Strategies for Combinatorial Organic Synthesis: Solution and Polymer-Supported Synthesis of 4-Thiazolidinones and 4-Metathiazanones Derived from Amino Acids

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Both the solution and polymer-supported synthesis of 4-thiazolidinones and 4-metathiazanones derived from amino acids are described. Solution studies showed that moderate to high yields of 4-thiazolidinones could be obtained from the one-pot, three-component condensation of amino acid esters (glycine, alanine, β-alanine, phenylalanine, and valine), an aldehyde (benzaldehyde, *o*-tolualdehyde, *m*-tolualdehyde, *p*-tolualdehyde, and 3-pyridinecarboxaldehyde), and an α-mercapto carboxylic acid (thiolactic and mercaptoacetic acid). Acylation of standard peptide synthesis resins with an Fmoc-protected amino acid, followed by deprotection of the Fmoc group and condensation with aldehydes and an α-mercapto or β-mercapto carboxylic acid, lead to the formation of the five- and six-membered heterocycles. The stepwise assembly of 4-thiazolidinones by treatment of the intermediate imine with an α-mercapto carboxylic acid was also demonstrated. Cleavage from the support under acidic (trifluoroacetic acid) conditions gave high yields and high purities of the liberated 4-thiazolidinones and lower yields of 4-metathiazanones.

Introduction

Combinatorial organic synthesis is a rapidly expanding field which has sparked a renaissance in the use of solid phase chemistry to assemble biologically active molecules.[1] While workers in this field initially directed their attention toward the preparation of oligomeric structures (e.g. peptides, *N*-alkylglycines, polycarbamates, polyureas),[2] a large number of laboratories have begun to target diverse collections of nonoligomeric "small molecule" compounds. For example, the polymer-supported synthesis of benzodiazepines,[3,4] hydantoins,[4] pyrrolidines,[5] and other classes[1b,6] of molecules have recently been disclosed. Synthesis of organic compounds on solid supports provides a convenient format for diversity generation because byproducts and excess reagents can be easily removed, and mild cleavage methods exist where often products released from the support are of sufficient purity to be directly submitted to bioassays. In addition to developing new methods for monitoring reactions on solid supports[7] and new reagents for orthogonal cleavage,[8] we were interested in exploring chemistries leading to new sources of diversity. One of the richest sources of diversity for the medicinal chemist is small heterocyclic rings, which in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities.

Two such heterocycles are thiazolidinones and metathiazanones. Thiazolidinones have been reported to possess a wide range of biological activities including antifungal, antibacterial, antihistaminic, antimicrobial, and anti-inflammatory activities among others.[9] 4-Thiazolidinones and 4-metathiazanones are most conveniently made by the three-component condensation of a primary amine, an aldehyde, and either a mercaptoacetic or mercaptopropionic acid.[10] The reaction proceeds through the intermediate imine, and the *stepwise* assembly of 4-thiazolidinones has also been described.[9,11] In adapting this chemistry to the solid phase, we chose to utilize amino acids as the source of primary amines with the carboxylic acid function serving as the site of attachment to the support. Thus, we could rely on established immobilization procedures for amino acids and moreover, have ready access to chiral starting materials as well as a wide variety of functionalities present in natural and unnatural amino acids. As a prelude to the generation and screening of combinatorial libraries, one must first "rehearse" the chemistry using a variety of building

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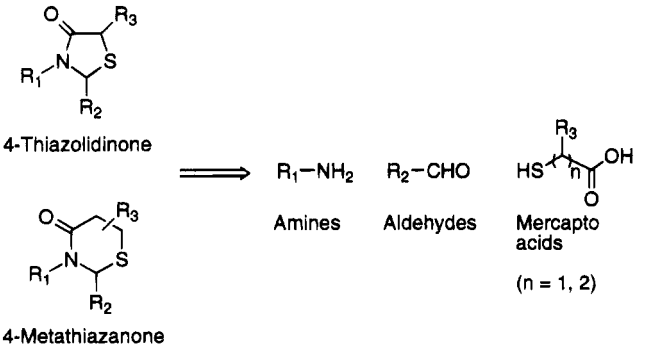
Table 1. Isolated Yields and Crude Purities of Solution and Polymer-Supported Synthesis of 4-Thiazolidinones and 4-Metathiazanones (Scheme 1)

entry	1	2 (equiv)	3 (equiv)	equiv of DIEA	% yield[a]	% yield[b]	product	method[c]	% yield[d]	% purity[e]
1	**1a**	**2a** (2.0)	**3a** (3.0)	1.3	85	60	**4**	A	69	98
2	**1a**	**2a** (1.1)	**3b** (1.2)	1.2	92	97	**4**	A	71	96
3	**1a**	**2b** (1.1)	**3a** (1.2)	1.3	42	92	**4**	A	72	98
4	**1a**	**2c** (1.1)	**3a** (1.2)	1.2	32	91	**4**	A	84	97
5	**1a**	**2d** (1.1)	**3a** (1.2)	1.3	58	100	**4**	A	81	95
6	**1a**	**2e** (1.1)	**3a** (1.2)	1.2	85	55	**4**	A	89	99
7	**1b**	**2a** (1.1)	**3a** (1.2)	1.2	38	82	**4**	A	90	92
8	**1b**	**2a** (2.0)	**3a** (3.0)	1.6	82		**4**			
9	**1e**	**2a** (2.0)	**3a** (3.0)	1.3	91	94	**5**	A	88	96
10	**1c**	**2a** (1.1)	**3a** (1.2)	1.6	6		**4**			
11	**1c**	**2a** (2.2)	**3a** (3.7)	1.7	88	86	**4**	A	69	84
12	**1c**	**2a** (2.2)	**3a** (3.7)	4.1	27		**4**			
13	**1d**	**2a** (1.1)	**3a** (1.2)	1.3	14	99	**4**	A	29	47
14	**1d**	**2a** (2.2)	**3a** (3.7)	1.7	68		**4**	B	60	88
15	**1d**	**2a** (2.2)	**3a** (3.7)	4.1	4		**4**			
16	**1a**	**2a** (2.0)	**3c** (3.0)	1.3	40	93	**6**	B	25	64
17	**1b**	**2a** (2.0)	**3c** (4.5)	1.3	8	78	**6**	B	<2	<10
18	**1c**	**2a** (2.0)	**3c** (8.0)	1.3	3	67	**6**	B	<2	<10

