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Synthesis of 2,3-diaminopyridine-derived 4-azabenzimidazoles and (benzylimino)pyridine analogues as potential anti-plasmodial agents

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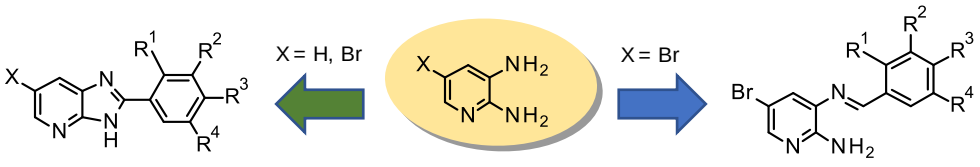
Abstract

Azabenzimidazoles are frequently found in small-molecule drugs due to their broad-spectrum biological activity. Newer drugs are continually needed to replace existing drugs which encounter microorganism drug resistance. The reaction of 2,3-diaminopyridine precursors with variously substituted benzaldehydes has provided convenient and efficient access to a series of 4-azabenzimidazole derivatives and, regioselectively, to a series of 2-amino-5-bromo-3-(benzylimino)pyridine derivatives, while sodium cyanoborohydride reduction of the latter has afforded the corresponding 2-amino-5-bromo-3-(benzylimino)pyridine analogues. Bioassays of these and other compounds have been undertaken to explore their cytotoxicity and their activity against the parasitic protozoans, *Plasmodium falciparum* and *Trypanosoma brucei*. A number of the compounds show promising selective activity against *T. brucei* with IC_{50} values as low as 1.3 μM while two of them exhibit encouraging activity against both *T. brucei* and *P. falciparum*.



Keywords: Azabenzimidazoles, (benzylimino)pyridines, 2,3-diaminopyridines, anti-malarial, anti-trypanosomal

Introduction

Plasmodium falciparum (*P. falciparum*) and *Trypanosoma brucei* (*T. brucei*), the parasitic protozoans responsible for malaria and trypanosomiasis (African Sleeping Sickness), are transmitted by their respective vectors, female *Anopheles* mosquitos and Tsetse flies.[1,2] Both infections are often experienced together as a co-infection and, if untreated, either can prove fatal. The health and consequential economic effects of these diseases exact a heavy burden on many African countries, and trypanosomiasis remains a neglected tropical disease.[3]

4-Azabenzimidazole (IUPAC: 1*H*-imidazo[4,5-*b*]pyridine) derivatives appear to exhibit broad-spectrum biological activity. The 2-aminoazabenzimidazole derivative **1**, for example, has been reported to be orally active against *P. falciparum* with an IC_{50} value of 0.04 μM,[4] and 2-(4-methoxyphenyl)azabenzimidazoles **2** have been shown to be viable against TANK-Binding Kinase 1 *(TBK1)* and Nuclear Factor Kinase subunit epsilon *(TBK1/IKK-*ε*)*.[5] *N*-Arylated azabenzimidazoles **3** have been reported by Ansell and co-workers as inhibitors of *P. falciparum* and Calcium-Dependent Protein Kinase 1 (*Pf*CDPK1),[6] while compound **4** is a potent allosteric inhibitor of AKT kinases.[7] The inhibitory activity of polycyclic 5-azabenzimidazoles has also been observed, e.g., compound **5** inhibits the Ataxia-Telangiectasia and Rad-3 related protein (ATR),[8] and the aminofurazanyl-azabenzimidazole **6** inhibits Rho-kinase (ROCK1) selectively.[9]

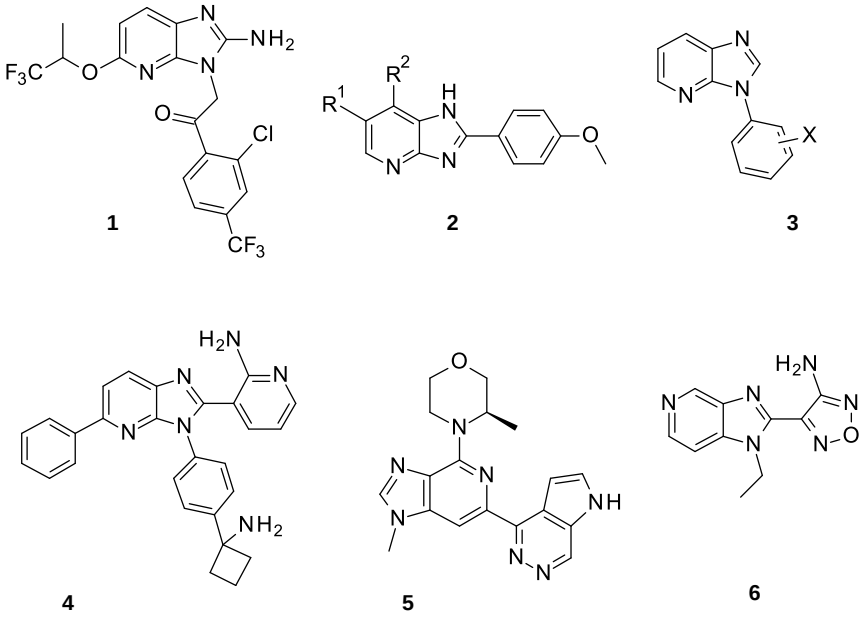
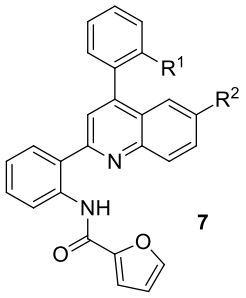


Figure 1. Examples of bioactive azabenzimidazoles.

The development of resistance to existing anti-malarial[10-12] and anti-trypanosomal drugs[13-15] is a motivating factor in the search for replacement drugs. Our previous contributions have included the synthesis and screening of 2,4-diarylquinolines (**7**) and 4-azabenzimidazoles (**8**) against these parasites.[16,17] In this paper, we report the synthesis of series of 2-phenyl-4-azabenzimidazoles (**14** and **15**) and 2-amino-3-(benzylimino)- and 2-amino-3-(benzylamino)pyridines (**16** and **17**) and an evaluation of their efficacy against *P. falciparum* and *T. brucei.*



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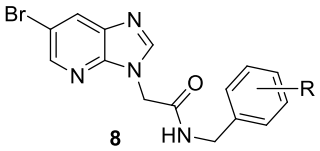

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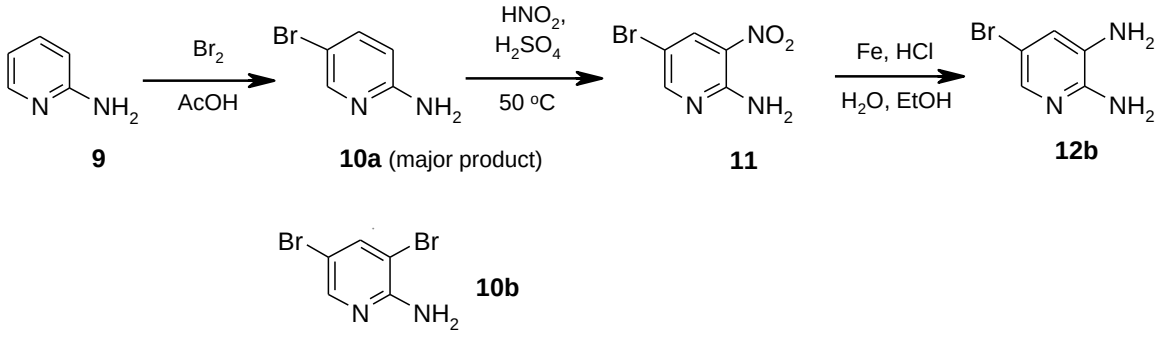
Results and Discussion

Both series of compounds (**14**) and (**15**) were accessed from the 2,3-diaminopyridines **12a** and/or **12b**. 2,3-Diaminopyridine **12a** was commercially available. The 2,3-diamino-5-bromopyridine analogue **12b** was obtained from 2-aminopyridine **9** *via* a 3-step synthesis involving sequential bromination, nitration and hydrogenation as reported by Fox and Threlfall[18] (Scheme 1). Bromination of 2-aminopyridine **9** is expected to occur at the β-positions (3 and 5) and, in this case, substitution at position 5 is favoured, affording 2-amino-5-bromopyridine **10a** as the major product, together with a small quantity of the 3,5-di-substituted analogue **10b**.

