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# Synthesis and activity of azaterphenyl diamidines against *Trypanosoma brucei rhodesiense* and *Plasmodium falciparum*

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ABSTRACT

A series of azaterphenyl diamidines has been synthesized and evaluated for in vitro antiprotozoal activity against both *Trypanosoma brucei rhodesiense (T. b. r.)* and *Plasmodium falciparum (P. f.)* and in vivo efficacy in the STIB900 acute mouse model for *T. b. r.* Six of the 13 compounds showed $IC_{50}$ values less than 7 nM against *T. b. r.* Twelve of those exhibited $IC_{50}$ values less than 6 nM against *P. f.* and six of those showed $IC_{50}$ values $\leqslant$0.6 nM, which are more than 25-fold as potent as furamidine. Moreover, two of them showed more than 40-fold selectivity for *P. f.* versus *T. b. r.* Three compounds **15b**, **19d** and **19e** exhibited in vivo efficacy against *T. b. r.* much superior to furamidine, and equivalent to or better than azafuramidine. The antiparasitic activity of these diamidines depends on the ring nitrogen atom(s) location relative to the amidine groups and generally correlates with DNA binding affinity.



## 1. Introduction

Human African trypanosomiasis (HAT) and malaria, which are caused by the protozoan parasites *Trypanosoma brucei* and *Plasmodium* sp., infect millions of people in large parts of the world each year.[1] Numerous aromatic or heterocyclic diamidines exhibit potent antiprotozoal activity against HAT and malaria.[2] However, pentamidine **1** (Fig. 1) is the only one of this class which has seen significant human clinical use and it has been used to treat 1st stage HAT for over half a century.[2] Furamidine **2a**, a diphenyl furan diamidine analogue, has been shown to be more potent and less toxic than pentamidine in murine models of trypanosomiasis.[3] The oral prodrug of furamidine **2b** (pafuramidine) showed promising results in Phase I and II clinical trials against both HAT and malaria.[1–3] Unfortunately, in an additional safety study of pafuramidine parallelling the Phase III trials, liver and kidney toxicities in some volunteers were found and the development of pafuramidine was suspended.[3] Introduction of an *N*-atom into one of phenyl ring of furamidine resulted in an aza-analogue of furamidine **3a**, which exhibited more potent in vivo antitrypanosomal activity than pentamidine and furamidine, although all three have similar in vitro activities.[4] The methoxyamidine prodrug of azafuramidine **3b** was found to be quite effective against 2nd stage HAT.[5] Although diamidines have been used therapeutically since the 1950s, the antiparasitic mode of action of such diamidines is not well understood. A long-hypothesized mechanism of action arose from their binding to the minor groove of DNA at AT rich sites in the nucleus or kinetoplast,[6] which has been suggested to interfere with DNA-associated enzymes, such as topoisomerase II, and possibly direct inhibition of transcription.[7] Recent investigations have shown that both furamidine **2a** and azafuramidine **3a** accumulated within trypanosomes at millimolar concentration, with intracellular concentrations over 15,000-fold higher than mouse plasma concentrations.[8] Although the results of this study showed that the extent of accumulation is not directly correlated with killing of the trypanosomes, the selective concentration of diamidines in parasite mitochondria (kinetoplast) appears to represent a pivotal step in their antiparasitic activity.[8]

The previous design of DNA minor groove binding diamidine analogues has focused on crescent shaped molecules which closely fit the curvature of the groove, such as pentamidine, furamidine and their analogues.[2,9] Recently, linear dicationic diamidines CGP40215A **4** and a benzimidazole diamidine **5** have shown strong DNA minor groove binding and potent antiparasitic activity.[10] Both compounds were found to simulate the curved structure of DNA minor groove by incorporation of a water molecule into the recognition complex with DNA.[10] Based on the discovery of this new binding mode, we recently prepared a series of linear terphenyl diamidines which showed significant DNA minor groove binding

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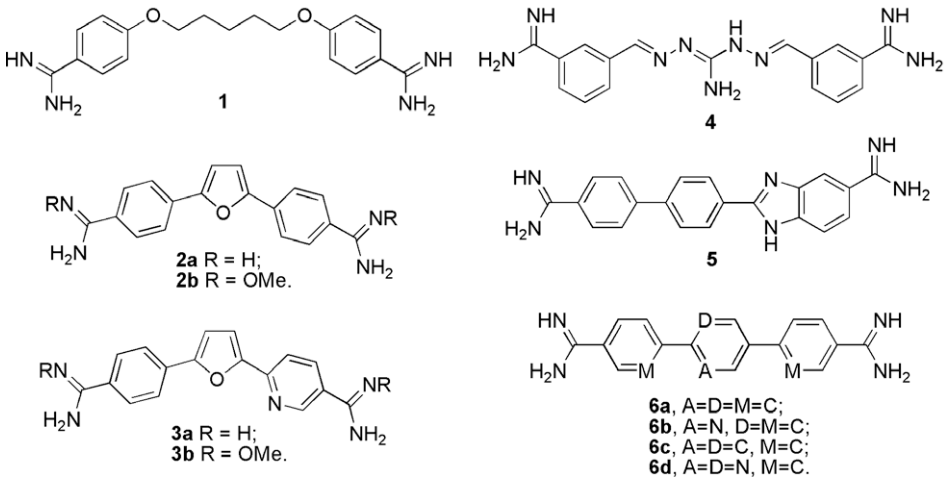



**Figure 1.** Aromatic or heterocyclic diamidine antiprotozoal agents.

affinity and low nanomolar antiprotozoal activity against *Trypanosoma brucei rhodesiense* (*T. b. r.*) and *Plasmodium falciparum* (*P. f.*).[11] The parent terphenyl compound **6a** is more effective than furamidine in an acute mouse model for *T. b. r.* STIB 900. Due to the promising results found in the furan diamidine system, we first synthesized three aza-analogues **6b–d** of terphenyl diamidine **6a** by introduction of a nitrogen atom into the central phenyl ring or both of the terminal phenyl rings.[11] Both aza-diamidine compounds **6b–c** in which a nitrogen atom has been placed in the central phenyl ring or *meta* to both of the amidine groups in the terminal phenyl rings are more effective than furamidine in an acute mouse model for *T. b. r.* STIB 900. The diaza-analogue **6d** is of particular interest because it exhibits very strong activity ($IC_{50}$ = 0.5 nM) against *P. f.* and at the same time shows a 32-fold selectivity for *P. f.* compared to antitrypanosomal activity.[11] More interestingly, **6d** binds specifically to a GC-rich sequence more strongly than to the usual AT recognition, which is the first non-polyamide, synthetic compound to specifically recognize a DNA sequence with a majority of GC base pairs.[12] Therefore, we prepared additional analogues of this series of azaterphenyl diamidines in order to investigate structure–activity relationships (SAR) and their DNA binding profiles. More recently, we have reported that this series of terphenyl and azaterphenyl diamidines exhibit potent in vitro antileishmanial activity.[13] The results indicate that the antileishmanial activity of these dications strongly depends on the ring *N*-atom position relative to the amidine groups and correlates with the DNA minor groove binding affinity. Here, we describe their synthesis, in vitro activities against *T. b. r.* and *P. f.* and in vivo efficacy in the *T. b. r.* STIB 900 acute mouse model.

