Synthesis, DNA Affinity, and Antiprotozoal Activity of Linear Dications: Terphenyl Diamidines and Analogues

Mohamed A. Ismail,[†] Reem K. Arafa,[†] Reto Brun,[‡] Tanja Wenzler,[‡] Yi Miao,[†] W. David Wilson,[†] Claudia Generaux,[§] Arlene Bridges,[§] James E. Hall,[§] and David W. Boykin*,[†]

Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, Atlanta, Georgia 30303-3083, Swiss Tropical Institute, Basel CH4002, Switzerland, and Molecular Pharmaceutics, UNC School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599

Received April 20, 2006

Diamidines **10a**−**g** and **18a**,**b** were obtained from dinitriles **9a**−**g** and **15a**,**b** by treatment with lithium trimethylsilylamide or upon hydrogenation of bis-*O*-acetoxyamidoximes. Dinitriles **9a**−**g** were prepared via Suzuki reactions between arylboronic acids and arylnitriles. Potential prodrugs **12a**−**f** and **17** were prepared via methylation of the diamidoximes **11a**−**f** and **16a**. Significant DNA affinities for rigid-rod molecules were observed. Compounds **10a**, **10b**, **10d**, **18a**, and **18b** show IC_{50} values of 5 nM or less against *Trypanosoma brucei rhodesiense* (*T. b. r.*) and **10a**, **10b**, **10e**, **18a**, and **18b** gave similar ones against *Plasmodium falciparum* (*P.f.*). The dications, **10a**, **10d**, **10f**, and **10g** are more active than furamidine in vivo. The prodrugs are only moderately effective on oral administration. Mouse liver microsome bioconversion of the methamidoxime prodrugs is significantly reduced from that of pafuramidine and suggests that the in vivo efficacy of these prodrugs is, in part, due to poor bioconversion.

Introduction

Pentamidine (**1**) has been known for its antimicrobial activity for over 50 years, and it remains the only aromatic diamidine to have seen significant human use.[1,2] Pentamidine is used against antimony-resistant leishmaniasis, initial stage human African trypanosomiasis (HAT), and also as a secondary drug for AIDS-related *P. jiroveci* (formerly *P. carinii*) pneumonia.[1] A prodrug of furamidine (**2**), which is administered orally, is currently in Phase II clinical trials against malaria and Phase III trials against pneumocystis pneumonia and HAT.[1,3−7] These dicationic molecules bind in the minor groove of DNA at AT rich sites, and this interaction is believed to be key to their antimicrobial activity.[1] The molecules are concentrated in the kinetoplast, which is thought to be the first step in their antitrypanosomal action.[1b] Minor groove binding is postulated to lead to the inhibition of DNA dependent enzymes or the direct inhibition of transcription.[1,8−11] For the trypanosomes, the selectivity of the dications is likely to include uptake by amidine transporters.[12] For about two decades, a fundamental element in the design of new minor groove binding molecules has been that the molecular scaffold bearing the amidine units should present crescent shape geometry complementary to the curve of the minor groove of DNA.[13] In addition to the shape complementary component of these molecules, van der Waals contacts with the walls of the groove have been shown to be an important contributor to binding affinity.[14−16] A recent theoretical review of the binding interactions of over 20 minor groove binders concluded that the curvature of the small molecule was important to provide energetically favorable van der Waals contacts.[17] Pentamidine, furamidine, and many analogues have been shown to meet this crescent shape requirement.[1,13,18,19] In contrast, recent reports have shown that diamidine (**3**) (CGP **3**), which despite the fact that it is a nearly linear molecule, binds quite strongly to the AT rich minor groove.[20−22] A careful analysis of binding data, crystal structure, and molecular dynamic simulations leads to the conclusion that water mediated interactions between **3** and the DNA minor groove, in effect, provide the needed curvature.[21,22] Recently, we reported strong DNA affinities and excellent antiprotozoan activity for the near linear biphenylbenzimidazoles (**4**).[23] A detailed study of the DNA binding of **4**, including a crystal structure of its cocrystal with the Dickerson dodecamer, shows that the linear molecule binds quite strongly to the minor groove.[24] As with CGP 40215, a bound water molecule provides a key interaction between **4** and the floor of the groove to, in effect, provide curvature.[24] A review of the literature reveals that other linear dicationic molecules exhibit marked antiprotozoan activity. For example, bis-4,4′-amidinobiphenyl (**5**) and bis-4,4′-amidinophenylethyne (**6**) have been reported to show significant in vivo activity in a trypanosomal mouse model for *Trypanosoma rhodesiense*.[25] In view of these several examples of linear dicationic molecules that show promising antimicrobial activity and significant DNA minor groove affinity, we have undertaken a study of linear systems based upon the rigid-rod terphenyl scaffold. Rigid-rod molecules, which cannot be compressed or bent, have received considerable attention in material science[26] and are receiving growing attention in the biological sciences.[27] Such compounds ,which do not match the curvature of the minor groove, may represent a new class of dicationic antimicrobial agents that exhibit a new type of antiparasitic effect. We report the synthesis of novel dicationic terphenyls and their evaluation as potential minor groove binders and antiprotozoan agents.

The p*K* of aromatic amidines is greater than 10, and consequently, such molecules are charged at physiological pH.[28] The lack of oral bioavailability of diamidines such as pentamidine, furamidine and analogues is well known.[19,29] In addition, several analogues of furamidine show excellent activity on intravenous dosing but are ineffective on oral administration.[18,19] Generally, oral administration is the preferred dosing regime, and hence, prodrug strategies for diamidines that have the potential to overcome their limited oral bioavailability merit attention. We have reported that bis-amidoximes and bis-*O*-alkylamidoximes

* To whom correspondence should be addressed. Tel: (404) 651-3798. Fax: (404) 651-1416. E-mail: dboykin@gsu.edu.
[†] Georgia State University.
[‡] Swiss Tropical Institute.
[§] University of North Carolina.

10.1021/jm060470p CCC: $33.50
Published on Web 07/29/2006

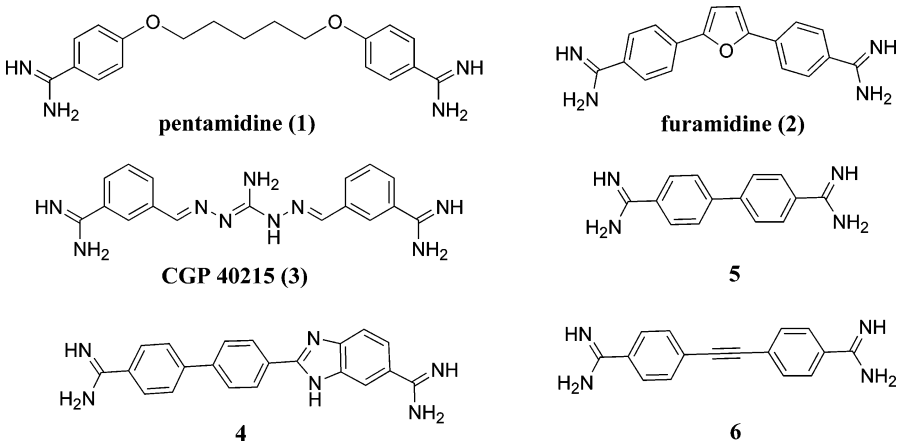
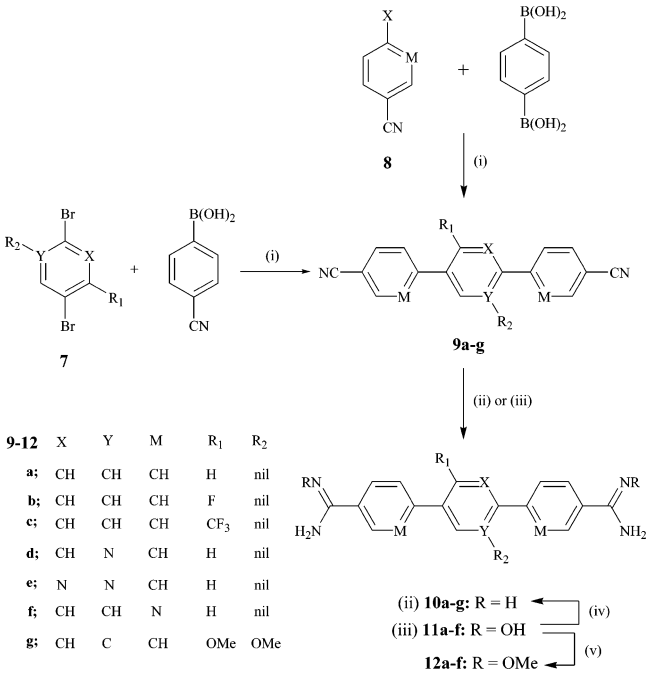


Figure 1. Structures of key dicationic antiprotozoan agents.

Scheme 1[a]



9-12	X	Y	M	R_1	R_2
a;	CH	CH	CH	H	nil
b;	CH	CH	CH	F	nil
c;	CH	CH	CH	CF_3	nil
d;	CH	N	CH	H	nil
e;	N	N	CH	H	nil
f;	CH	CH	N	H	nil
g;	CH	C	CH	OMe	OMe

[a] Reagents and conditions: (i) $Pd(PPh_3)_4$, Na_2CO_3, toluene, 80 °C; (ii) (a) $LiN(TMS)_2$, THF, r.t., overnight; (b) HCl(gas), dry ethanol, r.t., overnight; (iii) $NH_2OH.HCl$/KO-*t*-Bu, DMSO; (iv) (a) $AcOH/Ac_2O$; (b) H_2/Pd−C, AcOH; (v) $LiOH/(CH_3)_2SO_4$.

of a number of diamidine systems are effective prodrugs.[30−32] As part of our continuing effort to develop orally effective antimicrobial agents, we include the synthesis of examples of these two types of potential prodrugs in the terphenyl series.

