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Rapid Access to Multiple Classes of Peptidomimetics from Common γ-AApeptide Building Blocks

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Herein we report a highly efficient new method for preparing γ-AApeptides capable of theoretically containing any functionality; the method uses a few common *N*-alloc γ-AApeptide building blocks. More importantly, using the same approach, new classes of peptidomimetics bearing novel backbone scaffolds can also be readily generated. Our results not only demonstrate the versatility of this new synthetic method, but also highlight the possibility that the resulting novel peptidomimetics may find discrete biomedical/biomaterial applications in the future.

Introduction

Peptides are involved in virtually all aspects of life processes and display a remarkable repertoire of biological activities.[1] However, they also have a few intrinsic drawbacks for biological applications. Principal among these drawbacks are their susceptibility to proteolytic degradation. Alternatively, the development of peptidomimetics has been a vibrant research area in the past two decades, since such mimetics are designed to emulate the structures and functions of peptides yet possess enhanced stability and enable access to broadened structural diversity.[2] Peptidomimetics have been used to study protein surface recognition processes, disruption of protein–protein interactions and other important biological functions.[3] However, as peptides and proteins display an endless diversity of structures and functions,[2] development of new classes of peptidomimetics with novel backbones remains a highly significant pursuit.[4]

In pursuing the development of new peptidomimetics and related enabling synthetic technologies, we recently designed a new class of peptide mimics termed "γ-AApeptides" (Figure 1).[5] γ-AApeptides contain *N*-acylated *N*-aminoethyl amino acid units (Figure 1) derived from γ-PNAs.[6] In each unit (building block), the chiral side chain is derived from an α-amino acid, whereas the other side chain is introduced through acylation of the backbone nitrogen with assorted carboxylic acids or acyl chlorides. Accordingly, each monomeric unit of γ-AApeptides is structurally, and possibly functionally, comparable to two monomeric residues in α-peptides. That is to say, γ-AApeptides essentially project an identical number of functional groups as α-peptides of the same length. Additionally, the potential for generating γ-AApeptides with chemically diverse functional groups is limitless. Furthermore, half of the side chains of γ-AApeptides remain chiral, possibly imposing conformational biases that are reflected in peptide/peptidomimetic secondary structure. Similar to other classes of known peptidomimetics, γ-AApeptides are highly resistant to proteolytic degradation,[5,7] making them promising candidates for modulation and perturbation of biological processes. For instance, some γ-AApeptides can permeate mammalian cell membranes,[8] bind to HIV-1 RNA with affinity and specificity akin to Tat peptide,[9] modulate p53/MDM2 protein-protein interactions,[5] and selectively disrupt bacterial membranes by mimicking natural host-defense peptides.[10] Furthermore, γ-AApeptides can even form novel nanostructures,[11] suggesting their potential applications in the arena of biomaterials science. To further expand the versatility of γ-AApeptides in biomedical and materials applications, we report herein a method to prepare γ-AApeptides with high efficiency. More importantly, using the same synthetic approach, a few new classes of peptidomimetics with novel backbones, including oligocarbamates, oligosulfonamides, and oligoureas, can be conveniently generated. These peptidomimetics are different from classic oligocarbamates, oligosulfonamides and oligoureas,[12] and thus, may find novel functions and applications in biomedical and materials sciences in the future.

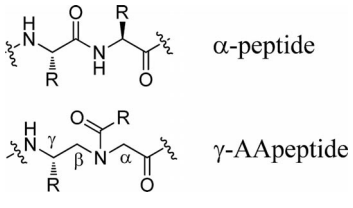

Figure 1. General structure of α-peptide and γ-AApeptide backbone scaffolds.

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Results and Discussion

The synthesis of γ-AApeptides was originally carried out on solid phase resin using the building-block approach.[10b] Although this approach is well established and reliably provides products in good yields, this strategy is not ideal for quickly generating derivatives with diverse groups since each building block has to be prepared separately prior to solid phase synthesis. We recently developed a submonomeric approach for the synthesis of γ-AApeptides that circumvents the need to generate γ-AApeptide building blocks.[13] However, the basic units, Fmoc-amino aldehydes, are not stable at room temperature, and thus need to be used immediately following their preparation. Moreover, the synthetic procedure is tedious requiring several steps for each cycle of monomer addition; this can significantly attenuate the overall yields when preparing longer sequences of peptidomimetics. Consequently, solid phase synthesis as it is most commonly practiced, is impractical for preparing γ-AApeptide libraries with large structural diversity.

