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FROM PEPTIDES TO PEPTIDOMIMETICS: CHEMICAL AND STRUCTURAL STRATEGIES FOR DEVELOPING DRUG-LIKE THERAPEUTICS: A STRATEGY-FOCUSED NARRATIVE REVIEW FOR MEDICINAL CHEMISTRY AND DRUG DISCOVERY

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Abstract:

Peptides have important properties in between small molecules and biologics; they are able to bind broadly and with high affinity and selectivity to protein surfaces that are shallow, dynamic and rich in conformational and nonpolar interactions, but are often hindered for clinical translation by factors such as proteolysis, conformational flexibility, lack of membrane permeability, rapid clearance and low oral exposure. Peptidomimetics solve these disadvantages by preserving the spatial geometry of essential recognition components while substituting some of the peptide's components with noncanonical residues, backbone modifications, bioisosteres, conformational constraints, and/or physicochemical-property modifiers. The present review offers a strategy-oriented framework for the development of a bioactive peptide to a drug-like peptidomimetic. The following six interconnected design classes are explored: (i) incorporation of unnatural and noncanonical amino-acids, (ii) backbone engineering and peptide-bond replacement, (iii) terminal and side-chain modification, (iv) cyclization and macrocyclization, (v) stapling and other conformational-locking strategies, and (vi) integrated molecular optimization of affinity, selectivity, stability, permeability, and pharmacokinetics. Special attention is given to structure–activity relationships, targeting of protein–protein interactions, oral delivery, intracellular delivery and optimization using computation. Examples of antiviral, anticancer, antimicrobial and enzyme-inhibitor and receptor-directed drug discovery demonstrate how single changes can address individual liabilities, but can also result in trade-offs. A practical design workflow is proposed that sees structural information, medicinal-chemistry iteration, biophysical characterization, permeability/stability assays and pharmacokinetic profiling are not optimized independently but rather integrated. It is concluded that successful peptidomimetic design is not about maximising any single property, but about an appropriate combination of recognition geometry and physicochemical and pharmacokinetic properties.

Keywords: *Peptidomimetics; peptide drug discovery; unnatural amino acids; noncanonical amino acids; backbone engineering; macrocyclization; stapled peptides; conformational restriction; protein–protein interactions; medicinal chemistry; drug-like peptides.*

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1. INTRODUCTION:

Peptide drug discovery has been revived, and the key advantage of peptide-sized ligands is that their large molecular surfaces enable them to mimic interaction motifs which are hard to capture by classical small molecule. Over 30 years of peptide medicinal chemistry has resulted in clinically useful hormone analogues, receptor agonists and antagonists, enzyme inhibitors, and antimicrobial agents. Today, sophisticated discovery approaches involve chemical synthesis, display methods, structural biology and computational design to produce more and more interesting peptide scaffolds. However, a native peptide is not a "best drug" candidate. It has an amide rich backbone that is susceptible to proteases, a broad conformational ensemble, a high polar surface that can hinder passive membrane diffusion, and it can have a short half-life in the body. The foregoing restrictions encourage the intentional transformation of a peptide pharmacophore to a peptidomimetic structure. Recent reviews highlight the shift in the field from the study of simple peptide mimics to systematic control of local structure, global conformation and physicochemical properties. [1–10]

The key idea of a peptidomimetic is therefore not just structural – it should possess the important recognition groups of a parent peptide and it should have fewer drawbacks. This can include the replacement of a natural residue with a D- or β-amino acid, N-methylation of an amide, the replacement of the peptide bond with a bioisostere, cyclization of a linear chain, stapling of an α-helix, or gradually removing the peptide character until only the important pharmacophore is left. The design space is not binary, but continuous from peptides to peptides with modified peptide bond, macrocyclic peptidomimetic to nonpeptidic small molecule. [8–18]