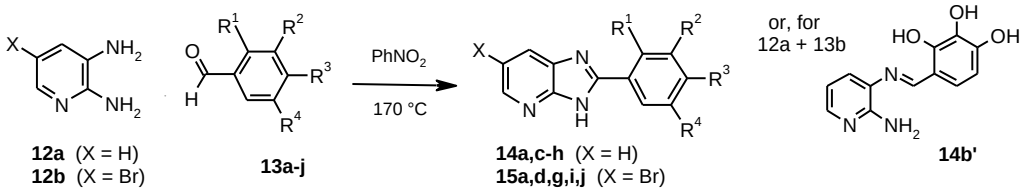


9 **10a** (major product) **11** **12b**

10b

Scheme 1. Synthesis of 2,3-diamino-5-bromopyridine **12b.**

According to Viron[19] and Kasman,[20] nitration of 2-amino-5-bromopyridine **10a** proceeds *via* a 2-nitroamino-5-bromopyridine intermediate which rearranges to 2-amino-5-bromo-3-nitropyridine **11** at *ca*. 50 °C. Iron/hydrochloric acid-catalysed reduction of the nitro compound **11** afforded the required 2,3-diamino-5-bromopyridine **12b** in 78% yield.

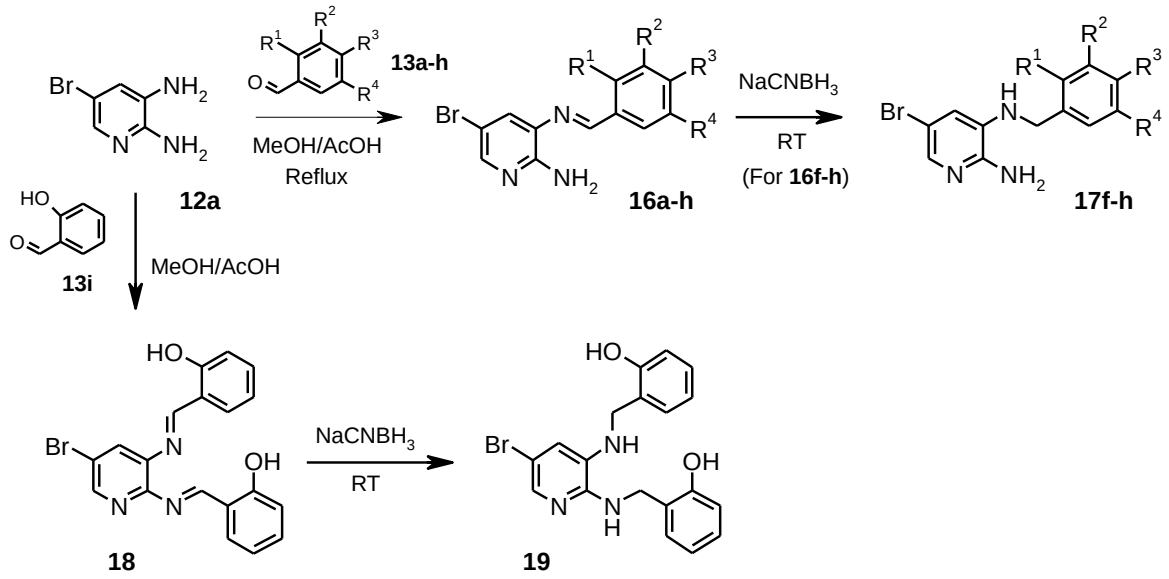


	a	b	c	d	e	f	g	h	i	j
R^1	OH	OH	OH	OH	H	H	OH	NO_2	OH	H
R^2	H	OH	Cl	OH	OH	H	H	OCH_3	OCH_3	OH
R^3	H	OH	H	H	H	Cl	H	H	H	OH
R^4	NO_2	H	Cl	H	H	H	Cl	H	H	H

Scheme 2. Synthesis of 2-phenyl-4-azabenzimidazoles **14a,c-h** and **15a**,**d**,**g**,**i**,**j** and the 2-amino-3-(2,3,4-trihydroxybenzylimino)pyridine **14b'.**

Access to 2-phenylazabenzimidazoles *via* acetic acid-mediated condensation of 2,3-diaminopyridines and triethyl orthoformate, followed by C-2 arylation, has been reported previously,[17,21] but the C-2 arylation step requires the use of expensive reagents, and the number of possible derivatives appears to be limited. Consequently, we employed a modification of the method reported by Singh *et al*.,[22] who condensed selected benzaldehydes with diaminopyridines in refluxing nitrobenzene, and purified the crude product by flash chromatography. However, given the high boiling point of nitrobenzene (211 °C) and the high polarity of the azabenzimidazole products, we found it possible to conduct reactions of the 2,3-diaminopyridines **12a,b** with selected benzaldehydes (Scheme 2) in nitrobenzene at a lower temperature (170 °C). The crude mixtures were allowed to cool to room temperature, and the products were precipitated by dilution with ethyl acetate, which was also used to wash away unreacted starting materials and the nitrobenzene to afford compounds **14a,c-h** and **15a**,**d**,**g**,**i**,**j** in yields of 61-89% (Table 1). Uncharacteristically under these conditions, reaction of 2,3-diaminopyridine **12a** with the trihdroxybenzaldehyde **13b** afforded, in 73% yield, the 2-amino-3-(2,3,4-trihydroxybenzylimino)pyridine **14b'** instead of the expected azabenzimidazole **14b**. Most of these products are new and were fully characterised by ^{1}H- and ^{13}C-NMR and HRMS analysis. Wah and Bangarigadu-Sunasy[23] isolated the 2-(2,3-dihydroxyphenyl)-4-azabenzimidazole **14d** in 2013 and reported ^{1}H NMR multiplets at 6.72-8.32 ppm for the six aromatic protons. At higher field (600 MHz), however, we have been able to resolve all the signals, including the amino and hydroxy proton signals.

In order to increase conformational flexibility between the pyridyl and aryl rings, we had hoped to prepare 2-amino-3-(benzylimino)pyridine, a putative intermediate in azabenzimidazole synthesis.[24] NMR analysis of the crude mixture following premature cooling of a reaction of 2,3-diaminopyridine **12a** with benzaldehyde, however, failed to provide any evidence of this intermediate. On the other hand, the brominated analogues, the 2-amino-5-bromo-3-(benzylimino)pyridines **16a-h** could be generated by regioselective condensation of 2,3-diamino-5-bromopyridine **12b** with the substituted benzaldehydes **13a**-**h** under mild acidic conditions using a catalytic quantity of glacial acetic acid and methanol as a solvent system (Scheme 3). The α-amino group is less nucleophilic than the β-amino group due to delocalisation of the nitrogen lone-pair electrons in the α-amino group towards the pyridyl nitrogen.[25-27] After reaction of the starting materials for 20 minutes under reflux, the desired products were obtained in yields of 65--88% (Table 1).

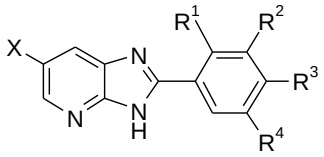


Scheme 3. Synthesis of 2-amino-5-bromo-3-(benzylimino)pyridines **16a-h** and related compounds.

Selected benzylimino derivatives (**16f-h**) were treated with sodium cyanoborohydride in methanol to afford the corresponding benzylamino analogues **17f**-**h** with a view to assessing the influence of the imino moiety on bioactivity. Regioselective reaction of the β-amino group of 2,3-diamino-5-bromopyridine **12b** was attempted using one equivalent of salicylaldehyde **13i**, but 5-bromo-2,3-bis-(2-hydroxybenzylimino)pyridine **18** was the only product isolated. Reduction of the bis-imino compound **18** to 5-bromo-2,3-bis-(2-hydroxybenzylamino)pyridine **19** was effected using two equivalents of sodium cyanoborohydride. 2-Amino-5-bromo-3-(3,4-dihydroxybenzylimino)pyridine **16b** has been isolated previously by Ramos *et al*.,[28] who used microwave-assisted methodology. All of the other 2-amino-5-bromo-3-(benzylimino)pyridines (**16a, c-h)** are new.

