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Assessment of numerous novel peptidomimetics

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Abstract
Because of the availability of massive amounts of genomic and proteomic data, peptides have great pharmaceutical potential as active drugs and diagnostics in a variety of clinical areas such as endocrinology, urology, obstetrics, oncology, and so on, as well as as functional to overcome tissue and cellular membrane barriers, excipients are used in drug delivery systems. The importance of peptidomimetics in molecular recognition and signalling, particularly in living systems, drives their design and synthesis. Peptidomimetics canbe designed from a variety of angles, and they can be classified in a variety of ways. Accordingto a review of the literature, medicinal and organic chemists who work with peptide mimics use these methods in a various ways. This manuscript is an attempt to discuss a variety of methodologies and strategies for developing and establishing systematic tools for the transformation of peptides into peptidomimetics or further into small drug-like molecules and their pharmacological activities relevant tomodern drug design.

Key words: Peptidomimetics, active drugs, obstetrics, oncology, endocrinology, urology.

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Introduction

Medicinal chemists have used drug discovery methods to design and develop novel drug molecules that can be used effectively in the treatment of a variety of human diseases. A brief overview of some of the most recent drug design techniques, such as molecular docking, quantitative structure-activity relationship, chemogenomic, and marine pharmacology, with a focus on peptidomimetics.

A wide range of naturally occurring peptides have been discovered over the last three decades. These peptides have numerous biological functions, including hormones, enzyme inhibitors, substrates, neurotransmitters, and immunomodulators. They can influence cell- cell communication and control a variety of vital functions such as metabolism, immune defence, digestion, respiration, pain sensitivity, reproduction, behaviour, and electrolyte levels after binding to their corresponding receptors or enzymes. As a result, extensive research has been conducted to better understand the physiological effects of these peptidic molecules in order to design new peptide-based therapeutic agents. Peptides have great pharmaceutical potential as active drugs and diagnostics in a variety of clinical areas such as endocrinology, urology, obstetrics, oncology, and others, as well as as functional To overcome tissue and cellular membrane barriers, excipients are used in drug delivery systems [1]. Peptides fall somewhere between traditional organic drug substances and high molecular weight biopharmaceuticals in terms of pharmaceutical importance. The importance of peptides in life can be seen from the most primitive organism to man. Peptides play a wide range of roles in humans, including hormonal, neuromodulatory, mucosal defence, and so on. Despite the obvious importance of peptides in

human homeostasis, there are Few peptides derived from medicinal chemistry are commercialised pharmaceutical products in the United States and Europe. Peptides' shortcomings as pharmaceutical products have long been recognised: typically short duration of action, lack of receptor subtype selectivity, and lack of oral bioavailability. However, medicinal chemistry provides solutions to the first two limitations, and oral bioavailability issues have been addressed by novel routes of administration (e.g., intranasal, inhalation) and injectable depot formulations [2]. The goal of this paper is to create molecules that can manipulate disease-related biological targets for beneficial effects while being low in toxicity.

Peptide design considerations

The physical and chemical properties of peptides and proteins are determined by the nature of the constituent amino acid side chains as well as the polyamide peptide backbone itself. The 20 primary amino acid structures. Hydrophobic or hydrophilic amino acid residues exist.. The first category includes those with aliphatic side chains (Ala, Val, Ile, Leu, Met) and those with aromatic side chains (Phe, Tyr, Trp). The hydrophilic group includes amino acids with neutral, polar side chains (Ser, Thr, Asn, Gln), acidic (Asp and Glu), or basic side chains (Lys, Arg, and His). Two amino acids, Cys and Pro, have unique properties that set them apart. Cys with a thiol group that can be oxidatively coupled to another Cys residue to form a disulfide bond that stabilises secondary and/or tertiary structure or to hold two different peptide chains together Free thiols, on the other hand, are found in some proteins and act as metal chelation ligands, nucleophiles in proteolitic enzymes, or carboxyl activators in acyl transferases. Pro is a cyclic residue that has specific conformational effects on the backbone of a peptide or protein. Indeed, the cyclic structure holds the Pro backbone dihedral angle at about -75°. Furthermore, several residues can undergo post-translational modification to yield new amino acids. Small peptides typically exhibit high conformational flexibility due to the multiple conformations that are energetically possible for each residue. The peptide backbone conformation can be described by three torsional angles (Figure 1): Ψ, which is defined by C(O)—N—C—C(O); and which is defined by C—C(O)—N—C. Except for the Xaa-Pro bond, the peptide bond angle is generally trans (= 180°). Ramachandran plots that limit the allowed torsional angle values to the majority of amino acids. L-amino acids have access to roughly one-third of the total structural space. However, the remaining degrees of freedom make structure prediction extremely difficult. Only a few examples of short to medium-sized peptides (30-50 residues) forming stable structures in aqueous solution have been reported in the literature [3]. Most of the time, they exist in a variety of dynamically interconvertible conformations. The most significant The x-ray diffraction analysis on single crystal is a technique for structural determination of biomolecules, even though it is debatable whether the solid state conformations determined by X-ray analysis are identical to those occurring in solution or during interactions with the biological target [4]. NMR spectroscopy has emerged as an important tool for determining the structural properties of biomolecules in solution over the last decade. The advancement of magnet technology, as well as the speed and data storage capacity of modern PCs, enabled the development of multidimensional NMR methods that allow for the detailed resolution of biomolecule resonance assignments and the determination of proton-proton distances at the foundation of NMR structure determination. Fluorescence and circular dichroism (CD) studies, in addition to these powerful techniques, provide useful information. data on the peptide's solution conformation and ability to interact with target molecules [5].

