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Dicationic DNA-targeted antiprotozoal agents: Naphthalene replacement of benzimidazole

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Abstract—A series of naphthalene analogues of highly active benzimidazole diamidines were synthesized using sequential Stille and Suzuki coupling reactions for preparation of the bis-nitrile intermediates. All of the diamidines showed strong DNA affinities as judged by high ΔT_m values with poly(dA–dT). The dicationic compounds were quite active in vitro versus *Trypanosoma brucei rhodesiense* (*T. b. r.*) exhibiting IC_{50} values ranging from 4 to 98 nM. These compounds were also active versus *Plasmodium falciparum* (*P. f.*) giving IC_{50} values ranging from 4 to 33 nM. Two of the compounds showed good activity in vivo in the STIB900 model for acute African trypanosomiasis; one gave 3/4 cures and the other gave 4/4 cures on ip dosage of 20 mg/kg for 4 days. The amidoxime prodrugs of the naphthalene analogues were essentially ineffective.
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1. Introduction

Aromatic diamidines have been studied since the 1930s when they were first reported to have significant antiprotozoan activity.[1] Despite extensive studies of various classes of dications, pentamidine (**I**), reported in 1942,[2] is the only compound from this class which has seen significant human use. Pentamidine is used against early stage human African trypanosomiasis (HAT), antimony-resistant leishmaniasis, and for AIDS-related *P. jiroveci* pneumonia.[1] Furamidine (**IIa**) and analogues have been demonstrated to have significant antiprotozoan activities and pafuramidine (**IIb**), an orally effective prodrug of **IIa**, is currently in Phase II clinical trials against malaria, and Phase III trials against HAT and pneumocystis pneumonia.[1,3–6] It has been suggested that these dicationic molecules act by binding in the minor groove of DNA at AT-rich sites.[1] There is evidence that minor-groove binding leads to inhibition of DNA-dependent enzymes or possibly direct inhibition of transcription.[1,7–10] The selectivity of these molecules, most probable for trypanosomes, seems likely to involve uptake by amidine transporters[11] and appears to involve initial concentration in kinetoplast DNA.[1b] Compound **III** a benzimidazole analogue of **IIa** and numerous related dicationic benzimidazoles exhibit significant activity against a variety of protozoan diseases.[12] However, because the diamidines are charged at physiological pH these molecules have limited bioavailability. Bioavailability has been significantly improved by prodrug approaches for a number of classes of diamidines,[13] however, potential prodrugs reported to date for benzimidazole compounds have not functioned effectively.[14] An alternate strategy for capitalizing on this type dicationic system is to replace the benzimidazole ring with other ring systems, which may yield functional prodrugs. We decided to make a substantial change in the physical properties of the ring system without too large change in overall geometry by replacing the benzimidazole unit with a naphthalene ring and determine if biological activity was retained. The lead compound would have the framework illustrated by **VI**. Early results on these type systems gave excellent activity. We now report the synthesis of several novel naphthalene-based dications and their initial evaluation as minor-groove binders and antiprotozoan agents (see Fig. 1).

Keywords: Antiprotozoal agents; Diamidines; Minor-groove binders; Prodrugs.
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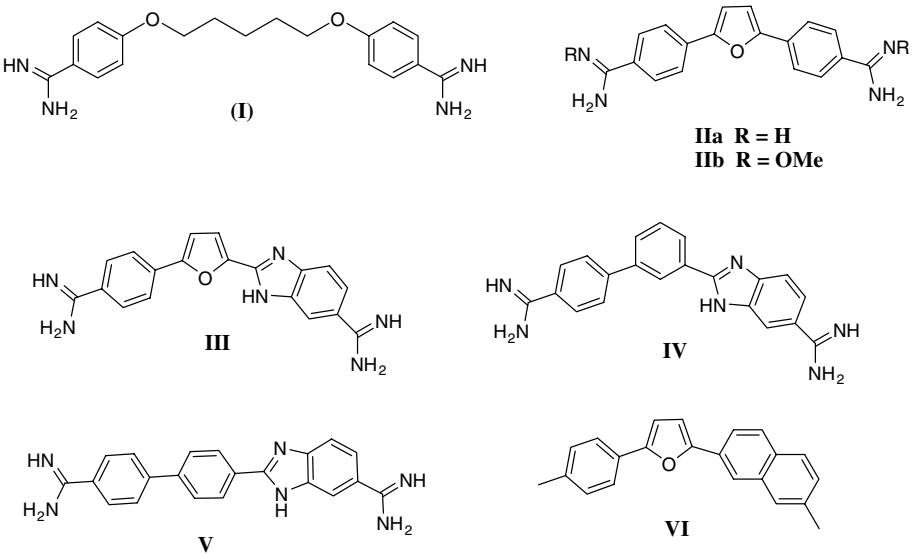


Figure 1. Structures of important dicationic antiprotozoan agents and lead naphthalene framework.

2. Results and discussion

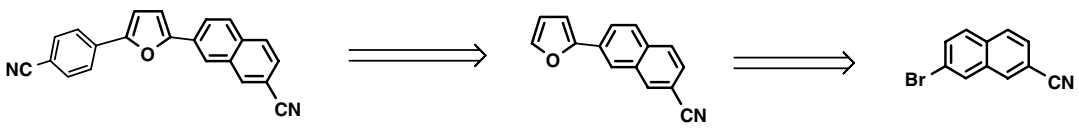
2.1. Chemistry

A retrosynthetic approach for obtaining the key bis-nitrile needed for preparation of **VI** is shown in Scheme 1. This approach is envisioned to involve sequential Stille and Suzuki coupling reactions to synthesize the desired triaryl systems.

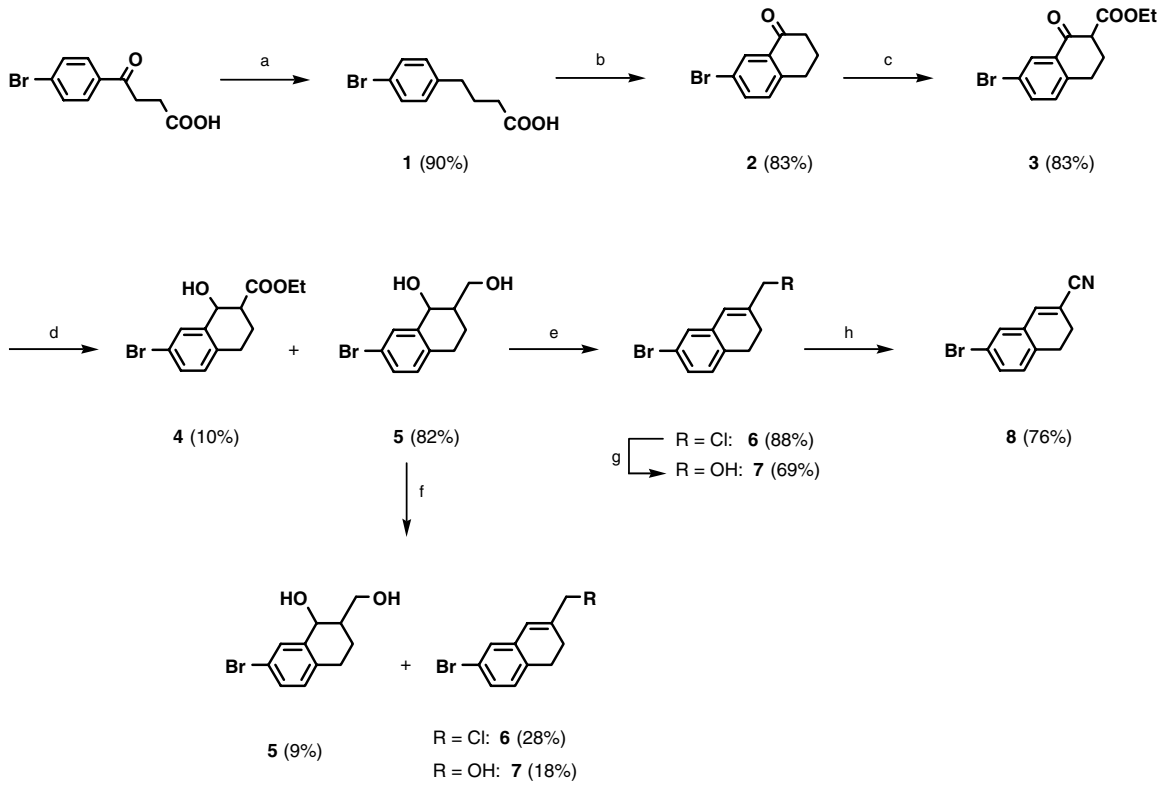
Initially, we attempted to make 7-bromo-2-cyanonaphthalene needed to introduce the naphthalene ring by a conventional Hayworth-type synthesis as outlined in Scheme 2. The starting material, 3-(4-bromobenzoyl)propionic acid, was converted to **1** using a modified Wolff–Kishner procedure.[15,16] Cyclization of **1** with polyphosphoric acid[15] gave the tetralone **2**, which was treated with ethyl formate to yield the β-ketoester **3**. The expected selective reduction of **3** into the alcohol-ester **4** failed using many of the procedures described previously[17] for analogous compounds. The $NaBH_4$ approach, according to previous reports, was expected to lead to the desired reduced compound **4** in good yield. But in our case, the fully reduced compound **5** in 82% yield was obtained. Recently, a heterogeneous Pd-ethylenediamine complex catalyst has been developed.[18] This catalyst possesses less activity than Pd/C because the coordinated ethylenediamine acts as a mild catalyst-poison. We tried to use this catalyst to selectively reduce the ketone **3** into alcohol **4** without reduction of the ester function but this method only afforded the recovery of starting material. On heating **5** at reflux in 1,4-dioxane with hydrochloric acid it did not produce the dehydration product **7** but the unexpected chloro analogue **6**, however, the latter derivative was readily hydrolyzed to alcohol **7**. Treatment of **5** in aqueous HCl over an extended period produced a mixture of **5**, **6**, and **7**. Using manganese dioxide and ammonia in 2-propanol–THF, containing magnesium sulfate at room temperature, we carried out the direct conversion of the primary alcohol **7** into the corresponding nitrile **8**. This step proceeds via an in situ oxidation–imination–aldimine oxidation sequence. Numerous attempts, including [(DDQ, dioxane/benzene or xylene), and (SeO_2, AcOH), (NBS, benzoyl peroxide, CCl_4), (10% Pd/C, xylene), (S, Pd/C, xylene), and (S, Pd/C)], to dehydrogenate **8** to yield 7-bromo-2-cyanonaphthalene failed.

