Solid Phase Syntheses of Oligoureas

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Abstract: Isocyanates **7** were formed from monoprotected diamines **3** or **6**, which in turn can be easily prepared from commercially available *N*-BOC- or *N*-FMOC-protected amino acid derivatives. Isocyanates **7**, formed *in situ*, could be coupled directly to a solid support functionalized with amine groups or to amino acids anchored on resins using CH_2Cl_2 as solvent and an 11 h coupling time at 25 °C. Such couplings afforded peptidomimetics with an *N*-phthaloyl group at the *N*-terminus. The optimal conditions identified for removal of the *N*-phthaloyl group were to use 60% hydrazine in DMF for 1−3 h. Several sequences of amino acids coupled to ureas ("peptidic ureas") and of sequential urea units ("oligoureas") were prepared via solid phase syntheses and isolated by HPLC. Partition coefficients were measured for two of these peptidomimetics, and their water solubilities were found to be similar to the corresponding peptides. A small library of 160 analogues of the YGGFL-amide sequence was prepared via Houghten's tea bag methodology. This library was tested for binding to the *anti-β*-endorphin monoclonal antibody. Overall, this paper describes methodology for solid phase syntheses of oligourea derivatives with side chains corresponding to some of the protein amino acids. The chemistry involved is ideal for high-throughput syntheses and screening operations. The products can be expected to have an interesting range of pharmacological properties and enhanced proteolytic stabilities relative to the corresponding peptides.

Introduction

Much of the combinatorial chemistry[1−6] now practiced in pharmaceutical companies around the world originated from research involving solid phase peptide syntheses.[7,8] This was not a coincidence. Peptide chemistry was one of the few areas for which techniques in solid phase syntheses were sufficiently well developed to permit experiments like those conceived by Furka,[9] Houghten,[10] Lam,[11] and others.[12] Paradoxically, however, peptides are not ideal candidates for many avenues of pharmaceutical development. Their major attribute is that they can present an infinite number of pharmacological profiles by forming permutations of acidic, basic, hydrophobic, hydrophilic, and aromatic side chains. The main reason peptides are not used more extensively as pharmaceuticals is that their bioavailabilities are not high, mainly due to proteolytic degradation. The focus of combinatorial research is therefore moving away from peptides toward other molecular types that can be prepared on a support thereby facilitating separations. Research on solid phase syntheses of small molecules is proliferating as a consequence.[13−15] There is also considerable interest in the formation of supported oligomers with a defined sequence.[16,17] Well-designed oligomers can be formed on a support by repeating the same types of coupling reactions. They can have chemically diverse side chains, but they need not have proteolytically labile amide bonds.

At the present time there are several approaches to the formation of novel oligomers of defined sequence. "Peptoids" [poly(*N*-alkylglycines)][18−21] and per-*N*-methylated peptides[22] illustrate the concept of using unusual polyamide structures. As the initial stages of the work reported in this manuscript were in progress, a paper by Schultz and co-workers appeared describing oligocarbamates prepared and tested on a plate with small photochemically addressable zones.[23] Since then there has been other research in this area[24] (including the preliminary communication of the work reported in this paper).[25] Somewhat later, Janda and co-workers christened azapeptides[26,27] contain-

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ing several consecutive urea bonds as "azatides" and described an elegant method for preparation of these materials on poly(ethylene glycol) as a liquid phase support.[28]

Other recent studies complement our current research in other ways, with respect to either formation of isocyanates or coupling of isocyanates to amines in supported reactions. The synthetic basis of Nowick's studies on molecular scaffolds[29,30] involves urea bond formation by reaction of amines with isocyanates in solution. Those researchers have developed pertinent ways to produce isocyanates from amino acid derived materials in the course of these studies.[31,32] Phosgene or triphosgene can be used for such reactions.[33] Meanwhile Hutchins and Chapman have been exploring solid phase methods to prepare small molecules containing urea bonds. To achieve this goal, supported amines were reacted with bis(4-nitrophenyl)carbonate or (4-nitrophenyl)chlorocarbonate to give anchored (4-nitrophenyl)carbamates, which were then coupled with other amines in solution.[34,35] Since that work, others have used urea bond formation in syntheses of small molecules on a solid phase wherein that particular step was not the focus.[36,37]

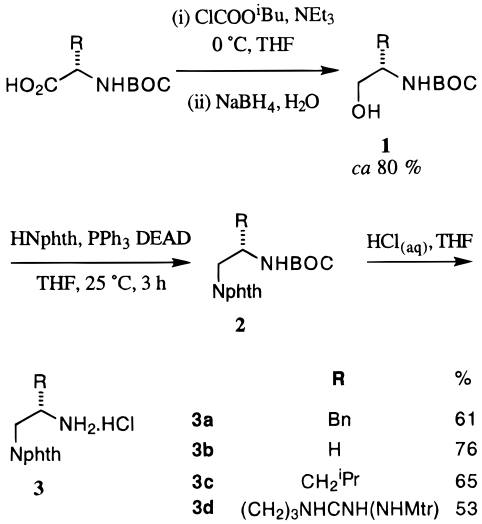
The objective of the work reported here was to study the potential of solid phase syntheses of oligoureas.[25] Oligourea backbones of the type outlined here have the potential to support a selection of chemically diverse side chains on a framework that is unlikely to be easily hydrolyzed by proteases. Preparations of starting materials are described, and details of the coupling steps used in the solid phase syntheses are given. Solubility properties of some of the products have been elucidated using partition coefficients. Finally, the expertise accumulated in the course of this work was then used to prepare a 160-member pilot library for a test screen using a monoclonal antibody.

Results and Discussion

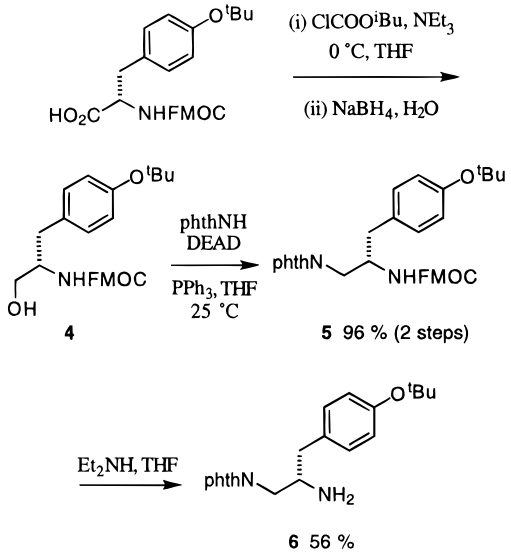
Preparation of the Monomers. Monoprotected diamines were required for the syntheses of oligoureas and peptide/oligourea chimeras. Scheme 1 gives the route followed to obtain these starting materials from amino acids which do not have reactive side-chain functional groups. This sequence was outlined in the communication of this work,[25] and experimental details are given in the appropriate section of this paper.

The corresponding protected diamine derived from tyrosine was required for the work that is described here, in addition to those derivatives shown in Scheme 1. Masking of the phenolic hydroxyl functionality was assumed to be necessary if this compound was to be used in solid phase synthesis. The ideal type of side-chain protecting group would be one that can be removed under the conditions employed for cleavage of the

Scheme 1. Preparation of Monoprotected Diamines from *N*-BOC-Protected Amino Acids

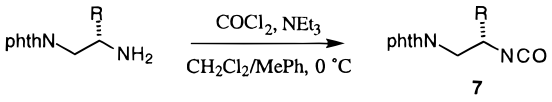


Scheme 2. Preparation of a Monoprotected Diamine from FMOC-Tyr(^{t}Bu)



peptidomimetics from the resin. Scheme 2 shows the route used to obtain the *tert*-butyl- and phthaloyl-protected phenolic diamine **5**, which meets this requirement.

Experimentally, both Schemes 1 and 2 are convenient and begin with commercially available starting materials. Monoprotected diamines are accessible through BOC-protected amino acids (Scheme 1) whereas FMOC-Tyr(*t*-Bu) provides the requisite acid labile side-chain protecting group required for the synthesis of compound **6** (Scheme 2). For long-term storage of starting materials in this project, the differentially protected diamines **2** and **5** were chosen; the selective *N*-deprotection and isocyanate formation steps to give **7** were performed immediately prior to the coupling reactions, as indicated below. Alternatively, the starting materials could be stored as hydrochloride salts of the amines after removal of the BOC group from compounds **2**.



