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The $HgCl_2$-Promoted Guanylation Reaction: The Scope and Limitations

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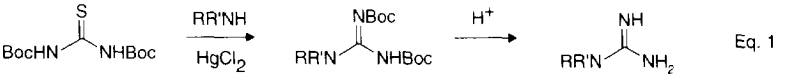
Abstract: The $HgCl_2$-promoted guanylation reaction was studied with various substituted thiourea starting materials and the scope and limitations are presented. The process was found to be effective with thioureas containing at least one N-conjugated substituent. Such activating groups include N-carbonyl- (acyl, alkoxycarbonyl, carbamoyl, etc.), N-cyano-, N-sulfonyl-, and N-aryl- substituents.

The guanidine functional group, often found in natural products, plays important roles in biological systems. Its high affinity for carboxylates, phosphates, and metals is an important aspect in interactions between receptors and their ligands. For this reason, it is often present in many drug compounds as well, covering a wide range of pharmacological activities.[1] The chemistry of guanidines has recently been reviewed,[2] but new synthetic methods for this important functional group continue to emerge, manifesting the interests in this area as well as the need for alternative preparative routes satisfying particular synthetic requirements.

One such new method utilizes $HgCl_2$, which promotes a reaction between bis-Boc-protected thiourea and amines.[3] The products, bis-Boc-protected guanidines, are deprotected to form mono-substituted *terminal* guanidines (Eq. 1). This process works well even with unreactive amines such as aromatic amines, and finds a wide use for the synthesis of terminal guanidines.



Eq. 1

Difficulties are sometimes encountered, on the other hand, in the synthesis of N,N'-disubstituted *internal* guanidines. Recent developments in this area include $CuSO_4$/silica gel-promoted guanylation of (bis)substituted thioureas,[4] water-soluble carbodiimide-promoted guanylation of N-alkyl-N'-Boc-thioureas,[5] and regioselective N-alkylation of bis-Boc-protected terminal guanidines.[6] Each of these methods is quite effective for the preparation of bis-alkyl substituted internal guanidines, but not suitable for many other substituents.

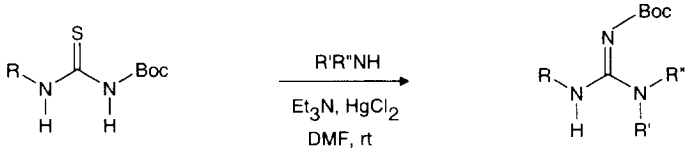
In an effort to expand the $HgCl_2$-promoted guanylation reaction further, to include substituted internal guanidine products, we have explored the original process with various thiourea starting materials. Reported herein are its scope and limitations.

RESULTS AND DISCUSSION

Mono-Boc Protected Guanidines: The Boc group in the $HgCl_2$-process, and other carbamate groups in related guanylation processes, play an interesting role: more than just a protecting group, they actually render the reactions possible.[7] We were therefore interested to know if the $HgCl_2$-process might work with just one Boc group in the starting material, i.e., N-Boc-N'-substituted thioureas. If successful, this process followed by Boc-deprotection would provide an efficient access to internal guanidines.[8]

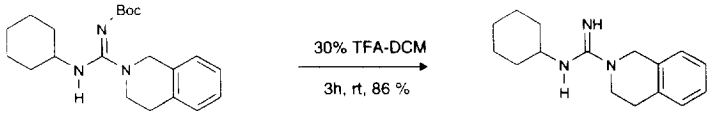
N-Substituted thioureas were treated with $(Boc)_2O$ in the presence of base (NaH or DMAP) to obtain the required substrates. Following the original procedure, the N-Boc-N'-substituted thioureas were treated with an amine in the presence of $HgCl_2$.[3] The results are summarized in Table 1.

Table 1. N-Boc-Guanylations



Entry	R	R'R"NH	Time	Yield
1	cyclohexyl-	tetrahydroisoquinoline	3.5 h	63 %
2	cyclohexyl-	aniline	4 h	70 %
3	*p*-nitrophenyl-	*p*-methoxyaniline	0.5 h	85 %

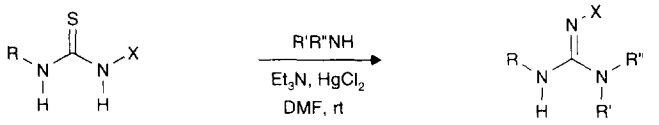
N-Boc-N'-substituted thioureas reacted smoothly with an amine in the presence of $HgCl_2$. The substituent on the starting N-Boc-thioureas may be alkyl or aryl; as can the incoming amine. The products, N-Boc-N',N"-disubstituted guanidines, can be easily deprotected, as exemplified in Eq. 2. Thus, this process provides a very efficient route to N,N'-disubstituted (internal) guanidines. It compares very favorably with the existing methods for the preparation of internal guanidines, in that the present methods are effective for diaryl-substituted internal guanidines (entry 3) as well as alkyl-substituted ones.



Eq. 2

N-Carbonyl-, N-Cyano-, and N-Sulfonyl-Guanidines: The success with N-Boc-N'-substituted guanidines in the $HgCl_2$-promoted process prompted us to try other conjugated substituents such as acyl, cyano

and sulfonyl groups (Eq. 3). These substituents are often found in many drug compounds. In this study, we fixed the substituent R to be cyclohexyl and the incoming amine, R'R"NH, to be tetrahydroisoquinoline as these groups were judged to be electronically and sterically neutral, thus enabling us to study fully the effects of the conjugated substituents, X.

