determinant factor in AA and LA activities which, in turn, confirms the nonspecific character of both activities. Similar findings have been reported recently on related β-adrenoceptor blocking monoethers in relation to their in vivo and in vitro cardiodepressant activities.[5] Table IV compares the observed activities with those predicted by the optimal equations.

Experimental Section

Melting points were determined on a Reichert microscope with Kofler heating and are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60 instrument using $CDCl_3$ or D_2O as solvents and Me_4Si or sodium 3-(trimethylsilyl)propanesulfonate (TMSPS) as internal standards. Elemental analyses indicated were within ±0.4% of the theoretical values. All *o*-dihydroxyarenes were from commercial sources except for 2,3-dihydroxy-5,6,7,8-tetrahydronaphthalene which was prepared from veratrole according to Haworth and Mavin;[10] the final step, namely, demethylation of the methoxy groups, was accomplished in 96% yield by treatment with BBr_3 in CH_2Cl_2 according to McOmie et al.[11]

1,1′-(3-Methylphenylene-1,2-dioxy)bis(3-chloro-2-propanol) (2a). A solution of 12.4 g (0.1 mol) of 3-methylcatechol, 37.0 g (0.4 mol) of epichlorohydrin and 0.4 mL of 10 N NaOH was stirred under N_2 at 40 °C for 48 h. After evaporation of the epichlorohydrin in vacuo at 40 °C, the residual oil was taken up in $CHCl_3$, washed twice, and concentrated. Molecular distillation yielded 21.3 g of impure **2a**.

1,1′-(3-Methylphenylene-1,2-dioxy)bis(3-isopropylamino-2-propanol) (2). A solution of 13.1 g of impure **2a**, 14.8 g (0.25 mol) of *i*-$PrNH_2$, and 15.0 mL of C_6H_6 was heated in a Carius tube at 80 °C for 8 h. After concentration, the product was taken up in 4 N AcOH and extracted carefully with $CHCl_3$. The amino ether was liberated with 2 N NaOH, taken up in $CHCl_3$, washed, and concentrated to give 0.0252 mol of **2** in a purity of 99.6% (potentiometric titration): yield, as calculated with reference to 3-methylcatechol, 43%. The compound was taken up in anhydrous Et_2O and treated with the calculated amount of ethereal HCl solution to afford the dihydrochloride salt. On TLC (silica gel GF_{254}, 20 vol % Me_2CO in $CHCl_3$) of the original $CHCl_3$ extract only one spot appeared. GLC (20% SE-30 on Chromosorb W 60–80) confirmed[12] it to consist of a mixture of 2-hydroxymethyl-5- and -8-methylbenzodioxane. Single molecular distillation gave 0.0206 mol: n^{20}D 1.5510 (lit.[12] n^{25}D 1.5488 and 1.5510 for the 5-methyl and 8-methyl isomer, respectively); total yield of amino ether and benzodioxanes, 0.0458 mol. Anal. ($C_{10}H_{12}O_3$) C, H.

On amination of molecular distilled 1,1′-(3-isopropylphenylene-1,2-dioxy)bis(3-chloro-2-propanol), prepared from an equimolar amount of 3-isopropylcatechol, 0.0141 mol of amino ether and 0.0332 mol of 2-hydroxymethyl-5- and -8-isopropylbenzodioxane [n^{20}D 1.5359. Anal. ($C_{12}H_{16}O_3$) C, H] were obtained: total yield 0.0473 mol. The similarity of the total yields demonstrates that on amination of the impure bis(3-chloro-2-hydroxypropyl) ethers, the monoethers still present were converted virtually quantitatively into 2-hydroxymethyl-1,4-benzodioxanes.

1,1′-(Naphthalene-2,3-dioxy)bis(2,3-epoxypropane) (7a). A solution of 16.0 g (0.1 mol) of 2,3-dihydroxynaphthalene, 15 mL of EtOH, 37.0 g of epichlorohydrin, and 0.4 mL of 10 N NaOH was stirred under N_2 at 40 °C for 54 h. After concentration in vacuo at 40 °C, the oil was taken up in 28.0 g of epichlorohydrin and stirred vigorously with 42.0 mL of 5 N NaOH, saturated with Na_2CO_3, at room temperature for 20 h.[13] After addition of Et_2O and H_2O the product was extracted, washed, concentrated, and crystallized from Et_2O: mp 83.5–87.5 °C; yield 17.9 g (66%). The ^{1}H NMR spectrum was consistent with the structure.