Having the bromonitrile **8** in hand, we decided to make the dihydro analogue of the target structure **VI** and evaluate its biological properties (vide infra). The bis-nitrile **10** was synthesized from intermediate **8**, which underwent a Stille coupling reaction with 2-tributylstannylfuran to give **9**, followed by a Heck reaction of the latter with *p*-bromobenzonitrile (Scheme 3).

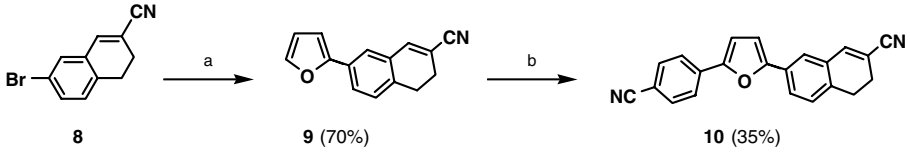
Returning to the initial target structure **VI**, we noted that 7-cyanonaphthalene-2-yl triflate has been described in the literature[19] and we decided to use it in place of 7-bromo-2-cyanonaphthalene for synthesis of the system **VI**. The approach outlined in Scheme 4 differs in certain steps from that previously described.[19] Commercially available 2-hydroxy-7-methoxynaphthalene was first converted to triflate **11** by using a Tf_2O/pyridine system instead of the expensive previously described



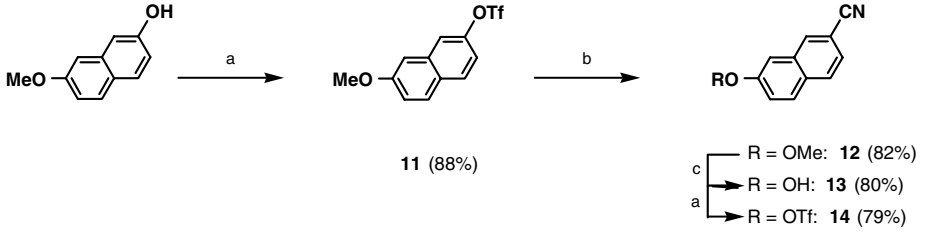
Scheme 1. Approach to key naphthalene intermediate.



Scheme 2. Reagents and conditions: (a) NH_2NH_2, KOH, triethyleneglycol, reflux, 2 h; (b) PPA, 90 °C, 20 min; (c) NaH, $(EtO)_2CO$, benzene, reflux, 3 h; (d) $NaBH_4$, EtOH, rt, overnight; (e) HCl 37%, 1,4-dioxane, reflux, 2 h 30 min; (f) HCl 1 N, reflux, 3 days; (g) $AgNO_3$, H_2O, acetone, rt, overnight; (h) MnO_2, $MgSO_4$, NH_3–IPA, THF, rt, overnight.



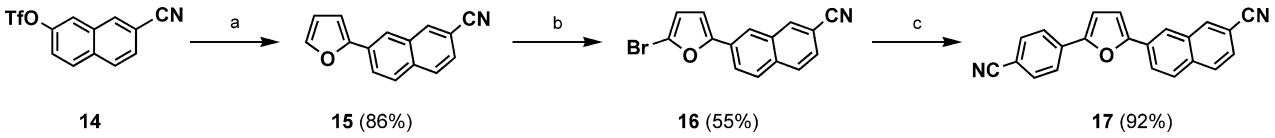
Scheme 3. Reagents and conditions: (a) 2-tributylstannylfuran, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 3 h; (b) *p*-bromobenzonitrile, $Pd(PPh_3)_4$, KOAc, DMF, 120 °C, overnight.



Scheme 4. Reagents and conditions: (a) Tf_2O, pyridine, toluene, rt, 2 h; (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 150 °C, 3 h; (c) BBr_3, CH_2Cl_2, rt, 48 h.

$PhN(SO_2CF_3)_2/Et_3N$ system. According to Kehr and Neidlein,[19] the conversion of triflate **11** by $Zn(CN)_2$ into nitrile **12** was readily completed in the presence of $Pd(OAc)_2$, PPh_3, in NMP at 150 °C, however, we were not successful with this approach. A recent study from Kubota and Rice[20] showed that DMF is an excellent solvent for this kind of reaction. The catalysts were also examined: neither $Pd(PPh_3)_2Cl_2$ nor $Pd(OAc)_2$ gave the desired product, however, use of $Pd(PPh_3)_4$ worked very well for this cyanation. By using $Pd(PPh_3)_4$ (0.02 equiv), $Zn(CN)_2$ (2 equiv), and DMF at 150 °C, we obtained **12** in 82% yield. The cleavage of the methylether **12** was achieved using BBr_3 at room temperature to afford **13**, which was converted to triflate **14** using Tf_2O/pyridine.

As shown in Scheme 5 the bis-nitrile **17** was prepared from intermediate **14** in three steps starting with a Stille coupling to produce the furan analogue **15** in a good yield. Bromination of **15** with NBS in DMF afforded **16** in a moderate yield. A subsequent Suzuki coupling



Scheme 5. Reagents and conditions: (a) 2-tributylstannylfuran, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 1 h; (b) NBS, DMF, rt, overnight; (c) 4-cynanophenyl boronic acid, $Pd(OAc)_2$, K_2CO_3, TBAF, DME/H_2O, reflux, 1 h.

of **16** with 4-cyanophenyl boronic acid gave the desired **17** in very good yield.

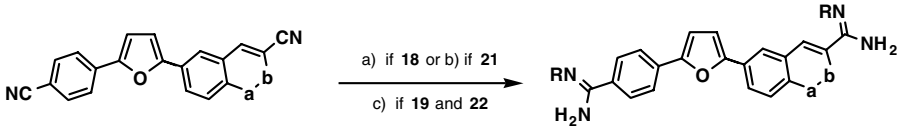
Scheme 6 summarizes the conversion of the bis-nitriles into the desired diamidines and their corresponding potential prodrugs. The bis-nitrile **10** was converted to amidine **18** by a classical Pinner sequence. For the conversion of **17** into amidine **21** we used the more elegant and simpler method of transforming nitrile into amidine using $LiN(TMS)_2$, followed by hydrolysis of the silyl groups with ethanolic HCl work-up to yield the desired compound.[21] This method is faster than the Pinner one and gave high yields. Treatment of **10** and **17** with hydroxylamine hydrochloride, potassium *tert*-butoxide in DMSO at room temperature allowed conversion of the cyano group into amidoximes **19** and **22**, respectively, in excellent yield. The *O*-methylamidoxime **20** was obtained in 39% yield by treating the amidoxime **19** with dimethylsulfate in the presence of aqueous NaOH in 1,4-dioxane. For the *O*-methylamidoxime **23**, the method involving the system LiOH, H_2O/DMF[22] was used and gave **22** in a 69% yield.

Earlier, we have reported that diamidines of both linear **IV** and curved **V** biphenylbenzimidazoles exhibit impressive antiprotozoan activities.[12] Consequently, we have prepared the naphthalene analogues **26a**,**b** for evaluation. The synthesis of the compounds **26a**,**b**–**28a**,**b** required the corresponding bis-nitriles **25a**,**b** and is outlined in Scheme 7. The preparation of **25a**,**b** involved two consecutive Suzuki couplings with first 3- or 4-bromophenyl boronic acid and then 4-cyanophenyl boronic acid. The diamidines **26a**,**b**, diamidoximes **27a**,**b**, and di-*O*-methoxyamidoximes **28a**,**b** were obtained as previously described above for the furan analogues.

