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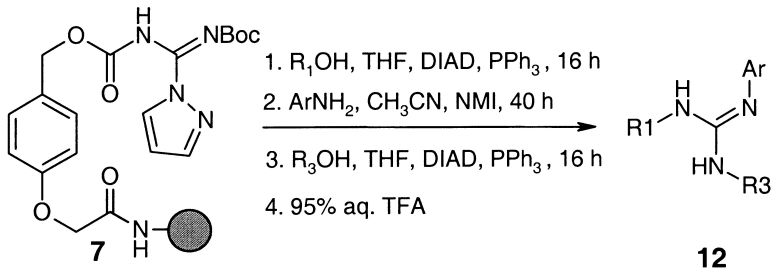

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Solid-Phase Synthesis of Substituted Guanidines Using a Novel Acid Labile Linker

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A novel acid labile linker for solid-phase synthesis of substituted guanidines has been developed. Its synthetic utility is exemplified by high-yielding pyrazole displacement with structurally and electronically diverse sets of aliphatic and aromatic amines. The final cleavage is achieved by treatment with 95:5 trifluoroacetic acid/water for 1 h. The corresponding guanidines were obtained in high purity (80−95%) and good isolated yields (50−95%). The scope and limitations of this linker were further demonstrated by the solid-phase synthesis of an 880-member library of individual trisubstituted arylguanidines employing pyrazole displacement with a set of 11 anilines and two subsequent Mitsunobu N-alkylations with sets of 10 and 8 alcohols, respectively.

Introduction

Compounds containing guanidine functionality have been widely utilized in the area of pharmaceuticals or as probes for investigating biochemical processes.[1] Reported biological activities of organic molecules containing the (alkyl)-guanidine moiety can be mainly attributed to the strongly basic carboxamidine group (pK_a ∼ 12). The guanidinium moiety, which is fully protonated under physiological conditions, may interact with other functional groups present in receptors or enzymes on the basis of hydrogen bonds and electrostatic interactions. Substituted guanidines including less basic arylguanidines have also been reported to exhibit antihypertensive, H_2 antagonist/agonist, and antiglaucoma activities.[1]

The current literature reveals a growing number of examples of solid-phase syntheses of guanidines utilizing either linkers or guanylating reagents.[2] Moreover, a number of solution-phase methods and reagents for converting amines to guanidines have been recently published.[3] In developing a new strategy for the synthesis of "guanidine"- based combinatorial libraries, we focused on the ability to synthesize a fully protected and structurally defined form of a guanidine precursor that could be easily attached to solid support prior to the synthesis.

Results and Discussion

Inspired by the recently published guanylating agent 1-*H*-pyrazole-1-[*N*,*N*′-bis(*tert*-butoxycarbonyl)]carboxamidine,[4] we envisioned a straightforward protecting group linker strategy for synthesis of *p*-alkoxybenzyl carbamate-based linker **1**. As illustrated in Scheme 1, dicyclohexylamine salt of the linker **1** was obtained in five steps from commercially available (4-hydroxymethyl)phenoxyacetic acid **2** in 36% overall yield. In the first step, (4-hydroxymethyl)phenoxyacetic acid **2** was reacted with an excess of allylbromide in the presence of $KHCO_3$−Aliquat 336 to provide **3** in 80% yield. Reaction of **3** with 4-nitrophenyl chloroformate in the presence of pyridine afforded "activated" carbonate **4** in 84% yield after 12 h.[5] Treatment of **4** with THF solution of 1-*H*-pyrazole-1-carboxamidine for 3 h at room temperature provided **5** in 80% yield. Subsequent protection of the amidine nitrogen of **5** to give **6** was achieved using 3-fold excess of Boc_2O in the presence of 2 equiv of NaH. To minimize N-diacylation, optimal reaction conditions required 1 h reflux in dry THF. Final deprotection of allyl ester using Pd(0)-mediated deallylation with subsequent addition of dicyclohexylamine provided linker **1** as a white crystalline solid after crystallization from $CHCl_3$/EtOAc (1:2). The structural identity of linker **1** was determined by ^1H, ^{13}C NMR, and ES-MS. Using this protocol, we were able to synthesize 26 g of the linker **1** in three batches. It should be mentioned that the overall synthesis sequence was not optimized and that flash-column chromatography purifications were routinely done after steps 1−4.

To investigate the scope and limitations of the new linker, a series of structurally different amines were reacted with the solid-phase-bound linker **7** (Table 1). Attachment of the linker to the TentaGel-NH_2 resin was accomplished using "acidic" coupling conditions to prevent direct displacement of pyrazole with TentaGel-NH_2. Entries **a**−**m** exemplify the general applicability of the linker to a variety of amines. Most primary and secondary aliphatic amines react efficiently with **7**, affording nearly quantitative conversion to **8a**−**m**.[6] Poor nucleophiles such as arylamines did not adversely affect the outcome of the reaction, regardless of the substituents, and provided the corresponding guanidines **8c**,**d** in yields comparable to that of the aliphatic amine series. However, a drop

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Scheme 1

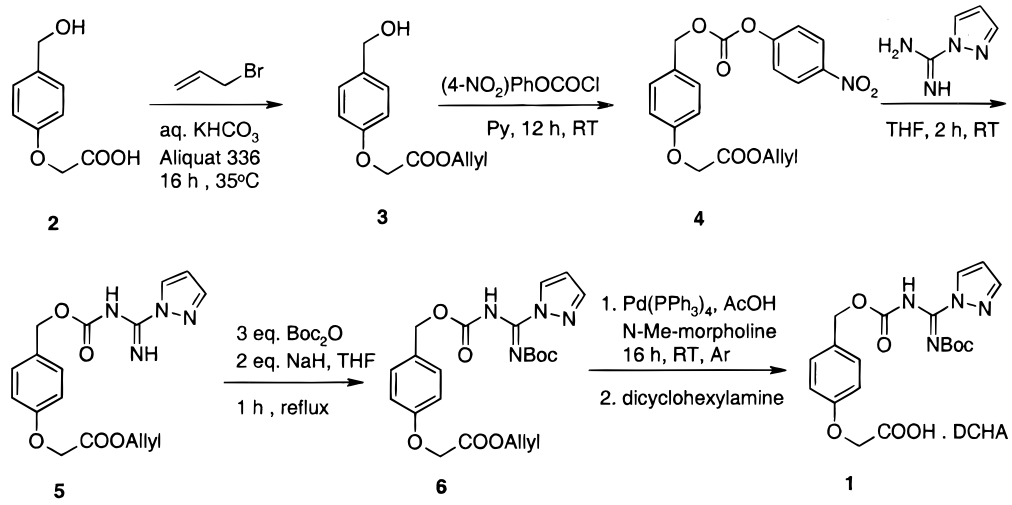
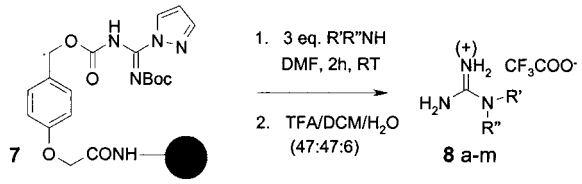
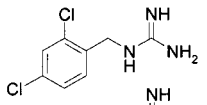
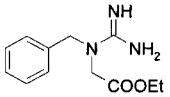
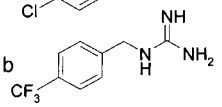
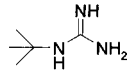
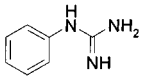
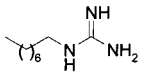
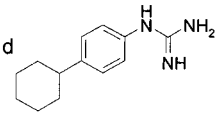
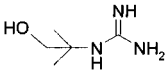
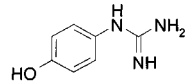
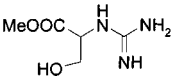
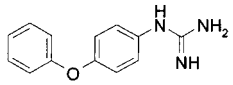
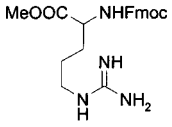
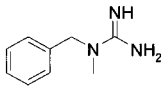