As the work reported here was approaching the final stages, Nowick and co-workers reported a method for forming very

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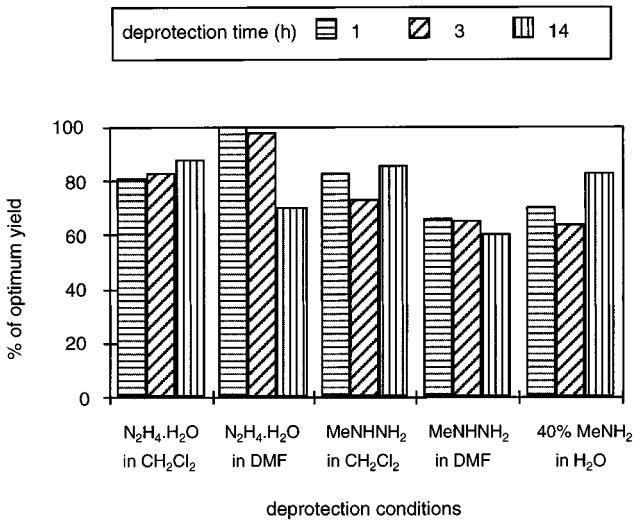
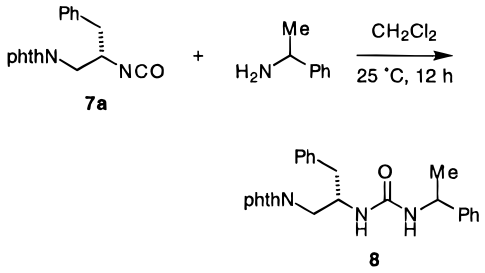


Figure 1. Variation of yield in the phthaloyl deprotection step as a function of reagent, solvent, and reaction time.

similar isocyanates but using aqueous conditions.[31] We have briefly tested the same conditions with our amine starting materials and find that method to be equally suitable and perhaps even more convenient.

Racemization in the formation of the monoprotected diamine products **3** and/or in couplings of the corresponding isocyanates was considered to be unlikely given the nature of the transformations involved. Nevertheless, we thought it prudent to check, at least in one case. The isocyanate derived from phenylalanine **7a** was therefore reacted with optically pure 1-phenylethylamine and with a racemic sample of the same amine, in two separate experiments. Only one of the two diastereomeric ureas **8** formed in the second reaction could be detected in the first.



Conditions for Coupling and Deprotection. Attempts were made to optimize the conditions for coupling of the isocyanates **7** to solid supported amines. To do this it was desirable to identify an appropriate internal standard. 4-Methylbenzenesulfonamide was chosen because its maximum absorbance at 220 nm is close to the typical λ_{max} for the oligourea compounds (210 nm). Thus a batch of Rink's amide resin was treated with 4-methylbenzenesulfonyl chloride such that approximately 20% of the reactive amine groups were converted to sulfonamides. The remainder of the reactive amines were coupled with FMOC-Phe. FMOC deprotection then gave a batch of resin with a convenient internal standard for HPLC analyses. Typically, portions of the resin were packaged in "tea bags"[38] so that aliquots could be conveniently removed and analyzed at intervals.

The first issue to be addressed in the optimization process was the coupling step. Preparation of the isocyanates used in this research were performed in dichloromethane, and this solvent was also selected for the coupling reactions. Removal of excess phosgene and solvent after the isocyanate formation and prior to the coupling reactions was shown to be unnecessary, so the crude reaction mixtures were used. After a specific coupling time with isocyanate **7a**, a tea bag was removed from the reaction mixture and the contents were treated with hydrazine in DMF for 12 h and then cleaved from the resin by treatment with TFA overnight. A series of experiments performed in this way indicated that the yield of the corresponding urea was optimal after approximately 11 h coupling time at room temperature; the product yields were suboptimal after 22 h and diminished further after 40 h.

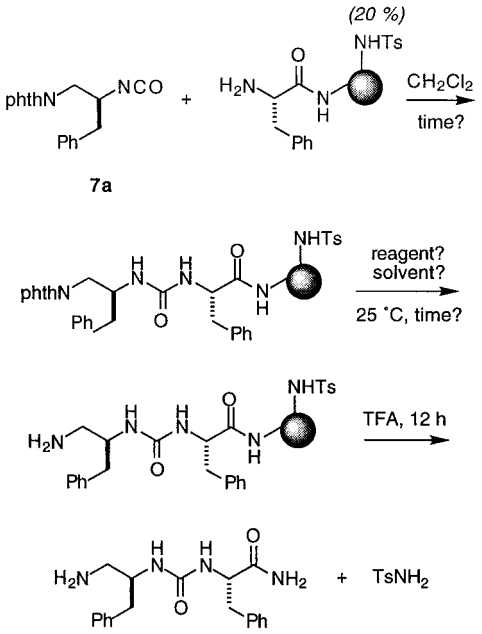


Figure 1 depicts some data concerning the various reagents and reaction times examined for the deprotection step. A 60% hydrazine in DMF for 1−3 h, gave the optimal yield of product. Use of extended reaction times, other reagents (*e.g.*, methylhydrazine and methylamine), and other solvents each gave less of the desired material. Use of the tetrachlorophthaloyl protecting group[39,40] in place of phthaloyl was briefly examined (data not shown), but it was evident that this change afforded no advantage.

Syntheses of Oligoureas and Peptidic Oligoureas. Figure 2 shows some of the products that were made via solid phase syntheses, cleaved from the resin, and isolated in the yields indicated after HPLC purification. A solid supported amine intermediate is generated in each cycle; consequently, a positive ninhydrin test[41] was used to test for the presence of this group after the deprotection steps, and evidence for complete coupling was derived from a negative ninhydrin test. The overall yields are in the 9−46% range, after four or five cycles of coupling and deprotection. Each compound was prepared only once, so these yields depicted are from initial synthetic attempts and might be improved with practice. The HPLC trace of the crude reaction product from the preparation of $CH_2Y^u{\cdot}CH_2G^u{\cdot}CH_2G^u{\cdot}CH_2F^u{\cdot}CH_2L^u$-amide is typical; this is shown in the Supporting Information.

Figure 2 also illustrates the abbreviations that we use to depict the sequence. For example, a CH_2F^u indicates a urea moiety arranged in such a way that if the peptidomimetic is arranged with the "*N*-terminus" on the left, then the methylene group

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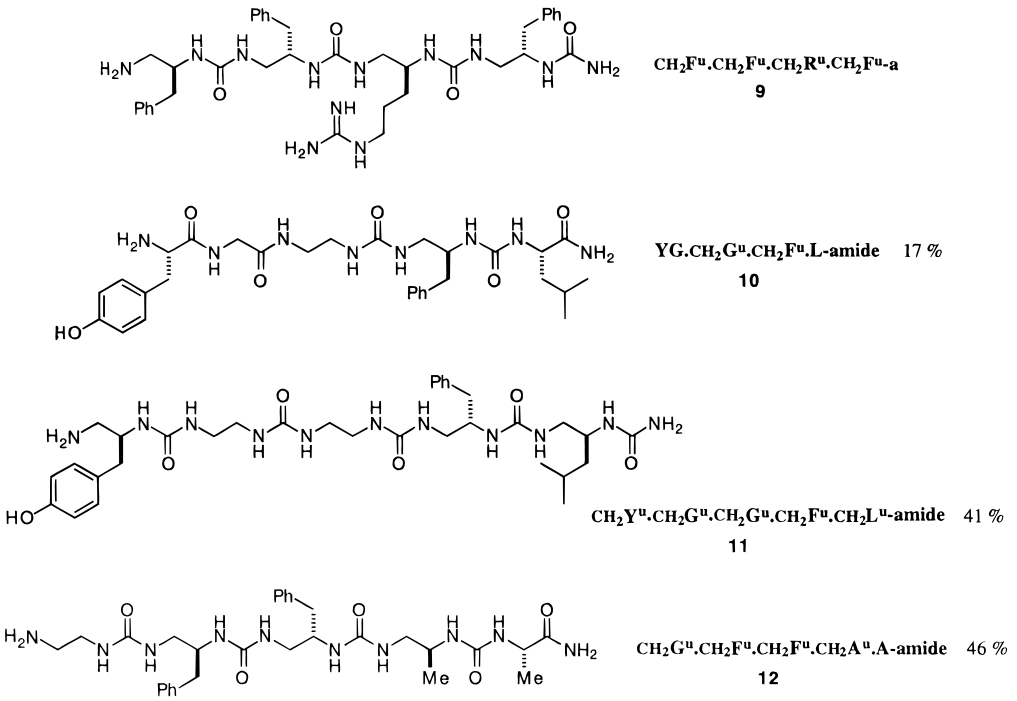


Figure 2. Some oligoureas prepared on a solid phase and isolated by HPLC.

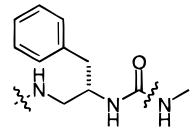
Table 1. Partition Coefficients for Two Peptides and the Corresponding Oligoureas[a]

$$P = \frac{[\text{pH 7.4 buffer}]}{[\text{octanol}]}$$

sequence	partition coefficient *P*
FFRF-amide	0.77
CH_2F^u-CH_2F^u-CH_2R^u-CH_2F^u-amide	1.50
YGGFL-amide	3.12
CH_2Y^u-CH_2G^u-CH_2G^u-CH_2F^u-CH_2L^u-amide	2.18

[a] Measured for the peptide/peptidomimetic partitioned between pH 7.4 phosphate buffer and 1-octanol; see the Experimental Section for details.

precedes the side chain substituent derivative of L-phenylalanine (F).



