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Synthesis and Antiprotozoal Activity of Dicationic *m*-Terphenyl and 1,3-Dipyridylbenzene Derivatives

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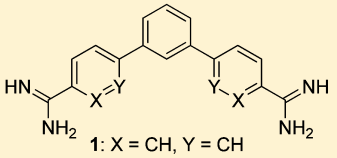
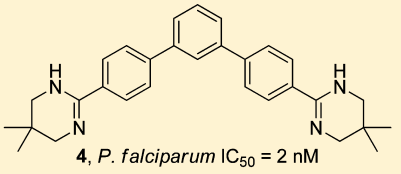
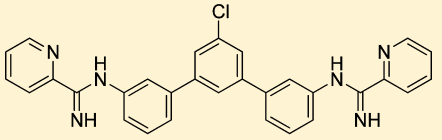


1: X = CH, Y = CH
23: X = N, Y = CH
25: X = CH, Y = N
T. b. rhodesiense in vivo
Each cured 4/4 mice at 4 x 5 mg/kg i.p.



4, *P. falciparum* IC_{50} = 2 nM



31, *T. cruzi* IC_{50} = 53 nM

ABSTRACT: 4,4″-Diamidino-*m*-terphenyl (**1**) and 36 analogues were prepared and assayed in vitro against T*rypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *Plasmodium falciparum*, and *Leishmania amazonensis*. Twenty-three compounds were highly active against *T. b. rhodesiense* or *P. falciparum*. Most noteworthy were amidines **1**, **10**, and **11** with IC_{50} of 4 nM against *T. b. rhodesiense*, and dimethyltetrahydropyrimidinyl analogues **4** and **9** with IC_{50} values of ≤ 3 nM against *P. falciparum*. Bis-pyridylimidamide derivative **31** was 25 times more potent than benznidazole against *T. cruzi* and slightly more potent than amphotericin B against *L. amazonensis*. Terphenyldiamidine **1** and dipyridylbenzene analogues **23** and **25** each cured 4/4 mice infected with *T. b. rhodesiense* STIB900 with four daily 5 mg/kg intraperitoneal doses, as well as with single doses of ≤10 mg/kg. Derivatives **5** and **28** (prodrugs of **1** and **25**) each cured 3/4 mice with four daily 25 mg/kg oral doses.

INTRODUCTION

The vector borne protozoal diseases trypanosomiasis, malaria, and leishmaniasis continue to affect some of the poorest areas of the world.[1−5] Human African trypanosomiasis (HAT), which occurs in over 20 sub-Saharan African countries, was largely controlled by the 1960s but has since re-emerged. After continued control efforts, fewer than 10 000 new cases were reported in 2009 for the first time in 50 years, and the World Health Organization (WHO) estimates that 30 000 actual cases currently exist (vs 300 000 cases in 1988).[1,6] The disease progresses from an early hemolymphatic stage to a late central nervous system (CNS) stage and has a 100% mortality rate if not treated.[7] Two forms of HAT exist. A chronic infection due to *Trypanosoma brucei gambiense*, prevalent in western and central Africa, accounts for about 95% of reported cases. The remaining cases arise from an acute infection of *T. brucei rhodesiense*, prevalent in eastern and southern Africa.[8]

American trypanosomiasis, or Chagas disease, is caused by *Trypanosoma cruzi*. An estimated 10 million people were infected in 2010, and an estimated 10 000 died in 2008 because of the disease. Originally endemic to Latin America, the disease has now spread to other continents. It progresses from an acute phase lasting about 2 months after infection, in which the

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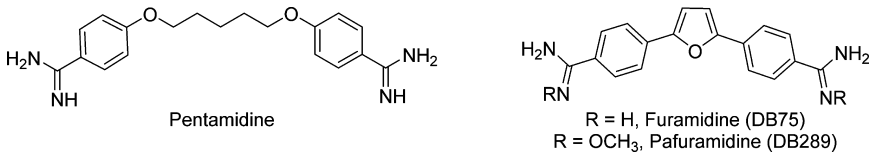

Figure 1. Structures of 1,5-bis(4-amidinophenoxy)pentane (pentamidine), 2,5-bis(4-amidinophenyl)furan (furamidine), and 2,5-bis(4-*N*′-methoxyamidinophenyl)furan (pafuramidine).

parasites are concentrated in the blood, to a chronic phase, in which the parasites are hidden in the heart and digestive muscle. Myocardial damage can lead to death.[4]

Malaria is concentrated in sub-Saharan Africa but is also endemic to other continents, affecting approximately 100 countries. The WHO has estimated 216 million cases of malaria in 2010 and 655 000 deaths.[2] Most of the deaths occur in Africa, primarily among young children. Four *Plasmodium* species are recognized as human pathogens. Among these, *P. falciparum* causes the most deadly infection.[2,7]

Infections due to various species of *Leishmania* affect nearly 12 million people in 88 countries. The diseases range in severity from a spontaneously healing cutaneous form due to *L. mexicana* to a life-threatening visceral form, 90% of which occurs in Bangladesh, India, Nepal, and Sudan (due to *L. donovani*) or in Brazil (due to *L. chagasi*).[5,8] Cases of patients infected with both visceral leishmaniasis (VL) and human immunodeficiency virus (HIV) continue to be reported.[9−16]

The need for safe, orally active, and economical drugs against HAT persists. Available therapies are scarce, antiquated, toxic, prone to resistance, and require parenteral (usually intravenous) administration.[1,6,7,17−19] Suramin, a polysulfonated naphthylurea, and pentamidine (Figure 1), an aromatic diamidine, are the two drugs used to treat early stage HAT. Late-stage therapies are generally more problematic. The organoarsenical melarsoprol is associated with an encephalopathy leading to death in about 5% of the cases.[7,20] Eflornithine is the only new anti-HAT drug introduced in the past 60 years. Although better tolerated than melarsoprol, eflornithine is ineffective against *T. b. rhodesiense*, and high doses must be given intravenously four times daily over long periods.[6] A combination of eflornithine and nifurtimox (nifurtimox−eflornithine combination therapy, NECT) was licensed in 2009.[1] It is easier to administer and has a shorter treatment duration than the eflornithine monotherapy and is currently the best choice to treat late stage patients with *T. b. gambiense* infections.

Drugs of choice against Chagas disease are benznidazole and nifurtimox, both of which are given orally. Both drugs are highly effective in curing the disease if treatments begins at the onset of the acute stage, but the efficacy of each diminishes with delayed initiation of treatment.[4,7] Severe side effects have also been reported for both drugs.[21] No drugs are currently approved for the chronic phase of the disease, but at least two drug candidates are currently in clinical trials.[4,7]

Although a number of economical orally active antimalarial drugs are available, drug resistance is a growing problem.[22] Resistance to chloroquine, observed in Thailand in the 1960s, has been followed by resistance in other locations and to other drugs, including sulfadoxine−pyrimethamine and mefloquine. Resistance to artemisinin led to the development of artemisinin-based combination therapy, but resistance to at least one combination, artesunate−mefloquine, has also been reported.[7]

Pentavalent antimonial compounds, including sodium stibogluconate and meglumine antimoniate, introduced in the 1940s, continue to be the drugs of choice against VL in most endemic countries despite their toxicity. High rates of treatment failures have been reported in Bihar, India, since the 1980s.[23] Antimony resistant VL was treated with pentamidine in the past, but the efficacy of pentamidine against VL has decreased,[24] and the use of pentamidine against leishmaniasis is now restricted to some forms of cutaneous disease that occur in South America.[25] Amphotericin B is an effective option in the treatment of VL,[26] but the less toxic liposomal formulations of the drug are limited by their expense. The aminoglycoside paromomycin has shown high efficacy in India and low toxicity, but a 3-week course of daily injections is required.[27] Miltefosine is orally active but is teratogenic, nephrotoxic, and hepatotoxic.[28] Various miltefosine combination therapies have been under recent investigations.[8,23,28]

Furamidine[29] (DB75, Figure 1) is a conformationally restricted analogue of pentamidine. These positively charged molecules have poor oral bioavailability; however, their *N*′-hydroxy and *N*′-methoxy derivatives with lower pK_a values have shown potential as orally active prodrugs.[30] Pafuramidine (DB289, Figure 1),[31] the methamidoxime prodrug of furamidine, advanced to phase III clinical trials against early stage HAT and phase II trials against malaria.[32,33] The compound exhibited nephro- and hepatotoxicity in a recent expanded phase I trial,[34] resulting in a suspension of phase III trials.[35]

Numerous analogues of pentamidine and furamidine, including those with modifications of both the central and outer rings, have been prepared and assayed against various organisms,[36−56] with the intent of finding comparably efficacious but less toxic drug candidates. A number of arylimidamides (AIAs), or "reversed" amidines, have been prepared and tested primarily against *T. cruzi* or *Leishmania* species.[57−60] A few diamidine derivatives of *o*-, *m*-, and *p*-terphenyl were originally prepared as serine protease inhibitors.[61] More recently, a larger number of dicationic *p*-terphenyls and their aza-analogues have been prepared as antiprotozoals.[62−64] Dicationic *m*-terphenyl derivatives have remained virtually unexplored, with respect to both the number of molecules synthesized and their potential antiprotozoal activities. While the *p*-terphenyls are linear in shape, the *m*-terphenyls are more conformationally similar to furamidine. The present work describes the synthesis of a rather diverse group of dicationic *m*-terphenyl derivatives and their biological evaluation against four parasites.

CHEMISTRY

A total of 37 cationically substituted *m*-terphenyl analogues were prepared (Table 1). This group consists of 29 diamidine derivatives (**1**−**29**), six bis-arylimidamides (bis-AIAs, **30**−**35**), and two mono-AIAs (**36** and **37**). The amidine group includes 16 simple amidines (**1**, **7**−**8**, **10**−**13**, **19**−**26**, and **29**), seven *N*-

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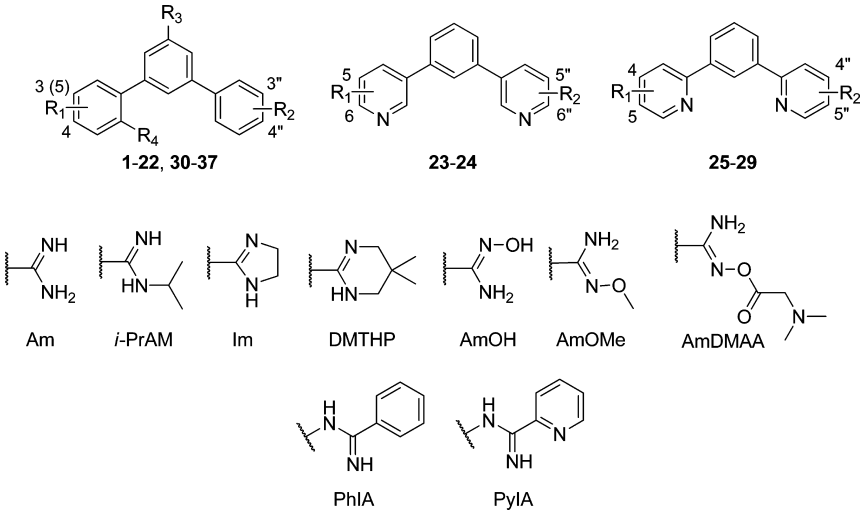
Table 1. Structures of Cationic *m*-Terphenyl and 1,3-Dipyridylbenzene Derivatives 1−37[a]



compd	R_1	R_2	R_3	R_4
1	4-Am	4″-Am	H	H
2	4-*i*-PrAm	4″-*i*-PrAm	H	H
3	4-Im	4″-Im	H	H
4	4-DMTHP	4″-DMTHP	H	H
5	4-AmOH	4″-AmOH	H	H
6	4-AmOMe	4″-AmOMe	H	H
7	4-Am	4″-Am	Cl	H
8	4-Am	4″-Am	NO_2	H
9	4-DMTHP	4″-DMTHP	NO_2	H
10	4-Am	4″-Am	NH_2	H
11	4-Am	4″-Am	OH	H
12	4-Am	4″-Am	OMe	H
13	3-Am	3″-Am	H	H
14	3-*i*-PrAm	3″-*i*-PrAm	H	H
15	3-Im	3″-Im	H	H
16	3-DMTHP	3″-DMTHP	H	H
17	3-AmOH	3″-AmOH	H	H
18	3-AmOMe	3″-AmOMe	H	H
19	3-Am	3″-Am	Cl	H
20	3-Am	3″-Am	OMe	H
21	3-Am	4″-Am	H	H
22	3-Am	4″-Am	Cl	H
23	6-Am	6″-Am		
24	5-Am	5″-Am		
25	5-Am	5″-Am		
26	5-Am	5″-Am		
27	5-AmOMe	5″-AmOMe		
28	5-AmDMAA	5″-AmDMAA		
29	4-Am	4″-Am		
30	3-PhIA	3″-PhIA	Cl	H
31	3-PyIA	3″-PyIA	Cl	H
32	3-PhIA	4″-PhIA	H	H
33	3-PyIA	4″-PyIA	H	H
34	3-PhIA	4″-PhIA	Cl	H
35	3-PyIA	4″-PyIA	Cl	H
36	4-PyIA	H	Cl	O-*i*-Pr
37	5-PyIA	H	Cl	O-*i*-Pr

[a]All compounds were isolated as hydrochloride salts except **26** (acetate salt) and **28** (free base).

alkyl and *N*,*N*′-alkylene derivatives (**2**−**4**, **9**, and **14**−**16**), and six prodrugs (**5**, **6**, **17**, **18**, **27**, and **28**). Structural variations include the orientation of the cationic groups, substituents on the amidine nitrogen atoms and/or on the central aromatic ring, and the insertion of nitrogen atoms in the outer aromatic rings. Compounds **1**−**22** and **30**−**37** have *m*-terphenyl nuclei,

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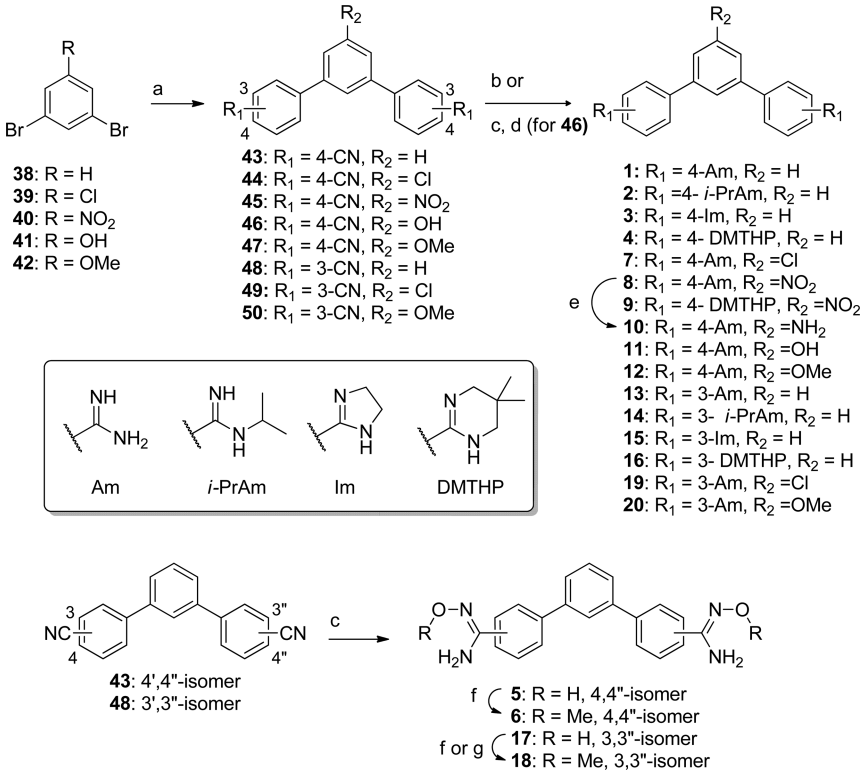
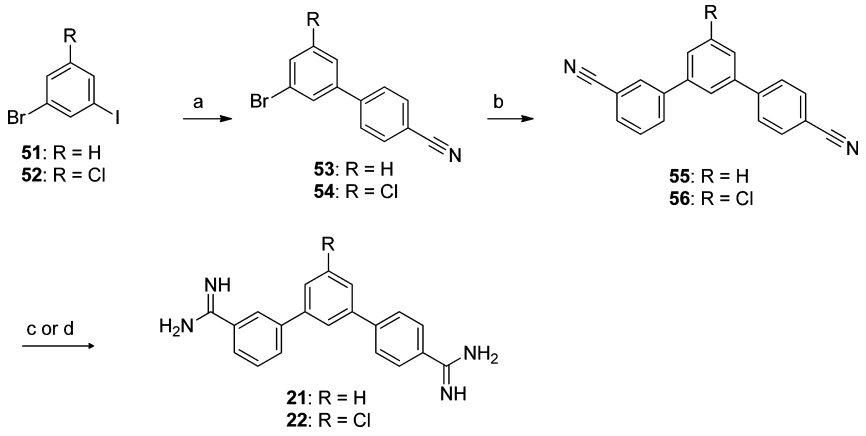
Scheme 1. Synthesis of Symmetric *m*-Terphenylamidine Derivatives and Prodrugs[a]



[a]Reagents and conditions: (a) 3- or 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, aq Na_2CO_3, DME, reflux (52−81%); (b) EtOH, HCl, 1,4-dioxane, and then NH_3 or amine, EtOH; (c) $NH_2OH{\cdot}HCl$, *t*-BuOK, DMF; (d) Ac_2O, AcOH, and then H_2, 10% Pd/C, EtOH, AcOH; (e) H_2, 10% Pd/C, EtOH; (f) CH_3I, *t*-BuOK, DMSO; (g) $(CH_3)_2SO_4$, aq NaOH, dioxane.

Scheme 2. Synthesis of Asymmetric *m*-Terphenyldiamidines[a]



[a]Reagents and conditions: (a) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, aq Na_2CO_3, DME; (b) (3-cyanophenyl)boronic acid, $Pd(PPh_3)_4$, aq Na_2CO_3, DME; (c) EtOH, HCl, 1,4-dioxane and then NH_3, EtOH; (d) $LiN(TMS)_2$, THF.

while analogues **23**−**24** and **25**−**29** have 1,3-bis(pyridin-3-yl)benzene and 1,3-bis(pyridin-2-yl)benzene scaffolds, respectively. All 37 compounds are novel except **13**, which was previously reported but as a different salt.[61] The activities of analogues **7**, **19**, **23**, and **24** against *T. cruzi* have been reported,[65,66] although details of their syntheses have yet to be reported. All target compounds were isolated as their hydrochloride salts except acetate salt **26** (an alternative salt form of **25**) and free base **28**.