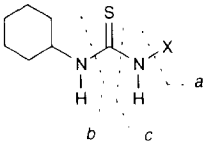


X = COR^1, CN, SO_2R^1, etc

Eq. 3

The required thiourea starting material was prepared following one of three disconnections (Scheme 1). Thus, for N-Boc-, N-acetyl-, and N-benzylcarbamoyl-substituted compounds, N-cyclohexylthiourea was treated with $(Boc)_2O$, Ac_2O and BnNCO, respectively (disconnection *a*). N-Tosyl- and N-benzoyl-N'-cyclohexylthioureas were prepared by reacting cyclohexylamine with TsNCS and BzNCS, respectively (disconnection *b*). The difficulty in preparing TsNCS,[9] coupled with easy availability of $TsNH_2$ prompted us to

Scheme 1. Synthesis of N-acyl-, N-cyano-, and N-sulfonyl-thioureas.



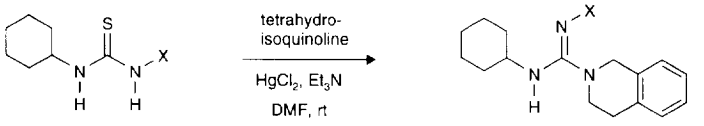
disconnection *a*	**disconnection *b***	**disconnection *c***
X = Boc (67 %)	X = Ts (30 %)	X = Ts (in situ)
Ac (84 %)	Bz (57 %)	CN (in situ)
CONHBn (32 %)		

consider an alternative route for the N-sulfonyl-guanidine. Thus, cyclohexylisothiocyanate was treated with the anion of tosylamide (disconnection *c*). Similarly, treatment with the anion of cyanamide provided the N-cyano-compound. The thioureas prepared *via* disconnection *c* were not isolated, but used *in situ* in their anionic forms for the $HgCl_2$-promoted guanylation steps (*vide infra*).

The cyclohexylthioureas substituted with conjugated groups thus prepared were subjected to the $HgCl_2$ procedure in the presence of tetrahydroisoquinoline.[3] The results are summarized in Table 2.

As shown already, N-Boc-N'-cyclohexylthiourea reacted smoothly with tetrahydroisoquinoline in the presence of $HgCl_2$ to yield the desired guanidine product (entry 1). As anticipated from this result, N-acetyl, N-benzoyl-, and N-benzylcarbamoyl-substituted thioureas were also converted easily to the corresponding guanidines (entries 2-4). N-Tosyl-N'-cyclohexylthiourea, prepared from TsNCS and cyclohexylamine

Table 2. N-Carbonyl-, N-Cyano-, and N-Sulfonyl-Guanylations



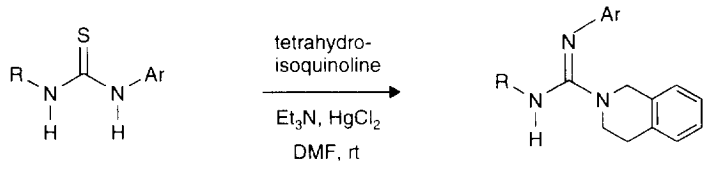
Entry	X	Time	Yield
1	Boc	3.5 h	63 %
2	Ac	5 h	75 %
3	Bz	2 h	75 %
4	CONHBn	1.5 h	67 %
5	Ts	0.6 h	83 %
6[a]	Ts	4 h	41 %[b]
7[a]	CN	2 h	61 %[b]

a: in-situ reaction.
b: over-all yield

(disconnection *b*, Scheme 1), was even more reactive than the N-carbonyl-substituted thioureas: the $HgCl_2$-reaction with tetrahydroisoquinoline was complete in 40 min to yield the N-tosylguanidine product in 83 % yield (entry 5).[10] The reaction between cyclohexylisothiocyanate and the anion of tosylamide (disconnection *c*, Scheme 1) initially produced the anion of N-cyclohexyl-N'-tosylthiourea. The anion was also presumed to be the first intermediate of the reaction of entry 5, Table 2, when Et_3N was added to the thiourea. It was therefore envisaged that the tosylamide anion reaction could be coupled with the $HgCl_2$ step *in situ* without isolating the tosylthiourea. Thus, tosylamide was deprotonated with KO*t*-Bu in DMF and treated with cyclohexylisothiocyanate (1 h, rt). When all the isothiocyanate had been consumed (TLC), the reaction mixture was cooled in an ice bath and treated with Et_3N, tetrahydroisoquinoline and $HgCl_2$. The guanylation under these conditions took *ca.* 4 h to complete and the desired N-tosylguanidine product (the same as obtained in entry 5) was obtained in 41 % overall yield (entry 6). Thus, the *in situ*, one-pot procedure compares favorably with the two-step process (entry 5) in terms of the overall yields and the convenience. Following the one-pot protocol, cyanamide was similarly incorporated in the N-cyanoguanidine structure in 61 % overall yield (entry 7).[11] As the N-cyanoguanidine functional group occupies an important place in medicinal chemistry, this one-pot protocol will find much use.[12]

N-Aryl-Guanidines: The above results point to a certain trend in the $HgCl_2$-promoted guanylation process: a conjugated substituent on one of the nitrogens of a thiourea is enough to cause the reaction to work. Therefore we turned our attention to N-aryl substitutions. We had already glimpsed an indication that a certain

Table 3. N-Aryl-Guanylations



Entry	R	Ar	Time	Yield
		Ar = *p*-X-C_6H_4-		
1	cyclohexyl-	X = NO_2	0.5 h	89 %
2	"	X = CF_3	24 h	86 %
3	"	X = COOMe	7 h	93 %
4	"	X = Cl	25.5 h	76 %
5	"	X = H	24 h	84 %
6	"	X = OMe	48 h	82 %
7	"	X = NMe_2	96 h	48 %
8	*p*-Cl-C_6H_4-	X = CF_3	0.7 h	96 %
9	cyclohexyl-	Ar = C_6F_5-	0.5 h	95 %

aryl group on the nitrogen of thiourea starting material could activate the process considerably (*vide supra* entry 3, Table 1). Thus, a series of N-arylthioureas were subjected to the $HgCl_2$ procedure.[3] Once again, the electronically and sterically neutral cyclohexyl group and tetrahydroisoquinoline were chosen in most cases for the R-substituent and for the incoming amine, R'R''NH, respectively. The N-aryl groups studied in this series were all *para*-substituted phenyls, except for one case, in order to weigh the electronic effects of the substituents to the fullest without steric interference. The results are summarised in Table 3.

