JOURNAL OF combinatorial CHEMISTRY

Subscriber access provided by American Chemical Society

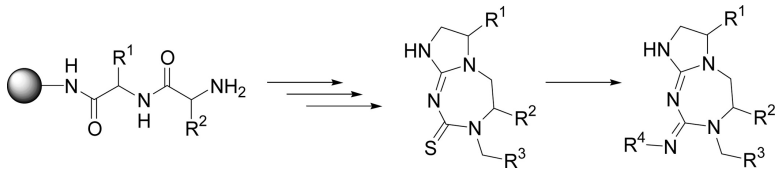
Article

Solid Phase Synthesis of 3,4,7-Trisubstituted 4,5,8,9-Tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2(7*H*)-thiones and *N*-Alkyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2-amines

Cornelia E. Hoesl, John M. Ostresh, Richard A. Houghten, and Adel Nefzi

J. Comb. Chem., **2006**, 8 (1), 127-131• DOI: 10.1021/cc050094e • Publication Date (Web): 12 November 2005

Downloaded from http://pubs.acs.org on March 22, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ACS Publications
High quality. High impact.

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solid Phase Synthesis of 3,4,7-Trisubstituted 4,5,8,9-Tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2(7*H*)-thiones and *N*-Alkyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2-amines

Cornelia E. Hoesl, John M. Ostresh, Richard A. Houghten, and Adel Nefzi*

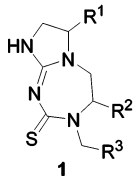
Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, California 92121

Received July 18, 2005

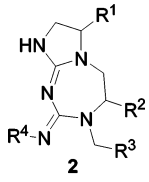
The solid-phase parallel synthesis of 3,4,7-trisubstituted 4,5,8,9-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2(7*H*)-thiones and *N*-alkyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2-amines starting from resin-bound dipeptides is described. The key synthetic steps involve the cylization of an amino and a guanidino functionality using thiocarbonyldiimidazole and the subsequent transformation of the resulting thiourea moiety to a substituted guanidine group using $HgCl_2$ and various amines. Following cleavage from the resin, the desired products were obtained in good yields and good to moderate purities, depending on the building blocks employed.

Introduction

With the advent of combinatorial chemistry, solid-phase chemistry has gained wide acceptance as a valuable tool for the rapid production of chemical collections used in lead structure identification and optimization. Considerable effort has been channeled to the synthesis of "druglike" nitrogen-containing heterocycles on solid supports. In recent years, we have developed efficient solid-phase methods for the chemical transformation of amino acids and small peptides to various heterocyclic compounds.[1] In parallel and combinatorial heterocyclic chemistry, amino acids remain unmatched as a source of diverse, enantiomerically pure building blocks. In continuation of our efforts toward the solid-phase synthesis of heterocycles using amino acids and peptides as precursors and the identification of highly active compounds, we report here an efficient strategy for the solid-phase synthesis of tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]-triazepine-2-(7*H*)-thiones **1** and tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepine-2-(7*H*)-imines **2** encompassing three or four positions of diversity, respectively.

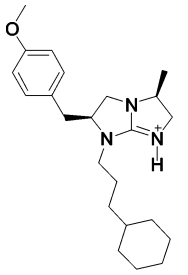


1



2

Both structures **1** and **2** incorporate a guanidine moiety either in conjugation to a thiocarbonyl or to an imine functionality. The guanidine motif appears in a diverse array of biologically active compounds. Reported examples, such as cimetidine for the treatment of ulcers and pinacidil as an antihypertensive agent, are already marketed.[2] Among many other therapeutical applications, guanidines have been shown to act as adrenergic neuron-blocking agents;[3] antitumor agents;[4] HIV-1 protease inhibitors;[5] and as antihistaminic, antiinflammatory, antidiabetic, and antibacterial drugs.[6] Recent studies from our laboratory showed that conformationally constrained trisubstituted bicyclic guanidines[7] exhibit antifungal activity against *Candida albicans* and *Cryptococcus neoformans*.[8] The deconvolution of the same bicyclic guanidine positional scan synthetic combinatorial library (PS-SCL) in a radioreceptor binding assay specific for the kappa opioid receptor led to the identification of active compounds.[7b] The most active individual bicyclic guanidine identified has IC_{50} = 37 nM. In the compounds reported herein, the guanidine moiety is incorporated into a 1,3,5-triazepine ring system that belongs to a group of pharmacologically less explored triazepines. Rare reports on the biological activity of 1,3,5-triazepine analogues, such as 1,3,5-triazacycloheptane-2,4-dione derivatives, include effective inhibitors of multidrug resistance dependent on P-glycoprotein.[9] The combination of the 1,3,5-triazepine moiety and the guanidine pharmacophore in compounds **1** and **2** leads to a new heterocyclic ring system with promising biological and pharmacological properties with respect to Lipinski's rules of five.[10]