## 2. Results and discussion

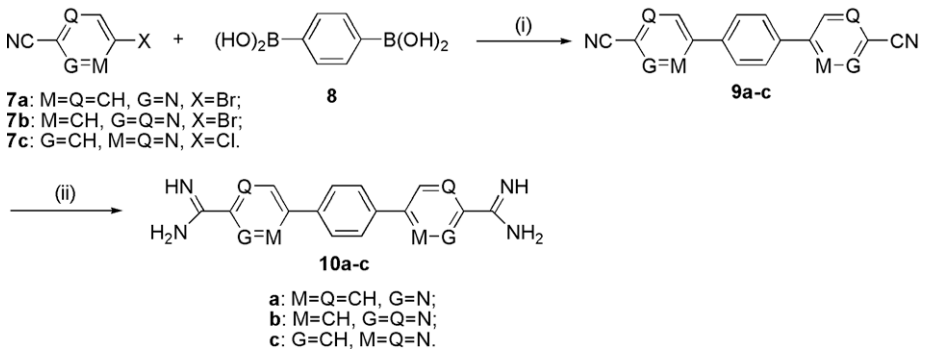
### 2.1. Chemistry

The syntheses of the azaterphenyl diamidines begins with Suzuki coupling of the appropriate aryl halides with the corresponding aryl boronic acids or esters to yield the azaterphenyl bis-nitriles (Schemes 1–3).[11] The bis-nitriles were converted to the diamidines by the action of lithium trimethylsilylamide [$LiN(TMS)_2$] in THF. As illustrated in Scheme 1, azaterphenyl diamidine analogues **10a–c** with nitrogen atom(s) in both of the terminal aryl rings (pyridyl, pyrimidinyl and pyrazinyl ring) were prepared from 5-bromo-2-pyridinecarbonitrile **7a**, 5-bromo-2-pyrimidinecarbonitrile **7b** and 5-chloro-2-pyrazinecarbonitrile **7c**[14] by coupling with 1,4-phenylenebisboronic acid **8** in two steps. Scheme 2 shows the syntheses of the diamidines **10a–c** with the two nitrogen atoms in the central aryl ring (pyrazinyl, pyridazinyl and pyrimidnyl ring) as well as pyridinyl rings as both the terminal units. Scheme 3 outlines the approach used to prepare the compounds **19a–g** with phenyl or pyridyl ring in the central ring and nitrogen atom(s) in one terminal aryl ring. The bis-nitriles **18a–g** were obtained from 4-bromophenylboronic acid **16a** or 2-chloropyridine-5-boronic acid **16b** in two step Suzuki coupling reactions.

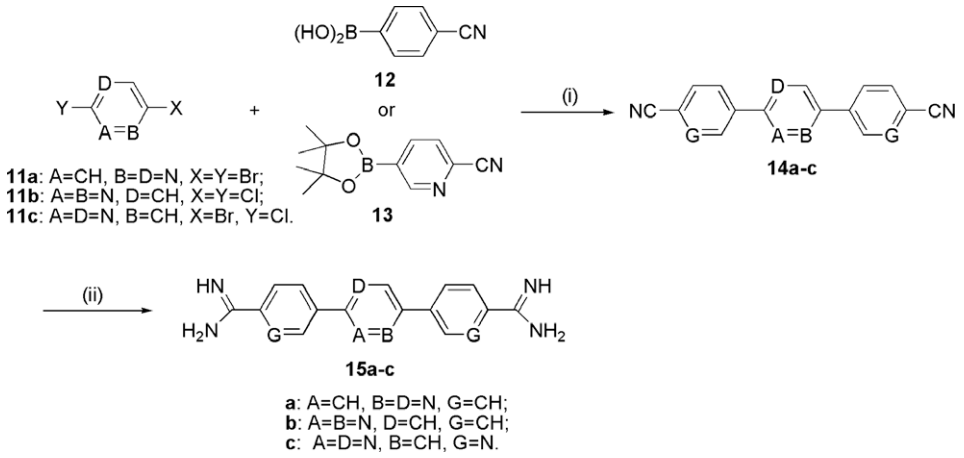
### 2.2. Biology

The results for the evaluation of the 13 azaterphenyl diamidine analogues against *T. b. r.* STIB900 and *P. f.* K1[16] and their DNA binding affinities[13] are shown in Table 1. For comparative and SAR purposes, the analogous data for pentamidine **1**, furamidine **2a**, azafuramidine **3a** and the terphenyl analogues **6a–d** are also included in Table 1. Six of the 13 compounds showed antitrypanosomal $IC_{50}$ values $\leqslant$7 nM, comparable to that of pentamidine and furamidine. Another six compounds exhibited $IC_{50}$ values between 7 and 32 nM, and only one compound **10c** gave poor antitrypanosomal activity ($IC_{50}$ > 7 μM). More interestingly, these azaterphenyl dications exhibited very potent activities against *P. f.* in vitro. Six of the 13 compounds showed $IC_{50}$ values $\leqslant$0.6 nM, which are over 25-fold more potent than furamidine ($IC_{50}$ = 15.5 nM). Another six of the compounds exhibited $IC_{50}$ values between 1.1 and 5.7 nM, and only one compound **10c** gave moderate antimalaria activity ($IC_{50}$ = 65 nM). Two of the most active compounds **15a** and **15c** showed more than 40-fold selectivity for *P. f.* compared to *T. b. r.* Compound **15c** was 106 times more active against *P. f.* ($IC_{50}$ = 0.3 nM) than against *T. b. r.* ($IC_{50}$ = 32 nM). Compound **15c** is one of the most potent compounds against *P. f.* K1 in the STI in vitro screen.

