Bis-Cationic Heteroaromatics as Macrofilaricides: Synthesis of Bis-Amidine and Bis-Guanylhydrazone Derivatives of Substituted Imidazo[1,2-*a*]pyridines

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A series of guanylhydrazone, amidine, and hydrazone derivatives of 2-phenylimidazo[1,2-*a*]-pyridine have been prepared and evaluated for macrofilarial activity against *Acanthocheilonema viteae* and *Brugia pahangi* in jirds. Compounds with 4′,6-bis-substitution by cyclic guanylhydrazone groups show activity. 4′,6-Bis-amidines show some activity but are more toxic; 4′- or 6-monosubstituted compounds are inactive. 2,6-Bis-substituted compounds lacking the phenyl ring are inactive. 4′,6-Bis-substituted compounds having additional double bonds inserted between the heterocyclic ring and the phenyl ring or between the substituent and the ring system show reduced activity.

Filarial infection is responsible for a number of significant human pathologies in various parts of the world.[1] *Onchocerca volvulus* is responsible for "river-blindness" which is endemic to large areas of Africa and to more localized regions of Central and South America.[2] Community-wide control programs based on diethylcarbamazine (DEC) and, more recently, ivermectin are highly effective in reducing microfilarial infestations for periods of several months to a year.[3] While ivermectin suppresses the fertility of adult *O. volvulus*, they retain sufficient reproductive potential to cause reinfestation.[4] As a result, development of an effective macrofilaricide has been adopted as a WHO goal, and a screening program based on *Brugia pahangi* and *Acanthocheilonema viteae* infestation in jirds was initiated.[5]

In this paper we report the synthesis of a series of bis-guanylhydrazones and bis-amidines derived from substituted imidazo[1,2-*a*]pyridines and their evaluation for macrofilaricidal activity. Bis-guanylhydrazones and bis-amidines are normally considered to be included in the DNA groove binding category and have frequently been found to have activity against trypanosomes[6] and also against *Pnuemocystis carinii*.[7] The lead compound grew out of a program aimed at developing trypanocides.[8]

Chemistry

Six separate series of compounds were investigated, represented by structures **1**−**6**. In addition to the 4′,6-disubstituted compounds (series **3**), the 4′- (**1**) and 6- (**2**) monosubstituted analogues, a truncated series (**4**), and two extended structures incorporating a double bond between the imidazo[1,2-*a*]pyridine ring and phenyl substituent (**5**) or between the two substituents and the 2-phenylimidazo[1,2-*a*]pyridine nucleus (**6**) were examined. The substituents used were mainly guanylhydrazones or amidines, although some hydrazones were also prepared (Chart 1).

The guanylhydrazones were prepared from aldehyde precursors while the amidines were prepared from nitriles, making the corresponding aldehydes and nitriles the key synthetic intermediates. Halo-substituted 2-arylimidazo[1,2-*a*]pyridines were used as starting materials. The preparation of **1b**,**c** has already been reported.[9] The 6-substituted intermediates were prepared from 6-iodo-2-phenylimidazo[1,2-*a*]pyridine by use of cuprous cyanide displacement under traditional CuCN substitution conditions.[10] The 6-aldehyde was obtained by formylation of the 6-lithio intermediate[11] (Scheme 1).

While dinitrile **3b** can be prepared using classical CuCN substitution conditions, a $Pd(Ph_3P)_4$-catalyzed procedure[12] was much more convenient and avoided handling large quantities of cyanide waste. Dialdehyde **3d** was most effectively prepared from lithium/bromide exchange of **3c** followed by formylation with DMF (Scheme 2).

The truncated dialdehyde **4c** was prepared starting with ethyl 6-iodoimidazo[1,2-*a*]pyridine-2-carboxylate. The iodine was effectively displaced by cyanide using the $Pd(Ph_3P)_4$/CuI procedure. Selective reduction of both the nitrile and ester group was accomplished by DIBAL at −78 °C to give the dialdehyde **4c** (Scheme 3).

The 2-styryl series (**5**) was synthesized starting with 6-iodoimidazo[1,2-*a*]pyridine-2-carboxaldehyde (**4d**) and diethyl 4-cyanobenzylphosphonate via a Wadsworth−Emmons reaction giving **5a**.[13] The dinitrile **5b** was prepared by $Pd(Ph_3P)_4$/CuI cyanation. A good yield of dialdehyde **5c** was obtained by DIBAL reduction in CH_2Cl_2 at −78 °C (Scheme 4).

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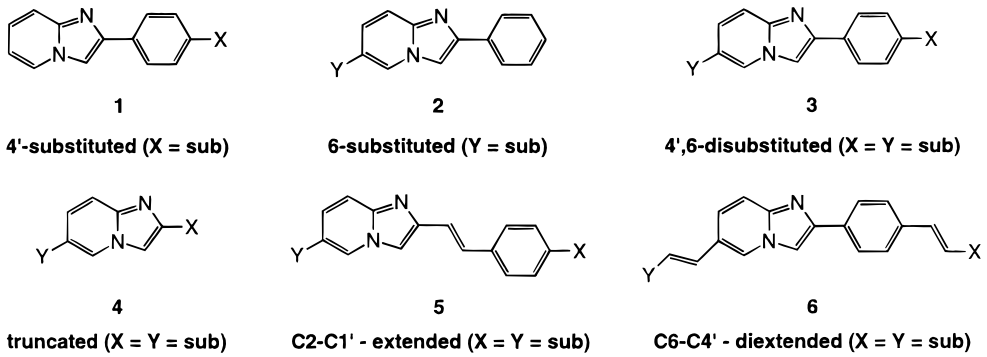
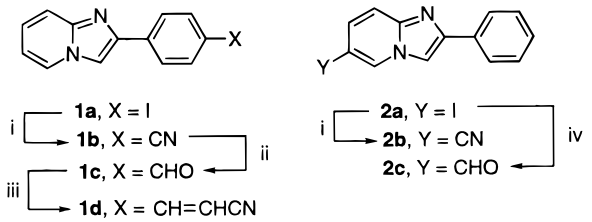
Chart 1

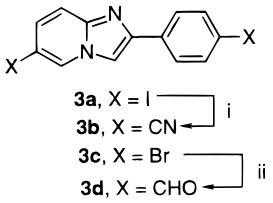


Scheme 1[a]



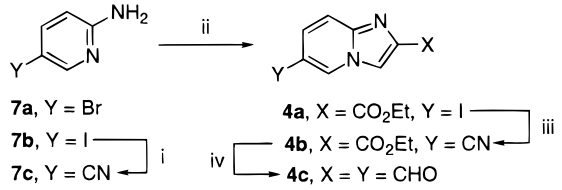
[a] Reagents: (i) CuCN/DMF; (ii) DIBALH; (iii) $NCCH_2PO(OEt)_2$/*n*-BuLi; (iv) *n*BuLi, DMF.

Scheme 2[a]



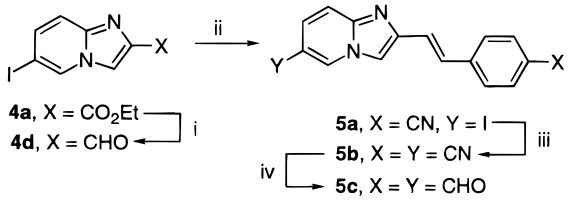
[a] Reagents: (i) KCN, CuI, $Pd(Ph_3)_4$, 18-crown-6; (ii) *n*BuLi, DMF.

Scheme 3[a]



[a] Reagents: (i) CuCN; (ii) ethyl pyruvate; (iii) KCN, CuI, $Pd(Ph_3)_4$, 18-crown-6; (iv) DIBAL/−78 °C.

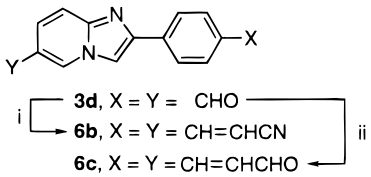
Scheme 4[a]



[a] Reagents: (d) DIBAL/−78 °C; (ii) diethyl cyanobenzylphosphonate/NaH; (iii) KCN, CuI, $Pd(Ph_3)_4$, 18-crown-6; (iv) DIBAL/−78 °C.

Efforts to obtain the bis-unsaturated nitrile **6b** from 2-(4-iodophenyl)-6-iodoimidazo[1,2-*a*]pyridine by the Heck reaction were only partially successful. The diiodo compound gave up to 40% conversion to **6b** using tri-(*o*-tolyl)phosphine and $Pd(OAc)_2$, but the product was a mixture of cis and trans isomers which was difficult to purify. A Wadsworth−Emmons reaction using the lithium salt of diethyl cyanomethylphosphonate[14] was much more satisfactory, giving **6b** in 70% yield as the pure trans−trans isomer (Scheme 5). Attempts to convert **6b** to **6c** by Raney nickel reduction[15] gave only modest yields. The best route to **6c** was from **3d**. While neither formylmethylenetriphenylphosphorane[16] nor diethyl diethoxymethylphosphonate[17] worked well, good results were achieved using the 2-(*tert*-butylamino)-vinylphosphonate reagent developed by Meyers.[18]

Scheme 5[a]



[a] Reagents: (i) $CNCH_2P(O(OEt)_2$/*n*-BuLi; (ii) (a) $^tBuN(Li)CH{=}CHP(O)(OEt)_2$ (b) aq $(CO_2H)_2$.