The cytotoxicity of the phenyl-4-azabenzimidazoles **14a-h** and **15a**,**d**,**g**,**i**,**j** was assessed against HeLa (human cervix adenocarcinoma) cells at a concentration of 20 μM. A resazurin-based assay was used to determine the percentage of surviving cells. Of the compounds tested, only **14a** showed significant toxicity against HeLa cells (< 50% survival, Table 1; Figure 2). Unsurprisingly, perhaps, two of the compounds containing nitro groups in this series exhibited the lowest HeLa survival levels (**14a**: 41%; **14h**: 55%). However, the 5-bromo analogue **15a**, which also contains a nitro group, exhibited a much higher HeLa cell viability of 87%, illustrating the generally lower toxicity of the 5-bromo derivatives (**15**).

Table 1. Yields and bioassay data for 2-phenyl-4-azabenzimidazoles **14a-h** and **15a**,**d**,**g**,**i**,**j** at 20 μM, with standard deviations in parentheses



Compd.	Yield (%)	R^1	R^2	R^3	R^4	X	HeLa cell viability[a] (%)	*P.falciparum* viability[b] (%)	*T. brucei* viability[c] (%)	IC_{50} (μM)
14a	78	OH	H	H	NO_2	H	41 (1.5)	148 (4.2)	88 (2.8)	
14b[d]	73	OH	OH	OH	H	H	70 (0.3)	123 (2.7)	17 (0.9)	1.3
14c	80	OH	Cl	H	Cl	H	86 (10.8)	128 (0.3)	104 (7.0)	
14d	68	OH	OH	H	H	H	75 (2.4)	51 (9.0)	20 (3.1)	11.8
14e	61	H	OH	H	H	H	79 (4.0)	125 (15.4)	83 (3.2)	
14f	88	H	H	Cl	H	H	80 (5.0)	113 (26.9)	99 (0.5)	
14g	77	OH	H	H	Cl	H	94 (6.6)	71 (4.4)	97 (0.1)	
14h	81	NO_2	OCH_3	H	H	H	55 (8.0)	83 (11.8)	61 (2.1)	
15a	75	OH	H	H	NO_2	Br	87 (14.5)	112 (10.6)	33 (3.1)	
15d	67	OH	OH	H	H	Br	107 (8.7)	93 (0.3)	20 (0.9)	11.9
15g	89	OH	H	H	Cl	Br	94 (0.8)	124 (6.1)	111 (2.2)	
15i	63	OH	OCH_3	H	H	Br	81 (14.3)	106 (3.4)	36 (0.5)	
15j	63	H	OH	OH	H	Br	82 (3.0)	100 (12.9)	43 (3.1)	

[a] Control: Emetine IC_{50} 0.02 - 0.09 μM. [b] Control: Chloroquine IC_{50} -0.01 – 0.03 μM. [c]Control: Pentamidine IC_{50} 0.0005 - 0.02 μM. [d] 2-amino-3-(2,3,4-trihydroxybenzylimino)pyridine.

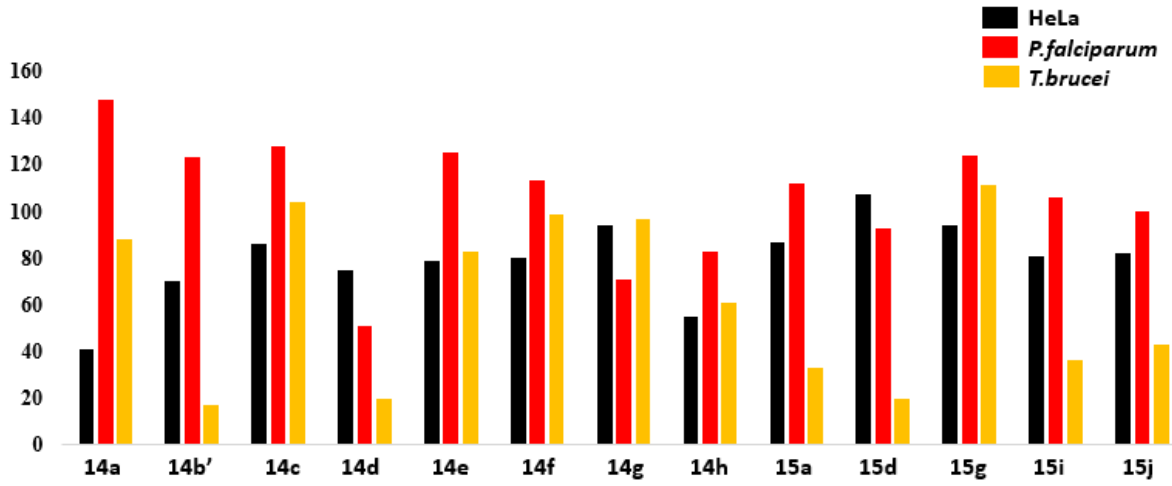


Figure 2. Biological activity of compounds **14a**,**c-h**, **14b'** and **15a**,**d**,**g**,**i**,**j** at 20 μM**.** Activity against *T. brucei and P. falciparum* measured as % survival of the parasites. Tabulated data, including standard deviations, are to be found in Table 1 and in the Supplementary Material.

When compounds **14a**,**c-h**, **14b'** and **15a**,**d**,**g**,**i**,**j** were screened for antimalarial activity (Table 1 and Figure 2), compound **14d** displayed modest activity (51% *P. falciparum* viability) but the remaining compounds showed little if any significant activity against *P. falciparum*. These compounds were also screened against *T. brucei* at 20 μM, with compounds **14b'**, **14d** and **15a,d,i,j** showing significant activity. Interestingly, while compound **14a** decreased *T. brucei* parasite viability to 88%, the 5-bromo analogue **15a** was far more active with percent parasite viability dropping to 33%. In contrast, compound **14d** and its 5-bromo analogue **15d** exhibited similar activity against *T. brucei* (20% parasite viability). With a parasite viability of 20% and a HeLa cell viability of 93%, compound **15d** exhibited the best "selectivity index" against *T. brucei*.

Compounds **16a-h**, **17f-h, 18** and **19**, in which the imidazole ring is absent, were also assessed for their cytotoxicity and activity against *P. falciparum* and *T. brucei* (Figure 3, Table 2). None of them were found to be significantly cytotoxic with viability of the HeLa cells ranging from 53% to 109%. The PLDH (*P. falciparum,* strain 3D7) bioassays were conducted at 20 μM, and revealed that compounds **16a** and **16d** exhibited promising activities against *P. falciparum* with percentage viabilities of 35 and 32%, respectively. The *T. brucei* data indicated that, at 20 μM, five of these compounds **16a**,**d**,**h**, **17h**, and **18** were active against the parasite (*ca.* 20% viability or less). 5-Bromo-2,3-bis-(2-hydroxybenzylimino)pyridine **18** showed the greatest activity, limiting *T. brucei* viability to 7%, but having an IC_{50} value (43 μM) somewhat higher than those of the other active compounds. The bis-amino analogue **19**, however, proved to be completely inactive against *T. brucei*.

