Synthetic Routes to *N*-Pmc-*N*′,*N*″-Disubstituted Guanidines via EDCI-Mediated Guanylation of Amines with *N*-Pmc-*N*′-Substituted Thioureas

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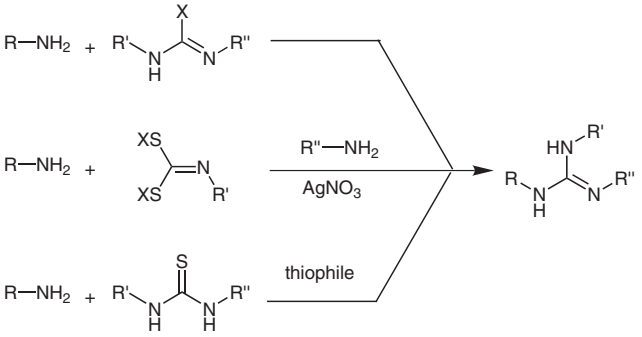
Abstract: An overview of the facile and high-yielding EDCI-mediated reaction of amines with *N*-Pmc-N′-alkyl thioureas to afford guanidines is presented, in which the general scope and limitations of the reaction are probed. It was found that the *N*-sulfonyl-*N*′-substituted thioureas cannot possess internal nucleophiles or disubstitution, and that the incoming amine must possess adequate nucleophilicity in order for the reaction to be viable. However, it is noted that the guanidine products can be accessed through two possible synthetic approaches, and that a simple reversal of amine and thiourea substituents allows the reaction to proceed successfully.

Key words: guanidine, guanylation, thiourea, EDCI, *N*-sulfonyl

Guanidines represent an important class of compounds in organic and bioorganic chemistry. The guanidine framework has been used as an organic superbase,[1] while oligomeric guanidines have seen frequent application as effective germicides and pesticides.[2] In enzymes, the guanidine headgroup of arginine is responsible for a diverse array of processes including protein-enzyme ion-pairing,[3] NO synthesis,[4] and insulin sensitivity.[5] Furthermore, arginine-rich peptide sequences such as HIV-1 TAT and Penetratin are known for their cell membrane translocating properties.[6]

Since alkyl-substituted guanidines are present in natural products[7] and arginine-containing peptide systems,[8] methods for the synthesis of guanidines with multiple substitution patterns are desirable. A review of the literature illustrates numerous examples of synthetic entries into substituted guanidine systems. These transformations generally involve a condensation reaction between an amine and a guanylating agent (Scheme 1).[9] Guanylation of an amine involves either the direct displacement of a leaving group from the central carbon atom of the guanyl transfer agent by the amine,[10–14] utilization of various dithiocarboimidate derivatives with amine nucleophiles,[15,16] or attack of the amine on what is generally accepted to be an in situ generated carbodiimide from a thiourea.[17–19] The latter methodology has become the more accepted one, as it has been established that thioureas bearing an electron-withdrawing group presumably afford activated carbodiimides.[20] Classically, heavy metal thiophiles (i.e., Hg salts) have been necessary to effect transformation of a thiourea into the putative carbodiimide intermediate. However, as discovered by Atwal et al. in 1989[18a] and further developed by Hamilton and coworkers in 1999,[21] discrete substituted guanidine systems were accessible through the gentle EDCI-mediated condensation of urethane-protected, substituted thioureas with amines. It is noteworthy, however, that in this protocol the alkoxycarbonyl moiety was not readily deprotected by acidic conditions. Most recently, the research groups of Anslyn and Fan have utilized this approach toward the solid-phase synthesis of guanidine oligomers,[22,23] with the development of sulfonyl-based, acid-labile guanidine protection protocol for these solid-phase oligomeric systems allowing for concurrent deblocking and cleavage at the end of the synthesis.



Scheme 1 Three general types of synthetic entry into substituted guanidine systems

The present research explores the EDCI-mediated reaction of *N*-Pmc-*N*′-alkylthioureas (Pmc = 2,2,5,7,8-pentamethylchroman-6-sulfonyl) with amines to afford *N*-Pmc-protected guanidines that may then be cleanly and conveniently deprotected with TFA. One of the compelling attributes of this chemistry was the ability to access the desired guanidines through two possible approaches (Scheme 2). It quickly became evident during this investigation that, in many cases, while one approach failed to furnish the desired guanidine, reversing the substitutions on the thiourea and amine allowed facile access to the target guanidine. This dual approach illustrates very nicely the flexible utility of this method.

For facile entry into this framework, we envisioned the use of Pmc-isothiocyanate **1** as the key precursor (Scheme 3). Reaction of isothiocyanate **1** with an array of amine nucleophiles afforded *N*-Pmc-*N*′-alkylthioureas **2** in excellent yields, comprising a wide range of N′-substi-

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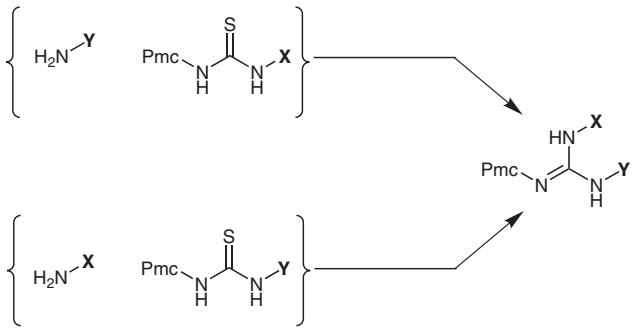
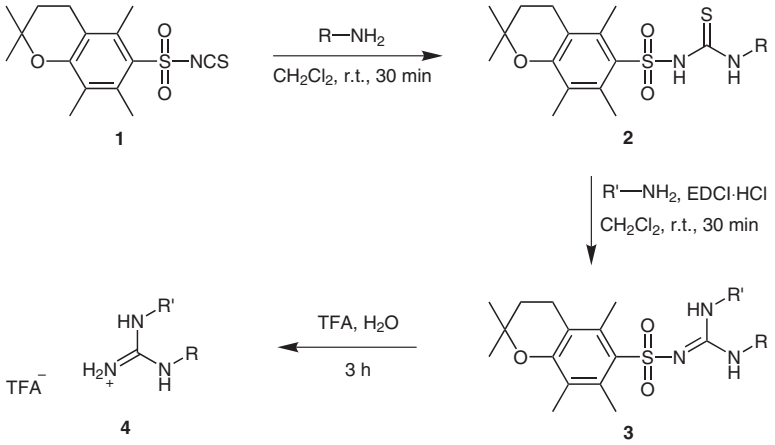


Scheme 2 Dual synthetic approach into each guanidine system is made possible by reversing the substitution patterns on the thiourea and amine partners

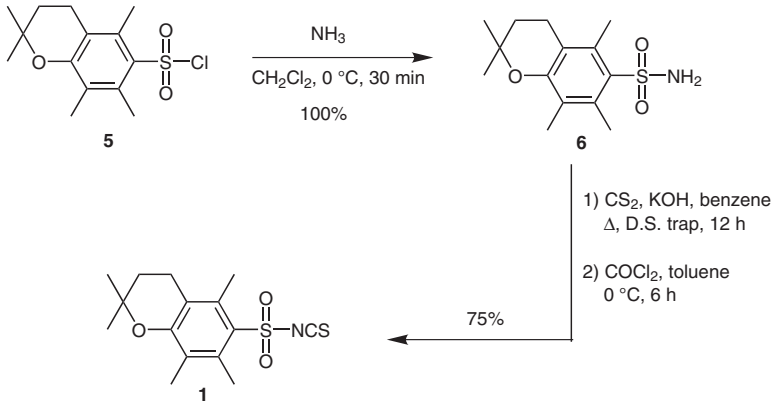
tution. Treatment of these electron-deficient thioureas with EDCI·HCl (to generate a highly-activated carbodiimide intermediate) in the presence of a primary (or secondary) amine smoothly and cleanly afforded an array of Pmc-protected guanidines **3**. Finally, treatment of compounds **3** with TFA promoted the Pmc-deprotection to yield the substituted guanidine compounds **4** as their corresponding TFA salts.

The synthesis of sulfonyl isothiocyanates has been accomplished through either reaction of sulfonyl chlorides with $NCS^{(-)}$[24a,25] or through the reaction of a (dithiomethylene)sulfonamide intermediate with phosgene.[27] Although the first method is more direct, we investigated the second method instead due to the lower cost of $Bu_4N^+NCS^-$. Commercial PmcCl **5** was converted into Pmc-sulfonamide **6** in quantitative yield by treatment with NH_3 in CH_2Cl_2. Reaction of Pmc-NH_2 with CS_2 and KOH followed by phosgene (as described) afforded Pmc-isothiocyanate **1** in 50% yield. Although this yield was consistent with published yields,[26] there was room for optimization of this transformation. We found that by using benzene as a co-solvent to azeotropically remove water, Pmc-isothiocyanate **1** could be obtained in 75% yield (Scheme 4). In addition, it was found that triphosgene[27] could be used instead of phosgene without compromising the yield of Pmc-isothiocyanate **1**. Reagent **1**, once isolated, was stable for months at –20 °C with minimal degradation observed. Prior to use, trituration of the compound in hexanes followed by filtration of accumulated solid impurities yielded regenerated **1** following solvent removal.

With Pmc-isothiocyanate **1** in hand, we began the preparation of a number of *N*-Pmc-thioureas. As summarized in Table 1, isothiocyanate **1** was allowed to react with a number of different primary amines and anilines to yield a variety of structurally diverse thioureas **2a**–**r** in excellent yields.