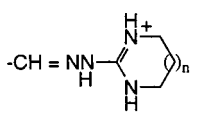
The aldehyde and nitrile intermediates were used to prepare guanylhydrazones, amidines, and substituted hydrazones. The functional groups which were included are designated in Chart 2. The guanylhydrazones were prepared from the corresponding substituted hydrazines, as described previously.[8] Some of the amidines could be prepared efficiently by a standard Pinner reaction (methods A−C).[19] For others, a procedure developed by Garigipati[20] in which the amine is first converted to an aluminum amide by trimethylaluminum was more effective (method D). The cyclic amidines **1p**−**5p** and **1q**−**5q** were prepared by heating the corresponding ethyl imidate intermediates with ethylenediamine or 1,3-diaminopropane.[21] Hydrazones **3s**−**w** were prepared by warming **3d** with the appropriate hydrazine in ethanol. The vinylthiazolines **1x** and **3x** were prepared by a Wadsworth−Emmons reaction using diethyl 2-thiazolinylmethylphosphonate.[22]

Biological Evaluation

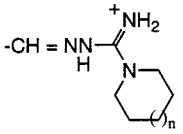
Biological activity was assayed using male Mongolian jirds (*Meriones unguiculatus*) which were transplanted subcutaneously with 10 (5 male, 5 female) adult *A. viteae* worms. After 2 weeks, 20 (10 male, 10 female) *B. pahangi* worms were transplanted into the peritoneal cavity. These doubly infected jirds were treated according to the doses of test compounds in Table 1 on five successive days. A positive control using a dosage of 2.0 mg/day flubendazole for five successive days was run

Chart 2

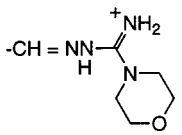
Guanylhydrazones:



e, n = 0; **f**, n = 1



g, n = 0; **h**, n = 1



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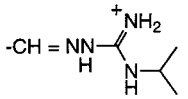

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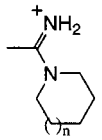
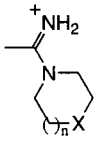
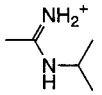
Amidines:



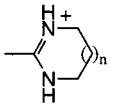
k, n = 0; **l**, n = 1



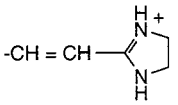
m, X = O, n = 1; **n**, X = NMe, n = 1



o



p, n = 0; **q**, n = 1



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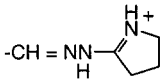
Hydrazones:



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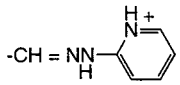

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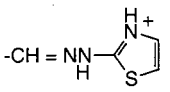

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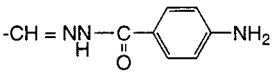

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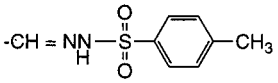
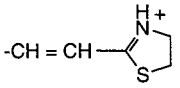


w

Thiazoline:



x

with each series. After 56 days, the jirds were killed and the number of each species of worm was counted. The percentage of worms was compared with the negative control;[5] 60% reduction was considered to constitute activity.

Results

The initial observation of activity against *A. viteae* was made with compound **3e**. As shown in Table 1, it caused 70−100% suppression of *A. viteae* at doses from 12.5 to 100 mg/day by sc administration for a period of 5 days. No significant suppression of *B. pahangi* was observed. The first objective undertaken was to delineate the scope of this activity. Several guanylhydrazones and amidines with single substituent group at C4′ or C6 were prepared, but no significant activity was observed. Attention was then focused on disubstituted analogues of the lead compound. Two additional guanylhydrazones (**3f**,**g**), two amidines (**3k**,**p**), and several hydrazones (**3s**−**w**) were prepared. Both of the guanylhydrazones showed significant activity. While **3g** showed evidence of toxicity, **3f** appeared to be somewhat more active than the lead compound with suppression of 60−100% at dose rates from 1.56 to 100 mg/day (see Table 1) for *A. viteae*.

The final structure variable explored was the relationship between activity and separation of the functional groups. Derivatives in which this distance was shortened by removal of the phenyl ring or lengthened by insertion of one or two double bonds were prepared. The truncated compounds (**4e**−**g**) showed no activity. The mono-extended guanylhydrazone **5f** was active, while **5e** was not. The bis-extended guanylhydrazones **6e**,**f** showed some activity but did not appear to be any more potent than the parent analogues. Again the six-membered guanylhydrazone appears to be more active than the five-membered compound. The bis-extended amidines **6m**,**n** were marginally active, effecting 50−60% reduction at 12.5 mg/kg, but were more toxic than the corresponding guanylhydrazones.

Discussion

The compounds reported in this study are related to a series of heteroaromatic guanylhydrazones synthesized and examined for activity against African trypanosomes.[8] Compound **3e** was synthesized at that time, although it was not included in the published report. This compound showed activity against *A. viteae*, and the present study was undertaken to establish the structural features required for activity and to search for more active analogues.

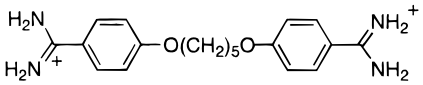
Compounds such as **3e**,**f** are similar in general structural features to various aromatic bis-cationic compounds. This broad group includes bis-amidines

Table 1. Macrofilarial Reduction

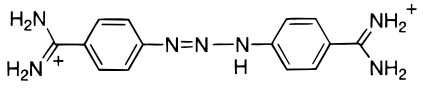
compd	dose (sc) (mg/kg) × 5 days	macrofilarial reduction *B. pahangi*	macrofilarial reduction *A. viteae*	compd	dose (sc) (mg/kg) × 5 days	macrofilarial reduction *B. pahangi*	macrofilarial reduction *A. viteae*
1e	100	0	60	**3g**	100, 100[a]	0,0[a]	60, 73[a]
1f	100	0	0	**3j**	100	32	100
1g	100	0	47	**3k**	3.12	0	39
1i	100	12	0	**3p**	100	35	0
1k	100	36	0	**3s**	100	5	24
1l	100	15	0	**3t**	100	0	0
1m	100	29	0	**3u**	100	38	0
1p	100	8	20	**3v**	100	8	0
1q	100	0	0	**3w**	100	16	0
1r	100	18	28	**3x**	100	0	0
1x	100	0	0	**4e**	100	5	13
2e	100	0	20	**4f**	100	5	0
2f	100	0	30	**4g**	100	5	0
2k	100	25, 0	60, 27	**5e**	100	4	24
2m	100	12	0	**5f**	100	32	100
2p	100	42	0	**5k**	100	toxic	toxic
3e	100	11, 18	100, 78	**5o**	100	toxic	toxic
	50	0, 0	100, 100	**5p**	100	toxic	toxic
	25	28, 0	73, 82	**6e**	100	18	71
	12.5	0	82	**6f**	100	41, 12	100, 64
3f	100	0, 9	100, 100		50	38	100
	75	0	100		25	13	73
	50	0	100	**6g**	12.5	38	50
	25	0	100, 100	**6k**	6.25	0	72
	12.5	0, 34	64, 100	**6m**	12.5	0	50
	6.25	0, 39	100, 75	**6n**	12.5	0	57
	3.12	11	88				
	1.56	16	63				

[a] Toxicity noted at this dosage.

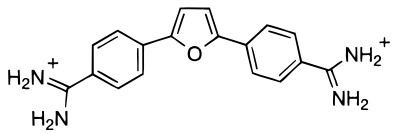
such as berenil, pentamidine, and furamidine. Many



Pentamidine



Berenil



Furamidine

such bis-cations possess trypanocidal activity.[6] These and related bis-cationics also show activity against *P. carinii*.[7] Heteroaromatic bis-guanylhydrazones have shown similar profiles of activity.[23] We are unaware of previous reports that bis-cationics have macrofilaricidal activity. Compounds which have previously been demonstrated to have macrofilaricidal activity include benzimidazole-2-carbamates[1,24] and benzothiazoles.[25] More preliminary indications of activity have been observed with aminoisoquinolines[26] and β-carbolines.[27]

Several bis-cations have been shown to bind to oligonucleotides in the minor groove and have been classified as groove binders.[28] Bis-cations also bind to RNA[29] and to DNA−RNA triple helices.[30] Precisely how (or if) this binding affects the viability of the protozoa has not been established. Bis-cations have demonstrated a range of other biological activities, including inhibition of RNA−protein interactions[31] and inhibition of topoisomerase.[32] Bis-cations have activity in mitochondria as evidenced by generation of petite mutants in *S. cerevisae*.[33]

The observation that certain bis-cations inhibit the filarial nematode *A. viteae* is, so far as we are aware, a novel result. This activity appears to have a much higher degree of structural specificity than the trypanocidal activity of bis-cations, and indeed, the minimal effect of the present compounds on *B. pahangi* also indicates a considerable degree of species specificity. In considering mechanisms by which the bis-guanylhydrazones might function, we can remark on one possibility. Both trypanosomes and nematodes utilize posttranslational trans-splicing of m-RNA, involving the addition of spliced leader sequences in processing of pre-mRNA. While trans-splicing is, along with RNA editing, a universal part of RNA processing in trypanosomes,[34] it is also prevalent in some nematodes.[35] It is known that certain cationic antibiotics and drugs inhibit RNA processing. Specific examples include the inhibition of group I intron splicing in *P. carinii* by pentamidine and dibenzimidazole bis-amidine.[36] Other basic compounds, including arginine peptides[37] and tuberactinomycin antibiotics,[38] are known to inhibit RNA splicing. While it would be premature to indicate RNA processing is the target of the activity of **3e**,**f**, the susceptibility of trypanosomes, *P. carinii*, and certain nematodes to bis-cations suggests RNA processing is at least one of the possibilities that might be investigated.