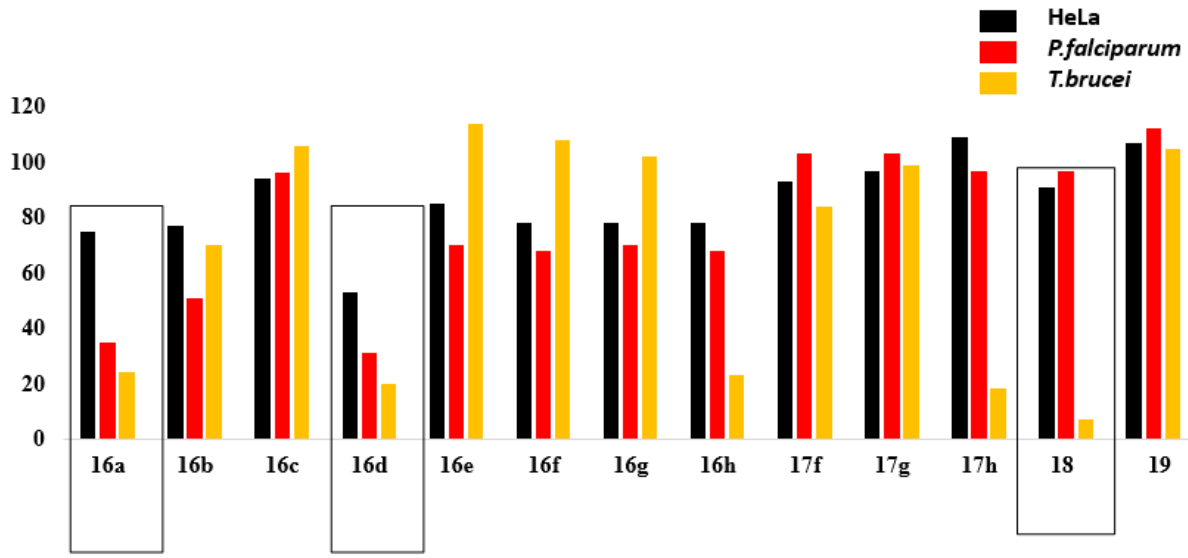
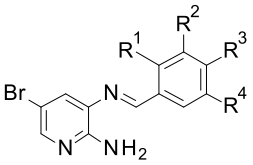
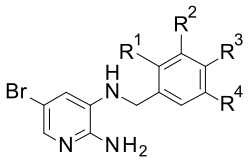
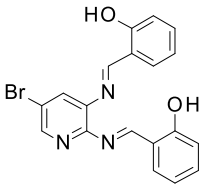
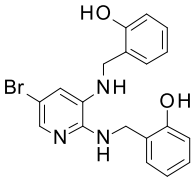


Figure 3. Biological activity of compounds **16a-h, 17f-h, 18 and 19** at 20 μM. Activity against *T. brucei* and *P. falciparum* measured as % survival of the parasites. Tabulated data, including standard deviations, are to be found in Table 2 and in the Supplementary Material.

Table 2. Yields and bioassay data for 2,3-diamino-5-bromopyridine derivatives **16a-h**, **17f-h**, **18** and **19** at 20 μM, with standard deviations in parentheses

Compd.	Yield (%)	R^1	R^2	R^3	R^4	Hela cell viability[a] (%)	*P.falciparum* viability[b] (%)	*T.brucei* viability[c] (%)	IC_{50} (μM)
									
16a	65	OH	OH	OH	H	75 (1.0)	35 (17.6)	24 (0.2)	1.3
16b	71	H	OH	OH	H	77 (12.1)	51 (1.6)	70 (3.6)	
16c	76	OH	H	H	Cl	94 (11.8)	96 (19.1)	106 (6.6)	
16d	76	OH	Cl	H	Cl	53 (0.5)	31 (9.7)	20 (0.3)	6.6
16e	86	OH	OCH_2CH_3	H	H	85 (0.9)	70 (1.1)	114 (6.2)	
16f	81	OH	OCH_3	H	H	78 (3.0)	68 (3.4)	108 (1.4)	
16g	78	OH	H	OCH_3	H	78 (1.8)	70 (8.4)	102 (4.5)	
16h	88	OH	Br	H	Br	78 (6.4)	68 (7.0)	23 (1.7)	11.2
									
17f	89	OH	OCH_3	H	H	93 (15.6)	103 (3.6)	84 (1.5)	
17g	94	OH	H	OCH_3	H	97 (4.9)	103 (2.7)	99 (1.4)	
17h	90	OH	Br	H	Br	109 (5.1)	97 (7.7)	18 (0.7)	6.5
18	72					91 (2.3)	97 (12.7)	7 (1.8)	42.8
19	81					107 (14.0)	112 (6.6)	105 (3.6)	

[a] Control: Emetine IC_{50} 0.02 - 0.09 μM. [b] Control: Chloroquine IC_{50} -0.01 – 0.03 μM. [c] Control: Pentamidine IC_{50} 0.0005 - 0.02 μM.

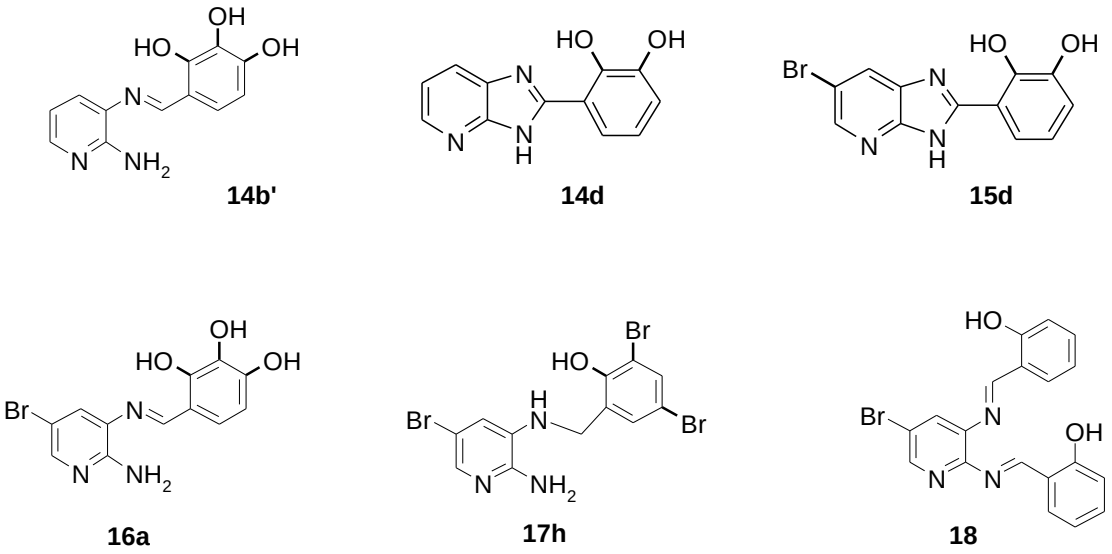


Figure 4. Structures of selected synthesised compounds exhibiting promising trypanocidal activities.

Based on the bioassay data summarised in Tables 1 and 2 and illustrated in Figures 2,3 and 5, several interesting structure-activity patterns may be identified.

i) With two exceptions (**14b'** and **14d**), the initial series of compounds (Table 1) exhibit little, if any, activity against either *P. falciparum* or *T. brucei*. The 2,3-dihydroxyphenyl and 2,3,4-trihydroxyphenyl groups in compounds **14b'** and **14d**, respectively, appear to be critical activating features (Figure 4) producing corresponding IC_{50} values of 1.3 and 11.8 μM against *T. brucei* (Figure 5).

ii) Introduction of the 5-bromo substituent enhances activity against *T. brucei*, with four of the five brominated analogues (**15a**,**d**,**i** and **j**) decreasing *T. brucei* viability to below 44% (compound **15i** with an IC_{50} value of 11.2 μM). This effect is clearly evident on comparing the *T. brucei %* viability data for compound **14a** (88%) and its 5-bromo analogue **15a** (33%).

iii) A number of the (phenylimino)pyridine derivatives (**16**; Figure 3) were found to exhibit interesting activity against *P. falciparum* and/or *T. brucei*. Common features amongst the active compounds were the presence of 2,3,4-trihydroxyphenyl (**16a**), 2-hydroxy-3,5-dichlorophenyl (**16d**) or 2-hydroxy-3,5-dibromophenyl (**16h**) moieties.

iv) Reduction of the imino group in the (benzylimino)pyridine derivatives **16f-g** to afford the corresponding benzylamino analogues **17f-g** resulted in the loss of the weak antimalarial activity of all three of the former compounds (*ca*. 70% parasite viability). Compound **17h** retains the promising activity against *T. brucei* exhibited by its benzylimino precursor **16h** (both compounds containing the 2-hydroxy-3,5-dihalophenyl motif); compound **17h**, however, exhibits selective activity against *T. brucei*.

v) Reduction of the imino group in the highly active 5-bromo-2,3-bis-(2-hydroxybenzylimino)pyridine **18** to the diamino analogue **19** is accompanied by a complete loss of the promising activity (7% parasite viability) of the precursor **18** against *T. brucei*.

vi) Most of the synthesised compounds exhibit relatively little, if any, toxicity against HeLa cells.

