Solid-Phase Syntheses of β-Turn Analogues To Mimic or Disrupt Protein−Protein Interactions

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ABSTRACT

Protein−protein interactions are difficult targets in medicinal chemistry, but they will become increasingly important as data from The Human Genome Project is interpreted. Our work focuses on β-turn mimics that are designed to mimic or disrupt some of these interactions. Solid-phase syntheses and preferred conformations of β-turn mimics that incorporate dipeptide units are discussed. The activity of one illustrative compound that potentiates the interaction of the nerve growth factor with its transmembrane tyrosine kinase receptor TrkA is outlined. Finally, the importance of dimeric turn mimics and some new approaches to these are described.

More DNA sequence data have been generated in the course of The Human Genome Project than the scientific community can deal with at this time. Its interpretation will reveal the structure and function of proteins that were previously unknown, and hitherto unrealized combinations of proteins that interact with each other. Numerous new targets for medicinal chemistry involving protein−protein interactions will inevitably emerge from these efforts.[1]

Protein−protein interactions are, however, difficult targets in medicinal chemistry.[2] Most involve contacts between faces that span more than 600 Å^2 total area,[3] but, within these contact regions, only a few of the amino acid residues at the interface tend to contribute significantly (>3.5 kcal/mol) to the binding, and these tend to be clustered in hot spots near the center of the interface.[4] These may be surrounded by peripheral amino acids that form hydrophobic "O-rings" to enhance binding at the hot-spot regions by excluding water molecules and providing a low-dielectric environment.[4] Hot spots and the interfaces that encapsulate them tend to be discontinuous, in terms both of special separation and amino acid sequence.[5]

Designing compounds to mimic aspects of protein−protein interfaces[6] requires a paradigm shift away from the small molecules that comply with Lipinski's rules (i.e., molecules should have 5 or fewer H-bond donors, 10 or fewer H-bond acceptors, Log *P* less than 5, and molecular mass less than 500).[7] The main challenge is finding leads that mimic hot spots, even if these leads are less bioavailable than small-molecule pharmaceuticals. A typical problem would be to find compounds that mimic or disrupt binding of the dimeric nerve growth factor (NGF, Figure 1) to its transmembrane receptor TrkA. These mimics probably must resemble the nature and orientation of the pharmacophores on NGF that are involved in the key hot spots. It is also quite probable that one hot-spot mimic might not be sufficient; linking two or more in a dimeric or multimeric arrangement may be required. This Account focuses on mimicking and disrupting protein−protein interactions that involve β-turns. Critical hot spots for the NGF/TrkA interaction include the NGF β-turn regions, and this Account describes how β-turn mimics have been produced and validated for this particular target.

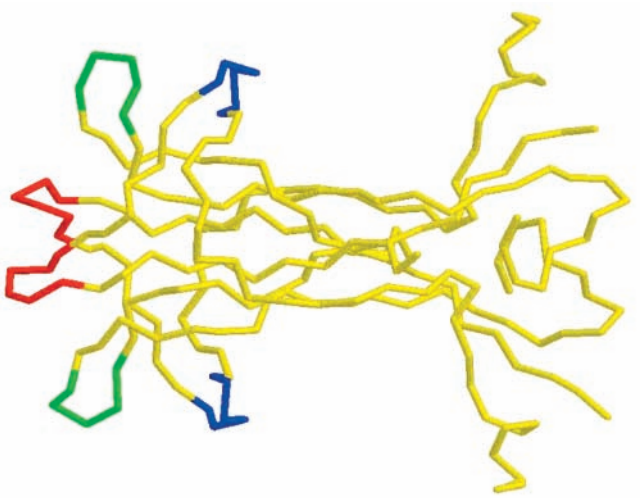

FIGURE 1. Structure of NGF homodimer with key turn regions highlighted.

Figure 2 outlines a strategy for dealing with new targets involving protein−protein interactions. In this, structural models (X-ray, NMR, or computer-aided simulations guided by homology) reveal points of contact at the target protein−protein interface.[8] Conclusions regarding the characteristics of the hot spots may be partially validated by mutagenesis studies, but model peptides that resemble these regions are also valuable. If the model peptides have no secondary structure constraints, they usually must be relatively large to interact effectively with the protein because the peptide must provide interactions that compensate for the entropic penalty of docking a flexible peptide in a relatively ordered and static orientation.[9] Smaller peptides that are constrained using disulfide linkages sometimes provide more suitable models. Constrained peptides that have measurable activities can be used to facilitate studies in which amino acids are systematically substituted (cf. "alanine scan") to identify

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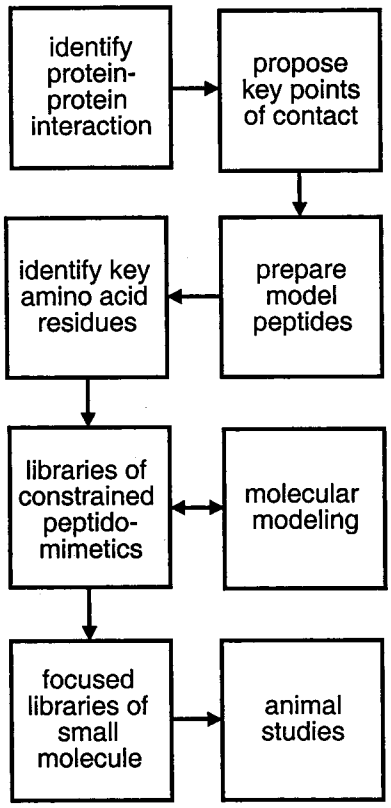


