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Solid-Phase Synthesis of Acyclic and Cyclic Amino Acid Derived Urea Peptidomimetics Using Phoxime Resin†

Yoshitomo Hamuro,[§,||] William J. Marshall,[⊥] and Mark A. Scialdone*,[§]

DuPont Life Sciences Enterprise, Biochemical Science and Engineering, P.O. Box 80328, Experimental Station, Wilmington, Delaware 19880-0328, DuPont Corporate Center for Analytical Sciences, P.O. Box 80228, Experimental Station, Wilmington, Delaware 19880-0328, Department of Biochemistry and Biophysics, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6059

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The use of Phoxime resin **2** (phosgenated *p*-nitrophenyl(polystyrene)ketoxime) in the synthesis of acyclic and heterocyclic amino acid derived ureas is described. Resin **2** was previously shown to be a useful precursor in the solid-phase preparation of nonsymmetric ureas from thermolysis of corresponding primary amine oxime carbamates and subsequent trapping with an amine in solution. Generation of functionalized polymer-supported primary amine oxime carbamates (**3** and **9**) for further diversification was accomplished by addition of amino acids or substituted hydrazines to resin **2**. The use of these functionalized oxime carbamate resins for the generation of acyclic α-ureidoacetamides **5**, 3-aminohydantoins **7**, and 1,2,4-triazine-3,6-diones **8** is suitable for combinatorial library generation.

Introduction

In recent years, combinatorial synthesis has rapidly emerged as a powerful methodology for the preparation of a wide variety of diverse molecular structures. The generation of nonoligomeric, small molecule libraries has especially attracted great attention for new drug lead discovery and optimization due to their preferable physiochemical and pharmacokinetic properties.[1,2] In general, solid-phase synthesis, rather than solution-phase synthesis, can be the preferred method for the generation of combinatorial libraries because of the greater ability to automate a solid-phase protocol, primarily due to the use of excess reagents in solution to effect cleaner reactions and ease of workup by simple filtration. Furthermore, split and mix strategies enable a rapid escalation in the numbers of possible compounds in the library obtainable from functionalized resins.[3,4] However, purification cannot be performed until after release of the final product, thus reactions with high yields involving reactive intermediates are critical for the successful generation of combinatorial libraries. Accordingly, facile manipulation of reactive functionality would be very important in combinatorial synthesis. Because of their high reactivity with nucleophiles, isocyanates or activated synthetic equivalents have been widely employed as reagents for small molecule combinatorial library generation such as ureas,[5−15] amidinoureas,[16] sulfonylureas,[17−19] azatides,[20] carbamates,[21−24] hydantoins,[25−30] 5,6-dihydropyrimidine-2,4-diones,[31] and quinazoline-2,4-diones.[32−35] The synthesis of nonsymmetric ureas using phosgenated *p*-nitrophenyl(polystyrene)ketoxime (Phoxime resin, **2**) has been previously demonstrated.[6] Primary amine derived oxime carbamates of resin **2** serve as solid-phase, heat-labile isocyanate equivalents.[5,36,37] Generation of functionalized polymer-supported oxime carbamates for further diversification can be a useful method to expand the number of these latent isocyanate equivalents beyond the limited number of commercially available isocyanates or where separate isocyanate generation and handling may be problematic.[7,20] This can be accomplished by the addition of amino acids or substituted hydrazines to resin **2** where, in both cases, these functionalized resins present carboxyl and amino groups, respectively, suitable for further transformations such as amide bond formation. Thermolysis of these further functionalized resins can either result in acyclic urea products upon trapping with an amine in solution or heterocyclic urea products by intramolecular cyclization.

Peptidic molecules are often good leads for inhibitor design; however, peptides seldom serve as drug candidates due to poor bioavailability. Therefore, molecules which can mimic the function of peptides with increased bioavailability and pharmacological behavior have been the focus of many research groups. In that sense, ureas and urea derivatives have attracted a lot of attention as a peptidomimetic inhibitors.[38−43] A class of urea peptidomimetics, α-ureidoacetamide derivatives (acyclic α-urea amides) **5**, has been used as non-peptide CCK-B/gastrin receptor antagonists.[44−47] Acyclic α-ureidoacetamides **5** can be synthesized utilizing resin **2** from the combinations of two amines and one α-amino acid as illustrated in Scheme 1. Key to this strategy

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* To whom correspondence should be addressed. E-mail: mark.a.scialdone@usa.dupont.com.

‡ To whom correspondence should be addressed regarding X-ray crystallographic studies. E-mail: will.marshall@usa.dupont.com.

§ DuPont Life Sciences Enterprise.

|| University of Pennsylvania.

⊥ DuPont Corporate Center for Analytical Sciences.

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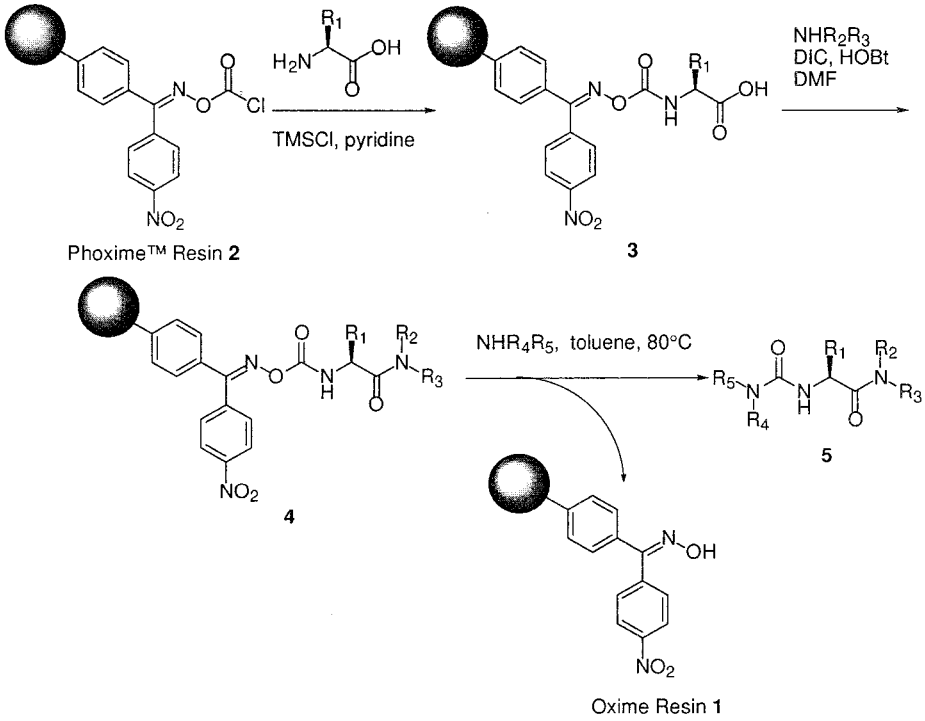
Scheme 1. Synthesis of α-Ureidoacetamides **5** Phoxime Resin **2**



is access to the amino acid derived carbamate resin **3** which can be further utilized to synthesize two other families of urea peptidomimetics, namely 3-aminohydantoins **7** and 1,2,4-triazine-3,6-diones **8**. Although similar functionality density and pharmacological behavior as hydantoins[25−29] can be expected for **7** and **8**, only a few investigations on the preparation of these compounds have been reported in the literature.[48−53] 1,2,4-Triazine-3,6-diones **8** and their ring isomer 3-aminohydantoins **7** are a relatively underinvestigated class of nitrogen heterocycles which can be viewed as constrained cyclic dipeptidomimetics.[54−58] There was also some dispute over the synthesis of **8** in the literature.[51,59] This article describes the methodology to prepare these three classes of compounds in a way suitable for combinatorial library generation.

