

# The chemical synthesis of peptidomimetic libraries

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Molecular diversity as a source of potential drug candidates has been an area of tremendous growth during the past year. The field has been dominated by investigations featuring diverse peptide libraries, generated by both chemical and biological methods. Yet the many undesirable properties of peptides as drugs, such as poor oral availability and low *in vivo* stability, have prompted chemists to develop methods for the efficient synthesis of conformationally constrained peptide, biopolymer and non-polymeric compound collections.

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## Introduction

The systematic screening of diverse compound collections from microbial fermentation broths, plants, marine organisms, and synthetic compound collections has yielded a substantial number of pharmaceutical lead compounds in drug discovery programs in recent years [1]. These screening strategies rely not on the knowledge of a target's structure but rather on the random testing of a sufficiently large number of chemical entities. The success of these screening programs suggests that a highly diverse set of chemical structures generated by rapid combinatorial synthesis could similarly provide drug candidates.

Within the past two years, molecular biologists and peptide chemists have developed schemes for the rapid generation and screening of diverse peptide libraries [2]. Peptides are an ideal class of molecules for the generation of combinatorial libraries because they are composed of 20 reasonably diverse amino acid building blocks which can be efficiently assembled either by chemical synthesis or by transcription/translation of DNA. In several cases, peptide libraries have provided moderate- to high-affinity ligands to cellular receptors (S Fong *et al.*, unpublished data) [3,4•] and to proteins [5–7] with no known natural peptide ligand. However, peptides are less than ideal when considered as drug candidates. Poor oral availability and low *in vivo* stability are among the undesirable features of peptides [8].

In order to avoid these problems, chemists are now applying the methodologies used with synthetic peptide libraries [9,10•,11,12•,13,14•] to collections of cyclic peptides, novel biopolymers, and even non-polymers. New synthesis technologies and chemistries that facilitate the synthesis and screening of diverse chemical libraries have recently been developed. One of the most significant of these is the 'resin-splitting' mixture synthesis method, a polymer-supported multiple synthesis procedure that

allows a high degree of control over the composition of a peptide mixture [15]. Mixtures are generated by dividing a solid support into equal portions, coupling a different amino acid to each portion, and then combining the portions. Equimolarity of mixtures is ensured as competition between the amino acids is eliminated. The method generates for each particle of solid support one polymer sequence that can facilitate screening [12•], and can generate mixtures containing more than one million different components [4•,11,12•]. The synthesis procedure has recently been fully automated [16••], and should be extendable to a variety of new chemistries.

Chemistries that are amenable to combinatorial library synthesis would ideally have the following characteristics: be polymer-supported to facilitate the resin-splitting method; be assembled in high yield with automatable chemistry; and allow the incorporation of a wide variety of chemical functionalities. In addition, the chemistry should generate classes of compounds that are biostable and bioavailable, and have the appropriate conformational properties.

## Cyclic peptides

Peptides that are cyclic often show increased resistance to enzymatic degradation [10] and constrained flexibility compared with the linear form. There are several recent examples of peptides where the increased rigidity induced by cyclization has led to enhanced receptor-binding affinity; these include potent cyclic RGD anti-thrombotics [17•], cyclic oxytocin antagonists [18], and cyclic  $\alpha$ -melanotropin analogues [19].

In order to generate libraries of cyclic peptides, it is important that the cyclization reaction can be performed in high yield and with a minimum of additional manipula-

## Abbreviation

Fmoc—9-fluorenylmethoxycarbonyl.

tions. Unfortunately, cyclization reaction yields are highly sequence-dependent [20], making the uniform cyclization of a peptide mixture difficult. But, recent advances in the cyclization of peptides directly on the solid support have greatly simplified the synthetic procedure, allowing the automation of cyclization reactions. In the past, cyclizations were typically performed in solution under conditions of high dilution. Polymer-supported cyclizations however take advantage of the 'pseudo-dilution' phenomenon [21•], which avoids potential side reactions such as oligomerization and facilitates product purification. For example, on-resin cyclization methods have recently been used to prepare cyclopeptides with bridges formed of thioethers [17•,22], disulfides [23] or lactams between two side chains [19], lactam between the amino terminus and a side chain [24], and lactams between the amino and carboxyl termini [21•,25].