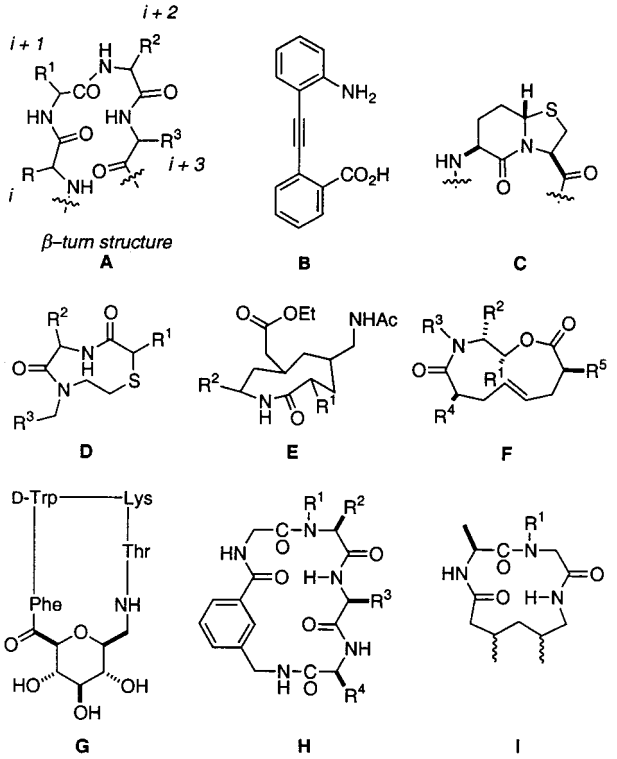
FIGURE 2. Strategy for designing small molecules that mimic or disrupt protein−protein interactions.

the critical side chains and necessary conformations. The next stage entails design and synthesis of conformationally constrained peptidomimetics presenting the critical side chains in the correct orientations to test positive in the biological assays. Libraries of such analogues enable "structure−conformation−activity relationships" (SCARs) to be delineated, that have one more dimension than conventional structure−activity relationships (SARs).

Several generalities apply to the conformationally constrained peptidomimetics alluded to in Figure 2. First, they should be accessible via syntheses that conveniently allow introduction of any protein amino acid side chain, since all types (lypophilic, hydrophilic, charged, and neutral) are found at hot spots.[4,5] Second, the conformations of these peptidomimetics should mimic one of the common elements of protein secondary structure (helices, sheets, or turns) frequently found at protein−protein interfaces.[4,5] Appropriate conformational constraints not only increase the free energy of binding (see above) but also facilitate studies in which preferred solution-phase structures can be used for predicting the structure of more rigid compounds that resemble the hot spots. Finally, syntheses of the peptidomimetics should enable rapid production of libraries because the optimal combinations of structural and conformational features are subtle, hence there will always be an element of trial and error. Solid-phase syntheses are most easily adapted to high-throughput automated parallel formats, so preparation of the compounds on a support is a valuable feature.

***β*-Turn Mimics: Background.** The term "β-turn mimic" has been applied liberally, so it is important to delineate the type that we required and how they differ from others.

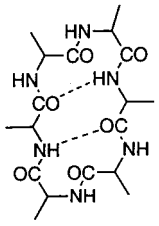
Most of the compounds made to resemble β-turns (**A**)



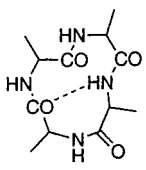
would be of little value for exploring protein−protein interactions. For instance, many analogues produced to initiate β-sheet formation in studies of protein folding (e.g., **B**) are unsuitable because they do not incorporate side chains corresponding to the $i + 1$ and $i + 2$ amino acids.[10] Similarly, few of the numerous ring-fused β-turn mimics (e.g., **C**)[11] are relevant here. Most of these were not obtained via solid-phase syntheses, do not contain an amide-based turn backbone, do not have a good overlap with ideal turn conformations,[12] and/or do not permit facile introduction of side chains corresponding to the functionalized amino acids. In any case, these types of compounds have not proved to be particularly useful in medicinal chemistry. Ellman's solid-phase syntheses of compounds **D**[13] enabled rapid production of libraries, and screens of these were used to discover active somatostatin analogues.[14] However, these compounds are relatively flexible in solution (computer-aided molecular dynamics; with S. Jin, unpublished). In that respect they are reminiscent of the nine-membered macrocycles prepared by Olsen, Kahn, and others in solution (e.g., **E**).[15] Similar macrocycles, not particularly targeted toward β-turns, recently have been prepared on a solid phase (e.g., **F**).[16] Screening large libraries of these types of materials (10^4−10^5 compounds) may reveal active components, but the hit rate is likely to be higher (and the requisite library size therefore smaller) for mimics that resemble natural β-turns of peptides more closely. This is important because unacceptably low hit rates are common in high-through-

put screens involving protein−protein interactions. Our strategy to increase the hit rate has been to maintain a turn or partial turn comprised of amino acids in the mimic. Some compounds in the literature relate to this design. For instance, Kessler's carbohydrate-based materials **G**,[17] DeGrado's Mamb derivatives **H**,[18] and Aubé's 13-membered-ring Ala-Gly turn analogues **I**[19] are relevant. The only drawback with these is that efficient solid-phase routes to libraries of compounds like this have not been reported.