Results and Discussion

Synthesis of α-Ureidoacetamides (5). The synthesis of a α-ureidoacetamides **5** is illustrated in Scheme 1.

Resin **2** was first reacted with 4 equiv of an α-amino acid in TMS-Cl/pyridine,[60] and the resulting carbamate acid resin **3** was then coupled with an amine under standard carbodiimide protocol (HOBt/DIC in DMF) to obtain the carbamate amide resin **4**. Resin **4** was cleaved thermolytically in the presence of another amine in toluene at 80 °C to form α-ureidoacetamide **5**. Representative results of this synthesis (Table 1) illustrate products with HPLC purities from 73% to 96% (average 84%) and mass recovery between 45% and 100% (average 65%).

In some cases, the major impurities of this synthesis were identified as urea dipeptide amides by LC−MS (8.5% for **5h** and 7.8% for **5i**). Reiterative washing of resin **3** before the amine coupling, assuming dipeptide formation was by the contamination of the amino acid into the amine coupling step, did not appear to improve the purity of the product.

Table 1. Synthesis of α-Ureidoacetamides **5**

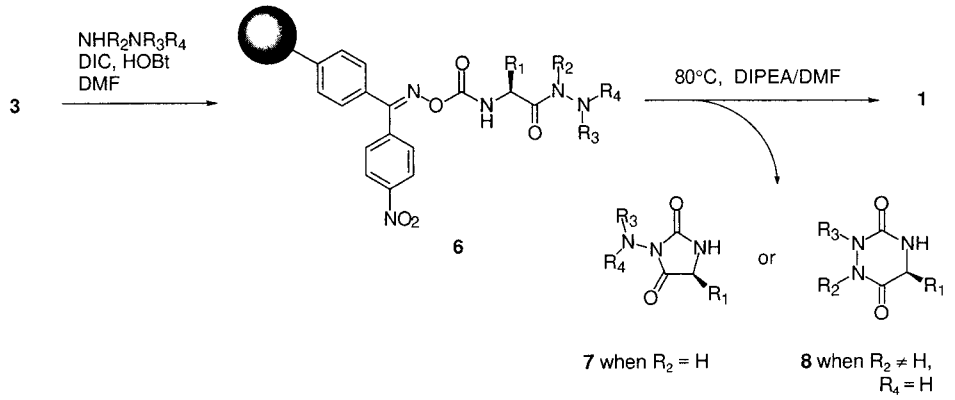
	amino acid	first amine	second amine	HPLC[a] rt (min)	HPLC[a] purity (%)	mass[b] (%)
5a	Ala	$BnNH_2$	morpholine	24.7	91	62
5b	Ala	$BnNH_2$	Et_2NH	26.9	83	66
5c	Ala	$BnNH_2$	$BnNH_2$	27.5	78	100
5d	Ala	Et_2NH	morpholine	23.7	94	45
5e	Ala	2-$PyNH_2$	morpholine	21.9	81	79
5f	Ala	Phe-O^{t}Bu	morpholine	28.3	78	71
5g	Phe	$BnNH_2$	morpholine	27.8	96	49
5h	Val	$BnNH_2$	morpholine	26.7	84	57
5i	Asp(O^{t}Bu)	$BnNH_2$	morpholine	27.9	73	65
5j	Lys(Boc)	$BnNH_2$	morpholine	28.0	78	58

[a] HPLC retention time and purity of crude product at 220 nm (see Experimental Section for the detailed conditions). [b] Mass recovery of crude product from resin **2** assuming the substitution level of resin **2** is 0.60 mmol/g (see Experimental Section for the determination of the substitution level).

Thus, the dipeptide formation probably occurs during the amino acid attachment to resin **2** via the corresponding mixed anhydride of resin **2** and the amino acid in the analogous mechanism proposed by Lapastanis.[61] The key step for the synthesis is the thermolysis of the carbamate resin **4**, which presumably occurs through isocyanate formation.[13,62] Therefore, resin **4** can be viewed as a solid-phase-attached, heat-labile isocyanato−carboxamide equivalent.[63]

To demonstrate the usefulness of this method for the generation of a small combinatorial library, a Nautilus 2400 automated synthesizer[64] was employed using the protocol described above to generate 80 α-ureidoacetamides **5** from five amino acids in the initial coupling (Ala, Phe, Val, Asp(O^{t}Bu) and Lys(^{t}Boc)) × four amines in the amide bond formation (*n*-propylamine, benzylamine, Val-*tert*-butyl ester, and 2-aminopyridine) × four in the thermolytic urea formation (2-tetrahydrofurylmethylamine, benzylamine, diethyl-

Scheme 2. Synthesis of 3-Aminohydantoins **7** vs 1,2,4-Triazine-3,6-diones **8**



amine, and morpholine). In this case, all of the amines utilized in the thermolysis step were volatile under high vacuum to eliminate the need for purification of the products obtained. Purification of products obtained from nonvolatile amines in this step can be done by ion exchange chromatography with Dowex AG 50W-X8 resin.[6] The mass recoveries of the three-step syntheses varied from 18% to 100% (average 49%) and the HPLC purities of the crude compounds varied from 25% to 94% (average 59%).

Synthesis of 3-Aminohydantoins (7) vs 1,2,4-Triazine-3,6-diones (8). The coupling of resin **3** with mono- or disubstituted hydrazine under standard carbodiimide conditions (HOBt/DIC in DMF) afforded carbamate hydrazide resin **6** (Scheme 2).

This resin was then thermolyzed in DIPEA/DMF at 80 °C to affect intramolecular cyclization to give either 3-aminohydantoins **7** or 1,2,4-triazine-3,6-diones **8**. In this synthesis, there are two regioselectivity issues in the case of monosubstituted hydrazines: (1) Which nitrogen of the hydrazine attacks the activated carboxylate of resin **3**? (2) Which nitrogen of the hydrazide attacks the isocyanate upon thermolysis of resin **6**, when $R_2 = H$?

Our strategy was to address both of these regioselectivity issues by synthesizing 3-aminohydantoin **7k** and 1,2,4-triazine-3,6-dione **8a** (Figure 1) unambiguously to identify unique features in the ^{13}C NMR spectra for the two different classes of compounds.[65]

These fingerprints would then serve as a facile means to determine the ring structure of products synthesized by the general procedures outlined in Scheme 2. To generate **7k**, 1,1-dimethylhydrazine was used. Since only the unsubstituted nitrogen of this hydrazine can serve as a productive nucleophile in the synthesis, the 3-aminohydantoin was formed. To generate **8a**, 1,2-dimethylhydrazine was used. There is no regioselectivity issue for the formation of the corresponding carbamate hydrazide due to the symmetry of the hydrazine. Since there is only one productive nucleophile in the intramolecular cyclization step, the 1,2,4-triazine-3,6-dione was synthesized unequivocally.