N-Cyclohexyl-N'-arylthioureas reacted with tetrahydroisoquinoline under the $HgCl_2$-conditions to produce the corresponding guanidines. There seemed to be a clear correlation between the electronic effects of the substituent (on the N-aryl) and the reaction rate. Thus, electron-withdrawing groups on the N-phenyl substituents facilitated the reaction greatly. The electron-withdrawing effects could be either conjugative (entries 1 and 3) or inductive (entries 2 and 9). The effects also seemed to be additive: N-*p*-chlorophenyl-N'-trifluoromethylphenyl-substituted thiourea underwent the guanylation faster than when either substituent was present alone (entry 8). On the other hand, the guanylation proceeded very sluggishly when the N-phenyl substituents contained electron-donating groups (entries 6 and 7).

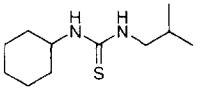
In the course of the guanylations with slow-reacting N-arylthioureas (entries 2-7), a less-polar intermediate was observed first, which was then slowly converted to the desired guanidine product. The intermediates were presumed to be carbodiimides; the isolation and characterization of these compounds were

not successful.[13] These observations are consistent with the reaction mechanism proposed for the guanylation of bis-Boc thiourea:[3] $HgCl_2$ promotes a formal elimination of H_2S from thiourea starting material to produce carbodiimide intermediates; amines then add to the carbodiimides to yield guanidine products. It appears that $HgCl_2$ causes the first step to proceed efficiently regardless of the nature of the substituents. It is in the second step (addition of amines to carbodiimides) that the N-substituents exert their electronic effects on the reaction rates. The observed effects of the substituents –faster reactions with electron withdrawing groups and slower ones with electron donating groups– can be explained in terms of stabilization/destabilization of the transition state in the addition step; there is little evidence that $HgCl_2$ participates in this step.[13b]

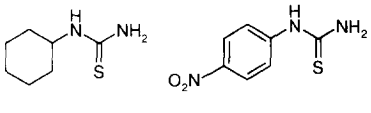
Limitations: The $HgCl_2$-promoted guanylation is effective only with thioureas containing N-conjugated substituents. Thus, treatment of N,N'-bis-alkyl-substituted thioureas with $HgCl_2/Et_3N$ produced the corresponding carbodiimides, which failed to react with amine nucleophiles under the standard $HgCl_2$-conditions employed. While carbodiimides are known to react with amines to produce the corresponding guanidines, the reactions generally require excess reagents and/or longer reaction times.[14]

Abating steric hindrance, as in N-monosubstituted (terminal) thioureas, did not help the guanylation to work. In fact, terminal guanidines, even those substituted with activating conjugated groups, failed to produce the guanidine products under the conditions employed (Scheme 2).

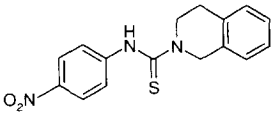
Scheme 2. Representative Unsuccessful Thioureas



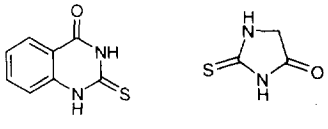
bis-alkyl thioureas



terminal thioureas



thioureas lacking an N-H



small-ring thioureas

In line with the proposed carbodiimide intermediacy in the $HgCl_2$-promoted guanylation process, the successful thiourea substrates require one hydrogen on each of the nitrogens to be present. Also as expected from the postulated reaction mechanism, the 5- and 6-membered cyclic thioureas substituted with N-carbonyl groups failed to react under the standard conditions. Note that the corresponding acyclic thioureas containing the same substituents would undergo guanylation easily under the $HgCl_2$ conditions.

Conclusion: The $HgCl_2$-promoted guanylation process has a wide synthetic applicability. One conjugated substituent on the nitrogen of thiourea starting material is enough to cause the reaction to proceed at room temperature. Such activating groups include N-carbonyl- (acyl, alkoxycarbonyl, carbamoyl, etc.), N-cyano-, N-sulfonyl-, and N-aryl- substituents.

EXPERIMENTAL PART

General Procedure for the $HgCl_2$-promoted Guanylation: The starting thiourea, the amine (1.1 equiv), and triethylamine (2.2 equiv) were dissolved in dimethylformamide (5 mL/mmol substrate) at rt. The mixture was cooled in an ice bath. Mercury(II) chloride (1.1 equiv) was added and the mixture was stirred for 20 min, before it was warmed to rt. When the reaction was judged complete (TLC), the reaction mixture was diluted with ethyl acetate and filtered through Celite, washing the Celite cake with additional ethyl acetate. The filtrate was washed with water, then with brine, and the organic phase was dried with $MgSO_4$. The crude product thus obtained was purified by flash chromatography on a silica column.[15]

N-Boc-N'-cyclohexyl-thiourea. To a solution of N-cyclohexylthiourea (1.10 g, 7 mmol) in tetrahydrofuran (THF, 40 mL), sodium hydride (60 %, 0.28 g, 7 mmol) was added and the mixture was stirred at room temperature for 10 min, under a N_2 atmosphere. The reaction mixture was cooled in an ice bath, and di-*tert*-butyl-dicarbonate (1.78 g, 8 mmol) was added as a solution in THF (15 mL). The mixture was stirred in the ice bath for 30 min, then warmed to room temperature It was stirred at rt overnight. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried with magnesium sulfate, and concentrated *in vacuo*. Unreacted starting material was recovered by crystallization (ethyl acetate-hexane, 0.37 g, 33 %). The residue was purified by flash chromatography using ethyl acetate-hexane(1:9) to yield the N-Boc-protected title compound (1.21 g, 67 %). ^{1}H NMR ($CDCl_3$) δ 9.61(1H,s,br), 7.74(1H,s,br), 4.24(1H,m), 2.11-1.99(2H,m), 1.81-1.55(3H,m), 1.47(9H,s), 1.42-1.15(5H,m); IR 3254(m), 2932(m), 1718(s), 1548(s), 1528(s), 1014(m) cm^{-1}; MS *m/e* 258(M^+), 121(100%); mp 109-111 °C.

