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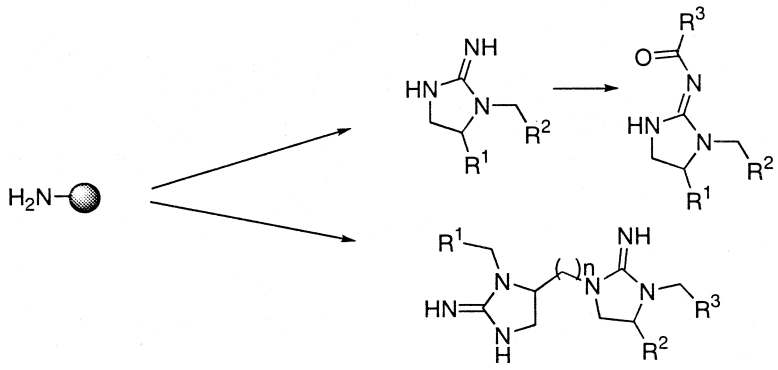

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A Novel Approach for the Solid-Phase Synthesis of Substituted Cyclic Guanidines, Their Respective Bis Analogues, and N-Acylated Guanidines from N-Acylated Amino Acid Amides

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An efficient method for the solid-phase synthesis of cyclic guanidines from N-acylated amino acid amides, bis cyclic guanidines from N-acylated dipeptides derived from orthogonally protected diamino acids, and N-acylated guanidines from disubstituted cyclic guanidines is described. The exhaustive reduction of N-acylated amino acid amides yields diamines that on treatment with cyanogen bromide lead to the formation of cyclic guanidines. Resin-bound orthogonally protected diamino acids (i.e., N^{α}-Fmoc-N^{x}-(Boc)-diamino acid, $x = \beta, \gamma, \delta, \epsilon$) were N-acylated following removal of the Fmoc group. Removal of the Boc functionality from the side chain then generated a primary amine. Subsequent coupling of Boc amino acids, followed by removal of the Boc group, generated dipeptides that were N-acylated. Exhaustive reduction of amide bonds of the N-acylated dipeptides generated tetraamines having four secondary amines, which upon cyclization with cyanogen bromide afforded the resin-bound trisubstituted bis cyclic guanidines. Treatment of the resin-bound disubstituted cyclic guanidines with carboxylic acids gave N-acylated guanidines. On the basis of their high yield and purity, bis cyclic guanidines derived from N^{α}-Fmoc-N^{ϵ}-Boc-lysine and N-acylated guanidines were chosen for preparation of mixture-based combinatorial libraries. Details of the preparation of these positional scanning libraries using the "libraries from libraries" concept are presented.

Introduction

Guanidines are structurally novel molecules reported to exhibit remarkable biological and pharmacological activities. The hydrogen-bonding acceptor and donor abilities of the guanidino group play an important role in their diverse properties. Recent studies revealed that a striking variety of novel guanidino alkaloids (e.g., ptilomycalin A and crambescidins, isolated from marine sponges) are reported to exhibit antiviral activity against herpes simplex virus (type 1), antifungal activity against *Candida albicans*, and anti-HIV activities.[1−4] Other members of this family also exhibited cytotoxicity against a range of human cancer cell lines, including lung carcinoma A-549, colon carcinoma HT-29, and melanoma MEL-28, and in vitro against L1210 murine leukemia cells.[1,4,5] Furthermore, these alkaloids inhibit Na^+-, K^+-, and Ca^{2+}-ATPase by interaction with ATP at its binding site.[6] They are also reported to be the most potent in vitro agonists as Ca^{2+} channel blockers ($IC_{50} = 0.15$ nM, nifedipine = 1.2 nM in this assay).[1] Examples of pharmacologically active synthetic nonpeptidic guanidines include neuronal Na^+ and Ca^{2+} channel blockers,[7] glutamate release inhibitors, anti-ischemic agents,[8] antiseizure agents,[9] adrenergic neuron blocking agents,[10] NO synthase inhibitors,[11] influenza neuraminidase inhibitors,[12] cardiotonic agents,[13] histamine H_3 receptor antagonists,[14] H_2 receptor agonists/antagonists,[15] potassium/ATP channel openers, antitumor agents, and antihistaminic, antiinflammatory, antidiabetic, antibacterial, and antihypertensive drugs.[16] Nonpeptidic cyclic cyanoguanidines are reported to be powerful HIV-1 protease inhibitors.[17] Notably, a guanidino moiety has previously been incorporated into a known antiulcer drug, cimetidine.[18] Moreover, a cyclic guanidine analogue reported by Lehn et al. is used as an enantioselective anion recognizer.[19] Therefore, the development of solid-phase syntheses of cyclic guanidines, their bis analogues, and N-acylated guanidines merits investigation.

Several approaches for the solid-phase synthesis of guanidines have appeared in the literature. There are four different approaches most commonly used for the solid-phase synthesis of guanidines, namely, the reaction of thioureas with amines,[13,20] the formation of resin-bound carbodiimides and their reaction with amines,[21] the solid-phase synthesis involving electrophiles in solution,[22] and the use of guanylating agents.[23] The major drawback of these approaches is the limitations of existing building blocks due to the need to use at least one of the three possible substituents of the guanidine moiety for attachment to the polymeric solid support. In addition, purities are typically in the range 50−75%. Recently, the synthesis of solution-phase cyclic guanidines and N-acylated guanidines through the cyclization of thioureas and ethoxycarbonylated thioureas, respectively, using 2-chloro-1,3-dimethylimidazolinium chloride (DMC) has been reported.[24] However, we have not come across any report on the synthesis of cyclic guanidines from peptides on the solid phase. We describe, herein, the straightforward synthesis of disubstituted cyclic guanidines from N-acylated

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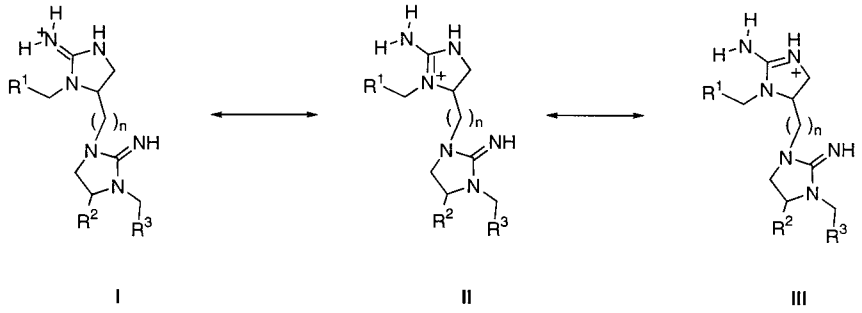
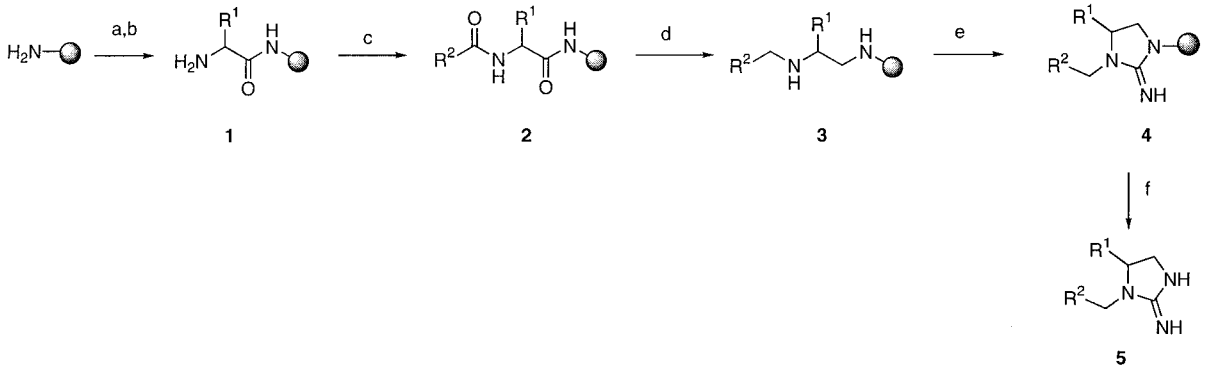
Scheme 1. Resonance Structures of Monoprotonated Trisubstituted Bis Cyclic Guanidines



I II III

Scheme 2[a]



1 2 3 4 5

[a] (a) Boc-NHCH(R^1)CO_2H (6 equiv, 0.1 M in DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, room temp; (b) 55% TFA/45% DCM, 30 min, room temp; (c) R^2CO_2H (10 equiv, 0.1 M in DMF), DIC (10 equiv), HOBt (10 equiv), room temp, overnight; (d) (i) BH_3−THF, 65 °C, 4 days; (ii) piperidine, 65 °C, 20 h; (e) CNBr (10 equiv, 0.1 M in DCM), room temp, overnight; (f) HF, anisole, 0 °C, 1.5 h.