Dissociation constants and partition coefficients, 1-octanol–phosphate buffer, pH 7.40, were determined as described previously.[1]

Acknowledgment. The authors are very grateful to Miss G. J. Bijloo for expert computational assistance.

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Synthesis and Antiprotozoal Activity of 2,5-Bis(4-guanylphenyl)furans

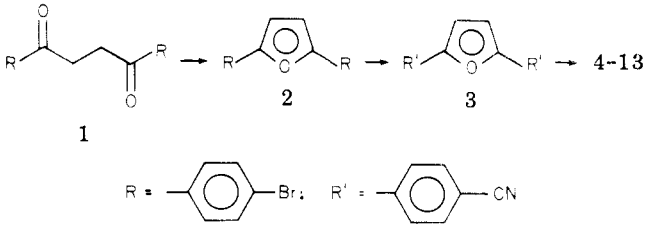
Bijan P. Das and David W. Boykin*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303. *Received August 10, 1976*

Eighteen substituted 2,5-bis(4-guanylphenyl)furans and related analogues, including "masked" amidines in which the guanyl function is incorporated into a heterocyclic ring, have been synthesized and their antimalarial and antitrypanosomal activity has been evaluated. None of the compounds exhibited high orders of antimalarial activity; however, 11 were very active against *Trypanosoma rhodesiense* in mice. Six compounds, including 2,5-bis(4-guanylphenyl)furan (**4**) and its 3-chloro (**32**), 3,4-dichloro (**31**), 3-methyl (**25**), 3,4-dimethyl (**20**), and 3-chloro-4-methyl (**38**) derivatives, produced cures in mice at submilligram dosage levels; the 3,4-dimethyl (**20**) analogue exhibited a prolonged curative effect providing protection for 30 days after a single dose against a challenge by *T. rhodesiense*. These six compounds are somewhat more active in this screen than stilbamidine, hydroxystilbamidine, and pentamidine. The "masked" amidines generally exhibited lower antitrypanosomal activity than their true guanyl counterparts. Compound **4** was synthesized from 1,4-di-*p*-bromophenyl-1,4-butanedione by cyclodehydrative furanization to 2,5-bis(4-bromophenyl)furan (**2**) which was allowed to react with $Cu_2(CN)_2$ to produce the corresponding bis-nitrile **3**. The latter compound was ultimately converted by way of an imidate ester into **4**. Similarly, the 3- and/or 4-substituted derivatives of **2** were employed to prepare the other members of the series.

A number of aryldiamidines have been found to be valuable for the treatment of various protozoan diseases.[1-4] Diminazene,[2] imidocarb,[3] stilbamidine,[2] hydroxystilbamidine,[2,4] pentamidine,[2,4] congocidin,[1a] and the tere-

Scheme I



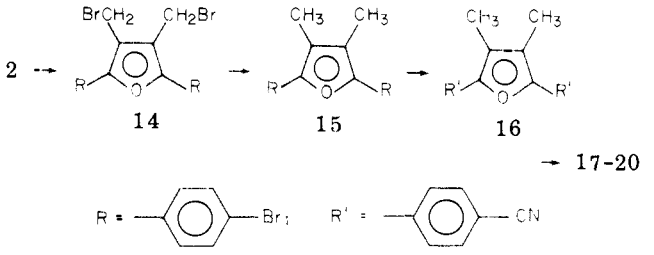
phthanilide amidines[5] are active against several protozoan diseases but are perhaps most notable as trypanocides. Some time ago, stilbamidine and pentamidine were reported to have some activity against avian malarias;[6] more recently, diminazene and pentamidine were reported to be 125 and 317 times more active than chloroquine against *Plasmodium vinckei*.[7] In light of the significant antimalarial activity for these compounds, and our continuing interest in the malarial problem, we were led to prepare new aryldiamidines as potential antimalarials.