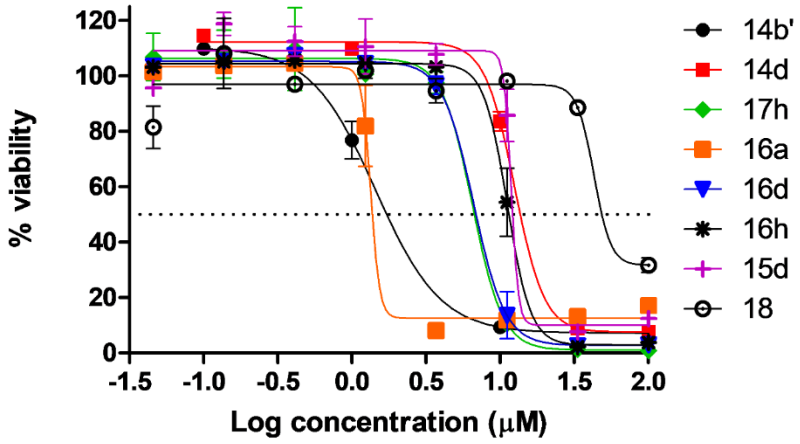


Figure 5. The anti-trypanosomal activity of compounds **14b'**, **14d, 16a, 15d, 16d, 16h, 17h** and **18** showing IC_{50} values against *T. brucei*.

Conclusions

A series of 2-phenyl-4-azabenzimidazole derivatives and 2-amino-5-bromo-3-(benzylimino)pyridine derivatives have been successfully obtained in yields of 61-88% from reactions of various benzaldehyde precursors with 2,3-diaminopyridine and its 5-bromo analogue. Reduction of selected 3-(benzylimino)pyridine derivatives and the 5-bromo-2,3-bis-(2-hydroxybenzylimino)pyridine with sodium cyanoborohydride afforded the corresponding amino analogues in good yield (81-94%). The synthesised compounds were screened for cytotoxicity against HeLa cells and for activity against the protozoan parasites, *P. falciparum* and *T. brucei*. A number of the compounds exhibited promising activity against *T. brucei*, and inspection of the bioassay data has revealed several significant structure-activity relationship trends involving the phenyl substitution patterns and the presence of the bromo substituent in the pyridine moiety.

Experimental Section

General. Reagents were purchased from Sigma-Aldrich. Thin layer chromatography (TLC) was performed using pre-coated silica gel plates (visualized under a UV lamp) and column chromatography was conducted using silica gel with hexane/ethyl acetate gradient solvent systems. NMR spectra were obtained using Bruker Avance 300 and 400 MHz NMR spectrometers; chemical shifts (δ/ppm) are reported relative to residual proton signals in the deuterated solvents (Chloroform, 7.26 ppm and DMSO-d_6, 2.5 ppm), and the data were analysed using Mestrenova®. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer with a diamond window, and melting points were measured using a hot stage apparatus. HRMS analyses were performed at Rhodes University and at the Central Analytical Facility of the University of Stellenbosch.

Synthetic methods. Preparative methods and analytical data are provided below. NMR spectra are provided in the Supplementary Material file. The absence of ^{13}C signals in some cases is attributed to tautomerism-induced line-broadening effects.

General procedure for the synthesis of the 2-phenyl-4-azabenzimidaoles (14) and (15) is illustrated by the following example. A solution of 2,3-diaminopyridine (100 mg, 0.9 mmol) and 2-hydroxy-5-nitrosalicylaldehyde (154 mg, 0.9 mmol) in nitrobenzene (10 mL) was heated (*ca*. 170 °C) under reflux with vigorous stirring, and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and diluted with EtOAc (50 mL), stirred and filtered under vacuum. The filtrate was washed with EtOAc (2 x 40 mL) to remove the nitrobenzene and give *2-(2-hydroxy-5-nitrophenyl)-4-azabenzimidazole* **14a** as a brown solid (184 mg, 78%), mp > 300 °C (dec.); δ_H (400 MHz; DMSO-d_6) 14.14 (1H, s, NH), 9.18 (1H, d, *J* 2.8 Hz, Ar-H), 8.46 (1H, dd, *J* 4.8, 1.4 Hz, Ar-H), 8.28 (1H, dd, *J* 9.2, 2.8 Hz, Ar-H), 8.15 (1H, dd, *J* 8.0, 1.2 Hz, Ar-H), 7.37 (1H, dd, *J* 8.1, 4.8 Hz, Ar-H) and 7.24 (1H, d, *J* 9.2 Hz, Ar-H); δ_C (100 MHz; DMSO-d_6) 164.3, 151.8, 145.3, 139.9, 128.0, 124.0, 119.6, 118.8 and 113.1 (Ar-C); HRMS: *m/z* Calc. for $C_{12}H_9N_4O_3$ (MH^+) 257.0675, Found 257.0671.

2-Amino-3-(2,3,4-trihydroxyphenylimino)pyridine (14b') was isolated as a brown solid (163 mg, 73%); mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6): 12.70 (1H, s, OH), 8.67 (1H, s, N=CH), 7.85 (1H, d, *J* 5.7 Hz, Ar-H), 7.35 (1H, d, *J* 7.5 Hz, Ar-H), 6.97 (1H, d, *J* 8.5 Hz, Ar-H), 6.62 (1H, m, *J* 7.5, 4.9 Hz, Ar-H), 6.44 (1H, d, *J* 8.4 Hz, Ar-H) and 5.76 (2H, s, NH_2); δ_C/ppm (100 MHz; DMSO-d_6) 163.4, 154.0, 150.3, 150.2, 145.4, 132.4, 130.2, 124.8, 123.8, 113.0 and 107.8 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{12}N_3O_3$ $(M+H)^+$ 246.0879, Found 246.0874.

2-(3,5-Dichloro-2-hydroxyphenyl)-4-azabenzimidazole (14c). Brown solid (206 mg, 80%), mp > 300 °C (dec,); δ_H/ppm (400 MHz; DMSO-d_6) 14.03 (1Hs, NH), 8.45 (1H, d, *J* 4.6 Hz, Ar-H), 8.20 (1H, d, *J* 2.4 Hz, Ar-H), 8.14 (1H, d, *J* 7.9 Hz, Ar-H), 7.72 (1H, d, *J* 2.4 Hz, Ar-H) and 7.37 (1H, dd, *J* 8.1, 4.8 Hz, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 153.4, 151.5, 145.2, 131.4, 124.8, 122.8, 122.3, 119.3 and 114.2 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_8Cl_2N_3O$ $(M+H)^+$ 280.0044, Found 280.0045.

2-(2,3-Dihydroxyphenyl)-4-azabenzimidazole (14d). Brown solid (142 mg, 68%). mp > 300 °C (dec.); δ_H/ppm (600 MHz; DMSO-d_6) 13.01 (1H, s, NH or OH), 9.21 (1H, s, OH), 8.40 (1H, s, Ar-H), 8.07 (1H, d, *J* 51.9 Hz, Ar-H), 7.56 (1H, s, Ar-H), 7.32 (1H, dd, *J* 8.0, 4.8 Hz, Ar-H), 6.94 (1H, d, *J* 7.6 Hz, Ar-H) and 6.84 (1H, t, *J* 7.4 Hz, Ar-H); δ_C/ppm (150 MHz; DMSO-d_6) 153.8, 147.5, 146.4, 144.4, 129.9, 125.9 – 125.3, 123.4, 119.1, 118.7, 118.1, 116.9 – 116.6 and 112.1 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.0773, Found 228.0752.

