Novel Dicationic Imidazo[1,2-*a*]pyridines and 5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridines as Antiprotozoal Agents

Mohamed A. Ismail,[†] Reto Brun,[‡] Tanja Wenzler,[‡] Farial A. Tanious,[†] W. David Wilson,[†] and David W. Boykin*[,†]

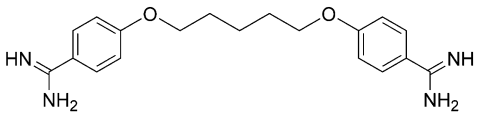
Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, Atlanta, Georgia 30303-3083, and Swiss Tropical Institute, Basel, CH4002, Switzerland

Received January 13, 2004

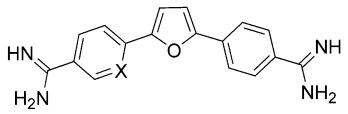
2-[5-(4-Amidinophenyl)-furan-2-yl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine acetate salt (**7**) was synthesized from 2-[5-(4-cyanophenyl)-furan-2-yl]-imidazo[1,2-*a*]-pyridine-6-carbonitrile (**4a**), through the bis-*O*-acetoxyamidoxime followed by hydrogenation in glacial acetic acid. Compound **4a** was obtained in four steps starting with two succesive brominations of 2-acetylfuran first with *N*-bromosuccinimide, and second with bromine to form α-bromo-2-acetyl-5-bromofuran (**2**) in a moderate yield. The product (**3a**), of the condensation reaction between 6-amino-nicotinonitrile and **2**, undergoes Suzuki coupling with 4-cyanophenylboronic acid to furnish **4a** in good yield. Acetate salt of 2-[5-(4-amidinophenyl)-furan-2-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine (**8a**) was obtained from **4a**, through the bis-*O*-acetoxyamidoxime followed by hydrogenation in a mixture of ethanol/ethyl acetate. *N*-Methoxy-2-{5-[4-(*N*-methoxyamidino)-phenyl]-furan-2-yl}-imidazo[1,2-*a*]pyridine-6-carboxamidine (**6**) was prepared via methylation of the respective diamidoxime **5a** with dimethyl sulfate. By these approaches eight new diamidines and four potential prodrugs were prepared. All of the diamidines showed strong DNA affinities as judged by high ΔT_m values. Six of the eight diamidines gave in vitro IC_{50} values of 63 nM or less vs *T. b. rhodesiense* with two exhibiting values of 6 nM and 1 nM. Also, six of the eight diamidines gave in vitro IC_{50} values of 88 nM or less vs *P. falciparum* with two exhibiting values of 14 nM. Excellent in vivo activity in the trypanosomal STIB900 mouse model was found for five of the diamidines on ip dosage; these compounds gave 4/4 cures in this model. The oral activity of the prodrugs was modest with only one showing 2/4 cures in the same mouse model.

Introduction

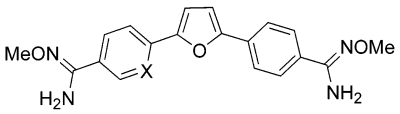
Aromatic diamidines exhibit broad-spectrum antimicrobial activity including effectiveness against the protozoan diseases caused by *Trypanosoma* sp and *Plasmodium* sp.[1] Despite the broad activity shown by aromatic diamidines, pentamidine (**I**) is the only compound of this class to see significant human use.[1] 2,5-Bis[4-(methoxyamidino)phenyl]furan (**IIIa**), a prodrug of furamidine, [2,5-bis(4-amidinophenyl)furan] (**IIa**), is an effective antitrypanosomal compound which is currently entered into Phase II clinical trials as an oral drug versus human African trypanosomiasis.[1] Recently, we have studied alterations of the 2,5-phenyl groups of furamidine by replacing phenyl group(s) with pyridyl group(s) [e.g **IIb** and **IIIb**]. Several prodrugs of these aza-analogues show excellent oral activity in vivo which are superior to that of their respective furamidines.[2] These biologically active aromatic diamidines bind to the minor groove of DNA at AT rich sites.[3−9] It is thought that the minor groove binding leads to inhibition of one or more DNA dependent enzymes which gives rise to the antimicrobial effect.[10−12] A number of effective aromatic diamidines include one or more benzimidazole units as part of the aromatic framework were studied.[13−16] One of these benzimidazole analogues, (**IV**), has been found to bind to DNA in an unusual stacked dimer array which offers the potential for development of new gene regulation molecules.[17−20]



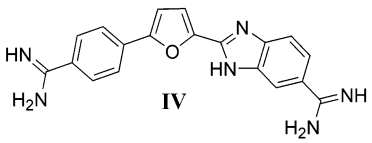
I



IIa; X = CH
IIb; X = N



IIIa; X = CH
IIIb; X = N



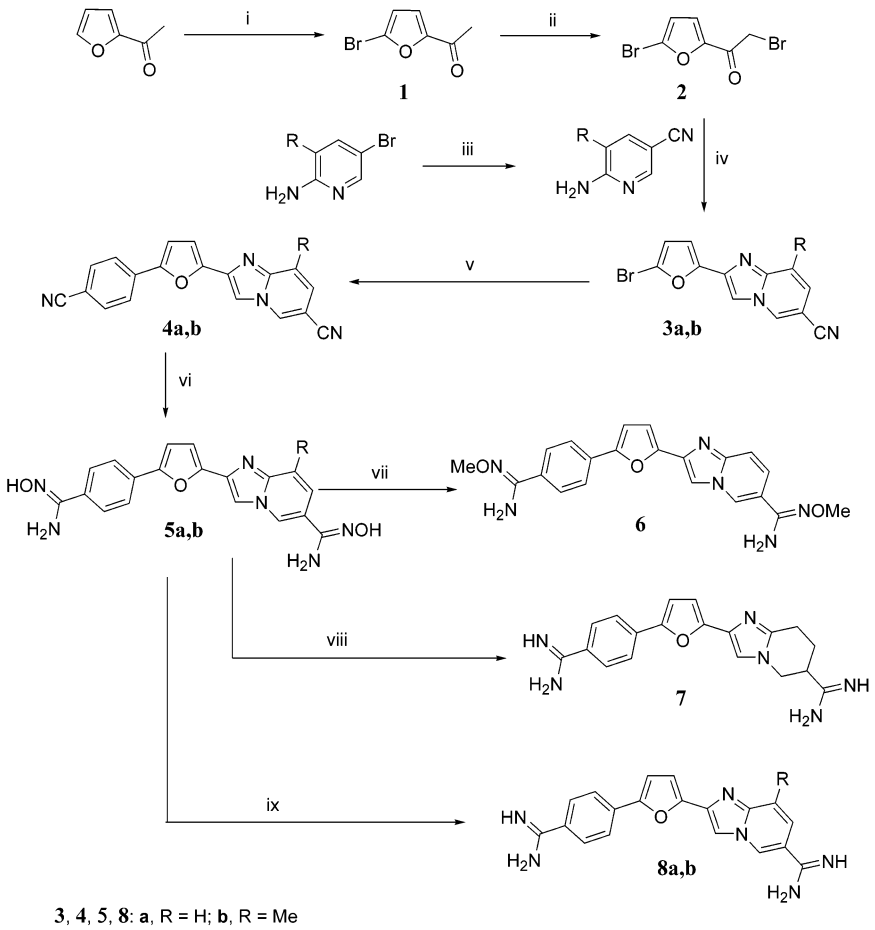
IV

Given the promising properties of these various benzimidazole aromatic diamidines, we decided to study the effect of replacing the benzimidazole group with

* To whom correspondence should be addressed. E-mail: dboykin@gsu.edu.
[†] Georgia State University.
[‡] Swiss Tropical Institute.

