Prodrugs for Amidines: Synthesis and Anti-*Pneumocystis carinii* Activity of Carbamates of 2,5-Bis(4-amidinophenyl)furan

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Syntheses of several carbamate analogues of 2,5-bis(4-amidinophenyl)furan (**1**) under mild conditions and their evaluation as prodrugs against *Pneumocystis carinii* pneumonia (PCP) in an immunosuppressed rat model are described. Thus, nine new bis-carbamates: methoxycarbonyl (**2**), 2,2,2-trichloroethoxycarbonyl (**3**), ethylthiocarbonyl (**4**), benzyloxycarbonyl (**5**), (4-methyl-2-oxo-1,3-dioxol-4-en-5-yl)methoxycarbonyl (**6**), phenoxycarbonyl (**7**), 4-fluorophenoxycarbonyl (**8**), 4-methoxyphenoxycarbonyl (**9**), and (1-acetoxy)ethoxycarbonyl (**10**) and a bis-carbonate ethoxycarbonyloxy (**11**) of the bis-amidine **1** have been synthesized and evaluated. The in vivo results show that the 4-fluorophenyl carbamate **8** and the 4-methoxyphenyl carbamate **9** in this series had the best anti-PCP activity by both intravenous and oral administration at a dosage level of 22 mol and 33 μmol/kg/day, respectively. Compounds **3**−**7** were also more active than the parent drug (**1**) on oral administration. The acute toxicity usually exhibited by the parent amidine **1** at a dosage level of 22 μmol/kg/day on intravenous administration has been significantly reduced by the prodrug modifications, with the exception of compound **10** which exhibited some toxicity. This report also describes the synthesis of several aryl−alkyl and aryl−aryl carbonates (**12**−**14, 16**−**23**) as efficient reagents for the preparation of carbamate derivatives from bis-arylamidines.

Introduction

Pneumocystis carinii pneumonia (PCP) is a leading cause of mortality and morbidity in patients suffering from AIDS (acquired immunedeficiency syndrome).[1] It has been estimated that approximately 80% of AIDS patients contract PCP. Pentamidine [1,5-bis(4-amidinophenoxy)pentane] has been used as a therapeutic agent for the treatment of PCP by intravenous infusion and as a prophylactic agent by aerosol dosage.[2] However, it is limited in use because of its toxicity, which includes hypotension, hypoglycemia, and cardiac arrhythmia.[2] In an effort to find a more efficient therapeutic agent for the treatment of PCP, studies from our laboratories have shown that a number of aromatic diamidines show excellent anti-PCP activity.[3−6] Recently we reported that 2,5-bis(4-amidinophenyl)furan (**1**) was more active and less toxic than pentamidine against PCP in an immunosuppressed rat model. However, the activity of **1** in the rat model was significantly less on oral administration.[3] Earlier, it was reported that compound **1** was effective in vivo in both mouse and simian models for *Trypanosoma rhodesiense*.[7,8] More recently we have reported that several *N*-alkyl substituted amidinophenylfurans were more active than the parent amidinophenylfuran **1** in the immunosuppressed rat model of PCP;[9] however, the low oral bioavailability of the amidines limits their utility, and therefore we have investigated prodrug approaches to improve the oral effectiveness of these compounds.

Chemical modification of drugs into prodrugs potentially can improve physicochemical properties such as water solubility and lipophilicity, transport of drug to the site of action, and presystemic degradation and hence can improve the oral bioavailability.[10,11] Although numerous reports exist on the prodrug modification of carboxyl, hydroxyl, thiol, and amino compounds,[12−16] very few reports are found on prodrug approaches for arylamidines.[17,18] Weller and co-workers have demonstrated that amidoximes and carbamate derivatives of monoamidines are effective prodrugs which provide significantly improved oral bioavailability for fibrinogen antagonists.[18] We have also reported that the bis-amidoxime and *O*-methylamidoxime of **1** were effective anti-PCP agents on both oral and intravenous administration.[19] Although there appears to be no carbamate-specific enzymes in mammals,[20] several electronically activated alkyl carbamates synthesized from amines have been reported to behave well as prodrugs and their activation has been attributed to enzymatic hydrolysis.[21] Moreover, a carbamate of a monoamidine has been demonstrated to be orally effective in the clinic for platelet inhibition.[22] As part of our continuing efforts to modify the physicochemical properties of amidines to achieve better oral activity, we have examined amidine carbamates as potential prodrugs. The (oxo-dioxolenyl)methyl functionality has been reported to function as an efficient prodrug moiety for alcohols, carboxylic acids, and amines.[23−27] A number of prodrugs employing this functionality have been reported,[28] and

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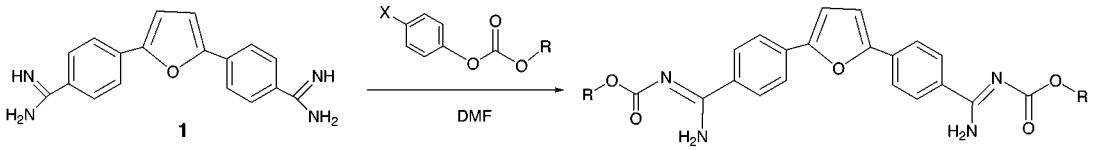
Scheme 1. Synthesis of Carbamates from 2,5-Bis(4-amidinophenyl)furan



we have also adapted this approach to amidines. Two examples of amidine prodrugs involving two-step transformations to the active drug (double prodrugs), an acetoxy carbamate and a carbonate of amidoxime of **1,** are also described.

Chemistry

2,5-Bis(4-amidinophenyl)furan (**1**) required for making the carbamates was synthesized from 2,5-bis(4-cyanophenyl)furan, via the imino ester by treatment with ammonia, by a previously reported method.[7] However, the bis-nitrile was prepared from 4-cyanobenzaldehyde by a more recently described two-step modified Stetter method involving the addition of divinyl sulfone to a solution of aldehyde in the presence of a thiazolium catalyst.[29] No problems have been encountered in scaling up the procedure to a 5-g size.