The approach taken for the design of new aryldiamidines was based, in part, upon the fact that numerous workers have cited the ability of these compounds to bind to DNA as an important factor which contributes to their biological activity.[8] The mechanism of interaction between DNA and the aryldiamidines studied has been reported to involve binding outside the helix, presumedly resulting from the electrostatic interaction between the negative phosphate groups on DNA and the positive guanyl centers of the diamidines.[9,10] Upon examination of molecular models of a number of aryldiamidines which exhibit useful biological activity, it was noted that they seem to fall into two spatial classes. One group has the guanyl functions separated by approximately 12 Å and the other has the amidine units separated by approximately 20 Å. It is probably only coincidental that these values correspond reasonably well with the distance across the minor and major grooves of DNA, since, for example, it has been proposed that congocidin, a 20-Å type, binds in the minor groove.[10] Nevertheless, we undertook to prepare several series of aryldiamidines which fall into one of the two groups. This paper describes the synthesis and biological evaluation of a series of 2,5-bis(4-guanylphenyl)furans which fall into the 12-Å category. Subsequent papers will deal with other 2,5-diaryl-substituted five-membered ring heterocyclic systems, as well as some 20-Å types. After completion of the synthetic work, a report appeared describing significant activity against *Trypanosoma rhodesiense* for 2,5-bis(4-guanylphenyl)furan (**4**).[11] In addition to preparing true diamidines, we were interested in assessing, in these systems, the effect on biological activity of masking the amidine function by incorporating it in a heterocyclic ring. The "masked" or cyclic amidine unit has been a useful variant in other areas where the amidine function has exhibited interesting biological properties.[12]

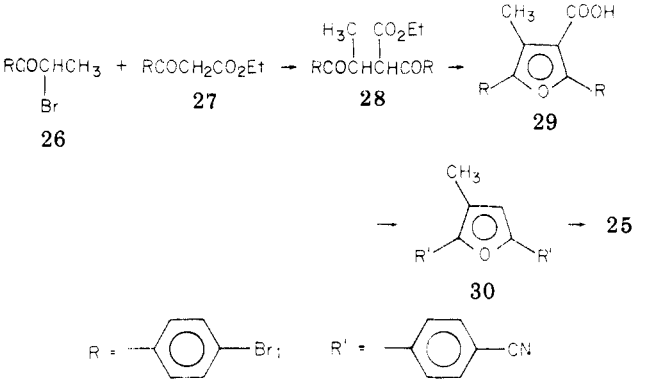
Chemistry. The 2,5-bis(4-guanylphenyl)furans and related compounds shown in Table I were prepared from the corresponding 2,5-bis(4-cyanophenyl)furans by conversion into imidate esters followed by reaction of these intermediates with ammonia or the appropriate diamine.[12] Purification of the hydrochloride salts of the diamidines was plagued with the usual difficulties encountered during purification of guanyl derivatives arising from their insolubility in organic solvents and their propensity to form hydrates.

2,5-Bis(4-bromophenyl)furan (**2**), precursor of 2,5-bis(4-cyanophenyl)furan (**3**) and ultimately for compounds **4–14**, was prepared by employing well-known cyclodehydration techniques for furanization of 1,4-diketones[13] (Scheme I). 2,5-Bis(4-bromophenyl)furan (**2**) was also used as an intermediate for the preparation of the 3,4-dimethyl-2,5-bis(4-guanylphenyl)furan analogues **17–20** and is patterned after a reported method of preparation of 2,5-diphenyl-3,4-dimethylfuran[14] (Scheme II).

Scheme II



Scheme III

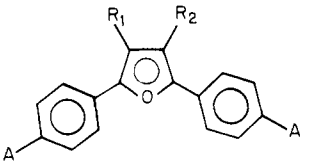


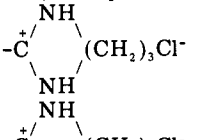
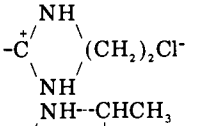
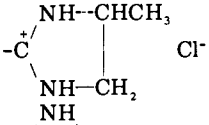
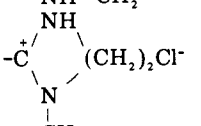
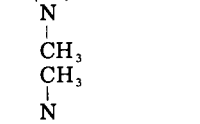
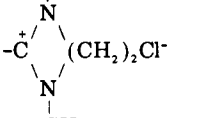
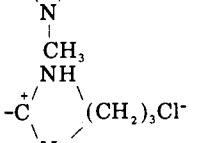
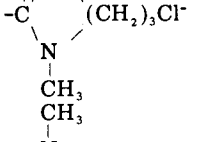
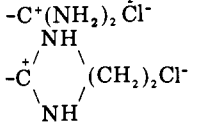
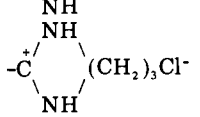
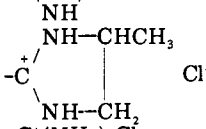
It has been reported that 2,5-bis(*p*-bromophenyl)-3-bromo-4-bromomethylfuran could be converted into 2,5-bis(*p*-bromophenyl)-3-methylfuran by a two-step process.[15] The procedure involved, first, nitric acid oxidation to form *cis*-1,2-bis(*p*-bromobenzoyl)-1-bromo-2-bromomethylethylene which was allowed to react with stannous chloride to give reductive debromination and furanization. We attempted to take advantage of the availability of 2,5-bis(4-bromophenylfuran)-3-chloro-4-bromomethylfuran (**21**) (see below) to attempt to prepare 2,5-bis(*p*-bromophenyl)-3-methylfuran (**22**). The furan **21** was successfully oxidized to *cis*-1,2-bis(*p*-bromobenzoyl)-1-chloro-2-bromomethylethylene (**23**); however, reaction with stannous chloride produced **24**, which presumably arises from reduction of the bromomethyl function followed by furanization. As a result of the failure of the reductive furanization route 3-methyl-2,5-bis(4-guanylphenyl)furan (**25**) was prepared by introduction of the methyl group into the carbon skeleton prior to ring closure.[16] The approach employed is detailed in Scheme III.