Relative Solubilities of Oligoureas and the Corresponding Peptides. Aqueous buffer/octanol partition coefficients were measured for two peptides and for the corresponding oligourea sequence (Table 1). In one case the oligourea was more hydrophilic, and in the other it was less. Thus the relative hydrophilicity of peptides and oligoureas can be comparable, but the solubilities of both classes of compounds will be influenced by factors other than molecular composition, including association of molecules and folding into relatively long lived conformations in solution. Solubility factors are sequence dependent, but so far, we have not prepared an oligourea that is markedly insoluble in water. Concerns that oligoureas might be very insoluble due to intermolecular hydrogen binding were thereby alleviated, at least for these sequences of four to five residues.

Assignment of ^{1}H NMR Resonances for the Peptidodomimetics. The one-dimensional proton NMR spectra of these molecules are complicated due to overlapping peaks. However, we found that proton assignments were possible using much the same techniques as are employed for peptides and proteins.[42] DQF-COSY spectra[43] facilitated assignment of most of the proton signals; several illustrative spectra of this kind are given in the Supporting Information. There were, however, breaks in connectivities caused by the urea bonds. Consequently, more complete assignments required use of ROESY spectra[44] to define N*H* protons which are associated with the same urea linkage. An illustrative ROESY spectra of one product is also given in the Supporting Information. The only remaining ambiguities arise from overlapping CH_2 resonances of the backbone. On the basis of these observations, we predict that conformational assignments of oligoureas in solution are possible.

Synthesis of a Library of Leu-Enkephalin Analogues. A 160-membered pilot library of peptidic oligoureas was prepared to illustrate that more ambitious screening projects would be possible using this methodology. The library was designed with YGGFL-amide as a basis; this peptide is shown in the top left of Figure 3. The plate was arranged in such that, progressing down and to the right, more D-amino acids and more ureas units (from both L- and D-amino acids) were incorporated.

Full details of the library preparation are given in the experimental section, but the salient details are summarized here. Rink's amide resin was packaged into tea bags. Amide bonds were formed via coupling FMOC-protected amino acids activated using PyBOP/HOBt, and the urea bonds were formed by direct reactions of isocyanates as described above. Deprotections of the amino acids were performed using piperidine in the usual way,[45] and the ureas were deprotected using hydrazine as outlined above. Finally, the peptides and peptidomimetics were cleaved from the resin using a TFA, phenol, water, ethanedithiol, thioanisole "cocktail". The scavengers in that mixture were included to protect the phenolic side chains from

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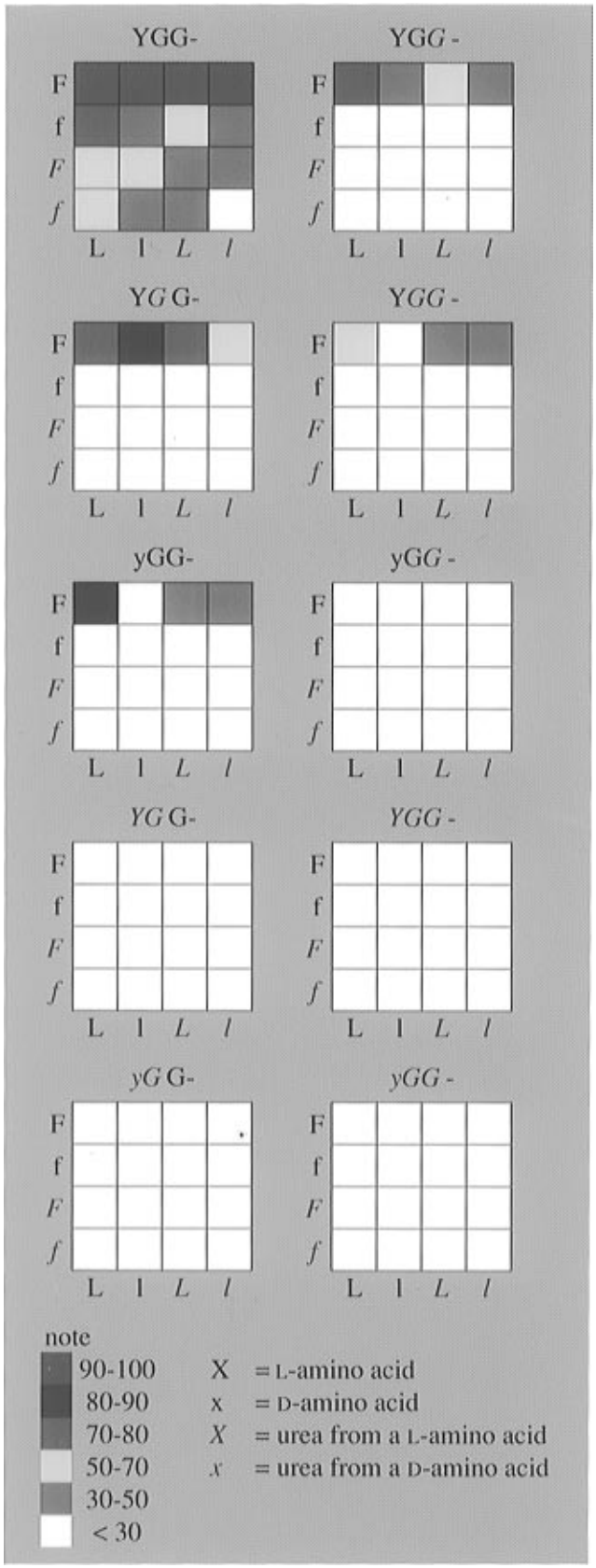


Figure 3. Screening of a peptidomimetic library with the *anti-β*-endorphin antibody. X = L-amino acid; x = D-amino acid; *X* = an urea entity formed from L-amino acid; *x* = an urea entity formed from a D-amino acid.

the *tert*-butyl cations liberated from the Tyr-derived residues. After filtration (effectively performed by agitating the tea bags which contained only the spent resin) and removal of the cleavage cocktail under vacuum, the peptide/peptidomimetic residues in small vials were dissolved in 2:1 H_2O:MeCN. The hydrophobic impurities were then extracted via treatment with diethyl ether. Evaporation of the aqueous portions (speed vac) gave colorless residues. Analyses of these via HPLC (215 nm) showed one major peak in almost every case. MALDI analyses showed a peak corresponding to the molecular ion for all the samples.

Table 2. IC_{50} Values for Binding of Peptides/Peptidomimetics to the *anti-β*-endorphin Antibody in a Competitive Radioimmunoassay

entry	sequence	IC_{50} (μM)
1	YGGFL-OH	0.0794
2	YGGFL-NH_2	0.295
3	Y$G_{CH_2}G^{u}$FL-NH_2	108
4	Y$_{CH_2}G^{u}$GFL-NH_2	50.1
5	Y$_{CH_2}G^{u}$GF(D-L)-NH_2	25.1
6	Y$_{CH_2}G^{u}GF_{CH_2}L^{u}$-$NH_2$	63.1
7	Y$_{CH_2}G^{u}$FL-NH_2	79.4

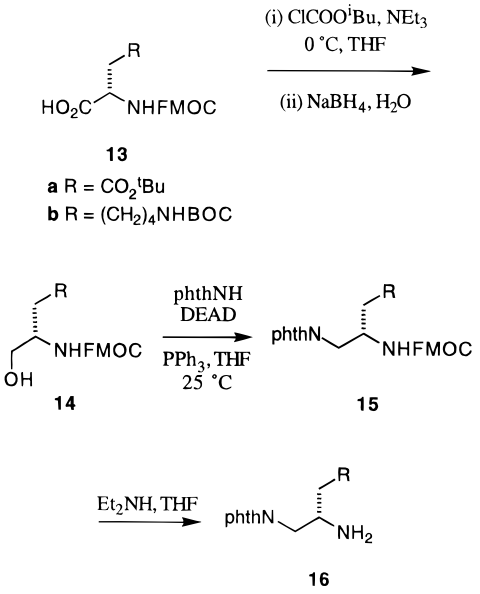
Screening a Library of Leu-enkephalin Analogues in a Competitive Radioimmunoassay. A monoclonal antibody (mAb) selective for the YGGF sequence was used to screen the pilot library shown in Figure 3. The sequence YGGFL-OH is known to be a good substrate for this mAb, but the mAb had less affinity for the peptides/peptidomimetics prepared here, all of which had carboxamide residues at the *C*-terminus. This was not a concern in this project, however, because the overall objective of the screening exercise was to probe the effect of systematically introducing more urea linkages on the binding efficiency, *i.e.* the change in binding affinity on progressing from top/left to bottom/right in Figure 3. The absolute values of the binding efficiency were really of little consequence in this work.

Peptides/peptidomimetics that had 70% or more of the binding affinity of YGGFL-amide with respect to the *anti-β*-endorphin antibody are shown in Figure 3. These data indicated that five peptidic-oligoureas were relatively tight binders to the mAb. To confirm this, these five compounds were resynthesized and purified by HPLC for determination of IC_{50} values. These data are given in Table 2. It emerges that, relative to YGGFL-amide, the IC_{50} values are decreased by approximately 2 orders of magnitude when a urea bond is incorporated at the G^2 and/or the L^5 position. The mAb has less affinity for substrates with other amide-for-urea substitutions. Substitution of G^2 and G^3 with a single urea entity was also explored in one case. Table 2, entry 7, shows that the peptide Y$_{CH_2}G^{u}$FL-NH_2 bound with approximately the same affinity as the analogues comprised of five residues.