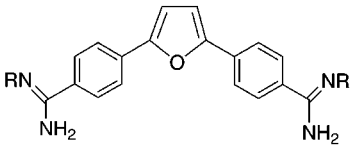
The traditional method for preparing a carbamate from amines or amidines involves reaction with an appropriate chloroformate in the presence of a base, usually aqueous sodium hydroxide or sodium/potassium bicarbonate.[18] However, the use of sodium hydroxide suffers from hydroxide ion-mediated hydrolysis of some of the chloroformate and the carbamate product. Moreover, the reaction medium is heterogeneous, and the yields of the carbamates by this method are often less than 50%. Many chloroformates cannot be stored at room temperature for long periods, whereas carbonates are solids, easy to handle, and stable at room temperature for long periods. Therefore, the use of aryl−alkyl and aryl−aryl carbonates provides an attractive alternative for the making of carbamates from amidines. Carbonates are often prepared by the reaction of chloroformates with alcohols mediated by a base. Dealkylation reactions involving tertiary amines and chloroformates have been reported,[30,31] and recently, dealkylation of tertiary aliphatic amines with phenyl chlorothionoformate was described.[32] Therefore, in this work pyridine was employed as the base for formation of the carbonates. The 4-nitrophenyl alkyl carbonates (**12**, **14**, **19**) were readily prepared by reacting 4-nitrophenol with the corresponding alkyl or aryl chloroformates in CH_2Cl_2 using pyridine as a base. The (1-acetoxy)ethyl 4-nitrophenyl carbonate (**17**) was prepared from 1-chloroethyl chloroformate by a two-step method involving reaction of 4-nitrophenol with the chloroformate followed by displacement of the chlorine by acetate, according to published procedures.[33,34] The ethylthio 4-nitrophenyl carbonate (**18**) was obtained by reaction of 4-nitrophenol with ethylthio chloroformate in pyridine/CH_2Cl_2. The symmetrical carbonates, diphenyl and bis(4-fluoro)- and bis(4-methoxy)phenyl carbonates (**20**−**22**), were synthesized by reaction of phenol, 4-fluorophenol, and 4-methoxyphenol with phenyl, 4-fluorophenyl, and 4-methoxyphenyl chloroformates, respectively, in pyridine/CH_2Cl_2 medium. The (5-methyl-2-oxo-1,3-dioxol-4-en-1-yl)methyl 4-nitrophenyl carbonate (**23**) was synthesized from commercially available 4,5-dimethyl-1,3-dioxol-2-one by a four-step process basically as outlined in the literature.[23] A modification to the reported procedure has been made in the bromination step ultimately leading to the carbonate **23**. Refluxing the reaction mixture for 15 min,[23] in our hands, leaves considerable amount of starting material. Thus, bromination of dimethyl dioxolone with *N*-bromosuccinimide, in the presence of α,α-azoisobutyronitrile as an initiator in carbon tetrachloride, when heated at reflux for 16 h afforded the monobromide as a major product (90%) and the dibromide as a minor product (10%). Attempted purification of the monobromo derivative by vacuum distillation was unsuccessful. Therefore, the reaction product was used directly. Displacement of the bromide by formate followed by acid-catalyzed hydrolysis to give hydroxymethyl derivative was carried out according to a more recent modification of the original procedure.[26] All carbonates (**12**, **14**, **19**−**23**) showed a strong IR absorption band at 1765−1780 cm^{-1} attributed to O−CO−O stretching vibrations. In the ^{13}C NMR spectra of the carbonates, the carbonyl carbon chemical shift appeared at 152−160 ppm, depending on substitution.

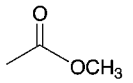
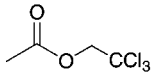
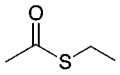
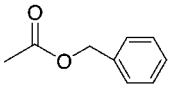
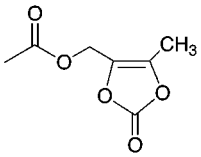
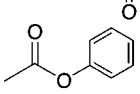
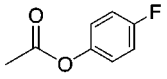
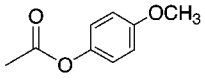
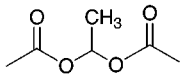
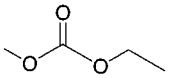
Several reports exist for the synthesis of carbamates from amines; however, few reports exist for the synthesis of carbamates of aromatic amidines. The methyl carbamate **2** was synthesized by the traditional method of reacting bis-amidine **1** with methyl chloroformate in CH_2Cl_2 employing NaOH as the base, in less than 50% yield. As an alternative approach, which improved the yield and purity of the carbamate, the bis-amidine **1** was reacted with methyl 4-nitrophenyl carbonate in DMF to obtain the methyl carbamate **2**, in 80% yield. The carbamates **3**−**10** listed in Table 1 were synthesized from bis-amidine **1** and the appropriate carbonates in DMF or THF/CH_3CN (Scheme 1). When DMF was used as the solvent, it was unnecessary to use an additional base, whereas in THF/CH_3CN medium, diisopropylethylamine was employed as a base. The symmetrical carbonates **20**−**22** were reacted with bis-amidine **1** to obtain the expected carbamates **7**−**9**. All carbamates (**2**−**10**) showed a strong IR absorption band in the region of 1667−1682 cm^{-1} and a broad band at 3000−3500 cm^{-1} attributed to N−C═O and NH stretching vibrations, respectively. In the ^{13}C NMR spectra of carbamates **2**−**10**, the carbonyl carbon chemical shift of NCOO group appeared at 164.3−166.8 ppm. Carbamoylation of amidine **1** causes a downfield shift of the amidine C═N carbon (163.4 ppm) by approximately 1 ppm, as seen at 164.3 ppm in methyl carbamate **2**.

Biological Results

Table 1 contains the results of evaluation of the new carbamate and carbonate prodrugs **2**−**11** against PCP in the immunosuppressed rat model[35] by both oral and intravenous administration. Most of the prodrugs (**2**−**11**) appear to be metabolically activated in vivo since,

Table 1. In Vivo Activity of Carbamate and Carbonate Prodrugs of 2,5-Bis(4-amidinophenyl)furan versus *P. carinii*



Compound	R	Dosage[a] (μmol/kg/day)	Cysts/g of lung[b] (% of control)	Toxicity[c]
Saline		--	100.0 ± 13.24	0
Pentamidine		iv@22.0	3.06 ± 0.90	++
1	H	iv@13.3 Oral@39.8	0.83 ± 0.36 44.52 ± 13.30	0 0
2		iv@22.0 Oral@33.0	6.91 + 6.01 49.68 + 20.50	0 0
3		iv@22.0 Oral@33.0	1.85 ± 1.79 8.59 ± 9.14	0 0
4		iv@22.0 Oral@33.0	83.01 ± 43.65 19.52 + 14.22	0 0
5		iv@11.0 Oral@33.0	0.03 ± 0.02 18.09 ± 9.16	0 0
6		iv@22.0 Oral@33.0	0.02 ± 0.01 18.73 + 11.87	0 0
7		iv@22.0 Oral@33.0	3.61 ± 1.80 5.70 ± 5.15	0 0
8		iv@22.0 Oral@33.0	0.02 + 0.01 2.21 ± 0.33	0 0
9		iv@22.0 Oral@33.0	0.02 + 0.01 2.10 ± 2.08	0 0
10		iv@11.0 Oral@33.0	1.21 ± 1.02 57.16 ± 10.19	++ 0
11		iv@34.7 Oral@33.0	1.66 ± 0.58 96.90 + 48.48	0 0