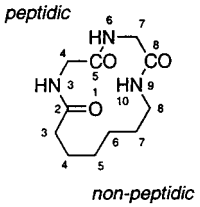
If the turn mimics most likely to give hits contain amino acids, why not use cyclic peptides? Cyclic hexapeptides, for instance, are known to adopt interchangeable turn−extended-turn conformations, and the conformational ensemble can be biased by placing D-amino acids at selected positions.[20] However, solid-phase syntheses of libraries of cyclic hexapeptides, though possible,[21] are difficult for a variety of reasons. The requisite macrolactamization reactions are sequence dependent and, in many cases, will not give sufficiently high purities. Another problem is that epimerization can be facile in these syntheses. Furthermore, difficult amino acid sequences will be encountered, making even some of the linear peptide precursors hard to form. Similar considerations apply to cyclic penta- and tetrapeptides, except that the macrolactamization step can be even more difficult for these compounds. For these reasons, turn mimics composed of only amino acids are not ideal, and in any case, compounds of this kind may have unfavorable bioavailability characteristics.



cyclic hexapeptide turn-extended-turn conformation



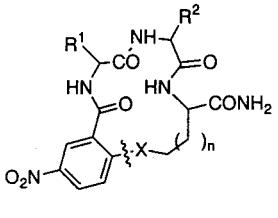
cyclic tetrapeptide



14-membered ring having a "ring-fused" C^{10} arrangement

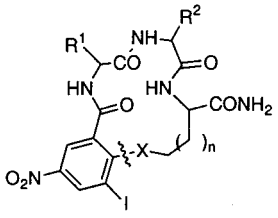
β-Turn Mimics Designed To Resemble Hot Spots at Protein−Protein Interfaces. Our designs of β-turn hot spot mimics are based on "ring-fused C^{10} motifs" or "back-to-back β-turns" as shown above. Such molecules resemble cyclic hexapeptides in turn-extended-turn conformations, but the extended region is not present. These 14-membered-ring macrocycles are easier to form than the ring-strained cyclic tetrapeptides, can incorporate exactly the amino acids found at target turn hot spots, and the non-peptidic part can include organic fragments to improve bioavailability. That non-peptidic sector can also contain the anchor to the solid phase. Macrocyclization can be achieved by forming a bond in this part of the molecules via reactions that are orthogonal to amide bond formation and potentially more efficient.

Solid-Phase Syntheses of Ring-Fused C^{10} Motifs. We designed compounds **1**−**6** to have back-to-back turn conformations and developed solid-phase syntheses of these materials via the disconnections indicated below.



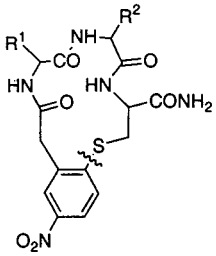
1

n = 0, X = O, S
n = 1, X = NH, O
n = 2, 3, X = NH



2

n = 0, X = O, S
n = 1, X = NH, O
n = 2, 3, X = NH



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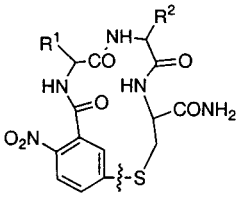
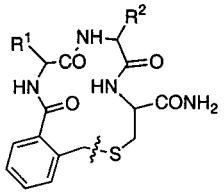
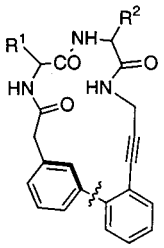