To overcome this obstacle, we report herein a new method that combines both building-block and submonomeric approaches. In this approach, only a few *N*-alloc γ-AApeptide building blocks need to be synthesized by either Route 1 or Route 2 (Figure 2, panel a),[5,10b,10c] in order to prepare γ-AApeptides containing virtually limitless functional diversity. When the stereoisomerically projected R group contains acid-labile protecting groups such as Boc, Route 2 has to be adopted to remove the benzyl group prior to alloc *N*-protection. It is notable that 1% AcOH is critical during debenzylation in order to protonate the secondary amine, which otherwise always leads to Fmoc group removal.

The key step of this solid phase synthesis is the removal of the alloc protecting group. Briefly, on the solid phase, the alloc protecting group is removed by 10 mol-% equiv. $Pd(PPh_3)_4$ and 6 equiv. $Me_2NH{\cdot}BH_3$ in DCM.[14] This reaction is extremely efficient and only takes 10 min to give the desired product with quantitative conversion. Following removal of the alloc group, a variety of carboxylic acids or acyl chlorides can then be used to acylate the backbone nitrogen of the γ-AApeptide. To test the efficiency of this methodology, we synthesized a tetra-block sequence **γ-AA1** and a penta-block sequence **γ-AA2** (Figure 3). As shown in Figure 3, panel c, using just one *N*-alloc γ-AApeptide building block, **γ-AA2** was synthesized. Importantly, **γ-AA2**, despite requiring only one monomer for construction, bears diverse *N*-tethered side chains, the result of different acylating agents employed. Using multiple *N*-alloc γ-AApeptide building blocks and different acylating agents, peptidomimetic **γ-AA1** containing a wide variety of random side chains was prepared (Figure 3, panel b). The purity of the crude preparations for both **γ-AA1** and **γ-AA2** exceeds 80% (Figure 3, b and 3c), thus demonstrating the feasibility of this approach for efficient preparation of γ-AApeptides with structurally diverse side chains. Compared to previous

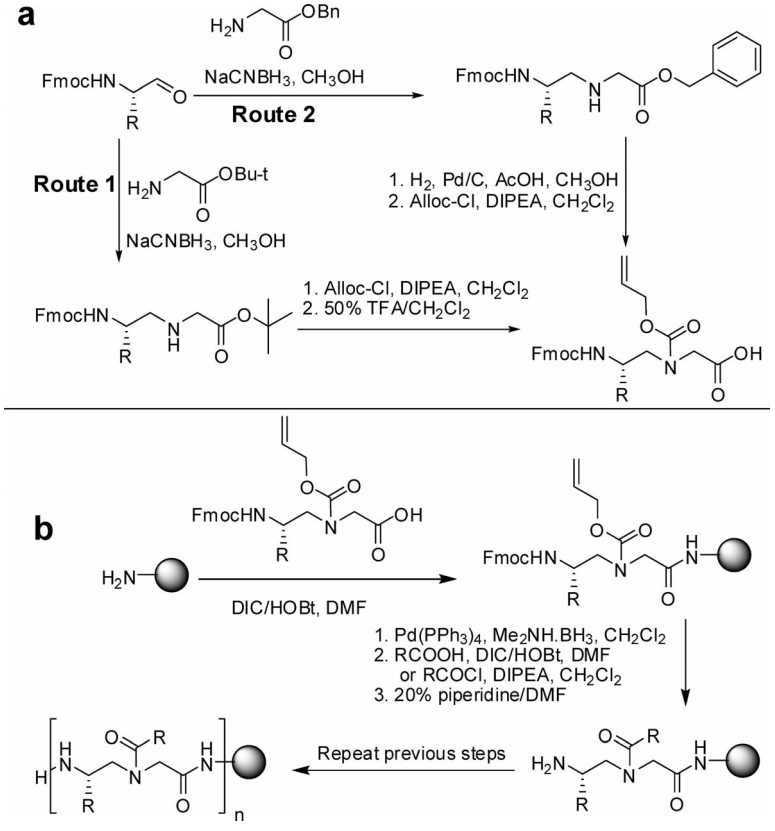

Figure 2. Synthesis of γ-AApeptides by a combined building-block and monomeric approach. **a**, synthesis of *N*-alloc γ-AApeptide building blocks. **b**, synthesis of γ-AApeptide sequences; Alloc = allyloxycarbonyl.