2.2. Biology

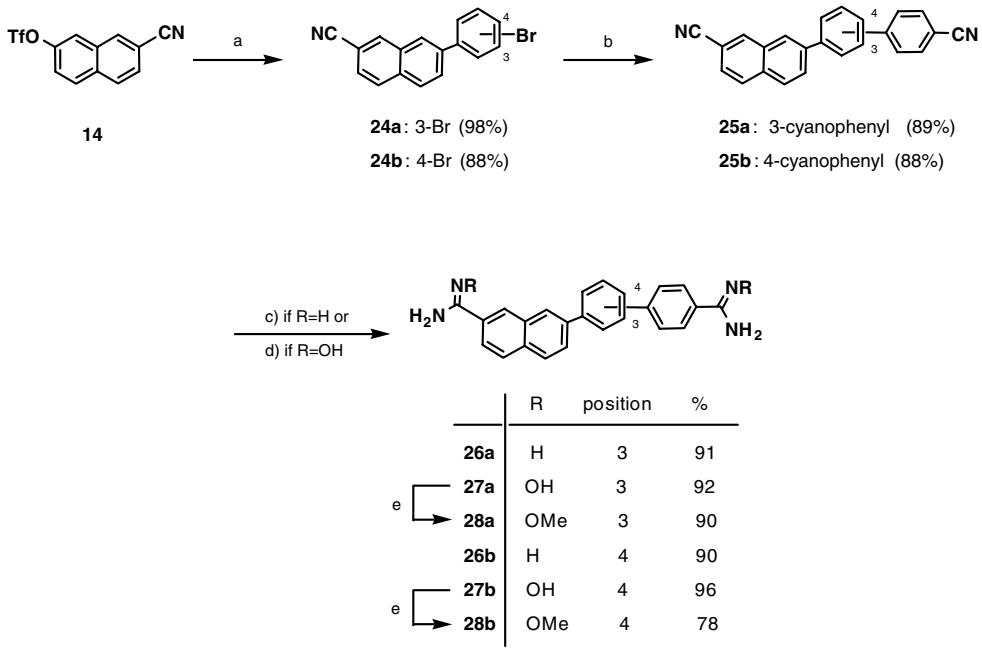
The DNA affinities and in vitro evaluation of the newly synthesized dicationic naphthalene analogues against *T. b. r.* and *P. f.* are given in Table 1. We also include data in Table 1 for **IIa** and the benzimidazole analogues **III**–**V** for comparison. The DNA affinities for the diamidines as indicated by ΔT_m values for their complexes with poly(dA–dT) are reduced by 10–30% in comparison to the corresponding benzimidazole analogue with the exception of **26b** which gives a comparable value to its benzimidazole analogue. The small drop in affinity is likely due to the absence of the benzimidazole NH hydrogen-bond donor. On comparison of the ΔT_m values of **18** and **21** it is noted that the affinity for the dihydro analogue is about 20% less than that of the fully aromatic one. This is consistent with better van der Waals contacts with the walls of the groove for the aromatic compound **21**. Since the NH is known to play an important role in the groove binding of **V** it is interesting that the affinities of **26b** and **V** are comparable despite the absence of an NH H-bond donor for **26b**.[24] Thus, **26b** merits further biophysical study to gain insight into the details of its minor-groove binding.

The IC_{50} values for the dicationic naphthalene derivatives against *T. b. r.* range from 4 to 98 nM. For the furan core systems, both **18** and **21** exhibit greater activity against *T. b. r* than **III**, and with **21** approximately 8-fold more active. For the biphenyl types, **26a** shows lower activity than its benzimidazole **IV** counterpart, whereas **26b** shows somewhat improved activity compared to its benzimidazole analogue **V**. These naphthalene compounds were generally somewhat more active in vitro versus *P. f.* giving



		R	a	b	%
	18	H	CH_2	CH_2	77
d	**19**	OH	CH_2	CH_2	87
d	**20**	OMe	CH_2	CH_2	39
	21	H	CH	CH	90
e	**22**	OH	CH	CH	84
e	**23**	OMe	CH	CH	69

Scheme 6. Reagents and conditions: (a) 1—EtOH/HCl, rt, 10 days; 2—EtOH/NH_3, rt, 10 days; (b)1—$LiN(TMS)_2$, THF, rt, overnight; 2—EtOH/HCl, rt, 12 h; (c) $NH_2OH \cdot HCl$, KO*t*Bu, DMSO, rt, overnight; (d) NaOH 2 N, dimethylsulfate, 1,4-dioxane, rt, overnight; (e) LiOH, dimethylsulfate, H_2O/DMF, rt, 72 h.



Scheme 7. Reagents and conditions: (a) 3- or 4-bromophenyl boronic acid, $Pd(OAc)_2$, K_2CO_3, TBAF, DME/H_2O, rt, 1 h; (b) 4-cynanophenyl boronic acid, $Pd(OAc)_2$, K_2CO_3, TBAF, DME/H_2O, reflux, 3 h; (c) $LiN(TMS)_2$, THF, rt, overnight; 2 EtOH/HCl, rt, 12 h; (d) $NH_2OH \cdot HCl$, KO*t*Bu, DMSO, rt, overnight; (e) LiOH, dimethylsulfate, H_2O/DMF, rt, overnight.

Table 1. DNA affinities and in vitro antiprotozoan activity

Compound	ΔT_m[a] poly(dA–dT)	*T. b. r.*[b] IC_{50} (nM)	*P. f.*[b] IC_{50} (nM)	IC_{50}[c] L-6 cells (nM)
IIa	25	4.3	15.5	6,400
III	24.6	122	96	10,100
IV	25.6	4.4	27.5	23,000
V	>28	7.7	0.5	17,000
18	17.6	98	4	27,300
19		10.1K	166	99,200
20		14.1K	849	17,900
21	22.2	16	6	11,100
22		7.5K	687	67,100
23		6.1K	833	>160,000
26a	20.9	59	29	11,100
27a		11.4K	6.5K	15,100
28a		6.9K	6.2K	161,000
26b	>28	4	33	6,600
27b		8.9K	8.5K	>179,000
28b		2.7K	5.2K	15,900

[a] DNA, poly(dA–dT); buffer MES10; compound/DNA ratio = 0.3. For compounds with ΔT_m values listed as >28 °C, no melting was observed at the highest temperature of the experiment, 96 °C; all prodrugs tested have insignificant ΔT_m values.

[b] The *T. b. r.* strain employed was STIB900 and the *P.f.* strain was K1; see Refs. 13b and 23. IC_{50} values are the average of duplicate determinations.

[c] Cytotoxicity was evaluated using cultured L-6 rat myoblast cells using the Alamar Blue assay, see Ref. 23.

IC_{50} values ranging from 4 to 33 nM. The two furan-based compounds **18** and **21** were approximately 20-fold more active than their benzimidazole parent **III**. The curved biphenyl analogue **26a** exhibited approximately the same activity as its benzimidazole predecessor **IV**, whereas the linear analogue **26b** was significantly less active than its counterpart **V**. As expected the potential prodrugs were inactive in the in vitro screens. The selectivity ratios of the diamidines, based upon cytotoxicity in L-6 myoblast cells, range from 200 to 6825. Consequently, these compounds are promising candidates for animal model studies.

The results from evaluating these compounds in the STIB900 mouse model for acute African trypanosomasis are presented in Table 2. The four diamidines **18**,

Table 2. In vivo antitrypanosomal activity of dicationic compounds in the STIB900 mouse model[a]

Compound	Cures[b]	Survival (days)[c]
IIa	0/4	52.5
III	1/4	>27.75
IV	4/4	>60
V	0/4	>36.5
18	0/3	16.75
19	0/4	8.5
20	NT	NT
21	3/4	>54
22	0/4	14.5
23	0/4	7.25
26a	1/4	>29.25
27a	0/4	9
28a	0/4	7.5
26b	4/4	>60
27b	1/4	>52
28b	0/4	13.75

[a] See Refs. 13b and 25 for details of STIB900 model. Dosage for diamidines was intraperitoneal at 20 mg/kg for 4 days. Dosage for prodrugs was po at 100 mg/kg for 4 days.

[b] 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.

21, **26a**, and **26b** all extend the life of treated animals beyond that of the untreated controls. Compounds **21** and **26b** are the most active in vivo giving 3/4 and 4/4 cures, respectively, on ip dosage. The potential prodrugs are generally ineffective, the only even moderately effective one **27b** provided just 1/4 cures and a significant increase in average survival time of the treated animals on oral dosage.

The strategy to replace a benzimidazole ring with a naphthalene one for these type minor-groove binders worked quite well as judged from their DNA binding affinity and intrinsic antiprotozoan activity. However, the hope that the amidoxime prodrugs of these compounds would be effective in mice was not realized. The lack of efficacy of the amidoxime prodrugs of the benzimidazole and naphthalene minor-groove binders merits further study.