### Polymeric diversity

Polymers are well suited for the generation of chemical diversity, as relatively few monomers (e.g. the standard 20 amino acids) can be combined with a common linking chemistry to generate a tremendous number of compounds. This combinatorial approach has recently been applied to non-peptide polymers to allow the generation of diverse peptidomimetic libraries. Such polymers would be expected to display an even more diverse array of side-chain functionalities than peptides, have different structural characteristics, be resistant to enzymatic degradation, and perhaps exhibit better bioavailability.

### Amide polymers

The chemistry of amide-bond formation has been used to generate a variety of polymers with alternative peptide backbones. A straightforward approach has been taken by Wang and coworkers [26] in which a large set of peptides containing D-amino acids were synthesized and assayed for receptor binding. Hagihara and coworkers [27••] reported the synthesis of vinylogous polypeptides, in which an (*E*)-ethenyl unit was inserted between the carbonyl carbon and the  $\alpha$ -carbon (Fig. 1). Trimeric vinylogous peptides and tetrameric hybrid peptides were synthesized by solution-phase chemistry and shown using X-ray crystallography to possess novel secondary structures. The vinylogous amino acid monomers were readily prepared by the homologation of amino aldehydes protected at their amino termini, and coupled by conventional amide-bond formation chemistry.

Amide-bond formation has also been used to synthesize oligonucleotide analogues. Huang and coworkers [28] have reported the (solution-phase) synthesis of nylon-based acyclic nucleic acid oligomers up to six residues in length (Fig. 2a). Nucleic acid surrogates based on a peptide backbone have been reported in which serine residues are modified at the side-chain hydroxyl group with a nucleobase and are oligomerized with glycine as al-

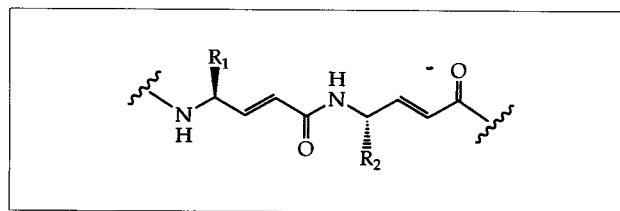


Fig. 1. The vinylogous polypeptide backbone.

ternating copolymers (Fig. 2b) [29]. The solution-phase synthesis of tetrameric structures was achieved. Similarly, the side-chain hydroxyl groups of serine and threonine have been modified with N-acetyl galactose, allowing the solid-phase synthesis of multiply glycosylated peptides [30]. Oligonucleotide analogues of up to 10 residues in length based on an N-aminoethylglycine backbone (Fig. 2c) have been synthesized by solid-phase methods [31•]. These polyamide nucleic acids were shown to bind to complementary DNA strands with high affinity.