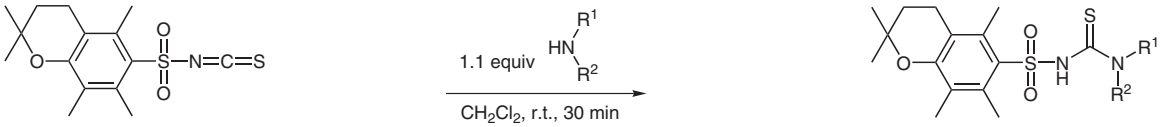


Scheme 3

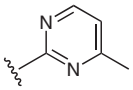
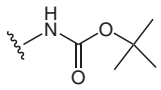
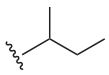
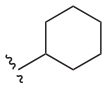
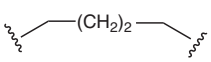
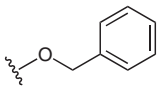
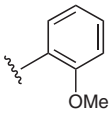
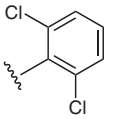
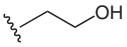
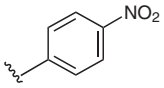
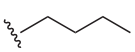
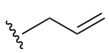
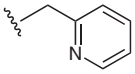
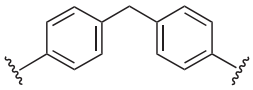
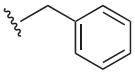
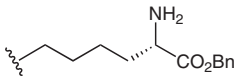


Scheme 4

Table 1 Substitution Patterns for *N*-Pmc-thioureas **2**[a]



1 **2a–r**

Entry	R^1	Yield (%)	Entry	R^1	Yield (%)
2a		~100	**2j**		83
2b		99	**2k**		81
2c		94	**2l**		44
2d		42	**2m**		81
2e		78	**2n**		81
2f		88	**2o**		90[b]
2g		82	**2p**		99
2h		58	**2q**		87
2i		~100	**2r**		nd[c]

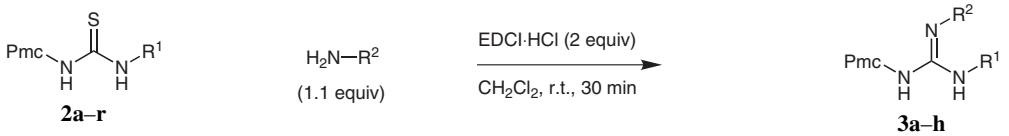
[a] R^2 = H in all cases except thiourea **2l**, in which R^1 and R^2 comprise a pyrrolidine carbocycle.
[b] The yield for thiourea **2o** includes traces of its dissociated components.
[c] Not determined.

The reaction of most amines proceeded to completion with Pmc-isothiocyanate within 15 minutes with the exception of 2-(4-methylpyrimidyl)amine and 2,6-dichloroaniline, which required 24 hours reaction time. Disubstituted thiourea **2l**, in addition to requiring extended reaction time, was obtained in low yield and exhibited a tendency to decompose within a few hours of chromatographic purification. Subsequently, guanylation reactions requiring this thiourea were carried out immediately following its synthesis and purification. *p*-Nitrophenyl derivative **2o** proved to be an exceptionally difficult compound to work with, as it was always contaminated with *p*-nitroaniline. This contaminant persisted regardless of how carefully the compound was chromatographically purified. It is hypothesized that, once dissolved in solution, **2o** is in equilibrium with the Pmc-isothiocyanate **1** and *p*-nitroaniline (Scheme 9, vide infra).

The general methodology for the synthesis of guanidines **3** involved stirring the thiourea, the reacting amine, and one equivalent Hünig's base in CH_2Cl_2 while adding 2 equivalents of EDCI·HCl in one portion to the reaction mixture (Scheme 3). TLC analysis of the resulting solution generally showed the reaction to be complete within a few minutes. Analytical samples for compound characterization were typically purified chromatographically over silica gel.

Table 2 illustrates the detailed preparation of the series of guanidines, demonstrating the utility of having dual synthetic approaches toward each target molecule. Interestingly, for the majority of guanidines, one approach was favored over the other. As expected, certain of the guanidines could be synthesized via either route (**3g** and **3h**). However, the more interesting results arose when only one approach was successful.

Table 2 Synthetic Routes to Substituted Guanidines **3a–h**, Illustrating Dual Potential for Entry into Each System



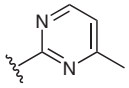
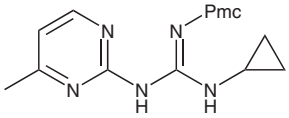
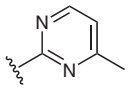
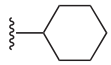
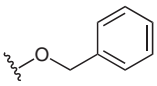
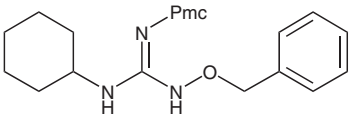
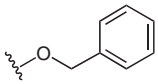
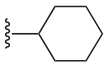
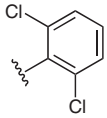
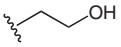
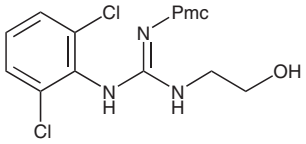
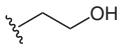
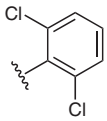
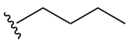
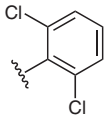
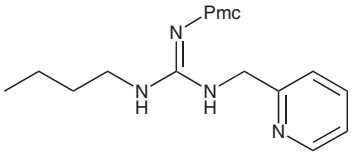
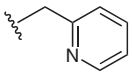
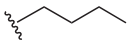
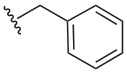
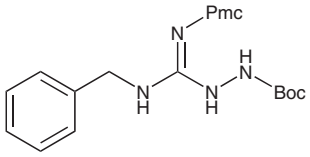
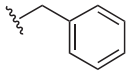
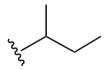
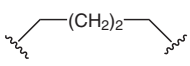
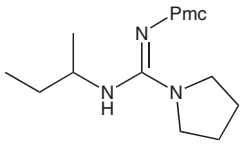
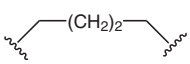
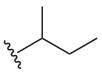
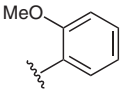
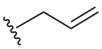
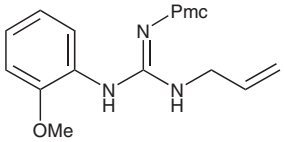
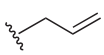
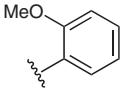
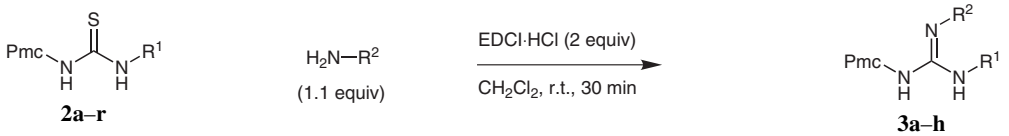
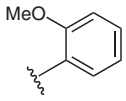
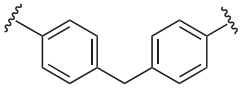
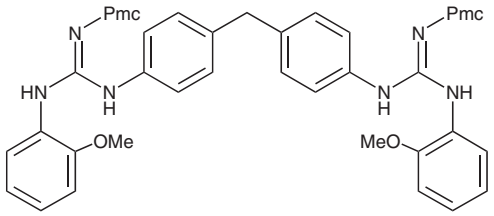
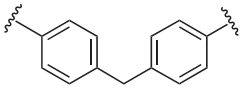
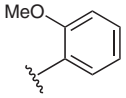
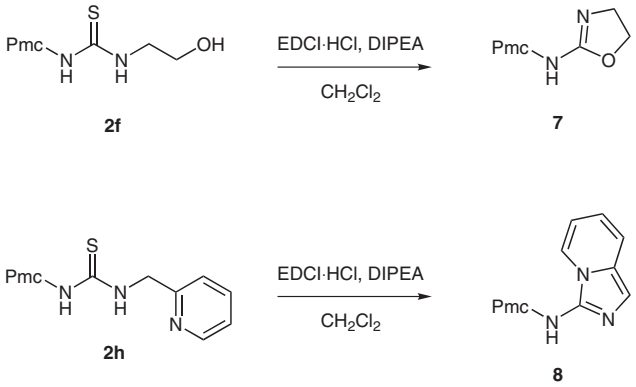
	Thiourea R^1	Amine R^2	Guanidine product	Yield (%)
2a				82
2b			**3a**	0
2c				74
2d			**3b**	0
2e				67
2f			**3c**	0
2g				91
2h			**3d**	0
2i				98
2j			**3e**	0
2k				100
2l			**3f**	0
2m				99
2p			**3g**	88

Table 2 Synthetic Routes to Substituted Guanidines **3a–h**, Illustrating Dual Potential for Entry into Each System (continued)



	Thiourea R^1	Amine R^2	Guanidine product	Yield (%)
2m				91
2q			**3h**	70

The synthesis of guanidine **3a** was only viable through the reaction of cyclopropylamine on 3-methylpyrimidyl-derived transfer agent **2a**, as the opposite approach afforded an intractable mixture. The inability to form guanidines **3c** and **3d** via the routes in which the substituents on the transfer agents were 2-hydroxyethyl- and 2-methylpyridyl, respectively, was a unique occurrence. Both thioureas possess an internal nucleophile (the hydroxyl on **3c** and the pyridyl nitrogen on **3d**), that cyclized intramolecularly on the EDCI-generated carbodiimide, even in the presence of a reacting amine. In both cases, reversing the substitution patterns on the thiourea and the amine afforded the desired guanidines in good yield. Products from the intramolecular cyclization of thioureas **2f** and **2h** (**7** and **8**, respectively) were easily isolated and characterized (Scheme 5). The product **8** was found to quickly change color in solution to deep blue. Interestingly, although highly colored within a few minutes of being dissolved in a solvent, its ^{1}H NMR spectrum did not show the buildup of significant amounts of any degradation product, or give any indication of chemical change of the dissolved sample.