amino acid amides, trisubstituted bis cyclic guanidines from N-acylated dipeptides using different orthogonally protected diamino acids (amino acids having two amine functionalities), and N-acylated guanidines from disubstituted cyclic guanidines using cyanogen bromide (CNBr) for guanidine formation.[25] It is noteworthy to point out that different substituent building blocks were varied independently around the cyclic guanidine moiety. The resulting products were obtained in high yield (>90%) and excellent purity (>80%) and enabled the synthesis of large combinatorial libraries of these compounds. N-acylation of cyclic guanidines would be expected to reduce their basicity by approximately 4−5 orders of magnitude.[17]

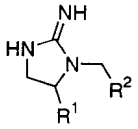
It was recently revealed that the imino group is susceptible to proton attack as illustrated by formamidine, acetamidine, and guanidines.[26] These cyclic guanidines and their bis analogues were protonated at their exocyclic imine nitrogen(s), both at physiological pH and under the enzyme inhibition assay conditions. On protonation, the positive charge could be delocalized over the π-system in a qualitative manner by the resonance structures presented in Scheme 1. Protonation at the exocyclic nitrogen is favorable because there are three resonance structures describing the delocalization of the positive charge over the π-system. This suggests an interesting system in which one or both guanidino moieties may be protonated. In turn, the free imine group or the guanidinium moiety(s) could be expected to influence numerous biological and pharmacological activities. This can also be used as an anion recognizer[19] or as a strong organic base or superchiral base.[24] We have synthesized a mixture-based positional scanning library[27] of the resulting trisubstituted bis cyclic guanidines from orthogonally protected lysine (N^{α}-Fmoc- N^{ϵ}-Boc-lysine) and N-acylated guanidines.

Results and Discussion

The synthetic strategy involves the preparation of (i) disubstituted cyclic guanidines from reduced N-acylated amino acid amides, (ii) bis cyclic guanidines from N-acylated dipeptides derived from N^{α}-Fmoc-N^{x}-(Boc)-diamino acids ($x = \beta, \gamma, \delta, \epsilon$), and (iii) N-acylated guanidines from disubstituted cyclic guanidines.

(i) Disubstituted Cyclic Guanidines. Individual Boc-protected amino acids were coupled to 4-methylbenzhydrylamine (MBHA) resin, followed by deprotection of the Boc group to generate the primary amines **1** (Scheme 2). The resulting free amines were N-acylated with specific carboxylic acids. Exhaustive reduction of the amide bonds of the N-acylated amino acid amides **2** by treatment with BH_3−THF generated diamines **3** having two secondary amines. The diamines **3** were treated with cyanogen bromide to provide the resin-bound cyclic guanidines **4**. Initially we prepared 20 cyclic guanidines using 5 different amino acids (Ala, Phe, Leu, Val, and Ile) and 5 different carboxylic acids (phenylacetic acid, butyric acid, isovaleric acid, acetic acid, and benzoic acid) (Table 1). The guanidines were cleaved from the solid support using anhydrous HF, generating compounds **5**. The N-benzylic moiety (N-acylation using benzoic acid, **2**, Scheme 2) was completely cleaved during 1.5 h of HF cleavage. Uncyclized compound was not observed by LC−MS. The crude products were extracted with 95% AcOH in water and purified by reverse-phase high-

Table 1. RP-HPLC Purity and Masses Found for the Cyclic Guanidines **5**[a]



product	R^1	R^2	purity[b] (%)	MW (calcd)	MW (found)
5a	$-CH_3$	$-CH_2CH(CH_3)_2$	95	169.3	170.4 ($M + H^+$)
5b	$-CH_2C_6H_5$	$-CH_2C_6H_5$	91	279.4	280.5 ($M + H^+$)
5c	$-CH_2C_6H_5$	$-(CH_2)_2CH_3$	91	231.3	232.5 ($M + H^+$)
5d	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	95	245.4	246.3 ($M + H^+$)
5e	$-CH_2CH(CH_3)_2$	$-CH_2C_6H_5$	95	245.4	246.9 ($M + H^+$)
5f	$-CH_3$	$-CH_2C_6H_5$	94	203.3	204.2 ($M + H^+$)

[a] The yields obtained were greater than 93% in all cases with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

pressure liquid chromatography (RP-HPLC). The crude yield and purity of the final compounds were greater than 93% and 80%, respectively, by LC−MS and RP-HPLC (see Table 1). The purified compounds were analyzed by high-resolution mass spectra (HRMS), ^{1}H NMR, and ^{13}C NMR to confirm their identity and structure. Three proton signals appearing at δ_H ~7.9−8.1 ppm in the ^{1}H NMR spectra corresponded to two protons of the protonated guanidino moiety and an imidazolyl proton.[28,29] In addition, a peak appearance at δ ~157−158 ppm in the ^{13}C NMR spectra confirmed the presence of a guanidino moiety.[30,31]

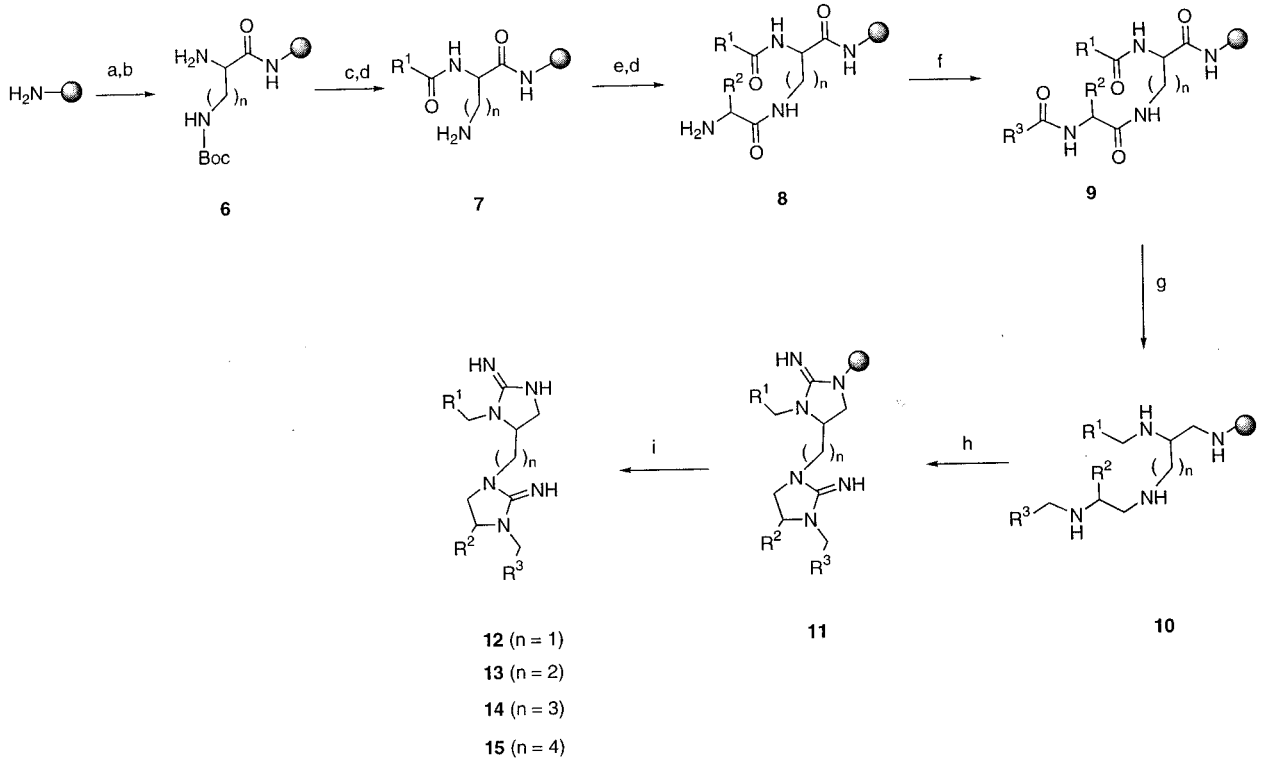
Our goal was to gain the ability to synthesize by solid-phase synthetic strategies thousands of heterocycles while keeping the essential scaffold the same. Variation of the structural diversity at different positions of the heterocycle in chemical libraries yields a greater opportunity to identify active molecules during high-throughput screening.[32] Having only two positions of diversity, the above cyclic guanidines are limited. To increase the number of diversity, we decided to prepare bis cyclic guanidines having three positions of diversity from N-acylated dipeptides using different orthogonally protected diamino acids. These novel scaffolds offer two five-member heterocycles, each having a cyclic guanidino moiety and each also having at least one position of diversity.