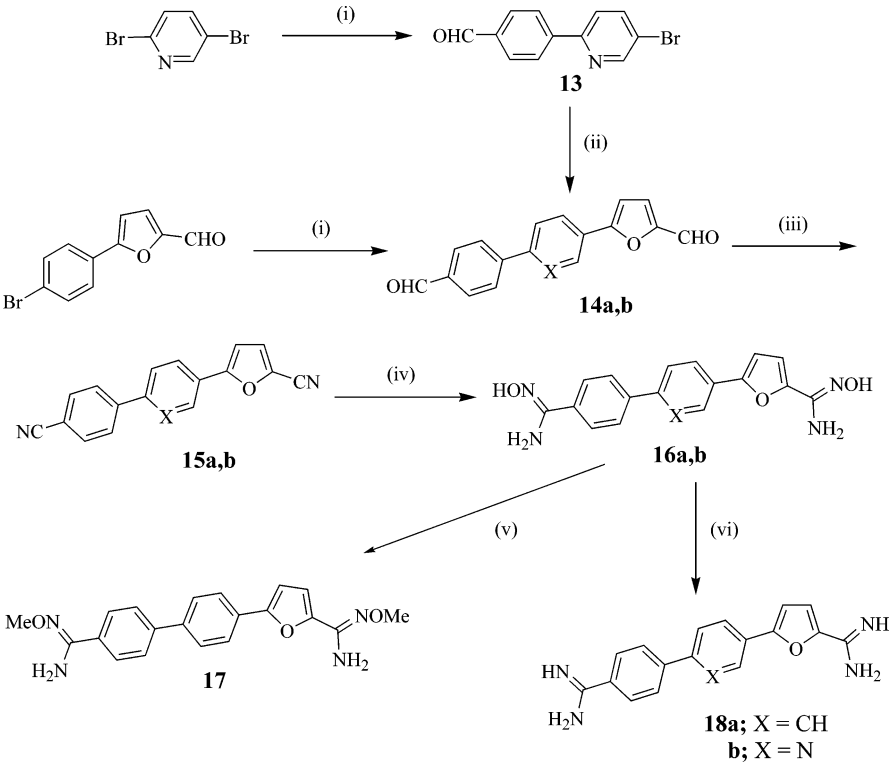
Chemistry. As shown in Scheme 1, a series of linear terphenyl diamidines and their aza-analogues was obtained from the respective dinitriles **9a**−**g** either by direct reaction using lithium trimethylsilylamide (cf. **10b**, **c**, **e**−**g**) or from the bis-*O*-acetoxyamidoxime followed by hydrogenation in glacial acetic acid (cf. **10a**, **d**). The dinitriles **9a**−**g** were prepared via a Suzuki coupling reaction either employing bis-1,4-phenyleneboronic acid with 4-bromobenzonitrile or 6-chloronicotinonitrile or by employing 4-cyanophenylboronic acid with 1,4-dibromobenzene and its derivatives. The potential prodrugs **12a**−**f** were prepared via methylation of the respective diamidoxime **11a**−**f** with dimethyl sulfate in DMF solution and using Li(OH) as a base. The hydrochloride salts of the amidoximes **11a**−**f** and **12a**−**f** were obtained by passing hydrogen chloride gas into an ethanolic solution of their free bases.

As outlined in Scheme 2, dinitrile compound **15a** was obtained in two steps starting with a Suzuki coupling reaction of 5-(4-bromophenyl)furan-2-carboxaldehyde with 4-formylphenylboronic acid to yield dialdehyde **14a**. Reaction of **14a** with hydroxylamine hydrochloride in the presence of Na_2CO_3, followed by acetic anhydride induced dehydration of the oxime furnished **15a**. The acetate salt of **18a** was obtained from dinitrile **15a** through bis-*O*-acetoxyamidoxime followed by hydrogenation in glacial acetic acid. In a similar way, diamidine **18b** was prepared starting from compound **15b**. Dinitrile **15b** was obtained employing a selective Suzuki coupling reaction of 2,5-dibromopyridine with 4-formylphenylboronic acid to give bromoaldehyde **13**. A Stille coupling reaction between **13** and 5-(diethoxymethyl-furan-2-yl)-tributyltin, followed by acid hydrolysis of the acetal gave **14b**, a key precursor of **15b**. The potential prodrug, *N*-methoxy-5-[4′-(*N*-methoxyamidino)-biphenyl-4-yl]-furan-2-carboxamidine (**17**) was prepared via methylation of the respective diamidoxime **16a**. The hydrochloride salts of the amidoximes, **16a**,**b** and **17**, were made by passing hydrogen chloride gas into an ethanolic solution of their free bases.

Biology. Table 1 contains the results from DNA binding studies and in vitro antiparasitic evaluations for the new linear dications. The ΔT_m values reflect the DNA affinities of these compounds. Although the ΔT_m value for **10a** is about 20% less than that of furamidine, it is significantly greater than that of pentamidine. Despite the fact that **10a** is a linear rigid-rod it shows impressive DNA affinity, perhaps using a water molecule to effectively provide curvature as has been shown for other linear dicationic molecules.[21,22,24]

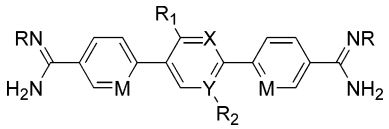
Although aromatic diamidines have been universally observed to be minor groove binding compounds in AT base pair sequences of DNA, the compounds have generally been crescent shaped systems that fit into the double helix groove and directly interact with the A and T bases at the floor of the groove. The linear compounds in this study are more similar to **3** and **4**, which are also minor groove binding compounds, but it is important to test the binding mode of the new linear compounds. A characteristic feature of groove binding diamidines is that they have a strong positive induced CD signal when they bind to AT DNA sequences. Intercalation binding gives weak induced CD signals that are generally negative. Consistent with a minor groove binding mode, the linear diamidines in this article give a positive induced CD signal when added to polydA.polydT, and the spectra are similar to those obtained for **3** and **4**. An example set of CD spectra for **10a** are shown in Supporting Information Figure 1, and the strong, positive induced CD signals at the maximum absorption wavelength of **10a** are clearly seen.

Scheme 2[a]



[a] Reagents and conditions: (i) 4-Formylphenylboronic acid, $Pd(PPh_3)_4$; (ii) (a) 5-(diethoxymethyl-furan-2-yl)-tributyltin, $Pd(PPh_3)_4$; (b) Hydrolysis with 2M HCl; (iii) (a) $NH_2OH.HCl$; (b) Ac_2O; (iv) $NH_2OH.HCl/KO$-*t*-Bu, DMSO; (v) $LiOH/(CH_3)_2SO_4$; (vi) (a) $AcOH/Ac_2O$; (b) $H_2/Pd-C$, AcOH.

Table 1. DNA Affinities and in Vitro Antiprotozoan Data for Linear Dications



code	R	R_1	R_2	X	Y	M	ΔTm[a] (° C)	*T. b. r.*[b] IC_{50} (nM)	P. f.[b] IC_{50} (nM)	cytotoxicity[c] IC_{50} (μM)
1	NA	NA		NA	NA	NA	12.6	2.2	NT	2.1
2	NA	NA		NA	NA	NA	25	4.5	15.5	6.4
10a	H	H	nil	CH	CH	CH	18.2	5	1	22.1
11a	OH	H	nil	CH	CH	CH	ND	22.8K	>11.8K	>211
12a	OMe	H	nil	CH	CH	CH	ND	13.8K	371	118.3
10b	H	F	nil	CH	CH	CH	15.1	2	1	6.4
11b	OH	F	nil	CH	CH	CH	ND	> 201K	925	29.1
12b	OMe	F	nil	CH	CH	CH	ND	51.5K	4.2K	8.5
10c	H	CF_3	nil	CH	CH	CH	10.1	48	15	9.4
11c	OH	CF_3	nil	CH	CH	CH	ND	29.9K	3.1K	13.3
12c	OMe	CF_3	nil	CH	CH	CH	ND	36.9K	3.8K	42.2
10d	H	H	nil	CH	N	CH	18.7	2	10	49.9
11d	OH	H	nil	CH	N	CH	ND	9.3K	7.6K	>184
12d	OMe	H	nil	CH	N	CH	ND	34.7K	3.2K	>166
10e	H	H	nil	N	N	CH	8.1	16	0.5	40.9
12e	OMe	H	nil	N	N	CH	ND	49K	5.7K	>177
10f	H	H	nil	CH	CH	N	9.2	47	10	26.6
12f	OMe	H	nil	CH	CH	N	ND	82.9K	1.2K	>158
10g	H	OMe	OMe	CH	C	CH	5.2	15	37	>100
18a	H	NA	NA	NA	NA	NA	19.1	5	1	56.1
16a	OH	NA	NA	NA	NA	NA	ND	67K	6.6K	106
17	OMe	NA	NA	NA	NA	NA	ND	24K	1.6K	>205
18b	H	NA	NA	NA	NA	NA	17.6	2	10	30.9

[a] Poly(d(A-T)$_2$ in MES10 buffer; ratio compound/DNA is 0.3. [b] The *T. b. r.*(*Trypanosoma brucei rhodesiense*) strain was STIB900, and the *P. f.* (*Plasmodium falciparum*) strain was K1. The values are duplicate determinations; see refs 23 and 31. [c] Cytotoxicity was evaluated using cultured L6 rat myoblast cells using the same assay procedure for *T. b. r.*

The central ring substituted terphenyldiamidines **(10a−c**, **10g)** show a progressive decrease (from 18.2 to 5.2 ΔTm) in binding affinity as larger and more substituents are added to the aryl rings. The substituents can cause an increase in the torsion angles between the aryl rings because of increased repulsive van der Waals interactions. A second important feature of the substit-

uents is that they increase the energy required to reduce the angle between directly bonded aryl systems. Reduced twist appears to be an important feature of unfused compound complexes with the DNA minor groove. The biphenyl torsional angle in **4**, for example, is 28° relative to the unbound value of 44°.[24] Large twists in the compound molecular shape are expected to decrease favorable interactions of the compounds with the DNA minor groove and increase steric clash with the walls of the groove. We conducted molecular mechanics calculations to compare the equilibrium torsional angles in the substituted compounds (angle between the substituted phenyl and the unsubstituted phenyl bonded adjacent to the substituent) as well as the energies of the compounds when the angle was reduced to 20°. The values are 44° and 17 kcal/mol for **10a**; 46° and 26 kcal/mol for **10b**; and 55° and 92 kcal/mol for **10c**, in agreement with the decreasing order of their ΔT_m values. For **10g**, the values are 50° and 41 kcal/mol, but presumably because it has two aryl ring junctions, **10g** has the lowest ΔT_m value in this set of compounds. These results suggest that a near planar array enhances the fit of linear rigid-rod molecules in the DNA minor groove.