4



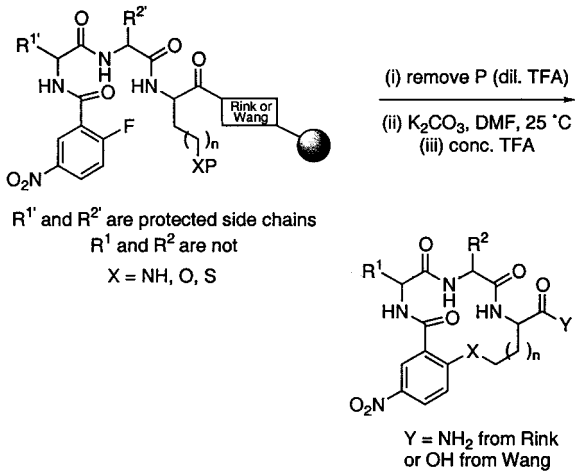
5



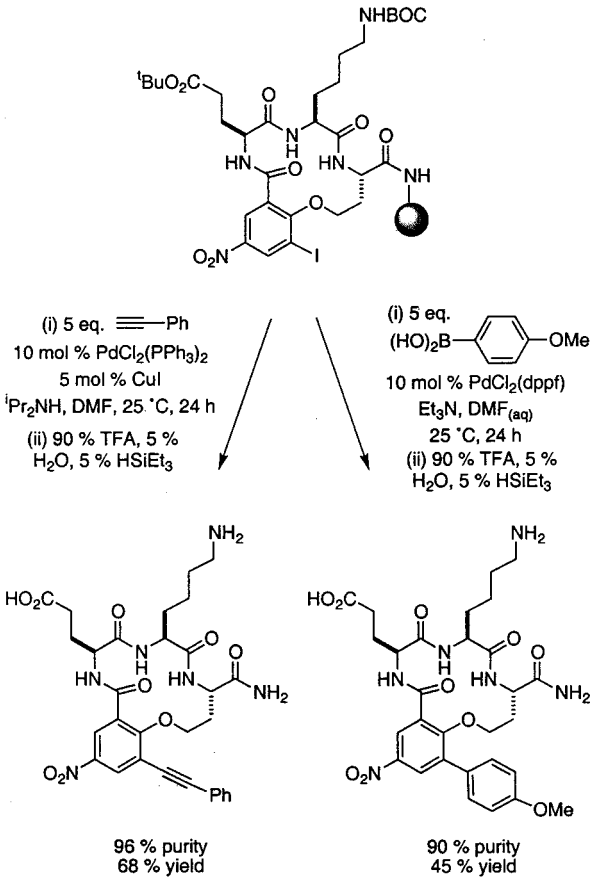
6

Preparation of the macrocycles **1**[22,23] and **2**[24] involves S_NAr displacements as shown below. The most difficult aspect of these syntheses is generating supported precursors with unprotected side chains at the first amino acid residue, while all the other side chains remain protected. This is nontrivial because that first amino acid side chain must be protected for the initial coupling and then deprotected on the resin without cleaving the handle that links the peptide to the support. To do this, various resins functionalized with the Rink or Wang handles have been used.[25] The protecting group strategy varies according to the nature of the first residue attached to the resin. For serine and homoserine, the side chain is protected with a trityl group so that it can be deprotected under mildly acidic conditions that do not cause cleavage from the resin or loss of ^{t}Bu/BOC protection on the other amino acids side chains. Similarly, the sulfur side chain was protected with (4-methoxyphenyl)diphenylmethyl (Mmt). Protection of nitrogen side chains was achieved by using the (4-methylphenyl)diphenylmethyl (Mtt) group, or by effecting an on-resin Hoffman degradation of Gln or Asn immediately prior to the cyclization.

The efficiency of the cyclization illustrated below is dependent upon the nucleophile X and the ring size.[22,23,25]

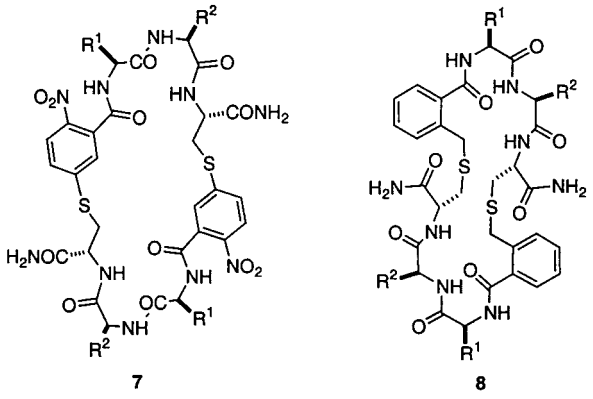


For the Lys and Orn derivatives (X = NH, n = 3 and 2, respectively) and for the Gln and Asn Hoffman degradation products (X = NH, n = 1 and 0, respectively), the purities of the crude materials are in the 90% range. Cyclizations using Ser or homoserine (HSer) at that first position (X = O, n = 1 and 0, respectively) are more difficult; the serine derivatives give unsatisfactory purities (less than 85% in most cases), but the HSer derivative purities are acceptable (most over 85%). O-Nucleophiles are not as effective as nitrogen ones, and 13-membered rings (n = 0, corresponding to Ser) are harder to form than 14-membered macrocycles (n = 1, from HSer). The Cys derivatives (X = S, n = 0) give acceptable cyclizations because sulfur is a good nucleophile, even though the macrocycle formed is a 13-membered ring.



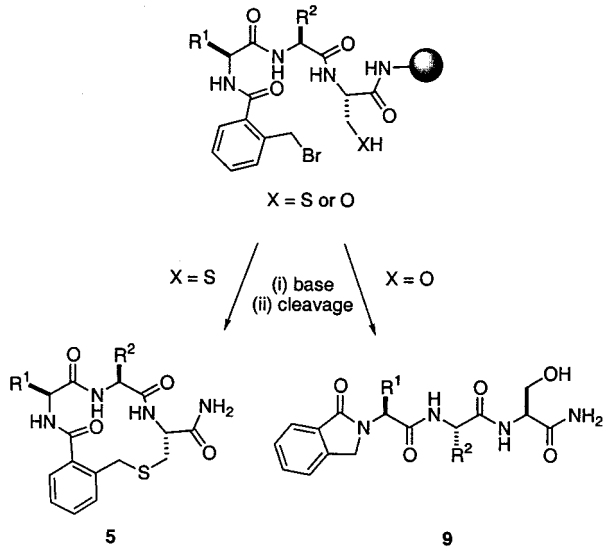
Purities of crude materials isolated after cleavage from the resin are critical in solid-phase syntheses, especially if the crude samples are to be taken directly into biological assays. Consequently, modifications to increase purities can be important. Compounds **2** illustrate a modification in which an iodine atom was used to accelerate the S_NAr displacement; the halogenated products **2** were obtained in higher purities than compounds **1**.[24] The aryl iodide functionality can also be used to diversify the library via on-resin organometallic coupling reactions as illustrated above.

Of the S_NAr macrocyclization products **3** and **4**, only **3** potentially has a back-to-back turn conformation. These products were made in comparative studies to test if back-to-back turn conformations could be instrumental in obtaining highly efficient macrocyclizations. In the event, on-resin cyclizations to give compounds **3** uniformly did proceed to give higher purities than the similar cyclizations to give compounds **4**.[26,27] The latter were consistently contaminated with head-to-tail dimers **7**. We find that formation of dimers like these is indicative of more difficult macrocyclizations.