The syntheses of the symmetric *m*-terphenylamidines and prodrugs **1**−**20** are depicted in Scheme 1. Dibromobenzene starting materials **38**, **39**, and **41** were commercially available. Nitro analogue **40**[67] was prepared by deamination of 2,6-dibromo-4-nitroaniline. Methoxy derivative **42** was prepared by bromination[68]−deamination[67] of *p*-anisidine. Double Suzuki couplings involving dibromobenzenes **38**−**42** and 2−2.5 equiv of 3- or (4-cyanophenyl)boronic acid catalyzed by tetrakis(triphenylphosphine)palladium(0) readily gave terphenyldinitriles **43**−**50** in yields of 52−81%. The nitriles (except **46**) were then subjected to modified Pinner reaction conditions (ethanol, HCl gas, dioxane cosolvent)[50,51] to generate the corresponding imidate esters, which were then reacted immediately with

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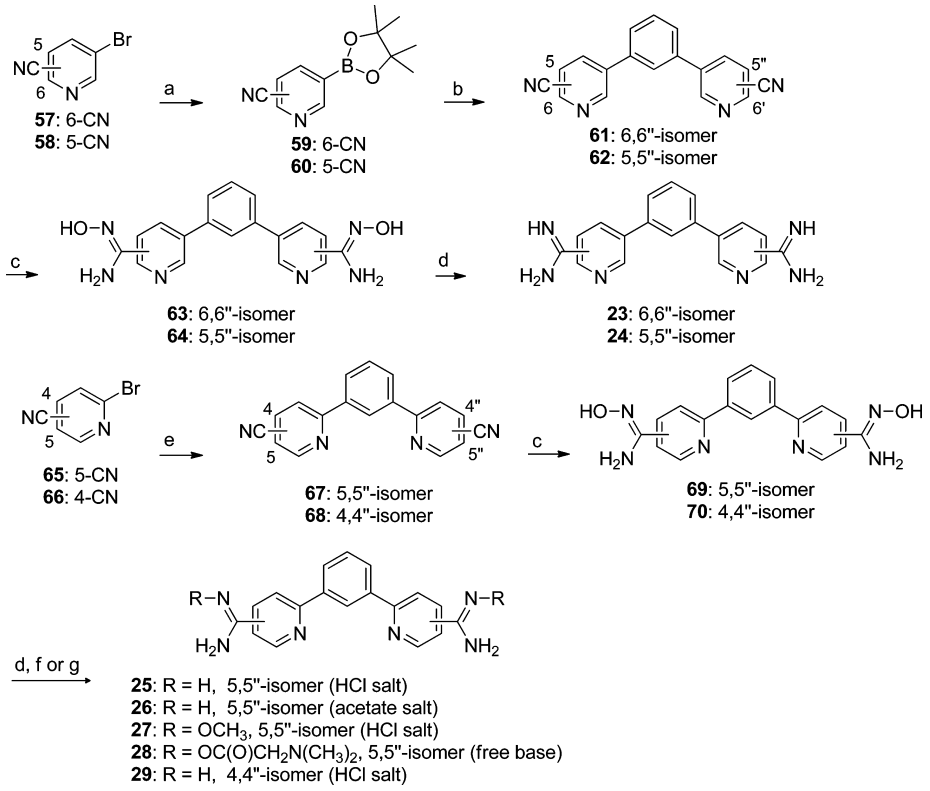
Scheme 3. Synthesis of 1,3-Dipyridylbenzeneamidines and Prodrugs[a]



[a]Reagents and conditions: (a) bis(pinacolato)diboron, $PdCl_2(dppf)$, KOAc, DMSO; (b) 1,3-diiodobenzene, $Pd(PPh_3)_4$, Ag_2CO_3, THF; (c) $NH_2OH{\cdot}HCl$, *t*-BuOK, DMSO; (d) Ac_2O, AcOH, and then H_2, 10% Pd/C; (e) 1,3-benzenediboronic acid, $Pd(PPh_3)_4$, Ag_2CO_3, THF; (f) Me_2SO_4, $LiOH{\cdot}H_2O$, DMF; (g) dimethylaminoacetyl chloride·HCl, K_2CO_3, DMF.

ammonia (for simple amidines **1**, **7**, **8**, **12**, **13**, **19**, and **20**), isopropylamine (for *N*-isopropylamidines **2** and **14**), ethylenediamine (for imidazolines **3** and **15**), or 2,2-dimethylpropane-1,3-diamine (for 5,5-dimethyl-1,4,5,6-tetrahydropyrimidin-2-yl (DMTHP) derivatives **4**, **9**, and **16**). Catalytic hydrogenation of nitro-substituted diamidine **8** gave the amino analogue **10**. Conversion of nitrile **46** to its amidoxime derivative using excess hydroxylamine in DMSO,[69] followed by O-acylation and catalytic hydrogenation,[50] gave 5′-hydroxydiamidine **11**. Amidoxime prodrugs **5** and **17** were prepared by similar treatment of nitriles **43** and **48** with hydroxylamine.[69] The amidoxime bases were converted to their hydrochloride salts for biological testing or underwent O-methylation to methamidoxime derivatives **6** and **18**, which were also converted to their hydrochloride salts.

Syntheses of asymmetric *m*-terphenyldiamidines **21** and **22** (Scheme 2) were similar to those of their symmetric counterparts, but their dinitrile precursors were prepared by successive single Suzuki couplings. High selectivity for single over double coupling has resulted from the use of bromoiodobenzene rather than dibromobenzene starting materials.[70] The coupling between bromoiodobenzene **51** and (4-cyanophenyl)boronic acid gave biphenyl **53** in 71% isolated yield. An analogous Suzuki coupling involving bromoiodide **52** (prepared by iodination−deamination of 4-bromo-2-chloroaniline)[71,72] gave biphenyl **54** in 59% yield. Successive couplings of bromobiphenyls **53** and **54** with (3-cyanophenyl)boronic acid gave the desired asymmetric terphenyldinitriles **55** and **56** (83% and 74% yields). A Pinner synthesis employing dinitrile **55** gave asymmetric diamidine **21**. Similar strategy using chloro analogue **56** failed, presumably because of the extremely low solubility of the nitrile in the reaction medium. Diamidine **22** was successfully prepared from dinitrile **56** using lithium bis(trimethylsilyl)amide in THF.[64]

The preparation of dipyridylbenzene derivatives **23**−**29** is shown in Scheme 3. 3-Bromopyridyl starting materials **57** (also commercially available) and **58** were prepared by treatment of 5-bromo-*N*-(*tert*-butyl)picolinamide[73] or 5- bromonicotinamide with phosphorus oxychloride.[73] The reactions of compounds **57** and **58** with bis(pinacolato)diboron and catalytic $PdCl_2(dppf)$[74] gave boronate esters **59** and **60**, which underwent Suzuki coupling with 1,3-diiodobenzene under anhydrous conditions ($Pd(PPh_3)_4$, Ag_2CO_3, THF)[75] to give 1,3-di(pyridin-3-yl)benzenedinitriles **61** and **62** (60% and 69% yields). Attempted Pinner syntheses of amidines **23** and **24** from dipyridylbenzenenitriles **61** and **62** were unsuccessful. The nitriles were treated with excess hydroxylamine in DMSO to give amidoxime intermediates **63** and **64**. The amidoximes were treated with acetic anhydride in acetic acid to generate the *N*′-acetoxy derivatives in situ, which were hydrogenated at 60 psi over 10% Pd/C in acetic acid.[69] The use of neat acetic acid in place of acetic acid−ethanol[69] proved to be necessary for selective cleavage of the oxygen−nitrogen bond (amidine deprotection) over the oxygen−carbon bond (reversion to the amidoxime).

Similar strategy was employed for the syntheses of the di(pyridin-2-yl)benzene analogues except for the reversal of functional groups for the Suzuki couplings. 2-Bromopyridylnitriles **65** and **66** were prepared by dechlorobromination of 6-chloronicotinonitrile[76] or 2-chloro-4-cyanopyridine using phos-

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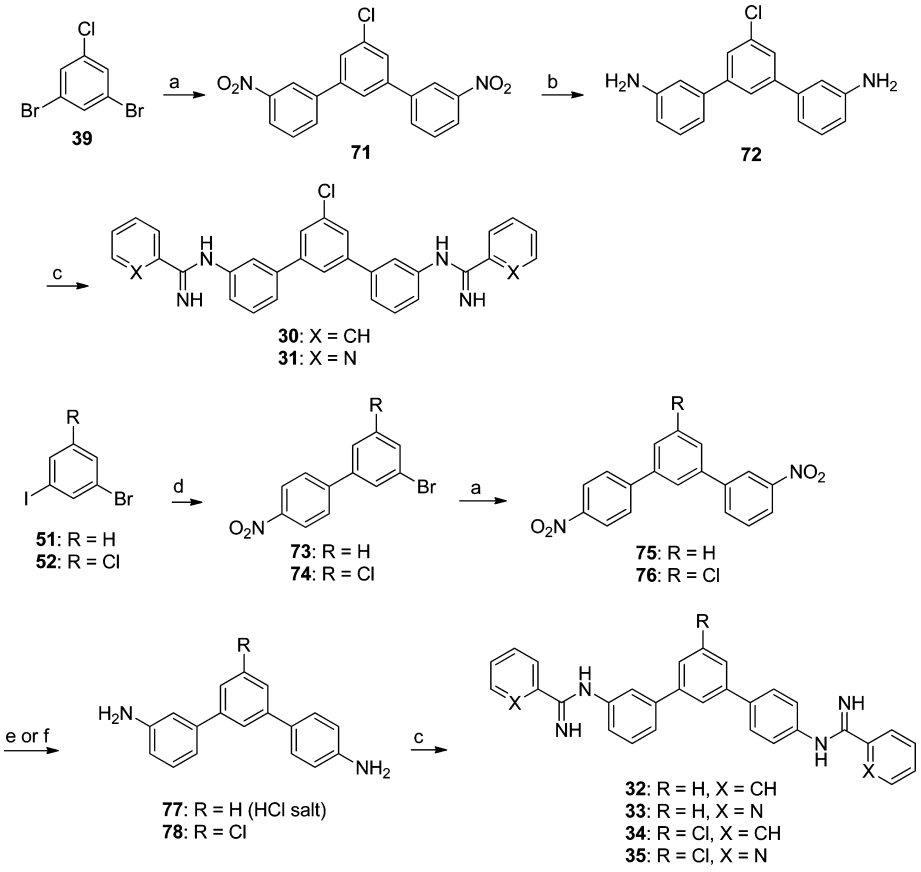
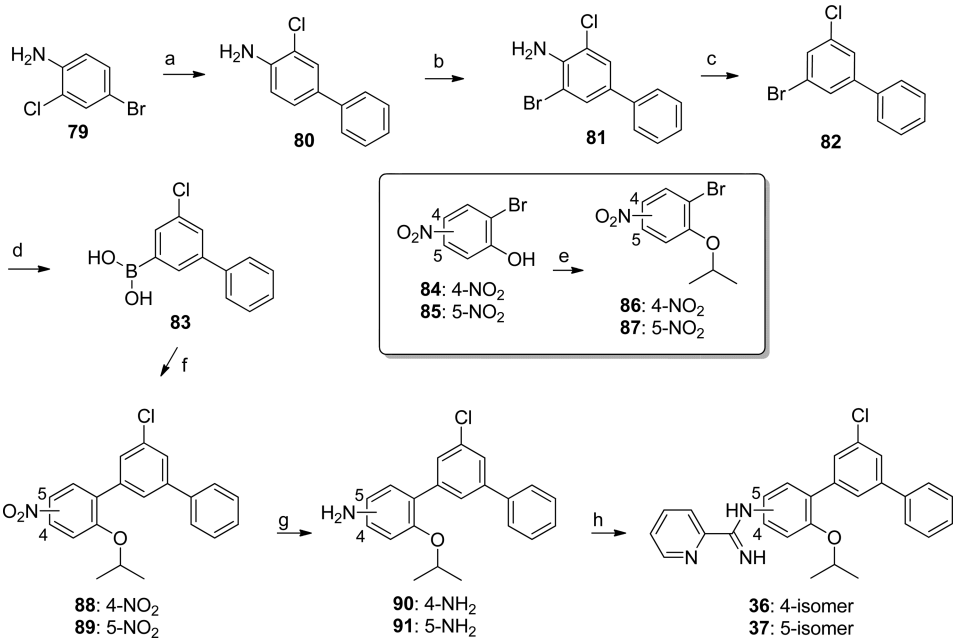
Scheme 4. Synthesis of *m*-Terphenyl-bis-arylimidamides (Bis-AIAs)[a]



[a]Reagents and conditions: (a) 3-nitrophenylboronic acid, $Pd(PPh_3)_4$, aq Na_2CO_3, DME, reflux; (b) $SnCl_2{\cdot}2H_2O$, EtOH; (c) Et_3N (for **77** only), benzonitrile or 2-cyanopyridine, $NaN(TMS)_2$, THF; (d) 4-nitrophenylboronic acid pinacol ester, $Pd(PPh_3)_4$, aq Na_2CO_3, DME; (e) H_2, 60 psi, 10% Pd/C, EtOH; (f) Fe, NH_4Cl, aq EtOH.

Scheme 5. Synthesis of *m*-Terphenyl Monoarylimidamides (Mono-AIAs)[a]



[a]Reagents and conditions: (a) phenylboronic acid, $Pd(PPh_3)_4$, aq Na_2CO_3, DME; (b) NBS, THF; (c) $NaNO_2$, H_2SO_4, EtOH; (d) BuLi, THF and then triisopropyl borate; (e) $(CH_3)_2CHI$, Cs_2CO_3, K_2CO_3, DMF; (f) **86** or **87**, $Pd(PPh_3)_4$, aq Na_2CO_3, DME; (g) $SnCl_2{\cdot}2H_2O$, EtOH; (h) benzonitrile or 2-cyanopyridine, $NaN(TMS)_2$, THF.

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Table 2. Antiprotozoal Activities, Cytotoxicities, and Selectivity Indices of Compounds 1−37 in Vitro

	T. b. rhodesiense[a]		*T. cruzi*[b]		*P. falciparum*[c]		*L. amazonensis*[d]		
compd	IC_{50} (μM)[f]	SI_{Tb}[g]	IC_{50} (μM)[f]	SI_{Tc}[h]	IC_{50} (μM)[f]	SI_{P}[i]	IC_{50} (μM)[j]	SI_{L}[k]	cytotox[e] IC_{50} (μM)[f]
1	0.004	8494	71.6	<1	0.024	1279			31.2
2	0.047	2157	>150	<1	0.016	6583			102
3	0.068	37	18.9	<1	0.073	35			2.55
4	0.140	871	151	<1	0.002	49347			122
5	10.9	>14	>150	ND[l]	>10	ND[l]			>150
6	4.44	4	92.6	<1	>10	<2			19.2
7	0.031	700	65.5	<1	0.039	561			21.9
8	0.020	>7481	57.2	>2	0.018	>8376			>150
9	0.692	>217	>150	ND[l]	0.003	>46781			>150
10	0.004	>39791	149	>1	0.136	>1103			>150
11	0.004	>37500	>150	<1	0.038	>3947			>150
12	0.005	7266	59.1	<1	0.048	693			33.0
13	0.055	2268	35.0	4	0.038	3319			125
14	0.617	>243	141	>1	0.031	>4194			>150
15	1.60	20	20.4	2	0.619	51			31.7
16	0.809	70	45.4	1	0.006	9498			56.6
17	2.55	2	11.2	<1	8.23	<1			5.60
18	11.3	2	24.1	<1	9.31	2			20.3
19	0.044	709	50.2	<1	0.033	944			30.9
20	0.029	4695	55.9	2	0.028	4964			137
21	0.052	544	27.1	1	0.015	1947			28.5
22	0.097	130	46.6	<1	0.010	1248			12.7
23	0.006	3720	43.4	<1	0.015	1485			22.3
24	0.527	>285	>150	ND[l]	0.058	>2577			>150
25	0.017	>8824	>150	ND[l]	0.040	>3763			>150
26	0.022	>6856	>150	ND[l]	0.045	>3339			>150
27	26.3	>6	117	>1	3.56	>42			>150
28	9.84	6	72.3	<1	0.486	129			62.9
29	1.17	>128	>150	ND[l]	0.077	>1939			>150
30	0.533	8	2.09	2	0.071	58	2.43	2	4.10
31	0.019	133	0.053	47	0.006	450	0.095	26	2.50
32	0.635	4	2.14	1	0.038	66	0.907	3	2.52
33	1.94	1	0.388	7	0.208	13	0.123	22	2.72
34	0.178	13	2.04	1	0.039	58	1.02	2	2.27
35	0.109	24	1.54	2	0.219	12	0.211	13	2.64
36	32.4	<1	4.18	2	>10	<1	0.933	10	9.69
37	12.3	<1	2.98	1	3.075	1	1.88	2	3.77
PMD[m]	0.003	11436			0.046	1004			46.6
FMD[n]	0.003	2000	23.3	<1	0.014	464			6.40
MSP[o]	0.004	1275							5.12
BNZ[p]			1.30	115					>150
CQ[q]					0.125	612			76.5
ATM[r]					0.004	34884			150
AMB[s]							0.124		
PPT[t]									0.017

[a] *Trypanosoma brucei rhodesiense* (STIB900).[83] [b] *Trypanosoma cruzi* Tulahuen C2C4 Lac Z.[83] [c] *Plasmodium falciparum* (K1, chloroquine resistant).[83] [d] *Leishmania amazonensis* infected CD-1 mouse intracellular amastigotes.[82] [e] Cytotoxicity to L6 rat myoblast cells.[83] [f] The IC_{50} values are the mean of two independent assays. Individual values differed by less than 50% of the mean value. [g] Selectivity index for *T. b. rhodesiense* expressed as the ratio IC_{50}(L6 cells)/IC_{50}(*T. b. rhodesiense*). [h] Selectivity index for *T. cruzi* expressed as the ratio IC_{50}(L6 cells)/IC_{50}(*T. b. cruzi*). [i] Selectivity index for *P. falciparum* expressed as the ratio IC_{50}(L6 cells)/IC_{50}(*P. falciparum*). [j] The IC_{50} values are the mean of three independent assays. The standard deviations varied from the mean values by 8−64%. [k] Selectivity index for *L. amazonensis* expressed as the ratio IC_{50}(L6 cells)/IC_{50}(*L. amazonensis*). [l] Value not determinable. [m] Pentamidine. [n] Furamidine. [o] Melarsoprol. [p] Benznidazole. [q] Chloroquine. [r] Artemisinin. [s] Amphotericin-B. [t] Podophyllotoxin.