Experimental Section

2-(4′-Iodophenyl)imidazo[1,2-*a*]pyridine (1a). A solution of 2-aminopyridine (9.27 g, 98.5 mmol) and 2-bromo-4′-iodoacetophenone (32 g, 98.5 mmol) in dry acetone (230 mL) was stirred under reflux for 12 h. A white solid precipitated. After being cooled, it was filtered and resuspended in methanol (200 mL) containing 48% HBr (30 mL). The reaction mixture

was then stirred and refluxed for 2 h. After cooling to room temperature, the mixture was neutralized (pH 7) with 10% NaOH. The solid was filtered and dried in air to furnish **1a** (26.6 g) as a white solid: 83%; ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 6.6 Hz, 1H), 7.86 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.18 (t, J = 9.0 Hz, 1H), 6.81 (t, J = 6.6 Hz, 1H).

2-(4′-Cyanophenyl)imidazo[1,2-*a*]pyridine (1b). A mixture of 2-(4′-iodophenyl)imidazo[1,2-*a*]pyridine (10.3 g, 32.2 mmol) and CuCN (3.45 g, 38.6 mmol) in dry DMF (200 mL) was refluxed for 48 h. The hot reaction mixture was poured into 1:4 ethylenediamine−water mixture (1000 mL) and extracted with $CHCl_3$ (5 × 100 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. Excess DMF was azeotropically removed with benzene until the volume was reduced to ∼20 mL. The product was precipitated with hexane. The solid was collected, and the mother liquor was subjected to the same procedure twice to afford the desired nitrile **1b** as a white solid: 5.1 g, 72%; mp 215−7 °C (recrystallized from CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 6.9 Hz, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.95 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 9.0 Hz, 1H), 7.23 (t, J = 9.0 Hz, 1H), 6.83 (t, J = 6.9 Hz, 1H). Anal. ($C_{14}H_9N_3$), C, H, N.

2-(4′-Formylphenyl)imidazo[1,2-*a*]pyridine (1c). To a stirred solution of 2-(4′-cyanophenyl)imidazo[1,2-*a*]pyridine (3.0 g, 13.64 mmol) in toluene (60 mL) at 0 °C was slowly added DIBAL (11 mL, 1.5 M in toluene, 16.4 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with methanol (1 mL), and stirred for 10 min. Then cold 10% H_2SO_4 (50 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. A white solid precipitated and was filtered. It was dissolved in hot water and basified (pH 12) with 10% NaOH. The aldehyde was isolated by filtration and dried in air to provide **1c** as a white solid: 2.31 g, 77%; mp 208−9 °C (recrystallized from $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.04 (s, 1H), 8.16 (d, J = 6.6 Hz, 1H), 8.12 (d, J = 8.1 Hz, 2H), 7.98 (s, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.23 (t, J = 9.0 Hz, 1H), 6.83 (t, J = 6.6 Hz, 1H). This compound was also prepared by a metal−halogen exchange reaction from the corresponding iodo compound **1a** following the procedure described for **2c**. Anal. ($C_{14}H_{10}N_2O$) C, H, N.

2-[4′-(2-Cyanoethenyl)phenyl]imidazo[1,2-*a*]pyridine (1d). To a stirred solution of diethyl cyanomethylphosphonate (5.8 g, 33 mmol) in THF (100 mL) was added *n*-BuLi (13.2 mL, 2.5 M in hexane, 33 mmol) at 5−10 °C. After the addition, stirring was continued at 10 °C for 15 min and then at room temperature for 1.5 h. A solution of **1c** (5.0 g, 22.5 mmol) in THF (50 mL) was added to the lithium enolate solution at 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. Saturated NH_4Cl was added to the reaction mixture. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 70 mL). The organic solutions were combined, extensively washed with water and brine, and dried over $MgSO_4$. After removal of solvent, the crude solid was recrystallized from absolute EtOH to furnish **1d** as a brown solid: 4.1 g, 74%; ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.78 (br d, J = 8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.84 (m, 2H), 7.65 (d, J = 16.8 Hz, 1H), 7.38 (t, J = 6.6 Hz, 1H), 6.58 (d, J = 16.8 Hz, 1H).

2-Phenyl-6-iodoimidazo[1,2-*a*]pyridine (2a). Following the procedure described for **1a**, 2-amino-5-iodopyridine[39] (10 g, 45.5 mmol) and 2-bromoacetophenone (9.05 g, 45.5 mmol) in dry acetone (100 mL) gave **2a** as a white solid: 13.52 g, 93%; ^{1}H NMR (DMSO-d_6) δ 8.86 (s, 1H), 8.27 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.39 (m, 4H), 7.28 (t, J = 7.2 Hz, 1H); MS (CI) 321 (M + 1).

2-Phenyl-6-cyanoimidazo[1,2-*a*]pyridine (2b). Following the procedure for **1b**, 2-phenyl-6-iodoimidazo[1,2-*a*]pyridine (8 g, 25 mmol) and CuCN (5 g) in dry DMF (80 mL) provided **2b** as an off-white solid: 3.72 g, 68%; mp 247−9 °C (recrystallized from $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 9.29 (s, 1H), 8.46 (s, 1H), 7.97 (d, J = 7.2 Hz, 2H), 7.71 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H). This compound was also prepared by palladium-catalyzed cyanation from **2a** as described for **3b**. Anal. ($C_{14}H_9N_3$) C, H, N.

2-Phenyl-6-formylimidazo[1,2-*a*]pyridine (2c). To a stirred suspension of 2-phenyl-6-iodoimidazo[1,2-*a*]pyridine (8 g, 25 mmol) and TMEDA (5.7 mL, 37.5 mmol) in toluene (200 mL) was added dropwise *n*-BuLi (15 mL of 2.5 M solution in hexane, 37.5 mmol) at −78 °C. The brown-colored thick reaction mixture was allowed to slowly warm to −20 °C and then stirred at −20 °C for 30 min. A solution of DMF (6 mL, 75 mmol) in toluene (20 mL) was added dropwise to the reaction mixture at −20 °C. Stirring was continued at −20 °C for 30 min, and then the mixture was allowed to slowly warm to room temperature and stirred overnight. Saturated NH_4Cl (50 mL) was added to the reaction mixture at 0 °C, and it was stirred for 10 min. Then it was poured into a biphasic mixure of $CHCl_3$ (100 mL) and saturated $NaHCO_3$ (100 mL). After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ extract was washed with water and brine and then dried over $MgSO_4$. Removal of solvent under reduced pressure provided a crude brownish solid which was recrystallized from CH_2Cl_2 to furnish aldehyde **2c** as a yellow solid: 4.05 g, 73%; mp 219−20 °C (recrystallized from $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 9.92 (s, 1H), 9.27 (s, 1H), 8.58 (s, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 9.3 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H). This compound was also prepared starting with nitrile **2b** by partial reduction using DIBAL following the procedure described for **5c**. Anal. ($C_{14}H_{10}N_2O$) C, H, N.

6-Iodo-2-(4′-iodophenyl)imidazo[1,2-*a*]pyridine (3a). Following the procedure described for **1a**, 2-amino-5-iodopyridine[39] (8.1 g, 36.9 mmol) and 2-bromo-4′-iodoacetophenone (12 g, 36.9 mmol) in dry acetone (70 mL) gave diiodo derivative **3a** as a cream-colored solid: 18 g, 90%; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.80 (s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 9.3 Hz, 1H), 7.33 (d, J = 9.3 Hz, 1H).

6-Cyano-2-(4′-cyanophenyl)imidazo[1,2-*a*]pyridine (3b). A mixture of 6-iodo-2-(4′-iodophenyl)imidazo[1,2-*a*]pyridine (446 mg, 1 mmol), powdered dry KCN (390 mg, 6 mmol), CuI (1.14 g, 6 mmol), $Pd[PPh_3]_4$ (25 mg, 0.02 mmol), and 18-crown-6 (50 mg, 0.18 mmol) in dry DMF (2 mL) was stirred at room temperature for 20 min under a nitrogen atmosphere.[12] The thick dark-green reaction mixture was refluxed in a preheated oil bath (195 °C). The solution was stirred under reflux for 2 h and then cooled to room temperature. The thick dark-gray mass was suspended in concentrated NH_4OH (80 mL) and stirred overnight. The solid was isolated by filtration, thoroughly washed with water, and then dried in air. This solid was stirred under reflux with $CHCl_3$ (80 mL) overnight and then filtered hot to remove undissolved material. Removal of $CHCl_3$ under reduced pressure afforded a crude gray solid which was recrystallized from absolute ethanol to furnish the desired dinitrile **3b** as a yellowish brown solid: 150 mg, 60%; mp 257−9 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.07 (d, J = 8 Hz, 2H), 8.04 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 7.71 (s, 1H), 7.33 (m, 1H). This compound was also prepared by treating diiodo derivative **3a** with CuCN by the procedure described for **1b**. Anal. ($C_{15}H_8N_4 \cdot 0.5H_2O$) C, H, N.

6-Bromo-2-(4′-bromophenyl)imidazo[1,2-*a*]pyridine (3c). Following the procedure for **1a**, 2-amino-5-bromopyridine[40] (8.58 g, 45.5 mmol) and 2,4′-dibromoacetophenone (15.6 g, 45.5 mmol) in dry acetone (120 mL) gave **3c** as a white solid: 15.5 g, 88%; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.81 (s, H), 7.54 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 9.6 Hz, 1H), 7.23 (dd, J_1 = 9.6 and J_2 = 1.8 Hz, 1H).

