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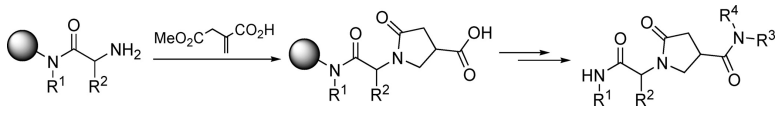

Solid-Phase Synthesis of a 4-Substituted γ-Lactam Library

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Pyrrolidin-2-one (γ-lactam) derivatives have shown a wide range of activities as ligands to diverse receptors, e.g., integrin, CCR5, and CCK. Therefore, we have prepared a large library of these derivatives for high-throughput screening against various protein targets, after developing a synthesis of pyrrolidin-2-ones on solid phase. Exploration of the ring formation was key to the success of this synthesis. First, acylation of resin-bound amines with *N*-Fmoc-protected amino acids and subsequent deprotection of the Fmoc group were accomplished readily. The resulting resin-bound primary amines were treated with β-monomethyl itaconate under gentle heat in a mixture of methanol and toluene to yield the desired intermediates. Finally, saponification, amide formation, and cleavage from the resin led to the production of a library of 12 000 pyrrolidin-2-one derivatives. These products were isolated as diastereomeric mixtures of high purity and were obtained in good yields.

Introduction

The pyrrolidin-2-one (γ-lactam) scaffold appears in diverse naturally occurring molecules. For example, as a pyroglutamyl group, it caps the amino terminus of peptide hormones such as gonadotropin releasing hormone.[1] The function of this γ-lactam is to stabilize the peptide's N-terminus against aminoprotease-mediated degradation. In other cases, the γ-lactam serves as a conformationally rigid scaffold, as in the 3-amino γ-lactam derivative **1** (Figure 1). When this residue is incorporated into peptides, a β-turn conformation is stabilized.[2,3]

More highly substituted γ-lactams have also shown a wide range of activities. Examples include antagonist **2** of the integrins (αvβ3, αvβ5, and αvβ6)[4] and antagonist **3** of the chemokine receptor CCR5.[5] Other γ-lactams have been used to inhibit fatty acid and cholesterol biosynthesis for the treatment of lipoprotein disorders (compound **4**)[6] and to inhibit phosphodiesterase IV, which is an enzyme linked to allergic and inflammatory diseases (compound **5**).[7] Finally, 4-substituted γ-lactams such as **6** exhibit improved antiepileptic activity, as compared to levetiracetam. This specific example possesses a 10-fold improvement in the ED_{50} over levetiracetam for protection against seizure activity in sound-sensitive mice.[8]

Since compounds such as **2**−**6** possess a wide range of biological activity, we decided to develop a solid-phase synthesis that would be amenable to the production of a library of 4-substituted γ-lactams. In addition, the formation of the functionalized γ-lactam during synthesis using itaconic acid derivatives is an interesting and viable approach.[8,9] However, to our knowledge, no reports of this conjugate addition/cyclization on resin have been reported. Recently, a synthesis of a solution phase library followed by diastereomer separation of the γ-lactam products was reported.[10] Diastereomeric pairs were formed, as expected. The main emphasis of that report was the ability to separate the diastereomers via high-throughput preparative high-performance liquid chromatography (HPLC). It is recognized that, even with automated high-throughput purification methods, the diastereomeric separation of a combinatorial library of the size we have envisioned is a daunting task. Therefore, we envisioned diastereomeric separation for only the active compounds in any high-throughput screens.

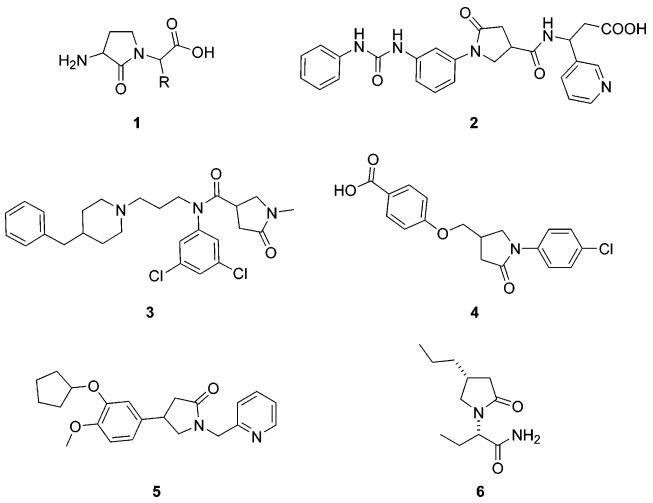

Figure 1. Examples of pyrrolidin-2-one derivatives.

To introduce diversity, the two points of attachment (the nitrogen and the acid) of the γ-lactam core were used. Since a primary amine was necessary for ring formation, a set of diverse amino acids coupled to resin-bound amines through the amino acid carboxyl group were selected. Finally, secondary amines were chosen to make diverse tertiary carboxamides at the 4-carboxyl position, leading to the design of the target molecule **7** (Figure 2). The synthesis of **7** was