N-Boc-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 63 % yield after flash chromatographic purification with ethyl acetate-hexane (1:1). ^{1}H NMR ($CDCl_3$) δ 7.95(1H,s,br), 7.23-7.07(4H,m), 4.56(2H,s), 3.63(2H,t,*J*=5.9Hz), 3.29(1H,m), 2.95(2H,t,*J*=5.9Hz), 2.01-1.86(2H,m), 1.81-1.5(3H,m), 1.53(9H,s), 1.45-1.18(5H,m); IR 3199(w), 2938(m), 1670(s), 1574(m), 1514(m) cm^{-1}; MS *m/e* 358(MH^+,100%); mp 136-139 °C; Anal. Found: C,68.01; H,8.97; N,11.30. Calcd for $C_{21}H_{31}N_3O_2 \cdot 0.75H_2O$: C,67.98; H,8.83; N,11.30.

N-Cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. N-Boc-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine (0.209 g, 0.58 mmol) was dissolved in dichloromethane (2.5 mL) and

trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temperature for 3h. Evaporation of the solvent afforded a white solid. The product was purified by flash chromatography using dichloromethane-methanol (9:1) to obtain the title compound as the di-trifluoroacetate salt (0.244 g, 86 %). ^{1}H NMR (d_6-DMSO) δ 7.65(1H,s), 7.34(1H,d,*J*=9Hz), 7.24-7.12(4H,m), 6.0(1H,br s), 4.58(2H,s), 3.63(2H,t,*J*=6Hz), 3.48(1H,m), 2.92(2H,t,*J*=6Hz), 1.95-1.55(5H,m), 1.45-1.0(5H,m); IR 3465(m), 3309(m), 2948(m), 1653(s), 1616(s), 1213(s), 1180(s), 1142(s) cm^{-1}; MS *m/e* 258(MH$^+$,100%).

N(1)-Boc-N(2)-cyclohexyl-N(3)-phenyl-guanidine. The guanylation was carried out following the general procedure. The title compound was obtained in 70 % yield after flash chromatographic purification with ethyl acetate-hexane (1:9). ^{1}H NMR ($CDCl_3$) δ 7.49-6.96(5H,m), 6.5(1H,br s), 4.73(1H, br), 3.99(1H,m), 2.15-0.98(10H,m), 1.50(9H,s); IR 3350(w), 2931(m), 1725(m), 1636(m), 1593(s), 1545(m) cm^{-1}; MS *m/e* 318(MH$^+$), 262(100%).

N-Boc-N'-p-nitrophenyl-thiourea. The N-Boc protection was carried out as described above. The title compound was obtained in 42 % yield after flash chromatographic purification with ethyl acetate-hexane (1:9). ^{1}H NMR ($CDCl_3$) δ 11.98(1H,s,br), 8.25(2H,d,*J*=7.7Hz), 7.99(2H,d,*J*=9.6Hz), 8.10(1H,s), 1.55(9H,s); IR 3178(m), 1721(m), 1589(m), 1519(s), 1325(s) cm^{-1}; MS *m/e* 298(MH$^+$), 242(100%); mp 99-101 °C.

N(1)-Boc-N(2)-p-methoxyphenyl-N(3)-p-nitrophenyl-guanidine. The guanylation was carried out following the general procedure. The title compound was obtained in 85 % yield after flash chromatographic purification with ethyl acetate-hexane (1:9). ^{1}H NMR ($CDCl_3$) δ 10.13(1H,s), 8.18(2H,d,*J*=10Hz), 7.86(1H,d,*J*=10.3Hz), 7.42(1H,d,*J*=10.3Hz), 7.10(1H,s,br), 6.98-6.75(4H,m), 3.81(3H,s), 1.48(9H,s); IR 3310(w), 1720(m), 1665(m), 1584(m), 1554(m), 1511(m), 1336(s) cm^{-1}; MS *m/e* 387(MH$^+$), 331(100%); Anal. Found: C,58.93; H,5.66; N,14.54. Calcd for $C_{19}H_{22}N_4O_5$: C,59.06; H,5.74; N,14.50.

N-Acetyl-N'-cyclohexyl-thiourea. To a solution of cyclohexylthiourea (0.482 g, 3 mmol) in THF (10 mL) was added acetic anhydride (0.472 mL, 5 mmol), pyridine (0.407 g, 5 mmol) and a catalytic amount of dimethylaminopyridine. The reaction mixture was stirred at reflux under a N_2 atmosphere. After 7 h, the solvent was evaporated, and the product was purified by flash chromatography using ethyl acetate-hexane (1:6) to yield the title compound (0.512 g, 84 %). ^{1}H NMR ($CDCl_3$) δ 10.47(1H,s,br), 8.83(1H,s,br), 4.23(1H,m), 2.12(3H,s), 2.10-1.97(2H,m), 1.80-1.55(3H,m), 1.50-1.20(5H,m); IR 3178(m), 3045(w), 2931(m), 2853(m), 1692(s), 1548(s), 1237(m), 1195(w), 1166(w) cm^{-1}; MS *m/e* 200(M$^+$), 98(100%) ; mp 96-102°C.

N-Acetyl-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 75 % yield after flash chromatographic purification with dichloromethane-methanol (9:1). ^{1}H NMR (d_6-DMSO) δ 7.23-7.15(4H,m), 4.47(2H,s), 3.52(2H,d,*J*=6Hz), 3.5-3.35(1H,m), 3.15(1H,s), 2.84(2H,t,*J*=5.8Hz), 1.86(3H,s), 1.85-1.12(10H,m); IR 3246(w), 2930(m), 2853(m), 1590(s), 1561(s), 1486(s), 1431(m) cm^{-1}; MS *m/e* 300 (MH$^+$,100%); mp 58-60°C.