6-Formyl-2-(4′-formylphenyl)imidazo[1,2-*a*]pyridine (3d). Following the procedure for **2c**, 6-bromo-2-(4′-bromophenyl)imidazo[1,2-*a*]pyridine, **3c** (3.52 g, 10 mmol), and TMEDA (4.5 mL, 30 mmol) in toluene (75 mL) were treated dropwise at −78 °C with *n*-BuLi (15 mL of 2 M solution in toluene, 30

mmol). After the mixture slowly warmed to −20 °C, additional toluene (20 mL) was added and stirring was continued at −20 °C for 30 min. A solution of DMF (4.6 mL, 58.6 mmol) in toluene (5 mL) was added dropwise to the reaction mixture. Stirring was continued at −20 °C for 30 min; then the mixture was allowed to slowly warm to room temperature and stirred overnight. Saturated NH_4Cl (50 mL) was added at 0 °C and stirred for 10 min. The mixture was poured into a biphasic mixure of $CHCl_3$ (80 mL) and saturated $NaHCO_3$ (80 mL). The sparingly soluble dialdehyde was recovered from the $CHCl_3$ extract and $CHCl_3$ extraction of the filtered solid. Evaporation of the $CHCl_3$ afforded a brown solid which was purified by recrystallization from CH_2Cl_2 to furnish desired dialdehyde **3d** (1.2 g) as a yellow solid: mp 203−5 °C. Additional product was obtained by chromatography of the mother liquor using silica gel: total yield 1.4 g, 56%; ^{1}H NMR ($CDCl_3$) δ 10.06 (s, 1H), 9.99 (s, 1H), 8.72 (s, 1H), 8.16 (d, J = 8 Hz, 2H), 8.11 (s, 1H), 7.99 (d, J = 8 Hz, 2H), 7.75 (m, 2H). Anal. ($C_{15}H_{10}N_2O_2$) C, H, N.

2-Amino-5-cyanopyridine (7c). Following the procedure described for **1b**, a suspension of 2-amino-5-iodopyridine[39] (60 g, 272 mmol) and CuCN (36.5 g, 407 mmol) in dry DMF (600 mL) was refluxed for 48 h. The crude product was purified by recrystallization from ethanol to furnish **7c** as a light-greenish white solid: 24.5 g, 77%; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 2.1 Hz, 1H), 7.54 (dd, J_1 = 8.7 and J_2 = 2.1 Hz, 1H), 6.47 (d, J = 8.7 Hz, 1H), 5.27 (br s, 2H). This compound was also obtained by palladium-catalyzed cyanation from iodo compound **7b** following the procedure described for **3b**.

2-Carbethoxy-6-iodoimidazo[1,2-*a*]pyridine (4a). A mixture of 2-amino-5-iodopyridine[39] (5 g, 23 mmol) and ethyl bromopyruvate (4.9 g, 23 mmol) in ethanol was refluxed for 18 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in a minimum volume of 10% HCl. The acidic suspension was neutralized to pH 8 with saturated $NaHCO_3$. The precipitate was filtered, dried in air, and purified by recrystallization from EtOAc to give **4a** as a cream-colored solid: 4.6 g, 65%; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.10 (s, 1H), 7.46 (d, J = 9.3 Hz, 1H), 7.38 (dd, J_1 = 9.3 and J_2 = 0.9 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H).

2-Carbethoxy-6-cyanoimidazo[1,2-*a*]pyridine (4b). A solution of 2-amino-5-cyanopyridine (24 g, 200 mmol) and ethyl bromopyruvate (39 g, 200 mmol) in ethanol (300 mL) was stirred under reflux for 15 h. The solvent was evaporated, and the residue was dissolved in a minimum volume of 10% HCl. The solution was neutralized (pH 8) with saturated $NaHCO_3$. The precipitate was filtered and dried in air to give cyano ester **4b** as a creamy solid: 25.8 g, 59%; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.27 (s, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.33 (dd, J_1 = 9.3 and J_2 = 1.5 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). This compound was also prepared by palladium-catalyzed cyanation from iodo compound **4a** following the procedure described for **3b**.

Imidazo[1,2-*a*]pyridine-2,6-dicarboxaldehyde (4c). To a solution of 2-carbethoxy-6-cyanoimidazo[1,2-*a*]pyridine (5 g, 23 mmol) in CH_2Cl_2 (200 mL) was added dropwise DIBAL (62 mL, 1.5 M in toluene, 93 mmol) at −78 °C. Stirring was continued at −78 °C for 30 min. The reaction mixture was quenched with cold methanol and then stirred for 10 min. The resulting mixture was poured into a biphasic mixture of saturated $NaHCO_3$ (100 mL) and $CHCl_3$ (150 mL) and allowed to warm to room temperature with occasional stirring. It was then passed through a Celite bed to remove a gelatinous mass, and the bed was thoroughly washed with $CHCl_3$. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined filtrate and extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude solid was purified by recrystallization from EtOAc to provide **4c** as an off-white crystalline solid: 2.5 g, 62%; mp 226−8 °C (recrystallized from EtOAc); ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 10.0 (s, 1H), 8.73 (s, 1H), 8.29 (s, 1H), 7.78 (br s, 2H).

6-Iodoimidazo[1,2-*a*]pyridine-2-carboxaldehyde (4d). Following the procedure described for **4c**, 2-carbethoxy-6-iodoimidazo[1,2-*a*]pyridine (7.28 g, 23 mmol) in CH_2Cl_2 (100 mL) was added dropwise to DIBAL (30.4 mL, 1.5 M in toluene, 45.6 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 1.5 h. Excess DIBAL was decomposed with methanol (2 mL), and stirring continued for 10 min. A standard workup gave a crude solid which was purified by recrystallization from EtOAc to provide **4d** as a cream-colored crystalline solid: 4 g, 63%; ^{1}H NMR ($CDCl_3$) δ 10.15 (s, 1H), 8.45 (s, 1H), 8.08 (s, 1H), 7.47 (m, 2H).

6-Iodo-2-(4′-cyanophenylethenyl)imidazo[1,2-*a*]pyridine (5a). To a stirred suspension of NaH (60% dispersion in mineral oil, 1.06 g, 22 mmol) that had been washed with hexane (2 × 5 mL) in THF (15 mL) was added dropwise a solution of diethyl 4-cyanobenzylphosphonate[13] (4.83 g, 19 mmol) in THF (13 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The resulting dark-greenish sodium enolate solution was added to the suspension of aldehyde **4d** (4 g, 14.7 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min and then heated under reflux with stirring for 2 h. After being cooled, the mixture was poured into crushed ice−water mixure. The brown solid which precipitated was filtered, dried, and recrystallized from $CHCl_3$ to provide desired iodonitrile **5a** as a cystalline off-white solid: 4.9 g, 90%; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.61 (m, containing a singlet at 7.62 and a doublet at 7.60, J = 9 Hz, 5H), 7.38 (m, 2H), 7.22 (d, J = 16.5 Hz, 2H).

6-Cyano-2-(4′-cyanophenylethenyl)imidazo[1,2-*a*]pyridine (5b). Following the procedure for **3b**, a mixture of compound **5a** (1 g, 2.69 mmol), CuI (1.6 g, 8.4 mmol), freshly dry powdered KCN (0.55 g, 8.4 mmol), $Pd[PPh_3]_4$ (0.095 g, 0.08 mmol 3 mol %), and 18-crown-6 (67 mg, 0.25 mmol) in dry DMF (2 mL) was stirred at room temperature for 20 min and then immediately brought to reflux in an oil bath preheated to about 200 °C for 2 h. The reaction was worked up as described for **3b** to give **5b** as a dark-brown solid: 700 mg, 96%; mp 265−7 °C (recrystallized from $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 7.64 (m, 5H), 7.37 (s, 1H), 7.32 (m, 1H), 7.23 (d, J = 17 Hz, 2H).

6-Formyl-2-(4′-formylphenylethenyl)imidazo[1,2-*a*]pyridine (5c). To a stirred solution of dinitrile **5b** (0.56 g, 2.07 mmol) in CH_2Cl_2 (50 mL) was added DIBAL (8.3 mL, 1.5 M in toluene, 12.44 mmol) slowly at −78 °C. Stirring was continued at this temperature for 10 min. After the reaction mixture was quenched with methanol (1 mL) at −78 °C, it was immediately poured into a vigorously stirred cold (0 °C) biphasic mixture of 5% $KHSO_4$ (65 mL, 24.8 mmol) and $CHCl_3$ (100 mL). The resulting mixture was stirred at 0 °C for 30 min and at room temperature overnight. Insoluble material was removed by passing through a Celite bed. After the organic layer was separated, the aqueous layer (pH ∼ 6) was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. Evaporation of solvent afforded a crude solid which was purified by flash chromatography of silica gel using 10% EtOAc in $CHCl_3$ as the eluant to furnish **5c** as a yellow solid: 280 mg, 45%; mp 238−42 °C dec (recrystallized from $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.01 (s, 1H), 9.96 (s, 1H), 8.65 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.77 (s, 1H), 7.68 (m, containing a doublet at 7.71, J = 8.5 Hz, 4H), 7.30 (d, J = 15.87 Hz, 2H).

6-(2-Cyanoethenyl)-2-[4′-(2-cyanoethenyl)phenyl]imidazo[1,2-*a*]pyridine (6b). To a stirred solution of diethyl cyanomethylphosphonate (2.12 g, 11.96 mmol) in THF (20 mL) was added *n*-BuLi at 5−10 °C. Stirring was continued at 10 °C for 15 min and then at room temperature for 1.5 h. The resulting lithium enolate was added to a suspension of dialdehyde **3d** (1.0 g, 4 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 18 h. It was then decomposed with saturated NH_4Cl. After the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). After drying and removal of solvent, the gray solid was recrystallized from absolute EtOH to furnish **6b** as a brown solid: 830 mg,

70%; mp 214−6 °C dec (recrystallized from EtOH); ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 8.00 (d, J = 8 Hz, 2H), 7.95 (s, 1H), 7.68 (d, J = 9.7 Hz, 1H), 7.54 (d, J = 8 Hz, 2H), 7.43 (d, J = 16.48 Hz, 1H), 7.34 (m, containing a doublet J = 16.48 Hz, 2H), 5.93 (d, J = 16.48 Hz, 1H), 5.89 (d, J = 16.48 Hz, 1H). Anal. ($C_{19}H_{12}N_4 \cdot 0.25H_2O$) C, H, N.