[a] Evaluation of iv dosage of the furan dications against *P. carinii* in rats as described in refs 35−37. Oral dosage by gavage. [b] Lower numbers of cysts/g of lung refer to higher activity versus PCP. Values below 1% of control are within experimental error and can be considered as complete cure of infection in the immunosuppressed rats. Mean cyst count for pooled controls: saline ($n = 98$) 47.04×10^6 cysts/g of lung tissue; pentamidine ($n = 89$) 1.44×10^6 cysts/g of lung tissue. [c] Toxicity of the test compounds is evaluated according to a five-level scale ranging from 0 to 5+. The toxicity information reported for the in vivo studies should not be considered definitive and is mainly anecdotal. However, these values do allow for comparison of relative toxicities of the test compounds with the control drug pentamidine.

with the exception of **4**, all were quite effective against PCP when administered intravenously. The possibility that the carbonates and carbamates themselves are active against PCP cannot be rigorously excluded from these studies. However, since we have shown for several cases of these type systems that dicationic molecules are required for anti-PCP activity,[3,6,9,19] the most likely origin of the activity is the diamidine metabolites. On oral administration varying degrees of effectiveness were observed. The alkyl carbamates **3**−**5** were more effective than the parent bis-amidine **1** on oral administration, whereas **2** was not. The alkyl carbamates **3**−**5** were more effective than **1** by a factor of from 2−5. In contrast, the phenyl carbamates **7**−**9** were all quite effective when given orally, ranging from 8 (for **7**) to 20 (for **8** and **9**) times more active than **1**. The level of oral activity for **8** and **9** is comparable to that of the oxime prodrugs of **1**, which we have previously described.[19]

The acetoxy carbamate double prodrug **10**, while effective on intravenous dosage, was moderately effective when given orally. The carbonate prodrug **11**, which requires both in vivo hydrolysis and reduction to yield

1, was effective on intravenous administration but was ineffective on oral administration. While these findings suggest that double prodrugs of amidines may be feasible, the current results are insufficiently encouraging to justify further work in this series.

The phenyl carbamates are the most promising of the prodrugs investigated in this study. The observed oral activity of the phenyl carbamates justifies further evaluation of these compounds, and such investigations are underway.

Experimental Section

Melting points were recorded using a Thomas-Hoover (Uni-Melt) capillary melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets (0.20-mm layer thickness) (E. Merck) and detected under UV light. ^{1}H and ^{13}C NMR spectra were recorded employing a Varian GX400 or Varian Unity Plus 300 spectrometer, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were recorded on a VG Analytical 70-SE spectrometer (Georgia Institute of Technology, Atlanta, GA). IR spectra were recorded using a Perkin-Elmer 2000 instrument. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within 0.4% of the theoretical values unless otherwise mentioned. All chloroformates were purchased from Aldrich Chemical Co. 4,5-Dimethyl-1,3-dioxol-2-one was purchased from TCI America Inc. Other chemicals and solvents were purchased from either Acros, Aldrich, or Fischer Scientific. 2,5-Bis(4-cyanophenyl)-furan,[29] 2,5-bis(4-amidinophenyl)furan,[7] and 2,5-bis[4-(*N*-hydroxyamidino)phenyl]furan[19] were synthesized as previously described. Anti-PCP activity screening was carried out according to published methods.[35−37] Compounds were routinely tested orally at 33 μmol/kg/day and intravenously at 22 μmol/kg/day. Saline- and pentamidine-treated groups of rats were included as negative and positive controls, respectively.

2,5-Bis[4-(*N*-methoxycarbonylamidino)phenyl]furan (2). Methyl 4-Nitrophenyl Carbonate (12). To an ice-cold solution of 4-nitrophenol (7.36 g, 0.053 mol) and pyridine (4.3 g, 0.054 mol) in CH_2Cl_2 (80 mL) at 0−5 °C was added a solution of methyl chloroformate (5 g, 0.053 mol) in CH_2Cl_2 (20 mL) and the mixture stirred for 15 min and then at room temperature overnight (16 h). The mixture was extracted with CH_2Cl_2 (50 mL), washed successively with water (50 mL), NaOH (0.5 N, 50 mL), saturated aqueous NaCl solution (50 mL), and water (3 × 50 mL), and dried (Na_2SO_4). The CH_2Cl_2 solution was passed through a silica gel column using chloroform (100%) as eluent to furnish pure carbonate **12** (10 g, 96%) as white solid. Purification of the carbonate by recrystallization from hexane gave 80% yield: mp 111−112 °C; TLC (R_f) 0.50 (100% $CHCl_3$); IR (KBr) 3121, 3086, 1766, 1618, 1602, 1522, 1443, 1366, 938, 858, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.24 (d, 2H, J = 9.05 Hz), 7.34 (d, 2H, J = 9.05 Hz), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$) 155.7, 153.3, 145.6, 125.5, 122.0, 56.1; MS *m*/*e* (EI$^+$, relative intensity, %) 197 (M$^+$, 25), 153 (33), 123 (100), 95 (21), 92 (45), 77 (46), 64 (32), 63 (33), 59 (55).

To a stirring suspension of bis-amidine **1** (0.5 g, 0.00164 mol) in dry DMF (8 mL) at room temperature was added a solution of carbonate **12** (0.72 g, 0.0036 mol) in DMF (2 mL) and the mixture was stirred overnight (16 h). Water (20 mL) was added to the mixture, stirred for few minutes, filtered, washed with water (2 × 10 mL) and ether (10 mL), and dried. Crystallization from ethanol gave pure carbamate **2** (80%) as a white solid: mp >300 °C dec; TLC (R_f) 0.49 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3500−3100, 3010, 2956, 1672, 1609, 1566, 1518, 1476, 1442, 1266, 1198, 1147, 1124, 1086, 1030, 940, 856, 806, 786, 764, 674, 604, 548 cm^{-1}; ^{1}H NMR (DMSO-d_6) 9.11 (s, 4H), 8.07 (d, 4H, J = 8.18 Hz), 7.95 (d, 4H, J = 8.30 Hz), 7.30 (s, 2H), 3.63 (s, 6H); ^{13}C NMR (DMSO-d_6) 165.6, 164.4, 152.6, 133.0, 132.8, 128.4, 123.3, 110.5, 51.8 MS *m*/*z* (FAB, thioglycerol) 421 (M + 1), 389, 363, 346, 321, 305, 289, 271, 257, 237, 230. Anal. ($C_{22}H_{20}N_4O_5$) C, H, N.

