

Unnatural oligomers and unnatural oligomer libraries

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Within the past few years, a variety of compounds that mimic biopolymers have been developed. All of these unnatural oligomers are prepared by iterative syntheses, which are amenable to combinatorial strategies. Peptides continue to be popular targets for mimicry, and there is growing interest in targeting oligosaccharides. The incorporation of unnatural oligomers into compounds that adopt defined structures, such as helices or sheets, has emerged as an exciting new area of unnatural oligomer research.

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Introduction

Polypeptides, oligosaccharides, and nucleic acids are central to the life processes of all organisms. These naturally occurring biopolymers are the actors in the dramas of molecular recognition, catalysis, signal transduction, and transport processes that make cellular life possible. Because of their roles in these processes, these compounds are especially interesting to bioorganic and medicinal chemists. An enhanced understanding of natural biopolymers offers the promise of an improved understanding of cellular processes. Synthetic compounds that mimic the natural biopolymers can modulate cellular processes and serve as new drugs.

Combinatorial chemistry is changing the way in which chemists discover new drugs [1,2,3*]. Rather than synthesizing and testing individual compounds for biological activity, chemists can now synthesize and screen libraries of compounds. Because these libraries can comprise hundreds, thousands, or even millions of compounds, the chances of discovering biologically active lead compounds are greatly increased. Compounds consisting of linked subunits are well suited for combinatorial libraries, because each subunit can be varied and the subunits can be connected to each other by an iterative process. For this reason, oligomers are especially good candidates for combinatorial drug discovery efforts.

This review describes the chemistry of unnatural oligomers and focuses upon developments from 1995 to the present. It is organized into two major sections. The first section describes unnatural oligomers inspired by polypeptides, oligosaccharides, and oligonucleotides and discusses gen-

eral strategies for the syntheses of these compounds. The second section focuses on the incorporation of unnatural oligomers into compounds that mimic biopolymer structure and function.

Unnatural oligomers inspired by biopolymers

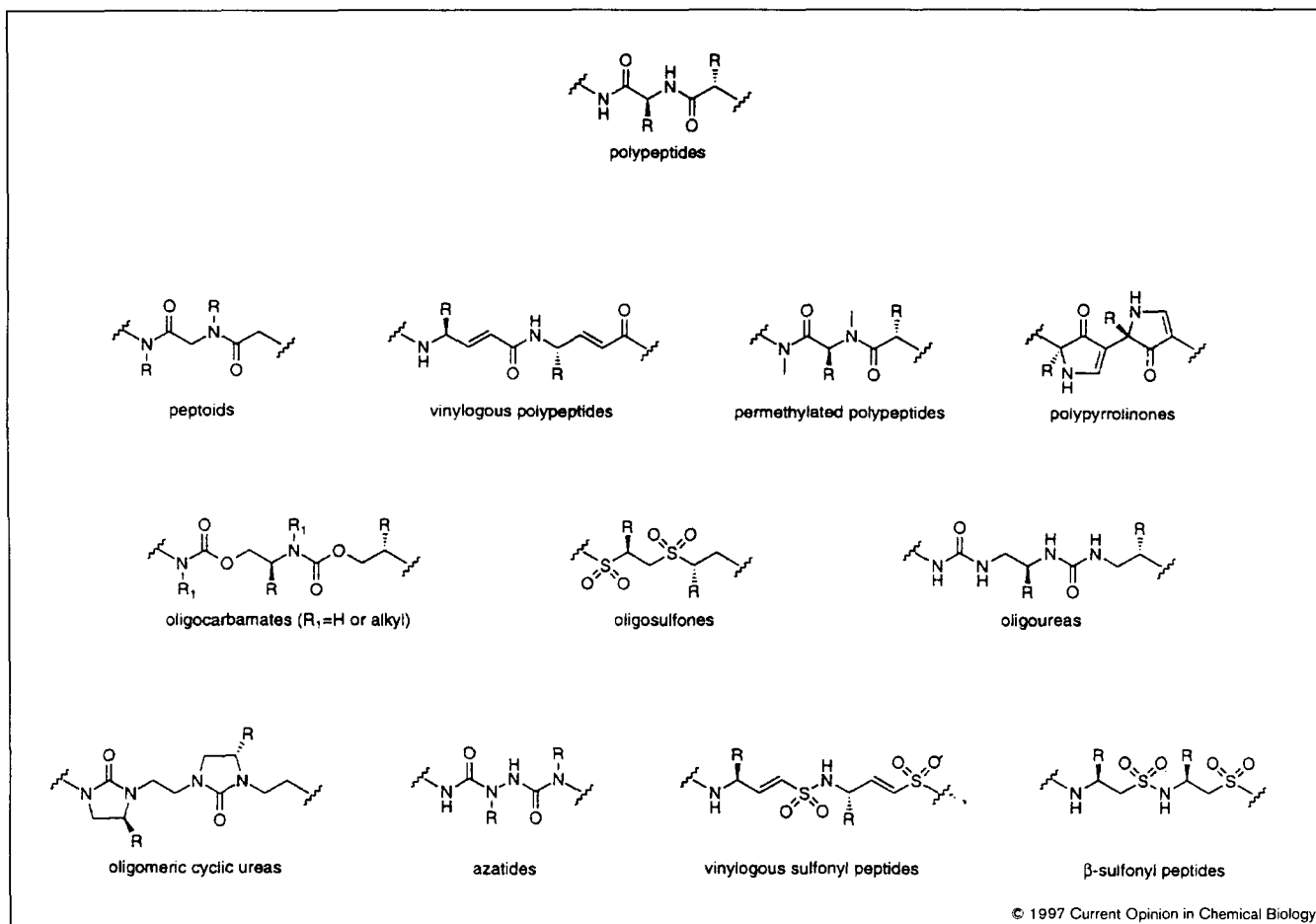
Polypeptides, oligosaccharides, and oligonucleotides are composed of repeating monomers bearing different substituents. Within the past few years, there has been considerable interest in developing unnatural oligomers that resemble these natural biopolymers. These oligomers are expected to be more stable *in vivo* than their natural counterparts, since they are unlikely to be substrates for the enzymes that degrade the polymers. Central to these efforts has been the invention of novel monomers and the development of iterative syntheses that permit the efficient preparation of oligomers and oligomer libraries.