phorus tribromide.[77] Various attempts at preparing boronic acids or esters from **65**, **66**, or their 2-chloro precursors were unsuccessful. Suzuki couplings of 2-bromopyridines **65** and **66** with 1,3-phenyldiboronic acid under anhydrous conditions ($Pd(PPh_3)_4$, Ag_2CO_3, THF)[75] gave 1,3-di(pyridin-2-yl)-benzenedinitriles **67** and **68** (63% and 87% yields). Compound **67** was also prepared in 91% yield by the coupling of 6-chloronicotinonitrile[76] and the diboronic acid in toluene/2 M aqueous Na_2CO_3.[47] Nitriles **67** and **68** were reacted with excess hydroxylamine in DMSO to give amidoxime intermediates **69**

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and **70**, which underwent O-acetylation followed by catalytic hydrogenation to give amidine hydrochlorides **25** and **29**. The former compound was also isolated as acetate salt **26**. Amidine **25** was also prepared directly from nitrile **67** using lithium bis(trimethylsilyl)amide in THF.[64] The prodrugs, methamidoxime **27** (hydrochloride salt) and dimethylaminoacetoxyamidine **28** (free base), were prepared by O-methylation or O-acylation of amidoxime **69**. Compound **27** was also prepared as the hydrochloride salt (59% yield) directly from nitrile **67** using methoxylamine hydrochloride in the presence of triethylamine and thioglycolic acid.[78]

The syntheses of bis-AIAs **30**–**35** are depicted in Scheme 4. A double Suzuki coupling between dibromobenzene **39** and 3-nitrophenylboronic acid gave the symmetric dinitroterphenyl **71** in 76% isolated yield. Reduction of **71** with tin(II) chloride dihydrate in ethanol gave the diamine **72**, which was reacted with benzonitrile or 2-cyanopyridine in the presence of sodium bis(trimethylsilyl)amide in THF[79] to give symmetric bis-phenylimidamide **30** and the corresponding di(pyridin-2-yl) derivative **31**. Similar strategy was employed for the asymmetric analogues **32**–**35** except for the requirement of successive single Suzuki couplings. Bromoiodobenzenes **51** and **52**[71,72] were coupled with 4-nitrophenylboronic acid pinacol ester to give bromobiphenyls **73** and **74**, which in turn were coupled with 3-nitrophenylboronic acid to give terphenyls **75** and **76** (52% and 55% yields overall). Hydrogenation of dinitroterphenyl **75** over 10% Pd in ethanol gave diamine **77** (72% yield as the HCl salt). The chloro-substituted dinitro analogue **76** was reduced to diamine **78** (69% yield) using iron powder and ammonium chloride in aqueous ethanol. Diamines **77** and **78** were reacted with benzonitrile or 2-cyanopyridine in the presence of sodium bis(trimethylsilyl)amide in THF[79] to give bis-AIAs **32**–**35** (34–64% yields).

The syntheses of mono-AIAs **36** and **37** (Scheme 5) began with the Suzuki coupling of bromoaniline **79** and phenylboronic acid to give biphenylamine **80** (70%). This intermediate underwent bromination to **81** (*N*-bromosuccinimide in THF, 83%), followed by deamination to bromobiphenyl **82** (sodium nitrite and sulfuric acid in ethanol, 86%). The latter underwent lithiation followed by quenching with triisopropyl borate to give crude boronic acid **83**. This intermediate underwent Suzuki couplings with bromoisopropoxynitrobenzenes **86**[80] and **87**[81] (prepared by Williamson ether syntheses from the corresponding phenols **84** and **85**[81]) to give nitroterphenyls **88** (82%) and **89** (91%). The nitro compounds were reduced to the corresponding amines **90** (83%) and **91** (94%) using tin(II) chloride dihydrate in ethanol. The amines were reacted with 2-cyanopyridine in the presence of sodium bis(trimethylsilyl)amide in THF to give mono-AIAs **36** (41%) and **37** (50%) as their HCl salts.

IN VITRO ANTIPROTOZOAL ACTIVITIES, SELECTIVITIES, AND STRUCTURE–ACTIVITY RELATIONSHIPS

In vitro activities of target compounds against *T. b. rhodesiense* strain STIB900, the intracellular amastigote form of the *T. cruzi* Tulahuen strain C2C4, the chloroquine resistant *P. falciparum* strain K1, and *L. amazonensis* intracellular amastigotes were measured following established protocols,[82,83] and the results are shown in Table 2. Cytotoxicities against L6 rat myoblast cells[83] were determined to calculate the selectivity indices (the ratios of cytotoxic IC_{50} values to antiprotozoal IC_{50} values) of each compound for each of the four parasites. Standard drugs include pentamidine and furamidine (against *T. b. rhodesiense* and *P. falciparum*), melarsoprol (against *T. b. rhodesiense*), benznidazole (against *T. cruzi*), chloroquine and artemisinin (against *P. falciparum*), amphotericin B (against *L. amazonensis*), and podophyllotoxin (against L6 cells).

T. b. rhodesiense. A total of 17 compounds were highly active with IC_{50} values below 100 nM, and 11 of these analogues had selectivity indices above 2000 (more selective than furamidine and melarsoprol). Five congeners exhibited IC_{50} values below 10 nM (comparable in potency to the three standard drugs). The most potent were lead compound **1** and derivatives **10** and **11**, all exhibiting IC_{50} values of 4 nM and selectivity indices above 8000, followed by analogues **12** (IC_{50} = 5 nM, SI = 7270) and **23** (IC_{50} = 6 nM, SI = 3720). Eight congeners (**2**, **7**, **8**, **19**, **20**, **25**, **26**, and **31**) exhibited IC_{50} values between 10 and 50 nM, of which analogues **8**, **25**, and **26** had selectivity indices above 6000 and derivatives **2** and **20** had selectivity indices above 2000. Four derivatives (**3**, **13**, **21**, and **22**) showed IC_{50} values between 50 and 100 nM, of which congener **13** had a selectivity index greater than 2000. Another nine compounds (**4**, **9**, **14**, **16**, **24**, **30**, **32**, **34**, and **35**) exhibited IC_{50} values between 100 nM and 1.0 μM.

The group of 17 most highly active compounds with IC_{50} values below 100 nM included 14 simple diamidines, *N*-isopropylamidine **2**, imidazoline **3**, and AIA derivative **31**. The diamidines included all 11 of the terphenyldiamidines (**1**, **7**, **8**, **10**–**13**, and **19**–**22**) and three of the five dipyridyl diamidines **23**, **25**, and **26**.

Among the terphenylamidine derivatives **1**–**22**, optimal potency and selectivity were observed when both cationic groups were oriented para to the central ring. Lead compound **1** (IC_{50} = 4 nM, SI ≈ 8500), was over 10 times more potent and over 4 times more selective than its regioisomer **13** (IC_{50} = 55 nM), with both amidine functions situated meta to the central ring. The asymmetric 3,4″-diamidine **21** was similar in potency (IC_{50} = 52 nM) to **13** but about 4 times less selective.

The introduction of substituents on the amidine nitrogen atoms resulted in diminished activity. The *N*-isopropylamidines **2** and **14** were more than 10 times less potent than the corresponding simple amidines **1** and **13**. The corresponding imidazoline derivatives **3** and **15** showed a further 2-fold decrease in potency. The DMTHP derivatives **4**, **9**, and **16** showed varied degrees of decreased potencies relative to the corresponding amidines **1**, **8**, and **13**. The prodrugs **5**, **6**, **17**, and **18** were inactive in vitro, as expected.[30,33]

The introduction of substituents on the central ring had varied effects upon activity, depending upon the orientation of the cationic groups. The potency of lead compound **1** was retained in its amino and hydroxy derivatives **10** and **11**, and these two analogues also had the highest selectivity indices (above 37 500). The methoxy derivative **12** was similar in both potency and selectivity to parent molecule **1**, while methoxy analogue **20** was slightly more potent and selective than its parent molecule **13**. None of the chloro analogues **7**, **19**, and **22** showed advantages of both potency and selectivity compared to parent molecules **1**, **13**, and **21**, respectively. The nitro analogue **8** was quite potent (IC_{50} = 20 nM), albeit 5 times less potent than parent amidine **1**, and showed at least comparable selectivity.

The orientation of both amidine functions para to the central ring was also required for optimal potency among the regioisomeric dipyridylbenzenediamidines **23**–**25** and **29**. The points of attachment of the pyridine rings proved to be

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less crucial. Analogues **23** (IC_{50} = 6 μM, SI ≈ 3700) and **25** (IC_{50} = 17 μM, SI > 8800), with both cationic groups positioned para to the central ring, were highly potent and highly selective for the parasite, and their potencies varied by less than 3-fold. Their regioisomers with both amidine moieties situated meta to the central ring were over 50 times less potent (**23** vs **24**, **25** vs **29**). The hydrochloride salt **25** and acetate salt **26** (different salts of the same diamidine base) gave similar results in the in vitro assays.

The AIA derivatives **30**−**37** were, as a whole, less potent and less selective compared to the amidine derivatives **1**−**29**. Even though the bis-pyridylimidamide **31** was the sixth most potent overall (IC_{50} = 19 nM), it was the least selective (SI = 133) of the 13 compounds with IC_{50} values below 50 nM. None of the other AIA derivatives had IC_{50} values below 100 nM.

T. cruzi. The bis-pyridylimidamides **31**, **33**, and **35** were most potent against the intracellular amastigote form of the *T. cruzi* Tulahuen strain. The order of decreasing potencies continued with the bis-phenylimidamide, monopyridylimidamide, and diamidine derivatives. The pyridylimidamide **31** (IC_{50} = 53, SI = 47) showed the most promising results, being about 25 times more potent than benznidazole (IC_{50} = 1.30 μM, SI = 115). The other pyridyl analogues **33** (IC_{50} = 388 nM) and **35** (IC_{50} = 1.54 μM) showed potencies greater than or comparable to benznidazole but selectivity indices below 10. Compound **31** merits further investigation, as selectivity indices above 10 are a common cutoff value for in vivo testing against *T. cruzi*. None of the other compounds exhibited IC_{50} values below 2 μM.

P. falciparum. Twenty-one compounds exhibited IC_{50} values below 50 nM (compared to IC_{50} = 46 nM for pentamidine) against the chloroquine resistant *P. falciparum* strain K1. The two most potent derivatives **4** and **9**, with IC_{50} values of 2 and 3 nM, respectively, and each having a selectivity index above 45 000, were more potent and selective for the parasite than artemisinin (IC_{50} = 4 nM, SI = 34 900). Analogues **16** and **31** each had IC_{50} values of 6 nM, while congener **22** had an IC_{50} value of 10 nM and a selectivity index of 1250. Only analogue **16** had a selectivity index below 1000. Four derivatives (**2**, **8**, **21**, and **23**) exhibited IC_{50} values between 10 and 20 nM. All had selectivity indices above 1000, with those of **2** and **8** being above 5000. Twelve compounds (**1**, **7**, **11**−**14**, **19**, **20**, **25**, **26**, **32**, and **34**) had IC_{50} values between 20 and 50 nM, of which seven analogues (**1**, **11**, **13**, **14**, **20**, **25**, and **26**) had selectivity indices above 1000. Four derivatives (**3**, **24**, **29**, and **30**) were less potent, with IC_{50} values between 50 and 100 nM. Overall, 15 compounds (**1**, **2**, **4**, **8**, **9**, **11**, **13**, **14**, **16**, **20**−**23**, **25**, and **26**) exhibited IC_{50} values below 50 nM and selectivity indices above 1000.

The group of 21 compounds with IC_{50} values below 50 nM includes 13 simple amidines (10 terphenyl and three dipyridylbenzene derivatives), five *N*-alkylamidines, and three AIA analogues. In contrast to the structural requirements for antitrypanosomal activity, antiplasmodial potency was less dependent on the positions of the cationic groups and was enhanced by alkylation of the amidine nitrogen atoms. The regioisomeric diamidines **1**, **13**, and **21** lacking central ring substituents showed rather small differences in potency (IC_{50} values of 24, 38, and 15 nM, respectively) but with activity favored by at least one cation in the para position. The chloro analogue **22** (a derivative of **21**) was the most potent of the terphenyl simple diamidines (IC_{50} = 10 nM).

The DMTHP derivatives **4**, **9**, and **16** (IC_{50} values of 2, 3, and 6 nM, respectively, and SI > 45 000 for **4** and **9**) were the most potent terphenyl *N*-alkyldiamidines, accounting for three of the four most potent and the three most highly selective analogues overall. They were also highly specific for this parasite, being 70−230 times more potent against *P. falciparum* compared to *T. b. rhodesiense*. The *N*-isopropylamidines **2** and **14** (IC_{50} of 16 and 31 nM, respectively, and SI > 4000 for each) also exhibited enhanced potencies and selectivities relative to corresponding amidines **1** and **13** and were the eighth and twelfth most potent overall. The imidazoline derivatives **3** and **15** (IC_{50} of 73 and 620 nM, respectively) were both less potent and less selective than the corresponding amidines **1** and **13**. Thus, diamidine **1** and its N-substituted derivatives **2**−**4** were all more potent than the corresponding 3,3″-isomers **13**−**16**.

The introduction of substituents on the central ring had varied effects upon activity, depending on the nature of the substituent and the position of the cationic groups. Both the potency and selectivity of the 4,4″-diamidine **1** were diminished by the presence of chloro, amino, and methoxy substituents on the central ring (derivatives **7**, **10**, and **12**). The nitro analogue **8** was slightly more potent than **1** with significantly enhanced selectivity. The potency of 3′3″-diamidine **13** was enhanced by a chloro or methoxy group on the central ring (analogues **19** and **20**), but selectivity was enhanced only in the latter instance. The potency of asymmetric diamidine **21** was enhanced, but its selectivity was diminished, by a chlorine atom on the central ring (derivative **22**).

The order of potencies of the four dipyridylbenzene diamidines was the same as that against *T. b. rhodesiense*. Analogues **23** (IC_{50} = 15 nM) and **25** (IC_{50} = 40 nM), each having both amidine groups positioned para to the central ring, were more potent than their respective counterparts **24** (IC_{50} = 58 nM) and **29** (IC_{50} = 77 nM) having two meta-amidine functions. Selectivity indices ranged from around 1500 for **23** to greater than 3500 for **25**. Acetate salt **26**, an alternative salt form of **25**, gave results similar to those of hydrochloride salt **25**. The difference in IC_{50} values between the most potent (**23**) and the least potent (**29**) analogues was just over 5-fold, compared to a nearly 200-fold differences in their IC_{50} values against *T. b. rhodesiense*.

The AIA derivatives, as a whole, were less potent and less selective compared to the amidine derivatives. The symmetric bis-pyridylimidamide **31** (IC_{50} = 6 nM, SI = 450) was the most potent AIA derivative and most selective for this parasite, followed by the asymmetric bis-phenylimidamides **32** and **34**, with IC_{50} values around 40 nM but selectivity indices below 100. These three compounds had the three lowest selectivity indices among the 21 compounds with IC_{50} values below 50 nM, despite the fact that analogue **31** was the third most potent overall. Congener **30** was the only other AIA derivative with an IC_{50} value below 100 nM.

L. amazonensis. Given that other AIAs have shown outstanding in vitro and promising in vivo antileishmanial activity in past work,[57,59,60,84] compounds **30**−**37** were assayed against *L. amazonensis* in the intracellular amastigote model.[82] The bis-pyridylamidamides **31**, **33**, and **35** were the three most potent compounds (in descending order). Analogue **31** (IC_{50} = 95 nM) was slightly more potent than amphotericin B (IC_{50} = 124 nM), while congener **33** (IC_{50} = 123 nM) showed comparable potency and derivative **35** (IC_{50} = 211 nM) showed lower potency. The IC_{50} values for the five mono- and bis-phenylimidamides ranged between 907 nM and 2.43 μM for

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bis-AIAs **32** and **30**, respectively. Thus, pyridylimidamide **31** and the corresponding phenyl analogue **30** were the most and least potent. For the relatively small number of compounds tested, the antileishmanial data are somewhat similar to anti-*T. cruzi* data. Bis-pyridylimidamides **31**, **33**, and **35** were the three most potent compounds (in descending order) against both parasites. However, the orders of activity of the phenylimidamides differed, without the clear distinction of potencies between mono- and bis-phenylimidamides, as observed against *T. cruzi*.

IN VIVO ACTIVITIES AND STRUCTURE–ACTIVITY RELATIONSHIPS

T. b. rhodesiense. Twenty compounds (including six prodrugs) were tested in mice infected with the *T. b. rhodesiense* strain STIB900 (Table 3).[85] The amidines and *N*-alkylamidines were given intraperitoneally (four daily doses of 5 mg/kg), while the prodrugs were given orally (four daily doses of 25 mg/kg). Mice that survived for 60 days after infection without showing a parasitemia relapse were considered as cured. This model is highly stringent, mimicking the acute stage of HAT, and the low doses applied allowed for the distinction of activities among the highly trypanocidal compounds. Pentamidine and furamidine attained 1/4 cures at 4 × 5 mg/kg ip, and any compound attaining a higher cure rate is considered to have enhanced activity in vivo.

