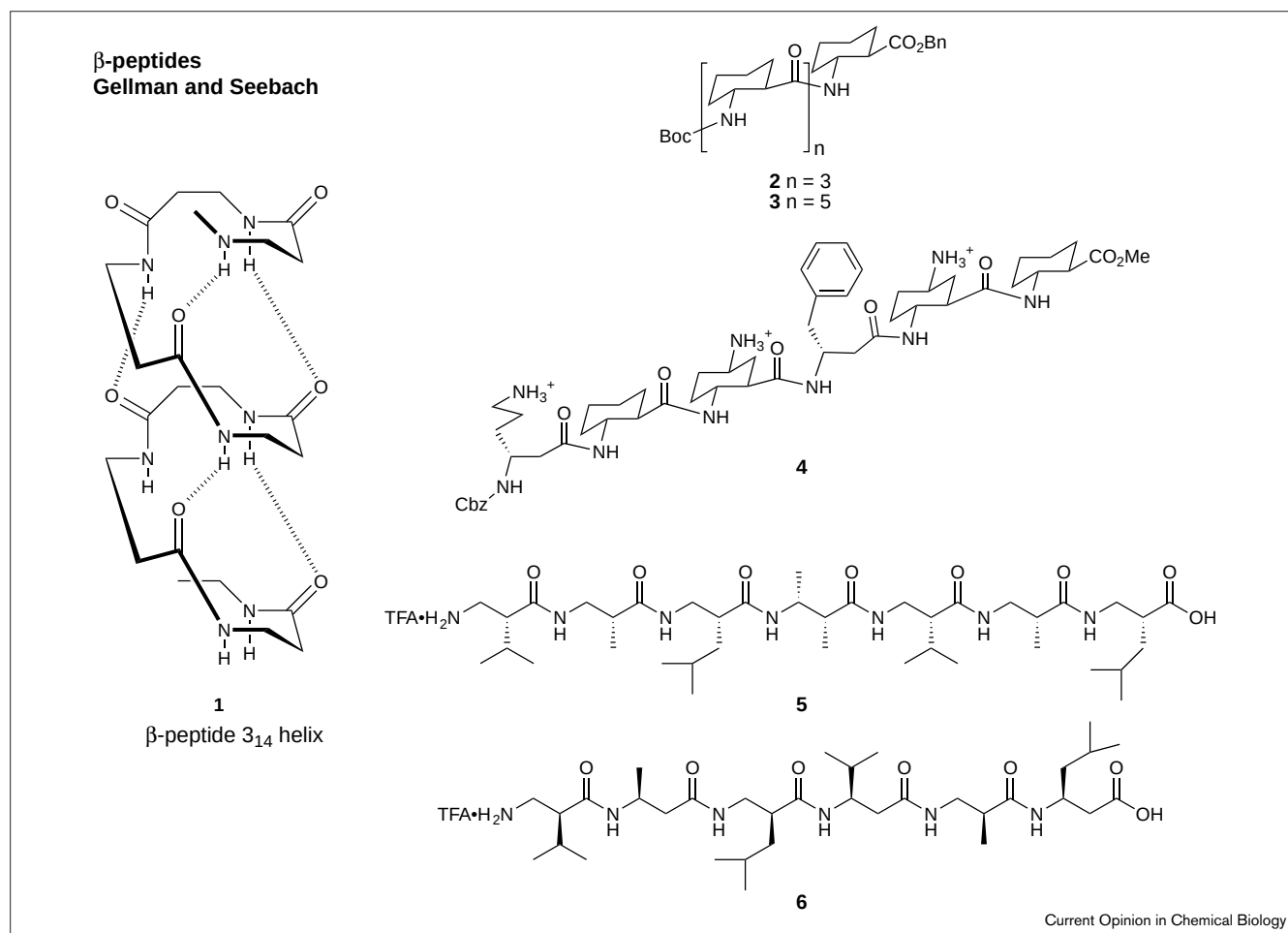
In pioneering studies, the Gellman and Seebach groups [4–6] independently produced helical oligomers based upon β -peptides in 1996. Unlike conventional peptides, which are composed of α -amino acids, β -peptides are composed of β -amino acids. These compounds form stable 3_{14} helices (Figure 1; **1**), containing three β -amino acid residues per turn, in which the amino group of each residue (*i*) hydrogen bonds to the carboxyl group of the second neighbor residue toward the carboxyl terminus (*i* + 2) to form a 14-membered hydrogen-bonded ring [(*i*) NH...O=C (*i* + 2)].

The Gellman group's first β -peptides consisted of oligomers of *trans*-2-aminocyclohexanecarboxylic acid. Crystal structures of the tetramer (**2**, *n* = 3) and hexamer (**3**, *n* = 5) verified the solid-state helical conformation [7••]. Extensive packing interactions of the cyclohexane rings of the hexamer suggest that tertiary structures based on these helices may be developed. Gellman and co-workers [8••] have recently reported the synthesis of a water-soluble β -peptide that maintains a stable 3_{14} helix in aqueous solution (**4**). This structure incorporates functionalized side chains, laying the groundwork for creating bio-active β -peptides with defined secondary and tertiary structures. Other water-soluble β -peptides have also been developed [9•].