Table 1. Preparation of Substituted Guanidines **8a**−**m**



	Product	Yield (%)[a]		Product	Yield (%)[a]
a		74	h		2[b]
b		85	i		50
c		78	j		71
d		95	k		84
e		70	l		86
f		92	m		56
g		73			

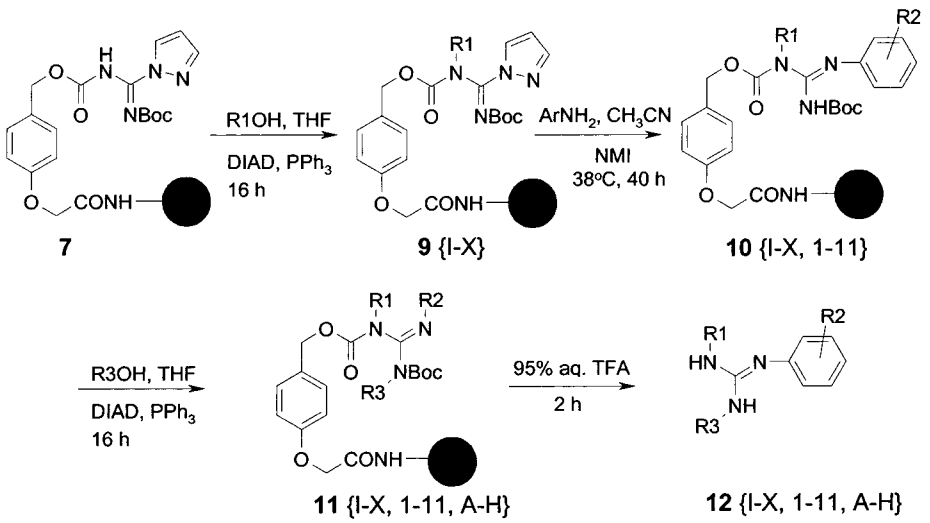
[a] Isolated yields based on the guanidine-TFA salt, purified by reverse-phase HPLC. [b] 95% of 1-*H*-pyrazole-1-carboxamidine was recovered after workup.

in yield ascribable to steric factors was observed in case of *tert*-butylamine. Moderate success was realized using amino acid esters as representatives of bifunctional building blocks. The reactions of Fmoc-Orn-OMe and H-Ser-OMe gave the corresponding Fmoc-Arg-OMe, **8m**, and guanylated serine methylester, **8l**, in 56% and 86% yields, respectively. As a notable exception, *N*-benzyl glycine ethyl ester did not give satisfactory results and provided only 2% of the expected product **8h** with 95% of recovered 1-*H*-pyrazole-1-carboxamidine. The compounds **8a**−**m** were fully characterized by ^{1}H NMR, ^{13}C NMR, and ES-MS.[7]

Library Development

Having established the generality of reaction of amines with linker **7**, we considered the applicability of linker **1** for solid-phase synthesis of trisubstituted guanidines **12 (**Scheme 2**)**. To explore the scope of this reaction sequence[3a] as well as compatibility of building blocks, we tested larger sets of anilines and alcohols by systematically screening entire sets of building blocks while fixing two other positions. Thus, a set of 30 alcohols was evaluated in a model array, keeping 4-aminobiphenyl and 2-bromophenethyl alcohol constant throughout the whole array. Analogous experiments were performed with a set of 22 anilines, while keeping 2-bromophenethyl alcohol in the first position and furfuryl alcohol in the third position constant. Similarly, 30 alcohols were tested in R3-position while fixing furfuryl alcohol and 4-aminobiphenyl. On the basis of the results of such orthogonal building block evaluation (in total, 82 compounds were synthesized), sets of 10 alcohols (I−X), 11 anilines (1−11), and 8 alcohols (A−H) were chosen for the production library of 880 substituted guanidines (Scheme 3). The most important criteria for selection of building blocks were maximum possible structural differences between building blocks and purity of the final products.[8] Since incomplete alkylation was observed for certain alcohols in the third randomization, several conditions for Mitsunobu N-alkylation (solvent, concentration, time) were examined to overcome this problem. Optimal conversions were achieved when using 25 equiv of an alcohol, PPh_3, and diisopropyl azodicarboxylate (DIAD) in THF for 16 h. However, extensive multiple washes of the resin (DCE, DMF, THF) were then necessary to remove remaining $P(O)Ph_3$ before the final cleavage. Satisfactory results were obtained after three optimization runs providing an additional 264 compounds in three 96-deep-well microtiter plates. The expected compounds were observed in 98% of the cases, with 34% of compounds having UV 220 nm purity greater than 75%. When purity was assessed at 50% threshold, the number of accepted compounds increases to 94%. In general, heterocyclic