10.1021/jm0400092 CCC: $27.50
Published on Web 05/28/2004

Scheme 1[a]



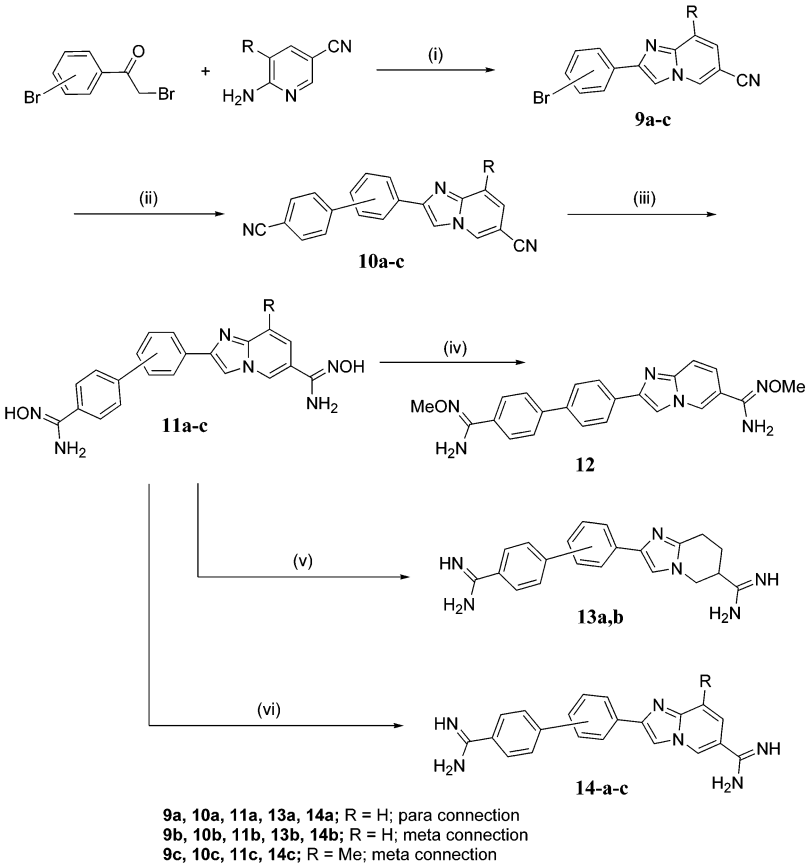
[a] Reagents and conditions: (i) NBS, DMF; (ii) Br_2; (iii) Cu(I)CN, DMF; (iv) EtOH, reflux; (v) 4-cyanophenyl boronic acid, $Pd(PPh_3)_4$; (vi) $NH_2OH{\cdot}HCl$/K-O-t-Bu, DMSO; (vii) $(Me)_2SO_4$; (viii) (a) Ac_2O/AcOH, (b) H_2/Pd−C, AcOH; (ix) (a) Ac_2O/AcOH, (b) H_2/Pd−C, EtOH.

imidazo[1,2-*a*]pyridines or 5,6,7,8-tetrahydro-imidazo-[1,2-*a*]pyridines. The imidazo[1,2-*a*]pyridine units appear as important building blocks in both natural and synthetic bioactive compounds.[21−23] Such alterations in structure offer the potential to change the base pair recognition on DNA binding and to yield different pharmacokinetic profiles. We report the synthesis of novel diamidino imidazo[1,2-*a*]pyridines and 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridines and their corresponding *N*-hydroxy and *N*-methoxy analogues which are potential prodrugs for this series and their evaluation versus *Trypanosoma b. rhodesiense* (*T. b. rhodesiense*) and *Plasmodium falciparum* (*P. falciparum*).

Chemistry

Compound **4a** was obtained in four steps starting with two successive brominations of 2-acetylfuran first with *N*-bromosuccinimide, and second with bromine to form 2-bromo-1-(5-bromofuran-2-yl)-ethanone (**2**) in a moderate yield (Scheme 1). A condensation reaction between 6-amino-nicotinonitrile and compound **2** gave 2-(5-bromofuran-2-yl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (**3a**). A subsequent Suzuki coupling of **3a** with 4-cyanophenylboronic acid furnished **4a** in good yield. The acetate salt of 2-[5-(4-amidinophenyl)-furan-2-yl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine (**7**) was obtained from 2-[5-(4-cyanophenyl)-furan-2-yl]-imidazo[1,2-*a*]pyridine-6-carbonitrile (**4a**), through the bis-*O*-acetoxyamidoxime followed by hydrogenation in glacial acetic acid. Intrestingly, 2-[5-(4-amidinophenyl)-furan-2-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine acetate salt (**8a**) was obtained from **4a**, through the bis-*O*-acetoxyamidoxime followed by hydrogenation in a mixture of ethanol/ethyl acetate. Thus, by choice of hydrogenation solvent the saturated or unsaturated imidazo[1,2-*a*]pyridine can be obtained. A recent study of the effect of solvent on the course of catalytic hydrogenation of nitrogen heterocyles illustrates the potential of such approaches.[24] In a similar way, diamidine **8b** was prepared starting from **4b** which was obtained by an analogous procedure to that described for **4a** employing 2-(5-bromofuran-2-yl)-8-methyl-imidazo[1,2-*a*]pyridine-6-carbonitrile (**3b**) instead of **3a**. However, in this case, the tetrahydro analogue of the diamidine **8b** was not obtained by using acetic acid as the hydrogenation solvent as described for the diamidine **7**, and this may be due to the steric effect of the methyl group.[24] The potential prodrug, *N*-methoxy-2-{5-[4-(*N*-methoxyamidino)-phenyl]-furan-2-yl}-imidazo[1,2-*a*]pyridine-6-carboxamidine (**6**), was prepared via methylation of the respective diamidoxime **5a** with dimethyl sulfate in aqueous sodium hydroxide solution at 0 °C in a reasonable yield (Scheme 1). The hydrochloride salts of the amidoximes, **5a** and **6** were made by passing hydrogen chloride gas into ethanolic solution of their free bases.

Scheme 2[a]



[a] Reagents and conditions: (i) EtOH, reflux; (ii) 4-cyanophenyl boronic acid, $Pd(PPh_3)_4$; (iii) $NH_2OH{\cdot}HCl$/K-O-t-Bu, DMSO; (iv) $(Me)_2SO_4$; (v) (a) Ac_2O/AcOH, (b) H_2/Pd−C, AcOH; (vi) (a) Ac_2O/AcOH, (b) H_2/Pd−C, EtOH.

