Synthesis and Antiprotozoal Activity of Aza-Analogues of Furamidine

Mohamed A. Ismail,[†] Reto Brun,[‡] Judy D. Easterbrook,[‡] Farial A. Tanious,[†] W. David Wilson,[†] and David W. Boykin*,[†]

Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, Atlanta, Georgia 30303-3083, USA, and Swiss Tropical Institute, Basel, CH4002, Switzerland

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6-[5-(4-Amidinophenyl)furan-2-yl]nicotinamidine (**8a**) was synthesized from 6-[5-(4-cyanophenyl)furan-2-yl]nicotinonitrile (**4a**), through the bis-*O*-acetoxyamidoxime followed by hydrogenation. Compound **4a** was prepared via selective bromination of 6-(furan-2-yl)nicotinonitrile (**2a**) with *N*-bromosuccinimide, followed by Suzuki coupling with 4-cyanophenylboronic acid. In a similar way, diamidines **8b** and **8c** were prepared from the dicyano derivatives **4c** and **4d**, respectively. *N*-Methoxy-6-{5-[4-(*N*-methoxyamidino)phenyl]-furan-2-yl}-nicotinamidine (**6a**) was prepared via methylation of the respective diamidoxime **5a** with dimethylsulfate. Prodrugs **6b** and **6c** were also prepared by methylation of the respective diamidoximes **5b** and **5d**. The symmetrical diamidines **14a**,**b** were synthesized through the corresponding bis-*O*-acetoxyamidoxime followed by hydrogenation. The key compounds **11a**,**b** were conveniently obtained by Stille coupling between 2,5-bis(tri-*n*-butylstannyl)furan and the corresponding heteroaryl halides. These compounds have been evaluated in vitro for activity against *Trypanosoma b. rhodesiense* (*T. b. r.*) and *P. falciparum* (*P. f.*). The diamidines **8a**, **8c**, and **14b** gave IC_{50} values versus *T. b. r.* of less than 10 nM. Against *P. f.* **8a**, **8b**, and **14b** exhibited IC_{50} values less than 10 nM. In an in vivo mouse model for *T. b. r.* four compounds **6a**, **6c**, **6d**, and **8a** were curative. Compound **6a** produced cures at an oral dosage of 5 mg/kg.

Introduction

The diamidine furamidine [2,5-bis(4-amidinophenyl)-furan] (**I**) exhibits broad spectrum antimicrobial activity including effectiveness against *Trypanosoma rhodesiense* in mice[1,2] and *Pneumocystis carinii pneumonia* (PCP) in an immunosuppressed rat model.[3] 2,5-Bis[4-(methoxyamidino)phenyl]furan (**II**), a furamidine prodrug, has satisfactorily completed phase I clinical trials and is currently in phase II trials as an oral drug versus human African trypanosomiasis and PCP.[4,5] Despite the broad range of activity exhibited by diamidines, to date only one compound of this chemical type, pentamidine (**III**), has seen significant clinical use. Pentamidine has been used clinically against African trypanosomiasis,[6] antimony-resistant leishmaniasis,[7] and PCP.[8,9] Pentamidine is currently being used against these three pathogenic organisms despite the fact that it is not effective when given orally, and it displays several untoward clinical effects.[10−12] Pentamidine has been shown to have significant in vitro activity against *P. falciparum*[13] and furamidine exhibited modest in vivo activity in a *P. berghei* mouse model.[1] A recent report describes pentamidine as an excellent lead for antimalarial drug discovery.[14] Given the need for new antimalarials with different modes of action, evaluation of other diaryl diamidines is warranted.

A number of compounds in this class of dicationic molecules have been shown to bind to the minor-groove of DNA at AT-rich sites, and the details of their interaction with the minor-groove have been elucidated from biophysical studies,[15−17] including crystal structures.[18,19] It is hypothesized that these types of molecules exert their biological activity by first binding to DNA and then by inhibiting one or more of several DNA dependent enzymes or perhaps by direct inhibition of transcription.[16,20,21] During the past several years, we have explored several approaches to improve the antimicrobial efficacy of furamidine-type minor-groove binders. Several investigations have suggested that groups that would increase the van der Waals interactions of minor groove binders with the walls of the groove would increase the DNA affinity of these types of molecules.[22,23] In an effort to increase efficacy of these furamidine types, we made a series of bis-*N*-alkyl analogues and evaluated their effectiveness on intravenous injection in the immunosuppressed rat model for PCP.[24] More fundamental structural variations on the cationic centers which involve exchange of the amidine group with guanidines and reversed amidines were investigated.[25] In addition to modification of the terminal amidino units, we have modified the furan ring and replaced the central furan ring with a number of other heterocyclic ring systems.[26−30] These modifications led to a number of compounds with both significant DNA affinity and antimicrobial activity; however, none appeared to have significant advantages over the furan analogues. Recently, these studies were reviewed.[5]

We have not previously explored alterations of the 2,5-phenyl groups of furamidine. Consequently, we decided to study the effect of introduction of nitrogen atoms into those rings by replacing phenyl group(s) with pyridyl group(s). Such alterations in structure offer the potential to change the base pair recognition of DNA binding by providing new hydrogen bond acceptor sites. Moreover, introduction of nitrogen atoms will change the

[†] Georgia State University.
[‡] Swiss Tropical Institute.
* Corresponding author.

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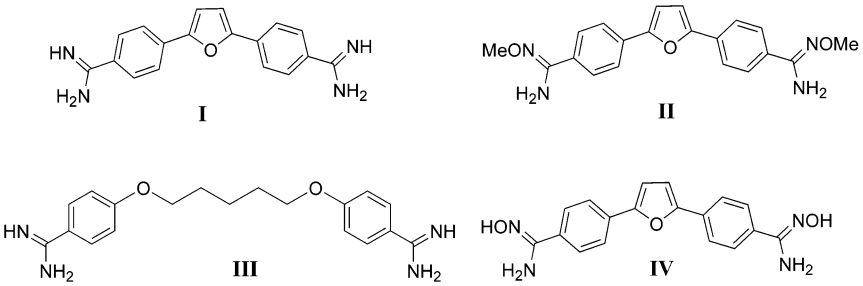
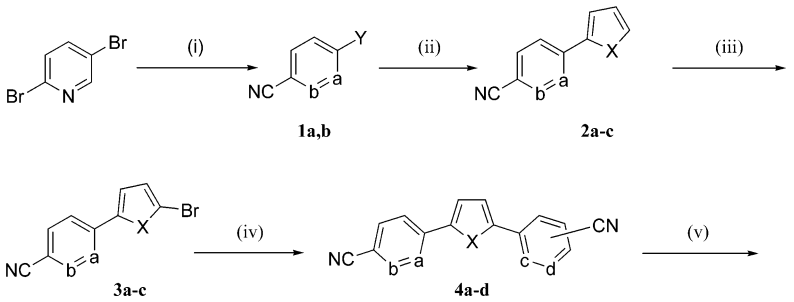
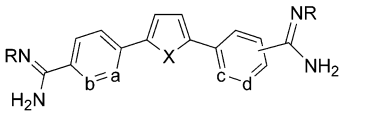


Figure 1. Diamidines and Prodrugs.