Peptidomimetic compounds

Peptides and proteins play central roles in many biological processes, acting as enzymes, substrates, antibodies, antigens, receptors, ligands, regulators of gene expression and so on. Because of their extensive biological role, peptides and proteins are particularly attractive targets for mimicry [4–6], and a wide variety of peptidomimetic oligomers have been created. These oligomers include peptoids [7,8], vinylogous polypeptides [9], permethylated polypeptides [10], polypyrrolinones [11], oligocarbamates [12,13**], oligosulfones [13**], oligoureas [14], oligomeric cyclic ureas [15], azatides [16*], vinylogous sulfonyl peptides [17], and β -sulfonyl peptides [18] (Fig. 1).

The development of peptoid libraries demonstrates the utility of unnatural oligomer libraries. Peptoids are oligomers of glycine with peptidelike side chains attached to the nitrogen atoms. Invented in 1992 by researchers at Chiron Corporation in collaboration with scientists at other institutions, these unnatural oligomers have been used to create combinatorial libraries and to identify biologically active compounds. After developing an efficient solid-phase synthesis of peptoids [19], the Chiron team used robotic technology to synthesize a 5000-member library of peptoid dimers and trimers. Screening of the library yielded high-affinity ligands for seven-transmembrane-domain G-protein-coupled receptors [20]. The peptoids were found to be resistant to degradation by protease enzymes, which normally break down peptides [21]. The peptoid story illustrates some important goals in the development of unnatural oligomers and oligomer libraries: facile synthesis, bioactivity, and improved metabolic stability. Libraries of oligocarbamates [12,13**] and permethylated polypeptides [10] have also been reported; both oligomer

Figure 1



Peptidomimetic oligomers. In these compounds, peptide-like sidechains are attached to nonpeptide backbones. The unnatural oligomers are expected to be more bioavailable and biologically stable than peptides.

types were shown to be resistant to proteolytic degradation and one of the libraries [10] afforded compounds with antimicrobial activity.