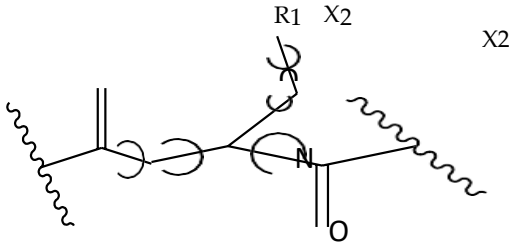

Fig.1. Backbone and side chain torsional angles.

Methodologies for design peptides

One of the most difficult challenges in the design of biologically active peptides remains conformational considerations in peptide synthesis. Peptides in solution are typically an ensemble of conformation states. When biological activity is limited to a single discrete conformer, this conformational ensemble represents a dilution of the biologically active species. This problem is exacerbated in peptides designed to mimic a portion of a protein structure, where the protein structure's intramolecular interactions are lost. The introduction of local or global constraints into peptide sequences could be used to reduce the number of accessible conformations and make the selectivity of synthetic

peptides more stringent than that provided by the sequence.

Global restrictions

Cyclization is the most straightforward way to introduce a conformational constraint into a peptide sequence. When compared to their linear analogues, cyclic peptides typically have higher in vivo stability. Cyclization can be accomplished by connecting the N-terminus to the C-terminus (head-to-tail) of the peptide sequence, or by connecting either the N- or C-terminus to one of the side chains (backbone-to-side chain), or by connecting side chains that are not involved in specific interactions with other side chains (side chain-to-side chain). The formation of a disulfide bond between two Cys residues is the most common side chain-to-side chain cyclization. An amide bond can also form between the side chains of Lys and Asp/Glu. One of the limitations of side chain- The constraint of to-side chain cyclization is that only a small portion of the polypeptide is constrained. To address this issue, multiple covalent bridges can be incorporated into a single sequence [6].

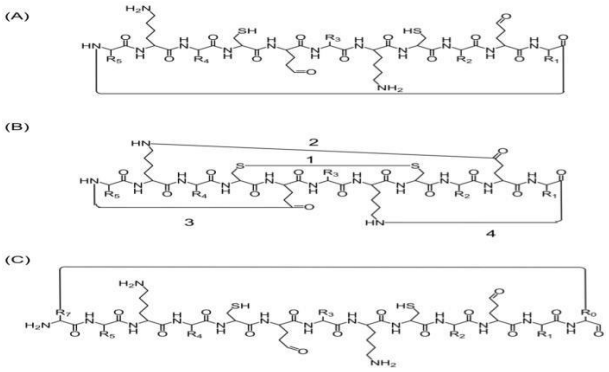

Fig.2. Peptide cyclization:
(A) Head to tail
(B) Backbone to side chain
(C) Sidechain to sidechain.