Seebach *et al.* [4,5] have investigated oligomers of acyclic β -amino acids, which although ostensibly more conformationally mobile than the cyclic β -amino acids investigated by Gellman [6], also form helices. Oligomers composed of acyclic β -amino acids, such as **5**, form a 3_{14} helix similar to **2** and **3** [4,5]. Differing substitution patterns of the acyclic monomers result in alternative helix conformations. For example, the β -peptide **6** adopts a 12/10/12 helix, in which the central hydrogen bond forms a 10-membered ring [(*i*) C=O...HN (*i* – 1)] and the terminal hydrogen bonds form 12-membered rings [(*i*) C=O...HN (*i* + 3)] [10•]. This helix can be viewed as incorporating two types of turns (see below). Seebach and co-workers [11] have begun to develop biologically active compounds that incorporate β -peptide groups and have found that nonapeptide analogues containing β -homalanine oligomers bind to a class I major histocompatibility complex protein.

Longer amino acid homologues have also begun to attract attention. The research groups of Hanessian and Seebach

Figure 1



β-Peptides that fold into helical structures. The β-peptides **2–5** fold into 3_{14} helices (**1**), whereas β-peptide **6** forms a 12/10/12 helix in which the outer turns are twelve-membered and the central turn is ten-membered. Bn, benzyl; Boc, *t*-butoxycarbonyl; Cbz, benzyloxycarbonyl; TFA, trifluoroacetic acid.

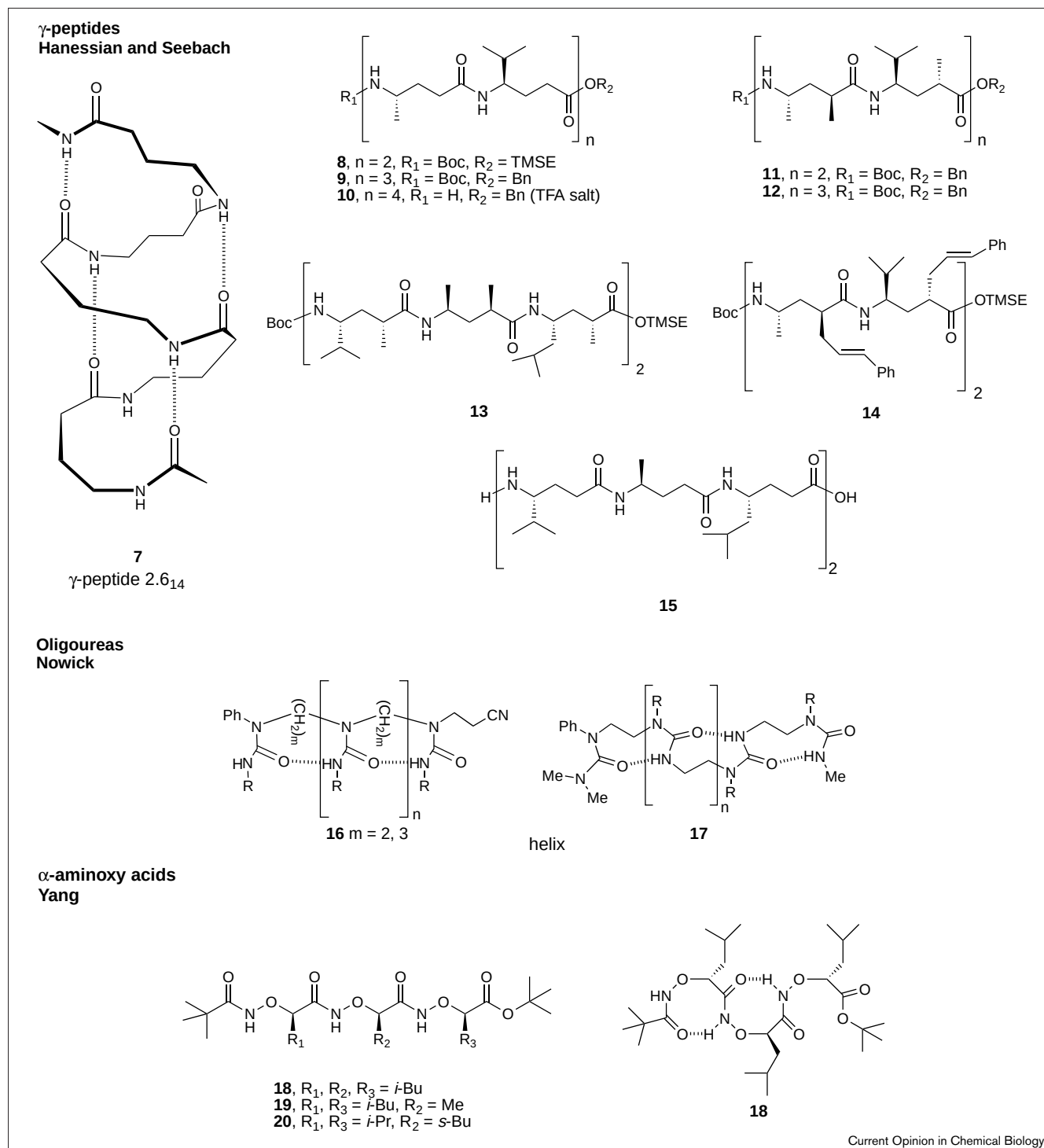
have independently reported that oligomers of γ -amino acids are also capable of forming stable helical structures (e.g. 2.6_{14} helix **7**, Figure 2). Hanessian *et al.* [12,13[•]] studied γ -peptides **8–14**, and Seebach and co-workers [14] studied **15**. NMR experiments, complemented by molecular modeling studies, demonstrated that **8–12**, **14**, and **15** adopt helical structures that contain 14-membered hydrogen-bonded rings [*i* C=O...HN (*i* + 3)]. γ -Peptide **13** does not adopt a helical structure because of unfavorable steric interactions between the sidechains.