2,5-Bis[4-(*N*-(2,2,2-trichloroethoxycarbonyl)amidino)phenyl]furan (3). 4-Nitrophenyl 2,2,2-Trichloroethyl Carbonate (14). To an ice-cold solution of 4-nitrophenol (2.0 g, 14.4 mmol) and triethylamine (1.6 g, 15.8 mmol) (or pyridine) in CH_2Cl_2 (20 mL) at 0−5 °C was added a solution of 2,2,2-trichloroethyl chloroformate (3.2 g, 15 mmol) in CH_2Cl_2 (10 mL) and the mixture stirred for 15 min and then at room temperature overnight (16 h). Aqueous workup as described above and purification of the product by silica gel column chromatography using chloroform (100%) as eluent furnished pure carbonate **14** (4.3 g, 91%). Alternatively, the product could also be purified by recrystallization from hexane in 60% yield: mp 59−60 °C; TLC (R_f) 0.56 (100% $CHCl_3$); IR (KBr) 3123, 3093, 3012, 2967, 2871, 2462, 2365, 2343, 1771, 1630, 1541, 1496, 1432, 1362, 1288, 1251, 1020, 954, 843, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.33 (d, 2H, J = 9.36 Hz), 7.45 (d, 2H, J = 9.36 Hz), 4.91 (s, 2H); ^{13}C NMR ($CDCl_3$) 155.2, 151.7, 145.9, 125.6, 121.9, 93.9, 77.6; MS *m*/*e* (EI$^+$, relative intensity, %) 314 (M$^+$ + 1), 313 (5), 280 (17), 278 (26), 196 (14), 182 (25), 166 (74), 139 (100), 135 (20), 133 (57), 131 (58), 122 (24), 109 (40), 95 (32), 63 (22). Anal. ($C_9H_6NO_5Cl_3$) C, H.

To a suspension of bis-amidine **1** (0.5 g, 0.00164 mol) and diisopropylethylamine (0.43 g, 0.0033 mol) in THF/CH_3CN mixture (20 mL, 1:1 v/v) at room temperature was added a solution of carbonate **14** (1.1 g, 0.0035 mol) in THF (10 mL) and the mixture stirred for 24 h. The solvents were removed under reduced pressure and the residue was cooled in ice, triturated with anhydrous diethyl ether (20 mL), filtered, washed with ether (2 × 20 mL), dried, and crystallized from $CHCl_3$−ether mixture to obtain 2,2,2-trichloroethyl carbamate **3** (0.65 g, 60% yield) as a yellow solid: mp 134−136 °C; TLC (R_f) 0.6; ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3509−3020, 3010, 2997, 2952, 1682,1615, 1600, 1517, 1492, 1485, 1412, 1377, 1251, 1147, 1130, 1120, 1058, 1028, 939, 849, 798, 730, 716, 634, 560 cm^{-1}; ^{1}H NMR (DMSO-d_6) 9.80−9.60 (br s, 4H), 8.07 (d, J = 8.73 Hz, 4H), 8.02 (d, J = 8.73 Hz, 4H), 7.39 (s, 2H), 4.98 (s, 4H); ^{13}C NMR (DMSO-d_6) 166.3, 152.6, 133.6, 129.2, 123.4, 111.2, 95.6, 74.5; MS *m*/*z* (FAB, thioglycerol) 656 (M + 1, 9 isotopic peaks), 507 (7 peaks), 481 (8 peaks), 481 (8 peaks), 464.0 (6 peaks), 357 (3 peaks), 314 (3 peaks), 304, 288, 271, 262, 245, 232. Anal. ($C_{24}H_{18}N_4O_5Cl_6$) C, H, N.

2,5-Bis[4-(*N*-ethylthiocarbonylamidino)phenyl]-furan (4). Ethylthio 4-Nitrophenyl Carbonate (18). Thiocarbonate **18** was synthesized from 4-nitrophenol and ethylthio chloroformate in pyridine/CH_2Cl_2 as described above, in 92% yield, and subsequently purified by silica column chromatography to afford pure colorless crystals: mp 65−66 °C; TLC (R_f) 0.6 (100% $CHCl_3$); IR (KBr) 3120, 3089, 2944, 2588, 2000, 1942, 1740, 1528, 1454, 1352, 1198, 1102, 894, 748, 660, 526 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.25 (dd, 2H, J = 4.92, 2.07 Hz), 7.33 (dd, 2H, J = 4.92, 2.22 Hz), 2.96 (q, 2H, J = 7.46 Hz), 1.38 (t, 3H, J = 7.46 Hz); ^{13}C NMR ($CDCl_3$) 169.7, 155.8, 145.5, 125.4, 122.2, 26.0, 14.8; MS *m*/*e* (EI$^+$, relative intensity, %) 227 (M$^+$, 4), 139 (12), 109 (19), 89 (100), 63 (12). Anal. ($C_9H_9NO_4S$) C, H.

To a suspension of bis-amidine **1** (0.6 g, 0.002 mol) in DMF (10 mL) at room temperature was added a solution of carbonate **18** (0.9 g, 0.004 mol). The resulting solution was stirred for 24 h. Ice water (40 mL) was added to the mixture, filtered, washed with water (3 × 30 mL) and ether (30 mL), and dried. The crude solid was purified by crystallization from ethanol−ether to furnish carbamate **4** (0.6 g, 62%) as a yellow solid: mp >300 °C; TLC (R_f) 0.58 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3445−3200, 3040, 2970, 2928, 2866, 1668, 1610, 1592, 1562, 1469, 1413, 1382, 1320, 1305, 1283, 1208, 1130, 1110, 1090, 1016, 939, 885, 842, 768 cm^{-1}; ^{1}H NMR (DMSO-d_6) 9.26 (s, 4H), 8.07 (d, 4H, J = 8.42 Hz), 7.96 (d, 4H, J = 8.30 Hz), 7.31 (s, 2H), 2.78 (q, 4H, J = 7.32 Hz), 1.24 (t, 6H, J = 7.32 Hz); ^{13}C NMR (DMSO-d_6) 181.4, 162.7, 152.6, 132.9, 132.3, 128.7, 123.4, 110.8, 24.1, 15.3; MS *m*/*z* (FAB, *m*-nitrobenzoic acid) 481 (M + 1), 429, 413, 397, 321, 298, 272, 257, 231. Anal. ($C_{24}H_{24}N_4O_3S_2\cdot 0.25H_2O$) C, H, N.