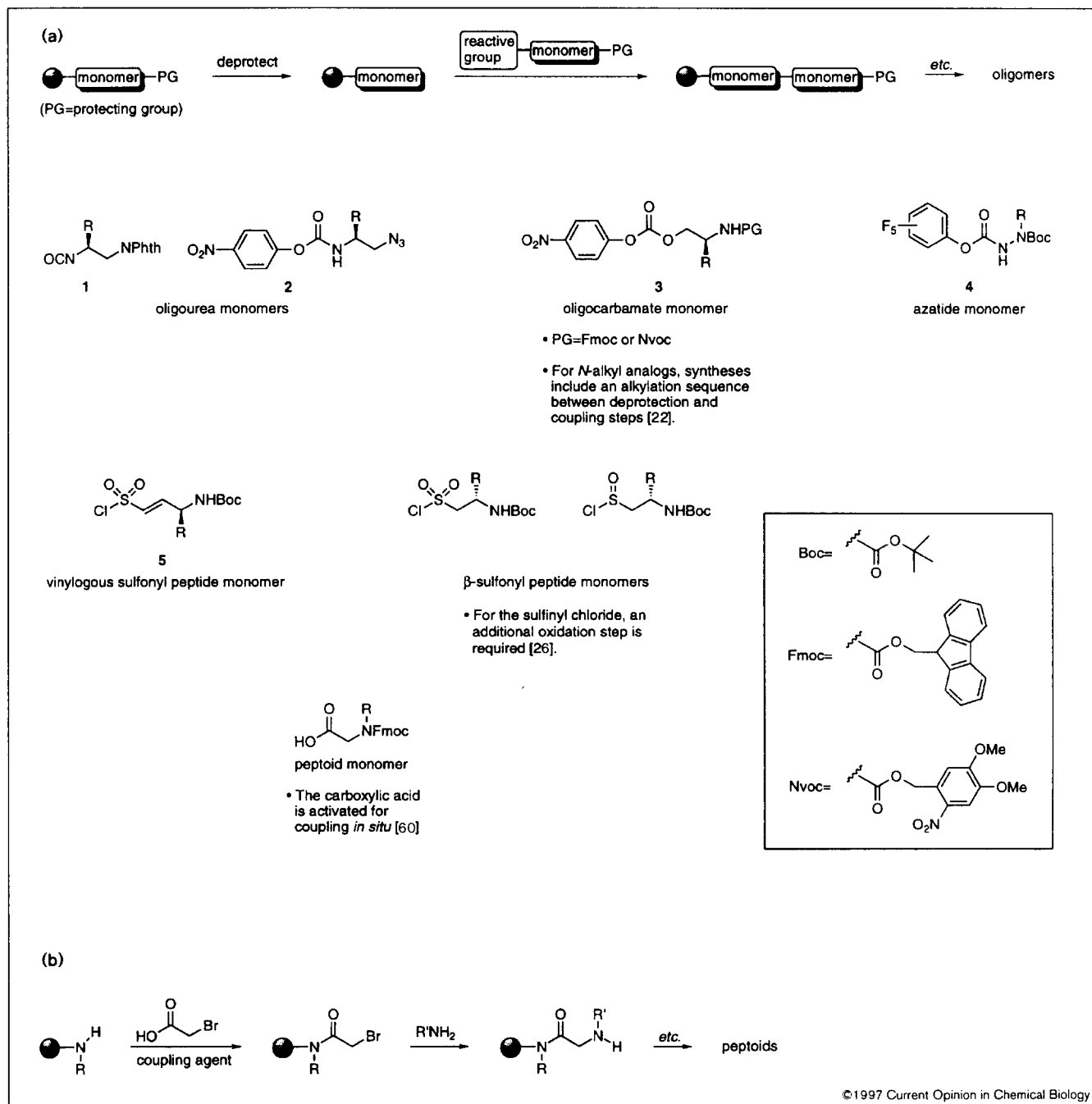
Most of the recent research on peptidomimetic oligomers has focused upon the development of efficient syntheses of the oligomers and has not yet led to the development of libraries. In general, these efforts have involved first developing solution-phase syntheses of the oligomers, then adapting the syntheses to solid-phase methods. The solid-phase methods are important, because they allow the efficient removal of synthetic by-products and excess reagents and make the oligomers easier to handle, facilitating the combinatorial syntheses of large numbers of different compounds. In the past two years, solid-phase syntheses have been reported for oligocarbamates [13•], oligo(*N*-alkylcarbamates) [22], oligoureas [14,23], azatides [16•], vinylogous sulfonyl peptides [24], and β -sulfonyl peptides [25,26].

Many of these syntheses involve repeated coupling of monomers bearing protected and reactive ends and are

conceptually similar to the Merrifield peptide synthesis [27]. The first monomer is attached to a polymer support, and the oligomer is constructed by a series of deprotection and coupling steps (Fig. 2a). In some cases, a few intermediate steps are required between the deprotection and coupling steps. If the free oligomer is desired, it may be liberated by cleavage from the solid support.

One of the problems associated with the synthesis of unnatural oligomers is that the monomers are often more difficult to make than the oligomers. In creating combinatorial libraries of unnatural oligomers, the synthesis of a diverse supply of monomers can prove to be the most time-consuming part of the process. The Chiron team developed an elegant solution to this problem—a 'submonomer' approach to peptoids [19]. In the submonomer approach, each *N*-alkylglycine unit is constructed on the solid support from bromoacetic acid and a readily available primary amine (Fig. 2b). The bromoacetic acid unit is coupled to the growing peptoid chain, and the amine is introduced by nucleophilic displacement of the bromine. A particularly attractive