One of the hallmarks of helices is that they have regular and repeating structures: each residue in the helix has the same relationship to the residues that come after it as the subsequent residue has to those that follow it (e.g. *i* is hydrogen bonded to *i* + 4; *i* + 1 is hydrogen bonded to *i* + 5, etc.). A number of unnatural oligomers exhibit this type of helix-like repeating structure, but do not form spiral structures, the other hallmark of helices. Building upon earlier

work on *N,N*-linked oligoureases (**16**), which form hydrogen-bonded repeating structures [15[•]], Wilson and Nowick [16[•]] have prepared *N,N'*-linked oligoureases (**17**). X-ray crystallographic studies indicate that these compounds form hydrogen-bonded helix-like structures in the solid state, whereas IR studies indicate that α -branched substituents enhance their hydrogen-bonded structure in chloroform solution (ME Wilson, JS Nowick, JW Ziller, unpublished data).

Yang *et al.* [17[•]] have developed another such structure consisting of α -aminoxy acids, which are analogues of β -amino acids. Oligomers of these aminoxy acids (e.g. **18–20**) form a helix made up of hydrogen-bonded eight-membered rings [*i* C=O...HN (*i* + 2)]. This is the smallest possible inter-residue hydrogen-bonded ring for a β -peptide analogue, and the β -peptide examples studied so far do not access such a conformation. The structure appears to be independent of the sidechain and characteristic even of short

Figure 2



Current Opinion in Chemical Biology

Hydrogen-bonding oligomers that form helices and helix-like structures. γ -peptides **8–12**, **14** and **15** form 2.6₁₄ helices (**7**). γ -peptide **13** does not form a helix due to unfavorable steric interactions. *N,N*-linked oligoureas **16** form a repeating hydrogen-bonded turn structure that can

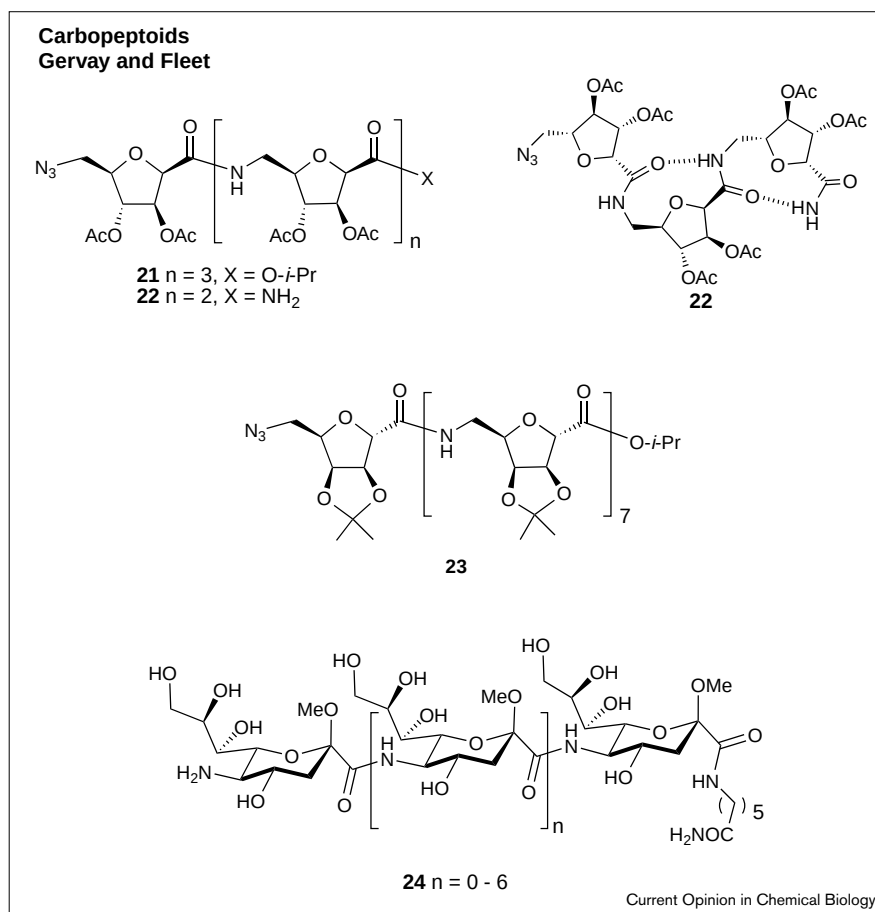
be used to hold peptide and peptidomimetic strands in proximity to form sheets. *N,N*-linked oligoureas **17** and α -aminoxy acids **18–20** form helix-like structures. Bn, benzyl; Boc, *t*-butoxycarbonyl; TFA, trifluoroacetic acid; TMSE, 2-(trimethylsilyl)ethyl.