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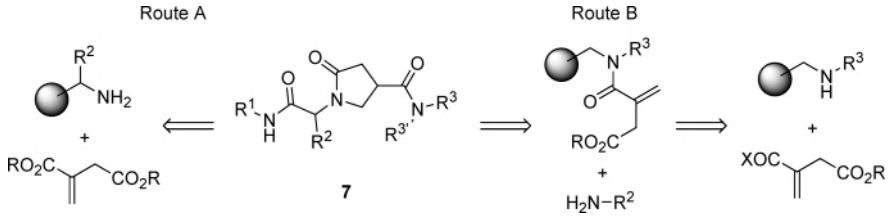
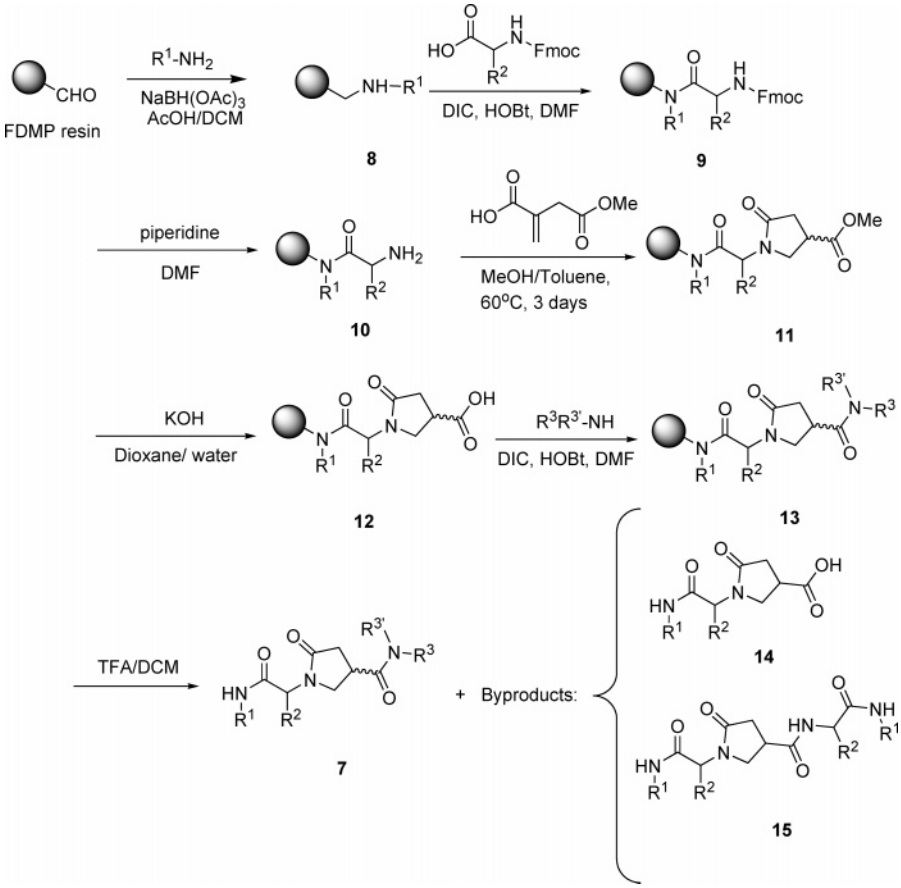


Figure 2. γ-Lactam derivative.

Scheme 1. Solid-Phase Synthetic Scheme for 4-Carboxamidopyrrolidin-2-ones and Identified Byproduct Structures



designed and optimized but its success relied particularly on the exploration of γ-lactam ring formation. The robustness of the final synthetic scheme was illustrated by the production of a large library of these γ-lactam derivatives.

Results and Discussion

For the γ-lactam ring formation to occur on resin, we envisioned two possible synthetic routes (see Figure 2). Route A involves the reaction of an itaconic acid derivative in solution with a resin-bound primary amine, and route B involves the reaction of a primary amine in solution with a resin-bound itaconate derivative. It was anticipated that, with route B, synthetic problems might occur during acylation with the itaconate in solution, as well as with the subsequent reaction with the amine. The first step would require specific carboxyl group activation and prevention of Michael addition of the resin-bound amine to the itaconate. The second step would require that the primary amine, most likely in excess, react via a Michael addition without an additional amine molecule reacting with the pendant carboxyl group. Because of these anticipated synthetic challenges, route A was adopted for this solid-phase synthesis involving three major steps: (i) coupling of a resin-bound amine to an amino acid, (ii) addition−cyclization to form the γ-lactam core, and (iii) coupling of the acid to a primary or a secondary amine, as shown in Scheme 1.

First, the amine was loaded onto the FDMP resin (2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene) by reductive amination, using sodium triacetoxyborohydride in a mixture of acetic acid in dichloromethane (DCM). The resulting secondary amine was coupled with *N*-Fmoc-protected amino acids using *N*,*N*-diisopropyl carboimide (DIC) and *N*-hydroxybenzotriazole (HOBt) as coupling agents. The resin loading of this intermediate was quantified by measuring the absorbance of the dibenzofulvene-containing solution from deprotection of the Fmoc group of a resin aliquot. Loadings ranged from 84 to 97%. The Fmoc group was then deprotected using a solution of 20% piperidine in *N*,*N*-dimethylformamide (DMF).

The formation of the γ-lactam core was composed of two steps: the Michael addition of a resin-bound primary amine