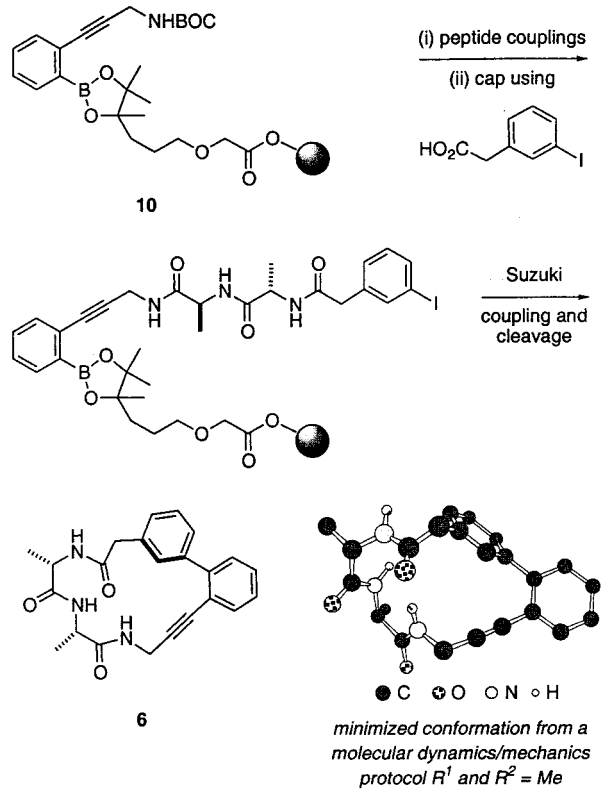


S_N2, rather than S_NAr, displacements were used to prepare the peptidomimetics **5**. These proceeded to give products with purities of around 80%, which ordinarily would not be satisfactory. However, the head-to-tail dimers **8** accounted for most of the other material; the reactions cleanly went to those two products. This dimer formation can be suppressed by decreasing the resin loading. These S_N2 macrocyclizations did not proceed in the same way when oxygen nucleophiles were used (with tetramethylguanidine as base); in that case, five-membered-ring lactams **9** were formed via cyclization onto the amide backbone of the peptide. Consistent with this, macrocyclizations of peptide-based materials reported by other groups tend to feature *S*-nucleophiles.[28]

Synthesis of the biaryl-linked turn mimics **6** requires preparation of the specialized handle shown attached to a resin in compound **10**.[29] Standard amino acid couplings, then capping of the sequence with an aryl iodide, facilitates production of turn mimics **6** via a Suzuki coupling. Only material that cyclizes cleaves from the resin, so the crude product is relatively pure. Strictly, systems **6** are not



ring-fused C^{10} motifs, but the Chem3D diagram shown below illustrates how turn conformations could be obtained.



A group at Amgen has also been investigating solid-phase S_NAr macrocyclizations.[30] However, their products are not designed to relate specifically to β-turn conformations.

Conformational Analyses of Ring-Fused C^{10} Motifs. Figure 3 shows the $i + 1$ and $i + 2$ ϕ,ψ dihedral angles in the common idealized β-turns.[31] There is little difference between type I and III turns, but type II turns *are* fundamentally different in that they involve a radical twist of the amide bond connecting the $i + 1$ and $i + 2$ residues. Type I′, II′, and III′ turns usually involve D-amino acids

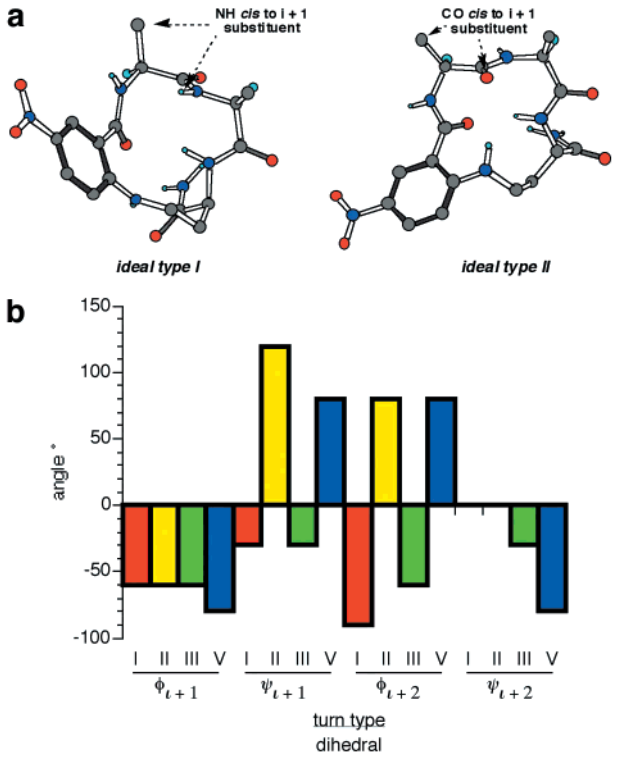


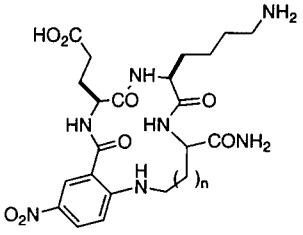
FIGURE 3. Comparisons of different β-turn types.

and so do not relate directly to protein hot spots; they can be regarded as "conformational mirror images" of the parent turns (e.g., ϕ,ψ dihedral angles for the $i + 1$ and $i + 2$ residues are −60°, −30°, −90°, and 0° for type I, and +60°, +30°, +90°, and 0° for type I′). Other turn types (IV and above) are less common in proteins and share some similarities with type I and/or type II turns.[32] Therefore, *flexible turn analogues may be classified as type I-like or type II-like, while recognizing that they sample other conformational states in solution*. In fact, the significance of differences between turn types is sometimes questionable, even in single-crystal X-ray diffraction studies. For example, there are two crystallographic data sets for uncomplexed NGF; one of the turn regions is type I in one analysis (2.3 Å resolution)[33] and a type II in the other (2.8 Å resolution).[34]

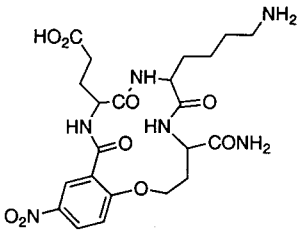
Our hypothesis that 14-membered rings corresponding to "ring-fused C^{10} motifs" would tend to give the most ideal turn conformations was tested via conformational analyses on compounds **11** which have 13- to 16-membered rings. Several techniques were used to do this. One-dimensional NMR studies revealed abnormal chemical shifts and provided coupling constants from which bond angles were estimated. Variations of chemical shifts with temperature were used to highlight N*H* protons that are hydrogen-bonded and/or solvent-shielded. Where possible, rates of exchange of amide N*H* protons with D_2O were used to check the conclusions from the temperature coefficient studies. Two-dimensional NMR studies showed the close contacts between protons. Circular dichroism was used to obtain information about the overall secondary structures. Finally, computer simulations without constraints were performed to generate virtual confor-

mational ensembles for comparison with the physical data. Correspondence between the virtual and experimental data provides pictorial models of the preferred conformations.