oligomers. Toniolo, Wakamiya and co-workers [18] have reported 'flat peptides' based on C α , β -didehydro- α -amino acids that form flat helix-like structures.

Others have developed helix-like carbohydrate oligomers. Fleet and co-workers [19,20] have used sugar-based δ -amino acid oligomers **21–23** (Figure 3) to form two distinct

Figure 3

Carbohydrate oligomers that fold into helices. 1,4-*cis*-carbopeptoids **21** and **22** form repeating β -turn type helices, whereas 1,4-*trans*-carbopeptoid **23** forms a left-handed helix. Preliminary studies in aqueous solution suggest that all oligomers of **24** except the heptamer ($n = 5$) adopt an ordered secondary structure that may be helical. Ac, acetate.



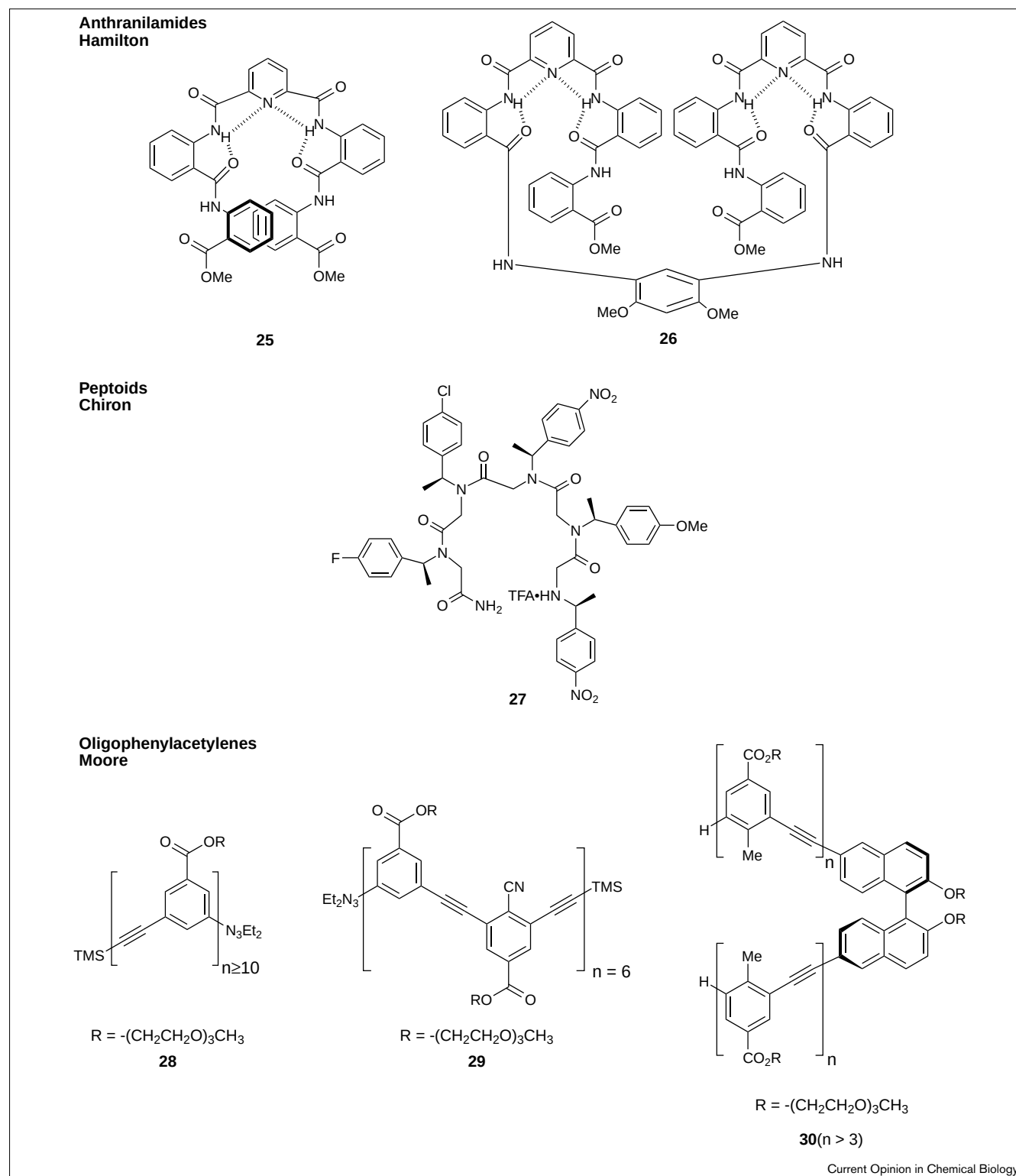
helices. The 1,4-*cis* tetramer and trimer (**21**, **22**) form a helix-like structure comprising hydrogen-bonded 10-membered rings [(*i*) C=O...HN (*i* + 2)] resembling a series of linked β -turns. The 1,4-*trans* octamer (**23**) forms a left-handed helix composed of 16-membered hydrogen-bonded rings [(*i*) C=O...HN (*i* + 3)] [21[•]]. Similarly, Gervay and co-workers [22] have used *N*-acetylneuraminic (NeuAc) acid as a naturally occurring, highly functionalized sugar-based δ -amino acid. Oligomers of NeuAc (**24**) are soluble in water, and preliminary NMR studies in aqueous dimethylsulfoxide solution suggest that all oligomers except the heptamer (**24**, $n = 5$) adopt an ordered secondary structure that may be helical. Their novel structures, high degree of functionality, ease of synthesis, and water solubility make these compounds attractive candidates for disrupting protein–protein interactions.

