Diguanidino and "Reversed" Diamidino 2,5-Diarylfurans as Antimicrobial Agents

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Dicationic 2,5-bis(4-guanidinophenyl)furans **5a**−**5f**, 2,5-bis[4-(arylimino)aminophenyl]furans **6a**−**6b** and **6e**−**6k**, and 2,5-bis[4-(alkylimino)aminophenyl]furans **6c**−**6d** have been synthesized starting from 2,5-bis[tri-*n*-butylstannyl]furan. Thermal melting studies with poly dA•dT and the duplex oligomer d(CGCGAATTCGCG)$_2$ demonstrated high DNA binding affinities for a number of the compounds. The binding affinities are highly dependent on structure and are significantly affected by substituents both on the phenyl rings of the 2,5-diphenylfuran nucleus and on the cationic centers. Of the 17 novel dicationic compounds synthesized, six (**6a**, **6b**, **5b**, **6f**, **6h**, **6i**) exhibited MICs of 2 μg/mL or less versus *Mycobacterium tuberculosis*. Of the compounds screened against *Candida albicans*, three gave MICs of 2 μg/mL or less (**5b**, **6h**, **6i**), and two (**5b**, **6i**) were fungicidal, unlike a standard antifungal drug fluconazole, which was fungistatic. In addition, one of the tested compounds (**6i**) exhibited a MIC of <1 μg/mL against *Aspergillus fumigatus*, while also being a fungicidal against this organism. Finally, when evaluated against an expanded fungal panel, compound **6h** showed good activity against *Cryptococcus neoformans* and *Rhizopus arrhizus*.

Introduction

The antimicrobial properties of dicationic molecules have been studied since the 1930s.[1] Compounds of this type have typically utilized amidine groups as the cationic moieties, and their activities against a number of pathogens including *Cryptosporidium parvum*,[2] *Giardia lamblia*,[3] *Leishmania* sp.,[4,5] *Plasmodium* sp.,[4,6] *Pneumocystis carinii*,[7−10] *Toxoplasma gondii*,[11] *Trypanosoma* sp.,[12−14] *Candida albicans*,[15−17] *Aspergillus* sp.,[15−17] and *Cryptococcus neoformans*[15−17] have been reported. Despite the broad range of activity exhibited by diamidines, only one compound of this chemical type, pentamidine, has seen significant clinical use. Pentamidine has been used clinically against African trypanosomiasis,[18] antimony-resistant leishmaniasis,[19] and *P. carinii* pneumonia.[7,20] A number of compounds in this class of dicationic molecules has been shown to bind to the minor-groove of DNA at AT-rich sites, and the details of their interaction with the minor-groove have been elucidated from biophysical studies[21−24] and from several crystal structures.[8,25−27] It is hypothesized that these types of molecules exert their biological activity by first binding to DNA and then by inhibiting one or more of several DNA dependent enzymes (i.e., topoisomerases, nucleases, etc.) or possibly by direct inhibition of transcription.[23,28−33]

In previous work from our laboratories, 2,5-diphenylfuran and 2,4-diphenylfuran diamidines have been found to be highly effective treatments in animal models for *Pneumocystis carinii* and *Cryptosporidium parvum*.[8−10,34] Furthermore, these diamidines have shown antifungal activity in vitro against *Candida albicans* and *Cryptococcus neoformans*.[15−17] In an effort to improve upon this antifungal activity and to discover other antimicrobial activities through continued broad-screen evaluation, we have become interested in the effect of structural variations on the cationic centers of these compounds. For instance, although there are reports of antimicrobial activity of guanidino compounds,[35] this class of cationic compounds has not been studied as extensively as their amidino analogues and has yet to be explored within the diarylfuran series. Therefore, this report describes, for the first time, the synthesis, DNA-binding affinities, and some in vitro antimicrobial (antifungal, antimycobacterial) activitites of diguanidino analogues in the 2,5-diphenylfuran series. In addition, the synthesis, DNA-binding affinities, and the same antimicrobial properties of 2,5-bis-{[alkyl (or aryl) imino]aminophenyl}furans are also detailed. These latter compounds have the imino group of the amidine attached to an "anilino" nitrogen in contrast to the original amidino furans in which the imino group is directly attached to the aryl ring. These compounds, hereafter, are referred to as "reversed" amidines. Finally, this report also describes, for the first time, some of the interesting effects of placing various substituents on the central phenyl rings of the 2,5-diphenylfuran framework.

Chemistry

The syntheses for the target diguanidines **5** and reversed diamidines **6** require the corresponding di-

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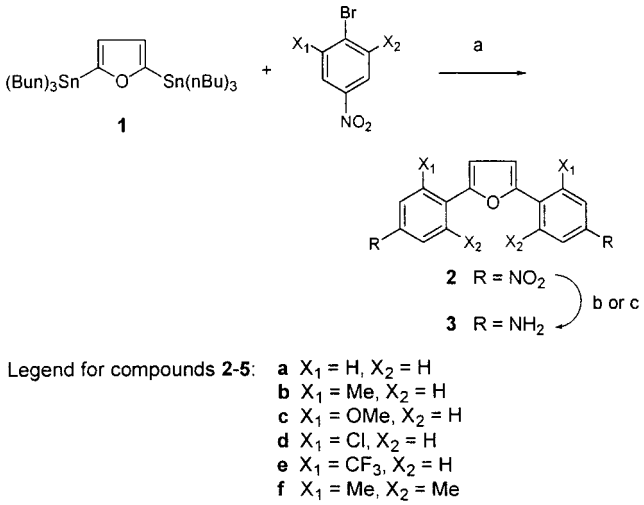
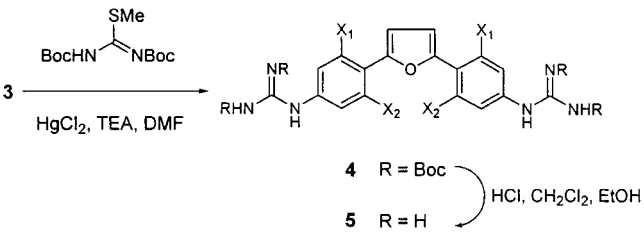
Scheme 1[a]



[a] (a) $Pd(PPh_3)_4$, 1,4-dioxane, Δ; (b) H_2, Pd/C, EtOAc, EtOH; (c) $SnCl_2$ dihydrate, EtOH, DMSO, Δ.

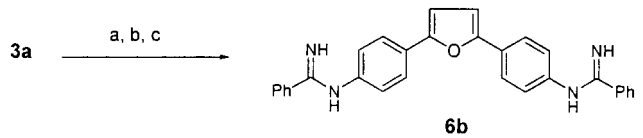
Scheme 2



amino compounds **3** as a common precursor (Scheme 1). The preparation of the diamino compounds **3** was conveniently achieved in two steps starting with a Stille coupling between 2,5-bis(tri-*n*-butylstannyl)furan and a substituted 4-bromonitroarene to form the corresponding 2,5-bis(4-nitrophenyl)furans **2**. This general reaction, which has been described by us in a communication,[36] typically gave good yields (65−88%) of the dinitro compounds, and, in contrast to previously reported syntheses,[37] allowed for the straightforward incorporation of substituents onto the two phenyl rings of the 2,5-diphenylfuran framework. Reduction of the 2,5-bis(4-nitrophenyl)furans **2** was achieved either by catalytic hydrogenation or by the action of stannous chloride and generally produced the desired diamino compounds **3** in excellent overall yields. With the diamines **3** in hand, the diguanidino analogues **5** were prepared in a two-step process which involved first the reaction of **3** with Boc-protected *S*-methylthiourea in the presence of mercuric chloride (Scheme 2).[38] Deprotection of the Boc-protected guanidine analogues **4** was subsequently accomplished using anhydrous HCl in dichloromethane/EtOH to give the diguanidines in good overall yield.