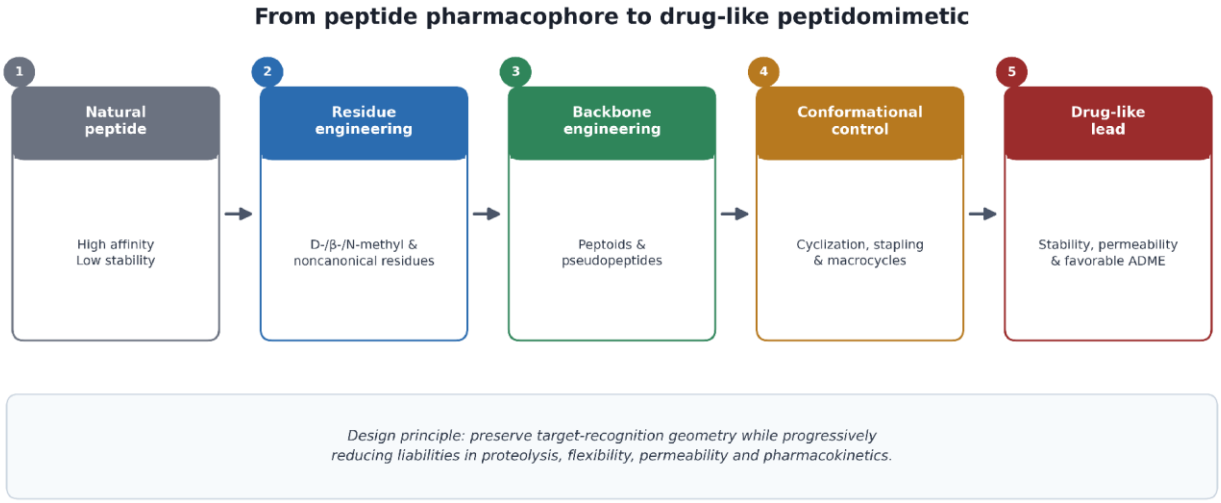

Figure 1. Conceptual workflow for converting a bioactive peptide into a peptidomimetic lead.

2. Why Convert a Peptide into a Peptidomimetic?

These major design drawbacks of native peptides can be summarized under five interconnected domains: chemical stability, conformational behavior, permeability, pharmacological behavior and manufacture. The active species can be quickly removed by proteolysis, the population of the binding-competent conformation may be decreased by excessive flexibility, extensive hydrogen-bonding may decrease passive membrane permeation, and high clearance may decrease systemic exposure. Of importance, if one property gets better, another one gets worse. For instance, introduction of a hydrophobic group may lead to enhanced permeability while simultaneously leading to enhanced aggregation or nonspecific binding. Cyclisation can improve stability and binding affinity to receptor, but it can also result in reduced solubility. N-methylation can alter both the hydrogen-bond donation and permeability, but it also alters the binding geometry. [6, 19–32]

Table 1. Major liabilities of native peptides and corresponding design responses

Peptide liability	Underlying cause	Typical design response	Desired outcome
Proteolytic instability	Flexible amide-rich backbone	D-/noncanonical residues; backbone replacement; cyclization	Longer half-life
Low passive permeability	High polarity; exposed H-bond donors/acceptors	N-methylation; macrocyclization; hydrophobic masking	Higher cellular exposure
Conformational flexibility	Many accessible conformers	Stapling; macrocyclization; turn/helix mimetics	Preorganization
Rapid systemic clearance	Proteolysis; renal filtration; metabolism	Size/conformation tuning; lipidation; conjugation	Improved exposure
Weak oral exposure	GI degradation + low permeability	Backbone modification; N-methylation; protease resistance	Potential oral activity
Off-target activity	Large or flexible interaction surface	Hot-spot mapping; conformational selection; SAR	Higher selectivity

3. Strategy I — Unnatural and Noncanonical Amino Acids

A residue-level substitution is the simplest intervention. Noncanonical amino acids can be used to change the geometry of side chains, steric volume, polarity, hydrogen-bonding, lipophilicity, and conformational preference while keeping the peptide structure intact. D-amino acids can decrease proteolytic recognition, β-amino acids can increase the backbone length and bring about alternative secondary structures, and N-methyl residues can protect the amide NH groups, and α,α-disubstituted residues can favor helices or turns. Unnatural amino acids have recently received considerable attention in the medicinal chemistry literature for their ability to tune peptide physicochemical properties and their potential for the expansion of the chemical space accessible by peptide and peptidomimetic drugs [23–25, 33–38].