Figure 2



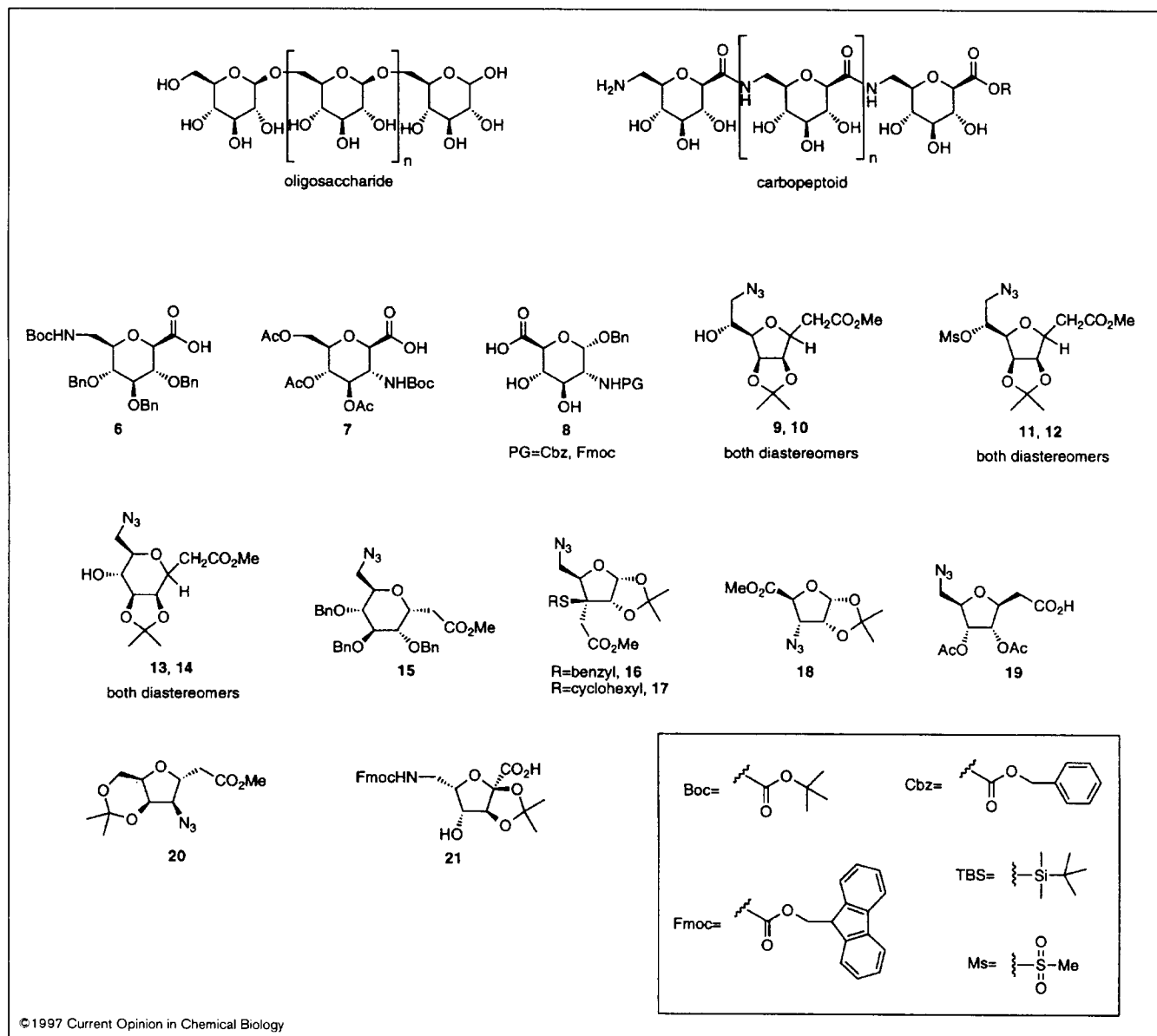
Strategies for the solid-phase synthesis of peptidomimetic oligomers. For additional information see [22,26,60]. **(a)** Monomers containing both reactive and protected ends are linked together by repeated coupling and deprotection steps. **(b)** A conceptually different 'submonomer' approach has been used to prepare peptoids.

feature of this synthesis is that it requires no protective groups. Schultz and co-workers are currently exploring a conceptually similar approach to prepare oligosulfones [13••].

Since 1995, several new unnatural oligomers have been reported. Burgess *et al.* [14] developed oligoureas and reported a solid-phase synthesis of these compounds. The

key coupling step in this synthesis involves the reaction of a monomer containing an isocyanate group with the amino group of the growing oligomer. The monomers **1** (Fig. 2a) are prepared in three steps from Boc-protected amino acids and have isocyanate and phthalimide groups as the reactive and protected ends. Using these monomers they prepared a pentaurea analog of Gly-Phe-Phe-Ala-Ala in 46% overall yield.

