

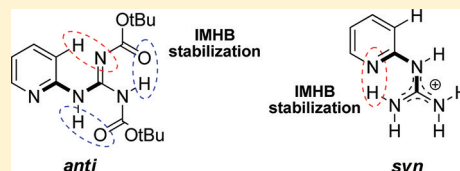
Pyridin-2-yl Guanidine Derivatives: Conformational Control Induced by Intramolecular Hydrogen-Bonding Interactions

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Supporting Information

ABSTRACT: The synthesis and conformational analysis of a series of pyridin-2-yl guanidine derivatives using NMR, X-ray crystallography, and B3LYP/6-31+G** theoretical studies are reported. A remarkable difference was observed in the ¹H NMR spectra of the guanidinium salts as compared with their *N,N'*-di-Boc protected and neutral analogues. This difference corresponds to a 180° change in the dihedral angle between the guanidine/ium moiety and the pyridine ring in the salts as compared to the Boc-protected derivatives, a conclusion that was supported by theoretical studies, X-ray data, and NMR analysis. Moreover, our data sustain the existence of two intramolecular hydrogen-bonding systems: (i) between the pyridine N1 atom and the guanidinium protons in the salts and (ii) within the *tert*-butyl carbamate groups of the Boc-protected derivatives. To verify that the observed conformational control arises from these intramolecular interactions, a new series of *N*-Boc-*N'*-propyl-substituted pyridin-2-yl guanidines were also prepared and studied.



INTRODUCTION

Guanidine derivatives have a wide range of applications throughout the field of medicinal chemistry. During the last 10 years, our group has been working on the synthesis¹ and biological evaluation of aromatic guanidine derivatives both as α -adrenoceptor ligands for the treatment of CNS disorders^{2–5} and as DNA minor groove binders.^{6,7} The biological importance of guanidines is highlighted by the prevalence of guanidine-carboxylate salt bridges in protein structures, a feature that is often closely linked to protein function.⁸ In addition, aromatic guanidines have found use in a diverse range of therapeutic and biological applications.⁹ Guanidines have also proven effective as catalysts for a wide variety of organic transformations^{10,11} and have been studied as ligands both in metalloproteins¹² and in synthetic metal complexes.¹³

The structure of guanidine in the solid state was recently resolved, revealing the high tendency of this molecule to form hydrogen bond (HB) interactions.¹⁴ Tautomerism in guanidines has been the object of a recent ¹⁵N NMR study,¹⁵ as have its vibrational properties, which have been the subject of a theoretical study.¹⁶ In an attempt to elucidate their mode of binding to biological receptors, Kleinmaier et al. have investigated the conformational preferences of monoalkylated acyl guanidines.¹⁷ Moreover, we have recently published a theoretical study of the π -cation interactions in solution between the guanidinium and simple aromatic systems.¹⁸ In spite of all of these studies, the molecular basis for ligand–receptor interactions in aromatic guanidines remains poorly understood, and further knowledge of their conformational preferences would be of great benefit in elucidating their mode of binding to biological receptors.

Moreover, carbamates and amides are important building blocks in artificially folded molecules, in conjunction with

pyridines. This topic has been thoroughly reviewed by Huc, who found that aromatic oligoamide foldamers can be efficiently designed, are easy to synthesize, and permit one to obtain many different stable folded states. Furthermore, he describes that conformational rearrangements may be induced by changing the conformational preference of aryl–amide bonds.¹⁹ In addition, pH-active pyridines are considered as interesting units in molecular motion controlled by pH. Thus, Kolomiets et al. using NMR and circular dichroism have studied how oligopyridine carboxamide strands experience reversible folding/unfolding when protonated.²⁰

In our search for new aromatic guanidine derivatives, we present here not only the preparation of a number of novel 2-guanidino pyridines (Figure 1) following our own synthetic

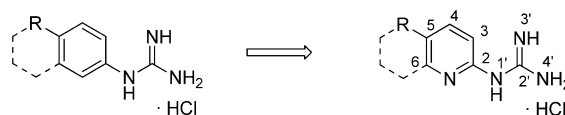


Figure 1. General structures of previously prepared phenyl guanidines and new pyridine-2-yl guanidine derivatives, indicating the numbering scheme used throughout this work.

approach¹ but also a thorough structural study at both experimental (¹H NMR and X-ray spectroscopy) and computational (density functional theory, DFT) levels.

To the best of our knowledge, these pyridin-2-yl guanidines have not yet been studied, and only a few pyridinyl guanidine derivatives have been reported to date. These include those in which the pyridine and guanidine moieties are separated by a

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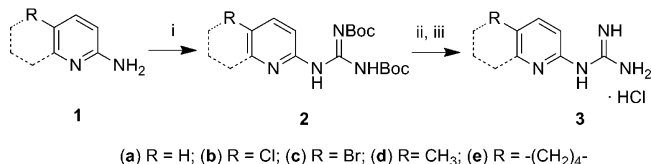
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linker, several cobalt²¹ and zinc²² complexes that were studied for their potential in sensor technology and as lactide polymerization catalysts, respectively, and a number of 2-pyridinylguanidines prepared as urokinase inhibitors.²³ Additionally, the crystal structures and conformational properties of *N,N'*-diphenylguanidine and its *N*-methylated derivatives have been previously investigated by X-ray crystallography and NMR by Kagechika and co.²⁴

RESULTS AND DISCUSSION

Synthesis and Characterization of *N*-(Pyridin-2-yl)-guanidinium Salts. A series of novel *N*-(pyridin-2-yl)-guanidinium salts and the closely related bicyclic analogue *N*-(5,6,7,8-tetrahydroquinolin-2-yl)guanidinium were synthesized following our standard synthetic procedure for the preparation of aromatic guanidines¹ (Scheme 1).

Scheme 1. General Synthetic Pathway^a



^aReagents and conditions: (i) HgCl₂, Et₃N, *N,N'*-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea, CH₂Cl₂, 0 °C to rt, 18 h. (ii) CF₃CO₂H, CH₂Cl₂, 3 h. (iii) Amberlite IRA-400(Cl⁻ form), H₂O, 24 h.

Starting from commercial or synthetically prepared²⁵ 2-aminopyridines (**1**), guanidylation was performed in the presence of mercury(II) chloride using Boc-protected 2-methyl-2-thiopseudourea to afford the corresponding *N,N'*-di-Boc-protected intermediates (**2**). Removal of the Boc groups

using trifluoroacetic acid followed by anion exchange with Amberlite IRA-400 resin afforded the desired guanidinium chloride salts (**3**) in good to excellent overall yields (65–93%).

Significantly, in the course of the characterization of these compounds, a striking difference was observed in the ¹H NMR chemical shifts of hydrogen H3 recorded for the neutral di-Boc-protected compounds **2** as compared to those recorded for the hydrochloride salts **3** (Figure 2).

This difference was preserved across a variety of R substituents with varying electronic properties (Cl, Br, H, and CH₃), in both CDCl₃ and DMSO-*d*₆. For the sake of this discussion, only shifts acquired in DMSO-*d*₆ will be quoted, unless otherwise stated. Regardless of the electronic effect induced by these R substituents, the difference in the ¹H NMR spectra between series **2** and **3** remained significant, thereby indicating that this phenomenon might be the result of conformational restraints. Considering the importance of conformation in the potential pharmacological application of these compounds, a complete structural study (NMR spectroscopy, DFT calculations, and X-ray crystallographic analysis) of these molecules was carried out.

Theoretical Studies on Conformation and Tautomerism of Aromatic Guanidines. Considering the relative position of the guanidine/ium and pyridine moieties with respect to the N1–C2–N1'–C2' dihedral angle, two extreme geometries result, which can be labeled as *anti* and *syn* conformations (Figure 3).

It is known that in pyridyl guanidinium systems, the *syn* conformation can be stabilized by intramolecular hydrogen-bonding interactions (IMHB) when the guanidinium carrying group is placed in the *ortho* position.²⁶ Hence, a theoretical DFT study at the B3LYP/6-31+G** computational level of all possible geometries of the neutral 2-pyridinoguanidine series (including *E/Z* isomers, *syn/anti* rotamers, and tautomers) was

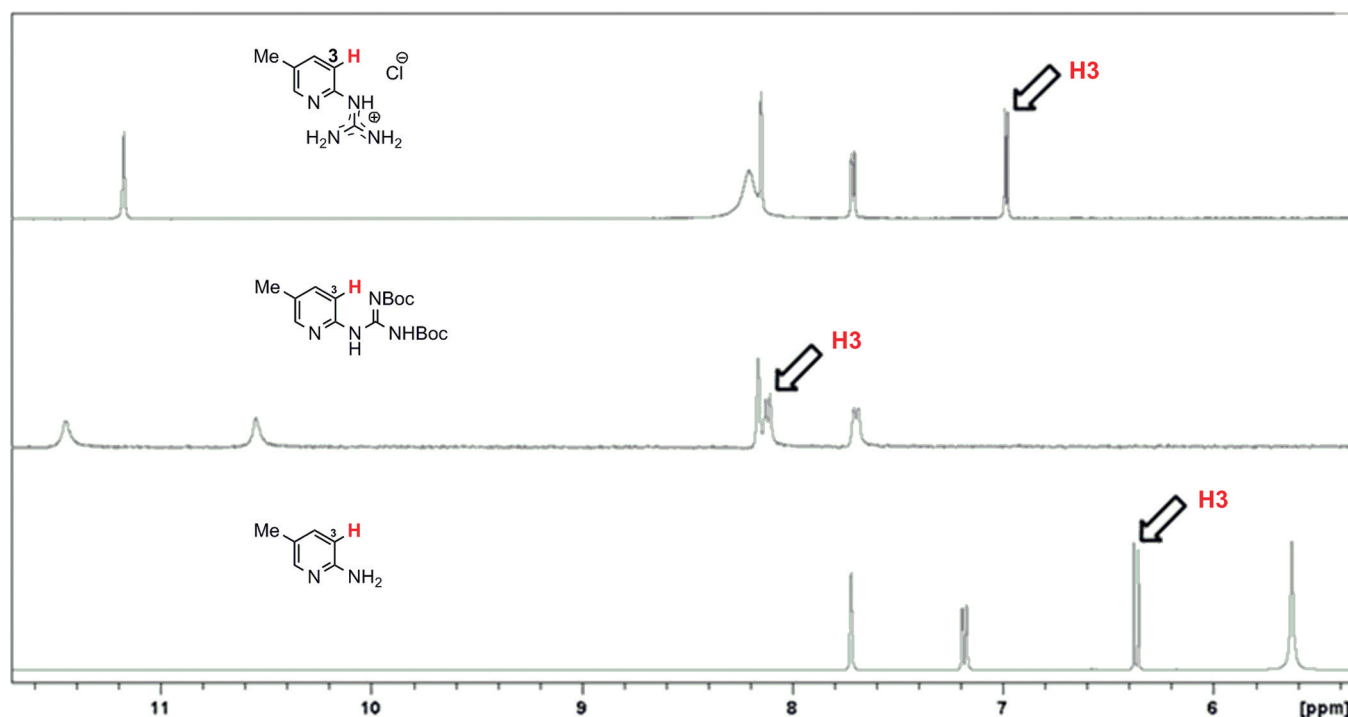


Figure 2. Aromatic region of the ¹H NMR spectra (DMSO-*d*₆) of 5-methyl-2-aminopyridine **1d** (bottom), 1-[2,3-di-(*tert*-butoxycarbonyl)guanidino]-5-methylpyridine **2d** (middle), and *N*-(5-methylpyridin-2-yl)guanidinium chloride **3d** (top).