6-(3-Oxo-1-propenyl)-2-[4′-(3-oxo-1-propenyl)phenyl]-imidazo[1,2-*a*]pyridine (6c). To a cooled and stirred solution of lithium diisopropylamide prepared from diisopropylamine (3.5 mL, 25.2 mmol) and *n*-BuLi (10.1 mL of 2.5 M in hexane, 25.2 mmol) in THF (15 mL) at −78 °C under nitrogen atmosphere was added acetaldehyde *N*-*tert*-butylimine [41] (1.6 mL, 12 mmol). Stirring was continued at −78 °C for 30 min, and then a solution of distilled diethyl chlorophosphate (2.08 g, 12 mmol) in THF (2 mL) was added. After addition was complete, the reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to −10 °C over a period of 5 h. The resulting yellow solution of lithioenaminophosphonate[18] was stirred at −10 °C for 20 min, then again cooled to −40 °C, and added through a cannula to the cold suspension of dialdehyde **3d** (1 g, 4 mmol) in THF (80 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 min and then slowly allowed to warm to room temperature. Stirring was continued at room temperature overnight, and a clear red-colored solution resulted. The reaction mixture was then treated with aqueous oxalic acid (3.45 g in 80 mL water, 27.3 mmol) followed by addition of benzene (80 mL). The biphasic mixture was stirred at room temperature, and after 3 h a yellow solid started to separate out from the reaction mixture. Stirring was continued at room temperature for overnight. The yellow solid was filtered through Celite bed and then washed with water. The yellow solid along with Celite was boiled under reflux with $CHCl_3$. Then this mixture was again passed through a Celite bed. The filtrate was washed with water and brine and then dried over $MgSO_4$. Removal of solvent provided pure **6c** as a yellow solid which was directly used for making hydrazones without further purification. After separating the organic layer from the original filtrate, the aqueous layer was made alkaline (pH 9) with 10% NaOH and then extracted with $CHCl_3$ (3 × 30 mL). The combined organic layer was washed with water followed by brine and then dried over $MgSO_4$. Concentration of the filtrate resulted in a semisolid which was crystallized from $CHCl_3$ to get additional **6c** to yield: 785 mg, 65%; mp 207−8 °C dec (recrystallized from $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.73 (d, J = 7.3 Hz, 2H), 8.34 (s, 1H), 8.03 (d, J = 8 Hz, 2H), 7.98 (s, 1H), 7.68 (m, containing a doublet at 7.66, J = 8 Hz, 3H), 7.48 (m, 3H), 6.77 (dd, J_1 = 12.8 and J_2 = 7.3 Hz, 1H), 6.72 (dd, J_1 = 12.8 and J_2 = 7.3 Hz, 1H). Anal. ($C_{19}H_{14}N_2O_2$) C, H, N.

General Procedure for the Preparation of (*N*-Alkylguanyl)hydrazones (Functional Groups e−j). A stirred suspension of 1.8−2 equiv of substituted aminoguanidinium iodide or bromide and the appropriate aldehyde (1 mmol) or 3 equiv of aminoguanidinium iodide or bromide with dialdehyde (1 mmol) in absolute ethanol (3 mL) was slowly heated to provide a clear solution. Stirring was continued under reflux for 24 h. The product generally precipitated out from the solution during reflux. The reaction mixture was then cooled, acidified (pH < 2) with concentrated HBr, and stirred for 30 min. The solid product was filtered and purified by recrystallization from aqueous ethanol containing HBr to provide the desired guanylhydrazones in 80−90% yield.

1e: 90%; ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1H), 8.77 (d, J = 6.9 Hz, 1H), 8.21 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 9 Hz, 1H), 7.76 (br t, 1H), 7.34 (t, J = 6.3 Hz, 1H), 3.72 (s, 4H). Anal. ($C_{17}H_{16}N_6 \cdot 2HBr$) C, H, N, Br.

1f: 91%; ^{1}H NMR (DMSO-d_6) δ 8.84 (s, 1H), 8.80 (d, J = 6.6 Hz, 1H), 8.35 (br s, 2H), 8.16 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.85 (m, 2H), 7.40 (t, J = 6.6 Hz, 1H), 3.35 (br t, 4H), 1.89 (br t, 2H). Anal. ($C_{18}H_{18}N_6 \cdot 2HBr \cdot H_2O$) C, H, N, Br.

1g: 50%; ^{1}H NMR (DMSO-d_6) δ 11.36 (s, 1H), 8.89 (s, 1H), 8.84 (d, J = 6.6 Hz, 1H), 8.44 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.91 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 3.47 (s, 4H), 1.94 (s, 4H); MS (CI) 333 (M + 1). Anal. ($C_{19}H_2ON_6 \cdot 2HBr \cdot 2H_2O$) C, H, N, Br.

1i: 56%; ^{1}H NMR (DMSO-d_6) δ 11.69 (s, 1H), 8.89 (s, 1H), 8.84 (d, J = 6.6 Hz, 1H), 8.42 (s, 1H), 8.31(s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.91 (t, J = 8.7 Hz, 1H), 7.45 (t, J = 6.6 Hz, 1H), 3.69 (m, 4H), 3.56 (m, 4H); MS (CI) 349 (M + 1). Anal. ($C_{19}H_{20}N_6 \cdot 2HBr \cdot 2H_2O$) C, H, N, Br.

2e: 60%; ^{1}H NMR (DMSO-d_6) δ 12.46 (s, 1H), 9.08 (s, 1H), 8.65 (s, 1H), 8.26 (s, 1H), 8.24 (d, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.84 (d, J = 9.3 Hz, 1H), 7.51 (t, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 3.75 (s, 4H); MS (CI) 305 (M + 1). Anal. ($C_{17}H_{16}N_6 \cdot 2HBr \cdot 0.5H_2O$) C, H, N, Br.

2f: 62%; ^{1}H NMR (DMSO-d_6) δ 11.73 (s, 1H), 9.10 (s, 1H), 8.67 (s, 1H), 8.42 (s, 1H), 8.30 (d, 1H), 8.23 (s, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.85 (d, J = 9.3 Hz, 1H), 7.54 (t, J = 7.2 Hz, 2H), 7.47 (t, J = 8.4 Hz, 1H), 3.56 (br s, 4H), 1.89 (br s, 2H); MS (CI) 319 (M + 1). Anal. ($C_{18}H_{18}N_6 \cdot 2HBr \cdot 2H_2O$) C, H, N, Br.

3e: 89%; ^{1}H NMR (DMSO-d_6) δ 8.91 (s, 1H), 8.59 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H), 8.07 (d, J = 9 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 9 Hz, 1H), 3.70 (br s, 8H). Anal. ($C_{21}H_{22}N_{10} \cdot 3HBr \cdot 2H_2O$) C, H, N, Br.

3f: 81%; ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.57 (s, 1H), 8.34 (br s, 1H), 8.30 (br s, 1H), 8.16 (s, 1H), 8.13 (s, 1H), 8.08 (d, J = 9.3 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 9.3 Hz, 1H), 3.33 (br t, 8H), 1.87 (br t, 4H). Anal. ($C_{23}H_{26}N_{10} \cdot 3HBr \cdot 0.5H_2O$) C, H, N, Br.

3g: 87%; ^{1}H NMR (DMSO-d_6) δ 9.01 (s, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 8.37 (s, 1H), 8.26 (d, J = 9.6 Hz, 1H), 8.02 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 9.6 Hz, 1H), 3.45 (br t, 8H), 1.93 (br t, 8H). Anal. ($C_{25}H_{50}N_{10} \cdot 3HBr \cdot 1.5H_2O$) C, H, N, Br.

3j: 71%; ^{1}H NMR (DMSO-d_6) δ 11.35 (s, 1H), 11.22 (s, 1H), 9.01 (s, 1H), 8.66 (s, 1H), 8.22 (m, 2H), 7.99 (m, containing a doublet at 8.00, J = 8 Hz, 9H), 7.80 (m, 3H), 3.88 (sept, J = 7.3 Hz, 2H), 1.19 (d, J = 6.8 Hz, 12H). Anal. ($C_{23}H_{33}N_{10} \cdot 3HBr$). Quadruplicate analysis gave empirical formula $C_{23}H_{33}N_{10}Br_{2.7}O_{3.9}$.

4e: 73%; ^{1}H NMR (DMSO-d_6) δ 9.23 (s, 1H), 8.76 (br s, 2H), 8.54 (s, 1H), 8.33 (s, 1H), 8.29 (d, J = 9.3 Hz, 1H), 8.26 (s, 1H), 7.80 (d, J = 9.3 Hz, 1H), 3.75 (s, 4H), 3.73 (s, 4H). Anal. ($C_{15}H_{18}N_{10} \cdot 3HBr \cdot 2H_2O$).

4f: 80%; ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1H), 8.60 (s, 1H), 8.53 (br s, 1H), 8.50 (d, J = 9.3 Hz, 1H), 8.46 (br s, 1H), 8.31 (s, 1H), 8.24 (s, 1H), 7.84 (d, J = 9.3 Hz, 1H), 3.36 (br s, 8H), 1.88 (br s, 4H). Anal. ($C_{17}H_{22}N_{10} \cdot 3HBr \cdot H_2O$) C, H, N, Br.

4g: 52%; ^{1}H NMR (DMSO-d_6) δ 9.32 (s, 1H), 8.68 (s, 1H), 8.58 (d, J = 9.6 Hz, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.06 (br s, 4H), 7.85 (d, J = 9.6 Hz, 1H), 3.48 (br s, 4H), 1.94 (br s, 4H). Anal. ($C_{19}H_{26}N_{10} \cdot 3HBr \cdot 2H_2O$) C, H, N, Br.