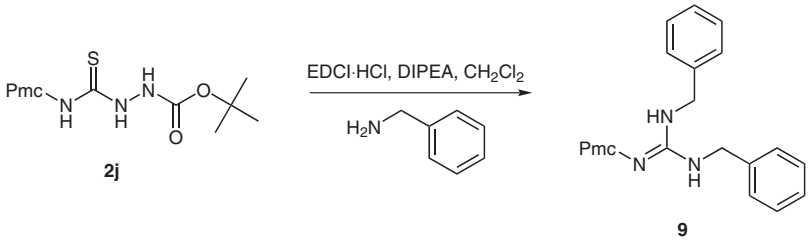


Scheme 5 Self-condensation reactions of thioureas **2f** and **2h**

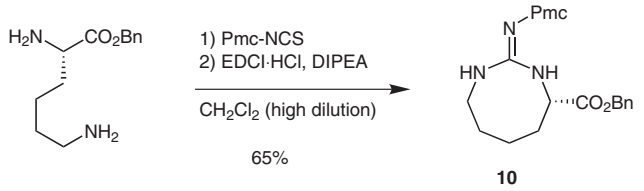
Some interesting results were observed during attempts at the synthesis of guanidine **3e**. The reaction pathway involving *N*-Pmc-*N*′-benzylthiourea **2i** and *tert*-butyl carbazate smoothly afforded the desired product in 98% yield. However, the reaction of benzylamine with *N*-Pmc-*N*′-NHCO$_2$*t*-Bu thiourea **2j** gave the dibenzyl guanidine **9** in 24% yield (Scheme 6) instead of the expected guanidine **3e**. It thus appears that *tert*-butyl carbazate is a sufficiently good leaving group to be displaced by benzylamine.

While *N*-Pmc-*N*′,*N*′-disubstituted thioureas (e.g., reaction of thiourea **2l** with *s*-butylamine) failed to afford guanidines under our reaction conditions, the target guanidines can still be accessed. For example, *N*-Pmc-*N*′-*s*-butylthiourea cleanly reacts with pyrrolidine affording guanidine **3f** in quantitative yield. This particular limitation was previously noted by Hamilton in his urethane-protected guanidine study.[21]

As shown in Scheme 7, the synthesis of cyclic guanidine **10** was achieved through a one-pot procedure. Under conditions of high dilution, an excess of lysine benzyl ester was treated sequentially with Pmc-isothiocyanate **1** fol-



Scheme 6 Unexpected product from the reaction of thiourea **2j** with benzylamine under EDCI-mediated guanylation conditions



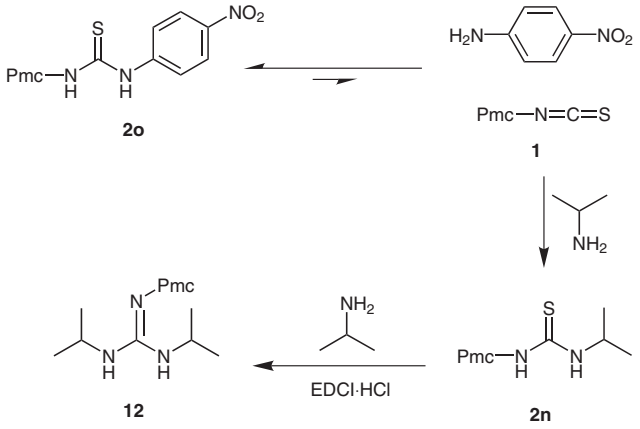
Scheme 7 One-pot, sequential formation of cyclic guanidine **10**, derived from lysine benzyl ester

lowed by EDCI·HCl to give **10** in 65% yield. The synthesis of this compound is significant in that it can offer a non-iterative, general approach toward the conversion of alkyldiamines into cyclic guanidines.

Interestingly, the reaction of *N*-Pmc-*N*′-*p*-nitrophenylthiourea **2o** with isopropylamine afforded none of the expected guanidine, but rather a mixture of bis(*p*-nitrophenyl)guanidine **11** and diisopropyl guanidine **12** in 35% and 22% yield, respectively (Scheme 8). The formation of these bis-substituted compounds supports the hypothesis that *N*-Pmc-*N*′-*p*-nitrophenylthiourea **2o** is in equilibrium with Pmc-isothiocyanate **1** and nitroaniline (Scheme 9). Isopropylamine attacks isothiocyanate **1** irreversibly, and the thiourea intermediate **2n** can subsequently react with another equivalent of isopropylamine to yield diisopropylguanidine **12**. Disubstituted guanidine **11** is probably derived from a similar disproportionation of released *p*-nitroaniline with **2o**.

Direct synthesis of bis(*p*-nitrophenyl) guanidine **11** was achieved in a one-pot fashion by the addition of two equivalents of *p*-nitroaniline to a solution of Pmc-isothiocyanate **1**, followed by direct addition of EDCI·HCl and Hünig's base (Scheme 10). Chromatographic purification of the reaction product proved tedious, as unreacted *p*-nitroaniline co-eluted with the desired guanidine. Purification of **11** was achieved through the treatment of the crude reaction mixture with *tert*-butyl nitrite in DMF[28] in order to selectively convert the free nitroaniline to nitrobenzene via its diazonium salt (Scheme 11).

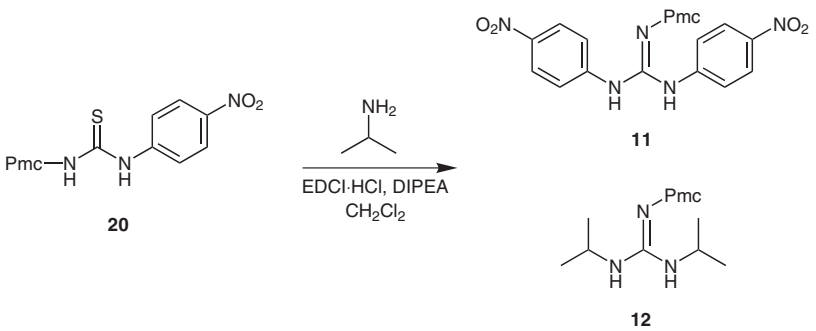
We have explored the amenability of this two-step guanylation chemistry toward a general one-pot process. As shown in Scheme 12, two of the Pmc-guanidine structures **3d** and **3f** were constructed via sequential addition of re-



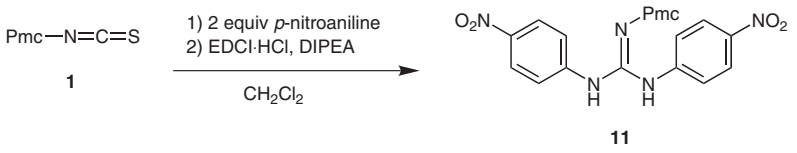
Scheme 9 Putative mechanism of **2o** disproportionation in the presence of isopropylamine and EDCI·HCl

agents to a solution of Pmc-isothiocyanate **1** in CH_2Cl_2. Since these two compounds could only be formed through one of their two possible synthetic pathways, synthesis of **3d** involved the addition of one equivalent of *n*-butylamine followed (shortly after) by the sequential addition of two equivalents of EDCI·HCl and one equivalent of 2-(aminomethyl)pyridine. Similarly, the synthesis of **3f** involved the addition of one equivalent of *sec*-butylamine followed (shortly after) by two equivalents of EDCI·HCl and one equivalent of pyrrolidine. Aqueous workup and purification over silica gel yielded **3d** and **3f** in 55% and 87%, respectively.

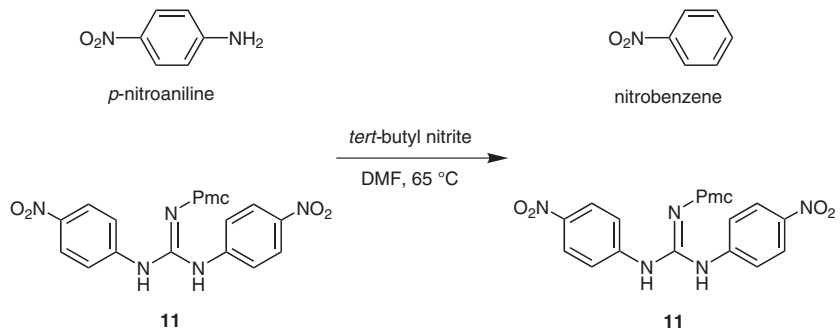
An advantage of this guanylation methodology is its amenability toward removal of the sulfonyl blocking group. Table 3 illustrates the ease with which most of the Pmc-guanidines **3** underwent deprotection, using TFA–H_2O (98:2) for six hours. After removal of excess TFA followed by trituration of the crude deprotection product with cold diethyl ether, the majority of the isolates were pure enough for immediate spectrographic characterization as their TFA salts. Occasionally, the crude isolate proved somewhat more impure, and chromatographic purification over silica gel was necessary using the unusual solvent system formic acid–MeOH–EtOAc (1:2:7) to afford guanidines **4** as their corresponding formate salts.