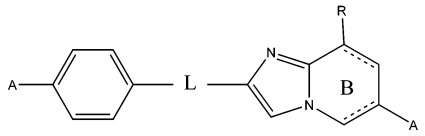
As part of this study we also prepared target diamidines containing 1,4-phenyl and 1,3-phenyl rings instead of the furan ring as the spacer. As shown in Scheme 2, the synthesis of 2-(4′-amidinobiphenyl-4-yl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine acetate salt (**13a**) employed an analogous synthetic approach to that used for **7** starting from the corresponding bis-*O*-acetoxyamidoxime. The required dinitrile **10a** was obtained using a similar synthetic approach to that employed for **4a** by starting with 4-bromophenacyl bromide instead of **2** in the preparation of 2-(4-bromophenyl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (**9a**). On the other hand, the synthesis of 2-(4′-amidinobiphenyl-4-yl)-imidazo[1,2-*a*]pyridine-6-carboxamidine (**14a**) employed the analogous synthetic approach as used for **8a**. *N*-Methoxy-2-[4′-(*N*-methoxyamidino)-biphenyl-4-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine (**12**), a potential prodrug of diamidine **14a**, was prepared in a similar way to that of **6** starting with the respective diamidoxime **11a**. The hydrochloride salts of the amidoximes **11a** and **12** were made by passing hydrogen chloride gas into ethanolic solution of their free bases.

Biological Results

Table 1 contains the results from the DNA binding studies for the new diamidines and the in vitro results for the compounds tested against *T. b. rhodesiense* and *P. falciparum*. The diamidines **8a**, **8b**, **14a**, **14b**, and **14c** all contain the unsaturated imidazo[1,2-*a*]pyridine unit and consistent with the presence of the planar aromatic systems show high DNA affinities as reflected by large ΔT_m values (24 to > 27). Changing the central ring from furanyl to 1,3-phenylene or 1,4-phenylene does not result in major differences in the observed DNA affinity. The diamidino tetrahydroimidazo[1,2-*a*]pyridine analogues **7**, **13a**, and **13b** all exhibit somewhat lower ΔT_m values (15 to 21) than their unsaturated analogues. This diminution in DNA affinity is consistent with the presence of partially saturated rings which deviate from planarity and thus do not form as effective stacking partners with the walls of the minor groove. Although the saturated analogues exhibit lower observed DNA affinity than their unsaturated counterparts, the affinities are relatively strong when compared to pentamidine ($\Delta T_m = 12$).[2] It is well-known that due to much lower p*K* values, the *N*-hydroxy and *N*-methoxy potential prodrugs of amidines do not bind well to DNA;[2] a representative example (**12**) of this class of compounds was evaluated and gave a ΔT_m value of only 0.3.

The in vitro evaluation of these compounds (Table 1) shows quite promising results against both *T. b. rhodesiense* and *P. falciparum*. Six of the eight diamidines gave IC_{50} values of 63 nM or less against *T. b. rhodesiense*. Two of the unsaturated analogues **8b** and **14a** gave quite low IC_{50} values of 6 and 1 nM against *T. b. rhodesiense*. Six of the eight diamidines gave IC_{50} values of 88 nM or less against *P. falciparum*. The two most active compounds in vitro against *P. falciparum* are **8a** and **13a**, and both gave an IC_{50} value of 14 nM. One of these is a saturated analogue and the other is unsaturated. As expected, the prodrug molecules show es-

Table 1. DNA Affinities and in Vitro Anti-Protozoan Data



code	L	B	R	A	ΔT_m[a] poly(dA.dT)$_2$	*T. b. rhodesiense*:[b] IC_{50}, nM	*P. falciparum*:[b] IC_{50}, nM
I	na	na	na	(C=NH)NH_2	12.6	2.2	NT
IIIa	na	na	na	(C=NH)NH_2	25	4.5	15.5
IIa	na	na	na	(C=NOMe)NH_2		14.6×10^3	11.4×10^3
8a	2,5-furanyl	unsatd	H	(C=NH)NH_2	26.2	63	14
5a	2,5-furanyl	unsatd	H	(C=NOH)NH_2		2.2×10^3	1.6×10^3
8b	2,5-furanyl	unsatd	Me	(C=NH)NH_2	>27	6	88
7	2,5-furanyl	satd	H	(C=NH)NH_2	15.6	52	1.2×10^3
6	2,5-furanyl	unsatd	H	(C=NOMe)NH_2		3×10^3	2.8×10^3
14b	1,3-phenylene	unsatd	H	(C=NH)NH_2	>27	22	107
14c	1,3-phenylene	unsatd	Me	(C=NH)NH_2	>27	49	86
13b	1,3-phenylene	sat'd	H	(C=NH)NH_2	19.1	226	86
14a	1,4-phenylene	unsat'd	H	(C=NH)NH_2	24.2	1	43
13a	1,4-phenylene	sat'd	H	(C=NH)NH_2	21.3	116	14
11a	1,4-phenylene	unsat'd	H	(C=NOH)NH_2		$>166 \times 10^3$	521
12	1,4-phenylene	unsat'd	H	(C=NOMe)NH_2	0.3	5.3×10^3	395

[a] See ref 2. [b] Average of duplicate determinations, see ref 2.

Table 2. In Vivo Anti-Trypanosomal Activity of Imidazo[1,2-*a*]pyridines and 5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridines Analogues in the STIB900 Mouse Model[a,b]

compound	dosage route[c]	dosage (mg/kg)	cures[d]	survival (days)[e]
pentamidine(**I**)	ip	20	0/4	40.8
furamidine (**IIa**)	ip	20	0/4	52.5
IIIa	po	100	4/4	>60
8a	ip	20	4/4	>60
5a	po	50	1/4	>19.5
8b	ip	20	4/4	>60
7	ip	20	4/4	>60
		5	2/4	>51
6	po	100	2/4	>39.5
14b	ip	20	4/4	>60
14c	ip	20	3/4	>50
14a	ip	20	4/4	>60
13a	ip	10	3/4	>51.5
11a	po	75	0/4	28
12	po	75	0/4	20

[a] See ref 2 for details of STIB900 model. [b] IC_{50} value for **13b** did not meet criteria for entry into animal studies. [c] ip = intraperitoneal; po = oral. [d] Number of mice that survive and are parasite free for 60 days. [e] Average days of survival; untreated control animals expire between day 7 and 8 postinfection.

sentially no in vitro activity due to the absence of the enzymes needed for bioconversion to the active diamidines.