Structural hypothesis is an important principle: substitutions should be based on a structural hypothesis. A change in a residue may decrease affinity even when there is an increase in stability if the residue is a binding hot spot. On the other hand, a substitution at a solvent-exposed and/or protease-sensitive position may offer a high benefit-to-risk ratio. Alanine scanning, D-residue scanning, positional scanning and systematic noncanonical residue libraries can then be used to distinguish those residues that must be present for recognition from those that primarily serve the conformational or degradation function.

3.1 D-Amino acids and stereochemical editing

D-amino acids invert local stereochemistry and frequently decrease recognition by proteases evolved for L-amino-acid substrates. Their use is particularly valuable when the parent peptide does not require a highly constrained global fold. Retro-inverso design takes this idea further by reversing sequence direction while inverting stereochemistry so that side chains can approximate the topology of the original peptide. However, preservation of side-chain arrangement does not guarantee preservation of the complete three-dimensional fold; retro-inverso analogues therefore require target-specific structural validation. [19–22, 39]

3.2 β-Amino acids, α,α-disubstituted residues and other conformational directors

β-amino acids introduce an additional backbone carbon and can generate β-peptides or mixed α/β architectures with distinctive helices and turns. α,α-Disubstituted residues such as Aib restrict backbone torsion and can increase helical propensity. These building blocks are especially useful when the medicinal-chemistry objective is to preserve a peptide recognition motif while reducing conformational entropy. The trade-off is synthetic complexity and the possibility that an artificial conformation no longer matches the target-bound geometry. [23–25, 40–43]

4. Strategy II — Backbone Engineering and Peptide-Bond Replacement

Backbone engineering directly addresses one of the central vulnerabilities of peptides: the repeating amide bond. Peptide bonds can be replaced, reduced or altered to change hydrogen-bonding, polarity, protease recognition and conformational behavior. Common architectures include peptoids, reduced amides, hydroxyethylene or hydroxyethylamine isosteres, thioamides, urea or carbamate linkages, azapeptides, depsipeptides and other pseudopeptides. The objective is not simply to remove peptide bonds but to preserve the

geometry and interaction vectors that matter for target recognition. [8–12, 44–48]

4.1 Peptoids and backbone N-substitution

Peptoids substitute the α-carbon-linked side chain of a peptide by an N-substituent on glycine. This alters conformational preferences and eliminates backbone NH donors, often increasing resistance to proteolysis. Peptoids are also well suited for highly modular library synthesis and are thus attractive for discovery and screening. Their higher conformational diversity can be a benefit for molecular recognition, but also presents a larger optimization problem than conventional peptides. [44,45]

4.2 Bioisosteric replacement and protease-inhibitor design

Example of transition-state mimics for peptide-bond replacement in medicinal chemistry. Hydroxyethylene, hydroxyethylamine and related motifs mimic important transition-state geometry and are non-cleavable. This approach has been particularly successful in the discovery of protease inhibitors where the goal is to mimic a substrate or transition state, but not become one. [46–48]

5. Strategy III — Terminal and Side-Chain Modification

Relatively small structural changes with large pharmacological consequences can be produced by terminal capping and side-chain modification. N-terminal acetylation or other caps may reduce exopeptidase susceptibility; C-terminal amidation may alter charge and receptor interactions; lipidation may increase membrane association and the duration of exposure; and selective side-chain substitution may modulate potency and selectivity. In the case of peptidomimetics these are usually applied in conjunction with residue or backbone modifications and not as singular interventions. [1, 6, 26,49]

A pragmatic solution is to consider the peptide as a modular pharmacophore. The central recognition motif is protected from unwanted modification, and termini and solvent-exposed side chains are examined for opportunities to improve stability, solubility and permeability. Such 'peripheral optimization' is especially useful where structural biology reveals a handful of hot-spot residues embedded within a larger peptide sequence.