With the goal of developing synthetic macromolecules that can either catalyze reactions like enzymes or bind ligands like antibodies, Hamilton and co-workers [23,24[•]] have been developing hybrid oligomers that are based upon functionalized aromatic monomers. Oligomers of anthranilamide form strands; incorporating a pyridine-2,6-dicarboxylic acid monomer into the strand induces a turn [23]. Combining two turn units (**25**,

Figure 4) with a 1,5-dimethoxy-2,4-diaminobenzene linker creates a helix **26** [24[•]]. Hybrid oligomer **26** crystallized in two different morphologies, both of which have helical conformations containing extensive hydrogen bonding and π -stacking interactions.

Other oligomers fold into helix-like structures without hydrogen bonds. Since the early 1990s, researchers at Chiron Corporation (Emeryville, CA, USA; <http://www.chiron.com/>) have been investigating *N*-substituted glycine oligomers (peptoids), with the goal of developing biologically active compounds. In 1998, this team demonstrated that bulky chiral side chains give peptoids a helical structure [25^{••}]. These helices are particularly significant because their folding is not driven by intramolecular hydrogen bonding, so the structures are stable in competitive solvents. Notably, aqueous solutions of the pentapeptoid **27**, an oligomer of five (*S*)-*N*-(1-phenylethyl)glycines, have circular dichroism characteristics similar to those observed for peptide α -helices [26]. Because the tertiary amide groups make peptoids conformationally heterogeneous, several minor conformers are evident in the NMR spectrum of **27**. NMR and molecular modeling established that the structure of the major conformation is a right-handed