Table 3. In Vivo Antiprotozoal Activity of Select *m*-Terphenyl and Dipyridylbenzene Derivatives[a]

compd	dose (mg/kg)[b]	route[c]	cured/infected[d]	MSD (days)[e]
1	4 × 5	ip	4/4	>60
	1 × 10	ip	4/4	>60
2	4 × 5	ip	0/4	13.5
3	4 × 5	ip	0/4	9.25
5	4 × 25	po	3/4	>51.25
6	4 × 25	po	1/4	>34.25
7	4 × 5	ip	0/4	15.25
8	4 × 5	ip	0/4	20
10	4 × 5	ip	0/4	>35
11	4 × 5	ip	1/4	>41.25
12	4 × 5	ip	2/4	>38
13	4 × 5	ip	0/4	18.5
17	4 × 25	po	0/4	7.25
18	4 × 25	po	0/4	17.75
20	4 × 5	ip	0/4	10
21	4 × 5	ip	0/4	34.75
23	4 × 5	ip	4/4	>60
	1 × 5	ip	4/4	>60
25	4 × 5	ip	4/4	>60
	1 × 10	ip	4/4	>60
26	4 × 5	ip	4/4	>60
27	4 × 25	po	2/4	>53.75
28	4 × 25	po	3/4	>52
MLSP[f]	4 × 5	ip	4/4	>60
FMD[g]	4 × 5	ip	1/4	>46
PMD[h]	4 × 5	ip	1/4	>38

[a]Female NMRI mice infected with *Trypanosoma brucei rhodesiense* (STIB900).[85] [b]Administration was once per day on 4 consecutive days for all compounds, and single doses for select compounds. [c]Route of administration: intraperitoneal (ip) or oral (po). [d]Mice that survived for 60 days after infection without showing a parasitemia relapse were considered as cured. [e]Mean survival days after infection. All mice were used to calculate the MSD (the relapsed mice and the cured mice, where MSD > 60 days). [f]Melarsoprol. [g]Furamidine. [h]Pentamidine.

Three diamidines, lead compound **1** and dipyridyl analogues **23** and **25**, each cured 4/4 infected mice at the 4 × 5 mg/kg ip regimen, exhibiting excellent cure rates comparable to that of melarsoprol. These three compounds also attained 4/4 cures in single doses of 10 mg/kg for diamidines **1** and **25** and 5 mg/kg for analogue **23**. Acetate salt **26**, a different salt form of **25**, also effected 4/4 cures at the 4 × 5 mg/kg regimen. Diamidines **12** and **11** cured 2/4 and 1/4 infected mice, respectively. Prodrugs of diamidines **1** and **25** demonstrated efficacy with the 4 × 25 mg/kg oral regimen. Compound **5**, the amidoxime derivative of **1**, cured 3/4 mice, while methamidoxime derivative **6** attained 1/4 cures. Compound **28**, the dimethylaminoacetoxy derivative of dipyridyl analogue **25**, cured 3/4 mice, and the methamidoxime derivative **27** attained 2/4 cures. Mean survival rates exceeded 50 days for prodrugs **5**, **27**, and **28**..

Two simple amidine moieties oriented para to the central ring, regardless of the presence or position of nitrogen atoms in the outer rings, were required for maximum efficacy in vivo (compounds **1**, **23**, and **25**). Among the terphenyl analogues, the introduction of alkyl substituents on the amidine nitrogen (**1** vs **2**, **1** vs **3**) or meta orientations of one or both amidine groups (**1** vs **13**, **1** vs **21**, **12** vs **20**) resulted in loss of efficacy. In these respects, a high correlation exists between potencies in vitro and efficacies in vivo. All analogues of diamidine **1** with substituents on the central ring were less effective in vivo. Derivatives **10**–**12** had potencies in vitro similar to that of the parent molecule, but the methoxy (**12**), hydroxy (**11**), and amino (**10**) analogues attained 2/4, 1/4, and 0/4 cures, respectively, but all with significantly prolonged mean survival times (exceeding 35 days) compared to untreated mice (10 days or less). The chloro and nitro derivatives **7** and **8**, which were less potent in vivo, cured no mice but with less prolonged survival times. In cases where prodrugs exist, the prodrugs reflected the efficacies of the parent amidines. Prodrugs of the highly effective amidines **1** and **25** demonstrated oral efficacy, as stated above. Neither amidine **13** nor its prodrugs (**17** and **18**) were effective in vivo.

L. donovani. On the basis of their in vitro antileishmanial efficacy and selectivity, compounds **31**, **33**, and **35** were selected for in vivo evaluation. These molecules were first tested in groups of two uninfected BALB/c mice at five daily doses of 30 mg/kg intraperitoneally to ensure that they were well tolerated in the animals prior to evaluation of in vivo antileishmanial efficacy in larger groups. Compounds **31** and **33** were toxic at this dose, with the animals displaying tremors and hyperactivity after the second and first doses, respectively. Mice were euthanized after these adverse effects were observed, and compounds **31** and **33** were not tested further in vivo. After no overt signs of toxicity were observed when compound **35** was given at 5 × 30 mg/kg ip, an in vivo antileishmanial efficacy test[82] was carried out with this compound. Unfortunately, only 23 ± 11% inhibition of liver parasitemia (mean ± standard deviation, n = 4) was observed when *L. donovani*-infected BALB/c mice were given compound **35** at 5 × 30 mg/kg ip. In the same experiment, miltefosine treatment of infected BALB/c mice at 5 × 10 mg/kg orally resulted in 96 ± 2% inhibition of liver parasitemia (n = 4).

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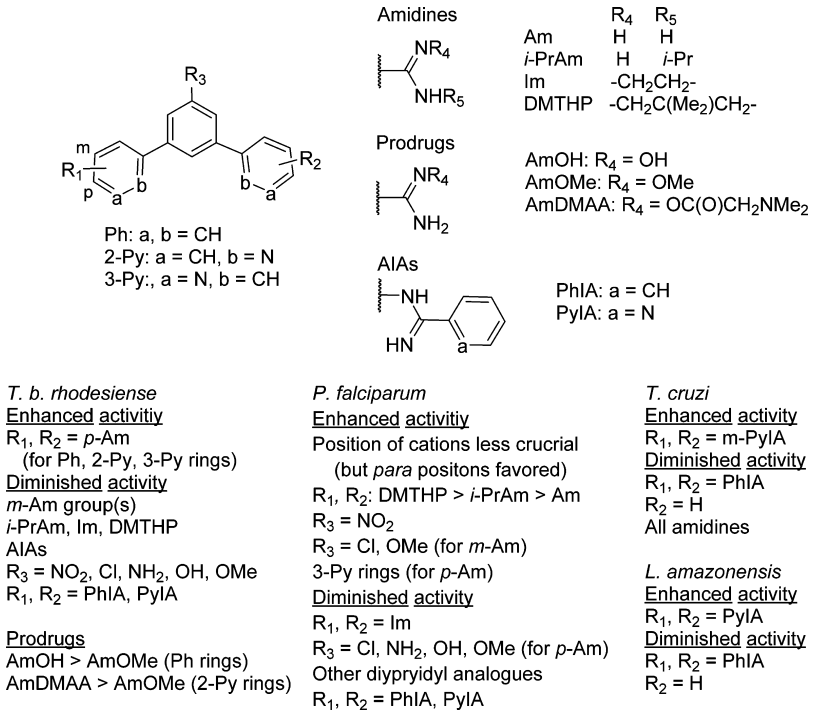

Figure 2. Summary of antiprotozoal SARs of *m*-terphenyl derivatives.

DISCUSSION

The *m*-terphenyl derivatives exhibited complementary SAR profiles against the four parasites, as summarized in Figure 2. In general, the amidine derivatives were more active against *T. b. rhodesiense* and *P. falciparum*, while the AIAs showed more promising results against the other parasites. The orientation of both amidine moieties para to the central ring, regardless of the presence or position of nitrogen atoms in the outer rings, was required for optimal activity against *T. b. rhodesiense*. Altered positions of the amidine groups, alkylation of the amidine nitrogen atoms, and substituents on the central ring all resulted in diminished activity either in vitro or in vivo. A general trend of diminished activities of *N*-alkyl analogues has been observed,[37,38,40,41,50,51,86,87] but the effects of substituents on the central or outer rings have varied from one class of compounds to another.[29,38,51] The insertion of nitrogen atoms into phenyl rings has resulted in retained or enhanced activity in the diphenylfuran and *p*-terphenyl analogues.[46,62,64,85] The replacement of a central furan ring with 1,3-phenylene was clearly beneficial with respect to the diamidine analogues but not for the prodrugs. Compound **1** attained 4/4 cures in the STIB900 acute model, compared to 1/4 cures for furamidine. Its similarly efficacious dipyridyl analogues **23** and **25** were also more active in vivo than the corresponding dipyridyl derivatives of furamidine.[46,85] Pafuramidine was more efficacious than the corresponding amidoxime[88] and has been one of few prodrugs to attain 4/4 cures in the STIB900 model at four daily 25 mg/kg oral doses.[85] By contrast, methamidoxime **6** (a prodrug of **1**) cured 1/4 mice under the same conditions, while the corresponding amidoxime **5** attained 3/4 cures. Methamidoxime **27** (a prodrug of **25**) and the di(pyridin-2-yl) analogue of pafuramidine[85] each cured 2/4 mice. Another prodrug of **25**, dimethylaminoacetoxy derivative **28**, attained 3/4 cures.

Antiplasmodial activity was less dependent upon the position of the cationic groups (although still favored by at least one para cation) and was enhanced by alkylation of the amidine nitrogen atoms, especially in the DMTHP derivatives and to a lesser extent in the *N*-isopropyl analogues. The imidazoline derivatives, however, were less potent than the corresponding amidines. In other examples from this lab, the effect of N-alkylation has varied from one class of compounds to another.[36−38,50,51] The effects of substituents on the central ring varied with the nature of the substituents and the orientation of the cationic groups. Only one dipyridyl analogue, the bis(6-amidinopyridin-3-yl) derivative **23**, was more potent than the corresponding terphenyldiamidine.

The bis-pyridylimidamide **31** was unique in demonstrating activity against all four parasites in vitro. Despite its high potencies against *T. b. rhodesiense* and *P. falciparum*, it was much less selective for these parasites over mammalian cells compared to the amidine derivatives. This compound, having both cations in the meta position and a chlorine atom attached to the central ring, was also the most active against *T. cruzi* and *L. amazonensis*. The SAR of these compounds against *T. cruzi* was rather clearly defined: the bis-pyridylimidamides were the most potent, followed by the bis-phenylamidamides, the mono-AIAs, and the amidine derivatives. The bis-pyridylimidamides were also the most active against *L. amazonensis*; however, the IC_{50} values of the less potent bis-phenylamidamides and mono-AIAs overlapped, and the amidine derivatives were not tested in this model.

A large number of mechanisms of antimicrobial activity have been proposed for the diamidine class of molecules.[89−101] These positively charged molecules bind to many negatively charged surfaces and receptors and accordingly have numerous potential sites of action. The antimicrobial action of these compounds probably occurs at multiple sites, and the primary site of action may vary from organism to organism. This is a huge problem with regard to drug design but is advantageous with regard to the potential development of drug resistance. It has been suggested that the highly selective toxicity of many of the compounds in this class toward pathogenic organisms over

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mammalian cells is due to active transport mechanisms. For example, trypanosomes have a number of active transport systems that allow cationic molecules to be concentrated in the parasites at levels over 1000 times higher than in mammalian cells.[97] Thus, the only way to optimize these compounds for specific targets is via focused parallel synthesis and in vitro testing or focusing on the active transport systems. Unfortunately, not enough is known with regard to the specificities of the transporters to aid in the drug design process.

Because of the propensity of dications to bind to numerous sites, the toxicity of these molecules is always a concern with regard to drug design.[85,102−108] The nature of the toxicity does not appear class related but may vary from compound to compound. For instance, hypoglycemia is the major concern with regard to pentamidine,[104,106] while nephrotoxicity resulted in the cancellation of human clinical trials with pafuramine.[85] An obvious approach to decreasing host toxicity is to produce more potent compounds against the targeted organisms. However, even the most potent diamidine compounds must be subjected to a battery of toxicity tests.

A number of the *m*-terphenyl analogues, as well as diamidine derivatives of other classes of compounds,[36−41,50,51] have shown high potencies against *P. falciparum* in vitro. However, the lack of a reliable animal model has been a major obstacle in their further development against malaria. Standard rodent models, which must use *Plasmodium* species that are nonpathogenic to humans due to the high specificity of *P. falciparum* for human erythrocytes, do not necessarily predict the efficacy of a given drug in human malaria,[109] and their relevance to human malaria has been questioned.[110,111] For example, pafuramidine, which is known to be effective in human malaria,[33] was inactive in a commonly used *P. berghei* mouse model,[112] as were pentamidine and other analogues of furamidine.[29,56,112] Murine *P. falciparum* models employing immunodeficent mice engrafted with human erythrocytes or hepatocytes (humanized mice)[110,112−114] should more accurately predict the efficacies of new therapies in human malaria, although they are generally more costly and more difficult to handle than standard rodent models.[114] These models may be useful in determining which standard rodent model offers better correlation with *P. falciparum* for given compounds; for example, one study suggested that *P. vinckei* may be a better surrogate than *P. berghei* for diamidines.[112] These findings may provide at least a starting point in the further evaluation of other diamidines.

CONCLUSIONS

This communication describes several novel diamidine derivatives that show excellent in vitro potency against *T. b. rhodesiense*, are curative in a mouse model of early stage HAT, and have the potential for reduced toxicity when compared to the prototype molecule furamidine. Most outstanding were diamidines **1**, **23**, and **25**, which attained 4/4 cures not only in four daily intraperitoneal doses of 5 mg/kg but also in single doses of 10 mg/kg or lower. Prodrugs of compounds **1** and **25** (derivatives **5** and **28**) also attained 3/4 cure rates in this model with four daily 25 mg/kg oral doses. Further evaluations of these compounds against other *T. brucei* strains and a mouse model of late stage HAT are in progress. A number of compounds, most significantly the DMTHP derivatives **4**, **9**, and **16**, showed promising antiplasmodial potencies in vitro and merit in vivo evaluation, contingent upon the selection of appropriate animal models. Although these compounds, as a class, did not show promising results against *T. cruzi*, AIA derivative **31** proved to be 25 times more potent than the clinical standard benznidazole and thus warrants further evaluation against this parasite.

EXPERIMENTAL SECTION

General Experimental Methods. In vitro antiprotozoal activities against *T. b. rhodesiense* (STIB900), *T. cruzi* (Tulahuen C2C4), *P. falciparum* (chloroquine resistant K1),[83] and *L. amazonensis* intracellular amastigotes,[82] cytotoxicities against L6 rat myoblast cells,[83] and in vivo activities against *T. b. rhodesiense* (STIB900)[85] and *L. donovani* (LV82)[82] were measured following established protocols. All protocols and procedures used in the current study were reviewed and approved by the local veterinary authorities of the Canton Basel-Stadt, Switzerland, or the Institutional Animal Care and Use Committee at The Ohio State University. The data in the *T. b. rhodesiense* model were generated at the time when the determination of survival was still accepted by the authorities.

Uncorrected melting points were measured on a Thomas-Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian Gemini 2000 or Unity Plus 300 MHz spectrometer or a Varian Inova 400 MHz spectrometer. Spectra were recorded at 300 MHz unless the higher field strength is specified. ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Unity Plus operating at 75 MHz. Anhydrous EtOH was distilled over Mg/I_2 immediately prior to use. Other anhydrous solvents were purchased from Aldrich Chemical Co., Milwaukee, WI, in Sure-seal containers and were used without further purification. Reaction mixtures were monitored by TLC on silica gel or by reverse phase HPLC. Organic layers of extraction mixtures were neutralized as necessary with acidic or basic washes, washed with saturated NaCl solution, and dried over $MgSO_4$ or Na_2SO_4 before being evaporated under reduced pressure. Normal phase gravity and flash column chromatography were performed using Davisil grade 633, type 60A silica gel (200−425 mesh). Reverse phase flash chromatography was performed as previously described.[41] Analytical HPLC chromatograms were recorded on a Hewlett-Packard 1090 series II or Agilent 1200 chromatograph using a Zorbax Rx C8 column (4.6 mm × 75 mm, 3.5 μm) maintained at 40 °C and UV photodiode array detection at 230, 254, 265, 290, and 320 nm. Area % values are reported at the wavelengths where the strongest signals of the products were observed. Mobile phases consisted of mixtures of acetonitrile (0−75%) or methanol (0−95%) in water containing formic acid (80 mM), ammonium formate (20 mM), and triethylamine (15 mM). Samples were eluted at appropriate gradients at a flow rate of 1.5 mL/min. Similar analyses were performed on a Hewlett-Packard 1100 system using a Zorbax SB C8 column (3.0 mm × 100 mm, 3.5 μm), eluting at 0.6 mL/min. Preparative reverse phase HPLC was performed on a Varian ProStar chromatography workstation configured with two PS-215 pumps fitted with 50 mL pump heads, a Dynamax Microsorb C18 (60 Å) column (41.4 cm × 25 cm, 8 μm), PS-320 variable wavelength UV−vis detector, and a PS-701 fraction collector. Mobile phases consisted of mixtures of acetonitrile (0−75%) or methanol (0−95%) in water containing formic acid (40 mM) and ammonium formate (10 mM). Flow rates were maintained at 40 mL/min. Select fractions were analyzed for purity by analytical HPLC as described above. Pooled purified fractions were evaporated under reduced pressure, reconstituted in water, and lyophilized on a VirTis BenchTop 2K or 6K lyophilizer. Low resolution ESI mass spectra were recorded on an Agilent Technologies 1100 series LC/MSD trap mass spectrometer or a VG analytical 70-SE spectrometer. Elemental analyses were performed by Atlantic Microlab, Norcross, GA, and, unless stated otherwise, were within ±0.4% of calculated values. CHN analyses were performed by combustion using a Perkin-Elmer 2400 or Carlo Erba 1108 automatic analyzer. Chlorine analyses were performed by flask combustion followed by ion chromatography. The compounds reported as salts were frequently analyzed correctly for fractional moles of water and/or other solvents; in each case ^{1}H NMR spectra

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were consistent with the analysis. The purity of all final compounds was determined to be ≥95% by combustion analysis.

General Procedure for Amidines 1−4, 7−9, 12−16, and 19−21. The nitrile was added to a mixture of anhydrous EtOH and 1,4-dioxane that had been saturated with hydrogen chloride at 0 °C in a dry three-neck flask equipped with a gas inlet tube, a thermometer, and a drying tube. The reaction mixture was then sealed and stirred at ambient temperature until the nitrile was no longer detectable. The reaction mixture was diluted with ether. The crude imidate was filtered off, dried under high vacuum over KOH, and then reacted immediately with an excess of ammonia or the appropriate amine in EtOH. The reaction mixture was diluted with ether, and the crude product was filtered off. The product was purified by direct recrystallization or by reverse phase HPLC or flash chromatography followed by conversion to the dihydrochloride salt using aqueous or ethanolic HCl.