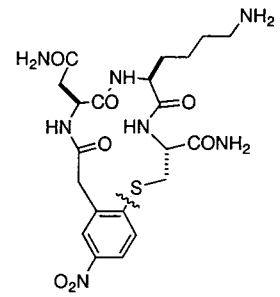
All the ring systems, 13- to 16-membered, were shown to adopt type I turn conformations, but the fit to the ideal parameters was, gratifyingly, best for the 14-membered-ring compound ($n = 1$).[22,35] Thus, the hypothesis that led us to this design is validated in this case. Moreover, analysis of the LLL isomer of compound **12** (i.e., the oxygen analogue of **11**, $n = 1$) showed an even better correspondence to an ideal type I β-turn conformation than the nitrogen analogue (**11**, $n = 1$). Most turns in proteins are type I,[22,35] but we had to find a way to introduce conformational diversity to mimic the others. Thus, we sought to find the positions at which D-amino acid substitutions would exert maximal effects on the conformation. When the isomeric series **12** was studied, all the compounds had type I-like conformations, except the LDL isomer.[36] D-Amino acids sandwiched between two L-amino acids therefore have a maximal effect on the conformations of these molecules.



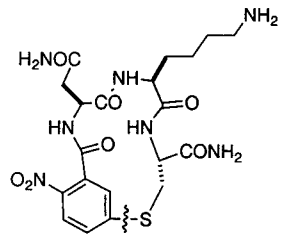
11
n = 0 - 3



12
LLL, DLL, LDL, LLD



13



14

Some molecules designed to have ring-fused C^{10} motifs did not show a conformational preference for β-turns. For instance, neither of the compound types **13** or **14** have a strong conformational bias toward a β-turn, even though physical models of compound **13** indicate that it could adopt such conformations.[26] Studies on several S_NAr products are ongoing to probe interdependence of heteroatom type and conformation, and how peripheral substituents may cause perturbations.

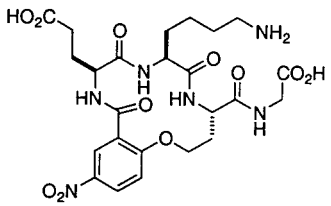
The S_N2 macrocyclization products **5** have a tendency to adopt type II β-turn conformations, but this preference is sequence dependent.[37] Circular dichroism studies indicate that some molecules in this series populate both type II and type I conformations, and these assertions are supported by modeling studies.

Relatively few compounds **6** have been prepared so far.[29] Our conformational studies on these have been limited to modeling work that indicates turn conformers are accessible.

Ring-Fused C^{10} Motifs as Mimics of NGF. All the analogues prepared in our methods-development work encapsulate amino acids found in turns involved in protein−protein interactions, mostly that of NGF with its high-affinity transmembrane tyrosine kinase receptor TrkA. Interventions targeted toward NGF/TrkA have considerable potential in medicinal chemistry. TrkA agonists or compounds that potentiate the effects of endogenous NGF could be useful in treatment of neurodegenerative diseases like Alzheimer's disease[38] and of neuronal damage resulting from traumatic accidents.[39] Antagonists of TrkA could be useful for treatment of neuroblastoma (cancer of the nervous system) or other tumor types; for instance, TrkA receptors are overexpressed in breast tumor cells, so these may respond selectively to TrkA antagonists.[40]

There is no structural information to show how the β-turns in NGF can interact with TrkA,[41] but disulfide-linked cyclic octapeptide mimics of the turn regions in NGF (Figure 1) are antagonists.[42] Therefore, many of the analogues we prepared contain amino acids corresponding to the $i + 1$ and $i + 2$ residues of the NGF turn regions.

Several assays are necessary to test if a small molecule mimics or disrupts the TrkA/NGF interaction by binding TrkA. Without multiple assays, small molecules that function in other ways can be confused with real leads. For instance, a molecule could up-regulate the production of NGF, bind NGF rather than TrkA, or bind TrkA without precipitating any response. Our collaborator, Uri Saragovi, has more than seven assays available to test for molecules that give a functional response via TrkA binding; hence, he is well positioned to distinguish these from compounds having other modes of action. Saragovi and co-workers have discovered that several of our compounds are active in all their assays. An early lead (patent application in progress) is compound **D3**.[43] We prepared a biotinylated analogue of **D3** (via nitro group reduction on a solid phase, and addition of a biotin-containing fragment) to facilitate direct studies of binding of the **D3** core to the Trk receptors.