2,5-Bis[4-(*N*-benzyloxycarbonylamidino)phenyl]-furan (5). Benzyl 4-Nitrophenyl Carbonate (19). Carbon-

ate **19** is commercially available. However, it was synthesized from 4-nitrophenol and benzyl chloroformate as described above for **12**, in 80% yield.

To a suspension of bis-amidine **1** (0.5 g, 0.0016 mol) in DMF (10 mL) at room temperature was added carbonate **19** (1.6 g, 0.006 mol). The resulting solution was stirred for 24 h and ice water (40 mL) was then added and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ extract was washed with NaOH (1 N, 40 mL), satd NaCl (40 mL), and water (50 mL) and dried (Na_2SO_4). The solution was filtered, concentrated under reduced pressure, cooled in an ice bath, triturated with ether (30 mL), filtered, washed with ether (3 × 20 mL), and dried under vacuum for 16 h to afford carbamate **5** as a shiny pale yellow solid (0.77 g, 52%). The yield was improved to 91% by precipitation of the product after the reaction, by addition of ice−water instead of chloroform extraction: mp 225 °C dec; TLC (R_f) 0.76 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3480−3140, 3111, 3087, 3063, 3032, 2960, 2866, 1667, 1612, 1570, 1507, 1497, 1375, 1296, 1266, 1145, 926, 859, 787, 744, 702 cm^{-1}; ^1H NMR (DMSO-d_6) 9.16 (s, 4H), 8.09 (d, 4H, J = 8.57 Hz), 7.95 (d, 4H, J = 8.57 Hz), 7.42−7.31 (2 d + 3t, 10H), 7.30 (s, 2H), 5.13 (s, 4H); ^{13}C NMR (DMSO-d_6) 166.0, 163.7, 152.6, 137.1, 132.9, 132.9, 128.4, 128.3, 128.0, 127.8, 123.3, 110.6, 66.0; MS *m/e* (FAB, *m*-nitrobenzoic acid) 573 (M + 1), 460, 439, 421, 378. Anal. ($C_{34}H_{28}N_4O_5 \cdot 2H_2O$) C, H, N.

A mixture of the carbamate free base **5** (0.4 g, 0.0007 mol), maleic acid (0.18 g, 0.0016 mol), and dry ethanol (20 mL) was stirred at room temperature for 4 h. The mixture was cooled in an ice bath, triturated with dry Et_2O (25 mL), filtered, washed with Et_2O (3 × 10 mL), and dried in a vacuum oven at 50 °C overnight to afford **5** dimaleate salt as a yellow solid (0.53 g, 94%): mp 155−157 °C dec; IR (KBr) 3480−3140, 3111, 3087, 3063, 3032, 2960, 1667, 1612, 1570, 1507, 1497, 1375, 1266, 1145, 926, 859, 787, 744, 702 cm^{-1}; ^1H NMR (DMSO-d_6) 9.40−9.80 (br s, 2H), 8.03 (d, 4H, J = 8.56 Hz), 7.99 (d, 4H, J = 8.56 Hz), 7.42−7.31 (2 d + 3 t, 10H), 7.35 (s, 2H), 6.18 (s, 2H), 5.19 (s, 4H); ^{13}C NMR (DMSO-d_6) 166.8, 165.5, 152.6, 136.4, 133.3, 132.1, 128.9, 128.4, 128.1, 128.0, 123.4, 111.0, 66.7; MS *m/e* (FAB, *m*-nitrobenzoic acid) (free base) 573.2, 460.1, 421.2, 378.2. Anal. ($C_{42}H_{36}N_4O_{13}$) C, H, N.

2,5-Bis{4-[*N*-(5-methyl-2-oxo-1,3-dioxol-4-en-1-yl)-methoxycarbonylamidino]phenyl}furan (6). 4-Bromomethyl-5-methyl-1,3-dioxol-2-one. A mixture of 4,5-dimethyl-1,3-dioxol-2-one (15.0 g, 0.132 mol), α,α-azobis(isobutyronitrile) (AIBN) (1.08 g, 0.0066 mol), and *N*-bromosuccinimide (23.4 g, 0.132 mol) in freshly distilled carbon tetrachloride (350 mL) was refluxed under nitrogen for 16 h. The mixture was concentrated to one-half the initial volume and cooled in an ice bath and the white solid was filtered. Concentration of the filtrate (CCl_4 solution) under reduced pressure gave 4-bromomethyl-5-methyl-1,3-dioxol-2-one as a pale brown liquid in 90% yield (25 g). Due to the instability of the product at room temperature, it was used without purification for the next step. A small amount of the crude product (100 mg) was purified for NMR analysis, through a short pad of silica gel using $CHCl_3$ (100%) as eluent: ^1H NMR ($CDCl_3$) 4.21 (s, 2H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$) 151.7, 138.1, 134.6, 18.0, 9.51.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl Formate. To an ice-cold solution of 4-bromomethyl-5-methyl-1,3-dioxol-2-one (24 g, 0.124 mol) and formic acid (19.5 g, 0.43 mol) in acetonitrile (250 mL) at 0 °C was added triethylamine (44 g, 0.44 mol) dropwise over a period of 15 min. The ice bath was then removed and the mixture was stirred at room temperature for 2 h. The mixture was concentrated to one-half the initial volume under reduced pressure and extracted with ethyl acetate (2 × 150 mL). The organic extract was washed successively with satd $NaHCO_3$ (200 mL), satd NaCl (200 mL), and water (200 mL) and dried (Na_2SO_4). Concentration of the filtrate gave crude formate ester as a colorless liquid (20 g): ^1H NMR ($CDCl_3$) 8.06 (s, 1H), 4.91 (s, 2H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$) 160.3, 152.1, 140.6, 133.1, 53.1, 9.42.