The in vivo activities of these compounds in the STIB900 model for acute *T. b. rhodesiense* infection are shown in Table 2. The standard drugs **I** and **IIa** are not very effective on ip or po administration due to poor pharmacokinetic profiles consistent with their dicationic nature. The pharmacokinetic profiles of dicationic molecules are quite variable depending upon structure. In this model, five of the diamidines (**8a**, **8b**, **7**, **14b**, **14a**) give 4/4 cures and one **14c** gives 3/4 cures on ip dosage. These are highly active diamidines that clearly merit expanded evaluation. The four prodrugs (**5a**, **6**, **11a**, **12**) showed only moderate in vivo effectiveness on oral dosage. The most effective compound **6** gave 2/4 cures at 100 mg/kg. This is in contrast to the prodrug **IIIa** and a number of the azafuramidine prodrug analogues[2] that achieve 4/4 cures. Currently, it is unclear why the prodrugs described here are not very effective. It has been previously noted that similar prodrugs of related benzimidazole analogues are also not effective.[25] Metabolism studies are underway to attempt to gain insight into this result.

A new class of diaryl diamidines have been prepared which show strong DNA affinity and high in vitro activity against *T. b. rhodesiense* and *P. f.* The diamidines show excellent in vivo activity against *T. b. rhodesiense* on ip dosage. The oral activity of the potential prodrugs is only modest. Given the potent in vivo activity of the diamidines, the study of other prodrug approaches to provide orally active compounds of this type are merited.

Experimental Section

Biology. The DNA binding studies and both the in vitro and in vivo antiprotozoan studies were performed as previously described.[2] Both ip and po dosage for the in vivo model used drug candidate dissolved in 10% DMSO−water solution.

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. ^1H and ^{13}C NMR spectra were recorded employing a Varian GX400 or Varian Unity Plus 300 spectrometer, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA) and are within ±0.4 of the theoretical values. The compounds are reported as salts and analyzed 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, Frontier., or Lancaster.

1-(5-Bromofuran-2-yl)-ethanone (1). To a solution of 2-acetylfuran (2.2 g, 20 mmol) in DMF (20 mL) was added portionwise *N*-bromosuccinimide (3.91 g, 22 mmol) with stirring. The reaction mixture was stirred overnight, and then poured onto cold water. The product was extracted with ether (200 mL, 3 ×). Yield 61%, mp 92−93 °C (hexanes/ether, lit.[26] mp 94−95 °C). ^1H NMR ($CDCl_3$); δ 2.45 (s, 3H), 6.49 (d, J = 3.9 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H). ^{13}C NMR; δ 185.4, 154.4, 128.2, 118.9, 114.3, 25.7.

2-Bromo-1-(5-bromofuran-2-yl)-ethanone (2). To a solution of 1-(5-bromofuran-2-yl)-ethanone (1.88 g, 10 mmol) in 12

mL of dioxane/ether (1:2) with cooling at 0−5 °C and stirring was portionwise added bromine (0.52 mL, 10 mmol) over 1 h. The reaction mixture was further stirred with cooling, and after TLC indicated complete bromination, the reaction mixture was diluted with ether (50 mL) and water (100 mL). The ethereal layer was separated, washed with 1 M sodium bicarbonate aqueous solution, and dried over Na_2SO_4. The ether extract was distilled off to afford **2** in 65% yield, mp 96−97 °C (hexanes/ether, lit.[27] mp 98.5−99.5 °C). ^{1}H NMR ($CDCl_3$); δ 4.24 (s, 2H), 6.55 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H). ^{13}C NMR; δ 179.0, 151.9, 129.4, 121.1, 115.0, 29.5.

2-(5-Bromofuran-2-yl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (3a). A mixture of 6-amino-nicotinonitrile (1.19 g, 10 mmol) and 2-bromo-1-(5-bromofuran-2-yl)-ethanone (2.66 g, 10 mmol) in ethanol (50 mL) was refluxed for 24 h. The precipitated salt was filtered suspended in water and neutralized with aqueous $NaHCO_3$ solution. The free base precipitate was filtered, and dried to furnish **3a** in 74% yield, mp 212−214 °C (EtOH). ^{1}H NMR (DMSO-d_6); δ 6.75 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 8.29 (s, 1H), 9.30 (s, 1H). ^{13}C NMR; δ 150.5, 144.2, 137.3, 134.3, 125.4, 121.9, 117.2, 116.9, 113.9, 110.4, 109.8, 97.2. MS (*m*/*z*, rel int); 288 (M^+, 100), 161 (8). Anal. ($C_{12}H_6BrN_3O$) C, H.

2-[5-(4-Cyanophenyl)-furan-2-yl]-imidazo[1,2-*a*]pyridine-6-carbonitrile (4a). To a stirred solution of **3a** (10 mmol), and tetrakis(triphenylphosphine)palladium (350 mg) in toluene (20 mL) under a nitrogen atmosphere was added 10 mL of a 2 M aqueous solution of Na_2CO_3 followed by 4-cyanophenylboronic acid (1.64 g, 12 mmol) in 10 mL of methanol. The vigorously stirred mixture was warmed to 80 °C for 24 h and then cooled, and the precipitate was filtered. The precipitate was partitioned between methylene chloride (500 mL) and 2 M aqueous Na_2CO_3 (50 mL) containing 6 mL of concentrated ammonia. The organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure to afford **4a**. Yield 82%, mp 298−300 °C (DMF). ^{1}H NMR (DMSO-d_6); δ 7.11 (d, J = 3.6 Hz, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.72 (d, J = 9.6 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.45 (s, 1H), 9.32 (s, 1H). ^{13}C NMR; δ 152.0, 150.4, 145.1, 138.6, 135.0, 134.4, 133.6, 126.1, 124.6, 119.5, 118.0, 117.6, 112.2, 111.3, 110.2, 98.1. MS (*m*/*z*, rel int); 310 (M^+, 100), 281 (10), 208 (5), 180 (10). High-resolution mass calcd. for $C_{19}H_{10}N_4O$: 310.08546. Observed: 310.07852. Anal. ($C_{19}H_{10}N_4O$) C, H, N.

***N*-Hydroxy-2-{5-[4-(*N*-hydroxyamidino)-phenyl]-furan-2-yl}-imidazo[1,2-*a*]pyridine-6-carboxamidine Hydrochloride Salt (5a).** A mixture of hydroxylamine hydrochloride (5.2 g, 75 mmol, 10 eq.) in anhydrous DMSO (40 mL) was cooled to 5 °C under nitrogen and potassium *tert*-butoxide (8.4 g, 75 mmol, 10 equiv) was added in portions. The mixture was stirred for 30 min. This mixture was added to the bis cyano derivative **4a** (7.5 mmol, 1 equiv). The reaction mixture was stirred overnight at room temperature. The reaction mixture was then poured slowly onto ice−water (200 mL). The precipitate was filtered and washed with water to afford **5a** (free base) in 96% yield, mp 207−210 °C. ^{1}H NMR (DMSO-d_6); δ 5.85 (s, 2H), 5.97 (s, 2H), 6.97 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 7.54−7.56 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 8.35 (s, 1H), 8.80 (s, 1H), 9.70 (s, 1H), 9.83 (s, 1H). ^{13}C NMR; δ 152.1, 150.3, 149.2, 148.5, 144.7, 136.9, 132.1, 130.2, 125.8, 124.1, 123.7, 123.0, 119.2, 115.6, 109.5, 109.1, 108.5. (**5a**, hydrochloride salt), mp 289−291 °C. Anal. ($C_{19}H_{16}N_6O_3\cdot 3.0HCl\cdot 1.9H_2O$) C, H, N, Cl.