6. Strategy IV — Cyclization and Macrocyclization

Cyclization converts conformationally mobile linear peptides into more restricted structures. Head-to-tail cyclization, side-chain-to-side-chain bridges, disulfides, lactams, triazoles and other macrocyclization methods can reduce the entropic cost of binding and shield proteolytic sites. Macrocycles can also create hydrophobic and polar surface arrangements that are distinct from those of linear peptides, sometimes enabling access to intracellular targets. [29–34, 50–55]

Macrocyclization should nevertheless be considered a design variable rather than a universal solution. Ring size, linker identity, stereochemistry and closure position can strongly influence the conformational ensemble. A poorly positioned bridge can distort the active conformation or reduce solubility. Modern macrocycle discovery therefore combines library screening with structure-guided optimization and explicit consideration of permeability and metabolic stability. [29–34]

Figure 2. Six complementary strategy classes used in peptidomimetic optimization.

7. Strategy V — Stapling and Other Conformational Locks

Stapling is particularly successful in conformational engineering. A constrained peptide resulting from covalently linking two residues on a suitable face of an α-helix can retain the helical recognition motif and, in some cases, acquire resistance to proteolysis and, in some instances, cellular uptake. Ring-closing metathesis was used to form hydrocarbon staples in a broadly applicable platform, and lactamization, triazole formation, thioether cross-linking, oxime chemistry, perfluoroaryl cysteine chemistry and other techniques have further broadened the accessible chemical space. [34–43, 56–72]

The most prominent examples in translation are stapled BH3 helices against BCL-2 family proteins and stapled p53-derived inhibitors against MDM2/MDMX. These systems provide an important lesson: the staple is not a passive brace. It can modify hydrophobic surface area, cellular uptake, protease susceptibility and sometimes direct target contacts. Therefore the biological effect of stapling has to be evaluated experimentally and can not be inferred on the basis of an enhanced helicity alone. [37, 38, 56–69]

7.1 Staple placement and optimization

Important side-chain contacts must be retained in staple positioning. The common α-helical spacings are i,i+4 and i,i+7 but the best topology is target and sequence dependent. Structure-based design, alanine scanning, molecular modeling and parallel synthesis permit comparison of multiple staple positions. The further development of stapling toward native residues and nonsymmetric cross-linking in recent work provides ways to modify peptides with less dependence on preinstalled noncanonical residues. [34, 35, 56–72]

8. Strategy VI — Integrated Molecular Optimization for Drug-Like Properties

The final strategy is not a single chemical transformation but an iterative medicinal-chemistry process that balances potency, selectivity, stability, permeability, solubility and pharmacokinetics. The central mistake in peptidomimetic development is to optimize each property independently. A molecule with nanomolar biochemical affinity may fail because it cannot reach the target compartment; a highly permeable analogue may be nonspecific; and a very stable analogue may lose the target-bound conformation. Drug-like optimization therefore requires multiparameter design. [1–7, 29–34]

Figure 3. Qualitative strategy–property map. Scores are conceptual and are intended to illustrate design leverage rather than quantitative performance.