3. Experimental

3.1. Biology

In vitro assays with *T. b. r*. STIB 900 and *P. f.* K1 strain as well as efficacy study in an acute mouse model for *T. b. r.* STIB 900 were carried out as previously reported.[12,13,23,25]

3.2. T_m measurements

Thermal melting experiments were conducted with a Cary 300 spectrophotometer. For the experiment cuvettes are mounted in a thermal block and the solution temperatures are monitored by a thermistor in a reference cuvette. Temperatures are under computer control and are increased at 0.5 °C/min. The experiments were conducted in Mes 10 buffer (Mes 10 mM, EDTA 1 mM, and NaCl 100 mM) using 1 cm path length quartz cuvettes. 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.

3.3. 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 F254 precoated aluminum sheets and detected with UV light. ^{1}H and ^{13}C NMR spectra were recorded employing a Varian Unity Plus 300 spectrometer, with peak assignments relative to residual DMSO (2.49 ppm) or $CHCl_3$ (7.24 ppm). Mass spectra were recorded on a VG analytical 70-SE spectrometer at the Georgia Institute of Technology, Atlanta, GA. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. All chemicals and solvents (including anhydrous) were purchased from Aldrich Chemical Co., Fisher Scientific, Across, Frontier or Lancaster and used as received. Ethanol (Mg/I_2) was distilled from the indicated drying agent.

3.3.1. 4-(*p*-Bromophenyl)butanoic acid (1). Potassium hydroxide (15.25 g, 0.27 mol) powder was added to a well-stirred solution of 3-(4-bromobenzoyl)propionic acid (20 g, 77.8 mmol) in triethyleneglycol (70 ml); then hydrazine (8.5 ml, 0.27 mol) was added dropwise under nitrogen. The mixture was refluxed for 2 h under nitrogen. After cooling to room temperature, the reaction mixture was neutralized with 4 N HCl and extracted several times with dichloromethane. The combined organic layers were washed with water, saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The crude oily product was subjected to column chromatography (silica gel, 50% ethyl acetate-hexanes). Removal of the solvents afforded an oil, which precipitated in petroleum ether. Filtration yielded 90% of **1** as a white powder; mp 62.2 °C (heptane). ^{1}H NMR ($CDCl_3$) δ 1.94 (p, J = 7.6 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 7.40 (dd, J = 1.5, 8.1 Hz, 2H), 11.2 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 179.98, 140.08, 131.47, 130.23, 119.82, 34.34, 33.2, 25.99; EI-MS *m/z*: 244 ($^{81Br}M^+$, 26), 242 ($^{79Br}M^+$, 26), 184 (98), 182 (100), 171 (35), 169 (36); Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.38; H, 4.52. Found: C, 49.19; H, 4.57.

3.3.2. 7-Bromo-3,4-dihydro-2*H*-naphthalen-1-one (2). Compound **1** (15 g, 61.72 mmol) was added portionwise to stirred PPA (150 g) at 90 °C. After being stirred for 20 min, the dark orange mixture was poured into ice/water. The yellow precipitate was collected, washed with water, and dried under vacuum to afford **2** in 83% yield; mp 77.5 °C (heptane). ^{1}H NMR ($CDCl_3$) δ 2.13 (p, J = 6.4 Hz, 2H), 2.65 (t, J = 6.3 Hz, 2H), 2.91 (t, J = 6.0 Hz, 2H), 7.14 (d, J = 8.1 Hz, 1H), 7.57 (dd, J = 2.1, 8.1 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 196.98, 143.1, 136.06, 133.99, 130.61, 129.92, 120.58, 38.74, 29.11, 22.93; EI-MS *m/z*: 226 ($^{81Br}M^+$, 95), 224 ($^{79Br}M^+$, 100), 211 (18), 209 (19), 198 (76), 196 (77), 170 (53), 168 (55), 145 (22), 115 (35), 89 (45); Anal. Calcd for $C_{10}H_9BrO$: C, 53.33; H, 4.0. Found: C, 53.46; H, 4.10.

3.3.3. 7-Bromo-1-oxo-1,2,3,4-tetrahydro-2-naphthoic acid ethyl ester (3). Diethylcarbonate (43.1 ml, 0.35 mol) was added to a suspension of NaH 60% (5.33 g, 0.13 mol) in 100 ml of dry benzene under nitrogen. This mixture was heated to 65 °C, and a solution of **2** (10 g, 44.44 mmol) in 50 ml of dry benzene was added dropwise over a period of 20 min. After the addition was completed, the mixture was refluxed for 3 h. After cooling to room temperature, acetic acid (10 ml) was added dropwise. Then ice-cold water was added and the mixture was stirred until the solid material has been dissolved. Organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The organic layers were washed with ice-cold water, saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The residual material was subjected to column chromatography (silica gel, 10% ethyl acetate-hexanes). Removal of the solvents afforded a dark pink oil, which precipitated in ice water. Precipitate was collected, washed with water, and dried to yield 83% of **3** as a pale yellow powder; mp 67.6 °C (petroleum ether). ^{1}H NMR (DMSO-d_6) δ 1.19 (t,

J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 2.25H), 2.28 (m, 2H), 2.76 (m, 1.5H), 2.94 (m, 2H), 3.82 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.2 Hz, 1.5H), 7.25 (d, J = 8.1 Hz, 0.75H), 7.36 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 2.1, 8.1 Hz, 0.75H), 7.73 (d, J = 2.1 Hz, 0.75H), 7.76 (dd, J = 2.1, 8.1 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 192.91, 172.59, 170.45, 162.85, 144.14, 139.09, 137.10, 133.98, 133.76, 132.35, 132.08, 130.62, 129.58, 126.75, 120.46, 120.18, 98.76, 61.55, 61.36, 54.23, 27.09, 26.99, 26.54, 20.64, 14.75; EI-MS m/z: 296 ($^{81Br}M^+$, 96), 298 ($^{79Br}M^+$, 100), 269 (10), 267 (10), 252 (85), 250 (89), 224 (67), 222 (66), 198 (33), 196 (35), 170 (185), 143 (64), 115 (100), 89 (28); Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.52; H, 4.37. Found: C, 52.32; H, 4.47.

3.3.4. 7-Bromo-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalen-1-ol (5). A solution of **3** (3 g, 10.10 mmol) in EtOH (30 ml) was treated with $NaBH_4$ (0.77 g, 20.20 mmol) overnight at room temperature. After addition of saturated aqueous ammonium chloride, followed by extraction with dichloromethane, organic layer was washed with water, saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The oily residue was purified by column chromatography (silica gel, 70% ethyl acetate-hexanes) to afford **5** in 82% yield as a white powder and the partially reduced compound **4** in 10% yield; mp 127 °C (ethyl acetate). ^{1}H NMR (DMSO-d_6) δ 1.47 (m, 1/3H), 1.65 (m, 4H), 1.96 (m, 1/3H), 2.65 (m, 8/3H), 3.58 (m, 4/3H), 4.30 (t, J = 8.1 Hz, 1/3H), 4.41 (t, J = 8.1 Hz, 1H), 4.55 (m, 4/3H), 5.00 (d, J = 5.7 Hz, 1H), 5.35 (d, J = 6.9 Hz, 1/3H), 7.01 (d, J = 8.4 Hz, 1/3H), 7.04 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 2.4, 8.4 Hz, 1/3H), 7.32 (dd, J = 2.1, 8.1 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.5 (d, J = 2.1.8 Hz, 1/3H); ^{13}C NMR (DMSO-d_6) δ 143.5, 142.3, 135.9, 135.8, 132.2, 130.7, 130.2, 129.6, 128.9, 118.5, 118.0, 68.0, 66.0, 62.4, 62.0, 43.8, 41.8, 27.7, 27.4, 23.5, 19.3; EI-MS m/z: 258 ($^{81Br}M^+$, 8), 256 ($^{79Br}M^+$, 8), 240 (29), 238 (30), 209 (56), 207 (51), 128 (100), 115 (18); Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.06. Found: C, 51.69; H, 5.20.

3.3.5. 7-Bromo-2-chloromethyl-3,4-dihydronaphthalene (6). To a solution of **5** (4.61 g, 17.94 mmol) in 1,4-dioxane (10 ml) was added concd HCl (5.5 ml, 0.18 mol) and the mixture was refluxed for 2 h 30 min. After cooling to room temperature, reaction mixture was poured into water. The precipitate was collected, washed with water, dried, and subjected to column chromatography (silica gel, 10% ethyl acetate-hexanes). After removal of the solvents, oily product, which precipitated in water, was collected and dried under vacuum to give **6** as a white powder in 88% yield; mp 86.3 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 2.32 (t, J = 8.4 Hz, 2H), 2.75 (t, J = 8.1 Hz, 2H), 4.37 (s, 2H), 6.06 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 2.4, 5.7 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 24.33, 26.44, 48.77, 119.16, 124.86, 128.53, 129.34, 128.87, 133.66, 135.46, 138.31; EI-MS m/z: 258.5 ($^{81Br}M^+$, 53), 256.5 ($^{79Br}M^+$, 42), 223 (98), 221 (100), 142 (80), 128 (36), 115 (21); Anal. Calcd for $C_{11}H_{10}BrCl$: C, 51.26; H, 3.88. Found: C, 51.66; H, 3.87.