The chemical shifts of the amide carbonyls in the ^{13}C spectra for these two compounds were distinctively different: the one for **7k** appeared at 172 ppm and the one for **8a** appeared at 165 ppm in DMSO-d_6, while the α-carbons for **7k** and **8a** appeared at almost the same places, 55.4 and 55.6 ppm, respectively, as did the urea carbonyls at 155.3 and 155.5 ppm (see Table 2 and Experimental Section). Also, the amide carbonyl for **7g**, which is electronically very different from **7k**, appeared at 174 ppm which is very similar

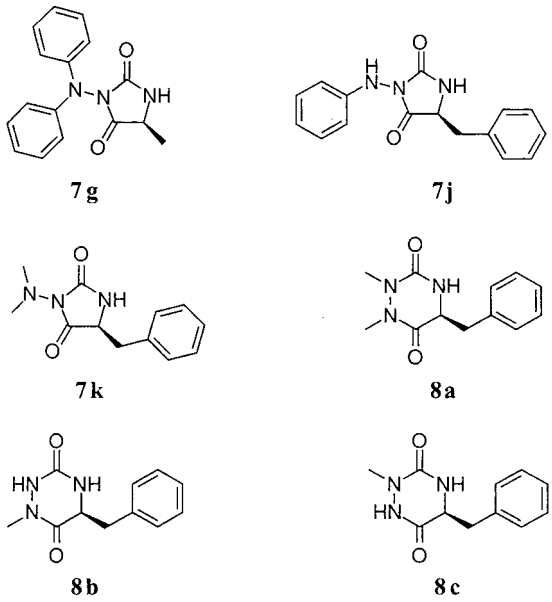


Figure 1. Products from intramolecular cyclization of resin **6**.

Table 2. Synthesis of 3-Aminohydantoins **7** vs 1,2,4-Triazine-3,6-diones **8**

	amino acid	hydrazine	HPLC[a] rt (min)	HPLC[a] purity (%)	mass[b] (%)	^{13}C NMR[c] (ppm)
7a	Ala	H_2NNHBn	24.5	85	52	173.2
7b	Ala	H_2NNH-(2-Py)	3.1	90	75	174.0
7c	Ala	H_2NNHPh-OMe-p	23.4	96	59	173.9
7d	Ala	H_2NNHPh	23.1	96	80	173.9
7e	Ala	H_2NNHPh-NO_2-p	24.0	95	70	173.4
7f	Ala	$H_2NNHTos$	25.5	63	70	172.3
7g	Ala	H_2NNHPh_2	28.6	35	53	173.5
7h	Phe	H_2NNHBn	27.9	73	53	174.1
7i	Phe	$H_2NNHCH_2CO_2Et$	26.1	85	68	171.3
7j	Phe	H_2NNHPh	27.5	75	52	172.0
7k	Phe	H_2NNMe_2	25.3	80	61	171.8
8a	Phe	MeNHNHMe	24.3	87	49	164.8
8b	Phe	H_2NNHMe	21.5	47	48	161.4

[a] HPLC retention time and purity of crude product at 220 nm (see Experimental Section for the detailed conditions). [b] Mass recovery of crude product from resin **2** assuming the substitution level of resin **2** is 0.60 mmol/g (see Experimental Section for the determination of the substitution level). [c] ^{13}C NMR chemical shift of amide carbonyl.

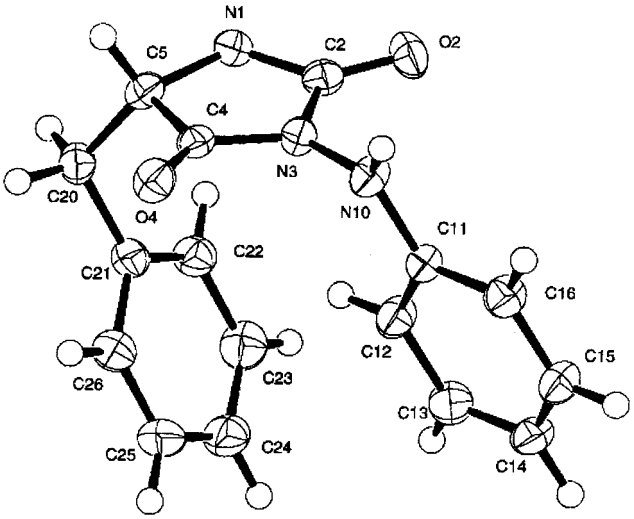


Figure 2. X-ray crystal structure of **7j**.

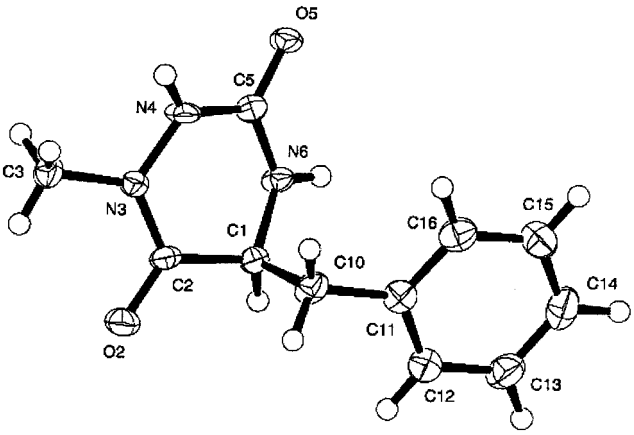


Figure 3. X-ray crystal structure of **8b**.

to the value for **7k**. Therefore, it is hypothesized that if the chemical shift of amide carbonyl appeared at 170 ppm or greater, the product is a 3-aminohydantoin; otherwise the product is 1,2,4-triazine-3,6-dione. According to this hypothesis, all compounds synthesized from monosubstituted hydrazines turned out to be 3-aminohydantoins **7**, except the combination of phenylalanine and methylhydrazine (**8b**). The ^{13}C NMR chemical shift analysis was supported by a couple of observations. First, the X-ray crystal structures of **7j** and **8b** were obtained (Figures 2 and 3, respectively) and indeed showed that **7j** was the 3-aminohydantoin and **8b** was 1,2,4-triazine-3,6-dione as predicted by the ^{13}C NMR chemical shift analysis.

Second, in the ^{1}H NMR spectra, the hydrazine-NH peaks of **7a**, **7h**, and **7i** (Table 2) were triplets, indicating that these protons were coupled with vicinal methylene groups of the hydrazine substituents. Therefore, these were assigned as 3-aminohydantoins because the 1,2,4-triazine-3,6-diones cannot have vicinal H−C−N−H couplings and should give singlet hydrazine-NH peaks, which is also in accordance with the ^{13}C NMR chemical shift analysis.