Scheme 2



Scheme 3

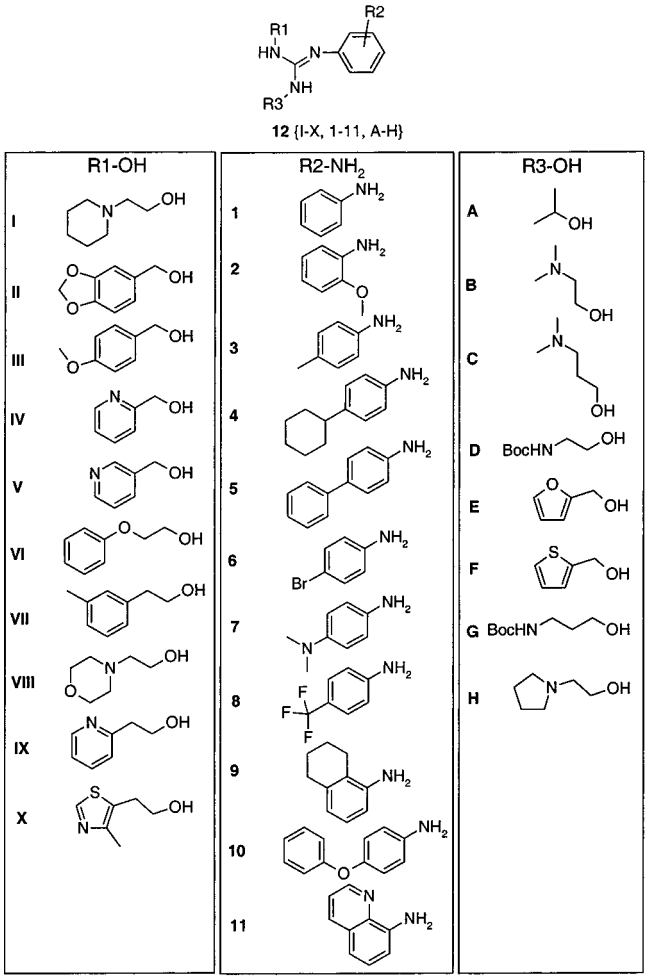
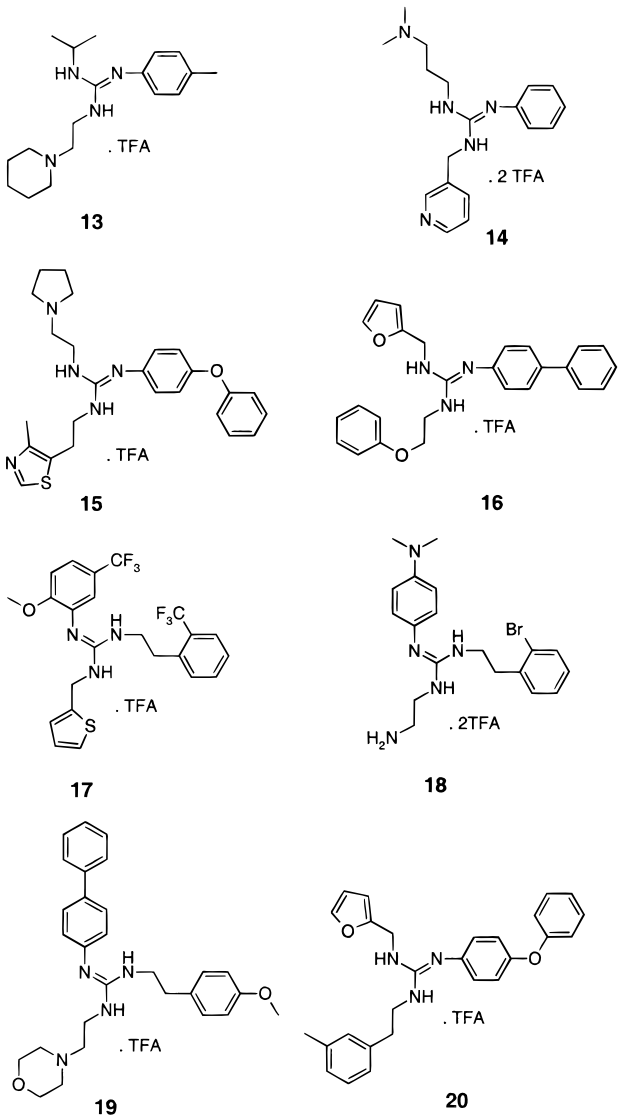


Chart 1



arylamines failed to provide correct compounds, and less hindered alcohols were preferred for the third randomization. Quality and relative quantity of synthesized guanidines were assessed by LC/MS analysis. To estimate chemical yields in a library as well as to confirm the structural identity of library members, eight model compounds **13**−**20** (Chart 1) were synthesized in a larger scale. The structural identity of compounds **13**−**20** was further confirmed by ^{1}H NMR, ^{13}C NMR, and MS. HPLC purity of crude compounds was >95% (220 nm) while isolated yields of intended compounds after preparative HPLC purification were in a range of 17−76%. Stoichiometry of their corresponding trifluoroacetate salts was deduced from ^{13}C NMR spectra.

Library Production

Having developed the basic methodology, we approached our next objective—library synthesis. The first two reaction steps were performed in 20 mL plastic syringes equipped with a polyethylene fritt at the bottom. Following the attachment of linker **7** to TentaGel-NH_2 resin under "acidic" HOBt/DIC conditions, Mitsunobu reaction of the resins **7** with a set of 10 alcohols in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD) in THF provided the resin-bound intermediates **9** {I−X}. A slurry of resin-bound monosubstituted guanidines in DMF was then distributed into 10 96-deep-well microtiter plates. Plate number thus corresponded to the R1 substituent while rows A−H and columns 1−11 corresponded with the R3 and R2 substituents, respectively. Following pyrazole displacement with a set of 11 anilines added in columns afforded disubstituted arylguanidines **10** {I−X, 1−11} after 40 h reaction at 38 °C. The R3 substituents were introduced by the second Mitsunobu alkylation using 25 equiv of the corresponding alcohol, PPh_3, and DIAD in THF for 16 h at room temperature. The resins **11** {I−X, 1−11, A−H} were then washed sequentially with THF, DMF, DCE, DMF, THF, and DCM. Cleavage of the guanidines from the resin and the final Boc-deprotection were effected with 95% TFA for 2 h. After evaporation of the cleavage solution using a Genevac high-speed evaporator, the reaction products were extracted into shallow titer plates using THF and acetonitrile. Library analysis was done with the following sampling protocol: 80 samples with the fixed 4-bromoaniline, 110 samples with a variety of fixed R1's, and 46 randomly chosen samples were analyzed by LC/MS at 220 and 270 nm (in total, 26.8% of the library). Cross-sectional plate analysis revealed that 98% of the library contained correct compounds, 26% library members had purity >75%, and 83% library members had purity >50%. Analysis of random samples (5.2% of the library) revealed that 96% of the library contained correct compounds, 21% library members had purity >75%, and 73% library members had purity >50%. Surprisingly, furfuryl alcohol, which was successfully used in the optimization studies, failed to give the expected compounds as the major components across the entire library. This, perhaps experimental failure, obviously lowered the overall purity profile of the library.