5e: 80%; ^{1}H NMR (20% D_2O in DMSO-d_6) δ 8.85 (s, 1H), 8.20 (m, containing a s at 8.19, 2H), 8.09 (s, 1H), 8.03 (s, 1H), 7.73 (m, containing a doublet at 7.74, J = 8 Hz, 3H), 7.62 (d, J = 8 Hz, 2H), 7.30 (m, 2H), 3.67 (d, J = 4.3 Hz, 8H). Anal. ($C_{23}H_{24}N_{10} \cdot 3HBr \cdot 2H_2O$) C, H, N, Br.

5f: 85%; ^{1}H NMR (DMSO-d_6) δ 11.75 (s, 1H), 11.51 (s, 1H), 9.17 (s, 1H), 8.41 (m, containing a s at 8.42, 3H), 8.31 (s, 2H), 8.20 (s, 1H), 8.11 (s, 1H), 7.88 (d, J = 8 Hz, 2H), 7.83 (d, J = 9 Hz, 1H), 7.68 (d, J = 8 Hz, 2H), 7.53 (d, J = 16.5 Hz, 1H), 7.46 (d, J = 16.5 Hz, 1H), 3.34 (d, J = 3.7 Hz, 8H), 1.87 (br s, 4H). Anal. ($C_{25}H_{28}N_{10} \cdot 3HBr \cdot 3H_2O$) C, H, N, Br.

5g: ^{1}H NMR (DMSO-d_6) δ 11.52 (s, 2H), 11.28 (s, 2H), 9.28 (s, 1H), 8.53 (d, J = 9.8 Hz, 1H), 8.48 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 7.98 (m, containing a doublet at 7.93, J = 8.5 Hz, 4H), 7.83 (d, J = 9.7 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.52 (m, 2H), 3.46 (s, 8H), 1.92 (s, 8H). Anal. ($C_{27}H_{32}N_{10} \cdot 3HBr \cdot 2H_2O$) C, H, N, Br.

6e: ^{1}H NMR (30% D_2O in DMSO-d_6) δ 8.85 (s, 1H), 8.62 (s, 1H), 8.03 (d, J = 9.3 Hz, 1H), 7.91 (m, 4H), 7.79 (d, J = 9.3 Hz, 1H), 7.69 (d, J = 8 Hz, 2H), 7.13 (dd, J_1 = 15.6 and J_2 =

8 Hz, 2H), 6.97 (m, 2H), 3.64 (s, 8H). Anal. ($C_{25}H_{26}N_{10}$·3HBr·2H_2O) C, H, N, Br.

6f: ^{1}H NMR (DMSO-d_6) δ 11.49 (s, 1H), 11.44 (s, 1H), 8.95 (s, 1H), 8.78 (s, 1H), 8.22 (m, containing a doublet J = 9.8 Hz, 4H), 7.93 (m, 6H), 7.73 (d, J = 7.94 Hz, 2H), 7.20 (2d, J = 16.48 Hz, 2H), 6.96 (2d, J = 16.48 Hz, 2H), 3.29 (s, 8H), 1.84 (br s, 4H). Anal. ($C_{27}H_{30}N_{10}$·3HBr·3H_2O) C, H, N, Br.

6g: ^{1}H NMR (DMSO-d_6) δ 11.24 (s, 1H), 11.20 (s, 1H), 8.98 (s, 1H), 8.79 (s, 1H), 8.25 (m, 2H), 8.05 (d, J = 9 Hz, 1H), 7.99 (d, J = 8 Hz, 2H), 7.87 (d, J = 9 Hz, 1H), 7.79 (m, containing a doublet at 7.74, J = 8 Hz, 4H), 7.26 (d, J = 15.87 Hz, 1H), 7.17 (d, J = 15.87 Hz, 1H), 7.02 (m, 2H), 3.41 (s, 8H), 1.90 (s, 8H). Anal. ($C_{29}H_{34}N_{10}$·3HBr·1.5H_2O) C, H, N, Br.

General Procedure for the Preparation of Amidines. Method A: Dry HCl gas was bubbled through a solution of nitrile (12.2 mmol) in nitrobenzene (50 mL) and absolute EtOH (10 mL) at 0 °C for 1 h, and the resulting mixture was stirred at room temperature for 16−20 h. The imino ether hydrochloride was precipitated by addition of dry Et_2O and then filtered. Excess nitrobenzene was removed by washing with copious amounts of Et_2O. The solid was dried under vacuum and directly reacted with appropriate amine to make corresponding amidines.

Method B: A suspension of dinitrile **5b** (0.45 g, 1.66 mmol) in dry dioxane (10 mL) and absolute ethanol (5 mL) was cooled in an ice−water bath, and dry HCl gas was bubbled through it. A creamy solid precipitated from the reaction mixture within 15 min, but the solid slowly went back in solution and the reaction mixture was a clear red-colored thick solution after 1 h. A yellow-colored solid slowly started to precipitate from the solution, and HCl gas stream was continued for next 2 h. The cold reaction mixture was then stoppered, slowly allowed to warm to room temperature, and left standing at room temperature for 3 days with occasional shaking. The reaction mixture was concentrated to dryness, keeping the water bath temperature below 30 °C, and the resulting solid residue was dried under vacuum overnight to provide the imidate intermediate as a brown solid (763 mg).

Method C: Dry HCl gas was bubbled at 0 °C into a stirred suspension of dinitrile **6a** (0.51 g, 1.72 mmol) in dry dioxane (6 mL) and absolute ethanol (3.6 mL). A yellow solid precipitated from the reaction mixture within 15 min, and passage of HCl gas was continued for 1 h. The reaction mixture turned nearly clear and became thick. It was slowly allowed to warm to room temperature with continuous stirring and left standing at room temperature overnight. The reaction mixture was concentrated to dryness, keeping the water bath temperature below 30 °C, and the resulting solid residue was dried in a vacuum for 2 h to provide the imidate intermediate (850 mg) as a tan-colored solid.

Method D: To a stirred cold suspension of the corresponding amine hydrochloride (30 mmol) in toluene (20 mL) was slowly added trimethylaluminum (15 mL, 2 M in toluene, 30 mmol) through a dropping funnel at 0 °C. Stirring was continued at this temperature for the next 15 min and at room temperature for 1.5 h. The resulting clear colorless solution of aluminum amide reagent was added to the suspension of dinitrile (4.8 mmol) in toluene (20 mL) by cannulation at 0 °C. After addition was complete, the reaction mixture was stirred at room temperature for 30 min and then heated to 80 °C for 24 h. During heating, the suspended reaction mixture became clear and dark red in color. After being cooled, the mixture was poured into a stirred slurry of silica gel (30 g) in chloroform (80 mL), and the solid material was completely transferred with methanol. The resulting mixture was stirred at room temperature for 30 min. The silica gel was filtered off and washed with hot methanol (3 × 50 mL). The filtrate and washings were combined and concentrated under reduced pressure to obtain crude amidine salts.

N-Substituted Amidines (Functional Groups k−o). Compounds **1l,m** and **2k,m** were prepared following method A. Compounds **1k**, **3k**, **5k**, and **6k,m,n** were prepared following method D (compound **1k** was also made by method A). Compound **5o** was prepared following method C.

1k. The crude residue was recrystallized from aqueous acetone to provide a creamy solid which was converted to the corresponding hydrochloride salt by bubbling HCl gas through the methanolic solution followed by concentration to dryness to provide amidine **1k** as a light-greenish white solid: 73%; ^{1}H NMR (DMSO-d_6) δ 8.77 (s, 1H), 8.76 (d, 1H), 8.10 (d, J = 8.1 Hz, 2H), 7.85 (t, J = 9 Hz, 1H), 7.80 (d, J = 6.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.36 (t, J = 9 Hz, 1H), 3.51 (t, J = 6.9 Hz, 2H), 3.39 (t, J = 6.6 Hz, 2H), 2.02 (t, J = 6.6 Hz, 2H), 1.83 (t, J = 6.9 Hz, 2H); MS (CI) 291 (M + 1). Anal. ($C_{18}H_{18}N_4$·2HCl·2H_2O) C, H, N, Cl.

1l. To a suspension of imidate intermediate from **1b** (2.9 g, 13.3 mmol) in absolute EtOH (50 mL) was added freshly distilled piperidine (2.63 mL, 26.6 mmol) at 0 °C. The mixture was stirred at room temperature overnight. After removal of solvent the residue was dissolved in minimum volume of 3 N HCl. The solid was precipitated out by addition of acetone and filtered. It was then purified by several recrystallizations from aqueous acetone. The final product was recrystallized from aqueous EtOH containing HCl to provide amidine **1l** as an off-white solid: 2.25 g, 45%; ^{1}H NMR (DMSO-d_6) δ 9.47 (br s, 1H), 9.36 (s, 1H), 8.91 (s, 1H), 8.85 (d, J = 6.9 Hz, 1H), 8.27 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 6.6 Hz, 1H), 3.75 (m, 4H), 1.6 (m, 6H); MS (CI) 305 (M + 1). Anal. ($C_{19}H_{20}H_4$·2HCl·2H_2O) C, H, N, Cl.

1m. Reaction of imidate ester hydrochloride from **1b** with morpholine as described above for **1l** gave amidine **1m** as an off-white solid: 35%; ^{1}H NMR (DMSO-d_6) δ 9.71 (s, 1H), 9.64 (s, 1H), 8.89 (d, J = 6.6 Hz, 1H), 8.30 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 6.7 Hz, 1H), 7.90 (t, J = 6.6 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 6.7 Hz, 1H), 3.82 (br s, 4H), 3.63 (br s, 2H), 3.54 (br s, 2H); MS (CI) 307 (M + 1). Anal. ($C_{18}H_{18}N_4O$·2HCl·H_2O) C, H, N, Cl.