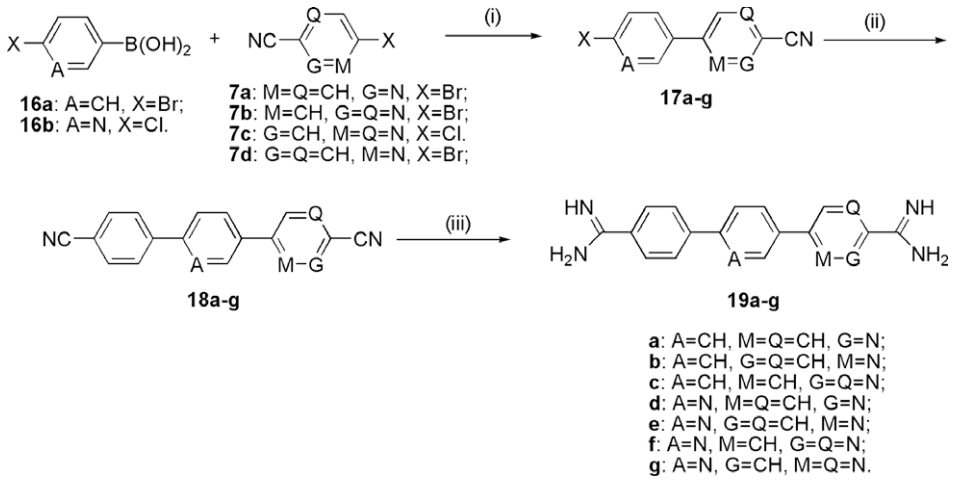
Our previous study has shown that the number and location of nitrogen atoms has a significant impact on the antileishmanial activity for these linear rigid-rod systems.[13] The results from the current study of these azaterphenyl compounds against *T. b. r.* and *P. f.* are generally consistent with that observed in the antileishmanial study. Compounds **10a** and **19a**, in which a nitrogen atom has been replaced *ortho* to one or both of the amidine groups, showed a five- and two-fold increase in potency compared to the parent terphenyl diamidine **6a** against *T. b. r.* and a three- and four-fold increased potency against *P. f.* The two isomeric compounds **6b** and **19b**, in which the nitrogen atom is *meta* to the amidine, exhibited a significant loss in potency against both *T. b. r.* and *P. f.*, compared to **10a** and **19a**. Introduction of two nitrogen atoms




**Scheme 1.** Reagents and conditions: (i) $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, 80 °C; (ii) (a) $LiN(TMS)_2$, THF; (b) HCl (gas), EtOH.



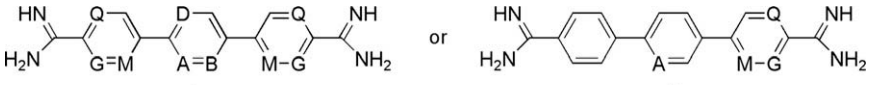

**Scheme 2.** Reagents and conditions: (i) $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, 80 °C; (ii) (a) $LiN(TMS)_2$, THF; (b) HCl (gas), EtOH.




**Scheme 3.** Reagents and conditions: (i) $Pd(pph_3)_4$, $NaCO_3$, toluene. 80 °C; (ii) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, $NaCO_3$, toluene, 80 °C; (iii) (a) $LiN(TMS)_2$, THF; (b) HCl (gas), EtOH.

*ortho* to one amidine, **19c**, resulted in a modest reduction of activity against both *T. b. r.* and *P. f.* compared to **19a**. Interestingly, if two nitrogen atoms are introduced *ortho* to both of the amidine groups, **10b**, a six-fold reduction in activity against *T. b. r.* was observed, conversely a slight enhancement in activity against *P. f.* was seen. For compound **10c**, in which one of the nitrogen atoms is *meta* and another is *ortho* to both amidine units, a significant reduction in activity against both *T. b. r.* and *P. f.* was seen. Introduction of one nitrogen atom in the central ring (**6c**) led to a two-fold increase in activity against *T. b. r.*, however, a seven-fold reduction in activity against *P. f.*, compared to the parent terphenyl compound **6a**.[11] In contrast, introduction of two nitrogen atoms in the central ring (**6d**, **15a–c**) resulted in a more than two-fold reduction in activity against *T. b. r.*, however, a three-fold increase in activity against *P. f.*, except **15b** which showed comparable activity, compared to the parent terphenyl compound **6a**. Introduction of one nitrogen atom in the central ring (**6d**) in compound **19a** with a nitrogen atom in one terminal aryl ring, led to moderate

**Table 1**
DNA affinities and antiprotozoan activity for azaterphenyl diamidines




I II

| Code | Aryl type | A | B | D | M | G | Q | ΔTm[a] (°C) | *T. b. r.*[b] $IC_{50}$ (nM) | *P. f.*[b] $IC_{50}$ (nM) | Selectivity [c] | Cytotoxicity[d] $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | / | / | / | / | / | / | / | 12.6 | 2.2 | 46.4 | 0.05 | 2100 |
| **2a** | / | / | / | / | / | / | / | 25 | 4.5 | 15.5 | 0.3 | 6400 |
| **3a** | / | / | / | / | / | / | / | 19.3 | 6.5 | 6.5 | 1.0 | 77,900 |
| **6a** | I | CH | CH | CH | CH | CH | CH | 17.1 | 5 | 1.4 | 3.6 | 22,100 |
| **6b** | I | CH | CH | CH | N | CH | CH | 9.2 | 47 | 10.1 | 4.7 | 25,600 |
| **6c** | I | N | CH | CH | CH | CH | CH | 18.7 | 2 | 10 | 0.2 | 49,900 |
| **6d** | I | N | CH | N | CH | CH | CH | 8.1 | 16 | 0.9 | 17.8 | 40,900 |
| **10a** | I | CH | CH | CH | CH | N | CH | 17 | 1 | 0.4 | 2.5 | 1200 |
| **10b** | I | CH | CH | CH | CH | N | N | 12.8 | 6 | 0.6 | 10.0 | 2200 |
| **10c** | I | CH | CH | CH | N | CH | N | 3.9 | 7131 | 65.4 | 109.0 | 46,500 |
| **15a** | I | CH | N | N | CH | CH | CH | 8.0 | 18 | 0.4 | 45.0 | 42,500 |
| **15b** | I | N | N | CH | CH | CH | CH | 16.9 | 14 | 1.3 | 10.8 | 31,300 |
| **15c** | I | N | CH | N | CH | N | CH | 6.8 | 32 | 0.3 | 106.7 | 5300 |
| **19a** | II | CH | / | / | CH | N | CH | 19.5 | 3 | 0.3 | 10 | 2800 |
| **19b** | II | CH | / | / | N | CH | CH | 11.7 | 11 | 1.3 | 8.5 | 26,700 |
| **19c** | II | CH | / | / | CH | N | N | 16.0 | 4 | 0.6 | 6.7 | 4700 |
| **19d** | II | N | / | / | CH | N | CH | 15.2 | 6 | 1.1 | 5.5 | 19,900 |
| **19e** | II | N | / | / | N | CH | CH | 13.8 | 7 | 2.5 | 2.8 | 28,300 |
| **19f** | II | N | / | / | CH | N | N | 14.9 | 12 | 1.5 | 8.0 | 6400 |
| **19g** | II | N | / | / | N | CH | N | 12.1 | 14 | 5.7 | 2.5 | 93,400 |

[a] Increase in thermal melting of poly(dA–dT)$_2$; see Refs. 11 and 13.
[b] The *T. b. r.* (*Trypanosoma brucei rhodesiense*) strain was STIB900, and the *P. f.* (*Plasmodium falciparum*) strain was K1. The Values were average of duplicate determinations; see Ref. 16.
[c] Selectivity was the ratio [$IC_{50}$ (*T. b. r.*)/$IC_{50}$ (*P. f.*)].
[d] Cytotoxicity was evaluated using cultured L6 rat myoblast cells; see Refs. 13 and 17.

reduction in activity against *T. b. r.* and *P. f.* However, it is noteworthy that introduction of two nitrogen atoms in the central ring (**6e** and **6f**) in the compounds **19b** and **19c** showed no apparent effect on either antitrypanosomal or antiplasmodial activity.