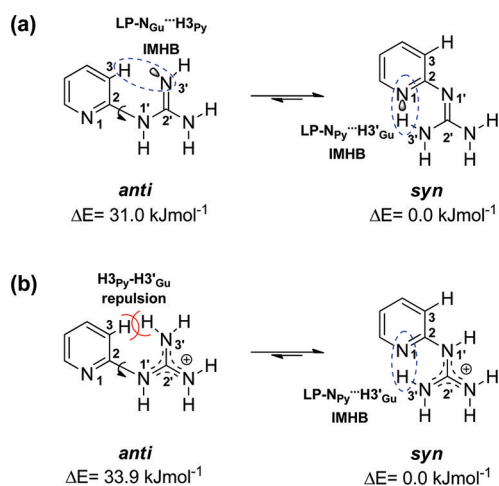


Figure 3. *Anti* and *syn* conformations available to (a) 2-pyridinoguanidine and (b) 2-pyridinoguanidinium (series 3) via rotation around the C2–N1' bond.

initially performed to approach our systems. We found that, as expected, the absolute minimum corresponds to one of the *syn* geometries (Figure 3a), which is 30 kJ mol^{−1} more stable than the best of the minima found in the *anti* conformation (for the sake of clarity, only the most stable *anti/syn* minima are shown). Thus, in 5-substituted-2-guanidinopyridines, the stabilization induced by the IMHB through the pyridine nitrogen [LP–N_{Py}···H3_{Gu}] is considerably larger than that through the guanidine nitrogen [LP–N_{Gu}···H3_{Py}], in the absence of electronic or steric secondary factors.

As mentioned before, we have experimentally observed that the guanidinium salts showed a NMR pattern very different to that observed in their Boc derivatives and that this could be due to important differences in their geometries. Hence, using B3LYP/6-31+G**, we continued with our theoretical study to confirm this hypothesis. In the case of the protonated series 3, a quantum theoretical intrinsic reaction coordinate (IRC) study of the C2–N1' rotation process^{27,28} was carried out (gas phase), resulting in two energetic minima and two transition states (Figure 4). As in the case of the neutral guanidine (Figure 3a), the global minimum of the guanidinium series corresponds to the *syn* conformation and features a coplanar arrangement of the guanidinium and pyridine moieties stabilized by the same type of IMHB interaction [LP–N_{Py}···H3_{Gu}]. In this case, the prevalence of the *syn* conformation is also favored by steric constraints in the *anti* rotamer (H3···H3' repulsion, Figure 3b), which was also localized as a second local minimum exhibiting a “twisted” geometry to minimize the aforementioned repulsion. Fur-

thermore, two stationary states were localized as follows: TS1, which corresponds to the transition between the *anti* and the *syn* minima, and TS2, which results from the transition between the two possible degenerate *anti* minima (“twisted” above and below the pyridine ring). Although the calculated barriers to the rotation are not high enough to completely restrict the C2–N1' rotation (36.9 and 45.7 kJ mol^{−1}), the energetic difference between the *anti* and the *syn* minima (34.0 kJ mol^{−1}) suggests an almost quantitative preference for the *syn* conformation.

The study of conformation and rearrangement in the Boc-protected series 2 is considerably more complicated. In this case, the guanidine subunit is not only triply substituted but also neutral; therefore, the localization of the C2=N(3',4') bond results in a number of tautomers. Additionally, *E/Z* isomerism in the imino group, and the possible internal rotation of the adjacent secondary amines results in further geometries. Unlike guanidinium series 3, the combination of these issues for the Boc-protected series 2 results in a vast array of possible conformations/isomers/tautomers, and any *a priori* prediction of geometrical preference becomes untenable. To approach this problem in a systematic way, we have carried out a complete screening (by means of a conformational systematic search) of the less computationally demanding diacyl analogues of series 2. Those structures showing total energies within a range of 30 kJ mol^{−1} from the minimum were used as templates for the di-Boc derivatives, which were then fully optimized until a minimum energy geometry was obtained (see the Supporting Information).

The ¹H NMR spectra of the majority of the *N,N'*-di-Boc-protected phenylguanidine derivatives previously synthesized in our group^{3–5} show the CH₃ protons of the *tert*-butyl groups as two separate signals integrating for nine protons each, suggesting the chemical inequivalence of the two *N*-Boc groups. This could be explained by the formation of two IMHBs involving the Boc carbonyl groups and guanidine hydrogens H1' and H4', which is supported by the deshielding recorded for these two protons' signals (>10 ppm). In addition, these two Boc groups are not equivalent because one is connected to an amino-N and the other one is connected to an imino-N group.

The proposed IMHB network confers rigidity to the *N,N'*-di-Boc-substituted guanidine system, which could be considered as a single “pseudo bicyclic” structure similar to that previously described for β -diketones.²⁹ Thus, the conformational problem in these Boc derivatives is reduced to a simple rotation around the C1–N1' bond connecting the phenyl ring and the rigid Boc-protected guanidine. Because of the symmetry of the phenyl ring, this rotation results in a degenerate pair of conformations stabilized by IMHBs between the guanidine N3' and the phenyl protons H2 or H6, respectively (Figure 5a).

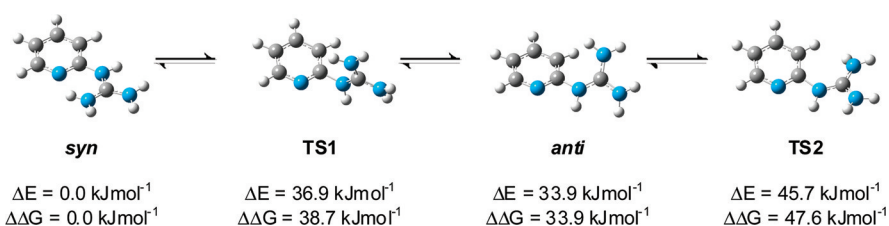


Figure 4. Stationary structures resulting from the IRC study at B3LYP/6-31+G** computational level of the C2–N1' rotation in the guanidinium derivative 3a. ΔE refers to the difference in total energy between a given state and the global energetic minimum in the gas phase, while $\Delta\Delta G$ is the difference in free energy.

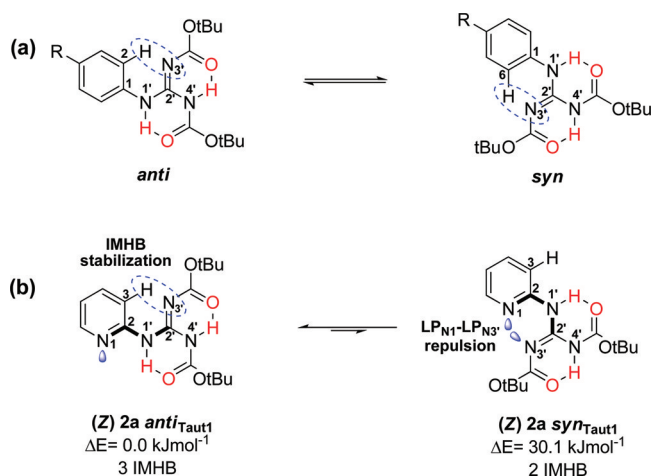


Figure 5. (a) Degenerate conformations for *N,N'*-di-Boc substituted phenylguanidines and (b) *anti* and *syn* conformations for Boc-protected pyridin-2-ylguanidine **2a** (Z isomer, same tautomer 1), indicating the calculated relative energies (B3LYP/6-31+G**). Highlighted in bold is the N1–C2–N1'–C2' dihedral angle, and in red is the NH...OC IMHB interaction.

This kind of C(Ar)–H...N IMHB has previously been described for compounds such as 2,2'-bipyridine,³⁰ 1,1'-bipyrazole,³¹ and 9-azaphenyl-9H-carbazoles,³² and C–H...X (X = O, S, N) HBs have been widely discussed in the literature by Desiraju, among others.³³

Similarly, in the Boc-protected pyridin-2-yl guanidines **2**, the conformational issue could be reduced to a rotation around the N1–C2–N1'–C2' dihedral angle. However, in this series **2**, the resulting *anti* and *syn* conformations are no longer degenerate (Figure 5b). In the *syn* conformation, a repulsive effect may exist between the N1 and the N3' lone pairs, while in the *anti* conformation, a stabilizing IMHB involving N3' and H3 may be present [LP–N_{Gu}...H3_{Py}]. B3LYP/6-31+G** calculations performed for the Z isomer of compound **2a** (same tautomer 1) confirmed that the *anti* conformation [(Z)-**2a anti-Taut1**] was 30.1 kJ mol^{−1} more stable than the *syn* one [(Z)-**2a syn-Taut1**], which shows a twisted geometry (N1–C2–N1'–C2' dihedral angle = 53.0°), resulting from the N1 and N3' lone pairs repulsion (Figure 5b).