κ opioid receptor

IC_{50}: 37 nM

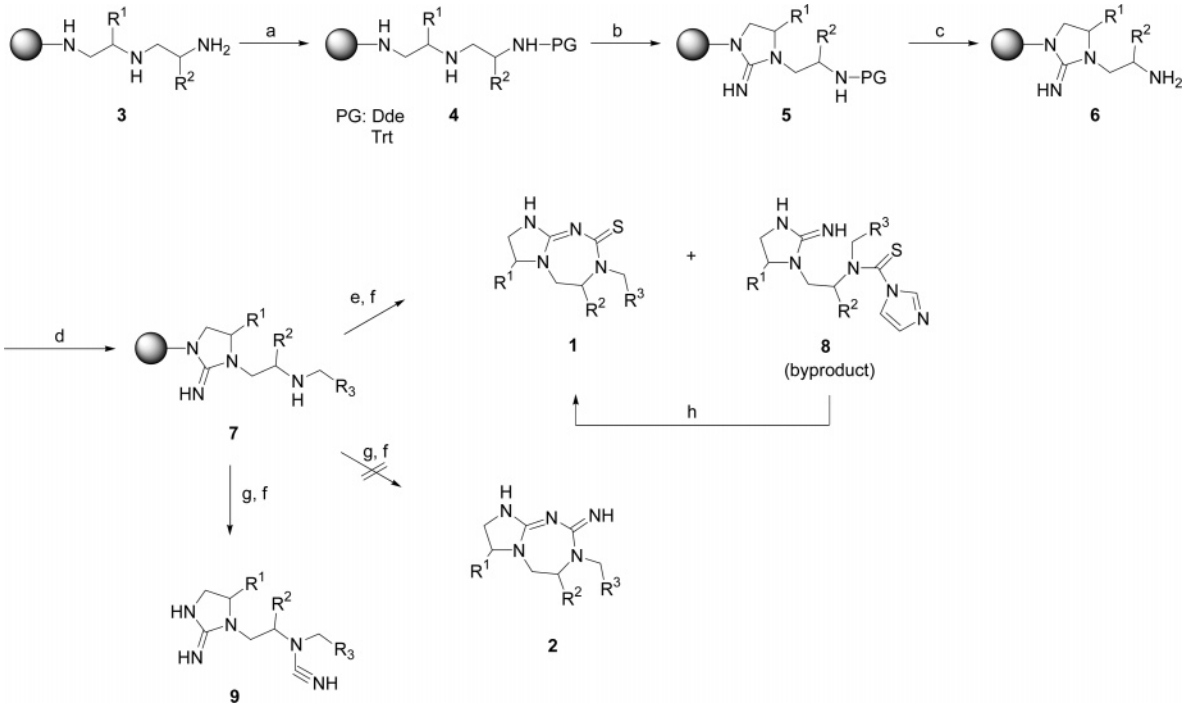
Results and Discussion

The synthetic strategy leading to the target structures is depicted in Scheme 1. Using the "tea bag methodology",[11] a dipeptide was assembled on *p*-methylbenzhydrylamine

* To whom correspondence should be addressed. Phone: 858-455-3823. Fax: 858-455-3804. E-mail: adeln@tpims.org.