4-Hydroxymethyl-5-methyl-1,3-dioxol-2-one. To a solution of the crude formate (19.9 g) and 80% methanol (250 mL) at room temperature was added concentrated HCl (1 mL) and the mixture stirred for 6 h. Methanol was evaporated at 30 °C under reduced pressure and the residue was extracted with ethyl acetate. Passage through a short pad of silica gel and concentration gave 4-hydroxymethyl-5-methyl-1,3-dioxol-2-one as a colorless oil (7.0 g, 43%): ^1H NMR ($CDCl_3$) 4.37 (s, 2H), 2.80 (s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$) 152.9, 137.6, 135.0, 53.3, 9.33.

(4-Methyl-2-oxo-1,3-dioxol-4-en-5-yl)methyl 4-Nitrophenyl Carbonate (23). Carbonate **23** was synthesized from 4-methyl-5-hydroxymethyl-2-oxo-1,3-dioxol-4-ene and 4-nitrophenyl chloroformate in CH_2Cl_2/pyridine as described earlier for compound **14** and purified by crystallization from chloroform to give colorless crystals in 76% yield: mp 120−121 °C (lit.[31] mp 116−117 °C); TLC (R_f) 0.23 (100% $CHCl_3$); IR (KBr) 3115, 3096, 2928, 2854, 1811, 1780, 1742, 1619, 1593, 1525, 1494, 1352, 1308, 1246, 1221, 1054, 860, 768 cm^{-1}; ^1H NMR ($CDCl_3$) 8.29 (d, 2H, J = 9.04 Hz), 7.39 (d, 2H, J = 9.20 Hz), 5.03 (s, 2H), 2.22 (s, 3H); ^{13}C NMR ($CDCl_3$) 155.4, 152.46, 151.8, 145.9, 141.6, 132.4, 125.6, 121.9, 58.4, 9.65; MS *m/e* (EI^+, relative intensity, %) 295 (M^+, 1), 139 (9), 113 (100), 69 (23), 43 (74). Anal. ($C_{12}H_9NO_8$) C, H, N.

To a suspension of bis-amidine **1** (0.7 g, 0.0023 mol) in DMF (15 mL) at room temperature was added a solution of carbonate **23** (1.5 g, 0.0052 mol) in DMF (5 mL) and the mixture stirred for 24 h. Ice water (50 mL) was added and the solid was filtered, washed with water (3 × 20 mL) and ether (30 mL), and dried under vacuum. The crude product was crystallized from $CHCl_3$−ether mixture to yield pure carbamate **6** (1.26 g, 89%) as a yellow solid: mp 153−155 °C; TLC (R_f) 0.33 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3500−3120, 3105, 3075, 2866, 3037, 1825, 1667, 1660, 1618, 1610, 1521, 1497, 1417, 1394, 1266, 1230, 1145, 1094, 989, 927, 787, 687 cm^{-1}; ^1H NMR (DMSO-d_6) 9.19 (s, 4H), 8.09 (d, J = 8.43 Hz), 7.96 (d, 4H, J = 8.24 Hz), 7.31 (s, 2H), 4.95 (s, 4H), 2.18 (s, 6H); ^{13}C NMR (DMSO-d_6) 166.2, 162.9, 152.6, 152.0, 139.5, 134.1, 133.0, 132.6, 128.5, 123.3, 110.7, 54.2, 8.82; MS *m/z* (FAB, *m*-nitrobenzoic acid) 617 (M + 1), 505, 487, 460, 443, 424, 375, 357. Anal. ($C_{36}H_{24}N_4O_{11}$) C, H, N.

2,5-Bis[4-(*N*-phenoxycarbonylamidino)phenyl]furan (7). Diphenyl Carbonate (20). Carbonate **20** is commercially available. However, it was prepared by reaction of phenol with phenyl chloroformate in pyridine/CH_2Cl_2 followed by aqueous workup as described above to give a white solid (90% yield): mp 79−80 °C. Physical data were identical with the standard.

To a suspension of bis-amidine **1** (0.5 g, 0.0016 mol) in DMF (10 mL) at room temperature was added carbonate **20** (0.77 g, 0.0036 mol). The resulting solution was stirred for 24 h, ice water (40 mL) was then added, and the resulting solid was filtered, washed with plenty of water (3 × 30 mL) and ether (2 × 30 mL), and dried under vacuum in a desiccator for 16 h to furnish carbamate **7** (0.53 g, 63%) as a yellow solid: mp >300 °C; TLC (R_f) 0.68 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3680−3000, 1674, 1615, 1562, 1515, 1488, 1412, 1382, 1266, 1199, 1170, 1145, 1030, 1016, 939, 969, 864, 798, 738, 693, 589 cm^{-1}; ^1H NMR (DMSO-d_6) 9.30 (s, 4H), 8.12 (d, 4H, J = 7.61 Hz), 7.98 (d, 4H, J = 7.30 Hz), 7.44 (m, 4H,), 7.33 (s, 2H), 7.22 (t, 2H, J = 6.19 Hz), 7.20 (d, 4H, J = 8.57 Hz); ^{13}C NMR (DMSO-d_6) 166.8, 162.1, 152.7, 151.6, 133.1, 132.6, 129.2, 128.6, 124.9, 123.4, 122.0, 115.2, 110.8; MS *m/z* (FAB, *m*-nitrobenzoic acid) 545 (M + 1), 460, 451, 425, 408, 391, 357, 329. Anal. ($C_{32}H_{24}N_4O_5 \cdot 1.3H_2O$) C, H, N.

2,5-Bis[4-(*N*-(4-fluorophenoxy)carbonylamidino)phenyl]-furan (8). Bis(4-fluorophenyl) Carbonate (21). Reaction of 4-fluorophenol with 4-fluorophenyl chloroformate in pyridine/CH_2Cl_2 as described earlier afforded carbonate **21** after silica gel column chromatography in 85% yield as a white solid: mp 122−123 °C; TLC (100% $CHCl_3$) 0.7; IR (KBr) 3130, 3091, 1885, 1764, 1649, 1610, 1508, 1304, 1234, 1176, 1094, 1010, 902, 838, 729, 576, 510 cm^{-1}; ^1H NMR ($CDCl_3$) 7.24 (dd, 4H, J = 9.05, 4.44 Hz), 7.08 (dd, 4H, J = 8.89, 8.09 Hz); ^{13}C NMR ($CDCl_3$) 161.9, 159.5, 152.3, 147.1, 147.0, 122.6, 122.5, 116.6, 116.4; MS *m/e* (EI^+, relative intensity, %) 250 (M^+, 82),

206 (27), 178 (12), 177 (43), 139 (11), 112 (25), 111 (20), 95 (100), 83 (32), 75 (19), 57 (17). Anal. ($C_{13}H_8F_2O_3$) C, H.