Substitution of amide bonds with the urea fragments used in this work elongates the backbone of the peptidomimetics by several atoms. This study shows that incorporation of urea units does not necessarily negate all the binding efficiency, but it was reduced in the limited number of compounds screened. This is not a surprising observation. The changes effected in this library were systematic, but they were not designed to logically enhance any particular activity.

Preparation of Monomers For Preparation of Other Oligoureas. The monomer building blocks used to prepare the library described above were derived from amino acids without side-chain functionalities (Scheme 1) except for the tyrosine derivative **6**. Preparations of other monomers will be necessary if the methodology described in this paper is to be expanded to other situations. In preliminary work toward that goal, the monomer units corresponding to Asp and Lys were also prepared as shown in Scheme 3. These two syntheses demon-

Scheme 3



strate production of synthons with acidic side chains protected as *tert*-butyl esters and with basic side chains protected as *tert*-butoxycarbonyl groups. In summary, simple monomers can be prepared from BOC-protected amino acids (Scheme 1), and we anticipate that most of the side-chain functionalized monomers corresponding to the protein amino acids will be available from FMOC-protected amino acids (Schemes 2 and 3).

Conclusions

We suspect that oligoureas may have unrealized potential with regard to developing leads for pharmaceutical development. The reactions described in this paper facilitate formation of isocyanate monomers from amino acids and the formation of oligoureas from these via solid phase reactions. This chemistry is amenable to formation of supported libraries via split syntheses and to solution phase libraries. We envisage that the techniques could be adapted for automated syntheses providing one compound per well or for generation of mixtures and deconvolution via the iterative screening[10,46] or positional scan[47] approaches most closely associated with Houghten. For target-oriented applications, attempts would be made to match the steric demands of the urea group with the intended receptor and small biased libraries could be formed. Alternatively, the "alphabet" of isocyanate monomers could be expanded to facilitate random screening of larger libraries. In general, proteolytic stabilities are likely to be increased when amide bonds are substituted with ureas. Moreover, pharmaceutically interesting ureas have been proved to be efficacious,[48,49] and it seems reasonable that other bioactive compounds in this class would be discovered if screening efforts in this area were intensified. Consequently, we have considerable optimism regarding the potential of this category of compounds in biomedical applications.

Our optimism regarding the potential of this group of compounds is shared by others in the field. Very recently, approximately 1 year after we communicated our preliminary results,[25] another group has reported syntheses of oligourea compounds on a solid phase.[50,51] Their approach is slightly different. They used (4-nitrophenyl)carbamates instead of isocyanates as the "activiated" coupling partners (although these carbamates possibly react via isocyanates formed *in situ*). Moreover, they used azides rather than phthaloyl functionality to mask the "*N*-terminal" nitrogen. It appears that approach works well for coupling several simple monomer units but does not offer any very significant advantage over the route we originally communicated and elaborated here. In unpublished work, we have designed synthetic routes for preparation of appropriately side-chain protected monomers corresponding to nearly all the protein amino acids. The latter results will be reported in due course.

Experimental Section

General Synthetic Procedures. Melting points were uncorrected. High-field NMR spectra were recorded on a Varian XLAA 200 (^{1}H at 200 MHz, ^{13}C at 50 MHz), a Varian Unity+ 300, a Varian XLR 300, a Varian XL-400, or a Varian Unity+ 500 machine. ^{1}H chemical shifts are reported in δ relative to C*H*Cl$_3$ (7.24 ppm) as internal standard, and ^{13}C chemical shifts are reported in ppm relative to *C*DCl$_3$ (77.0 ppm) unless otherwise specified. Multiplicities in ^{1}H NMR are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet. IR spectra were recorded on a Mattson RS/1. Centrifuge evaporation system is Jouan RC 10.22 system. Thin layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography was performed on SP silica gel 60 (230−600 mesh ASTM). Other chemicals were purchased from commercial suppliers and used as received. The alcohols **1** and **4** were formed via the reduction process outlined in Schemes 1 and 2 or, for most of this work, purchased directly from Advanced ChemTech Chemical Co.

(*S*)-*N*^{2}-*tert*-Butoxycarbonyl-3-phenyl-*N*^{1}-phthaloyl-1,2-diaminopropane (2a). Diethyl azodicarboxylate (3.2 mL, 16.4 mmol, 1.0 equiv) was added over 10 min to an ice-cold mixture of *N*-BOC phenylglycinol **1a** (2.91 g, 16.4 mmol, 1.0 equiv), PPh_3 (5.25 g, 20.0 mmol, 1.2 equiv), and phthalimide (2.70 g, 18.4 mmol, 1.1 equiv) in 80 mL of THF. The reaction mixture was stirred for 3 h, the THF was evaporated under vacuum, and the residue was purified via flash chromatography (4.5:1 hexane:EtOAc eluant) to afford 3.73 g (73%) of the product as a white powder: mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 3, 5 Hz, 2H), 7.69 (dd, J = 3, 5 Hz, 2H), 7.33−7.22 (m, 5H), 4.64 (d, J = 8 Hz, 1H), 4.32 (br s, 1H), 4.28−3.65 (m, 2H), 2.95−2.83 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.33, 155.38, 137.16, 133.81, 132.35, 129.26, 128.59, 126.70, 123.26, 79.41, 50.85, 41.93, 39.45, 28.18; IR (KBr) 3367, 2979, 2939, 1772, 1720, 1677, 1641, 1510, 1431 cm^{-1}; FAB-HRMS for $C_{22}H_{25}N_2O_4$ [MH] calcd *m*/*z* 381.1814, found 381.1818.

***N*^{1}-*tert*-Butoxycarbonyl-*N*^{2}-phthaloyl-1,2-diaminoethane (2b).** This compound was prepared using *N*-BOC glycinol **1b** (10.1 g, 62.7 mmol) in essentially the same procedure as outlined for the conversion of **1a** into **2a** (*vide supra*). The product **2b** was formed as a white powder (17.1 g, 94%): mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2H), 7.73−7.70 (m, 2H), 4.82 (br s, 1H), 3.83 (t, J = 6 Hz, 2H), 3.43 (q, J = 6 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.31, 155.86, 133.87, 132.30, 123.26, 79.50, 39.83, 38.16, 28.27; IR (KBr) 3394, 2971, 2944, 1772, 1703, 1519, 1434 cm^{-1}; FAB-HRMS for $C_{15}H_{19}N_2O_4$ [MH] calcd *m*/*z* 291.1344, found *m*/*z* 291.1367.

(*S*)-*N*^{2}-*tert*-Butoxycarbonyl-4-methyl-*N*^{1}-phthaloyl-1,2-diaminopentane (2c). This compound was prepared using *N*-BOC leucinol **1c** (0.9 g, 4.4 mmol) in essentially the same procedure as outlined for the conversion of **1a** into **2a** (*vide supra*). The product **2c** was formed as a white powder (1.3 g, 86%): mp 124−129 °C; ^{1}H NMR (300 MHz,

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acetone-d_6) δ 7.86 (m, 4H), 5.81 (m, 1H), 4.11 (m, 1H), 3.66 (m, 2H), 1.56 (m, 1H), 1.39 (m, 1H), 1.20 (s, 9H), 0.99 (d, $J = 7$ Hz, 3H), 0.94 (d, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 164.90, 157.35, 130.76, 129.33, 119.63, 74.48, 44.50, 39.63, 37.88, 24.40, 21.62, 19.42, 18.17; IR (KBr) 3248, 2953, 2870, 1770, 1708, 1685, 1529, 1431 cm^{-1}; FAB-HRMS for $C_{19}H_{27}N_2O_4$ [MH] calcd *m*/*z* 347.1971, found *m*/*z* 347.1977.

(*S*)-N^2-*tert*-Butoxycarbonyl-1-[(4-methoxy-2,3,5-trimethylbenzenesulfonyl)guanidino]-N^1-phthaloyl-1,2-diaminopentane (2d). This compound was prepared using *N*-BOC argininol **1d** (4.1 g, 8.7 mmol) in essentially the same procedure as outlined for the conversion of **1a** into **2a** (*vide supra*). The product **2d** was formed as an oil (3.5 g, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.61 (m, 2H), 7.50−7.47 (m, 2H), 6.51 (s, 1H), 6.46 (br s, 2H), 4.80 (br s, 1H), 4.41 (m, 1H), 3.80 (s, 3H), 3.54 (m, 2H), 3.17 (m, 2H), 2.70 (s, 3H), 2.63 (s, 3H), 2.11 (s, 3H), 1.51−1.37 (m, 4H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.38, 155.09, 153.46, 135.42, 133.37, 130.85, 129.61, 128.22, 121.47, 120.15, 108.52, 76.18, 73.69, 52.29, 46.39, 39.16, 37.63, 26.90, 24.97, 22.81, 21.11; IR (neat) 3340, 2978, 1772, 1712, 1439, 1367 cm^{-1}; FAB-HRMS for $C_{29}H_{39}N_5O_7SNa$ [MNa] calcd *m*/*z* 624.2468, found *m*/*z* 642.2478.