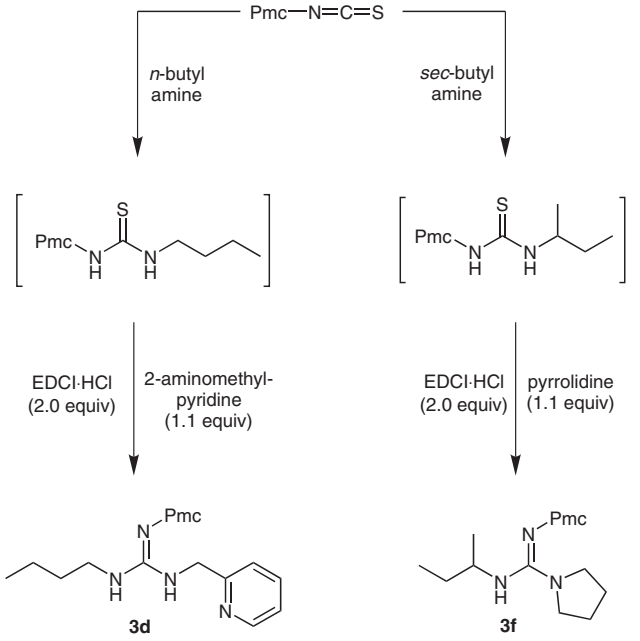
Scheme 8 Guanylation product profile from the disproportionation of thiourea **2o** with isopropylamine



Scheme 10 Direct synthesis of guanidine **11**



Scheme 11 Separation of residual *p*-nitroaniline from guanidine **11** via selective reduction of *p*-nitroaniline impurity using *tert*-butyl nitrite

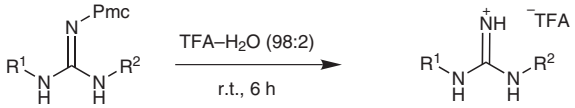


Scheme 12 One-pot synthesis of representative *N*-Pmc-guanidines **3d** and **3f**

In conclusion, we have investigated the scope and limitations of the guanidine-forming reaction sequence between *N*-sulfonyl-*N*′-substituted thioureas and amines under EDCI-mediated conditions. The general reaction is shown to easily tolerate a diversity of substitution patterns on the thiourea and amine fragments, affording products in generally high yield and purity. The four types of limitations encountered in this study were as follows:

1. The substituent on the *N*-Pmc-thiourea cannot possess an internal nucleophilic center.
2. The *N*-Pmc-thiourea can only tolerate monosubstitution patterns.
3. The amine component of the reaction must possess sufficient nucleophilicity to attack the in situ derived carbo-

Table 3 TFA Deprotection of *N*-Pmc-Protected Guanidines



3a–i,k **4a–i,k**

Pmc-protected guanidine	Pmc-deprotected guanidine
3a	**4a**: 96% R^1 = 3-methylpyrimidyl R^2 = cyclopropyl
3b	**4b**: 86% R^1 = cyclohexyl R^2 = benzyloxy
3d	**4d**: 84% R^1 = *n*-Bu R^2 = 2-methylpyridyl
3e	**4e**: 83% R^1 = Bn R^2 = NH_2-
3f	**4f**: ~100% R^1 = 1-methylpropyl R^2 = pyrrolidyl
3g	**4g**: ~100% R^1 = 2-methoxyphenyl R^2 = allyl
3h	**4h**: 89% R^1 = 2-methoxyphenyl R^2 = bis(4-methylenephenyl)
3i (= **10**)	**4i**: ~100% R^1,R^2 = lysyl benzyl ester
3k	**4k**: 71% R^1 = R^2 = *p*-nitrophenyl

diimide. Amines and anilines bearing an electron-withdrawing substituent can be problematic in the formation of both the thiourea and the guanidine component.

Finally, due to the ability of accessing these guanidine systems through two possible synthetic routes (i.e., the 'pairs approach'), all of the systems prohibited by these limitations using one approach could be realized by switching the substitution patterns on the thiourea and the amine.

Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. CH_2Cl_2 was distilled from CaH_2. All reactions were carried out under N_2 atmosphere. Flash chromatography was carried out on Sorbent Technologies silica gel (230–400 mesh). Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained using a PerkinElmer 2000 FT-IR spectrometer. 500 MHz and 125 MHz 1D NMR spectra were collected using standard pulse sequences provided by Bruker. Low-resolution mass spectrometric data were obtained using a Finnigan EI-CI mass spectrometer. High-resolution mass spectra were acquired from the Mass Spectrometry Resource of Washington University. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

2,2,5,7,8-Pentamethylchroman-6-sulfonamide (6)

2,2,5,7,8-Pentamethylchroman-6-sulfonyl chloride (**5**; 5.0 g, 0.017 mL) was dissolved in CH_2Cl_2 (75 mL). The resulting solution was brought to 0 °C in an ice bath, and gaseous ammonia was bubbled through it for 20 min. At the end of this time, it was noted that a white solid had precipitated out of the solution. This slurry was poured into a 500 mL separatory funnel containing EtOAc (150 mL) and H_2O (150 mL). After repeated shaking, the organic layer was separated, dried ($MgSO_4$) and concentrated to give the sulfonamide as a colorless solid (4.67 g, ~100%); mp 157–159 °C.

IR (film): 3287 cm^{-1} (NH).

^1H NMR (500 MHz, acetone-d_6): δ = 6.20 (br s, 2 H), 2.68 (t, *J* = 6.2 Hz, 2 H), 2.54 (s, 3 H), 2.52 (s, 3 H), 2.11 (s, 3 H), 1.84 (t, *J* = 6.5 Hz, 2 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 154.4, 135.9, 135.6, 134.3, 124.4, 119.0, 74.5, 33.2, 26.8, 21.8, 18.6, 17.5, 12.1.

MS (CI): *m*/*z* = 284 (M + H).

Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.40; H, 7.66; N, 5.00.

2,2,5,7,8-Pentamethylchroman-6-sulfonyl Thiocyanate (1)

2,2,5,7,8-Pentamethylchroman-6-sulfonamide (**6**; 4.67 g, 0.017 mol) and KOH (2.00 g, 0.036 mol) were refluxed for 24 h in a 4:1 mixture of benzene–CS_2 (100 mL) under Dean–Stark conditions. At the end of this time, most of the residual solvent had been distilled away and to the mixture was added additional benzene (75 mL) and redistilled again until the solvent was reduced to about 0.75 of its original volume. This was repeated one more time with additional benzene (75 mL) in order to remove any residual CS_2. The resulting yellow slurry was cooled to 0 °C in an ice bath and phosgene (20% in toluene; 15 mL, 2 equiv) was added dropwise over 30 min with vigorous stirring. The mixture was allowed to reach r.t. overnight, at which time N_2 was bubbled through it for 20 min in order to remove the remaining phosgene. The solvent was removed in vacuo and the residue was taken up and triturated in hexane (100 mL). Filtration of the solids and concentration in vacuo afforded **1** as a light yellow gum, which was used without further purification (4.15 g, 75%).

IR (film): 1898 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 6.8 Hz, 2 H), 2.59 (s, 3 H), 2.57 (s, 3 H), 2.14 (s, 3 H), 1.85 (t, *J* = 6.8 Hz, 2 H), 1.34 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 154.9, 137.31, 137.27, 129.4, 125.2, 118.8, 74.8, 32.5, 26.8, 21.4, 18.4, 17.4, 12.2.

MS (CI): *m*/*z* = 205, 267, 326 (M + H).

Anal. Calcd for $C_{15}H_{19}NO_3S_2$: C, 55.36; H, 5.88; N, 4.30. Found: C, 55.30; H, 6.01; N, 4.12.

***N*-Pmc-*N*′-Substituted Thioureas 2a–r; General Procedure**

To a 0 °C solution of Pmc-thiocyanate **1** (0.5 g, 1.5 mmol) in CH_2Cl_2 (15 mL) was added dropwise the respective primary amine (1.05 equiv) dissolved in CH_2Cl_2 (10 mL). After 30 min, the solvent was removed in vacuo to yield crude product, which was purified by flash chromatography on silica gel using 20% EtOAc–hexanes as eluent, except for *N*′-4-methyl-2-pyrimidyl-derived thiourea which was purified by way of trituration with CH_2Cl_2–hexanes (1:1) and filtration.

***N*-Pmc-*N*′-2-(4-methylpyrimidyl)thiourea (2a)**

Yield: 0.67 g (~100%); amorphous colorless solid; mp 160–162 °C (dec.).

IR (KBr): 3415, 1153 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 14.27 (br s, 1 H), 8.73 (br s, 1 H), 6.94 (d, *J* = 5.2 Hz, 1 H), 2.61–2.70 (m, 8 H), 2.57 (s, 3 H), 2.14 (s, 3 H), 1.84 (t, *J* = 6.7 Hz, 2 H), 1.34 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.4, 156.7, 155.7, 138.0, 137.5, 127.0, 124.6, 118.2, 115.7, 74.1, 32.6, 26.7, 23.9, 21.5, 17.9, 17.1, 12.3.

MS (CI): *m*/*z* = 204, 267, 435 (M + H).

Anal. Calcd for $C_{20}H_{26}N_4O_3S_2$: C, 55.28; H, 6.03; N, 12.89. Found: C, 55.29; H, 6.03; N, 12.71.

***N*-Pmc-*N*′-cyclopropylthiourea (2b)**

Yield: 0.58 g (99%); colorless friable foam; mp 142–143 °C.

IR (film): 3333, 1138 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (br s, 1 H), 7.79 (br s, 1 H), 2.90–2.93 (m, 1 H), 2.65 (t, *J* = 6.8 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.13 (s, 3 H), 1.84 (t, *J* = 6.8 Hz, 2 H), 1.33 (s, 6 H), 0.75–0.78 (m, 2 H), 0.30 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.9, 155.7, 136.9, 136.8, 127.3, 125.3, 118.9, 74.5, 32.4, 27.7, 26.6, 21.3, 18.2, 17.2, 12.1, 7.2.