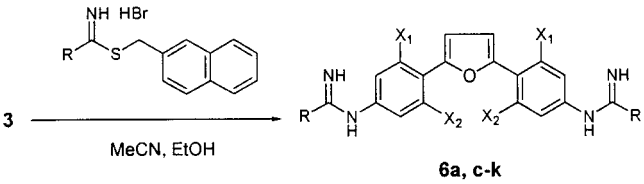
As shown in Scheme 3, the first of the reversed diamidines (**6b**) was prepared from the corresponding diamide via a two-step process which involved conversion of the latter to the diimidoyl chloride using $SOCl_2$, followed by reaction with anhydrous ammonia.[9] Unfortunately, this approach gave inconsistent results in other cases, apparently due to the low solubility of the intermediate diamides and/or the sensitivity of the furan nucleus to thionyl chloride. Alternatively, the remainder of the diamidines **6** were conveniently pre-

Scheme 3[a]



[a] (a) PhCOCl, TEA, MeCN; (b) $SOCl_2$, DMF, CH_2Cl_2, Δ; (c) NH_3, EtOH.

Scheme 4



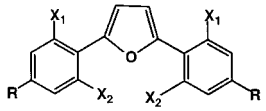
pared by reaction of the diamines **3** with 2 equiv of a nonodoriferous *S*-(2-naphthylmethyl)thioimidate[39,40] in EtOH/MeCN (Scheme 4). Analogous to the literature,[39] this reaction gave good yields (60−80%) when the diamine was unsubstituted or substituted with electron-donating groups; however, when the diamine was substituted with the deactivating chloro group, the yield was reduced considerably (25%), and with the strongly deactivating trifluoromethyl group, the diamidine could not be isolated.

Biological Results

Melting temperatures were measured for the compounds **5** and **6** bound to poly dA•dT to obtain a qualitative evaluation of the DNA binding affinity of these drug candidates (Table 1). Since several of the compounds bound very strongly to poly dA•dT (Table 1), the interaction of these compounds with the Dickerson-Drew dodecamer d $(CGCGAATTCGCG)_2$, a DNA with a different and shorter AT sequence and different groove characteristics, was also studied. The reduced binding of the drugs to the dodecamer, reflected by the lower ΔTm values of the drug-dodecamer complexes (Table 1), allowed for a better relative comparison of the DNA binding affinity of these putative minor-groove binding compounds. Although ΔTm values provide only a relative ranking of the compounds binding affinities, we have found that they are directly correlated with binding constants for a set of related diphenylfuran dications.[41]

The parent diguanidino compound **5a** showed a strong affinity for DNA as judged by the ΔTm values for both poly dA•dT (21.6) and the dodecamer (10.8). These values compare well to those (25 and 11.7, respectively) previously reported[8] for the parent diamidine, 2,5-bis-[4-amidinophenyl]furan (furamidine), suggesting little difference in affinity of the amidine and guanidine cationic centers within the 2,5-diarylfuran system. Based on the comparison of ΔTm values for binding to the dodecamer for the parent diguanidine **5a** and for the various parent reversed diamidines **6a**−**6d**, several interesting effects resulting from structural variation of the terminal groups are noted. First, reversed diamidines bearing phenyl (**6b**) or cyclohexyl (**6c**) terminal groups showed an increase in affinity over that of the parent diguanidine **5a**. In a related series of diamidines,

Table 1. In Vitro Antimicrobial Activities and DNA Binding Results for 2,5-Diarylfuran Dicationic Molecules **5** and **6**[c]



			C. albicans		*A. fumigatus*			DNA affinity[b]	
compd no.	X_1X_2	R	MIC (μg/mL)	MFC (μg/mL)	MIC (μg/mL)	MFC (μg/mL)	*M. tub.* MIC (μg/mL)	ΔTm (AT)	ΔTm (oligo)
5a	$X_1 = X_2 = H$	NHAm	12.5	25	100	>100	3.13	21.6	10.8
6a	$X_1 = X_2 = H$	NHC(=NH)−2-Pyr	nt	nt	nt	nt	1.56	19.6	7.5
6b	$X_1 = X_2 = H$	NHC(=NH)Ph	25	50	nt	nt	1.56	28.6	15.0
6c	$X_1 = X_2 = H$	NHC(=NH)-c-Hex	>100	nt	100	>100	≤6.25	26.7	12.8
6d	$X_1 = X_2 = H$	NHC(=NH)CH_3	>100	nt	100	>100	nd[a]	15.9	6.0
5b	$X_1 = H, X_2 = CH_3$	NHAm	1.04	2.08	33.4	33.4	≤1	17.8	6.9
5c	$X_1 = H, X_2 = OCH_3$	NHAm	10	100	100	100	16	15.2	2.8
5d	$X_1 = H, X_2 = Cl$	NHAm	10	100	100	100	4	26.1	4.7
5e	$X_1 = H, X_2 = CF_3$	NHAm	10	10	100	100	8	5.9	0
5f	$X_1 = X_2 = CH_3$	NHAm	nt	nt	nt	nt	nt	2.7	1.4
6e	$X_1 = H, X_2 = CH_3$	NHC(=NH)Ph	3.12	6.25	nt	nt	3.13	24.9	7.8
6f	$X_1 = H, X_2 = CH_3$	NHC(=NH)−2-Pyr	10	10	10	100	≤1	22.6	8.9
6g	$X_1 = H, X_2 = CH_3$	NHC(=NH)−2-Qu	100	100	100	nt	nt	7.5	1.1
6h	$X_1 = H, X_2 = CH_3$	NHC(=NH)−2-Pyr-5-CH_3	≤1	10	10	>100	2	24.3	10.8
6i	$X_1 = H, X_2 = OCH_3$	NHC(=NH)−2-Pyr	≤1	≤1	≤1	≤1	≤1	19.0	7.8
6j	$X_1 = H, X_2 = Cl$	NHC(=NH)−2-Pyr	100	>100	>100	nt	8	5.2	0
6k	$X_1 = X_2 = CH_3$	NHC(=NH)−2-Pyr	10	>100	10	>100	nt	5.7	1.2
	furamidine		6.25	25	nt	nt		25	11.7
	fluconazole		0.25	NA					
	rifampin						0.062		

[a] No activity observed at 6.25 μg/mL. [b] AT = poly dA•dT; oligo = d(CGCGAATTCGCG)$_2$. [c] nt = not tested; nd = not determined.

such an increase in affinity with increasing bulk of terminal groups was attributed to increased van der Waals interactions of the terminal groups with the walls of the minor-groove and such is likely the case in this system.[9] Interestingly, the ΔTm value for the compound with a terminal 2-pyridyl group (**6a**) is significantly lower than that for its phenyl counterpart **6b**. The lower affinity of **6a** may suggest a different binding mode or different base pair selectivity for the two closely related dicationic analogues. However, introduction of a methyl group onto each of the two central phenyl rings of the amidine with a terminal phenyl group, **6e**, resulted in lowering of the ΔTm value to one similar to that of its pyridyl counterpart, **6f**. Finally, the use of a small alkyl terminal group, a methyl group as found in **6d**, led to a significant drop in binding affinity.

