2,4-Diphenyl Furan Diamidines as Novel Anti-*Pneumocystis carinii* Pneumonia Agents

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Dicationic 2,4-bis(4-amidinophenyl)furans **5**−**10** and 2,4-bis(4-amidinophenyl)-3,5-dimethylfurans **14** and **15** have been synthesized. Thermal melting studies revealed high binding affinity of the compounds to poly(dA-dT) and to the duplex oligomer d(CGCGAATTCGCG)$_2$. All of the new compounds were effective against *Pneumocystis carinii* pneumonia in the immunosuppressed rat model with up to 200-fold increase in activity compared to the control compound pentamidine. No toxicity was noted for **5**, **7**−**10** at the dose of 10 μmol/kg/d; however, the isopropyl analogue **7** showed toxicity comparable to pentamidine at the dosage of 20 μmol/kg/d. Dimethylation of the parent compound on the furan ring resulted in reduced activity and increased toxicity.

Introduction

The primary goals of optimum pneumocystosis treatment are immediate alleviation of symptoms, a microbicidal effect on the organism, and prevention or minimization of adverse drug reactions without causing a reduction in efficacy. Efficacy and safety therefore play a primary role in the selection of therapeutic agents.[1] Pentamidine is an effective agent for the treatment of *Pneumocystis carinii* pneumonia (PCP), but clinical development of pentamidine-type molecules has been severely limited not only by the toxicity of several of the compounds but also by the lack of understanding of their mechanisms of toxicity and action, pharmacokinetics, and structure−activity relationships. Recent evidence from studies of various aromatic amidines related to pentamidine supports the hypothesis of initial binding of these drug candidates to AT-rich regions of the minor groove of DNA and subsequent inhibition of microbial enzymes. However, no quantitative correlation has been established between DNA binding and biological activity.

The broad anti-infective, in particular anti-PCP activity, reported for 2,5-bis(4-amidinophenyl)furan[10] and its low in vivo toxicity led to the design of a new set of dicationic diphenyl furans. Modifications of the lead compound were intended to increase nonbonding interactions between the drugs and the minor groove of the DNA. A change in the substitution pattern as well as dimethylation of the central furan ring was assumed to induce an out-of-plane twist, which could result in enhanced isohelicity of these compounds with the inner surface of the minor groove. Different positioning in the minor groove could favor additional H-bonding as well as electrostatic interactions. This report describes the synthesis of 2,4-bis(4-amidinophenyl)furans, their relative binding affinity to the minor groove of AT-rich DNA, and their biological evaluation against *P. carinii* pneumonia in the immunosuppressed rat model.

Chemistry

The synthesis for target compounds **5**−**10** employed a base-catalyzed condensation of 4-cyanobenzaldehyde with 4-cyanoacetophenone (Scheme 1). Addition of bromine to the α,β-unsaturated ketone **1** and subsequent treatment with sodium methoxide gave an enol ether[2−5] which was used for the next reaction step without further identification or purification. The key step for the furan formation employed highly reactive dimethyl sulfonium methylide generated in dimethyl sulfoxide.[6] This insertion reaction gave a furanoid product **3**, readily identified as a 2,4-diarylfuran. The classical Pinner method was employed to transform the cyano into amidine groups.[7] The imidate ester **4**, generated as an intermediate product, was very hygroscopic and tended to hydrolyze fairly rapidly if left exposed to the atmosphere. However, immediate reaction with the appropriate amine gave the desired amidines **5**−**10**.[8−11] The low solubility of free amidines with an extended aromatic backbone in aqueous systems is a major reason amidines are converted to salts prior to in vitro or in vivo testing.

Target compounds **14** and **15** were prepared from bis-(4-bromophenyl)furan (Scheme 2) by bromomethylation with formaldehyde and HBr and subsequent reduction using LAH to give **11**.[8] Substitution of the aromatic bromo groups employing Cu(I)CN led to the cyano-substituted intermediate **12**[12] which was transformed into the amidine derivatives **14** and **15** employing the Pinner method.[7−11] The free amidine bases were precipited as HCl salts.