Figure 4

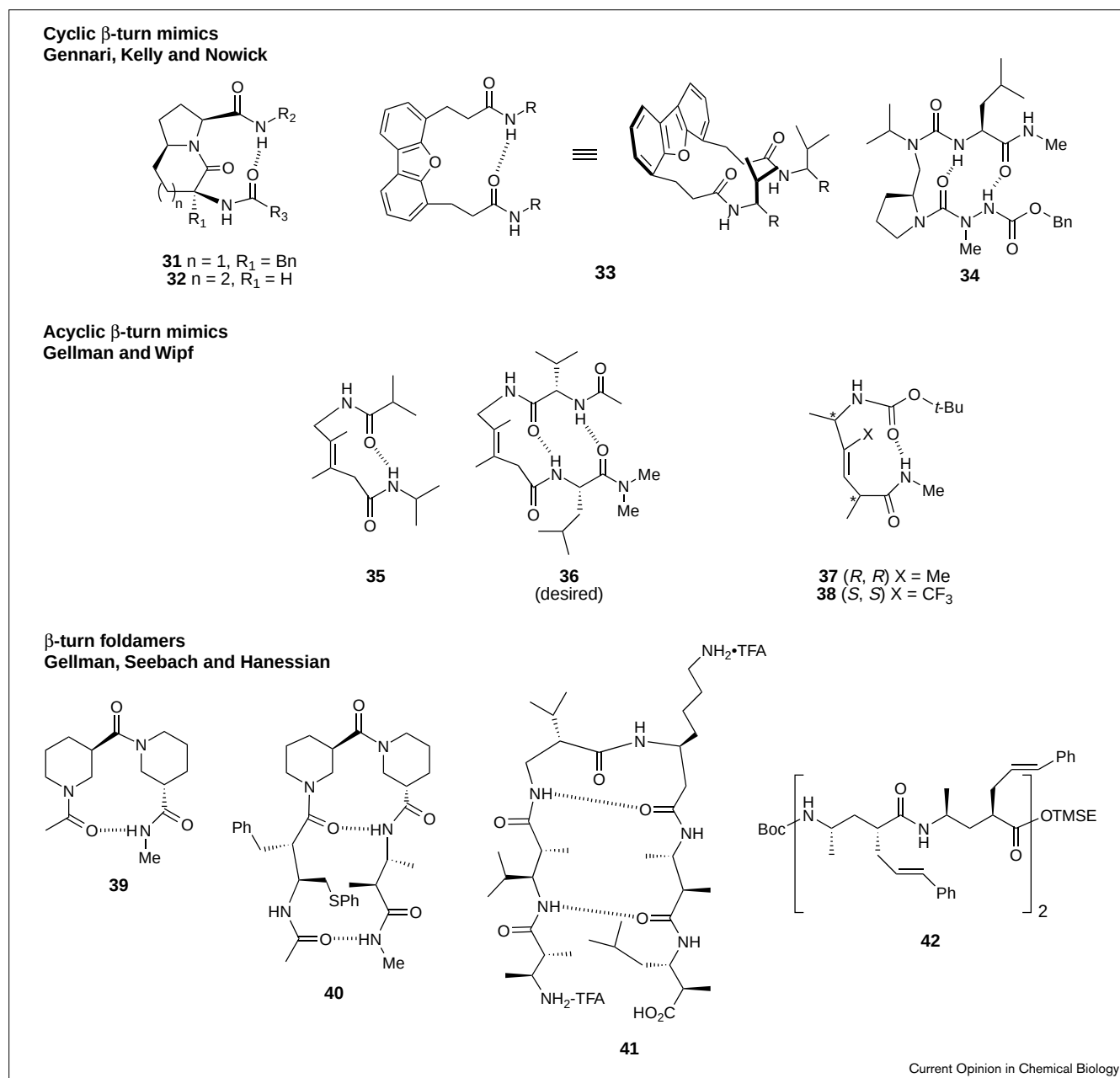


Other oligomers that fold into helices: anthranilamides **25–26**; a peptoid with bulky α -substituents **27**; and *meta*-phenylacetylenes **28–30**. TFA, trifluoroacetic acid; TMS, trimethylsilyl.

helix with three residues per turn. These helices may eventually lead to biologically active compounds, as SH3 and

WW domain proteins have been shown to bind polyproline II helices containing *N*-alkylglycine residues [27].

Figure 5



β -turn mimics that nucleate sheet structure. Cyclic turn units **31–34** are conventional β -turn mimics that nucleate sheets or sheet-like structures. Alternative turn units **35–38** depend on acyclic conformational control

effects (e.g. allylic strain). Homologated peptide oligomers that fold into turn structures (**39–42**) have also been reported recently. Bn, benzyl; Boc, *t*-butoxycarbonyl; TFA, trifluoroacetic acid; TMSE, 2-(trimethylsilyl)ethyl.

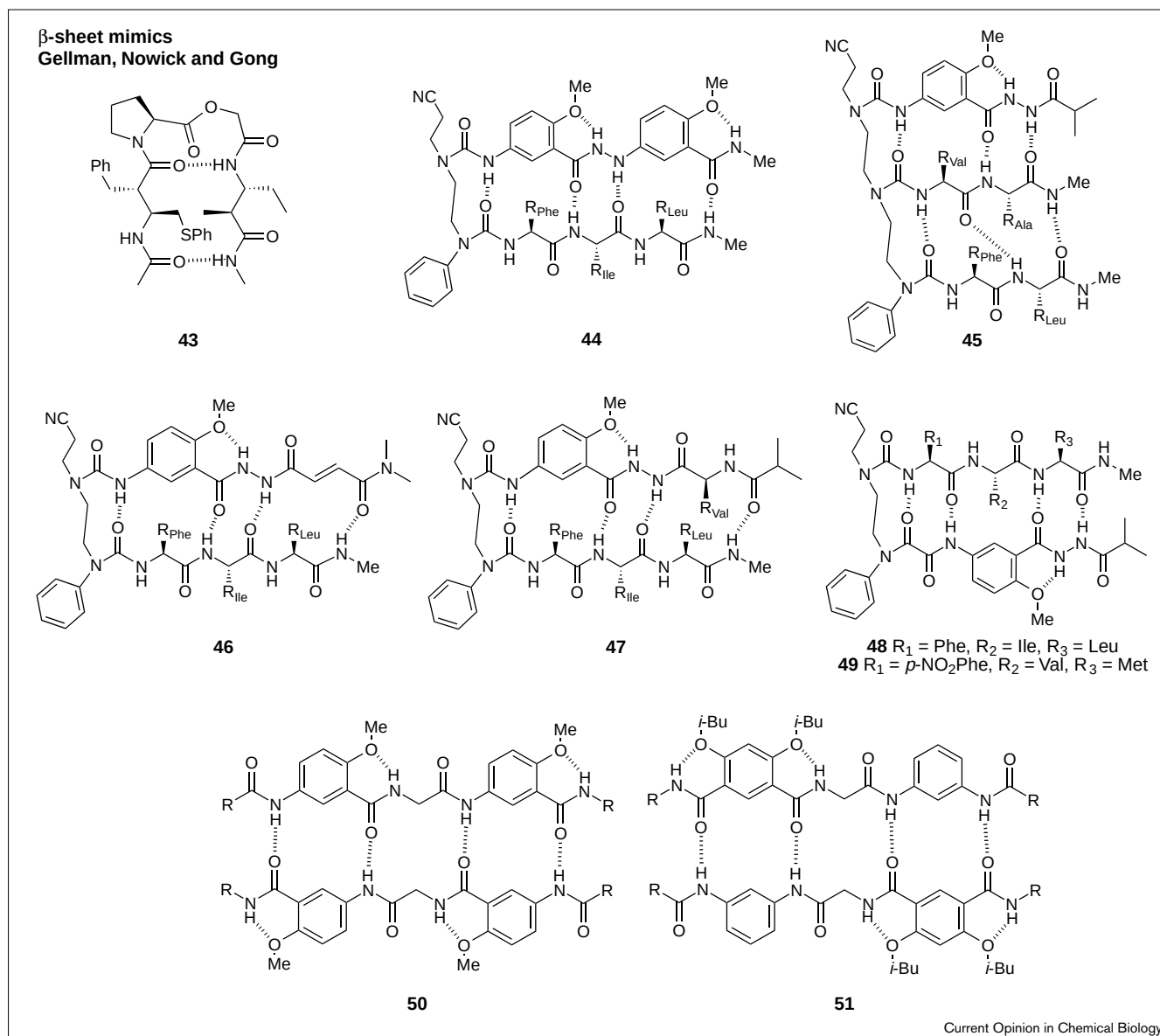
Moore and co-workers [28,29*] have designed another system that folds into a helix without hydrogen bonding. This system is based upon *meta*-phenylacetylene oligomers (**28**), which can fold if they comprise at least ten monomers. Solvophobic forces drive the folding; the octadecamer folds in polar solvents, such as acetonitrile, but not in less polar solvents, such as chloroform. In an interesting extension of this work, Moore and co-workers [30] synthesized oligomer **29**, which contains nitrile groups that induce