10.1021/cc050094e CCC: $33.50 © 2006 American Chemical Society
Published on Web 11/12/2005

Scheme 1[a]

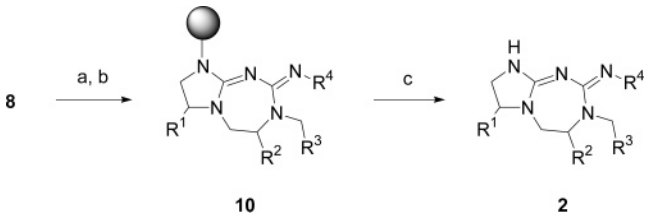


[a] (a) DdeOH in DMF or TrtCl in DCM; (b) CNBr in DCM; (c) N_2H_4, DMF or 1 % TFA in DCM; (d) R^3CHO, $NaCNBH_3$, 1% AcOH in DCM; (e) $CSIm_2$ in DCM; (f) HF, anisole; (g) CNBr in DCM; (h) 1 % TFA in AcCN/$H_2$0 (50/50).

resin (MBHA) starting from Boc-α-amino acids. The resin-bound dipeptide was treated with borane in THF, resulting in exhaustive reduction of the amides, to yield the corresponding solid-supported triamines **3**. The primary amine functionality in triamines **3** was selectively protected using either 2-acetyldimedone (Dde-OH) in DMF or trityl chloride in DCM. Complete protection was monitored via the ninhydrin test.[12] Trityl chloride proved to be preferable as a protection group, since deprotection of Dde was found to be difficult in some cases (for R^2 = 1-methylethyl, 1-hydroxyethyl). Compounds **4** were obtained in excellent purities (>90%) and quantitative yields. The resin-bound cyclic guanidine **5** was formed following treatment of **3** with cyanogen bromide (CNBr). [13] Following deprotection of Dde or trityl, respectively, compounds **6** were obtained. We found resin-bound products bearing the cyclic guanidine moiety to be much more labile to acidolytic cleavage, as compared to the resin-bound triamine **3**. Whereas the cleavage of triamines **3** from the solid support using HF/anisole at 0 °C requires a rather long reaction time of 7 h, the guanidine derivatives **6** can be readily cleaved within 1.5 h, similar to heterocycles linked via an amide bond to the MBHA resin. Next, a third position of diversity was introduced by reductive alkylation of the primary amino moiety, leading to compounds **7**.

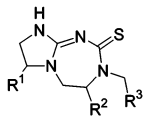
Products **7** were characterized by electrospray LC/MS and one representative compound by ^{1}H NMR. One proton signal appearing at δ = 8.35 ppm and two proton signals appearing at δ = 8.22 ppm correspond to two protons of the protonated guanidino moiety and an imidazolyl proton in accordance with the literature.[13,14] The construction of the 1,3,5-triazepine ring was achieved employing $CSIm_2$ for the synthesis of derivatives **1** or CNBr for the synthesis of derivatives **2** (R^4 = H). $CSIm_2$ and CNBr have proven to be valuable reagents for solid-phase cyclization reactions leading to to cyclic thiourea, thiohydantoin, and cyclic guanidine derivatives.[15] The cyclization reaction was performed using 10 equiv of $CSIm_2$ (0.1 M in DCM) overnight. Following cleavage from the resin, two products were obtained according to LC/MS. On the basis of ^{13}C NMR spectroscopy, we found that the uncyclized compounds **8** had been formed as a byproduct. Optimization studies using extended reaction times or elevated reaction temperatures did not improve the purity of **1**. We observed that the byproducts **8** reacted to the products **1** when the samples were treated with 1% TFA in AcCN/H_2O (50/50). We assume that subsequent activation of the thio functionality by protonation leads to ring closure, affording the desired seven-membered tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepine-2-(7*H*)-thiones **1**. Thus, following cleavage from the resin, each sample was subjected to acidic treatment (1% TFA in AcCN/H_2O (90/10)), affording compounds **1** in high purity according to LC/MS. The synthesis was repeated starting from a ^{15}N-labeled amino acid (R^1 = CH_2Ph, R^2 = CH_2Ph, R^3 = Ph) for the first position of diversity, and an NMR analysis was performed on the resulting ^{15}N-labeled product to confirm the proposed structures [^{15}N]-**1a** and [^{15}N]-**10a**.

Scheme 2[a]

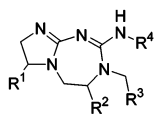


[a] (a) $HgCl_2$, DMF; (b) R^4NH_2, DMF; (c) HF, anisole.