Biological Results

Melting temperatures were measured for the compounds **5**−**10** and **14**−**15** bound to poly(dA-dT)$_2$ to obtain a qualitative evaluation of the DNA binding

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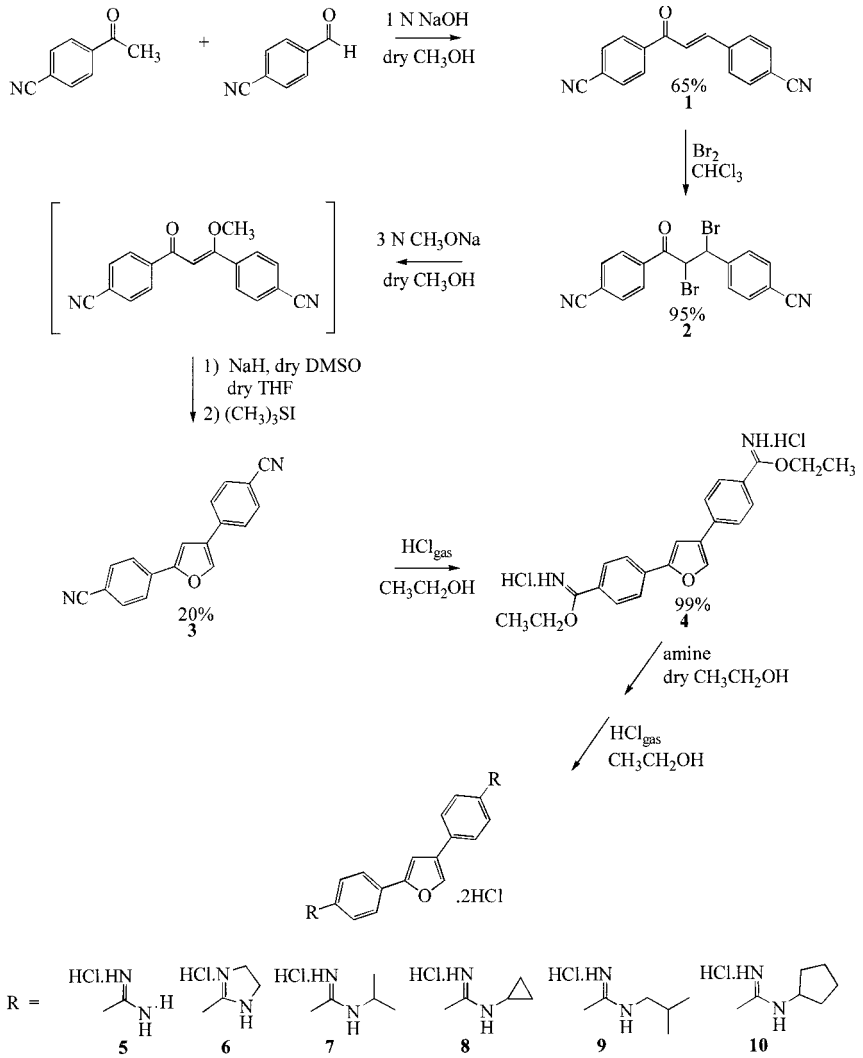
Scheme 1



affinity of these drug candidates. The difference in T_m values between the drug−DNA complexes and free DNA in solution provides a useful tool to assess the interaction strength of the molecules with DNA. Since all compounds bound very strongly to poly(dA-dT) (Table 1), the Dickerson−Drew dodecamer d(CGCGAATTCGCG)$_2$, a DNA with different groove dimensions, was employed. The reduced binding affinity of the drugs to the dodecomer, reflected by the lower T_m values of the drug−docedamer complexes (Table 1), allowed a better relative comparison of the DNA binding affinity of these minor groove binding compounds.

Docking experiments suggested that the compounds **5**−**10** fit well into the minor groove at the center of the AT-rich region with the hydrogen on carbon 3 of the central furan ring pointing toward the bottom of the groove. Steric hindrance derived from the unfavorable interaction of this hydrogen atom with the bottom of the groove seemed to be responsible for a somewhat decreased binding affinity to DNA of this set of 2,4-substituted diphenylfuran diamidines in comparison to a set of correspondingly substituted 2,5-diphenylfuran diamidines, previously reported in the literature.[10] Steric interactions between the phenyl ring on carbon 4 and the hydrogen atoms on the central furan ring of compounds **5**−**10** seemed to induce an out-of-plane twist, suggested also by preliminary crystal structure data and by AM1 calculations performed on the intermediate product 2,4-bis(4-bromophenyl)furan. A significantly larger twist was expected for compounds **14** and **15** due to the methyl groups on carbon 3 and 5 of the central furan ring, which may contribute to the lower binding affinity of these compounds in comparison to compounds **5**−**10**. In the approach of the compounds **14** and **15** toward the bottom of the groove, the methyl group on carbon 3 was not expected to contribute additional steric hindrance compared to the hydrogen atom of compounds **5**−**10**, as according to unpublished data on *N*-methyl-substituted pyrrole systems the minor groove seemed to be able to accommodate methyl groups quite well.