(ii) Bis Cyclic Guanidines from Orthogonally Protected Diamino Acids. The orthogonally protected (Fmoc)-(Boc)-L-diamino acids (e.g., N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid, N^{α}-Fmoc-N^{γ}-Boc-diaminobutyric acid, N^{α}-Fmoc-N^{δ}-Boc-ornithine, and N^{α}-Fmoc-N^{ϵ}-Boc-lysine) were coupled to MBHA resin followed by removal of the N^{α}-Fmoc group, generating primary amines **6** (Scheme 3). These were then N-acylated with a wide variety of available carboxylic acids, followed by removal of the Boc group from the side chain to generate compounds with the general structure of **7**. The primary amine of each compound was coupled with different Boc-protected amino acids, followed by deprotection of the Boc group, to generate dipeptides **8**. Subsequent N-acylation at the primary amine of the dipeptides **8** with a carboxylic acid yielded compounds **9**. Exhaustive reduction of the amide bonds of the compounds **9** by treatment with BH_3−THF generated tetraamines **10** having four secondary amines.[30] The tetraamines **10** were treated with cyanogen bromide to generate the resin-bound bis cyclic guanidines **11**. As expected, the bis cyclic guanidines **11** were generated because of the energetically favorable formation of five-membered rings. Uncyclized starting materials as detected by LC−MS or RP-HPLC were not observed. Cleavage from the solid support using anhydrous HF, followed by extraction with 95% AcOH in water, yielded compounds **12**−**15**. The crude samples were purified by RP-HPLC. The chromatographed products were characterized by LC−MS, HRMS, ^{1}H NMR, and ^{13}C NMR to confirm their identity and structure. Five proton signals appeared at δ ~7.9−8.3 ppm in the ^{1}H NMR spectra in DMSO-d_6. These downfield chemical shifts suggested that these protons were those of an amine or imine or both.[29] This corresponded to two protons for each protonated guanidino moieties and an imidazolyl proton from one of the rings. This was further supported by the appearance of two peaks at δ ~155−158 ppm in the ^{13}C NMR spectra that confirmed the presence of two guanidino moieties.[30,31]

The choice of tether length between the two guanidino moieties in the bis cyclic guanidine merits discussion. A single-carbon tether derived from the N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid generated a mixture of cyclic guanidine (i.e., possibly cyclization between two internal secondary nitrogens) and its bis analogue. This may be due to the competition between formation of the five-member cyclic guanidine and its bis analogue during the cyclization reaction. We used a two-carbon tether derived from the N^{α}-Fmoc-N^{γ}-Boc-diaminobutyric acid, but the cyclization reaction yielded several undesirable byproducts. The three-carbon tether derived from N^{α}-Fmoc-N^{δ}-Boc-ornithine resulted in a final product with reasonable purity (see Table 2). The four-carbon spacer derived from the N^{α}-Fmoc-N^{ϵ}-Boc-lysine gave high purity (>80%) of the final product (see Tables 2 and 3) with no impurity greater than 3%. Considering the purity of the final product and cost of the precursor (see Tables 2 and 3), N^{α}-Fmoc-N^{ϵ}-Boc-lysine, having a four-carbon spacer, was chosen for preparation of the bis cyclic guanidine library.[33]

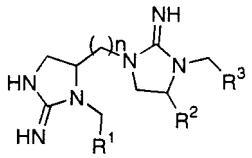
To determine the possibility of racemization during either the BH_3−THF reduction step or the final cyclization step, two diasteriomeric analogues of both intermediate **10** and final compound **15** known not to coelute were prepared. RP-HPLC data revealed that there was negligible racemization (>99% optically pure) during exhaustive reduction of amide

Scheme 3[a]



[a] (a) Fmoc-(Boc)-L-diamino acids (2.5 equiv, 0.05 M in DMF), DIC (2.5 equiv), HOBt (2.5 equiv), room temp, overnight; (b) 20% piperidine/80% DMF, room temp, 30 min; (c) R^1CO_2H (10 equiv, 0.1 M in DMF), DIC (10 equiv), HOBt (10 equiv), room temp, overnight; (d) 55% TFA/45% DCM, room temp, 30 min; (e) Boc-NHCH(R^2)CO_2H (6 equiv, 0.1 M in DMF), DIC (6 equiv), HOBt (6 equiv), room temp, 2 h; (f) R^3CO_2H (10 equiv, 0.1 M in DMF), DIC (10 equiv), HOBt (10 equiv), room temp, overnight; (g) (i) BH_3−THF, 65 °C, 4 days; (ii) piperidine, 65 °C, 20 h; (h) CNBr (10 equiv, 0.1 M in DCM), room temp, overnight; (i) HF, anisole, 0 °C, 1.5 h. "*n*" denotes the tether carbon length between two guanidine rings.

Table 2. Comparison of Purity of Tethered Bis Cyclic Guanidine Analogues **12**−**15**



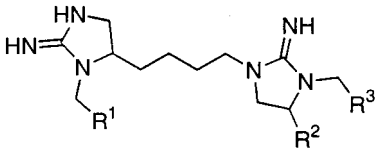
				purity (%)[a]			
entry	R^1	R^2	R^3	**12** ($n = 1$)	**13** ($n = 2$)	**14** ($n = 3$)	**15** ($n = 4$)
a	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	69 (480.6) [481.1][b]	80 (494.7) [495.1][b]	89 (508.7) [509.2][b]	91 (522.7) [523.8][b]
b	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-(CH_2)_2CH_3$	67 (432.6) [433.1][b]	75 (446.6) [447.1][b]	80 (460.7) [461.2][b]	88 (474.7) [475.7][b]
c	$-CH_2C_6H_5$	$-CH_3$	$-CH_2C_6H_5$	72 (404.6) [405.0][b]	82 (418.6) [419.0][b]	85 (432.6) [433.1][b]	80 (446.6) [447.2][b]

[a] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm. "*n*" denotes the carbon spacer length (Scheme 2). [b] Values in the parentheses and brackets denote MW (calcd) and MW [M + H^+] (found), respectively.

bonds, in conformity with our earlier observations.[30,31] In addition, RP-HPLC and ^1H NMR data indicated negligible racemization (<1%) during cyclization of tetraamines with cyanogen bromide.

After optimization of all the synthetic steps, we tested 46 carboxylic acids at the first (R^1) and third (R^3) positions of diversity and 36 amino acids for the second (R^2) position of diversity for possible inclusion in a positional scanning combinatorial library.[27] Substituted benzoic acids were excluded for N-acylation at the first (R^1) and third (R^3) positions of diversity because of the resulting complete cleavage of the N-benzylic functionality under the final cleavage conditions used.[30,31] We found that the biphenylmethyl moiety, obtained upon N-acylation of biphenylcarboxylic acid or 4-ethyl-4′-biphenylcarboxylic acid at the first (R^1) and third (R^3) positions of diversity, was partially cleaved during HF cleavage. Hence, substituted biphenylcarboxylic acids were not considered for use in the library at the first (R^1) and third (R^3) positions of diversity. Substituted phenylacetic acids and aliphatic carboxylic acids were included for the N-acylation at the first (R^1) and third (R^3) positions of diversity. Those amino acids, which have either an extra amine functionality (for example, lysine or arginine) or generate an extra amine functionality after reduc-

Table 3. RP-HPLC Purity and Masses Found for the Bis Cyclic Guanidines **15**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
15d	$-CH(CH_3)_2$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	474.7	475.2 ($M + H^+$)	91
15e	$-CH_2CH(CH_3)C_2H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	502.7	503.5 ($M + H^+$)	91
15f	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH(CH_3)_2$	474.7	475.2 ($M + H^+$)	80
15g	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-(CH_2)_2CH(CH_3)_2$	502.7	503.4 ($M + H^+$)	90
15h	$-CH_2CH_2C_6H_{11}$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	542.8	543.6 ($M + H^+$)	86
15i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-C_6H_{11}$	514.7	515.4 ($M + H^+$)	90
15j	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH_2C_5H_9$	528.8	529.4 ($M + H^+$)	89
15k	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_4(4\text{-}C_6H_5)$	598.8	599.4 ($M + H^+$)	92
15l	2-norbornaneacetyl	$-CH_2C_6H_5$	$-CH_2C_6H_5$	540.8	541.4 ($M + H^+$)	87
15m	$-CH_2C_6H_5$	$-C_6H_5$	$-CH_2C_6H_5$	508.7	509.3 ($M + H^+$)	90
15n	$-CH_2C_6H_5$	$-CH_2C_{10}H_7$	$-CH_2C_6H_5$	572.8	573.3 ($M + H^+$)	88

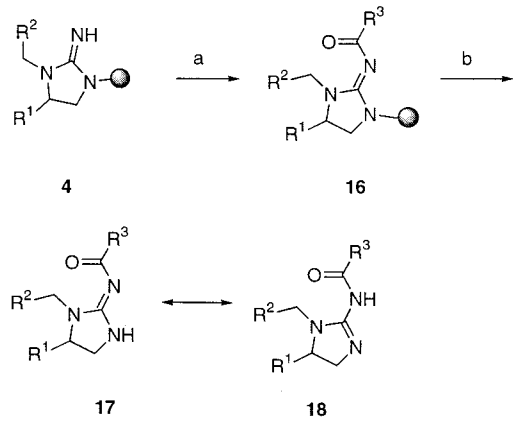
[a] The yields obtained were greater than 93% in all cases with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

tion (for example, glutamine or asparagine), were excluded for the second (R^2) position of diversity.