In this preparation, for most monosubstituted hydrazines, the unsubstituted nitrogen attacked the activated carboxylate of resin **3** (which leads to $R_2 = R_3 = H$ in resin **6**), and then the same nitrogen attacked isocyanate upon themolysis of resin **6**. In the case of methylhydrazine, however, the X-ray structure showed that the 1,2,4-triazine-3,6-dione **8b** is formed and not the regioisomer **8c**, indicating that the nitrogen bearing the methyl group attacked the activated carboxylate of resin **3** (Figure 3).

This suggests that in the carbodiimide coupling reaction of resin **3**, the substituted nitrogen in the monomethyl hydrazine group is more nucleophilic than the other nitrogen due to the electron-donating character of the methyl group, albeit more sterically hindered. Furthermore, there is no hydrogen left on that nitrogen to form the 3-aminohydantoin for this particular synthesis ($R_2 = Me$, $R_3 = R_4 = H$ of resin **6**). Overall, in the scope of our investigation, as long as $R_2 = H$ in resin **6**, the products were the 3-aminohydantoins **7**, and only in the case $R_2 \neq H$ in resin **6** were the products 1,2,4-triazine-3,6-diones **8**.[66] Table 2 lists the representative results of the syntheses of **7** or **8** from resin **6**. The HPLC purities of the crude products were better than 80% in most cases, and the crude mass recoveries for **7** were over 50% for all cases.

Synthesis of 1,2,4-Triazine-3,6-diones (8). 1,2,4-Triazine-3,6-diones **8** can be synthesized explicitly by the route illustrated in Scheme 3.

Resin **2** was reacted with monosubstituted hydrazine in CH_2Cl_2 to form carbazate resin **9** where the unsubstituted nitrogen adds to the oxime chloroformate. Resin **9**, which can be viewed as a solid-phase-attached, heat-labile hydrazino isocyanate equivalent, [20,57] was coupled with Boc-protected amino acid under standard carbodiimide conditions (HOBt/DIC in DMF) to give resin **10**, which was then deprotected in 25% TFA in CH_2Cl_2 for 30 min to give resin **11**. Resin **11** was thermolyzed under analogous conditions as **7** to give 1,2,4-triazine-3,6-dione **8**. The purities and yields (Table 3) in this synthesis of **8** are not as good as those for the synthesis of **7**, presumably due to the fact that the thermolytic intramolecular cyclization to give the six-membered ring is not as favorable as the five-membered ring formation.

Conclusion

The application of phosgenated *p*-nitrophenyl(polystyrene)ketoxime (Phoxime, **2**) resin in the synthesis of acyclic and heterocyclic amino acid derived ureas was described. Functionalization by the addition of free amino acids or substituted hydrazines to resin **2** gave polymer-supported oxime carbamates that undergo amide bond formation, and unlike conventional approaches to urea libraries using commercially available isocyanates or isocyanate equivalents, this approach enables diversification of the isocyanate equivalent through the oxime carbamate linkage to the resin. These functionalized resins were employed in the preparation of acyclic α-ureidoacetamides via thermolysis in the presence of a trapping amine in solution and heterocyclic 3-aminohydantoins and 1,2,4-triazine-3,6-diones via thermolytic intramolecular cyclization of the isocyanato hydrazides. A general rule for probing 3-aminohydantoin vs 1,2,4-triazine-3,6-dione formation selectivity using the ^{13}C chemical shift of the amide carbonyl was illustrated. Further use of these protocols in the preparation of biologically active combinatorial libraries is currently under investigation.

Scheme 3. Synthesis of 1,2,4-Triazine-3,6-diones **8**

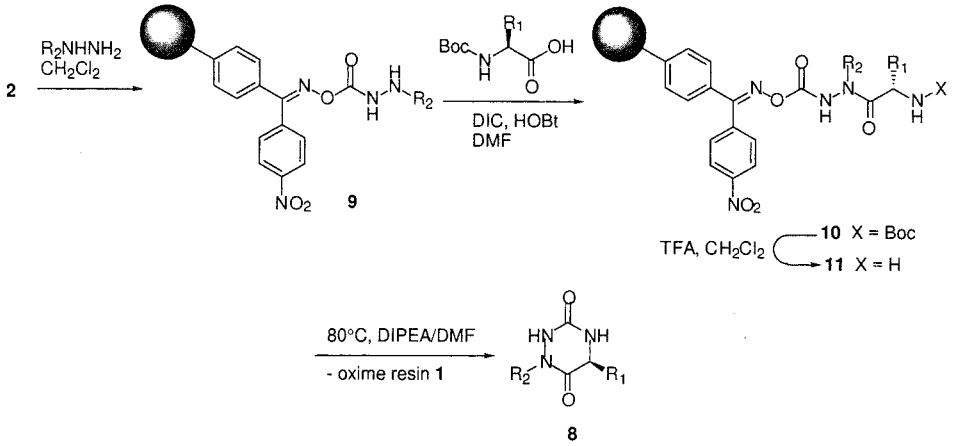


Table 3. Synthesis of 1,2,4-Triazine-3,6-diones **8**

	amino acid	hydrazine	HPLC[a] rt (min)	HPLC[a] purity (%)	mass[b] (%)	^{13}C NMR[c] (ppm)
8d	Phe	H_2NNHBn	27.1	70	62	161.2
8e	Phe	$H_2NNHCH_2CO_2Et$	25.7	58	44	n/a
8f	Phe	H_2NNH(2-Py)	27.0	66	58	163.8
8g	Phe	H_2NNHPh	27.5	22	32	n/a

[a] HPLC retention time and purity of crude product at 220 nm (see Experimental Section for the detailed conditions). [b] Mass recovery of crude product from resin **2** assuming the substitution level of resin **2** is 0.60 mmol/g (see Experimental Section for the determination of the substitution level). [c] ^{13}C NMR chemical shift of amide carbonyl.

Experimental Section

General Experimental Aspects. Oxime resin **1** was prepared by the literature procedure[67] using Biobeads SX-1 (1% cross-linked polystyrene) from Biorad. Loading was determined to be 0.60 mmol/g resin based on picric acid analysis (see below). Thermolytic cleavage reactions were carried out in 20 mL scintillation vials from Kimble Glass Inc. of Vineland, NJ. All protected amino acids were purchased from BACHEM, Bioscience Inc., of King of Prussia, PA. All other chemicals were purchased from Aldrich. IR spectra of the functionalized resins were obtained with a Perkin-Elmer FT1600 infrared spectrometer using a KBr die. Low-resolution mass spectra were obtained with a VG Trio-2000 quadruple mass spectrometer using the electrospray atmospheric pressure chemical ionization (APCI) technique. High-resolution mass spectra were obtained with a Micromass VG-70SE. ^{1}H NMR were carried out on Bruker DRX-500 and DRX-400 spectrometers. HPLC analyses were performed on a Hewlett-Packard 1090 liquid chromatography system using a photodiode array detector and a Vydac C18 column, 2.1 m × 150 mm, 1.0 mL/min flow rate, a nonlinear gradient elution from 0% to 100% acetonitrile in 0.1% TFA buffered water. HPLC purities in the text were determined by the area integration at 220 nm.