Local restrictions

The simplest local constraints that can be imposed on a given residue involve the substitution of a methyl group for a hydrogen adjacent to a rotable bond. One substitution that has received a lot of attention in recent years is - hydrogen yielding C-tetrasubstituted-amino acids [7]. For example, replacing the -hydrogen on alanine with a methyl group yields - aminoisobutyric acid (Aib). This residue was discovered in fungal peptide sequences the rotational freedom of the two peptide backbone angles was reduced due to the steric bulk of the methyl group. In the case of Aib, the allowable and backbone angles in peptides are limited to values near -57°, -47°, and +57°, +47° [8]. The introduction of an alkyl group, either at the - or on position the aromatic ring of naturally occurring amino acids rigidifies the side chain's conformational flexibility. Three natural amino acids have - disubstitutions: Val (two methyl groups), Ile (a methyl and an ethyl), and Thr (a methyl and a hydroxyl). Furthermore, - substitution creates a second asymmetric centre in the amino acid structure. These modifications do not significantly alter the backbone, allowing the peptide backbone and side chain some flexibility, which is often critical for peptide mimetic activity. Another advantage of these modifications is that the additional alkyl groups increase the lipophilicity of the peptide, allowing it to cross the membrane barrier [9]. Certainly, the formation of a covalent bond between the aromatic ring of a -amino acid residue and the peptide backbone has proven to be a useful additional conformation restriction. N-alkylated residues, particularly N-methylation, are important peptide bond modifications that affect the conformational freedom of the peptide backbone. The steric constraints introduced by the N-alkyl group have an effect on the side chain freedom of neighbouring amino acids. Furthermore, the removal of the backbone NH groups reduces the number of inter- and intra-molecular hydrogen bonds, destabilising both -helix and - sheet conformations. Finally, the attached carbonyl group exhibits increased basicity and decreased polarity. -peptoids are oligomers of N-substituted glycines with the side chain attached to the amine nitrogen rather than the -carbon [10]. The conformational change in N-substituted glycines causes the α - carbon achiral, so peptoids have less spatial constraint. Because of the lack of amide protons, neither peptoids nor peptides can form intramolecular hydrogen bonds through backbone-backbone interactions. The same backbone structure, however, makes peptoids extremely resistant to proteases. A further investigated group of local constraints are proline derivatives. Proline analogues with the properties of other amino acids are known as proline-amino acid chimeras, and they have been used to investigate the spatial requirements for receptor affinity and biological activity in both natural amino acids and peptides. 3-carboxyproline, 3-phenylproline, and 3-dimethylproline, for example, combine amino acid side chain functionality with the conformational rigidity of proline. These are examples of some cases, replacing natural amino acids in peptides with proline-amino acid

chimaeras improved understanding of the bioactive conformations of peptides binding to receptors [11].

Backbone modification

The backbone of a peptide can be altered in a variety of ways through isosteric or isoeletronic substitution [12]. Various peptidomimetics containing pseudopeptides or peptide bond surrogates, in which peptide bonds have been replaced with other chemical groups, are designed and synthesised in order to obtain peptide analogues with improved pharmacological properties. This is primarily due to the fact that such approaches generate an amide bond surrogate with defined three-dimensional structures and significant differences in polarity, hydrogen bonding capability, and acid-base character. Importantly, the structural and stereochemical integrities of the adjacent pair of -carbon atoms in these pseudopeptides remain unchanged. This type of modification employs A. Spatola's psi-bracket ([]) nomenclature. Such peptide sequence modifications are expected to completely Preventing protease cleavage of the amide bond improves peptide metabolic stability significantly. However, such modifications may have a negative impact on the biophysical and biochemical properties of peptides, particularly their conformation, flexibility, and hydrophobicity. As a result, selecting an amide bond surrogate is a trade-off between positive effects on pharmacokinetics and bioavailability and potential negative effects on activity and specificity [13]. The ability of the surrogate to mimic the steric, electronic, and solvation properties of the amide bond is undoubtedly the most important factor in determining the potency of pseudopeptide analogues. Synthetically, the methods for assembling peptidosulfonamides, phosphonopeptides, oligoureas, depsides, depsipeptides, peptoids, and azapeptides are similar to those for standard solid-phase peptide synthesis, though different reagents and coupling agents are used and safeguarding strategies are required [14].

Methods of synthesis

Synthesis of N, N′-orthogonally protected trithiocarbonate-linked dipeptidomimetics:

N-Protected amino alkyl thiols were treated with carbon disulphide in the presence of triethylamine (TEA) to generate trithiocarbonate salt, which when reacted with appropriate halides yielded dipeptidomimetics in good yields. The procedure was further developed for the synthesis of N, N′-orthogonally protected trithiocarbonate-linked dipeptidomimetics (figure 3) [15].