[a] Yield of the intermediate ester from the solution phase reaction after purification. [b] Yield of the acid from the solution phase saponification after purification. [c] Reagent concentrations employed for the polymer-supported reaction: method A: 0.25 M aldehyde **2**, 0.50 M mercapto acid **3**; method B: 0.75 M aldehyde **2**, 2.0 M mercapto acid **3**. [d] Yield of the acid from the polymer-supported reaction after TFA cleavage and purification. [e] Purity of the crude acid cleaved from the polymer support via HPLC analysis (220 nm detection).

blocks to learn the peculiarities of the process. We now wish to report our efforts on both the solution and solid phase assembly of 4-thiazolidinones and 4-metathiazanones derived from amino acids.



Results and Discussion

There have been no reports describing the solid phase synthesis of 4-thiazolidinones and few reports where the nitrogen of this heterocycle originates from an α-amino acid.[12,13] We therefore initially examined the solution phase condensation of amino acid esters with aldehydes and mercapto carboxylic acids to explore whether amino acids would serve as a suitable nitrogen source. We found that a one-pot, three-component condensation in refluxing benzene with azeotropic removal of water afforded moderate to high yields of the 4-thiazolidinones **4** and **5** after purification (Table 1). A relative stoichiometry of 1:2:3 of amine:aldehyde:mercapto acid, respectively, proved to be optimum for preparing ample quantities of material for further study. The use of fewer equivalents of aldehyde and mercaptoacetic acid gave dramatically lower yields with the substituted amino acids alanine, phenylalanine, and valine (compare entries 7 to 8, 10 to 11, and 13 to 14). One equivalent of tertiary amine was necessary to neutralize the amino acid hydrochloride salt, and excess amine was found to inhibit the reaction (compare entries 11 and 12, 14 and 15). A substituent at the 5 position of the ring was well tolerated in the reaction (entry 2), and additional alkyl substituents (Et, Pr, *i*-Pr, Bu; data not shown) were also readily tolerated.

Analogous condensations to form 4-metathiazanones **6** were more sensitive to the steric demands of the amine component, with yields decreasing in the series glycine–alanine–phenylalanine (entries 16–18). Sufficient material was obtained to continue, and no further attempts were made to improve yields of the solution phase reactions as our primary goal was to exploit the inherent advantages of solid phase organic synthesis techniques to drive the reactions to completion.

Saponification of the esters to the corresponding acids afforded high yields of authentic standards for the subsequent solid phase study (Table 1). The polymer-supported synthesis was performed on commercial solid supports bearing the 9-fluorenylmethoxycarbonyl (Fmoc)-protected amino acid attached to an acid- or photocleavable linker.[14] In a series of control experiments we demonstrated that both 4-thiazolidinones and 4-metathiazanones were stable to typical acidolysis conditions used for the deprotection of side chain protecting groups and resin-cleavage (e.g. 90% TFA containing phenol, thioanisole, water, and ethanedithiol), although for this study we routinely liberated the compounds from the resin with 50% TFA/dichloromethane. The observed acid stability of the 4-thiazolidinones is in contrast to the related *N*-acylthiazolidines, which have been reported to be sensitive to TFA treatment.[6g,16] We had previously demonstrated that 4-thiazolidinones could be assembled on a photolabile support and were stable to UV photolysis conditions employed to cleave them from supports.[8]

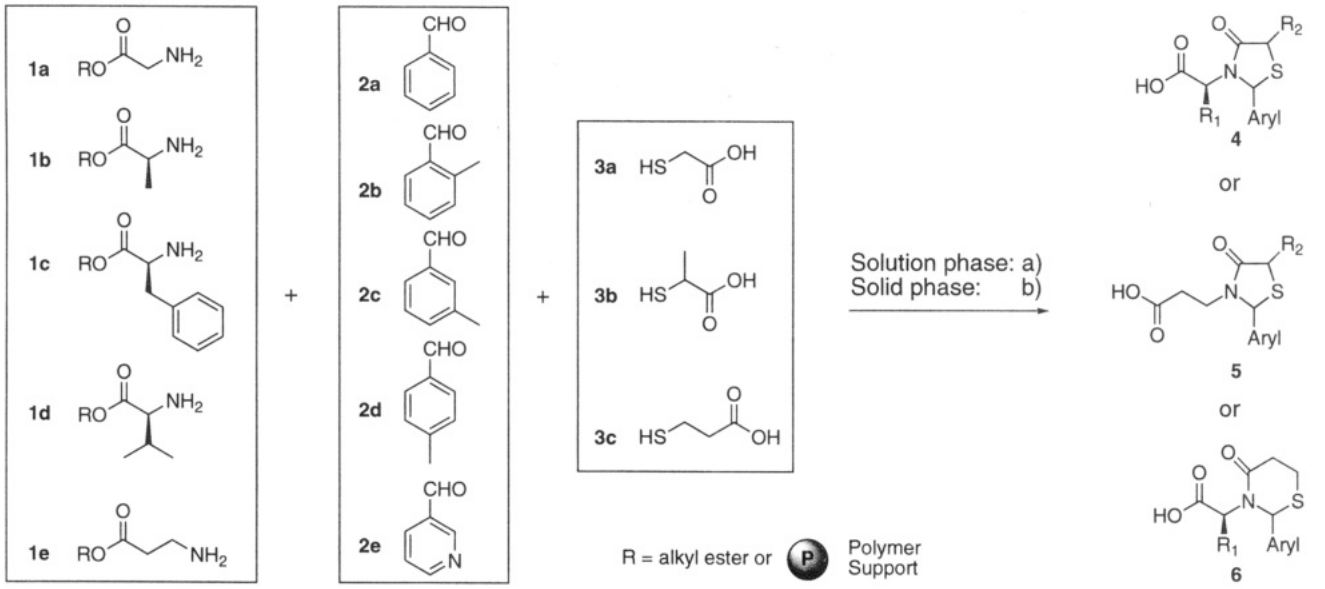
(12) Walsh, D. A.; Uwaydah, I. M. U.S. Patent 5 061 720, 1991.