The Δ*T*m values of these linear azaterphenyl diamidines, which range from high values of 17–19 °C to low ones of 4–6 °C, are lower than that of crescent shape molecules e.g. furamidine (Δ*T*m = 25 °C).[13] Our previous study found that the compounds which exhibit the higher Δ*T*m values showed the higher antileishmanial activity and the weaker binding compounds show low activity.[13] A similar trend is found for *T. b. r.*, but not for *P. f.* The potent antitrypanosomal compounds, which showed $IC_{50}$ values less than 7 nM, exhibited higher Δ*T*m values (12 °C or greater). On the other hand, the less potent antitrypanosomal compounds, which showed $IC_{50}$ values of more than 18 nM, exhibited lower Δ*T*m values (less than 10 °C). These results are generally consistent with the observed relationship between DNA binding affinities and antileishmanial activity of this series azaterphenyl diamidines. However, the correlation between Δ*T*m values and antiplasmodial activity is complex. For example, the potent compounds **6d**, **15a** and **15c** which $IC_{50}$ values of $\leqslant$0.9 nM showed Δ*T*m values of 6.8–8.1 °C. In contrast, the potent compounds **10a**, **10b**, **19a** and **19c** with $IC_{50}$ values of $\leqslant$0.6 nM showed significantly higher Δ*T*m values of 12.8–19.5 °C. Clearly, other factors such as transport, induced changes in DNA topology or protein–DNA complex inhibition, are important in determining the antiplasmodial activity of these linear-rod molecules. It is perhaps also significant that diamidine compounds localize only in the nuclear DNA of plasmodia[15] but they are in both the mitochondrial kinetoplast DNA and in the nucleus in trypanosomes.[8c]

Given the promising in vitro *T. b. r.* activity of these analogues, we have evaluated them in the stringent STIB900 acute mouse model for *T. b. r.*[16] The results are shown in Table 2 and for comparative purposes the in vivo data for pentamidine **1**, furamidine **2a**, azafuramidine **3a** and the terphenyl analogues **6a–d** in the same model are also presented. On intraperitoneal dosing all of the dications showed a significant increase in survival time for the treated animals compared to untreated controls. Three of the thirteen

**Table 2**
In vitro and in vivo anti-trypanosomal activity of azaterphenyl diamidines in the STIB900 mouse model[a]

| Code | *T. b. r.* $IC_{50}$ (nM) | Dosage[b] (ip, mg/kg) | Cures [c] | Survival (days) [d] |
|---|---|---|---|---|
| **1** | 2.2 | 20 | 2/4 | >57.5 |
| | | 5 | 1/4 | >38 |
| **2a** | 4.5 | 20 | 3/4 | >57.75 |
| | | 5 | 1/4 | >46 |
| **3a** | 6.5 | 20 | 4/4 | >60 |
| | | 5 | 3/4 | >54.5 |
| **6a** | 5 | 20 | 2/4 | >47.75 |
| **6b** | 47 | 5 | 2/4 | >60 |
| **6c** | 2 | 5 | 2/4 | >42 |
| **6d** | 16 | 5 | 0/4 | 23.5 |
| **10a** | 1 | 5 | 0/4 | >51.5 |
| **10b** | 6 | 5 | 1/4 | >43.25 |
| **10c** | 7131 | NA | | |
| **15a** | 18 | 5 | 0/4 | 36.5 |
| **15b** | 14 | 5 | 3/4 | >49.25 |
| **15c** | 32 | 5 | 0/4 | 34 |
| **19a** | 3 | 5 | 0/4 | >48.75 |
| **19b** | 11 | 5 | 1/4 | >56.0 |
| **19c** | 4 | 5 | 1/4 | >46.25 |
| **19d** | 6 | 5 | 3/4 | >60.0 |
| **19e** | 7 | 5 | 4/4 | >60.0 |
| **19f** | 12 | 5 | 0/4 | >43.25 |
| **19g** | 14 | 5 | 1/4 | >31.75 |

[a] See Ref. 16 for details of STIB900 mouse model.
[b] Dosage was for four days; ip, intraperitoneal.
[c] Number of mice that survive and are parasite free for 60 days.
[d] Average days of survive; untreated control expires between day 7 and 9 post-infection.

compounds, **15b**, **19d** and **19e**, gave superior and four compounds, **10b**, **19b**, **19c** and **19g**, identical results to that for furamidine in this model at the dose of 5 mg/kg. Five compounds were not able to cure any mice although they extended the survival significantly. Two compounds **15b** and **19d** were as effective as the azafuramdine **3a** giving 3/4 cures at 5 mg/kg. The best result obtained was for compound **19e**, which showed 4/4 cures at a dose of 5 mg/kg. It is noteworthy that although the compounds **6b** and **19b**, in which the nitrogen atom is *meta* to the amidine, exhibited a significant loss of in vitro potency against *T. b. r.* compared to their isomeric compounds **10a** and **19a**, in which the nitrogen atom is *ortho* to the amidine, the in vivo efficacy of **6b** and **19b** (2/4 and 1/4 cure, respectively) was superior to the *ortho* isomers **10a** and **19a** (0/4 cure). The pyridinyl analogue **19e** was also more effective than the *ortho* isomer **19d** in this mouse model, even though these two isomers exhibited almost similar in vitro antitrypanosomal activity. These results are consistent with those observed for the azafuramidine system.[4] Since previous study of the bis-amidoximes and bis-*O*-methylamidoximes prodrugs of the terphenyl diamidine analogues showed poor bioconversion and were not effective on oral administration,[11] we did not prepare their bis-amidoximes and bis-*O*-methylamidoximes prodrugs during this study. However, further studies to develop novel orally effective prodrugs of this highly active series of azaterphenyl diamidines are underway.

In summary, we have prepared a series of azaterphenyl diamidine analogues that exhibit potent in vitro activity against both *T. b. r.* and *P. f.*, and showed promising activity on intraperitoneal administration in the *T. b. r.* STIB900 acute mouse model. Six of the 13 compounds showed $IC_{50}$ values $\leqslant$0.6 nM against *P. f.*, and two of them showed more than 40-fold selectivity for *P. f.* versus *T. b. r.* Three compounds **15b**, **19d** and **19e** exhibited in vivo efficacy (3/4 or 4/4 cure at 5 mg/kg dosage, ip) in the stringent STIB900 model much superior to that of furamidine, and comparable to or better than azafuramidine. SAR information shows that the number and location of nitrogen atoms has a significant effect on antiparasitic activity. This series of azaterphenyl diamidines merit further investigation as novel potent antiparasitic agents.