***N*-Methoxy-2-{5-[4-(*N*-methoxyamidino)-phenyl]-furan-2-yl}-imidazo[1,2-*a*]pyridine-6-carboxamidine Hydrochloride Salt (6).** To a solution of **5a** (1.12 g, 3 mmol) in dioxane (5 mL) and 2 N NaOH (24 mL) at 0−5 °C was slowly added dimethyl sulfate (9 mmol) in dioxane (5 mL). The reaction mixture was further stirred for 2 h and then extracted with ethyl acetate (200 mL, three times). The solvent was evaporated, and the residue was purified (SiO_2, hexanes/EtOAc, 2:8) to give **6** (free base) in 43% yield, mp 126−127 °C. ^{1}H NMR (DMSO-d_6); δ 3.77 (s, 6H), 6.12 (s, 2H), 6.23 (s, 2H), 6.99 (d, J = 3.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.55 (s, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 8.38 (s, 1H), 8.84 (s, 1H). ^{13}C NMR; δ 152.1, 150.6, 149.2, 148.9, 144.8, 137.0, 131.3, 130.7, 126.2, 124.7, 123.8, 123.0, 118.4, 115.7, 109.6, 109.2, 108.7, 60.7, 60.6. MS (*m*/*z*, rel int); 404 (M^+, 100), 373 (10), 357 (50), 326 (20), 310 (25). High-resolution mass calcd. for $C_{21}H_{20}N_6O_3$: 404.15969. Observed: 404.15957. (**6**, hydrochloride salt), mp 208−209 °C. Anal. ($C_{21}H_{20}N_6O_3\cdot 3.0HCl\cdot 1.5H_2O$) C, H, N.

2-[5-(4-Amidinophenyl)-furan-2-yl]-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (7). To a solution of **5a** (1 mmol) in glacial acetic acid (10 mL) was slowly added acetic anhydride (0.35 mL). After the mixture was stirred overnight, TLC indicated complete acylation of the starting material, and then the solvent was evaporated under reduced pressure. To the formed product (the product of acylation step) in glacial acetic acid (20 mL) was added 10% palladium on carbon (80 mg), and then the mixture was placed on Parr hydrogenation apparatus at 50 psi for 6 h at room temperature. The reaction 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 **7** in 86% yield, mp 195−197 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.80−2.10 (br s, 2.8 × CH_3 + 3H), 2.80 (br s, 1H), 3.07 (br s, 1H), 4.10 (br s, 1H), 4.37 (br s, 1H), 6.64 (d, J = 3.6 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 7.57 (s, 1H), 7.81−7.90 (m, 4H). MS (*m*/*z*, rel int); 348 (M^+, 5), 314 (100), 300 (5), 261 (8). Anal. ($C_{19}H_{20}N_6O\cdot 2.8AcOH\cdot 2.0H_2O$) C, H, N.

2-[5-(4-Amidinophenyl)-furan-2-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (8a). To a solution of **5a** (1 mmol) in glacial acetic acid (10 mL) was slowly added acetic anhydride (0.35 mL). After the mixture was stirred overnight, TLC indicated complete acylation of the starting material, and then the solvent was evaporated under reduced pressure. To the formed product (the product of acylation step) in a mixture of ethanol/EtOAc (50 mL, 1:1) was added 10% palladium on carbon (80 mg), and then the mixture was placed on Parr hydrogenation apparatus at 50 psi for 4 h at room temperature. The reaction 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 71% yield, mp 257−259 °C.^{1}H NMR (D_2O/DMSO-d_6); δ 1.76 (s, 2.7 × CH_3 of acetate), 7.09 (d, J = 3.6 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.59 (d, J = 9.6 Hz, 1H), 7.71 (d, J = 9.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 8.52 (s, 1H), 9.13 (s, 1H). MS (*m*/*z*, rel int); 344 (M^+, 5), 327 (20), 310 (100), 290 (55). Anal. ($C_{19}H_{16}N_6O\cdot 2.7AcOH\cdot 2.0H_2O$) C, H, N.

6-Amino-5-methylnicotinonitrile. A mixture of 2-amino-5-bromo-3-methylpyridine (15.49 g, 82.8 mmol) and Cu(1)CN (9.27 g, 103.5 mmol) in DMF (160 mL) was heated at 150 °C for 24 h. The reaction mixture was poured onto water, and the solid which formed was extracted by using ethyl acetate (600 mL, 3 times) from aq NH_4OH. The solvent was evaporated and the precipitate purified by chromatography (SiO_2, hexanes/EtOAc 4:6). Yield 70%, mp 198−200 °C, (lit.[28] mp 203−205 °C, lit.[29] melting point not reported via palladium-catalyzed cyanation).

2-(5-Bromofuran-2-yl)-8-methyl-imidazo[1,2-*a*]pyridine-6-carbonitrile (3b). The same procedure described for **3a** was used employing 6-amino-5-methylnicotinonitrile instead of 6-amino-nicotinonitrile. Yield 72%, mp 204.5−205 °C. ^{1}H NMR (DMSO-d_6); δ 2.52 (s, 3H), 6.74 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 7.36 (s, 1H), 8.26 (s, 1H), 9.16 (s, 1H). ^{13}C NMR; δ 150.6, 144.8, 136.7, 131.9, 127.4, 123.3, 121.6, 117.0, 113.8, 110.4, 110.1, 97.1, 16.3. Anal. ($C_{13}H_8BrN_3O$) C, H.

2-[5-(4-Cyanophenyl)-furan-2-yl]-8-methyl-imidazo[1,2-*a*]pyridine-6-carbonitrile (4b). The same procedure described for **4a** was used starting with **3b**. Yield 77%, mp 276−277 °C. ^{1}H NMR (DMSO-d_6); δ 2.54 (s, 3H), 7.12 (d, J = 3.6 Hz, 1H), 7.38 (s, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.45 (s, 1H), 9.19 (s, 1H). ^{13}C NMR; δ 151.1, 149.7, 144.9, 137.2, 133.6, 132.8, 132.0,

127.4, 123.8, 123.3, 118.8, 117.0, 111.4, 111.0, 110.3, 109.3, 97.1, 16.3. MS (*m*/*z*, rel int); 324 (M^+, 100), 295 (7), 222 (8), 194 (15), 162 (15). High-resolution mass calcd for $C_{20}H_{12}N_4O$: 324.10111. Observed: 324.10070.

***N*-Hydroxy-2-{5-[4-(*N*-hydroxyamidino)-phenyl]-furan-2-yl}-8-methyl-imidazo[1,2-*a*]pyridine-6-carboxamidine (5b).** The same procedure described for **5a** was used starting with **4b**. Yield 92%, mp 255−258 °C. ^{1}H NMR (DMSO-d_6); δ 2.54 (s, 3H), 5.91 (br s, 4H), 6.99 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.41 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H), 8.36 (s, 1H), 8.68 (s, 1H), 9.73 (s, 1H), 9.79 (s, 1H). ^{13}C NMR; δ 152.0, 150.4, 149.4, 148.7, 145.2, 136.4, 132.0, 130.3, 125.8, 125.1, 123.0, 121.9, 119.1, 110.1, 108.9, 108.4, 16.7. Anal. ($C_{20}H_{18}N_6O_3$·0.5H_2O) C, H.