(13) Amino acid-derived 4-thiazolidinones have been prepared via *N*-alkylation of 4-thiazolidinones with α-haloacetic acids: (a) Rida, S. M.; Salama, H. M.; Labouta, I. M.; A.-Ghany, Y. S. *Pharamzie* **1985**, *40*, 727–728. (b) Enomoto, M.; Kojima, A.; Komuro, Y.; Morooka, S.; Aono, S.; Sanemitsu, Y.; Mizutani, M.; Tanabe, Y. U.S. Patent 4 992 455, 1991.

(14) We have used Sasrin resin (polystyrene) from Bachem Bio-Science Inc, TentaGel (a polystyrene-polyethyleneglycol copolymer) from Rapp Polymere, and Novasyn PR 500 (a polydimethylacrylamide/polyhipe support) from Nova Biochem with equal success.

(15) We have used 3 Å molecular sieves or trimethyl orthoformate as desiccant with equal results.

Scheme 1[a]



[a] Reaction Conditions: (a) (i) amino acid ester hydrochloride salt (1 equiv), aldehyde (2 equiv), mercapto acid (3 equiv), benzene, 80 °C, Dean–Stark trap; (ii) NaOH, MeOH; (b) (i) support-bound amino acid, aldehyde (0.25 M), mercapto acid (0.5 M), tetrahydrofuran, 3 Å mol sieves, 70 °C; (ii) 50% TFA/CH_2Cl_2.

Deprotection of the Fmoc group with piperidine, followed by condensation of the support-bound amine with several aldehydes and mercaptoacetic acids in a one-pot reaction for 2 h at 70 °C with removal of water[15] afforded the desired heterocycles. Cleavage of the compounds from the support with TFA and subsequent product purification with preparative HPLC afforded moderate to high yields of 4-thiazolidinones (Table 1). The products were characterized by conventional techniques (HPLC, ^1H and ^{13}C NMR, MS, and elemental analysis). Reagent concentrations of 0.25 M for the aldehyde **2** and 0.5 M for the mercapto acid **3** (method "A", entries 1–13) in several solvents (tetrahydrofuran, acetonitrile, methanol, benzene) afforded 4-thiazolidinones of high purity; tetrahydrofuran was found to be the most general solvent due to its resin-swelling properties and solubility of reactants. The isolated yields are quite respectable in their own right, but the principle advantage of having assembled the molecules on the solid support is demonstrated by the purities of the crude material: no further purification is necessary before assaying for biological activity.

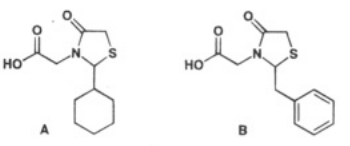
We routinely employ from 15 to 25 equiv of solution reactants relative to the resin loading in order to assure complete reaction. Fast ^{13}C NMR analysis of the support prior to cleavage was previously used to demonstrate near quantitative conversion of support-bound glycine to the 4-thiazolidinone.[7a] The use of large stoichiometric excesses was insufficient to drive the ring closure to completion with sterically demanding valine as amine and benzaldehyde as the aldehyde, however, and 4-thiazolidinone **4** was initially formed in only 47% purity (29% isolated yield, entry 13) under method A. A significant amount of benzaldehyde was observed after cleavage by HPLC, indicative of complete imine formation (which decomposes during the TFA treatment) but incomplete 4-thiazolidinone formation (Figure 1). We found that the reaction could be driven to near completion through the use of higher concentrations of both aldehyde (0.75 M) and mercaptoacetic acid (2.0 M), affording a mixture of the two products in 88% purity (60% yield, entry 14, method B). These higher concentrations of reagents were then adopted as standard for all further solid phase work.

The stepwise approach was also successful on the solid phase, with high overall yields of 4-thiazolidinones being obtained by treatment of the support-bound amine with an aldehyde, followed by subsequent exposure of the resultant imine to a solution of mercaptoacetic acid.[7a] The use of aromatic aldehydes leads to highly stabilized benzylidine imines which facilitates such a stepwise approach, and we have observed little decomposition of the imine after brief washes with organic solvents. The use of alkyl aldehydes in a stepwise approach is expected to be more difficult due to imine stability, and to date we have successfully employed alkyl aldehydes under the one-pot reaction conditions.[17]

Analogous solid phase condensations to generate 4-metathiazanones **6** were less successful. The 4-metathiazanone derived from glycine, benzaldehyde, and mercaptopropionic acid was observed to be only 64% pure after cleavage from the support and could be isolated in only 25% yield (entry 16). Little or no product was observed with the more demanding alanine and phenylalanine examples (entries 17 and 18), perhaps indicating the

(16) Sheppard, G. S.; Pireh, D.; Carrera, G. M.; Bures, M. G.; Heyman, H. R.; Steinman, D. H.; Davidsen, S. K.; Phillips, J. G.; Guinn, D. E.; May, P. D.; Conway, R. G.; Rhein, D. A.; Calhoun, W. C.; Albert, D. H.; Magoc, T. J.; Carter, G. W.; Summers, J. B. *J. Med. Chem.* **1994**, *37*, 2011–2032.