The approaches used to prepare the 3,4-dichloro- and 3-chloro-2,5-bis(4-guanylphenyl)furans **31** and **32** employ selective dichloro- and chloro furanization reactions of di-*p*-bromobenzoylethylene (**33**) with phosphorus pentachloride and acetyl chloride, respectively.[17] It is interesting to note that the difference in reactivity of aryl bromide and aryl chloride to nucleophilic displacement is successfully taken advantage of in the preparation of the bis-nitrile intermediates used as precursors of **31** and **32** (Scheme IV). Preparation of 3-chloro-4-methyl-2,5-bis(4-guanylphenyl)furan (**38**) follows the route employed for the synthesis of **17** and used, as the key intermediate, 3-chloro-2,5-bis(4-bromophenyl)furan (**36**) (Scheme V).

Table I contains the physical data on the target bisamidines. Table II includes the physical data on the furan intermediates used to prepare the various guanyl compounds.

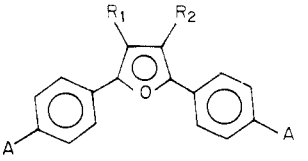
Table I. 2,5-Bis(4-guanylphenyl)furans



Compd[a] no.	R_1	R_2	A	Mp,[b] °C dec	% yield[c]	Mol formula
4[d]	H	H	$-C^+(NH_2)_2Cl^-$	400-401	60	$C_{18}H_{18}Cl_2N_4O$
5	H	H		430-431	90	$C_{24}H_{26}Cl_2N_4O$
6	H	H		409-410	90	$C_{22}H_{22}Cl_2N_4O$
7	H	H		398-400	75	$C_{24}H_{26}Cl_2N_4O$
8	H	H		195-210	63	$C_{24}H_{26}Cl_2N_4O \cdot 0.5H_2O$
9	H	H		130-133	80	$C_{26}H_{30}Cl_2N_4O \cdot 2H_2O$
10	H	H		205-210	64	$C_{24}H_{30}Cl_2N_4O \cdot H_2O$
11	H	H		155-160	86	$C_{28}H_{34}Cl_2N_4O \cdot H_2O$
12[e]	H	H		180-190	80	$C_{32}H_{50}Cl_4N_6O$
13	H	H	$-CONHNH_2$	>480	50	$C_{18}H_{16}N_4O_3$
17	CH_3	CH_3	$-C^+(NH_2)_2Cl^-$	368-369	73	$C_{20}H_{22}Cl_2N_4O$
18	CH_3	CH_3		390-392	70	$C_{24}H_{26}Cl_2N_4O \cdot 0.5H_2O$
19	CH_3	CH_3		396-398	45	$C_{26}H_{30}Cl_2N_4O \cdot H_2O$
20	CH_3	CH_3		273-275	49	$C_{26}H_{30}Cl_2N_4O \cdot 1.5H_2O$
25	H	CH_3	$-C^+(NH_2)_2Cl^-$	364-366	45	$C_{19}H_{20}Cl_2N_4O \cdot 0.5H_2O$
31	Cl	Cl	$-C^+(NH_2)_2Cl^-$	255-260	85	$C_{18}H_{16}Cl_4N_4O$
32[f]	H	Cl	$-C^+(NH_2)_2Cl^-$	355-356	57	$C_{18}H_{17}Cl_3N_4O$
38	CH_3	Cl	$-C^+(NH_2)_2Cl^-$	344-346	75	$C_{19}H_{19}Cl_3N_4O$