2-[5-(4-Amidinophenyl)-furan-2-yl]-8-methyl-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (8b). The same procedure described for **8a** was used, starting with **5b**. Yield 68%, mp 229−231 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.84 (s, 3 × CH_3), 2.58 (s, 3H), 7.02 (d, J = 3.6 Hz, 1H), 7.24 (d, J = 3.6 Hz, 1H), 7.48 (s, 1H), 7.82−7.92 (m, 4H), 8.40 (s, 1H), 8.89 (s, 1H). Anal. ($C_{20}H_{18}N_6O$-3.0AcOH-1.35H_2O) C, H, N.

2-(4-Bromophenyl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (9a). The same procedure described for **3a** was used, employing 4-bromophenacyl bromide instead of 2-bromo-1-(5-bromofuran-2-yl)-ethanone (**2**). Yield 67%, mp 262−264 °C. ^{1}H NMR (DMSO-d_6); δ 7.73 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 9.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 8.69 (s, 1H), 9.48 (s, 1H). Anal. ($C_{14}H_8BrN_3$) C, H.

2-(4′-Cyanobiphenyl-4-yl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (10a). The same procedure described for **4a** was used, starting with **9a**. Yield 78%, mp 276−278 °C. ^{1}H NMR (DMSO-d_6); δ 7.51 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.92−7.98 (m, 4H), 8.14 (d, J = 7.8 Hz, 2H), 8.58 (s, 1H), 9.33 (s, 1H). ^{13}C NMR; δ 145.6, 144.2, 143.9, 137.9, 134.3, 133.2, 132.8, 127.5, 127.4, 126.6, 125.0, 118.8, 117.4, 117.1, 110.9, 110.0, 97.1. MS (*m*/*z*, rel int); 320 (M^+, 100), 293 (5), 217 (8), 190 (8), 160 (10). High-resolution mass calcd. for $C_{21}H_{12}N_4$: 320.10620. Observed: 320.10275. Anal. ($C_{21}H_{12}N_4$·0.25H_2O) C, H, N.

***N*-Hydroxy-2-[4′-(*N*-hydroxyamidino)-biphenyl-4-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine Hydrochloride Salt (11a).** The same procedure described for **5a** was used starting with **10a**. Free base yield 97%, mp 300−302 °C. ^{1}H NMR (DMSO-d_6); δ 5.86 (s, 2H), 5.94 (s, 2H), 7.55 (s, 2H), 7.72−7.80 (m, 6H), 8.07 (d, J = 8.1 Hz, 2H), 8.47 (s, 1H), 8.80 (s, 1H), 9.69 (s, 1H), 9.83 (s, 1H). ^{13}C NMR; δ 150.4, 148.5, 144.6, 144.4, 139.9, 138.7, 133.0, 132.3, 126.8, 126.16, 126.11, 125.9, 124.0, 123.2, 119.0, 115.8, 110.0. (**11a**, hydrochloride salt), mp 291−293 °C. Anal. ($C_{21}H_{18}N_6O_2$·3.0HCl·1.9H_2O·0.25EtOH) C, H, N.

***N*-Methoxy-2-[4′-(*N*-methoxyamidino)-biphenyl-4-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine Hydrochloride Salt (12).** The same procedure described for **6** was used starting with **11a**. Free base yield 48%, mp 224−226 °C (SiO_2: hexanes/EtOAc; 2:8). ^{1}H NMR (DMSO-d_6); δ 3.77 (s, 3H), 3.79 (s, 3H), 6.12 (s, 2H), 6.23 (s, 2H), 7.50−7.59 (m, 2H), 7.77 (s, 4H), 7.81 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 8.50 (s, 1H), 8.83 (s, 1H). ^{13}C NMR; δ 150.6, 148.8, 144.6, 144.5, 140.3, 138.5, 133.0, 131.4, 126.8, 126.2, 126.1, 126.0, 124.5, 123.2, 118.1, 115.8, 110.0, 60.6, 60.5. MS (*m*/*z*, rel int); 414 (M^+, 60), 384 (10), 367 (50), 320 (100), 294 (10). High-resolution mass calcd. for $C_{23}H_{22}N_6O_2$: 414.18042. Observed: 414.18122. (**12**, hydrochloride salt), mp 234−236 °C. Anal. ($C_{23}H_{22}N_6O_2$·3.0HCl·1.4H_2O·0.25EtOH) C, H, N.

2-(4′-Amidinobiphenyl-4-yl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (13a). The same procedure described for **7** was used starting with **11a**. Yield 85%, mp 240−242 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 2.03 (br s, 3 × CH_3 + 3H), 2.86 (br s, 1H), 3.03 (br s, 1H), 4.16 (br s, 1H), 4.36 (br s, 1H), 7.57 (s, 1H), 7.75−7.77 (m, 2H), 7.85−7.91 (m, 6H). Anal. ($C_{21}H_{22}N_6$·3.0AcOH·1.5H_2O) C, H, N.

2-(4′-Amidinobiphenyl-4-yl)-imidazo[1,2-*a*]pyridine-6-carboxamidine acetate salt (14a). The same procedure described for **8a** was used, starting with **11a**. Yield 81%, mp 243−246 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.90 (s, 3 × CH_3), 7.61−7.69 (m, 2H), 7.89−7.94 (m, 6H), 8.13 (s, 2H), 8.62 (s, 1H), 9.12 (s, 1H). MS (*m*/*z*, rel int); 354 (M^+, 10), 321 (100), 311 (90), 296 (35). Anal. ($C_{21}H_{18}N_6$·3.0AcOH·2.5H_2O) C, H, N.

2-(3-Bromophenyl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (9b). The same procedure described for **9a** was used, employing 3-bromophenacyl bromide instead of 4-bromophenacyl bromide. Yield 64%, mp 205−206.5 °C. ^{1}H NMR (DMSO-d_6); δ 7.43−7.47 (m, 1H), 7.52−7.58 (m, 2H), 7.75−7.78 (m, 1H), 8.03 (s, 1H), 8.22 (s, 1H), 8.61−8.65 (m, 1H), 9.37 (s, 1H). ^{13}C NMR; δ 144.6, 144.1, 135.2, 134.3, 130.9, 128.3, 125.1, 124.7, 122.2, 117.5, 116.9, 111.2, 97.2. MS (*m*/*z*, rel int); 298 (M^+, 100), 161 (10). Anal. ($C_{14}H_8BrN_3$) C, H.