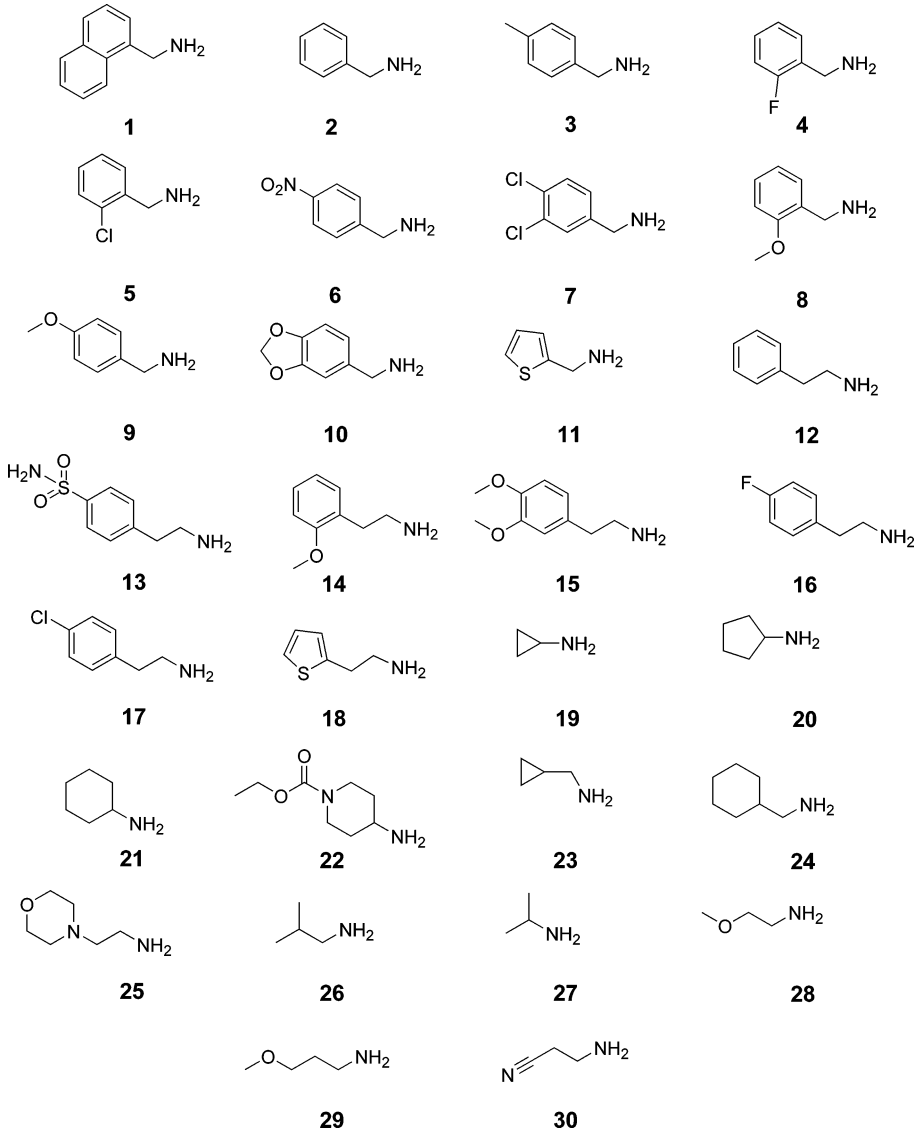


Figure 3. Amines $\mathbf{R^1}$.

to the double bond of an itaconate ester, followed by cyclization. To our knowledge, conditions for this reaction on a resin have not been reported; therefore, this reaction required optimization. Previously published conditions[9−12] for the synthesis in solution could not be used for the following reasons: high temperature would distort the Irori MicroKans; aqueous or methanolic solvents would be incompatible with the polystyrene-based resin, and finally use of an acid (like *p*-toluenesulfonic acid) to promote the reaction presented the potential to prematurely cleave the product from the acid-sensitive FDMP resin. The following parameters were varied: solvent (mixture of methanol with DMF, toluene, or DCM); itaconate derivatives (dimethyl, monomethyl, or monoethyl); the reagent concentration (0.2−0.75 M); the reaction duration (12 h, 24 h, 2 days, and 3 days); and the reaction temperature (50−65 °C). From these experiments, it was concluded that (i) the best solvent mixtures were methanol/toluene (4:1) or methanol/DCM (4:1), (ii) itaconic acid monomethyl ester reacted better than its ethyl derivative, (iii) an increase in the concentration of itaconate improved the formation of product, though not greatly; (iv) the reaction worked well at 65 °C for 18 h but the same results were obtained at 60 °C for 3 days. Interestingly, when dimethyl itaconate was used, Michael addition occurred but no γ-lactam formation was observed.

Reaction with monomethyl itaconate in methanol/DCM (4:1) at 60 °C for 3 days resulted in complete consumption of the resin-bound primary amine. However, a mixture of the desired acid and its corresponding methyl ester was observed. The esterification probably occurred due to the extensive exposure of the carboxylic acid to methanol during the cyclization. This observation led us to include a saponification step after the addition−cyclization reaction. The saponification[13] was accomplished using potassium hydroxide in a mixture of dioxane/water.

Finally, the resin-bound acid was coupled with primary and secondary amines using conditions similar to those used in the second step. The products were cleaved from the resin with a solution of 10% trifluoroacetic acid in DCM. The resin was washed with DCM and both eluants were combined. The products were analyzed by liquid chromatography−mass spectroscopy (LC−MS) and nuclear magnetic resonance (NMR) after evaporation of the solvents and dissolution in acetonitrile.

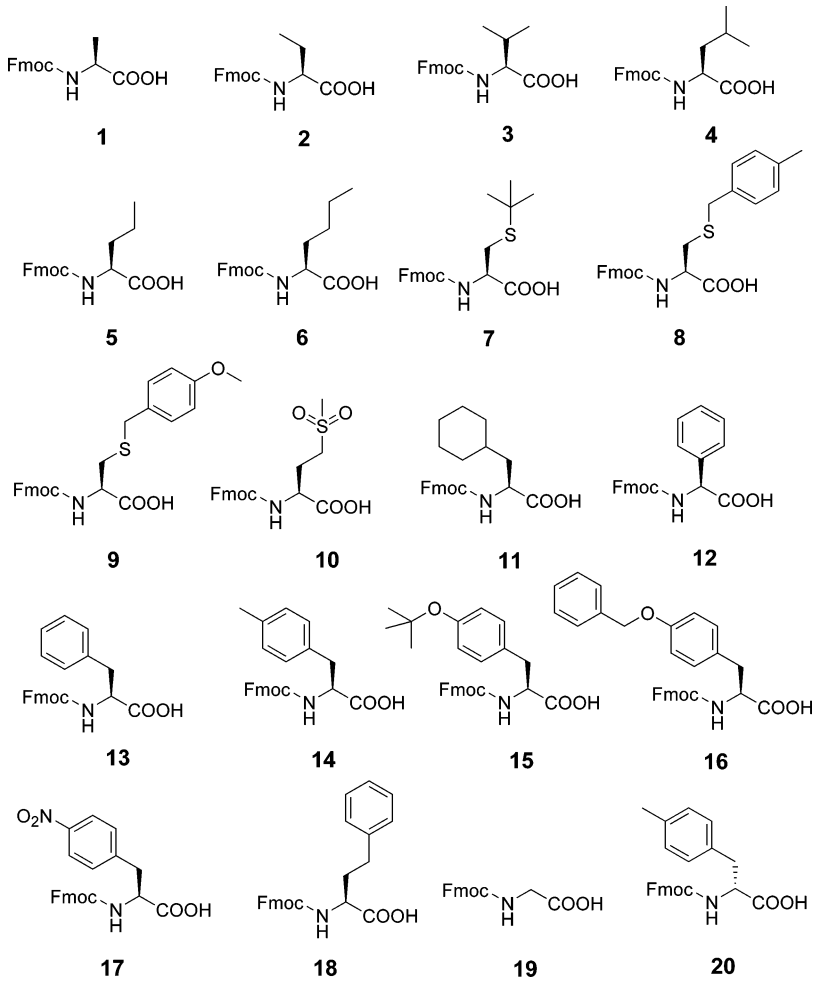


Figure 4. Fmoc-Amino acids $\mathbf{R^2}$.

Fifteen compounds were synthesized according to Scheme 1 and analyzed by LC−MS (ELS). The purities ranged from 72 to 99.9%, and the average mass recovery was 63%. The study of a few NMR spectra revealed the doubling of many peaks and, in particular, the amide N*H* and the amino acid C*H* protons. These protons systematically appeared as two peaks of similar integrations but very different chemical shifts. In many spectra, the amide N*H* was observed at ∼8.6 and 7.0, whereas C*H* appeared at ∼5.2 and 4.6. This confirmed the expected formation of the two diastereomers in almost-equal amounts during the cyclization step.