MS (CI): *m*/*z* = 204, 267, 383 (M + H).

Anal. Calcd for $C_{18}H_{26}N_2O_3S_2$: C, 56.51; H, 6.85; N, 7.32. Found: C, 56.78; H, 6.92; N, 7.29.

***N*-Pmc-*N*′-cyclohexylthiourea (2c)**

Yield: 0.61 g (94%); colorless friable foam; mp 72–76 °C.

IR (film): 3335, 3335, 1123 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (br s, 1 H), 7.67 (d, *J* = 7.3 Hz, 1 H), 3.97–4.07 (m, 1 H), 2.65 (t, *J* = 6.8 Hz, 2 H), 2.59 (s, 3 H), 2.57 (s, 3 H), 2.12 (s, 3 H), 1.83 (t, *J* = 6.8 Hz, 2 H), 1.76–1.79 (m, 2 H), 1.54–1.56 (m, 3 H), 1.29–1.32 (m, 8 H), 1.17–1.23 (m, 1 H), 1.05–1.12 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 155.7, 136.9, 136.8, 127.4, 125.3, 118.9, 74.5, 54.0, 32.4, 31.4, 26.6, 25.3, 24.1, 21.3, 18.3, 17.3, 12.1.

MS (CI): *m*/*z* = 205, 425 (M + H).

Anal. Calcd for $C_{21}H_{32}N_2O_3S_2$: C, 59.40; H, 7.60; N, 6.60. Found: C, 59.50; H, 7.73; N, 6.46.

***N*-Pmc-*N′*-benzyloxythiourea (2d)**
Yield: 0.29 g (42%); amorphous colorless solid; mp 128–129 °C.

IR (film): 3228, 1150 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.72 (br s, 1 H), 7.29–7.48 (m, 5 H), 4.88 (s, 2 H), 2.64 (t, *J* = 6.1 Hz, 2 H), 2.53 (s, 3 H), 2.52 (s, 3 H), 2.11 (s, 3 H), 1.81 (t, *J* = 6.4 Hz, 2 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 137.3, 133.8, 129.3, 129.0, 127.0, 124.9, 118.5, 78.9, 74.3, 32.6, 26.7, 21.5, 18.1, 17.2, 12.3.

MS (MALDI): *m*/*z* = 449 (M + H).

HRMS: *m*/*z* calcd for $C_{22}H_{29}N_2O_4S_2$: 449.1570; found: 449.1565 (M + H).

***N*-Pmc-*N′*-(2,6-dichlorophenyl)thiourea (2e)**
Yield: 0.58 g (78%); colorless friable foam; mp 75–78 °C.

IR (film): 3291, 1521 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.02 (br s, 1 H), 8.98 (br s, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 7.9 Hz, 1 H), 2.55–2.76 (m, 8 H), 2.12 (s, 3 H), 1.82 (t, *J* = 6.3 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6, 155.8, 136.9, 134.6, 132.9, 129.6, 128.3, 127.6, 125.3, 118.9, 74.5, 32.4, 26.6, 21.2, 18.4, 17.4, 12.0.

MS (MALDI): *m*/*z* = 488 (M + H).

Anal. Calcd for $C_{21}H_{24}Cl_2N_2O_3S_2$: C, 51.74; H, 4.96; N, 5.75. Found: C, 51.69; H, 5.00; N, 5.66.

***N*-Pmc-*N′*-(2-hydroxyethyl)thiourea (2f)**
Yield: 0.52 g (88%); colorless gum.

IR (film): 3331, 1547 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.98 (br s, 1 H), 8.16 (br s, 1 H), 3.64 (s, 4 H), 2.65 (t, *J* = 6.1 Hz, 2 H), 2.58 (s, 3 H), 2.56 (s, 3 H), 2.12 (s, 3 H), 1.82 (t, *J* = 6.5 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5, 155.6, 137.0, 136.9, 127.1, 125.0, 118.8, 74.4, 60.3, 60.1, 47.6, 32.2, 26.5, 21.2, 18.0, 17.1, 14.0, 12.0.

MS (MALDI): *m*/*z* = 388 (M + H).

Anal. Calcd for $C_{17}H_{26}N_2O_4S_2$: C, 52.82; H, 6.78; N, 7.25. Found: C, 52.97; H, 6.95; N, 7.22.

***N*-Pmc-*N′*-butylthiourea (2g)**
Yield: 0.50 g (82%); colorless transparent gum.

IR (film): 3337, 1549 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.56 (br s, 1 H), 7.79 (s, 1 H), 3.45–3.50 (m, 1 H), 2.65 (t, *J* = 6.4 Hz, 2 H), 2.58 (s, 3 H), 2.57 (s, 3 H), 2.12 (s, 3 H), 1.83 (t, *J* = 6.6 Hz, 2 H), 1.36–1.44 (m, 2 H), 1.32 (s, 6 H), 1.11–1.20 (m, 2 H), 0.84 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0, 155.6, 136.8, 136.6, 127.5, 125.2, 118.8, 74.4, 45.3, 32.3, 30.2, 26.6, 21.2, 19.5, 18.2, 17.2, 13.5, 12.0.

MS (CI): *m*/*z* = 399 (M + H).

Anal. Calcd for $C_{19}H_{30}N_2O_3S_2$: 57.25; H, 7.59; N, 7.03. Found: C, 57.09; H, 7.44; N, 7.02.

***N*-Pmc-*N′*-(2-methylpyridyl)thiourea (2h)**
Yield: 0.39 g (58%); colorless friable foam; mp 51–54 °C.

IR (film): 3276, 1532 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.01 (br s, 1 H), 8.52 (d, *J* = 3.7 Hz, 1 H), 7.59 (t, *J* = 7.3 Hz, 1 H), 7.19 (t, *J* = 6.1 Hz, 1 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 4.77 (d, *J* = 3.6 Hz, 2 H), 2.52–2.75 (m, 8 H), 2.08 (s, 3 H), 1.78 (t, *J* = 6.5 Hz, 2 H), 1.28 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 155.5, 154.3, 148.7, 136.9, 136.6, 127.5, 125.0, 122.4, 121.3, 118.7, 74.3, 50.3, 32.4, 26.6, 21.2, 18.1, 17.2, 12.1.

MS (APCI): *m*/*z* = 434 (M + H).

Anal. Calcd for $C_{21}H_{27}N_3O_3S_2$: C, 58.17; H, 6.28; N, 9.69. Found: C, 58.45; H, 6.38; N, 9.50.

***N*-Pmc-*N′*-benzylthiourea (2i)**
Yield: 0.65 g (~100%); colorless friable foam; mp 60–66 °C.

IR (film): 3336, 1123 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 7.96 (br s, 1 H), 7.21–7.27 (m, 3 H), 6.94–6.96 (m, 2 H), 4.67 (d, *J* = 5.3 Hz, 2 H), 2.61 (t, *J* = 6.8 Hz, 2 H), 2.49 (s, 3 H), 2.48 (s, 3 H), 2.10 (s, 3 H), 1.84 (t, *J* = 6.8 Hz, 2 H), 1.35 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2, 155.8, 136.9, 136.7, 135.9, 128.7, 127.8, 127.4, 125.5, 119.0, 74.6, 49.8, 32.5, 26.7, 21.3, 18.2, 17.2, 12.2.

MS (CI): *m*/*z* = 205, 267, 433 (M + H).

Anal. Calcd for $C_{22}H_{28}N_2O_3S_2$: C, 61.08; H, 6.52; N, 6.48. Found: C, 61.38; H, 6.64; N, 6.37.

***N*-Pmc-*N′*-(*tert*-butoxycarbonyl)aminothiourea (2j)**
Yield: 0.57 g (83%); colorless friable foam; mp 84–87 °C.

IR (film): 3228, 1150 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.06 (br s, 1 H), 7.15 (br s, 1 H), 2.65 (t, *J* = 6.3 Hz, 2 H), 2.58 (s, 3 H), 2.57 (s, 3 H), 2.12 (s, 3 H), 1.82 (t, *J* = 6.5 Hz, 2 H), 1.44 (s, 9 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 153.9, 137.4, 137.1, 127.1, 125.2, 118.8, 82.6, 74.5, 32.4, 28.0, 26.7, 21.3, 18.1, 17.3, 12.1.

MS (MALDI): *m*/*z* = 400 (M – *t*-Bu).

Anal. Calcd for $C_{20}H_{31}N_3O_5S_2$: 52.49; H, 6.83; N, 9.18. Found: C, 52.72; H, 6.95; N, 9.15.

***N*-Pmc-*N′*-(1-methylpropyl)thiourea (2k)**
Yield: 0.50 g (81%); light yellow transparent gum.

IR (film): 3332, 1542 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (br s, 1 H), 7.54 (d, *J* = 6.9 Hz, 1 H), 4.13–4.19 (m, 1 H), 2.65 (t, *J* = 6.3 Hz, 2 H), 2.60 (s, 3 H), 2.58 (s, 3 H), 2.12 (s, 3 H), 1.83 (t, *J* = 6.6 Hz, 2 H), 1.35–1.44 (m, 2 H), 1.32 (s, 6 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 0.71 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1, 155.7, 136.8, 136.7, 127.4, 125.3, 118.9, 74.5, 53.0, 32.4, 28.7, 26.6, 21.3, 18.9, 18.2, 17.2, 12.0, 9.6.

MS (CI): *m*/*z* = 399 (M + H).

Anal. Calcd for $C_{19}H_{30}N_2O_3S_2$: 57.25; H, 7.59; N, 7.03. Found: C, 57.42; H, 7.61; N, 6.98.