The placement of a single substituent on each of the two phenyl rings of the 2,5-diphenylfuran framework produced striking differences in ΔTm values for both the diguanidine and reversed diamidine series. For the diguanidine series, it is noted that placement of single substituent of roughly the same size but of differing electronic properties (e.g., Me, OMe, Cl, CF_3) on the phenyl rings resulted in a lowering of the ΔTm values; compare the values of **5a** with **5b**−**5e**. The most dramatic effect was observed for the strongest electron-withdrawing group, the CF_3 of **5e**, which reduced the ΔTm value (dodecamer) to zero. This seems likely to be a p*K* effect and may reflect the presence of nonprotonated quanidinium groups under the test conditions, which would greatly affect the DNA binding affinity. The introduction of two methyl groups on the aryl rings (**5f**) also dramatically reduced the ΔTm value from that of the parent diguanidine **5a**. The presence of two methyl groups on each aryl ring of these furan systems is thus not well accommodated in the DNA minor groove, perhaps because of the torsional twist that such substitution would induce on the system.

The ΔTm values for a series of reversed diamidines with terminal 2-pyridyl groups (**6a**, **6f**, **6h**−**k**) showed a different sensitivity to substituents. In this case, the introduction of a single substituent on each of the two phenyl rings of the 2,5-diarylfuran framework caused little effect on the ΔTm values when the substituent was methyl (**6f**) or methoxy (**6i**). However, introduction of a chloro group (**6j**) resulted in significant reduction of the value, perhaps in part due to a p*K* effect. Interestingly, the detrimental effect of the chloro group on the ΔTm was much greater for the pyridyl derivative **6j** than for the analogous guanidine **5d**, perhaps due to the lower basicity of the reversed amidine in comparison to the guanidine. In agreement with the results from the diguanidine series, the introduction of two methyl groups on each of the core phenyl rings (**6k**) also dramatically reduced the DNA affinity. Interestingly, replacement of the terminal 2-pyridyl with a 2-quinolyl group (**6g**) resulted in a significant reduction of the ΔTm, suggesting definite limits on the dimensions of the terminal group. On the other hand, the introduction of a methyl group on the terminal pyridyl ring (**6h**) slightly enhanced the binding affinity.

The antimicrobial data for these compounds are also summarized in Table 1. The greatest activity among the diguanidino compounds was found for **5b**, which showed good in vitro activity against both *C. albicans* and *M. tuberculosis*. These compounds gave MIC values of approximately 1 μg/mL against both organisms and was fungicidal against *C. albicans*. The reversed amidines bearing a terminal alkyl group (**6c**−**d**), in general, did not show significant antimicrobial activity, although compound **6c**, with the larger cyclohexyl group, did exhibit some activity against *M. tuberculosis*. In con-

Table 2. Evaluation of **6h** Against an Expanded Fungus Panel[a]

genus, species, isolate number	MIC 80%	MIC 100%	MFC
Aspergillus flavus 194.99	3.12	6.25	>100
Aspergillus flavus 107.96	3.12	50	>100
Aspergillus flavus 141.88	3.12	50	>100
Aspergillus fumigatus 168.95	10	50	>100
Aspergillus fumigatus 182.99	3.12	50	>100
Aspergillus fumigatus 119.00	3.12	50	>100
Aspergillus fumigatus 165.86	50	50	>100
Aspergillus fumigatus 153.90	3.12	50	>100
Fusarium solani 152.89	3.12	50	50
Rhizopus arrhizus 117.89	0.78	1.56	1.56
Candida albicans 116.98	1.56	1.56	>100
Candida albicans 159.95	0.79	1.58	3.12
Candida albicans 149.97	0.78	1.56	6.25
Candida albicans 156.97	1.56	3.15	>100
Candida albicans 126.97	1.56	3.12	3.12
Candida albicans 117.00	0.78	3.12	25
Candida albicans A39	1.56	1.56	25
Cryptococcus neoformans H99	1.56	1.56	>100

[a] MIC and MFC values are μg/mL. MIC 80% = 80% of inoculum is inhibited. MIC 100% = 100% of inoculum is inhibited. MFC = minimum fungicidal concentration.

trast, the amidines bearing a terminal phenyl group (**6b**, **6e**) showed good activity against *M. tuberculosis* (MIC = 1.56 and 3.13 μg/mL, respectively) as well as some antifungal activity. In addition, four of the compounds containing a terminal pyridyl group (**6a**, **6f**, **6h**, and **6i**) showed promising activity against *M. tuberculosis*, with MIC values ranging from 1.0 to 2.0 μg/mL. Compounds **6h** and **6i** also showed activity at the MIC level of ≤ 1.0 μg/mL against *C. albicans*, and **6i** showed a similar level of activity against *Aspergillus fumigatus*. Finally, it is of interest to note that the pyridyl-substituted compounds which exhibited the greatest antimicrobial activity also showed at least moderate DNA affinity, a correlation which may offer insight into the mode of action of these compounds.

To evaluate the spectrum of antifungal activity of these compounds, pyridyl-substituted diamidines **6h** and **6i** were selected for studies against other pathogenic fungi (Table 2). Compound **6h** was quite effective against an expanded panel of *C. albicans*, while exhibiting fungicidal activity against several strains. This compound was also quite active against *Cryptococcus neoformans* and *Rhizopus arrhizus*, while being fungicidal against the latter. In contrast, **6h** was not very active gainst the mold *Fusarium solani* or the two *Aspergillus* species. Compound **6i** did not show significant activity in the expanded fungus panel.

In conclusion, the data presented in this report indicate that both the diguanidines and the reversed diamidines in the 2,5-diarylfuran series have strong DNA binding properties, which are highly dependent on structure. Substituents on the central phenyl rings of the 2,5-diarylfuran framework as well as on the terminal cationic centers have significant influences on DNA-binding affinity. It seems likely that the different series bind by different modes; an understanding of these differences in DNA interactions awaits the results of various biophysical studies that are in progress. Compounds from both of these new classes of dicationic antimicrobial agents show promising in vitro results. It is striking that compounds in these classes show both antifungal and antimycobacterial activity. In addition, they show the potential to be broad-spectrum antifungal agents. Finally, the clinical potential of these types of compounds awaits the results of additional structure−activity studies and the in vivo evaluation of their efficacies.

Experimental Section

The difference in thermal melting values (ΔTm) were determined, and DNA samples were prepared as previously described.[9,10]

***Mycobacterium tuberculosis* Susceptibility Testing.** The compounds were tested against *M. tuberculosis* H37Rv in BACTEC 12B medium using a fluorometric broth microdilution assay, the Microplate Alamar Blue Assay (MABA).[41] Compounds were initially assessed at 6.25 ug/mL, and those effecting a reduction in fluorescence of at least 90% relative to untreated cultures were further evaluated for MIC by testing at lower concentrations. The MIC was defined as the lowest concentration of compound effecting a reduction of ≥90% of the relative fluorescence units relative to a control culture. Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF)) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases.