Analysis of the crude products showed the presence of two byproducts (Scheme 1) in varying quantities (2 to 20%). Compound **14** was formed when the coupling of the secondary amine failed, whereas **15** resulted from the cross reaction of the unreacted resin-bound primary amine **10** with the pyrrolidin-2-one carboxylic acid **12**. The latter byproduct was avoided if the resin-bound primary amine was completely consumed during the γ-lactam formation.

Library Design and Synthesis

Using the DirectedDiversity tools,[14] we studied the diversity and physicochemical properties of the virtual library of compound **7** to eliminate products with undesirable properties. Specifically, controlling the molecular weight and cLogP were key criteria in this selection process. This analysis led to the selection of 50 primary amines $\mathbf{R^1}$, 41 enantiomerically pure *N*-Fmoc-amino acids $\mathbf{R^2}$, and 55 secondary amines $\mathbf{R^3}$. For $\mathbf{R^3}$, many of the secondary amines were chosen to reduce the cLogP of the virtual products. These monomers were then rehearsed to determine their reactivity in our synthetic pathway. The rehearsals were accomplished by fixing two monomers while varying the third. Most of the monomers reacted well, except for a few amino acids. Protected aspartate and glutamate derivatives along with their amides did not result in highly pure products. Significant levels of byproducts, probably generated by reaction between the side chains and the itaconate during the cyclization step, were obtained instead. In addition, hindered amino acids such as aminoisobutyric acid resulted in incomplete γ-lactam formation. Based on the rehearsal results, 30 primary amines for $\mathbf{R^1}$, 20 *N*-Fmoc-amino acids for $\mathbf{R^2}$, and 20 secondary amines for $\mathbf{R^3}$ were selected for use in the production library (see Figures 3, 4, and 5, respectively).

Twelve thousand 4-carboxamide γ-lactams were produced and subsequently analyzed by LC−MS (ELS); 85.2% of the compounds had purities of above 80%, and the average purity was 91.3%. The average mass recovery was 13 mg (61%). The average molecular weight was 514.4 g/mol, and the average cLogP was 1.69. Twenty representative products **7** were also analyzed by NMR and are detailed in the Experimental Section.

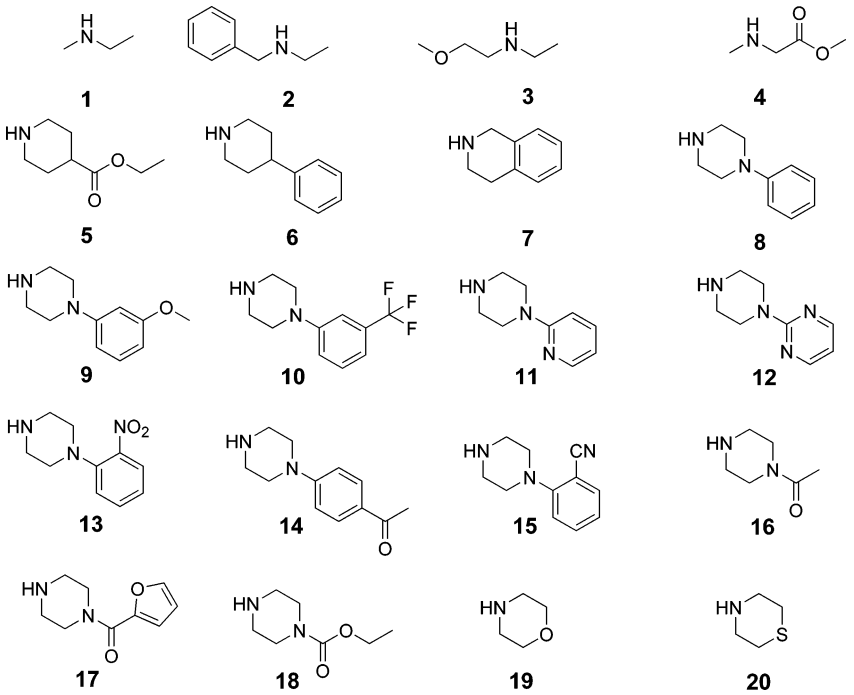


Figure 5. Secondary amines $\mathbf{R^3}$.

Conclusion

A synthesis of 4-carboxamide γ-lactams was designed and developed on solid phase. The successful optimization of the pyrrolidin-2-one ring formation on solid support was key to the success of this synthesis leading to the production of a 12 000-member library. The desired products were obtained as 1:1 diastereomeric mixtures in high purity and moderate to high yields.

Experimental Section

General Information. The 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (FDMP) beads of 150−300 μm (loading 1.5 mmol/g) were purchased from Polymer Laboratories (Amherst, MA). All other reagents were purchased from standard commercial sources and used without further purification. The solvents were purchased from Aldrich Chemical and Co. (Milwaukee, WI) in 18-L stainless-steel containers.

The LC−MS data were recorded on a Waters ZQ electrospray mass spectrometer equipped with four-channel MUX capabilities (Milford, MA) with ELS detection using Phenomenex columns 60 Å, 5 μm, 3 × 50 mm). (The ^{1}H NMR spectra and ELS LC−MS traces for all the compounds detailed in the Experimental Section are given as Supporting Information.) Two mobile phases (A, which is composed of 99.9% water and 0.1% TFA, and B, which is composed of 99.9% acetonitrile and 0.1% TFA) were used as a gradient from 25% B to 100% B in 1.8 min and 100% B for 0.45 min with a flow rate of 6.0 mL/min. ^{1}H NMR spectra were recorded in 5-mm tubes on a 300 MHz Varian in $CDCl_3$, unless otherwise stated.

Approximately 25 mg of FDMP resin was dispensed in MicroKans along with an RF tag (MicroKans and RF tags were purchased from Discovery Partners, San Diego, CA). After each step, the cans were sorted using the AutoSort-10K. At the final step, the resin was cleaved and the products recovered in deep well plates, using the Accucleave96. The quantitation and archiving of the products were done by transferring them from the deep well to tared barcoded Matrix minitubes (Hudson, NH) using the Robbins Hydra (Sunnyvale, CA) and weighing them using the Mettler-Toledo Bohdan Balance Automator (Mt. Vernon, IL).

The following abbreviations are used: DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; HOBt, *N*-hydroxybenzotriazole; DIC, *N*,*N*-diisopropyl carbodiimide; and TFA, trifluoroacetic acid.