2-(3-Hydroxyphenyl)-4-azabenzimidazole (14e). Brown solid (119 mg, 61%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.49 (1H, s, OH), 13.10 (1H, s, OH) [may be due to rotational isomerism], 9.80 (1H, s NH), 8.34 (1H, dd, *J* 22.4, 4.0 Hz, Ar-H), 8.04 (1H, d, *J* 7.9 Hz, Ar-H), 7.63 (2H, d, *J* 9.4 Hz, Ar-H), 7.36 (1H, q, *J* 8.2 Hz, Ar-H), 7.24 (1H, dd, *J* 8.0, 4.8 Hz, Ar-H) and 6.99 – 6.89 (1H, m, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 158.1, 144.2, 131.0, 130.6, 118.6, 118.2, 118.0 and 113.9 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{10}N_3O$ $(M+H)^+$ 212.0824, Found 212.0820.

2-(4-Chlorophenyl)-4-azabenzimidazole (14f). Brown solid (186 mg, 88%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.50 (1H, s, NH), 8.35 (1H, d, *J* 3.8 Hz, Ar-H), 8.24 (2H, d, *J* 8.5 Hz, Ar-H), 8.02 (1H, d, *J* 5.1 Hz, Ar-H), 7.65 (2H, d, *J* 8.5 Hz, Ar-H) and 7.26 (1H, dd, *J* 8.0, 4.8 Hz, Ar-H). δ_C/ppm (100 MHz; DMSO-d_6) 144.1, 135.2, 129.1, 128.5, 128.4, and 118.3 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9ClN_3$ $(M+H)^+$ 230.0485, Found 230.0502.

2-(5-Chloro-2-hydroxyphenyl)-4-azabenzimidazole (14g). Brown solid (174 mg, 77%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.89, 13.42, 13.11 and 12.81 (2H, m, NH and OH), 8.43 (s, 1H), 8.24 (s, 1H), 8.15 (IH, s, Ar-H), 7.45 (1H, dd, *J* 8.8, 2.4 Hz, Ar-H), 7.35 (1H, dd, *J* 8.0, 4.8 Hz, Ar-H) and 7.10 (IH, d, *J* 8.8 Hz, Ar-H); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9ClN_3O$ $(M+H)^+$ 246.0434, Found 246.0451.

2-(4-Methoxy-3-nitrophenyl)-4-azabenzimidazole (14h). Brown solid (201 mg, 81%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.78 (1H, S, NH), 8.40 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 7.78 – 7.69 (2H, m, Ar-H), 7.53 (1H, d, *J* 8.2 Hz, Ar-H), 7.29 (1H, dd, *J* 8.0, 4.7 Hz, Ar-H) and 3.96 (3H, s, O-CH_3); δ_C/ppm (100 MHz; DMSO-

d_6) 151.0, 144.8, 139.7, 131.8, 122.1 and 115.5 (Ar-C) and 57.0 (OCH_3); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{11}N_4O_3$ $(M+H)^+$ 271.0831, Found 271.0854.

6-Bromo-2-(2-hydroxy-5-nitrophenyl)-4-azabenzimidazole (15a). Black solid (133 mg, 75 %), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.83 (1H, s, NH), 9.12 (1H, s, Ar-H), 8.50 (1H, s, Ar-H), 8.36 (1H, s, Ar-H), 8.26 (1H, d, *J* 8.4 Hz, Ar-H) and 7.22 (1H, d, *J* 9.1 Hz, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 163.7, 152.4, 145.3, 139.6, 127.7, 124.0, 118.4 and 113.8 and 112.8 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_8N_4O_3$ $(M+H)^+$ 334.9780; Found 334.9775.

6-Bromo-2-(2,3,-dihydroxyphenyl)-4-azabenzimidazole (15d). Black solid (115 mg, 71 %), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.95, 12.63 (2H, br s x 2, OH), 9.34 (1H, s, Ar-H), 8.45 (1H, s, Ar-H), 7.57 (1H, d, *J* 7.8 Hz, Ar-H), 6.96 (1H, d, J 7.6 Hz Hz, Ar-H) and 6.83 (1H, t, *J* 7.8 Hz, Ar-H).. δ_C/ppm (100 MHz; DMSO-d_6) 155.0, 146.4, 144.6, 119.2, 118.3, 116.9 and 113.4 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9BrN_3O_2$ $(M+H)^+$ 305.9878, Found 305.9879.

6-Bromo-2-(2-hydroxy-5-chlorophenyl)-4-azabenzimidazole (15g). Black solid (153 mg, 89%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 13.19 (2H, s, NH or OH), 8.46 (1H, s, Ar-H), 8.31 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 7.43 (1H, d, *J* 8.1 Hz, Ar-H) and 7.06 (1H, d, *J* 8.7 Hz, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 156.9, 153.0, 145.0, 132.2, 126.4, 123.0, 119.2 and 113.6 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_8BrClN_3O$ $(M+H)^+$ 323.9539, Found 323.9514.

6-Bromo-2-(2-hydroxy-3-methoxyphenyl)-4-azabenzimidazole (15i). Black solid (107 mg, 63%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 12.80, 12.46 (1H, br s x 2, NH), 12.68 (1H, d, *J* 156.7 Hz, OH), 8.47 (1H, s, Ar-H), 8.23 (1H, d, *J* 7.9 Hz, Ar-H), 7.68 (1H, dd, *J* 11.9, 7.7 Hz, Ar-H), 7.13 (1H, d, *J* 7.8 Hz, Ar-H), 6.96 (1H, t, *J* 8.0 Hz, Ar-H), 3.84 (3H, s, OCH_3); δ_C/ppm (100 MHz; DMSO-d_6) 148.6, 144.7, 135.3, 129.8, 123.3, 119.0, 118.2, 114.7 and 113.5 (Ar-C) and 55.8 (O-CH_3); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{11}BrN_3O_2$ $(M+H)^+$ 320.0035, Found 320.0041.

6-Bromo-2-(3,4-dihydroxyphenyl)-4-azabenzimidazole (15j). Black solid (108 mg, 66.8%), mp > 300 °C (dec.); δ_H/ppm (400 MHz; DMSO-d_6) 9.65 (1H, s, OH), 9.32 (1H, s, OH), 8.32 (1H, s, Ar-H), 8.23 (1H, d, *J* 8.1 Hz, ArH), 7.65 (1H, s,Ar-H), 7.53 (1H, d, *J* 7.8 Hz, Ar-H) and 6.89 (1H, d, *J* 8.1 Hz, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 148.6, 145.7, 135.3, 129.9, 123.3, 120.4, 119.0, 115.8 and 114.4(Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9BrN_3O_2$ $(M+H)^+$ 305.9878, Found 305.9877.

General procedure for the synthesis of the 2-amino-5-bromo-3-(benzylimino)pyridines **16a-h** is illustrated by the following example. In a 50 ml round-bottom flask equipped with a reflux condenser, 2,3-diamino-5-bromopyridine (100 mg, 0.5 mmol) was dissolved in methanol (20 mL). One equivalent of 2,3,4-trihydroxybenzaldehyde (81.7 mg, 0.5 mmol) and acetic acid (0.2 mL) were added. The resulting mixture was stirred at *ca.* 50 °C and the progress of the reaction was monitored by thin layer chromatography. At the completion of the reaction, the crude solution was cooled to room temperature, diluted with hexane (50 mL) and the precipitate filtered under vacuum and washed with hexane (3 × 50 mL) to afford *2-amino-5-bromo-3-(2,3,4-trihydroxybenzylimino)pyridine* **16a** as a yellow solid (112 mg, 65%), mp 150-152 °C; ν_{max}/cm^{-1}: 3459, 3296 (NH), 3147 (OH), 1645 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 8.70 (1H, s, N=C-H), 7.90 (1H, d, *J* 2.1 Hz, Ar-H), 7.57 (1H, d, *J* 2.1 Hz, Ar-H), 7.00 (1H, d, *J* 8.5 Hz, Ar-H), 6.45 (1H, d, *J* 8.5 Hz, Ar-H) and 6.03 (2H, s, NH_2); δ_C/ppm (100 MHz; DMSO-d_6) 164.5 (N=C-H), 153.2, 150.7, 150.1, 145.0, 132.4, 131.7, 126.8, 124.1, 113.0, 107.9 and 105.7 (Ar-C); ESI LC-MS: *m/z* Calc. for $C_{12}H_{11}BrN_3O_3$ $(M+H)^+$ 323.9984, Found 323.9994.