4,4″-Diamidino-*m*-terphenyl Dihydrochloride (1). **1** was prepared from nitrile **43** (0.56 g, 2.01 mmol) with ammonium carbonate used in place of ammonia. After purification by preparative HPLC, the product was recrystallized from ethanolic HCl−ether to give a white solid (346 mg, 44%): mp >350 °C; ^{1}H NMR δ 9.50 (br s, 3H), 9.24 (br s, 3H), 8.14 (t, J = 1.6 Hz, 1H), 8.10 (d, J = 8.7 Hz, 4H), 7.99 (d, J = 8.2 Hz, 4H), 7.87 (dd, J = 7.7 and 1.6 Hz, 2H), 7.68 (t, J = 7.7 Hz, 1H); ESI MS m/z 315.1 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{18}N_4$·2HCl·0.7H_2O) C, H, N, Cl.

4,4″-Bis(*N*-isopropyl)amidino-*m*-terphenyl Dihydrochloride (2). **2** was prepared from nitrile **43** and isopropylamine. The product was purified by reverse phase flash chromatography and recrystallized from aqueous HCl to give a solid (690 mg, 61%): mp 253−254 °C; ^{1}H NMR δ 9.69 (d, J = 8.2 Hz, 2H), 9.57 (br s, 2 H), 9.21 (br s, 2H), 8.07 (m, 5H), 7.86 (m, 6H), 7.69 (t, J = 7.8 Hz, 1H), 4.13 (m, 2H), 1.31 (d, J = 6.4 Hz, 12H); ESI MS m/z 399.2 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{26}H_{30}N_4$·2HCl·1.4H_2O) C, H, N, Cl.

4,4″-Bis(imidazolin-2-yl)-*m*-terphenyl Dihydrochloride (3). **3** was prepared from nitrile **43** and ethylenediamine. The crude precipitated product was recrystallized from aqueous HCl to give a white solid (1.26g, 79%): mp >250 °C (dec); ^{1}H NMR δ 10.90 (br s, 3H), 8.22 (m, 5H), 8.16 (d, J = 8.7 Hz, 4H), 7.91 (dd, J = 7.8 and 1.7 Hz, 2H), 7.68 (t, J = 7.8 Hz, 1H), 4.04 (s, 8H); ESI MS m/z 367.2 ([M + H]$^+$ of free base); HPLC 99.0 area %. Anal. ($C_{24}H_{22}N_4$·2HCl·2.8H_2O) C, H, N, Cl.

4,4″-Bis[(5,5-dimethyl)-1,4,5,6-tetrahydropyrimidin-2-yl]-*m*-terphenyl Dihydrochloride (4). **4** was prepared from nitrile **43** (961 mg, 3.43 mmol) and 2,2-dimethylpropane-1,3-diamine. The product was recrystallized from aqueous HCl to give white granules (1.33 g, 74%): mp >350 °C (dec); ^{1}H NMR δ 10.39 br s, 3H), 8.14 (t, J = 1.7 Hz, 1H), 8.11 (d, J = 8.6 Hz, 4H), 7.97 (d, J = 8.6 Hz, 4H), 7.87 (dd, J = 7.7 and 1.6 Hz, 2H), 7.68 (t, J = 7.8 Hz, 1H), 3.24 (s, 8H), 1.07 (s, 12H); ESI MS m/z 451.2 ([M + H]$^+$ of free base); HPLC 99.0 area %. Anal. ($C_{30}H_{34}N_4$·2HCl·1.25H_2O) C, H, N, Cl.

4,4″-Bis(*N*′-hydroxy)amidino-*m*-terphenyl Dihydrochloride (5). Potassium *tert*-butoxide (8.42 g, 75.0 mmol) was added to a stirred solution of hydroxylamine hydrochloride (5.25 g, 75.6 mmol) in dry DMSO (45 mL). After 30 min nitrile **43** (2.11 g, 7.52 mmol) was added, and the mixture was stirred overnight. The reaction mixture was poured over ice−water, and the precipitated amidoxime base was filtered off (2.05 g, 79%): mp >215 °C (dec); ^{1}H NMR δ 9.71 (br s, 2H), 7.98 (s, 1H), 7.80 (s, 8H), 7.71 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.7 Hz, 1H), 5.89 (br s, 4 H); HPLC 100 area %. Anal. ($C_{20}H_{18}N_4O_2$·0.1H_2O) C, H, N.

An aliquot of the base (478 mg, 1.38 mmol) was recrystallized from aqueous HCl to give a white solid (221 mg, 38%): mp >260° (dec); ^{1}H NMR δ 11.33 (br s, 2H), 9.16 (br s, 4H), 8.11 (s, 1H), 8.08 (d, J = 8.5 Hz, 4H), 7.87 (m, 6H), 7.67 (t, J = 7.7 Hz, 1H); ESI MS m/z 347.2 ([M + H]$^+$ of free base); HPLC 99 area %. Anal. ($C_{20}H_{18}N_4O_2$·2HCl) C, H, N, Cl.

4,4″-Bis(*N*′-methoxy)amidino-*m*-terphenyl Dihydrochloride (6). A mixture of amidoxime base **5** (1.56 g, 4.49 mmol) and potassium *tert*-butoxide (1.07 g, 9.53 mmol) in DMSO (20 mL) was stirred for 2 h followed by the addition of iodomethane (0.9 mL, 14 mmol). The reaction mixture was stirred overnight and poured over ice. The precipitated crude product was chromatographed on silica, eluting with $CHCl_3$/MeOH (20:1) and recrystallized twice from MeOH−H_2O to give white crystals (532 mg, 32%): mp 141−142 °C; ^{1}H NMR δ 8.04 (s, 1H), 7.96 (d, J = 8.3 Hz, 4H), 7.86 (d, J = 8.4 Hz, 4H), 7.79 (dd, J = 7.7 and 1.6 Hz, 2H), 7.03 (t, J = 8.1 Hz, 2H), 3.48 (s, 6H). Anal. ($C_{22}H_{22}N_4O_2$) C, H, N.

The base was converted to the HCl salt using aqueous HCl to give a white solid (570 mg, 87% from salt conversion, 28% from the amidoxime): mp 192 °C (dec); ^{1}H NMR δ 8.08 (m,1H), 8.01 (d, J = 8.5 Hz, 4H), 7.46 (d, J = 8.5 Hz, 4H), 7.82 (dd, J = 7.6 and 1.6 Hz, 2H), 7.65 (t, J = 7.7 Hz, 1H), 3.87 (s, 6H); ESI MS m/z 375.5 ([M + H]$^+$ of free base); HPLC 99 area %. Anal. ($C_{22}H_{22}N_4O_2$·1.95HCl·1.3H_2O) C, H, N.

4,4″-Diamidino-5′-chloro-*m*-terphenyl Dihydrochloride (7). **7** was prepared from nitrile **44** (1.03 g, 3.28 mmol). The product was purified by reverse phase flash chromatography and converted to the HCl salt using aqueous HCl to give a solid (532 mg, 53%): mp >250 °C (dec); ^{1}H NMR δ 9.52 (br s, 4H), 9.27 (br s, 4H), 8.16 (d, J = 8.5 Hz, 4H), 8.12 (t, J = 1.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 4H), 7.96 (d, J = 1.5 Hz, 2H); ESI MS m/z 349.2 ([M + H]$^+$ of free base); HPLC 99.4 area %. Anal. ($C_{20}H_{17}ClN_4$·2HCl·2.3H_2O) C, H, N, Cl.

4,4″-Diamidino-5′-nitro-*m*-terphenyl Dihydrochloride (8). **8** was prepared from nitrile **45** (1.64 g, 5.03 mmol). The product was purified by reverse phase flash chromatography and converted to the HCl salt using aqueous HCl to give a solid (929 mg, 42%): mp >350 °C (dec); ^{1}H NMR δ 9.58 (br s, 4H), 9.34 (br s, 4H), 8.62 (d, J = 1.5 Hz, 2H), 8.59 (t, J = 1.6 Hz, 1H), 8.25 (d, J = 8.6 Hz, 4H), 8.05 (d, J = 8.5 Hz, 4H); ESI MS m/z 360.1 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{17}N_5O_2$·2.2HCl·1.9H_2O) C, H, N, Cl.

4,4″-Bis[(5,5-dimethyl)-1,4,5,6-tetrahydropyrimidin-2-yl]-5′-nitro-*m*-terphenyl Dihydrochloride (9). **9** was prepared analogously to **4** from nitrile **45** (1.66 g, 5.11 mmol), but the imidate intermediate was prepared in neat ethanolic HCl. The product was purified by preparative HPLC and converted to the HCl salt using ethanol HCl and ether to give an off-white solid (1.37g, 47%): mp >389 °C (dec); ^{1}H NMR δ 10.70 (br s, 4H), 8.61 (m, 3H), 8.27 (d, J = 8.5 Hz, 4H), 8.01 (d, J = 8.6 Hz, 4H), 3.25 (s, 8H), 1.08 (s, 12H); ESI MS m/z 496.4 ([M + H]$^+$ of free base); HPLC 99.0 area %. Anal. ($C_{30}H_{33}N_5O_2$·2HCl·H_2O) C, H, N, Cl.

4,4″-Diamidino-5′-amino-*m*-terphenyl Dihydrochloride (10). Nitro compound **8** (0.536 g, 1.24 mmol) was hydrogenated for 3 h at 60 psi over 10% Pd/C (90 mg, 0.055 mmol) in EtOH/H_2O (2:1, 150 mL). The reaction mixture was filtered through Celite and evaporated to a white solid. The product was recrystallized from EtOH−H_2O to give white crystals (401 mg, 80%): mp >250 °C (dec); ^{1}H NMR δ 9.48 (br s, 4H), 9.25 (br s, 4H), 7.97 (d, J = 9.1 Hz, 4H), 7.93 (d, J = 9.1 Hz, 4H), 7.22 (t, J = 1.5 Hz, 1H), 7.01 (t, J = 1.5 Hz, 2H), 5.53 (br s, 2H); ESI MS m/z 330.2 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{19}N_5$·2HCl·2.7H_2O) C, H, N, Cl.

4,4″-Diamidino-5′-hydroxy-*m*-terphenyl Dihydrochloride (11). Dinitrile **46** (0.77 g, 2.6 mmol) was converted to 4,4″-bis(*N*′-hydroxy)amidino-5′-hydroxy *m*-terphenyl (free base) in 99% yield following the procedure for compound **5**: mp 160−163 °C; ^{1}H NMR δ 9.68 (br s, 3H), 7.76 (d, J = 9 Hz, 4H), 7.69 (d, J = 9 Hz, 4H), 7.37 (s, 1H), 7.05 (s, 2H), 5.84 (br s, 4H); ^{13}C NMR δ 158.4, 151.5, 141.5, 141.0, 131.6, 126.6, 126.2, 116.2, 112.9; MS (ESI) m/z 363 ([M + H]$^+$).

To a solution of the diamidoxime (0.36 g, 1 mmol) in glacial acetic acid (10 mL) was slowly added acetic anhydride (0.35 mL). After stirring overnight, the solvent was evaporated to dryness under reduced pressure and the oily residue obtained was used without further purification, where it was dissolved in absolute ethanol (25 mL) and glacial AcOH (10 mL) followed by addition of 10% palladium on carbon (80 mg). The mixture was hydrogenated on a Parr apparatus at 50 psi for 4 h at room temperature. The mixture was filtered through a filter aid and the filter pad washed with water. The filtrate was evaporated under reduced pressure and the residue was collected and washed with ether to give **11** as an acetate salt. The diamidine was purified by neutralization with Na_2CO_3 followed by filtration of the resultant solid and washing with water (3×). Finally,

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the free base was stirred with ethanolic HCl overnight, diluted with ether, and the solid formed was filtered and dried to give the diamidine hydrochloride salt **11** (77%): mp >300 °C; ^{1}H NMR δ 10.12 (br s, 1H), 9.48 (br s, 4H), 9.26 (br s, 4H), 7.98 (d, J = 9 Hz, 4H), 7.95 (d, J = 9 Hz, 4H), 7.52 (s, 1H), 7.23 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 165.19, 158.7, 145.1, 140.6, 128.8, 127.3, 126.9, 116.8, 114.2. HRMS calcd for $C_{20}H_{19}N_4O$ m/z 331.1559 ([M + H]$^+$ for free base); observed 331.1564. Anal. ($C_{20}H_{18}N_4O$·2.0HCl·0.8H_2O·0.5EtOH) C, H, N.

4,4″-Diamidino-5′-methoxy-*m*-terphenyl Dihydrochloride (12). **12** was prepared from nitrile **47** (1.01 g, 3.22 mmol). The product was purified by reverse phase flash chromatography and converted to the HCl salt using aqueous HCl to give a gray solid (960 mg, 71%): mp >225 °C (dec); ^{1}H NMR δ 9.51 (br s, 4H), 9.28 (br s, 4H), 8.11 (d, J = 8.5 Hz, 4H), 7.99 (d, J = 8.5 Hz, 4H), 7.71 (m, 1H), 7.40 (d, J = 1.3 Hz, 2H), 3.95 (s, 3H); ESI MS m/z 345.2 ([M + H]$^+$ of free base); HPLC 98.4 area %. Anal. ($C_{21}H_{20}N_4O$·2HCl·1.6H_2O) C, H, N, Cl.

3,3″-Diamidino-*m*-terphenyl Dihydrochloride (13). **13** was prepared from nitrile **48** (1.01 g, 3.60 mmol). The product was purified by preparative HPLC and converted to the HCl salt using aqueous HCl to give a solid (716 mg, 51%): mp >350 °C; ^{1}H NMR δ 9.69 (br s, 4H), 9.34 (br s, 4H), 8.48 (s, 1H), (8.37, s, 2H), 8.18 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 7.8 Hz, 4H), 7.75 (t, J = 7.8 Hz, 2H), 7.67 (t, J = 2.8 Hz, 1H); ESI MS m/z 315.3 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{18}N_4$·2HCl·0.6H_2O) C, H, N, Cl.

3,3″-Bis(*N*-isopropyl)amidino-*m*-terphenyl Dihydrochloride (14). An aliquot (0.95 g 2.13 mmol) of the imidate intermediate prepared from nitrile **48** was reacted with isopropylamine and purified analogously to **2** as a white solid (681 mg, 68%): mp >240 °C (dec); ^{1}H NMR δ 9.83 (d, J = 8.0 Hz, 2H), 9.68 (br s, 2H), 9.22 (br s, 2H), 8.50 (s, 1H), (8.23, s, 2H), 8.13 (d, J = 7.4 Hz, 2H), 7.86 (dd, J = 7.5 and 1.5 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.73 (t, J = 7.6 Hz, 2H), 7.67 (t, J = 7.7 Hz, 1H), 4.13 (m, 1H), 1.33 (d, J = 6.4 Hz, 12H); ESI MS m/z 398.3 ([M + H]$^+$ of free base); HPLC 98.7 area %. Anal. ($C_{26}H_{30}N_4$·2HCl·1.2H_2O) C, H, N, Cl.

3,3″-Bis(imidazolin-2-yl)-*m*-terphenyl Dihydrochloride (15). **15** was prepared from an aliquot of the imidate above (0.99 g, 2.22 mmol) and ethylenediamine. The product was purified by reverse phase flash chromatography and then converted to the HCl salt using ethanolic HCl–ether to give a white solid (775 mg, 79%): mp 325–327 °C (dec); ^{1}H NMR δ 11.04 (br s, 3H), 8.75 (s, 2H), 8.43 (s, 1H), 8.26 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 7.9 Hz, 2H), 7.90 (dd, J = 7.5 and 1.5 Hz, 2H), 7.78 (t, J = 7.9 Hz, 2H), 7.67 (t, J = 7.8 Hz, 1H), 4.05 (s, 8H); ESI MS m/z 367.4 ([M + H]$^+$ of free base); HPLC 99.5 area %. Anal. ($C_{24}H_{22}N_4$·2HCl·1.6H_2O) C, H, N, Cl.

3,3″-Bis[(5,5-dimethyl)-1,4,5,6-tetrahydropyrimidin-2-yl]-*m*-terphenyl Dihydrochloride (16). **16** was prepared from nitrile **48** (1.02 g, 3.64 mmol) and 2,2-dimethylpropane-1,3-diamine. After purification by preparative HPLC, the crude HCl salt (prepared using aqueous HCl) was dissolved in water and treated with aqueous NaOH to precipitate the free base. This was converted to the HCl salt using a mixture of ethanolic HCl, dioxane, and ether to give a white solid (671 mg, 35%): mp >335 °C (dec); ^{1}H NMR δ 10.51 (br s, 4H), 8.58 (s, 1H), 8.37 (s, 2H), 8.16 (d, J = 8.0 Hz, 2H), 7.88 (dd, J = 8.7 and 1.6 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.75 (t, J = 7.8 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H), 3.52 (s, 8H), 1.07 (s, 12H); ESI MS m/z 451.3 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{30}H_{34}N_4$·2.3HCl·0.55H_2O) C, H, N, Cl.

3,3″-Bis(*N*′-hydroxy)amidino-*m*-terphenyl Dihydrochloride (17). **17** was prepared following the procedure for amidoxime **5** from nitrile **48** (2.81 g, 10.0 mmol). The amidoxime base was recrystallized from EtOH to give white crystals (3.57 g, 103%): mp 212–213 °C; ^{1}H NMR δ 9.70 (br s, 2H), 8.03 (t, J = 1.6 Hz, 2H), 8.01 (t, J = 1.5 Hz, 1H), 7.78 (dm, J = 7.7 Hz, 2H), 7.73 (m, 2H), 7.71 (m, 2H), 7.60 (dd, J = 8.4 and 7.9 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 5.98 (br s, 4H). Anal. ($C_{20}H_{18}N_4O_2$·0.9EtOH.) C, H, N.

An aliquot of the base (511 mg, 1.27 mmol) was converted to the HCl salt using ethanolic HCl–ether to give a white solid (546 mg, 88%): mp >110 °C (dec); ^{1}H NMR δ 11.32 (br s, 2H), 9.14 (br s, 4H), 8.33 (s, 1H), 8.21 (s, 2H), 8.14 (d, J = 7.5 Hz, 2H), 7.87 (dd, J = 7.7 and 1.6 Hz, 2H), 7.78 (dm, J = 7.8 Hz, 2H), 7.73 (t, J = 7.7 Hz, 2H), 7.67 (t, J = 7.8 Hz, 1H); ESI MS m/z 347.2 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{18}N_4O_2$·2HCl·0.7H_2O·0.8EtOH) C, H, N, Cl.