The aza analogues (**10d**−**f**) do not show a recognizable pattern for the effect of the introduction of a heterocyclic nitrogen atom into the various phenyl rings. The ΔT_m for **10d** with one N-atom and the parent molecule **10a** are equivalent, and thus, essentially, there is no effect of the introduction of one heterocyclic nitrogen in the central ring. Unexpectedly, the introduction of two nitrogen atoms in the central ring as exemplified by **10e** dramatically reduces the ΔT_m value. The origin of this effect is unclear. Similarly, the introduction of one nitrogen atom in each of the terminal rings also significantly lowers the ΔT_m value. Further biophysical studies are underway to attempt to understand the effect of N-atom introduction on DNA affinities of these linear rigid-rods. Replacement of one of the benzamidine units with a furamidine one (**18a**, **18b**) gives ΔT_m values quite close to that of the parent **10a**, showing that replacing a terminal phenyl with furan has little effect on DNA affinity. A more detailed analysis of the DNA binding properties of these linear systems will be forthcoming in due course.

These linear dications also exhibit significant in vitro antiparasitic activity (Table 1). Five dications (**10a**, **10b**, **10d**, **18a**, **18b**) show IC_{50} values of 5 nM or less against *T. b. r.* In addition, five molecules (**10a**, **10b**, **10e**, **18a**, **18b**) exhibit IC_{50} values of near 5nM or less against *P.f.* The diaza analogue **10e** is of particular interest because it shows a 30-fold selectivity for *P. f.* As expected, the prodrugs do not show significant in vitro activity.

The promising in vitro activities of these analogues lead us to evaluate them in the STIB900 acute mouse model for *T. b. r.* (Table 2). Most of the dications on intraperitoneal dosing show a significant increase in survival time of treated animals compared to untreated controls. Four of the linear dications (**10a**, **10d**, **10f**, **10g**, **18b**) gave results superior to that of furamidine in this model.

Given the encouraging in vivo activities found for several of these dications, the amidoxime and methamidoxime potential prodrugs were evaluated on oral administration in the same animal model. Although several of the prodrugs (**12b**, **11d**, **12d**) significantly increased the survival time of treated animals versus that of untreated controls, none of the compounds approximated the efficacy of pafuramidine (Table 2). This disappointing result clearly suggests significant differences in pharmacodynamics and/or metabolism of the linear prodrugs.

Because we have found that methoxymes generally show greater in vivo efficacy than amidoximes,[2] we sought to gain some insight into the low efficacy of these linear prodrugs by comparing the rates of metabolic transformation of selected methamidoximes (**12a**, **12b**, **12d**−**12f**) to that of pafuramidine when exposed to mouse liver microsomes (Table 3). The substrate depletion data presented in Table 3 shows that pafuramidine rapidly disappears on exposure to mouse liver microsomes with a $t_{1/2}$ value <15 min. In contrast, the linear methamidoximes are much more metabolically stable with $t_{1/2}$ values greater than 90 min for all compounds studied except for **12d**, which gave a $t_{1/2}$ value of 55 min. The results from the mouse liver microsome studies are consistent with the in vivo efficacy results from the STIB900 mouse model and suggest that the slow metabolism of the linear prodrugs in mice

Table 2. Antitrypanosomal Activity in Vivo of Linear Dications in the STIB900 Mouse Model[a]

compd	dosage mg/kg	cures[b]	survival (days)[c]
1	20 ip	0/4	>42.75
2	20	0/4	> 52.5
	5 ip	0/4	35.5
pafuramidine[d]	25 po	1/4	>60
10a	20 ip	2/4	>47.75
11a	100 po	0/4	24.75
12a	100 po	0/4	20.75
10b	5 ip	0/4	>51.75
11b	25 po	0/4	22.25
12b	25 po	0/4	37.25
10c	5 ip	0/4	17.25
11c	25 po	0/4	9
12c	25 po	0/4	7.25
10d	20	4/4	>60
	5 ip	2/4	>42
11d	100 po	1/4	>35.75
12d	25 po	0/4	>42.75
10e	5 ip	0/4	23.5
12e	25 po	0/4	12.5
10f	5 ip	2/4	>60
12f	25 po	0/4	12
10g	5 ip	2/4	>51.75
18a	20 ip	0/4	21.25
16a	25 po	0/4	16
17	25 po	0/4	6.25
18b	20	3/4	>53.5
	5 ip	2/4	>41.75

[a] See refs 23 and 31 for details of the STIB900 mouse model. Dosage was for 4 days and was either intraperitoneal (ip) or oral (po) as noted. [b] The number of mice that survive 60 days and are parasite free. [c] Average days of survival; untreated controls died between day 7 and 8 post infection. [d] Pafuramidine = 2,5-bis(4-methoxyamidinophenyl)furan.

Table 3. Results from an in Vitro Metabolic Transformation Investigation of Selected Methoxamidines

compd	$t_{1/2}$[a]
pafuramidine	<15
12a	>90
12b	>90
12d	55
12e	>90
12f	>90

[a] $t_{1/2}$ in minutes for methoxamidine disappearance.

significantly contributes to their low efficacy. The bioconversion of these linear prodrugs needs to be investigated in other species.

We have shown that linear rigid-rod dications effectively bind to DNA, exhibit low nanomolar IC_{50} values against *T. b. r.* and *P. f.*, and show promising activity on intraperitoneal administration in the STIB900 mouse model. However, the prodrugs show only modest efficacy on oral dosing in the same mouse model, and they are significantly more slowly metabolized than pafuramidine by mouse liver microsomes. To capitalize on the efficacy of these potent dications, other prodrugs that rely on different bioconversion pathways need to be developed.

Experimental Section

Molecular Mechanics Calculations. Calculations were performed with the Spartan 04 software package (Wavefunction, Inc.) and the SYBYL force field. The compounds were first energy minimized with geometry optimization, and the phenyl−phenyl (or substituted phenyl) torsion angle was determined. The torsion was then locked into a 20° angle and a single-point energy calculated with the same software to give an idea of the energy cost of making the aromatic system more planar, as is usually required for minor groove binding (see ref 23, for example).

Efficacy Evaluations. In vitro assays with *T. b. r.* STIB 900 and the *P. f.* K1 strain as well as the efficacy study in an acute mouse model for *T. b. r.* STIB 900 were carried out as previously reported.[23,31]

***T*m Measurements.** Thermal melting experiments were conducted with a Cary 300 spectrophotometer. Cuvettes for the experiment were mounted in a thermal block, and the solution temperatures were monitored by a thermistor in the reference cuvette. Temperatures were maintained under computer control and were increased at 0.5 C/min. The experiments were conducted in 1 cm path length quartz cuvettes in MES 10 buffer (MES 10mM, EDTA 1mM, NaCl 100mM). The concentrations of DNA were determined by measuring the absorbance at 260 nm. A ratio of 0.3 compound per base was used for the complex, and DNA with no compound was used as a control.

Metabolic Stability Experiments.[33] Dimethyl sulfoxide, magnesium chloride, potassium dihydrogen phosphate, anhydrous disodium hydrogen phosphate, and β-nicotinamide adenine dinucleotide 2′-phosphate tetrasodium salt were purchased from Sigma (St. Louis, MO). Microsomes from pooled male mice B6C3F1 (n = 126) were purchased from XenoTech LLC (Lenexa, KS).

To determine the metabolic stability of prodrugs, **12a**, **12b**, **12d**, **12e**, **12f**, and pafuramidine were incubated with microsomal protein from mice (0.5 mg/mL final target concentration), phosphate buffer (100 mM, pH 7.4), and $MgCl_2$ (5 mM) in a total incubation volume of 0.5 mL. Incubations were performed in duplicate. The prodrugs were prepared as 10 mM stock solutions in DMSO and were added to the incubation mixtures in 2.5 μL of DMSO to keep the organic solvent at 0.5% (v/v) in the final incubations. Samples were preincubated at 37 °C for 3 min, and the reactions were started by the addition of 50 μL of β-NADPH (2 mM final target concentration). Reactions were stopped at 0, 5, 10, 15, 20, 25, and 30 min by quenching with 100 μL of acetonitrile. The samples were centrifuged at 3000 rpm for 5 min. Pafuramidine was used as the internal standard for all other compounds. **12b** was used as the internal standard for pafuramidine. Samples were analyzed immediately after centrifugation using LC-MS/MS systems as described below.