The amidine groups at the termini of the molecules seemed to contribute significantly to the complex stability between the dications and the DNA through H-bonding and electrostatic interactions. Different positioning of the cationic groups due to a larger twist of compounds **14** and **15** might have resulted in less favorable interactions and therefore lower binding affinity of these compounds in comparison to compounds **5**−**10**. The extended aromatic core region of the molecules **5**−**10** is expected to favor extensive contacts between the compounds and the hydrophobic surface of the groove. However, the suggested large twist of compounds **14** and **15** might have had the opposite effect

Scheme 2

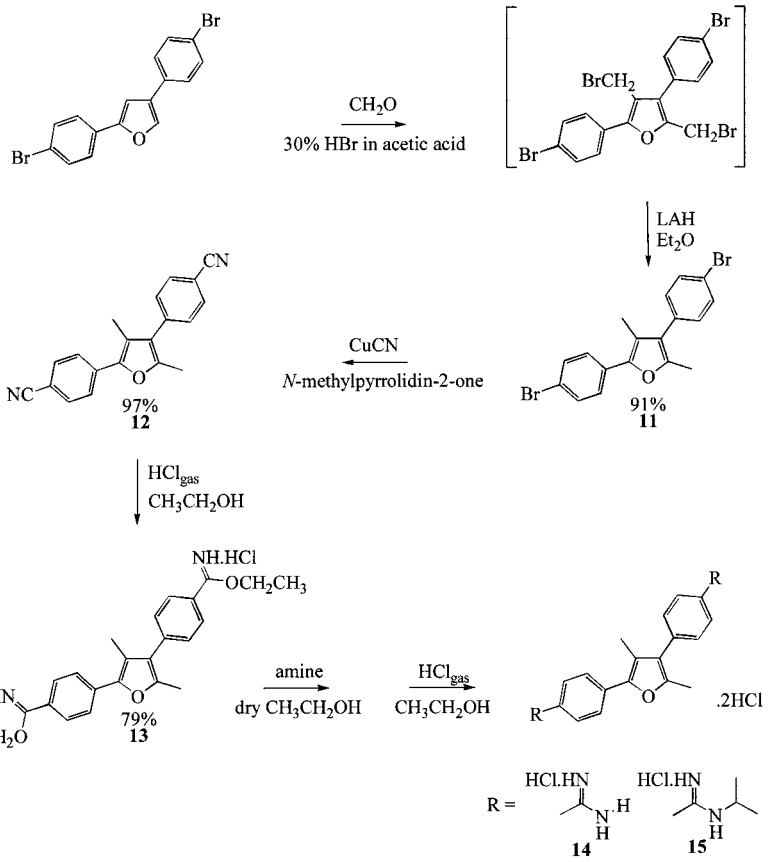


Table 1. Nucleic Acid Binding Results of 2,4-Bis(4-amidinophenyl)furans

R	ΔT_m[a] (DNA)	ΔT_m[b] (oligomer)
pentamidine	12.6	4.8
5	19.0	9.1
6	16.8	7.2
7	17.6	10.9
8	23.2	10.9
9	20.4	9.3
10	20.4	13.6
14	17.0	6.5
15	12.5	5.4

[a] Increase in thermal melting of poly(dA-dT)$_2$.[18] [b] Increase in thermal melting of d(CGCGAATTCGCG)$_2$.[19]

Table 2. In Vivo anti-*Pneumocystis carinii* Pneumonia Activity of 2,4-Bis(4-amidinophenyl)furans

compound	dosage (μmol/kg/d)	cyst/g of lung[a] (% of control)	toxicity[b]
saline		100.00 ± 22.28[c]	
pentamidine	22.0	2.30 ± 1.08[c]	++
5	10.0	0.30 ± 0.24	0
7	20.0	0.00 ± 0.00	++
	10.0	0.04 ± 0.02	0
	5.0	0.08 ± 0.02	0
	1.0	2.42 ± 1.00	0
	0.25	110.50 ± 25.38	0
8	10.0	0.01 ± 0.00	0
10	10.0	0.16 ± 0.14	0
	1.0	1.79 ± 0.61	0
14	10.0	0.89 ± 0.46	+
15	10.0	24.43 ± 10.68	0

[a] Lower numbers of cysts/g of lung refer to higher activity against *Pneumocystis carinii* pneumonia. Values below 1% of control are within the experimental error and can be considered as complete cure of the pneumonia infections in the immunosuppressed rats.[13−15] [b] Toxicity of the test compounds is evaluated according to a five-level scale ranging from 0 to 5+. The toxicity information reported in the in vivo studies should not be considered definitive and is mainly anectotal in nature. These values though do allow for a comparison of the relative toxicities of the compounds and of the control drug pentamidine.[13−15] [c] Mean cyst count for pooled controls: saline (n = 46) 100.0 ± 22.28 cysts/g of lung tissue; pentamidine (n = 42) 2.30 ± 1.08.

and reduce favorable van der Waals interactions of the aromatic rings with the walls of the groove. Alkyl substitution on the amidino nitrogen of the compounds **7**−**10** resulted in higher affinity for DNA compared to the unsubstituted parent compound **5**. These results were consistent with increased van der Waals interactions between the alkyl groups and the walls of the minor groove. The slightly reduced binding affinity of the *isobutyl* compound **9** could be due to the greater flexibility of this alkyl group. Entropic factors may have also contributed to the stability of the complex. The significantly reduced binding affinity of the isopropyl derivative **15** could in part be due to unfavorable positioning of the alkyl groups which probably resulted in steric hindrance rather than in additional van der Waals interactions.