## 3. Experimental

### 3.1. Biology

#### 3.1.1. Efficacy evaluation

In vitro assays with *T. b. r.* STIB900 and *P. f.* K1 strain as well as the efficacy study in an acute mouse model for *T. b. r.* STIB900 were carried out as previously reported.[16]

### 3.2. Chemistry

Melting points were determined on a Mel-Temp 3.0 melting point apparatus, and are uncorrected. TLC analysis was carried out on Silica Gel 60 F254 precoated aluminum sheets using UV light for detection. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Unity Plus 300 MHz or Bruker 400 MHz spectrometer using indicated solvents. Mass spectra was obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA. Elemental analysis were performed by Atlantic Microlab Inc., Norcross, GA, and are within ±0.4 of the theoretical values. The compounds reported as salts frequently analyzed correctly for fractional moles of water and/or ethanol of solvation. In each case, proton NMR showed the presence of the indicated solvents. All chemicals and solvents were purchase from Aldrich Chemical Co., VWR International or Frontier Scientific.

#### 3.2.1. 1,4-Bis-(2′-cyanopyridin-5′-yl)phenylene (9a)

To a stirred solution of 5-bromo-2-pyridinecarbonitrile **7a** (6.60 g, 36.0 mmol), and tetrakis(triphenylphosphine) palladium (1.80 g, 1.56 mmol) in toluene (100 mL) under a nitrogen atmosphere was added 50 mL of a 2 M aqueous solution of $Na_2CO_3$ followed by 1,4-phenylenebisboronic acid **8** (3.90 g, 24.0 mmol) in 50 mL of methanol. The vigorously stirred mixture was heat at 80 °C overnight. After cooling, the solution was filtered, and the precipitate was washed with toluene, water and ether, to afford the title compound as a white solid **9a** (4.70 g, 92% yield); mp > 300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.99 (s, 4H), 8.08 (d, $J$ = 8.0 Hz, 2H), 8.38 (dd, $J$ = 2.0, 8.0 Hz, 2H), 9.14 (d, $J$ = 2.0 Hz, 2H). Anal. Calcd for $C_{18}H_{10}N_4$–0.3$H_2O$: C, 75.14; H, 3.71; N, 19.47. Found: C, 75.37; H, 3.51; N, 19.15.

#### 3.2.2. 1,4-Bis-(2′-amidinopyridin-5′-yl)-phenylene hydrochloride salt (10a)

The dinitrile **9a** (570 mg, 2.0 mmol), suspended in freshly distilled THF (30 mL), was treated with lithium trimethylsilylamide (1 M solution in THF, 15 mL, 15.0 mmol), and the reaction was allowed to stir overnight at room temperature. The reaction mixture was then cooled to 0 °C and HCl saturated ethanol (15 mL) was added, whereupon a precipitate started forming. The mixture was left to stir overnight, after which it was diluted with ether, and the resultant solid was collected by filtration. The diamidine was purified by neutralization with 1 N NaOH followed by filtration of the resultant solid and washing with water (3×). Finally, the dried free base was stirred with ethanolic HCl overnight and diluted with ether, and the solid which formed was filtered and dried to give diamidine salt **10a** in 68% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.11 (s, 4H), 8.47 (d, $J$ = 8.4 Hz, 2H), 8.60 (dd, $J$ = 2.0, 8.4 Hz, 2H), 9.24 (d, $J$ = 2.0 Hz, 2H), 9.41 (s, 4H), 9.66 (s, 4H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 161.6, 147.4, 142.5, 138.5, 135.8, 135.4, 127.8, 123.1. HRMS: $m/z$ 317.1517 (M+1) (calculated for $C_{18}H_{17}N_6$, 317.1515). Anal. Calcd for $C_{18}H_{16}N_6$–2.0HCl–0.3$H_2O$: C, 54.78; H, 4.75; N, 21.29. Found: C, 55.03; H, 4.60; N, 21.01.

#### 3.2.3. 1,4-Bis-(2′-amidinopyrimidin-5′-yl)-phenylene hydrochloride salt (10b)

The same procedure described for 1,4-bis-(2′-cyanopyridin-5′-yl)phenylene **9a** was used by employing 5-bromo-2-pyrimidinecarbonitrile **7b** and 1,4-phenylenebisboronic acid **8** to furnish 1,4-bis-(2′-cyanopyrimidin-5′-yl)-phenylene **9b** in 69% yield; mp >300 °C.$^1$H NMR (DMSO-$d_6$): $\delta$ 8.16 (s, 4H), 9.50 (s, 4H). The compound was used directly in the next step.

The same procedure described for the preparation of **10a** was used starting with the dinitrile **9b**; 68% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.24 (s, 4H), 9.57 (s, 4H), 9.60 (s, 4H), 9.76 (s, 4H). HRMS: $m/z$ 319.1418 (M+1) (calculated for $C_{16}H_{15}N_8$, 319.1420). Anal. Calcd for $C_{16}H_{14}N_8$–2.0HCl–2.5$H_2O$: C, 44.05; H, 4.83; N, 25.68. Found: C, 44.39; H, 4.55; N, 25.28.

#### 3.2.4. 1,4-Bis-(2′-cyanopyrazin-5′-yl)phenylene (9c)

The same procedure described for 1,4-bis-(2′-cyanopyridin-5′-yl)phenylene **9a** was used by employing 5-chloro-2-pyrazinecarbonitrile **7c**[14] and 1,4-phenylenebisboronic acid **8** to furnish the title compound **9c** in 74% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.39 (s, 4H), 9.22 (s, 2H), 9.69 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 151.1, 147.2, 145.9, 136.2, 129.1, 128.0, 116.1. HRMS: $m/z$ 285.0886 (M+1) (calculated for $C_{16}H_9N_6$, 285.0889).

#### 3.2.5. 1,4-Bis-(2′-amidinopyrazin-5′-yl)-phenylene hydrochloride salt (10c)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **9c**; 55% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.64 (s, 4H), 9.47 (s, 2H), 9.71 (s, 4H), 9.78 (s,

2H), 9.92 (s, 4H). HRMS: *m*/*z* 319.1419 (M+1) (calculated for $C_{16}H_{15}N_8$, 319.1420). Anal. Calcd for $C_{16}H_{14}N_8$–2.0HCl–0.65$H_2O$: C, 47.69; H, 4.33; N, 27.81. Found: C, 48.04; H, 4.18; N, 27.52.

### 3.2.6. 2,5-Bis-(4′-cyanophenyl)-pyrazine (14a)

The same procedure described for 1,4-bis-(2′-cyanopyridin-5′-yl)phenylene **9a** was used by employing 2,5-dibromopyrazine **11a**[18] and 4-cyanophenylboronic acid **12** to furnish the title compound **14a** in 52% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.99 (d, *J* = 8.4 Hz, 4H), 8.39 (d, *J* = 8.4 Hz, 4H), 9.42 (s, 2H). Anal. Calcd for $C_{18}H_{10}N_4$–0.3$H_2O$: C, 75.14; H, 3.71; N, 19.47. Found: C, 75.26; H, 3.47; N, 19.70.