Automated sample analysis was performed using Analyst software (version 1.3.1, Applied Biosystems, Foster City, CA). The Analyst controlled HPLC-MS/MS system consisted of two Shimadzu Scientific (Columbia, MD) solvent delivery pumps, a thermostated (6 °C) LEAP HTC autosampler (Carrboro, NC), and an Applied Biosystems API4000 triple quadrupole mass spectrometer. Reversed-phase gradient chromatography was used to elute the prodrugs from an Aquasil (C_{18} 5μ, 50 × 2.1 mm) analytical column at a flow rate of 1 mL/min, following a 3μL injection. Starting conditions for each injection were 90:10, water/methanol with 0.1% formic acid in each. The relative amounts of water/methanol were held constant for 0.5 min while the column eluted to waste. After 0.5 min, the eluent was directed to the mass spectrometer and the relative amount of methanol increased linearly to 90% at 3 min postinjection. This amount of methanol was held for 0.5 min to wash the column. The column was reequilibrated under the starting conditions for the final 0.5 min. Total run time was 4 min.

The mass spectrometer was connected to the HPLC system by a TurboIonSpray interface. Nitrogen, from a Peak Scientific (Bedford, MA) nitrogen generator, was used as the curtain, nebulizer, and collision gas. User controlled voltages, gas pressures, and source temperature were optimized for the detection of the parent and product ions of the prodrugs. All compounds were analyzed in positive ion mode using multiple reaction monitoring. Care was taken to not inject compounds with similar transitions in succession.

Microsoft Excel 2003 for Windows (Seattle, WA) was used for the calculation of the percent substrate loss and to calculate half-lives. Ratios of peak areas obtained at different times were compared to that at zero time point and were multiplied by 100 to get the percent parent drug left intact. The in vitro half-lives were determined by plotting ln % remaining versus time, then measuring the slope (k) of this plot by using the first-order decay formula ($C = C_0\ e^{-kt}$): $t_{1/2} = 0.693/\text{slope}$

Synthetic Protocols. 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 and detected under UV light. ^{1}H and ^{13}C NMR spectra were recorded by employing a Varian Unity Plus 300 spectrometer (Varian, Inc., Palo Alto, California), and chemical shifts (δ) are in ppm relative to TMS as the internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer (VG Analytical, Ltd., Manchester, United Kingdom). Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values, except for **12a** and **18a**, which were validated by HRMS. The compounds reported as salts frequently analyzed correctly for fractional moles of water and/or ethanol of solvation. In each case, proton NMR showed the presence of indicated solvents. All chemicals and solvents were purchased from Aldrich Chemical Co., Fisher Scientific, Frontier Scientific, or Lancaster Synthesis, Inc.

4,4″-Bis-cyano[1,1′;4′,1″]terphenyl (9a). To a stirred solution of 4-bromobenzonitrile (0.91 g, 5 mmol), and tetrakis(triphenylphosphine) palladium (200 mg) in toluene (10 mL) under a nitrogen atmosphere was added 5 mL of a 2 M aqueous solution of Na_2CO_3 followed by 1,4-phenylenebisboronic acid (0.41 g, 2.5 mmol) in 5 mL of methanol. The vigorously stirred mixture was warmed to 80 °C for 12 h. The solvent was evaporated, and the precipitate was partitioned between methylene chloride (200 mL) and 2 M aqueous Na_2CO_3 (15 mL) containing 3 mL of concentrated ammonia. The organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure to afford **9a** as a white solid in 73% yield; mp 299−300 °C (DMF) (Lit.[34] mp 272 °C). ^{1}H NMR (DMSO-d_6): δ 7.89 (s, 4H), 7.94−7.96 (m, 8H). MS (ESI) m/e (rel int.): 280 (M^+, 100).

[1,1′;4′,1″]Terphenyl-4,4″-bis-*N*-hydroxyamidine (11a). A mixture of hydroxylamine hydrochloride (1.83 g, 26.3 mmol, 10 equiv) in anhydrous DMSO (30 mL) was cooled to 5 °C, and then

potassium *t*-butoxide (2.95 g, 26.3 mmol, 10 equiv) was added portion wise. To the mixture was added dinitrile **9a** (728 mg, 2.6 mmol), and the reaction was kept stirring overnight at room temperature. The reaction mixture was poured onto ice/water, whereupon a white precipitate of the diamidoxime formed. The product was collected by filtration and washed with water to afford **11a** (free base) in 68% yield; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 5.67 (br s, 4H), 7.71−7.79 (m, 12H), 9.60 (br s, 2H). MS (ESI) *m*/*e* (rel int.): 347 (M^++1, 40), 279 (100). High-resolution Calc. for $C_{20}H_{19}N_4O_2$ ms 347.1508. Observed: 347.1500.

Hydrochloride Salt of 11a. The hydrochloride salt of **11a** was prepared by suspending the free base in dry ethanol, cooling the mixture in an ice bath, and passing HCl gas for about 10 min; mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 7.28−7.35 (m, 4H), 7.77−7.80 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 156.1, 138.3, 137.3, 134.9, 127.7, 127.1, 124.7. Anal. Calc. for $C_{20}H_{18}N_4O_2$-2.0HCl-0.25H_2O-0.25C_2H_5OH: C, 56.56; H, 5.09; N, 12.87. Found: C, 56.56; H, 5.12; N, 12.55.

[1,1′;4′,1″]Terphenyl-4,4″-bis-amidine Acetate Salt (10a). To a solution of **11a** (347 mg, 1 mmol) in glacial acetic acid (10 mL) was slowly added acetic anhydride (0.35 mL). After stirring overnight and TLC indicated complete acylation of the starting material, 10% palladium on carbon (80 mg) was then added. The mixture was placed on a Parr hydrogenation apparatus at 50 psi for 4 h at room temperature. The mixture was filtered through Hyflo and the filter pad washed with water. The filtrate was evaporated under reduced pressure, and the precipitate was collected and washed with ether to give **10a**; mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 1.78 (s, 2 × CH_3), 7.52−7.54 (m, 4H), 7.58−7.61 (m, 2H), 7.76−7.90 (m, 6H). MS (ESI) *m*/*e* (rel int.): 315 (M^++1, 33), 158 (100), 121 (40). Anal. Calc. For $C_{20}H_{18}N_4$-2.0CH_3CO_2H-0.5H_2O: C, 64.99; H, 6.13; N, 12.63. Found: C, 64.97; H, 6.01; N, 12.60.

[1,1′;4′,1″]Terphenyl-4,4″-bis-*N*-methoxyamidine (12a). To a suspension of the amidoxime **11a** (347 mg, 1 mmol) in DMF (15 mL) was added LiOH·H_2O (252 mg, 6 mmol, in 3 mL of H_2O), which was followed by dimethyl sulfate (630 mg, 5 mmol). The reaction mixture was kept stirring overnight, after which it was poured onto ice/water, and the precipitate was filtered, washed with water, and dried to give the desired compound in 72% yield; mp 270−272 °C. ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 6H), 6.10 (br s, 4H), 7.75−7.80 (m, 12H).

Hydrochloride Salt of 12a. Mp 240−242 °C. ^{1}H NMR (DMSO-d_6): δ 3.86 (s, 6H), 7.95−7.90 (m, 12H), 8.45 (br s, 4H). MS (ESI) *m*/*e* (rel int.): 375 (M^+ +1, 100), 346 (25). High-resolution Calc. for $C_{22}H_{23}N_4O_2$ ms 375.1821. Observed: 375.1819. Anal. Calc. for $C_{22}H_{22}N_4O_2$-2.0HCl: C, 59.07; H, 5.41; N, 12.52. Found: C, 59.54; H, 5.44; N, 12.10.

2′-Fluoro-[1,1′;4′,1″]terphenyl-4,4″-bis-carbonitrile (9b). Adopting the same procedure used for the preparation of **9a**, a Suzuki coupling reaction was performed using 2,5-dibromo-1-flourobenzene (3.50 g, 13.78 mmol) and 4-cyanophenylboronic acid (4.45 g, 30.32 mmol) to yield the target bis-cyano derivative in 89% yield; mp 289−291 °C. ^{1}H NMR (DMSO-d_6): δ 7.72−7.83 (m, 5H) 7.90−7.99 (m, 6H). Anal. Calc. for $C_{20}H_{11}FN_2$: C, 80.52; H, 3.71. Found: C, 80.24; H, 3.95.

2′-Fluoro-[1,1′;4′,1″]terphenyl-4,4″-bis-amidine Hydrochloride Salt (10b). Dinitrile **9b** (498 mg, 1.67 mmol), suspended in freshly distilled THF (5 mL), was treated with lithium trimethylsilylamide (1 M solution in THF, 4 mL, 4 mmol), and the reaction was allowed to stir overnight. The reaction mixture was then cooled to 0 °C and to which was added HCl saturated ethanol (100 mL), whereupon a precipitate started forming. The mixture was left to run overnight, after which it was diluted with ether, and the resultant solid was collected by filtration. The diamidine was purified by neutralization with 1 N NaOH followed by filtration of the resultant solid and washing with water (3×). Finally, the free base was stirred with ethanolic HCl overnight and diluted with ether, and the solid formed was filtered and dried to give diamidine salt **10b**; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 7.72−7.89 (m, 5H), 7.97−8.07 (m, 6H), 9.34 (br s, 4H), 9.54 (br s, 4H). MS (ESI) *m*/*e* (rel int.): 333 (M^+, 100), 316 (23), 299 (27). Anal. Calc. for $C_{20}H_{17}FN_4$-2.0HCl-0.75H_2O: C, 57.35; H, 4.93; N, 13.37. Found: C, 57.54; H, 4.88; H, 13.35.

2′-Fluoro-[1,1′;4′,1″]terphenyl-4,4″-bis-*N*-hydroxyamidine (11b). The same procedure described for the preparation of **11a** was used starting with **9b**; yield 96%; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 5.83 (br s, 4H), 7.62−7.73 (m, 5H), 7.79−7.81 (m, 6H), 9.60 (br s, 2H). MS (ESI) *m*/*e* (rel int.): 364 (M^+, 100), 183 (42).