2-Amino-5-bromo-3-(3,4-dihydroxybenzylimino)pyridine (16b) Yellow solid (116 mg, 71%), mp 138-140 °C; ν_{max}/cm^{-1}: 3421, 3344 (NH_2), 3076 (OH), 1588 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 9.49 (2H, br s, OH), 8.49 (1H, s, Ar-H), 7.85 (1H, d, *J* 2.0 Hz, Ar-H), 7.52 (1H, d, *J* 2.0 Hz, Ar-H), 7.43 (1H, d, *J* 1.6 Hz, Ar-H), 7.28 (1H, dd, *J* 8.1, 1.6 Hz, Ar-H), 6.84 (1H, d, *J* 8.1 Hz, Ar-H), 6.02 (2H, s, NH_2); δ_C/ppm (100 MHz; DMSO-d_6) 160.8 (N=C-H),

153.8, 149.6, 145.6, 144.7, 132.8, 127.9, 125.1, 122.7, 115.4, 115.1 and 105.5 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{11}BrN_3O_2$ $(M+H)^+$ 308.0035, Found 308.0047.

2-Amino-5-bromo-3-(5-chloro-2-hydroxybenzylimino)pyridine (16c). Yellow solid (132 mg, 76%), mp 116-118 °C; ν_{max}/cm^{-1}: 3483, 3295 (NH), 3143 (OH), 1579 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 11.56 (1H, br s, OH), 8.84 (1H, s, N=C-H), 7.94 (1H, d, *J* 2.2 Hz, Ar-H), 7.90 (1H, d, *J* 2.7 Hz, Ar-H), 7.58 (1H, d, *J* 2.2 Hz, Ar-H), 7.44 – 7.39 (1H, dd, Ar-H), 7.00 (1H, d, *J* 7.3 Hz, Ar-H), 6.24 (2H, s, NH_2); δ_C/ppm (100 MHz; DMSO-d_6) 160.2 (N=C-H), 157.7, 153.7, 146.1, 132.8, 131.42, 129.7, 126.6, 123.0 , 122.0, 118.5 and 105.4 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{10}BrClN_3O$ $(M+H)^+$ 325.9696, Found 325.9702.

2-Amino-5-bromo-3-(3,5-dichloro-2-hydroxybenzylimino)pyridine (16d). Orange solid (145.4 mg, 76%), mp 108-110 °C; ν_{max}/cm^{-1}: 3464, 3376 (NH), 1574 (C=N); δ_H/ppm 400 MHz; DMSO-d_6) 13.19 (1H, br s, OH), 9.42 (1H, s, N=C-H), 7.97 (1H, d, *J* 2.5 Hz, Ar-H), 7.78 (1H, d, *J* 1.9 Hz, Ar-H), 7.74 (1H, d, *J* 2.4 Hz, Ar-H), 7.38 (1H, d, *J* 2.0 Hz, Ar-H) and 5.85 (2H, s, NH_2). Δ_C/ppm (100 MHz; DMSO-d_6) 162.8 (N=C-H), 154.4, 153.4, 146.8, 132.2, 130.4, 130.2, 127.8, 122.7, 121.8, 121.6 and 105.3 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9BrCl_2N_3O$ $(M+H)^+$ 359.9306, Found 359.9301.

2-Amino-5-bromo-3-(3-ethoxy-2-hydroxybenzylimino)pyridine (16e). Orange solid (153 mg, 86%), mp 130-132 °C; ν_{max}/cm^{-1}: 3439, 3352 (NH), 3235 (OH), 1591 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 12.07 (1H, br s, OH), 9.41 (1H, s, N=C-H), 7.75 (1H, d, *J* 2.1 Hz, Ar-H), 7.41 (1H, d, *J* 7.2 Hz, Ar-H), 7.33 (1H, d, *J* 2.1 Hz, Ar-H), 7.13 (1H, d, *J* 7.2 Hz, Ar-H), 6.89 (1H, t, *J* 7.9 Hz, Ar-H), 5.71 (2H, s, NH_2), 4.08 (2H, q, *J* 6.9 Hz, O-CH_2), 1.36 (3H, t, *J* 6.9 Hz, CH_3); δ_C/ppm (100 MHz; DMSO-d_6) 161.01 (N=C-H), 150.3, 147.1), 142.8, 140.7, 135.3, 123.8, 123.7), 119.9, 118.9, 118.8 and 116.9 (Ar-C), 64.1 (O-CH_2) and 14.7 (CH_3); ESI HPLC-MS: *m/z* Calc. for $C_{15}H_{15}BrN_2O_2$ $(M+H)^+$ 336.0348, Found 336.0348.

2-Amino-5-bromo-3-(2-hydroxy-3-methoxybenzylimino)pyridine (16f). Brown solid (138 mg, 81%), mp 136-140 °C; ν_{max}/cm^{-1}: 3441, 3349 (NH), 3237 (OH), 1590 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 11.90 (1H, br s, O-H), 9.42 (1H, s, N=C-H), 7.74 (1H, d, *J* 2.1 Hz, Ar-H), 7.44 (1H, dd, *J* 7.9, 1.1 Hz, Ar-H), 7.33 (1H, d, *J* 2.1 Hz, Ar-H), 7.15 (1H, dd, *J* 8.0, 1.1 Hz, Ar-H), 6.91 (1H, t, *J* 7.9 Hz, ArH) and 5.70 (2H, s, NH_2), 3.84 (3H, s, O-CH_3); δ_C/ppm (100 MHz; DMSO-d_6) 160.6 (N=C-H), 150.0, 148.0, 143.0, 140.8, 135.3, 123.7, 123.3, 120.1, 118.9, 118.8 and 115.7 (Ar-C) and 56.0 (OCH_3); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{13}BrN_3O_2$ $(M+H)^+$ 322.0191, Found 322.0187.

2-Amino-5-bromo-3-(2-hydroxy-4-methoxybenzylimino)pyridine (16g). Yellow solid; mp 116-118 °C; (133 mg, 78%); ν_{max}/cm^{-1}: 3483, 3297 (NH_2), 3155 (OH), 1605 (N=C); δ_H/ppm (400 MHz; DMSO-d_6) 12.32 (1H, s, OH), 8.78 (1H, s, N=C-H), 7.91 (1H, d, *J* 2.0 Hz, Ar-H), 7.61 (1H, d, *J* 8.7 Hz, Ar-H), 7.58 (1H, d, *J* 2.0 Hz, Ar-H), 6.58 (1H, dd, *J* 8.6, 2.3 Hz, Ar-H), 6.58 (1H, dd, *J* 8.6, 2.3 Hz, Ar-H), 6.51 (1H, d, *J* 2.2 Hz, Ar-H), 6.51 (1H, d, *J* 2.2 Hz, Ar-H), 6.07 (2H, s, NH_2), 3.81 (3H, s, OCH_3); δ_C/pp (100 MHz; DMSO-d_6) 163.8 (N=C-H), 163.3, 162.0, 153.3, 145.2, 133.8, 131.7, 126.8, 113.7, 106.9, 105.6, 100.8 (Ar-C) and 55.5 (OCH_3); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{13}BrN_3O_2$ $(M+1)^+$ 322.0191, Found 322.0189.

2-Amino-5-bromo-3-(3,5-dibromo-2-hydroxbenzylimino) (16h). Orange solid (210 mg, 88%), mp 118-120 °C; ν_{max}/cm^{-1}: 3461, 3373 (NH),3067 (OH), 1615 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 13.47 (1H, s, OH), 9.38 (1H, s, N=C-H), 8.09 (d, *J* 2.3 Hz, 1H, Ar-H), 7.95 (d, *J* 2.2 Hz, 1H, Ar-H), 7.79 (d, *J* 2.0 Hz, 1H, Ar-H), 7.39 (d, *J* 2.0 Hz, 1H, Ar-H) and 5.83 (s, 2H, NH_2); δ_C/ppm (100 MHz; DMSO-d_6) 160.1 (N=C-H), 156.3, 149.3, 141.0, 137.7, 135.7, 134.6, 124.7, 121.9, 119.7, 111.3 and 110.3 (Ar-C); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_9Br_3N_3O$ $(M+H)^+$ 446.8217, Found 446.8214.