### 3.2.7. 2,5-Bis-(4′-amidinophenyl)-pyrazine hydrochloride salt (15a)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **14a**; 76% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.05 (d, *J* = 8.4 Hz, 4H), 8.45 (d, *J* = 8.4 Hz, 4H), 9.37 (s, 4H), 9.53 (s, 2H), 9.58 (s, 4H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.1, 149.0, 142.1, 140.2, 129.2, 129.0, 127.0. Anal. Calcd for $C_{18}H_{16}N_6$–2.0HCl–0.55$H_2O$: C, 54.16; H, 4.82; N, 21.05. Found: C, 54.41; H, 4.75; N, 20.71.

### 3.2.8. 2,5-Bis-(4′-cyanophenyl)-pyridazine (14b)

The same procedure described for 1,4-bis-(2′-cyanopyridin-5′-yl)phenylene **9a** was used employing 3,6-dichloropyridazine **11b** and 4-cyanophenylboronic acid **12** to furnish the title compound **14b** in 80% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.05 (d, *J* = 8.4 Hz, 4H), 8.43 (d, *J* = 8.4 Hz, 4H), 8.51 (s, 2H). MS: *m*/*z* 282 (M+1). Anal. Calcd for $C_{18}H_{10}N_4$–0.25$H_2O$: C, 75.38; H, 3.69; N, 19.54. Found: C, 75.11; H, 3.56; N, 19.75.

### 3.2.9. 2,5-Bis-(4′-amidinophenyl)-pyridazine hydrochloride salt (15b)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **14b**; 72% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.61 (d, *J* = 8.4 Hz, 4H), 8.06 (d, *J* = 8.4 Hz, 4H), 8.13 (s, 2H), 8.83 (s, 4H), 9.10 (s, 4H). Anal. Calcd for $C_{18}H_{16}N_6$-2.5HCl-0.5EtOH: C, 53.00; H, 5.03; N, 19.52. Found: C, 53.27; H, 4.85; N, 19.38.

### 3.2.10. 2,5-Bis-(2′-cyanopyridin-5′-yl)-pyrimidine (14c)

The same procedure described for 1,4-bis-(2′-cyanopyridin-5′-yl)phenylene **9a** was used employing 5-bromo-2-chloropyrimidine **11c** and 2-cyanopyridine-5-boronic acid pinacol ester **13** to furnish the title compound **14c** in 78% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$):): $\delta$ 8.24 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 2.0, 8.4 Hz, 1H), 8.93 (dd, *J* = 2.0, 8.4 Hz, 1H), 9.32 (d, *J* = 2.0 Hz, 1H), 9.50 (s, 2H), 9.68 (d, *J* = 2.0 Hz, 1H). HRMS: *m*/*z* 285.0884 (M+1) (calculated for $C_{16}H_9N_6$, 285.0875).

### 3.2.11. 2,5-Bis-(2′-amidinopyridin-5′-yl)-pyrimidine hydrochloride salt (15c)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **14c**; 67% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.51 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.77 (dd, *J* = 2.0, 8.4 Hz, 1H), 9.08 (dd, *J* = 2.0, 8.4 Hz, 1H), 9.40 (d, *J* = 2.0 Hz, 1H), 9.47 (s, 4H), 9.60 (s, 2H), 9.72 (s, 2H), 9.75 (s, 2H), 9.76 (d, *J* = 2.0 Hz, 1H). HRMS: *m*/*z* 319.1425 (M+1) (calculated for $C_{16}H_{15}N_8$, 319.1420). Anal. Calcd for $C_{16}H_{14}N_8$–2.0HCl–0.8$H_2O$: C, 47.37; H, 4.37; N, 27.62. Found: C, 47.47; H, 4.14; N, 27.32.

### 3.2.12. 5-(4′-Bromophenyl)-2-pyridinecarbonitrile (17a)

5-Bromo-2-cyanopyridine **7a** and 4-bromophenylboronic acid **16a** were reacted under the above-mentioned Suzuki coupling conditions to give the target nitrile **17a**, which was purified by column chromatography (EtOAc/hexane, 80:20); yield 82%; mp 138–140 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.73 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.34 (dd, *J* = 2.4, 8.0 Hz, 1H), 9.08 (d, *J* = 2.4 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 149.2, 137.8, 135.4, 134.5, 132.2, 131.4, 129.5, 129.1, 123.2, 117.6. HRMS: *m*/*z* 258.9866 (M+1) (calculated for $C_{12}H_8N_2Br$, 258.9871).

### 3.2.13. Phenyl[1,1′]phenyl[4′,5″]pyridinyl-4,2″-bis-carbonitrile (18a)

The nitrile **17a** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18a**; yield 84%; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.90–7.97 (m, 8H), 8.08 (d, *J* = 8.4 Hz, 1H). 8.38 (dd, *J* = 2.0, 8.4 Hz, 1H), 9.13 (d, *J* = 2.0 Hz, 1H). Anal. Calcd for $C_{19}H_{11}N_3$–0.3$H_2O$: C, 79.59; H, 4.08; N, 14.66. Found: C, 79.65; H, 3.91; N, 14.43.

### 3.2.14. Phenyl[1,1′]phenyl[4′,5″]pyridinyl-4,2″-bis-amidine hydrochloride salt (19a)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18a**; 65% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.97 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.58 (dd, *J* = 2.0, 8.4 Hz, 1H), 9.16 (s, 2H), 9.22 (d, *J* = 2.0 Hz, 1H), 9.40 (s, 2H), 9.44 (s, 2H), 9.64 (s, 2H). HRMS: *m*/*z* 316.1551 (M+1) (calculated for $C_{19}H_{18}N_5$, 316.1562). Anal. Calcd for $C_{19}H_{17}N_5$–2.0HCl–0.6$H_2O$: C, 57.18; H, 5.10; N, 17.55. Found: C, 57.46; H, 5.08; N, 17.25.

### 3.2.15. 2-(4′-Bromophenyl)-5-pyridinecarbonitrile (17b)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used by employing 2-bromo-5-cyanopyridine **7d** and 4-bromophenylboronic acid **16a** to furnish the title compound **17b** in 78% yield; mp 157–159 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.74 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.40 (dd, *J* = 2.4, 8.4 Hz, 1H), 9.09 (d, *J* = 2.4 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 157.9, 152.6, 141.1, 136.1, 132.0, 129.2, 124.4, 120.2, 117.2, 107.7. HRMS: *m*/*z* 258.9871 (M+1) (calculated for $C_{12}H_8N_2Br$, 258.9871).

### 3.2.16. Phenyl[1,1′]phenyl[4′,2″]pyridinyl-4,5″-bis-carbonitrile (18b)

The nitrile **17b** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18b**; yield 94%; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.68 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 8.0 Hz, 1H). 8.42 (dd, *J* = 2.0, 8.0 Hz, 1H), 9.17 (d, *J* = 2.0 Hz, 1H). HRMS: *m*/*z* 282.1038 (M+1) (calculated for $C_{19}H_{12}N_3$, 282.1031).