3.3.6. 7-Bromo-2-hydroxymethyl-3,4-dihydronaphthalene (7). A solution of **6** (4.1 g, 15.88 mmol) in acetone (30 ml) was added dropwise to a stirred suspension of silver nitrate (4.05 g, 23.82 mmol) in acetone (60 ml) and water (60 ml) at room temperature. After being stirred overnight, the mixture was filtered and the filtrate was extracted with chloroform. Organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Oily residue was subjected to column chromatography (silica gel, 30% ethyl acetate-hexanes). Removal of the solvents yielded 69% of **7** as a white powder; mp 92 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 2.15 (t, J = 8.7 Hz, 2H), 2.69 (t, J = 8.4 Hz, 2H), 4.01 (d, J = 4.8 Hz, 2H), 5.02 (t, J = 5.7 Hz, 1H), 6.39 (s, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.22 (dd, J = 2.1, 6.6 Hz, 2H), 7.24 (d, J = 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 144.30, 136.55, 133.64, 129.17, 128.64, 127.74, 119.11, 119.08, 63.68, 26.52, 23.68; EI-MS m/z: 240 ($^{81Br}M^+$, 53), 238 ($^{79Br}M^+$, 54), 209 (24), 207 (22), 159(37), 141 (54), 128 (100), 115 (23); Anal. Calcd for $C_{11}H_{11}BrO$: C, 55.23; H, 4.6. Found: C, 55.40; H, 4.67.

3.3.7. 7-Bromo-2-cyano-3,4-dihydronaphthalene (8). A 2 M solution of ammonia in 2-propanol (15 ml) and anhydrous magnesium sulfate (14.61 g, 0.12 mol) were added to a stirred solution of **7** (1.94 g, 8.11 mmol) in THF (40 ml). Activated manganese dioxide (10.6 g, 0.12 mol) was added to the solution. The resulting mixture was stirred at room temperature overnight and then diluted with dichloromethane. The mixture was filtered through Celite®, the Celite® washed well with dichloromethane, and the filtrate concentrated. The solid residue was purified by column chromatography (silica gel, 5% ethyl acetate-hexanes). Removal of the solvents afforded **8** as a white powder in 76% yield; mp 93.5 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 2.49 (t, J = 8.4 Hz, 2H), 2.81 (t, J = 7.8 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H), 7.45 (dd, J = 2.1, 8.1 Hz, 1H), 7.51 (d, J = 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 140.13, 134.57, 133.06, 132.45, 130.13, 129.92, 119.41, 119.26, 110.77, 25.21, 23.68; EI-MS m/z: 235 ($^{81Br}M^+$, 62), 233 ($^{79Br}M^+$, 65), 154 (100), 127 (37); Anal. Calcd for $C_{11}H_8NBr$: C, 56.41; H, 3.42. Found: C, 56.70; H, 3.39.

3.3.8. 2-(2-Cyano-3,4-dihydronaphthalen-7yl)furan (9). To a solution of **8** (1.64 g, 7.0 mmol) and tetrakis(triphenylphosphine)palladium (0.24 g, 0.21 mmol) in 1,4-dioxane (15 ml) was added 2-tributylstannylfuran (3.3 ml, 10.41 mmol) and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into ice/water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The concentrate was purified by column chromatography (silica gel, 20% ethyl acetate-hexanes). Removal of the solvent yielded 70% of **9** as a white powder; mp 117 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 2.49 (t, J = 7.8 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 6.58 (m, J = 1.8 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.50 (s, 4H), 7.53 (d, J = 6.6 Hz, 2H), 7.74 (d, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 153.13, 143.66, 142.03, 135.26, 132.16, 129.92, 129.19, 125.76, 123.56, 120.33, 112.81, 110.62, 106.58, 26.34, 24.66; ESI-MS m/z: 222

$(M+H)^+$, 443 $(2M+H)^+$; Anal. Calcd for $C_{15}H_{11}NO$: C, 81.44; H, 4.97. Found: C, 81.34; H, 4.96.

3.3.9. 2-(2-Cyano-3,4-dihydronaphthalen-7yl)-5-(4-cyanophenyl)furan (10). To a solution of **9** (1.3 g, 5.88 mmol) in DMF (15 ml) was added *p*-bromobenzonitrile (1.6 g, 8.82 mmol), tetrakis(triphenylphosphine)palladium (0.2 g, 0.17 mmol), and potassium acetate (0.86 g, 8.82 mmol). The mixture was heated at 120 °C under nitrogen overnight. The reaction mixture was poured onto ice/water and the precipitate was collected, washed with water, hexanes, and ether, dried, and purified by column chromatography (silica gel, 30–50% dichloromethane-hexanes). Removal of the solvents gave **10** as a yellow powder in 35% yield; mp 208.5 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 2.50 (t, J = 7.8 Hz, 2H), 2.89 (t, J = 7.8 Hz, 2H), 7.12 (d, J = 3.3 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 3.3 Hz, 1H), 7.51 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 153.55, 150.76, 141.09, 135.25, 133.80, 132.86, 131.48, 128.49, 128.42, 125.37, 123.77, 123.14, 119.50, 118.85, 111.7, 110.02, 109.23, 108.62, 25.62, 23.85; EI-MS *m*/*z*: 322 (M^+, 100), 190 (10), 130 (19), 102 (14); Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.98; H, 4.34. Found: C, 81.81; H, 4.31.

3.3.10. 7-Methoxynaphthalene-2-yl trifluoromethanesulfonate (11). Triflic anhydride (21.24 ml, 0.13 mol) was added dropwise to a suspension of 7-methoxy-2-naphthol (20 g, 0.11 mol) and pyridine (9.28 ml, 0.11 mol) in toluene (150 ml). After stirring for 2 h at room temperature, the solution was poured onto water and extracted several times with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The dark oily residue was purified by column chromatography (silica gel, 15% ethyl acetate-hexanes). Removal of the solvents afforded **11** as an oil in 88% yield; ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 7.25 (dd, J = 2.7, 9.0 Hz, 1H), 7.40 (dd, J = 2.4, 9.0 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H), 7.93 (d, J = 9.3 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 158.49, 147.34, 134.71, 130.60, 129.42, 127.53, 120.10, 117.96, 116.82, 116.15, 106.29, 55.34; EI-MS *m*/*z*: 306 (M^+, 25), 173 (10), 145 (100), 130 (12), 102 (34), 69 (15); Anal. Calcd for $C_{12}H_9F_3O_4S \cdot 0.1$EtOAc: C, 47.27; H, 3.13. Found: C, 47.62; H, 2.93.

3.3.11. 7-Methoxy-2-cyanonaphthalene (12). To a suspension of **11** (32.19 g, 0.11 mol) and $Zn(CN)_2$ (24.70 g, 0.21 mol) in deoxygenated dry DMF (80 ml) was added $Pd(PPh_3)_4$ (2.43 g, 2.1 mmol) in DMF (60 ml). The mixture was then stirred at 150 °C under nitrogen atmosphere for 3 h. After cooling to room temperature, the reaction mixture was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, 10% ethyl acetate-hexanes). Removal of the solvents gave **12** as a white powder in 82% yield; mp 81.7 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 7.35 (dd, J = 2.7, 9.0 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.60 (dd, J = 1.8, 8.4 Hz, 1H), 7.95 (d, J = 9.3 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 159.08, 134.17, 133.44, 130.60, 130.31, 129.80, 124.81, 122.59, 120.05, 109.55, 107.17, 56.17; EI-MS *m*/*z*: 183 (M^+, 85), 153 (26), 140 (100), 126 (5), 113 (13), 84 (39), 49 (64); Anal. Calcd for $C_{12}H_9NO$: C, 78.68; H, 4.91. Found: C, 78.79; H, 4.90.

3.3.12. 7-Hydroxy-2-cyanonaphthalene (13). In an ice bath, a solution of BBr_3 (9.77 ml, 0.1 mol) in dichloromethane (35 ml) was added to a solution of **12** (7.57 g, 41.36 mmol) in dichloromethane (45 ml). After 48 h at room temperature, the mixture was poured into water and the suspension filtered. The precipitate was washed with dichloromethane, dried, and purified by column chromatography (silica gel, 20% ethyl acetate-hexanes). The filtrate was extracted several times with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The dark residue was purified by column chromatography (silica gel, 20% ethyl acetate-hexanes). Removal of the solvents yielded **13** (80%) as a white crystalline powder; mp 187.1 °C (water/acetic acid). ^{1}H NMR (DMSO-d_6) δ 7.25 (s, 1H), 7.27 (dd, J = 2.4, 7.8 Hz, 1H), 7.50 (dd, J = 1.8, 8.1 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 156.69, 133.67, 132.34, 129.73, 129.06, 128.97, 123.05, 121.93, 119.49, 109.17, 108.55; EI-MS *m*/*z*: 169 (M^+, 100), 140 (49), 114 (17); Anal. Calcd for $C_{11}H_7NO$: C, 78.10 ; H, 4.14. Found: C, 78.16; H, 3.99.