Antifungal Test Organisms. The fungi used in this study for all the compounds in Table 1 included two reference strains, *C. albicans* A39 and *A. fumigatus* (strain 168.95). Expanded studies on **6h**−**i** employed the fungi listed in Table 2.

Medium. Antifungal susceptibility testing was performed with RPMI 1640 medium (Sigma Chemical Co., St. Louis, MO) with glutamine, but without sodium bicarbonate, and was buffered at pH 7.0 with 0.165 M morpholinopropanesulfonic acid.

Antifungal in Vitro Susceptibility Testing. Experiments for determination of MICs of yeasts were performed by the broth macrodilution method according to the recommendations of the National Committee for Clinical Laboratory Standards.[42] The only difference compared to the standardized method was the choice of drug dilutions, which ranged from 100 to 0.09 μg/mL. Briefly, this method specifies the use of an inoculum grown at 35 °C and adjusted to a concentration of 0.5×10^3 to 2.5×10^3 CFU/mL, incubation of the culture at 35 °C, and reading at 48 h for all yeasts except for *C. neoformans*, for which the results are interpreted at 72 h. The MIC was defined as the culture with the lowest drug concentration in which a visual turbidity less than or equal to 80% inhibition compared to that produced by the growth control tube was observed.

The minimum fungicidal concentration (MFC) was determined by plating 100 μL aliquots from tubes showing complete inhibition of growth on Sabouraud agar plates. The lowest drug concentration that yielded three or fewer colonies was recorded as the MFC.

Moulds were tested by the same method,[42] but with the following modifications. Isolates were grown on Sabouraud dextrose agar at 30 °C; after adequate sporulation occurred (4−14 days), conidia were harvested by flooding the colonies with a sterile solution of 0.85% NaCl and 0.05% Tween 80 in sterile distilled water. Inocula were prepared with a hemocytometer for counting and were then diluted with RPM1 1640 medium to obtain a final inoculum size of approximately 0.5×10^3 to 2.5×10^3 CFU/mL. The inoculum size was verified by plating an aliquot of the inoculum. The cultures were incubated at 30 °C for 48 to 72 h or until growth in the control tube was visible.

Chemistry. Melting points were determined with a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance spectra were recorded on a Varian Unity+300 or a Varian VRX 400 instrument, with peak assignments relative to residual DMSO (2.49 ppm) or $CHCl_3$ (7.24 ppm). Mass spectra were recorded on a VG Instruments 70-SE spectrometer at the Georgia Institute of Technology, Atlanta, GA. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Unless otherwise stated, all reagent chemicals and solvents (including anhydrous

solvents) were purchased from Aldrich Chemical Co., Fisher Scientific, or Lancaster Synthesis and used as received. Acetonitrile (CaH_2), triethylamine (CaH_2), and ethanol (Mg/I_2) were distilled from the indicated drying agent. 2,6-Dimethyl-4-nitrobromobenzene[44,45] and *S*-(2-naphthylmethyl) thioacetimidate[39] were prepared according to the literature.

Preparation of 2,5-Bis(4-nitrophenyl)furans 2. The following representative procedure is a slight variation of that previously described.[36]

2,5-Bis(2-methyl-4-nitrophenyl)furan (2b). To a solution of 2-bromo-5-nitrotoluene (4.32 g, 20 mmol) and tetrakis-(triphenylphospine)palladium(0) (0.40 g) in anhydrous 1,4-dioxane (50 mL) was added 2,5-bis(tri-*n*-butylstannyl)furan (6.46 g, 10 mmol), and the mixture was heated overnight under nitrogen at 95−100 °C. The resulting orange suspension was diluted with hexanes (15 mL), cooled to room-temperature, and filtered to give, after rinsing with hexanes, an orange solid (3.10 g), mp 241−243 °C. The product was recrystallized from DMF (100 mL) to give a bright orange fluffy solid (2.87 g, 85%), mp 242−243 °C. ^{1}H NMR (DMSO-d_6): 2.69 (s, 6H), 7.31 (s, 2H), 8.12 (m, 4H), 8.23 (s, 2H). Anal. Calcd. for $C_{18}H_{14}N_2O_5$ (338.31): C, H, N.

2,5-Bis(4-nitrophenyl)furan (2a). Yield: 88%; orange fluffy solid; mp 269−270 °C lit.[46] mp 270−272 °C.

2,5-Bis(2-methoxy-4-nitrophenyl)furan (2c). Yield: 77%; bright orange granular solid; mp 308−310 °C (DMF).^{1}H NMR (DMSO-d_6): 4.10 (s, 6H), 7.37 (s, 2H), 7.90 (s, 2H), 7.94 (d, 2H), 8.22 (d, 2H). Anal. Calcd. for $C_{18}H_{14}N_2O_7 \cdot 0.1H_2O$ (372.11): C, H, N.

2,5-Bis(2-chloro-4-nitrophenyl)furan (2d). Yield: 71%; fluffy orange solid; mp 247−247.5 °C (DMF/MeOH).^{1}H NMR (DMSO-d_6): 7.70 (s, 2H), 8.29 (dd, J = 8.8, 2.2 Hz, 2H), 8.36 (d, J = 8.8 Hz, 2H), 8.43 (d, J = 2.2 Hz, 2H). Anal. Calcd. for $C_{16}H_8Cl_2N_2O_5$ (379.15): C, H, N.

2,5-Bis(4-nitro-2-trifluoromethylphenyl)furan (2e). Yield: 74%; fluffy golden needles; mp 158.5−159 °C (EtOH). ^{1}H NMR (DMSO-d_6): 7.38 (s, 2H), 8.24 (d, J = 8.7 Hz, 2H), 8.57 (d, J = 2.4 Hz, 2H), 8.62 (dd, J = 8.6, 2.4 Hz, 2H). Anal. Calcd. for $C_{18}H_8F_6N_2O_5$ (446.26): C, H, N.

2,5-Bis(2,6-dimethyl-4-nitrophenyl)furan (2f). Yield: 65%; yellow needles; mp 156.5−157.5 °C (DMF/EtOH/H_2O). ^{1}H NMR (DMSO-d_6): 2.34 (s, 12H), 6.85 (s, 2H), 8.04 (s, 4H). Anal. Calcd. for $C_{20}H_{18}N_2O_5$ (366.36): C, H, N.

Preparation of 2,5-Bis(4-aminophenyl)furans 3. The following procedure is representative.

2,5-Bis(4-amino-2-methylphenyl)furan (3b). To a suspension of the bis-nitro derivative **2b** (2.87 g) in EtOAc (90 mL) and dry EtOH (10 mL) was added Pd/C (10%) (0.40 g), and the mixture was hydrogenated on a Parr apparatus at an initial pressure of ∼50 psi. After the uptake of hydrogen subsided (generally 3−6 h), the resulting solution was filtered over Celite, and the pale yellow to colorless filtrate was concentrated in vacuo to near dryness to give, after dilution with hexanes, the pure diamine as a pale yellow/tan solid (2.17 g, 91%), mp 174−176 °C, which required no purification. ^{1}H NMR (DMSO-d_6): 2.33 (s, 6H), 5.15 (br s, 4H), 6.42 (s, 2H), 6.46 (m, 4H), 7.35 (d, 2H). MS (EI): m/z 278 (M^+).