approaches, this new strategy significantly reduces the number of steps, shortens the time required for synthesis, and greatly improves the yield and purity of γ-AApeptides. Furthermore, *N*-alloc building blocks are much more stable than Fmoc-amino aldehydes, the basic units historically used in the synthesis of γ-AApeptides by the submonomeric approach.[13] As a result *N*-alloc-protected monomers can be prepared in large batches and used for a long period of

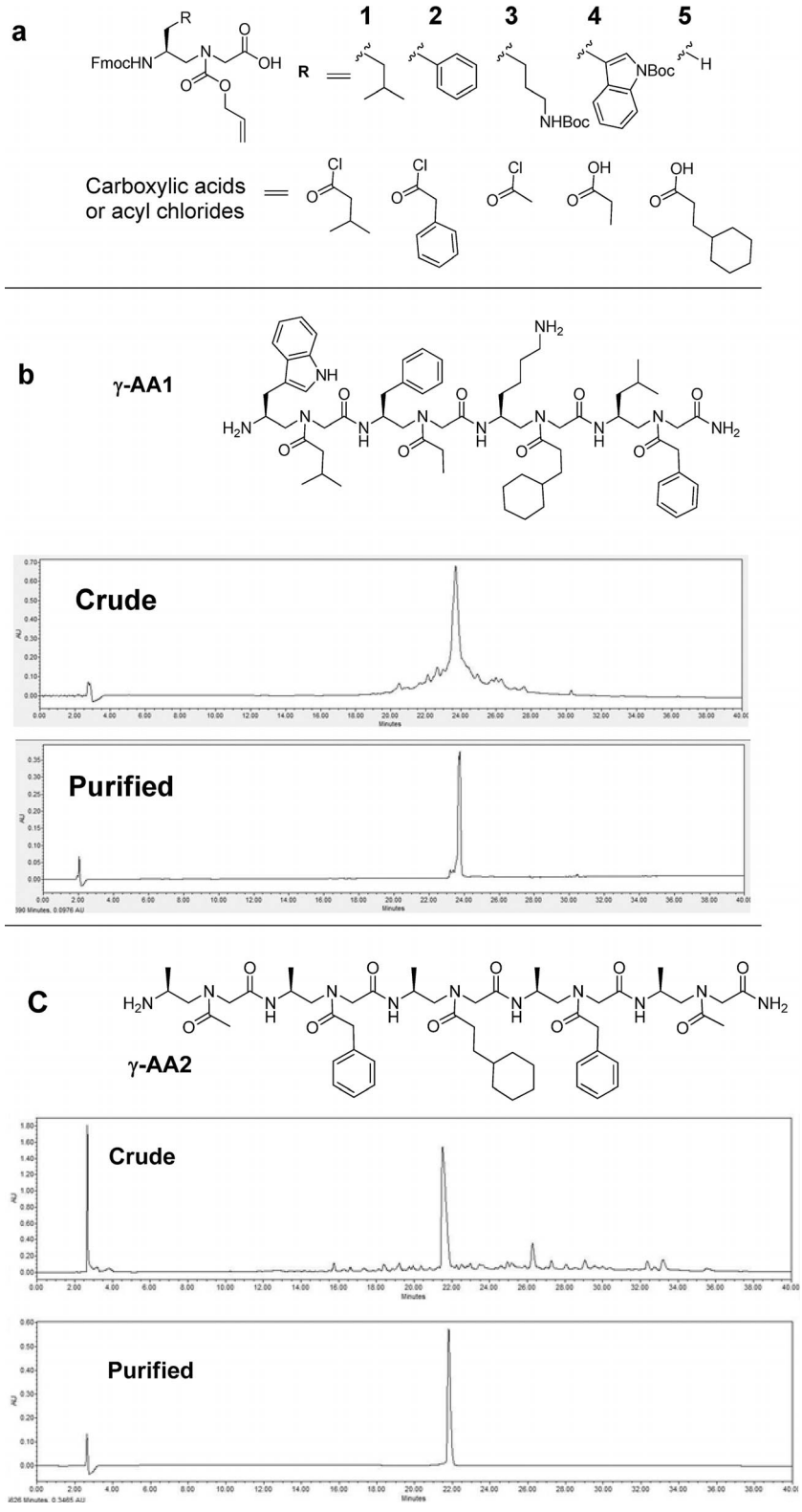

Figure 3. **a**. *N*-Alloc γ-AApeptide building blocks **1**–**5** and acylating agents used for the synthesis of the sequences. **b**. The structure of **γ-AA1**, and its crude and purified analytical HPLC traces. **c**. The structure of **γ-AA2**, and its crude and purified analytical HPLC traces.

time, in stark contrast to Fmoc-amino aldehydes. This feature adds another dimension of versatility to the new synthetic method.

It is known that peptidomimetics such as oligocarbamates, oligosulfonamides, and oligoureas have important biological applications,[12] implying what could be the great promise of new peptidomimetics with novel functional backbones. However, the synthesis of these classes of peptidomimetics is not trivial, as reflected by the scarcity of reports of their biological applications. Indeed, many more reports, both synthetically- and functionally-oriented, are known for β-peptides and peptoids. We envisioned that, using these same *N*-alloc γ-AApeptide building blocks, new peptidomimetic classes with novel backbones could be readily accessed.