Hydrochloride Salt of 11b. Mp 282−284 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 7.74−7.86 (m, 9H), 8.02−8.05 (m, 2H). Anal. Calc for $C_{20}H_{17}FN_4O_2$-2.0HCl-0.5H_2O: C, 53.82; H, 4.51; N, 12.55. Found: C, 53.88; H, 4.43; N, 12.29.

2′-Fluoro-[1,1′;4′,1″]terphenyl-4,4″-bis-methoxyamidine (12b). The target compound was prepared by adopting the same procedure mentioned for **12a** starting with **11b**; yield 74%; mp 172−174 °C. ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 6H), 6.11 (br s, 4H), 7.60−7.78 (m, 11H). MS (ESI) *m*/*e* (rel int.): 393 (M^+ + 1, 100), 197 (28).

Hydrochloride Salt of 12b. Mp 250−252 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.85 (s, 6H), 7.71−7.88 (m, 9H), 7.96 (d, J = 7.8 Hz, 2H). Anal. Calc. for $C_{22}H_{21}FN_4O_2$-2.0HCl-0.25H_2O-0.25C_2H_5-OH: C, 56.14; H, 5.23; N, 11.63. Found: C, 56.13; H, 4.93; N, 11.43.

2′-Trifluoromethyl-[1,1′;4′,1″]terphenyl-4,4″-bis-carbonitrile (9c). Following the same synthetic procedure employed for **9a** using l,4-dibromo-2- triflouromethylbenzene (3.33 g, 10 mmol) and 4-cyanophenylboronic acid (3.23 g, 22 mmol) yielded dinitrile **9c** as a white solid (87%); mp 181−183 °C. ^{1}H NMR (DMSO-d_6): δ 7.55−7.58 (m, 3H), 7.94−8.02 (m, 6H), 8.04−8.16 (m, 2H). Anal. Calc. for $C_{21}H_{11}F_3N_2$: C, 72.41; H, 3.18. Found: C, 72.68; H, 3.34.

2′-Trifluoromethyl-[1,1′;4′,1″]terphenyl-4,4″-bis-amidine Hydrochloride Salt (10c). The diamidine was prepared following the procedure used for **10b**; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 7.56−7.64 (m, 3H), 7.96−8.18 (m, 8H), 9.36 (br s, 4H), 9.57 (br s, 4H). MS (ESI) *m*/*e* (rel int.): 383 (M^+ + 1, 23), 192 (100). Anal. Calc. for $C_{21}H_{17}F_3N_4$-2.0HCl-0.5H_2O-0.1C_2H_5OH: C, 54.30; H, 4.42; N, 11.94. Found: C, 54.11; H, 4.24; N, 11.66.

2′-Trifluoromethyl-[1,1′;4′,1″]terphenyl-4,4″-bis-*N*-hydroxyamidine (11c). The same procedure described for the preparation of **11a** was used starting with **9c**; yield 94%; mp 204−206 °C. ^{1}H NMR (DMSO-d_6): δ 5.96 (br s, 4H), 7.37 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 2H), 7.80−7.82 (m, 4H), 8.03−8.07 (m, 2H), 9.76 (br s, 2H). MS (ESI) *m*/*e* (rel int.): 415 (M^+ + 1, 26), 208 (100).

Hydrochloride Salt of 11c. Mp 229−231 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 7.55−7.61 (m, 3H), 7.84−7.92 (m, 4H), 8.07−8.18 (m, 4H). Anal. Calc. for $C_{21}H_{17}F_3N_4O_2$-2.0HCl-1.25H_2O-0.25C_2H_5-OH: C, 49.53; H, 4.44; N, 10.74. Found: C, 49.55; H, 4.40; N, 10.55.

2′-Trifluoromethyl-[1,1′;4′,1″]terphenyl-4,4″-bis-methoxyamidine (12c). Amidoxime **11c** was used to prepare the corresponding methoxime using the above-mentioned method in 72% yield; mp 186−188 °C. ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 3H), 3.76 (s, 3H), 6.14 (br s, 4H), 7.36 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 2H), 7.80−7.82 (m, 4H), 8.03−8.07 (m, 2H). MS (ESI) *m*/*e* (rel int.): 443 (M^+ + 1, 59), 222 (100).

Hydrochloride Salt of 12c. Mp 214−216 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.84 (s, 6H), 7.51 (m, 3H), 7.83 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.1 Hz, 2H), 8.11−8.15 (m, 2H). Anal. Calc. for $C_{23}H_{21}F_3N_4O_2$-2.0HCl-1.25H_2O-0.5C_2H_5OH: C, 51.39; H, 5.12; N, 9.98. Found: C, 51.54; H, 4.84; N, 9.94.

Phenyl[1,1′]pyridyl[4′,1″]phenyl-4,4″-bis-carbonitrile (9d). 2,5-Dibromopyridine and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **9d**, which was purified by column chromatography (EtOAc/Hexane, 80:20); yield 84%; mp 270−272 °C (Lit.[35] mp 264−266 °C). ^{1}H NMR (DMSO-d_6): δ 7.97−8.05 (m, 6H), 8.25 (dd, J = 1.8, 8.1 Hz, 1H), 8.33−8.38 (m, 3H), 9.13 (d, J = 1.8 Hz, 1H). MS (ESI) *m*/*e* (rel int.): 281 (M^+, 100).

Phenyl[1,1′]pyridyl[4′,1″]phenyl-4,4″-bis-*N*-hydroxyamidine (11d). The diamidoxime was obtained from dinitrile **9d** using the standard procedure in 97% yield; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 5.89 (br s, 4H), 7.79−7.81 (m, 6H), 8.08−8.23 (m, 4H), 9.03 (d, J = 1.5 Hz, 1H), 9.74 (br s, 2H). ^{13}C NMR (DMSO-d_6): δ 154.3, 150.4, 150.3, 147.2, 138.3, 136.8, 134.6, 133.7, 133.4, 132.8, 126.1, 125.9, 125.8, 125.5, 119.9. MS (ESI) *m*/*e* (rel int.): 348 (M^+ + 1, 52), 174 (100).

Hydrochloride Salt of 11d. Mp 292−294 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 7.89−7.91 (m, 4H), 8.09 (d, J = 8.7 Hz, 2H), 8.27 (d, J = 8.7 Hz, 1H), 8.36−8.40 (m, 3H), 9.15 (d, J = 1.8 Hz, 1H). Anal. Calc. for $C_{19}H_{17}N_5O_2$-3.0HCl-1.0H_2O-0.3C_2H_5OH: C, 48.18; H, 4.90; N, 14.33. Found: C, 48.18; H, 4.74; N, 14.18.

Phenyl[1,1′]pyridyl[4′,1″]phenyl-4,4″-bis-amidine Acetate Salt (10d). Diamidine **10d** was synthesized in two consecutive steps as described for **10a**. First by acetylation of amidoxime **11d** to give the bis-acetoxime intermediate and second by direct reduction; mp 273−275 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 1.70 (s, 2.8 x CH_3), 7.84−7.89 (m, 4H), 8.06−8.25 (m, 6H), 8.95 (s, 1H). MS (ESI) *m*/*e* (rel int.): 316 (M^+ + 1, 100), 158 (98). ^{13}C NMR (D_2O/DMSO-d_6, of hydrochloride salt): δ 165.9, 154.8, 148.4, 143.5, 142.2, 136.5, 134.2, 129.3, 129.0, 128.5, 127.9, 127.8, 127.7, 122.0. Anal. Calc. for $C_{19}H_{17}N_5$-2.8CH_3CO_2H-0.75H_2O: C, 59.44; H, 6.02; N, 14.09. Found: C, 59.27; H, 5.92; N, 14.16.

Phenyl[1,1′]pyridyl[4′,1″]phenyl-4,4″-bis-*N*-methoxyamidine (12d). Diamidoxime **11d** was used to prepare the target compound using the standard procedure in 89% yield; mp 245−247 °C. ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 6H), 6.13 (br s, 4H), 7.78−7.84 (m, 6H), 8.08−8.23 (m, 4H), 9.03 (d, J = 2.4 Hz, 1H).^{13}C NMR (DMSO-d_6): δ 154.3, 150.6, 150.5, 147.5, 138.8, 137.4, 134.9, 133.5, 133.0, 132.2, 126.4, 126.3, 126.1, 126.0, 120.2, 60.6. MS (ESI) *m*/*e* (rel int.): 376 (M^+ + 1, 100).

Hydrochloride Salt of 12d. Mp 241−242 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.88 (s, 6H), 7.94 (d, J = 8.7 Hz, 4H), 8.05 (d, J = 8.7 Hz, 2H), 8.27 (d, J = 8.7 Hz, 1H), 8.34−8.41 (m, 3H), 9.14 (d, J = 2.4 Hz, 1H). Anal. Calc. for $C_{21}H_{21}N_5O_2$-3.0HCl-1.75H_2O-0.5C_2H_5OH: C, 48.98; H, 5.69; N, 12.98. Found: C, 48.99; H, 5.56; N, 12.75.

2,5-Bis-(4′-cyanophenyl)-pyrimidine (9e). 2-Chloro-5-bromopyrimidine[36] and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give target dinitrile **9e**; 91% yield; mp 305−306.5 °C (DMF). ^{1}H NMR (DMSO-d_6): δ 7.98−8.07 (m, 6H), 8.58 (s, 2H), 9.34 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 161.1, 155.5, 140.4, 137.8, 132.6, 132.3, 129.9, 128.0, 127.4, 118.1, 118.0, 113.0, 111.3. MS (ESI) *m*/*e* (rel int.): 282 (M^+, 100), 141 (10), 127 (80). Anal. Calc. for $C_{18}H_{10}N_4$: C, 76.58; H, 3.57. Found: C, 76.25; H, 3.82.