The percentage of crude yield for each individual control compound was determined with respect to the theoretical loading of the resin (1.10 mequiv/g). The percentage of crude purity was calculated from the relative peak areas of the HPLC chromatograms. Only those compounds having crude yield and purity greater than 80% were considered for inclusion in the synthesis of the positional scanning library.[27] We chose 40 carboxylic acids for the first (R^1) and third (R^3) positions of diversity and 26 amino acids for the second (R^2) position of diversity for inclusion in the synthesis of the library (included in the Supporting Information). Predetermined isokinetic ratios of different carboxylic acids and Boc-amino acids[34] were used for coupling of mixtures. The compounds were cleaved from the solid support using anhydrous HF and extracted with 95% AcOH in water.

(iii) N-Acylated Guanidines from Disubstituted Cyclic Guanidines. Resin-bound disubstituted cyclic guanidines **4** were treated with a wide variety of available carboxylic acids in the presence of 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*′-diisopropylethylamine (DIEA), generating resin-bound N-acylated guanidines **16** (Scheme 4). Complete acylation was observed in all cases under these experimental conditions. Little or no racemization (<1%) was observed by RP-HPLC as described previously.[30,31] The resulting compounds were cleaved from the solid support using standard HF (1.5 h) cleavage conditions and were extracted with 95% AcOH in water, affording compounds **17**. The samples were purified by RP-HPLC (Table 4). Purified samples were characterized by LC−MS, HRMS, ^{1}H NMR, and ^{13}C NMR. Two downfield peaks appearing in the ^{13}C NMR spectrum corresponded to the presence of one guanidine carbon (∼157 ppm) and one acyl group carbon (∼180 ppm).[30,31] Two strong downfield proton signals (i.e., δ_H ∼9.2−9.4 ppm for imidazolyl −N(H) proton and ∼11.5 ppm for acetamide −N(H)−CO− proton) in the ^{1}H NMR spectrum corresponded to the possible equilibrium between imidazolyl−N(H) and acetamide −N(H)−CO− protons.[24,29] This indicated a 1:1 equilibrium between the imino form exocyclic ═NC(O)R^3 (**17**) and amino form exocyclic −NHC(O)R^3 (**18**). It has been reported that the substituted guanidines can exist in two tautomeric forms, conventionally named the imino form (exocyclic ═NH) and amino form (exocyclic $-NH_2$).[29] However, the tautomeric preference is sensitive to their neutral form and the electronic nature of the substituents at the second (R^2) and third (R^3) positions of diversity.[29]

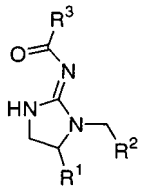
Scheme 4[a]



[a] (a) R^3CO_2H (25 equiv, 0.16 in DMF), HBTU (25 equiv), DIEA (50 equiv), 26 H, room temp; (b) HF, anisole, 1.5 h, 0 °C.

We tested 40 amino acids for the first position of diversity (R^1) and 44 carboxylic acids for the second (R^2) and third (R^3) positions of diversity to determine their acceptability for inclusion in a positional scanning library. Serine and threonine analogues were excluded for the first position (R^1) of diversity because of formation of undesirable byproducts (i.e., >30%). However, tyrosine analogues were included only for the first position (R^1) of diversity because of their moderate purity (i.e., 80%). Similarly, *p*-NO_2-phenylalanine analogues yielded undesirable byproducts, likely due to partial reduction of the NO_2 group during BH_3−THF reduction.[35] Both *p*-NO_2-(*R*)-phenylalanine and *p*-NO_2-(*S*)-phenylalanine analogues were not included in the synthesis

Table 4. RP-HPLC Purity and Masses Found for the N-Acylated Guanidines **17**[a]



product	R^1	R^2	R^3	MW (calcd)	MW (found)	purity[b] (%)
17a	$-CH_3$	$-CH_3$	$-CH_2C_6H_5$	245.3	245.9 ($M + H^+$)	85
17b	$-CH_3$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	321.4	321.8 ($M + H^+$)	84
17c	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	397.5	397.9 ($M + H^+$)	85
17d	$-CH(CH_3)_2$	$-CH_2C_6H_5$	$-CH_2C_6H_5$	349.5	349.9 ($M + H^+$)	86
17e	$-CH_2C_6H_5$	$-CH_3$	$-CH_2C_6H_5$	321.4	321.8 ($M + H^+$)	85
17f	$-CH_2C_6H_5$	$-(CH_2)_2CH_3$	$-CH_2C_6H_5$	349.5	349.8 ($M + H^+$)	84
17g	$-CH_2C_6H_5$	$-C_4H_7$	$-CH_2C_6H_5$	361.5	362.0 ($M + H^+$)	84
17h	$-CH_2C_6H_5$	$-CH_2C_6H_5(4\text{-}OC_2H_5)$	$-CH_2C_6H_5$	441.6	442.1 ($M + H^+$)	91
17i	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2CH(CH_3)_2$	363.5	363.9 ($M + H^+$)	89
17j	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-(CH_2)_2CH_3$	349.5	349.8 ($M + H^+$)	87
17k	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_2C_6H_5(3\text{-}CH_3)$	411.5	412.0 ($M + H^+$)	91
17l	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-C_4H_7$	361.5	361.9 ($M + H^+$)	88

[a] The yields obtained were greater than 93% in all cases with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at 214 nm.

of the library. Other amino acids either having an extra amine functionality (for example, lysine, arginine, etc.) or generating an extra amine functionality after reduction (for example, glutamine, asparagine, etc.) were excluded for the first (R^1) position of diversity. Benzoic acid derivatives (obtained upon N-acylation using benzoic acid derivatives, **2**, Scheme 2) were excluded for N-acylation at the second (R^2) position of diversity because of complete or partial cleavage of the N-benzylic moiety during HF cleavage.[30,31] Biphenylcarboxylic acid and its derivatives (for example, 4-ethyl-4′-biphenylcarboxylic acid) were not considered for N-acylation at the second (R^2) position of diversity because of partial cleavage of the bulkier *N*-methylbiphenyl group during HF cleavage. However, 4-ethyl-4′-biphenylcarboxylic acid was included for the third (R^3) position of diversity because of its high purity (i.e., >80%). Similarly, cinnamic acid derivatives were excluded from the second (R^2) position of diversity because of formation of undesirable byproducts during BH_3−THF reduction. However, these carboxylic acids were used for N-acylation at the third position (R^3) of diversity.

The crude yield and purity were determined as described previously. From the groups tested, those building blocks having crude purity greater than 80% were included in the synthesis of the positional scanning library.[36] Thus, 34 amino acids were chosen for the first position of diversity (R^1), 37 carboxylic acids for the second position of diversity (R^2), and 36 carboxylic acids for the third (R^3) position of diversity for the synthesis of the positional scanning library (included in Supporting Information). Predetermined isokinetic ratios for different Boc-amino acids for the first (R^1) position of diversity were used for coupling of mixtures.[34] Two different sets of predetermined isokinetic ratios for different carboxylic acids were used for N-acylation of amines vs guanidines; amines were N-acylated using *N*,*N*′-diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt),[34] and guanidines were N-acylated using HBTU and DIEA (see Supporting Information) for the second (R^2) and third (R^3) positions of diversity, respectively, for coupling of the mixtures. The compounds were cleaved from the solid support using anhydrous HF and extracted with 95% AcOH in water.