Conclusions

In conclusion, we have introduced a new acid labile linker for synthesis of substituted guanidines. The synthesis of *N*-aryl *N*′,*N*″-dialkyl guanidines has been completed in a library format, thus demonstrating the applicability of the new linker to solid-phase combinatorial synthesis. The linker was efficiently and selectively functionalized via Mitsunobu alkylations and pyrazole displacement to afford expected products, most showing a purity better than 50% at 220 nm. The limitations of this methodology include the multistep synthesis of the linker with four purification steps involving flash column chromatography. A significant advantage of the described method is that mono-, di-, and trisubstituted guanidines can be synthesized on solid phase by using a structurally defined and purified guanidine linker being attached to the solid support prior to the synthesis. Such concept of using this acid labile "guanidine" linker offers another attractive tool to solid-phase chemists working in the fields of organic and peptide synthesis.

Experimental Section

General. Commercial reagents were used as received without additional purification. Unless otherwise noted, solvents were of the reagent grade available from commercial sources and used without further purification. TentaGel resin was purchased from Rapp Polymere, Tübingen, Germany (90 μm, 0.22 mmol/g). ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and are referenced to an internal standard of tetramethylsilane. High-pressure liquid chromatography (HPLC) was performed using YMC ODS-AM C18 (4.6 × 250 mm) and Vydac C18 (22 × 250 mm) columns with UV detection at 230 nm and gradient elution from 0% to 100% CH_3CN in 30 min. Infrared spectra were recorded on a FTIR spectrometer, and only characteristic absorptions are reported. HRMS spectra were recorded using the FAB technique (Xe gun at 10 kV, glycerol: thioglycerol:3-nitrobenzyl alcohol as the matrix) by the Department of Chemistry at University of Arizona, Tucson, AZ. Melting points are not corrected.

Linker Synthesis: Allyl 2-(4-(hydroxymethyl)phenoxy)-acetate (3). To a stirred mixture of 2-(4-(hydroxymethyl)-phenoxy)acetic acid (15.4 g, 0.085 mol) in CH_2Cl_2 (120 mL), $NaHCO_3$ (14.6 g, 0.174 mol), and water (146 mL) was added allylbromide (22.2 mL, 0.254 mol) at 0 °C followed by Aliquat 336 (33 g). After the mixture was stirred for 16 h at 35 °C, the organic and aqueous phases were separated, the aqueous portion was washed with CH_2Cl_2 (2 × 20 mL), and combined organic portions were dried over $MgSO_4$. Following filtration and concentration gave a colorless residue which was purified by flash chromatography (hexane:AcOEt 70:30) to give **3** (15.1 g, 80%) as a colorless liquid: IR (neat) 3320, 1762 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\boldsymbol{\delta}$ 2.95 (bs, 1 H), 4.52 (bs, 2 H), 4.60 (s, 2 H), 4.66 (dt, 2 H, J = 5.8 Hz, J = 1.3 Hz)), 5.25−5.43 (m, 2 H), 5.88 (ddt, 1 H, J_{trans} = 17.8 Hz, J_{cis} = 10.4 Hz, J = 5.8 Hz), 6.78−6.87 (m, 2 H), 7.20−7.29 (m, 2 H); ^{13}C NMR ($CDCl_3$) $\boldsymbol{\delta}$ 64.17 t, 65.09 t, 65.59 t, 114.37 d, 118.83 t, 128.29 d, 131.19 d, 134.25 s, 156.93 s, 168.50 s; HRMS calcd for ($M^{+\bullet}$) $C_{12}H_{14}O_4$ *m*/*z* 222.0892, measured 222.0884.

Allyl 2-(4-((4-Nitrophenoxycarbonyloxy)methyl)phenoxy)acetate (4). Pyridine (25 mL, 0.31 mol) was slowly added to a stirred solution of **3** (16.0 g, 0.072 mol) and 4-nitrophenyl chloroformate (14.5 g, 0.072 mol) in CH_2Cl_2 (155 mL) at room temperature, and the mixture was stirred for 12 h. The mixture was washed three times with 10% $KHSO_4$, dried ($MgSO_4$), and concentrated under vacuum. Flash chromatography (hexane:AcOEt 70:30) provided **4** as an pale oil (23.4 g, 84% yield): IR (neat) 1760, 1732, 1353 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.67 (s, 2 H), 4.70 (dt, 2 H), 5.21 (s, 2 H), 5.21−5.36 (m, 2 H), 5.85−5.98 (m, 1 H), 6.91 (m, 2 H), 7.33−7.39 (m, 4 H), 8.24 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 64.9 t, 65.6 t, 70.4 t, 114.6 d, 118.7 t, 121.5 d, 124.9 d, 127.3 s, 130.4 d, 131.2 d, 145.1 s, 152.1 s, 155.3 s, 158.1 s, 168.1 s; HRMS calcd for ($M^{+\bullet}$) $C_{19}H_{17}NO_8$ *m*/*z* 387.0954, measured 387.0954.

Allyl 2-(4-((*N*-(Iminopyrazolylmethyl)carbamoyloxy)-methyl)phenoxy)acetate (5). A solution of 1-*H*-pyrazole-1-carboxamide·HCl (16.2 g, 0.110 mol) in 2 M NaOH (55 mL, 0.110 mol) was extracted three times with THF. The combined organic extracts were dried over $MgSO_4$ and mixed with **4** (21.0 g, 0.054 mol). The mixture was allowed to stir for 2 h followed by evaporation and flash chromatography (AcOEt:hexane:NEt_3, 25:70:5) to yield **5** as a white solid (15.6 g, 80%): mp 94−95 °C (MeOH); IR (neat) 3440, 3328, 1760, 1657, 1622, 1502 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.65 (s, 2 H), 4.71 (bd, 2 H), 5.14 (s, 2 H), 5.24−5.38 (m, 2 H), 5.85−5.99 (m, 1 H), 6.40−6.42 (m, 1 H,), 6.85−6.95 (m, 2 H), 7.35−7.45 (m, 2 H), 7.65 (bs, 1 H), 7.68 (bs, 1 H), 8.43 (d, 1 H, J = 2.8 Hz), 9.02 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 65.4 t, 65.8 t, 67.1 t, 109.2 d, 114.6 d, 119.1 d, 128.8 t, 129.7 s, 130.1 d, 131.4 d, 143.6 d, 155.1 s, 157.7 s, 163.9 s, 168.5 s; HRMS calcd for $(M + H)^+$ $C_{17}H_{19}N_4O_5$ *m*/*z* 359.1355, measured 359.1352.