To test our hypothesis, we synthesized oligosulfonamide **γ-AA3**, oligocarbamate **γ-AA4**, oligourea **γ-AA5**, and the sequence **γ-AA6** containing assorted backbone functionalities using one *N*-alloc γ-AApeptide building block on solid phase (Figures 4 and 5). These syntheses were accomplished by acylating the backbone nitrogens with a variety of commercially available sulfonyl chlorides, chloroformates, and isocyanates (Figure 4, panel a). HPLC chromatograms for both crude and purified peptidomimetics demonstrate the efficiency of the executed syntheses (Figure S3). It should be noted that these new peptidomimetics differ from classic oligocarbamates, oligosulfonamides and oligoureas[12] in that they are based on the γ-AApeptide backbone and may therefore have discrete structures and functions. Our results vividly demonstrate that, with common γ-AApeptide building blocks, different classes of peptidomimetics can be readily obtained.

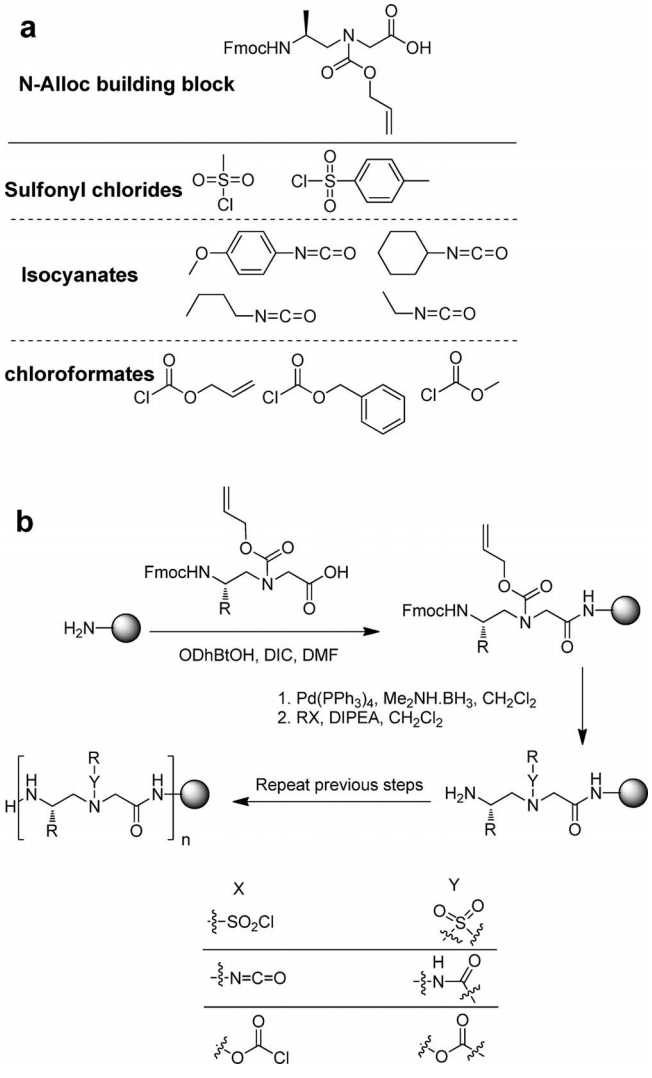

Figure 4. **a**. The *N*-alloc γ-AApeptide building block, sulfonyl chlorides, chloroformates, and isocyanates used to prepare new classes of peptidomimetics. **b**. Solid-phase synthesis of peptidomimetic backbone sequence with different *N*-tethered functionalities.