Conclusion

A novel approach to the preparation of three separate guanidines, (i) substituted cyclic guanidines, (ii) bis cyclic guanidines, and (iii) N-acylated guanidines, was presented. The solid-phase synthesis of these compounds is straightforward, resulting in high yield of the desired compounds that retain their enantiomeric purity and have low side products. The carbon spacer length between the two guanidino moieties in bis cyclic guanidines was varied by using different orthogonally protected diamino acids. The bis cyclic guanidines obtained from N^{α}-Fmoc-N^{ϵ}-Boc-lysine were preferred for preparation of a combinatorial library. We have prepared a positional scanning library of trisubstituted bis cyclic guanidines from orthogonally protected lysine using the "libraries from libraries" approach.[36] We have also prepared a positional scanning library of the trisubstituted N-acylated guanidines using the "libraries from libraries" approach.[36] The use of these libraries for the identification of active individual compounds will be reported elsewhere.

Experimental Section

4-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.1 mequiv/g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex International (Wood Dale, IL). Boc, Fmoc-diamino acid derivatives, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience, Inc. (Philadelphia, PA). HF was purchased from Air Products (San Marcos, CA). All other reagents and anhydrous solvents were purchased from Aldrich Chemical

Co. (Milwaukee, WI). Analytical RP-HPLC was performed on a Beckman System Gold Instrument (Fullerton, CA). Purification of the samples was made using a Vydac 218TP54 C18 column (0.46 cm × 25 cm). LC−MS (ESI and APCI) were recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at $\lambda = 214$ nm, using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column. High-resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Facility of the University of California at Riverside.

Typical Procedure for the Individual Synthesis of Cyclic Guanidines, Their Bis Analogues, and N-Acylated Guanidines. A total of 100 mg of MBHA resin was sealed inside a polypropylene mesh packet.[37] Polypropylene bottles were used for all the reactions. The resin was washed with dichloromethane (DCM) followed by neutralization with 5% DIEA in DCM and washed with DCM.

(1) Coupling of an Amino Acid to the Resin. (a) Disubstituted Cyclic Guanidines (See Scheme 2). Boc-amino acid (6 equiv, 0.1 M in DMF) was coupled to MBHA resin using the classical coupling reagents DIC and HOBt (6 equiv each) for 2 h at room temperature followed by washes with DMF (3 times) and DCM (3 times). The Boc group was deprotected using 55% TFA in DCM for 30 min followed by neutralization with 5% DIEA in DCM. N-acylation at the primary amine of the amino acids was carried out with a carboxylic acid (10 equiv, 0.1 M in DMF, overnight) using DIC and HOBt (10 equiv each), followed by washes with DMF (3 times) and DCM (3 times).

(b) Trisubstituted Bis Cyclic Guanidines from Orthogonally Protected Diamino Acids (See Scheme 3). Orthogonally protected diamino acid, Fmoc-(Boc)-diamino acid (2.5 equiv, 0.05 M in DMF, overnight) (e.g., N^{α}-Fmoc-N^{β}-Boc-diaminopropionic acid, N^{α}-Fmoc- N^{γ}-Boc-diaminobutyric acid, N^{α}-Fmoc-N^{δ}-Boc-ornithine, and N^{α}-Fmoc-N^{ϵ}-Boc-lysine), was coupled to MBHA resin using DIC and HOBt (2.5 equiv each) at room temperature. After washes with DMF (4 times), the Fmoc group was removed using 20% piperidine in DMF for 30 min, followed by washing with DMF (4 times) and DCM (3 times). After neutralization, N-acylation with a carboxylic acid, deprotection of the Boc group from the side chain, coupling of the Boc-amino acid, followed by deprotection of the Boc group, and N-acylation of the dipeptide with a carboxylic acid were performed in the same manner as described above. Completeness of the coupling was verified by the ninhydrin test.[38]

(2) Exhaustive reduction of amide groups by BH_3−THF. Exhaustive reduction of the N-acylated amino acid amides or N-acylated dipeptides was carried out in 50 mL glass conical tubes under nitrogen. To each tube was added the resin packet (0.110 mequiv of resin, 100 mg of starting resin) and boric acid (12 equiv) followed by trimethyl borate (12 equiv). Borane−THF complex (1 M, 40 equiv) was added slowly. After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h followed by decantation of the reaction solution and quenching with MeOH. After washes with DMF and MeOH (4 times), the resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[30] After decantation of the piperidine−borane solution, the resin packet was washed with DMF (4 times), DCM (4 times), and MeOH (2 times) and was dried.

(3) Cyclization To Form the Cyclic Guanidines and Their Bis Analogues. The resin-bound diamines and tetraamines were treated with cyanogen bromide (10 equiv, 0.1 M in DCM, overnight) for both disubstituted guanidines (see Scheme 2) and their bis analogues (see Scheme 3), respectively, under nitrogen followed by washes with DCM (3 times), IPA (2 times), and DCM (3 times). The resin was cleaved by anhydrous HF in the presence of anisole at 0 °C for 1.5 h,[39] and the cleaved product was extracted with 95% acetic acid in H_2O and was lyophilized.

(4) N-Acylation of Resin-Bound Cyclic Guanidines. The resin-bound cyclic guanidines were N-acylated with a range of carboxylic acids (25 equiv, 0.16 M in DMF) in the presence of HBTU (25 equiv) and DIEA (50 equiv) at room temperature for 26 h (see Scheme 4). The resin was washed with DMF (5 times), IPA (2 times), and DCM (3 times). The final product was cleaved from the solid support using anhydrous HF in the presence of anisole for 1.5 h at 0 °C.[39] The final compound was extracted with 95% acetic acid in water and lyophilized. All washes with DCM, DMF, IPA, MeOH, or 5% DIEA in DCM were for 2 min each.

1-Isopentyl-5-methylimidazolidin-2-imine (5a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88−0.90 (dd, $J = 4.5$ Hz, $J = 6.6$ Hz, 6H), 1.20−1.21 (d, $J = 6.1$ Hz, 3H), 1.27−1.35 (m, 1H), 1.39−1.45 (m, 1H), 1.53−1.58 (m, 1H), 3.07−3.13 (m, 2H), 3.38−3.44 (m, 1H), 3.66 (t, $J = 9.1$ Hz, 1H), 3.98−4.02 (m, 1H), 8.00−8.03 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.57, 22.13, 22.40, 25.27, 34.91, 47.70, 53.88, 157.76. HRMS (DCI): m/z 170.1665 found ($[M + H]^+$), 170.1657 calculated for $C_9H_{20}N_3$ ($[M + H]^+$).

5-Benzyl-1-(2-phenylethyl)imidazolidin-2-imine (5b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.73−2.77 (m, 2H), 2.87−2.88 (m, 1H), 3.04−3.06 (d, $J = 10.3$ Hz, 1H), 3.22−3.23 (d, $J = 6.1$ Hz, 1H), 3.38−3.44 (m, 2H), 3.73−3.76 (m, 1H), 4.14 (m, 1H), 7.23−7.31 (m, 10H), 7.79 (s, 1H), 7.91 (s, 2H).

5-Benzyl-1-butylimidazolidin-2-imine (5c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88 (t, $J = 7.3$ Hz, 3H), 1.23−1.28 (m, 2H), 1.43−1.48 (m, 1H), 1.51−1.55 (m, 1H), 2.74−2.79 (dd, $J = 8.3$ Hz, $J = 13.6$ Hz, 1H), 3.05−3.08 (dd, $J = 4.3$ Hz, $J = 13.6$ Hz, 1H), 3.16−3.25 (m, 2H), 3.43−3.49 (m, 2H), 4.22−4.24 (m, 1H), 7.23−7.33 (m, 5H), 8.01 (s, 2H), 8.05 (s, 1H).

5-Benzyl-1-isopentylimidazolidin-2-imine (5d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84−0.86 (d, $J = 6.6$ Hz, 3H), 0.88−0.89 (d, $J = 6.5$ Hz, 3H), 1.32−1.36 (m, 1H), 1.42−1.45 (m, 1H), 1.49−1.53 (m, 1H), 2.76−2.81 (dd, $J = 7.9$ Hz, $J = 13.6$ Hz, 1H), 3.01−3.05 (dd, $J = 4.7$ Hz, $J = 13.7$ Hz, 1H), 3.11−3.17 (m, 1H), 3.22−3.25 (dd, $J = 6.0$ Hz, $J = 9.5$ Hz, 1H), 3.45−3.50 (m, 2H), 4.22−4.25 (m, 1H), 7.23−7.25 (m, 5H), 7.91 (s, 1H), 7.91 (s, 2H).