2,5-Bis(4-aminophenyl)furan (3a). Yield: 94%; pale yellow/tan solid; mp 218−221 °C, lit.[46] mp 213-216 °C. MS (EI): m/z 250 (M^+).

2,5-Bis(4-amino-2-methoxyphenyl)furan (3c). The original oil was reconcentrated with benzene to give a yellow/tan solid which was triturated with ether. Yield: 79%; mp 201−202.5 °C. ^{1}H NMR (DMSO-d_6): 3.80 (s, 6H), 5.25 (br s, 4H), 6.24 (dd, J = 8.3, 2.0 Hz, 2H), 6.30 (d, J = 1.9 Hz 2H), 6.56 (s, 2H), 7.48 (d, J = 8.4 Hz, 2H). MS (EI): m/z 310 (M^+).

2,5-Bis(4-amino-2-trifluoromethylphenyl)furan (3e). Original red oil crystallized from EtOAc/hexanes in two crops as a red/orange solid. Combined yield: 81%; mp (first/major crop) 89.5−91 °C; mp (second crop) 91.5−92 °C. ^{1}H NMR (DMSO-d_6): 5.79 (br s, 4H), 6.52 (s, 2H), 6.82 (dd, J = 8.4, 2.4 Hz, 2H), 6.98 (d, J = 2.2 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H). MS (EI): m/z 386 (M^+).

2,5-Bis(4-amino-2,6-dimethylphenyl)furan (3f). Yield: 99%; white fluffy solid; mp 144.5−146 °C. ^{1}H NMR (DMSO-d_6): 2.01 (s, 6H), 5.06 (br s, 4H), 6.24 (s, 2H), 6.29 (s, 4H). MS (EI): m/z 306 (M^+).

2,5-Bis(4-amino-2-chlorophenyl)furan (3d). To a suspension of the corresponding bis-nitro derivative **2d** (1.22 g, 3.2 mmol) in dry EtOH (100 mL) and DMSO (20 mL) was added $SnCl_2 \cdot 2H_2O$ (5.80 g, 25.7 mmol), and the mixture was heated under nitrogen at 80 °C. After 4−5 h, TLC showed that starting material had been consumed, and thus the mixture was cooled, neutralized with NaOH (aq), and extracted with EtOAc. The extract was washed with water and brine, then dried (Na_2SO_4), and concentrated. The resulting oil was crystallized from benzene/hexane with partial concentration to give a light brown solid (0.74 g, 71%), mp 191.5−193 °C. Catalytic hydrogenation was not explored. ^{1}H NMR (DMSO-d_6): 5.60 (br s, 4H), 6.61 (dd, J = 8.6, 2.2 Hz, 2H), 6.68 (d, J = 2.2 Hz 2H), 6.82 (s, 2H), 7.56 (d, J = 8.6 Hz, 2H). MS (EI): m/z 318 (M^+).

Preparation of 2,5-Bis(4-*N*,*N*′-di-BOCguanidinophenyl)furan Derivatives 4 (Scheme 2). The following experimental is representative. The yields ranged from 62 to 89%.

2,5-Bis(4-*N*,*N*′-di-BOCguanidinophenyl)furan (4a). To a room-temperature solution of 2,5-bis(4-aminophenl)furan (0.626 g, 2.5 mmol) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.56 g, 5.3 mmol) in anhydrous DMF was added triethylamine (1.59 g, 15.7 mmol) followed by mercury-(II) chloride (1.57 g, 5.8 mmol), and the resulting suspension was stirred at room-temperature for 22 h. After diluting with CH_2Cl_2 and sodium carbonate solution, the suspension was filtered over Celite, and the filtrate was washed well with water (3×) and finally with brine. After drying (Na_2SO_4), the solvent was removed in vacuo, and the residue was diluted with MeOH to give the BOC-protected bis-guanidine as a pale yellow solid. The collected product was purified by reprecipitation from CH_2Cl_2/MeOH (with partial concentration) to give a fluffy yellow solid (1.25 g, 68%), mp >400 °C dec. ^{1}H NMR ($CDCl_3$): 1.50 and 1.53 (2s, 36H), 6.65 (s, 2H), 7.66 (s, 8H), 10.38 (br s, 2H), 11.61 (br s, 2H).

Deprotection of *N*,*N*′-Di-BOCguanidines. The following procedure is representative.

2,5-Bis(4-guanidinophenyl)furan Dihydrochloride (5a). A solution of the corresponding *N*,*N*′-di-BOCguanidine (1.19 g, 1.62 mmol) in CH_2Cl_2 (15 mL) was diluted with dry EtOH (10 mL) and saturated at ice−water bath temperature with anhydrous HCl. The solution was then stirred at room-temperature for 2−3 days (drying tube), with the product slowly precipitating (shorter reaction times generally gave incomplete deprotection). After removing the solvent, the solid was dissolved in hot EtOH, and the solution was filtered and then concentrated to near dryness to give a suspension. After dilution with ether, the solid was collected and dried in vacuo at 50−60 °C for 2 days to yield the bis-guanidine dihydrochloride as an off-white/tan solid (0.66 g, quantitative), mp >300 °C dec. ^{1}H NMR (DMSO-d_6): 7.12 (s, 2H), 7.31 (d, 4H), 7.58 (br s, 8H), 7.86 (d, 4H), 10.09 (br s, 2H). MS (FAB, thioglycerol): m/z 335.3 (MH^+, 100). Anal. Calcd. for $C_{18}H_{18}N_6O \cdot 2HCl \cdot 0.25EtOH$ (407.30): C, H, N. In some cases, the product only solidified after completely removing the solvent and placing the residue under high vacuum.

2,5-Bis(4-guanidino-2-methylphenyl)furan Dihydrochloride (5b). Tan solid, mp 265−271 °C dec. ^{1}H NMR (DMSO-d_6): 2.53 (s, 6H), 6.93 (s, 2H), 7.17 (m, 4H), 7.56 (br s, 8H), 7.82 (d, 2H), 10.06 (br s, 2H). MS (FAB, thioglycerol): m/z 363.3 (MH^+, 100). Anal. Calcd. for $C_{20}H_{22}N_6O \cdot 2HCl \cdot 1.5H_2O \cdot 0.66EtOH$ (496.93): C, H, N.

2,5-Bis(4-guanidino-2-methoxyphenyl)furan Dihydrochloride (5c). Light brown hygroscopic solid. ^{1}H NMR (DMSO-d_6): 3.95 (s, 6H), 6.92 (dd, 2H), 6.99 (d, 2H), 7.02 (s, 2H), 7.58 (br s, 8H), 7.95 (d, 2H), 10.08 (br s, 2H). MS (EI): m/z 352 ($M^+ - NH_2CN$, 38.0), 310 (100), 267 (38.9), 251 (8.8), 155 (18.7). Anal. Calcd. for $C_{20}H_{22}N_6O_3 \cdot 2HCl \cdot 1.0H_2O \cdot 0.33EtOH$ (500.57): C, H, N.

2,5-Bis(2-chloro-4-guanidinophenyl)furan Dihydrochloride (5d). Tan solid, mp 300−304 °C dec. ^{1}H NMR (DMSO-d_6): 7.31 (s, 2H), 7.33 (d, 2H), 7.47 (s, 2H), 7.72 (br s, 8H), 8.04 (d, 2H). MS (DCI, ammonia): *m/z* 365, 363, 361 ($MH^+ - NH_2CN$, 8, 52, 78), 323, 321, 319 (11, 66, 100). Anal. Calcd. for $C_{18}H_{16}Cl_2N_6O\cdot 2HCl\cdot 0.5H_2O$ (485.21): C, H, N, Cl.