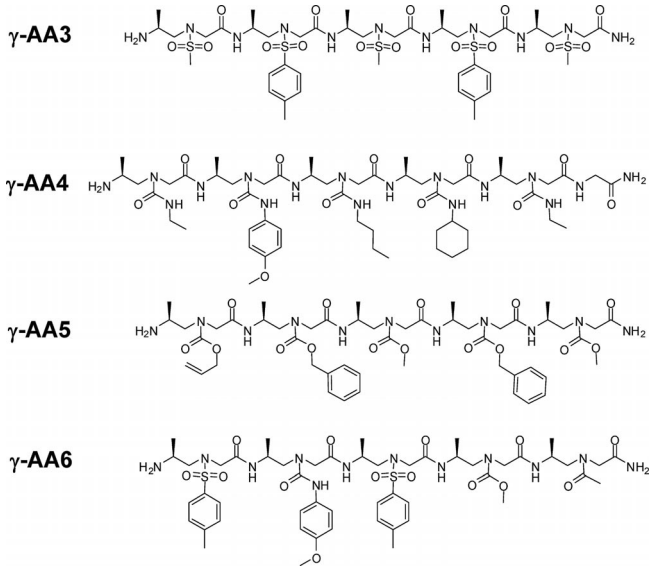

Figure 5. The sequences of oligosulfonamide (**γ-AA3**), oligourea (**γ-AA4**), oligocarbamate (**γ-AA5**), and the sequence containing all possible backbone functionalities (**γ-AA6**).

Conclusions

In summary, we have developed a modified method for efficient preparation of γ-AApeptides and a few new classes of peptidomimetics such as oligosulfonamides, oligoureas and oligocarbamates, using common *N*-alloc γ-AApeptide building blocks. Generation of chemically diverse libraries of γ-AApeptides with virtually limitless potential is now feasible. We demonstrate here the versatility of this new synthetic approach which is, in part, highlighted by the creation of new families of unprecedented peptidomimetics bearing diverse functional backbones and side chains. Further development of these novel peptidomimetics may reveal that they have important biological applications in the future. As such, the potential scope of research on γ-AApeptides will be significantly expanded.

Experimental Section

1. General Experimental Methods: All Fmoc-protected α-amino acids and Rink amide resins (0.7 mmol/g, 200–400 mesh, 1% DVB)

were purchased from Chem-Impex International, Inc. (Wood Dale, IL, USA). All other solvents and reagents were purchased from assorted vendors and used without further purification. NMR spectroscopic data for building blocks was obtained with a 400 MHz NMR spectrometer. High resolution masses of building blocks were determined with a Liquid Chromatography/Quadrupole Time-of Flight mass spectrometer. Masses of peptidomimetics were obtained using a Proteomics Analyzer. Solid-phase synthesis was conducted in peptide synthesis vessels on a shaker. Oligomers were analyzed and purified with an HPLC system, and then lyophilized.

2. Preparation of γ-AApeptide Building Blocks: *N*-Alloc γ-AApeptide building blocks **1**, **2**, **5** were synthesized using Route 1 in Figure 2 by following previously reported methods.[5,15] Building blocks **3** and 4 were synthesized by Route 2 in Figure 2 and the procedure for preparation of **3** is briefly shown as follows. To benzyl ester[5,15] (2 g, 1.66 mmol) in methanol (50 mL) containing 1% acetic acid was added Pd/C (0.2 g, 10 wt.-%). Hydrogenation was conducted at atmospheric pressure and room temperature for 2 h. After filtration and evaporation, the remaining solid was suspended in CH_2Cl_2 (50 mL) and *N*,*N*-diisopropylethylamine (434 μL, 2.49 mmol, 1.5 equiv.) was added. The reaction mixture was cooled to 0 °C, then a solution of allyl chloroformate (176 μL, 1.66 mmol, 1 equiv.) in CH_2Cl_2 was slowly added over 1 h. The mixture was allowed to stir at room temperature for another 2 h, and then washed with saturated citric acid (30 mL × 3) and brine solution, dried with Na_2SO_4, and concentrated under vacuum. The pure building block **3** was obtained as a white foam solid after flash chromatography with 10% MeOH/CH_2Cl_2 (1.68 g, 85% yield).