2,5-Bis-(4′-amidinophenyl)-pyrimidine (10e). The same procedure described for the preparation of **10b** was used starting with **9e**; 86% yield; mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 7.91−8.00 (m, 6H), 8.54 (s, 2H), 9.26 (s, 2H). ^{13}C NMR (D_2O/DMSO-d_6): δ 166.1, 166.0, 162.4, 156.3, 142.0, 139.3, 131.1, 130.3, 129.4, 129.0, 128.5, 128.0, 122.2. MS (ESI) *m*/*e* (rel int.): 317 (M^+ + 1, 100), 159 (45). Anal. Calc. for $C_{18}H_{16}N_6$-3.0HCl-0.25H_2O: C, 50.24; H, 4.57; N, 19.53. Found: C, 50.33; H, 4.80; N, 19.47.

2,5-Bis-[4′-(*N*-hydroxyamidino)phenyl]-pyrimidine (11e). The same procedure described for the preparation of **11a** was used starting with **9e**; 97% yield; mp 290−292 °C. ^{1}H NMR (DMSO-d_6): δ 5.71 (s, 4H), 7.84−7.87 (m, 6H), 8.42 (s, 2H), 9.23 (s, 2H), 9.58 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 161.6, 154.7, 150.2, 150.1, 136.9, 135.2, 133.7, 133.4, 130.2, 127.0, 126.0, 125.8, 125.3. MS (ESI) *m*/*e* (rel int.): 349 (M^+ + 1, 100), 332 (15), 315 (10), 282 (60).

2,5-Bis-[4′-(*N*-methoxyamidino)phenyl]-pyrimidine (12e). The same procedure described for the preparation of **12a** was used starting with **11e**; free base yield 64%; mp 217−218 °C (DMF). ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 6H), 6.19 (s, 4H), 7.83−7.88 (m, 6H), 8.43 (s, 2H), 9.28 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 161.6, 155.0, 150.5, 150.4, 137.4, 134.5, 134.3, 132.6, 130.3, 127.2, 126.3, 126.2, 125.9, 60.5. MS (ESI) *m*/*e* (rel int.): 377 (M^+ + 1, 100), 347 (30), 330 (25).

Hydrochloride Salt of 12e. Mp 242−243 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.81 (s, 6H), 7.81−7.84 (m, 4H), 7.99 (s, 2H), 8.49 (s, 2H), 9.26 (s, 2H). Anal. Calc. for $C_{20}H_{20}N_6O_2$-2.6HCl-0.75C_2H_5-OH): C, 51.05; H, 5.40; N, 16.61. Found: C, 51.35; H, 5.46; N, 16.44.

1,4-Bis-(5′-cyanopyridin-2′-yl)phenylene (9f). The same procedure described for **9a** was used by employing 6-chloronicotinonitrile (2 equiv) and 1,4-phenylenebisboronic acid (1 equiv) to furnish **9f** in 94% yield; mp >300 °C (DMF). ^{1}H NMR (DMSO-d_6): δ 8.10−8.40 (m, 8H), 9.18 (s, 2H). MS (ESI) *m*/*e* (rel int.): 282 (M^+, 100), 254 (10), 179 (20). Anal. Calc. for $C_{18}H_{10}N_4$: C, 76.58; H, 3.57. Found: C, 76.33; H, 3.71.

1,4-Bis-(5′-amidinopyridin-2′-yl)-phenylene (10f). The same procedure described for the preparation of **10b** was used starting with **9f**; 90% yield; mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 8.42 (m, 8H), 9.15 (s, 2H). ^{13}C NMR (D_2O/DMSO-d_6): δ 164.5, 160.3, 149.1, 139.3, 138.0, 128.5, 123.6, 121.3. MS (ESI) *m*/*e* (rel int.): 317 (M^+ + 1, 100), 300 (70), 283 (50), 273 (15), 246 (35). Anal. Calc. for $C_{18}H_{16}N_6$-4.0HCl: C, 46.77; H, 4.36; N, 18.18. Found: C, 46.98; H, 4.55; N, 17.89.

1,4-Bis-[5′-(*N*-hydroxyamidinopyridin-2′-yl)]-phenylene (11f). The same procedure described for the preparation of **11a** was used starting with **9f**; 96% yield; mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 5.88 (s, 4H), 8.03 (d, J = 8.1 Hz, 2H), 8.13 (d, J = 8.1 Hz, 2H), 8.23−8.36 (m, 4H), 8.99 (s, 2H), 9.75 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 155.3, 148.7, 146.4, 138.6, 133.6, 127.6, 126.6, 119.3. MS (ESI) *m*/*e* (rel int.): 349 (M^+ + 1, 100), 334 (30), 282 (20).

1,4-Bis-[5′-(*N*-methoxyamidinopyridin-2′-yl)]-phenylene (12f). The same procedure described for the preparation of **12a** was used starting with **11f** to furnish the free base of **12f** in 70% yield; mp 218−219 °C (DMF). ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 6H), 6.29 (s, 4H), 8.05−8.15 (m, 4H), 8.26 (s, 4H), 8.95 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 155.7, 149.0, 146.8, 138.7, 134.3, 127.1, 126.9, 119.7, 60.8. MS (ESI) *m*/*e* (rel int.): 377 (M^+ + 1, 100), 330 (10), 189 (25).

Hydrochloride Salt of 12f. Mp 251−253 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.82 (s, 6H), 8.20 (s, 4H), 8.26 (s, 4H), 8.94 (s, 2H). Anal. Calc. for $C_{20}H_{20}N_6O_2$-4.0HCl-2.0H_2O-0.2C_2H_5OH): C, 43.17; H, 5.18; N, 14.80. Found: C, 43.32; H, 5.04; N, 14.42.

2,5-Bis(4-cyanophenyl)-1,4-dimethoxybenzene (9g). The same procedure described for **9a** was used by employing 1,4-dibromo-2,5-dimethoxybenzene (1 equiv) and 4-cyanophenylboronic acid (2 equiv) to furnish **9g** in 87% yield; mp 299−301 °C (DMF), Lit.[37] mp 278 °C. ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 6H), 7.13 (s, 2H), 7.78 (d, J = 8.4 Hz, 4H), 7.91 (d, J = 8.4 Hz, 4H).

2,5-Bis(4-amidinophenyl)-1,4-dimethoxybenzene (10g). The same procedure described for the preparation of **10b** was used starting with **9g**; yield 90%; mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.80 (s, 6H), 7.13 (s, 2H), 7.81 (d, J = 7.2 Hz, 4H), 7.91 (d, J = 7.2 Hz, 4H). ^{13}C NMR (D_2O/DMSO-d_6): δ 165.8, 150.9, 143.4, 130.1, 129.6, 128.0, 126.7, 115.2, 56.9. MS (ESI) *m*/*e* (rel int.): 375 (M^+ + 1, 20), 358 (25), 345 (40), 328 (100). Anal. Calc. for $C_{22}H_{22}N_4O_2$-2.0HCl-2.25H_2O: C, 54.15; H, 5.88; N, 11.48. Found: C, 54.05; H, 5.81; N, 11.16.

5-(4′-Formylbiphenyl-4-yl)-furan-2-carboxaldehyde (14a). The same procedure described for **9a** was used employing 5-(4-bromophenyl)-furan-2-carboxaldehyde (1.25 g, 5 mmol), and 4-formylphenyl-boronic acid (894 mg, 6 mmol) to afford **14a** in 85% yield; mp 173−174 °C (SiO_2, hexanes/EtOAc, 70:30). ^{1}H NMR (DMSO-d_6); δ 7.42 (d, J = 3.6 Hz, 1H), 7.70 (d, J = 3.6 Hz, 1H), 7.93−8.01 (m, 8H), 9.64 (s, 1H), 10.07 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 192.7, 177.9, 157.6, 151.8, 144.6, 139.6, 135.3, 130.2, 128.6, 127.9, 127.3, 125.7, 109.5. MS (ESI) *m*/*e* (rel int.): 276 (M^+, 100), 247 (5), 219 (25), 189 (25). Anal. Calc. for $C_{18}H_{12}O_3$: C, 78.24; H, 4.37. Found: C, 77.99; H, 4.44.

5-(4′-Cyanobiphenyl-4-yl)-furan-2-carbonitrile (15a). To a stirred solution of **14a** (552 mg, 2 mmol) in 10 mL of methanol was slowly added an aqueous solution (8 mL) of hydroxylamine hydrochloride (280 mg, 4 mmol) and sodium carbonate (424 mg, 4 mmol). The reaction mixture was allowed to reflux for 6 h. The solvent was evaporated, the precipitate was partitioned between

water and ethyl acetate (150 mL), and the organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure. The crude oxime was allowed to reflux in acetic anhydride (8 mL) for 4 h. The reaction mixture was poured slowly onto ice−water and the precipitate was filtered and washed with water to afford **15a** in 59% yield; mp 216−218 °C. ^{1}H NMR (DMSO-d_6); δ 7.38 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 3.6 Hz, 1H), 7.88−7.96 (m, 8H). ^{13}C NMR ((DMSO-d_6); δ 157.4, 143.4, 138.9, 132.9, 128.3, 127.8, 127.5, 125.8, 125.4, 124.3, 118.7, 112.0, 110.4, 108.3. MS (ESI) *m*/*e* (rel int.): 270 (M^+, 100), 241 (5), 214 (10). Anal. Calc. for $C_{18}H_{10}N_2O$: C, 79.99; H, 3.73. Found: C, 79.85; H, 3.91.

5-[4′-(*N*-Hydroxyamidino)-biphenyl-4-yl]-furan-2-*N*-hydroxyamidine (16a). The same procedure described for **11a** was used starting with **15a** to furnish **16a** (free base) in 92% yield; mp 229−230 °C. ^{1}H NMR (DMSO-d_6); δ 5.87 (s, 4H), 6.85 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 7.71−7.87 (m, 8H), 9.70 (s, 2H).