(*S*)-3-Phenyl-N^1-phthaloyl-1,2-diaminopropane hydrochloride (3a). A solution of compound **1a** (1.04 g, 2.7 mmol) in 10 mL of 6 M HCl_{aq} (60 mmol, 22 equiv) and 10 mL of THF was stirred at 25 °C for 12 h. A white powder precipitated. This was collected and washed with diethyl ether to afford 0.72 g (84%) of the product as a white powder: mp 263−264 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (br s, 2H), 7.86−7.81 (m, 4H), 7.32 (d, $J = 4$ Hz, 4H), 7.22 (m, 1H), 3.82 (dd, $J = 9$, 14 Hz, 1H), 3.73 (m, 1H), 3.63 (dd, $J = 4$, 14 Hz, 1H), 3.15 (dd, $J = 5$, 14 Hz, 1H), 2.86 (dd, $J = 9$, 14 Hz, 1H);^{13}C NMR (50 MHz, DMSO-d_6) δ 167.62, 135.75, 133.87, 131.62, 128.67, 128.20, 126.43, 122.57, 50.14, 38.94, 36.26; IR (KBr) 3468, 3053, 3024, 1773, 1710, 1600, 1434 cm$^{-1;}$ FAB-HRMS for $C_{17}H_{17}N_2O_2$ [MNa] calcd *m*/*z* 281.1290, found *m*/*z* 281.1293.

N^2-Phthaloyl-1,2-diaminoethane (3b). This compound was prepared using **2b** (17.1 g, 59 mmol) in essentially the same procedure as outlined for the conversion of **2a** into **3a** (*vide supra*). The product **3b** was formed as a white powder (10.9 g, 81%): mp 268−270 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (br s, 3H), 7.88−7.82 (m, 4H), 3.86 (t, $J = 6$ Hz, 2H), 3.06 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 167.98, 134.38, 132.12, 123.07, 37.30, 35.45; IR (KBr) 3475, 3011, 2909, 2886, 1779, 1709, 1432 cm^{-1}; FAB-HRMS for $C_{10}H_{10}N_2O_2$ [MH] calcd *m*/*z* 191.0821, found *m*/*z* 191.0837.

(*S*)-4-Methyl-N^1-phthaloyl-1,2-diaminopentane (3c). This compound was prepared using **2c** (1.45 g, 4.2 mmol) in essentially the same procedure as outlined for the conversion of **2a** into **3a** (*vide supra*). The product **3c** was formed as a white powder (0.87 g, 74%): mp 252−255 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (br s, 2H), 7.89 (m, 4H), 3.76 (m, 2H), 3.43 (m, 1H), 1.86 (m, 1H), 1.52 (m, 2H), 0.95 (d, $J = 6$ Hz, 1H), 0.91 (d, $J = 6$ Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.62, 131.76, 129.32, 120.45, 45.39, 41.63, 36.46, 21.18, 19.97, 19.14; IR (KBr) 3477, 3010, 2873, 1776, 1716, 1608, 1429 cm^{-1}; FAB-HRMS for $C_{14}H_{19}N_2O_2$ [MH] calcd *m*/*z* 247.1446, found *m*/*z* 247.1465.

(*S*)-1-[(4-Methoxy-2,3,5-trimethylbenzenesulfonyl)guanidino]-N^1-phthaloyl-1,2-diaminopentane (3d). This compound was prepared using **2d** (0.11 g, 0.18 mmol) in essentially the same procedure as outlined for the conversion of **2a** into **3a** (*vide supra*). The product **3d** was formed as a oil (0.05 g, 53%): ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (m, 4H), 6.63 (s, 1H), 3.76 (s, 3H), 3.52 (m, 1H), 3.30 (m, 2H), 3.26 (m, 2H), 2.67 (s, 3H), 2.61 (s, 3H), 2.09 (s, 3H), 1.69 (m, 2H), 1.29 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 165.46, 155.33, 153.63, 134.91, 133.40, 131.20, 130.35, 128.83, 121.17, 119.99, 108.29, 66.12, 51.55, 47.92, 35.54, 27.69, 25.07, 24.33, 21.24, 19.81; IR (neat) 3367, 3070, 2953, 2926, 2854, 1716, 1458, 1378 cm^{-1}; FAB-HRMS for $C_{24}H_{32}N_5O_5S$ [MH] calcd *m*/*z* 502.2124, found *m*/*z* 502.2110.

(*S*)-N^2-[(9-Fluorenylmethoxy)carbonyl]-3-[(4-*tert*-butyloxy)benzyl]-N^1-phthaloyl-1,2-diaminopropane (5). Diethyl azodicarboxylate (1.1 mL, 6.5 mmol, 1.5 equiv) was added over 10 min to an ice-cold mixture of *N*-FMOC tyrosinol **4** (0.96 g, 4.4 mmol, 1.0 equiv), PPh_3 (1.71 g, 6.5 mmol, 1.5 equiv), and phthalimide (1.71 g, 6.5 mmol, 1.5 equiv) in 50 mL of THF. The solution was stirred for 3 h, the THF was evaporated under vacuum, and the residue was purified via flash chromatography (2.3:1 hexane:EtOAc eluant) to afford 2.4 g (96%) of the product as a white powder: mp 132−134 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.85 (d, $J = 7$ Hz, 2H), 7.81 (m, 4H), 7.65−7.55 (m, 2H), 7.44−7.30 (m, 4H), 7.27 (d, $J = 8$ Hz, 2H), 6.91 (d, $J = 8$ Hz, 2H), 6.53 (m, 1H), 4.33 (m, 1H), 4.12−4.01 (m, 2H), 3.89 (m, 2H), 3.04 (dd, $J = 6$, 14 Hz, 1H), 2.94 (dd, $J = 9$, 14 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 164.98, 152.85, 151.00, 141.22, 139.02, 130.90, 130.04, 129.15, 124.46, 123.93, 122.30, 122.14, 120.70, 119.76, 116.73, 74.42, 63.01, 48.93, 43.96, 38.62, 34.65; IR (KBr) 3377, 2981, 2964, 2930, 1776, 1709, 1700, 1434 cm^{-1}; FAB-HRMS for $C_{36}H_{34}N_2O_5Na$ [MNa] calcd *m*/*z* 597.2365, found *m*/*z* 597.2374.

(*S*)-3-[(4-*tert*-Butyloxy)benzyl]-N^1-phthaloyl-1,2-diaminopropane (6). Diethylamine (0.36 mL, 3.5 mmol, 10 equiv) was added to the solution of 0.2 g of compound **5** (0.35 mmol) in 5 mL of THF. The mixture was stirred at 25 °C for 12 h, the THF was evaporated under vacuum, and the residue was purified via flash chromatography (1:4 hexane:EtOAc eluant) to afford 0.07 g (56%) of the product as an oil: ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.81 (s, 4H), 7.03 (d, $J = 9$ Hz, 2H), 6.81 (d, $J = 9$ Hz, 2H), 4.06 (m, 1H), 3.73 (dd, $J = 5$, 7 Hz, 2H), 2.89 (dd, $J = 4$, 13 Hz, 1H), 2.61 (dd, $J = 9$, 13 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 168.87, 154.43, 134.71, 132.77, 130.41, 124.30, 123.42, 109.65, 78.00, 60.49, 43.65, 40.18; IR (neat) 3228, 2976, 2931, 1714, 1646, 1435 cm^{-1}; FAB-HRMS for $C_{22}H_{25}N_2O_3$ [MH] calcd *m*/*z* 353.1865, found *m*/*z* 353.1862.

Procedure for Formation of Isocyanates *in Situ*. The conversion of amine **3a** into isocyanate **7a** is typical of the isocyanate formation procedure used throughout this work. Compound **7a** was prepared by mixing 95 mg of **3a** (0.3 mmol), triethylamine (0.34 mL, 2.4 mmol, 8 equiv), and 0.2 mL of a 2 M phosgene solution (0.39 mmol, 1.3 equiv) in 5 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 2 h, then added to the solid supported amine.