### 3.2.17. Phenyl[1,1′]phenyl[4′,2″]pyridinyl-4,5″-bis-amidine hydrochloride salt (19b)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18b**; 75% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.98 (d, *J* = 8.4 Hz, 4H), 8.04 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.33–8.37 (m, 4H), 9.11 (s, 1H), 9.26 (s, 2H), 9.38 (s, 2H), 9.49 (s, 2H), 9.66 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.2, 163.8, 159.3, 149.0, 144.2, 140.0, 137.5, 137.1, 128.9, 127.9, 127.7, 127.6, 127.1, 123.0, 119.9. Anal. Calcd for $C_{19}H_{17}N_5$–2.0HCl–0.9$H_2O$: C, 56.42; H, 5.18; N, 17.30. Found: C, 56.74; H, 4.94; N, 16.90.

### 3.2.18. Phenyl[1,1′]phenyl[4′,5″]pyrimidinyl-4,2″-bis-carbonitrile (18c)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used by employing 5-bromo-2-cyanopyr-

imidine **7b** and 4- bromophenylboronic acid **16a** to furnish 5-(4′-Bromophenyl)-2-pyrimidinecarbonitrile **17c** in 58% yield; mp 202–204 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.79 (d, $J$ = 8.4 Hz, 2H), 7.88 (d, $J$ = 8.4 Hz, 2H), 9.39 (s, 2H). The compound was used directly in the next step. The above nitrile **17c** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18c**; yield 74%; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.95–8.01 (m, 6H), 8.08 (d, $J$ = 8.4 Hz, 2H), 9.47 (s, 2H). HRMS: $m/z$ 283.0983 (M+1) (calculated for $C_{18}H_{11}N_4$, 283.0984).

### 3.2.19. Phenyl[1,1′]phenyl[4′,5′′]pyrimidinyl-4,2′′-bis-amidine hydrochloride salt (19c)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18c**; 75% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.97 (d, $J$ = 8.4 Hz, 2H), 8.03 (d, $J$ = 8.4 Hz, 2H), 8.06 (d, $J$ = 8.4 Hz, 2H), 8.15 (d, $J$ = 8.4 Hz, 2H), 9.13 (s, 2H), 9.44 (s, 2H), 9.54 (s, 2H), 9.57 (s, 2H), 9.76 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.1, 159.5, 155.6, 151.6, 144.0, 139.7, 135.0, 132.5, 128.9, 128.4, 128.0, 127.3, 127.2. Anal. Calcd for $C_{18}H_{16}N_6$–2.0HCl–0.6$H_2O$: C, 54.04; H, 4.84; N, 21.00. Found: C, 54.29; H, 4.68; N, 20.86.

### 3.2.20. 5-(2′-Chloropyridin-5′-yl)-2-pyridinecarbonitrile (17d)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used by employing 5-bromo-2-cyanopyridine **7a** and 2-chloropyridine-5-boronic acid **16b** to furnish the title compound **17d** in 98% yield; mp 220–224 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.22 (d, $J$ = 8.0 Hz, 1H), 8.41 (d, $J$ = 8.4 Hz, 1H), 8.51 (dd, $J$ = 2.0, 8.4 Hz, 1H), 8.75 (dd, $J$ = 2.0, 8.0 Hz, 1H), 9.19 (d, $J$ = 2.0 Hz, 1H), 9.48 (d, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 151.1, 149.4, 148.6, 135.9, 135.0, 132.0, 130.6, 129.1, 124.6, 117.5. HRMS: $m/z$ 216.0334 (M+1) (calculated for $C_{11}H_7N_3Cl$, 216.0329).

### 3.2.21. Phenyl[1,2′]pyridinyl[5′,5′′]pyridinyl-4,2′′-bis-carbonitrile (18d)

The nitrile **17d** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18d**; yield 80%; mp 270–272 °C. $^1$H NM R$^1$H NMR (DMSO-$d_6$): $\delta$ 7.99 (d, $J$ = 8.4 Hz, 2H), 8.07 (d, $J$ = 8.4 Hz, 2H), 8.17 (d, $J$ = 8.4 Hz, 1H), 8.32 (d, $J$ = 8.4 Hz, 1H), 8.39 (dd, $J$ = 2.0, 8.4 Hz, 1H), 8.75 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.18 (d, $J$ = 1.6 Hz, 1H), 9.52 (d, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 151.6, 148.9, 148.0, 140.5, 136.3, 135.5, 134.9, 133.7, 132.5, 132.3, 128.6, 127.4, 121.4, 118.1, 117.0, 110.9. HRMS: $m/z$ 283.0974 (M+1) (calculated for $C_{18}H_{11}N_4$, 283.0984).

### 3.2.22. Phenyl[1,2′]pyridinyl[5′,5′′]pyridinyl-4,2′′-bis-amidine hydrochloride salt (19d)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18d**; 71% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.00 (d, $J$ = 8.4 Hz, 2H), 8.33 (d, $J$ = 8.4 Hz, 1H), 8.43 (d, $J$ = 8.4 Hz, 2H), 8.47–8.51 (m, 2H), 8.66 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.18 (s, 2H), 9.26 (d, $J$ = 2.0 Hz, 1H), 9.30 (d, $J$ = 2.0 Hz, 1H), 9.42 (s, 2H), 9.46 (s, 2H), 9.66 (s, 2H). HRMS: $m/z$ 317.1502 (M+1) (calculated for $C_{18}H_{17}N_6$, 317.1515). Anal. Calcd for $C_{18}H_{16}N_6$–2.0HCl–1.0$H_2O$: C, 53.08; H, 4.95; N, 20.63. Found: C, 53.28; H, 4.59; N, 20.34.

### 3.2.23. 2-(2′-Chloropyridin-5′-yl)-5-pyridinecarbonitrile (17e)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used by employing 2-bromo-5-cyanopyridine **7d** and 2-chloropyridine-5-boronic acid **16b** to furnish the title compound **17e** in 83% yield; mp 198–200 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.68 (d, $J$ = 8.4 Hz, 1H), 8.29 (d, $J$ = 8.4 Hz, 1H), 8.45 (dd, $J$ = 2.0, 8.4 Hz, 1H), 8.55 (dd, $J$ = 2.4, 8.4 Hz, 1H), 9.12 (d, $J$ = 2.0 Hz, 1H), 9.15 (d, $J$ = 2.4 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 155.8, 152.7, 152.0, 148.7, 141.3, 138.1, 132.0, 124.6, 120.8, 117.0, 108.4. HRMS: $m/z$ 216.0323 (M+1) (calculated for $C_{11}H_7N_3Cl$, 216.0329).