2k. Treatment of the imidate intermediate from **2b** with pyrrolidine following the procedure described for **1l** gave amidine **2k** as an off-white solid: 44%; ^{1}H NMR (DMSO-d_6) δ 9.61 (s, 1H), 9.14 (s, 1H), 9.11 (d, 1H), 8.78 (s, 1H), 8.03 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 9.3 Hz, 1H), 7.74 (d, J = 9.3 Hz, 1H), 7.51 (t, J = 6.9 Hz, 2H), 7.43 (t, J = 7.5 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 3.49 (t, J = 6.9 Hz, 2H), 2.06 (quintet, J = 6.6 Hz, 2H), 1.86 (quintet, J = 6.6 Hz, 2H); MS (CI) 291 (M + 1). Anal. ($C_{18}H_{18}H_4$·2HCl·1.5H_2O) C, H, N, Cl.

2m. Reaction of morpholine with the imidate intermediate from **2b** as described for **1l** gave amidine **2m** as an off-white solid: 39%; ^{1}H NMR (DMSO-d_6) δ 9.89 (s, 1H), 9.72 (s, 1H), 9.11 (s, 1H), 8.78 (s, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 9.3 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 3.81 (br s, 4H), 3.64 (br s, 2H), 3.45 (br s, 2H); MS (CI) 307 (M + 1). Anal. ($C_{18}H_{18}N_4O$·2HCl·H_2O) C, H, N, Cl.

3k. The crude residue obtained from the reaction between dinitrile **3b** and pyrrolidine hydrochloride was recrystallized from aqueous acetone and subsequently converted to the corresponding hydrochloride salt following the procedure as described for **1k** to give amidine **3k**: 62%; ^{1}H NMR (DMSO-d_6) δ 9.60 (br s, 1H), 9.34 (br s, 1H), 9.10 (br s, 1H), 9.08 (s, 1H), 8.91 (br s, 1H), 8.82 (s, 1H), 8.20 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 9.6 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 9.6 Hz, 1H), 3.52 (m, 3H), 3.43 (t, J = 6.6 Hz, 1H), 2.04 (m, 2H), 1.86 (m, 2H). Anal. ($C_{23}H_{26}N_6$·3HCl·2H_2O) C, H, N, Cl.

5k. The residue from the reaction between dinitrile **5b** and pyrrolidine hydrochloride was dissolved in water, basified (pH > 12), and then extracted with $CHCl_3$ (4 × 25 mL). The $CHCl_3$ solution was washed with water followed by brine and dried over $MgSO_4$. Removal of solvent afforded crude amidine as free base. A methanolic solution was heated with MeOH/HCl at 0 °C for 30 min and at room temperature for 1 h. After concentrating to dryness, the resulting residue was dried under vacuum and recrystallized from absolute EtOH/acetone containing HCl to furnish amidine **5k** as a creamy solid: 60%; ^{1}H NMR (D_2O) δ 9.01 (s, 1H), 8.24 (s, 1H), 7.93 (m, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 17.1

Hz, 1H), 7.32 (d, J = 17.1 Hz, 1H), 3.54 (m, 8H), 2.10 (m, 4H), 1.90 (m, 4H). Anal. ($C_{25}H_{28}N_6$·2.3HCl·2.5H_2O) C, H, N, Cl.

5o. The bis-imino ether HCl salt from **5b** (450 mg, 1.66 mmol) was suspended in absolute EtOH (6 mL). Freshly distilled isopropylamine (0.57 mL, 6.71 mmol) was added at 0 °C and stirred at room temperature for 24 h. After removal of solvent, the residue was dried under vacuum. A methanolic HCl (10 mL) solution of this residue was stirred at 0 °C for 30 min and at room temperature for 2 h. Removal of methanol afforded a tan-colored solid which was recrystallized from aqueous acetone in the presence of HCl to furnish amidine **5o** as a creamy solid: 500 mg, 58%; ^{1}H NMR (D_2O) δ 9.08 (s, 1H), 8.23 (s, 1H), 7.92 (m, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 16.48 Hz, 1H), 7.29 (d, J = 16.48 Hz, 1H), 3.92 (sept, J = 6.7 Hz, 2H), 1.28 (t, J = 6.1 Hz, 12H). Anal. ($C_{23}H_{28}N_6$·3HCl·H_2O) C, H, N, Cl.

6k. The crude solid isolated from the reaction of dinitrile **6a** with pyrrolidine hydrochloride was recrystallized from aqueous acetone to provide amidine (1.65 g) as a greenish solid which was stirred with MeOH/HCl (30 mL) at 0 °C for 30 min and at room temperature for 1 h. Evaporation of methanol afforded a crude residue which was purified by recrystallization from aqueous EtOH to give amidine **6k** as a yellow solid: 1.4 g, 54%; ^{1}H NMR (D_2O) δ 8.41 (s, 1H), 8.11 (s, 1H), 7.77 (d, J = 9.3 Hz, 1H), 7.52 (m, 5H), 7.31 (d, J = 16.1 Hz, 1H), 7.20 (d, 16.1 Hz, 1H), 6.63 (d, J = 16 Hz, 1H), 6.50 (d, J = 16.1 Hz, 1H), 3.60 (m, 4H), 3.32 (m, 4H), 1.97 (m, 8H). Anal. ($C_{27}H_{30}N_6$·2.6HCl·3.2H_2O) C, H, N, Cl.

6m. The crude residue from the reaction between dinitrile **6a** and morpholine hydrochloride was first purified and then converted to the corresponding hydrochloride salt following the procedure as described for **6k** to give amidine **6m** as a yellow solid: 50%; ^{1}H NMR (DMSO-d_6) δ 9.59 (br s, 1H), 9.45 (br s, 1H), 9.14 (br s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.14 (d, J = 8.55 Hz, 3H), 7.86 (m, containing a doublet at 7.88, J = 8.54 Hz, 3H), 7.66 (t, J = 16.48 Hz, 2H), 7.26 (t, J = 16.48 Hz, 2H), 3.71 (s, 16H). Anal. ($C_{27}H_{31}N_6O_2$·3HCl·H_2O) C, H, N, Cl.

6n. The crude yellow solid obtained by reacting dinitrile **6a** with 1-methylpiperazine hydrochloride was stirred with MeOH/HCl (15 mL) at 0 °C for 30 min and at room temperature for 1 h. It was then evaporated to dryness under reduced pressure to give a creamy solid which was purified by recrystallization from aqueous EtOH to provide amidine **6n** as a brown solid: 52%; ^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H), 8.58 (s, 1H), 8.05 (d, J = 9.15 Hz, 1H), 7.93 (d, J = 8.54 Hz, 2H), 7.79 (m, 3H), 7.50 (2d, J = 15 Hz, 2H), 7.05 (t, J = 15 Hz, 2H), 4.20 (s, 16H), 2.79 (s, 6H). Anal. ($C_{29}H_{36}N_8$·5HCl·3H_2O) C, H, N, Cl.

Cyclic *N,N′*-Dialkylamidines (Functional Groups p−r). Compounds **1p**−**r**, **2p**, and **3p** were prepared following method A. Compounds **5p** and **6p** were prepared following methods B and C, respectively.

1p. To a suspension of imidate intermediate from **1b** (2.9 g, 13.3 mmol) in absolute EtOH (50 mL) was added freshly distilled ethylenediamine (2.13 mL, 32 mmol) at 0 °C. The mixture was stirred under reflux overnight. After being cooled to room temperature, the reaction mixture was concentrated to 1/5 volume and diluted with ether. The solid precipitate was purified by several recrystallizations from aqueous acetone. The final product was recrystallized from aqueous EtOH containing HCl to provide amidine **1p** as a white solid: 1.8 g, 40%; ^{1}H NMR (DMSO-d_6) δ 10.74 (s, 1H), 8.82 (s, 1H), 8.75 (d, J = 6.6 Hz, 1H), 8.27 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 6.6 Hz, 1H), 3.99 (s, 4H); MS (CI) 263 (M + 1). Anal. ($C_{16}H_{14}N_4$·2HCl·2H_2O) C, H, N, Cl.

1q. The imidate ester hydrochloride from **1b** was treated with freshly distilled 1,3-diaminopropane as outlined above for **1p** and provided amidine **1q** as an off-white solid: 1.7 g, 37%; ^{1}H NMR (DMSO-d_6) δ 10.18 (s, 1H), 8.88 (s, 1H), 8.81 (d, J = 6.6 Hz, 1H), 8.27 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H), 7.80 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 6.3 Hz, 1H), 3.47 (br s, 4H), 1.95 (m, 2H); MS (CI) 277 (M + 1). Anal. ($C_{17}H_{16}N_4$·2HCl·2H_2O) C, H, N, Cl.

1r. To a suspension of imidate intermediate from **1d** (3 g, 12.2 mmol) in absolute EtOH (20 mL) was added freshly distilled ethylenediamine (1 mL, 15 mmol) at 0 °C. The mixture was refluxed for 18 h. The residue obtained after removing solvent was recrystallized from aqueous EtOH containing HCl to give amidine **1r** as a yellow solid: 2.8 g, 62%; ^{1}H NMR (DMSO-d_6) δ 8.51 (d, J = 6.6 Hz, 1H), 8.20 (s, 1H), 7.77 (t, J = 6.9 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 6.9 Hz, 1H), 7.13 (d, J = 16.8 Hz, 1H), 6.38 (d, J = 16.8 Hz, 1H), 4.75 (s, 4H). Anal. ($C_{18}H_{16}N_4$·2HCl·0.5H_2O) C, H, N, Cl.