3.3.13. 7-Cyanonaphthalene-2-yl trifluoromethanesulfonate (14). Triflic anhydride (6.65 ml, 39.57 mmol) was added dropwise to a suspension of **13** (6.08 g, 35.97 mmol) and pyridine (2.9 ml, 35.97 mmol) in toluene (50 ml). After stirring for 2 h at room temperature, the solution was poured onto water and extracted several times with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The dark oily residue was purified by column chromatography (silica gel, 10% ethyl acetate-hexanes). Removal of the solvents gave an oil that precipitated in heptane to give **14** as a beige powder in 79% yield; mp 75.1 °C (CH_2Cl_2/heptane). ^{1}H NMR (DMSO-d_6) δ 7.84 (dd, J = 2.4, 9.0 Hz, 1H), 7.92 (dd, J = 1.8, 8.7 Hz, 1H), 8.26 (t, J = 9.6 Hz, 2H), 8.30 (s, 1H), 8.71 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 147.65, 134.51, 133.46, 132.06, 131.52, 129.61, 127.95, 123.05, 120.16, 119.58, 118.67, 110.32; EI-MS *m*/*z*: 301 (M^+, 20), 168 (37), 140 (100), 113 (16), 69 (23); Anal. Calcd for $C_{12}H_6F_3NO_3S$: C, 47.84; H, 1.99. Found: C, 47.87; H, 1.84.

3.3.14. 2-(2-Cyanonaphthalen-7-yl)furan (15). To a solution of **14** (2 g, 6.64 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.19 mmol) in 1,4-dioxane (20 ml) was added 2-tributylstannylfuran (3.14 ml, 9.96 mmol) and the reaction mixture was refluxed for 1 h. After cooling to room temperature, the reaction mixture was poured into ice/water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The concentrate was purified by column

chromatography (silica gel, 10% ethyl acetate-hexanes). Removal of the solvent yielded **15** as a yellow powder in 86% yield; mp 120.5 °C (heptane). ^{1}H NMR (DMSO-d_6) δ 6.73 (m, J = 1.8 Hz, 1H), 7.17 (d, J = 3.3 Hz, 1H), 7.4 (dd, J = 1.5, 8.4 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 8.07 (s, 3 H), 8.33 (s, 1H), 8.6 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 152.26, 143.92, 134.42, 133.45, 132.23, 129.28, 128.82, 126.39, 125.40, 121.60, 119.19, 112.50, 109.19, 107.92; EI-MS *m/z*: 219 (M^+, 100), 190 (65); Anal. Calcd for $C_{15}H_9NO$: C, 82.19; H, 4.10. Found: C, 82.00; H, 3.87.

3.3.15. 2-Bromo-5-(2-cyanonaphthalen-7-yl)furan (16). To a solution of **15** (0.8 g, 3.65 mmol) in DMF (5 ml) cooled to 0 °C was added NBS (0.72 g, 4.01 mmol) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into ice/water. The precipitate was filtered, washed with water and hexanes, dried under vacuum, and purified by column chromatography (silica gel, 10% ethyl acetate-hexanes). Removal of the solvent afforded **16** as a pale yellow powder in 55% yield; mp 131.9 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 6.79 (d, J = 3.3 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.76 (dd, J = 1.5, 8.7 Hz, 1H), 8.03 (dd, J = 1.5, 8.7 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 8.31 (s, 1 H), 8.62 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 154.39, 134.48, 133.58, 132.11, 129.25, 128.91, 128.14, 126.63, 124.83, 122.59, 121.55, 119.11, 114.45, 110.48, 109.28; EI-MS *m/z*: 299 ($^{81Br}M^+$, 45), 297 ($^{79Br}M^+$, 42), 190 (100); Anal. Calcd for $C_{15}H_8NOBr \cdot 0.1H_2O$: C, 60.06; H, 2.75. Found: C, 60.01; H, 2.49.

3.3.16. 2-(4-Cyanobiphenyl)-5-(2-cyanonaphthalen-7-yl)furan (17). A mixture of **16** (0.94 g, 3.15 mmol), 4-cyanophenyl boronic acid (0.65 g, 4.42 mmol), tetrabutylammonium fluoride (1.33 g, 3.73 mmol), palladium acetate (14.2 mg, 0.06 mmol), and potassium carbonate (0.87 g, 6.30 mmol) in a mixture of water/DME (10 ml/10 ml) was refluxed and stirred vigorously for 1 h. After cooling to room temperature, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, 30–60% dichloromethane-hexanes). Removal of solvents afforded **17** (92%) as a yellow powder; mp 239.6 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 7.36 (d, J = 3.6 Hz, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.77 (dd, J = 1.5, 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.7 Hz, 2H), 8.18 (dd, J = 1.5, 8.7 Hz, 1H), 8.54 (s, 1H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 116.19, 114.47, 97.11, 96.53, 96.50, 95.66, 94.99, 92.05, 91.60, 91.40, 89.31, 88.12, 86.85, 85.22, 81.73, 81.55, 74.60, 73.20, 72.43, 72.13; EI-MS *m/z*: 320 (M^+, 100), 190 (31), 160 (38); Anal. Calcd for $C_{22}H_{12}N_2O$: C, 82.22; H, 3.54. Found: C, 82.50; H, 3.75.

3.3.17. 2-(2-Amidino-3,4-dihydronaphthalen-7-yl)-5-(4-amidinophenyl)furan hydrochloride salt (18). HCl gas was passed through an ethanolic solution (15 ml) of **10** (0.17 g, 0.53 mmol) and the mixture was stirred at room temperature for 10 days. After evaporation of the solvent, intermediate imidate ester was washed several times with dry ether and dried under vacuum. NH_3 gas was then passed through an anhydrous (freshly distilled EtOH) ethanolic solution (15 ml) of imidate and the mixture was stirred at room temperature for another 10 days. After evaporation of the solvent, the solid was washed several times with dry ether and dried under vacuum to afford **18** (free base) as a yellow powder in 77% yield; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 2.58 (t, J = 8.1 Hz, 2H), 2.92 (t, J = 8.1 Hz, 2H), 7.17 (d, J = 3.6 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 7.52 (s, 1H), 7.83 (m, 2H), 7.92 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H), 8.93 (br s, 1H), 9.06 (br s, 2H), 9.12 (br s, 2H), 9.43 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 165.85, 164.83, 153.50, 151.01, 136.15, 135.10, 134.57, 131.77, 128.93, 128.49, 128.35, 127.56, 125.87, 125.35, 123.62, 123.33, 111.49, 108.62, 26.16, 22.72; (**18**, hydrochloride salt) ESI-MS *m/z*: 357 $(M+H)^+$, 358 $(M+2H)^{2+}$, 179 $(M/2+H)^+$; Anal. Calcd for $C_{22}H_{20}N_4O \cdot 2HCl \cdot 1.3H_2O$: C, 58.36; H, 5.47; N, 12.37; Cl, 15.66. Found: C, 57.97; H, 5.18; N, 12.46; Cl, 16.03.

3.3.18. 2-(2-*N*-Hydroxyamidino-3,4-dihydronaphthalen-7-yl)-5-(4-*N*-hydroxyamidinophenyl)furan hydrochloride salt (19). A suspension of hydroxylamine hydrochloride (1.72 g, 24.84 mmol) in anhydrous DMSO (30 ml) under nitrogen was cooled to 5 °C and potassium *t*-butoxide (2.79 g, 24.84 mmol) was added portionwise. The mixture was stirred for 30 min. The bis-cyano derivative **10** (0.4 g, 1.24 mmol) was added at once and the reaction mixture was stirred overnight at room temperature. It was then slowly poured into ice/water and stirred for about 30 min. The precipitate was collected, washed with water, dichloromethane, ether, and hexanes, and dried under vacuum to afford **19** (free base) as a yellow powder in 87% yield; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 2.52 (t, J = 8.1 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H), 5.53 (br s, 2H), 5.86 (br s, 2H), 7.02 (d, J = 3.6 Hz, 1H), 7.07 (s, 1H), 7.11 (d, J = 3.6 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.75 (m, J = 8.7 Hz, 4H), 9.70 (s, 1H), 9.85 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 152.86, 151.94, 151.09, 150.38, 135.18, 134.15, 132.43, 132.09, 130.36, 128.44, 127.84, 125.81, 123.89, 122.95, 122.46, 121.39, 108.72, 107.71, 26.92, 21.72; (**19**, hydrochloride salt) ESI-MS *m/z*: 389 $(M+H)^+$, 390 $(M+2H)^{2+}$, 195 $(M/2+H)^+$, 777 $(2M+H)^+$; Anal. Calcd for $C_{22}H_{20}N_4O_3 \cdot 2HCl \cdot 1/3H_2O$: C, 56.66; H, 4.86; N, 12.01; Cl, 15.02. Found: C, 56.79; H, 4.89; N, 11.63; Cl, 14.72.