***N*-Pmc-*N″*,*N″*-bis(α,β-methylene)thiourea (2l)**
Yield: 0.26 g (44%); colorless amorphous solid; mp 126–128 °C.

IR (film): 3244, 1549 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.33 (br s, 1 H), 3.52–3.76 (m, 4 H), 2.67 (t, *J* = 6.0 Hz, 2 H), 2.63 (s, 6 H), 2.13 (s, 3 H), 1.85–2.09 (m, 4 H), 1.82 (t, *J* = 6.4 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 137.7, 137.1, 124.6, 123.0 (br), 118.2, 74.1, 52.2 (br), 49.3 (br), 32.7, 26.8, 26.4 (br), 24.5 (br), 21.6, 18.2, 17.3, 12.3.

MS (APCI): *m*/*z* = 397 (M + H).

Anal. Calcd for $C_{19}H_{28}N_2O_3S_2$: 57.54; H, 7.12; N, 7.06. Found: C, 57.31; H, 7.15; N, 6.98.

_N_-Pmc-_N_′-(_o_-methoxyphenyl)thiourea (2m)
Yield: 0.56 g (81%); colorless friable foam; mp 76–78 °C.

IR (film): 3272, 1123 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.94 (br s, 1 H), 8.36 (d, *J* = 7.9 Hz, 1 H), 8.04 (br s, 1 H), 7.12–7.16 (m, 1 H), 6.84–6.93 (m, 2 H), 3.84 (s, 3 H), 2.56–2.76 (m, 8 H), 2.12 (s, 3 H), 1.82 (t, *J* = 6.8 Hz, 2 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 155.7, 150.4, 136.8, 136.7, 127.7, 127.0, 126.4, 125.2, 122.7, 120.1, 118.8, 110.6, 74.4, 55.8, 32.4, 26.6, 21.3, 18.1, 17.1, 12.1.

MS (CI): *m*/*z* = 205, 267, 449 (M + H).

HRMS: *m*/*z* calcd for $C_{22}H_{28}N_2O_4S_2$: 449.1569; found: 449.1577 (M + H).

_N_-Pmc-_N_′-isopropylthiourea (2n)
Yield: 0.48 g (81%); colorless amorphous solid; mp 122–124 °C.

IR (film): 3334, 1541 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (br s, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 4.21–4.33 (m, 1 H), 2.65 (t, *J* = 6.2 Hz, 2 H), 2.59 (s, 3 H), 2.58 (s, 3 H), 2.12 (s, 3 H), 1.83 (t, *J* = 6.4 Hz, 2 H), 1.32 (s, 6 H), 1.05 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7, 155.5, 136.8, 136.7, 127.2, 125.0, 118.7, 74.3, 47.4, 32.2, 29.4, 26.4, 21.2, 21.1, 18.0, 17.0, 11.9.

MS (CI): *m*/*z* = 385 (M + H).

HRMS: *m*/*z* calcd for $C_{18}H_{28}N_2O_3S_2$: 384.1542; found: 384.1537 (M + H).

_N_-Pmc-_N_′-(_p_-nitrophenyl)thiourea (2o)
Yield: 0.64 g (90%); yellow solid; mp 144–146 °C.

IR (film): 3285, 1898 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.85 (br s, 1 H), 8.17 (d, *J* = 8.1 Hz, 2 H), 7.69 (d, *J* = 8.3 Hz, 2 H), 2.56–2.68 (m, 8 H), 2.11 (s, 3 H), 1.82 (t, *J* = 6.6 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 156.2, 145.0, 143.2, 137.0, 136.9, 127.1, 125.7, 124.5, 123.0, 119.2, 74.8, 32.3, 26.6, 21.3, 18.3, 17.3, 12.2.

MS (APCI): *m*/*z* = 464 (M + H).

Anal. Calcd for $C_{21}H_{25}N_3O_5S_2$: C, 54.41; H, 5.44; N, 9.06. Found: C, 54.23; H, 5.46; N, 8.91.

_N_-Pmc-_N_′-allylthiourea (2p)
Yield: 0.58 g (99%); colorless friable foam; mp 112–116 °C.

IR (film): 3341, 1146 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H), 7.90 (br s, 1 H), 5.65–5.72 (m, 1 H), 5.08 (d, *J* = 10.4 Hz, 1 H), 4.98 (d, *J* = 14.5 Hz, 1 H), 4.15 (dd, *J* = 4.3, 1.0 Hz, 2 H), 2.66 (t, *J* = 6.8 Hz, 2 H), 2.59 (s, 3 H), 2.58 (s, 3 H), 2.14 (s, 3 H), 1.85 (t, *J* = 6.8 Hz, 2 H), 1.34 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3, 155.7, 136.8, 136.7, 131.7, 127.3, 125.3, 118.9, 117.1, 74.5, 47.7, 32.4, 26.6, 21.2, 18.2, 17.2, 12.0.

MS (CI): *m*/*z* = 204, 267, 383 (M + H).

Anal. Calcd for $C_{18}H_{26}N_2O_3S_2$: C, 56.51; H, 6.85; N, 7.32. Found: C, 56.93; H, 6.95; N, 7.20.

Bis[_N_-(4,4′-methylene)]-_N_′-Pmc-thiourea (2q)
Yield: 1.30 g (87%); colorless friable foam; mp 120–123 °C.

IR (film): 3304, 2930 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.42 (br s, 2 H), 8.18 (br s, 2 H), 7.22 (d, *J* = 7.9 Hz, 4 H), 7.10 (d, *J* = 7.9 Hz, 4 H), 3.90 (s, 2 H), 2.53–2.68 (m, 16 H), 2.12 (s, 6 H), 1.81 (t, *J* = 6.4 Hz, 4 H), 1.31 (s, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.3, 155.9, 139.4, 136.9, 135.7, 129.3, 127.4, 125.5, 124.5, 119.0, 74.6, 40.9, 32.4, 26.6, 21.3, 18.2, 17.3, 12.1.

MS (APCI): *m*/*z* = 524 (M – PmcNCS).

Anal. Calcd for $C_{43}H_{52}N_4O_6S_4$: C, 60.82; H, 6.17; N, 6.60. Found: C, 60.80; H, 6.20; N, 6.61.

_N_-Pmc-_N_′,_N_″-Substituted Guanidines 3 from Thioureas 2 and Amines; General Two-Step Procedure
To a 100 mL round-bottomed flask containing a stirred solution of the representative thiourea transfer agent **2** (1.25 mmol) in CH_2Cl_2 (50 mL) was added EDCI·HCl (0.48 g, 2.50 mmol) in one portion. Following dissolution of the EDCI·HCl (~15 s), the appropriate amine (1.1 equiv) was added to the mixture and the solution was allowed to stir for 30 min. At the end of this time, the solvent was removed in vacuo. The crude product was then chromatographically purified over silica gel (20–40% EtOAc–hexanes).

_N_-Pmc-_N_′,_N_″-Substituted Guanidines 3 from Pmc-Isothiocyanate 1 and Sequential Addition of Amine and EDCI·HCl Reagents; General One-Pot Procedure
To a 100 mL round-bottomed flask containing a stirred solution of Pmc-isothiocyanate **1** (1.25 mmol) in CH_2Cl_2 (50 mL), was added the first amine (1.0 equiv) and allowed to stir for 30 min. To this solution was added EDCI·HCl (2 equiv) in one portion followed immediately by the second amine (1.1 equiv) and the solution was stirred for an additional 30 min. At the end of this time, the solvent was removed in vacuo. The crude product was then chromatographically purified over silica gel (EtOAc–hexane).

_N_-Pmc-_N_′-(4-methylpyrimid-2-yl)-_N_″-cyclopropylguanidine (3a)
Yield: 0.56 g (82%); colorless friable foam; mp 70–73 °C.

IR (film): 3261, 1442 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.31 (br s, 1 H), 9.79 (br s, 1 H), 8.29 (d, *J* = 4.8 Hz, 1 H), 6.82 (d, *J* = 4.8 Hz, 1 H), 6.83 (s, 1 H), 2.72 (s, 3 H), 2.69 (s, 3 H), 2.64 (t, *J* = 6.2 Hz, 2 H), 2.42 (s, 3 H), 2.12 (s, 3 H), 1.79 (t, *J* = 6.4 Hz, 2 H), 1.30 (s, 6 H), 0.79 (d, *J* = 6.2 Hz, 2 H), 0.58 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 157.1, 156.7, 153.4, 152.0, 135.5, 134.8, 133.5, 123.6, 117.7, 115.2, 73.4, 32.6, 26.5, 23.7, 23.6, 21.2, 18.3, 17.2, 11.9, 6.6.

MS (MALDI): *m*/*z* = 458 (M + H).

Anal. Calcd for $C_{23}H_{31}N_5O_3S$: C, 60.37; H, 6.83; N, 15.30. Found: C, 60.30; H, 6.88; N, 15.24.

_N_-Pmc-_N_′-cyclohexyl-_N_″-benzyloxyguanidine (3b)
Yield: 0.57 g (74%); colorless friable foam; mp 63–66 °C.

IR (film): 3306, 1576 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.22 (br s, 1 H), 7.25–7.43 (m, 3 H), 7.12–7.22 (m, 2 H), 5.28 (d, *J* = 6.6 Hz, 1 H), 4.69 (s, 2 H),

3.53–3.65 (m, 1 H), 2.65 (t, *J* = 6.1 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.13 (s, 3 H), 1.83 (t, *J* = 6.3 Hz, 2 H), 1.63–1.77 (m, 2 H), 1.49–1.63 (m, 3 H), 1.19–1.43 (m, 9 H), 1.03–1.17 (m, 1 H), 0.82–1.00 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.0, 153.5, 135.7, 135.0, 134.6, 133.2, 129.5, 129.1, 128.8, 124.0, 117.8, 79.0, 73.6, 49.1, 32.9, 32.7, 26.8, 25.3, 24.5, 21.5, 18.4, 17.3, 12.1.