Table 2. Strategy-to-property framework for peptidomimetic optimization

Strategy	Primary effect	Typical benefit	Potential trade-off	Useful assays
D-/noncanonical residues	Stereochemistry/side-chain editing	Protease resistance; potency tuning	Loss of native binding geometry	Proteolysis; SPR/ITC; SAR
N-methylation	Masks NH; changes conformation	Permeability; metabolic stability	Reduced H-bonding with target	PAMPA/Caco-2; NMR; proteolysis
Backbone bioisostere	Changes polarity and cleavage susceptibility	Stability; oral exposure	Synthetic complexity	LC–MS stability; PK
Macrocyclization	Restricts conformational ensemble	Affinity; stability; sometimes permeability	Solubility; ring strain	CD/NMR; permeability
Hydrocarbon stapling	Locks α-helix	Helicity; stability; PPI inhibition	Hydrophobicity; uptake variability	CD; FP/SPR; cellular uptake
Terminal capping	Blocks exopeptidases; tunes charge	Stability; exposure	Changed receptor recognition	Serum stability; receptor assay
Integrated multiparameter SAR	Balances multiple properties	Drug-like profile	Larger design space	Potency + ADME + PK panel

9. Peptidomimetics for Protein–Protein Interactions

Protein–protein interactions are attractive targets because many disease processes are driven by interfaces that are too large or shallow for classical small molecules. Peptides can reproduce short recognition motifs, while peptidomimetics can stabilize those motifs and introduce drug-like features. Helix mimetics, β-strand mimetics, macrocycles and stapled peptides have therefore become important tools for PPI drug discovery. [13–18, 56–72]

The design workflow for a PPI peptidomimetic begins with identification of the native interface and its energetic hot spots, followed by extraction of the minimal recognition motif. The motif is then stabilized or mimicked chemically, and the resulting molecules are evaluated for target affinity, selectivity, cell entry and intracellular target engagement. High-resolution structures are particularly valuable because they reveal whether the modification preserves the intended interface or introduces new contacts. [13–18, 56–72]

10. Computational and Structure-Based Design

Computational methods can reduce the enormous search space generated by peptide sequence and chemical modifications. Molecular docking can identify plausible binding orientations; molecular dynamics can characterize conformational ensembles; free-energy methods can rank analogues; and pharmacophore models can define essential interaction vectors. For peptidomimetics, ensemble-based thinking is especially important because the molecule can occupy different conformations in water, membrane-like environments and the target-bound state. [17, 18, 29–34, 73–76]

A practical computational workflow is: (1) identify a target bound peptide structure or experimentally validated motif; (2) map hot spots and non-essential positions; (3) generate residue/backbone/conformational variants; (4) filter for plausible geometry and synthetic accessibility; (5) estimate target affinity and conformational stability; (6) predict permeability and ADME liabilities; and (7) synthesize a focused set for experimental validation. This approach is becoming increasingly compatible with machine learning-assisted property prediction, but experimental validation is still essential as peptide permeability and conformational behavior are highly context dependent.

11. Representative Therapeutic Applications

Peptidomimetic chemistry has produced discovery programs in oncology, infectious disease, antiviral therapy, enzyme inhibition, inflammation and receptor pharmacology. In oncology, stapled and macrocyclic molecules have been employed to target BCL-2-family interactions, p53–MDM2/MDMX, β-catenin-associated interactions and other intracellular PPIs. Peptidomimetics have been developed as protease inhibitors and also as membrane-active or target-directed antimicrobials in infectious disease. Transition state and substrate-mimetic strategies (e.g. antiviral programs targeting viral proteases) have been especially effective. [38, 56–72, 77–90]

Table 3. Representative examples illustrating strategy-driven optimization

Application	Parent concept	Key modification	Main optimized property	Representative reference
BCL-2 family PPIs	BH3 α-helix	Hydrocarbon stapling	Helicity, stability, intracellular activity	Walensky et al.; DOI linked in Ref. 37
p53–MDM2/MDMX	p53 transactivation helix	Stapling / constrained helix	Affinity and cellular activity	Chang et al.; Ref. 38
Antiviral protease inhibition	Peptide substrate/transition state	Hydroxyethylene and related mimics	Protease resistance / potency	Jaskolski et al.; Ref. 76
Antiviral SARS-CoV-2 Mpro	Protease substrate motif	Structure-guided peptidomimetic design	Enzyme inhibition	Frecer & Miertus; Ref. 84
Antimicrobial peptidomimetics	Host-defense peptide motif	α/β substitution and backbone editing	Stability / antibacterial activity	Molchanova et al.; Ref. 81
Peptoid libraries	Peptide-like recognition motif	N-substituted glycine backbone	Protease resistance / library diversity	Simon et al.; Ref. 89