[a] All compounds were recrystallized from absolute ethanol and analyzed for C, H, and N and the analytical results were within ±0.4% of the calculated values. [b] Melting points are uncorrected. [c] Yields are based upon the imidate ester hydrochloride. [d] Reported in ref 11; however, the only physical data reported were equivalent weight and Cl analysis. [e] This compound appears to be a glass that shrinks at 170 °C. [f] This compound was prepared by another synthetic route[18] and reported as a dihydrochloride monohydrate; except for mp 338-339 °C, no other physical data were reported.

Table II. Furan Intermediates



Compd[a] no.	R_1	R_2	A	Mp, °C[b]	% yield	Recrysn solvent	Mol formula
2[c]	H	H	Br	198-199	93	HOAc	$C_{16}H_{10}Br_2O$
3[d]	H	H	CN	294-295	65	EtOH	$C_{18}H_{10}N_2O$
14	CH_2Br	CH_2Br	Br	194-195	83	EtOH-acetone	$C_{18}H_{12}Br_4O$
15	CH_3	CH_3	Br	175-176	92	Petr ether	$C_{18}H_{14}Br_2O$
16	CH_3	CH_3	CN	250-252	68	Acetone	$C_{20}H_{14}N_2O$
29	COOH	CH_3	Br	247-248	55	$CHCl_3$	$C_{18}H_{12}Br_2O_3$
30[e]	H	CH_3	CN	197-198	69	EtOH	$C_{19}H_{12}N_2O$
34[g]	Cl	Cl	Br	165-166	90	Acetone	$C_{16}H_8Br_2Cl_2O$
35[e]	Cl	Cl	CN	247-248	80	Acetone	$C_{18}H_8Cl_2N_2O$
36[f]	H	Cl	Br	119-120	80	EtOH	$C_{16}H_9Br_2ClO$
37	H	Cl	CN	213-214	85	EtOH-acetone	$C_{18}H_9ClN_2O$
39	Cl	CH_3	Br	165-166	62	EtOH	$C_{17}H_{11}Br_2ClO$
40	Cl	CH_3	CN	251-252	70	EtOH	$C_{19}H_{11}ClN_2O$
44	Cl	CH_2Br	Br	187-188	82	Acetone	$C_{17}H_{10}Br_3ClO$

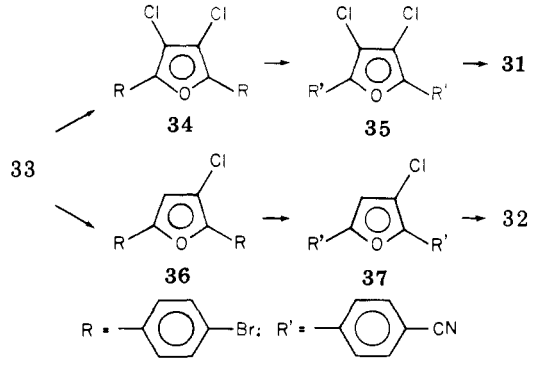
[a] All new compounds (except 30 and 35) were analyzed for C and H and the analytical results were within ±0.3% of the calculated values. [b] Melting points are uncorrected. [c] Lit.[13] mp 200-201 °C. [d] Lit.[11] mp 293-295 °C. [e] This nitrile did not analyze for C within ±0.3%; however, it had the expected spectral properties, including ^{13}C NMR, and was used in the next synthetic step. [f] Lit.[17] mp 120 °C. [g] Lit.[13] mp 165-166 °C.

Table III. Antitrypanosomal Activity of 2,5-Bis(4-guanylphenyl)furans[h]