Test for Racemization of 7a. The isocyanate **7a** (prepared *in situ* as described immediately above) was added to a solution of racemic 2-phenylethylamine (0.013 mL, 0.1 mmol, 0.33 equiv) in 0.5 mL of CH_2Cl_2. The reaction mixture was stirred for 12 h at 25 °C, the solvent was evaporated under vacuum, and the residue was purified by preparative RP-HPLC (Vydac C18 column, 22 mm × 25 cm, 10 μm) with a linear gradient obtained by mixing solvent A (0.1% TFA in water) and solvent B (0.1% TFA in acetonitrile) and programmed to increase from 50 to 65% B over 35 min with a flow rate of 5 mL min^{-1}. The peak with a retention time of 27.3 min was collected and lyophilized to afford 6 mg (14%) of a white powder: This material was a near 1:1 mixture of the two diastereoisomers of compound **8**: ^{1}H-NMR (300 MHz, acetone-d_6) δ 7.84−7.79 (m, 4H), 7.32−7.19 (m, 10H), 5.86 (m, 1H), 5.31 (m, 1H), 4.68 (m, 1H), 4.50 (m, 1H), 3.73 (m, 2H), 2.93 (m, 2H), 1.30 (d, $J = 7$ Hz, $^3/_2$H), 1.18 (d, $J = 7$ Hz, $^3/_2$H); FAB$^+$ for $C_{26}H_{26}N_3O_3$ [MH] calcd *m*/*z* 427, found *m*/*z* 427. When this experiment was repeated using **7a** and optically pure (*S*)-2-phenylethylamine, only one diastereomer of **8** was observed. This material was isolated as a white powder: ^{1}H-NMR (300 MHz, acetone-d_6) δ 7.83 (m, 4H), 7.27−7.15 (m, 10H), 5.88 (m, 1H), 5.34 (m, 1H), 4.68 (m, 1H), 4.50 (m, 1H), 3.70 (m, 2H), 2.89 (m, 2H), 1.14 (d, $J =$ 7 Hz, 3H); FAB+ for $C_{26}H_{26}N_3O_3$ [MH] calcd *m*/*z* 427, found *m*/*z* 427.

$CH_2F^uCH_2F^uCH_2R^uCH_2F^u$-$NH_2$ (9). The general procedure for formation of oligoureas via stepwise coupling of phthaloyl-protected isocyanates to Rink's amide resin was as follows. Manual oligourea synthesis was carried out in a 30 mL vessel fitted with a course glass frit and agitated using a manual wrist action shaker (Burrel, Model 75). All reactions were carried out at 25 °C. Phthaloyl deprotection was performed by shaking the resin with a 60% solution of 98% hydrazine hydrate in DMF (5 mL, 12 h). DMF (5 × 1 min, *ca*. 10 mL) and CH_2Cl_2 (5 × 1 min, *ca*. 10 mL) washing cycles were used after each coupling step and each deprotection step. The isocyanate **7a** was prepared by mixing 76 mg of **3a** (0.24 mmol), 0.27 mL triethylamine (1.92 mmol, 8 equiv), and 0.16 mL of a 2 M phosgene solution (0.32 mmol, 1.3 equiv) in 10 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 2 h, then used for the coupling reaction without further purification. Rink's amide resin (0.064 g of 0.62 mmol g^{-1} capacity) was first swelled in DMF (ca 10 mL) for 2 h, then reacted with the solution of **7a** (0.24 mmol, 3 equiv in 10 mL of CH_2Cl_2). The mixture was then shaken for 5 h and subjected to one washing cycle. The phthaloyl protecting group was removed, and then the resin was

washed, as described immediately above. Three cycles of deprotection and coupling were then performed in the same manner. After removal of the final phthaloyl protecting group, the resin was washed thoroughly with DMF then CH_2Cl_2.

Cleavage of the peptide from the resin was effected using the following procedure. The resin was completely dried under high vacuum, and then a phenol/1,2-ethanedithiol/thioanisole/water/TFA mixture (5:2.5:1:5:81.5, v/v/v/v/v, respectively, 15 mL) was added to the resin in a flask. The reaction mixture was agitated at 25 °C for 9 h. The resin was filtered and washed with TFA (5 mL), and the filtrate was evaporated to *ca*. 2 mL. Deionized water (20 mL) was added, and the resulting aqueous solution was washed with Et_2O (2 × 5 mL) and lyophilized. The crude peptidomimetic was further purified by preparative RP-HPLC (Vydac C18 column, 22 mm × 25 cm, 10 μm) with a linear gradient obtained by mixing solvent A (0.1% TFA in water) and solvent B (0.1% TFA in acetonitrile). The gradient was programmed to increase from 5 to 60% B over 37 min with a flow rate of 5 mL min^{-1}. The peak with a retention time of 34.3 min was collected and lyophilized to afford 5 mg (9%) of the product as a white powder: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.87 (br s, 2H), 7.62 (t, J = 5 Hz, 1H), 7.30−7.10 (m, 10H), 6.34 (d, J = 9 Hz, 1H), 6.19−6.03 (m, 10H), 5.70 (bs, 2H), 4.14 (m, 1H), 3.99 (m, 1H), 3.89 (m, 1H), 3.54 (m, 1H), 3.51−3.40 (m, 2H), 3.31−3.26 (m, 4H), 3.10−3.00 (m, 3H), 2.79−2.25 (m, 7H), 1.49−1.15 (m, 2H); FAB-HRMS for $C_{37}H_{55}N_{12}O_4$ [MH] calcd *m*/*z* 731.4469, found *m*/*z* 731.4468.

YGcH$_2$G^{u}cH$_2$F^{u}L-NH$_2$ (10). The crude peptide was prepared using a protocol very similar to that used for the oligourea **9** described above, except that the quantities were different. Rink's amide resin (0.46 g of 0.53 mmol g^{-1} capacity) was used. The isocyanates were prepared by mixing of **3** (0.73 mmol, 3 equiv), triethylamine (0.8 mL, 24 equiv), and 2 M phosgene solution (0.37 mL, 0.73 mmol, 3.9 equiv) in CH_2Cl_2 (10 mL) at 0 °C. Cleavage of the peptide from the resin was agitated in a mixture of phenol/1,2-ethanedithiol/thioanisole/water/TFA (3:1:2:2:40, w/v/v/v/v, respectively, 12 mL) at 25 °C for 9 h. The crude peptide was further purified by preparative RP-HPLC (Vydac C18 column, 22 mm × 25 cm, 10 μm) with a linear gradient obtained by mixing solvent A (0.1% TFA in water) and solvent B (0.1% TFA in acetonitrile). The gradient was programmed to increase from 20 to 80% B over 35 min with a flow rate of 5 mL min^{-1}. The peak with a retention time of 20.1 min was collected and lyophilized to afford 25 mg (17%) of the product as a white hygroscopic solid: mp 125−127 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.71 (t, J = 6 Hz, 1H), 8.07 (br d, J = 2 Hz, 1H), 7.96 (m, 1H), 7.28−7.24 (m, 3H), 7.19 (d, J = 7 Hz, 3H), 7.04 (d, J = 9 Hz, 2H), 6.91 (s, 1H), 6.70 (d, J = 9 Hz, 2H), 6.12 (s, 1H), 6.05−6.01 (m, 2H), 5.95 (d, J = 8 Hz, 1H), 4.05 (m, 1H), 3.97 (m, 1H), 3.79 (dd, J = 6, 17 Hz, 1H), 3.73−3.69 (m, 2H), 3.10−2.92 (m, 7H), 2.82 (dd, J = 8, 14 Hz, 1H), 2.70 (dd, J = 6, 14 Hz, 1H), 2.59 (dd, J = 7, 14 Hz, 1H), 1.60−1.51 (m, 1H), 1.42−1.28 (m, 3H), 0.87 (d, J = 4 Hz, 3H), 0.85 (d, J = 4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.37, 156.08, 155.99, 147.16, 143.90, 140.72, 137.59, 134.11, 132.19, 131.43, 129.81, 129.33, 127.56, 127.02, 125.35, 125.13, 120.09, 114.68, 66.30, 65.11, 46.74, 41.96, 34.42; IR (KBr) 3380, 2934, 1671, 1559, 1517, 1455, 1438 cm^{-1}; MALDI+ for $C_{30}H_{45}N_8O_6$ [MH] calcd *m*/*z* 613.3462, found *m*/*z* 613.3481.

cH$_2$Y^{u}cH$_2$G^{u}cH$_2$G^{u}cH$_2$F^{u}cH$_2$L^u-NH$_2$ (11). The crude peptide was prepared using a protocol very similar to that used for the oligourea **9** described above, except that the quantities were different. Rink's amide resin (0.161 g of 0.62 mmol g^{-1} capacity) was used. The isocyanates for each coupling step were prepared by mixing 76 mg of compound **3** (0.6 mmol), triethylamine (0.67 mL, 4.8 mmol), and 0.39 mL of a 2 M phosgene solution (0.78 mmol) in 10 mL of CH_2Cl_2 at 0 °C. The mixtures were stirred for 2 h, then used for the coupling reaction without further purification. The mixture used to cleave the peptidomimetic for the resin was phenol/1,2-ethanedithiol/thioanisole/water/TFA (5:2.5:1:5:81.5, v/v/v/v/v, respectively, 5 mL); this was applied for 9 h at 25 °C. The crude peptide was further purified by preparative RP-HPLC using the same column and solvent system programmed to increase from 30 to 35% B over 25 min with a flow rate of 5 mL min^{-1}. The peak with a retention time of 19.3 min was collected and lyophilized to afford 15 mg (21%) of the product as a white powder: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (br s, 1H), 7.80 (br s, 2H), 7.23−7.17 (m, 5H), 6.98 (d, J = 8 Hz, 2H), 6.67 (d, J = 8 Hz, 2H), 6.18 (br s, 1H), 6.13 (m, 1H), 6.11 (m, 1H), 6.07 (m, 1H), 6.05 (m, 1H), 6.02 (m, 1H), 5.99 (m, 1H), 5.97 (m, 1H), 5.86 (m, 1H), 5.60 (m, 2H), 3.97 (m, 1H), 3.81 (m, 1H), 3.64 (m, 1H), 3.29 (m, 2H), 3.27 (m, 2H), 3.19 (m, 1H), 3.14 (m, 1H), 3.09 (m, 2H), 3.04 (m, 2H), 2.84 (m, 2H), 2.73 (m, 1H), 2.60 (m, 2H), 2.58 (m, 2H), 1.59 (m, 1H), 1.13 (m, 1H), 0.86 (d, J = 6 Hz, 3H), 0.81 (d, J = 6 Hz, 3H); ^{13}C NMR (75 Hz, DMSO-d_6) δ 158.98, 158.54, 158.35, 158.09, 156.87, 138.92, 138.73, 129.97, 129.16, 128.11, 127.74, 125.90, 115.13, 60.35, 51.10, 49.13, 47.48, 44.88, 43.54, 41.78, 38.46, 37.43, 21.90, 14.56; IR (KBr) 3374, 2956, 2933, 1684, 1653, 1558, 1437 cm^{-1}; MALDI+ for $C_{33}H_{54}N_{11}O_6$ [MH] calcd *m*/*z* 700.8684, found *m*/*z* 700.4268.