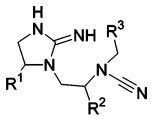
Table 1[a]



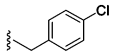
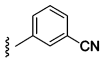
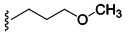
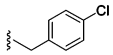
1



2



9

	R^1	R^2	R^3	R^4	mass (calcd.) $(M+H^+)$	mass (found) $(M+H^+)$	purity [%]
1a				-	441.2	441.3	92
1b				-	493.2	493.3	82
1c				-	477.2	477.3	80
1d				-	475.2	475.3.	71
1e				-	390.2	390.3	55
2a					480.3	480.6	72
2b					496.3	496.6.	61
2c					404.3	404.5.	45
2d					514.3	514.4	64
2e					532.3	532.4	82
2f					429.3	429.4	48
2g					576.3	576.5	40
2h					548.4	548.5	45
2i					480.3	480.5	43
9a				-	424.2	424.4	82
9b				-	272.2	272.4	75
9c				-	378.3	378.4	85
9d				-	398.2	398.4	74
9e				-	449.2	449.4	83
9f				-	440.3	440.3	85
9e				-	378.2	378.3	55
9f				-	458.2	458.6	75
9g				-	416.3	416.5	76
9e				-	278.2	278.3	55

[a] Purities were determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) over 10 min at 214 nm. Crude yields calculated on the basis of the initial loading of the resin (1.10 meq/g) were higher than 90%.

Cyclization of the guanidine derivatives **7** to the desired tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepine-2-(7*H*)-imines **2** (R^4 = H) using cyanogen bromide failed (Scheme 1). Instead, the cyanamide derivatives **9** were formed, which were easily identifiable by a signal at ~115 ppm in the ^{13}C spectrum. In contrast to compounds **8**, which could be cyclized by activation with acid, treatment using both, either a proton source or Lewis acid, did not lead to the cyclized products **2** (R^4 = H). In addition, we observed that although the cyanamide derivatives **9** were obtained in high purities, they were prone to hydrolysis, leading to urea derivatives.

To circumvent cyclization with CNBr, we decided to develop a synthetic route to tetrahydro-3*H*-imidazo[1,2-*a*]-[1,3,5]triazepine-2-(7*H*)-imine derivatives **2** starting from the resin-bound tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepine-2-(7*H*)-thiones **1**. Previously, we reported the transformation of thioureas to guanidines using $HgCl_2$ and various amines. We found that this synthetic method is also applicable for the synthesis of compounds **2**. Thus, resin-bound compounds **1** were treated with $HgCl_2$ in DCM. Subsequently, various amines were added (Scheme 2). Compounds **2** were obtained in high crude yield and in purities varying between 40 and 83%, depending on the amino acids and amines used (Table 1).

Overall, the heterocycles **1** were obtained via eight synthetic steps, including two amino acid couplings, one amide reduction, protection of the primary amine, first cyanogen bromide cyclization, deprotection, reductive alkylation, and cyclization to the 1,3,5-triazepine ring using $CSIm_2$. Subsequent treatment using $HgCl_2$ and amine led to heterocycles 2. Epimerization was found to be lower than 5% according to HPLC at 214 nm.

Conclusion

In summary, we have successfully synthesized 3,4,7-trisubstituted 4,5,8,9-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]-triazepin-2(7*H*)-imines and 4,5,8,9-tetrahydro-3*H*-imidazo-[1,2-*a*][1,3,5]triazepine-2(7*H*)-thiones from resin-bound dipeptides. The multistep synthesis on the solid phase led to the products in high yields and acceptable purities and was shown to be amenable to parallelization. The route to the bicyclic ring systems **1** and **2** also provided an example of divergent design, affording two heterocyclic core structures (X = S or NH), expected to have different pharmacological profiles, from a common intermediate.

Experimental Section

Commercially available reagents were used without further purification unless otherwise stated. Analytical RP-HPLC was performed on a Beckman System Gold instrument (Fullerton, CA). Purification of the samples was performed using a Vydac 218TP54 C18 column (0.46 × 25 cm). LC/MS (ESI) results were recorded on a Finnigan Mat LCQ (ThermoQuest Corporation, CA) using a Betasil C18 column (3 μm, 100 A, 3 × 50 mm) at 214 nm. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions at 500 MHz (^1H) and 125 MHz (^{13}C). The yield for purified products was determined on the basis of the loading of the polymeric support starting from 50 mg of the resin.