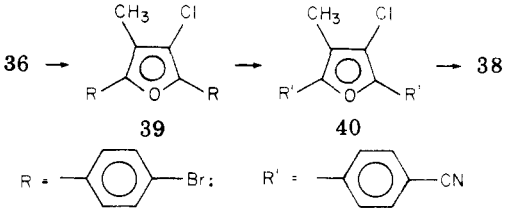
	Cures[a] or ΔMST[b] at dosage[c] (mg/kg)													
No.	0.21	0.42	0.63	0.83	1.06	1.25	2.5	5.0	10.0	20.0	40.0	80.0	160	320	640
4			3			4	4	5	5	5	5	5	5	5	5
5								2	4	5	5	5	5	2	
6									2	3	5	5	5	5	2
7							0.6d	3.2d	2	3	4	5	5	5	5
8										1.1d	5.5d	5	T[g]	T	T
9											T		T		T
10							0.3d	0.7d		T	T		T		T
11											T		T		T
17			2			3	4	5	5	5	5	5	5	5	
18						1.8d	18d	2	3	5	5	5	5	5	5
19						3.2d	3	4	5	5	5	5	4	T	T
25	2	3		5		5	5	5	5	5	5	5	5	5	
31	0.2d	0.4d		0.8d		2.0d	6.2d	4	5	5	5	5	5	5	
32	1	2		3		5	5	5	5	5					
38	2.1d	2		2		4	4	5	5	5	5	5	5	5	
41[e]						2	5	5	5	5	5	5	5	5	5
42[d]						2	5	5	5	5	5	5	5	5	5
43[f]						1	4	5	5	5	5	5	5	5	5

[a] A cure is defined as a 30-day increase in survival time of the treated animals over the controls. Five mice were used per dosage level; hence, five is the maximum number of cures. [b] ΔMST is the increase in mean survival time of test animals vs. controls in days. ΔMST is differentiated from cures by the use of d, i.e., 3.2d = 3.2 days. [c] Dosage is in milligrams of compound per kilogram of body weight of the test animal. [d] Hydroxystilbamidine. [e] Stilbamidine. [f] Pentamidine. [g] T = toxic death. [h] See ref 20.

Scheme IV



Scheme V



Biological Activities. The compounds shown in Table I were screened for antimalarial activity by testing against *P. berghei* in mice.[19] The cyclic amidines **5** and **6** have exhibited modest activity; for example, **5** increased the mean survival time (MST) of test animals in comparison to controls by approximately 12 days at a dosage of 320 mg/kg, and it was toxic at 640 mg/kg. The antimalarial activity of **6** was somewhat less, giving an increase in MST of approximately 5 days at a dosage of 640 mg/kg. All the

other compounds showed little, if any, antimalarial activity.

Because of the obvious structural relationship of these compounds to trypanocides of the 12-Å class (e.g., stilbamidine) they were tested against *T. rhodesiense*. The results of this screening by the method of Rane[20] may be found in Table III. When the antitrypanosomal activity of the compounds in Table I is compared with that for their 12-Å prototypes stilbamidine **41** and hydroxystilbamidine **42**, as well as with the longer molecule pentamidine **43**, it is apparent that these compounds, in general, are very good antitrypanosomal agents. The dimethyl analogue **17** exhibits a prolonged curative effect providing complete protection to mice for 30 days after a single 5 mg/kg dose against a challenge by *T. rhodesiense*.[21]

Examination of the antitrypanosomal test results allows one to draw only limited structure–activity conclusions. In general, the introduction of masked or cyclic amidines (**5–11, 18–20**) in place of the simple guanyl function seems to result in a reduction of antitrypanosomal activity and an increase in toxicity. This generalization especially applies to the quaternary cyclic amidines (**8–11**) which show very limited activity and are quite toxic. Most of the 2,5-bis(4-guanylphenyl)furans (**4, 17, 25, 32, 38**) show somewhat superior activity to stilbamidine, hydroxystilbamidine, and pentamidine in this test. Unfortunately, test results at lower dosage levels for stilbamidine and hydroxystilbamidine are not available for further comparison. The substitution of one methyl group on the furan ring (**25**) produces a slight enhancement of activity, whereas two methyl groups (**17**) do not cause much change in biological response in comparison to the parent compound **4**. Similarly, introduction of one chlorine (**32**) on the furan ring appears to slightly enhance activity, whereas two chlorine atoms (**31**) reduce the activity in comparison to **4**. A combination of methyl and chlorine functions on the furan ring (**38**) does not appreciably alter the biological response. The difference in activity of the cyclic amidines and those with a true guanyl function and the difference between the furan system substituted with electron donors and withdrawers may be due to differences in distribution or, if DNA binding is significant to their mode of action, due to differences in interaction with DNA. Studies of the interaction of these compounds with DNA are underway.

Experimental Section

Melting points reported under 300 °C were taken on a Thomas-Hoover melting point apparatus; the melting points of compounds melting above 300 °C were obtained on a Mel-Temp apparatus and all melting points are uncorrected. IR spectra were recorded on all new compounds with a Perkin-Elmer Model 337 spectrometer, ^{1}H NMR spectra were recorded on selected compounds with a Varian A-60A instrument, and ^{13}C NMR spectra on selected compounds were obtained with a JEOL FX-60 instrument. All spectra were in accord with the structures assigned. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga.