Four of the 2,4-diphenylfuran diamidines, **5**, **7**, **8**, and **10**, and the 3,5-dimethylated compounds **14** and **15** have been evaluated on intravenous administration against *Pneumocystis carinii* pneumonia in the immunosuppressed rat model.[13−15] Except for **15**, all test compounds showed significantly higher anti-PCP activity than the control compound pentamidine (Table 2). An investigation of the dose−response of the alkyl-substituted diamidines **7** and **10** showed an 11-fold decrease in the anti-*P. carinii* activity of compound **10** and a 60-fold decrease in activity of compound **7** when the dosage was reduced from 10 to 1 μmol/kg/d. A qualitative evaluation of the

toxicity in the same in vivo studies showed that the 2,4-diphenylfuran diamidines **5**, **7**, **8**, **10**, and **15** caused no toxic side effects at the administered dosages of 10 μmol/kg/d or less. At a dosage of 20 μmol/kg/d compound **7** showed side effects comparable to those of the control compound pentamidine; however, activity levels of these two compounds were significantly different. Introduction of the methyl groups on the central furan ring as seen in compound **14** and **15** resulted in reduced activity and, for compound **14**, in increased toxicity. A comparison of the 2,4-substituted furan diamidines **5**, **7**, **8**, and **10** to a set of correspondingly substituted 2,5-bis(4-amidinophenyl)furans showed that the correlation between DNA binding affinity and biological activity previously reported for the symmetrical set of compounds[10] cannot be confirmed for the 2,4-diphenyl derivatives. It is also noteworthy that despite weaker interaction with DNA, the 2,4-substituted compounds turned out to have higher biological activity against PCP in the immunosuppressed rat model than the 2,5-substituted analogues.[10]

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover and with a Mel-Temp 3.0 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer, ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian Unity +300 and a Varian VRX 400 instrument. Mass spectra were recorded on a VG Instruments 70-SE spectrometer by Georgia Institute of Technology, Atlanta, GA. Elemental analyses were performed on a Perkin-Elmer 2400 Series II C, H, N organic elemental analyzer or by Atlantic Microlab, Norcross, GA, and are within ±0.4 of the theoretical values unless otherwise noted. All chemical and solvents were purchased from Aldrich Chemical Co., Fisher Scientific, or Acros organics. In the cases where dry solvents were required, MeOH and EtOH were distilled from Mg metal, THF and Et_2O were distilled from Na/benzophenone, and DMSO was distilled from CaH_2.

1,3-Bis(4-cyanophenyl)prop-2-en-1-one (1). 4-Cyanobenzaldehyde (10.00 g, 76.3 mmol) and 4-acetylbenzonitrile (11.07 g, 76.3 mmol) were dissolved in 150 mL of dry MeOH and heated to reflux. NaOH (1 N) was added dropwise until precipitation occurred, and refluxing was continued for another 5 min. The suspension was cooled to room temperature, and the bright yellow solid was filtered, washed with Et_2O, and dried over $CaSO_4$ under vacuum. Yield: 12.89 g (65%), mp 113−115 °C, lit.[16] mp 111−114 °C. IR (KBr): 2228, 1670 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.30 (d, 2 H, J = 8.1 Hz), 8.10 (d, 2 H, J = 8.7 Hz), 8.09 (d, 1 H, J = 15.3 Hz), 8.06 (d, 2 H, 7.5 Hz), 7.80 (d, 1 H, J = 15.6 Hz). ^{13}C NMR (DMSO-d_6): δ 188.4, 142.8, 140.4, 138.8, 132.7, 132.6, 129.5, 129.1, 124.9, 118.4, 118.0, 115.2, 112.5. Anal. ($C_{17}H_{10}N_2O$) C, H, N.

1,3-Bis(4-cyanophenyl)-2,3-dibromopropan-1-one (2). Compound **1** (12.89 g, 49.9 mmol) was added to a solution of 2.6 mL of Br_2 (50.5 mmol) in 150 mL of $CHCl_3$. The suspension was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the solid was filtered, washed with Et_2O, and dried over $CaSO_4$ under reduced pressure. Yield: 19.78 g (95%), mp 187−189 °C. IR (KBr): 2228, 1691 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 2 H, J = 8.4 Hz), 7.87 (d, 2 H, J = 8.8 Hz), 7.75 (d, 2 H, J = 8.4 Hz), 7.64 (d, 2 H, J = 8.0 Hz), 6.70 (d, 1 H, J = 11.2 Hz), 5.62 (d, 1 H, J = 11.2 Hz). ^{13}C NMR ($CDCl_3$): δ 189.5, 142.9, 137.4, 133.1, 132.9, 129.5, 129.4, 118.2, 117.8, 117.7, 113.6, 47.5, 46.2. Anal. ($C_{17}H_{10}N_2OBr_2$) C, H, N.