Typical Procedure for the Preparation of Compounds 7. A 50-mg sample of MBHA resin (1.10 meq/g, 100−200 mesh) was contained in a polypropylene mesh packet. Following neutralization with 5% DIEA in DCM, the resin was washed with DCM. The first Boc amino acid (6 equiv, 0.1 M) was coupled using hydroxybenzotriazole (HOBt, 6 equiv, 0.1 M) and diisopropylcarbodiimide (DIC, 6 equiv, 0.1 M) for 90 min. Upon removal of the Boc group with 55% TFA in DCM (30 min), the packet was washed and neutralized with a solution of 5% DIEA in DCM. The second Boc amino acid was coupled accordingly. The Boc group was removed as described above. The exhaustive reduction of the resin-bound amides was carried out in 50-mL glass conical tubes under nitrogen. To each tube was added the resin packet and boric acid (12 equiv). Trimethylborate (12 equiv) was added, followed by the slow addition of borane/THF complex (40 equiv). After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h in a heating block, followed by decantation of the reaction solution and quenching with MeOH. The resin packet was then washed with DMF and MeOH. The resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complex. Following decantation of the piperidine/borane solution, the resin packet was washed with DMF, DCM, and MeOH and dried. The resin-bound amine was reacted with trityl chloride in DCM/DMF (9:1) in the presence of DIEA. Alternatively, the primary amino function was protected using Dde-OH (1.5 equiv, 0.03 M in DMF), followed by washes with DMF, DCM, IPA, and DCM. Cyclization to the five-membered guanidine ring was achieved by treatment with CNBr (10 equiv, 0.1 M in DCM) for 15 h under nitrogen. Removal of the trityl group was performed using 1% TFA in DCM repeatedly until the solution no longer turned yellow. The resin was washed with DCM, IPA, and DCM. Removal of the Dde group was achieved by treatment with 2% N_2H_4 in DMF for 1 h, followed by washes with DMF, DCM, IPA, and DCM. Following cleavage from the resin with HF/anisole (95/5) for 1.5 h at 0 °C, the desired products **7** were extracted with acetic acid/water (95/5) and lyophilized.

***N*-Benzyl-1-(5-benzyl-2-iminoimidazolin-1-yl)-3-phenylpropan-2-amine 7a.** ^1H NMR (DMSO-d_6): δ 2.31 (dd, J = 9.2, 13.4 Hz, 1H), 2.43 (dd, J = 3.0, 13.4 Hz, 1H), 2.87 (dd, J = 10.3, 13.8 Hz, 1 H), 3.13 (dd, J = 3.5, 9.6 Hz, 1H), 3.22 (t, J = 9.5 Hz, 1H), 3.39 (dd, J = 3.6, 15.8 Hz, 1H), 3.49 (dd, J = 3.5, 13.8 Hz, 1H), 3.85−3.92 (m, 2H), 4.10 (dd, J = 9.0, 15.8 Hz, 1H), 4.28 (d, J = 12.7 Hz, 1H), 4.45 (d, J = 12.7 Hz, 1H), 6.97 (d, J = 7.4 Hz, 2H), 7.21−7.31 (m, 4H), 7.39 (d, J = 4.5 Hz, 4H), 7.43−7.49 (m, 3H), 7.55 (d, J = 7.1 Hz, 2H), 8.21 (br, 1H), 8.35 (s, 2H), 9.45−9.60 (br, 1H), 9.65−9.75 (br, 1H). MS (ESI): calcd [MH^+] 399.2, found 399.4.

Typical Procedure for the Preparation of Compounds 1. The respective resin-bound compound **7** was treated with $CSIm_2$ (20 equiv, 0.1 M in DCM) for 15 h at room temperature under nitrogen, followed by washes with DCM, IPA, and DCM. Cleavage from the resin with HF/anisole (95/5) for 1.5 h at 0 °C, extraction with acetic acid/water (95/5), and lyophilization, followed by treatment with 1%

TFA in AcCN/H_2O (90/10) for 7 days led to the desired products **1**.