Compounds **4, 17, 25, 31, 32,** and **38** were prepared from the appropriate bis-nitrile by the method outlined for the preparation of **4**. The masked amidines **5–12** and **18–20** were prepared according to the method given for **6**. The bis-nitriles **3, 16, 37, 35,** and **40** were prepared from the appropriate aryl bromides by the method presented for **3**. The bromomethylation–$LiAlH_4$ reduction method described for the preparation of **14** and **15** was employed for the preparation of **44** and **39**.

2,5-Bis(*p*-bromophenyl)furan (2). The literature procedure[22] for preparation of *trans*-di-*p*-bromobenzoylethylene (**36**) from bromobenzene and fumaryl chloride was employed. The ethylene compound was reduced with Zn–HOAc as described earlier[23] to prepare 1,4-di-*p*-bromophenyl-1,4-butanedione. The saturated 1,4-diketone (7.9 g, 0.02 mol) was suspended in 80 mL of Ac_2O and the mixture was heated to reflux. Approximately 5 drops of concentrated H_2SO_4 was added and refluxing was continued for 5 min. The solution was poured into a mixture of water–ice (1 L), stirred well, and filtered: crude yield 7 g (93%). Recrystallization from acetic acid gave 5.6 g (75%), mp 198–199 °C (lit.[13] mp 200–201 °C).

2,5-Bis(*p*-cyanophenyl)furan (3). A mixture of 7.5 g (0.02 mol) of **2** and 4 g (0.02 mol) of $Cu_2(CN)_2$ in 45 mL of quinoline was refluxed for 2 h. The mixture was poured into approximately 300 mL of dilute HCl solution (caution, HCN is liberated) and filtered. The solid was washed with H_2O, dilute NaOH, dilute HCl, and finally again with H_2O. The solid bis-nitrile was dissolved in acetone, filtered to remove inorganic residue, and finally passed through a short alumina column to remove traces of copper salts. It is imperative that copper salts be removed at this stage since they carry over to the bis-amidines from which we were never able to remove the copper salts. A convenient method to determine that copper salts are removed is a flame test. Evaporation of the eluent from the alumina column and recrystallization from ethanol gave 3.5 g (65%), mp 294–295 °C.

2,5-Bis(4-guanylphenyl)furan Dihydrochloride (4). The dinitrile **3** (3 g, 0.011 mol) was dissolved in a mixture of 100 mL of dioxane and 25 mL of absolute EtOH and the solution was saturated with dry HCl gas at 5 °C. The solution was placed in a pressure bottle and shaken for 3 days at room temperature. The imidate ester hydrochloride, which precipitated as a yellow solid, was filtered and the solid was dried under vacuum at room temperature overnight. The IR spectra of the imidate confirmed the absence of the nitrile group and the imidate was used directly without further characterization. A suspension of 3.5 g of imidate in 100 mL of absolute ethanol was saturated at 5 °C with anhydrous ammonia. The suspension was placed in a pressure bottle and shaken for 3 days at room temperature. The reaction mixture was filtered, and the solid was collected, dried, and dissolved in warm absolute ethanol (ca. 1.5 L). The solution was acidified with anhydrous HCl at 5 °C and concentrated under vacuum at room temperature, and 2.5 g (60%) of yellow crystals appeared which on recrystallization from absolute ethanol gave mp 400–401 °C dec.

2,5-Bis[4-(2-imidazolinyl)phenyl]furan (6). A solution of the imidate ester hydrochloride, 2.1 g (0.005 mol), and 0.6 g (0.01 mol) of ethylenediamine in 50 mL of absolute ethanol was refluxed overnight. The solid which formed was filtered and recrystallized from absolute ethanol saturated with anhydrous HCl to yield 1.9 g (90%), mp 409–410 °C dec.

2,5-Bis(*p*-carboxyhydrazidophenyl)furan (13). A suspension of 0.4 g (0.0011 mol) of crude 2,5-bis(*p*-carbethoxyphenyl)furan (obtained from **3**) in 50 mL of diethylene glycol and 5 mL of hydrazine hydrate (75%) was heated to reflux. After approximately 10 min, dissolution occurred and after approximately 30 min, a precipitate appeared. After 1 h of refluxing the solution was filtered hot and the collected solid was washed several times with H_2O and EtOH. The yield was 0.19 g (50%) of material which did not melt up to 480 °C.