As mentioned, the conformational analysis in series **2a** was systematically extended to all of the possible isomers/tautomers/rotamers; hence, several reasonably stable **2a syn** minimum energy geometries were found showing at least one of the previously described IMHBs, plus a second IMHB involving pyridine N1 (Figure 6). These minima exhibited, in all cases, a coplanar arrangement of the pyridine and guanidine

subunits, strongly supporting the existence of the postulated IMHBs (N1–C2–N1'–C2' dihedral angle $\approx 0.0^\circ$). However, their relative energies reveal that the tautomer **1** of the Z isomer in its *anti* conformation (compound **2a anti-Taut1**, Figure 5b) remains the most stable by a significant energetic margin ($>15.0 \text{ kJ mol}^{-1}$). Therefore, these results strongly suggest that compounds in series **2** should preferentially adopt the *anti* conformation.

Summarizing, the Boc-protected derivatives **2** exhibit a clear preference for the *anti* conformation, while the guanidinium salts **3** and the neutral 2-pyridinylguanidine exist primarily in the *syn* conformation. In addition, the energetic differences computed between these two conformations seem large enough to allow prediction of the predominant conformation across series **2** and **3** under experimental conditions.

X-ray Analysis and NMR Studies of the New Pyridin-2-yl Guanidines. Confirmation of these computational predictions was achieved with the X-ray crystal structure of some of these pyridin-2-yl guanidine/ium derivatives (Figure 7). Thus, slow recrystallization from a mixture of hexane/EtOAc provided a crystal structure for the 5-chloro derivative of the di-Boc-protected pyridin-2-yl guanidines (**2b**). This structure is planar, and the N1–C2–N1'–C2' dihedral angle is 180°, in agreement with the predicted *anti* conformation (Figures 2b and 7). This crystal structure also reveals an extensive IMHB network involving the Boc CO and N3' lone pairs as HB acceptors and the H1', H4', and H3 as donors, as previously described in Figure 5b. Using the same solvent system, a second crystal structure was obtained for the di-Boc-protected guanidine-4-ethoxybenzene **4** (Figure 7), whose preparation has been described by us elsewhere⁴ and which is structurally related to series **2**. The crystal structure obtained exhibited the *anti* conformation and bears similar features to those of its pyridine analogue **2b**. A summary of the most relevant distances and angles of these crystal structures is presented in Table 1. The HB distances found for the O...H1' interaction ($\sim 1.9 \text{ \AA}$) in both compounds are in agreement with very strong HBs, while those distances found for the N3'...H3(C) contacts ($\sim 2.3 \text{ \AA}$) correspond to medium-weak HB interactions (see Table 1). However, the HB formed between O...H4' is shorter for compound **4** than for compound **2b**, indicating that even though medium to very strong HBs are established in both cases the one corresponding to compound **4** is stronger.

In addition, crystals for two of the 1-(pyridin-2-yl)-guanidinium chloride salts (**3d** and **3e**) were obtained, using a slow diffusion of diethyl ether in a cold methanolic solution, and resolved by X-ray crystallographic analysis (Figure 7). These structures **3d** and **3e** exhibit *syn* conformation featuring pyridine/guanidine coplanarity and an IMHB between the N1

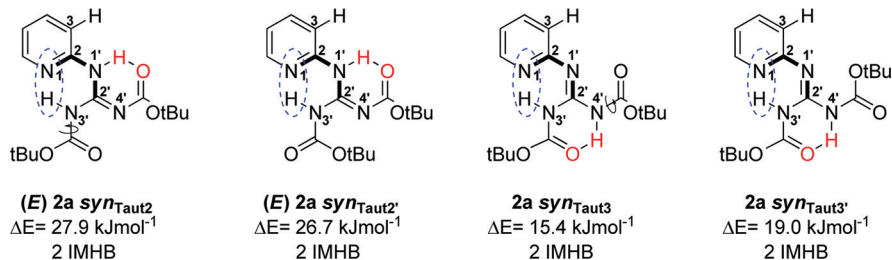


Figure 6. Relative energies, referred to the minimum energy structure [(Z) **2a anti-Taut1** in Figure 5b] calculated at B3LYP/6-31+G** level, for the most favorable energetic minima tautomers/rotamers selected in the *syn* geometry of compound **2a**. Highlighted in bold is the N1–C2–N1'–C2' dihedral angle, and in red is the NH...OC IMHB interaction.

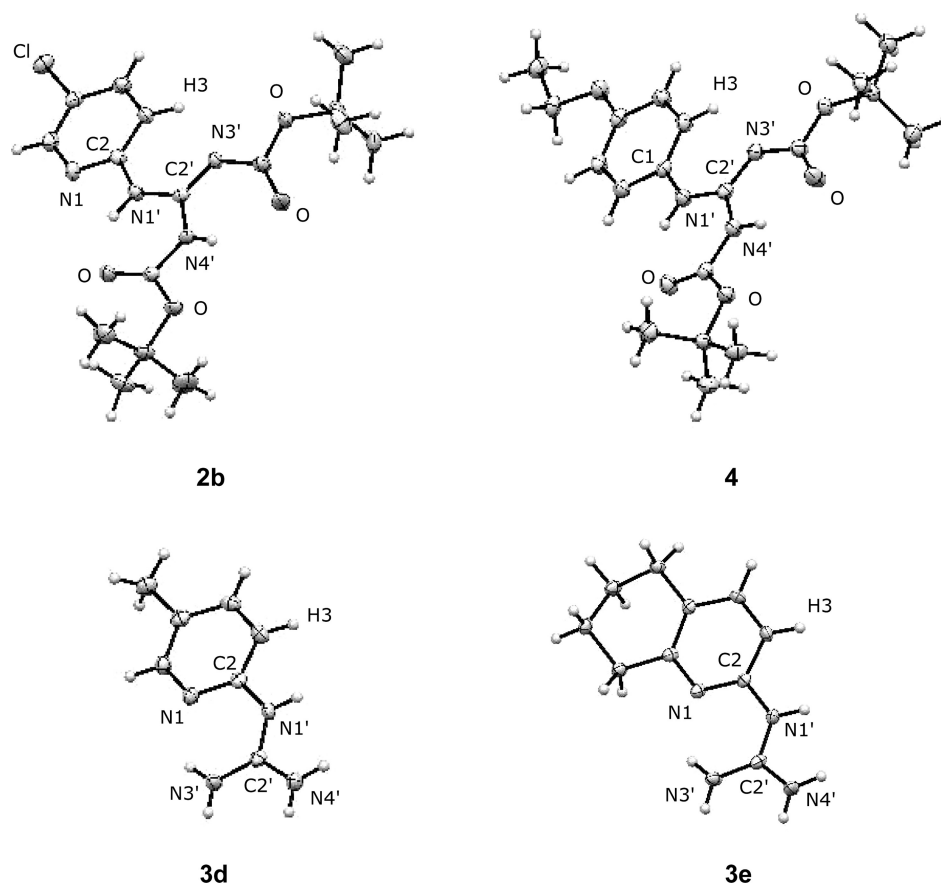


Figure 7. X-ray crystal structures of 2-[2,3-di-(*tert*-butoxycarbonyl)guanidino]-5-chloropyridine (**2b**), 1-[2,3-di-(*tert*-butoxycarbonyl)guanidino]-4-ethoxybenzene (**4**), *N*-(5-methylpyridin-2-yl)guanidinium chloride (**3d**), and *N*-(5,6,7,8-tetrahydroquinolin-2-yl)guanidinium chloride (**3e**).

Table 1. Relevant HB Distances (Å) and Angles (°) Found in the Crystal Structures of Compounds **4**, **2b**, **3d**, and **3e**

	N3'...H3	N3'...H3—C3	O...H1'	O...H1'—N1'	O...H4'	O...H4'—N4'
4	2.314	120.9	1.950	139.7	1.872	133.8
2b	2.311	119.2	1.952	139.3	2.109	123.7
	C2'—N1'	C2'—N3'	C2'—N4'	N1'...H3'	N1'...H3'—N3'	
4	1.339	1.385	1.315			
2b	1.354	1.388	1.300			
3d	1.343	1.315	1.326	2.091		129.8
3e	1.350	1.309	1.333	2.085		129.9

and the H3'/H4' guanidine protons. In both compounds, the distances observed for the N1'...H3' interaction (Table 1) correspond to strong HBs.

Furthermore, looking at the three C—N bond distances within the guanidine/ium moieties, it was noticed that in the neutral Boc-protected structures (**2b** and **4**), different values were observed ranging from clear single C—N bonds for C2'—N3' to C=N double bonds for C2'—N4', while C2'—N1' would be slightly shorter than a single bond, indicating a degree of delocalization. In the case of the guanidinium derivatives, **3d** and **3e**, the distances found for C2'—N1' and C2'—N4' are similar to the C2'—N1' in the Boc derivatives showing delocalization. The C2'—N3' bond corresponding to the N1'...H3' interaction was slightly shorter than the other two C—N bonds due to this IMHB. The relatively longest C—N bond corresponded, in both structures, to the C2'—N1' bond that connects to the pyridine system.

Curiously, in the crystal structure of *N,N'*-diphenylguanidine, one of the C—N bonds connected to a phenyl ring show double bond characteristics, while the other two (C—NH₂ and C—NHPh) appear as single bonds.²⁴ In the case of the neutral Boc derivatives, **2b** and **4**, it seems that the guanidine double bond is localized not over the N atom attached to the pyridine/phenyl ring but over the N atom connected to a Boc group not involved in hydrogen bonding with N1' (C2'—N4'). However, in the crystal structure of *N,N'*-dimethyl-*N,N'*-diphenylguanidine, the C=N double bond is localized over the unsubstituted N atom,²⁴ similar to what is observed in our neutral guanidines. Regarding the hydrochloride salts **3d** and **3e** and the hydrobromide salt of *N,N'*-dimethyl-*N,N'*-diphenylguanidine,²⁴ very similar C—N distances are obtained for the three C—N bonds involved in the guanidinium group (between 1.31 and 1.38 Å).

Significantly, NMR experiments in solution supported the persistence of the conformational effects that have been theoretically predicted (DFT calculations) and experimentally observed in the solid state by X-ray crystallographic studies (Table 2).