2,5-Bis(4-guanidino-2-trifluoromethylphenyl)furan Dihydrochloride (5e). Orange/red hygroscopic solid. ^{1}H NMR (DMSO-d_6): 6.99 (s, 2H), 7.63 (d, 2H), 7.69 (s, 2H), 7.79 (br s, 8H), 7.91 (d, 2H), 10.37 (br s, 2H). MS (CI, isobutane): *m/z* 471 (MH^+, 14), 429 (100), 387 (19). Anal. Calcd. for $C_{20}H_{16}F_6N_6O\cdot 2HCl\cdot 0.67H_2O\cdot 0.67EtOH$ (586.24): C, H, N.

2,5-Bis(4-guanidino-2,6-dimethylphenyl)furan Dihydrochloride (5f). Off-white solid, mp 296−300 °C dec. ^{1}H NMR (DMSO-d_6): 2.20 (s, 12H), 6.56 (s, 2H), 7.01 (s, 4H), 7.57 (br s, 8H), 10.09 (br s, 2H). MS (FAB, thioglycerol): *m/z* 391.2 (MH^+, 100). Anal. Calcd. for $C_{22}H_{26}N_6O\cdot 2HCl\cdot 0.5H_2O$ (472.41): C, H, N.

The original route to the reversed amidines (which was used to prepare **6b**) is as follows (Scheme 3).

2,5-Bis[4-(benzimidoylamino)phenyl]furan Dihydrochloride (6b). To a chilled solution of 2,5-bis(4-aminophenyl)-furan (0.25 g, 1.0 mmol) in dry acetonitrile (10 mL) was added triethylamine (0.22 g, 2.1 mmol) followed dropwise by benzoyl chloride (0.30 g, 2.1 mmol), and the resulting suspension was stirred at room-temperature for 3 h. Water (10 mL) was then added, and the precipitate was collected, rinsed with water, followed by MeOH, and finally dried in vacuo to give 2,5-bis-(4-benzamidophenyl)furan as a tan solid (0.44 g, 96%), mp 312−314.5 °C. ^{1}H NMR (DMSO-d_6): 6.98 (s, 2H), 7.52−7.62 (m, 6H), 7.80 (d, 4H), 7.89 (d, 4H), 7.97 (d, 4H), 10.33 (br s, 2H).

The intermediate bis(benzamide) (0.44 g, 0.96 mmol) was suspended in anhydrous dichloromethane (40 mL) and treated with freshly distilled thionyl chloride (0.68 g, 5.7 mmol) along with 2 drops of DMF, and the mixture was refluxed with vigorous stirring until a solution was obtained (20 h). The solution was then concentrated in vacuo to give a yellow solid, which was coevaporated with dry benzene. The obtained imidoyl chloride was dissolved in anhydrous dichloromethane (40 mL), and the solution was saturated at ice/water-bath temperature with anhydrous ammonia and sealed. After stirring overnight at room-temperature, the turbid mixture was concentrated to give a yellow solid, which was triturated with 0.5 N NaOH, collected, and air-dried. This free-base (0.44 g, 100%) was dissolved in boiling EtOH (50 mL), filtered, and at ice-bath temperature was treated with dry HCl. After dilution with ether, the solution was concentrated (high vacuum) to give the dihydrochloride as an orange hygroscopic solid, mp 242−248 °C. ^{1}H NMR (DMSO-d_6): 7.26 (s, 2H), 7.58 (d, 4H), 7.67 (t, 4H), 7.78 (t, 2H), 7.95 (d, 4H), 8.03 (d, 4H), 9.12 (br s, 2H), 9.94 (br s, 2H), 11.66 (br s, 2H). MS (EI): *m/z* 456 (M^+, 100), 353 (63), 250 (62), 221 (16), 130 (15), 103 (41), 76 (14), 44 (22). *Anal*. Calcd. for $C_{30}H_{24}N_4O\cdot 2HCl\cdot 0.5H_2O\cdot 0.1(C_2H_5)_2O$ (545.87): C, H, N.

Alternative Preparation of Bis{[alkyl(or aryl)imino]-aminophenyl}furan Derivatives 6 (Scheme 4). The following experimental is representative. In some cases, the product was purified by recrystallization.

2,5-Bis[2-methyl-4-(2-pyridylimino)aminophenyl]-furan (6f). To a solution of 2,5-bis(4-amino-2-methylphenyl)-furan (0.30 g, 1.08 mmol) in dry MeCN (5 mL) was added dry EtOH (15 mL), and the solution was chilled briefly in an ice−water bath. *S*-(2-Naphthylmethyl)thiobenzimidate hydrobromide (0.815 g, 2.27 mmol) was then added, and the mixture was stirred overnight at room-temperature. The resulting solution was concentrated to an oil, which was triturated with ether to give a yellow solid. The solid was collected, dissolved in EtOH, and basified with NaOH (1 N), and the free base was extracted into EtOAc. After drying (Na_2SO_4) and partially concentrating, the resulting suspension was diluted with ether to give a fluffy yellow solid (0.36 g, 69%), mp 188−189 °C, which required no purification.^{1}H NMR (DMSO-d_6): 2.51 (s, 6H), 6.60 (br s, 4NH), 6.77 (s, 2H), 6.87 (m, 4H), 7.55 (dd, 2H), 7.74 (d, 2H), 7.95 (m, 2H), 8.31 (d, 2H), 8.63 (d, 2H).

To prepare the hydrochloride salt, the free base was suspended in EtOH (40 mL) and treated with dry HCl gas for 5−10 min at ice-bath temperature. The resulting solution was then concentrated in vacuo to near dryness to give an orange suspension which was diluted with ether (40 mL) and filtered to yield an orange powder (0.40 g), mp >180 °C dec. ^{1}H NMR (DMSO-d_6): 2.62 (s, 6H), 7.08 (s, 2H), 7.44 (d, 2H), 7.47 (s, 2H), 7.85 (dd, 2H), 7.99 (d, 2H), 8.22 (t, 2H), 8.49 (d, 2H), 8.89 (d, 2H), 9.36 (br s, 2H), 10.13 (br s, 2H), 11.88 (br s, 2H). MS (EI): *m/z* 486 (M^+, 100), 382 (77.9), 278 (12.8), 104 (20.0), 78 (8.8), 43 (28.9). Anal. Calcd. for $C_{30}H_{26}N_6O\cdot 3.5HCl\cdot 0.5H_2O$ (623.20): C, H, N, Cl.

2,5-Bis[4-(2-pyridylimino)aminophenyl]furan (6a). Free base: yellow crystalline solid, mp 221−223 °C (DMF/EtOH/H_2O). Yield: 65% ^{1}H NMR (DMSO-d_6): 6.80 (br s, 4NH), 6.94 (s, 2H), 7.03 (d, 4H), 7.56 (m, 2H), 7.77 (d, 4H), 7.96 (m, 2H), 8.32 (d, 2H), 8.64 (m, 2H). Hydrochloride: Orange powder, mp >175 °C dec ^{1}H NMR (DMSO-d_6): 7.26 (s, 2H), 7.58 (d, 4H), 7.85 (dd, 2H), 8.03 (d, 4H), 8.22 (t, 2H), 8.52 (d, 2H), 8.89 (d, 2H), 9.39 (br s, 2H), 10.16 (br s, 2H), 11.91 (br s, 2H). MS (EI): *m/z* 458 (M^+, 100), 354 (49.1), 250 (27.6), 221 (8.9), 130 (9.4), 105 (13.6), 78 (8.6). Anal. Calcd. for $C_{28}H_{22}N_6O\cdot 3.5HCl$ (586.12): C, H, N, Cl.