2,4-Bis(4-cyanophenyl)furan (3). A suspension of 15.00 g (35.9 mmol) of **2** in 150 mL of dry MeOH was heated to reflux. Freshly prepared 3 M MeONa (2.49 g of Na in 36 mL of MeOH) was added dropwise, and stirring was continued for 30 min. The clear orange solution was cooled to room temperature and poured into 100 mL water. The aqueous suspension was extracted with CH_2Cl_2, the organic phase was dried over $NaSO_4$, and the solvent was removed under reduced pressure to give an oily orange residue. A suspension of 1.03 g (42.9 mmol) of NaH in 15 mL of dry DMSO was stirred at room temperature for 30 min. Dry THF (30 mL) was added, and the suspension was cooled in a salt/ice bath to 0 °C and treated dropwise with a solution of 8.78 g (43.0 mmol) of trimethylsulfonium iodide in 15 mL of dry DMSO. The suspension was stirred for 5 min and treated with a solution of the crude enol ether in 25 mL of dry THF. The dark suspension was stirred at ice bath temperature for 15 min, the ice bath was removed, and stirring was continued for 18 h. The mixture was poured into 300 mL of water and extracted with $CHCl_3$. The solvent was evaporated, and the oily residue was passed through a silica gel column to obtain an off-white crystalline solid. Yield: 1.89 g (20%), mp 229−231 °C. IR (KBr): 2222 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1 H), 7.81 (d, 2 H, J = 8.8 Hz), 7.72 (d, 2 H, J = 8.8 Hz), 7.71 (d, 2 H, J = 8.8 Hz), 7.63 (d, 2 H, J = 8.8 Hz), 7.12 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 153.9, 140.8, 136.5, 134.1, 133.0, 132.9, 127.8, 126.5, 124.5, 118.9, 111.5, 111.3, 106.5. Anal. ($C_{18}H_{10}N_2O$) C, H, N.

2,4-Bis(4-ethoxyiminoylphenyl)furan Dihydrochloride (4). Dinitrile **3** (0.50 g, 1.8 mmol) was suspended in 20 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. The flask was sealed, and stirring was continued at room temperature for another 3 d. The imidate ester hydrochloride was precipitated with 20 mL of dry Et_2O, filtered, and dried under vacuum at room temperature. Yield: 0.80 g (99%). Because of its hygroscopic nature and limited stability the imidate ester is used immediately for the formation of amidines without purification.

2,4-Bis(4-amidinophenyl)furan (5). A suspension of 0.80 g (1.8 mmol) of imidate ester hydrochloride **4** in 20 mL of dry EtOH was cooled to 0 °C in an ice bath and saturated with dry NH_3 gas. The ice bath was removed, the flask was sealed, and stirring was continued for 72 h. After addition of 20 mL of 1 M NaOH, the white suspension was stirred for 1 h. The solid was filtered, washed with water, and dried over $CaSO_4$ under reduced pressure. For purification the crude product was heated in dry EtOH for 30 min, again filtered, and dried over $CaSO_4$. A suspension of the free base in 20 mL of dry EtOH was saturated with dry HCl gas at 0 °C, and stirring was continued for 2 h at room temperature. The yellow solid was precipitated with 20 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.42 g (96%), mp > 346 °C decomposition. ^{1}H NMR (DMSO-d_6:D_2O 1:1): δ 8.33 (s, 1 H), 7.92 (d, 2 H, J = 8.4 Hz), 7.84−7.78 (m, 6 H), 7.60 (s, 1 H). ^{13}C NMR (DMSO-d_6:D_2O 1:1): δ 166.4, 166.3, 154.1, 142.9, 138.0, 135.6, 129.7, 129.7, 128.1, 127.4, 127.1, 127.1, 125.1, 107.9. MS: *m/e* 305 (M^+) free base. Anal. Calcd for $C_{18}H_{16}N_4O\cdot 2HCl\cdot 1H_2O$: C, 54.69; H, 5.10; N, 14.17. Found: C, 54.99; H, 4.98; N, 13.10.