In agreement with the *anti* conformation, the existence of an IMHB between N3' and H3 in the di-Boc-protected series (**2**) is strongly supported by the ¹H NMR data recorded for proton H3 (Table 2). Throughout series **2**, this signal is broadened and strongly shifted to high field (7.93–8.27 ppm). In contrast, the H3 signal recorded for the guanidinium salt series **3** consistently appears as a sharp doublet at 6.80–7.13 ppm, which is much closer to that observed for the corresponding

Table 2. ^1H NMR Shifts of Series 1–3 Obtained in $\text{DMSO}-d_6^a$

compd	R	δH3	δH4	δH6	$\delta\text{H1}'$	$\delta\text{H3}'$	$\delta\text{H4}'$
1a	H	6.41	7.33	7.88	5.85		
1b	Cl	6.45	7.39	7.88	6.14		
1c	Br	6.42	7.49	7.94	6.16		
1d	CH_3	6.37	7.18	7.72	5.63		
1e	$-(\text{CH}_2)_4-$	6.20	7.03		5.53		
2a	H	8.22 (+1.81)	7.87 (+0.54)	8.32 (+0.44)	11.44		10.59
2b	Cl	8.27 (+1.82)	8.02 (+0.63)	8.38 (+0.50)	11.36		10.65
2c	Br	8.22 (+1.80)	8.13 (+0.64)	8.44 (+0.50)	11.36		10.64
2d	CH_3	8.11 (+1.74)	7.69 (+0.51)	8.15 (+0.43)	11.46		10.54
2e	$-(\text{CH}_2)_4-$	7.93 (+1.73)	7.53 (+0.50)		11.53		10.49
3a	H	7.07 (+0.66)	7.88 (+0.55)	8.32 (+0.44)	11.39	8.30 ^b	
3b	Cl	7.13 (+0.68)	7.98 (+0.59)	8.35 (+0.47)	11.70	8.28 ^b	
3c	Br	7.06 (+0.64)	8.09 (+0.60)	8.43 (+0.49)	11.53	8.23 ^b	
3d	CH_3	6.98 (+0.61)	7.71 (+0.53)	8.15 (+0.43)	11.17	8.20 ^b	
3e	$-(\text{CH}_2)_4-$	6.80 (+0.60)	7.55 (+0.52)		11.08	8.22 ^b	

^aThe difference in chemical shift with reference to the corresponding 2-aminopyridine is shown in parentheses. ^bH3' and H4' are chemically equivalent due to free rotation around the C2'–N1', C2'–N3', and C2'–N4' bonds.

series of 2-aminopyridines (**1**) (6.20–6.45 ppm). As shown, this variation in the chemical shift of H3 is significant even considering electronic effects.

The effect of the Boc-guanidine subunit upon chemical shift generally resembles that of the guanidinium cation (Figure 8).

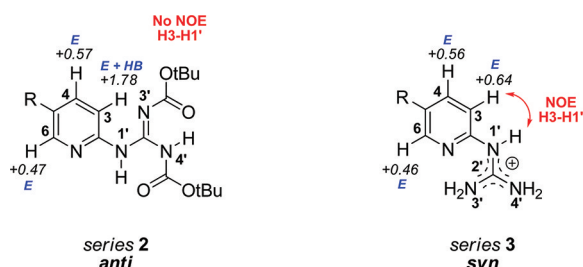


Figure 8. Average value of ^1H NMR deshielding in aromatic protons H3, H4, and H6 in series 2 and 3 with respect to the corresponding 2-aminopyridine **1**. *E* and *HB* indicate electronic or hydrogen-bonding effects, respectively.

Focusing on the conformationally unaffected protons H4 and H6, the average difference in chemical shift with reference to the starting 2-aminopyridine changes little between the Boc-guanidine and the guanidinium subunits (+0.57/+0.56 for H4 and +0.47/+0.46 for H6, respectively). However, in the case of H3, the average change in deshielding is considerably higher for the Boc-protected series **2** (+1.78) than for the guanidinium series **3** (+0.64); this marked discrepancy can be explained by the electronic effect of a IMHB interaction.

The chemical inequivalence of the Boc groups in series **2** was confirmed by the occurrence of two separate signals for the *tert*-butyl groups. The CH_3 protons appeared as two singlets each integrating for nine protons at 1.43–1.44 and at 1.44–1.51 ppm, in agreement with the rigid, “pseudo bicyclic” structure suggested for the Boc-guanidine subunit. In the case of the Boc-guanidine 4-ethoxybenzene derivative **4**, for which a corroborating X-ray crystal structure was obtained, these signals appear at 1.44 and 1.50 ppm.

Further evidence of the conformational arrangement was available via the ^1H NMR signals of the guanidine NH protons. In the Boc-protected series **2**, H1' and H4' are highly shifted (11.36–11.53 and 10.49–10.65 ppm, respectively) with respect

to the starting amine, suggesting the participation of these protons in the HB network proposed for the *anti* conformation. In the *syn* conformation of the guanidinium series **3**, H1' is highly deshielded (11.08–11.70 ppm) due to its acidity induced by the adjacent pyridine ring, while H3' and H4' appear as a single signal at 8.22–8.28 ppm as they are chemically equivalent. This value is higher than the corresponding chemical shift in unsubstituted guanidinium chlorides (7.07 ppm),³⁴ and this deshielding can be explained by the effect of the nearby pyridine nitrogen lone pair.

Nuclear Overhauser effect (NOE) experiments further supported the postulated conformational preferences. A through-space interaction was observed between H3 and H1' in the *N*-(pyridin-2-yl)guanidinium chlorides **3**, in agreement with the *syn* conformation. Conversely, the absence of an NOE signal for these same protons in the di-Boc protected series **2** suggests that they are not nearby in space, supporting the prevalence of the *anti* conformation.

Moreover, variable temperature ^1H NMR was carried out on compounds **2d** and **3d** to identify if equilibrium exists between the possible conformations in both series. Spectra were recorded in $\text{DMSO}-d_6$ at 10° increments from room temperature to 80 °C, and a final spectrum was recorded on recooling the sample to room temperature. Neither compound showed significant changes, the spectra indicating in each case that in fact a single conformer exists experimentally in solution, confirming our predictions. The characteristic downfield shift and broad nature of H3 in compound **2d** was maintained throughout, as was the high field shift of the NH protons at 10.5 and 11.4 ppm (see the Supporting Information). Some degradation of the compound was observed above 70 °C. The possibility that this was as a result of another conformation of the same molecule was ruled out by its persistence on recooling the compound to room temperature. For compound **3d**, no observable changes occurred on heating the solution (see the Supporting Information). In particular, the high shift seen for the NH signals was maintained. No degradation of the compound was observed in this case. This leads us to conclude that the *syn* conformation for compounds **3** dominates in solution as well as in the solid state.

On the basis of these experiments, we have calculated the temperature dependence of the ^1H NMR chemical shifts of

those hydrogens involved in the IHMB in compounds **2d** and **3d** (H3 and H3', respectively) as shown in Figure 9. It can be

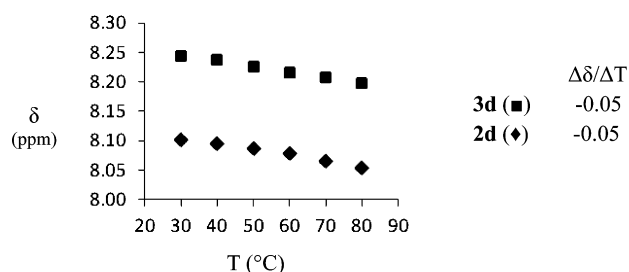


Figure 9. ^1H NMR chemical shifts of H3 (compound **2d**, ◆) and H3' (compound **3d**, ■) as a function of temperature ($^{\circ}\text{C}$). The corresponding $\Delta\delta/\Delta T$ coefficients are also shown.

observed that compound **3d** experiences more internal hydrogen bonding than **2d**, and both seem to show similar temperature dependence.

The $\Delta\delta/\Delta T$ coefficients obtained (-0.05 for **2d** and **3d**) are larger than those reported by Gellman et al. for IMHBs in diamides³⁵ (from -0.0025 to -0.0100), suggesting that the IMHB formed in both cases are solvent-exposed. It can be concluded that upon increasing the temperature the IMHBs have been slightly distorted since a small negative shift is observed for the corresponding signals and that this distortion is larger for compound **2d** than for **3d** in agreement with the strength of each of the IMHBs involved ($\text{C}-\text{H}\cdots\text{N}$ for **2d**, which is weaker than $\text{N}-\text{H}\cdots\text{N}$ for **3d**).

Conformational Control in *N*-Boc-*N'*-alkyl pyridin-2-yl Guanidines. Considering the theoretical and experimental evidence so far obtained, it was hypothesized that substitution of one of the Boc protecting groups by an alkyl chain could suppress the rigid IMHB network in series **2** and might thereby induce a change from the *anti* to the *syn* conformation. Thus, a new series of *N*-Boc-*N'*-alkyl-substituted pyridin-2-yl guanidines (**5**) was studied. As for the previous series, a systematic conformational study for **5a** was performed at the B3LYP/6-31+G** level showing that, in agreement with our hypothesis, the *syn* conformation is >25.9 kJ mol $^{-1}$ more stable than the best *anti* one (Figure 10). However, because of the asymmetry of this system, two different *syn/anti* energetic minima, **5a(i)** and **5a(ii)**, had to be analyzed. In the case of the *syn* conformers, these minima differ by only 5.0 kJ mol $^{-1}$, suggesting the existence of two possible *syn* conformers under experimental conditions.

Compounds **5b** and **5d**, *N*-Boc-*N'*-propylpyridin-2-yl guanidine-substituted analogues to **5a**, were experimentally prepared following a synthetic procedure recently developed within our research group.³⁶ The characterization of these compounds confirmed the theoretical prediction that the molecules of series **5** can exist as a nearly equimolar mixture of two isomers (see Figure 11).