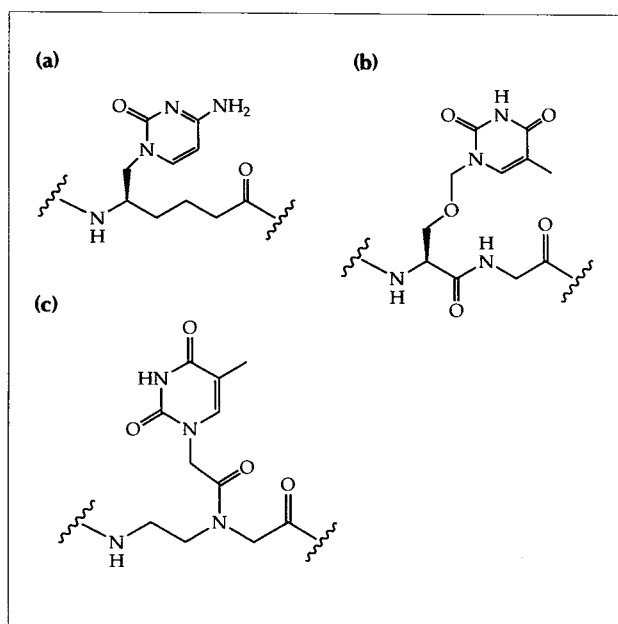
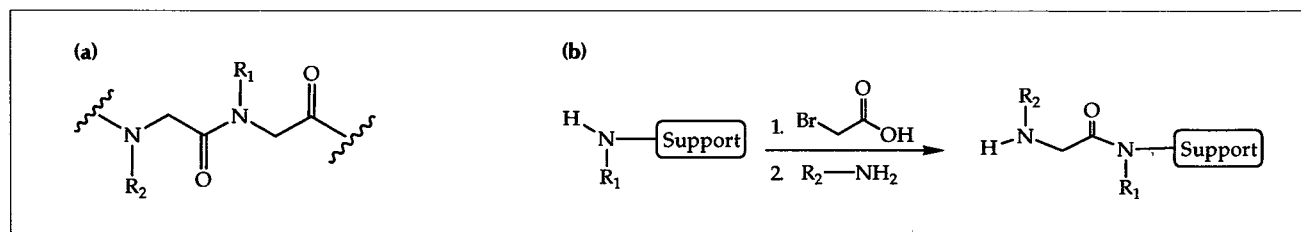


Fig. 2. (a) Nylon-based oligonucleotide analogues with a polyamide backbone. (b) Polyamide oligonucleotide analogues with an alternating Ser-Gly backbone. (c) Polyamide oligonucleotide analogues with an N-aminoethylglycine backbone.

Peptide analogues in which the side chains are substituted at the nitrogen atom rather than at the  $\alpha$ -carbon have recently been reported (Fig. 3a) [32••]. These peptoid oligomers (oligomeric N-substituted glycines) appear to have excellent resistance to proteases. The peptoids were prepared by solid-phase chemistry from a set of  $N^{\alpha}$ -Fmoc-N-substituted (Fmoc, 9-fluorenylmethoxycarbonyl) glycine monomers whose side chains closely resemble those of the natural amino acids. The recently reported synthesis of N-substituted glycine oligomers from readily available primary amine and  $\alpha$ -haloacetic acid 'submonomers' (Fig. 3b) avoids the use of  $N^{\alpha}$ -Fmoc-

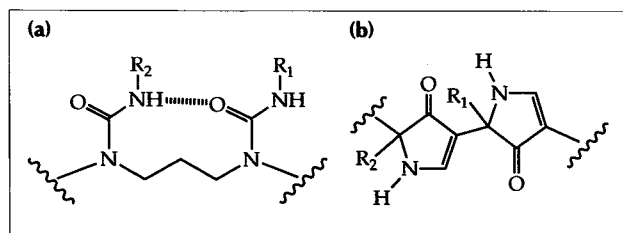


**Fig. 3.** (a) The N-substituted glycine (peptoid) backbone. (b) The solid-phase submonomer synthesis of oligo(N-substituted glycines) is achieved with readily available building blocks and requires no N<sup>α</sup> protection.

protected monomers entirely [33••]. The solid-phase submonomer method was used to synthesize efficiently several oligomers with a variety of 'non-natural' side-chain structures up to 25 residues in length.

### Non-amide polymers

The synthesis of functionalized oligomers without amide bonds has also been reported. Nowick and coworkers [34••] developed an oligoureia scaffold that is stabilized by internal hydrogen bonding, which may serve to orient side chains in a parallel fashion (Fig. 4a). Trimeric compounds were synthesized by solution-phase chemistry, in which a wide variety of side-chain structures were readily introduced as isocyanates. Smith and coworkers [35•] have synthesized 3,5-linked pyrrolin-4-one oligomers which mimic the  $\beta$ -strand conformation of peptides (Fig. 4b). Tetrameric compounds were synthesized by solution-phase methods and were characterized by X-ray crystallography.