2p. The imidate ester hydrochloride from **2b** (2.9 g, 13.3 mmol) was allowed to react with freshly distilled ethylenediamine as described above for **1p** to furnish amidine **2p** as an off-white solid: 2 g, 45%; ^{1}H NMR (DMSO-d_6) δ 11.19 (s, 1H), 9. 66 (s, 1H), 8.79 (s, 1H), 8.07 (d, J = 7.2 Hz, 2H), 8.02 (s, 1H), 7.96 (d, J = 8.7 Hz, 1H), 7.58 (s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.42 (t, J = 6.9 Hz, 1H), 3.99 (s, 4H); MS (CI) 263 (M + 1). Anal. ($C_{16}H_{14}N_4$·2HCl·2H_2O) C, H, N, Cl.

3p. The bis-imino ether intermediate from **3b** (3 g, 12.2 mmol) was treated with ethylenediamine (3.3 mL, 50 mmol) as described above for **1r**. After removal of EtOH, crude residue was recrystallized from aqueous acetone containing HCl to provide amidine **3p** as a creamy solid: 2.3 g, 40%; ^{1}H NMR (DMSO-d_6) δ 11.05 (br s, 1H), 10.78 (br s, 1H), 9.60 (s, 1H), 8.85 (s, 1H), 8.28 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 7.84 (s, 2H), 3.98 (br s, 8H). Anal. ($C_{19}H_{18}N_6$·3HCl·2H_2O) C, H, N, Cl.

5p. To a stirred suspension of crude bis-imino ether HCl salt from **5b** (450 mg, 1.66 mmol) in absolute EtOH (5 mL) was added ethylenediamine (0.35 mL, 4.04 mmol) at 0 °C. The clear red-colored reaction mixture was stirred at room temperature for 30 min and then refluxed overnight. The yellow precipitate was filtered and dried. The yellow solid was suspended in water (5 mL) and basified (pH > 9) with 10% NaOH. The precipitate was filtered, washed with water, and dried in air to give amidine as a free base (400 mg). To the stirred suspension of free base in MeOH (10 mL) was added methanolic HCl at 0 °C. The resulting clear solution was stirred at 0 °C for 15 min and at room temperature for 2 h. A gray solid was precipitated out. On warming to 60 °C the reaction mixture became clear. Stirring was continued at 60 °C for 1 h. Evaporation of methanol resulted in a light-greenish yellow solid which was recrystallized from aqueous EtOH containing HCl to provide amidine **5p** as a brown solid: 390 mg, 50%; ^{1}H NMR (DMSO-d_6) δ 10.97 (s, 2H), 10.71 (s, 2H), 9.57 (s, 1H), 8.31 (s, 1H), 8.03 (d, J = 8 Hz, 2H), 7.84 (m, containing a doublet at 7.86, J = 8 Hz, 4H), 7.60 (m, 2H), 3.97 (d, J = 4.9 Hz, 8H). Anal. ($C_{21}H_{20}N_6$·2.3HCl·2H_2O) C, H, N, Cl.

6p. To a stirred clear solution of imino ether HCl salt from **6b** (0.51 g, 1.72 mmol) in absolute EtOH (4 mL) was added ethylenediamine (0.5 mL, 7.47 mmol) at 0 °C. The mixture was stirred at room temperature for 15 min and then under reflux overnight. The yellow precipitate was filtered. The solid was suspended in water (8 mL) and basified (pH > 11) with 10% NaOH. The undissolved solid was filtered, washed with water, and dried in air to provide free base amidine (400 mg). Methanolic HCl (10 mL) was added to the stirred suspended free base in MeOH (10 mL) at 0 °C. The resulting mixture was stirred at room temperature for 30 min and then refluxed for 1 h (not all solid went in solution). After removal of methanol, the crude residue was purified by recrystallizaton from aqueous EtOH containing HCl to furnish amidine **6p** as a yellow solid: 425 mg, 50%; ^{1}H NMR (DMSO-d_6) δ 10.33 (s, 2H), 10.26 (s, 2H), 8.84 (s, 1H), 8.66 (s, 1H), 8.07 (d, J = 8 Hz, 2H), 7.93 (d, J = 16.48 Hz, 1H), 7.90 (d, J = 16.48 Hz, 1H), 7.72 (m, 4H), 6.82 (d, J = 16.48 Hz, 1H), 6.81 (d, J = 16.48 Hz, 1H), 3.87 (s, 8H). Anal. ($C_{23}H_{22}N_6$·2.6HCl·2H_2O) C, H, N, Cl.

General Procedure for the Preparation of N-Substituted Hydrazones (Functional Groups s−w). A stirred mixture of the dialdehyde **3d** (3.8 mmol) and hydrazine (8.17 mmol) in absolute ethanol (3 mL) was refluxed for 18 h. A

yellow solid precipitated from the solution during reflux. After being cooled, the reaction mixture was acidified (pH < 2) with concentrated HBr and stirred for 30 min. The undissolved solid was filtered, dried, and recrystallized from aqueous ethanol containing HBr to furnish hydrazones in 70−80% yield.

3s: starting with 2-hydrazinopyrroline[42] and following the standard procedure; 83%; ^{1}H NMR (DMSO-d_6) δ 13.14 (s, 1H), 13.04 (s, 1H), 10.45 (s, 1H), 10.37 (s, 1H), 9.11 (s, 1H), 8.68 (s, 1H), 8.11 (m, containing a doublet at 8.10, J = 8 Hz, 3H), 8.00 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 1H), 3.68 (m, 4H), 2.96 (m, 4H), 2.17 (m, 4H). Anal. ($C_{23}H_{24}N_8$·3HBr·2H_2O) C, H, N, Br.

3t: 61%; ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.75 (s, 1H), 8.39 (d, J = 9.6 Hz, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 8.13 (m, 4H), 8.11 (s, 4H), 7.85 (d, J = 9.6 Hz, 1H), 7.25 (t, J = 7.8 Hz, 2H), 7.11 (m, 2H). Anal. ($C_{25}H_{20}N_6$·3HBr·3H_2O) C, H, N, Br.

3u: 83%; ^{1}H NMR (DMSO-d_6) δ 9.08 (s, 1H), 8.82 (s, 1H), 8.20 (d, J = 9.6 Hz, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 9.6 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 3.9 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 6.96 (d, J = 3.9 Hz, 1H), 6.94 (d, J = 3.6 Hz, 1H). Anal. ($C_{21}H_{16}H_8S$·3HBr·3H_2O) C, H, N, S, Br.

3v: 76%; ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.82 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 8.27 (d, J = 9 Hz, 1H), 7.96 (m, 5H), 7.77 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H). Anal. ($C_{29}H_{26}N_6O_4$·3HBr·3H_2O) C, H, N, Br.

3w: 80%; ^{1}H NMR (DMSO-d_6) δ 11.77 (s, 1H), 11.57 (s, 1H), 8.94 (s, 1H), 8.68 (s, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.90 (m, 2H), 7.73 (m, 8H), 7.36 (m, 4H), 2.31 (s, 6H). Anal. ($C_{29}H_{26}N_6O_4S_2$·HBr·4H_2O)

Preparation of Diethyl 2-Thiazolinylmethylphosphonate. A mixture of 2-aminoethanethiol hydrochloride (9.62 g, 84.68 mmol), diethyl cyanomethylphosphonate (15 g, 84.68 mmol), and K_2CO_3 (11.71 g, 84.68 mmol) in absolute ethanol (125 mL) was refluxed for 6 h. The reaction mixture was filtered. After removal of ethanol, crude phosphonate was distilled under high vacuum to furnish 11.4 g as an oil: 52%; ^{1}H NMR (DMSO-d_6) δ 4.09 (t, J = 8.4 Hz, 2H), 3.98 (q, J = 7.2 Hz, 4H), 3.27 (t, J = 8.4 Hz, 2H), 3.12 (d, J = 21.3 Hz, 2H), 1.18 (t, J = 7.2 Hz, 6H).

General Procedure for the Preparation of Vinylthiazolines (Functional Group x). To a stirred solution of diethyl 2-thiazolinylmethylphosphonate[22] (2.2 mmol) in THF (20 mL) was added *n*-BuLi (2.5 M in hexane, 2.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. A solution of aldehyde **1c** (1.8 mmol) in THF (15 mL) was added to the reaction mixture or lithium enolate solution was added to a suspension of dialdehyde **3d** (0.8 mmol) in THF (15 mL) by a cannula and stirred at room temperature for 2 h. Saturated NH_4Cl was added to the reaction mixture, and the aqueous layer was extracted from $CHCl_3$. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and then concentrated. The crude product was purified by recrystallization from absolute EtOH.

1x. This compound was prepared following the general procedure from the phosphonate (2.1 g, 8.87 mmol) and compound **1c** (1.64 g, 7.39 mmol) as a white solid: 76%; ^{1}H NMR ($CHCl_3$) δ 8.11 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.89 (s, 1H), 7.62 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.19 (dt, J_1 = 9 and J_2 = 0.9 Hz, 1H), 7.11 (d, J = 16.2 Hz, 1H), 7.04 (d, J = 16.2 Hz, 1H), 6.79 (dt, J_1 = 6.6 and J_2 = 0.9 Hz, 1H), 4.38 (t, J = 8.1 Hz, 2H), 3.34 (t, J = 8.1 Hz, 2H).

3x. This compound was prepared following the general procedure from the phosphonate (4.74 g, 20 mmol) and compound **3d** (2 g, 8 mmol) as a white solid: 80%; ^{1}H NMR ($CHCl_3$) δ 8.19 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.88 (s, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 9.6 Hz, 1H), 7.12 (d, J = 16.2 Hz, 2H), 7.03 (d, J = 16.2 Hz, 2H), 4.40 (t, J = 8.1 Hz, 2H), 4.39 (t, J = 8.1 Hz, 2H), 3.37 (t, J = 8.1 Hz, 2H), 3.35 (t, J = 8.1 Hz, 2H).

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