D3

Saragovi and co-workers have observed the following about **D3**:

- (in its biotinylated form) it binds directly to TrkA expressing cells, and to a solubilized form of the TrkA receptor immobilized on glass;
- it competes with a monoclonal antibody known to bind TrkA;

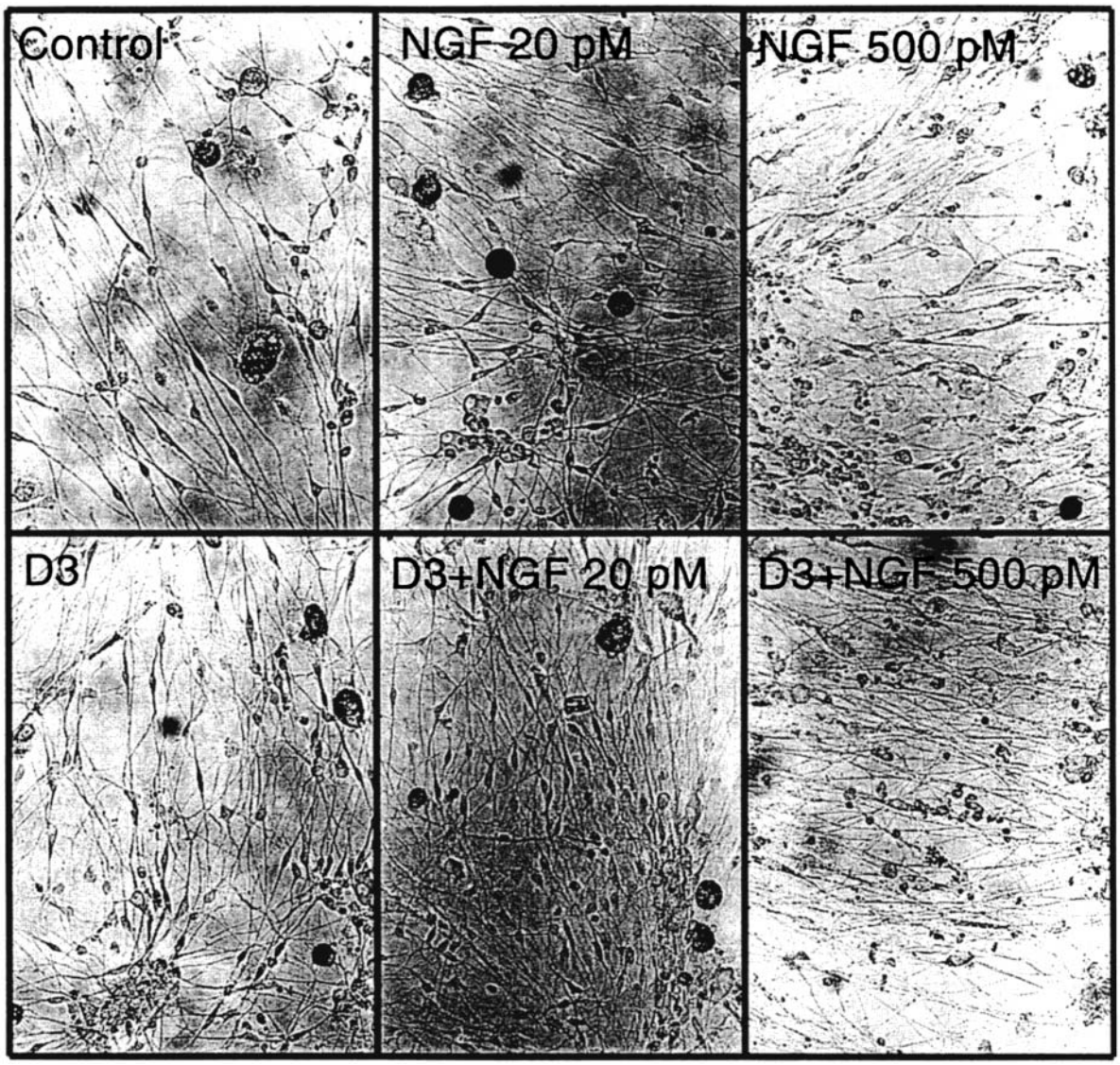


FIGURE 4. D3 potentiates the effects of NGF binding to TrkA. The photographs on the top row show unhealthy rat brain cells (dendrites show poor overlap) in the presence of increasing amounts of NGF. On the bottom row are equivalent experiments but in the presence of **D3**, and the dendrite outgrowth is enhanced in each case.

• it gives IC_{50} values of 4 μM and estimated K_d values of 2 μM in both binding assays;

• it up-regulates the production of choline acetyl transferase just as NGF does;

• it causes intracellular Tyr residues of TrkA to become phosphorylated;

• it potentiates the survival effect of suboptimal concentrations of NGF on TrkA expressing cells that are starved of other growth factors; and

• it potentiates the effect of endogenous NGF in promoting the outgrowth of dendrites on brain cells in vitro (Figure 4).

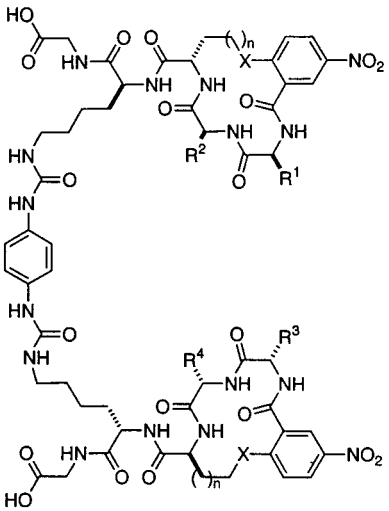
Compound **D3** is not a true agonist (it does not act in the absence of NGF), but this is not a disadvantage from a therapeutic standpoint because the central nervous system has endogenous NGF. The data summarized above are significant because outside of these studies there are no compounds that have been conclusively shown to mimic or disrupt binding of NGF to TrkA by binding the receptor.[44]

Multivalent β-Turn Mimics. It is surprising that **D3** acts in concert with NGF. It is widely held that when NGF binds to TrkA receptor, dimerization is crucial to cell signaling; hence, monovalent molecules like **D3** are more likely to be antagonists. The fact that it is not indicates that some other molecular pathway must be involved that is more complex than we had originally envisaged.