Scheme 1[a]



	a	b	Y	X	CN
1a;	N	CH	Cl		
1b;	CH	N	Br		
2a;	N	CH		O	
2b;	N	CH		S	
2c;	CH	N		O	
3a;	N	CH		O	
3b;	N	CH		S	
3c;	CH	N		O	
4a;	N	CH		O	*P*-CN
4b;	N	CH		S	*P*-CN
4c;	N	CH		O	*m*-CN
4d;	CH	N		O	*p*-CN



5a-d; R = OH

(vi) → **6a-c**; R = OMe, **6d**; R = OEt

(vii) → **7a-c**; X = O, R = OAc

(viii) → **8a-c**; X = O; R = H

	a	b	c	d	c-d ring
7a;	N	CH	CH	CH	para
7b;	N	CH	CH	CH	meta
7c;	CH	N	CH	CH	para

[a] Reagents and conditions: (i) Cu(1)CN, DMF 110-120 °C; (ii) 2-tributyltin furan or 2-tributyltin thiophene, $Pd(PPh_3)_4$; (iii) NBS, DMF; (iv) 3- or 4-cyanophenyl boronic acid, $Pd(PPh_3)_4$; (v) $NH_2OH{\cdot}HCl/KO$-*t*-Bu, DMSO; (vi) $(R)_2SO_4/NaOH$, dioxane, 0 °C; (vii) $AcOH/Ac_2O$; (viii) H_2/Pd-C, AcOH.

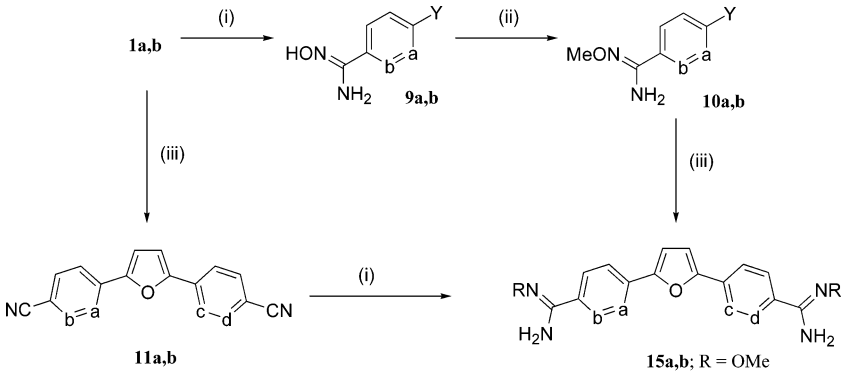
lipophilicity of the molecules and thereby could lead to different absorption and distribution profiles. We report the synthesis of disymmetric and symmetric aza-analogues of furamidine, a new class of heteroaryl diamidines.

It is well documented that the oral bioavailibility of the dicationic diamidines is limited.[5] A number of different analogues of furamidine show excellent in vivo activity on intravenous administration; however, they are ineffective when given orally.[3,24] It is also apparent, as a pragmatic consideration, that new drugs to treat human African trypanosomiasis should be orally effective. As noted above, we have found that certain bis-amidoximes and bis-*O*-methylamidoximes function as prodrugs of diamidines and are quite effective antimicrobial agents when administered orally.[4] Consequently, in this report we include the synthesis of these two types of potential prodrugs for the aza-analogues of furamidine.

Chemistry. 6-[5-(4-Amidinophenyl)furan-2-yl]nicotinamidine (**8a**) was synthesized from 6-[5-(4-cyanophenyl)furan-2-yl]nicotinonitrile (**4a**), through the bis-*O*-acetoxyamidoxime followed by hydrogenation (Scheme 1). Compound **4a** was obtained in three steps starting with a Stille coupling reaction between 2-tributylstannylfuran and 6-chloronicotinonitrile[31] (**1a**) to form the corresponding 6-(furan-2-yl)nicotinonitrile (**2a**). Bromination of **2a** with *N*-bromosuccinimide in DMF solution, furnished 6-(5-bromo-furan-2-yl)-nicotinonitrile (**3a**), in excellent yield. A subsequent Suzuki coupling of **3a** with 4-cyanophenyl boronic acid gave **4a** in good yield. In a similar way, diamidine **8b** was prepared from **4c** which was obtained by the same procedure described for **4a** employing 3-cyanophenyl boronic acid instead of 4-cyanophenyl boronic acid.

The potential prodrug, *N*-methoxy-6-{5-[4-(*N*-methoxyamidino)phenyl]-furan-2-yl}-nicotinamidine (**6a**), was prepared via methylation of the respective diamidoxime

Scheme 2[a]



	a	b	c	d
11a;	N	CH	N	CH
11b;	CH	N	CH	N
12a;	N	CH	N	CH
12b;	CH	N	CH	N
13a;	N	CH	N	CH
13b;	CH	N	CH	N
14a;	N	CH	N	CH
14b;	CH	N	CH	N
15a;	N	CH	N	CH
15b;	CH	N	CH	N

	a	b	Y
9a;	N	CH	Cl
9b;	CH	N	Br
10a;	N	CH	Cl
10b;	CH	N	Br

[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl$/KO-*t*-Bu, DMSO; (ii) $(CH_3)_2SO_4$/NaOH, dioxane, 0 °C; (iii) 2,5-bis(tributyltin) furan, $Pd(PPh_3)_4$, (iv) $AcOH/Ac_2O$; (v) H_2/Pd-C, AcOH.

5a with dimethylsulfate in aqueous sodium hydroxide solution at 0 °C in a reasonable yield (Scheme 1). The ethoxamidine **6d** was prepared in a similar manner using diethylsulfate. *N*-Methoxy-6-{5-[4-(*N*-methoxyamidino)phenyl]-thiophen-2-yl}-nicotinamidine (**6b**) was also prepared by methylation of the respective diamidoxime (**5b**), which was prepared by the same synthetic route of its furan-analogue **5a** starting with 6-(thiophen-2-yl)nicotinonitrile (**2b**).

As part of this study, we prepared a pyridine analogue of furamidine with the nitrogen atom next to amidine group. The synthesis of 5-[5-(4-amidinophenyl)-furan-2-yl]-pyridine-2-carboxamidine (**8c**) required the corresponding dinitrile **4d** (Scheme 1). The preparation of **4d** involved the same synthetic approach as employed for its isomer **4a**. In addition, 5-bromo-pyridine-2-carbonitrile, a precursor of 5-(furan-2-yl)pyridine-2-carbonitrile (**2c**), was synthesized by selective temperature-dependent cyanation of the commercially available 2,5-dibromopyridine with equimolar amount of Cu(1)CN at 110−120 °C. Our new currently reported method is an improvement and a simplification of the previously reported method involving cyanation of the noncommercially available 3-bromo-pyridine-1-oxide with trimethyl-silanecarbonitrile to give two products 5-bromopyridine-2-carbonitrile and 3-bromo-pyridine-2-carbonitrile.[32] *N*-Methoxy-5-{5-[4-(*N*-methoxyamidinophenyl]-furan-2-yl}-pyridine-2-carboxamidine (**6c**), a potential prodrug of diamidine **8c**, was prepared in a similar way to that of its analogue **6a** starting with the respective diamidoxime **5d**.

The symmetrical diamidine, 2,5-bis[5-amidino-2-pyridyl)furan (**14a**) was synthesized through the corresponding bis-*O*-acetoxyamidoxime followed by hydrogenation (Scheme 2). The required 2,5-bis(5-cyano-2-pyridyl)furan (**11a**) was conveniently obtained by Stille coupling between 2,5-bis(tri-*n*-butylstannyl)furan and 6-chloronicotinonitrile. The diamidine **14b** was prepared as previously described from **11b**.