(17) For instance, condensation of support-bound glycine with cyclohexane-carboxaldehyde and mercaptoacetic acid and subsequent TFA cleavage afforded 4-thiazolidinone **A** in 89% isolated yield. The analogous condensation of support-bound glycine with phenylacetaldehyde and mercaptoacetic acid gave 4-thiazolidinone **B** in 46% isolated yield, but the phenylacetaldehyde used was contaminated with 10% of styrene oxide which may account for the moderate yield.



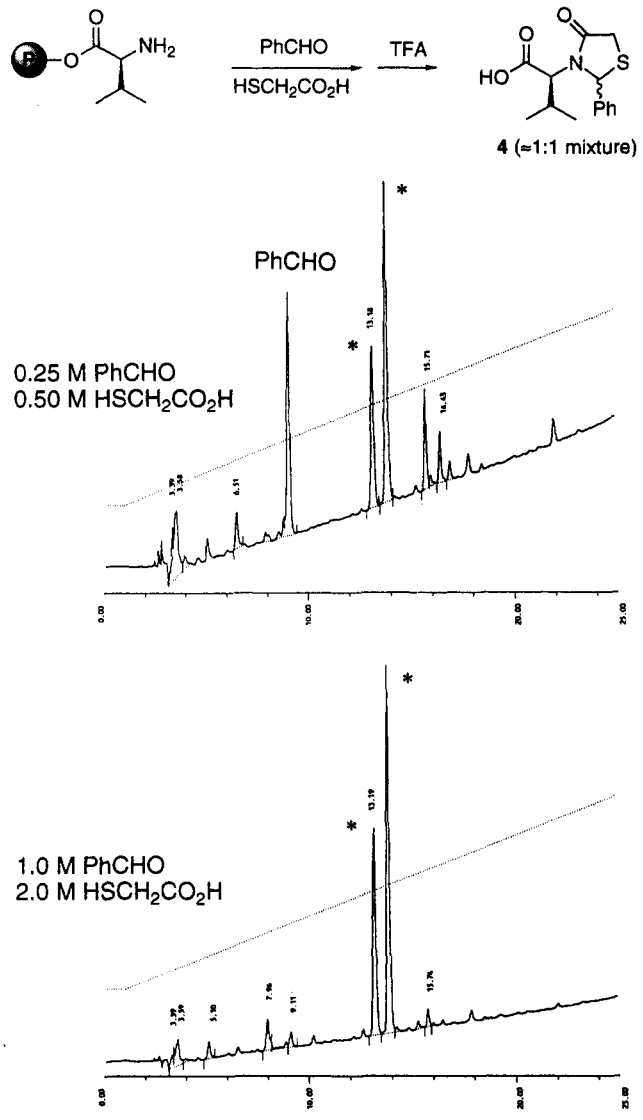


Figure 1. HPLC trace (220 nm) of diastereomeric 4-thiazolidinones **4** (13.2 and 13.9 min) produced from support-bound valine, benzaldehyde, and mercaptoacetic acid obtained after TFA cleavage. Top trace: method A; bottom trace: method B. The principle byproduct is benzaldehyde at 9.1 min.

upper bounds of tolerated substitution in the amine component under these reaction conditions. Efforts are underway to improve the polymer-supported synthesis of 4-metathiazanones.

As there are two new asymmetric centers formed in the reaction, diastereomeric products are observed via NMR and HPLC analysis. The elevated temperature of the reaction appears to override any thermodynamic control one might expect in the reaction, and roughly equal mixtures of cis and trans isomers are observed when no chiral center is present in the amine component (entry 2, and data not shown). The presence of a chiral center in the amino acid leads to mixtures of the two possible diastereomeric thiazolidinones (four diastereomers when a substituent is present at the 5 position), with more bulky substituents providing moderate levels of stereoinduction in the products (major:minor ≤ 4:1) (Figure 1). Other workers have been able to bias the distribution of product isomers at the 2 and 5 positions by altering the reaction conditions during 4-thiazolidinone formation,[18] and our efforts along these lines will be reported in the future.

In conclusion we have demonstrated the stepwise and one-pot three-component condensations of amino acids, aldehydes, and mercapto carboxylic acids to generate 4-thiazolidinones and 4-metathiazanones both in solution and on a polymer support. Attaching the amino acids to the support as their corresponding esters and subsequently forming the heterocycles allows one to drive the reactions to completion through the use of high concentrations and high molar excesses of reagents. The ability to join three classes of building block families in a combinatorial synthesis will allow for the generation of significant diversity which should find broad application in drug discovery. The documented bioactivity of these two classes of compounds, in addition to their ability to serve as molecular scaffolds to append additional functionality, makes them valuable targets for combinatorial organic synthesis. The chemistry described is currently being applied to combinatorial libraries, and the results of such endeavors will be reported in due course.

Experimental Section

General. All melting points are uncorrected. Unless otherwise noted, materials were of the highest grade available from commercial sources and used without further purification. Commercial resins (TentaGel-S-AC from Rapp Polymere, Tübingen, Germany; Sasrin resins from Bachem Bioscience Inc., Bubendorf, Switzerland; Novasyn PR 500 from Nova Biochem) were used without further characterization other than determination of the loading. ^{1}H NMR data were measured at 300 MHz and ^{13}C NMR at 75 MHz in the indicated solvent with tetramethylsilane as internal reference. HPLC analyses were conducted on a 2.1 × 250 mm-5 μ C_{18} column with a flow rate of 0.25 mL/min, monitoring at 220 nm. Solvent A: H_2O + 0.1% TFA; solvent B: ACN + 0.1%TFA; gradient: 0% B for 1 min and then to 90% B over 25 min. Mass spectra were obtained with either APCI or ESI as ionization method. Combustion analyses were performed by the Microanalytical Laboratory, University of California at Berkeley.