Determining the Substitution Level of Resin (2). Resin **2** was prepared from oxime resin **1** in the manner described in our previous paper.[6] The substitution level of resin **2** was measured by picric acid determination.[68,69] First, resin **2** was treated with excess piperazine in DMF to obtain piperazine carbamate. Then the free amino group was quantitated by picric acid. The substitution level of resin **2** was calculated as 0.60 mmol/g by this method. Although the chlorine analysis of the same resin gave the substitution level of 0.71 mmol/g, the contamination of phosgene in resin increases the chlorine content and tends to give a higher substitution level. The gravimetric yields of simple urea syntheses were also in better accordance with the substitution level obtained from the picric acid test. Therefore, the substitution value of 0.60 mmol/g was used for this study.

Preparation of Oxime−Piperazinocarbonyl Resin. To a solution of piperazine hexahydrate (601 mg, 3.1 mmol) in DMF or pyridine (5 mL) was added Phoxime resin **2** (1.00 g). The mixture was shaken at room temperature for 2 h. Resin was collected on a glass filter and washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3. (The washings were pale yellow for DMF and dark orange for pyridine.) The resin was dried to give the titled resin (1.00 g for DMF, 1.02 g for pyridine).

Picric Acid Test. A sample of the above resin (ca. 150 mg) was weighed accurately and placed in a glass filter. The resin was washed with 5% DIPEA in CH_2Cl_2 × 2, CH_2Cl_2 × 5, 0.1 M picric acid in 1/1 MeOH/CH_2Cl_2 × 2, and CH_2Cl_2 × 5. The washed resin was washed four times with 5% DIPEA in CH_2Cl_2, and the filtrates were collected. The collected filtrates were diluted to 25 mL with EtOH. A 1 mL sample of the EtOH solution was diluted with EtOH to 100 mL. The absorbance at 358 nm of the doubly diluted EtOH solution was measured. The concentration of the solution was calculated using the value of $\epsilon = 14\,500$ at 358 nm for DIPEA picrate salt. The substitution level of resin was calculated as 0.60 mmol/g.

General Procedure for the Preparation of Oxime Carbamate Carboxyl Resin (3). An amino acid (20 mmol) was dissolved in TMS-Cl (6.52 g, 60 mmol) and pyridine (40 mL). Resin **2** (6.45 g, 3.87 mmol) was added to the solution, and the mixture was shaken at room temperature for 2 h. The resulting resin **3** was collected on a glass filter and washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3 and dried: IR (for oxime alanine resin) 3411, 3025, 2920, 1943, 1871, 1747, 1664, 1601, 1524, 1491, 1449, 1346, 1184 cm^{-1}.

General Procedure for the Preparation of Oxime Carbamate Amide Resin (4). To a solution of HOBt·H_2O (367 mg, 2.4 mmol) and DIC (303 mg, 2.4 mmol) in DMF (10 mL) was added resin **3** (0.60 mmol). To the mixture, amine (2.4 mmol) was added and shaken at room temperature for 10 h. The resulting resin **4** was collected on a glass filter, washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3, and dried: IR (for oxime alanine benzylamide resin) 3404, 3025, 2919, 1943, 1867, 1735, 1684, 1600, 1521, 1490, 1451, 1343 cm^{-1}.

General Thermolysis Procedure for the Preparation of Acyclic α-Ureidoacetmide (5). To a solution of amine (3.0 mmol) in toluene (6 mL) resin **4** (0.30 mmol) was added. The mixture was shaken at 80 °C for 48 h. The resulting resin was filtered by a glass filter and washed with toluene × 2, CH_2Cl_2, ^{i}PrOH, and CH_2Cl_2 × 2. The combined filtrates were evaporated in vacuo, and the crude products were analyzed by HPLC, MS, and NMR.

***N*-((*N*-Morpholino)carbonyl)alanine Benzylamide (5a).** HPLC purity at 220 nm, 91%; mass recovery, 62%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (t, J = 6.0 Hz, 1H, PhCH_2N*H*), 7.4−7.2 (m, 5H, phenyl), 6.53 (d, 1H, Ala-N*H*), 4.29 (d, J = 6.0 Hz, 2H, PhCH_2), 4.21 (m, 1H, Ala-C*H*), 3.54 (m, 4H, OCH_2CH_2N), 3.31 (m, 4H, OCH_2CH_2N), 1.26 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 157.5, 140.0, 125.5, 127.3, 126.9, 66.3, 50.2, 44.3, 42.3, 18.7.

***N*-(Diethylaminocarbonyl)alanine Benzylamide (5b).** HPLC purity at 220 nm, 83%; mass recovery, 66%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (t, J = 5.9 Hz, 1H, Ph CH_2N*H*), 7.4−7.2 (m, 5H, phenyl), 6.07 (d, J = 7.6 Hz, 1H), 4.4−4.2 (m, 3H, Ala-NHC*H* + PhCH_2), 3.23 (q, J = 7.0 Hz, 4H, (CH_3CH_2)$_2$N), 1.27 (d, J = 7.2 Hz, 3H, Ala-CH_3), 1.04 (t, J = 7.0 Hz, 6H, (CH_3CH_2)$_2$N); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 156.7, 128.6, 127.3, 127.0, 50.1, 42.3, 39.5, 19.0, 14.2.

***N*-(Benzylaminocarbonyl)alanine Benzylamide (5c).** HPLC purity at 220 nm, 78%; mass recovery, 100%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (t, J = 5.7 Hz, 1H, Bn amide-N*H*), 7.3−7.1 (m, 10H, phenyl), 6.45, (t, J = 6.0 Hz, 1H, Bn urea-N*H*), 6.12 (d, J = 7.9 Hz, 1H, Ala-N*H*), 4.3−4.1 (m, 5H), 1.14 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.6, 157.8, 141.1, 139.8, 129.2, 129.0, 128.7, 127.4, 127.1, 126.9, 49.2, 43.2, 42.3, 20.0.

***N*-((*N*-Morpholino)carbonyl)alanine Diethylamide (5d).** HPLC purity at 220 nm, 94%; mass recovery, 45%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.13 (d, J = 7.9 Hz, 1H, Ala-N*H*), 4.62, (quintet, J = 7.1 Hz, 1H, Ala-NHC*H*), 3.56 (bs, 4H, OCH_2CH_2N), 3.30 (bs, 4H, OCH_2CH_2N), 3.3−3.1 (m, 6H, CH_2CH_3), 1.17 (d, J = 6.9 Hz, 3H, Ala-CH_3), 1.02 (t, J = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.1, 156.3, 66.5, 49.9, 45.9, 42.3, 18.6, 14.2.

***N*-((*N*-Morpholino)carbonyl)alanine 2-Pyridylamide (5e).** HPLC purity at 220 nm, 81%; mass recovery, 79%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 1H, PyN*H*), 8.37 (broad, 1H, Ala-N*H*), 8.04 (dd, J = 5.0, 1.4 Hz, 1H, Py-6H), 7.52 (td, J = 7.8, 1.9 Hz, 1H, Py-5H), 7.24 (d, J = 8.3 Hz, 1H, Py-3H), 6.78 (td, J = 8.0, 1.0 Hz, 1H, Py-4H), 4.63 (m, 1H, Ala-N*H*), 3.5−3.0 (m, 8H, O(CH_2CH_2)$_2$N), 1.10 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.2, 154.3, 153.7, 147.2, 138.5, 117.3, 112.0, 66.4, 45.3, 44.2, 19.2.