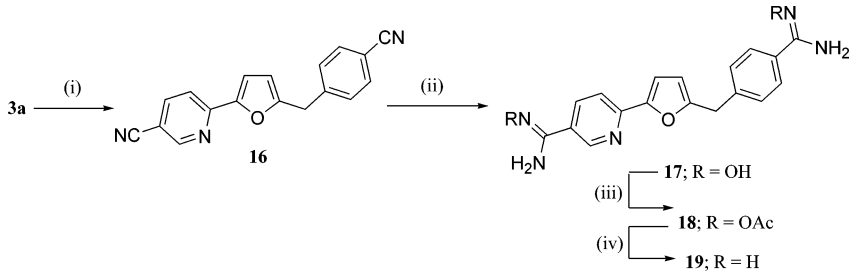
2,5-Bis[5-(*N*-methoxyamidino)-2-pyridyl)furan (**15a**), a potential prodrug of diamidine **14a**, was prepared using the synthetic pathway adopted for the preparation of **6a**−**c** but gave a poor yield (5%) apparently due to the low solubility of diamidoxime **12a** (Scheme 2). Interestingly, direct Stille coupling between 2,5-bis(tri-*n*-butylstannyl)furan and 6-chloro-*N*-methoxy-nicotinamidine (**10a**) proved to be a higher yielding route for the preparation of **15a**. The potential prodrug **15b** was synthesized from **10b** as previously described.

Finally, 6-[5-(4-amidinobenzyl)-furan-2-yl]-nicotinamidine (**19**) was synthesized from 6-[5-(4-cyanobenzyl)-furan-2-yl]nicotinonitrile (**16**), through the bis-*O*-acetoxyamidoxime followed by hydrogenation (Scheme 3). The dinitrile **16** was the product of direct Negishi coupling between *p*-cyanobenzyl zinc bromide and 6-(5-bromo-furan-2-yl)-nicotinonitrile (**3a**).

Biological Results

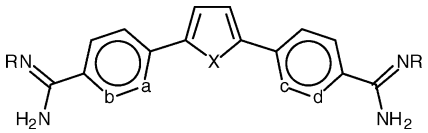
Six diamidine aza-analogues of furamidine (**I**) were prepared and evaluated against *T. b. rhodesiense* and *P. falciparum* in vitro (Table 1). The four compounds **8a**, **8c**, **14a**, and **14b** that closely match the shape and dimensions of furamidine show strong affinity for DNA as reflected by the ΔT_m values (Table 1) for binding to both poly(dA.dT)$_2$ and calf thymus DNA(CT-DNA). The ΔT_m values for CT-DNA are reduced, as expected, from that of poly(dA.dT)$_2$ as a result of the fewer AT units.

Scheme 3[a]



[a] Reagents: (i) 4-cyanobenzyl zinc bromide, $Pd(PPh_3)_4$; (ii) $NH_2OH.HCl/KO$-*t*-Bu, DMSO; (iii) $AcOH/Ac_2O$; (iv) H_2/Pd-C, AcOH.

Table 1. DNA Affinities and in Vitro Antiprotozoan Data



							DNA affinity[a]		*T. b. r.*[b]	*P. f.*[c]
code	a	b	c	d	X	R	ΔT_m poly $(dA.dT)_2$	ΔT_m CT DNA	IC_{50} nM	IC_{50} nM
pentamidine (**III**)	NA	NA	NA	NA	NA	NA	12.6	2.0	2.2	ND
furamidine (**I**)	CH	CH	CH	CH	O	H	25.0	8.9	4.5	15.5
8a	N	CH	CH	CH	O	H	19.3	6.6	7.0	6.5
5a	N	CH	CH	CH	O	OH	ND[g]		120K	4.3K
6a	N	CH	CH	CH	O	OMe	0.9		37.1K	4.9K
6d	N	CH	CH	CH	O	OEt	ND[g]		8.4K	7.3K
8b[d]	N	CH	CH	CH	O	H	7.3	3.3	40.7	8.8
5c[e]	N	CH	CH	CH	O	OH	ND[g]		13.3K	41.5K
5b	N	CH	CH	CH	S	OH	ND[g]		>187K	>10.4K
6b	N	CH	CH	CH	S	OMe	0		9.4K	4.9K
8c	CH	N	CH	CH	O	H	22.6	3.1	3.1	18.3
5d	CH	N	CH	CH	O	OH	ND[g]		200K	>11.7K
6c	CH	N	CH	CH	O	OMe	ND[g]		6.5K	8.5K
14a	N	CH	N	CH	O	H	15.5	5.4	21	83
12a	N	CH	N	CH	O	OH	0.9		55.8K	>10.2K
15a	N	CH	N	CH	O	OMe	ND[g]		11.1K	1.77K
14b	CH	N	CH	N	O	H	18.5	8.2	7.0	3.9
12b	CH	N	CH	N	O	OH	ND[g]		>21K	>10.5K
15b	CH	N	CH	N	O	OMe	−0.5		1.91K	1.31K
19[f]	CH	N	CH	CH	O	H	3.6	1.3	147	148

[a] See refs 24. [b] Average of duplicate determinations, refs 33 and 34. [c] Average of duplicate determinations, ref 35. [d] Amidine in cd ring is meta. [e] Amidoxime in cd ring is meta. [f] c−d ring phenylamidine is replaced by benzylamidine. [g] Since amidoximes bind very weakly only representative examples were studied, ND = not determined.

Consequently, the use of poly$(dA.dT)_2$ is helpful for scaling of the various compounds affinities.[3] Detailed DNA binding studies for the aza-analogues, including footprinting studies will be forthcoming. The ΔT_m values for the aza-analogues are reduced from that of **I**, but are significantly higher than that of pentamidine. The reduction in the ΔT_m values of the aza-analogues of furamidine is consistent with their increased hydrophilic properties as a result of additional nitrogen atoms. This result again suggests the importance of the hydrophobic component for minor-groove DNA binding affinity.[15,24] Compounds **8a**, **8c**, and **14b** also show high orders of in vitro activity against both organisms and give IC_{50} values comparable to that of **I**. The introduction of nitrogen(s) into the phenyl ring(s) of **I** yield compounds which show promising antimicrobial activity. The diamidines **8b** and **19** deviate significantly from the geometry of **I** and as expected, exhibit much lower DNA affinity as well as lower in vitro activity against *T. b. r.*; however, **8b** shows good activity versus *P. f.* Twelve potential prodrugs, amidoximes, *O*-methylamidoximes and one *O*-ethylamidoxime, in the aza-analogue system were prepared. As expected, these amidoxime analogues do not bind well to DNA, nor do they exhibit significant antiprotozoan activity when tested in vitro due to the absence of metabolizing enzymes. Two potential prodrugs in the thiophene series (**5b**, **6b**) were made for in vivo evaluation even though the synthetic approach described herein could not be used to prepare the corresponding diamidine.