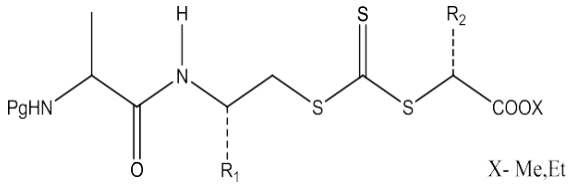

Fig.3. N,N-orthogonally protected trithiocarbonate-linked peptidomimitics.

Synthesis of pyrrolidinones and pyrrolidines peptidomimetics

Protected diaminoalcohols were synthesised by allyl addition to -amino acid-derived imines and subsequent hydroboration to produce pyrrolidinones and pyrrolidines. Pyrrolidinones were synthesised in moderate yields by oxidising the hydroxy function with tetrapropylammonium(figure 4) perruthenate/N-methylmorpholine-N-oxide and concomitant cyclization, whereas pyrrolidines were synthesised in good yields by tosylation of the hydroxy group and subsequent intramolecular nucleophilic substitution. Thus, accessible substrates were transferred into peptidomimetics via the attachment of amino acid moieties at both termini via conventional peptide coupling strategies [16].

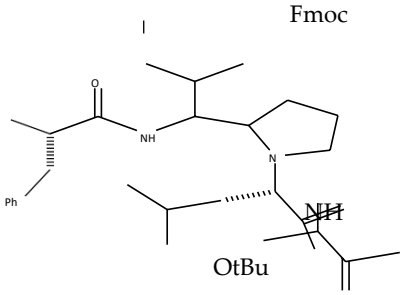

Fig. 4. Pyrrolidinones and pyrrolidines peptidomimetics

Synthesis of glyoxylamide peptidomimetics

Novel mono- and bis-glyoxylamide (figure. 5) peptidomimetics were synthesised by facile ring-opening of N-acylisatins with amino acids and peptide derivatives. The ring- opening of N-acylisatins with dipeptides and tripeptides was discovered to be the most efficient strategy for the synthesis of second and third generation glyoxylamides [17].

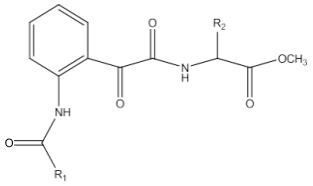

Fig. 5.Glyoxylamide peptidomimtic.

Peptido sulfonamides

Peptidosulfonamides can be synthesised by solid-phase synthesis methods using either a Merrifield or a Tentagel resin. The synthesis of cyclo-phenylalanyl [CH2S(O)2N]-glycine demonstrated the feasibility of preparing cyclic peptidosulfonamides(figure.6). However, the transition from solution to solid-phase peptidosulfonamide synthesis was time-consuming and requires careful optimization [18].

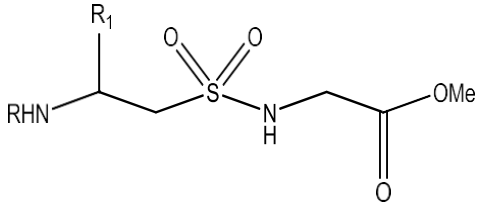

Fig. 6. Peptidosulfonamide.

Synthesis of C-hydroxyalkylamido peptidomimetics:

Using "volatilizable" aminoalkyl functionalized silica gels, we present a promising method for high-throughput synthesis of linear C-hydroxyalkylamido peptidomimetics and beta-turn cyclic peptidomimetics. Boc amino acids and carboxylic acids were coupled using a standard DIC/HOBt coupling protocol on functionalized aminoalkyl silica gels.Following peptide synthesis, the resin bound peptide was cleaved in two steps to yield the linear C- hydroxyalkylamido peptidomimetics [19].

Anti-microbial activity

To combat the growing health threat posed by resistant pathogenic microorganisms, we developed some novel peptidomimetic antibiotics based on the antimicrobial peptide protegrin I. Several rounds of optimization yielded a lead compound with nanomolar activity against Gram-negative Pseudomonas species. The peptidomimetics had a non- membrane-lytic mechanism of action, and a cellular target was identified as a homolog of the beta-barrel protein LptD (Imp/OstA), which functions in outer-membrane biogenesis. In a mouse septicemia infection model, the peptidomimetic showed potent antimicrobial activity against Pseudomonas aeruginosa [20].