***N*-((*N*-Morpholino)carbonyl)alanylphenylalanine *tert*-Butyl Ester (5f).** HPLC purity at 220 nm, 78%; mass recovery, 71%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 7.5 Hz, 1H, Phe-N*H*), 7.4−7.2 (m, 5H, phenyl), 6.49, (d, J = 7.7 Hz, 1H, Ala-N*H*), 4.33 (q, J = 7.3 Hz, 1H, Ala-C*H*), 4.20 (t, J = 7.3 Hz, Phe-C*H*), 3.54 (m, 4H, OCH_2-CH_2N), 3.27 (m, 4H, OCH$_2$CH_2N), 2.95 (m, 2H, Phe-CH_2), 1.32 (s, 9H, C(CH_3)$_3$), 1.21 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.7, 172.3, 170.7, 157.4, 137.5, 129.8, 128.4, 126.8, 80.9, 66.3, 54.5, 49.7, 44.3, 37.2, 27.9, 18.5.

***N*-((*N*-Morpholino)carbonyl)phenylalanine Benzylamide (5g).** HPLC purity at 220 nm, 96%; mass recovery, 49%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (t, J = 6.0 Hz, 1H, BnN*H*), 7.4−7.1 (m, 10H, phenyl), 6.61 (d, J = 8.4 Hz, 1H, Phe-N*H*), 4.4−4.2 (m, 3H), 3.48 (m, 4H, OCH_2-CH_2N), 3.3−2.8 (m, 4H, OCH$_2$CH_2N), 3.01 (dd, J = 13.5, 4.9 Hz, 1H, Phe-CH_2), 2.88 (dd, J = 13.5, 10.1 Hz, Phe-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.7, 157.6, 139.7, 139.0, 129.6, 128.5, 128.3, 127.4, 127.0, 126.4, 66.2, 56.4, 44.3, 42.4, 37.9.

***N*-((*N*-Morpholino)carbonyl)valine Benzylamide (5h).** HPLC purity at 220 nm, 84%; mass recovery, 57%: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (t, J = 5.7 Hz, 1H, PhCH_2N*H*), 7.4−7.2 (m, 5H, phenyl), 6.28 (d, J = 9.5 Hz, 1H, Val-N*H*), 4.34, (d, J = 4.2 Hz, 2H, PhCH_2), 4.04 (t, J = 8.1 Hz, 1H, Val-NHC*H*), 3.59 (m, 4H, OCH_2CH_2N), 3.36 (m, 4H, OCH$_2$CH_2N), 2.04 (m, 1H, C*H*(CH$_3$)), 0.90 (t, J = 6.1 Hz, 6H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.4, 157.9, 139.8, 128.4, 127.8, 127.4, 66.2, 60.3, 44.5, 42.3, 36.1, 19.8, 19.1.

***N*-(*N*-Morpholino)carbonyl-*β*-*tert*-butyl-aspartic Acid α-Benzylamide (5i).** HPLC purity at 220 nm, 73%; mass recovery, 65%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (t, J = 6.1 Hz, 1H, Ph CH$_2$N*H*), 7.4−7.2 (m, 5H, phenyl), 6.72 (d, J = 8.2 Hz, 1H, Asp-N*H*), 4.56, (q, J = 6.0 Hz, 1H, Asp-C*H*), 4.29 (d, J = 6.0 Hz, 2H, PhCH_2), 3.55 (m, 4H, OCH_2CH_2N), 3.30 (m, 4H, OCH$_2$CH_2N), 2.71 (dd, J = 15.5, 5.9 Hz, 1H, Asp-CH*H*), 2.52 (m, 1H, Asp-C*H*H), 1.39 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 170.1, 157.4, 139.8, 128.5, 127.3, 127.0, 80.2, 66.2, 51.6, 44.3, 42.4, 38.2, 36.1, 28.0.

α-*N*-(*N*-Morpholino)carbonyl-*ω*-*N*-Boc-lysine Benzylamide (5j). HPLC purity at 220 nm, 78%; mass recovery, 58%: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (t, J = 6.1 Hz, 1H, PhCH$_2$N*H*), 7.4−7.2 (m, 5H, phenyl), 6.73 (broad t, 1H, Lys-N*H*-*ω*), 6.43 (d, J = 7.9 Hz, 1H, Lys-N*H*-α), 4.29 (d, J = 5.9 Hz, 2H, PhCH_2), 4.11 (m, 1H, NHC*H*CO), 3.55 (m, 4H, OCH_2CH_2N), 3.30 (m, 4H, OCH$_2$CH_2N), 2.29 (m, 2H, Lys-CH_2NH-*ω*), 1.61 (m, 2H, Lys-CH_2CH$_2$NH-*ω*), 1.4−1.2 (m, 13H, Lys-CH_2CH_2CH_2CH_2NH-*ω* + C(CH_3)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 157.8, 155.9, 139.9, 128.4, 127.4, 127.0, 77.6, 66.1, 54.8, 44.3, 42.3, 36.1, 32.0, 29.6, 28.6, 23.5.

General Procedure for the Preparation of Oxime Carbamate Hydrazide Resin (6). To a solution of HOBt·

H_2O (306 mg, 2.0 mmol) in DMF (10 mL) was added resin **3** (0.50 mmol) followed by a hydrazine (2.0 mmol) then by DIC (252 mg, 2.0 mmol), and the mixture was shaken at room temperature for 11 h. The resulting resin **6** was collected on a glass filter, washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3, and dried: IR (for oxime phenylalanine phenylhydrazide resin) 3394, 3025, 2920, 1943, 1870, 1801, 1739, 1685, 1601, 1522, 1491, 1450, 1345 cm^{-1}.

General Thermolysis Procedure for the Preparation of 3-Aminohydantoin (7). To a solution of DIPEA (5.0 mmol) in DMF (10 mL) was added resin **6** (0.50 mmol), and the mixture was shaken at 80 °C for 24 h. The resulting resin was filtered by a glass filter and washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3. The combined filtrates were evaporated in vacuo, and the crude products were analyzed by HPLC, MS, and NMR.

(*S*)-5-Methyl-3-(benzylamino)hydantoin (7a). HPLC purity at 220 nm, 85%; mass recovery, 52%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a ivory wax (21%): mp 284−286 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (s, 1H, alanine N*H*), 7.41 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 4.7 Hz, 1H), 5.84 (t, J = 5.1 Hz, 1H, hydrazine N*H*), 4.10 (d, J = 5.1 Hz, 2H, PhC*H*$_2$NH), 4.01 (q, J = 6.9 Hz, 1H, CH$_3$C*H*), 1.19 (d, J = 6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.2, 155.9, 137.7, 129.1, 128.3, 127.5, 53.1, 50.7, 17.6; HRMS *m*/*e* calcd for $C_{11}H_{13}N_3O_2$ (CI, CH_4 reagent gas, M + H^+) 220.1086, found 220.1084.