The activity of these diamidines and their prodrugs were evaluated in an in vivo mouse model using the virulent STIB900 strain of *T. b. rhodesiense* (Table 2).[35] The diamidines were administered intraperitoneally and the prodrugs were given orally. The in vivo results of the aza-analogues are compared to **I**, **II**, and 2,5-bis-[4-(*N*-hydroxyamidinophenyl]furan (**IV**). In this model, **I**, **II**, and **IV** significantly extend the life of the treated animals; however, only compound **II** gave cures (2 of 5 animals). The diamidines **8a** and **14a** on the other hand cured all treated animals. All of the potential prodrugs show activity when they are administered orally to the mice. In cases where they did not cure the animals they extended the survival significantly as compared to untreated control mice which died on day 7 to 8 post-infection. Interestingly, the methoxymes are consistently

Table 2. In Vivo Antitrypanosomal Activity of Aza-Furamindine Analogues[a]

compound	dosage route[b]	dosage (mg/kg)	cures[c]	survival (days)[d]
pentamidine (**III**)	i.p.	20	0/4	40.8
furamidine (**I**)	i.p	20	0/4	52.5
IV	p.o.	100	0/4	50
II	p.o.	50	2/5	60
8a	i.p.	20	4/4	60
5a	p.o	100	0/4	54
6a	p.o	75	4/4	60
6a	p.o.	5	4/4	60
8b	i.p.	20	0/4	26.25
8c	i.p.	20	2/4	56.5
5d	p.o.	75	3/4	52.75
6c	p.o.	75	4/4	60
6c	p.o.	5	1/4	34.25
6d	p.o.	100	4/4	60
14a	i.p	20	4/4	60
12a	p.o.	75	0/4	18
15a	p.o.	50	4/4	60
15a	p.o.	5	1/4	40
14b	i.p.	20	3/4	59
12b	p.o.	50	1/4	30
15b	p.o.	100	0/4	21.75

[a] See experimental for details of STIB900 model. [b] i.p. = interpertional; p.o. = oral. [c] Number of mice that survive and are parasite free for 60 days. [d] Average days of survival; untreated control animals expire between day 7 and 8 post infection.

more effective than the amidoximes (see Table 1). The methoximes **6a**, **6c**, and **15a** resulted in cures of all animals. The methoxime **6a** is especially potent since it cured all animals at the oral dose of 5 mg/kg. In contrast to the results for the ethoxamidine of **I** against PCP,[4] the ethoxamidine **6d** was quite effective versus *T. b. r* in vivo. Contrary to the earlier observation this result suggests that ethoxamidines should be more carefully considered as potential prodrugs. Although the two thiophene based prodrugs **5b** and **6b** were not as effective as their furan counterparts, they did increase the survival time of treated animals >31 days (data not shown in Table 2).

In summary, we have prepared aza-analogues of **I** that exhibit high in vitro activity against both *T. b. rhodesiense* and *P. falciparum*. Several prodrugs of these aza-analogues show excellent oral activity in vivo which is superior to that of **I**, **II**, and **IV** against *T. b. rhodesiense* in this mouse model. We have found several excellent candidates for further evaluation against *T. b. rhodesiense*, and they will be tested for secondary stage (CNS involvement) efficacy. The results of these studies and the evaluation of these compounds in animal models for malaria will be forthcoming.

Experimental Section

Biology. In Vitro Assay for *T. b. rhodesiense*. Minimum essential medium (50 μl) supplemented according to Baltz et al.[33] with 2-mercaptoethanol and 15% heat-inactivated horse serum were added to each well of a 96-well microtiter plate. Serial drug dilutions were added to the wells. Then 50 μL of trypanosome suspension (*T. b. rhodesiense* STIB 900) was added to each well and the plate incubated at 37 °C under a 5% CO_2 atmosphere for 72 h. Alamar Blue (10 μL) was then added to each well and incubation continued for a further 2−4 h. Then the plate was read in a microplate fluorometer system (Spectramax Gemini by Molecular Devices) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm.[34] Fluorescence development was expressed as percentage of the control, and IC_{50} values determined.

In Vitro Assay for *P. falciparum*. Antiplasmodial activity was determined using the K1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). A modification of the [^{3}H]-hypoxanthine incorporation assay was used.[35] Briefly, infected human red blood cells in RPMI 1640 medium with 5% Albumax were exposed to serial drug dilutions in microtiter plates for 48 h. Viability was assessed by measuring the incorporation of [^{3}H]-hypoxanthine by liquid scintillation counting 24 h after the addition of the radiolabel. The counts were expressed as percentage of the control cultures, sigmoidal inhibition curves were drawn and IC_{50} values calculated.

In Vivo *T. b. rhodesiense* Mouse Model. Groups of four mice were infected intraperitoneally with 2×10^5 bloodstream forms of *T. b. rhodesiense* STIB 900 which originates from a patient in Tanzania. On days 3, 4, 5, and 6 post-infection the experimental groups were treated with the drugs either by the intraperitoneal or for prodrugs by the oral route. Usually the highest tolerated dose was used which was determined in a pretoxicological experiment. Parasitemia of the mice was checked daily up to day 14 post-infection and thereafter 2×/week up to day 60. One group of mice was not treated and acted as control. For relapsing mice the day of death was recorded and the survival time determined.

Chemistry. 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 employing a Varian GX400 or Varian Unity Plus 300 spectrometer, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were recorded on a a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values. 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 solvent (s). All chemicals and solvents were purchased from Aldrich Chemical Co., Fisher Scientific or Frontier.

6-(Furan-2-yl)nicotinonitrile (2a). A mixture of 6-chloronicotinonitrile (4.155 g, 30 mmol), 2-tributylstannylfuran (10.7 g, 30 mmol), and tetrakis(triphenylphosphine) palladium (500 mg) in dry dioxane (100 mL) was heated under nitrogen at reflux (100−110 °C) for 24 h. The solvent was evaporated under reduced pressure, the solid was dissolved in toluene, the solution was passed through Celite to remove Pd. The solution was evaporated, and the solid was filtered to give **2a** in 80.6% yield, mp 116.5−117 °C (hexanes/ether). Anal. ($C_{10}H_6N_2O$) C, H.

6-(5-Bromo-furan-2-yl)-nicotinonitrile (3a). To a solution of **2a** (5.1 g, 30 mmol) in DMF (20 mL) was added portionwise *N*-bromosuccinimide (5.87 g, 33 mmol) with stirring. The reaction mixture was stirred overnight at room temperature, and then poured onto cold-water. The precipitate which formed was collected, washed with water, and dried to give the analytically pure product **3a** in 90.4% yield, mp 196 °C MS (*m*/*z*, rel.int.); 248 (M^+, 100), 220 (10), 169 (25), 141 (80), 114 (30). Anal. ($C_{10}H_5BrN_2O$) C, H, N.

6-[5-(4-Cyano-phenyl)-furan-2-yl]-nicotinonitrile (4a). To a stirred solution of **3a** (1.245 g, 5 mmol), and tetrakis-(triphenylphosphine) palladium (288 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 4-cyanophenyl boronic acid (821 mg, 6 mmol) in 5 mL of methanol. The vigorously stirred mixture was warmed to 80 °C for 24 h, then cooled, and the precipitate was filtered. The precipitate was partitioned between methylene chloride (300 mL) and 2 M aqueous Na_2CO_3 (25 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 **4a** in 76% yield; mp 301−302 °C (DMF). MS (*m*/*z*, rel. int.); 271 (M^+, 100), 243 (10), 140 (20), 103 (20). High-resolution mass calcd. for $C_{17}H_9N_3O$: 271.07456. Observed 271.07392. Anal. ($C_{17}H_9N_3O$) C, H, N.