2,4-Bis[4,5-dihydro-1*H*-imidazol-2-yl)phenyl]furan Dihydrochloride (6). Dried and freshly distilled 1,2-diaminoethane (freshly distilled from KOH) (0.14 mL, 2.1 mmol) was added to a suspension of 0.41 g (0.9 mmol) of imidate ester hydrochloride **4** in 20 mL of dry EtOH, and under exclusion of water the solution was refluxed for 16 h. The solvent was removed under reduced pressure, the residue was suspended in 20 mL of 1 N KOH, and the suspension was stirred for 30 min. The solid was filtered, washed with H_2O, and dried in vacuo. The free imidazoline base was suspended in 20 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. After the solution was stirred for 2 h the imidazoline salt was precipitated with 20 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.22 g (49%), mp > 300 °C decomposition. ^{1}H NMR (DMSO-d_6): δ 8.21(s, 1 H), 7.90−7.78 (m, 8 H), 7.48 (s, 1 H), 3.96 (t, 8 H). ^{13}C NMR (DMSO-d_6): δ 167.0, 166.9, 154.7, 143.7, 139.1, 136.6, 130.5, 128.7, 127.9, 125.8, 122.3, 122.0, 108.6, 46.0. Anal. ($C_{22}H_{20}N_4O\cdot 2HCl\cdot 3H_2O$) C, H, N.

2,4-Bis[4-{*N*-(isopropylamidino)phenyl}]furan (7). In a sealed flask a mixture of 1.47 g (3.4 mmol) of imidate ester

hydrochloride **4** and 0.75 mL (8.8 mmol) of isopropylamine (freshly distilled from KOH) in 20 mL of dry EtOH was stirred at room temperature for 3 d. The solvent was removed under reduced pressure, and the residue was suspended in 1 N NaOH. After the mixture was stirred for 30 min, the white solid was filtered, washed with water, and dried in vacuo. The white solid was suspended in 30 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. Stirring was continued for 2 h, and the yellow solid was precipitated with 30 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.73 g (47%), mp >305 °C decomposition. ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 1 H), 7.80−7.67 (m, 8 H), 7.54 (s, 1 H), 3.81 (m, 2 H), 1.14 (d, 12 H, J = 4.8 Hz). ^{13}C NMR (DMSO-d_6): δ 153.6, 139.6, 136.6, 136.1, 132.4, 130.6, 127.4, 126.9, 126.8, 124.8, 122.8, 104.9, 43.4, 22.8. Anal. ($C_{24}H_{28}N_4O$·2HCl·5/4H_2O) C, H, N.

2,4-Bis[4-{*N*-(cyclopropylamidino)phenyl}]furan (8). In a sealed flask a mixture of 0.74 g (1.7 mmol) of imidate ester hydrochloride **4** and 0.29 mL (4.1 mmol) of cyclopropylamine (freshly distilled from KOH) in 15 mL of dry EtOH was stirred at room temperature for 2 d. The suspension was poured into 100 mL of water, and the free amidine base was precipitated with 20 mL of 1 M NaOH. The suspension was diluted with another 100 mL of water and stirred at room temperature for 30 min. The beige precipitate was filtered, washed with water, and dried in vacuo. The free base was suspended in 10 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. Stirring was continued for 2 h at room temperature, and the yellow hydrochloric salt was precipitated with 50 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.42 g (59%), mp > 240 °C decomposition. ^{1}H NMR (DMSO-d_6:D_2O): δ 8.36 (s, 1 H), 7.98 (d, 2 H, J = 8.0 Hz), 7.88 (d, 2 H, J = 7.2 Hz), 7.80 (d, 2 H, J = 8.4 Hz), 7.78 (d, 2 H, J = 8.0 Hz), 7.63 (s, 1 H), 2.79 (s, 2 H), 1.04 (d, 4 H, J = 5.2 Hz), 0.85 (s, 4 H). ^{13}C NMR (DMSO-d_6:D_2O): 166.6, 166.4, 154.6, 142.9, 138.1, 135.8, 129.8, 129.8, 128.5, 128.1, 127.8, 127.5, 125.5, 108.0, 25.1, 7.6. Anal. ($C_{24}H_{24}N_4O$·2HCl·2/3H_2O) C, H, N.