General Procedure for the Preparation of Library Compounds. 1. Preparation of the Resin-Bound Amine (8). The resin in MicroKans was swollen in 2.5% acetic acid in DCM, after which point amines (10 equiv, 0.375 M) were added and the reaction mixtures shaken for 2 h, followed by the addition of $NaBH(OAc)_3$ (13.4 equiv, 0.5 M). The mixtures were shaken overnight at room temperature, the reaction solvent was filtered, and the excess of $NaBH(OAc)_3$ was decomposed by the addition of DCM/methanol (1:1). The resin was finally washed with MeOH, DCM, then twice with DMF, MeOH and DCM successively and the resin was dried in vacuo overnight.

2. Preparation of the Resin-Bound Fmoc-amino-amide (9). In the reaction bottles, each *N*(Fmoc)-amino acid (5.35 equiv, 0.2 M) was dissolved in DMF and mixed with HOBt (5.35 equiv, 0.2 M) and DIC (5.35 equiv, 0.2 M). The mixture was shaken for 30 min, and then the resin-bound **8** amine in MicroKans were added to each bottle. The reaction mixture was shaken overnight at room temperature. The solvent was then drained and the **9** resin was washed three times with DMF, methanol (MeOH), and DCM successively. The resin was finally dried in vacuo overnight.

3. Preparation of the Resin-Bound Amino-amide (10). A mixture of 20% piperidine in DMF was added to the dried

9 resin and shaken for 30 min. After draining the solvent, a fresh mixture of piperidine in DMF was added to the resin and it was shaken for another 30 min. The solvent was drained and the **10** resin washed twice with DMF, MeOH, and DCM successively and then with MeOH and DCM, and the resin was dried in vacuo overnight.

4. Formation of Pyrrolidinone Methyl Ester (11). The **10** resin was mixed with mono-methyl itaconate (16 equiv, 0.6 M) in methanol/toluene (4:1). The reaction mixture was then shaken and heated at 60 °C for three and a half days. After cooling to room temperature, the solvent was drained and the resin washed with MeOH, toluene and DMF and then twice with DCM and MeOH successively. Finally, the resin was dried in vacuo overnight.

5. Formation of Pyrrolidinone Carboxylic Acid (12). The **11** resin was suspended in dioxane/water (3:1), followed by the slow addition of potassium hydroxide (KOH) (14.8 equiv, 0.55 M) over 1 h, and the mixture was shaken overnight at room temperature. The solvent was drained and the resin washed with water, dioxane, DCM, DMF, MeOH, DCM, MeOH, and DCM successively, and the resin was dried in vacuo overnight.

6. Amide Formation (13). The **12** resin was swollen in DMF and HOBt (5.35 equiv, 0.2 M) was added, followed by DIC (5.35 equiv, 0.2 M). After mixing for 30 min, each amine was added to the resin, and the reaction mixture was shaken overnight at room temperature. The solution was drained and the resin washed twice with DMF, MeOH, and DCM, then with MeOH and DCM, and the resin was dried in vacuo overnight.

7. Cleavage from the Resin (7). The compounds were cleaved from the resin by treating each MicroKan with 10% TFA in DCM for 30 min then the solutions were collected by filtration into 2 mL deep well plates. The resin was washed with DCM for another 30 min and the solutions were also collected. The two solutions were combined and evaporated. The **7** products were analyzed by LC−MS, as previously described. Twenty selected products were also analyzed by NMR, which is detailed below.

8. 1-[1-(4-Methylbenzylcarbamoyl)-2-phenylethyl]-5-oxopyrrolidine-3-carboxylic Acid Ethylmethylamide 7{*3,13,1*}. Yield: 12.7 mg (80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 and 6.8 and 6.54 and 6.22 (multiplets corresponding to the N*H* of each diastereomer), 7.12 (m, 9H), 4.79 and 4.61 (q, J = 7.2 Hz, C*H* of each diastereomer), 4.34 (m, 2H), 4.27 (d, J = 5.9 Hz, 2H), 3.68 (m, 1H), 3.57 (m, 1H), 2.99 (m, 1H), 2.75−2.54 (overlapping multiplets, 2H), 2.68 (s, 2H), 2.33 (s, 3H), 2.3 (d, J = 3.9 Hz, 3H), 1.41 (dd, J = 1.9, 7.2 Hz, 3H); LC−MS (ELS) m/z = 422.43 $[M + H]^+$ (93.96%, R_t = 1.21 min).

9. (Methyl-{1-[1-(4-methylbenzylcarbamoyl)-2-phenylethyl]-5-oxopyrrolidine-3-carbonyl}amino)acetic Acid Methyl Ester 7{*3,13,4*}. Yield: 10.2 mg (58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (m, N*H* of one diastereomer), 7.05 (overlapping multiplets, 9H), 6.54 (m, N*H* of second diastereomer), 5.18−4.54 (multiplets, C*H* of each diastereomer, 1H), 4.41−3.98 (overlapping multiplets, 2H + 2H), 3.72 (s, 3H), 3.65 (m, 2H), 3.33 (m, 2H), 3.12 (m, 1H), 3.05 (singlet, CH_3N of one diastereomer), 3.01 (singlet, CH_3N of second diastereomer), 2.71−2.45 (m, 2H), 2.29 (s, 3H); LC−MS (ELS) m/z = 466.45 $[M + H]^+$ (90.71%, R_t = 1.17 min).

10. 2-{4-[4-(4-Acetylphenyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-*N*-(4-methylbenzyl)-3-phenylpropionamide 7{*3,13,14*}. Yield: 15.8 mg (62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (m, N*H* of one diastereomer), 7.92 (dd, J = 2.6, 9.2 Hz, 2H), 7.27 (m, 4H), 7.18 (m, 3H), 7.08 (m, 2H), 7.01 (m, N*H* of the other diastereomer), 6.9 (m, 2H), 5.21 (q, J = 5.3, 11.9 Hz, C*H* of one diastereomer), 4.64 (t, J = 8.6 Hz, C*H* of second diastereomer), 4.43 (d, J = 5.9 Hz, 2H), 4.29 (qd, J = 5.9, 15.2, 23.7 Hz, 2H), 3.71 (m, 4H), 3.6 (m, 2H), 3.37 (m, 4H), 3.14 (m, 1H), 2.73 (m, 2H), 2.56 (s, 3H), 2.31 (s, 3H); LC−MS (ELS) m/z =567.53 $[M + H]^+$ (99.77%, R_t = 1.27 min).