5-Isobutyl-1-(2-phenylethyl)imidazolidin-2-imine (5e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.80−0.82 (d, $J = 6.0$ Hz, 3H), 0.87−0.88 (d, $J = 6.1$ Hz, 3H), 1.28−1.32 (dd, $J = 1.3$ Hz, $J = 11.5$ Hz, 1H), 1.50−1.55 (m, 2H), 2.73−2.77 (m, 1H), 2.82−2.86 (m, 1H), 3.16 (t, $J = 3.5$ Hz, 1H),

3.34−3.40 (m, 1H), 3.59 (t, J = 9.0 Hz, 1H), 3.66−3.70 (m, 1H), 3.78 (m, 1H), 7.22−7.33 (m, 5H), 8.02 (s, 2H), 8.05 (s, 1H).

5-Methyl-1-(2-phenylethyl)imidazolidin-2-imine (5f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20−1.21 (d, J = 6.2 Hz, 3H), 2.72−2.76 (m, 1H), 2.84−2.90 (m, 1H), 3.08 (t, J = 8.2 Hz, 1H), 3.33−3.39 (m, 1H), 3.59−3.69 (m, 2H), 3.93−3.98 (m, 1H), 7.22−7.32 (m 5H), 8.04 (s, 2H), 8.08 (m, 1H).

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]methyl}-4-benzyl-2-imidazolidinimine (12a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.73−2.78 (m, 4H), 2.84−2.88 (m, 3H), 2.95−3.01 (m, 3H), 3.25−3.51 (m, 4H), 3.69−3.72 (m, 1H), 3.79−3.82 (m, 1H), 3.93−3.96 (m, 1H), 4.04−4.07 (m, 1H), 7.20−7.34 (m, 15H), 8.15 (s, 2H), 8.21 (d, J = 3.93 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.29, 32.39, 36.78, 43.27, 43.40, 43.99, 46.11, 50.79, 55.40, 56.84, 126.88, 128.88, 128.93, 129.34, 135.79, 137.81, 156.75, 157.85.

3-Butyl-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]methyl}-4-benzyl-2-imidazolidinimine (12b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86 (t, J = 7.4 Hz, 3H), 1.21−1.26 (m, 2H), 1.39−1.42 (m, 1H), 1.49−1.53 (m, 1H), 2.73−2.79 (m, 2H), 2.86 (m, 1H), 2.96−2.99 (q, J = 5.2 Hz, J = 10.0 Hz, 1H), 3.01−3.05 (dd, J = 3.9 Hz, J = 13.7 Hz, 1H), 3.23−3.59 (m, 8H), 3.71 (m, 1H), 3.96−3.98 (m, 1H), 4.21−4.22 (m, 1H), 7.22−7.35 (m, 10H), 8.16 (s, 2H), 8.20 (s, 2H), 8.24 (s, 1H). HRMS (DCI): m/z 433.3076 found ([M + H]$^+$), 433.3079 calculated for $C_{26}H_{37}N_6$ ([M + H]$^+$).

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]ethyl}-4-benzyl-2-imidazolidinimine (13a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.40 (m, 1H), 1.72−1.74 (m, 1H), 2.71−2.92 (m, 5H), 3.03−3.06 (dd, J = 4.14 Hz, J = 13.7 Hz, 1H), 3.10 (t, J = 7.81 Hz, 2H), 3.24−3.29 (m, 5H), 3.32−3.53 (m, 2H), 3.66 (m, 1H), 3.78−3.83 (m, 1H), 4.10−4.11 (m, 1H), 7.22−7.33 (m, 15H), 8.03 (s, 1H), 8.05 (s, 2H), 8.07 (2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.58, 32.21, 32.47, 36.82, 40.24, 42.57, 43.31, 45.25, 55.75, 56.55, 126.57, 126.78, 128.36, 128.47, 128.88, 128.99, 129.40, 135.92, 137.84, 137.92, 155.90, 157.70.

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]ethyl}-4-methyl-2-imidazolidinimine (13c). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.21−1.22 (d, J = 6.0 Hz, 3H), 1.62−1.65 (m, 1H), 1.94−1.96 (m, 1H), 2.72−2.78 (m, 2H), 2.84−2.90 (m, 2H), 3.13−3.16 (q, J = 8.1 Hz, 1H), 3.25−3.28 (m, 2H), 3.33−3.42 (m, 3H), 3.55 (t, J = 9.7 Hz, 1H), 3.67−3.72 (m, 3H), 3.88−3.94 (m, 2H), 7.21−7.34 (m, 10H), 8.14 (s, 2H), 8.17 (s, 2H), 8.28 (s, 1H). HRMS (DCI) m/z 419.2927 found ([M + H]$^+$), 419.2923 calculated for $C_{25}H_{35}N_6$ ([M + H]$^+$).

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]propyl}-4-benzyl-2-imidazolidinimine (14a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.08−1.11 (m, 1H), 1.18−1.29 (m, 2H), 1.45−1.47 (m, 1H), 2.73−2.89 (m, 5H), 2.97−3.0 (dd, J = 4.0 Hz, J = 13.7 Hz, 1H), 3.10−3.17 (m, 3H), 3.24−3.28 (m, 2H), 3.48−3.51 (m, 2H), 3.57 (t, J = 9.7 Hz, 1H), 3.67−3.69 (m, 1H), 3.80−3.83 (m, 1H), 3.89−3.90 (m, 1H), 4.11−4.12 (m, 1H), 7.20−7.31 (m, 15H), 8.08 (s, 2H), 8.15 (s, 2H), 8.30 (s, 1H). HRMS (DCI): m/z 509.3349 found ([M + H]$^+$), 509.3393 calculated for $C_{32}H_{41}N_6$ ([M + H]$^+$).

3-Butyl-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]propyl}-4-benzyl-2-imidazolidinimine (14b). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.89 (t, J = 7.71 Hz, 3H), 1.12−1.13 (m, 2H), 1.25−1.30 (m, 3H), 1.43−1.56 (m, 3H), 2.57−2.58 (m, 1H), 2.63 (m, 1H), 2.70−2.75 (m, 1H), 2.78−2.87 (m, 1H), 2.98−3.02 (d, J = 4.13 Hz, 1H), 3.10−3.16 (m, 3H), 3.24−3.40 (m, 2H), 3.47−3.48 (m, 2H), 3.54−3.59 (m, 1H), 3.66 (m, 1H), 3.89 (m, 1H), 4.20 (m, 1H), 7.22−7.32 (m, 10H), 7.95 (s, 3H), 7.98 (2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.63, 19.17, 20.68, 27.37, 28.67, 32.22, 36.59, 39.01, 41.87, 42.41, 43.93, 45.31, 49.73, 56.37, 57.31, 126. 59, 126.75, 128.38, 128.45, 128.89, 129.45, 135.83, 137.85, 156.00, 157.73.

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.04 (m, 2H), 1.27−1.30 (m, 2H), 1.40−1.42 (m, 1H), 1.64−1.65 (m, 1H), 2.74−2.82 (m, 3H), 2.85−2.89 (m, 2H), 2.99−3.02 (dd, J = 4.2 Hz, J = 13.6 Hz, 1H), 3.07−3.17 (m, 3H), 3.23−3.26 (dd, J = 5.8 Hz, J = 9.8 Hz, 1H), 3.33−3.35 (m, 1H), 3.44−3.59 (m, 2H), 3.68−3.71 (m, 2H), 3.78−3.84 (m, 2H), 4.08−4.12 (m, 1H), 7.22−7.33 (m, 15H), 8.04 (s, 2H), 8.08 (s, 2H), 8.18 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.35, 25.77, 30.37, 32.39, 32.48, 36.86, 42.44, 43.35, 43.93, 45.53, 49.76, 56.51, 57.72, 126.54, 126.79, 128.36, 128.38, 128.47, 128.91, 128.99, 129.40, 135.95, 137.97, 155.95, 157.88.

3-(2-Phenylethyl)-1-[(3-isobutyl-2-imino-4-imidazolidinyl)butyl]-4-benzyl-2-imidazolidinimine (15d). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.82−0.84 (d, J = 6.4 Hz, 3H), 0.90−0.91 (d, J = 6.6 Hz, 3H), 1.04−1.06 (m, 2H), 1.28−1.32 (m, 2H), 1.40−1.42 (m, 1H), 1.64−1.65 (m, 1H), 1.88−1.90 (m, 1H), 2.88−2.89 (m, 1H), 2.74−2.80 (m, 2H), 2.95−3.03 (m, 2H), 3.07−3.11 (m, 2H), 3.16−3.26 (m, 4H), 3.46−3.50 (m, 1H), 3.65 (t, J = 9.4 Hz, 1H), 3.79 (m, 1H), 3.87−3.88 (m, 1H), 4.09−4.10 (m, 1H), 7.22−7.33 (m, 10H), 7.99−8.01 (m, 4H), 8.08 (s, 1H).