MS (MALDI): *m*/*z* = 514 (M + H).

Anal. Calcd for $C_{28}H_{39}N_3O_4S$: C, 65.47; H, 7.65; N, 8.18. Found: C, 65.27; H, 7.73; N, 8.08.

_N_-Pmc-_N′_-(2,6-dichlorophenyl)-_N″_-(2-hydroxyethyl)guanidine (3c)
Yield: 0.52 g (67%); colorless friable foam; mp 84–86 °C.

IR (film): 3294, 1107 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (br s, 1 H), 7.24–7.37 (m, 2 H), 3.63 (br s, 2 H), 3.41 (br s, 2 H), 2.61 (t, *J* = 6.0 Hz, 2 H), 2.55 (s, 3 H), 2.53 (s, 3 H), 2.10 (s, 3 H), 1.80 (t, *J* = 6.4 Hz, 2 H), 1.30 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.6, 135.7, 135.0, 134.6, 133.2, 129.2, 128.8, 123.8, 117.8, 73.6, 61.9, 44.0, 32.8, 26.7, 21.3, 18.5, 17.4, 12.0.

MS (MALDI): *m*/*z* = 514 (M + H).

Anal. Calcd for $C_{23}H_{29}Cl_2N_3O_4S$: C, 53.70; H, 5.68; N, 8.17. Found: C, 53.81; H, 5.68; N, 8.09.

_N_-Pmc-_N′_-(2-methylpyridyl)-_N″_-butylguanidine (3d)
Yield: 0.65 g (91%); colorless gummy semisolid.

IR (film): 3337, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 3.6 Hz, 1 H), 7.61 (br s, 1 H), 7.18 (d, *J* = 6.9 Hz, 2 H), 7.10 (br s, 1 H), 4.45 (br s, 2 H), 3.19 (d, *J* = 5.0 Hz, 2 H), 2.50–2.69 (m, 8 H), 2.03 (s, 3 H), 1.79 (t, *J* = 6.5 Hz, 2 H), 1.45–1.60 (m, 2 H), 1.21–1.40 (m, 8 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 155.1, 153.2, 148.5, 137.0, 135.4, 134.6, 134.0, 123.6, 122.5, 117.6, 73.4, 41.2, 32.8, 31.0, 26.6, 21.3, 19.8, 18.4, 17.3, 13.5, 11.9.

MS (MALDI): *m*/*z* = 476 (M + H).

Anal. Calcd for $C_{25}H_{36}N_4O_3S$: C, 63.53; H, 7.68; N, 11.85. Found: C, 63.32; H, 7.64; N, 11.66.

_N_-Pmc-_N′_-benzyl-_N″_-(*tert*-butoxycarbonyl)aminoguanidine (3e)
Yield: 0.67 g (98%); colorless friable foam; mp 79–84 °C.

IR (film): 3320, 1718 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (br s, 1 H), 7.16–7.24 (m, 5 H), 6.71 (br s, 1 H), 6.06 (br s, 1 H), 4.40 (d, *J* = 5.7 Hz, 2 H), 2.60 (t, *J* = 6.8 Hz, 2 H), 2.56 (s, 3 H), 2.53 (s, 3 H), 2.09 (s, 3 H), 1.80 (t, *J* = 6.8 Hz, 2 H), 1.41 (s, 9 H), 1.31 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 154.9, 153.7, 135.8, 135.1, 133.2, 128.5, 127.6, 127.4, 123.9, 117.8, 82.6, 73.6, 44.8, 32.9, 28.0, 26.8, 21.4, 18.5, 17.4, 12.0.

MS (MALDI): *m*/*z* = 531 (M + H), 553 (M + Na), 569 (M + K).

Anal. Calcd for $C_{27}H_{38}N_4O_5S$: C, 61.11; H, 7.22; N, 10.56. Found: C, 61.01; H, 7.28; N, 10.65.

_N_-Pmc-_N′_-(1-methylpropyl)-_N″_-bis(α,β-methylene)guanidine (3f)
Yield: 0.65 g (~100%); colorless viscous oil.

IR (film): 3319, 1576 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.33 (d, *J* = 8.2 Hz, 1 H), 3.42 (br s, 4 H), 3.30–3.38 (m, 1 H), 2.59–2.67 (m, 8 H), 2.10 (s, 3 H), 1.84 (br s, 4 H), 1.80 (t, *J* = 6.8 Hz, 2 H), 1.19–1.40 (m, 8 H), 0.90 (d, *J* = 6.2 Hz, 2 H), 0.80 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 153.1, 135.4, 134.6, 134.1, 123.6, 117.6, 73.3, 51.1, 49.0, 32.7, 30.1, 26.5, 25.1, 21.2, 20.2, 18.6, 17.4, 11.8, 10.1.

MS (APCI): *m*/*z* = 436 (M + H).

Anal. Calcd for $C_{23}H_{37}N_3O_3S$: C, 63.41; H, 8.56; N, 9.65. Found: C, 63.08; H, 8.59; N, 9.52.

_N_-Pmc-_N′_-allyl-_N″_-(*o*-methoxyphenyl)guanidine (3g)
Yield: 0.42 g (99%); colorless friable foam; mp 43–45 °C.

IR (film): 3314, 1582, 1558 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.14–7.21 (m, 1 H), 7.06–7.14 (m, 1 H), 7.00 (d, *J* = 6.4 Hz, 1 H), 6.83–6.91 (m, 1 H), 5.69–5.80 (m, 1 H), 4.95–5.10 (m, 2 H), 3.83 (s, 2 H), 3.74 (s, 3 H), 2.63 (br s, 2 H), 2.55 (s, 3 H), 2.53 (s, 3 H), 2.08 (s, 3 H), 1.81 (br s, 2 H), 1.29 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.4, 153.1, 135.5, 134.9, 133.7, 133.6, 127.1, 125.1, 123.7, 120.9, 117.7, 116.7, 111.5, 73.4, 55.6, 43.8, 32.8, 26.6, 21.3, 18.4, 17.3, 11.9.

MS (MALDI): *m*/*z* = 472 (M + H).

Anal. Calcd for $C_{25}H_{33}N_3O_4S$: C, 63.67; H, 7.05; N, 8.91. Found: C, 63.77; H, 6.99; N, 8.87.

Bis[_N_-(4,4′-methylene)-_N′_-Pmc-_N″_-(2-methoxyphenyl)guanidine (3h)
Yield: 0.70 g (91%); colorless friable foam; mp 103–107 °C.

IR (film): 3287, 1549 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (br s, 2 H), 7.84–7.98 (m, 2 H), 7.70 (br s, 2 H), 7.21 (s, 8 H), 7.04 (t, *J* = 6.6 Hz, 2 H), 6.88 (t, *J* = 7.5 Hz, 2 H), 6.79 (d, *J* = 7.9 Hz, 2 H), 3.99 (s, 2 H), 3.65 (s, 6 H), 2.57–2.73 (m, 16 H), 2.13 (s, 6 H), 1.80 (t, *J* = 6.4 Hz, 2 H), 1.31 (s, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.6, 150.6, 139.4, 135.6, 135.0, 134.1, 133.3, 129.9, 129.5, 126.0, 125.2, 123.9, 122.5, 120.8, 117.8, 110.5, 73.6, 55.6, 40.7, 32.7, 26.6, 21.3, 18.5, 17.4, 12.0.

MS (MALDI): *m*/*z* = 1028 (M + H).

Anal. Calcd for $C_{57}H_{66}N_6O_8S_2$: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.93; H, 6.70; N, 8.19.

_N_-Pmc-[_N′_-(α)-_N″_-(ε)-Lysine Benzyl Ester]guanidine (3i = 10); Typical Procedure
Lysine benzyl ester di-trifluoroacetate (0.490 g, 1.06 mmol) was suspended in CH_2Cl_2 (250 mL) under an inert atmosphere with rapid stirring. Hünig's base (910 μL, 10 equiv) was then added dropwise over 5 min, initiating dissolution of the reactant. After most of the starting material had dissolved, Pmc-isothiocyanate **1** (0.340 g, 1.0 equiv) dissolved in CH_2Cl_2 (5 mL) was added dropwise over 20 min. After TLC confirmation of the absence of **1** from the reaction (20 min), EDCI·HCl (0.202 g, 1.0 equiv) was added to the mixture in one portion. After 10 min, the solvent was removed in vacuo, and the crude product was purified via silica gel chromatography using 80% EtOAc–hexanes as eluent to yield **3i** (= **10**) as a colorless friable foam (0.36 g, 65%); mp 84–86 °C.

IR (film): 3245, 1741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59 (br s, 1 H), 7.27–7.43 (m, 5 H), 5.16 (s, 2 H), 4.62–4.74 (m, 1 H), 3.50–3.62 (m, 1 H), 3.36–3.48 (m, 1 H), 2.50–2.68 (m, 8 H), 2.08 (s, 3 H), 1.96–2.06 (m, 1 H), 1.83–1.95 (m, 1 H), 1.77 (t, *J* = 6.2 Hz, 2 H), 1.50–1.71 (m, 4 H), 1.28 (d, *J* = 4.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 156.5, 153.2, 135.8, 135.2, 134.8, 133.3, 128.6, 128.4, 123.7, 117.7, 73.4, 67.6, 54.1, 40.8, 34.0, 32.8, 29.0, 26.6, 26.5, 21.3, 20.0, 18.4, 17.3, 11.9.