Anti-cancer activity

Some novel unnatural amino acid-substituted (Hydroxyethyl)urea peptidomimetics inhibited secretase, neuronal differentiation of neuroblastoma cells, and interfered with tumorigenesis and neuroblastoma malignancy. This demonstrates that peptidomimetics can be used as lead compounds in the development of new anticancer drugs [21].

Anti-viral activity

Georgi et al. investigated a series of acyclovir analogues with a thiazole ring containing amino acids (glycine, alanine, valine, leucine) in their search for new and effective prodrugs against the herpes simplex virus. The chemical stability of some compounds containing variousresidues was investigated at pH 1 and pH 7.4 at 37°C. Some of the esters (Gly-thiazole, Ala- thiazole-acyclovir, Leu-thiazole-acyclovir) were highly unstable, especially in acidic conditions, and hydrolyzed rapidly into the chemical precursor acyclovir. Valthiazole-acyclovir peptidomimetic was extremely stable at pH 7.4. At this pH, the val-thiazole-acyclovir peptidomimetic was more stable than valacyclovir (the first effective acyclovir prodrug) [22].

Immuno detection activity

Murali et al. discovered that antibody-like binding peptidomimetics (ABiP) such as Anti-Her2/neu peptidomimetic (AHNP), a mimic of Herceptin, a mAb, are used for advanced breast cancer therapy. The AHNP has been used as a defining tool in the development of immunodetection probes that demonstrate a general process application. AHNP has been expressed as a streptavidin-oligomeric fusion protein. The immunodetection amplification technique was used to detect the Her2/neu antigen at extremely low concentrations using these Herceptin-like ABiPs (IDAT). A fully developed, highly diverse library of ABiPs represents an alternative to monoclonal antibody panels and may also be useful for target validation, antigen detection, therapeutics, and as a drug development platform[23].

Selectivity for DNA receptors

Jeffrey et al. tested a peptidomimetic template consisting of a hydrophobic scaffold, a dansyl fluorophore, and an Arg-His recognition sstrand as a simple mimic of the zinc finger of the Zif268 protein. Association constants (KAs) were on the order of 105 M1 for complexes formed between the mimetic and duplexes d(CGGGAATTCCCG)2 and (AAAAAAAAATTTTTTTT).

In a 0.5 M NaCl/buffer (0.1 M phosphate, pH 7.0) solution, modest selectivity for GC-rich DNA was observed[24] Differences in KAs, combined with observed CD profiles, suggest that the mimetic is associated with the duplexes via different binding modes. The DNA duplexes had weaker interactions with the free Arg-His recognition strand, the dansyl functional group, and a scaffold with only glycines as the recognition strand. The scaffold most likely provides

for greater van der Waal's interactions, a greater hydrophobic effect on association, and a reduction in side chain freedom of motion This last effect was confirmed by molecular mechanics calculations and the fact that the mimetic suffered a smaller loss of entropic energy upon association than the free recognition strand. These studies show that the synthetic scaffold is a promising platform for attaching peptides to increase their affinity and possibly selectivity for DNA targets [25].

Anti-malarial activity

Ettari et al. created some novel peptidomimetics with a protected aspartyl aldeyde warhead, resulting in thioacylal and acylal derivatives. Both compounds demonstrated increased antiplasmodial activity over the parent molecule. Furthermore, thioacylal has the potential to be a promising trypanocidal agent [26]

Anti-oxidant activity

N-acetylcarnosine (N-acetyl-h-alanyl-lhistidine) (NAC) and carcinine (h- alanylhistamine) are metabolically related to l-carnosine and have been shown to occur in tissues of many vertebrates, including humans; these compounds were shown to be resistant to enzymatic hydrolysis. In order to confer resistance to enzymatic hydrolysis and ex vivo improvement of protective antioxidative properties related to lcarnosine, a series of related biocompatible imidazole-containing peptidomimetics were synthesised [27]. Ex vivo, N-acetylcarnosine (NAC) and carcinine played a greater role in the prolongation and potentiation of physiological responses to therapeutic and cosmetic treatments containing l-carnosine as an antioxidant. NAC can function as a time release (carrier) stable version of l-carnosine in ophthalmic pharmaceutical and cosmetic formulations containing lubricants.