(4*S*,7*S*)-3,4,7-Tribenzyl-4,5,8,9-tetrahydro-3*H*-imidazo-[1,2-*a*][1,3,5]triazepine-2(7*H*)-thione (1a). ^{1}H NMR (DMSO-d_6): δ 2.70 ppm (dd, J = 10.0, 12.9 Hz, 1H), 2.91 (dd, J = 5.1, 10.1 Hz, 1H), 2.97−3.04 (m, 2H), 3.43−3.48 (m, 2H), 3.96 (s, 2H), 4.25−4.31 (m, 3H), 5.51 (d, J = 14.8 Hz, 1H), 7.18−7.25 (m, 8H), 7.28−7.39 (m, 7H), 7.98 (br, 1H), 11.6−12.0 (br, 1H). ^{13}C NMR (DMSO-d_6): δ 34.7 ppm, 35.8, 45.9, 46.4, 60.4, 60.9, 62.3, 126.8, 126.2, 128.0, 128.7, 129.0, 129.1, 134.4, 135.8, 136.4, 151.3, 178.1. MS (ESI): calcd [MH^+] 441.2, found 441.3.

Typical Procedure for the Preparation of Compounds 2. The respective resin-bound compound **7** was treated with $CSIm_2$ (20 equiv, 0.1 M in DCM) for 15 h at room temperature under nitrogen, followed by washes with DCM, IPA, and DCM. The resin was treated with 1% TFA in AcCN/H_2O (50/50) for 7 days; washed with DCM, IPA, and DCM; and dried. The resin-bound compound was reacted with 10 equiv of $HgCl_2$ (0.1 M in DMF) for 12 h at room temperature under nitrogen. The respective amine (20 equiv) was added, and the reaction mixture was shaken for 12 h at room temperature under nitrogen. The final compound **2** was obtained after cleavage from the resin by anhydrous HF in the presence of anisole for 1.5 h at 0 °C, extracted with 95% acetic acid in H_2O, and lyophilized.

(4*S*,7*S*)-3,4,7-Tribenzyl-*N*-butyl-4,5,7,8-tetrahydro-3*H*-imidazo[1,2-*a*][1,3,5]triazepin-2-amine (2a). ^{1}H NMR (DMSO-d_6): δ 0.85 ppm (d, J = 7.4 Hz, 3H), 1.16−1.21 (m, 2H), 1.42−1.45 (m, 2H), 2.59 (dd, J = 10.3, 13.1 Hz, 1H), 2.85−2.87 (m, 2H), 3.07 (dd, J = 3.9, 13.1 Hz, 1H), 3.25−3.33 (m, 3H), 3.39−3.42 (m, 2H), 3.53 (dd, J = 4.4, 13.6 Hz, 1H), 3.73 (d, J = 16.3 Hz, 1H), 4.01−4.05 (m, 1H), 4.18−4.24 (m, 1H), 4.60 (d, J = 16.3 Hz, 1H), 7.15−7.40 (m, 16H), 7.98 (br, 1H). ^{13}C NMR (DMSO-d_6): δ 13.7 ppm, 19.3, 31.2, 35.4, 36.6, 41.8, 44.7, 46.9, 55.3, 60.5, 61.6, 126.7, 126.9, 127.5, 127.8, 128.6, 128.6, 128.7, 129.1, 135.0, 136.4, 137.3, 154.7, 158.1. MS (ESI): calcd [MH^+] 480.3, found 480.6.

Typical Procedure for the Preparation of Compounds 9. The respective resin-bound compound **7** was treated with CNBr (10 equiv, 0.1 M in DCM) for 15 h under nitrogen, followed by washes with DCM, IPA, and DCM. Following cleavage from the resin with HF/anisole (95/5) for 1.5 h at 0 °C, the desired products **9** were extracted with acetic acid/water (95/5) and lyophilized.

Benzyl{(1*S*)-2-[(5*S*)-2-imino-5-methylimidazolidin-1-yl]-1-methylethyl}cyanamide (9b). ^{1}H NMR (DMSO-d_6): δ 1.19 ppm (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 3.12 (dd, J = 6.1, 9.0 Hz, 1H), 3.25 (dd, J = 4.2, 15.3 Hz, 1H), 3.51−3.54 (m, 1H), 3.58−3.64 (m, 2H), 3.90−3.93 (m, 1H), 4.26 (s, 2H), 7.18−7.25 (m, 8H), 7.35−7.42 (m, 5H), 8.08 (br, 2H), 8.18 (br, 1H). ^{13}C NMR (DMSO-d_6): δ 15.7 ppm, 17.4, 44.6, 47.6, 53.4, 53.5, 54.1,115.6, 128.3, 128.6, 128.7, 135.7, 158.0. MS (ESI): calcd [MH^+] 272.2, found 272.4.