Prior to the pharmacological studies of **D3**, we had assumed that to obtain a TrkA agonist it would be necessary to prepare molecules containing two turn mimics corresponding to combinations of turns, one from each of the NGF monomer units. Indeed, that may be a requirement for development of true TrkA agonists that act in the absence of NGF. Combinations of turn mimics of two different NGF bends in the same monomer are also

potentially valuable; these could form "super-antagonists" that bind more strongly than their single-turn components. These observations are consistent with a general realization that we share with others in the field:[45] *libraries of rationally designed small-molecule dimers, trimers, and tetramers will be critical in studies of cell signaling mediated by multimeric ligands causing aggregation of receptor molecules.*[46] Two methods for production of molecules containing more than one turn mimic have emerged from our laboratories so far.

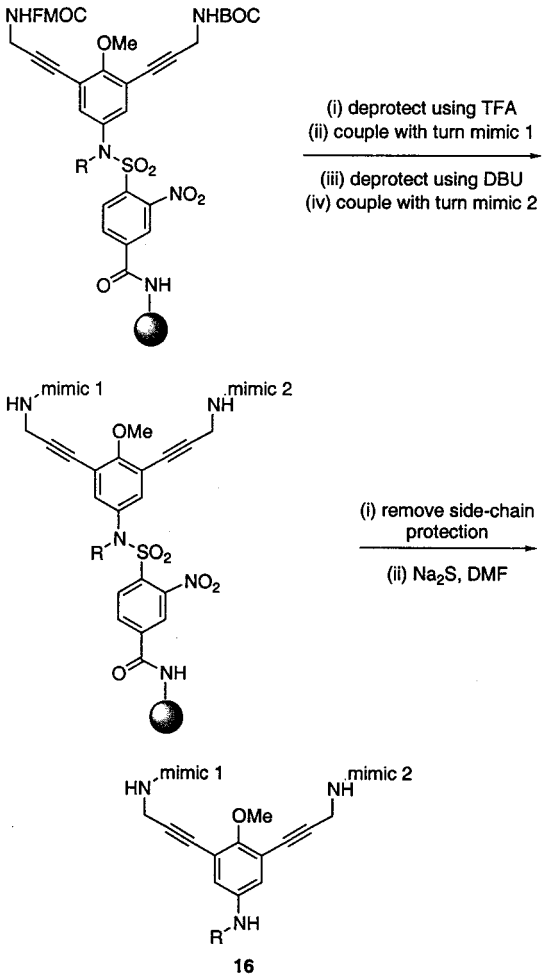
A library of compounds **15** was made via a "divergent convergent approach" involving reaction of a smaller library with itself. Briefly, six monomers were made with a lysine spacer between the Wang linker and the peptidomimetic. The Lys side chain was protected with a hydrazine-labile (ivDde)[47] protecting group, and each sample in the supported library was divided into two. One aliquot of each was cleaved from the resin, giving peptidomimetics with a free amino group on the Lys terminus (no other amino acids requiring side-chain protection were involved in this study). The other aliquots were treated with, in this order, hydrazine, a 1,4-diisocyanate benzene derivative, and finally each of the peptidomimetics that were liberated into solution. These operations were performed in a one-compound-per-well format. Reactions of libraries with libraries[48] like this offers considerable numerical advantages in combinatorial chemistry,[49] though our study was a very modest example since only 12 dimers were prepared.



15

The activities of the bivalent molecules **15** and their monovalent compoents were assayed using a cytosensor microphysiometer.[50] This device has multiple wells for suspending cells in nonbuffered media and allows them to be treated with the test compounds (or controls). The cytosensor microphysiometer then measures the pH of the media as a function of time. Molecules that bind cell surface receptors and initiate signaling of any type ultimately cause the cells to liberate protons into the medium, giving pH decreases at rates characteristic of the cell surface receptors that were activated. These assays indicated that the bivalent molecules induced a greater response than the monovalent ones from which they were formed, though these observations need to be confirmed using other assays.

Our other approach to preparing dimers has been via the tailor-made linker scaffold **16**.[51] This is designed so that the BOC protecting group can be cleaved and a peptidomimetic attached to one arm of the scaffold, and then the FMOC group can be removed and another peptidomimetic attached to the other arm of the scaffold. The functionalized scaffold is then disconnected from the resin using sodium sulfide in DMF. We developed this cleavage system because the ones commonly used to cleave nosylates[52] involve substances like thiophenate; these generate byproducts that interfere with biological assays performed on crude samples. Conversely, sodium sulfide protonates to hydrogen sulfide on workup after the cleavage reaction, leaving only sodium hydroxide than can be neutralized with a buffer. A library of simple dimers has been prepared to demonstrate proof of principle.[53] The spacing of the amine groups on the arms on the scaffold **16** is approximately 10 Å, a distance which is appropriate for some turn combinations in NGF.



16

Outlook

Several challenges remain in this area. First, a greater diversity of turn analogues is required. For this, clean on-

resin macrocyclization reactions are critical to enable crude products to be isolated from the resin in reasonably high purities. More conformational studies are necessary to understand the structural features that determine the shapes of these molecules in solution. More efficient ways of forming dimers are urgently needed. In practice, dimers are hard to make because the constituent monomers are generally prepared on relatively small scales.

Once the synthetic obstacles are overcome, libraries of monomers and dimers can then be tested in other systems involving protein−protein interactions to access the generality of our approach. This is a pivotal issue. If the strategy outlined above is applicable only to NGF, then we have been lucky to find it. However, if is applicable to other protein−protein interactions, then this is the basis of a major development in the field. In the latter case, relatively small focused libraries of secondary structure mimics that have a good probability of providing leads in assays involving protein−protein interactions, including new ones discovered via genomics and proteomics, could be extremely valuable.

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