Immunosuppressant activity

Dunehoo et al. discovered that RGD peptides/peptidomimetics have been marketed as anti-thrombotic agents and are being studied for their ability to inhibit tumour angiogenesis. Other cell adhesion peptides derived from ICAM- 1 and LFA-1 sequences were discovered to inhibit T-cell adhesion to vascular endothelial cells and epithelial cells; these peptides are being studied for they could be used to treat autoimmune diseases. Recent research suggests that cell adhesion receptors, such as integrins, can internalise their peptide ligands. As a result, many cell adhesion peptides (for example, RGD peptide) have been used to target drugs, particles, and diagnostic agents to a specific cell with increased expression of cell adhesion receptors. Cell adhesion peptides and receptors are used in specific targeted drug delivery, diagnostics, and tissue engineering. More information on the will be available in the future. Internalization and intracellular trafficking of cell adhesion molecules will be used to deliver drug molecules to specific types of cells or to diagnose cancer, heart disease, and autoimmune diseases [27].

Aminopeptidase N inhibition activity

Qianbin et al. performed biological characterization of piperidinedione peptidomimetic analogues, which revealed that most compounds had high inhibitory activity against aminopeptidase N. (APN). Furthermore, they demonstrated good activity in the HL-60 cell assay and the in vivo anti-metastasis assay. This intriguing activity profile may also serve as a guide for the development of new, specific inhibitors of target mammalian aminopeptidases with a 'one-zinc' active site.

Analgesic activity

Duggan et al. reported the synthesis and biological activity of a low molecular weight nonpeptidic mimic of the analgesic peptide -conotoxin GVIA. When compared to a previously reported lead, the molecular weight of this compound has decreased by 193 g/mol. When compared to the original lead, this compound has an EC50 of 5.8 M and can be synthesised in only six steps.

Anticancer activity

"Ceyda et al. synthesised some novel peptidomimetics with a 2 aminobenzathaiazole scaffold that target the PD-1/PDL-1 pathway in this compound decreased the proliferation of peripheral blood mono nuclear cell 10umconcentration." The novel compound may be able to block cancer immunotherapy [28].

Anti-tumor activty

Jaiwel Chen etal. developed molecular synthesis of mandelic acid peptidomimetic derivatives as amino peptidase N inhibitors. Because amino peptidase is overexpressed in tumour cells and plays a critical role in angiogenesis, the development of amino peptidase N inhibitors is warranted. When compared to other targets, the compound 9M was found to be the most potent. The molecular stimulations revealed that legand co-ordinates with the catalytic zinc ion, which is critical for inhibitory activity [29].

Hemolytic cactivity

Eight new sulfide-based cyclic Peptidomimetics analogues of solanamides A and B have been synthesised using a solid phase peptide synthesised and

SN2 reactin on a morita-baylis-hillman (MBH) residue introduced at the N terminakl of a tetrapeptide. The final step takes advantageof the electrophilic properties of the MBH. The analogues were prepared in a moderate overall yield and did not show toxic effect on stephylococcus aureus growth and were not toxic to human fibroblasts. One of them inhibited the hemolytic activity of S aureus, implying an interfering action in bacterial quorum sensing similar to that previously reported for solanamides [30].

Synthesis of oxetanyl peptides

Martin Mclaughlin et al. are working on the synthesis of novel oxetanyl peptides in which the amide bond is replaced by a non-hydrolyzable axetanylamine. The fragment has been reported. The discovery of a new class of sudodipeptides with the H bond doner or acceptor pattern found in proteins broadens the repertoire of peptidomimetics [31].

Conclusion

The goal of medicinal chemistry is to create molecules that can manipulate disease-related biological targets for beneficial effects with low toxicity. Peptides, as we have seen, have enormous potential as both active drugs and diagnostics. The discovery and development of peptide-based drugs involve both rational and empirical considerations. Random screening procedures can be used to identify ligands for known functional domains of target proteins, which can then be followed by structural and computational analysis. The primary medicinal chemistry challenges for a peptide chemist are to design molecules with a sufficient duration of action, sufficient receptor specificity, and a stable and appropriate formulation. Recently, studies of self-organizing peptides (amyloids) yielded important information for the development of long-acting peptides. Peptide Constraint has been used to both prevent proteolysis and to bias binding toward specific receptor subtypes. The latter activity appears to be evolving into a rational design approach, but it still requires attention to an appropriate strategy for successful commercial development.

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