Hydrochloride Salt of 16a. Mp >300 °C. ^{1}H NMR (D_2O/DMSO-d_6); 7.38 (d, J = 3.9 Hz, 1H), 7.82 (d, J = 3.9 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H). ^{13}C NMR (DMSO-d_6); δ 158.7, 158.5, 148.7, 143.5, 138.8, 138.4, 128.6, 128.5, 127.4, 126.9, 125.5, 124.6, 119.2, 108.8. MS (ESI) *m*/*e* (rel int.): 337 (M^+ + 1, 65), 322 (50), 307 (100), 272 (40). Anal. Calc. for $C_{18}H_{16}N_4O_3$-2.0HCl: C, 52.82; H, 4.43; N, 13.68. Found: C, 52.60; H, 4.45; N, 13.30.

5-[4′-(*N*-Methoxyamidino)-biphenyl-4-yl]-furan-2-*N*-methoxyamidine (17). The same procedure described for **12a** was used starting with **16a** to give free base of **17** in 92% yield; mp 214−215 °C. ^{1}H NMR (DMSO-d_6); δ 3.75 (s, 6H), 6.12 (s, 2H), 6.17 (s, 2H), 6.91 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.76−8.00 (m, 8H).

Hydrochloride Salt of 17. Mp 194−196 °C. ^{1}H NMR (D_2O/DMSO-d_6): δ 3.88 (s, 6H), 7.20 (d, J = 3.6 Hz, 1H), 7.34 (d, J = 3.6 Hz, 1H), 7.77−8.13 (m, 8H). Anal. Calc. for $C_{20}H_{20}N_4O_3$-2.0HCl: C, 54.92; H, 5.07; N, 12.81. Found: C, 54.88; H, 5.29; N, 12.99.

5-(4′-Amidinobiphenyl-4-yl)-furan-2-amidine Acetate Salt (18a). The same procedure described for **10a** was used starting with **16a** to give **18a** in 71% yield; mp 236−238 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.78 (s, 2 x CH_3), 7.31 (d, J = 3.6 Hz, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.85−8.11 (m, 8H). EIMS *m*/*e* (rel int.); 304 (M^+, 20), 287 (100), 270 (50), 216 (30), 190 (10). High-resolution Calc. for $C_{18}H_{16}N_4O$ ms 304.1324. Observed: 304.1320. Anal. Calc. for $C_{18}H_{16}N_4O$-2.0AcOH-1.75H_2O-0.25EtOH: C, 57.81; H, 6.25; N, 11.98. Found: C, 58.18; H, 5.90; N, 11.56.

4-(5-Bromopyridin-2-yl)-benzaldehyde (13). The same procedure described for **10a** was used by employing 2,5-dibromopyridine (1 equiv) and 4-formylphenylboronic acid (1 equiv); yield 71%; mp 120−121 °C (SiO_2, hexanes/EtOAc, 80:20). ^{1}H NMR (DMSO-d_6); δ 7.97 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.7 Hz, 1H), 8.16 (dd, J = 2.4, 8.7 Hz, 1H), 8.26 (d, J = 8.4 Hz, 2H), 8.80 (d, J = 2.4 Hz, 1H), 10.08 (s, 1H). MS (ESI) *m*/*e* (rel int.): 262 (M^+, 100), 232 (30), 153 (55). Anal. Calc. for $C_{12}H_8BrNO$: C, 54.99; H, 3.08. Found: C, 54.75; H, 3.14.

5-[6-(4-Formylphenyl)-pyridin-3-yl]-furan-2-carboxaldehyde (14b). To a stirred solution of **13** (2.62 g, 10 mmol) in 40 mL of dry 1,4-dioxane was added palladium tetrakis-triphenylphosphine (400 mg), followed by 5-(diethoxymethylfuran-2-yl)-tributyltin (4.59 g, 10 mmol), and the reaction mixture was refluxed at 100 °C for 24 h. The solvent was then evaporated to dryness to give a dark brown residue, which was suspended in water and extracted with CH_2Cl_2. The organic layer was passed over Hyflo, dried (Na_2SO_4), and evaporated to dryness under reduced pressure, followed by acid hydrolysis with 2 M HCl to furnish **14b**; yield 79%; mp 204−206 °C (EtOH). ^{1}H NMR (DMSO-d_6); δ 7.55 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 3.6 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 8.4 Hz, 1H), 8.37−8.41 (m, 3H), 9.24 (d, J = 2.1 Hz, 1H), 9.67 (s, 1H), 10.09 (s, 1H). ^{13}C NMR (DMSO-d_6); δ 192.8, 178.1, 155.2, 154.7, 152.3, 146.3, 142.9, 136.5, 133.3, 130.0, 127.2, 125.1, 124.3, 121.4, 110.6. Anal. Calc. for $C_{17}H_{11}NO_3$: C, 73.63; H, 3.99. Found: C, 73.75; H, 3.81.

5-[6-(4-Cyanophenyl)-pyridin-3-yl]-furan-2-carbonitrile (15b). The same procedure described for **15a** was used starting with **14b**; yield 40%; mp 203−205 °C. ^{1}H NMR (DMSO-d_6); δ 7.53 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 8.4 Hz, 1H), 8.35−8.37 (m, 3H), 9.21 (d, J = 2.1 Hz, 1H). MS (ESI) *m*/*e* (rel int.): 272 (M^+ + 1, 100), 182 (15). Anal. Calc. for $C_{17}H_9N_3O$: C, 75.26; H, 3.34. Found: C, 75.44; H, 3.54.

5-{6-[4-(*N*-Hydroxyamidino)-phenyl]-pyridin-3-yl}-furan-2-*N*-hydroxyamidine (16b). The same procedure described for **11a** was used starting with **15b**; yield 90%; mp 194−195 °C. ^{1}H NMR (DMSO-d_6); δ 5.89 (s, 2H), 5.95 (s, 2H), 6.90 (d, J = 3.6 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.07−8.26 (m, 4H), 9.11 (d, J = 2.1 Hz, 1H), 9.76 (s, 2H). MS (ESI) *m*/*e* (rel int.): 338 (M^+ + 1, 100), 323 (20). Anal. Calc. for $C_{17}H_{15}N_5O_3$: C, 60.52; H, 4.48. Found: C, 60.73; H, 4.22.

5-[6-(4-Amidinophenyl)-pyridin-3-yl]-furan-2-carboxamidine acetate salt (18b). The same procedure described for **10a** was used starting with **16b**; yield 57%; mp 239−241 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.93 (s, 3 x CH_3), 7.31 (d, J = 3.6 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.15−8.37 (m, 4H), 9.24 (s, 1H). EIMS *m*/*e* (rel int.); 306 (M^+ +1, 55), 289 (10), 273 (15), 237 (100). High-resolution Calc. for $C_{17}H_{16}N_5O$ ms 306.1354. Observed: 306.1349. Anal. Calc. for $C_{17}H_{15}N_5O$-3.0AcOH-2.4H_2O: C, 52.25; H, 6.02; N, 13.25. Found: C, 51.95; H, 5.70; N, 12.90.

Acknowledgment. This work was supported by an award from the Bill and Melinda Gates Foundation and NIH Grants GM-61587 and AI46365.

Supporting Information Available: Elemental analysis for new compounds and CD spectra titration of **10a** into poly(dA).poly(dT). This material is available free of charge via the Internet at http://pubs.acs.org

References

(1) (a) Tidwell, R. R.; Boykin, D. W. Dicationic DNA Minor Groove Binders as Antimicrobial Agents. In *Small Molecule DNA and RNA Binders; From Synthesis to Nucleic Acid Complexes*; Demeunynck, M.; Bailly, C.; Wilson, W. D., Eds.; Wiley-VCH: New York, 2003; Vol. 2, p 414. (b) Wilson, W. D.; Nguyen, B.; Tanious, F. A.; Mathis, A.; Hall, J. E.; Stephens, C. E.; Boykin, D. W. Dications That Target the DNA Minor Groove: Compound Design and Preparation, DNA Interactions, Cellular Distribution and Biological Activity. *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5*, 389−408. (c) Soeiro, M. N. C.; de Souza, E. M. Stephens, C. E.; Boykin, D. W. Aromatic Diamidines as Antiparasitic Agents, *Expert Opin. Invest. Drugs* **2005**, *14*, 957−972.

(2) Ashley, J. N.; Barber, H. J.; Ewins, A. J.; Newbery, G.; Self, A. D. H. Chemotherapeutic Comparison of the Trypanocidal Action of Some Aromatic Diamidines. *J. Chem. Soc.* **1942**, 103−106.

(3) Fairlamb, A. H. Chemotherapy of Human African Trypanosomiasis: Current and Future Prospects. *Trends Parasitol*. **2003**, *19*, 488−494.

(4) Bouteille, B.; Oukem, O.; Bisser, S.; Dumas, M. Treatment Perspectives for Human African Trypanosomiasis. *Fundam. Clin. Pharmacol.* **2003**, *17*, 171−181.

(5) Yeramian, P. D.; Castagnini, L. A.; Allen, J. A.; Umesh, L.; Gotuzzo, E. Efficacy and Safety of DB289, a New Oral Drug for Treatment of *Pneumocystis carinii* pneumonia (PCP) in AIDS Patients. Presented at the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting, Chicago, IL, September 14−17, 2003.

(6) Yeramian, P.; Krudsood, S.; Chalermrut, K.; Silachamroon, U.; Allen, J.; Brun, R.; Meshnick, S.; Tidwell, R.; Looareesuwan, S. Efficacy of DB289 in Acute Uncomplicated *P. falciparum*/*P. vivax* Malaria. Presented at the 52nd Annual Meeting of the American Society of Tropical Medicine and Hygiene, Philadelphia, PA, December 3−7, 2003.

(7) Yeramian, P.; Meshnick, S. R.; Krudood, S.; Chalermurut, K.; Silachamroon, U.; Tangukdee, N.; Allen, J.; Brun, R.; Kweik, J. J.; Tidwell, R. R.; Looareesuwan, S. Efficacy of DB289 in Thai Patients with *Plasmodium* vivax or Acute, Uncomplicated *Plasmodium falciparum* Infections. *J. Infect. Dis.* **2005**, *192*, 319−322.