In the case of compound **5b** ($\text{R} = \text{Cl}$), a 3:4 mixture of isomers (i) and (ii) was formed, adjudged by ^1H NMR integration. These isomers proved to be inseparable by either column chromatography (silica gel) or by recrystallization. For compound **5d** ($\text{R} = \text{CH}_3$), a 6:5 mixture of isomers (i) and (ii) was obtained, and in this case, isolation of the (i) isomer was possible using silica gel column chromatography (9:1, hexane:EtOAc). The similar isomeric ratios found in both compounds suggest little difference in their relative energies in

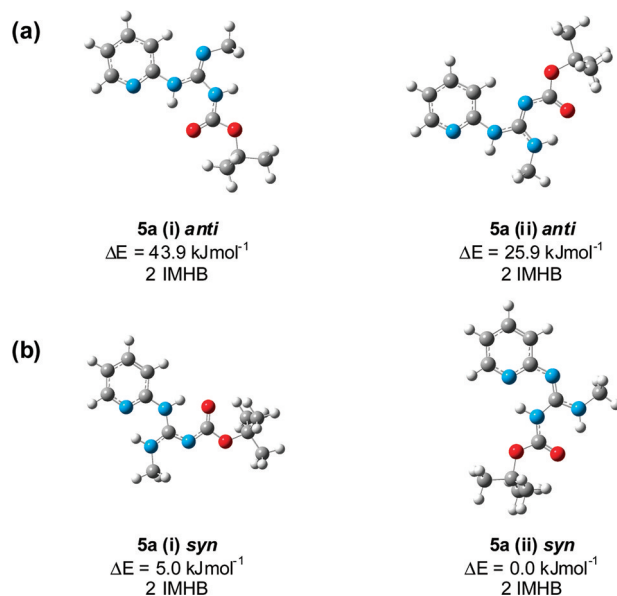


Figure 10. Energetic minima calculated for (a) the best *anti* conformation of *N*-Boc-*N'*-methyl-(pyridin-2-yl)guanidine **5a** and (b) the best *syn* conformation of the same molecule. To reduce the computational cost of these calculations, the propyl group present in the experimental compounds was replaced with a methyl group.

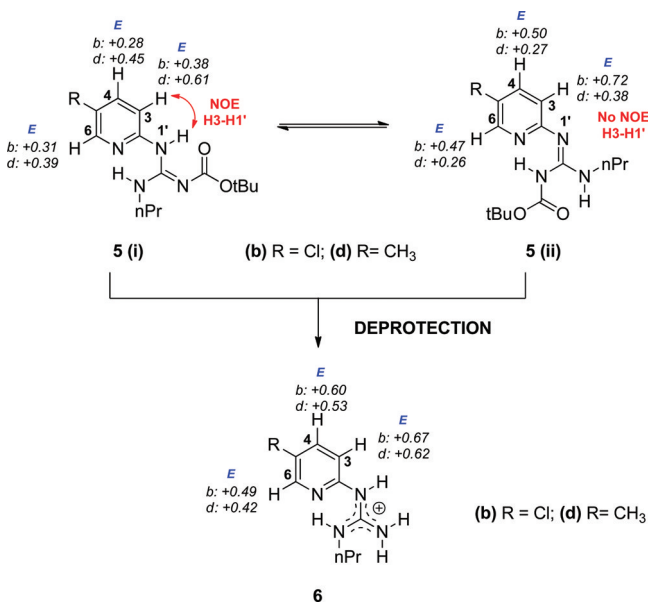


Figure 11. Isomers (i) and (ii) obtained for the *N*-Boc-*N'*-propylpyridin-2-yl guanidines **5b** and **5d**. Indicated are the ^1H NMR shifts of protons H3, H4, and H6 in compounds **5** and **6** with respect to the corresponding 2-aminopyridines **1**. *E* denotes electronic effects.

agreement with our calculations. Temperature-dependent ^1H NMR experiments were carried out with the mixture of **5b** isomers in $\text{DMSO}-d_6$ and heating from 20 to 100 $^{\circ}\text{C}$. It was observed that signals corresponding to **5b(ii)** increased with temperature (up to 75 $^{\circ}\text{C}$) until a 50:50 proportion with those of **5b(i)**, indicating that the equilibrium was reached, and finally, the compound decomposed at 100 $^{\circ}\text{C}$. More importantly, the ^1H NMR spectra of both isomers did not show the H3 shift characteristic of the *anti* conformation but one closer to that of the starting 2-aminopyridines (Table 3), suggesting that it is uninvolved in IMHB interactions, in

Table 3. ^1H NMR (DMSO- d_6) Shifts in Compounds **5** and **6**

compd	isomer	δH3	δH4	δH6	$\delta\text{H1}'$	$\delta\text{H3}'$	$\delta\text{H4}'$
5b R = Cl	i	6.83	7.67	8.19	12.42		7.89
	ii	7.17	7.89	8.35		11.89	9.74
5d R = CH ₃	i	6.98	7.63	8.11	11.74		10.12
	ii	6.75	7.45	7.98		13.09	10.11
6b R = Cl		7.12	7.99	8.37	11.47	9.17	8.58
6d R = CH ₃		6.99	7.71	8.14	11.34	9.43	8.59

agreement with the *syn* conformation. This *syn* conformation in isomer (i) was further evidenced by the presence of NOE signals between H1' and H3 and by the high-field shift recorded for H1', as expected for an IMHB with a CO lone pair [**5b**(i), 12.42; and **5d**(i), 11.74 ppm]. These NOE signals were not observed in isomers (ii), as expected.

The prevalence of the *syn* conformation in compounds **5** confirms that neither the *N*-Boc electronic effect, the unprotonated state of the molecules, nor the steric bulk around the guanidine subunit are sufficient to induce the *anti* conformation observed in the di-Boc derivatives **2**. Thus, the conformational control in pyridin-2-yl guanidines remains firmly rooted in the IMHB interactions established between the guanidine and the pyridine subunits.

As expected, cleavage of the Boc group in compounds **5** results in the abolition of any isomeric mixture as shown in the ^1H NMR of the corresponding *N*-propyl **6** derivatives, which exhibit the *syn* conformation (see Figure 11). It is worth noting that the introduction of an alkyl substituent in the protonated guanidinium **6** does not produce any significant variation in the chemical shift of protons H3, H4, and H6 with respect to the guanidiniums **3**.

CONCLUSIONS

During preparation of a new series of pyridin-2-yl guanidine derivatives following our standard synthetic method, a striking difference between the ^1H NMR spectra of the *N,N'*-di-Boc-protected and guanidinium salt derivatives (series **2** and **3**, respectively) was observed. This difference remained across the series regardless of the substituent in position 5 of the pyridine ring; we therefore considered that this effect might result from conformational constraints. Hence, we have carried out a complete theoretical and experimental structural study using B3LYP/6-31+G** calculations, NMR spectroscopy, and X-ray crystallographic analysis.

Considering the two possible conformational extremes (*anti* and *syn*), DFT theoretical studies yielded two main conclusions. First, the Boc-protected derivatives **2** exhibit a preference for the *anti* conformation, while the 2-pyridinoguanidine and the guanidinium salts **3** exist primarily in the *syn* conformation. Second, the computations suggested the formation of two IMHBs involving the Boc carbonyl groups and guanidine hydrogens, which confer rigidity to the *N,N'*-di-Boc-substituted guanidine system in series **2**, and in the final guanidinium salts (series **3**), another IMHB is suggested to be formed between the pyridine nitrogen and the protons H3' [LP–N_{py}···H3'_{Gua}] in the guanidinium moiety.

X-ray crystal structures obtained for two of the 1-(pyridin-2-yl)guanidinium chloride salts (**3d** and **3e**) confirm the existence of the *syn* conformation and demonstrate a coplanar arrangement of the pyridine and guanidinium subunits, and the

existence of a IMHB interaction between the pyridine nitrogen and the guanidine protons. Moreover, the X-ray crystal structures of the *N,N'*-di-Boc-protected pyridin-2-yl guanidine **2b** (R = Cl) and its phenyl analogue **4** (R = OEt) confirm the existence of an extensive IMHB network involving the adjoining carbamate and guanidine groups.

Furthermore, solution-phase ^1H NMR, variable temperature, and NOE experiments confirm that the conformational preferences suggested by our computational studies and found in solid-state X-ray crystallographic studies are maintained in solution.

Finally, to verify that conformational control results from IMHB interactions and not from electronic or steric effects, a new series of *N*-Boc-*N'*-propyl-substituted pyridin-2-yl guanidines **5** has been studied. B3LYP/6-31+G** studies predicted a shift from the *anti* to the *syn* geometry in these new derivatives. Preparation of the corresponding derivatives **5b** and **5d** (R = Cl and CH₃) followed by Boc deprotection to yield the propyl guanidinium salts (**6b** and **6d**) allowed us to confirm the existence of the predicted *syn* geometry by means of ^1H NMR studies. Hence, conformational control in pyridin-2-yl guanidines seems to be entirely dependent on the IMHB interactions within the guanidine group (in the case of the *N,N'*-di-Boc derivatives) and between the guanidine and the pyridine subunits (in the guanidinium salts).

EXPERIMENTAL SECTION

Geometries were fully optimized at the B3LYP theoretical level with the 6-31+G** basis set as implemented in the Gaussian03 program.³⁷ Harmonic frequency calculations verified the nature of the stationary points as minima (all real frequencies) or transition states (one imaginary frequency). The scanning of the rotation was performed using the IRC type calculation implemented in the Gaussian03 program at the same level. To reduce the computational cost, the initial optimization of all possible tautomers, isomers, and rotamers of the di-Boc-protected and *N*-Boc-*N'*-alkyl pyridin-2-yl guanidine derivatives (**2a** and **5a**, respectively) was performed using an *N*-acetyl group in place of the *N*-Boc group. The most significant conformers (only those structures with relative energies within 30 kJ mol^{−1} from the minimum) were then optimized using the full *N*-Boc structure. The complete data regarding these preliminary calculations are available in the Supporting Information.

A suitable crystal from each compound **2b**, **4**, **3d**, and **3e** was selected and mounted using inert oil on a 0.3 mm diameter glass fiber tip and placed on the goniometer head in a 123 K N₂ gas stream. Nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were placed into geometrically calculated positions and refined using a riding model. The temperature was 123 K in all cases. The agreement between the data and the model (R1) for all structures was 5% or below.

Spectra were recorded on a spectrometer operating at 600.1 MHz for ^1H NMR and 150.9 MHz for ^{13}C NMR. NMR peak assignments were confirmed using the following COSY and ROESY experiments: phase-sensitive gradient enhanced (ge) 2D multiplicity-edited HSQC using PEP and adiabatic pulses with gradients in back-incept (hsqcetgpcsp2), phase-sensitive ge-2D HMBC using a 2-fold low-pass J-filter (hmbcetgpl2nd), and selective gradient enhanced 1D ROESY (selrogy).