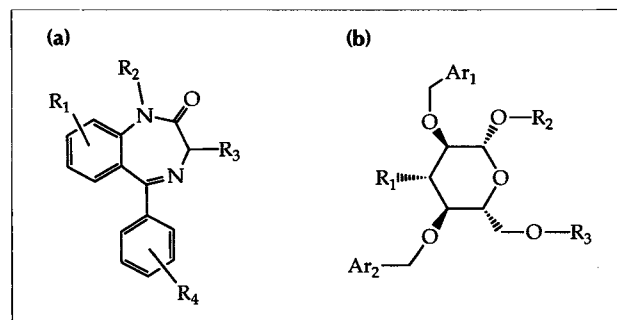


**Fig. 4.** (a) The oligoureia polymer backbone may orient side chains as a result of internal hydrogen bonding. (b) The pyrrolinone-based polymer backbone mimics the fully extended conformation of peptides.

### Non-polymeric diversity

The combinatorial synthesis of non-polymeric organic compounds would allow the rapid screening of 'drug-like' chemical structures. These systems are characterized by the display of a number of side chains around a structured cyclic scaffold. The advantage of libraries of this type is that any lead identified from it will already have many desirable characteristics (such as conformational rigidity and biostability) built into it. This may avoid the step of converting a lead generated from a peptide library into a peptidomimetic drug candidate, and may thus be a better starting point for drug discovery. Bunin and Ellman

[36••] have demonstrated this concept by developing a solid-phase method for the general and expedient synthesis of 1,4-benzodiazepine derivatives (Fig. 5a). Each derivative is prepared from three pieces: a 2-aminobenzophenone, an amino acid and an alkylating agent. Ten different benzodiazepene derivatives were prepared in excellent overall yields. Hirschmann and coworkers [37•] have reported the use of  $\beta$ -D-glucose as a scaffold upon which four to five side-chain functional groups were appended (Fig. 5b). Potent ligands for G-protein-coupled receptors have been discovered using this template.



**Fig. 5.** (a) 1,4-Benzodiazepines can be synthesized efficiently on a solid support. (b)  $\beta$ -D-Glucose can serve as a scaffold for potent peptidomimetics.

### Future directions

The past two years have seen rapid progress in the synthesis and screening of synthetic peptide libraries. There is currently a trend by chemists toward the synthesis of diverse compound libraries that are less peptide-like and more drug-like. In the near future, there will be wider use of polyamide-based oligomer libraries that contain non-natural amino acids, D amino acids, cyclization sites, N-alkylation and other conformational constraints. The development of novel biopolymer and non-polymeric diversity systems will continue to be an area of tremendous growth. Chemistries that are amenable to high-throughput solid-phase synthesis will be particularly useful. Mass screening of chemical libraries can require substantial quantities of synthetic building blocks, so movement toward both miniaturization [13] and chemistries that use readily available building blocks [33••] is likely.

The screening of diverse non-peptide libraries will surely present new analytical problems in identifying ligands

of interest, as they are not likely to be characterizable by conventional peptide analyses. One solution to this problem is to encode the sequence of novel building blocks that comprise a biopolymer or peptidomimetic with a covalently attached chemical tag, e.g. a sequence of amino acids or nucleotides, which can be readily analyzed using conventional methods. Kerr and coworkers [38•] have demonstrated the use of amino acid triplets to encode a library of 200 peptides that contain non-natural amino acids. Brenner and Lerner [39•] have proposed the use of oligonucleotides as the coding sequence. This procedure of tagging will allow selection experiments to be performed on very large libraries because the coding sequence can be amplified by PCR. These coding strategies do not, however, allow the free ligand to be assayed as the ligands must either be attached to a solid phase or to the chemical tag. The identity of the highest-affinity binders of a *free* ligand mixture must still be determined by iterative resynthesis procedures [4•,10•] or by affinity selection followed by mass spectrometry [14•,40].

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