Figure 3

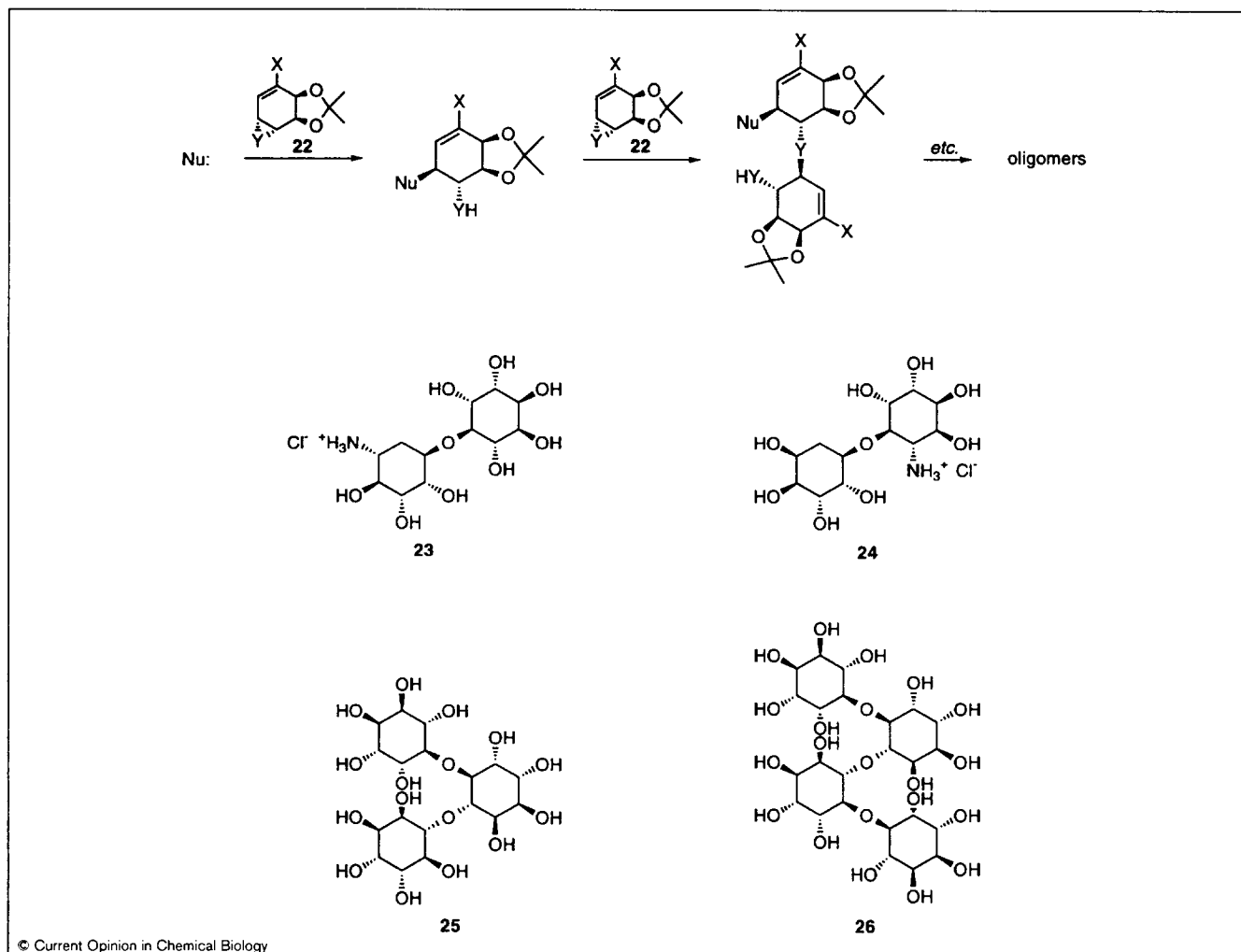


Carbopeptoids: oligosaccharide mimics in which the natural glycosidic linkage is replaced with an amide. A variety of monomers have been recently reported. Carbopeptoids should be easier to synthesize than oligosaccharides and are potentially more biologically stable.

One shortcoming of these syntheses is that the phthalimide protective group is difficult to remove. The deprotection step involves treatment with 60% hydrazine hydrate in dimethylformamide for 15 hours at 25°C. Because hydrazine is a powerful nucleophile, electrophilic functional groups, such as esters, are unlikely to be compatible with the reaction conditions. Schultz and co-workers have recently published a synthesis that overcomes this limitation [23]. This synthesis relies upon monomers **2** (Fig. 2a), which contain the azide group in lieu of the phthalimide group and the nitrophenyl carbamate group in lieu of the isocyanate group.

Although these oligoureases are easy to synthesize, they may not be good candidates for drug discovery, because compounds containing many hydrogen bonding groups do not cross cell membranes easily [11]. Each monomer unit of these oligoureases contains two NH groups—twice as many as are found in an amino acid. To address this issue, Schultz and co-workers developed oligomeric cyclic ureas (Fig. 1) [15]. Thus far, only a solution-phase synthesis of these compounds has been reported. The synthesis is iterative, with each iteration involving seven steps. Schultz and co-workers have also reported the synthesis of oligo(*N*-alkylcarbamates) [22], which may

Figure 4



Inositol oligomers: oligosaccharide mimics in which the endocyclic oxygen is replaced with a methylene unit. These oligomers can be prepared by repeated nucleophilic ring-openings of monomers **22** (X=halogen substituent; Y=O, NH), followed by alkene oxidation and acetal hydrolysis.

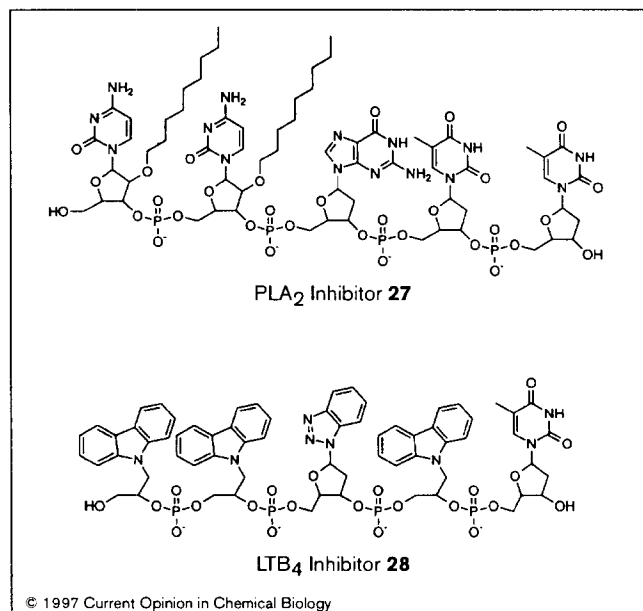
also cross cell membranes more efficiently than the nonalkylated oligomers reported earlier (Fig. 1) [12]. The oligo(*N*-alkylcarbamates) are prepared by an iterative solid-phase synthesis using monomers **3** (Fig. 2a). In this synthesis, the *N*-alkyl groups are introduced by acylation and reduction steps between the deprotection and coupling steps.