N-Benzoyl-N'-cyclohexyl-thiourea. N-benzoylisothiocyanate (0.13 mL, 1 mmol) was treated with cyclohexylamine (0.11 mL, 1 mmol) in ethyl acetate (5 mL) at rt for 3 h. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic phase was dried ($MgSO_4$) and filtered. Flash chromatographic purification with ethyl acetate-hexane (1:9) yielded the title compound (0.150 g, 57 %). ^{1}H NMR ($CDCl_3$) δ 10.70(1H,s,br), 8.88(1H,s), 7.83(2H,d,*J*=6.9Hz), 7.67-7.46(3H,m), 4.29(1H,m), 2.15-2.01(2H,m), 1.83-1.54(3H,m), 1.54-1.20(5H,m); IR 3170(m), 2927(m), 2954(m), 1672(m), 1595(w), 1544(s) cm^{-1}; MS *m/e* 262(M^+), 105(100%).

N-Benzoyl-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 75 % yield after flash chromatographic purification with dichloromethane-methanol (9:1), followed by recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 8.48(1H,d,*J*=10.5Hz), 8.3-8.2(2H,m), 7.5-7.35(3H,m), 7.28-7.12(4H,m), 4.68(2H,s), 3.76(2H,t,*J*=5.8Hz), 3.50(1H,m), 3.01(2H,t,*J*=5.9Hz), 2.1-1.9 (2H,m), 1.85-1.5(3H,m),1.45-1.2(5H,m); IR 3250(w), 3080(w), 2924(m), 2854(m), 1591(s), 1576(s), 1543(s), 1502(s) cm^{-1}; MS *m/e* 361(M^+), 105(100%); mp 183-185°C; Anal. Found: C,75.09; H,7.39; N,11.59. Calcd for $C_{23}H_{27}N_3O_1 \cdot 0.4H_2O$: C,74.93; H,7.60; N,11.40.

N-Benzylcarbamoyl- N'-cyclohexyl-thiourea. To a solution of N-cyclohexylthiourea (0.558 g, 3 mmol) in THF (20 mL) was added benzylisocyanate (0.562 g, 4 mmol) and a catalytic amount of dimethylaminopyridine. The reaction mixture was stirred at reflux under a N_2 atmosphere for 60 h. The solvent was evaporated and the product purified by flash chromatography using ethyl acetate-hexane (1:4) to yield the title compound (0.327 g, 32 %). ^{1}H NMR ($CDCl_3$) δ 10.29(1H, br), 9.79(1H,s), 7.38-7.20(5H,m), 6.40(1H, br), 4.35(2H,d,*J*=6Hz), 4.2-4.05(1H,m), 2.02-1.83(2H,m), 1.75-1.52(3H,m), 1.50-1.18(5H,m); IR 3385(m), 3270(m), 3070(w), 2927(m), 1688(m), 1649(s), 1524(s), 1452(m), 1201(m) cm^{-1}; MS *m/e* 291(M^+), 91(100%).

N-Benzylcarbamoyl- N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 67 % yield after flash chromatographic purification with ethyl acetate-hexane (3:1). ^{1}H NMR ($CDCl_3$) δ 8.79(1H,d,*J*=10.6Hz), 7.35-7.08(9H,m), 5.40(1H,m), 4.48(2H,s), 4.5-4.35 (2H,m), 3.55(2H,t,*J*=6.6Hz), 3.23(1H,m), 2.92(2H,t,*J*=6.6Hz), 1.99-1.5(5H,m), 1.45-1.18(5H,m) IR 3260(w), 3050(w), 2930(m), 2852(m), 1597(s), 1496(s), 1452(s), 1273(m), 1146(m) cm^{-1}; MS *m/e* 390(M^+), 132(100%).

N-Cyclohexyl-N'-tosyl-thiourea. The title compound was prepared from tosylisothiocyanate (crude[9]) and cyclohexylamine as described above for the N-benzoyl analogue. Flash chromatographic purification (ethyl acetate-hexane 1:2) yielded the product in 30 % yield. ^{1}H NMR ($CDCl_3$) δ 8.04(1H,d,*J*=8Hz), 7.75(2H,d,*J*=8.4Hz), 7.35(2H,d,*J*=8.3Hz), 4.10(1H,m), 2.44(3H,s), 2.0-1.85(2H,m), 1.75-1.55(3H,m), 1.45-1.2(5H,m) ; IR 3318(s), 3060(m), 2926(m), 2858(m), 1548(s), 1494(s), 1397(s), 1367(m), 1128(s), 1085(s) cm^{-1}; MS *m/e* 313(MH^+), 91(100%); mp 142-148°C.

N-Cyclohexyl-N'-tosyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 83 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 7.80(2H,d,*J*=8.0Hz), 7.26-7.08(6H,m), 6.72(1H,d,*J*=9.5Hz), 4.52(2H,s), 3.62(2H,t,*J*=5.5Hz), 3.20(1H,m), 2.95(2H,t,*J*=5.7Hz), 2.40(3H,s), 1.88-1.5(5H,m), 1.3-1.10(5H,m); IR 3333(m), 2913(m), 1577(s), 1486(s), 1444(m), 1180(m) cm^{-1}; MS *m/e* 412(MH^+, 100%); mp 140-142°C; Anal. Found: C,65.92; H,7.32; N,9.97. Calcd for $C_{23}H_{29}N_3SO_2 \cdot 0.5H_2O$: C,65.68; H,7.19; N,9.99.