2,4-Bis[4-{*N*-(isobutylamidino)phenyl}]furan (9). In a sealed flask a mixture of 0.64 g (1.5 mmol) of imidate ester hydrochloride **4** and 0.32 mL (3.2 mmol) of isobutylamine in 10 mL of dry EtOH was stirred for 2 d at room temperature. NaOH (10 mL, 1 M) was added to the light yellow suspension, and stirring was continued for another 1.5 h. The mixture was poured into 150 mL of H_2O, and the off-white precipitation was filtered, washed with H_2O, and dried over $CaSO_4$ under vacuum. The crude product was recrystallized from EtOH/Et_2O. The free base was dissolved in 10 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. Stirring was continued at room temperature for 2 h, and the light yellow solid was precipitated with 10 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.36 g (50%), mp > 278 °C decomposition. ^{1}H NMR (DMSO-d_6:D_2O 1:1): δ 8.47 (s, 1 H), 7.95 (d, 2 H, J = 8.0 Hz), 7.89 (d, 2 H, J = 8.0 Hz), 7.81−7.74 (m, 5 H), 3.23 (t, 4 H), 2.00 (m, 2 H), 0.96 (m, 12 H). ^{13}C NMR (DMSO-d_6:D_2O 1:1): δ 163.3, 163.2, 153.4, 142.3, 136.7, 134.4, 129.3, 129.2, 128.0, 127.7, 127.5, 126.2, 124.2, 107.3, 49.9, 27.3, 20.2. Anal. ($C_{26}H_{32}N_4O$·2HCl·1H_2O) C, H, N.

2,4-Bis[4-{*N*-(cyclopentylamidino)phenyl}]furan (10). In a sealed flask a mixture of 0.53 g (1.2 mmol) of imidate ester hydrochloride **4** and 0.27 mL (2.7 mmol) of cyclopentylamine (freshly distilled from KOH) in 20 mL of dry EtOH was stirred at room temperature for 24 h. NaOH (20 mL, 1 M) was added, and stirring was continued for 30 min. The solid was filtered, washed with H_2O, and dried under reduced pressure. The free amidine base was suspended in 20 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. After the mixture was stirred for 5 h, the yellow solid was precipitated with 20 mL of dry Et_2O, filtered, and dried under vacuum. Yield: 0.43 g (69%), mp > 302 °C decomposition. ^{1}H NMR (DMSO-d_6): δ 8.25 (s, 1 H), 7.87 (d, 2 H, J = 8.0 Hz), 7.77 (d, 2 H, J = 8.0 Hz), 7.67 (t, 4 H), 7.52 (s, 1 H), 4.00 (m, 2 H), 2.00 (m, 8 H), 1.62 (m, 8 H).^{13}C NMR (DMSO-d_6): δ 163.6, 154.4, 142.6, 137.4, 135.2 129.9, 129.8, 128.7, 128.4, 128.3, 127.1, 125.1, 107.7, 55.7, 32.5 24.6. MS: *m/e* 441 (M^+) free base. Anal. Calcd for $C_{28}H_{34}N_4O$·2HCl·5/4H_2O: C, 64.18; H, 7.02; N, 10.69. Found: C, 63.80, H, 6.51; N, 10.47.

2,4-Bis(4-bromophenyl)-3,5-dimethylfuran (11). Paraformaldehyde (1.24 g, 41.3 mmol) was added to 35 mL of a 30% solution of HBr in glacial acetic acid. 2,4-Bis(4-bromophenyl)-furan[17] (1.56 g, 4.1 mmol) was added, and the dark mixture was stirred at room temperature for 2 d. The solution was poured into 250 mL of H_2O and stirred for 15 min. The light green precipitate was filtered, washed with water, and dried under vacuum. Without further purification the 2.20 g (3.90 mmol) of bis(4-bromophenyl)-3,5-dibromomethyl-2,4-furan was added to a suspension of 0.59 g (15.5 mmol) of LAH in 30 mL of dry Et_2O. The suspension was stirred at room temperature for 1 h, then slowly poured into 100 mL H_2O. The precipitate was filtered over Celite and thoroughly washed with Et_2O, and the two phases of the filtrate were separated. The organic phase was washed with water, dried over Na_2SO_4, and reduced under vacuum. Yield: 1.44 g (91%), mp 167−169 °C. ^{1}H NMR ($CDCl_3$): δ 7.58−7.52 (m, 6 H), 7.17 (d, 2 H, J = 8.4 Hz), 2.34 (s, 3 H), 2.16 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 147.9, 146.4, 132.6, 131.9, 131.5, 130.9, 126.9, 124.3, 121.2, 120.6, 117.0, 12.6, 10.9. MS: *m/e* 406 (M^+). Anal. Calcd for $C_{18}H_{14}OBr_2$: C, 53.23; H, 3.47. Found: C, 53.72, H, 3.76.