3.3.19. 2-(2-*N*-Methoxyamidino-3,4-dihydronaphthalen-7-yl)-5-(4-*N*-methoxyamidinophenyl)furan hydrochloride salt (20). Bis-amidoxime **19** (240 mg, 0.62 mmol) was dissolved in 1,4-dioxane (10 ml) and cooled to 0–5 °C. Aqueous 2 N NaOH solution (9 ml) was slowly added followed by dimethylsulfate (0,6 ml, 6.2 mmol) dropwise in 1,4-dioxane (5 ml). After addition was completed, the mixture was stirred at room temperature for overnight. The reaction mixture was poured into water and extracted with ethyl acetate. Organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The concentrate was purified by column chromatography (silica

gel, 20% ethyl acetate-hexanes). Removal of the solvents afforded **20** (free base) as a pale yellow powder in 39% yield; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 2.51 (t, J = 8.1 Hz, 2H), 2.75 (t, J = 7.8 Hz, 2H), 3.72 (s, 3H), 3.75 (s, 3H), 5.76 (br s, 2H), 6.10 (br s, 2H), 7.03 (d, J = 3.6 Hz, 1H), 7.12 (s, 1H), 7.13 (d, J = 3.6 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 152.93, 151.86, 151.12, 150.64, 135.31, 133.93, 131.66, 131.22, 130.76, 128.43, 127.88, 126.19, 124.91, 122.96, 122.74, 121.55, 108.78, 107.81, 60.68, 60.61, 26.84, 21.80; (**20**, hydrochloride salt) ESI-MS m/z: 417 $(M+H)^+$, 418 $(M+2H)^{2+}$; Anal. Calcd for $C_{24}H_{24}N_4O_3 \cdot 1.5HCl \cdot 0.6H_2O$: C, 59.80; H, 5.58; N, 11.62; Cl, 11.03. Found: C, 59.92; H, 5.61; N, 11.24; Cl, 11.25.

3.3.20. 2-(2-Amidinonaphthalen-7-yl)-5-(4-amidinophenyl)furan hydrochloride salt (21). A solution of compound **17** (300 mg, 0.94 mmol) in THF (8 ml) was treated with $LiN(TMS)_2$ 1 M in THF (5 ml), stirred overnight at room temperature, treated with ethanolic HCl (10 ml), and stirred for another 12 h. The precipitate was then filtered, washed with ether, and dried. The salt of **21** was put into water, basified with aqueous NaOH 10%, and stirred vigorously. The precipitate was then filtered, washed with water, ether, and dried to afford **21** (free base) as a yellow powder in 90% yield; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 7.40 (d, J = 3.6 Hz, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.83 (dd, J = 1.5, 8.7 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 8.09–8.17 (m, 4 H), 8.20 (dd, J = 1.5, 8.4 Hz, 1H), 9.27 (br s, 2H), 9.40 (br s, 2H), 9.51 (br s, 2H), 9.60 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 166.73, 165.77, 154.14, 152.62, 135.25, 135.15, 132.74, 130.39, 129.68, 129.37, 129.31, 129.19, 126.90, 125.83, 124.62, 124.30, 123.69, 112.31, 110.98; (**21**, hydrochloride salt) ESI-MS m/z: 178 $(M/2+H)^+$, 355 $(M+H)^+$, 356 $(M+2H)^{2+}$; Anal. Calcd for $C_{22}H_{18}N_4O \cdot 2HCl \cdot H_2O$: C, 59.33; H, 4.97; N, 12.58. Found: C, 59.32; H, 4.66; N, 12.32.

3.3.21. 2-(2-*N*-Hydroxyamidinonaphthalen-7y-l)-5-(4-*N*-hydroxyamidinophenyl)furan hydrochloride salt (22). The same procedure described for **19** was used starting from **17**. Free base of **22**, yield 84%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 3.64 (br s, 3H), 7.39 (d, J = 3.6 Hz, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.74 (dd, J = 1.2, 8.7 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 8.07–8.20 (m, 5H), 8.46 (s, 1H), 8.57 (s, 1H), 9.07 (br s, 3H), 11.28 (s, 1H), 11.33 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 159.28, 158.61, 153.27, 151.84, 134.09, 133.99, 132.08, 129.34, 128.81, 128.67, 128.38, 124.86, 124.15, 123.86, 123.65, 122.73, 111.44, 110.36; (**22**, hydrochloride salt) ESI-MS m/z: 194 $(M/2+H)^+$, 387 $(M+H)^+$, 388 $(M+2H)^{2+}$; Anal. Calcd for $C_{22}H_{18}N_4O_3 \cdot 2HCl \cdot 1/2H_2O$: C, 56.42; H, 4.51; N, 11.96. Found: C, 56.15; H, 4.76; N, 11.56.

3.3.22. 2-(2-*N*-Methoxyamidinonaphthalen-7-yl)-5-(4-*N*-methoxyamidinophenyl)furan hydrochloride salt (23). To a solution of **22** (730 mg, 1.89 mmol) in DMF (15 ml) was slowly added lithium hydroxide hydrate (317.5 mg, 7.56 mmol) followed by dimethylsulfate (0.45 ml, 4.73 mmol). After addition was completed, the mixture was stirred at room temperature for 72 h. The reaction mixture was poured into water and the precipitate was collected, washed with water and heptane to afford **23** (free base) as a yellow powder in 69% yield; mp >260 °C (1,4-dioxane). ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 3.79 (s, 3H), 6.12 (br s, 3H), 6.19 (br s, 3H), 7.21 (d, J = 3.3 Hz, 1H), 7.26 (d, J = 3.6 Hz, 1H), 7.77 (m, J = 8.4 Hz, 3H), 7.88 (m, J = 8.4 Hz,3H), 7.98 (s, 2H), 8.32 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (DMSO-d_6) δ; (**23**, hydrochloride salt) ESI-MS m/z: 415 $(M+H)^+$; Anal. Calcd for $C_{24}H_{22}N_4O_3 \cdot 2HCl \cdot 1/2H_2O$: C, 58.82; H, 5.33; N, 10.97. Found: C, 58.84; H, 4.99; N, 10.62.

3.3.23. 7-(3-Bromophenyl)-2-cyanonaphthalene (24a). A mixture of triflate **14** (2 g, 6.64 mmol), 3-bromophenyl boronic acid (1.6 g, 7.97 mmol), tetrabutylammonium fluoride (2.10 g, 6.64 mmol), palladium acetate (30 mg, 0.13 mmol), and potassium carbonate (1.82 g, 13.28 mmol) in water/DME mixture (25 ml/25 ml) was stirred vigorously for about 1 h at room temperature. The precipitate was filtered, washed with water, dried under vacuum, and purified by column chromatography (silica gel, 50% dichloromethane-hexanes). Removal of the solvents afforded **24a** as a white powder in 98% yield; mp 147.3 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 7.49 (t, J = 7.8 Hz, 1H), 7.64 (m, J = 0.9, 8.1 Hz, 1H), 7.83 (m, J = 1.8, 9.0 Hz, 2H), 8.03 (t, J = 1.8 Hz, 1H), 8.08 (dd, J = 1.8, 8.7 Hz, 1H), 8.15 (d, J = 8.7 Hz, 2H), 8.42 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 141.54, 137.52, 134.72, 133.73, 132.16, 131.25, 130.84, 129.64, 129.16, 128.85, 128.25, 126.74, 126.33, 126.20, 122.59, 119.15, 108.95; EI-MS m/z: 309 ($^{81Br}M^+$, 90), 307 ($^{79Br}M^+$, 90), 227 (50), 100 (48); Anal. Calcd for $C_{17}H_{10}NBr$: C, 66.23; H, 3.24. Found: C, 66.21; H, 3.14.

3.3.24. 7-(4′-Cyanobiphenyl-3-yl)-2-cyanonaphthalene (25a). A mixture of compound **24a** (2.05 g, 6.65 mmol), 4-cyanophenyl boronic acid (1.37 g, 9.32 mmol), tetrabutylammonium fluoride (2.52 g, 7.98 mmol), palladium acetate (30 mg, 0.13 mmol), and potassium carbonate (1.84 g, 13.31 mmol) in water/DME mixture (25 ml/25 ml) was refluxed for about 3 h. After cooling to room temperature, the mixture was poured into water and the precipitate was filtered, washed with water, dried under vacuum, and purified by column chromatography (silica gel, 50% dichloromethane-hexanes). Removal of the solvents afforded **25a** as a white powder in 89% yield; mp 201.8 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 7.67 (t, J = 7.8 Hz, 1H), 7.79 (m, J = 1.8, 8.4 Hz, 2H), 7.90 (d, J = 7.8 Hz, 1H), 8.03 (q, J = 8.7 Hz, 4H), 8.16 (m, 4H), 8.5 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 144.25, 139.88, 139.02, 138.63, 134.32, 133.41, 132.61, 132.55, 132.07, 129.71, 128.89, 128.46, 128.29, 127.64, 127.19, 126.51, 126.19, 125.97, 125.64, 118.83, 118.53, 110.15, 108.74; EI-MS m/z: 330 (M^+, 80); Anal. Calcd for $C_{24}H_{14}N_2 \cdot 1/4H_2O$: C, 86.07; H, 4.36. Found: C, 86.16; H, 4.11.