Azatides are another unnatural oligomer type in which urea groups link the monomeric units. These peptidomimetic compounds were developed by Han and Janda [16•] and consist of repeating hydrazine units connected by urea linkages. Azatides are readily prepared by coupling monomers **4** (Fig. 2a); each monomer is synthesized from a substituted hydrazine by protection of the substituted nitrogen atom and conversion of the unsubstituted nitrogen to a reactive pentafluorophenyl carbamate group. Using liquid-phase (polymer-supported solution-phase) techniques, Han and Janda synthesized an analog of

Leu-enkephalin (Tyr-Gly-Gly-Phe-Leu) in 57% overall yield. Unfortunately, the azatide showed no propensity to compete with Leu-enkephalin for binding to an antibody raised against β -endorphin and which binds a number of opoid peptides, including Leu-enkephalin. The authors attributed the inactivity of the Leu-enkephalin analog to conformational differences between the azatide and the native peptide. Readers interested in liquid-phase synthesis should refer to the review by Gravert and Janda (pp 107–113) in this issue.

Vinylogous sulfonyl peptides form another class of unnatural oligomers that have recently been reported. First prepared by Gennari *et al.* in 1994 [17], these peptidomimetic compounds resemble vinylogous polypeptides, which were reported by Schreiber *et al.* in 1992 [9]. Vinylogous sulfonyl peptides are prepared by coupling sulfonyl chloride monomers **5** (Fig. 2a) using solution-phase or solid-phase techniques [17,24]. The

Figure 5



Drug leads discovered at Isis Pharmaceuticals (Carlsbad, CA) by screening phosphodiester pentamer libraries. The activities of these inhibitors are comparable to those of leads found by screening natural products [41*].

monomers are synthesized in three steps from Boc-protected α -amino aldehydes, which are prepared from amino acids. Gennari *et al.* [28*] have also reported extensive conformational and computer modeling studies on vinylogous sulfonyl peptides and have found that these peptidomimetic compounds adopt intramolecularly hydrogen bonded ring conformations. Both Gennari and co-workers [25] and Liskamp and co-workers [18,26] have subsequently reported related syntheses of β -sulfonyl peptides.

Oligosaccharide mimics

Oligosaccharides are involved in cellular recognition interactions and play key roles in immune response and inflammation when displayed on the surfaces of cells. With the growing understanding of their importance, oligosaccharides have also emerged as targets for mimicry.

Replacement of the glycosidic linkages of oligosaccharides with amide groups gives rise to unnatural oligomers (Fig. 3) that are more easily synthesized than oligosaccharides and that are potentially more resistant to hydrolysis and enzymatic degradation. Since 1995, a number of research groups have become interested in oligomers of this sort. Nicolaou *et al.* [29] named this class of compounds 'carbopeptoids' [29], McDevitt and Lansbury called them 'glycotides' [30], and others have termed them 'oligosaccharide mimetics'. Nicolaou *et al.* [29] have also reported the analogous 'carbonucleotoids', in which the glycosidic linkage has been replaced with a phosphodiester

group; this replacement offers the same advantages as the amide substitution in carbopeptoids.