helix formation by binding two equivalents of silver ions in tetrahydrofuran solution. Oligomers **28** and **29** form racemic helices. To impart a chiral bias to the helix, Moore and co-workers [31] incorporated chiral binaphthol derivatives into the chain of oligomer **30**.

Turns

Turns are important targets for mimicry, both because they serve as recognition sites in peptides and proteins and

Figure 6



Molecules designed to mimic β -sheet structure. Compounds **43–47** mimic intermolecular β -sheet interactions by combining turn mimics with peptide strands or strand mimics. β -Sheet mimic **48** not only folds intermolecularly

to form a β -sheet, but also self-associates to form a β -sheet dimer. Oligomers **50** and **51** self-associate in a similar fashion. Ala, alanine; Ile, isoleucine; Leu, leucine; Met, methionine; Phe, phenylalanine; Val, valine.

because they allow a protein chain to fold back upon itself to form a compact structure. One area of research has focused upon the creation of structures that mimic the conformations and functionality displayed by β -turns and related structures, whereas a second has focused upon the creation of ‘nucleating turn mimics’ that induce structure in attached groups (typically peptide strands) [1].

Cyclic structures were first used as turn mimics and nucleators in the mid-1980s and continue to be used for these purposes. Gennari, Scolastico and co-workers [32*] have investigated bicyclic lactams **31** and **32** (Figure 5) as turn mimics and have established that **31** nucleates β -sheet

structure when incorporated into certain peptides. Kelly and co-workers [33] have used dibenzofuran turn units to nucleate anti-parallel β -sheets in water. These compounds adopt conformations in which the dibenzofuran moiety folds against the sheet, forming a hydrophobic cluster with the side chains of the first residues of the sheet, thus stabilizing the turn. Recently, Kelly and co-workers [34] reported a dibenzofuran turn unit that aligns two peptide strands to form a parallel β -sheet-like structure (**33**). Soth and Nowick [35] have reported peptide/oligourea/azapeptide hybrid oligomer **34**, which adopts a hairpin turn containing two intramolecular hydrogen bonds in chloroform solution. Two separate groups have reported using a

cis-norbornenyl turn that induces β -sheet-like structure in attached peptides [36,37]. Smith, Hirschmann *et al.* [38] have extended earlier work on the use of 3,5-linked pyrrolin-4-one β -strand mimics to create a hydrogen-bonded turn-like structure.

More recently, acyclic structures containing alkenes have been developed, which exploit allylic strain and other acyclic conformational effects to mimic β -turns [39,40]. In these compounds, the alkene unit mimics the amide bond that would be present in a natural turn. Gellman and co-workers [41•] presented the first example of this strategy — alkene-based turn **35**. A longer peptidomimetic (**36**), with amino acids flanking the alkene-based turn, prefers a hairpin conformation in dichloromethane solution. Careful NMR studies suggest that other competing conformations are also present. Wipf *et al.* [42] have designed and synthesized related alkene-based turns **37** and **38**; the latter contains a trifluoromethyl-substituted alkene, which mimics the electronic properties of the amide group.