***N*-Hydroxy-6-{5-[4-(*N*-hydroxycarbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine hydrochloride salt (5a)**. A mixture of hydroxylamine hydrochloride (10.4 g, 150 mmol, 10 equiv) in anhydrous DMSO (80 mL) was cooled to 5 °C under nitrogen and potassium *t*-butoxide (16.8 g, 150 mmol, 10 equiv) was added in portions. The mixture was stirred for 30 min. This mixture was added to the bis cyano derivative **4a** (15 mmol, 1 equiv). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then poured slowly onto ice−water (200 mL of water and 200 mL of ice). The precipitate was filtered and washed with water and then ethanol to afford **5a** (free base) in 91% yield; mp 252−253 °C. ^{1}H NMR (DMSO-d_6); δ 5.87 (s, 2H), 6.01 (s, 2H), 7.20 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H). 7.92 (d, J = 8.1 Hz, 1H), 8.10 (dd, J = 8.1, 2.1 Hz, 1H), 8.88 (d, J = 2.1 Hz, 1H), 9.72 (s, 1H), 9.89 (s, 1H). ^{13}C nmr; δ 153.7, 152.5, 150.3, 148.7, 148.1, 146.7, 133.6, 132.6, 130.0, 127.2, 125.8, 123.4, 117.8, 111.7, 109.0. MS (*m*/*z*, rel.int.); 337 (M^+, 100), 312 (10), 273 (5), 137 (20), 109 (30). High-resolution mass calcd. for $C_{17}H_{15}N_5O_3$: 337.11749. Observed 337.11560. (**5a**, hydrochloride salt); mp 281−282 °C. ^{13}C NMR; δ158.7, 156.8, 153.6, 152.4, 151.0, 148.8, 137.2, 133.6, 128.8, 124.4, 124.2, 120.1, 118.2, 114.2, 111.6. Anal. ($C_{17}H_{15}N_5O_3$-3.0HCl-0.8H_2O) C, H, N, Cl.

***N*-Methoxy-6-{5-[4-(*N*-methoxy-carbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine Hydrochloride Salt (6a)**. To a solution of **5a** (10 mmol) in dioxane (15 mL) and 2 N NaOH (80 mL) at 0−5 °C was slowly added dimethyl sulfate (30 mmol) in dioxane (5 mL). The reaction mixture was further stirred for 2 h and then extracted with ethyl acetate (500 mL, 3 times). The solvent was evaporated and the residue was purified (SiO_2, hexanes/EtOAc, 40:60) to give **6a** (free base) in 50% yield; mp 166−167 °C. ^{1}H NMR (DMSO-d_6); δ 3.77 (s, 3H), 3.80 (s, 3H), 6.12 (s, 2H), 6.28 (s, 2H), 7.23 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 3.6 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H). 7.92 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.84 (s, 1H). ^{13}C NMR; δ 153.6, 152.5, 150.5, 149.0, 148.5, 146.9, 134.1, 131.8, 130.3, 126.5, 126.2, 123.5, 117.8, 112.0, 109.3, 60.7, 60.6. MS (*m*/*z*, rel. int.); 365 (M^+, 100), 334 (20), 318 (20), 287 (35). High-resolution mass Calcd. for $C_{19}H_{19}N_5O_3$: 365.14879. Observed: 365.14927. **(6a**, hydrochloride salt); mp 196−198 °C. Anal. ($C_{19}H_{19}N_5O_3$-3.0HCl-1.0H_2O) C, H, N, Cl.

***N*-Acetoxy-6-{5-[4-(*N*-Acetoxycarbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine (7a)**. To a solution of **5a** (337 mg, 1 mmol) in glacial acetic acid (10 mL) was slowly added acetic anhydride (0.35 mL). After stirring overnight TLC indicated complete acylation of the starting material. The reaction mixture was poured onto ice−water, and the precipitate was filtered, washed with water, and dried to give **7a** in 98% yield, mp 283−284 °C. Anal. ($C_{21}H_{19}N_5O_5$-0.25CH_3CO_2H) C, H, N.

6-[5-(4-Carbamimidoyl-phenyl)-furan-2-yl]-nicotinamidine Acetate Salt (8a). To a solution of **7a** (330 mg, 0.784 mmol) in glacial acetic acid (13 mL), and ethanol (20 mL) was added 10% palladium on carbon (80 mg). The mixture was placed on 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 **8a** in 84% yield, mp 264−266 °C. ^{1}H NMR (DMSO-d_6); δ 1.80 (s, 6H), 7.43 (s, 2H), 7.89 (d, J = 8.1 Hz, 2H), 8.08 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.98 (s, 1H). Anal. ($C_{17}H_{15}N_5O$-2.0CH_3CO_2H-1.7H_2O) C, H, N.

Free base of 8a was prepared by dissolving the acetate salt (50 mg) in water (5 mL) and by neutralization with 1 N NaOH. The precipitate was filtered, dried to afford free amidine of **7**, mp 232−233 °C. ^{1}H NMR (DMSO-d_6); δ 7.39 (s, 2H), 7.89 (d, J = 8.1 Hz, 2H), 8.05 (d, J = 8.1 Hz, 3H), 8.25 (d, J = 8.1 Hz, 1H), 8.99 (s, 1H). MS (*m*/*z*, rel.int.); 306 (M^++1, 100), 289 (10), 236 (10). High-resolution mass calcd. for $C_{17}H_{16}N_5O$: 306.13549. Observed: 306.13583.

6-(Thiophen-2-yl)nicotinonitrile (2b). The same procedure described for **2a** was used employing 2-tributylstannylthiophene instead of 2-tributylstannylfuran. Yield 82%, mp 110−111 °C (hexanes/ether). Anal. ($C_{10}H_6N_2S$) C, H.

6-(5-Bromo-thiophen-2-yl)nicotinonitrile (3b). The same procedure described for **3a** was used starting with **2b**. Yield 95%, mp 172−173 °C. Anal. ($C_{10}H_5BrN_2S$) C, H.

6-[5-(4-Cyano-phenyl)-thiophen-2-yl]nicotinonitrile (4b). The same procedure described for **4a** was used starting with **3b**. Yield 77.7%; mp 316−318 °C (DMF). Anal. ($C_{17}H_9N_3S$) C, H.

***N*-Hydroxy-6-{5-[4-(*N*-hydroxycarbamimidoyl)-phenyl]-thiophen-2-yl}-nicotinamidine hydrochloride salt (5b)**. The same procedure described for **5a** was used starting with **4b**. Free base of **5b**, yield 97%; mp 293−295 °C ^{1}H NMR (DMSO-d_6); δ 5.86 (s, 2H), 6.01 (s, 2H), 7.64 (d, J = 3.9 Hz, 1H), 7.74 (m, 4H), 7.86 (d, J = 3.9 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H). 8.06 (dd, J = 8.7, 1.8 Hz, 1H), 8.82 (d, J = 1.8 Hz, 1H), 9.73 (s, 1H), 9.89 (s, 1H). ^{13}C NMR; δ 151.5, 150.2, 148.7, 146.3, 144.8, 143.4, 133.8, 133.5, 132.7, 127.3, 126.8, 126.0, 125.2, 124.9, 117.8. **(5b**, hydrochloride salt), mp 301−303 °C. Anal. ($C_{17}H_{15}N_5O_2S$-3.0HCl-1.0H_2O): C, H, N.

***N*-Methoxy-6-{5-[4-(*N*-methoxy-carbamimidoyl)-phenyl]-thiophen-2-yl}-nicotinamidine Hydrochloride Salt (6b)**. The same procedure described for **6a** was used starting with **5b**. Free base of **6b**, yield 52%; mp 188−189 °C. ^{1}H NMR (DMSO-d_6); δ 3.76 (s, 3H), 3.79 (s, 3H), 6.16 (s, 2H), 6.28 (s, 2H), 7.65 (d, J = 3.9 Hz, 1H), 7.71−7.78 (m, 4H), 7.88 (d, J = 3.9 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H). 8.05 (dd, J = 8.4, 2.1 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H). ^{13}C nmr; δ 151.9, 150.4, 148.9, 146.5, 144.8, 143.4, 134.2, 134.0, 131.8, 127.0, 126.5, 126.3, 125.4, 124.9, 117.8, 60.7, 60.6. MS (*m*/*z*, rel. int.); 381 (M^+, 100), 350 (20), 334 (30), 303 (35), 288 (20). High-resolution mass calcd. for $C_{19}H_{19}N_5O_2S$: 381.12595. Observed: 381.12337. **(6b**, hydrochoride salt). mp 230−231 °C. Anal. ($C_{19}H_{19}N_5O_2S$-3.0HCl-0.3EtOH) C, H, N.