2,5-Bis[4-(cyclohexylimino)aminophenyl]furan (6c). Free base: pale yellow needles, mp 242−243 °C dec (EtOAc). Yield: 17%. ^{1}H NMR (DMSO-d_6): 1.18−1.90 (m, 20H), 2.14 (m, 2H), 5.71 (br s, 4NH), 6.82 (s, 2H), 7.63 (d, 4H). [In addition, a 41% yield of the monoamidine/monoamine (free base: yellow solid, mp 195−196 °C) was isolated by chromatography on silica (EtOAc−MeOH, 9:1). The insoluble nature of the reaction medium was the likely cause of the incomplete reaction.] Dihydrochloride: tan/peach solid, mp 244−248 °C dec. ^{1}H NMR (DMSO-d_6): 1.27 (m, 6H), 1.63−1.96 (m, 14H), 2.72 (m, 2H), 7.22 (s, 2H), 7.40 (d, 4H), 7.96 (d, 2H), 8.60 (br s, 2H), 9.34 (br s, 2H), 11.39 (br s, 2H). MS (FAB, thioglycerol): *m/z* 469.4 (MH^+, 100). Anal. Calcd. for $C_{30}H_{38}N_4O\cdot 2HCl\cdot 0.75EtOH\cdot 0.25H_2O$ (580.60): C, H, N.

2,5-Bis[4-(benzimidoyl)amino-2-methylphenyl]furan (6e). Free base: yellow crystalline solid. Yield: 60%. ^{1}H NMR (DMSO-d_6): 2.48 (s, 6H), 6.50 (br s, 4NH), 6.75 (s, 2H), 6.84 (s, 4H), 7.44 (m, 6H), 7.71 (d, 2H), 7.95 (d, 4H). Hydrochloride: orange/yellow hygroscopic solid. ^{1}H NMR (DMSO-d_6): 2.61 (s, 6H), 7.03 (s, 2H), 7.38−7.44 (m, 4H), 7.63−7.68 (m, 4H), 7.75−7.80 (m, 2H), 7.94 (d, 6H). MS (EI): *m/z* 484 (M^+, 100), 381 (87.2), 278 (37.9), 235 (5.4), 218 (3.1), 190 (5.5), 144 (11.1), 103 (32.8), 76 (9.3). Anal. Calcd. for $C_{32}H_{28}N_4O\cdot 2HCl\cdot 0.66H_2O$ (569.39): C, H, N.

2,5-Bis[2-methyl-4-(2-quinolylimino)aminophenyl]-furan (6g). Free base: orange powdery crystals, mp 168−169 °C (EtOH). Yield: 52%. ^{1}H NMR (DMSO-d_6): 2.54 (s, 6H), 6.80 (s, 2H), 6.95 (m, 4H), 7.69 (m, 2H), 7.78 (d, 2H), 7.84 (m, 2H), 8.07 (d, 2H), 8.12 (d, 2H), 8.44 (d, 2H), 8.50 (d, 2H). Dihydrochloride: orange solid, mp >185 °C dec. ^{1}H NMR (DMSO-d_6): 2.65 (s, 6H), 7.10 (s, 2H), 7.50 (m, 4H), 7.85 (m, 2H), 8.01 (m, 2H), 8.20 (d, 2H), 8.26 (d, 2H), 8.46 (d, 2H), 8.80 (d, 2H), 9.44 (br s, 2H), 10.21 (br s, 2H), 11.98 (br s, 2H). MS (FAB, thioglycerol): *m/z* 587.2 (MH^+, 100). Anal. Calcd. for $C_{38}H_{30}N_6O\cdot 2.0HCl\cdot 1.75H_2O$ (691.13): C, H, N, Cl.

2,5-Bis[2-methyl-4-(5-methyl-2-pyridylimino)amino-phenyl]furan (6h). Free base: yellow crystalline solid, mp 156−158 °C (Et_2O/hexanes). Yield: 74%. ^{1}H NMR (DMSO-d_6): 2.37 (s, 6H), 2.50 (s, 6H), 6.55 (br s, 4NH), 6.75 (s, 2H), 6.85 (m, 4H), 7.70−7.76 (m, 4H), 8.18 (d, 2H), 8.45 (s, 2H). Hydrochloride: orange solid, mp >175 °C dec. ^{1}H NMR (DMSO-d_6): 2.49 (s, 6H), 2.62 (s, 6H), 7.08 (s, 2H), 7.43 (d, 2H), 7.47 (s, 2H), 7.85 (dd, 2H), 7.98 (d, 2H), 8.03 (d, 2H), 8.42 (d, 2H), 8.74 (s, 2H), 9.29 (br s, 2H), 10.07 (br s, 2H), 11.83 (br s, 2H). MS (EI): *m/z* 514 (M^+, 19.2), 396 (100), 278 (34.5), 144 (8.0), 118 (33.6), 91 (13.6), 43 (22.8). Anal. Calcd. for $C_{32}H_{30}N_6O\cdot 3.25HCl\cdot 0.75H_2O$ (646.62): C, H, N, Cl.

2,5-Bis[2-methoxy-4-(2-pyridylimino)aminophenyl]-furan (6i). Free base: Bright yellow crystalline solid, mp 196−

197 °C (EtOAc/Et_2O). Yield: 75%. ^{1}H NMR (DMSO-d_6): 3.92 (s, 6H), 6.64 and 6.67 (d, 2H and s, 2H, overlapping a broad NH signal), 6.89 (s, 2H), 7.55 (dd, 2H), 7.86 (d, 2H), 7.95 (m, 2H), 8.32 (d, 2H), 8.63 (d, 2H). Dihydrochloride: brick orange solid, mp >180 °C dec. ^{1}H NMR (DMSO-d_6): 4.00 (s, 6H), 7.16 (s, 2H), 7.18 (d, 2H), 7.34 (s, 2H), 7.85 (dd, 2H), 8.13 (d, 2H), 8.22 (t, 2H), 8.49 (d, 2H), 8.89 (d, 2H), 9.39 (br s, 2H), 10.15 (br s, 2H), 11.89 (br s, 2H). MS (EI): *m*/*z* 518 (M^+, 100), 414 (90.0), 371 (13.3), 310 (12.7), 267 (9.7), 155 (6.02), 104 (25.9), 77 (9.6), 43 (13.6). Anal. Calcd. for $C_{30}H_{26}N_6O\cdot 2.0HCl\cdot 2.0H_2O$ (627.51): C, H, N, Cl.