Allyl 2-(4-((*N*-(*N*-Boc-Iminopyrazolylmethyl)carbamoyloxy)methyl)phenoxy)acetate (6). To a stirred solution of **5** (14.4 g, 40 mmol) and di-*tert*-butyl dicarbonate (26.3 g, 120 mmol) in dry THF (200 mL) was added portionwise a suspension of sodium hydride (3.5 g, 50% oil, 80 mmol) under argon atmosphere. The mixture was stirred for 15 min (gas evolution) followed by heating at reflux for 1 h. The slurry was filtered through a fritted glass funnel packed with Celite followed by THF (2 × 30 mL) washes. The filtrate was concentrated, and the crude product was purified by flash chromatography (AcOEt:hexane:AcOH 80:20:2) to afford 15.8 g (86%) of **6** as an oil. IR (neat) 1812, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 4.66 (d, 2 H, J = 3.0 Hz), 4.70 (dd, 2 H, J = 5.81 Hz, J = 1.26 Hz), 5.16 (d, 2 H, J = 8.03), 5.73−5.90 (m, 2 H), 5.85−6.00 (m, 1 H), 6.44 (dd, 1 H, J = 2.71 Hz, J = 1.62 Hz), 6.90 (dd, 2 H, J = 8.60 Hz, J = 1.71 Hz), 7.36 (dd, 2 H, J = 15.5 Hz, J = 8.0 Hz), 7.58−7.68 (m, 1 H), 8.29 (d, 1 H, J = 2.60 Hz), 9.06 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.9, 65.3, 65.8, 67.8, 83.7, 110.0, 114.6, 119.0, 128.8, 129.2, 130.3, 131.3, 138.8, 142.8, 149.4, 157.7, 158.3, 168.4; HRMS calcd for $(M + H)^+$ $C_{22}H_{26}N_4O_7$ *m*/*z* 459.1880, measured 459.1888.

2-(4-((*N*-(*N*-Boc-Iminopyrazolylmethyl)carbamoyloxy)-methyl)phenoxy)acetic Acid DCHA Salt (1). To a stirred solution of **6** (2.21 g, 4.8 mmol), acetic acid (3.3 mL, 58 mmol), and *N*-methylmorpholine (1.58 mL, 14 mmol) in DMF (17 mL) was added Pd $(PPh_3)_4$ (83.2 mg, 0.07 mmol) at ambient temperature, and the resulting solution was stirred overnight under argon. The mixture was evaporated to dryness, the residue was dissolved in EtOAc (72 mL), and the solution was washed with a cold (4 °C) aqueous solution of trisodium salt of citric acid (16%, 48 mL). Aqueous portion was extracted with EtOAc (72 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was redissolved in EtOAc (14.4 mL) followed by addition of dicyclohexylamine (0.956 mL, 4.80 mmol). The mixture was stirred in an ice bath for 40 min, at which time solid **1** precipitated. The product was filtered and dried under vacuum to yield 2.24 g (77%) of pure **1** as a white solid: mp 140−141 °C (dec), ($CHCl_3$:EtOAc, 1:2); IR (neat) 3344, 1766, 1708, 1639, 1513 cm^{-1}; ^1H ($CDCl_3$) δ 1.03−1.22 (m, 4 H), 1.27−1.65 (m, 8 H), 1.53 (s, 1 H), 1.68−1.78 (m, 4 H), 1.88−1.98 (m, 4 H), 2.82−2.93 (m, 2 H), 4.44 (s, 2 H), 5.14 (s, 2 H), 6.44 (dd, 1 H, 2.7 Hz, 1.5 Hz), 6.88 (d, 2 H, 8.4 Hz), 7.33 (d, 2 H, 8.4 Hz), 7.64 (d, 1 H, 1.5 Hz), 8.27 (d, 1 H, 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.1, 28.0, 28.9, 52.5, 67.7, 68.2, 83.2, 110.0, 114.6, 127.4, 128.8, 130.2, 138.6, 142.8, 159.1, 173.4; HRMS calcd for $(M + H)^+$ $C_{19}H_{23}N_4O_7$ *m*/*z* 419.1567, measured 419.1576.

Evaluation of the Guanidine Linker 1. Linker Attachment. A 50 mL syringe fitted with polyethylene filter was charged with TentaGel S-NH_2 resin (6.0 g, 1.32 mmol, 0.22 mmol/g). After being washed with DMF (2 × 20 mL), the resin was treated with a solution of HOBt·H_2O (5%, 20 mL, 3×) in DMF. The resin was washed with DMF (3 × 20 mL) and then treated with a mixture of DIC (0.77 g, 6.1 mmol), HOBt·H_2O (0.92 g, 6.0 mmol), and linker DCHA salt (**1**) (3.61 g, 6.0 mmol) in DMF (24 mL) for 22 h. Final resin wash was done as follows: DMF (2 × 20 mL), acetonitrile (2 × 20 mL), DCM (2 × 20 mL). Washed resin was then dried in lyophylizer for 16 h. A total of 24 g of the resin **7** was prepared in four batches.

General Method for Synthesis of Substituted Guanidines 8 a−m. A solution of the corresponding amine (2.2 mmol, 20 equiv) in CH_3CN (3 mL) was added to the resin **7** (0.50 g, 0.11 mmol), and the suspension was shaken at 38 °C for 2 h. The resin was then filtered and washed with CH_3CN (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL) to give resin-bound compounds **8 a−m**. The resins **8 a−m** (0.50 g, 0.11 mmol) were treated with a mixture of trifluoroacetic acid, CH_2Cl_2, and water (2.5 mL, 47:47:6) for 2 × 30 min at room temperature. The supernatants were then separated and evaporated in vacuo. The resulted crude products were further purified by preparative HPLC to give pure **8 a−m** as white solids.

(2,4-Dichlorobenzyl)guanidine·TFA (8a): ^1H NMR (DMSO-d_6) δ 4.41 (d, 2 H), 7.31 (d, 1 H), 7.48 (dd,1 H), 7.72 (d, 1 H), 7.48 (bs, 4 H) 8.15 (t, 1 H); ^{13}C NMR (DMSO-d_6) δ 41.9, 118.5 (q, $^2J_{CF}$ = 293 Hz), 127.6, 128.9, 129.7, 132.9, 133.3, 133.7, 157.2, 158.9, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_8H_{10}Cl_2N_3$ *m*/*z* 218.0252, measured 218.0247.