11. 2-[2-Oxo-4-(4-pyrimidin-2-ylpiperazine-1-carbonyl)-pyrrolidin-1-yl]pentanoic acid 2-fluorobenzylamide 7-{*4,5,12*}. Yield: 17.4 mg (78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, J = 5.9 Hz, 2H), 7.25 (m, 2H), 7.08 (m, 2H), 6.8 (m, 1H), 4.73 (dd, J = 3.9, 11.2 Hz, C*H* of one diastereomer), 4.53 (m, C*H* of the other diastereomer), 4.47 (dd, J = 6.6, 11.9 Hz, 2H), 3.94−3.45 (overlapping multiplets, 8H + 2H), 2.75 (m, 2H), 2.22−1.57 (m, 2H), 1.28 (overlapping multiplets, 2H + 1H), 0.95 (t, J = 7.2 Hz, CH_3 of one diastereomer), 0.93 (t, J = 7.2 Hz, CH_3 of the other diastereomer); LC−MS (ELS) m/z = 483.63 $[M + H]^+$ (93.41%, R_t = 0.85 min).

12. 3-*tert*-Butylsulfanyl-*N*-(2-chlorobenzyl)-2-[2-oxo-4-(4-phenylpiperidine-1-carbonyl)pyrrolidin-1-yl]propionamide 7{*5,7,6*}. Yield: 15.5 mg (74%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (m, N*H* of one diastereomer), 7.50 (m, N*H* of the other diastereomer), 7.32 (m, 4H), 7.20 (m, 5H), 4.94 (d, J = 11.9 Hz, C*H* of one diastereomer), 4.69 (d, J = 11.9 Hz, C*H* of the other diastereomer), 4.52 (m, 2H), 4.44 (q, J = 8.6, 15.2 Hz, 1H), 3.92−3.38 (overlapping multiplets, 2H + 2H), 3.14 (m, 2H), 2.94 (m, 1H), 2.76 (m, 2H), 2.63 (m, 2H), 1.93 (m, 2H), 1.62 (m, 2H), 1.34 (s, C(CH_3)$_3$ of one dias.), 1.32 (s, C(CH_3)$_3$ of the other diastereomer); LC−MS (ELS) m/z = 556.68 $[M + H]^+$ (93.30%, R_t = 1.62 min).

13. 2-[4-(4-Acetylpiperazine-1-carbonyl)-2-oxopyrrolidin-1-yl]hexanoic acid 4-nitro-benzylamide 7{*6,6,16*}. Yield: 16.3 mg (72%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (m, N*H* of one diastereomer), 8.16 (dd, J = 7.2, 8.6, 2H), 7.43 (dd, J = 8.6, 10.5 Hz, 2H), 7.20 (m, N*H* of the other diastereomer), 4.71 (dd, J = 3.9, 11.2 Hz, C*H* of one diastereomer), 4.52 (d, J = 6.5 Hz, 2H), 4.45 (m, C*H* of the other diastereomer), 3.79−3.63 (m, 4H), 3.48 (m, 4H), 3.25−2.74 (overlapping multiplets, 2H + 1H), 2.22−1.88 (m, 1H), 2.17 (s, 3H), 1.65−1.2 (m, 2H), 1.29 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); LC−MS (ELS) m/z = 488.53 $[M + H]^+$ (94.29%, R_t = 0.97 min).

14. *N*-Benzo[1,3]dioxol-5-ylmethyl-2-[2-oxo-4-(thiomorpholine-4-carbonyl)pyrrolidin-1-yl]-3-phenylpropionamide 7{*10,20,20*}. Yield: 14.2 mg (76%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (m, N*H* of one diastereomer), 7.24 (m, 5H), 6.91 (m, N*H* of the other diastereomer), 6.74 (m, 2H), 6.56 (s, 1H), 5.92 (s, 2H), 5.20 (dd, J = 4.6, 11.9 Hz, C*H* of one diastereomer), 4.24 (t, J = 7.9 Hz, C*H* of the other diastereomer), 4.36 (dd, J = 1.9, 5.3 Hz, 1H), 4.24 (dq, J = 5.9, 15.8 Hz, 1H), 3.71 (overlapping multiplets, 2H + 2H

+ 1H), 3.33 (m, 1H), 3.19 (m, 1H), 2.90 (m, 1H), 2.66 (m, 1H), 2.58 (d, $J = 5.3$ Hz, 4H), 2.45−2.34 (m, 1H); LC−MS (ELS) $m/z = 496.46$ $[M + H]^+$ (100%, $R_t = 1.16$ min).

15. 2-{4-[4-(2-Nitrophenyl)piperazine-1-carbonyl]-2-oxo-pyrrolidin-1-yl}-*N*-thiophen-2-ylmethylpropionamide 7{*11,1,13*}. Yield: 7.4 mg (33%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 and 6.83 (m, N*H* of each diastereomer), 7.82 (d, $J = 8.6$ Hz, 1H), 7.54 (m, 1H), 7.18 (m, 3H), 6.95 (m, 2H), 4.85 (q, $J = 7.2$ Hz, C*H* of one diastereomer), 4.7 (buried multiplet, C*H* of the other diastereomer), 4.59 (multiplets, 2H), 3.63 (overlapping multiplets, 2H + 4H), 3.44 (m, 1H), 3.06 (m, 4H), 2.86 and 2.56 (m, 2H); LC−MS (ELS) $m/z = 486.44$ $[M + H]^+$ (99.10%, $R_t = 1.23$ min).

16. 2-{4-[4-(2-Cyanophenyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-*N*-[2-(3,4-dimethoxyphenyl)ethyl]propionamide 7{*15,1,15*}. Yield: 7.7 mg (32%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 and 6.15 (m, N*H* of each diastereomer), 7.55 (dt, $J = 1.9$, 7.9 Hz, 1H), 7.47 (m, 1H), 7.04 (m, 1H), 6.95 (dd, $J = 1.9$, 7.9 Hz, 1H), 6.7 (q, $J = 7.2$ Hz overlapping with d, $J = 9.2$ Hz, 2H + 1H), 4.73 (q, $J = 7.2$ Hz, C*H* of one diastereomer), 4.49 (q, $J = 6.6$ Hz, C*H* of the other diastereomer), 3.81 (m, 6H), 3.79 (buried multiplet, 2H), 3.62 (m, 4H), 3.43 (overlapping multiplets, 2H + 1H), 3.12 (m, 4H), 2.87−2.65 (overlapping multiplets, 2H + 2H), 1.36 (2 doublets, $J = 7.2$ Hz, CCH_3 of one diastereomer), 1.32 (d, $J = 7.2$ Hz, CCH_3 of the other diastereomer); LC−MS (ELS) $m/z = 534.3$ $[M + H]^+$ (96.41%, $R_t = 1.22$ min).