3,3″-Bis(*N*′-methoxy)amidino-*m*-terphenyl Dihydrochloride (18). **18** was prepared from amidoxime base **17** either by the method employed for compound **6** or using dimethyl sulfate and aqueous NaOH in dioxane. The combined products from multiple experiments were chromatographed on silica, eluting with hexanes/EtOAc (2:1) and converted to the HCl salt using ethanolic HCl–ether to give a white solid (1.69 g, 88% from salt conversion, 21% from amidoxime): mp 235–237 °C (dec); ^{1}H NMR δ 8.78 (br s, 2H), 8.34 (s, 1H), 8.24 (s, 2H), 8.09 (d, J = 8.0 Hz, 2H), 7.85 (dd, J = 7.7 and 1.6 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.67 (m, 3H), 3.89 (s, 6H); ESI MS m/z 375.2 ([M + H]$^+$ of free base); HPLC 98.4 area %. Anal. ($C_{22}H_{22}N_4O_2$·2HCl·0.3H_2O) C, H, N, Cl.

3,3″-Diamidino-5′-chloro-*m*-terphenyl Dihydrochloride (19). **19** was prepared from nitrile **49** (973 mg, 3.09 mmol). The product was purified by reverse phase flash chromatography and converted to the HCl salt using aqueous HCl to give a white solid (469 mg, 26%): mp >350 °C; ^{1}H NMR δ 9.65 (br s, 4H), 9.32 (br s, 4H), 8.42 (s, 1H), 8.36 (s, 2H), 8.23 (d, J = 7.9 Hz, 2H), 7.99 (d, J = 1.4 Hz, 2H), 7.91 (d, J = 7.9 Hz, 2H), 7.76 (t, J = 7.8 Hz, 2H); ESI MS m/z 349.2 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{17}ClN_4$·2HCl·0.75H_2O) C, H, N, Cl.

3,3″-Diamidino-5′-methoxy-*m*-terphenyl Dihydrochloride (20). **20** was prepared from nitrile **50** (1.00 g, 3.23 mmol). The product was purified by reverse phase flash chromatography and converted to the HCl salt using aqueous HCl to give a light gray solid (990 mg, 73%): mp >325 °C; ^{1}H NMR δ 9.64 (br s, 4H), 9.27 (br s, 4H), 8.32 (s, 2H), 8.18 (d, J = 7.8 Hz, 2H), 7.97 (s, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.74 (t, J = 7.8 Hz, 2H), 7.44 (d, J = 1.2 Hz, 2H), 3.95 (s, 3H); ESI MS m/z 345.2 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{21}H_{20}N_4O$·2HCl·1.3H_2O) C, H, N, Cl.

3,4″-Diamidino-*m*-terphenyl Dihydrochloride (21). **21** was prepared from nitrile **55** (1.00 g, 3.58 mmol). The crude product was recrystallized from aqueous HCl to give a white solid (1.18 g, 85%): mp >220 °C (dec); ^{1}H NMR δ 9.61 (br s, 2H), 9.52 (br s, 2H), 9.32 (br s, 2H), 9.27 (br s, 2H), 8.29 (m, 1H), 8.23 (m, 1H), 8.18 (dm, J = 8.0 Hz, 1H), 8.12 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 8.7 Hz, 2H), 7.89 (m,3H), 7.75 (t, J = 7.8 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H); ESI MS m/z 315.1 ([M + H]$^+$ of free base); HPLC 97.5 area %. Anal. ($C_{20}H_{18}N_4$·2HCl·1.8H_2O) C, H, N, Cl.

3,4″-Diamidino-5′-chloro-*m*-terphenyl Dihydrochloride (22). Lithium bis(trimethylsilyl)amide (1 M solution in THF, 10 mL, 10 mmol) was added dropwise to a suspension of nitrile (1.00 g, 3.18 mmol) in dry THF (15 mL). The mixture was stirred overnight and then cooled to 0 °C (ice–salt bath) before the slow addition of saturated ethanolic HCl. After 2 h the stirred solution was diluted with ether to precipitate the crude product, which was purified by preparative HPLC. Conversion to the HCl salt using EtOH–aqueous HCl followed by recrystallization from water–acetone gave a white powder (750 mg, 56%): mp >260 °C (dec); ^{1}H NMR δ 9.50 (br s, 4H), 9.27 (br s, 4H), 8.30 (m, 1H), 8.23 (dm, J = 8.1 Hz, 1H), 8.20 (t, J = 1.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 2H), 8.00 (m, 3H), 7.95 (t, J = 1.7 Hz, 1H), 7.90 (dm, J = 8.3 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H); ESI MS m/z 349.1 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{20}H_{17}ClN_4$·2HCl·1.75H_2O) C, H, N, Cl.

General Procedure for 1,3-Dipyridylbenzenediamidines 23–25 and 29. A solution of the amidoxime (3–5 mmol) in acetic acid was treated with acetic anhydride (5 mL), giving a precipitate. The mixture was transferred to a hydrogenation bottle, and more AcOH and 10% Pd/C (10–20 mol %) were added. The mixture was hydrogenated at 60 psi until completion and filtered through Celite. The product was purified by preparative HPLC and converted to the HCl salt using aqueous HCl unless stated otherwise.

1,3-Bis(6-amidinopyridin-3-yl)benzene Dihydrochloride (23). **23** was prepared from amidoxime **63** (1.28 g, 3.65 mmol) as a white solid (668 mg, 47%): mp 342–343 °C; ^{1}H NMR δ 9.71 (br s,

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4H), 9.50 (br s, 4H), 9.31 (d, J = 2.2 Hz, 2H), 8.68 (dd, J = 8.4 and 2.3 Hz, 2H), 8.52 (d, J = 8.4 Hz, 2H), 8.38 (m, 1H), 8.05 (dd, J = 7.8 and 1.7 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H); ESI MS m/z 317.1 ($[M + H]^+$ of free base); HPLC 100 area %. Anal. ($C_{18}H_{16}N_6 \cdot 2HCl \cdot 1.5H_2O$) C, H, N, Cl.

1,3-Bis(5-amidinopyridin-3-yl)benzene Trihydrochloride (24). **24** was prepared from amidoxime **64** (1.04 g, 2.97 mmol) as a white solid (542 mg, 42%): mp >300 °C; ^{1}H NMR δ 9.79 (br s, 4H), 9.42 (br s, 4H), 9.38 (d, J = 2.1 Hz, 2H), 9.04 (d, J = 2.1 Hz, 2H), 8.78 (t, J = 2.1 Hz, 2H), 8.57 (m, 1H), 8.04 (dd, J = 7.7 and 1.7 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H); ESI MS m/z 317.1 ($[M + H]^+$ of free base); HPLC 97.5 area %. Anal. ($C_{18}H_{18}N_6 \cdot 2.8HC \cdot 0.8H_2O$) C, H, N, Cl.

1,3-Bis(5-amidinopyridin-2-yl)benzene Trihydrochloride (25). **25** was prepared from amidoxime **69** (1.17 g, 3.35 mmol). The product was converted to the HCl salt using ethanolic HCl−ether to give a white solid (992 mg, 76%): mp >350 °C; ^{1}H NMR δ 9.71 (br s, 4H), 9.41 (br s, 4H), 9.15 (t, J = 1.1 Hz, 2H), 9.01 (s, 1H), 8.44 (d, J = 8.5 Hz, 2H), 8.40 (dd, J = 8.7 and 2.0 Hz, 2H), 8.37 (dd, J = 7.8 and 1.8 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H); ESI MS m/z 317.1 ($[M + H]^+$ of free base); HPLC 100 area %. Anal. ($C_{18}H_{16}N_6 \cdot 3HCl \cdot 0.6H_2O$) C, H, N, Cl.

1,3-Bis(5-amidinopyridin-2-yl)benzene Diacetate 26). **26** was prepared and chromatographed analogously to **25** from amidoxime **69** (700 mg, 2.01 mmol). The product was converted to the free base using aqueous NaOH. A mixture of the free base in H_2O (20 mL) and AcOH (2 mL) was heated and filtered, and the filtrate was lyophilized to give the acetate salt (319 mg, 36%): mp >227−230 °C; ^{1}H NMR δ 10.24 (br s, 8H), 9.10 (d, J = 1.4 Hz, 2H), 8.96 (t, J = 1.5 Hz 1H), 8.33 (m. 6H), 7.73 (t, J = 7.8 Hz, 1H), 1.79 (s, 6H); ESI MS m/z 317.1 ($[M + H]^+$ of free base); HPLC 100 area %. Anal. ($C_{18}H_{18}N_6 \cdot 2.25CH_3CO_2H \cdot 2H_2O$) C, H, N, Cl.

1,3-Bis-(5-*N*′-methoxyamidinopyridin-2-yl)benzene Tetrahydrochloride 27. To a suspension of diamidoxime **69** (348 mg, 1.00 mmol) in DMF (10 mL) was added LiOH·H_2O (252 mg, 6.01 mmol, in 3 mL of H_2O) which was followed by dimethyl sulfate (630 mg, 4.99 mmol). The reaction mixture was stirred overnight, after which it was poured onto ice−water and the precipitate was filtered, washed with water, and dried to give the free base of **27** in 77% yield: mp 157−158 °C; ^{1}H NMR δ 8.96 (s, 2H), 8.84 (s, 1H), 8.09−8.22 (m, 6H), 7.63 (t, J = 7.8 Hz, 1H), 6.30 (br s, 4H), 3.78 (s, 6H); ^{13}C NMR δ 156.1, 149.0, 146.8, 138.6, 134.3, 129.4, 127.5, 127.1, 124.7, 119.8, 60.7.

The free base (200 mg, 0.53 nM) was converted to the tetrahydrochloride salt by stirring overnight in ethanol saturated with HCl(g) to yield a pale yellow solid (205 mg, 69%): mp 196−197.5 °C; MS m/z 377 ($[M + H]^+$ of free base). Anal. ($C_{20}H_{20}N_6O_2 \cdot 4.0$ HCl·1.1H_2O·0.5EtOH) C, H, N.

1,3-Bis[(5-[*N*′-dimethylaminoacetoxy]amidino)pyridin-2-yl]-benzene (28). To a stirred solution of diamidoxime **69** (348 mg, 1.00 mmol) and K_2CO_3 (966 mg, 7 mmol) in DMF (10 mL) was added dimethylaminoacetyl chloride hydrochloride (632 mg, 4 mmol). The reaction mixture was stirred overnight at room temperature and then poured onto brine solution. The precipitate was filtered, recrystallized from methanol to furnish **28** in a 79% yield: mp 156−157.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 2H), 8.90 (s, 1H), 8.19−8.25 (m, 6H), 7.66 (m, 1H), 7.05 (s, 4H), 3.39 (s, 4H), 2.30 (s, 12H); ^{13}C NMR (DMSO-d_6) δ 167.9, 157.2, 154.8, 147.6, 138.4, 135.6, 129.5, 127.9, 126.3, 125.0, 119.9, 58.2, 44.5; MS m/z 519 ($[M + H]^+$ of free base). HRMS calcd for $C_{26}H_{31}N_8O_4$ $[M + H]^+$ 519.2468; observed 519.2457. Anal. ($C_{26}H_{30}N_8O_4 \cdot 1.25H_2O$) C, H, N.

1,3-Bis(4-amidinopyryidin-2-yl)benzene Dihydrochloride (29). **29** was prepared by the general procedure from amidoxime **70** (2.19 g,5.34 mmol). The product was converted to the HCl salt using ethanolic HCl with a trace of water to give a pale pink solid (1.22 g, 59%): mp 309−310 °C; ^{1}H NMR δ 9.92 (br s, 4H), 9.59 (br s, 4H), 9.14 (s,1H), 9.00 (d, J = 5.1 Hz, 2H), 8.64 (s, 2H), 8.35 (dd, J = 8.7 and 1.7 Hz, 2H), 7.84 (dd, J = 5.1 and 1.6 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H); ESI MS m/z 317.1 ($[M + H]^+$ of free base); HPLC 97.7 area %. Anal. ($C_{18}H_{16}N_6 \cdot 2.4HCl \cdot 1.1H_2O$) C, H, N, Cl.

3,3″-Bis(benzimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (30). A solution of 5′-chloro-3,3″-diamino-*m*-terphenyl (**72**) in THF (30 mL) was added dropwise to a mixture of sodium bis(trimethylsilyl)amide (2 M solution in THF, 6.0 mL, 12.0 mmol) and THF (6.0 mL). The mixture was stirred for 20 min and then split into two portions.

To the first aliquot was added a solution of benzonitrile (0.75 mL, 7.3 mmol), and the mixture was stirred for 3 days. More sodium bis(trimethylsilyl)amide solution (3.0 mL, 6.0 mmol) was added, and the reaction mixture was stirred an additional 3 h before being poured over ice and extracted into CH_2Cl_2. The product was purified by preparative HPLC and lyophilized. A solution of the lyophilized product in EtOH, water, and 1 N HCl was evaporated, dissolved in hot water, filtered, and lyophilized to give the HCl salt as a white powder (682 mg, 42%): mp >200 °C (dec); ^{1}H NMR (400 MHz) δ 11.72 (br s, 2H), 9.95 (br s, 2H), 9.18 (br s, 2H), 8.07 (s, 1H), 8.02 (s, 2H), 7.97 (m, 6H), 7.89 (s, 2H), 7.80 (t, J = 7.4 Hz, 2H), 7.70 (m, 6H), 7.53 (d, J = 7.9 Hz, 2H); ESI MS m/z 501.3 ($[M + H]^+$ of free base); HPLC 98.8 area %. Anal. ($C_{32}H_{25}ClN_4 \cdot 2HCl \cdot 1.5H_2O$) C, H, N, Cl.

3,3″-Bis(picolimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (31). **31** was prepared analogously to **30** using the second aliquot from above and 2-cyanopyridine (0.89 g, 8.55 mmol) in place of benzonitrile to give an off-white powder (661 mg, 41%): mp >170 °C; ^{1}H NMR (400 MHz) δ 11.94 (br s, 2H), 10.19 (br s, 2H), 9.46 (br s, 2H), 8.91 (d, J = 4.0 Hz, 2H), 8.55 (d, J = 7.9 Hz, 2H), 8.24 (t, J = 7.6 Hz, 2H), 8.08 (s, 1H), 8.02 (s, 2H), 7.96 (d, J = 7.7 Hz, 2H), 7.87 (m, 4H), 7.70 (t, J = 7.8 Hz, 2H), 7.54 (d, J = 7.7 Hz, 2H); ESI MS m/z 503.3 ($[M + H]^+$ of free base); HPLC 98.1 area %. Anal. ($C_{30}H_{23}ClN_6 \cdot 2HCl \cdot 2H_2O$) C, H, N, Cl.

3,4″-Bis(benzimidoylamino)-*m*-terphenyl Dihydrochloride (32). Triethylamine (1.5 mL, 10.8 mmol) was added to a stirred suspension of 3,4″-diamino-*m*-terphenyl dihydrochloride (**77**, 1.01 g, 3.03 mmol) in THF (50 mL). After 1.5 h benzonitrile (1.0 mL, 9.80 mmol) was added, followed by the slow addition of sodium bis(trimethylsilyl)amide (2 M solution in THF, 8.0 mL, 16.0 mmol). The reaction mixture was stirred for 3 days, poured over ice, and extracted into $CHCl_3$. The product was purified by preparative HPLC and lyophilized. A solution of the lyophilized product in EtOH and 1 N HCl was evaporated, dissolved in hot water, filtered, and lyophilized to give the HCl salt as a white powder (558 mg, 34%): mp 216 °C; ^{1}H NMR (400 MHz) δ 11.70 (br s, 2H), 9.92 (br s, 2H), 9.15 (br s, 2H), 8.07 (s, 1H), 7.98 (m, 7H), 7.91 (d, J = 7.3 Hz, 1H), 7.79 (m, 4H), 7.70 (m, 6H), 7.61 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 7.3 Hz, 1H); ESI MS m/z 467.6 ($[M + H]^+$ of free base); HPLC 100 area %. Anal. ($C_{32}H_{26}N_4 \cdot 2HCl \cdot 1.5H_2O$) C, H, N, Cl.

3,4″-Bis(picolimidoylamino)-*m*-terphenyl Dihydrochloride (33). **33** was prepared analogously to **32** with 2-cyanopyridine used in place of benzonitrile as a yellow powder (1.04 g, 64%): mp 190 °C; ^{1}H NMR (400 MHz) δ 11.96 (br s, 1H), 11.95 (br s, 1H), 10.17 (br s, 1H), 10.15 (br s, 1H), 9.45 (br s, 1H), 9.39 (br s, 1H), 8.91 (s, 2H), 8.56 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 8.1 Hz, 1H), 8.24 (m, 2H), 8.08 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.97 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.87 (m, 2H), 7.80 (m, 2H), 7.71 (t, J = 7.9 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H); ESI MS m/z 469.6 ($[M + H]^+$ of free base); HPLC 98.9 area %. Anal. ($C_{30}H_{24}N_6 \cdot 2HCl \cdot 1.9H_2O$) C, H, N, Cl.

3,4″-Bis(benzimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (34). To a solution of 5″-chloro-3,4″-diamino-*m*-terphenyl (**78**, 1.01 g, 3.42 mmol) and benzonitrile (1.10 g, 10.7 mmol) in THF (40 mL) was slowly added sodium bis(trimethylsilyl)-amide (2 M solution in THF, 7.0 mL, 14.0 mmol). The mixture was stirred for 3 days. Workup and purification were analogous to **32**. The final product was recrystallized from hot water to give a gray powder (954 mg, 49%): mp >200 °C (dec); ^{1}H NMR (400 MHz) δ 11.71 (br s, 2H), 9.95 (br s, 2H), 9.19 (br s, 1H), 9.17 (br s, 1H), 8.06 (m, 4H), 7.98 (m, 5H), 7.87 (d, J = 8.4 Hz, 2H), 7.80 (t, J = 7.3 Hz, 2H), 7.70 (m, 5H), 7.63 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.7 Hz, 1H); ESI MS m/z 501.2 ($[M + H]^+$ of free base); HPLC 98.7 area %. Anal. ($C_{32}H_{25}ClN_4 \cdot 2HCl \cdot 2.4H_2O$) C, H, N, Cl.

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3,4″-Bis(picolimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (35). **35** was prepared analogously to **34** with 2-cyanopyridine used in place of benzonitrile. The HCl salt was prepared using ethanolic HCl to give a yellow powder (668 mg, 34%): mp >190 °C (dec); ^{1}H NMR (400 MHz) δ 11.94 (br s, 2H), 10.18 (br s, 1H), 10.16 (br s, 1H), 9.47 (br s, 1H), 9.41 (br s, 1H), 8.92 (m, 2H), 8.54 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.24 (m, 2H), 8.06 (t, J = 7.5 Hz, 4H), 7.97 (d, J = 7.9 Hz, 1H), 7.89 (m, 2H), 7.86 (m, 2H), 7.71 (t, J = 7.9 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 7.9 Hz, 1H); ESI MS m/z 503.5 ([M + H]$^+$ of free base); HPLC 98.9 area %. Anal. ($C_{30}H_{23}ClN_6 \cdot 2.5HCl \cdot 1.5H_2O$) C, H, N, Cl.