Acknowledgment. This research was supported by the National Cancer Institute Grant No. CA78040 (Houghten) and NIDA Grant No. 5 RO1 DA09410 (Houghten). The authors also thank the Multiple Sclerosis National Research Institute, Diabetes National Group, Alzheimer's and Aging Research Center, Pain Management Research Institute of America, and Osteoporosis and Breast Cancer Research Center for their support.

Supporting Information Available. Experimental procedures for the preparation of compounds **1**, **2**, and **9**. NMR data and spectra of [^{15}N]-**1a**, [^{15}N]-**1a** gHSQCDEPT, and [^{15}N]-**1a**: ^{13}C gHMBD, [^{15}N]-**1a**: ^{15}N gHMBC. ^{1}H NMR of **6a**, **9b**, **2a**. ^{13}C of **9b**, **2a**. ^{1}H and ^{13}C NMR data of **1b**, **1c**, **1d**, **1e**, **2b**, and **2c**. ^{1}H NMR data of **9c**−**f**. MS (ES) of all compounds.

References and Notes

(1) (a) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. M. *J. Med Chem.* **1999**, *42*, 3743−3778. (b) Hoesl, C. E.; Nefzi, A.; Ostresh, J. M.; Yu, Y.; Houghten, R. A. *Methods Enzymol.* **2003**, *369*, 496.

(2) Ganellin, C. R. In *Chronicles of Drug Discovery*; Bindra, J. S., Lednicer, D., Eds.; Wiley: New York, 1982; Vol. 1, pp 1−38.

(3) Gilman, A. G.; Goodman, L. S.; Goodman, A. *The Pharmacological Basis of Therapeutics*, 6th ed.; Macmillan Publishing Co.: New York, 1980; p 380.

(4) Ekelund, S.; Nygren, P.; Larsson, R. *Biochem. Pharmacol.* **2001**, *61*, 1183.

(5) Jhadav, P. K.; Woerner, F. J.; Lam, P. Y. S.; Hodge, C. N.; Eyermann, C. J.; Man, H. W.; Daneker, W. F.; Bacheler, L. T.; Rayner, M. M.; Meek, J. L.; Erickson-Viitanen, S.; Jackson, D. A.; Calabrese, J. C.; Schadt, M.; Chang, C. H.; *J. Med. Chem.* **1998**, *41*, 1446.

(6) Greenhill, J. L.; Lue, P. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5.

(7) (a) Ostresh, J. M.; Schoner, C. C.; Hamshin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622. (b) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. *J. Med. Chem.* **1999**, *42*, 3743−3778.

(8) Blondelle, S. E.; Crooks, E.; Ostresh, J. M.; Houghten, R. A. *Antimicrob. Agents Chemother.* **1999**, *43*, 106.

(9) Sawanishi, H.; Wakusawa, S.; Murakami, R.; Muramatsu, H.; Suzuki, H.; Takashima, A.; Aizawa, T.; Miyamoto, K. *J. Med. Chem.* **1995**, *38*, 5066.

(10) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.

(11) Houghten, R. A. *Proc. Nat. Acad. Sci. U.S.A.* **1985**, *28*, 5131−5135.

(12) Kaiser, E. T.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

(13) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 578.

(14) (a) Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, 1038. (b) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433.

(15) (a) Nefzi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931. (b) Nefzi, A.; Ostresh, J. M.; Guilianotti, M.; Houghten, R A. *J. Comb. Chem.* **1999**, *1*, 195. (c) Acharya, A. N.; Ostresh, J. M.; Hougthen, R. A. *J. Comb. Chem.* **2001**, *3*, 579. (d) Nefzi, A.; Guilianotti, M.; Truong, L.; Rattan, S.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem.* **2002**, *4*, 175. (e) Klein, G.; Ostresh, J. M.; Nefzi, A. *Tetrahedron Lett.* **2003**, *4*, 2211.

CC050094E