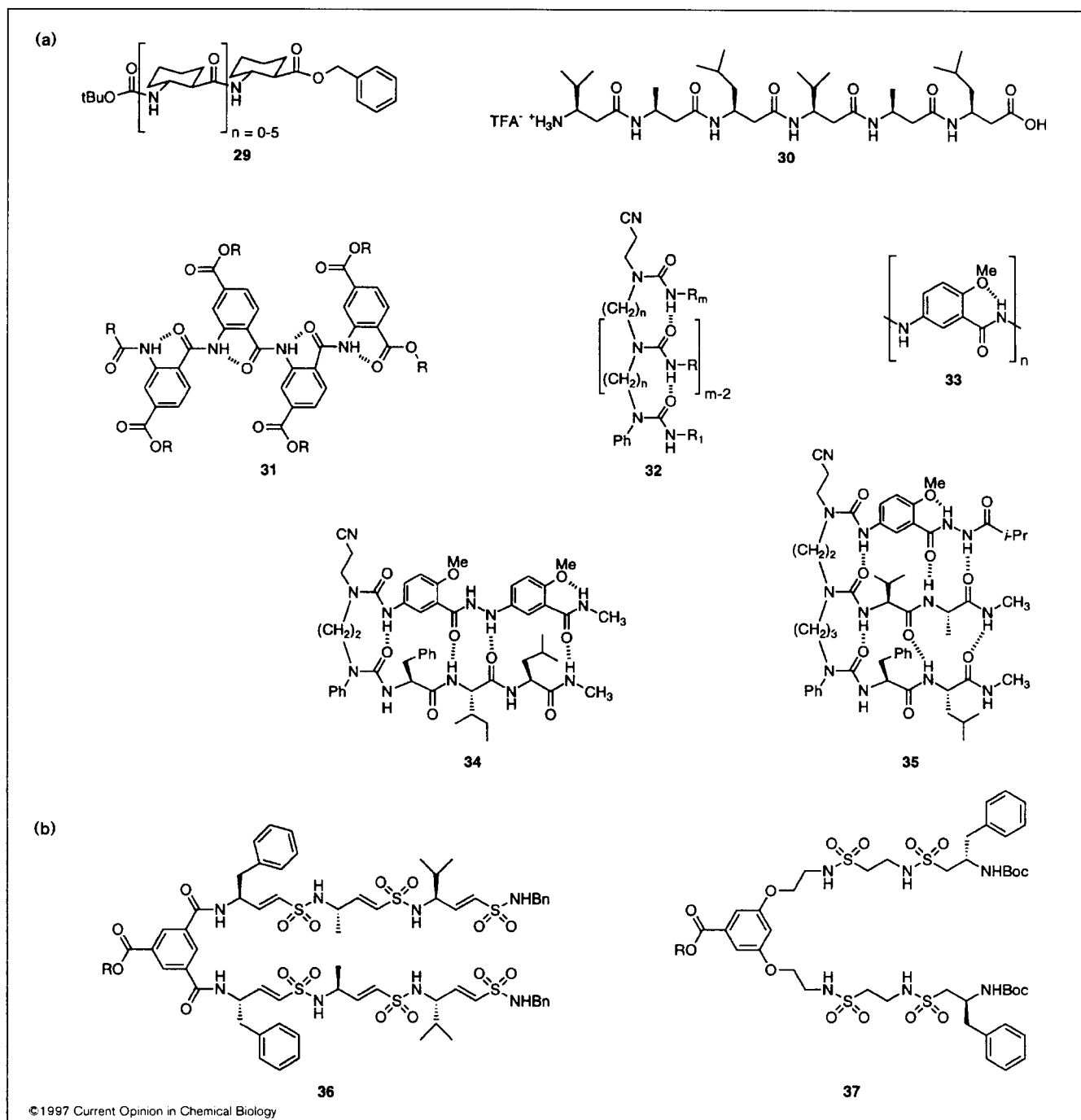
Carbopeptoids are synthesized by coupling the corresponding amino acid monomers using standard peptide synthesis techniques. A wide variety of carbopeptoid monomers have been prepared from the large pool of available sugar precursors. Ichikawa and co-workers [31,32] synthesized monomers 6 and 7 (Fig. 3), coupled them to form $\beta(1\rightarrow2)$ -linked and $\beta(1\rightarrow6)$ -linked tetrasaccharide mimics, and determined that the corresponding *O*-sulfated tetracarbopeptoids inhibit HIV infection of CD4⁺ and MT2 cells. Wessel and co-workers [33] have synthesized monomer 8 and used it in a solid-phase tetramer synthesis. McDevitt and Lansbury [30] have synthesized twelve monomers, 9–20, from a variety of sugars [30]. At least one carbopeptoid monomer is now commercially available (21, from Neosystem). The monomers will likely be used to generate carbopeptoid libraries in the future.

Hudlicky *et al.* [34*,35**] developed a different sort of oligosaccharide mimic based upon inositols and aminocyclitols (Fig. 4). These oligomers resemble oligopyranoses in which the ring oxygen has been replaced by a carbon. The oligomers are synthesized from chiral cyclohexenediol epoxide and aziridine monomers 22 (Fig. 4), which are prepared chemoenzymatically from bromo- or chlorobenzene [36,37]. Each monomer is coupled to the growing oligomer by nucleophilic attack of the oligomer on the allylic epoxide (or aziridine) group of the monomer. The alkene groups of the cyclohexene rings are further modified later in the synthesis; different alkenes can be differentiated by the presence or lack of halogen substituents. Using these procedures, Hudlicky *et al.* [34*,35**] synthesized dimers 23 and 24, trimer 25, and tetramer 26. X-ray crystallographic studies of a complex between dimer 24 and CaCl₂ and molecular modeling studies of larger oligomers suggest that extended oligomers should form helical structures. As discussed in the final section of this review, compounds that adopt defined structures are of special interest.

Oligonucleotide analogs

Unlike peptides, proteins, and oligosaccharides, oligonucleotides are primarily involved in the storage and transfer of genetic information. For this reason, much of the mimicry of oligonucleotides has been directed toward the development of antisense oligonucleotides, with the goal of modulating the transfer of genetic information. Typical strategies for the creation of these oligonucleotide analogs have involved replacement of the sugar and phosphate backbone. Although noteworthy research has been directed toward developing PNAs (peptide nucleic acids) and many other nucleic acid analogs as antisense agents, this work goes beyond the scope of this review and has been reviewed elsewhere [38,39]. Other applications of oligonucleotide analogs have only recently begun to receive attention.

Figure 6



Unnatural oligomers that mimic biopolymer structure and function. **(a)** Structured oligomers. In these compounds, intramolecular hydrogen-bonding induces formation of helices, linear strands or sheets. **(b)** Artificial receptors. The pocket formed between the unnatural oligomer strands can bind peptide substrates.

Libraries of up to 10^{15} oligonucleotides can be screened using *in vitro* selection to identify oligonucleotides that bind to other molecules or catalyze reactions [1,40]. Interested readers can refer to the reviews by Pan (pp 17–25) and Breaker (pp 26–31) in this issue. The major limitations of DNA and RNA molecules are that these natural oligomers each comprise only four monomers and

are prone to enzymatic degradation. To circumvent these limitations, researchers at Isis Pharmaceuticals (Carlsbad, CA) have used combinatorial methods to create biologically active oligonucleotide analogs [41•]. The Isis team developed a diverse collection of replacements for the bases that can achieve hydrophobic, hydrogen-bonding, aromatic stacking, dipolar, and ion pairing interactions.