2,5-Bis(*p*-bromophenyl)-3,4-dibromomethylfuran (14). A suspension of 6 g (0.02 mol) of **2** and 3 g (0.1 mol) of paraformaldehyde in 80 g of 30% HBr in glacial acetic acid was stirred at room temperature for 48 h during which time the mixture turned to a semisolid. The mixture was filtered, washed with H_2O, and recrystallized from acetone to yield 9.3 g (83%) of solid, mp 194–195 °C.

2,5-Bis(*p*-bromophenyl)-3,4-dimethylfuran (15). The dibromomethyl compound **14** (2.9 g, 0.005 mol) was added to a suspension of 1.0 g (0.026 mol) of $LiAlH_4$ in 100 mL of THF and the mixture stirred at room temperature for 15 min. After the excess $LiAlH_4$ was carefully destroyed by adding small amounts of wet Et_2O, the mixture was extracted (Et_2O), washed (H_2O), and dried ($CaSO_4$) and the solvent removed to yield 2 g (92%) of **15**. Recrystallization from petroleum ether (bp 30–60 °C) gave mp 195–196 °C.

Oxidation of 2,5-Bis(*p*-bromophenyl)-3-chloro-4-bromomethylfuran (21). A mixture of 150 mL of acetic acid, 5.0 mL of concentrated HNO_3, and 7 g (0.014 mol) of 2,5-di(*p*-bromophenyl)-3-chloro-4-bromomethylfuran was warmed at 40–50 °C for 1 h. The mixture on dilution with water gave a gum which on subsequent washing with water turned into solid *cis*-1,2-

bis(*p*-bromobenzoyl)-1-chloro-2-bromomethylethylene (**23**), 4.5 g (61%). Crystallization from ethanol gave mp 101–103 °C. Anal. ($C_{17}H_{10}Br_3ClO_2$) C, H.

Reduction of *cis*-1,2-Bis(*p*-bromobenzoyl)-1-chloro-2-bromomethylethylene (23). The diketone, 0.8 g (0.0015 mol), was added to a refluxing mixture of 6 mL of HOAc, 5 mL of concentrated HCl, and 0.36 g of $SnCl_2$. The mixture was refluxed for 5 min and poured into water, extracted (Et_2O), washed (H_2O), dried ($CaSO_4$), and evaporated to yield 0.4 g (64%) of solid. Crystallization from ethanol gave mp 163–164 °C. The ^1H NMR and IR of the compound were identical with that of **39**.

Preparation of 2,5-Di(*p*-bromophenyl)-3-methyl-4-carboxyfuran (29). To a solution of 4.8 g (0.11 mol) of 57% NaH (mineral oil) in 100 mL of ethanol was added 30 g (0.11 mol) of *p*-bromobenzoylethyl acetate,[24] under a nitrogen atmosphere, and the mixture was stirred for 30 min. The mixture was cooled to about 5 °C, and a solution of 32.3 g (0.11 mol) of 2,4-dibromopropiophenone[16a] in 250 mL of ethanol was added dropwise and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under vacuum, the residue was treated with water, extracted with ether, washed, and dried ($CaSO_4$), and ether was removed to yield 48 g (90%) of oil. The oil was dissolved directly into 150 mL of ethanol and cooled to 5 °C and dry HCl gas was passed through the solution for 30 min. The solid which formed was filtered and washed (cold ethanol and then petroleum ether) to yield 26 g (51%) of solid which was used in the next step. The crude ester (26 g, 0.055 mol) was refluxed for 8 h in 260 mL of 50% ethanol–H_2O solution containing 20 g of NaOH. The reaction mixture was evaporated under reduced pressure, treated with H_2O, and acidified. The resulting precipitate was collected (13.8 g, 55%). The product (**29**) on recrystallization from $CHCl_3$ gave mp 247–248 °C dec.

Preparation of 2,5-Di(*p*-cyanophenyl)-3-methylfuran (30). A mixture of 6 g (0.014 mol) of **29**, 6 g (0.03 mol) of $Cu_2(CN)_2$, and 50 mL of quinoline was refluxed for 2 h, poured in dilute HCl, filtered, washed, dried, and dissolved in acetone. The solution was passed through a column of alumina to remove copper salts. The eluent on concentration gave 2.7 g (69%) of solid; recrystallization from ethanol gave mp 197–198 °C.

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