6-[5-(3-Cyano-phenyl)-furan-2-yl]-nicotinonitrile (4c). The same procedure described for **4a** was used employing 3-cyanophenyl boronic acid instead of 4-cyanophenyl boronic acid. Yield 80%; mp 272−273 °C. MS (*m*/*z*, rel. int.); 271 (M^+, 100), 243 (10), 169 (5), 140 (10). High-resolution mass calcd. for $C_{17}H_9N_3O$: 271.07456. Observed: 271.07442.

***N*-Hydroxy-6-{5-[3-(*N*-hydroxycarbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine (5c)**. The same procedure described for **5a** was used starting with **4c**. Yield 94%; mp 217−218 °C. ^{1}H NMR (DMSO-d_6); δ 5.96 (s, 2H), 6.03 (s, 2H), 7.19 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H). 7.91 (d, J = 8.4 Hz, 1H), 8.11−8.15 (m, 2H), 8.89 (s, 1H), 9.75 (s, 1H), 9.90 (s, 1H). ^{13}C NMR; δ 153.7, 152.3, 150.3, 148.6, 148.1, 146.6, 133.9, 133.5, 129.5, 128.7, 127.1, 124.8, 124.1, 120.4, 117.6, 111.5, 108.7. (**5c**, hydrochloride salt), mp 271−273 °C. Anal. ($C_{17}H_{15}N_5O_3$-3.0HCl-0.5H_2O) C, H, N.

***N*-Acetoxy-6-{5-[3-(*N*-acetoxycarbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine (7b)**. The same procedure described for **7a** was used starting with **5c**. Yield 100%, mp 212−213 °C.

6-[5-(3-Carbamimidoyl-phenyl)-furan-2-yl]-nicotinamidine Acetate Salt (8b). The same procedure described for **8a** was used starting with **7b**. Yield 83%, mp 269−270 °C. ^{1}H NMR (DMSO-d_6); δ 1.80 (s, 2xCH_3), 7.34 (d, J = 3.6 Hz, 1H), 7.49 (d, J = 3.6 Hz, 1H), 7.65−7.80 (m, 2H), 8.01−8.14 (m, 2H), 8.21−8.32 (m, 2H). MS (*m*/*z*, rel. int.); 306 (M^++1, 100), 293 (10), 283 (25), 237 (28). High-resolution mass calcd. for $C_{17}H_{16}N_5O$: 306.13549. Observed: 306.13444. Anal. ($C_{17}H_{15}N_5O$-2.0CH_3CO_2H-1.5H_2O-0.25EtOH) C, H, N.

5-Bromo-pyridine-2-carbonitrile (1b). A mixture of 2,5-dibromopyridine (20 mmol) and Cu(1)CN (20 mmol) in DMF (120 mL) was heated at 110−120 °C for 12 h. The reaction mixture was poured onto water and the solid which formed was extracted by using ethyl acetate (250 mL, 3 times). The solvent was evaporated and the precipitate purified (SiO_2,

hexanes/EtOAc 90:10). Yield 74%, mp 125−126 °C (lit.[32] bp 100−110 °C).

5-(Furan-2-yl)pyridine-2-carbonitrile (2c). The same procedure described for **2a** was used starting with 5-bromopyridine-2-carbonitrile. Yield 83%, mp 115−116 °C. Anal. ($C_{10}H_6N_2O$) C, H, N.

5-(5-Bromo-furan-2-yl)pyridine-2-carbonitrile (3c). The same procedure described for **3a** was used starting with **2c**. Yield 93%, mp 173 °C. Anal. ($C_{10}H_5BrN_2O$) C, H, N.

5-[5-(4-Cyano-phenyl)-furan-2-yl]-pyridine-2-carbonitrile (4d). To a stirred solution of **3c** (1.245 g, 5 mmol), and tetrakis(triphenylphosphine) palladium (288 mg) in toluene (15 mL) under a nitrogen atmosphere was added 10 mL of a 1 M aqueous solution of $NaHCO_3$ followed by 4-cyanophenyl boronic acid (821 mg, 6 mmol) in 5 mL of methanol. The vigorously stirred mixture was warmed to 80 °C for 24 h, then cooled, and the precipitate was filtered. The precipitate was partitioned between methylene chloride (300 mL) and 1 M aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4), and then concentrated to dryness under reduced pressure to afford **4d** in 64% yield; mp 276−277 °C (DMF). Anal. ($C_{17}H_9N_3O$) C, H, N.

***N*-Hydroxy-5-{5-[4-(*N*-hydroxycarbamimidoyl)-phenyl]-furan-2-yl}-pyridine-2-carboxamidine hydrochloride salt (5d)**. The same procedure described for **5a** was used starting with **4d**. Free base of **5d**, yield 93%; mp 276−279 °C. ^{1}H NMR (DMSO-d_6); δ 5.85 (s, 4H), 7.20 (d, J = 3.3 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H). 7.92 (d, J = 8.4 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 9.04 (d, J = 1.8 Hz, 1H), 9.72 (s, 1H), 10.0 (s, 1H). ^{13}C nmr; δ 153.3, 150.3, 149.9, 149.2, 148.4, 143.4, 132.5, 130.9, 130.0, 126.0, 125.8, 123.3, 119.4, 110.3, 108.9. MS (*m*/*z*, rel.int.); 337 (M^+, 40), 322 (25), 288 (100), 272 (95), 246 (25). High-resolution mass calcd. for $C_{17}H_{15}N_5O_3$: 337.11749. Observed 337.11544. (**5d**, hydrochloride salt); mp 257−260 °C. Anal. ($C_{17}H_{15}N_5O_3$-2.0HCl-0.9H_2O) C, H, N.

***N*-Methoxy-5-{5-[4-(*N*-methoxycarbamimidoyl)-phenyl]-furan-2-yl}-pyridine-2-carboxamidine (6c)**. The same procedure described for **6a** was used starting with **5d**. Free base of **6c**, yield 50%; mp 142−143 °C. ^{1}H NMR (DMSO-d_6); δ 3.78 (s, 3H), 3.82 (s, 3H), 6.11 (s, 4H), 7.20 (s, 1H), 7.33 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H). 7.92 (d, J = 8.1 Hz, 1H), 8.22 (dd, J = 8.1, 2.1 Hz, 1H), 9.03 (d, J = 2.1 Hz, 1H). ^{13}C NMR; δ 153.3, 150.5, 149.9, 149.0, 147.4, 143.5, 131.6, 131.0, 130.3, 126.3, 126.2, 123.3, 119.8, 110.6, 109.1, 61.1, 60.6. (**6c**, hydrochloride salt); mp 235−237 °C. Anal. ($C_{19}H_{19}N_5O_3$-2.0HCl) C, H, N, Cl.