3.3.25. 7-(4′-Amidinobiphenyl-3-yl)-2-amidinonaphthalene hydrochloride salt (26a). The same procedure described for **21** was used starting from **25a**. Free base

of **26a**, yield 91%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 7.69 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 8.18–8.21 (m, 4H), 8.53 (s, 1H), 8.61 (s, 1H), 9.29 (br s, 3H), 9.38 (br s, 1H), 9.53 (br s, 3H), 9.61 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 165.96, 165.19, 145.03, 140.18, 139.31, 138.65, 134.35, 132.10, 130.08, 129.88, 128.84, 128.62, 128.51, 128.35, 127.35, 126.90, 126.76, 125.95, 123.96; (**26a**, hydrochloride salt) ESI-MS m/z: 365 $(M+H)^+$; Anal. Calcd for $C_{24}H_{20}N_4 \cdot 2HCl \cdot 1.7H_2O$: C, 61.59; H, 5.47; N, 11.97. Found: C, 61.72; H, 5.08; N, 11.60.

3.3.26. 7-(4′-*N*-Hydroxyamidinobiphenyl-3-yl)-2-*N*-hydroxyamidinonaphthalene hydrochloride salt (27a). The same procedure described for **19** was used starting from **25a**. Free base of **27a**, yield 92%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 5.88 (br s, 2H), 5.93 (br s, 2H), 7.78–8.09 (m, 12H), 8.27 (s, 1H), 8.32 (s, 1H), 9.70 (s, 1H), 9.79 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 159.09, 158.89, 144.88, 141.04, 140.22, 139.29, 134.58, 133.02, 130.64, 129.62, 129.23, 129.10, 128.45, 127.97, 127.21, 126.45, 126.06, 125.21, 124.68; (**27a**, hydrochloride salt) ESI-MS m/z: 397 $(M+H)^+$, 398 $(M+2H)^{2+}$; Anal. Calcd for $C_{24}H_{20}N_4O_2 \cdot 2HCl \cdot 0.1H_2O$: C, 61.18; H, 4.75; N, 11.89. Found: C, 61.12; H, 4.93; N, 11.49.

3.3.27. 7-(4′-*N*-Methoxyamidinobiphenyl-3-yl)-2-*N*-methoxyamidinonaphthalene hydrochloride salt (28a). The same procedure described for **23** was used starting from **27a** with additional purification by column chromatography (silical gel, 30% ethyl acetate-hexanes). Free base of **28a**, yield 90%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 3.79 (s, 3H), 6.13 (br s, 2H), 6.20 (br s, 2H), 7.61–8.09 (m, 12H), 8.34 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 156.48, 156.20, 143.68, 140.44, 139.66, 138.41, 133.68, 132.50, 130.10, 128.61, 128.23, 127.47, 127.25, 127.17, 126.56, 126.50, 125.96, 125.75, 124.10, 62.98, 62.75; (**28a**, hydrochloride salt) ESI-MS m/z: 425 $(M+H)^+$; Anal. Calcd for $C_{26}H_{24}N_4O_2 \cdot 2HCl \cdot EtOH \cdot 0.7H_2O$: C, 60.47; H, 6.05; N, 10.07. Found: C, 60.31; H, 6.07; N, 10.00.

3.3.28. 7-(4-Bromophenyl)-2-cyanonaphthalene (24b). The same procedure described for **24a** was used starting from **14** with 4-bromophenyl boronic acid. Yield 88%; mp 178.8 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 7.73 (m, 5H), 8.3 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.1 Hz, 2H), 8.36 (s, 1H), 8.6 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 138.31, 137.91, 134.67, 133.62, 132.22, 132.06, 129.19, 128.90, 128.14, 126.64, 125.91, 121.71, 119.16, 108.97; EI-MS m/z: 309 ($^{81Br}M^+$, 92), 307 ($^{79Br}M^+$, 90), 227 (50), 100 (51); Anal. Calcd for $C_{17}H_{10}NBr \cdot H_2O$: C, 62.59; H, 3.70. Found: C, 62.87; H, 3.37.

3.3.29. 7-(4′-Cyanobiphenyl-4-yl)-2-cyanonaphthalene (25b). The same procedure described for **25a** was used starting from **24b**. Yield 88%; mp 199.9 °C (butan-1-ol). ^{1}H NMR (DMSO-d_6) δ 7.8 (dd, J = 1.5, 8.7 Hz, 1H), 7.96 (m, 8H), 8.15 (m, 3H), 8.46 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 143.89, 139.33, 138.29, 137.77, 134.72, 133.67, 132.96, 132.30, 129.21, 128.89, 128.24, 127.83, 127.52, 126.62, 125.94, 119.22, 118.94, 110.21, 108.96; EI-MS m/z: 330 (M^+, 100%), 165 (45), 151 (38); Anal. Calcd for $C_{24}H_{14}N_2$: C, 87.27; H, 4.24. Found: C, 96.94; H, 4.30.

3.3.30. 7-(4′-Amidinobiphenyl-4-yl)-2-amidinonaphthalene hydrochloride salt (26b). The same procedure described for **21** was used starting from **25b**. Free base of **26b**, yield 90%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 7.82 (dd, J = 1.8, 8.4 Hz, 1H), 7.93–8.05 (m, 9H), 8.14 (dd, J = 1.8, 8.7 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.47 (s, 1H), 8.59 (s, 1H), 9.15 (br s, 3H), 9.25 (br s, 1H), 9.44 (br s, 3H), 9.55 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 165.92, 165.20, 144.43, 139.37, 138.09, 137.79, 134.35, 132.10, 129.92, 128.90, 128.74, 128.51, 127.96, 127.80, 126.93, 126.85, 126.38, 126.02, 124.01; (**26b**, hydrochloride salt) ESI-MS m/z: 365 $(M+H)^+$; Anal. Calcd for $C_{24}H_{20}N_4 \cdot 2HCl \cdot 3.5H_2O$: C, 57.60; H, 5.84. Found: C, 57.79; H, 5.63.

3.3.31. 7-(4′-*N*-Hydroxyamidinobiphenyl-4-yl)-2-*N*-hydroxyamidinonaphthalene hydrochloride salt (27b). The same procedure described for **19** was used starting from **25b**. Free base of **27b**, yield 96%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 5.89 (br s, 2H), 5.96 (br s, 2H), 7.78–7.94 (m, 11H), 8.02 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 8.31 (s, 1H), 9.71 (s, 1H), 9.81 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 158.96, 158.60, 143.76, 139.30, 138.05, 137.86, 133.98, 132.22, 129.29, 128.67, 128.46, 127.73, 127.58, 127.33, 126.95, 126.18, 124.74, 124.09, 123.92; (**27b**, hydrochloride salt) ESI-MS m/z: 397 $(M+H)^+$, 398 $(M+2H)^{2+}$; Anal. Calcd for $C_{24}H_{20}N_4O_2 \cdot 2HCl \cdot 1.8H_2O$: C, 57.44; H, 5.14; N, 11.16. Found: C, 57.36; H, 4.74; N, 10.77.

3.3.32. 7-(4′-*N*-Methoxyamidinobiphenyl-4-yl)-2-*N*-methoxyamidinonaphthalene hydrochloride salt (28b). The same procedure described for **23** was used starting from **27b** with additional purification by column chromatography (silical gel, 30% ethyl acetate-hexanes). Free base of **28b**, yield 78%; mp >260 °C (EtOH/ether). ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3H), 3.80 (s, 3H), 6.11 (br s, 2H), 6.19 (br s, 2H), 7.78–7.94 (m, 11H), 8.03 (d, J = 8.7 Hz, 1H), 8.28 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 157.00, 156.95, 143.36, 139.31, 137.92, 137.85, 133.77, 132.33, 128.65, 128.50, 128.18, 127.71, 127.67, 127.23, 126.78, 126.08, 125.62, 125.17, 124.12, 63.17, 62.97; (**28a**, hydrochloride salt) ESI-MS m/z: 425 $(M+H)^+$; Anal. Calcd for $C_{26}H_{24}N_4O_2 \cdot 2HCl \cdot EtOH$: C, 60.47; H, 6.05; N, 10.07. Found: C, 60.38; H, 5.97; N, 10.03.

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