General Solution Phase Condensation. A mixture of amine hydrochloride salt (12 mmol), aldehyde (24 mmol), mercapto acetic acid (36 mmol), and diisopropylethylamine (15 mmol) in 50 mL of benzene was heated to reflux with a Dean–Stark trap for 18 h during which time about 0.5 mL of water collected in the trap. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic phase was washed (saturated $NaHCO_3$, 1 N HCl, and saturated NaCl), dried ($MgSO_4$), and concentrated to give a colorless oil. Chromatography on silica gel (100% CH_2Cl_2 to 3% acetone/CH_2Cl_2) afforded pure product as a colorless oil. The ester was taken on to the acid without further characterization.

To a solution of the ester (5 mmol) in 35 mL of MeOH was added 1 N NaOH (7.5 mL, 7.5 mmol). After stirring for 2 h at room temperature, the reaction mixture was partitioned between EtOAc and 1 N HCl. The organic phase was dried ($MgSO_4$) and concentrated to give a white semisolid. Chromatography on silica gel (1% HOAc/10% MeOH/89% $CHCl_3$) gave pure product acid as a white solid.

General Solid Phase Reaction (one-pot condensation). Commercially available Fmoc-amino acid resins containing an acid-cleavable linker were used. The terminal Fmoc group was deprotected by immersing the resin in 30% piperidine/DMF for 30 min in a standard peptide synthesis vessel, followed by washing with DMF, CH_2Cl_2, MeOH, and Et_2O. The resin was dried under reduced pressure and transferred to glass vials equipped with Teflon caps (≈50 mg of resin in a 4 mL vial), and 2 mL of a solution of 0.25 M aldehyde and 0.5 M mercapto

(18) Tanabe, Y.; Kubota, Y.; Sanemitsu, Y.; Itaya, N.; Suzukamo, G. *Tetrahedron Lett.* **1991**, *32*, 383–386.

carboxylic acid in THF were added along with 20–30 pellets of 3 Å molecular sieves. The vial was capped and heated to 70 °C for 2 h with occasional shaking. The reaction mixture was cooled to room temperature and transferred to a disposable filter tube. The resin was washed (CH_2Cl_2, DMF, MeOH, and Et_2O), dried under reduced pressure, and treated with a solution of 50% TFA/CH_2Cl_2 for 30 min to release the polymer-bound heterocycle. Removal of the solvent under reduced pressure followed by preparative HPLC afforded the pure 4-thiazolidinone or 4-metathiazanone.

General Solid Phase Reaction (stepwise condensation). Analogous to the above procedure, deprotected resin was treated with a 0.25 M solution of aldehyde in THF for 2 h at 70 °C. The resin was washed (THF, MeOH, Et_2O) and subsequently treated a 0.5 M solution of mercapto carboxylic acid for 2 h at 70 °C. Washing and cleavage as above afforded the 4-thiazolidinones or 4-metathiazanones.

2-(2-Phenyl-4-oxothiazolidin-3-yl)acetic Acid (entry 1). Following the above solution procedure, 2.56 g (85% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.32 (d, J = 16.9 Hz, 1 H), 3.70 (s, 3 H), 3.80 (s, 2 H), 4.44 (d, J = 16.9 Hz, 1 H), 5.83 (s, 1 H), 7.30–7.42 (m, 5H).

From the solution procedure, 1.44 g (60% yield) of the acid was obtained as a white solid; from the support procedure, 10.3 mg (69% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 155–157 °C; ^{1}H NMR ($CDCl_3$) δ 3.36 (d, J = 16.9 Hz, 1 H), 3.82 (s, 2 H), 4.45 (d, J = 16.9 Hz, 1 H), 5.82 (s, 1 H), 6.70–7.05 (br s, 1 H), 7.31–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$ plus 2 drops DMSO-d_6) δ 32.6, 44.3, 63.6, 127.7, 127.8, 128.0, 128.3, 129.1, 139.1, 170.3, 171.6; MS (ESI) m/z 238 (MH^+). Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.35; H, 4.69; N, 5.76.

2-(2-Phenyl-5-methyl-4-oxothiazolidin-3-yl)acetic Acid (entry 2). Following the above solution procedure, 2.90 g (92% yield) of the methyl ester was obtained as a colorless oil (1:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 1.65 (d, J = 6.7 Hz, 1.5 H), 1.67 (d, J = 6.7 Hz, 1.5 H), 3.32 (d, J = 16.9 Hz, 1 H), 3.69 (s, 1.5 H), 3.71 (s, 1.5 H), 4.04 (br q, J = 6.7 Hz, 1 H), 4.43 (d, J = 16.9 Hz, 0.5 H), 4.45 (d, J = 16.9 Hz, 0.5 H), 5.77 (s, 0.5 H), 5.80 (d, J = 2.0 Hz, 0.5 H), 7.28–7.42 (m, 5 H).

From the solution procedure, 2.66 g (97% yield) of the acid obtained as a white solid; from the support procedure, 11.3 mg (71% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading) (1:1 mixture of diastereomers): mp 77–80 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (d, J = 6.7 Hz, 3 H), 3.35 (d, J = 17.2 Hz, 1 H), 4.00–4.10 (m, 1 H), 4.43 (d, J = 17.2 Hz, 0.5 H), 4.46 (d, J = 17.2 Hz, 0.5 H), 5.76 (s, 0.5 H), 5.79 (d, J = 2.0 Hz, 0.5 H), 7.28–7.42 (m, 5 H), 9.03–9.17 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ (19.7, 19.8), (40.5, 41.2), (44.0, 44.2), (60.7, 61.0), (127.2, 127.7), (128.9, 128.9), (128.7, 129.1), (138.3, 139.1), 169.1, (173.8, 173.9); MS (ESI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.31; H, 5.46; N, 5.37.