2-(4′-Cyanobiphenyl-3-yl)-imidazo[1,2-*a*]pyridine-6-carbonitrile (10b). The same procedure described for **4a** was used, starting with **9b**. Yield 61%, mp 290−292 °C. ^{1}H NMR (DMSO-d_6); δ 7.48−7.63 (m, 2H), 7.74−7.78 (m, 2H), 7.92−7.99 (m, 4H), 8.08 (d, J = 7.8 Hz, 1H), 8.36 (s, 1H), 8.64 (s, 1H), 9.33 (s, 1H). ^{13}C NMR; δ 146.7, 145.0, 144.9, 139.6, 135.0, 134.5, 133.6, 130.5, 128.4, 127.8, 126.9, 125.7, 125.2, 119.5, 118.2, 117.8, 111.7, 110.9, 97.9. MS (*m*/*z*, rel int); 320 (M^+, 100), 297 (3), 217 (5), 190 (8), 160 (10). High-resolution mass calcd. for $C_{21}H_{12}N_4$: 320.10620. Observed: 320.10619. Anal. ($C_{21}H_{12}N_4$) C, H.

***N*-Hydroxy-2-[4′-(*N*-hydroxyamidino)-biphenyl-3-yl]-imidazo[1,2-*a*]pyridine-6-carboxamidine (11b).** The same procedure described for **5a** was used, starting with **10b**. Yield 94%, mp 252−254 °C. ^{1}H NMR (DMSO-d_6); δ 5.89 (s, 2H), 5.98 (s, 2H), 7.52−7.58 (m, 3H), 7.67 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 7.8 Hz, 1H), 8.31 (s, 1H), 8.57 (s, 1H), 8.81 (s, 1H), 9.72 (s, 1H), 9.86 (s, 1H). ^{13}C NMR; δ 150.5, 148.5, 144.6, 144.5, 140.3, 139.9, 134.3, 132.4, 129.3, 126.3, 125.9, 124.8, 123.9, 123.6, 123.2, 119.0, 115.8, 110.1. Anal. ($C_{21}H_{18}N_6O_2$·2.0H_2O) C, H.

2-(4′-Amidinobiphenyl-3-yl)-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (13b). The same procedure described for **7** was used, starting with **11b**. Yield 65%, mp 236−238 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.90−2.17 (br s, 3 × CH_3 + 3H), 2.79 (br s, 1H), 3.03 (br s, 1H), 4.11 (br s, 1H), 4.33 (br s, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.90−7.96 (m, 4H), 8.09 (s, 1H). Anal. ($C_{21}H_{22}N_6$-3.0AcOH·2.85H_2O·0.25EtOH) C, H, N.

2-(4′-Amidinobiphenyl-3-yl)-imidazo[1,2-*a*]pyridine-6-carboxamidine Acetate Salt (14b). The same procedure described for **8a** was used, starting with **11b**. Yield 57%, mp 233−235 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.87 (s, 3 × CH_3), 7.55−7.69 (m, 4H), 7.72−7.92 (m, 4H), 8.05 (d, J = 7.5 Hz, 1H), 8.33 (s, 1H), 8.56 (s, 1H), 9.03 (s, 1H). Anal. ($C_{21}H_{18}N_6$·3.0AcOH·0.9H_2O) C, H, N.

2-(3-Bromophenyl)-8-methyl-imidazo[1,2-*a*]pyridine-6-carbonitrile (9c). The same procedure described for **9b** was used, employing 6-amino-5-methylnicotinonitrile instead of 6-amino-nicotinonitrile. Yield 70%, mp 168−169.5 °C. ^{1}H NMR (DMSO-d_6); δ 2.55 (s, 3H), 7.36 (s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 8.20 (s, 1H), 8.57 (s, 1H), 9.20 (s, 1H). MS (*m*/*z*, rel int); 312 (M^+, 60), 175 (100), 135 (10). Anal. ($C_{15}H_{10}BrN_3$) C, H.

2-(4′-Cyanobiphenyl-3-yl)-8-methyl-imidazo[1,2-*a*]pyridine-6-carbonitrile (10c). The same procedure described for **4a** was used, starting with **9c**. Yield 78%, mp 236−238 °C. ^{1}H NMR (DMSO-d_6); δ 2.56 (s, 3H), 7.34 (s, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.97 (s, 4H), 8.10 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H), 8.64 (s, 1H), 9.21 (s, 1H). ^{13}C NMR; δ 145.2, 144.7, 144.3, 138.7, 133.8, 132.8, 131.9, 129.6, 127.6, 127.5, 126.9, 126.1, 124.3, 122.8, 118.8, 117.1, 111.4, 110.1, 96.9, 16.3. Anal. ($C_{22}H_{14}N_4$) C, H.

***N*-Hydroxy-2-[4′-(*N*-hydroxyamidino)-biphenyl-3-yl]-8-methyl-imidazo[1,2-*a*]pyridine-6-carboxamidine (11c).** The same procedure described for **5a** was used, starting with **10c**. Yield 97%, mp 193−195 °C. ^{1}H NMR (DMSO-d_6); δ 2.56 (s, 3H), 5.89 (s, 2H), 5.93 (s, 2H), 7.39 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 9 Hz, 2H), 7.83 (d, J = 9 Hz, 2H), 8.02 (d, J = 7.8 Hz, 1H), 8.29 (s, 1H), 8.56

(s, 1H), 8.66 (s, 1H), 9.72 (s, 1H), 9.78 (s, 1H). ^{13}C NMR; δ 150.4, 148.6, 145.1, 144.0, 140.3, 139.9, 134.5, 132.4, 129.3, 126.4, 125.8, 125.2, 124.8, 123.6, 121.8, 121.5, 118.9, 110.6, 16.7.

2-(4′-Amidinobiphenyl-3-yl)-8-methyl-imidazo[1,2-*a*]-pyridine-6-carboxamidine Acetate Salt (14c). The same procedure described for **8a** was used starting with **11c**. Yield 81%, mp 237−239.5 °C. ^{1}H NMR (D_2O/DMSO-d_6); δ 1.75 (s, 3 × CH_3), 2.54 (s, 3H), 7.43 (s, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.95−7.99 (m, 4H), 8.11 (d, J = 7.8 Hz, 1H), 8.38 (s, 1H), 8.72 (s, 1H), 9.01 (s, 1H). Anal. ($C_{22}H_{20}N_6$·3.0AcOH·0.5H_2O) C, H, N.

Acknowledgment. This work was supported by the Bill and Melinda Gates Foundation and M. A. I. was awarded a Fellowship by ICSC-World Laboratory.

Supporting Information Available: Elemental analyses data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) 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, pp 414−460.

(2) Ismail, M. A.; Brun, R.; Easterbrook J. D., Tanious, F.; W. D. Wilson; Boykin, D. W. Synthesis and Antiprotozoal Activity of Aza-Analogues of Furamidine, *J. Med. Chem*. **2003**, *46*, 4761−4769.

(3) Boykin, D. W.; Kumar, A.; Spychala, J.; Zhou, M.; Lombardy, R.; Wilson, W. D.; Dykstra, C. C.; Jones, S. K.; Hall, J. E.; Tidwell, R. R.; Laughton, C.; Nunn, C. M.; Neidle, S. Dicationic diarylfurans as anti-*Pneumocystis carinii* agents. *J. Med. Chem*. **1995**, *38*, 912−916.