***N*-Ethoxy-6-{5-[4-(*N*-ethoxy-carbamimidoyl)-phenyl]-furan-2-yl}-nicotinamidine (6d)**. The same procedure described for **6a** was used by employing diethyl sulfate instead of dimethyl sulfate. Free base of **6d**, yield 67%; mp 179−179.5 °C. ^{1}H NMR (DMSO-d_6); δ 1.25 (t, J = 6.9 Hz, 6H), 4.03 (q, J = 6.9 Hz, 4H), 6.07 (s, 2H), 6.22 (s, 2H), 7.24 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H). 7.93 (d, J = 8.7 Hz, 1H), 8.11 (dd, J = 8.7, 1.8 Hz, 1H), 8.86 (d, J = 1.8 Hz, 1H). ^{13}C NMR; δ 153.6, 152.4, 150.3, 148.8, 148.4, 146.9, 134.0, 131.9, 130.2, 126.6, 126.1, 123.4, 117.7, 111.9, 109.1, 67.9, 67.8, 14.7. MS (*m*/*z*, rel. int.); 393 (M^+, 100), 365 (5), 332 (30), 304 (10), 272 (50). High-resolution mass calcd. for $C_{21}H_{23}N_5O_3$: 393.18009. Observed: 393.18106. (**6d**, hydrochloride salt); mp 199−201 °C. Anal. ($C_{21}H_{23}N_5O_3$-3.0HCl-1.3H_2O) C, H, N.

***N*-Acetoxy-5-{5-[4-(*N*-acetoxycarbamimidoyl)-phenyl]-furan-2-yl}-pyridine-2-carboxamidine (7c)**. The same procedure described for **7a** was used starting with **5d**. Yield 89%, mp 267−270 °C. Anal. ($C_{21}H_{19}N_5O_5$) C, H.

5-[5-(4-Carbamimidoyl-phenyl)-furan-2-yl]-pyridine-2-carboxamidine acetate salt (8c). The same procedure described for **8a** was used starting with **7c**. Yield 68%, mp 266−268 °C. ^{1}H NMR (DMSO-d_6); δ 1.80 (s, 9H), 7.41 (d, J = 3.6 Hz, 1H), 7.51 (d, J = 3.6 Hz, 1H), 7.94 (d, J = 8.7 Hz, 2H), 8.12 (d, J = 8.7 Hz, 2H), 8.28 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 9.28 (s, 1H). Anal. ($C_{17}H_{15}N_5O$-3.0CH_3CO_2H-2.1H_2O) C, H, N.

2,5-Bis(5-cyano-2-pyridyl)furan (11a). A mixture of 6-chloronicotinonitrile (1.38 g, 10 mmol), 2,5-bis(tri-*n*-butylstannyl)-furan (3.2 g, 5 mmol) and tetrakis(triphenyl-phosphine)-palladium(0) (125 mg) in dry 1,4-dioxane (40 mL) was heated under nitrogen at reflux (100−110 °C) for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in methylene chloride and the solution was passed through Celite to remove Pd. The solution was evaporated, filtered and the precipitate was washed with hexanes to afford **11a** in 85% yield, mp 311−312 °C (DMF). Anal. ($C_{16}H_8N_4O$) C, H, N.

2,5-Bis[5-(*N*-hydroxycarbamimidoyl)-2-pyridyl)furan hydrochloride salt (12a). The same procedure described for **5a** was used starting with **11a**. Free base of **12a**, yield 96%, mp 272−274 °C. ^{1}H NMR (DMSO-d_6); δ 6.00 (s, 4H), 7.31 (s, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.13 (dd, J = 8.4, 2.1 Hz, 2H). 8.91 (d, J = 2.1 Hz, 2H), 9.88 (s, 2H). ^{13}C NMR; δ 153.5, 148.7, 147.9, 146.7, 133.6, 127.6, 118.0, 111.7. MS (*m*/*z*, rel. int.); 338 (M^+, 40), 306 (45), 289 (100), 246 (10), 219 (15), 141 (45), 103 (88). High-resolution mass calcd. for $C_{16}H_{14}N_6O_3$: 338.11274. Observed 338.11255. (**12a** hydrochloride salt); mp 283−285 °C. Anal. ($C_{16}H_{14}N_6O_3$-3.65HCl-1.0H_2O) C, H, N, Cl.

2,5-Bis[5-(*N*-acetoxycarbamimidoyl)-2-pyridyl)furan (13a). The same procedure described for **7a** was used starting with **12a**. Yield 94%, mp 299−300 °C. Anal. ($C_{20}H_{18}N_6O_5$) C, H.

2,5-Bis[5-amidino-2-pyridyl)furan hydrochloride salt (14a). The free amidine **14a** prepared by dissolving the acetate salt which prepared via the same procedure described for **8a** starting with **13a**, (230 mg) in water (10 mL) and neutralization with 1 N NaOH. The precipitate was filtered and dried to give free amidine of **14a** (108 mg), mp 239−241 °C. MS (*m*/*z*, rel. int.); 307 (M^++1, 90), 247 (25), 237 (100). (**14a** hydrochloride salt): mp 316−317 °C. ^{1}H NMR (DMSO-d_6); δ 7.56 (s, 2H), 8.22 (d, J = 8.7 Hz, 2H), 8.33 (dd, J = 8.7 Hz, J = 2.1 Hz, 2H). 8.96 (d, J = 2.1 Hz, 2H). ^{13}C NMR; δ 165.3, 154.4, 152.7, 149.8, 139.1, 124.6, 121.1, 116.3. Anal. ($C_{16}H_{14}N_6O$-3.3HCl-2.2H_2O) C, H, N, Cl.

2,5-Bis(2-cyano-5-pyridyl)furan (11b). The same procedure described for **11a** was used employing 5-bromo-pyridine-2-carbonitrile instead of 6-chloronicotinonitrile. Yield 73%, mp 270−272 °C. MS (*m*/*z*, rel. int.); 272 (M^+, 100), 247 (5), 141 (15). High-resolution mass calcd. for $C_{16}H_8N_4O$: 272.06981. Observed: 272.06960. Anal. ($C_{16}H_8N_4O$) C, H.

2,5-Bis[2-(*N*-hydroxycarbamimidoyl)-5-pyridyl]furan (12b). The same procedure described for **5a** was used starting with **11b**. Yield 90%, mp 281−283 °C. ^{1}H NMR (DMSO-d_6); δ 5.86 (s, 4H), 7.35 (s, 2H), 7.93 (d, J = 8.4 Hz, 2H), 8.24 (dd, J = 8.4, 2.1 Hz, 2H). 9.07 (d, J = 2.1 Hz, 2H), 10.00 (s, 2H). ^{13}C nmr; δ 150.7, 149.2, 148.6, 143.5, 131.1, 125.7, 119.4, 110.2. (**12b**, hydrochloride salt), mp 270−272 °C. Anal. ($C_{16}H_{14}N_6O_3$-2.0HCl-3.0H_2O-0.25C_2H_5OH): C, H, N.

2,5-Bis[2-(*N*-acetoxycarbamimidoyl)-5-pyridyl)furan (13b). The same procedure described for **7a** was used starting with **12b**. Yield 97%, mp 273−275 °C.

2,5-Bis[2-amidino-5-pyridyl]furan Acetate Salt (14b). The same procedure described for **8a** was used starting with **13b**. Yield 88%, mp 256−259 °C. ^{1}H NMR (DMSO-d_6); δ 1.74 (s, 2xCH_3), 7.34 (s, 2H), 8.13 (s, 2H), 8.37 (s, 2H). 9.14 (s, 2H). MS (*m*/*z*, rel. int.); 306 (M^+, 10), 289 (30), 272 (100), 247 (25), 218 (8). High-resolution mass calcd. for $C_{16}H_{14}N_6O$: 306.12291. Observed: 306.12360. Anal. ($C_{16}H_{14}N_6O$-2.0CH_3CO_2H-1.0H_2O-0.3C_2H_5OH) C, H, N.