2,4-Bis(4-cyanophenyl)-3,5-dimethylfuran (12). To a suspension of 3.31 g (36.9 mmol) of Cu(I)CN in 30 mL of *N*-methylpyrrolidin-2-one was added 1.44 g (3.7 mmol) of 2,4-bis(4-bromophenyl)-3,5-dimethylfuran **11**. The suspension was heated to reflux for 2.5 h. After cooling to room temperature the suspension was poured into a solution of 41 mL of concentrated NH_4OH in 100 mL of water. The mixture was stirred for 15 min, and the precipitate was filtered, washed with water, and dried over $CaSO_4$ under reduced pressure. The dry precipitate was extracted with $CHCl_3$ in a Soxhlet extraction apparatus for 3 d. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel. Yield: 0.47 g (42%), mp 164−166 °C. IR (KBr): 2228 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 4 H, J = 7.6 Hz), 7.70 (d, 2 H, J = 8.8 Hz), 7.40 (d, 2 H, J = 8.4 Hz), 2.39 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 150.0, 146.1, 138.2, 135.7, 132.7, 132.6, 130.4, 125.4, 124.6, 119.4, 119.2, 118.9, 111.2, 110.0, 12.8, 11.2. MS: *m/e* 298 (M^+). Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 79.63; H, 4.83; N, 9.23.

3,5-Dimethyl-2,4-bis(4-ethoxyiminoylphenyl)furan Dihydrochloride (13). 2,4-Bis(4-cyanophenyl)-3,5-dimethylfuran **12** (0.30 g, 1.0 mmol) was suspended in 15 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. The flask was sealed and stirring was continued at room temperature for 1 d. The imidate ester hydrochloride was precipitated with 50 mL of Et_2O, filtered, and dried over $CaSO_4$ under vacuum. Yield: 0.37 g (79%). Because of its hygroscopic nature and limited stability the imidate ester is used immediately for the formation of amidines without further purification.

2,4-Bis(4-amidinophenyl)-3,5-dimethylfuran (14). 3,5-Dimethyl-2,4-bis(4-ethoxyiminoylphenyl)furan dihydrochloride **13** (0.62 g, 1.3 mmol) was suspended in 15 mL of dry EtOH, and the solution was saturated with dry NH_3 gas at ice bath temperature. The flask was sealed, and the suspension was stirred for 5 d. The solvent was removed under reduced pressure, and the oily residue was suspended in 200 mL of water. NaOH (30 mL, 1 M) was added to the clear solution, and the mixture was stirred for 30 min at room temperature. The precipitate was filtered, washed with water, and dried over $CaSO_4$ under vacuum. The free amidine base was dissolved in 10 mL of dry EtOH, and the solution was saturated with HCl gas at ice bath temperature. The suspension was stirred at room temperature for 1 h, and the hydrochloric salt was precipitated with 100 mL of dry Et_2O, filtered, and dried over $CaSO_4$ under vacuum. Yield: 0.31 g (82%), mp > 285 °C decomposition. ^{1}H NMR (DMSO-d_6:D_2O 1:1): δ 7.80 (d, 6 H, J = 8.4 Hz), 7.51 (d, 2 H, J = 8.1 Hz), 2.30 (s, 3 H), 2.16 (s, 3 H).

^{13}C NMR (DMSO-d_6:D_2O 1:1): δ 166.9, 151.4, 146.5, 139.5, 137.2, 131.3, 129.7, 129.4, 127.2, 126.2, 125.0, 120.8, 13.3, 11.6. Anal. ($C_{20}H_{20}N_4O$·2HCl·1/2H_2O) C, H, N.

2,4-Bis[4-{*N*-(isopropylamidino)phenyl}]-3,5-dimethylfuran (15). In a sealed flask a mixture of 0.61 g (1.3 mmol) of 3,5-dimethyl-2,4-bis(4-ethoxyiminoylphenyl)furan dihydrochloride **13** and 0.27 mL (3.2 mmol) of isopropylamine in 10 mL of dry EtOH was stirred at room temperature for 2 d. The solvent was removed under reduced pressure, and the oily residue was suspended in 200 mL of water. NaOH (10 mL, 1 M) was added to the clear solution, and the mixture was stirred at room temperature for 30 min. The light yellow precipitate was filtered under nitrogen atmosphere and dried under vacuum over $CaSO_4$. The free amidine base was dissolved in 10 mL of dry EtOH and the solution was saturated with HCl gas at ice bath temperature. The solution was stirred at room temperature for 2 h, and the hydrochloric salt was precipitated with 100 mL of dry Et_2O, filtered under nitrogen atmosphere, and dried over $CaSO_4$ under vacuum. Yield: 0.54 g (85%), mp 284−286 °C. ^{1}H NMR (DMSO-d_6:D_2O 1:1): δ 7.79−7.68 (m, 6 H), 7.48 (d, 2 H, J = 8.1 Hz), 3.89 (m, 2 H), 2.30 (s, 3 H), 2.15 (s, 3 H), 1.26 (s, 3 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (DMSO-d_6:D_2O 1:1): δ 163.4, 163.2, 151.3, 146.7, 139.0, 136.7, 131.3, 129.7, 129.4, 128.6, 127.7, 126.3, 125.2, 120.6, 46.9, 22.0, 13.4, 11.7. Anal. ($C_{26}H_2N_4O$·2HCl·9/4H_2O) C, H, N.

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