N-Cyclohexyl-N'-tosyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. In-situ Preparation: A solution of tosylamide (0.171 g, 1 mmol) in DMF (20 mL) was treated with KO*t*-Bu (1M in THF, 1 mL). The mixture was stirred for 20 min at rt. Cyclohexylisothiocyanate was then added and the mixture was stirred for a further 1 h. TLC indicated the complete consumption of cyclohexylisothiocyanate. The mixture was cooled in an ice bath. Et_3N (0.42 mL, 3 mmol) was added followed by tetrahydroisoquinoline (0.136 g, 1 mmol). Finally $HgCl_2$ (0.307 g, 1.1 mmol) was added and the mixture was stirred for 20 min. It was warmed to rt and stirred for a further 3.5 h. Work-up as described in the general procedure followed by flash chromatographic purification (ethyl acetate-hexane 1:2) and recrystallization from ethyl acetate and hexane yielded the product in 41 % overall yield. mp 140-143°C.

N-Cyano-N'-cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. In-situ Preparation: . The guanylation was carried out as described above for the N-tosylguanidine. The title compound was obtained in 61 % yield after flash chromatographic purification with ethyl acetate-hexane (1:1). ^{1}H NMR ($CDCl_3$) δ 7.26-7.09(4H,m), 4.68(1H,m), 4.61(2H,s), 3.88(1H,m), 3.71(2H,t,*J*=5.8Hz), 2.97(2H,t,*J*=5.8Hz), 2.14-1.97(2H,m), 1.84-1.57(3H,m), 1.56-1.13(5H,m); IR 3239(m), 3119(w), 2925(m), 2854(m), 2165(s), 1590(s), 1533(s), 1447(m) cm^{-1}; MS *m/e* 283(MH^+, 100%); mp 115-118°C; Anal. Found: C,71.10; H,8.35; N,19.54. Calcd for $C_{17}H_{22}N_4 \cdot 0.3H_2O$: C,70.95; H,7.92; N,19.47.

N-Cyclohexyl-N'-p-nitrophenyl-thiourea. *Para*-Nitrophenylisothiocyanate (0.90 g, 5 mmol) was treated with cyclohexylamine (0.58 mL, 5 mmol) in ethyl acetate (20 mL) at rt. Hexane was added and the resulting crystalline product was isolated by filtration (1.34 g, 96 %). ^{1}H NMR ($CDCl_3$) δ 8.26(2H,d,*J*=8.9Hz), 8.1(1H,br s), 7.39(2H,d,*J*=8.9Hz), 6.17(1H,br d,*J*=7.3Hz), 4.35-4.15(1H,m), 2.2-2.05(2H,m), 1.75-1.6(3H,m), 1.55-1.1(5H,m); IR 3347(s), 3189(m), 2933(s), 1594(s), 1530(s), 1500(s), 1370(s), 1319(s) 1246(s)cm^{-1}; MS *m/e* 279(M^+), 56(100%); mp 181-183°C.

N-Cyclohexyl-N'-p-nitrophenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 89 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 8.12(2H,d,*J*=9.1Hz), 7.28-7.05(4H,m), 6.85(2H,d,*J*=9.1Hz), 4.45(2H,s), 3.83(1H,m), 3.54(2H,t,*J*=5.8Hz), 3.29(1H,m), 2.91(2H,t,*J*=5.8Hz), 2.00-1.88(2H,m), 1.75-1.52(3H,m), 1.38-1.00(5H,m); IR 3377(m), 3080(w), 2934(m), 1590(w), 1568(m), 1550(s), 1507(s), 1280(s)

cm^{-1}; MS *m/e* 378(M^+), 132(100%); mp 150-153°C; Anal. Found: C,69.22; H,6.84; N,14.80. Calcd for $C_{22}H_{26}N_4O_2$: C,69.82; H,6.92; N,14.80.

N-Cyclohexyl-N'-p-trifluoromethylphenyl-thiourea. The title compound was obtained as above in 89 % yield after recrystallization from ethyl acetate and hexane. ^1H NMR ($CDCl_3$) δ 8.00(1H,s,br), 7.67(2H,d,*J*=8.5Hz), 7.32(2H,d,*J*=8.6Hz), 6.01(1H,d,*J*=7Hz), 4.28(1H,m), 2.16-2.0(2H,m), 1.8-1.55(3H,m), 1.5-1.05(5H,m); IR 3250(m), 3035(m), 2935(m), 1606(w), 1540(m), 1327(s), 1164(m) cm^{-1}; MS *m/e* 303(MH^+, 100%); mp 181-184°C.

N-Cyclohexyl-N'-p-trifluoromethylphenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 86 % yield after flash chromatographic purification with dichloromethane-methanol (9:1). ^1H NMR ($CDCl_3$) δ 7.51(2H,d,*J*=8.4Hz), 7.20-7.08(5H,m), 7.03-6.97(1H,m), 4.58(2H,s), 3.68(1H,m), 3.68(2H,t,*J*=5.8Hz), 2.98(2H,t,*J*=5.3Hz), 2.01-1.9(2H,m), 1.67-1.35(5H,m), 1.3-1.0(3H,m); IR 2932(m), 2856(m), 1621(s), 1352(s), 1165(m) cm^{-1}; MS *m/e* 401(M^+), 132(100%); mp 102-106°C; Anal. Found: C,61.45; H,5.92; N,9.30. Calcd for $C_{23}H_{26}N_3F_3 \cdot HCl \cdot 0.5H_2O$: C,61.81; H,6.32; N,9.40.

N-Cyclohexyl-N'-p-methoxycarbonylphenyl-thiourea. The title compound was obtained as above in 91 % yield after recrystallization from ethyl acetate and hexane. ^1H NMR ($CDCl_3$) δ 8.08(2H,d,*J*=8.7Hz), 7.85(1H,s), 7.23(2H,d,*J*=9.1Hz), 6.09(1H,d,*J*=8.3Hz), 4.28(1H,m), 3.91(3H,s), 2.15-2.04(2H,m), 1.74-1.55(3H,m), 1.55-1.08(5H,m); IR 3307(m), 2938(m), 1701(s), 1608(m), 1547(s), 1530(s), 1244(s), 766(m) cm^{-1}; MS *m/e* 293(MH^+,100%); mp 179-181°C.