### 3.2.24. Phenyl[1,2′]pyridinyl[5′,2′′]pyridinyl-4,5′′-bis-carbonitrile (18e)

The nitrile **17e** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18e**; yield 76%; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.00 (d, $J$ = 8.4 Hz, 2H), 8.29 (d, $J$ = 8.4 Hz, 1H), 8.39 (d, $J$ = 8.4 Hz, 3H), 8.48 (dd, $J$ = 2.0, 8.4 Hz, 1H), 8.68 (dd, *$J$ = 2.0, 8.4 Hz, 1H), 9.16 (d, $J$ = 2.0 Hz, 1H), 9.48 (d, $J$ = 2.0 Hz, 1H). HRMS:* $m/z$ 283.0976 (M+1) (calculated for $C_{18}H_{11}N_4$, 283.0984).

### 3.2.25. Phenyl[1,2′]pyridinyl[5′,2′′]pyridinyl-4,5′′-bis-amidine hydrochloride salt (19e)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18e**; 57% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.00 (d, $J$ = 8.4 Hz, 2H), 8.33 (d, $J$ = 8.4 Hz, 1H), 8.42–8.44 (m, 4H), 8.71 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.14 (d, $J$ = 2.0 Hz, 1H), 9.21 (s, 2H), 9.35 (s, 2H), 9.48 (s, 2H), 9.52 (d, $J$ = 2.0 Hz, 1H), 9.65 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.2, 163.7, 157.4, 155.4, 149.2, 148.5, 142.6, 137.7, 136.0, 132.3, 128.8, 128.7, 127.1, 123.7, 121.3, 120.4. Anal. Calcd for $C_{18}H_{16}N_6$–2.5HCl–1.5$H_2O$: C, 49.75; H, 4.99; N, 19.34. Found: C, 50.03; H, 4.73; N, 19.25.

### 3.2.26. 5-(2′-Chloropyridin-5′-yl)-2-pyrimidinecarbonitrile (17f)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used by employing 5-bromo-2-cyanopyrimidine **7b** and 2-chloropyridine-5-boronic acid **16b** to furnish the title compound **17f** in 27% yield; mp 158–160 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.77 (d, $J$ = 8.4 Hz, 2H), 8.41 (dd, $J$ = 2.4, 8.4 Hz, 1H), 8.97 (d, $J$ = 2.4 Hz, 1H), 9.46 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 156.5, 151.7, 148.7, 143.1, 138.6, 132.0, 127.8, 124.8, 116.1. HRMS: $m/z$ 217.0288 (M+1) (calculated for $C_{10}H_6N_4Cl$, 217.0281).

### 3.2.27. Phenyl[1,2′]pyridinyl[5′,5′′]pyrimidinyl-4,2′′-bis-carbonitrile (18f)

The nitrile **17f** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18f**; yield 77%; mp 272–274 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.01 (d, $J$ = 8.4 Hz, 2H), 8.34 (d, $J$ = 8.4 Hz, 1H), 8.40 (d, $J$ = 8.4 Hz, 2H), 8.53 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.28 (d, $J$ = 2.0 Hz, 1H), 9.55 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 156.4, 154.9, 148.5, 142.9, 141.8, 136.3, 132.9, 132.5, 127.9, 127.5, 121.3, 118.7, 116.2, 112.0. HRMS: $m/z$ 284.0949 (M+1) (calculated for $C_{17}H_{10}N_5$, 284.0936).

### 3.2.28. Phenyl[1,2′]pyridinyl[5′,5′′] pyrimidinyl -4,2′′-bis-amidine hydrochloride salt (19f)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18f**; 51% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.99 (d, $J$ = 8.4 Hz, 2H), 8.38 (d, $J$ = 8.4 Hz, 1H), 8.44 (d, $J$ = 8.4 Hz, 2H), 8.59 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.16 (s, 2H), 9.34 (d, $J$ = 2.0 Hz, 1H), 9.47 (s, 2H), 9.60 (s, 2H), 9.62 (s, 2H), 9.79 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.2, 159.5, 155.9, 155.1, 152.0, 148.7, 142.4, 136.5, 132.8, 128.8, 128.8, 128.1, 127.0, 121.2. HRMS: $m/z$ 318.1464 (M+1) (calculated for $C_{17}H_{16}N_7$, 318.1467). Anal. Calcd for $C_{17}H_{15}N_7$–2.0HCl–0.6$H_2O$: C, 50.91; H, 4.57; N, 24.45. Found: C, 50.68; H, 4.49; N, 24.13.

### 3.2.29. 5-(2′-Chloropyridin-5′-yl)-2-pyrazinecarbonitrile (17g)

The same procedure described for 5-(4′-bromophenyl)-2-pyridinecarbonitrile **17a** was used employing 2-chloro-5-cyanopyr-

azine **7c** and 2-chloropyridine-5-boronic acid **16b** to furnish the title compound **17g** in 47% yield; mp 118–120 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.75 (d, $J$ = 8.4 Hz, 1H), 8.58 (dd, $J$ = 2.4, 8.4 Hz, 1H), 9.18 (d, $J$ = 2.4 Hz, 1H), 9.25 (s, 1H), 9.65 (s, 1H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 152.4, 149.1, 148.7, 147.6, 146.0, 138.2, 129.6, 129.1, 124.8, 115.9. HRMS: $m/z$ 217.0273 (M+1) (calculated for $C_{10}H_6N_4Cl$, 217.0281).

### 3.2.30. Phenyl[1,2′]pyridinyl[5′,5″]pyrazinyl-4,2″-bis-carbonitrile (18g)

The nitrile **17g** and 4-cyanophenylboronic acid were reacted under the above-mentioned Suzuki coupling conditions to give the target dinitrile **18g**; yield 70%; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.01 (d, $J$ = 8.4 Hz, 2H), 8.33 (d, $J$ = 8.4 Hz, 1H), 8.39 (d, $J$ = 8.4 Hz, 2H), 8.68 (dd, $J$ = 2.0, 8.4 Hz, 1H), 9.25 (s, 1H), 9.48 (s, 1H), 9.72 (s, 1H). HRMS: $m/z$ 284.0948 (M+1) (calculated for $C_{17}H_{10}N_5$, 284.0936).

### 3.2.31. Phenyl[1,2′]pyridinyl[5′,5″]pyrizinyl-4,2″-bis-amidine hydrochloride salt (19g)

The same procedure described for the preparation of **10a** was used starting with the dinitrile **18g**; 75% yield; mp >300 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.80 (d, $J$ = 8.4 Hz, 2H), 8.38 (d, $J$ = 8.4 Hz, 1H), 8.46 (d, $J$ = 8.4 Hz, 2H), 8.97 (dd, $J$ = 2.4, 8.4 Hz, 1H), 9.20 (s, 2H), 9.49 (s, 3H), 9.67 (s, 2H), 9.74 (d, $J$ = 2.0 Hz, 1H), 9.79 (s, 1H), 9.91 (s, 2H). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 165.2, 160.7, 155.7, 148.9, 148.4, 146.5, 142.9, 142.4, 139.4, 136.4, 129.7, 128.8, 128.7, 127.1, 121.1. Anal. Calcd for $C_{17}H_{15}N_7$–2.7HCl–2.0$H_2O$: C, 45.19; H, 4.84; N, 21.70. Found: C, 45.52; H, 4.71; N, 21.34.

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