(4-Trifluoromethylbenzyl)guanidine·TFA (8b): ^1H NMR (DMSO-d_6) δ 4.55 (d, 2 H), 7.44 (bs, 4 H), 7.50 (d, 2 H), 7.81 (d, 2 H), 8.30 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 43.4, 118.5 (q, $^2J_{CF}$ = 293 Hz), 125.4, 127.7, 128.3, 142.3, 157.1, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_9H_{11}F_3N_3$ *m*/*z* 218.0905, measured 218.0900.

Phenylguanidine·TFA (8c): ^1H NMR (DMSO-d_6) δ 7.14−7.34 (m, 3 H), 7.37−7.47 (m, 2 H), 7.61 (bs, 4 H), 10.15 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 118.5 (q, $^2J_{CF}$ = 293 Hz), 124.8, 126.8, 130.1, 135.9, 156.4, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_7H_{10}N_3$ *m*/*z* 136.0875, measured 136.0877.

(4-Cyclohexylphenyl)guanidine·TFA (8d): ^1H NMR (DMSO-d_6) δ 1.20−1.50 (m, 5 H), 1.60−1.9 (m, 5 H), 7.13 (m, AA′BB′, 2 H), 7.28 (m, AA′BB′, 2 H), 7.37 (bs, 4 H), 9.66 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 26.0, 26.8, 34.3, 43.7, 70.2, 118.5 (q, $^2J_{CF}$ = 293 Hz), 124.8, 128.3, 133.5, 146.2,

156.4, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_{13}H_{20}N_3$ *m/z* 218.1657, measured 218.1662.

(4-Hydroxyphenyl)guanidine·TFA (8e): ^{1}H NMR (DMSO-d_6) δ 6.70−6.8 (m, AA′BB′, 2 H), 6.95−7.10 (m, AA′BB′, 2 H), 7.27 (bs, 4 H), 9.51 (s, 1 H); ^{13}C NMR (75 MHz) δ 118.5 (q, $^2J_{CF}$ = 293 Hz), 116.6, 126.2, 127.8, 157.0, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_7H_{10}N_3O$ *m/z* 152.0824, measured 152.0821.

(4-Phenoxyphenyl)guanidine·TFA (8f): ^{1}H NMR (DMSO-d_6) δ 6.97−7.10 (m, 4 H), 7.11−7.18 (m, 1 H), 7.21−7.28 (m, 2 H), 7.36−7.44 (m, 2 H), 7.58 (bs, 4 H), 9.99 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 118.5 (q, $^2J_{CF}$ = 293 Hz), 119.0, 120.1, 124.1, 127.7, 130.5, 130.3, 155.6, 156.8, 157.0, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_{13}H_{14}N_3O$ *m/z* 228.1137, measured 228.1135.

***N*-Methyl-*N*-benzylguanidine·TFA (8g):** ^{1}H NMR (DMSO-d_6) δ 2.92 (s, 3 H), 4.58 (s, 2 H), 7.17−7.24 (m, 2 H), 7.27−7.45 (m, 4 H), 7.55 (bs, 4 H); ^{13}C NMR (DMSO-d_6) δ 36.5, 53.1, 118.5 (q, $^2J_{CF}$ = 293 Hz), 127.5, 128.1, 129.2, 136.1, 157.4, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_9H_{14}N_3$ *m/z* 164.1188, measured 164.1186.

***tert*-Butylguanidine·TFA (8i):** ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 9 H), 6.97 (bs, 4 H), 7.49 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 29.0, 51.4, 118.5 (q, $^2J_{CF}$ = 293 Hz), 156.1, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_5H_{14}N_3$ *m/z* 116.1188, measured 116.1185.

***n*-Octylguanidine·TFA (8j):** ^{1}H NMR (DMSO-d_6) δ 0.84 (t, 3 H), 1.24 (m, 10 H), 1.44 (t, 2 H), 3.03−3.13 (m, 2 H), 7.19 (bs, 4 H), 7.71 (t, 3 H); ^{13}C NMR (DMSO-d_6) δ 13.9, 22.0, 26.0, 28.4, 28.5, 28.6, 31.2, 40.7, 118.5 (q, $^2J_{CF}$ = 293 Hz), 156.9, 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_9H_{22}N_3$ *m/z* 172.1814, measured 172.1822.

(2-Hydroxy-*tert*-butyl)guanidine·TFA (8k): ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 6 H), 3.40 (d, 2 H, J = 4.6 Hz), 6.07 (t, 1 H, J = 4.6 Hz), 7.23 (bs, 4 H), 7.31 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 24.1, 55.7, 69.4, 118.5 (q, $^2J_{CF}$ = 293 Hz), 163.5 (q, $^3J_{CF}$ = 35 Hz); HRMS calcd for $C_5H_{14}N_3O$ *m/z* 132.1137, measured 132.1133.

Methyl 2-(Amidinoamino)-3-hydroxypropanoate·TFA (8l): ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3 H), 3.60−3.74 (m, 1 H), 3.8−3.9 (m, 1 H), 4.35−4.45 (m, 1 H), 5.4−5.5 (m, 1 H), 7.34 (bs, 4 H), 7.55−7.75 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 52.9, 56.3, 61.7, 118.5 (q, $^2J_{CF}$ = 293 Hz), 157.6, 163.5 (q, $^3J_{CF}$ = 35 Hz), 170.3; HRMS calcd for $C_5H_{12}N_3O_3$ *m/z* 162.0879, measured 162.0882.

Fmoc-Arg-OMe·TFA (8m): ^{1}H NMR (DMSO-d_6) δ 1.35−1.77 (m, 4 H), 3.00−3.15 (m, 2 H), 3.62 (s, 3 H), 4.03 (q, 1 H, J = 4.9 Hz), 4.14−4.4 (m, 3 H), 7.06 (bs, 2 H), 7.26−7.35 (m, 2 H), 7.37−7.45 (m, 2 H), 7.50−7.60 (m, 1 H), 7.65−7.73 (m, 2 H), 7.75−7.83 (m, 1 H), 7.85−7.93 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 25.6, 28.2, 47.1, 52.3, 66.1, 70.2, 118.5 (q, $^2J_{CF}$ = 293 Hz), 120.6, 125.6, 127.5, 128.1, 141.2, 144.2, 156.6, 157.3, 163.5 (q, $^3J_{CF}$ = 35 Hz), 173.1; HRMS calcd for $C_{22}H_{27}N_4O_4$ *m/z* 411.2032, measured 411.2035.