cH$_2$G^{u}cH$_2$F^{u}cH$_2$F^{u}cH$_2$A^{u}A-NH$_2$ (12). The crude peptide was prepared using a protocol very similar to that used for the oligourea **9** described above, except that the quantities were different. Rink's amide resin (0.31 g of 0.62 mmol g^{-1} capacity) was used. The isocyanate for each coupling step were prepared from **3** (0.58 mmol, 3 equiv), triethylamine (0.65 mL, 24 equiv), and 0.29 mL of a 2 M phosgene solution (0.58 mmol, 3 equiv) in 10 mL of CH_2Cl_2 at 0 °C. The mixture used to cleave the peptidomimetic for the resin was phenol/1,2-ethanedithiol/thioanisole/water/ TFA (3:1:2:2:40, w/v/v/v/v, respectively); 12 mL of this was applied at 25 °C for 9 h. The crude peptide was further purified using the same column and solvent system. The gradient was programmed to increase from 20 to 80% B over 35 min with a flow rate of 5 mL min^{-1}. The peak with a retention time of 21.6 min was collected and lyophilized to afford 46.6 mg (46.3%) of the product as a white hygroscopic solid: mp 125−127 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (br s, 3H), 7.40 (s, 1H), 7.29−7.23 (m, 4H), 7.20−7.16 (m, 6H), 7.00 (s, 1H), 6.28 (m, 2H), 6.27−6.08 (m, 4H), 6.04 (m, 2H), 4.09 (m, 1H), 3.93 (m, 1H), 3.84 (m, 1H), 3.58 (m, 1H), 3.44 (m, 2H), 3.28 (m, 2H), 3.07 (m, 2H), 2.89 (m, 1H), 2.67 (m, 4H), 2.54 (m, 3H), 1.19 (d, J = 7 Hz, 3H), 0.91 (d, J = 7 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 175.17, 159.07, 158.73, 158.39, 157.53, 138.77, 129.09, 128.17, 125.99, 50.54, 49.91, 48.49, 45.83, 45.25, 44.54, 44.32, 37.01, 19.76, 18.70; IR (KBr) 3450, 2921, 1644, 1567, 1562, 1505, 1498, 1458 cm^{-1}; MALDI+ for $C_{30}H_{47}N_{10}O_5$ [MH] calcd *m*/*z* 626.37, found *m*/*z* 626.82, 649.20 [MNa], 664.99 [MK].

Syntheses of the Library of 160 Peptidomimetics (Figure 3). Stepwise coupling of phthaloyl-protected isocyanates to Rink's amide resin was used as outlined above, except that the resin (16.6 mg of 0.62 mmol g^{-1} capacity) was packaged into approximately 1 cm^2 "tea bags" formed from a permeable membrane (McMaster-Carr, Atlanta, GA: phone 404-346-7000). A 50 mL vessel was used and agitated using a horizontal shaker (Eberbach 6000). All reactions were carried out at 25 °C.

The following conditions were used for the formation of the urea bonds. The isocyanate of each phthaloyl amino acid derivative was prepared by mixing the appropriate amine (**3** or **6**) (3 equiv, relative to the resin, throughout), triethylamine (24 equiv), and 2 M phosgene solution (3.9 equiv) in 50 mL of CH_2Cl_2 at 0 °C. The Rink's amide resin in the tea bags was first swelled in DMF (*ca*. 50 mL) for 2 h, then reacted with the isocyanate solution. The mixture was shaken for 12 h, then washed (washing cycle as described in the preparation of compound **9**). The phthaloyl protecting group was removed using a 12 h reaction time, and then the resin was washed again.

The conditions used for the formation of amide bonds were as follows. FMOC amino acids were coupled using PyBOP/HOBt/NMM. FMOC deprotection was performed by shaking the tea bags twice with 20% piperidine in DMF (50 mL, 30 min × 2). After removal of the final protecting group, the resin was washed thoroughly with DMF. Cleavage of the peptide from the resin (still in the tea bags) was performed using individual vials containing a 1.5 mL of a mixture of phenol/1,2-ethanedithiol/thioanisole/water/TFA (5:2.5:1:5:81.5, v/v/v/v/v, respectively), agitated at 25 °C for 9 h. The solutions were transferred to 2 mL centrifuge tubes; residual material in the bags was collected and added to the centrifuge tubes by washing each bag with 0.5 mL of TFA. The solutions were evaporated to dryness on a vacuum centrifuge. Purified water (1 mL) and acetonitrile (0.5 mL) was added to each tube, and the resulting solutions were washed with Et_2O (0.5 mL × 2) and lyophilized. The crude peptidomimetics were characterized by MALDI and HPLC.

Preparation of Selected Compounds from the Library. Five interesting peptidomimetics identified in the library screen, were prepared again on a larger scale (0.1 mmol) using procedures very similar to those already described for compounds **9**−**12**. Throughout the solvents A and B used in the HPLC purification were 0.1% TFA in water and 0.1% TFA in acetonitrile, respectively. Only data for characterization is given here.

YCH_2G^{u}GFL-NH_2. Gradient: 20 to 30% B over 47 min with a flow rate of 5 mL min^{-1}. Retention time: 27.9 min. The product was formed as a white powder (9 mg, 15%): ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.36 (br s, 1H), 8.39 (m, 1H), 8.07 (br s, 2H), 8.06 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 7.26−7.16 (m, 5H), 7.10 (br s, 1H), 7.00 (d, J = 8 Hz, 2H), 6.99 (br s, 1H), 6.71 (d, J = 8 Hz, 2H), 6.25 (m, 1H), 6.19 (m, 1H), 4.49 (m, 1H), 4.19 (m, 1H), 3.79 (m, 1H), 3.65 (dd, J = 5, 17 Hz, 1H), 3.49 (dd, J = 5, 17 Hz, 1H), 3.14−2.91 (m, 6H), 2.82 (dd, J = 8, 14 Hz, 1H), 2.78 (dd, J = 10,14 Hz, 1H), 1.55 (m, 1H), 1.47 (m, 2H), 0.88 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H); IR (KBr) 3311, 3086, 2960, 1670, 1558, 1518, 1456 cm^{-1}; MALDI$^+$ for $C_{29}H_{42}N_7O_6$ [MH] calcd m/z 584.196, found m/z 584.388.

YCH_2G^{u}GFl-NH_2. Gradient: 22 to 29% B over 43 min with a flow rate of 5 mL min^{-1}. Retention time: 34.8 min. The product was formed as a white powder (20 mg, 34%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (br s, 1H), 8.41 (m, 1H), 8.18−8.05 (m, 4H), 7.27−7.16 (m, 6H), 7.01−6.98 (m, 3H), 6.71 (d, J = 9 Hz, 2H), 6.28 (m, 1H), 6.17 (m, 1H), 4.51 (m, 1H), 4.11 (m, 1H), 3.78 (m, 1H), 3.63 (dd, J = 5, 17 Hz, 1H), 3.54 (dd, J = 5, 17 Hz, 1H), 3.13−2.78 (m, 8H), 1.39 (m, 2H), 1.26 (m, 1H), 0.79(d, J = 6 Hz, 3H), 0.73 (d, J = 6 Hz, 3H); IR (KBr) 3374, 3033, 2958, 1668, 1556, 1518, 1441 cm^{-1}; MALDI$^+$ for $C_{29}H_{42}N_7O_6$ [MH] calcd m/z 584.196, found m/z 584.554.