(*S*)-5-Methyl-3-((2-pyridyl)amino)hydantoin (7b). HPLC purity at 220 nm, 90%; mass recovery, 75%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a clear oil (40%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H, N*H*), 8.33 (s, 1H, N*H*), 8.05 (d, J = 4.9 Hz, 1H), 7.58 (td, J = 7.8, 1.8 Hz, 1H), 6.78 (td, J = 7.2, 1.8 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 4.25 (q, J = 6.7 Hz, 1H, CH$_3$C*H*), 1.35 (d, J = 6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.0, 157.2, 155.4, 147.9, 138.0, 116.0, 107.6, 51.1, 17.9; HRMS *m*/*e* calcd for $C_9H_{10}N_4O_2$ (M^+) 206.0804, found 206.0804.

(*S*)-5-Methyl-3-((4-methoxy)phenylamino)hydantoin (7c). HPLC purity at 220 nm, 96%; mass recovery, 59%. The crude brown oil was one spot on TLC (R_f = 0.25, 1/20 MeOH/CH_2Cl_2) without purification: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H, N*H*), 8.01 (s, 1H, N*H*), 6.79 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 4.25 (q, J = 7.0 Hz, 1H, CH$_3$C*H*), 1.34 (d, J = 6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.9, 155.5, 153.7, 140.9, 114.8, 114.0, 55.7, 51.0, 17.8; HRMS *m*/*e* calcd for $C_{11}H_{13}N_3O_3$ (M^+) 235.0957, found 235.0957.

(*S*)-5-Methyl-3-(phenylamino)hydantoin (7d). HPLC purity at 220 nm, 96%; mass recovery, 80%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a ivory wax (47%): mp 181−183 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (s, 1H, N*H*), 8.32 (s, 1H, N*H*), 7.19 (t, J = 7.9 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 7.8 Hz, 2H), 4.28 (q, J = 6.9 Hz, 1H, CH$_3$C*H*), 1.36 (d, J = 6.9 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.9, 155.3, 153.7, 147.1, 129.3, 119.9, 112.4, 51.0, 17.8; HRMS *m*/*e* calcd for $C_{10}H_{12}N_3O_2$ (M^+) 205.0851, found 205.0855.

(*S*)-5-Methyl-3-((4-nitro)phenylamino)hydantoin (7e). HPLC purity at 220 nm, 95%; mass recovery, 70%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a yellow oil (35%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (broad s, 1H, N*H*), 8.55 (s, 1H, N*H*), 8.11 (d, J = 9.2 Hz, 2H), 6.82 (broad s, 2H), 4.35 (broad, 1H, CH$_3$C*H*), 1.38 (d, J = 5.0 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.4, 154.4, 153.0, 139.8, 126.2, 111.6, 51.3, 17.6; HRMS *m*/*e* calcd for $C_{10}H_{10}N_4O_4$ (M^+) 250.0702, found 250.0705.

(*S*)-5-Methyl-3-(*p*-toluenesulfonylamino)hydantoin (7f). HPLC purity at 220 nm, 63%; mass recovery, 70%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a pale brown oil (32%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (broad s, 1H, Tos-N*H*), 8.37 (s, 1H, Ala-N*H*), 7.73 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 4.18 (q, J = 6.9 Hz, Ala-C*H*), 2.41 (s, 3H, Tos-C*H*$_3$), 1.25 (d, J = 6.9 Hz, 3H, Ala-C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.3, 153.6, 143.9, 137.7, 129.7, 127.8, 50.9, 21.4, 17.7; HRMS *m*/*e* calcd for $C_{11}H_{13}N_3O_4S$ (M^+) 283.0627, found 283.0622.

(*S*)-5-Methyl-3-(diphenylamino)hydantoin (7g). HPLC purity at 220 nm, 35%; mass recovery, 53%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a pale brown oil (8%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H, N*H*), 7.34 (t, J = 8.0 Hz, 4H), 7.09 (d, J = 8.0 Hz, 4H), 6.99 (d, J = 8.0 Hz, 2H), 4.38 (q, J = 7.0 Hz, 1H, CH$_3$C*H*), 1.35 (d, J = 7.0 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.5, 154.3, 144.3, 144.2, 129.8, 129.7, 123.9, 123.7, 119.8, 119.1, 51.1, 17.7; HRMS *m*/*e* calcd for $C_{16}H_{15}N_3O_2$ (M^+) 281.1164, found 281.1173.

(*S*)-5-Benzyl-3-(benzylamino)hydantoin (7h). HPLC purity at 220 nm, 73%; mass recovery, 53%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a ivory solid (34%): mp 173−176 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H, Phe-N*H*), 7.4−7.1 (m, 10H), 5.64 (t, J = 5.6 Hz, 1H, PhCH$_2$N*H*), 4.30 (t, J = 4.5 Hz, 1H, PhCH$_2$C*H*), 3.72 (d, J = 5.5 Hz, 2H, PhC*H*$_2$NH), 2.94 (dd, J = 14.0, 4.8 Hz, 1H, Phe-PhCH*H*), 2.87 (dd, J = 14.0, 5.5 Hz, 1H, Phe-PhC*H*H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.1, 158.3, 140.1, 137.9, 132.4, 131.5, 131.0, 130.7, 129.8, 129.4, 58.1, 55.6, 39.3; HRMS *m*/*e* calcd for $C_{17}H_{17}N_3O_2$ (M^+) 295.1321, found 295.1322.

(*S*)-5-Benzyl-3-(ethoxycarbonylmethylamino)hydantoin (7i). HPLC purity at 220 nm, 85%; mass recovery, 68%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a pale yellow solid (41%): mp 136−137 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (s, 1H, Phe-N*H*), 7.4−7.1 (m, 5H), 5.56 (t, J = 5.7 Hz, 1H, NN*H*), 4.33 (td, J = 5.1, 1.1 Hz, 1H, PhCH$_2$C*H*), 4.07 (q, J = 7.1 Hz, 2H, CH$_3$C*H*$_2$O), 3.33 (m, 2H, C*H*$_2$NHN), 2.99 (dd, J = 14.0, 4.7 Hz, 1H, Phe-PhCH*H*), 2.94 (dd, J = 14.0, 5.5 Hz, 1H, Phe-PhC*H*H), 1.19 (t, J = 7.1 Hz, 3H, C*H*$_3$CH$_2$O); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 169.4, 155.5, 135.6, 130.0, 128.4, 127.1, 60.6, 55.8, 50.5, 36.9, 14.3; HRMS *m*/*e* calcd for $C_{14}H_{18}N_3O_4$ (M + H^+) 292.1297, found 292.1300.

(*S*)-5-Benzyl-3-(phenylamino)hydantoin (7j). HPLC purity at 220 nm, 75%; mass recovery, 52%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a white solid (34%): mp 212−213 °C; ^{1}H NMR (400 MHz, DMSO-

d_6) δ 8.49 (s, 1H, N*H*), 8.16 (s, 1H, N*H*), 7.4−7.2 (m, 5H), 6.97 (t, J = 7.5 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.97 (broad, 2H), 4.62 (t, J = 4.0 Hz, 1H, $PhCH_2CH$), 3.1−3.0 (m, 2H, $PhCH_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.0, 155.2, 135.1, 130.6, 129.0, 128.7, 127.3, 119.6, 112.0, 56.1, 36.2; HRMS *m*/*e* calcd for $C_{16}H_{15}N_3O_2$ (M^+) 281.1164, found 281.1166.