(4) 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 Anti-*Pneumocystis carinii* Agents. *J. Med. Chem*. **1998**, *41*, 124−129.

(5) Francesconi, I.; Wilson, W. D.; Tanious, F. A. et al. 2,4-Diphenyl furan diamidines as novel Anti-*Pneumocystis carinii* pneumonia agents. *J. Med. Chem*. **1999**, *42*, 2260−2265.

(6) Czarny, A.; Boykin, D. W.; Wood, A.; Nunn, C. M.; Neidle, S.; Zhao, M. R. J.; Wilson, W. D. 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.

(7) Laughton, C. A.; Tanious, F. A.; Nunn, C. M.; Boykin, D. W.; Wilson, W. D.; Neidle, S. A Crystallographic And Spectroscopic Study Of The Complex Between d(CGCGAATTCGCG)$_2$ And 2,5-Bis(4-guanylphenyl)furan, An Analogue Of Berenil: Structural Origins Of Enhanced DNA-Binding Affinity. *Biochemistry* **1996**, *35*, 5655−5661.

(8) Trent, J. O.; Clark, G. R.; Kumar, A.; Wilson, W. D.; Boykin, D. W.; Hall, J. E.; Tidwell, R. R.; Blagburn, B. L.; Neidle, S. Targeting the Minor Groove of DNA: Crystal Structures of Two Complexes between Furan Derivatives of Berenil and the DNA Dodecamer d(CGCGAATTCGCG)$_2$. *J. Med. Chem*. **1996** *39*, 4554−4562.

(9) 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 Intercalation Binding Modes. *J. Am. Chem. Soc.* **1998**, *120*, 10310−10321.

(10) 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.

(11) 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.

(12) 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 cells. *Antimicrob. Agents Chemother*. **1994**, *38*, 1890−1898.

(13) Tidwell, R. R.; Geratz, J. D.; Dann, O.; Volz, G.; Zeh, D.; Loewe, H Diarylamidine Derivatives With One or Both of the Aryl Moieties Consisting of an Indole or Indole-like Ring. Inhibitors of Arginine-Specific Esteroproteases. *J. Med. Chem*. **1978**, *21*, 613−23.

(14) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S. K.; Tidwell, R. R.; Czarny, A.; Bajic, M.; Bajic, M; Kumar, A.; Boykin, D.; Perfect, J. R. Structure-In Vitro Activity Relationships of Pentamidine Analogues and Dication-Substituted Bis-Benzimidazoles as New Antifungal Agents. *Antimicrob. Agents Chemother.* **1998**, *42*, 2495−2502.

(15) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S. K.; Tidwell, R. R.; Kumar, A.; Boykin, D. W.; Perfect, J. R. In Vitro Antifungal Activities of a Series of Dicationic-Substituted Carbazoles, Furans, and Benzimidazoles. *Antimicrob. Agents Chemother.* **1998**, *42*, 2503−2509.

(16) Lombardy, R. L.; Tanious, F. A.; Ramachandran, K.; Tidwell, R. R.; Wilson, W. D. Synthesis and DNA Interactions of Bisbenzimidazole Dications Which Have Activity against Opportunistic Infections. *J. Med. Chem*. **1996**, *39*, 1452−1462.

(17) Wang, L.; Bailly, C.; Kumar, A.; Ding, D.; Bajic, M.; Boykin, D. W.; Wilson, W. D. Specific molecular recognition of mixed nucleic acid sequences: An aromatic dication that binds in the DNA minor groove as a dimer. *Proc. Natl. Acad. U.S.A.* **2000**, *97*, 12−16.

(18) Hopkins, K. T.; Wilson, W. D.; Bender, B. C.; McCurdy, D. R.; Hall, J. E.; Tidwell R. R.; Kumar, A.; Bajic, M.; Boykin, D. W. Extended Aromatic Furan Amidino Derivatives as Anti-*Pneumocystis carinii* Agents. *J. Med. Chem*. **1998**, *41*, 3872−3878.

(19) Wang, L.; Carrasco, C.; Kumar, A.; Stephens, C. E.; Bailly, C.; Boykin, D. W.; Wilson, W. D. Evaluation of the Influence of Compound Structure on Stacked-Dimer Formation in the DNA Minor Groove. *Biochemistry* **2001**, *40*, 2511−2521.

(20) Bailly, C.; Tardy, C.; Wang, L.; Armitage, B.; Hopkins, K. T.; Kumar, A.; Schuster, G. B.; Boykin, D. W.; Wilson W. D. Recognition of ATGA Sequences by the Unfused Aromatic Dication DB293 Forming Stacked Dimers in the DNA Minor Groove. *Biochemistry* **2001**,*40*, 9770−9779.

(21) Hamdouchi, C.; Blas, J.; Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. 2-Amino-3-substituted-6-[(*E*)-1-phenyl-2-(*N*-methylcarbamoyl)vinyl]Imidazo[1,2-*a*]Pyridines as a Novel Class of Inhibitors of Human Rhinovirus: Stereospecific Synthesis and Antiviral Activity. *J. Med. Chem*. **1999**, *42*, 50−59.

(22) Hamama, W. S.; Zoorob, H. H. Chemistry of Bicyclic Pyridines Containing a Ring-Junction Nitrogen. *Tetrahedron* **2002**, *58*, 6143−6162.

(23) Sundberg, R. J.; Biswas, S.; Murthi, K. K.; Rowe, D. Bis-Cationic Heteroaromatics as Macrofilaricides: Synthesis of Bis-Amidine and Bis-Guanylhydrazone Derivatives of Substituted Imidazo-[1,2-*a*]pyridines. *J. Med. Chem*. **1998**, *41*, 4317−4328.

(24) Skupinska, K. A.; McEachern, E. J.; Skerij, R. T.; Bridger, G. J. Concise Preparation of Amino-5,6,7,8-tetrahydroisoquinolines via Catalytic Hydrogenation of Acetamidoquinolines and Acetamidoisoquinolines. *J. Org. Chem*. **2002**, *67*, 7890−7893.

(25) 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 Activies of Aromatic Diamidoxime Prodrugs. *Antimicrob. Agents Chemother.* **1998**, *42*, 666−674.

(26) Gilman, H.; Hewlett, A. P.; Wright, G. F. 5-Bromofurylacetylene. *J. Am. Chem. Soc.* **1931**, *53*, 4192−4196.

(27) Brown, E. The bromination of Furyl methyl ketone. *Iowa State Coll. J. Sci.* **1937**, *11*, 221−225.

(28) Dunn, A. D.; Norrie, R. The reaction of some brominated aminopicolines with acetic anhydride and with copper(1)cyanide. *J. Prakt. Chem./Chem. -Ztg* **1996**, *338* (7), 663−666.

(29) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. A highly catalytic robust palladium catalyzed cyanation of aryl bromides. *Tetrahedron Lett.* **1999**, *40*, 8193−8195.

JM0400092