Compound 1: Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 7.74 (d, J = 8 Hz, 2 H), 7.56 (t, J = 8 Hz, 2 H), 7.38 (t, J = 8 Hz, 2 H), 7.29 (t, J = 8 Hz, 2 H), 5.92–5.73 (m, 1 H), 5.29–5.06 (m, 2 H), 4.57–4.28 (m, 5 H), 4.17–3.83 (m, 3 H), 3.60–3.15 (m, 2 H), 1.69–1.23 (m, 3 H), 0.93–0.87 (m, 6 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) (two rotamers): δ = 173.6, 173.2, 157.8, 156.8, 156.7, 156.6, 156.2, 143.8, 141.3, 132.3, 124.5, 119.9, 118.2, 117.4, 66.8, 66.6, 52.3, 49.8, 48.7, 47.2, 41.7, 24.8, 23.2, 22.0, 21.8, 21.7, 14.2 ppm. HR-ESI: $[M + H]^+$ calc: 481.2333, found 481.2352.

Compound 2: Yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 8.74 (s, 1 H), 7.73 (d, J = 8 Hz, 2 H), 7.50–7.47 (m, 2 H), 7.36 (t, J = 8 Hz, 2 H), 7.28–7.18 (m, 7 H), 5.82–5.74 (m, 1 H), 5.21–5.07 (m, 2 H), 4.53–4.43 (m, 2 H), 4.34–4.25 (m, 2 H), 4.11–3.21 (m, 6 H), 2.82 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) (two rotamers): δ = 173.5, 157.5, 156.9, 156.5, 156.1, 143.8, 143.7, 141.3, 137.2, 132.2, 129.2, 129.1, 128.6, 127.7, 127.0, 126.7, 125.2, 119.9, 117.6, 66.9, 60.5, 51.7, 49.8, 49.0, 47.1, 38.8, 21.0, 14.2 ppm. HR-ESI: $[M + H]^+$ calc: 515.2177, found 515.2196.

Compound 3: Yield 85% (from intermediate **6a**). ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 8.74 (s, 1 H), 7.73 (d, J = 8 Hz, 2 H), 7.57 (d, J = 8 Hz, 2 H), 7.37 (t, J = 8 Hz, 2 H), 7.28 (t, J = 8 Hz, 2 H), 5.91–5.79 (m, 1 H), 5.28–5.07 (m, 2 H), 4.55–4.52 (m, 2 H), 4.37–3.92 (m, 5 H), 3.92–3.21 (m, 3 H), 3.06–3.02 (m, 2 H), 1.42–1.26 (m, 15 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) (two rotamers): δ = 172.8, 156.9, 156.7, 156.4, 156.3, 143.9, 143.8, 141.3, 132.4, 125.0, 119.9, 117.3, 79.3, 76.8, 66.7, 66.6, 52.1, 50.5, 49.8, 49.1, 47.2, 40.2, 32.1, 29.3, 28.4, 22.8 ppm. HR-ESI: $[M + Na]^+$ calc: 618.2786, found 618.2810.

Compound 4: Yield 80% (from intermediate **6b**). ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 9.08 (s, 1 H), 8.11 (d, J = 8 Hz, 1 H), 7.70 (d, J = 8 Hz, 2 H), 7.62–7.21 (m, 10 H), 5.84–5.61 (m, 1 H), 5.21–5.07 (m, 2 H), 4.55–4.50 (m, 2 H), 4.35–4.15 (m, 3 H), 4.02–3.71 (m, 3 H), 3.48–2.60 (m, 3 H), 1.61 (s, 9 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) (two rotamers): δ = 173.5, 157.0, 156.6, 156.4, 156.2, 149.6, 143.8, 141.2, 135.4, 132.2, 132.1, 127.6, 127.0, 125.2, 125.0, 124.5, 124.0, 123.8, 122.7, 119.9, 118.9, 118.3, 117.6, 116.1, 115.3, 83.7, 83.6, 67.0, 66.8, 51.7, 51.3, 50.6, 50.5, 49.9, 49.1, 47.1, 28.1 ppm. HR-ESI: $[M + H]^+$ calc: 654.2810, found 654.2826.