A new development in the creation of turn structures involves β -peptides. Gellman and co-workers [43••] have developed a heterochiral nipecotic acid dimer turn (**39**) that induces sheet structure in attached β -peptide strands. Incorporation of **39** into β -tetrapeptide **40** resulted in the formation of the β -peptide equivalent of a β -hairpin. This work is particularly exciting because it suggests that different types of β -amino acids can be used to create secondary structures in a predictable fashion. Seebach *et al.* [44•] have also created a β -peptide turn (**41**) based on the central turn of their 12/10/12 helix (see above). This turn comprises two homochiral β -amino acids — the first with a substituent at the α -position, the second with a substituent at the β -position. Seebach *et al.* [45] have also reported an α,α -disubstituted β -tripeptide that forms a similar turn. This result, taken with the helical β -peptides discussed above, demonstrates that the structures of β -peptides are substituent dependent and suggests rules for designing secondary structures.

The myriad of potential homologated amino acids and substitution patterns provides a plethora of opportunities for the creation of structure. Thus, Hanessian *et al.* [13•] recently reported that γ -tetrapeptide **42**, which has a substitution pattern similar to γ -peptide **13**, adopts a reverse turn conformation containing a 14-membered hydrogen-bonded ring [(*i*) C=O...HN (*i* + 3)].

Sheets

Like helices and turns, β -sheets occur widely in proteins. In addition to contributing to protein structure, β -sheets play key functional roles in proteolytic enzyme–substrate interactions, protein–protein recognition, protein dimerization, and peptide and protein aggregation. β -Sheets are arguably the most challenging structures in proteins to mimic because they involve interactions between remote residues. One approach to creating molecules that mimic

β -sheets involves the combination of turn mimics with peptide strands. Some of these β -sheet mimics contain turns that were discussed in the preceding section; these will either be mentioned briefly or omitted here.

β -amino acids with an appropriate substitution pattern preferentially adopt an extended conformation similar to that of a β -strand [46•]. Combining these *anti*- α,β -disubstituted β -amino acids with a known α -depsipeptide turn unit, Gellman and co-workers [46•] constructed the hybrid oligomer **43** (Figure 6). The X-ray crystallographic structure of **43** demonstrates a minimal antiparallel β -hairpin-type sheet. As described above, Gellman and co-workers [43••] have also incorporated their heterochiral nipecotic acid dimer turn into the middle of a β -tetrapeptide to form minimal sheet structure **40** (Figure 5). Similarly, Seebach *et al.* [44•] have used one of their turn structures to nucleate sheet formation in β -hexapeptide **41**. In combination with the results described in the previous two sections, these results establish that β -peptides can be used to create all three main types of protein structure.

Nowick and co-workers (see [15•]) developed a strategy for creating molecules that mimic protein β -sheets that involves combining peptide strands with two different molecular templates. One template is based on *N,N*-linked oligoureas **16** (Figure 2) that resemble turns, whereas the other is based on substituted aromatic groups that resemble the hydrogen bonding functionality of one edge of a peptide β -strand. The oligourea ‘molecular scaffold’ is designed to bring the peptide and peptidomimetic strands into proximity, whereas the β -strand mimic is designed to help align the peptide strands. Two-stranded and three-stranded structures **44** and **45** (Figure 6) are representative. Most of the studies of these compounds have been performed in chloroform solution, but a recent study has shown that these molecules can adopt partially folded structures in competitive solvents, such as methanol and aqueous methanol [47].

The latest efforts by Nowick *et al.* [48] have focused upon the development of β -sheet structures containing new β -strand mimics. β -Sheet mimics **46** and **47** are analogs of **44** that have fumaramic hydrazide and peptide hydrazide groups in place of its 5-hydrazino-2-methoxybenzamide group. β -Sheet mimic **48** has the β -strand mimic on its ‘bottom’ edge rather than its ‘top’ [49••].

In studying β -sheet mimic **48**, Nowick *et al.* [49••] discovered that this compound forms a β -sheet dimer with a well-defined structure in chloroform solution; mixtures of sheet mimics **48** and **49** form both heterodimers and homodimers. These findings are significant because of the widespread role of β -sheet formation in protein dimerization and protein–protein interactions. Analogues of these compounds may be useful in understanding and interfering with specific protein–protein interactions. In related work, Gong *et al.* [50] have reported that intermolecular hydrogen bonding can occur in

hydrogen-bond donor (D) and acceptor (A) strands derived from combinations of substituted aromatic groups. Two self-complementary sequences DADA (50) and DDAA (51) dimerize in chloroform.

Conclusions

As a result of the rapid advances in designing molecules that fold, chemists are now on the cusp of creating molecules that resemble proteins. β -peptides that fold into all the main secondary structures in a predictable fashion can now be prepared; ' β -proteins' with well-defined tertiary and quaternary structures are sure to follow! Other designed molecules that fold to mimic helices, turns, and sheets are being developed. These advances will allow the development of compounds with functions akin to those of proteins. One of the most exciting emerging applications of these compounds is blocking protein-protein interactions by mimicking the secondary structural elements central to protein-protein recognition.

Note added in proof

A related article that reviews many of the papers described here appeared shortly after this review was submitted [51].

Acknowledgements

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