N-Cyclohexyl-N'-p-methoxycarbonylphenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 93 % yield after flash chromatographic purification (dichloromethane-methanol 14:1; ethyl acetate-hexane 9:1). ^1H NMR ($CDCl_3$) δ 7.94(2H,d,*J*=8.7Hz), 7.21-7.08(4H,m), 6.88(2H,d,*J*=8.6Hz), 4.46(2H,s), 3.88(3H,s), 3.53(2H,t,*J*=5.9Hz), 3.5(1H,m), 3.18(1H,m), 2.93(2H,t,*J*=5.5Hz), 1.96-1.87(2H,m), 1.72-1.49(3H,m), 1.32-0.92(5H,m); IR 3360(w), 2929(m), 2852(m), 1714(m), 1589(s), 1512(m), 1274(s) cm^{-1}; MS *m/e* 391(M^+), 132(100%); mp 150-153°C; Anal. Found: C,70.31; H,7.13; N,10.30. Calcd for $C_{24}H_{29}N_3O_2 \cdot H_2O$: C,70.56; H,7.40; N,10.29.

N-Cyclohexyl-N'-p-chlorophenyl-thiourea. The title compound was obtained as above in 92 % yield after recrystallization from ethyl acetate and hexane. ^1H NMR ($CDCl_3$) δ 7.69(1H,br s), 7.40(2H,d,*J*=7Hz), 7.15(2H,d,*J*=7Hz), 5.79(1H,br d), 4.35-4.15(1H,m), 2.1-2.0(2H,m), 1.75-1.55(3H,m), 1.50-1.30(2H,m), 1.25-1.05(3H,m); IR 3250(br), 2932(s), 2853(m), 1579(m), 1541(s), 1490(s), 1335(s) cm^{-1}; MS *m/e* 269(MH^+,100%), 271(37%); mp 177-179°C.

N-Cyclohexyl-N'-p-chlorophenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 76 % yield after flash

chromatographic purification (dichloromethane-methanol 9:1) followed by recrystallization (methanol-ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 8.51(1H,d,*J*=6Hz), 7.23-6.93(8H,m), 4.60(2H,s), 3.80(1H,m), 3.68(2H,t,*J*=5.9Hz), 2.95(2H,t,*J*=6.0Hz), 2.03-1.89(2H,m), 1.72-1.48(5H,m), 1.29-1.10(3H,m); IR 2923(m), 2850(m), 1621(s), 1584(m), 1535(m), 1492(m), 1091(w) cm^{-1}; MS *m/e* 367(M^+), 132(100%); mp 249-251°C. Anal. Found: C,64.73; H,6.83; N,10.54. Calcd for $C_{24}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$: C,65.34; H,6.73; N,10.39.

N-Cyclohexyl-N'-phenyl-thiourea. The title compound was obtained as above in 94 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 7.7(1H,s), 7.47-7.20(5H,m), 5.88(1H,br d), 4.38-4.10(1H,m), 2.10-2.0(2H,m), 1.70-1.55(3H,m), 1.50-1.30(2H,m), 1.20-1.02(3H,m); IR 3210(br), 2938(m), 2852(m), 1542(s), 1508(s), 1241(m) cm^{-1}; MS *m/e* 234(M^+), 93(100%); mp 148-149°C.

N-Cyclohexyl-N'-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 84 % yield after flash chromatographic purification (dichloromethane-methanol 14:1). ^{1}H NMR ($CDCl_3$) δ 8.46(1H,s,br), 7.29-6.94(9H,m), 4.61(2H,s), 3.68(2H,t,*J*=5.8), 3.72(1H,m), 2.98-2.89(2H,m), 2.01-1.9(2H,m), 1.75-1.4(5H,m), 1.3-1.05(3H,m); IR 2930(s), 2854(s), 1619(s), 1550(m), 1452(m) cm^{-1}; MS *m/e* 334(MH^+,100%).

N-Cyclohexyl-N'-p-methoxyphenyl-thiourea. The title compound was obtained as above in 95 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 7.46(1H,s,br), 7.12(2H,d,*J*=9.0Hz), 6.95(2H,d,*J*=9.0Hz), 5.66(1H,d,*J*=10Hz), 4.34-4.16(1H,m), 3.83(3H,s), 2.09-1.97(2H,m), 1.7-1.3(5H,m), 1.3-1.0(3H,m); IR 3370(m), 3167(m), 2928(m), 1542(s), 1509(s) 1233(s), 1030(s) cm^{-1} ; MS *m/e* 265(MH^+,100%); mp 125-127°C.

N-Cyclohexyl-N'-p-methoxyphenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 82 % yield after flash chromatographic purification (dichloromethane-methanol 9:1). ^{1}H NMR ($CDCl_3$) δ 8.12(1H,s,br), 7.18-7.05(5H,m), 7.0-6.94(1H,m), 6.81(2H,d,*J*=9Hz), 4.55(2H,s), 3.76(3H,s), 3.63(2H,t,*J*=5.6Hz), 3.6(1H,m), 2.89 (2H,t,*J*=6Hz), 2.01-1.89(2H,m), 1.72-1.48(5H,m), 1.30-1.09(3H,m); IR 2931(s), 2854(m), 1618(s), 1555(m), 1512(s), 1243(m) cm^{-1}; MS *m/e* 363(M^+), 123(100%); mp 103-105°C; Anal. Found: C,63.37; H,6.83; N,9.51. Calcd for $C_{23}H_{29}N_3O \cdot 2HCl$: C,63.30; H,7.16; N,9.63.

N-Cyclohexyl-N'-p-dimethylaminophenyl-thiourea. The title compound was obtained as above in 89 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 7.30(1H,br s), 7.04(2H,d,*J*=9.2Hz), 6.70(2H,d,*J*=9.2Hz), 5.65(1H,br d), 4.35-4.17(1H,m), 3.0(6H,s), 2.15-1.97(2H,m), 1.67-1.29(5H,m), 1.22-0.97(3H,m); IR 3381(m), 3162(m), 2928(m), 1529(s), 1524(s), 1448(m), 1267(m) cm^{-1}; MS *m/e* 227(M^+), 136(100%); mp 126-128°C.