3-(2-Phenylethyl)-1-{[3-(3-methylpentyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15e). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.87 (d, J = 6.6 Hz, 6H), 1.03−1.15 (m, 4H), 1.27−1.31 (m, 2H), 1.38−1.43 (m, 2H), 1.49−1.56 (m, 2H), 1.64−1.66 (m, 1H), 2.74−2.80 (m, 2H), 2.87−2.89 (m, 1H), 2.99−3.18 (m, 5H), 3.23−3.26 (dd, J = 5.7 Hz, J = 9.8 Hz, 1H), 3.35−3.38 (m, 1H), 3.44−3.50 (m, 2H), 3.63 (t, J = 9.4 Hz, 1H), 3.78−3.80 (m, 1H), 3.88−3.90 (m, 1H), 4.08−4.10 (m, 1H), 7.21−7.33 (m, 10H), 8.03 (s, 4H), 8.14 (s, 1H).

3-Isobutyl-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15f). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.83−0.84 (d, J = 6.6 Hz, 3H), 0.89−0.90 (d, J = 6.4 Hz, 3H), 1.03−1.06 (m, 2H), 1.27−1.31 (m, 2H), 1.39−1.41 (m, 1H), 1.64−1.65 (m, 1H), 1.95−1.98 (m, 1H), 2.73−2.86 (m, 3H), 2.99−3.02 (dd, J = 4.0 Hz, J = 13.7 Hz, 1H), 3.08−3.16 (m, 4H), 3.16−3.26 (m, 4H), 3.50−3.68 (m, 2H), 3.82−3.84 (m, 1H), 4.16−4.18 (m, 1H), 7.21−7.33 (m, 10H), 7.96 (s, 2H), 8.04 (s, 2H), 8.09 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 19.13, 19.49, 20.34, 25.79, 26.04, 30.36, 32.37, 36.40, 42.42, 43.91, 45.50,

48.52, 49.47, 56.63, 57.71, 126.56, 126.79, 128.38, 128.46, 128.91, 129.42, 135.91, 137.95, 156.15, 157.83.

3-(4-Methylpentyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.87 (d, J = 6.70 Hz, 6H), 1.04−1.14 (m, 4H), 1.29−1.32 (m, 2H), 1.40−1.46 (m, 2H), 1.52−1.57 (m, 2H), 1.64 (m, 1H), 2.74−2.86 (m, 3H), 3.00−3.04 (dd, J = 4.1 Hz, J = 13.7 Hz, 1H), 3.12−3.33 (m, 6H), 3.46−3.58 (m, 2H), 3.68−3.70 (m, 2H), 3.81−3.83 (m, 1H), 4.19−4.20 (m, 1H), 7.22−7.33 (m, 10H), 8.09 (s, 2H), 8.15 (s, 2H), 8.32 (s, 1H). HRMS (DCI): *m*/*z* 503.3841 found ([M + H]$^+$), 503.3862 calculated for $C_{31}H_{47}N_6$ ([M + H]$^+$).

3-(2-Phenylethyl)-1-{[3-(3-cyclohexylpropyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15h). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.84−0.89 (m, 2H), 1.04−1.22 (m, 8H), 1.29−1.31 (m, 2H), 1.40−1.43 (m, 2H), 1.51−1.67 (m, 8H), 2.74−2.80 (m, 2H), 2.87−2.89 (m, 1H), 2.99−3.18 (m, 5H), 3.23−3.26 (dd, J = 5.6 Hz, J = 9.7 Hz, 1H), 3.35−3.49 (m, 2H), 3.63 (t, J = 9.5 Hz, 1H), 3.79−3.89 (m, 2H), 4.08−4.09 (m, 1H), 7.22−7.33 (m, 10H), 8.08 (s, 4H), 8.25 (s, 1H).

3-Cyclohexylmethyl-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15i). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86−0.96 (m, 3H), 1.02−1.30 (m, 5H), 1.40 (m, 1H), 1.56−1.68 (m, 6H), 2.74−2.86 (m, 3H), 2.97−3.01 (dd, J = 4.0 Hz, J = 13.7 Hz, 1H), 3.08−3.16 (m, 4H), 3.25−3.28 (dd, J = 5.1 Hz, J = 9.8 Hz, 1H), 3.31−3.39 (m, 3H), 3.54−3.61 (m, 3H), 3.65−3.70 (m, 1H), 3.81−3.83 (m, 1H), 4.15−4.16 (m, 1H), 7.22−7.33 (m, 10H), 7.97 (s, 2H), 8.09 (s, 2H), 8.21 (s, 1H).

3-(3-Cyclopentylpropyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15j). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05−1.06 (m, 4H), 1.22−1.32 (m, 4H), 1.41−1.50 (m, 4H), 1.55−1.59 (m, 3H), 1.64−1.75 (m, 4H), 2.74−2.86 (m, 3H), 3.00−3.04 (dd, J = 4.1 Hz, J = 13.7 Hz, 1H), 3.11−3.34 (m, 5H), 3.46−3.58 (m, 3H), 3.66−3.70 (m, 2H), 3.81−3.83 (m, 1H), 4.18−4.20 (m, 1H), 7.22−7.33 (m, 10H), 8.04 (s, 2H), 8.10 (m, 2H), 8.22 (m, 1H).

3-[2-(1,1′-Biphenyl-4-yl)ethyl]-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15k). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.03−1.04 (m, 2H), 1.25−1.37 (m, 3H), 1.61−1.63 (m, 1H), 2.73−2.94 (m, 6H), 3.02−3.15 (m, 4H), 3.24−3.31 (m, 2H), 3.48−3.57 (m, 3H), 3.67−3.69 (m, 1H), 3.80−3.85 (m, 2H), 4.14−4.15 (m, 1H), 7.23−7.46 (m, 14H), 7.61−7.65 (m, 4H), 8.07 (s, 2H), 8.09 (s, 2H), 8.20 (s, 1H). HRMS (DCI): *m*/*z* 599.3855 found ([M + H]$^+$), 599.3862 calculated for $C_{39}H_{47}N_6$ ([M + H]$^+$).

3-(2-Phenylethyl)-1-{[3-(2-bicyclo[2.2.1]hept-2-ylethyl)-2-imino-4-imidazolidinyl]butyl}-4-benzyl-2-imidazolidinimine (15l). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.04−1.14 (m, 6H), 1.19−1.51 (m, 10H), 1.63 (m, 1H), 2.00 (s, 1H), 2.17 (s, 1H), 2.74−2.82 (m, 2H), 2.86−2.90 (m, 1H), 2.99−3.18 (m, 5H), 3.23−3.26 (dd, J = 5.6 Hz, J = 9.7 Hz, 1H), 3.37−3.50 (m, 3H), 3.62 (t, J = 9.5 Hz, 1H), 3.79−3.81 (m, 1H), 3.88−3.90 (m, 1H), 4.09 (m, 1H), 7.22−7.33 (m, 10H), 8.05 (s, 4H), 8.18 (s, 1H).

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-phenyl-2-imidazolidinimine (15m). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.17−1.19 (m, 2H), 1.46−1.56 (m, 3H), 1.71−1.75 (m, 1H), 2.60−2.62 (m, 1H), 2.75−2.80 (m, 2H), 2.86−2.93 (m, 2H), 3.19 (t, J = 8.0 Hz, 1H), 3.30−3.38 (m, 3H), 3.43−3.46 (m, 2H), 3.59 (t, J = 9.4 Hz, 1H), 3.67−3.72 (m, 1H), 3.85−3.88 (m, 1H), 4.00 (t, J = 10.0 Hz, 1H), 4.92−4.95 (dd, J = 7.4 Hz, J = 9.6 Hz, 1H), 7.14−7.47 (m, 15H), 8.07 (s, 2H), 8.16 (s, 1H), 8.31 (s, 2H).

3-(2-Phenylethyl)-1-{[3-(2-phenylethyl)-2-imino-4-imidazolidinyl]butyl}-4-(1-naphthylmethyl)-2-imidazolidinimine (15n). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.94−0.95 (m, 2H), 1.11−1.16 (m, 2H), 1.26 (m, 1H), 1.50 (m, 1H), 2.73 (m, 1H), 2.82−2.85 (m, 1H), 2.91−2.98 (m, 2H), 3.04−3.10 (m, 3H), 3.16−3.19 (dd, J = 4.1 Hz, J = 13.7 Hz, 1H), 3.28−3.34 (m, 2H), 3.49−3.58 (m, 2H), 3.65−3.76 (m, 3H), 3.83−3.86 (m, 2H), 4.18−4.22 (m, 1H), 7.21−7.51 (m, 13H), 7.75 (s, 1H), 7.83−7.89 (m, 3H), 8.02 (s, 2H), 8.06 (s, 2H), 8.13 (s, 1H). HRMS (DCI): *m*/*z* 573.3700 found ([M + H]$^+$), 573.3705 calculated for $C_{37}H_{45}N_6$ ([M + H]$^+$).