To a suspension of bis-amidine **1** (0.5 g, 0.0026 mol) in DMF (10 mL) at room temperature was added a solution of carbonate **21** (0.87 g, 0.0035 mol). The resulting solution was stirred for 16 h. Ice water (40 mL) was added to the mixture, filtered, washed with water (3 × 30 mL) and ether (30 mL), and dried in a vacuum for 24 h to furnish 4-fluorophenyl carbamate **8** (0.92 g, 61%) as a yellow solid: mp >300 °C; TLC (R_f) 0.45 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3465−3000, 1667, 1621, 1491, 1260, 1187, 1139, 1078, 969, 859, 793, 665 cm^{-1}; ^1H NMR (DMSO-d_6) 9.31 (s, 4H), 8.12 (d, 4H, J = 8.73 Hz, Ar−CH), 7.98 (d, 4H, J = 8.57 Hz), 7.33 (s, 2H), 7.22 (d, 8H, J = 6.5 Hz); ^{13}C NMR (DMSO-d_6) 162.1, 161.9, 157.8, 156.5, 154.2, 153.4, 152.6, 147.8, 133.0, 132.4, 132.6, 128.8, 128.5, 127.8, 123.5, 123.4, 123.3, 116.0, 115.9, 115.6, 115.5, 115.4, 115.2; MS m/z (FAB, m-nitrobenzoic acid) 581 (M + 1), 469, 443, 426, 357, 331. Anal. ($C_{32}H_{22}N_4O_5F_2 \cdot 0.5H_2O$) C, H, N.

2,5-Bis[4-(*N*-(4-methoxyphenoxy)carbonylamidino)-phenyl]furan (9). Bis(4-methoxyphenyl) Carbonate (22). Reaction of 4-methoxyphenol with 4-methoxyphenyl chloroformate in pyridine/CH_2Cl_2 followed by aqueous workup as described above gave carbonate **22**, after silica gel column chromatography, in 93% yield as a white solid: mp 95 °C; TLC (R_f) 0.53 (100% $CHCl_3$); IR (KBr) 3076, 2958, 2848, 1772, 1610, 1514, 1470, 1286, 1242, 1182, 1028, 894, 836, 776, 726, 534 cm^{-1}; ^1H NMR ($CDCl_3$) 7.16 (d, 4H, J = 9.05 Hz), 6.88 (d, 4H, J = 9.04 Hz), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$) 157.7, 153.0, 144.8, 122.0, 114.7, 55.8; MS m/e (EI^+, relative intensity, %) 274 (M^+, 100), 230 (33), 215 (29), 187 (12), 124 (16), 123 (46), 107 (10), 95 (12), 77 (13), 64 (7), 52 (5), 41 (6). Anal. ($C_{15}H_{14}O_5$) C, H.

To a suspension of bis-amidine **1** (0.7 g, 0.0016 mol) in DMF (10 mL) at room temperature was added carbonate **22** (1.39 g, 0.0051 mol) and the mixture stirred for 24 h. Anhydrous ether (25 mL) was then added to the precipitated product, stirred for a few minutes, filtered, washed with ether (3 × 15 mL), and dried under vacuum in a desiccator for 48 h to furnish 4-methoxyphenyl carbamate **9** (0.9 g, 65%) as a yellow solid: mp >300 °C; TLC (R_f) 0.68 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3450−3100, 3010, 2934, 2836, 1683, 1484, 1256, 1184, 1142, 1078, 1033, 1010, 967, 928, 850, 801, 774, 753, 696, 659, 607, 583, 559, 531 cm^{-1}; ^1H NMR (DMSO-d_6) 9.26 (s, 4H), 8.11 (d, 4H, J = 8.54 Hz), 7.98 (d, 4H, J = 8.53 Hz), 7.34 (s, 2H), 7.09 (d, 4H, J = 9.04 Hz), 6.93 (d, 4H, J = 9.03 Hz), 3.75 (s, 6H), 2.88 (s, 3H, DMF), 2.72 (s, 3H, DMF); ^{13}C NMR (DMSO-d_6) 166.62, 156.3, 152.6, 145.1, 133.0, 132.6, 128.5, 123.4, 122.7, 114.1, 110.7, 55.4, 35.74 (DMF), 30.74 (DMF); MS m/z (FAB, thioglycerol) 605 (M + 1), 481, 429, 323, 303, 289, 273, 257, 247, 229. Anal. ($C_{34}H_{28}N_4O_7 \cdot 1DMF$) C, H, N.

2,5-Bis[4-(1-acetoxyethoxycarbonylamidino)phenyl]-furan (10). 1-Chloroethyl 4-Nitrophenyl Carbonate (16). To an ice-cold solution of 4-nitrophenol (2.0 g, 0.015 mol) and triethylamine (1.6 g, 0.016 mol) (or pyridine) in CH_2Cl_2 (20 mL) at 0−5 °C was added a solution of 1-chloroethyl chloroformate (2.1 g, 19 mmol) in CH_2Cl_2 (10 mL) and the mixture stirred for 15 min and then at room temperature overnight (16 h). The mixture was extracted with CH_2Cl_2 (50 mL), washed successively with water (50 mL), NaOH (0.5 N, 50 mL), satd NaCl solution (50 mL), and water (3 × 50 mL), and dried (Na_2SO_4). The CH_2Cl_2 solution was filtered and evaporated under reduced pressure and the residue was purified by silica gel column chromatography using chloroform (100%) as eluent to furnish pure carbonate **16** as a white solid: mp 70−71 °C (lit.[21] mp 69−70 °C); TLC (R_f) 0.75 ($CHCl_3$); IR (KBr) 3116, 3084, 2999, 2932, 2864, 2364, 2330, 1779, 1626, 1525, 1355, 1245, 1101, 914, 863, 779, 677 cm^{-1}; ^1H NMR ($CDCl_3$) 8.31 (dd, 2H, J = 5.08, 2.07 Hz), 7.43 (dd, 2H, J = 4.76, 2.22 Hz), 6.50 (q, 1H, J = 11.67 Hz), 1.93 (d, 3H, J = 5.87 Hz); ^{13}C NMR ($CDCl_3$) 155.2, 150.6, 145.9, 125.6, 121.9, 85.4, 25.3; MS m/e (EI^+, relative intensity) 210 (M^+ − HCl, 4), 139 (26), 122 (13), 109 (8), 76 (13), 75 (11), 65 (27), 64 (17), 63 (100), 50 (10), 43 (13).