General Procedure for the Synthesis of Di-Boc-Protected Guanidine Derivatives. To a solution of starting amine (1.0 equiv), *N,N'*-bis-(*tert*-butoxycarbonyl)-*S*-methylisothiourea (1.1 equiv) and triethylamine (3.5 equiv) in CH₂Cl₂ at 0 °C was added mercuric chloride (1.1 equiv). The mixture was stirred for 30 min at 0 °C, then warmed to RT, and stirred until the reaction was judged complete by TLC analysis. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite to remove any mercury byproduct. The filtrate was washed with brine (20 mL) and water (20 mL), dried over

anhydrous MgSO_4 , and concentrated under reduced pressure to yield a residue that was purified by silica gel column chromatography, eluting with the appropriate hexane:EtOAc mixture.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]pyridine (2a). Clear crystalline solid (282 mg, 79%); mp 138–140 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 1.44 (s, 9H, CH_3), 1.51 (s, 9H, CH_3), 7.16 (app. t, 1H, $J = 5.8, 5.6$ Hz, Ar), 7.87 (app. t, 1H, $J = 7.2, 7.7$ Hz, Ar), 8.22 (d, 1H, $J = 7.9$ Hz, Ar), 8.32 (d, 1H, $J = 3.8$ Hz, Ar), 10.59 (broad s, 1H, NH), 11.44 (broad s, 1H, NH). ^1H NMR (600 MHz, CDCl_3): δ 1.53 (s, 18H, CH_3), 7.01 (app. t, 1H, $J = 5.4$ Hz), 7.70 (app. t, 1H, $J = 7.3$ Hz), 8.29 (d, 1H, $J = 4.0$ Hz), 8.37 (broad s, 1H), 10.89 (broad s, 1H, NH), 11.53 (broad s, 1H, NH). ^{13}C NMR (150 MHz, CDCl_3): δ 28.0 (CH_3), 28.1 (CH_3), 79.9 (quat. 'Bu), 83.9 (quat. 'Bu), 116.0 (CH Ar), 119.7 (quat. Ar), 138.1 (CH Ar), 148.0 (CH Ar), 150.6 (quat. Ar), 152.6 (quat. C=O), 153.1 (quat. C=O), 163.2 (quat. C=N). IR (cm^{-1}): ν 3253 (NH), 2979 (NH), 1725 (C=N, Gua), 1621 (C=O, Boc), 1586, 1570, 1479, 1398, 1368, 1332, 1302, 1293, 1256, 1229, 1147, 1121, 1089, 1030, 994, 883, 848, 809, 763, 733, 710, 669. HRMS (m/z ESI^+): 337.1876 calcd for $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$; found, 337.1882.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]-5-chloropyridine (2b). White solid (433 mg, 75%); mp 124 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 1.44 (s, 9H, CH_3), 1.50 (s, 9H, CH_3), 8.02 (dd, 1H, $J = 8.8, 2.3$ Hz, Ar), 8.27 (d, 1H, $J = 8.7$ Hz, Ar), 8.38 (d, 1H, $J = 2.3$ Hz, Ar), 10.65 (broad s, 1H, NH), 11.36 (broad s, 1H, NH). ^1H NMR (400 MHz, CDCl_3): δ 1.53 (s, 9H, CH_3), 1.54 (s, 9H, CH_3), 7.67 (dd, 1H, $J = 8.9, 2.6$ Hz, Ar), 8.24 (d, 1H, $J = 2.6$ Hz, Ar), 8.40 (d, $J = 8.9$ Hz, Ar), 10.92 (broad s, 1H, NH), 11.51 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 28.0 (CH_3), 28.1 (CH_3), 80.1 (quat. 'Bu), 84.1 (quat. 'Bu), 116.8 (CH Ar), 126.9 (quat. Ar), 137.7 (CH Ar), 146.6 (CH Ar), 148.9 (quat. Ar), 152.6 (quat. C=O), 152.9 (quat. C=O), 163.0 (quat. Gua). IR (cm^{-1}): ν 3249 (NH), 2981 (NH), 1741 (C=N), 1716, 1633 (C=O), 1576, 1559, 1476, 1455, 1407, 1383, 1367, 1322, 1287, 1252, 1235, 1219, 1142, 1123, 1101, 1059, 1028, 1006, 967, 917, 880, 848, 837, 801, 782, 743, 728, 685. HRMS (m/z ESI^+): 371.1486 calcd for $\text{C}_{16}\text{H}_{23}\text{ClN}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$; found, 371.1489.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]-5-bromopyridine (2c). White solid (383 mg, 80%); mp 126 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 1.44 (s, 9H, CH_3), 1.50 (s, 9H, CH_3), 8.13 (dd, 1H, $J = 8.9, 1.9$ Hz, Ar), 8.22 (d, 1H, $J = 8.9$ Hz, Ar), 8.44 (d, 1H, $J = 1.9$ Hz, Ar), 10.64 (broad s, 1H, NH), 11.36 (broad s, 1H, NH). ^1H NMR (400 MHz, CDCl_3): δ 1.49 (s, 18H, CH_3), 7.75 (dd, $J = 8.7, 1.3$ Hz, Ar), 8.28 (d, 1H, $J = 2.1$ Hz, Ar), 8.31 (d, 1H, $J = 8.3$ Hz, Ar), 10.86 (broad s, 1H, NH), 11.49 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 27.8 (CH_3 , Boc), 27.9 (CH_3 , Boc), 79.9 (quat. 'Bu), 83.9 (quat. 'Bu), 114.7 (CH Ar), 117.2 (quat. Ar), 140.3 (CH Ar), 148.6 (CH Ar), 149.1 (quat. Ar), 152.5 (quat. C=O), 152.7 (quat. C=O), 162.8 (quat. Gua). IR (cm^{-1}): ν 3247 (NH), 2980 (NH), 1715 (C=N, Gua), 1632 (C=O, Boc), 1593, 1553, 1453, 1404, 1367, 1324, 1287, 1252, 1232, 1148, 1129, 1101, 1057, 1028, 1004, 878, 841, 793, 745. HRMS (m/z ESI^+): 415.0981 calcd for $\text{C}_{16}\text{H}_{23}\text{BrN}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$; found, 415.0990.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]-5-methylpyridine (2d). White crystalline solid (460 mg, 71%); mp 139 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 1.44 (s, 9H, CH_3), 1.51 (s, 9H, CH_3), 7.69 (d, 1H, $J = 8.4$ Hz, Ar), 8.11 (d, 1H, $J = 8.4$ Hz, Ar), 8.15 (s, 1H, Ar), 10.54 (broad s, 1H, NH), 11.46 (broad s, 1H, NH). ^1H NMR (400 MHz, CDCl_3): δ 1.48 (s, 9H, CH_3), 1.49 (s, 9H, CH_3), 2.23 (s, CH_3), 7.45 (dd, 1H, $J = 8.4, 1.9$ Hz, Ar), 8.07 (d, 1H, $J = 1.9$ Hz, Ar), 8.20 (broad s, 1H, Ar), 10.78 (broad s, 1H, NH), 11.52 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 17.8 (CH_3), 28.0 (CH_3), 28.1 (CH_3), 79.7 (quat. 'Bu), 83.7 (quat. 'Bu), 115.6 (CH Ar), 129.1 (quat. Ar), 138.6 (CH Ar), 147.9 (CH Ar), 148.4 (quat. Ar), 152.7 (quat. C=O), 153.0 (quat. C=O), 163.3 (quat. C=N). IR (cm^{-1}): ν 3244 (NH), 2978 (NH), 1720 (C=N), 1632 (C=O), 1585, 1560, 1475, 1454, 1404, 1374, 1324, 1305, 1289, 1268, 1252, 1230, 1151, 1136, 1107, 1058, 1025, 882, 856, 838, 803, 758, 749, 709. HRMS (m/z ESI^+): 351.2032 calcd for $\text{C}_{17}\text{H}_{26}\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$; found, 351.2036.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]-5,6,7,8-tetrahydroquinoline (2e). Brown solid (302 mg, 83%); mp 164–165 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 1.43 (s, 9H, CH_3), 1.44 (s, 9H, CH_3), 1.73 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 7.53 (d, 1H, $J = 8.7$ Hz, Ar), 7.93 (d, 1H, $J = 8.2$ Hz, Ar), 10.49 (broad s, 1H, NH), 11.53 (broad s, 1H, NH). ^1H NMR (400 MHz, CDCl_3): δ 1.52 (s, 18H, CH_3), 1.78 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 2.70 (t, 2H, $J = 6.3, 6.1$ Hz, CH_2), 2.78 (t, 2H, $J = 6.1, 6.3$ Hz, CH_2), 7.35 (d, 1H, $J = 8.3$ Hz, Ar), 8.04 (broad s, 1H, Ar), 10.64 (broad s, 1H, NH), 11.54 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 22.7 (CH_2), 22.9 (CH_2), 28.00 (CH_3), 28.02 (CH_2), 28.04 (CH_3), 32.0 (CH_2), 79.6 (quat. 'Bu), 83.6 (quat. 'Bu), 113.6 (CH Ar), 128.3 (quat. Ar), 138.7 (CH Ar), 147.6 (quat. Ar), 152.6 (quat. C=O), 152.0 (quat. C=O), 155.4 (quat. Ar), 163.3 (quat. Gua). IR (cm^{-1}): ν 3251 (NH), 2979 (NH), 1714 (C=N, Gua), 1645 (C=O), 1629, 1588, 1565, 1449, 1395, 1369, 1354, 1325, 1313, 1279, 1247, 1231, 1151, 1112, 1058, 1029, 996, 941, 899, 874, 864, 840, 804, 755, 713. HRMS (m/z ESI^+): 391.2345 calcd for $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4$ [$\text{M} + \text{H}$] $^+$; found, 391.2342.