***N*-[(2*Z*)-1-Ethyl-5-methylimidazolidin-2-ylidene]-2-phenylacetamide (17a).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.13 (t, J = 6.9 Hz, 3H), 1.27−1.28 (d, J = 6.0 Hz, 3H), 3.26−3.29 (q, J = 8.2 Hz, J = 18.5 Hz, 2H), 3.35−3.39 (m, 1H), 3.71−3.76 (m, 1H), 3.85 (t, J = 10.6 Hz, 1H), 3.92 (s, 1H), 4.11−4.14 (m, 1H), 7.26−7.34 (m, 5H), 9.34 (s, 1H), 11.61 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.61, 17.75, 36.97, 42.31, 48.99, 53.08, 127.01, 128.35, 129.53, 133.79. HRMS (DCI): *m*/*z* 246.1606 found ([M + H]$^+$), 246.1606 calculated for $C_{14}H_{20}N_3O$ ([M + H]$^+$).

***N*-[(2*Z*)-5-Methyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-2-phenylacetamide (17b).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.26−1.27 (d, J = 6.1 Hz, 3H), 2.80−2.85 (m, 1H), 2.89−2.95 (m, 1H), 3.26−3.29 (dd, J = 8.1 Hz, J = 9.8 Hz, 1H), 3.53−3.55 (m, 1H), 3.75−3.84 (m, 3H), 4.04−4.10 (m, 2H), 7.22−7.39 (m, 10H), 9.34 (s, 1H), 11.38 (s, 1H). HRMS (DCI): *m*/*z* 322.1912 found ([M + H]$^+$), 322.1919 calculated for $C_{20}H_{24}N_3O$ ([M + H]$^+$).

***N*-[(2*Z*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-2-phenylacetamide (17c).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.82−2.95 (m, 3H), 3.08−3.12 (dd, J = 4.6 Hz, J = 13.6 Hz, 1H), 3.37−3.41 (m, 1H), 3.53−3.56 (m, 1H), 3.60−3.64 (m, 1H), 3.71−3.82 (m, 2H), 4.15−4.16 (m, 1H), 4.32 (m, 1H), 7.21−7.35 (m, 15H), 9.27 (s, 1H), 11.58 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 32.71, 36.83, 43.68, 46.37, 57.13, 126.65, 126.88, 127.00, 128.33, 128.41, 128.55, 129.00, 129.20, 129.43, 129.46, 135.72, 137.78. HRMS (DCI): *m*/*z* 398.2224 found ([M + H]$^+$), 398.2232 calculated for $C_{26}H_{28}N_3O$ ([M + H]$^+$).

***N*-[(2*Z*)-5-Isopropyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-2-phenylacetamide (17d).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.75−0.77 (d, J = 6.6 Hz, 3H), 0.84−0.86 (d, J = 6.9 Hz, 3H), 2.17−2.20 (m, 1H), 2.84−2.95 (m, 2H), 3.45−3.49 (m, 2H), 3.65 (t, J = 11.2 Hz, 1H), 3.73−3.83 (m, 2H), 4.06 (m, 1H), 4.16−4.19 (m, 1H), 7.21−7.35 (m, 10H), 9.36 (s, 1H), 11.6 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-ethylimidazolidin-2-ylidene]-2-phenylacetamide (17e).** ^{1}H NMR (500 MHz, DMSO-d_6):

δ 1.17 (t, J = 6.9 Hz, 3H), 2.80−2.84 (q, J = 8.8 Hz, J = 12.6 Hz, 1H), 3.13−3.16 (dd, J = 4.2 Hz, J = 13.4 Hz, 1H), 3.63 (m, 3H), 3.82−3.89 (m, 3H), 4.37 (m, 1H), 7.24−7.35 (m, 10H), 9.35 (s, 1H), 11.55 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-butylimidazolidin-2-ylidene]-2-phenylacetamide (17f).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88 (t, J = 7.5 Hz, 3H), 1.23−1.29 (m, 2H), 1.48−1.59 (m, 2H), 2.82−2.87 (q, J = 8.0 Hz, J = 13.4 Hz, 1H), 3.09−3.13 (dd, J = 4.4 Hz, J = 13.6 Hz, 1H), 3.27−3.32 (m, 1H), 3.38−3.49 (m, 1H), 3.68 (t, J = 10.5 Hz, 1H), 3.77−3.83 (m, 1H), 3.89 (m, 2H), 4.36 (s, 1H), 7.23−7.35 (m, 10H), 9.33 (s, 1H), 11.6 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-(cyclobutylmethyl)imidazolidin-2-ylidene]-2-phenylacetamide (17g).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65−1.68 (m, 1H), 1.77−1.90 (m, 3H), 1.93−1.97 (m, 1H), 2.05−2.07 (m, 1H), 2.62−2.68 (m, 1H), 2.81 (m, 1H), 3.10−3.14 (dd, J = 4.3 Hz, J = 13.6 Hz, 2H), 3.64 (m, 2H), 3.89 (m, 3H), 4.26 (m, 1H), 7.24−7.35 (m, 10H), 9.35 (s, 1H), 11.55 (s, 1H).

***N*-{(2*Z*)-5-Benzyl-1-[2-(4-ethoxyphenyl)ethyl]imidazolidin-2-ylidene}-2-phenylacetamide (17h).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.28−1.31 (t, J = 7.0 Hz, 3H), 2.81−2.85 (m, 3H), 3.07−3.11 (dd, J = 4.5 Hz, J = 13.6 Hz, 1H), 3.62−3.79 (m, 5H), 3.91−3.97 (m, 2H), 4.08 (m, 1H), 4.32 (m, 1H), 6.82−6.84 (d, J = 8.2 Hz, 2H), 7.16−7.35 (m, 12H), 9.25 (s, 1H), 11.35 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-3-methylbutanamide (17i).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.88 (t, J = 6.6 Hz, 6H), 1.90−1.96 (m, 1H), 2.22−2.30 (m, 2H), 2.82−2.94 (m, 2H), 3.08−3.11 (dd, J = 4.5 Hz, J = 13.6 Hz, 1H), 3.42 (m, 2H), 3.53−3.56 (m, 1H), 3.65 (t, J = 10.2 Hz, 1H), 4.09−4.12 (m, 1H), 4.35 (m, 1H), 7.20−7.34 (m, 10H), 9.29 (s, 1H), 10.99 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-butanamide (17j).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86 (t, J = 7.0 Hz, 3H), 1.47−1.51 (m, 2H), 2.29−2.41 (m, 2H), 2.82−2.91 (m, 3H), 3.08−3.12 (dd, J = 4.6 Hz, J = 13.6 Hz, 1H), 3.39−3.42 (q, J = 5.8 Hz, J = 10.8 Hz, 1H), 3.51−3.56 (m, 1H), 3.65 (t, J = 10.7 Hz, 1H), 4.09−4.14 (m, 1H), 4.35 (m, 1H), 7.20−7.35 (m, 10H), 9.27 (s, 1H), 11.15 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-2-(3-methylphenyl)acetamide (17k).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.28 (s, 3H), 2.85−2.86 (m, 2H), 2.90−2.95 (m, 2H), 3.08−3.12 (dd, J = 4.6 Hz, J = 13.6 Hz, 1H), 3.63−3.72 (m, 4H), 4.11 (m, 1H), 4.32 (m, 1H), 7.02−7.09 (m, 3H), 7.20−7.34 (m, 11H), 9.28 (s, 1H), 11.34 (s, 1H).

***N*-[(2*Z*)-5-Benzyl-1-(2-phenylethyl)imidazolidin-2-ylidene]-cyclobutanecarboxamide (17l).** ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.76−1.81 (m, 1H), 1.89−1.94 (m, 1H), 2.04−2.12 (m, 4H), 2.81−2.91 (m, 3H), 3.08−3.11 (dd, J = 4.5 Hz, J = 13.6 Hz, 1H), 3.29−3.32 (m, 1H), 3.39−3.42 (q, J = 5.7 Hz, J = 10.8 Hz, 1H), 3.49−3.54 (m, 1H), 3.65 (t, J = 10.7 Hz, 1H), 4.09−4.14 (m, 1H), 4.35 (m, 1H), 7.19−7.34 (m, 10H), 9.30 (s, 1H), 11.11 (s, 1H).

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Supporting Information Available. LC−MS of individual cyclic guanidines, their bis analogues, and N-acylated guanidines, and HRMS and NMR spectra (both ^{1}H and ^{13}C) of some selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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