MS (MALDI): *m*/*z* = 528 (M + H).

Anal. Calcd for $C_{28}H_{37}N_3O_5S$: C, 63.73; H, 7.07; N, 7.96. Found: C, 63.78; H, 7.13; N, 7.85.

2-(Pmc)amino-3,4-dihydrooxazole (7)
Yield: 0.48 g (91%); colorless friable foam; mp 60–63 °C.

IR (film): 3390, 1635 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (br s, 1 H), 4.47 (t, *J* = 8.1 Hz, 2 H), 3.78 (t, *J* = 8.2 Hz, 2 H), 2.63 (t, *J* = 6.4 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.11 (s, 3 H), 1.80 (t, *J* = 6.6 Hz, 2 H), 1.30 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3, 154.0, 135.8, 135.4, 131.8, 124.0, 117.9, 73.6, 66.4, 42.5, 32.7, 26.6, 21.3, 18.3, 17.2, 11.9.

MS (CI): *m*/*z* = 353 (M + H).

Anal. Calcd for $C_{17}H_{24}N_2O_4S$: C, 57.93; H, 6.86; N, 7.95. Found: C, 57.75; H, 6.88; N, 7.90.

3-(Pmc)amino-2,4-diazaindene (8)
Yield: 0.56 g (93%); light yellow friable foam; mp 70–73 °C.

IR (film): 3294, 1599 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.2 Hz, 1 H), 6.97 (d, *J* = 9.3 Hz, 1 H), 6.80 (s, 1 H), 6.54 (t, *J* = 6.4 Hz, 1 H), 6.26 (t, *J* = 6.6 Hz, 1 H), 2.59–2.78 (m, 8 H), 2.11 (s, 3 H), 1.79 (t, *J* = 6.5 Hz, 2 H), 1.30 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.4, 139.9, 135.5, 134.8, 134.1, 123.9, 122.1, 121.1, 117.8, 117.5, 111.2, 100.2, 73.5, 32.8, 26.7, 21.4, 18.7, 17.6, 12.0.

MS (CI): *m*/*z* = 135 (M – Pmc).

N-Pmc-N′,N″-bis(*p*-nitrophenyl)guanidine (11)
Pmc-isothiocyanate **1** (0.230 g, 0.707 mmol) and *p*-nitroaniline (0.244 g, 2.5 equiv) were dissolved in DMF (15 mL) under an inert atmosphere and stirred for 30 min. EDCI·HCl (0.176 g, 1.3 equiv) was then added in one portion, and the mixture was stirred for an additional 12 h. After this time, the mixture was heated to 65 °C in an oil bath, and *tert*-butyl nitrite (94 μL, 1.0 equiv), dissolved in DMF (5 mL) was added dropwise via syringe over 5 min. After 5 min, gas evolution was evident and the mixture turned orange. The mixture was maintained at 65 °C until gas evolution had ceased. The contents of the reaction vessel were then poured into EtOAc (100 mL), and extracted with 2% aq HCl (3 × 50 mL). The organic portion was then dried ($MgSO_4$), and the solvent removed in vacuo to yield the crude product. Silica gel column purification (40% EtOAc–hexanes) afforded the pure product (0.16 g, 23%) as a yellow friable foam; mp 110–112 °C.

IR (film): 3284, 1622 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (br s, 2 H), 8.08 (d, *J* = 8.8 Hz, 4 H), 7.41 (d, *J* = 9.0 Hz, 4 H), 2.62 (t, *J* = 6.7 Hz, 2 H), 2.54 (s, 3 H), 2.52 (s, 3 H), 2.10 (s, 3 H), 1.82 (d, *J* = 6.7 Hz, 2 H), 1.32 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 149.1, 144.5, 142.3, 135.7, 135.4, 131.3, 125.0, 124.6, 122.4, 118.4, 74.1, 63.6, 32.6, 26.7, 21.3, 18.6, 17.5, 12.0.

HRMS: *m*/*z* calcd for $C_{27}H_{29}N_5O_7S$ + Li: 574.1788; found: 574.1972 (M + Li).

Deprotection of *N*-Pmc-*N*′,*N*″-Disubstituted Guanidines 4a,b,d–i,k; General Procedure
The *N*-Pmc-*N*′,*N*″-disubstituted guanidine **3** (0.50 mmol) was stirred in 98:2 TFA–H_2O for 6 h, followed by removal of the acidic supernatant in vacuo. The deprotected guanidine was isolated via trituration of the residue in Et_2O to afford the crude reaction product as a white powder. In most cases, the resulting deprotected guanidine was pure enough for spectroscopic characterization as its TFA salt. Occasionally, small amounts of residual pentamethylchroman within the crude product necessitated chromatographic purification over silica gel (eluent: 1:2:7 formic acid–MeOH–EtOAc), and the compound then characterized as its formate salt.

***N*-(4-Methylpyrimidyl)-*N*′-cyclopropylguanidine (4a)**
Yield: 0.15 g (96%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.30 (d, *J* = 4.9 Hz, 1 H), 6.95 (d, *J* = 4.9 Hz, 1 H), 2.53–2.60 (m, 1 H), 2.32 (s, 3 H), 0.82 (d, *J* = 5.9 Hz, 2 H), 0.62 (s, 2 H).

MS (MALDI): *m*/*z* = 192 (M + H).

***N*-Cyclohexyl-*N*′-benzyloxyguanidine (4b)**
Yield: 0.13 g (86%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.50 (s, 1 H), 7.28–7.47 (m, 5 H), 4.84 (s, 2 H), 3.29–3.41 (m, 1 H), 1.85–1.93 (m, 1 H), 1.77–1.85 (m, 1 H), 1.66–1.76 (m, 2 H), 1.54–1.66 (m, 1 H), 1.10–1.49 (m, 6 H).

MS (MALDI): *m*/*z* = 248 (M + H).

***N*-Butyl-*N*′-(2-pyridyl)methylguanidine (4d)**
Yield: 0.18 g (84%); isolated as its 2 × TFA salt.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.56 (s, 1 H), 7.84 (t, *J* = 7.0 Hz, 1 H), 7.66 (s, 1 H), 7.51 (s, 1 H), 7.30–7.40 (m, 2 H), 4.51 (s, 2 H), 3.09–3.22 (m, 2 H), 1.41–1.54 (m, 2 H), 1.23–1.37 (m, 2 H), 0.88 (t, *J* = 7.1 Hz, 3 H).

MS (MALDI): *m*/*z* = 207 (M + H).

***N*-Benzyl-*N*′-aminoguanidine (4e)**
Yield: 0.12 g (83%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.48 (br s, 1 H), 8.15 (br s, 1 H), 7.23–7.43 (m, 5 H), 4.47 (s, 2 H).

MS (MALDI): *m*/*z* = 165 (M + H).

***N*-(1-Methylpropyl)-*N*′-bis(α,β-methylene)guanidine (4f)**
Yield: 0.14 g (~100%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 3.38–3.50 (m, 1 H), 3.26–3.38 (m, 4 H), 1.85–2.00 (m, 4 H), 1.41–1.60 (m, 2 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 0.84 (t, *J* = 7.3 Hz, 3 H).

MS (MALDI): *m*/*z* = 170 (M + H).

***N*-(*o*-Methoxyphenyl)-*N*′-allylguanidine (4g)**
Yield: 0.16 g (~100%); isolated as its TFA salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.27 (t, *J* = 6.7 Hz, 1 H), 7.13 (t, *J* = 6.7 Hz, 1 H), 7.02 (d, *J* = 7.5 Hz, 1 H), 6.91 (t, *J* = 7.6 Hz, 1 H), 5.73–5.82 (m, 1 H), 5.22 (d, *J* = 17.2 Hz, 1 H), 5.12 (d, *J* = 10.4 Hz, 1 H), 4.78 (s, 3 H), 3.77–3.85 (m, 2 H).

MS (MALDI): *m*/*z* = 206 (M + H).

Bis[*N*-(4,4′-methylene)-*N*′-(2-methoxyphenyl)]guanidine (4h)
Yield: 0.32 g (89%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.28 (t, *J* = 7.2 Hz, 2 H), 7.12–7.25 (m, 10 H), 7.04 (d, *J* = 8.2 Hz, 2 H), 6.93 (t, *J* = 7.5 Hz, 2 H), 3.93 (s, 2 H), 3.82 (s, 6 H).

MS (MALDI): *m*/*z* = 575 (M + H).

***N*-(α)-*N*′-(ε)-(Lysine Benzyl Ester)guanidine (4i)**
Yield: 0.15 g (~100%); isolated as its formate salt.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.15 (br s, 1 H), 8.44 (br s, 1 H), 8.12 (br s, 1 H), 7.58 (br s, 1 H), 7.30–7.45 (m, 5 H), 5.22 (q, *J* = 9.6 Hz, 2 H), 5.01–5.12 (m, 1 H), 3.67–3.84 (m, 1 H), 3.01–3.13 (m, 1 H), 2.01–2.14 (m, 1 H), 1.61–1.85 (m, 4 H), 1.46–1.61 (m, 1 H).

MS (MALDI): *m*/*z* = 262 (M + H).

***N*,*N*′-Bis(*p*-nitrophenyl)guanidine (4k)**
Yield: 0.15 g (71%); isolated as its formate salt.

^{1}H NMR (500 MHz, CD_3OD): δ = 8.18 (d, *J* = 8.4 Hz, 4 H), 7.45 (d, *J* = 8.4 Hz, 4 H).

MS (CI): *m*/*z* = 302 (M + H).

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