General procedure for the hydrogenation of imines to amines **17f-h** and **19** is illustrated by the following example. The imino derivative **18** (100 mg, 0.3 mmol) was dissolved in methanol (10 mL) and the solution was cooled to below 10°C. Sodium cyanoborohydride (39.3 mg, 0.6 mmol) was added and the mixture stirred vigorously at room temperature. The progress of the reaction was monitored by thin layer chromatography. At

the completion of the reaction, the crude mixture was concentrated under pressure, ethyl acetate (50 mL) and deionized water (50 mL) were added, and the crude product was extracted into ethyl acetate, dried with anhydrous sodium sulphate, and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel; elution with ethyl acetate - hexane (1:1) to afford the product *5-bromo-2,3-bis(2-hydroxybenzylamino)pyridine* **19** as a white solid (92 mg, 92%), mp 94-98 ^{o}C; ν_{max}/cm^{-1}: 3388 (NH), 3069, 2957 (OH); δ_H/ppm (400 MHz; DMSO-d_6) 10.01 (1H, s, OH), 9.60 (1H, s, OH), 7.35 (1H, d, *J* 2.0 Hz, Ar-H), 7.15 (2H, dd, *J* 10.0, 3.9 Hz, Ar-H), 7.07 (2H, td, *J* 8.5, 1.5 Hz, Ar-H), 6.84 (1H, d, *J* 8.0 Hz, Ar-H), 6.76 (3H, dt, *J* 15.3, 7.6 Hz, Ar-H), 6.57 (d, *J* 2.0 Hz, 1H), 6.55 (1H, t, *J* 5.5 Hz, NH), 5.74 (1H, t, *J* 5.3 Hz, NH), 4.42 (2H, d, *J* 5.5 Hz, CH_2) and 4.19 (2H, d, *J* 5.3 Hz, CH_2); δ_C/ppm (100 MHz; DMSO-d_6) 155.3, 155.2, 146.3, 132.6, 132.4, 129.3, 128.7, 128.0, 127.9, 126.1, 124.1, 118.9, 118.8, 115.5, 115.0, 114.5, 106.6 (Ar-C), 41.3 and 21.0 (CH_2); ESI HPLC-MS: *m/z* Calc. for $C_{19}H_{19}BrN_3O_2$ $(M+H)^+$ 400.0660, Found 400.0665.

2-Amino-5-bromo-3-(2-hydroxy-3-methoxybenzylamino)pyridine (17f). White solid (90 mg, 90%), m.p 116-118 °C; ν_{max}/cm^{-1}: 3434, 3369, 3268 (NH), 2933 (OH); δ_H/ppm (400 MHz; DMSO-d_6) 9.50 (1H, s, OH), 7.36 (1H, d, *J* 2.1 Hz, Ar-H), 6.83 (1H, d, *J* 2.1 Hz, Ar-H), 6.76 (1H, dd, *J* 7.6, 1.4 Hz, Ar-H), 6.73 – 6.67 (2H, overlapping m, Ar-H), 6.32 (1H, t, *J* 5.7 Hz, NH), 5.16 (2H, s, NH_2), 4.42 (2H, d, *J* 5.7 Hz, CH_2), 3.76 (3H, s, O-CH_3); δ_C/ppm (100 MHz; DMSO-d_6) 147.8, 146.3, 144.4, 133.0, 132.5, 126.9, 121.2, 118.6, 118.5, 110.8, 106.1 (Ar-C) and 55.7 (OCH_3) and 45.2 (CH_2); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{15}BrN_3O_2$ $(M+H)^+$ 324.0348, Found 324.0347.

2-Amino-5-bromo-3-(2-hydroxy-4-methoxybenzylamino)pyridine (17g). White solid (89 mg, 89%), mp 122-124 °C ; ν_{max}/cm^{-1}: 3374, 3348, 3273 (NH), 2923, 2852 (OH); δ_H/ppm (400 MHz; DMSO-d_6) 9.63 (1H, s, O-H), 7.26 (1H, d, *J* 2.0 Hz, Ar-H), 7.05 (1H, d, *J* 8.4 Hz, Ar-H), 6.56 (1H, d, *J* 2.0 Hz, Ar-H), 6.41 (1H, d, *J* 2.5 Hz, Ar-H), 6.36 (1H, dd, *J* 8.4, 2.5 Hz, Ar-H), 5.75 (2H, s, NH_2), 5.45 (1H, t, *J* 5.5 Hz, N-H), 4.10 (2H, d, *J* 5.5 Hz, CH_2) and 3.67 (3H, s, O-CH_3); δ_C/ppm (100 MHz; DMSO-d_6) 159.3, 156.0, 147.4, 133.2, 132.2, 129.4, 116.7, 114.9, 106.9, 104.3 and 101.1 (Ar-C), 55.0 (CH_2) and 40.8 (O-CH_3); ESI HPLC-MS: *m/z* Calc. for $C_{13}H_{15}BrN_3O_2$ $(M+1)^+$ 324.0348, Found 324.0348.

2-Amino-5-bromo-3-(3,5-dibromo-2-hydroxybenzylamino)pyridine (17h). White solid (94 mg, 94.4%), mp 122-124 °C; ν_{max}/cm^{-1}: 3409, 3830 (NH), 2930 (OH); δ_H/ppm (400 MHz; DMSO-d_6) 11.97 (1H, s, O-H), 7.62 (1H, d, *J* 2.4 Hz, Ar-H), 7.41 (1H, d, *J* 2.1 Hz, Ar-H), 7.35 (1H, d, *J* 2.4 Hz, Ar-H), 6.90 (d, *J* 2.1 Hz, 1H, Ar-H), 6.84 (1H, t, *J* 6.0 Hz, N-H), 5.24 (2H, s, NH_2) and 4.41 (2H, d, *J* 6.0 Hz, CH_2); δ_C/ppm (100 MHz; DMSO-d_6) 152.0, 145.9, 133.3, 133.0, 132.2, 132.0, 130.8, 119.3, 112.3, 110.2 and 106.7 (Ar-C) and 40.9 (CH_2); ESI HPLC-MS: *m/z* Calc. for $C_{12}H_{11}Br_3N_3O$ $(M+1)^+$ 448.8374, Found 448.8372.

5-Bromo-2,3-bis(2-hydroxybenzylimino)pyridine (18). The procedure described for the synthesis of **16a** was followed using 2,3-diamino-5-bromopyridine (100 mg, 0.5 mmol), salicylaldehyde (0.1 mL, 1.6 mmol), methanol (20 mL) and glacial acetic acid (0.4 mL). 5-Bromo-2,3-bis(2-hydroxybenzylimino)pyridine **18** was isolated as a yellow solid (168 mg, 80%), mp 142-144 °C; λ_{max}/cm^{-1}: 1605 (C=N); δ_H/ppm (400 MHz; DMSO-d_6) 12.90 (1H, br s, OH), 12.45 (1H, s, OH), 9.50 (1H, s, N=C-H), 9.00 (1H, s, N=C-H), 8.52 (1H, s, Ar-H), 8.21 (1H, s, Ar-H), 7.80 (1H, d, *J* 7.4 Hz, Ar-H), 7.71 (1H, d, *J* 7.3 Hz, Ar-H), 7.46 (2H, d, *J* 5.5 Hz, Ar-H) and 7.00 (4-H, dd, *J* 12.6, 6.9 Hz, Ar-H); δ_C/ppm (100 MHz; DMSO-d_6) 166.4 (N=C-H), 164.3 (N=C-H), 161.1, 160.4, 150.3 – 149.8 (overlapping m), 146.7, 140.2 – 139.9 (overlapping m), 134.5, 134.2, 133.0, 132.3, 131.1, 119.6, 119.4, 119.3, 119.3, 118.7, 116.8 and 116.8 [Ar-C]; ESI HPLC-MS: *m/z* Calc. for $C_{19}H_{15}BrN_3O_2$ $(M+H)^+$ 396.0347, Found 396.0349.

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Supplementary Material

Copies of selected ^{1}H, ^{13}C and COSY NMR spectra are presented in the Supplementary Material file associated with this manuscript.

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