The sugar units to which the bases are attached are either deoxyribose or other diols; monomers containing propane-2,3-diol are prepared by reacting *R*-glycidol with the appropriate base analogs [42]. These oligonucleotide analogs are synthesized by coupling the corresponding monomers using standard oligonucleotide synthesis techniques. By screening libraries containing 20736 phosphodiester pentamers, the team identified inhibitors to the inflammatory mediators phospholipase A₂ (PLA₂) and leukotriene B₄ (LTB₄) (27 and 28, Fig. 5). Recently, researchers at PharmaGenics have reported a combinatorial library of phosphoramidate oligomers comprising a diverse range of functionalized and unfunctionalized diols [43]. Unfortunately, heavily modified oligonucleotide analogs, such as those developed at Isis and Pharmagenics, are not likely to be amenable to *in vitro* selection techniques. For this reason, libraries of these oligonucleotide analogs must be screened by standard chemical techniques and cannot contain 10¹⁵ members.

Unnatural oligomers that mimic biopolymer structure and function

Many of the functions of natural biopolymers arise from the modes in which they fold and self-assemble. The mimicry of biopolymer folding and interactions offers the promise of an enhanced understanding of these functions and may eventually lead to new drugs.

Structural mimics

Peptides, proteins, oligosaccharides, and nucleic acids often fold into well-defined secondary structures. A variety of unnatural oligomers that mimic these types of structures have been developed. Gellman and co-workers [44•] have termed molecules of this sort 'foldamers' [44•], and developments in this area have been highlighted recently [45•]. The oligosaccharide mimics of Hudlicky *et al.* [34•,35••] provide examples of foldamers, forming a helical molecular scaffold upon which hydroxy and amino groups are displayed (Fig. 4). Other foldamers include β -peptides, which were reported both by Appella *et al.* [45•] and by Seebach *et al.* [46••,47•] (Fig. 6). The Gellman group's structures consist of oligomers of *trans*-2-aminocyclohexanecarboxylic acid (29 in Fig. 6), which form highly stable intramolecularly hydrogen bonded helical structures; Seebach's structures consist of oligomers of various β -amino acids (30) and also form intramolecularly hydrogen bonded helices. Hamilton and co-workers have developed another type of β -amino acid oligomer, the oligoanthranilamides (31) [48]. These unnatural oligomers form extended linear strands; turn units can be inserted in the strands to give helical structures. Foldamers that form stacked aromatic structures have been developed by Lokey and Iverson [49] and by Vögtle *et al.* [50,51].

A foldamer adopts a defined conformation. An alternative approach to creating structured molecules involves the use of molecular templates [52]. For the past few years, the Nowick group have been developing molecules in

which oligomeric templates bearing peptide strands form folded β -sheet structures (Fig. 6) [53••,54•]. They have developed oligoureia template 32 to hold peptide strands in proximity [55], and they have developed β -strand mimic template 33 to help enforce an extended β -sheet structure by means of intramolecular hydrogen bonding [53••]. The β -strand mimic may be thought of as an oligomer of 5-amino-2-methoxybenzamide or 5-hydrazino-2-methoxybenzoic acid. Thus far they have prepared structures as large as (34) and (35), containing diurea- or triurea templates and monomeric or dimeric β -strand mimics. They have developed both solution-phase and solid-phase syntheses of these compounds and they have prepared and studied a combinatorial library of β -sheet structures to determine the effects of different amino acids upon β -sheet structure and stability. These β -sheet structures may eventually be used to create biomimetic receptors and catalysts.

Receptors

Natural biopolymers participate in a wide variety of intermolecular interactions. Interactions between enzymes and substrates, receptors and ligands, and proteins and nucleic acids play key roles in cellular processes. With the goals of creating unnatural molecules that mimic these processes, researchers have begun to develop receptors composed of unnatural oligomers (Fig. 6b).

Both Gennari *et al.* [56•] and Liskamp and co-workers [57] have reported studies on tweezerlike receptors based on sulfonyl peptides [56•,57]. In collaboration with Still and Nestler, Gennari's group synthesized vinylogous sulfonyl peptide receptor 36 and screened it against an encoded combinatorial library of 50625 tripeptides [56•]. The receptor bound approximately 250 of these peptides with significant sequence selectivities. The following year, Liskamp *et al.* [57] reported similar studies of β -sulfonyl peptide receptor 37. Both the Gennari and Liskamp receptors are similar to peptide-based models used earlier by Still *et al.* to generate combinatorial receptor libraries [58•,59].

Conclusions and outlook

Natural biopolymers play important roles in cellular processes, and synthetic compounds that mimic their effects can modulate cellular activity and serve as drugs. Efficient syntheses of a variety of unnatural oligomers resembling these biopolymers have now been developed, and it is likely that more syntheses will appear in the future. Combinatorial techniques have yielded bioactive versions of some of these unnatural oligomers; the utility of many of the others remains to be established. The activities of biopolymers are intimately related to their structures; an unnatural oligomer that mimics a biopolymer's primary sequence may have a completely different three-dimensional structure and therefore lack biological activity. To overcome this potential drawback, researchers are now creating unnatural oligomers that

mimic the secondary structures of biopolymers. Libraries of these structured oligomers may yield compounds with improved biological activities.

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