Model Library Compounds: *N*-(Isopropyl)-*N′*-(2-(1-piperidyl)ethyl)-*N″*-(4-methylphenyl)guanidine·TFA (13) was isolated in 58% yield as a colorless oil: IR (neat) 3267, 1681, 1650, 1514 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3 H), 3.20 (bs, 2 H), 3.24 (s, 2 H), 3.35 (s, 2 H), 3.76 (s, 2 H), 3.78 (bs, 2 H), 5.47 (s, 1 H), 5.53 (s, 1 H), 7.3−7.4 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ 40.1, 53.7, 55.5, 57.5, 57.7, 57.9, 59.6, 118.5 (q, $^2J_{CF}$ = 293 Hz), 124.2, 127.5, 129.1, 129.8, 136.3, 137.2, 163.5 (q, $^3J_{CF}$ = 35 Hz), 173.3; HRMS calcd for $C_{18}H_{31}N_4$ *m/z* 303.2545, measured 303.2549.

***N*-(3-Dimethylaminopropyl)-*N′*-(3-pyridylmethyl)-*N″*-(phenyl)guanidine·2TFA (14)** was isolated in 72% yield as a colorless oil: IR (neat) 3097, 1681, 1614, 1427 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.13 (bs, 2 H), 3.23 (s, 2 H), 3.35 (s, 2 H), 3.55 (bs, 2 H), 3.74 (s, 2 H), 4.00 (s, 2 H), 4.43 (s, 2 H), 5.23 (s, 1 H), 5.57 (s, 1 H), 7.2−7.4 (m, 9 H); ^{13}C NMR (DMSO-d_6) δ 25.4, 49.7, 53.0, 54.0, 56.7, 58.1, 59.3, 118.5 (q, $^2J_{CF}$ = 293 Hz), 124.9, 127.2, 127.4, 128.2, 128.4, 128.6, 129.1, 131.7, 136.1, 137.6, 163.5 (q, $^3J_{CF}$ = 35 Hz), 174.3; HRMS calcd for $C_{18}H_{26}N_5$ *m/z* 312.2188, measured 312.2180.

***N*-(2-Pyrrolidinylethyl)-*N′*-(2-(4-methyl(1,3-thiazole-5-yl)ethyl)-*N″*-(4-phenoxyphenyl)guanidine·TFA (15)** was isolated in 76% yield as a colorless oil: IR (neat) 3228, 1681, 1650, 1502 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3 H), 3.16 (s, 2H), 3.31 (s, 2 H), 3.61 (s, 2 H), 3.82 (s, 2 H), 5.45 (s, 1 H), 5.50 (s, 1 H), 7.1−7.6 (m, 10 H); ^{13}C NMR (DMSO-d_6) δ 39.8, 53.7, 56.9, 57.9, 58.1, 59.8, 118.5 (q, $^2J_{CF}$ = 293 Hz), 123.6, 127.1, 127.4, 128.9, 130.3, 132.1, 136.9, 139.2, 163.5 (q, $^3J_{CF}$ = 35 Hz), 174.1; HRMS calcd for $C_{25}H_{32}N_5$-OS *m/z* 450.2328, measured 450.2327.

***N*-(2-Furfurylmethyl)-*N′*-(2-phenoxyethyl)-*N″*-(4-biphenyl)guanidine·TFA (16)** was isolated in 41% yield as a colorless oil: IR (neat) 3072, 1684, 1600, 1490 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.1−2.3 (bs, 4 H), 3.59 (s, 2 H), 3.70 (s, 2 H), 3.88 (s, 2 H), 3.96 (bs, 4 H), 4.06 (s, 2 H), 5.66 (s, 1 H), 5.70 (s, 1 H), 7.3−7.8 (m, 5 H); ^{13}C NMR (DMSO-d_6) δ 51.8, 53.4, 57.7, 58.0, 59.6, 63.5, 117.7, 118.5 (q, $^2J_{CF}$ = 293 Hz), 126.2, 128.3, 128.7, 133.1, 134.7, 163.5 (q, $^3J_{CF}$ = 35 Hz), 172.0; HRMS calcd for $C_{26}H_{26}N_3O_2$ *m/z* 412.2025, measured 412.2026.

***N*-(2-Thienylmethyl)-*N′*-(2-(2-(trifluoromethyl)phenyl)-ethyl)-*N″*-(2-methoxy-5-(trifluoromethyl)phenyl)guanidine·TFA (17)** was isolated in 24% yield as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 2.85−3.08 (m, 2 H), 3.42−3.60 (m, 2 H), 3.78 (s, 3 H), 4.56−4.80 (m, 2 H), 6.94−7.12 (m, 2 H), 7.26−7.38 (d, 1 H, J = 5.1 Hz), 7.40−7.54 (m, 4 H), 7.55−7.65 (m, 1 H), 7.66−7.80 (m, 2 H), 8.07 (bs, 1 H), 8.33 (bs, 1 H), 9.46 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 31.5, 42.8, 56.6, 113.7, 124.4, 125.6, 126.3, 126.4, 126.5, 126.8, 126.9, 127.3, 127.6, 128.0, 132.0, 133.0, 137.0, 140.0, 154.3, 157.6, 158.3 (q, $^3J_{CF}$ = 33 Hz); ESMS (M + H)$^+$ *m/z* 502.

***N*-(2-Aminoethyl)-*N′*-(2-(2-bromophenyl)ethyl)-*N″*-(4-dimethylaminophenyl)guanidine·2TFA (18)** was isolated in 17% yield as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 2.91 (s, 6 H), 2.90−3.10 (m, 2 H), 3.30−3.60 (m, 4 H), 4.08 (bs, 3 H), 6.70−6.82 (m, 2 H), 6.94−7.06 (m, 2 H), 7.13−7.26 (m, 1 H), 7.30−7.46 (m, 2 H), 7.57−7.70 (m, 1 H), 7.94 (bs, 1 H), 9.26 (s, 1 H);); ^{13}C NMR (DMSO-d_6) δ 28.0, 34.8, 38.4, 41.6, 113.3, 117.4 (q, ^2J = 300 Hz), 123.3, 124.5, 127.7, 128.3, 129.3, 131.8, 133.1, 138.0, 149.9, 154.7, 158.8 (q, $^3J_{CF}$ = 33 Hz); ESMS (M + H)$^+$ *m/z* 404.

***N*-(2-Morpholinylethyl)-*N′*-(2-(4-methoxyphenyl)ethyl)-*N″*-(4-biphenyl)guanidine·TFA (19)** was isolated in 47% yield as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 2.70−2.88 (m, 2 H), 2.95−3.50 (m, 8 H), 3.52−4.00 (m, 6 H), 3.72 (s, 3 H), 6.75−6.94 (m, 2 H), 7.10−7.26 (m, 4 H), 7.31−7.42 (m, 1 H), 7.43−7.53 (m, 2 H), 7.60−7.78 (m, 4 H), 8.05 (bs, 2 H), 9.07 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 33.9, 36.9, 43.8, 52.0, 55.0, 64.0, 70.3, 114.4, 117.2 (q, ^2J = 300 Hz), 125.4, 127.0, 128.1, 128.2, 129.5, 130.3, 130.5, 135.6, 138.5, 139.6, 154.3, 158.5, 159.0 8 (q, $^3J_{CF}$ = 33 Hz); ESMS (M + H)$^+$ *m*/*z* 459.