6-Chloro-*N*-hydroxynicotinamidine (9a). The same procedure described for **5a** was used starting with 6-chloronicotinonitrile. Yield 93%, mp 185−186 °C (EtOAc). MS (*m*/*z*, rel. int.); 171 (M^+, 90), 153 (70), 139 (100), 112 (20).

6-Chloro-*N*-methoxynicotinamidine (10a). The same procedure described for **6a** was used starting with **9a**. Yield 70%, mp 105−105.5 °C (hexanes). Anal. ($C_7H_8ClN_3O$) C, H, N.

2,5-Bis[5-(*N*-methoxycarbamimidoyl)-2-pyridyl)furan Hydrochloride Salt (15a). The same procedure described for **11a** was used starting with **10a**. Free base of **15a**,

yield 35% (SiO_2, hexanes/EtOAc, 1:1), mp 228−230 °C. ^{1}H NMR (DMSO-d_6); δ 3.80 (s, 6H), 6.31 (s, 4H), 7.34 (s, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.13 (dd, J = 8.4, 2.4 Hz, 2H). 8.88 (d, J = 2.4 Hz, 2H). ^{13}C NMR; δ 153.5, 148.9, 148.3, 147.0, 134.1, 126.8, 118.1, 112.0, 60.7. MS (*m*/*z*, rel. int.); 366 (M^+, 100), 335 (25), 319 (30), 288 (40). High-resolution mass calcd. for $C_{18}H_{18}N_6O_3$: 366.14404. Observed: 366.14012. **(15a**, hydrochloride salt); mp 201−202 °C. Anal. ($C_{18}H_{18}N_6O_3$-3.25HCl-3.0H_2O-0.1C_2H_5OH) C, H, N, Cl.

5-Bromo-*N*-hydroxy-pyridine-2-carboxamidine (9b). The same procedure described for **9a** was used starting with 5-bromo-pyridine-2-carbonitrile. Yield 98%, mp 162−164 °C. MS (*m*/*z*, rel. int.); 215 (M^+, 45), 185 (100), 158 (20).

5-Bromo-*N*-methoxy-pyridine-2-carboxamidine (10b). The same procedure described for **6a** was used starting with **9b**. Yield 65%, mp 81−81.5 °C (SiO_2, hexanes/EtOAc, 9:1). Anal. ($C_7H_8BrN_3O$) C, H.

2,5-Bis[5-(*N*-methoxy-pyridine-2-carbamimidoyl)]furan Hydrochloride Salt (15b). The same procedure described for **15a** was used starting with **10b**. Free base of **15b**, yield 47%, mp 239−240 °C (SiO_2, hexanes/EtOAc, 1:1). ^{1}H NMR (DMSO-d_6); δ 3.82 (s, 6H), 6.14 (s, 4H), 7.39 (s, 2H), 7.92 (d, J = 8.4 Hz, 2H), 8.26 (dd, J = 8.4, 2.4 Hz, 2H). 9.09 (d, J = 2.4 Hz, 2H). ^{13}C NMR; δ 150.7, 149.0, 147.7, 143.7, 131.2, 126.1, 119.8, 110.5, 61.0. MS (*m*/*z*, rel. int.); 367 (M^++1, 10), 323 (35), 305 (10), 279 (100). High-resolution mass calcd. for $C_{18}H_{19}N_6O_3$: 367.15186. Observed: 367.15104. (**15b**, hydrochloride salt); mp 194−196 °C. Anal. ($C_{18}H_{18}N_6O_3$-2.0HCl-1.0H_2O-0.75EtOH) C, H, N.

6-[5-(4-Cyanobenzyl)furan-2-yl]nicotinonitrile (16). To a solution of **3a** (996 mg, 4 mmol) in tetrahydrofuran (25 mL) was added palladium tetrakis(triphenyl-phosphine) (228 mg) and *p*-cyanobenzyl zinc bromide (12 mL, 0.5 M in THF, 6 mmol). The reaction mixture was stirred 24 h at room temperature. The mixture was diluted with dichloromethane, washed with saturated NH_4Cl, and the organic layer was dried over anhydrous Na_2SO_4. After filtration and on concentration the residue was purified by chromatography (SiO_2), hexanes (100−40%)/EtOAc (0−60%), to afford **16** in 48% yield, mp 204−206 °C. MS (*m*/*z*, rel.int.); 285 (M^+, 100), 256 (15), 183 (10), 154 (15). High-resolution mass calcd. for $C_{18}H_{11}N_3O$: 285.09021. Observed: 285.08970.

***N*-Hydroxy-6-{5-[4-(*N*-hydroxycarbamimidoyl)benzyl]-furan-2-yl}-nicotinamidine (17)**. The same procedure described for **5a** was used starting with **16**. Yield 85%, mp 214−216 °C. ^{1}H NMR (DMSO-d_6); δ 4.08 (s, 2H), 5.76 (s, 2H), 5.96 (s, 2H), 6.33 (d, J = 3.3 Hz, 1H), 7.05 (d, J = 3.3 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 3H), 8.02 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 8.79 (d, J = 2.1 Hz, 1H), 9.57 (s, 1H), 9.84 (s, 1H). ^{13}C NMR; δ 155.7, 151.8, 150.6, 148.7, 148.4, 146.5, 138.5, 133.6, 131.7, 128.3, 126.9, 125.6, 117.1, 110.3, 109.3, 33.5. MS (*m*/*z*, rel.int.); 352 (M^++1, 25), 323 (100), 307 (20), 291 (10), 273 (10), 239 (15). High-resolution mass calcd. for $C_{18}H_{18}N_5O_3$: 352.14096. Observed: 352.14606.

***N*-Acetoxy-6-{5-[4-(*N*-acetoxycarbamimidoyl)benzyl]-furan-2-yl}-nicotinamidine (18)**. The same procedure described for **7a** was used starting with **17**. Yield 98%, mp 194−196 °C. MS (*m*/*z*, rel. int.); 436 (M^++1, 10), 400 (15), 378 (60), 360 (75), 320 (100), 303 (50), 279 (10), 237 (50).

6-[5-(4-Carbamimidoylbenzyl)-furan-2-yl]-nicotinamidine Acetate Salt (19). The same procedure described for **8a** was used starting with **18**. Yield 60%, mp 213-216 °C. ^{1}H NMR (DMSO-d_6); δ 1.78 (s, 2xCH_3), 6.43 (d, J = 3.3 Hz, 1H), 7.23 (d, J = 3.3 Hz, 1H), 7.43 (d, J = 7.8 Hz, 2H), 7.49−7.73 (m, 3H), 8.17 (d, J = 7.8 Hz, 1H), 8.89 (s, 1H). MS (*m*/*z*, rel. int.); 320 (M^++1, 100), 315 (10), 294 (5), 255 (10), 237 (18). High-resolution mass calcd. for $C_{18}H_{18}N_5O$: 320.15114. Observed: 320.15689. Anal. ($C_{18}H_{17}N_5O$-2.0AcOH-3.0H_2O-0.35EtOH) C, H, N.

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Supporting Information Available: Details of the synthesis and anitprotozoal activity of aza-analogues of furamidine. This material is available free of charge via the Internet at http://pubs.acs.org.

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