2-(2-*o*-Tolyl-4-oxothiazolidin-3-yl)acetic Acid (entry 3). Following the above solution procedure, 1.32 g (42% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.35 (d, J = 16.9 Hz, 1 H), 3.70 (s, 3 H), 3.75–3.78 (m, 2 H), 4.53 (d, J = 16.9 Hz, 1 H), 6.15 (br s, 1 H), 7.14–7.27 (4 H).

From the solution procedure, 1.15 g (92% yield) of the acid was obtained as a white solid; from the support procedure, 11.5 mg (72% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.40 (d, J = 16.9 Hz, 1 H), 3.71–3.85 (m, 2 H), 4.53 (d, J = 16.9 Hz, 1 H), 6.13 (s, 1 H), 6.78–7.06 (br s, 1 H), 7.15–7.29 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 18.4, 31.4, 44.1, 59.4, 125.9, 126.7, 128.4, 131.0, 135.7, 136.6, 169.2, 171.5; MS (ESI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.11; H, 5.28; N, 5.48.

2-(2-*m*-Tolyl-4-oxothiazolidin-3-yl)acetic Acid (entry 4). Following the above solution procedure, 1.01 g (32% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H), 3.33 (d, J = 17.0 Hz, 1 H), 3.70 (s, 3 H), 3.80 (s, 2 H), 4.45 (d, J = 17.0 Hz, 1 H), 5.80 (s, 1 H), 7.08–7.31 (M, 4 H).

From the solution procedure, 0.867 g (91% yield) of the acid was obtained as a white solid; from the support procedure, 13.3 mg (84% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 128–133 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.36 (d, J = 17.0 Hz, 1 H), 3.81 (d, J = 2.0 Hz, 2 H), 4.45 (d, J = 17.0 Hz, 1 H), 5.77 (br s, 1 H), 6.46–6.73 (br s, 1 H), 7.09–7.31 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 20.9, 31.7, 43.9, 62.5, 124.4, 127.7, 128.8, 129.7, 138.2, 139.0, 139.1, 171.2; MS (ESI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.06; H, 5.39; N, 5.19.

2-(2-*p*-Tolyl-4-oxothiazolidin-3-yl)acetic Acid (entry 5). Following the above solution procedure, 1.84 g (58% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.32 (d, J = 16.9 Hz, 1 H), 3.69 (s, 3 H), 3.78 (m, 2 H), 4.42 (d, J = 16.9 Hz, 1 H), 5.81 (br s, 1 H), 7.15–7.26 (m, 4 H).

From the solution procedure, 1.77 g (100% yield) of the acid was obtained as a white solid; from the support procedure, 12.9 mg (81% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 122–126 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.35 (d, J = 17.5 Hz, 1 H), 3.78 (s, 2 H), 3.96–4.32 (br s , 1 H), 4.42 (d, J = 17.5 Hz, 1 H), 5.79 (br s, 1 H), 7.15–7.27 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 20.8, 31.8, 43.9, 62.4, 127.4, 129.5, 136.0, 138.5, 169.2, 171.1; MS (ESI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S \cdot 0.05H_2O$: C, 57.15; H, 5.24; N, 5.55. Found: C, 56.88; H, 5.22; N, 5.34.

2-(2-(3-Pyridyl)-4-oxothiazolidin-3-yl)acetic Acid (entry 6). Following the above solution procedure, 2.55 g (85% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.33 (d, J = 16.9 Hz, 1 H), 3.71 (s, 3 H), 3.83 (s, 2 H), 4.45 (d, J = 16.9 Hz, 1 H), 5.86 (br s, 1 H), 7.38 (dd, J = 8.2, 6.5 Hz, 1 H), 7.75 (ddd, J = 8.2, 2.5, 2.5 Hz, 1 H), 8.57 (d, J = 2.5 Hz, 1 H), 8.65 (dd, J = 6.5, 2.5 Hz, 1 H).

From the solution procedure, 2.66 g (55% yield) of the acid was obtained as a white solid; from the support procedure, 19.7 mg (89% yield) of the acid (TFA-pyridinium salt) was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 216–220 °C; ^{1}H NMR (DMSO-d_6) δ 2.59 (d, J = 16.0 Hz, 1 H), 3.64 (d, J = 14.4 Hz, 1 H), 3.84 (dd, J = 14.4, 2.0 Hz, 1 H), 3.97 (d, J = 16.0 Hz, 1 H), 6.09 (d, J = 2.0 Hz, 1 H), 7.40 (dd, J = 8.2, 4.9 Hz, 1 H), 7.74 (ddd, J = 8.2, 2.0, 2.0 Hz, 1 H), 8.48 (d, J = 2.0 Hz, 1 H), 8.53 (dd, J = 4.9, 2.0 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 32.4, 46.2, 60.4, 124.0, 135.1, 135.8, 148.6, 149.9, 169.9, 170.4; MS (ESI) m/z 239 (MH^+).

(2*S*) 2-(2-Phenyl-4-oxothiazolidin-3-yl)propanoic Acid (entries 7, 8). Following the above solution procedure, 2.33 g (82% yield) of the methyl ester was obtained as a colorless oil (1:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 7.3 Hz, 0.5 H), 1.43 (d, J = 7.3 Hz, 0.5 H), 3.49 (s, 1.5 H), 3.65 (d, J = 16.0 Hz, 0.5 H), 3.70 (d, J = 16.0 Hz, 0.5 H), 3.74 (s, 1.5 H), 3.81 (dd, J = 16.0, 2.0 Hz, 0.5 H), 3.83 (dd, J = 16.0, 2.0 Hz, 0.5 H), 3.97 (q, J = 7.3 Hz, 0.5 H), 4.30 (q, J = 7.3 Hz, 0.5 H), 5.72 (br s, 0.5 H), 5.75 (d, J = 2.0 Hz, 0.5 H), 7.33–7.46 (m, 5 H).