(8) Dykstra, C. C.; McClernon, D. R.; Elwell, L. P.; Tidwell, R. R. Selective Inhibition of Topoisomerases from *Pneumocystis carinii* Compared with that of Topoisomerases from Mammalian Cell. *Antimicrob. Agents Chemother.* **1994**, *38*, 1890−1898.

(9) Bailly, C.; Dassonneville, L.; Carrascol, C.; Lucasl, D.; Kumar, A.; Boykin, D. W.; Wilson, W. D. Relationships between Topoisomerase II Inhibition, Sequence-specificity and DNA Binding Mode of Dicationic Diphenylfuran Derivatives. *Anti-Cancer Drug Des.* **1999**, *14*, 47−60.
(10) Fitzgerald, D. J.; Anderson, J. N. Selective Nucleosome Disruption by Drugs that Bind in the Minor Groove of DNA. *J. Biol. Chem.* **1999**, *274*, 27128−27138.
(11) Henderson, D.; Hurley, L. H. Molecular Struggle for Transcription Control. *Nat. Med. (N.Y.)* **1995**, *1*, 525−527.
(12) Matovu, E.; Stewart, M. L.; Geiser, F.; Brun, R.; Maser, P.; Wallace, L. J. M.; Burchmore, R. J.; Enyaru, J. C. K.; Barrett, M. P.; Kaminsky, R.; Seebeck, T.; de Koning, H. P. Mechanisms of Arsenical and Diamidine Uptake and Resistance in *Trypanosoma brucei*. *Eukaryotic Cell* **2003**, *2*, 1003−1008.
(13) (a) Goodsell, D.; Dickerson, R. E. Isohelical Analysis of DNA Groove-binding Drugs. *J. Med. Chem.* **1986**, *29*, 245−255. (b) Cory, M.; Tidwell, R. R.; Fairley, T. A. Structure and DNA Binding Activity of Analogues of 1,5-Bis(4-amidinophenoxy)pentane (pentamidine). *J. Med. Chem.* **1992**, *35*, 431−438.
(14) Czarny, A.; Boykin, D. W.; Wood, A. A.; Nunn, C. M.; Neidle, S.; Zhao, M. R. J.; Wilson, W. D. Differential Experimental Analysis of van der Waals and Electrostatic Contributions in the Interactions of Minor-Groove Binding Benzimidazoles with DNA. *J. Am. Chem. Soc.* **1995**, *117*, 4716−4717.
(15) Mazur, S.; Tanious, F. A.; Ding, D.; Kumar, A.; Boykin, D. W.; Neidle, S.; Wilson, W. D. Large Hydrophobic Contributions are Involved in DNA Minor-Groove Complex Formation with a Series of Diphenylfuran Dications: Surface Plasmon Resonance and Isothermal Titration Calorimetry Studies. *J. Mol. Biol.* **2000**, *300*, 321−337.
(16) Wilson, W. D.; Tanious, F. A.; Ding, D.; Kumar, A.; Boykin, D. W.; Colson, P.; Houssier, C.; Bailly, C. Nucleic Acid Interactions of Unfused Aromatic Cations: Evaluation of Proposed Minor Groove, Major Groove and Interaction Modes. *J. Am. Chem. Soc.* **1998**, *120*, 10310−10321.
(17) Shaikh, S. A.; Ahmed, S. R.; Jayaram, B. A. Molecular Thermodynamic View of DNA-Drug Interactions: A Case Study of 25 Minor-Groove Binders. *Arch. Biochem. Biophys.* **2004**, *429*, 81−99.
(18) Boykin, D. W.; Kumar, A.; Xiao, G.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R; Hall, J. E.; Tidwell, R. R. 2,5-Bis-[4(N-alkylamidino)phenyl]furans as *Pneumocystis carinii* Agents. *J. Med. Chem.* **1998**, *41*, 124−129.
(19) Boykin, D. W.; Kumar, A.; Spychala, J.; Zhou, M.; Lombardy, R. L.; Wilson, W. D.; Dykstra, C. C.; Jones, S. K.; Hall, J. E.; Tidwell, R. R.; Laughton, C.; Nunn, C. M.; Neidle, S. Dicationic Diaryl Furans as Anti-*Pneumocystis carinii* Agents. *J. Med. Chem.* **1995**, *38*, 912−916.
(20) Brun, R.; Buhler, Y.; Sandmeier, U.; Kaminsky, R.; Bacchi, C. J.; Rattendi, D.; Lane, S.; Croft, S. L.; Snowdon, D.; Yardley, Caravatti, G.; Frei, J.; Stanek, J.; Mett, H. In Vitro Trypanocidal Activities of New *S*-Adenosylmethionine Decarboxylase Inhibitors. *Antimicrob. Agents Chemother.* **1996**, *40*, 1442−1447.
(21) Nguyen, B.; Lee, M. P. H.; Hamelberg, D.; Joubert, A.; Bailly, C.; Brun, R.; Neidle, S.; Wilson, D. W. Strong Binding in the DNA Minor Groove by an Aromatic Diamidine with a Shape That Does Not Match the Curvature of the Groove. *J. Am. Chem. Soc.* **2002**, *124*, 13680−13681.
(22) Nguyen, B.; Hamelberg, D.; Bailly, C.; Colson, P.; Stanek, J.; Brun, R.; Neidle, S.; Wilson, D. W. Characterization of a Novel DNA Minor-Groove Complex, *Biophys. J.* **2004**, *86*, 1028−1041.
(23) Ismail, M. A.; Batista-Parra, A.; Miao, Y.; Wilson, W. D.; Wenzler, T.; Brun, R.; Boykin, D. W. Dicationic Near-Linear Biphenyl Benzimidazole Derivatives as Antiprotozoal Agents. *Bioorg. Med. Chem.* **2005**, *13*, 6718−6726.
(24) Miao, Y.; Lee, M.; Batista-Parra, A.; Ismail, M. A.; Neidle, S.; Boykin, D. W.; Wilson, W. D. Out of Shape DNA Minor Groove Binders: Induced Fit Interactions of Heterocyclic Dications with the DNA Minor Groove. *Biochemistry* **2005**, *44*, 14701−14708.
(25) Steck, E. A.; Kinnamon, K. E.; Rane, D. S.; Hanson, W. L. *Leishmanina donovani*, *Plasmodium berghi*, Trypanosoma rhodensiense: Antiprotozoal Effects of Some Amidine Types. *Exp. Parasitol.* **1981**, *52*, 404−413.
(26) Schwab, P. F. H.; Levin, M. D.; Michl, J. Simple Axial Rods. *Chem. Rev.* **1999**, *99*, 1863−1934.
(27) Sakai, N.; Mareda, J.; Matile, S. Rigid-Rod Molecules in Biomembrane Models: From Hydrogen-Bonded Chains to Synthetic Multifuntional Pores. *Acc. Chem. Res.* **2005**, *38*, 79−87.
(28) Oszczapowicz, J. In *The Chemistry of Amidines and Imidates*; Patai, S. Ed.; Wiley and Sons: Chichester, U. K., 1991; Vol. 2, pp 623−688.
(29) Hall, J. E.; Kerrigan, J. E.; Ramachandran, K.; Bender, B. C.; Stanko, J. P.; Jones, S. K.; Patrick, D. A.; Tidwell, R. R. Anti-*Pneumocystis* Activity of Aromatic Diamidoxime Prodrugs. *Antimicrob. Agents Chemother.* **1998**, *42*, 666−674.
(30) Boykin, D. W.; Kumar, A.; Bender, B. C.; Hall, J. E.; Tidwell, R. R. Anti-*Pneumocystis* Activity of Bis-amidoximes and Bis-*O*-alkylamidoximes Prodrugs. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3017−3020.
(31) Ismail, M. A.; Brun, R.; Easterbrook, J. D.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. Synthesis and Anti-Protozoal Activity of Aza-Analogues of Furamidine. *J. Med. Chem.* **2003**, *46*, 4761−4769.
(32) Ansede, J.; Anbazhagan, M.; Brun, R.; Easterbrook, J.; Hall, J. E. *O*-Alkoxyamidine Prodrugs of Furamidine: In Vitro Transport and Microsomal Metabolism as Indicators of In Vivo Efficacy in a Mouse Model of *Trypanosoma Brucei Rhodesiense* Infection. *J. Med Chem.* **2004**, *47*, 4335−4338.
(33) Thompson, T. N. Early ADME in Support of Drug Discovery: The Role of Metabolic Stability Studies. *Curr. Drug Metab.* **2000**, *1*, 215−241.
(34) Colonge, J.; Buendia, J.; Sabadie, J. Synthesis of *p*-Terphenyl Derivatives Substituted in the 4- and 4,4″-Positions. *Bull. Soc. Chim. Fr.* **1967**, *11*, 4370−4374.
(35) Kumar, A.; Rhodes, R. A.; Spychala, J.; Wilson, W. D.; Boykin, D. W.; Tidwell, R. R.; Dykstra, C. C.; Hall, J. E.; Jones, S. K.; Schinazi, R. F. Synthesis of Dicationic Diarylpyridines as Nucleic Acid Binding Agents. *Eur. J. Med. Chem.* **1995**, *30*, 99−106.
(36) Brown, D. J.; Lyall, J. M. Pyrimidine Reactions. *Aust. J. Chem.* **1964**, *17*, 794−802.
(37) Palmgren, A.; Thorarensen, A.; Baeckvall, J. Efficient Synthesis of Symmetrical 2,5-Disubstituted Benzoquinones via Palladium-Catalyzed Double Negishi Coupling. *J. Org. Chem.* **1998**, *63*, 3764−3768.

JM060470P