2,5-Bis[2-chloro-4-(2-pyridylimino)aminophenyl]-furan (6j). Free base: orange crystalline solid, mp 189−190 °C (EtOH). Yield: 25%. ^{1}H NMR (DMSO-d_6): 6.85 (br s, 4NH), 7.02 (dd, 2H), 7.08 (d, 2H), 7.17 (s, 2H), 7.56 (m, 2H), 7.93−7.98 (m, 4H), 8.29 (d, 2H), 8.64 (m, 2H). Dihydrochloride: yellow/orange solid, mp >180 °C dec. ^{1}H NMR (DMSO-d_6): 7.45 (s, 2H), 7.60 (d, 2H), 7.80 (s, 2H), 7.86 (dd, 2H), 8.23 (m, 4H), 8.50 (d, 2H), 8.90 (d, 2H), 9.54 (br s, 2H), 10.23 (br s, 2H), 11.98 (br s, 2H). MS (EI): *m*/*z* 530, 528, 526 (M^+, 13.2, 69.8, 100), 426, 424, 422 (7.9, 48, 72.4), 322, 320, 318 (2.6, 17.4, 26.6). Anal. Calcd. for $C_{28}H_{20}Cl_2N_6O\cdot 2.0HCl\cdot 1.5H_2O$ (627.35): C, H, N, Cl.

2,5-Bis[2,6-dimethyl-4-(2-pyridylimino)aminophenyl]-furan (6k). Free base: pale yellow crystals, mp 206−207 °C (EtOH). Yield: 80%. ^{1}H NMR (DMSO-d_6): 2.19 (s, 12H), 6.47 (s, 2H), 6.55 (br s, 4NH), 6.69 (s, 4H), 7.54 (m, 2H), 7.94 (m, 2H), 8.29 (d, 2H), 8.62 (d, 2H). Hydrochloride: fluffy yellow solid. ^{1}H NMR (DMSO-d_6): 2.28 (s, 12H), 6.68 (s, 2H), 7.28 (s, 4H), 7.84 (m, 2H), 8.21 (t, 2H), 8.48 (d, 2H), 8.88 (d, 2H), 9.37 (br s, 2H), 10.12 (br s, 2H), 11.87 (br s, 2H). MS (EI): *m*/*z* 514 (M^+, 8.5), 410 (38.7), 306 (100), 291 (16.0), 148 (45.4), 104 (56.3). Anal. Calcd. for $C_{32}H_{30}N_6O\cdot 3.75HCl\cdot 0.5H_2O$ (660.35): C, H, N, Cl.

2,5-Bis[4-(acetimidoyl)aminophenyl]furan Dihydrobromide (6d). This compound was purified and characterized as the HBr salt without conversion to the free base. Fluffy tan/orange solid, mp 307−309.5 °C dec (MeOH/EtOAc). Yield: 57%. ^{1}H NMR (DMSO-d_6, 70 °C): 2.37 (s, 6H), 7.17 (s, 2H), 7.40 (d, 4H), 7.94 (d, 4H), 8.52 (br s, 2H), 9.43 (br s, 2H), 11.13 (br s, 2H). MS (FAB, thioglycerol): *m*/*z* 333.2 (MH^+, 100). Anal. Calcd. for $C_{20}H_{20}N_4O\cdot 2.0HBr$ (494.23): C, H, N.

Pyridine-2-thiocarboxamide. According to the general method of Taylor,[47] 2-cyanopyridine (7.28 g, 7.0 mmol) and thioacetamide (10.52 g, 14.0 mmol) were treated with 60 mL of HCl-saturated DMF, and the solution was stirred vigorously in an open flask on an oil bath set initially at 80 °C (the temperature gradually rising to 95 °C over the course of the reaction). After 80 min (TLC monitoring), the orange suspension was cooled, neutralized with concentrated NaOH/ice, and extracted with EtOAc. The extract was washed with water (3×) and concentrated to a brown solid which was triturated with warm water and collected. The product was chromatographed (SiO_2) with EtOAc:hexanes (2:1) to give a yellow crystalline solid (6.36 g, 66%), mp 136−137 °C; lit.[48] mp 137 °C.

5-Methylpyridine-2-thiocarboxamide. Prepared as above from 2-cyano-5-methylpyridine[49] with a reaction time of 30 min. Yield: 59%. Gold crystals, mp 172.5−173 °C. ^{1}H NMR ($CDCl_3$): 2.39 (s, 3H), 7.60 (br s, NH), 7.61 (dd, 1H), 8.31 (d, 1H), 8.57 (d, 1H), 9.42 (br s, NH).

The following new *S*-(2-naphthylmethyl)thioimidates were prepared according to the literature[39] by reaction of the appropriate thioamide with (2-bromomethyl)naphthalene in refluxing $CHCl_3$ (EtOH-free) for 1.5 h.

***S*-(2-Naphthylmethyl)cyclohexanethioimidate·HBr.** Yield: 91%. White solid, mp 192−192.5 °C. ^{1}H NMR (DMSO-d_6): 1.14−1.32 (m, 3H), 1.45−1.53 (m, 2H), 1.63 (d, 1H), 1.76 (d, 2H), 1.87 (d, 2H), 2.84 (t, 1H), 4.73 (s, 2H), 7.53−7.56 (m, 3H), 7.89−7.97 (m, 3H), 8.01 (s, 1H).

***S*-(2-Naphthylmethyl)thiobenzimidate·HBr.** Yield: 94%. White solid, mp 210−212 °C dec. ^{1}H NMR (DMSO-d_6): 4.90 (s, 2H), 7.54−7.62 (m, 2H), 7.62−7.66 (m, 3H), 7.78−7.82 (m, 1H), 7.88−7.99 (m, 5H), 8.06 (s, 1H).

***S*-(2-Naphthylmethyl)-2-pyridylthioimidate·HBr.** Yield: 58%. White fluffy solid, mp 192 °C dec. ^{1}H NMR (DMSO-d_6): 4.80 (s, 2H), 7.53−7.57 (m, 2H), 7.59−7.62 (dd, 1H), 7.76−7.79 (m, 1H), 7.90−7.97 (m, 3H), 8.05 (s, 1H), 8.10−8.14 (m, 1H), 8.26 (d, 1H), 8.78−8.80 (m, 1H).

***S*-(2-Naphthylmethyl)-5-methyl-2-pyridylthioimidate·HBr.** Yield: 65%. White fluffy solid, mp 190−191 °C dec. ^{1}H NMR (DMSO-d_6): 2.42 (s, 3H), 4.79 (s, 2H), 7.53−7.57 (m, 2H), 7.59−7.62 (dd, 1H), 7.90−7.97 (m, 4H), 8.05 (s, 1H), 8.17 (d, 1H), 8.64 (s, 1H).

***S*-(2-Naphthylmethyl)-2-quinolylthioimidate·HBr.** Yield: 23%. Light tan fluffy solid, mp 184−186 °C dec. ^{1}H NMR (DMSO-d_6): 4.73 (s, 2H), 7.53−7.55 (m, 2H), 7.62−7.64 (dd, 1H), 7.78 (t, 1H), 7.87−7.97 (m, 4H), 8.07 (s, 1H), 8.12 (d, 2H), 8.28 (d, 1H), 8.66 (d, 1H). Quinoline-2-thiocarboxamide was prepared from quinoline-2-carbonitrile according to the general method of Taylor.[47]

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Supporting Information Available: Yields, mp, and ^{1}H NMR data for 2,5-bis(4-*N*,*N*′-di-BOCguanidinophenyl)furans **4b**−**f.** This material is available free of charge via the Internet at http://pubs.acs.org.

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