***N*-(2-Furfurylmethyl)-*N′*-(2-(3-methylphenyl)ethyl)-*N″*-(3-phenoxyphenyl)guanidine·TFA (20)** was isolated in 25% yield as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3 H), 2.72 (t, 2 H, J = 5.2 Hz), 3.40−3.59 (m, 2 H), 4.38−4.57 (m, 2 H), 6.30−6.38 (m, 1 H), 6.42−6.48 (m, 1 H), 6.90−7.10 (m, 1 H), 7.12−7.22 (m, 2 H), 7.35−7.48 (m, 2 H), 7.67 (s, 1 H), 7.68 (bs, 1 H), 8.23 (bs, 1 H), 9.48 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 21.4, 34.6, 38.7, 43.2, 108.5, 111.1, 119.2, 119.8, 124.3, 126.3, 127.3, 127.5, 128.8, 129.9, 130.6, 131.1, 137.9, 138.6, 143.5, 150.4, 154.4, 155.6, 156.8, 158.4 (q, $^3J_{CF}$ = 32 Hz); ESMS (M + H)$^+$ *m*/*z* 426.

Library Synthesis. Linker Attachment: See Evaluation of the Guanidine Linker 1. Resin Distribution: Suspension of resin **7** (1.8 g) in DMF (26 mL) was equally distributed into 88 wells in one 96-deep-well plate using an eight-channel pipettor. DMF was removed by aspiration, and the resin was washed with dry THF (200 μL per well, 10×). This procedure was repeated until all 10 plates were filled with all batches of resin **7**.

First Randomization (Mitsunobu Alkylation I): Stock solutions (8.0 mL, dry THF) of 10 selected alcohols **I-X** (8.8 mmol, Scheme 3) and PPh_3 (2.31 g, 8.8 mmol) were prepared in glass vials. Another stock solution of DIAD (17.84 g, 88.3 mmol, 1.66M) in dry THF (53 mL) was prepared in single glass vial. Each stock solution of alcohols/PPh_3 was distributed into a corresponding plate (90 μL/well) precooled in a refrigerator at 4 °C for 20 min. Then the DIAD stock solution was distributed into plates (60 μL/well). The covered plates were shaken at room temperature for 16 h, followed by reagents removal and resin wash.

Resin Wash: Reagents were removed by aspiration followed by resin wash done by a customized Zymark robot as follows: dry THF (300 μL per well, 2×), DMF (300 μL, 2×), DCE/DMF (4:6) (300 μL, 2×). This sequence cycle was repeated three times with final wash using acetonitrile (300 μL, 7×).

Second Randomization (Pyrazole Displacement): Stock solutions (13.0 mL, acetonitrile) of 11 anilines **1**−**11** (9.6 mmol, Scheme 3) and NMI (0.116 g, 1.6 mmol) were prepared in glass vials. Each stock solution was distributed into a corresponding plate (160 μL/well) using an 11-channel pipettor. Covered plates were put into oven at 38 °C for 40 h.

Resin Wash: Reagents were removed by aspiration followed by resin wash done by a customized Zymark robot as follows: acetonitrile (300 μL per well, 8×), DMF (300 μL, 8×), dry THF (300 μL, 7×).

Third Randomization (Mitsunobu Alkylation II): Stock solutions (10.0 mL, dry THF) of eight alcohols **A**−**H** (11.0 mmol, Scheme 3) and PPh_3 (2.88 g, 11.0 mmol) were prepared in glass vials. Another stock solution of DIAD (17.84 g, 88.3 mmol, 1.66 M) in dry THF (53 mL) was prepared in a single glass vial. Each stock solution of alcohols/PPh_3 was distributed into a corresponding plate (90 μL/well) precooled in a refrigerator at 4 °C for 20 min. The DIAD stock solution was then distributed into plates (60 μL/well). The covered plates were shaken at room temperature for 16 h followed by reagents removal and resin wash.

Resin Wash: Reagents were removed by aspiration followed by resin wash done by a customized Zymark robot as follows: dry THF (400 μL per well, 3×), DMF (400 μL, 3×), DCE/DMF (4:6) (500 μL, 3×). This sequence cycle was repeated three times with final wash using THF (400 μL, 7×). The complete set of 10 plates was dried in a Genevac HT-12 Atlas evaporator.

Cleavage: A solution of 95% TFA/water (200 μL) was distributed into each well. A complete set of 10 plates was shaken at room temperature for 2 h followed by drying in a Genevac HT-12 Atlas evaporator.

Compounds Extraction: The library was extracted by a customized Zymark robot as follows: THF (450 μL) was added into each well, and plates were shaken for 2 h. A solution of cleaved compound was aspirated, and additional portions of THF were added (300 μL, 2×). Extraction continued with acetonitrile (150 μL, 2×) followed by solvent evaporation and drying in a Genevac HT-12 Atlas evaporator.

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Supporting Information Available. LC/MS spectra of selected library members. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(6) 1,2- and 1,3-diamines provided corresponding cyclic guanidines.
(7) Applicability of linker **1** to other resins was demonstrated by synthesis of compounds **8b**, **8f**, and **8l** on aminomethyl polystyrene resin (125−160 μm, 1.18 mmol/g, Rapp Polymere, Tübingen, Germany). Substituted guanidines of nearly identical purity were obtained under similar reaction conditions (DMF used instead of CH_3CN) with the following isolated yields: **8b** (68%), **8f** (65%), **8l** (83%).
(8) Process of building blocks selection was as follows: building blocks for R1, R2, and R3 were obtained from Available Chemicals Database (ACD). Large data sets of structures were first filtered applying internal criteria such as unwanted fragments, reactive groups, MW cutoff, and library size. In the next step, a virtual library of substituted guanidines was enumerated with the filtered R-groups. Further selection of building blocks was done using 2D fingerprints and Tanimoto index (cutoff at 0.85) as implemented in Diversity Manager software (Tripos). At this stage, 29 alcohols and 22 anilines were identified for chemistry evaluation in plates. The final list of building blocks for each position (10 + 8 alcohols and 11 anilines) was "fine-tuned" to reflect chemistry performance (purity criteria).

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