(*S*)-5-Benzyl-3-(dimethylamino)hydantoin (7k). HPLC purity at 220 nm, 80%; mass recovery, 61%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a ivory solid (23%): mp 202−205 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H, Phe-N*H*), 7.3−7.1 (m, 5H), 4.28 (td, J = 4.5, 1.0 Hz, 1H, $PhCH_2CH$), 2.98 (dd, J = 13.9, 4.5 Hz, 1H, Phe-PhCH*H*), 2.93 (dd, J = 14.0, 4.7 Hz, 1H, Phe-PhC*H*H), 2.48 (s, 6H, $(CH_3)_2NN$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.8, 155.3, 135.1, 130.3, 128.3, 127.1, 55.4, 43.7, 36.7; HRMS *m*/*e* calcd for $C_{12}H_{15}N_3O_2$ (M^+) 233.1164, found 233.1178.

1,2-Dimethyl-(*S*)-5-benzyl-1,2,4-triaza-3,6-dione (8a). HPLC purity at 220 nm, 87%; mass recovery, 49%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a yellow oil (26%): ^1H NMR (400 MHz, DMSO-d_6) δ 7.4−7.1 (m, 6H, aromatics and N*H*), 4.01 (td, J = 5.5, 2.7 Hz, 1H, $PhCH_2CH$), 3.03 (s, 3H, CH_3), 2.89 (d, J = 5.5 Hz, 2H, $PhCH_2$), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.8, 155.5, 136.4, 130.1, 128.6, 127.1, 55.6, 38.8, 33.7, 32.4; HRMS *m*/*e* calcd for $C_{12}H_{15}N_3O_2$ (M^+) 233.1164, found 233.1163.

1-Methyl-(*S*)-5-benzyl-1,2,4-triaza-3,6-dione (8b). HPLC purity at 220 nm, 47%; mass recovery, 48%; purified by column chromatography (SiO_2, 1/20 MeOH/CH_2Cl_2) to give a white solid (13%): mp 180−182 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H, N*H*), 7.4−7.1 (m, 6H, aromatics + N*H*), 4.02 (m, 1H, NHC*H*), 3.0−2.8 (m, 5H, CH_3 + $PhCH_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 154.1, 136.8, 130.1, 128.5, 126.9, 55.3, 37.9, 33.1; HRMS *m*/*e* calcd for $C_{11}H_{13}N_3O_2$ (M^+) 219.1008, found 219.1017.

General Procedure for the Preparation of Oxime Carbazate Resin (9). A hydrazine or hydrazine HCl salt (4 mmol; in the case of the HCl salt, 1 equiv of DIPEA was added to neutralize the mixture) was dissolved in CH_2Cl_2 (15 mL). Resin **2** (1.29 g, 0.77 mmol) was added to the solution, and the mixture was shaken at room temperature for 2 h. The resulting resin **9** was collected on a glass filter and washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3, and dried: IR (for oxime phenylcarbazate resin) 3025, 2920, 1944, 1866, 1750, 1601, 1520, 1490, 1456, 1346 cm^{-1}.

General Procedure for the Preparation of Boc-Amino Hydrazide Oxime Resin (10). To a solution of Boc-amino acid (4 mmol), HOBt·H_2O (612 mg, 4.0 mmol), and DIC (505 mg, 4.0 mmol) in DMF (15 mL) was added resin **9** (1.0 mmol), and the mixture was shaken at room temperature for 12 h. The resulting resin **10** was collected on a glass filter, washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3, and dried: IR (for Boc-phenylalanine phenylhydrazide oxime resin) 3345, 3024, 2920, 1943, 1757, 1601, 1523, 1492, 1450, 1345, 1153 cm^{-1}.

General Procedure for the Preparation of Amino Carbazate Oxime Resin (11). To a solution of TFA (5 mL) and CH_2Cl_2 (15 mL) was added resin **10** (1.0 mmol), and the mixture was shaken at room temperature for 30 min. The resulting resin **11** was collected on a glass filter, washed with CH_2Cl_2 × 2, 10% DIPEA in CH_2Cl_2 × 2, and CH_2Cl_2 × 3, and dried: IR (for phenylalanine phenylhydrazide oxime resin) 3344, 3024, 2920, 1943, 1872, 1755, 1601, 1523, 1492, 1450, 1345 cm^{-1}.

General Thermolysis Procedure for the Preparation of 1,2,4-Triaza-3,6-dione (8). To a solution of DIPEA (5.0 mmol) in DMF (10 mL) was added resin **11** (0.50 mmol), and the mixture was shaken at 80 °C for 24 h. The resulting resin was collected on a glass filter and washed with DMF × 4, MeOH × 4, and CH_2Cl_2 × 3. The combined filtrates were evaporated in vacuo and the crude products were analyzed by HPLC, MS, and NMR.

2-Benzyl-(*S*)-5-benzyl-1,2,4-triaza-3,6-dione (8d). HPLC purity at 220 nm, 70%; mass recovery, 62%; purified by column chromatography (SiO_2, 1/50 MeOH/CH_2Cl_2) to give a yellow oil (10%): ^1H NMR (500 MHz, DMSO-d_6) δ 9.14 (broad s, 1H, N*H*), 7.4−7.0 (m, 10H), 4.84 (s, 1H, N*H*), 4.62 (q, J = 14.3 Hz, 2H, $PhCH_2N$), 4.11 (t, J = 5.5 Hz, 1H, CH_3CH), 2.95 (m, 2H, $PhCH_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 154.3, 136.8, 136.2, 130.2, 129.0, 128.7, 128.6, 127.7, 126.9, 55.4, 48.7, 37.5; HRMS *m*/*e* calcd for $C_{17}H_{17}N_3O_2$ (M^+) 295.1321, found 295.1320.

2-(2-Pyridyl)-(*S*)-5-benzyl-1,2,4-triaza-3,6-dione (8f). HPLC purity at 220 nm, 66%; mass recovery, 58%. Purified by trituration in Et_2O to give an ivory solid (37%): mp 190−192 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1H, N*H*), 8.40 (dd, J = 5.0, 1.2 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.87 (td, J = 7.2, 1.4 Hz, 2H), 7.64 (s, 1H, N*H*), 7.3−7.1 (m, 6H), 4.17 (m, 1H, CH_3CH), 3.03 (m, 2H, $PhCH_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.8, 155.5, 148.2, 147.5, 139.5, 136.8, 129.9, 128.6, 127.0, 124.1, 121.7, 115.9, 110.8, 57.0, 36.3; HRMS *m*/*e* calcd for $C_{15}H_{14}N_4O_2$ (M^+) 282.1117, found 282.1119.

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Supporting Information Available. Representative IR spectra of functionalized resins, ^1H and ^{13}C NMR spectra, HPLC and HRMS of products, and X-ray data for **7a** and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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