17. 1-{1-[2-(3,4-Dimethoxyphenyl)-ethylcarbamoyl]-propyl}-5-oxopyrrolidine-3-carboxylic Acid Ethyl-(2-methoxyethyl)amide 7{*15,2,3*}. Yield: 5.3 mg (31%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (m, N*H* of one diastereomer), 6.69 (m, 3H), 6.16 (m, N*H* of the other diastereomer), 4.49 (multiplet, C*H* of one diastereomer), 4.19 (multiplet, C*H* of the other diastereomer), 3.80 (s, 2 × (CH_3O) of one diastereomer), 3.78 (s, 2 × (CH_3O) of the other diastereomer), 3.42 (overlapping multiplets, 2H + 2H + 2H + 2H), 3.26 (s, 3H), 3.20−2.80 (m, 1H), 2.70 (overlapping multiplets, 2H + 2H), 2.49−2.19 (m, 2H), 1.89−1.41 (m, 2H), 1.08 (dt, $J = 7.9$, 21.0 Hz, 3H), 0.83 (m, 3H); LC−MS (ELS) $m/z = 464.3$ $[M + H]^+$ (99.52%, $R_t = 0.89$ min).

18. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-{4-[4-(furan-2-carbonyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-4-phenylbutyramide 7{*15,18,17*}. Yield: 11.4 mg (42%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 and 6.08 (m, N*H* of each diastereomer), 7.45 (s, 1H), 7.12 (m, 5H), 7.04 (t, $J = 3.9$ Hz, 1H), 6.73 (m, 1H), 6.66 (m, 2H), 6.45 (m, 1H), 4.64 (m, C*H* of one diastereomer), 4.29 (t, $J = 7.2$ Hz, C*H* of the other diastereomer), 3.77 (s, 6H), 3.63 (overlapping multiplets, 2H + 2H), 3.45 (m, 8H), 3.19 (m, 1H), 2.88−2.35 (overlapping multiplets, 2H + 2H + 2H), 2.16−1.77 (m, 2H); LC−MS (ELS) $m/z = 617.3$ $[M + H]^+$ (96.46%, $R_t = 1.25$ min).

19. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[2-oxo-4-(4-phenylpiperazine-1-carbonyl)pyrrolidin-1-yl]-3-phenylpropionamide 7{*15,20,8*}. Yield: 14.3 mg (55%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 and 6.32 (m, N*H* of each diastereomer), 7.67 (d, $J = 7.9$ Hz, 2H), 7.49 (m, 2H), 7.41 (m, 1H), 7.2 (m, 5H), 6.68 (m, 3H), 5.14 (dd, $J = 5.3$, 11.2 Hz, C*H* of one diastereomer), 4.53 (t, $J = 8.6$ Hz, C*H* of the other diastereomer), 4.18 (m, 2H), 3.85 (s, 6H), 3.66 (buried multiplet, 2H), 3.46 (m, 8H), 3.31 (buried multiplet, 1H), 3.05 (m, 2H), 2.80 (m, 2H), 2.57 (m, 2H); LC−MS (ELS) $m/z = 585.3$ $[M + H]^+$ (96.90%, $R_t = 1.37$ min).

20. *N*-[2-(4-Chlorophenyl)-ethyl]-2-[4-(3,4-dihydro-1*H*-isoquinoline-2-carbonyl)-2-oxopyrrolidin-1-yl]-3-(4-methoxybenzylsulfanyl)propionamide 7{*17,9,7*}. Yield: 18.3 mg (81%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 and 7.81 (m, N*H* of each diastereomer), 7.21 (m, 10H), 6.83 (dd, $J = 5.9$, 7.9 Hz, 2H), 4.89 (dd, $J = 3.3$, 11.9 Hz, C*H* of one diastereomer), 4.28 (q, $J = 7.9$ Hz, C*H* of the other diastereomer), 4.66 (q, $J = 7.2$, 32.9 Hz, 2H), 3.78 (s, 3H overlapping with a multiplet, 2H), 3.65 (multiplet, 2H), 3.63−3.41 (overlapping multiplets, 2H + 2H), 3.29 (dd, $J = 3.9$, 14.5 Hz, 1H), 2.87 (overlapping multiplets, 2H + 2H + 2H), 2.51 (m, 2H); LC−MS (ELS) $m/z = 606.66$ $[M + H]^+$ (100%, $R_t = 1.57$ min).

21. 3-(4-Hydroxyphenyl)-2-[2-oxo-4-(4-phenylpiperazine-1-carbonyl)pyrrolidin-1-yl]-*N*-(2-thiophen-2-ylethyl)-propionamide 7{*18,15,8*}. Yield: 7.2 mg (29%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 and 6.83 (m, N*H* of each diastereomer), 7.42 (t, $J = 7.2$ Hz, 2H), 7.25 (multiplet overlapping with the solvent peak, 3H), 7.11 (m, 1H), 7.02 (d, $J = 7.2$ Hz, 2H), 6.9 (m, 1H), 6.73 (d, $J = 8.6$ Hz, 3H), 5.09 (dd, $J = 4.6$, 11.9 Hz, C*H* of one diastereomer), 4.52 (t, $J = 7.9$ Hz, C*H* of the other diastereomer), 3.9 (m, 2H), 3.57 (m, 2H), 3.35 (m, 8H), 3.20 (m, 1H), 3.19−2.88 (m, 2H + 2H), 2.82−2.49 (m, 2H), 1.25 and 0.83 (impurities from the deprotection of the *tert*-butyl group on the tyrosine); LC−MS (ELS) $m/z = 547.75$ $[M + H]^+$ (100%, $R_t = 1.02$ min).