From the solution procedure, 0.833 g (82% yield) of the acid was obtained as a white solid; from the support procedure, 13.8 mg (90% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-alanine (0.612 mmol/g loading): mp 176–182 °C (3:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ major isomer 1.15 (d, J = 7.4 Hz, 3 H), 3.65 (d, J = 16.0 Hz, 1 H), 3.86 (dd, J = 16.0, 2.0 Hz, 1 H), 4.40 (q, J = 7.3 Hz, 1 H), 5.83 (d, J = 2.0 Hz, 1 H), 7.28–7.48 (m, 5 H); minor isomer 1.44 (d, J = 7.3 Hz, 3 H), 3.64 (q, J = 7.3 Hz, 1 H), 3.71 (m, 2 H), 5.76 (br s, 1 H), 7.28–7.48 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ major isomer 14.5, 31.4, 52.1, 61.5, 126.8, 127.8, 128.7, 141.6, 171.2, 171.5; minor isomer 14.3, 32.1, 52.9, 64.0, 126.8, 128.7, 129.0, 139.8, 171.0, 171.5; MS (ESI) m/z 274 ($M + Na^+$). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.16; H, 5.31; N, 5.53.

3-(2-Phenyl-5-methyl-4-oxothiazolidin-3-yl)propanoic Acid (entry 9). Following the above solution procedure, 2.47 g (91% yield) of the ethyl ester was obtained as a colorless

oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3 H), 2.40 (dt, J = 16.5, 7.2 Hz, 1 H), 2.65 (dt, J = 16.5, 7.2 Hz, 1H), 3.08 (dt, J = 15.0, 7.2 Hz, 1 H), 3.68 (d, J = 15.9 Hz, 1 H), 3.76 (dt, J = 15.0, 7.2 Hz, 1 H), 3.80 (dd, J = 15.9, 2.0 Hz, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.74 (d, J = 2.0 Hz, 1 H), 7.30–7.44 (m, 5 H).

From the solution procedure, 2.08 g (94% yield) of the acid was obtained as a white solid; from the support procedure, 8.0 mg (88% yield) of the acid was obtained from 200 mg of TentaGel Fmoc-β-alanine (0.180 mmol/g loading): mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (dt, J = 16.5, 7.0 Hz, 1 H), 2.69 (dt, J = 16.5, 7.0 Hz, 1 H), 3.10 (dt, J = 14.4, 7.0 Hz, 1 H), 3.70 (d, J = 16.0 Hz, 1 H), 3.75 (dt J = 16.0, 7.0 Hz, 1 H), 3.81 (dd, J = 16.0, 2.0 Hz, 1 H), 5.74 (d, J = 2.0 Hz, 1 H), 7.28–7.44 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ 31.4, 31.8, 38.6, 62.1, 126.9, 128.8, 128.9, 140.3, 170.6, 172.4; MS (APCI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.04; H, 5.22; N, 5.29.

(2S)-3-Phenyl-2-(2-phenyl-4-oxothiazolidin-3-yl)propanoic Acid (entries 10, 11). Following the above solution procedure, 2.08 g (88% yield) of the methyl ester was obtained as a colorless oil (2:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 3.20–3.42 (m, 2 H), 3.57 (s, 1/3 3 H), 3.72 (s, 2/3 3 H), 3.58–3.79 (m, 2.7 H), 4.17 (dd, J = 8.2, 8.2 Hz, 0.3 H), 4.41 (br s, 0.7 H), 5.63 (br s, 0.3 H), 6.93–7.41 (m, 10 H).

From the solution procedure, 1.21 g (86% yield) of the acid was obtained as a white solid; from the support procedure, 13.5 mg (69% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-phenylalanine (0.601 mmol/g loading): mp 75–81 °C (1:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 3.21–3.50 (m, 2 H), 3.65–3.96 (m, 3 H), 4.37 (br s, 0.5 H), 5.67 (br s, 0.5 H), 6.86–7.45 (m, 10 H); (1:1 mixture of diastereomers) ^{13}C NMR ($CDCl_3$) δ (32.6, 33.0), (33.9, 34.3), (59.0, 59.2), (65.4, 65.9), (126.6, 127.3), (128.5, 128.5), (128.6, 129.0), (128.8, 128.8), (129.2, 129.3), (129.4, 129.7), (136.4, 137.0), (137.2, 137.3), (172.1, 172.7), (173.9, 174.0); MS (ESI) m/z 328 (MH^+). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.04; H, 5.23; N, 4.28. Found: C, 65.79; H, 5.44; N, 4.65.

(2S)-3-Methyl-2-(2-phenyl-4-oxothiazolidin-3-yl)butanoic Acid (entries 13, 14, 15). Following the above solution procedure, 1.79 g (68% yield) of the methyl ester was obtained as a colorless oil: diastereomers could be resolved by flash chromatography, minor (less polar) isomer ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 2.39–2.53 (m, 1H), 3.13 (s, 3 H), 3.65 (d, J = 15.7 Hz, 1 H), 3.92 (dd, J = 15.9, 2.0 Hz, 1 H), 4.39 (d, J = 11.1 Hz, 1 H), 5.58 (d, J = 2.0 Hz, 1 H), 7.22–7.48 (m, 5 H); major (more polar) isomer ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 7.2 Hz, 3 H), 0.91 (d, J = 7.2 Hz, 3 H), 2.02–2.17 (m, 1 H), 3.70 (s, 3 H), 3.70 (d, J = 16.1 Hz, 1 H), 3.84 (d, J = 8.6 Hz, 1 H), 3.90 (dd, J = 16.1, 2.0 Hz, 1 H), 5.74 (d, J = 2.0 Hz, 1 H), 7.32–7.48 (m, 5 H).