1-[2,3-Di(*tert*-butoxycarbonyl)guanidino]-4-ethoxybenzene (4). White solid (330 mg, 76%); mp 118–120 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.42 (t, 3H, $J = 7.1$ Hz, CH_3), 1.51 (s, 9H, CH_3), 1.56 (s, 9H, CH_3), 4.03 (q, 2H, $J = 7.1$ Hz, CH_2), 6.87 (d, 2H, $J = 8.7$ Hz, Ar), 7.47 (d, 2H, $J = 8.7$ Hz, Ar) 10.20 (br s, 1H, NH), 11.67 (br s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 14.4 (CH_3), 27.6 (CH_3), 27.8 (CH_3), 63.1 (CH_2), 79.0 (CH_3), 83.1 (CH_3), 114.2 (CH Ar), 123.4 (CH Ar), 129.2 (quat. Ar), 152.9 (quat. Ar), 153.2 (quat. C=O), 155.7 (quat. C=O), 163.2 (quat. Gua). IR (cm^{-1}): ν 3280 (NH), 3165 (NH), 2933, 1716 (C=N), 1630 (C=O), 1605, 1573, 1511 (Aryl), 1390, 1345, 1227, 1155, 1117, 1057. HRMS (m/z ESI^+): 380.2185 calcd for $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$; found, 380.2181.

General Procedure for the Synthesis of *N*-Boc-*N'*-Propyl Guanidine Derivatives. To a solution of *N*-*tert*-butoxycarbonyl-*N'*-propylthiourea (7, described below), the starting amine (1.0 equiv), and triethylamine (3.5 equiv) in CH_2Cl_2 at 0 °C was added mercuric chloride (1.2 equiv). The mixture was stirred for 30 min at 0 °C, then warmed to RT, and stirred until reaction was adjudged complete by TLC analysis. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite to remove any mercury byproduct. The filtrate was washed with brine (20 mL) and water (20 mL), dried over anhydrous MgSO_4 , and concentrated under reduced pressure to yield a residue that was purified by silica gel column chromatography, eluting with the appropriate hexane:EtOAc mixture.

***N*-*tert*-Butoxycarbonyl-*N'*-propylthiourea (7).** To a solution of thiourea (500 mg, 6.58 mmol) in dry THF (120 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 1184 mg, 29.60 mmol), followed by di-*tert*-butyl dicarbonate (3155 mg, 14.47 mmol). After 8 h of stirring at RT, the reaction was cooled again to 0 °C, and a second portion of NaH (442 mg, 11.05 mmol) was added followed 1 h later by trifluoroacetic anhydride (1.41 mL, 10.13 mmol). After 45 min, 1-propylamine (0.83 mL, 10.13 mmol) was added neat, and the reaction was stirred at RT for 18 h. The reaction was quenched with dropwise H_2O (20 mL) followed by extraction with EtOAc (3 $\times$ 20 mL). The organic phase was dried over MgSO_4 , solvents were removed under vacuum, and the crude product was purified by flash chromatography (4:1 hexane:EtOAc, Rf 0.3). Recrystallization from hexanes afforded the product as a white, crystalline solid (1019 mg, 71%); mp 58–60 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.01 (t, 2H, $J = 7.3$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.52 (s, 9H, Boc), 1.71 (q, 2H, $J = 7.3$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.63 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 7.97 (br s, 1H, NH), 9.74 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ 11.3 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 21.5 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 27.8 (CH_3 , Boc), 47.1 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 83.4 (Cq Boc), 151.8 (C=O), 179.4 (C=S). IR (cm^{-1}): ν 3245, 3175 (NH), 2961, 2934, 2875, 1720 (C=O), 1523 (C=N), 1243, 1206, 1142 (C=S), 1073, 1008. HRMS (m/z ESI^+): 219.1167 calcd for $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$; found, 219.1167.

1-[2-(*tert*-Butoxycarbonyl)-3-propylguanidino]-5-chloropyridine (5b). Clear gum (247 mg, 39%, 4:3 mixture of isomers). ^1H NMR (600 MHz, DMSO): δ 0.91 (m, 6H, CH_3), 1.43 (s, 9H, CH_3), 1.48 (s, 9H, CH_3), 1.56 (m, 4H, CH_2), 3.31 (m, 4H, CH_2), 6.83 (d,

1H, $J = 8.8$ Hz, Ar), 7.17 (d, 1H, $J = 8.0$ Hz, Ar), 7.67 (dd, 1H, $J = 8.8$, 2.6 Hz, Ar), 7.89 (dd, 1H, $J = 8.8$, 2.5 Hz, Ar), 7.89 (broad s, 1H, NH), 8.19 (d, 1H, $J = 2.6$ Hz, Ar), 8.35 (d, 1H, $J = 2.5$ Hz, Ar), 9.74 (broad s, 1H, NH), 11.89 (broad s, 1H, NH), 12.42 (broad s, 1H, NH). ^{13}C NMR (600 MHz, CDCl_3): δ 1.00 (m, 4H, CH_3), 1.53 (s, 9H, CH_3), 1.54 (s, 9H, CH_3), 1.65 (app. sex, 4H, $J = 7.3$ Hz, CH_2), 3.41 (broad s, 2H, CH_2), 3.49 (m, 2H, $J = 7.0$, 5.5 Hz, CH_2), 6.82 (d, 1H, $J = 8.8$ Hz, Ar), 6.88 (broad s, 1H, Ar), 7.46 (d, 1H, $J = 6.9$ Hz, Ar), 7.60 (dd, 1H, $J = 8.8$, 2.3 Hz, Ar), 7.87 (broad s, 1H, NH), 8.12 (broad s, 1H, Ar), 8.17 (d, 1H, $J = 2.3$ Hz, Ar), 9.77 (broad s, 1H, NH), 12.28 (broad s, 1H, NH), 12.62 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 22.5 (CH_2), 28.2 (CH_3), 28.4 (CH_3), 42.6 (CH_2), 78.8 (quat. ^tBu), 114.2 (CH Ar), 121.8 (CH Ar), 122.8 (quat. Ar), 124.9 (quat. Ar), 137.6 (CH Ar), 138.4 (CH Ar), 143.8 (CH Ar), 144.5 (CH Ar), 149.8 (quat. Ar), 151.4 (quat. Ar), 153.7 (quat. $\text{C}=\text{O}$), 157.2 (quat. $\text{C}=\text{O}$), 160.1 (quat. Gua), 164.4 (quat. Gua). IR (cm^{-1}): ν 3359 (NH), 2968 (NH), 1730 ($\text{C}=\text{N}$), 1645 ($\text{C}=\text{O}$), 1585, 1560, 1476, 1455, 1406, 1380, 1329, 1322, 1288, 1259, 1234, 1170, 1156, 1120, 1032, 980, 832, 799, 734, 689. HRMS (m/z ESI^+): 335.1251 calcd for $\text{C}_{14}\text{H}_{21}\text{ClN}_4\text{O}_2$ [$\text{M} + \text{Na}$] $^+$; found, 335.1246.

1-[2-(tert-Butoxycarbonyl)-3-propylguanidino]-5-methylpyridine (5d). Column chromatography (5:1 Hexane:EtOAc) on the mixture of isomers **5d(i)** and **5d(ii)**, followed by recrystallization (hexane/EtOAc) yielded **5d** as a white powder (75.0 mg, 28%, single isomer); mp 102–104 °C, clean melt. ^1H NMR (400 MHz, DMSO): δ 0.91 (t, 3H, $J = 7.4$ Hz, CH_3), 1.42 (s, 9H, CH_3), 1.54 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 3.31 (m, 2H, CH_2), 6.98 (d, 1H, $J = 8.2$ Hz, Ar), 7.63 (d, 1H, $J = 8.2$ Hz, Ar), 8.11 (s, 1H, Ar), 10.12 (broad s, 1H, NH), 11.74 (broad s, 1H, NH). ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, 3H, $J = 7.4$ Hz, CH_3), 1.51 (s, 9H, CH_3), 1.62 (app. sex, 2H, $J = 7.6$, 7.2 Hz, CH_2), 2.24 (s, 3H, CH_3), 3.46 (m, 2H, CH_2), 6.72 (d, 1H, $J = 8.4$ Hz, Ar), 7.42 (dd, 1H, $J = 8.4$, 2.1 Hz, Ar), 10.17 (broad s, 1H, NH), 11.97 (broad s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3): δ 11.5 (CH_3), 17.5 (CH_3), 22.5 (CH_2), 28.4 (CH_3), 42.4 (CH_2), 78.4 (quat. ^tBu), 112.7 (CH Ar), 126.7 (quat. Ar), 139.2 (CH Ar), 145.3 (CH Ar), 150.9 (quat. Ar), 157.5 (quat. $\text{C}=\text{O}$), 164.2 (quat. Gua). IR (cm^{-1}): ν 3355 (NH), 2965 (NH), 2930, 2875, 1712 ($\text{C}=\text{N}$), 1638, 1597 ($\text{C}=\text{O}$), 1562, 1495, 1474, 1347, 1300, 1245, 1172, 1154, 1125, 1056, 1026, 961, 909, 821, 805, 774, 739, 665. HRMS (m/z ESI^+): 315.1797 calcd for $\text{C}_{15}\text{H}_{24}\text{N}_4\text{O}_2$ [$\text{M} + \text{Na}$] $^+$; found, 315.1792.

General Procedure for the Synthesis of Guanidinium Chloride Salts. To starting 1-[2,3-di-Boc-guanidino]pyridine (1.0 equiv) was added slowly a solution of trifluoroacetic acid (TFA) in CH_2Cl_2 (25.0 equiv, 25% v/v). Stirring at RT was continued until the reaction was adjudged complete by TLC analysis (≤ 3 h). Solvent and excess TFA were removed under reduced pressure to yield the trifluoroacetate salt as an off-white solid. This was dissolved in H_2O , to which Amberlite IRA-400 resin in its chloride form (excess) was added. The mixture was stirred for 36 h at room temperature after which the Amberlite resin was removed by vacuum filtration. The aqueous layer was washed with DCM and concentrated under reduced pressure to yield an off-white solid, which was purified by small-scale reverse-phase chromatography using C-8 silica with 100% H_2O as mobile phase. Conversion to the chloride salt was checked by ^{19}F NMR and if necessary stirring in Amberlite was repeated.