2-Isopropoxy-4-(picolimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (36). **36** was prepared analogously to **34** from 4-amino-5′-chloro-2-isopropoxy-*m*-terphenyl (**90**, 1.20 g, 3.55 mmol), 2-cyanopyridine (0.67 g, 6.44 mmol), and sodium bis(trimethylsilyl)-amide (2 M solution in THF, 3.0 mL, 6.0 mmol) in THF (60 mL). The product was converted to the HCl salt using ethanolic HCl and ether to give a solid (699 mg, 41%): mp >154 °C (dec); ^{1}H NMR (400 MHz) δ 11.88 (br s, 1H), 10.14 (br s, 1H), 9.38 (br s, 1H), 8.91 (d, J = 4.3 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.24 (td, J = 7.8 and 1.4 Hz, 1H), 7.87 (td, J = 7.4 and 4.8 Hz, 1H), 7.76 (m, 2H), 7.74 (s, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 1.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.43 (tt, J = 7.3 and 2.1 Hz, 1H), 7.32 (s, 1H), 7.15 (dd, J = 8.1 and 1.4 Hz, 1H), 4.71 (septet, J = 6.0 H, 1H), 1.31 (d, J = 6.0 Hz, 6H); ESI MS m/z 442.8 ([M + H]$^+$ of free base); HPLC 100 area %. Anal. ($C_{27}H_{24}ClN_3O \cdot 2HCl \cdot 0.25H_2O$) C, H, N, Cl.

2-Isopropoxy-5-(picolimidoylamino)-5′-chloro-*m*-terphenyl Dihydrochloride (37). **37** was prepared analogously to **36** from 5-amino-5′-chloro-2-isopropoxy-*m*-terphenyl (**91**, 1.42 g, 4.20 mmol) to give a solid (1.01 g, 50%): mp 172–177 °C; ^{1}H NMR (400 MHz) δ 11.68 (br s, 1H), 10.03 (br s, 1H), 9.26 (br s, 1H), 8.89 (dd, J = 3.9 and 0.8 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.22 (td, J = 7.8 and 1.2 Hz, 1H), 7.85 (m, 2H), 7.75 (t, J = 7 1.6 Hz, 1H), 7.73 (s, 1H), 7.71 (t, J = 1.0 Hz, 1H), 7.67 (t, J = 1.7 Hz, 1H), 7.65 (d, J = 2.6 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.43 (m, 2H), 7.33 (d, J = 9.1 Hz, 1H), 4.76 (septet, J = 6.0 H, 1H), 1.31 (d, J = 6.0 Hz, 6H); ESI MS m/z 442.9 ([M + H]$^+$ of free base); HPLC 99.1 area %. Anal. ($C_{27}H_{24}ClN_3O \cdot 2HCl \cdot 0.1H_2O$) C, H, N, Cl.

General Suzuki Coupling Procedure for Cyano-Substituted Terphenyls and Biphenyls 43–45, 47–50, and 53–56. A solution of tetrakis(triphenylphosphine)palladium(0) (5–10 mol %) and the dibromobenzene (1 equiv) in DME (50 mL) was stirred for 15–30 min under Ar. The boronic acid (2.2–2.5 equiv for double couplings, 1–1.2 equiv for single couplings) was added, followed by Na_2CO_3 (10% solution, 75 mL). The mixture was refluxed until reaction was complete. The cooled reaction mixture was worked up by extraction into an appropriate solvent. The product was purified by chromatography on silica gel and recrystallization from an appropriate solvent.

4,4″-Dicyano-*m*-terphenyl (43). **43** was prepared from 1,3-dibromobenzene (**38**, 1.97 g, 8.35 mmol) and 4-cyanophenylboronic acid (2.61g, 17.8 mmol). Column chromatography by gradient elution using hexanes/EtOAc mixtures followed by recrystallization from EtOAc–hexanes gave an ivory colored solid (1.59 g, 68%): mp 199–203 °C; ^{1}H NMR δ 8.09 (t, J = 1.8 Hz, 1H), 8.04 (d, J = 8.5 Hz, 4H), 8.97 (d, J = 8.4 Hz, 4H), 7.84 (dd, (d, J = 7.7 and 1.5 Hz, 2H), 7.66 (t, J = 7.8 Hz, 1H); HPLC 100 area %. Anal. ($C_{20}H_{12}N_2$) C, H, N.

4,4″-Dicyano-5′-chloro-*m*-terphenyl (44). **44** was prepared from dibromobenzene **39** (1.62g, 6.00 mmol) and 4-cyanophenylboronic acid (2.21 g, 15.0 mmol). Column chromatography, eluting with $CHCl_3$ followed by recrystallization from toluene containing a trace of DMF, gave a white solid (1.48 g, 78%): mp 297–301 °C; ^{1}H NMR δ 8.09 (m, 5H), 7.98 (d, J = 8.4 Hz, 4H), 7.92 (d, J = 1.5 Hz, 2H). Anal. ($C_{20}H_{11}ClN_2$) C, H, N.

4,4″-Dicyano-5′-nitro-*m*-terphenyl (45). **45** was prepared from dibromobenzene **40** (1.69 g, 6.01 mmol) and 4-cyanophenylboronic acid (2.21g, 15.0 mmol). The reaction mixture was poured over ice to precipitate the crude product, which was recrystallized from DMF–EtOH to give a solid (1.18 g, 60%): mp 319–320 °C; ^{1}H NMR δ 8.58 (d, J = 1.5 Hz, 2H), 8.55 (t, J = 1.5 Hz, 1H), 8.18 (d, J = 8.3 Hz, 4H), 8.03 (d, J = 8.3 Hz, 4H). Anal. ($C_{20}H_{11}N_3O_2 \cdot 0.1H_2O$) C, H, N.

4,4″-Dicyano-5′-hydroxy-*m*-terphenyl (46). To a stirred solution of 3,5-dibromophenol (**41**, 1.25 g, 5.0 mmol) and tetrakis(triphenylphosphine)palladium (200 mg) in toluene (10 mL) under a nitrogen atmosphere was added 5 mL of a 2 M aqueous solution of Na_2CO_3 followed by 4-cyanophenylboronic acid (0.37 g, 2.5 mmol) in methanol (5 mL). The vigorously stirred mixture was warmed to 80 °C for 12 h. The solvent was evaporated, and the precipitate was partitioned between methylene chloride (200 mL) and 2 M aqueous Na_2CO_3 (15 mL) containing 3 mL of concentrated ammonia. The organic layer was dried and then concentrated to dryness under reduced pressure to afford **46** as a white solid in 76% yield: mp 290–292 °C; ^{1}H NMR δ 10.00 (br s, 1H), 7.92–7.94 (m, 8H), 7.58 (s, 1H), 7.15 (s, 2H); ^{13}C NMR δ 158.5, 144.4, 140.5, 132.8, 127.8, 118.8, 116.9, 114.2, 110.3.

4,4″-Dicyano-5′-methoxy-*m*-terphenyl (47). **47** was prepared from dibromobenzene **42** (1.60 g, 6.03 mmol) and 4-cyanophenylboronic acid (2.21g, 15.0 mmol). Purification by column chromatography, eluting with C_2HCl_2/hexanes (4:1) followed by recrystallization from CH_3CN–H_2O, gave a solid (1.51 g, 81%): mp 239–241 °C; ^{1}H NMR δ 8.04 (d, J = 8.6 Hz, 4H), 7.95 (d, J = 8.5 Hz, 4H), 7.66 (t, J = 1.5 Hz, 1H), 7.37 (d, J = 1.5 Hz, 2H), 3.93 (s, 3H). Anal. ($C_{21}H_{14}N_2O_2$) C, H, N.

3,3″-Dicyano-*m*-terphenyl (48).[61] **48** was prepared from 1,3-dibromobenzene (**38**, 2.66 g, 11.3 mmol) and 3-cyanophenylboronic acid (3.75 g, 25.5 mmol). Column chromatography, eluting with hexanes/EtOAc (3:1) mixtures followed by recrystallization from CH_3CN, gave a white solid (2.38 g, 75%): mp 165–167 °C (lit.[61] 164–165°); ^{1}H NMR δ 8.37 (t, J = 1.5 Hz, 2H), 8.18 (ddd, J = 8.0, 1.9, and 1.1 Hz, 2H), 8.13 (t, J = 1.6 Hz, 1H), 7.87 (dt, J = 7.7 and 1.4 Hz, 2H), 7.82 (dd, J = 8.0 and 1.5 Hz, 2H), 7.71 (t, J = 7.8 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H). Anal. ($C_{20}H_{12}N_2$) C, H, N.

3,3″-Dicyano-5′-chloro-*m*-terphenyl (49). **49** was prepared from dibromobenzene **39** (1.63 g, 6.03 mmol) and 3-cyanophenylboronic acid (2.22 g, 15.1 mmol). Purification by column chromatography, eluting with $CHCl_3$ followed by recrystallization from DMF, gave a light gray solid (991 mg, 52%): mp 279–277 °C; ^{1}H NMR δ 8.43 (t, J = 1.6 Hz, 2H), 8.23 (dm, J = 8.0 Hz, 2H), 8.11 (t, J = 1.6 Hz, 1H), 7.93 (d, J = 1.6 Hz, 2H), 7.90 (dt, J = 7.9 and 1.3 Hz, 2H), 7.71 (t, J = 7.9 Hz, 2H). Anal. ($C_{20}H_{11}ClN_2 \cdot 0.1H_2O$) C, H, N.

3,3″-Dicyano-5′-methoxy-*m*-terphenyl (50). **50** was prepared from dibromobenzene **42** (1.33 g, 5.01 mmol) and 3-cyanophenylboronic acid 1.84 g, 12.5 mmol). The product was chromatographed on silica, eluting with CH_2Cl_2/hexanes (4:1) and recrystallized from CH_3CN–H_2O to give a solid (1.32 g, 71%): mp 194–196 °C; ^{1}H NMR δ 8.38 (t, J = 1.5 Hz, 2H), 8.19 (dm, J = 8.7 Hz, 2H), 7.87 (dt, J = 7.8 and 1.3 Hz, 2H), 7.70 (t, J = 1.5 Hz, 1H), 7.69 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 1.5 Hz, 2H), 3.93 (s, 3H). Anal. ($C_{21}H_{14}N_2O$) C, H, N.

3-Bromo-4′-cyanobiphenyl (53). **53** was prepared from iodobenzene **51** (3.06 g, 10.8 mmol) and 4-cyanophenylboronic acid (1.50 g, 10.2 mmol). The product was chromatographed on a silica column, eluting with hexanes/EtOAc (9:1) and recrystallized from toluene–hexanes to give white crystals (1.86 g, 71%): mp 56–57 °C; ^{1}H NMR δ 7.97 (t, J = 1.8 Hz, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H), 7.77 (ddd, J = 7.7, 1.6, and 1.0 Hz, 1H), 7.66 (ddd, J = 8.1, 2.0, and 1.1 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H). Anal. ($C_{13}H_8BrN$) C, H, N.

3-Bromo-5-chloro-4′-cyanobiphenyl (54). **54** was prepared from iodobenzene **52** (868 mg, 2.73 mmol) and 4-cyanophenylboronic acid (402 mg, 2.73 mmol). The product was purified on a silica column, eluting with hexane/EtOAc (9:1) to give a solid (0.47 g, 59%): mp 128–129 °C; ^{1}H NMR δ 7.96 (m, 5H), 7.86 (m, 1H), 7.81 (m, 1H); HPLC 100 area %. Anal. ($C_{13}H_7BrClN$) C, H, N.

3,4″-Dicyano-*m*-terphenyl (55). **55** was prepared from bromobiphenyl **53** (2.59 g, 10.0 mmol) and 3-cyanophenylboronic acid (1.77 g, 12.1 mmol). The product was chromatographed on a silica column, eluting with $CHCl_3$ and recrystallized from CH_3CN–H_2O to give white crystals (2.35 g, 83%): mp 139–142 °C; ^{1}H NMR δ 8.37 (t, J =

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1.5 Hz, 1H), 8.16 (dm, J = 8.0 Hz, 1H), 8.12 (t, J = 1.8 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.97 (d J = 8.7 Hz, 2H), 7.87 (dt, J = 7.8 and 1.3 Hz, 1H), 7.82 (m, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H). Anal. ($C_{20}H_{12}N_2$) C, H, N.

5′-Chloro-3,4″-dicyano-*m*-terphenyl (56). **56** was prepared from **54** (1.20 g, 4.11 mmol) and 3-cyanophenylboronic acid (788 mg, 5.36 mmol). The reaction mixture was diluted with water to precipitate the product, which was then recrystallized from CH_3CN to give a solid (950 mg, 74%): mp 235−236 °C; ^{1}H NMR δ 8.42 (d, J = 1.6 Hz, 1H), 8.21 (ddd, J = 8.0, 1.8, and 1.1 Hz, 1H), 8.09 (m, 3H), 7.98 (d, J = 8.5 Hz, 2H), 7.94 (t, J = 1.7 Hz, 1H), 7.89 (m, 2H), 7.71 (t, J = 7.8 Hz, 1H); HPLC 97.1 area %. Anal. ($C_{20}H_{11}ClN_2$) C, H, N.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-picolinonitrile (59). A mixture of 5-bromopicolinonitrile (**57**, 2.93 g, 16.0 mmol), bis(pinacolato)diboron (4.50 g, 17.7 mmol), $PdCl_2{\cdot}CH_2Cl_2$ (401 mg, 0.191 mmol), and potassium acetate (4.75 g, 48.4 mmol) in DMSO (45 mL) was heated for 90 °C for 6 h. The reaction mixture was partitioned between water and toluene and then filtered through Celite, and the aqueous layer was extracted with toluene. The dried extracts were evaporated to a solid (3.11 g, 85%) which was used directly in the next step: ^{1}H NMR δ 8.88 (m, 1H), 8.22 (m, 1H), 8.04 (m, 1H), 1.33 (s, 12H).

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-nicotinonitrile (60). **60** was prepared analogously to **59** from 5-bromonicotinonitrile (**58**, 5.16 g, 28.19 g) to give a solid (6.37 g, 98%) which was used directly in the next step: ^{1}H NMR δ 9.14 (d, J = 2.1 Hz, 1H), 8.99 (d, J = 1.5 Hz, 1H), 8.40 (t, J = 1.9 Hz,, 1H), 1.33 (s, 12H).

General Suzuki Coupling Procedure for Dipyridylbenzene Derivatives 61, 62, 67, and 68. A mixture of the appropriate aryl halide and boronic acid or ester, tetrakis(triphenylphosphine)-palladium(0) (0.05 equiv), and silver carbonate (2.5 equiv) was stirred in refluxing THF until reaction was complete (2−3 h). The reaction mixture was filtered through Celite, and the Celite pad was rinsed with hot THF. The evaporated filtrate was purified by column chromatography or by direct recrystallization.

1,3-Bis(6-cyanopyridin-3-yl)benzene (61). **61** was prepared from 1,3-diodobenzene (2.02 g, 6.12 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (**59**, 3.11 g, 13.5 mol). Column chromatography on silica, eluting with 2% MeOH in $CHCl_3$ followed by recrystallization of the crude product from CH_3CN−ether, gave a white solid (1.04 g, 60%): mp 233−236 °C; ^{1}H NMR δ 9.27 (d, J = 2.2 Hz, 2H), 8.53 (dd, J = 8.2 and 2.3 Hz, 2H), 8.30 (t, J = 1.8 Hz, 1H), 8.19 (d, J = 8.1 Hz, 2H), 7.98 (dd, J = 7.8 and 1.8 Hz, 2H), 7.83 (t, J = 7.8 Hz, 1H); HPLC 98.0 area %. Anal. ($C_{18}H_{10}N_4$) C, H, N.

1,3-Bis(5-cyanopyridin-3-yl)benzene (62). **62** was prepared from 1,3-diiodobenzene (1.65 g, 5.00 mmol) and boronate ester **60** (2.88 g, 12.5 mmol). The crude product was directly recrystallized from CH_3CN−ether to give a white solid (981 mg, 69%): mp 254−255 °C; ^{1}H NMR δ 9.37 (d, J = 2.3 Hz, 2H), 9.07 (d, J = 1.9 Hz, 2H), 8.86 (t, J = 2.2 Hz, 2H), 8.30 (t, J = 1.8 Hz, 1H), 7.97 (dd, J = 7.8 and 1.8 Hz, 2H), 7.71 (t, J = 7.8 Hz, 1H); HPLC 98.2 area %. Anal. ($C_{10}H_{10}N_4{\cdot}0.2H_2O$) C, H, N.

General Procedure for Amidoximes 63, 64, 69, and 70. Potassium *tert*-butoxide (10 equiv) was added to a solution of hydroxylamine hydrochloride (10 equiv) in DMSO (0.5−0.6 mL/mmol hydroxylamine hydrochloride). After 1 h the nitrile (1 equiv) was added and the reaction mixture was stirred overnight. The reaction mixture was poured over ice. The resulting precipitated product was filtered off and dried.

1,3-Bis(6-*N*′-hydroxyamidinopyridin-3-yl)benzene (63). **63** was prepared from nitrile **61** (1.03 g, 3.65 mmol) to give a white solid (1.28 g, 101%): ^{1}H NMR δ 10.06 (s, 2H), 9.02 (d, J = 2.3 Hz, 2H), 8.26 (dd, J = 8.4 and 2.3 Hz, 2H), 8.14 (t, J = 1.6 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 7.7 and 1.6 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 5.91 (br s, 4H); HPLC 97.2 area %. The product was used in the next step without further purification.

1,3-Bis(5-*N*′-hydroxyamidinopyridin-3-yl)benzene (64). **64** was prepared from nitrile **62** (858 mg, 3.04 mmol) to give a light gray solid (1.07 g, 101%): ^{1}H NMR δ 9.92 (s, 2H), 9.02 (d, J = 2.2 Hz, 2H), 8.90 (d, J = 1.9 Hz, 2H), 8.38 (t, J = 2.0 Hz, 2H), 8.19 (m, 1H), 7.87 (dd, J = 7.8 and 1.5 Hz, 2H), 7.68 (t, J = 8.0 Hz, 1H), 6.14 (br s, 4H). The product was used in the next step without further purification.