From the solution procedure, 0.568 g (99% yield) of the acid was obtained as a white solid; from the support procedure, 4.6 mg (29% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-valine (0.550 mmol/g loading) under method A and 9.5 mg (60% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-valine (0.550 mmol/g loading) under method B: mp 119–134 °C (1:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 0.76–1.04 (m, 6 H), 2.48–2.69 (m, 1 H), 3.38 (d, J = 10.3 Hz, 0.5 H), 3.65–3.94 (m, 2.5 H), 5.63 (br s, 0.5 H), 5.65 (br s, 0. H), 7.28–7.45 (m, 5 H); (1:1 mixture of diastereomers) ^{13}C NMR (DMSO-d_6) δ (19.1, 19.3), (20.2, 20.4), (26.7, 27.6), (31.1, 31.5), (61.5, 62.1), (62.8, 63.1), (126.7, 127.7), (128.3, 128.8), (128.4, 128.4), (140.6, 140.7), (169.9, 170.1), (171.4, 172.1); MS (APCI) m/z 280 (MH^+). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.02. Found: C, 60.22; H, 6.18; N, 4.62.

2-(2-Phenyl-4-oxometathiazan-3-yl)acetic Acid (entry 16). Following the above solution procedure, 1.27 g (40% yield) of the methyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.78–2.98 (m, 4 H), 3.34 (d, J = 17.2 Hz, 1 H), 3.70 (s, 3 H), 4.72 (d, J = 17.2 Hz, 1 H), 5.70 (s, 1 H), 7.27–7.44 (m, 5 H).

From the solution procedure, 1.12 g (93% yield) of the acid was obtained as a white solid; from the support procedure, 3.9 mg (25% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-glycine (0.631 mmol/g loading): mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 2.78–2.90 (m, 2 H), 2.91–3.01 (m, 2 H), 3.38 (d, J = 17.2 Hz, 1 H), 4,72 (d, J = 17.2 Hz, 1 H), 5.70 (s, 1 H), 7.27–7.43 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ 21.7, 34.2, 48.3, 62.2, 126.8, 128.0, 128.4, 139.1, 169.0, 169.8; MS (APCI) m/z 252 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.16; H, 5.37; N, 5.39.

(2S)-2-(2-Phenyl-4-oxometathiazan-3-yl)propanoic Acid (entry 17). Following the above solution procedure, 0.601 g (8% yield) of the methyl ester was obtained as a colorless oil (1:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7.3 Hz, 1.5 H), 1.43 (d, J = 7.3 Hz, 1.5 H), 2.74–2.97 (m, 4 H), 3.55 (s, 1.5 H), 3.75 (s, 1.5 H), 4.15 (q, J = 7.3 Hz, 0.5 H), 4.53 (q, J = 7.3 Hz, 0.5 H), 5.62 (s, 0.5 H), 5.71 (s, 0.5 H), 7.24–7.50 (m, 5 H).

From the solution procedure, 66 mg (78% yield) of the acid was obtained as a white solid; from the support procedure, <0.2 mg (<2% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-alanine (0.612 mmol/g loading): mp 65–75 °C; (1:1 mixture of diastereomers) ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 7.0 Hz, 1.5 H), 1.39 d, J = 7.0 Hz, 1.5 H), 2.62–3.07 (m, 4 H), 3.75 (q, J = 7.0 Hz, 0.5 H), 4.25 (q, J = 7.0 Hz, 0.5 H), 5.60 (s, 0.5 H), 5.73 (s, 0.5 H), 7.20–7.54 (m, 5 H), 8.03–8.52 (br s, 1 H); (1:1 mixture of diastereomers) ^{13}C NMR ($CDCl_3$ plus DMSO-d_6) δ (14.1, 14.8), (21.3, 22.9), (34.0, 35.0), (54.8, 57.3), (60.7, 64.4), (126.3, 127.0), (127.6), (128.1, 128.3), (138.3, 139.7), (169.3, 170.0), (172.5, 172.7); MS (ESI) m/z 266 (MH^+), 288 $(M + Na)^+$.

(2S)-3-Phenyl-2-(2-phenyl-4-oxometathiazan-3-yl)propanoic acid (entry 18). Following the above solution procedure, 75 mg (3% yield) of the ethyl ester was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.0 Hz, 3 H), 2.70–2.98 (m, 4 H), 3.06 (dd, J = 14.0, 7.0 Hz, 1 H), 3.42 (dd, J = 14.0, 7.0 Hz, 1 H), 3.68–3.82 (m, 1 H), 3.84–3.97 (m, 1 H), 4.60 (t, J = 7.0 Hz, 1 H), 5.81 (s, 1 H), 6.93–7.45 (m, 10 H).

From the solution procedure, 46 mg (67% yield) of the acid obtained as a white solid; from the support procedure, <0.2 mg (<2% yield) of the acid was obtained from 100 mg of Sasrin Fmoc-phenylalanine (0.601 mmol/g loading): mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 2.80–3.00 (m, 4 H), 3.07 (dd, J = 14.1, 7.4 Hz, 1 H), 3.46 (dd, J = 14.1, 7.4 Hz, 1 H), 4.01 (t, J = 7.4 Hz, 1 H), 5.76 (s, 1 H), 6.74–7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.6, 35.6, 36.0, 62.7, 65.2, 126.5, 127.9, 128.3, 128.7, 128.9, 129.4, 137.0, 137.9, 172.5, 173.8; MS (ESI) m/z 342 (MH^+).

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