12. Challenges and Design Trade-Offs

Although significant progress has been made, peptidomimetics do not necessarily have to be drug-like. The biggest hurdles are the compromise between permeability and solubility, affinity and conformational flexibility, metabolic stability and target compatible geometry and chemical complexity and scaleable synthesis. Macrocyclization of peptides may lead to stereochemical or regioisomeric mixtures, hydrophobicity can be added by staples, noncanonical residues can complicate the synthetic and analytical characterization of the peptide, and highly modified peptides may be hard to synthesize reproducibly. [29–38, 56–72]

Translation of biochemical potency to cellular or in vivo efficacy is another challenge. PPIs can have a high affinity for the purified target, but don't penetrate to the appropriate compartment. Similarly, a better serum stability does not ensure good oral absorption. Therefore assays that are orthogonal should be included in the development pipeline early: biochemical potency, target engagement, serum/GI stability, membrane permeability, cellular uptake, endosomal escape (if applicable), microsomal stability, plasma protein binding and pharmacokinetics.

13. Future Perspectives

The future peptidomimetics will not be limited to a single new scaffold but will be characterized by integration. The areas of noncanonical amino-acid chemistry, selective native-residue stapling, macrocycle synthesis, display technologies, and structural biology and computational design are rapidly merging. The most useful design paradigm will be multiparameter optimization--the consideration of recognition geometry, conformational ensemble and ADME properties. [23–25, 29–34, 56–72]

Three directions seem to hold great potential. First, expanded chemical alphabets will give rise to residues and backbones that cannot be found in natural peptides, thereby gaining access to conformations that are not accessible through such peptides. Second, the structural guidance of macrocyclization and stapling will enhance targeting of intracellular PPIs. Third, computational and machine-learning tools can be used to prioritize combinations of sequence, backbone and chemical modifications, thus minimizing the number of compounds that need to be synthesized. It is not a goal to make peptides behave exactly like a small molecule, but to develop a balanced molecular class with the recognition ability of the biologics and some of the drug-like properties of a small molecule.

14. CONCLUSIONS:

Peptidomimetic drug discovery can best be viewed as a toolbox for maintaining recognition for the peptide, while minimizing undesirable characteristics that discount the use of native peptides as drugs. The unnatural residues ensure local control, backbone engineering provides a change in the chemistry of the scaffold, the terminal and side-chain modification controls peripheral properties, cyclization/macrocyclization controls the global shape, stapling stabilises defined secondary structure, and integrated multiparameter optimization brings the resulting molecule toward a viable pharmacological profile. The most successful programs follow these strategies in a recursive manner and test each structural hypothesis by experiment. The peptidomimetics are thus a significant stepping stone between peptide biology and medicinal chemistry, and hold special potential for use on hard-to-access protein surfaces, and for intracellular targets.

15. ABBREVIATIONS:

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism and excretion
Aib	α-Aminoisobutyric acid
AMP	Antimicrobial peptide
CD	Circular dichroism
GI	Gastrointestinal
ITC	Isothermal titration calorimetry
MD	Molecular dynamics
Mpro	Main protease
ncAA	Noncanonical amino acid
NMR	Nuclear magnetic resonance
PAMPA	Parallel artificial membrane permeability assay
PPI	Protein–protein interaction
PK	Pharmacokinetics
RCM	Ring-closing metathesis
SAR	Structure–activity relationship
SPPS	Solid-phase peptide synthesis
SPR	Surface plasmon resonance

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