1,3-Bis(5-cyanopyridin-2-yl)benzene (67). **67** was prepared analogously to **61** from bromopyridine **65** (2.02 g, 11.0 mmol) and 1,3-benzenediboronic acid (912 mg, 5.5 mmol). The product was purified on a column of silica, eluting with a gradient of 0−2% MeOH in $CHCl_3$ followed by recrystallization from CH_3CN to give a solid (976 mg, 63%): mp 241−242 °C; ^{1}H NMR δ 9.16 (dd, J = 2.0 and 0.9 Hz, 2H), 8.99 (t, J = 1.9 Hz, 1H), 8.46 (dd, J = 8.4 and 2.1 Hz, 2H), 8.37 (dd, J = 8.3 and 1.0 Hz, 2H), 8.33 (dd, J = 7.9 and 1.8 Hz, 2H), 7.73 (t, J = 7.8 Hz, 1H); HPLC 98.0 area %. Anal. ($C_{18}H_{10}N_4$) C, H, N.

1,3-Bis(4-cyanopyridin-2-yl)benzene (68). **68** was prepared analogously to **61** from bromopyridine **66** (4.50 g, 24.6 mmol) and 1,3-benzenediboronic acid (2.00 g, 12.1 mmol). After filtration of the reaction mixture through Celite, the filtrate was concentrated and diluted with ether to give a precipitate (2.98 g, 87%): mp 238−239 °C; ^{1}H NMR δ 8.96 (dd, J = 5.0 and 0.9 Hz, 2H), 8.91 (t, J = 1.7 Hz, 1H), 8.69 (t, J = 1.1 Hz, 2H), 8.32 (dd, J = 7.8 and 1.8 Hz, 2H), 7.88 (dd, J = 5.0 and 1.4 Hz, 2H), 7.71 (t, J = 7.8 Hz, 1H); HPLC 99.0 area %. Anal. ($C_{10}H_{18}N_4$) C, H, N.

1,3-Bis(5-*N*′-hydroxyamidinopyryidin-2-yl)benzene (69). **69** was prepared analogously to **63** from nitrile **67** (0.960 g, 3.40 mmol) to give a light gray solid (1.20 g, 101%): ^{1}H NMR δ 9.92 (s, 2H), 9.01 (dd, J = 1.8 and 1.2 Hz, 2H), 8.87 (t, J = 1.6 Hz, 1H), 8.20 (dd, J = 7.8 and 1.8 Hz, 2H), 8.15 (m, 4H), 7.68 (t, J = 7.8 Hz, 1H), 6.07 (br s, 4H); HPLC 98.5 area %. The product was used in the next step without further purification.

1,3-Bis(4-*N*′-hydroxyamidinopyryidin-2-yl)benzene (70). **70** was prepared analogously to **63** from nitrile **68** (1.51 g, 5.34 mmol). The sticky, filtered precipitate was dissolved in hot ethanol, and the solution was evaporated to a light gray solid (2.19 g, 118%, wet): ^{1}H NMR δ 10.12 (s, 2H), 8.88 (t, J = 1.6 Hz, 1H), 8.71 (d, J = 5.1 Hz, 2H), 8.30 (s, 2H), 8.21 (dd, J = 7.8 and 1.7 Hz, 2H), 7.66 (m, 3H), 6.20 (br s, 4H); HPLC 98.0 area %. The product was used in the next step without further purification.

Nitro-Substituted Terphenyl and Biphenyl Derivatives 71 and 73−76. Compounds **71** and **73−76** were prepared by Suzuki coupling reaction conditions analogous to those for compounds **43−45**, **47−50**, and **53−56**.

5′-Chloro-3,3″-dinitro-*m*-terphenyl (71). **71** was prepared from dibromide **39** (1.35 g, 5.00 mmol) and 3-nitrophenylboronic acid (1.85 g, 11.1 mmol). The reaction mixture was poured over ice, and the precipitated crude product was recrystallized from DMF as a gray solid (1.35 g, 76%): mp 242−243 °C; ^{1}H NMR δ 8.66 (t, J = 2.0 Hz, 2H), 8.34 (dm, J = 8.5 Hz, 2H), 8.29 (dm, J = 8.2 Hz, 2H), 8.16 (t, J = 1.6 Hz, 1H), 7.97 (d, J = 1.6 Hz, 2H), 7.81 (t, J = 8.0 Hz, 2H). Anal. ($C_{18}H_{11}ClN_2O_4{\cdot}0.2H_2O$) C, H, N.

5′-Chloro-3,3″-diamino-*m*-terphenyl (72). A mixture of dinitroterphenyl **71** (2.98 g, 8.40 mmol) and tin(II) chloride dihydrate (3 × 10.0 g portions, 133 mmol) in EtOH (100 mL) was refluxed for 3 h. The reaction mixture was diluted with water, neutralized by cautious addition of $NaHCO_3$, and extracted into CH_2Cl_2. Both layers were filtered through Celite, and the aqueous layer was extracted with CH_2Cl_2. Combined dried extracts were evaporated to a white solid (2.16 g, 87%), which was recrystallized from EtOH to give a white solid (1.24 g, 50%): mp 153−154 °C; ^{1}H NMR δ 7.65 (t, J = 1.6 Hz, 1H), 7.53 (d, J = 1.6 Hz, 2H), 7.13 (t, J = 7.8 Hz, 2H), 6.92 (t, J = 1.9 Hz, 2H), 6.86 (dd, J = 7.6 and 0.9 Hz, 2H), 6.62 (ddd, J = 8.0, 2.2, and 0.9 Hz, 2H), 5.20 (br s, 4H); ESI MS m/z 295.7 ($[M + H]^+$). Anal. ($C_{18}H_{15}ClN_2{\cdot}0.1H_2O$) C, H, N.

3-Bromo-4′-nitrobiphenyl (73). **73** was prepared from iodobenzene **51** (5.76 g, 20.4 mmol) and 4-nitrophenylboronic acid pinacol ester (5.04 g, 20.2 mmol). The product was purified on a column of silica, eluting with a gradient of 0−40% EtOAc in hexanes and recrystallized from EtOAc/hexanes to give yellow crystals (4.60 g, 82%): mp 88 °C; ^{1}H NMR δ 8.31 (d, J = 8.8 Hz, 2H), 8.01 (m, 3H),

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7.87 (dm, J = 7.8 Hz, 1H), 7.69 (dm, J = 9.0 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H); HPLC 98.8 area %. Anal. ($C_{12}H_8BrN_2O$) C, H, N.

3-Bromo-5-chloro-4′-nitrobiphenyl (74). **74** was prepared from iodobenzene **52** (2.55 g, 8.04 mmol) and 4-nitrophenylboronic acid pinacol ester (2.00 g, 8.04 mmol). The product was purified on a column of silica, eluting with hexanes/EtOAc (19:1) and recrystallized from EtOAc–hexane to give white crystals (1.51 g, 60%): mp 147–148 °C; ^{1}H NMR δ 8.30 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 8.00 (t, J = 1.6 Hz, 1H), 7.92 (t, J = 1.7 Hz, 1H), 7.84 (t, J = 1.7 Hz, 1H); HPLC 100 area %.

3,4″-Dinitro-*m*-terphenyl (75). **75** was prepared from bromobiphenyl **73** (4.53 g, 16.3 mmol) and 3-nitrophenylboronic acid (2.82 g, 16.9 mmol). Column chromatography, eluting with a gradient from hexanes/EtOAc (4:1) to neat EtOAc followed by recrystallization from EtOH, gave a white solid (3.27 g, 63%): mp 188–189 °C; ^{1}H NMR δ 8.60 (t, J = 2.0 Hz, 1H), 8.34 (dm, J = 8.9 Hz, 2H), 8.28 (m, 2H), 8.17 (t, J = 1.7 Hz, 1H), 8.13 (dm, J = 8.9 Hz, 2H), 7.89 (m, 2H), 7.81 (t, J = 8.0 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H). Anal. ($C_{18}H_{12}N_2O_4$·0.05H_2O) C, H, N.

5′-Chloro-3,4″-dinitro-*m*-terphenyl (76). **76** was prepared from bromobiphenyl **74** (2.09 g, 6.68 mmol) and 3-nitrophenylboronic acid (1.69 g, 8.33 mmol). The reaction mixture was diluted with water. The resulting precipitate was filtered off, dried, and purified by suspension in hot ethanol to give a light gray solid (2.18 g, 92%): mp 216–218 °C; ^{1}H NMR δ 8.64 (t, J = 2.0 Hz, 1H), 8.33 (m, 3H), 8.29 (ddd, J = 8.2, 2.2, and 0.9 Hz, 1H), 8.17 (d, J = 8.9 Hz, 2H), 8.14 (t, J = 1.6 Hz, 1H), 7.99 (t, J = 1.7 Hz, 1H), 7.95 (t, J = 1.7 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H); HPLC 100 area %. Anal. ($C_{18}H_{11}ClN_2O_4$·0.5H_2).

3,4″-Diamino-*m*-terphenyl Dihydrochloride (77). A mixture of dinitroterphenyl **75** (3.00 g, 9.37 mmol) and 10% Pd/C (0.60 g, 0.56 mmol) in EtOH (300 mL) was hydrogenated at 60 psi. The reaction mixture was filtered through Celite. The filtrate was concentrated to a small volume, treated with saturated ethanolic HCl, and diluted with ether to give the hydrochloride salt as a white solid (2.24 g, 72%): mp >250 °C (dec); ^{1}H NMR δ 10.10 (br s, 4H), 7.89 (m, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.77 (dm, J = 7.8 Hz, 1H), 7.72 (m, 2H), 7.61 (m, 3H), 7.43 (d, J = 8.5 Hz, 2H), 7.36 (dm, J = 7.8 Hz, 1H). Anal. ($C_{18}H_{16}N_2$·2HCl·0.2H_2O) C, H, N, Cl.

5″-Chloro-3,4″-diamino-*m*-terphenyl (78). Iron powder (3.60 g, 64.5 mmol) was added to a mixture of dinitroterphenyl **76** (2.19 g, 6.15 mmol) and ammonium chloride 1.02 g, 19.1 mmol) in refluxing EtOH/H_2O (2:1 mixture, 90 mL), and refluxing was continued for 2.5 h. The reaction mixture was cooled and filtered through Celite. The filtrate was diluted with water and extracted into ether. The extract was concentrated to ∼50 mL and treated with saturated ethanolic HCl (3 mL) to precipitate the HCl salt (1.94 g, 85%). The salt was dissolved in hot water, filtered, and diluted with NaOH solution to precipitate the free base as a white solid (1.26 g, 69%) which was used directly in the next step: ^{1}H NMR δ 7.62 (t, J = 1.5 Hz, 1H), 7.51 (t, J = 1.7 Hz, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.39 (t, J = 1.7 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.91 (t, J = 1.9 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 6.65 (d, (t, J = 8.5 Hz, 2H), 6.60 (d, J = 7.9 Hz, 1H), 5.34 (br s, 2H), 5.17 (br s, 2H); HPLC 96.3 area %.

4-Amino-3-chlorobiphenyl (80). **80** was prepared analogously to compound **71** from 4-bromo-2-chloroaniline (**79**, 5.25 g, 25.4 mmol) and phenylboronic acid (3.75 g, 30.8 mmol). The product was chromatographed on a column of silica, eluting with 15–20% EtOAc in hexanes followed by recrystallization from hexanes to give a solid (3.62 g, 70%): mp 69–70 °C; ^{1}H NMR δ 7.56 (d, J = 7.3 Hz, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.38 (m, 3H), 7.25 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 5.48 (s, 2H); HPLC 100 area %. Anal. ($C_{12}H_{10}ClN$) C, H, N.

4-Amino-3-bromo-5-chlorobiphenyl (81). *N*-Bromosuccinimide (3.84 g, 21.6 mmol) was added to a solution of aminobiphenyl **80** (4.33 g, 21.3 mmol) in THF (60 mL) at 0 °C. After 1 h the reaction mixture was quenched with $NaHSO_3$ solution, neutralized with $NaHCO_3$ solution, and extracted into EtOAc. Column chromatography on silica, eluting with hexanes/EtOAc (9:1) followed by recrystallization from EtOAc–hexanes, gave crystals (5.00 g, 83%): mp 111–112 °C; ^{1}H NMR δ 7.71 (d, J = 2.1 Hz, 1H), 7.61 (t, J = 2.0 Hz, 2H), 7.59 (m, 1H), 7.41 (tm, J = 7.6 Hz, 2H), 7.30 (tm, J = 7.3 Hz, 1H), 5.54 (s, 2H); HPLC 100 area %. Anal. ($C_{12}H_9BrClN$) C, H, N.

3-Bromo-5-chlorobiphenyl (82). A solution of 4-amino-3-bromo-5-chlorobiphenyl (**81**, 4.51 g, 16.0 mmol) in EtOH (25 mL) was treated dropwise with H_2SO_4 (5 mL). Sodium nitrite (2.74 g, 39.7 mmol) was added, and the mixture was refluxed for 30 min. The reaction mixture was poured over ice and excess $NaHCO_3$ and then extracted into EtOAc. Column chromatography on silica, eluting with hexanes, gave a clear oil that solidified upon standing (4.52 g, 86%): mp 32–33 °C; ^{1}H NMR δ 7.85 (t, J = 1.5 Hz, 1H), 7.77 (t, J = 1.6 Hz, 1H), 7.73 (m, 3H), 7.49 (m, 2H), 7.43 (m, 1H); HPLC 99.5 area %. Anal. ($C_{12}H_8BrCl$) C, H, N.

(5-Chloro-biphenyl-3-yl)boronic Acid (83). Butyllithium (2.5 M/hexanes, 4.5 mL, 11.25 mmol) was added dropwise over 15 min to a solution of 3-bromo-5-chlorobiphenyl (**82**, 2.49 g, 9.31 mmol) in THF (150 mL) at −78 °C. The mixture was maintained for 1 h before the dropwise addition of triisopropyl borate (4.5 mL, 19.6 mmol). The mixture was maintained another hour at −78 °C before being warmed to ambient temperature. The reaction mixture was quenched with 1 N HCl (150 mL) and extracted with ether. The dried extract was evaporated to a white solid (2.12 g, 98%) which was used in the next step without further purification.

5′-Chloro-2-isopropoxy-4-nitro-*m*-terphenyl (88). **88** was prepared analogously to compounds **43–50** from bromobenzene **86** (1.35 g, 5.17 mmol) and boronic acid **83** (1.54 g, 6.62 mmol). The product was purified on a column of silica, eluting with hexanes/EtOAc (50:1) followed by recrystallization from EtOH to give yellow crystals (1.57 g, 82%): mp 100–101 °C; ^{1}H NMR δ 7.89 (m, 2H), 7.80 (t, J = 1.8 Hz, 1H), 7.76 (m, 4H), 7.63 (t, J = 1.7 Hz, 1H), 7.50 (tm, J = 7.4 Hz, 2H), 7.42 (tm, J = 7.3 Hz, 1H), 4.87 (septet, J = 6.0 Hz, 1H), 1.30 (d, J = 6.0 Hz, 6H); HPLC 96.2 area %. Anal. ($C_{21}H_{18}ClNO_3$) C, H, N.

5′-Chloro-2-isopropoxy-5-nitro-*m*-terphenyl (89). **89** was prepared analogously to compounds **43–50** from bromobenzene **87** (1.30 g, 5.01 mmol) and boronic acid **83** (1.50 g, 1.29 mmol). The product was purified on a column of silica, eluting with hexane/EtOAc (17:3) to give a white solid (1.68 g, 91%): mp 111 °C; ^{1}H NMR δ 8.28 (dd, J = 7.5 and 2.9 Hz, 1H), 8.26 (d, J = 2.9 Hz, 1H), 7.80 (t, J = 1.5 Hz, 1H), 7.77 (d, J = 1.4 Hz, 1H), 7.74 (t, J = 1.8 Hz, 2H), 7.63 (t, J = 1.7 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.41 (m, 2H), 4.91 (septet, J = 6.0 Hz, 1H), 1.32 (d, J = 6.0 Hz, 6H); HPLC 100%. Anal. ($C_{21}H_{18}ClNO_3$) C, H, N.

4-Amino-5′-chloro-2-isopropoxy-*m*-terphenyl (90). A solution of nitroterphenyl **88** (1.57 g, 4.26 mmol) in EtOH (75 mL) was brought to reflux. Tin(II) chloride dihydrate (5.18 g, 29.6 mmol) was slowly added via the condenser, and refluxing was continued for 1.5 h. The reaction mixture was portioned between ether and water basified with 1 N NaOH, and the aqueous layer was extracted twice with ether. Combined extracts were filtered through Celite. Column chromatography on silica, eluting with hexanes/EtOAc (3:2), gave a glass (1.20 g, 83%): ^{1}H NMR δ 7.70 (d, J = 7.2 Hz, 2H), 7.66 (t, J = 1.5 Hz, 1H), 7.48 (m, 4H), 7.40 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 6.25 (dd, J = 8.2 and 2.0 Hz, 1H), 5.30 (s, 2H), 4.47 (septet, J = 6.1 Hz, 1H), 1.25 (d, J = 6.0 Hz, 6H). The product was used in the next step without further purification.

5-Amino-5′-chloro-2-isopropoxy-*m*-terphenyl (91). **91** was prepared analogously to compound **90** from nitroterphenyl **89** (1.64 g, 4.46 mmol). Column chromatography on silica, eluting with hexane/EtOAc (2:1), gave a glass (1.42 g, 94%): ^{1}H NMR δ 7.72 (m, 3H), 7.64 (t, J = 1.8 Hz, 1H), 7.51 (m, 3H), 7.41 (tm, J = 7.3 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 2.9 Hz, 1H), 6.57 (dd, J = 8.6 and 2.8 Hz, 1H), 4.79 (s, 2H), 4.15 (septet, J = 6.1 Hz, 1H), 1.11 (d, J = 6.0 Hz, 6H); HPLC 97.5 area %. The product was used in the next step without further purification.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

AIA, arylimidamide; DMTHP, 5,5-dimethyl-1,4,5,6-tetrahydropyrimidin-2-yl; HAT, human African trypanosomiasis; NECT, nifurtimox−eflornithine combination therapy; pK_a, ionization constant; SI, selectivity index; VL, visceral leishmaniasis; WHO, World Health Organization

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