22. *N*-Cyclopropyl-2-{4-[4-(furan-2-carbonyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-4-methanesulfonylbutyramide 7{*19,10,17*}. Yield: 18.2 mg (80%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 and 6.99 (m, N*H* of each diastereomer), 7.52 (s, 1H), 7.12 (t, $J = 3.9$ Hz, 1H), 6.53 (m, 1H), 4.76 (q, $J = 5.3$, 9.9 Hz, C*H* of one diastereomer), 4.56 (q, $J = 6.6$, 15.2 Hz, C*H* of one diastereomer), 3.88 (m, 4H), 3.73 (m, 2H), 3.61 (multiplet, 4H), 3.48−3.05 (m, 2H), 2.95 (2 singlets, 3H), 2.9 (buried multiplet, 1H), 2.85−2.65 (m, 2H), 2.43 (m, 2H), 2.18 (m, 1H), 0.76−0.53 (m, 4H); LC−MS (ELS) $m/z = 495.52$ $[M + H]^+$ (100%, $R_t = 0.26$ min).

23. *N*-Cyclohexyl-2-{4-[4-(furan-2-carbonyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-3-(4-nitrophenyl)propionamide 7{*21,17,17*}. Yield: 8.2 mg (32%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, $J = 2.6$, 8.6 Hz, 2H), 7.87 and 6.47 (d, $J = 7.9$ Hz, 1H), 7.52 (s, 1H), 7.40 (dd, $J = 2.6$, 8.6 Hz, 2H), 7.12 (d, $J = 3.3$ Hz, 1H), 6.54 (m, 1H), 5.21 and 4.54 (dd, $J = 5.3$, 11.8 Hz and t, $J = 7.9$ Hz, 1H), 3.87 (m, 4H), 3.74 (m, 4H), 3.54 (two overlapping multiplets, 2H + 1H), 3.32 (m, 2H), 2.99 (m, 1H), 2.67 (d, $J = 7.2$ Hz, 1H), 1.95−1.56 (m, 5H), 1.42−1.00 (m, 6H); LC−MS (ELS) $m/z = 566.66$ $[M + H]^+$ (94.69%, $R_t = 1.13$ min).

24. 4-{2-[2-Oxo-4-(4-pyridin-2-ylpiperazine-1-carbonyl)pyrrolidin-1-yl]propionylamino}piperidine-1-carboxylic Acid Ethyl Ester 7{*22,1,11*}. Yield: 8.4 mg (31%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7.96 (q, $J = 7.2$, 15.2 Hz, 1H), 7.9 and 6.55 (m, 1H), 7.00 (overlapping

quadruplet and multiplet, $J = 8.6$, 15.8 Hz, 2H), 4.79 and 4.47 (q, $J = 7.9$, 15.2 Hz and m, 1H), 4.12 (q, $J = 6.6$, 13.8 Hz, 2H), 4.07 (m, 2H + 1H), 3.96−3.71 (m, 4H + 2H), 3.63−3.48 (m, 2H), 2.90 (m, 2H), 2.90 and 2.71 (m, 2H), 1.87 (m, 2H + 1H), 1.44 (d, $J = 7.2$ Hz, 3H), 1.39 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H overlapping with a multiplet, 2H); LC−MS (ELS) $m/z = 501.66$ $[M + H]^+$ (100%, $R_t = 0.28$ min).

25. *N*-Cyclopropylmethyl-2-{4-[4-(3-methoxyphenyl)-piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-2-phenyl-acetamide 7{*23,12,9*}. Yield: 13.5 mg (59%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 and 5.92 (m, 1H), 7.19 (m, 5H + 1H), 6.63 (m, 2H), 5.81 and 5.7 (doublet, $J = 34.3$ Hz, 1H), 3.8 and 3.41 (m, 1H), 3.64 (s, 3H), 3.62 (m, 2H), 3.27−3.02 (m, 4H), 2.96 (m, 2H), 2.86−2.52 (m, 2H + 1H), 0.93 and 0.75 (m, 2H), 0.34 (m, 2H), 0.07 (two multiplets, 2H); LC−MS (ELS) $m/z = 491.63$ $[M + H]^+$ (100%, $R_t = 1.06$ min).

26. 1-(1-Isobutylcarbamoyl-2-*p*-tolylethyl)-5-oxopyrrolidine-3-carboxylic Acid Ethylmethylamide 7{*26,14,1*}. Yield: 9.6 mg (66%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 and 6.7 (m, N*H* of each diastereomer), 7.08 (s, 4H), 5.15 (dd, $J = 4.6$, 12.5 Hz, C*H* of one diastereomer), 4.45 (t, $J = 7.9$ Hz, C*H* of the other diastereomer), 3.63 (m, 2H), 3.33 (m, 2H), 3.26 and 3.10 (m, 2H), 2.94 (dd, $J = 7.2$, 13.8 Hz, 3H), 2.94 (buried multiplet, 2H), 2.86 (m, 1H), 2.70−2.49 and 2.35 (overlapping multiplets, 2H + 1H), 2.29 (s, 3H), 1.87 and 1.66 (m, 1H), 1.17 and 1.08 (two multiplets, 3H), 0.89 and 0.78 (two doublets, $J = 6.6$ Hz, 6H); LC−MS (ELS) $m/z = 563.84$ $[M + H]^+$ (95.87%, $R_t = 1.17$ min).

27. 2-{4-[4-(4-Acetylphenyl)piperazine-1-carbonyl]-2-oxopyrrolidin-1-yl}-*N*-(2-cyanoethyl)-3-*p*-tolylpropiona-mide 7{*30,14,14*}. Yield: 17.6 mg (73%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 and 7.43 (m, N*H* of each diastereomer), 7.89 (d, $J = 8.6$ Hz, 2H), 7.08 (2 singlets, 4H), 6.86 (dd, $J = 2.6$, 8.6 Hz, 2H), 5.19 (dd, $J = 3.9$, 12.5 Hz, C*H* of one diastereomer), 4.50 (dd, $J = 7.2$, 8.6 Hz, C*H* of the other diastereomer), 3.76 (m, 2H), 3.61 (m, 4H), 3.38 (overlapping multiplets, 4H + 2H), 3.32 (m, 2H), 3.13 and 2.77 (dd, $J = 9.2$, 13.8 Hz and m, 1H), 2.84 and 2.60 (m, 2H), 2.67 (m, 2H), 2.54 (s, 3H), 2.30 (2 singlets, 3H); LC−MS (ELS) $m/z = 530.64$ $[M + H]^+$ (99.71%, $R_t = 1.07$ min).

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Supporting Information Available. ^{1}H NMR spectra and ELS LC−MS traces for all the compounds detailed in the Experimental Section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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