YCH_2G^{u}GFCH_2L^u-NH_2. Gradient: 22 to 28.5% B over 40 min with a flow rate of 5 mL min^{-1}. Retention time: 30.9 min. The product was isolated as a white powder (9 mg, 15%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (br s, 1H), 8.40 (t, J = 5 Hz, 1H), 8.06−8.01 (m, 4H), 7.23−7.16 (m, 5H), 7.00 (d, J = 8 Hz, 2H), 6.70 (d, J = 8 Hz, 2H), 6.25 (t, J = 6 Hz, 1H), 6.14 (t, J = 6 Hz, 1H), 5.79 (d, J = 8 Hz, 1H), 5.45 (br s, 1H), 4.43 (m, 1H), 3.78 (m, 1H), 3.71 (dd, J = 5, 16 Hz, 1H), 3.63 (m, 1H), 3.50 (dd, J = 5, 16 Hz, 1H), 3.12−2.91 (m, 8H), 2.82 (dd, J = 8, 14 Hz, 1H), 2.78 (dd, J = 10, 14 Hz, 1H), 1.59 (m, 1H), 1.15 (m, 2H), 0.86 (d, J = 7 Hz, 3H), 0.81 (d, J = 7 Hz, 3H); IR (KBr) 3374, 3093, 2958, 1670, 1558, 1518, 1438 cm^{-1}; MALDI$^+$ for $C_{30}H_{45}N_8O_6$ [MH] calcd m/z 613.743, found m/z 613.791.

YGCH_2G^{u}FL-NH_2. Gradient: 20 to 40% B over 45 min with a flow rate of 5 mL min^{-1}. Retention time: 29.1 min. The product was isolated as a white powder (7 mg, 12%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (br s, 1H), 8.17 (t, J = 6 Hz, 1H), 8.00 (br s, 2H), 7.92 (d, J = 8 Hz, 1H), 7.90 (d, J = 4 Hz, 1H), 7.25−7.17 (m, 5H), 7.05 (d, J = 9 Hz, 2H), 6.98 (br s, J = 9 Hz, 2H), 6.69 (d, J = 9 Hz, 2H), 6.20 (m, 1H), 6.10 (d, J = 8 Hz, 1H), 4.35 (m, 1H), 4.21 (m, 1H), 3.96 (m, 1H), 3.89−3.62 (m, 2H), 3.02−2.93 (m, 6H), 2.79 (dd, J = 9, 14 Hz, 1H), 2.75 (dd, J = 9, 14 Hz, 1H), 1.54 (m, 1H), 1.44 (m, 2H), 0.86 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H); IR (KBr) 3390, 3087, 2960, 1670, 1558, 1541, 1518, 1437 cm^{-1}; MALDI$^+$ for $C_{29}H_{42}N_7O_6$ [MH] calcd m/z 584.196, found m/z 584.418.

YCH_2G^{u}FL-NH_2. Gradient: 20 to 32% B over 40 min with a flow rate of 5 mL min^{-1}. Retention time: 33.0 min. The product was isolated as a white powder (6.4 mg, 20%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (br s, 1H), 8.48 (br s, 1H), 8.16 (br s, 2H), 8.06 (br d, J = 9 Hz, 1H), 7.36−7.28 (m, 7H), 7.11 (d, J = 9 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 6.31 (m, 1H), 6.24 (d, J = 8 Hz, 1H), 4.48 (m, 1H), 4.33 (q, J = 8 Hz, 1H), 3.84 (t, J = 7 Hz, 1H), 3.62−3.56 (m, 1H), 3.53−3.49 (m, 1H), 3.21−3.00 (m, 4H), 2.94−2.83 (m, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 0.98 (d, J = 6 Hz, 3H), 0.94 (d, J = 6 Hz, 3H); IR (KBr) 3406, 3089, 2958, 1670, 1558, 1518, 1439 cm^{-1}; FAB-HRMS for $C_{27}H_{39}N_6O_5$ [MH] calcd m/z 527.298, found m/z 527.297.

***tert*-Butyl (*S*)-N^3-[(9-Fluorenylmethoxy)carbonyl]-N^4-phthaloyl-3,4-diaminobutanate (15a).** This compound was prepared using **13a** (0.21 g, 0.53 mmol) in essentially the same procedure as outlined for the conversion of FMOC-Tyr(*t*Bu)-OH into **5** (*vide supra*). The product **15a** was purified via flash chromatography (3.3:1 hexane:EtOAc eluant) as a white solid (0.20 g, 72%): mp 156−157.5 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86−7.80 (m, 4H), 7.66 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.5 Hz, 2H), 7.42 (m, 2H), 7.31 (m, 2H), 6.56 (d, J = 9 Hz, 1H), 4.37 (m, 1H), 4.24 (m, 1H), 4.11 (t, J = 6.1 Hz), 3.89 (d, J = 6.1 Hz, 2H), 2.64 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.40, 156.68, 145.26, 142.05, 135.10, 134.01, 128.50, 127.97, 126.14, 123.82, 120.77, 81.08, 67.13, 61.74, 48.76, 48.00, 39.16, 28.26; IR (KBr) 3244, 3062, 3045, 2989, 1774, 1730, 1701, 1605, 1533, 1369 cm^{-1}; $[\alpha]^{20}_D$ = +11.33; FAB-HRMS for $C_{31}H_{30}N_2O_6Na$ [MNa] calcd m/z 549.2002, found m/z 549.2012.

***tert*-Butyl (*S*)-N^4-Phthaloyl-3,4-diaminobutanate (16a).** Diethylamine (0.07 mL, 0.67 mmol, 10 equiv) was added to the solution of 0.036 g of compound **15a** (0.068 mmol) in 1 mL of THF. The mixture was stirred at 25 °C for 12 h, the THF was evaporated under vacuum, and the residue was purified via flash chromatography (1:4 hexane: EtOAc eluant) to afford 8 mg (39%) of the product as an oil. This product can be used for the preparation of isocyanates without further purification: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.90−7.88 (m, 4H), 3.90 (m, 1H), 3.72 (dd, J = 7, 14 Hz, 1H), 3.57 (dd, J = 6, 14 Hz, 1H), 2.95 (br s, 2H), 2.28−1.89 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 172.97, 168.85, 135.14, 133.02, 123.82, 80.17, 58.07, 43.22, 32.50, 28.26; FAB$^+$MS for $C_{17}H_{23}N_2O_4$ [MH] calcd m/z 305, found m/z 305.

(*S*)-N^2-[(9-Fluorenylmethoxy)carbonyl]-N^1-phthaloyl-N^6-*tert*-butyloxycarbonyl-1,2,6-triaminohexane (15b). This compound was prepared using **13a** (2.87 g, 6.3 mmol) in essentially the same procedure as outlined for the conversion of FMOC-Tyr(*t*Bu)-OH into **5** (*vide supra*). The product **15b** was purified via flash chromatography (3:2 hexane:EtOAc eluant) as a white solid (1.68g, 59%): mp 167−168 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89−7.24 (m, 12H), 6.78 (m, 1H), 4.14 (m, 1H), 4.03 (m, 2H), 3.78 (m, 1H), 3.62 (m, 2H), 2.90 (m, 2H), 1.45−1.14 (m, 6H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.96, 156.03, 155.56, 144.01, 140.59, 134.20, 131.61, 128.68, 127.56, 126.97, 125.30, 120.04, 77.32, 74.20, 65.70, 50.00, 46.65, 36.70, 31.04, 29.24, 28.26, 22.95; $[\alpha]^{20}_D$ = +21.03; IR (KBr) 3350, 3329, 3049, 2978, 2943, 1776, 1709, 1689, 1529, 1446, 1438, 1400 cm^{-1}; FAB-HRMS for $C_{34}H_{37}N_3O_6Na$ [MNa] calcd m/z 606.2580, found m/z 606.2592.

N^1-Phthaloyl-N^6-*tert*-butyloxycarbonyl-1,2,6-triaminohexane (16b). Diethylamine (0.32 mL, 3.1 mmol, 10 equiv) was added to the solution of 0.20 g of compound **16a** (0.34 mmol) in 3 mL of THF. The mixture was stirred at 25 °C for 12 h, the THF was evaporated under vacuum, and the residue was purified via flash chromatography (1:4 hexane: EtOAc eluant) to afford 0.07 g (58%) of the product as an oil. This product can be used for the preparation of isocyanates without further purification: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.90−7.88 (m, 9H), 5.97 (br s., 1H), 3.80 (m, 1H), 3.02 (m, 2H), 1.70−1.14 (m, 6H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.85. 156.66, 135.04, 133.01, 123.75, 78.28, 69.46,58.95, 40.96, 34.46, 31.89. 28.70, 24.13; IR (neat) 3384, 2977, 2933, 2869, 2559, 2046, 1776, 1712, 1525, 1427, 1400 cm^{-1}; FAB$^+$MS for $C_{19}H_{28}N_3O_4$ [MH] calcd m/z 362, found m/z 362.

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Supporting Information Available: One- and two-dimensional NMR data for a selection of the peptidomimetics prepared in this work and an HPLC trace for the crude sample of CH_2Y^u•CH_2G^u•CH_2G^u•CH_2F^u•CH_2L^u-amide before HPLC purification (19 pages). See any current masthead page for ordering and Internet instructions.

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