1-Acetoxyethyl 4-Nitrophenyl Carbonate (17). To a solution of 1-chloroethyl 4-nitrophenyl carbonate (2.0 g, 0.0082 mol) in glacial acetic acid (50 mL) at room temperature was added mercuric acetate (3.8 g, 0.012 m) and the mixture was stirred for 40 h. Water (100 mL) was then added to the mixture and extracted with ether (2 × 75 mL). The ethereal phase was washed with NaOH (0.5 N, 30 mL), satd NaCl (30 mL), and water (2 × 50 mL) and dried (anhydrous Na_2SO_4). The solution was filtered, concentrated under reduced pressure, and purified by silica gel column chromatography to afford pure carbonate **17** (1.9 g, 89%) as a colorless liquid: TLC (R_f) 0.65 ($CHCl_3$); IR (film) 1779, 1749, 1615, 1592, 1528, 1491, 1266, 1110, 1070, 857 cm^{-1}; ^1H NMR ($CDCl_3$) 8.29 (d, 2H, J = 9.05 Hz), 7.41 (d, 2H, J = 9.04 Hz), 6.84 (q, 1H, J = 10.95 Hz), 2.14 (s, 3H), 1.62 (d, 3H, 5.4 Hz); ^{13}C NMR ($CDCl_3$) 169.1, 155.3, 150.7, 145.8, 125.5, 121.9, 92.5, 20.96, 19.61; MS m/e (EI^+, relative intensity) 210 (M^+), 166 (4), 122 (5), 87 (33), 63 (6), 50 (3), 43 (100).

A mixture of bis-amidine **1** (0.4 g, 0.0013 mol), diisopropylethylamine (0.35 g, 0.0026 mol), and THF/CH_3CN (1:1 mixture, 15 mL) was stirred at room temperature. A solution of carbonate **17** (0.71 g, 0.00264 mol) in THF (5 mL) was then added and stirring was continued for 24 h. Solvents were removed under reduced pressure at 40 °C, triturated with anhydrous ether (20 mL), filtered, washed with ether (2 × 25 mL), dried in air, and crystallized from $CHCl_3$−ether to yield 1-acetoxyethyl carbamate **10** as a yellow solid in 71% yield (0.52 g): mp 165−167 °C dec; TLC (R_f) 0.5 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3690−2900 (br), 3458 (s), 3324 (s), 3131 (s), 2945 (s), 1734, 1667, 1640, 1607, 1562, 1488, 1412, 1362, 1279, 1243, 1147, 1117, 1089, 1057, 1022, 992, 932, 885, 842, 797, 597, 566 cm^{-1}; ^1H NMR (DMSO-d_6) 9.33 (s, 4H), 8.09 (d, 4H, J = 8.54 Hz), 7.96 (d, 4H, J = 8.54 Hz), 7.34 (s, 2H), 6.79 (q, 2H, J = 10.87 Hz), 2.03 (s, 6H), 1.55 (d, 6H, J = 5.39 Hz); ^{13}C NMR (DMSO-d_6) 168.9, 166.8, 161.5, 152.6, 133.1, 132.6, 128.6, 123.4, 110.8, 89.2, 20.8, 19.6; MS m/z (FAB, thioglycerol) 565 (M + 1), 479, 461, 435, 375, 357, 331, 314, 288, 271. Anal. ($C_{28}H_{28}N_4O_9$) C, H, N.

2,5-Bis[4-(*N*-ethoxycarbonyloxyamidino)phenyl]-furan (11). NaOH method: To a suspension of the bis-amidoxime (2,5-bis[4-(*N*-hydroxyamidino)phenyl]furan) (0.86 g, 0.0028 mol) and CH_2Cl_2 (15 mL) was added a solution of ethyl chloroformate (1.22 g, 0.011 mol) in CH_2Cl_2 (15 mL) and the mixture stirred for 10 min. NaOH (1 N, 12 mL) was then added dropwise and stirred at room temperature for 6 h. Ice water (10 mL) was added and the solid was filtered, washed with water (3 × 30 mL), dried in air, and crystallized from ethanol to give pure ethyl carbonate **11** (0.67 g, 50% yield) as a white solid.

Carbonate method: Ethyl 4-Nitrophenyl Carbonate (13). Reaction of 4-nitrophenol with ethyl chloroformate in pyridine/CH_2Cl_2 as described above, gave carbonate 1**3** as colorless crystals in 92% yield by silica gel chromatographic purification and 82% by crystallization: mp 70−71 °C; TLC (R_f) 0.48 (100% $CHCl_3$); IR (KBr) 3124, 3092, 3010, 2920, 2866, 1772, 1622, 1600, 1536, 1278, 1112, 1060, 1006, 908, 860, 774, 732, 662, 527, 502 cm^{-1}; ^1H NMR ($CDCl_3$) 8.29 (d, 2H, J = 9.05 Hz), 7.38 (d, 2H, J = 9.05 Hz), 4.36 (q, 2H, J = 14.28 Hz), 1.38 (t, 3H, J = 7.07 Hz); ^{13}C NMR ($CDCl_3$) 155.8, 152.6, 145.6, 125.5, 122.0, 65.7, 14.3; MS m/e (EI^+, relative intensity, %) 212 (M^+, 1.4), 211 (1), 139 (100), 109 (60), 89 (100), 93 (13), 81 (11), 65 (21), 63 (13).

Reaction of the bis-amidoxime with carbonate **13** in DMF at room temperature gave the bis-ethoxycarbonyloxy derivative in 85% yield as a white solid: mp >300 °C dec. The physical data for compound **11** obtained by both methods were identical. TLC (R_f) 0.5 ($CHCl_3$, MeOH, NH_4OH, 4:1:0.2, v/v); IR (KBr) 3700−3100, 3056, 2989, 2937, 2915, 2890, 1770, 1668, 1635, 1481, 1414, 1370, 1266, 1208, 1124, 1035, 1013, 939, 857, 834, 775, 686 cm^{-1}; ^1H NMR (DMSO-d_6) 7.91 (d, 4H, J = 7.21 Hz), 7.78 (d, 4H, J = 7.20 Hz), 7.24 (s, 2H), 6.89 (s, 4H), 4.20

(q, 4H, $J = 14$ Hz), 1.26 (t, 6H, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6) 156.0, 153.5, 152.4, 131.6, 130.2, 127.3, 123.3, 109.7, 63.6, 14.20; MS *m/z* (FAB, thioglycerol) 481 (M + 1), 429, 393, 377, 347, 323, 305, 288, 271, 237. Anal. ($C_{24}H_{24}N_4O_7$) C, H, N.

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