N-(Pyridin-2-yl)guanidinium Chloride (3a). Orange/white solid (46 mg, 81%); mp 78 °C, clean melt. ^1H NMR (600 MHz, DMSO): δ 7.07 (d, 1H, $J = 8.2$ Hz, Ar), 7.18 (dd, 1H, $J = 6.9$, 5.4 Hz, Ar), 7.88 (app t, 1H, Ar), 8.30 (broad s, 4H, NH_2), 8.32 (d, 1H, $J = 4.1$ Hz, Ar), 11.39 (broad s, 1H, NH). ^{13}C NMR (150 MHz, DMSO): δ 113.2 (CH Ar), 119.3 (quat. Ar), 139.5 (CH Ar), 146.7 (CH Ar), 151.9 (quat. Ar), 155.3 (quat. CN). IR (cm^{-1}): ν 3312 (NH), 3180 (NH), 3130 (NH), 1679 ($\text{C}=\text{N}$), 1622, 1596, 1561, 1462, 1416, 1319, 1274, 1244, 1154, 1054, 1020, 998, 874, 775. HRMS (m/z ESI^+): 137.0827 calcd for $\text{C}_6\text{H}_8\text{N}_4$ [$\text{M} + \text{H}$] $^+$; found, 137.0827. Purity by HPLC: 97.2% (tR 16.81 min).

N-(5-Chloropyridin-2-yl)guanidinium Chloride (3b). Oily white solid (95 mg, 85%); mp 164 °C, clean melt. ^1H NMR (600 MHz, DMSO): δ 7.13 (d, 1H, $J = 8.8$ Hz, Ar), 7.98 (dd, 1H, $J = 8.8$, 2.6 Hz, Ar), 8.28 (broad s, 1H, NH), 8.35 (d, 1H, $J = 2.6$ Hz, Ar),

11.70 (broad s, 1H, NH). ^{13}C NMR (150 MHz, DMSO): δ 115.0 (CH Ar), 126.6 (quat. Ar), 139.2 (CH Ar), 144.7 (CH Ar), 151.0 (quat. Ar), 155.7 (quat. CN). IR (cm^{-1}): ν 3313 (NH), 3178 (NH), 2953, 1685 ($\text{C}=\text{N}$), 1617, 1587, 1551, 1465, 1364, 1310, 1274, 1236, 1136, 1113, 1022, 1009, 924, 876, 828, 757, 734, 718. HRMS (m/z ESI^+): 171.0437 calcd for $\text{C}_6\text{H}_7\text{ClN}_4$ [$\text{M} + \text{H}$] $^+$; found, 171.0433. Purity by HPLC: 99.0% (tR 22.68 min).

N-(5-Bromopyridin-2-yl)guanidinium Chloride (3c). Oily white solid (118 mg, 74%); mp 74–81 °C. ^1H NMR (600 MHz, DMSO): δ 7.06 (d, 1H, $J = 8.8$ Hz, Ar), 8.09 (dd, 1H, $J = 8.8$, 2.5 Hz), 8.23 (broad s, 1H, NH), 8.43 (d, 1H, $J = 2.5$ Hz, Ar), 11.53 (broad s, 1H, NH). ^{13}C NMR (150 MHz, DMSO): δ 114.7 (quat. Ar), 116.1 (CH Ar), 142.9 (CH Ar), 148.1 (CH Ar), 151.7 (quat. Ar), 155.9 (quat. CN). IR (cm^{-1}): ν 3313 (NH), 3218 (NH), 3011 (NH), 1684.0 ($\text{C}=\text{N}$), 1618, 1582, 1551, 1465, 1360, 1308, 1275, 1234, 1137, 1094, 1006, 925, 874, 825, 732. HRMS (m/z ESI^+): 214.9932 calcd for $\text{C}_6\text{H}_7\text{BrN}_4$ [$\text{M} + \text{H}$] $^+$; found, 214.9926. Purity by HPLC: 99.1% (tR 23.88 min).

N-(5-Methylpyridin-2-yl)guanidinium Chloride (3d). Clear crystalline solid (94 mg, 84%); mp 188–192 °C, clean melt. ^1H NMR (600 MHz, DMSO): δ 2.27 (s, 3H, CH_3), 6.98 (d, 1H, $J = 8.3$ Hz, Ar), 7.71 (dd, 1H, $J = 8.3$, 1.9 Hz, Ar), 8.15 (broad s, 1H, Ar), 8.21 (broad s, 4, NH), 11.17 (broad s, 1H, NH). ^{13}C NMR (150 MHz, DMSO): δ 17.1 (CH_3), 112.7 (CH Ar), 128.5 (quat. Ar), 140.1 (CH Ar), 146.1 (CH Ar), 149.7 (quat. Ar), 155.2 (quat. CN). IR (cm^{-1}): ν 3268 (NH), 2889 (NH), 1677 ($\text{C}=\text{N}$), 1621, 1601, 1563, 1489, 1376, 1315, 1285, 1242, 1086, 1035, 1023, 1002, 909, 873, 832, 798, 738, 718. HRMS (m/z ESI^+): 151.0984 calcd for $\text{C}_7\text{H}_{10}\text{N}_4$ [$\text{M} + \text{H}$] $^+$; found, 151.0979. Purity by HPLC: 98.3% (tR 21.57 min).

N-(5,6,7,8-Tetrahydroquinolin-2-yl)guanidinium Chloride (3e). Brown solid (71 mg, 85%); mp 224–228 °C (decomposed). ^1H NMR (600 MHz, DMSO): δ 1.73 (m, 2H, $J = 5.8$, 6.0 Hz, CH_2), 1.80 (m, 2H, $J = 6.1$, 5.9 Hz, CH_2), 2.68 (app. t, 2H, $J = 6.2$, 6.0 Hz, CH_2), 2.78 (app. t, 2H, $J = 6.1$, 6.0 Hz, CH_2), 6.80 (d, 1H, $J = 8.2$ Hz, Ar), 7.55 (d, 1H, $J = 8.2$ Hz, Ar), 8.22 (broad s, 4H, NH), 11.08 (broad s, 1H, NH). ^{13}C NMR (150 MHz, DMSO): δ 22.1 (CH_2), 22.2 (CH_2), 27.2 (CH_2), 31.5 (CH_2), 110.5 (CH Ar), 127.3 (quat. Ar), 140.1 (CH Ar), 149.2 (quat. Ar), 154.0 (quat. Ar), 155.2 (quat. CN). IR (cm^{-1}): ν 3323 (NH), 3149 (NH), 2961 (NH), 1679 ($\text{C}=\text{N}$), 1634, 1597, 1566, 1465, 1031, 813. HRMS (m/z ESI^+): 191.1297 calcd for $\text{C}_{10}\text{H}_{14}\text{N}_4$ [$\text{M} + \text{H}$] $^+$; found, 191.1293. Purity by HPLC: 98.1% (tR 27.00 min).

1-(5-Chloropyridin-2-yl)-3-propylguanidinium Chloride (6b). Yellow crystalline solid (120 mg, 93%); mp 102–104 °C, clean melt. ^1H NMR (600 MHz, DMSO): δ 0.94 (t, 3H, $J = 7.4$ Hz, CH_3), 1.59 (app. sex, 2H, $J = 7.2$, 7.3 Hz, CH_2), 3.29 (m, 2H, $J = 6.7$ Hz, CH_2), 7.12 (s, 1H, Ar), 7.99 (dd, 1H, $J = 8.8$, 2.5 Hz, Ar), 8.37 (d, 1H, $J = 2.5$ Hz, Ar), 8.58 (broad s, 2H, NH), 9.17 (broad s, 2H, NH), 11.47 (broad s, 2H, NH). ^{13}C NMR (150 MHz, DMSO): δ 11.3 (CH_3), 21.9 (CH_2), 42.9 (CH_2), 115.0 (CH Ar), 125.7 (quat. Ar), 139.7 (CH Ar), 145.1 (CH Ar), 154.1 (quat. Gua). IR (cm^{-1}): ν 3268 (NH), 3097 (NH), 3059, 2958, 2931, 2875, 1673, 1646, 1629 ($\text{C}=\text{N}$), 1591, 1558, 1469, 1385, 1371, 1342, 1315, 1271, 1243, 1145, 1109, 1075, 1044, 1012, 966, 903, 869, 828, 772, 737, 658. HRMS (m/z ESI^+): 211.0745 calcd for $\text{C}_{10}\text{H}_{14}\text{N}_4$ [$\text{M} - \text{H}$] $^-$; found, 211.0750. Purity by HPLC: 99.3% (tR 26.40 min).

1-(5-Methylpyridin-2-yl)-3-propylguanidinium Chloride (6d). Yellow crystalline solid (32 mg, 90%); mp 102–104 °C, clean melt. ^1H NMR (600 MHz, DMSO): δ 0.94 (t, 3H, $J = 7.5$ Hz, CH_3), 1.58 (app. sex, 2H, $J = 7.5$, 7.1 Hz, CH_2), 2.25 (s, 3H, CH_3), 3.29 (m, 2H, $J = 6.6$ Hz, CH_2), 6.99 (broad s, 1H, Ar), 7.71 (dd, 1H, $J = 8.4$, 1.9 Hz, Ar), 8.14 (d, 1H, $J = 1.9$ Hz, Ar), 8.59 (broad s, 2H, NH), 9.43 (broad s, 2H, NH), 11.34 (broad s, 2H, NH). ^{13}C NMR (150 MHz, DMSO): δ 11.0 (CH_3), 17.2 (CH_3), 21.6 (CH_2), 42.5 (CH_2), 112.6 (CH Ar), 128.3 (q Ar), 140.3 (CH Ar), 145.8 (CH Ar), 150.0 (q Ar), 154.1 (q, Gua). IR (cm^{-1}): ν 2965 (NH), 1674 ($\text{C}=\text{N}$), 1632, 1608, 1572, 1484, 1343, 1283, 1244, 1136, 1079, 1029, 968, 831, 743. HRMS (m/z ESI^+): 193.1453 calcd for $\text{C}_{10}\text{H}_{17}\text{N}_4$ [$\text{M} + \text{H}$] $^+$; found, 193.1458. Purity by HPLC: 96.9% (tR 24.57 min).

■ ASSOCIATED CONTENT

● Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all compounds described in series 2–6; characterization data for the 2-aminopyridines described in series 1; X-ray crystal structural data for compounds 2b, 3d, 3e, and 4; copies of the variable temperature ^1H NMR spectra of compounds 2d and 3d, and Cartesian coordinates of all of the structures optimized at the B3LYP/6-31+G** level. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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