N-Cyclohexyl-N'-p-dimethylaminophenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 48 % yield after flash

chromatographic purification (dichloromethane-methanol 9:1). ^{1}H NMR ($CDCl_3$) δ 8.10(1H,s,br), 7.18-6.97(6H,m), 6.61(2H,d,*J*=8.8Hz), 4.54(2H,s), 3.62(2H,t,*J*=5.7Hz), 3.60(1H,m), 2.95(2H,t,*J*=6.7Hz), 2.89(6H,s), 2.04-1.87(2H,m), 1.87-1.48(5H,m), 1.32-1.06(3H,m); IR 2930(s), 2854(m), 1676(m), 1614(s), 1584(m), 1554(m), 1522(s) cm^{-1}; MS *m/e* 376(M^+,100%); mp 107-111°C; Anal. Found: C,62.77; H,7.30; N,12.23. Calcd for $C_{24}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$: C,62.92; H,7.64; N,12.22.

N-p-Chlorophenyl-N'-p-trifluoromethylphenyl-thiourea. The title compound was prepared from *p*-trifluoromethylphenylisothiocyanate and *p*-chloroaniline. The product was obtained in 94 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR (d_6-DMSO) δ 10.13(1H,s,br), 7.78(2H,d,*J*=9.1Hz), 7.70(2H,d,*J*=9.1Hz), 7.55(2H,d,*J*=8.9Hz), 7.41(2H,d,*J*=8.9Hz), 3.29(1H,s); IR 3187(m), 3021(m), 1592(m), 1535(s), 1490(m), 1322(s), 1178(m), 1067(m), 830(m) cm^{-1}; MS *m/e* 330(M^+), 127(100%).

N-p-Chlorophenyl-N'-p-trifluoromethylphenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 96 % yield after flash chromatographic purification with ethyl acetate-hexane (1:3). ^{1}H NMR ($CDCl_3$) δ 7.48(2H,d,*J*=8.4Hz), 7.25-7.08(7H,m), 6.96(2H,d,*J*=8.1Hz), 6.84(2H,d,*J*=8.1Hz), 4.58(2H,s), 3.61(2H,d,*J*=6Hz), 2.87(2H,t,*J*=5.8Hz); IR 3050(w), 1614(s), 1575(s), 1489(m), 1323(s), 1159(m), 1110(s), 1065(s) cm^{-1}; MS *m/e* 429(M^+), 132(100%); mp 139-141°C; Anal. Found: C,64.27; H,4.54; N,9.76. Calcd for $C_{23}H_{19}ClF_3N_3$: C,64.26; H,4.46; N,9.78.

N-Cyclohexyl-N'-pentafluorophenyl-thiourea. The title compound was obtained as above in 95 % yield after recrystallization from ethyl acetate and hexane. ^{1}H NMR ($CDCl_3$) δ 6.05-5.85(1H,m), 4.2-4.05(1H,m), 2.2-2.05(2H,m), 1.85-1.60(3H,m), 1.5-1.1(5H,m); IR 3222(br), 2937(m), 1530(s), 1507(s), 1234(m) cm^{-1}; MS *m/e* 324(M^+), 183(100%); mp 159-162°C.

N-Cyclohexyl-N'-pentafluorophenyl-3,4-dihydro-1H-isoquinoline-2-carboxamidine. The guanylation was carried out following the general procedure. The title compound was obtained in 95 % yield after flash chromatographic purification with ethyl acetate-hexane (1:6). ^{1}H NMR ($CDCl_3$) δ 7.2-7.04(4H,m), 4.46(2H,s), 3.68(1H,d,*J*=10.6Hz), 3.53(2H,t,*J*=5.6Hz), 3.4-3.22(1H,m), 2.87(2H,t,*J*=5.6Hz), 2.0-1.88(2H,m), 1.75-1.55(3H,m), 1.38-0.97(5H,m); IR 3390(br), 3140(br), 2935(m), 2854(m), 1566(s), 1496(s), 1426(m) cm^{-1}; MS *m/e* 423(M^+,100%), 414(28.5%); mp 131-134°C; Anal. Found: C,62.20; H,5.17; N,9.91. Calcd for $C_{22}H_{22}N_3F_5$: C,62.41; H,5.24; N,9.92.

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13. (a) We were able to isolate the less-polar intermediates when the guanylation reactions were performed, with selected thiourea substrate, either in the absence of, or in the presence of less than 1 equivalent of the incoming amine (tetrahydroisoquinoline). The intermediates were characterized to be the corresponding carbodiimides. (b) The carbodiimides thus obtained were treated in a separate step with tetrahydroisoquinoline in the absence of $HgCl_2$. Their reactivities showed a trend similar to what had been observed in the $HgCl_2$-promoted guanylation process, i.e., faster reactions with electron-withdrawing substituents and slower reactions with electron-donating groups.
14. For a review on the chemistry of carbodiimides, see: Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233.
15. (a) Elemental analyses indicate that the guanidine products were obtained, depending on the nature of the substituents, as either free base, the mono-, or di-hydrochloride salt forms. Thus, the guanidines substituted with electron-withdrawing groups (e.g., the products of Tables 1 and 2, *p*-nitrophenyl- and *p*-methoxycarbonylphenyl-substituted guanidines [entries 1 and 3, Table 3]) were obtained as free-base; *p*-trifluoromethylphenyl- and *p*-chlorophenyl-substituted guanidines (entries 2 and 4, Table 3) were obtained as the mono-hydrochloride forms; electron-donating group-substituted phenyl-guanidines (entries 5-7, Table 3) were obtained as the di-hydrochloride salts. (b) The stoichiometry of the salt forms simply reflects the basicity of the substituted guanidine products. See reference 2 for the effects of the substituents on the basicity of substituted guanidines.

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