Compound 5: Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 7.73 (d, J = 8 Hz, 2 H), 7.55 (t, J = 8 Hz, 2 H), 7.37 (t, J = 8 Hz, 2 H), 7.29 (t, J = 8 Hz, 2 H), 5.85–5.76 (m, 1 H), 5.29–5.09 (m, 2 H), 4.55–4.54 (m, 2 H), 4.36–4.15 (m, 3 H), 4.04–3.89 (m, 2 H), 3.64–3.58 (m, 1 H), 3.43–3.13 (m, 2 H), 1.16–0.99 (m, 3 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) (two rotamers): δ = 173.1, 157.0, 156.5, 143.8, 141.3, 132.3, 124.9, 119.9, 117.5, 66.9, 66.7, 53.2, 52.9, 49.8, 49.0, 47.2, 46.4, 18.4 ppm. HR-ESI: $[M + H]^+$ calc: 439.1864, found 439.1872.

3. Solid Phase Synthesis of γ-AApeptides and Other Classes of Peptidomimetics: Solid phase synthesis was conducted in peptide synthesis vessels on a Burrell Wrist-Action shaker. 100 mg of Rink amide resin (0.07 mmol) was treated with 20% Piperidine/DMF solution (3 mL) for 15 min (×2) to remove the Fmoc protecting group. The solution was drained and beads were washed with DCM (3× 3 mL) and DMF (3× 3 mL). A solution of *N*-alloc γ-AApeptide building block (2 equiv.), HOBt (38 mg, 0.28 mmol), and DIC (44 μL, 0.28 mmol) in DMF (3 mL) was agitated for 5 min, and then added to the resin. The mixture was allowed to react at room temperature for 6 h and drained. The beads were washed with DCM (3× 3 mL) and DMF (3× 3 mL), followed by a capping reaction with acetic anhydride (500 μL in 3 mL pyridine). After washing with DMF (3× 3 mL) and DCM (3× 3 mL), to the beads were added $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) and $Me_2NH{\cdot}BH_3$ (25 mg, 0.42 mmol) in DCM (3 mL).[14] The alloc deprotection reaction was agitated for 10 min and repeated one more time. The beads were washed with DCM and DMF, followed by the reaction with acylating agents (4 equiv.) and DIPEA (6 equiv.) in 3 mL of DCM for 30 min (×2) or with carboxylic acid (4 equiv.), HOBt (8 equiv.), and DIC (8 equiv.) for 4 h (×2). The previous steps were repeated until the desired sequences were obtained. After that, the resin were washed with DCM and dried in vacuo. Peptide cleavage was done in a 4 mL vial by treating resin with TFA/H_2O/TIS (95:2.5:2.5) for 2 h. The solvent was evaporated and the crude reaction was analyzed and purified on an analytical (1 mL/min) and

Table 1. Purity, yield and MALDI-TOF analysis of γ-AApeptides.

γ-AApeptide	Purity (based on crude HPLC trace)	Yield [%] (based on loading of the resin)	Exact mass (theoretical)	Mass ($[M + H]^+$ as determined by MALDI-TOF)
γ-AA1	82%	15	1159.7522	1160.8005
γ-AA2	86%	18	1045.6324	1046.5728
γ-AA3	80%	17	1129.3735	1130.4100
γ-AA4	50%	15	1159.7190	1160.6294
γ-AA5	55%	12	1055.5288	1056.5046
γ-AA6	60%	11	1144.5045	1145.5491

preparative (20 mL/min) HPLC columns, respectively using a Waters HPLC. The HPLC gradient system employed a program of 5% to 100% linear gradient of solvent B (0.1% TFA in acetonitrile) in A (0.1% TFA in water) over the duration of 40 min. HPLC detection wavelength was set to 215 nm and products identified were confirmed by MALDI-TOF (Table 1).

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, HPLC traces.

Acknowledgments

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