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3,5-Diaryl-2-aminopyridines as a Novel Class of Orally Active Antimalarials Demonstrating Single Dose Cure in Mice and Clinical Candidate Potential

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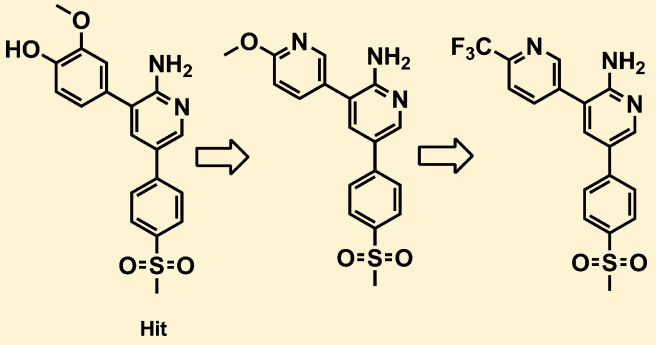
Supporting Information

ABSTRACT: A novel class of orally active antimalarial 3,5-diaryl-2-aminopyridines has been identified from phenotypic whole cell high-throughput screening of a commercially available SoftFocus kinase library. The compounds were evaluated in vitro for their antiplasmodial activity against K1 (chloroquine and drug-resistant strain) and NF54 (chloroquine-susceptible strain) as well as for their cytotoxicity. Synthesis and structure−activity studies identified a number of promising compounds with selective antiplasmodial activity. One of these frontrunner compounds, **15**, was equipotent across the two strains (K1 = 25.0 nM, NF54 = 28.0 nM) and superior to chloroquine in the K1 strain (chloroquine IC_{50} K1 = 194.0 nM). Compound **15** completely cured *Plasmodium berghei*-infected mice with a single oral dose of 30 mg/kg. Dose−response studies generated ED_{50} and ED_{90} values of 0.83 and 1.74 mg/kg for **15** in the standard four-dose Peters test. Pharmacokinetic studies in the rat indicated that this compound has good oral bioavailability (51% at 20 mg/kg) and a reasonable half-life ($t_{1/2}$ ∼ 7−8 h).



INTRODUCTION

Malaria is a disease that is prevalent in many developing countries. According to the World Health Organization 2011 report, malaria is responsible for 216 million clinical cases and 655000 deaths in 2010, especially among children and pregnant women.[1] Malaria is caused by protozoan parasites of the genus *Plasmodium* that infect and destroy red blood cells, leading to fever, severe anemia, cerebral malaria, and, if untreated, death.[2] *Plasmodium falciparum* is the dominant species in sub-Saharan Africa and is responsible for the most deaths. The disease burden is heaviest in African children under 5 years of age. *Plasmodium vivax* causes 25−40% of the global malaria burden, particularly in South and Southeast Asia and Central and South America. The other two main species that are known to infect humans are *Plasmodium ovale* and *Plasmodium malariae*.[1,2]

Various medications are presently used for the treatment of malaria. However, some of these exhibit significant toxicity and undesirable side effects in humans. Drugs used to treat malaria include chloroquine (CQ), quinine, mefloquine, atovaquone/proguanil, doxycycline, hydroxychloroquine, halofantrine, pyrimethamine-sulfadoxine, primaquine, artesunate, and other

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artemisinin derivatives.[3−6] On the other hand, the most promising drug candidates at various stages of clinical testing include OZ439,[7] ferroquine,[8] and T3/SAR97276.[9]

The recent widespread emergence of drug resistance in many tropical countries has compromised many of the current chemotherapies and justifies the continued search for new chemotherapeutic agents capable of circumventing resistance.[10]

3,5-Diaryl-2-aminopyridines were identified from an imaged-based[11] high-throughput screen (HTS) of a BioFocus DPI SoftFocus kinase library[12] as promising selective in vitro antiplasmodial hits (Figure 1). A literature search at the

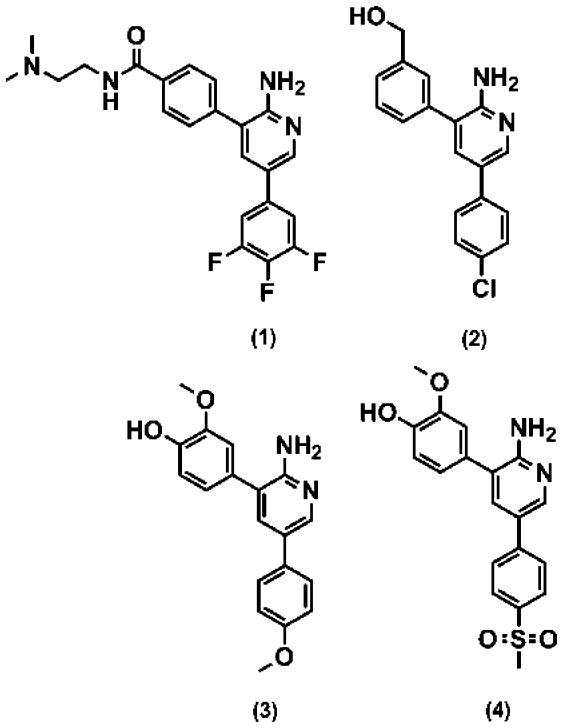

Figure 1. Selected structures of HTS hits.

beginning of this work showed no prior art relating to the antiplasmodial activity of 3,5-disubstituted-2-aminopyridines, although subsequently some examples of this class have been reported in the published GlaxoSmithKline (GSK) Tres Cantos Antimalarial Set (TCAMS).[13] However, antimalarial amino-pyridine-based molecules such as bis-2-aminopyridines and their corresponding ammonium salt derivatives have previously been reported.[14] In addition, 2-aminopyridines have been reported with various pharmacological properties including their mechanism as kinase inhibitors,[15,16] G protein-coupled receptor (GPCR) antagonists,[17] and ion channel modulators.[13,18,19]

The HTS was performed on 36608 compounds of which 442 demonstrated 50% activity at a concentration of 1.82 μM against the 3D7 and Dd2 *P. falciparum* strains. This HTS campaign delivered a number of actives with varying aryl groups at positions 3 and 5 of the aminopyridine core.

These actives are exemplified by compounds **1**−**4** (Figure 1). Analysis of the HTS structure−activity relationship (SAR) from 739 compounds tested gave eight compounds with >80% inhibition at the screening dose of 1.82 μM and revealed that analogues with a methylsulfonylphenyl group at position 5 of the aminopyridine core displayed the best potencies. Compound **4** was selected as a representative example for subsequent hit validation through resynthesis, retesting, and absorption, distribution, metabolism, and excretion (ADME) profiling. This compound, IC_{50} = 49.0 nM, K1 and NF54, was profiled for its in vitro ADME properties and found to have moderate metabolic stability in human liver microsomes with a predicted human hepatic extraction ratio (E_H) of 0.48 and, therefore, was not expected to perform well in vivo. The obvious metabolic hot spot in this compound is in the 2-methoxyphenyl moiety at position 3 of the aminopyridine core. Accordingly, this metabolic hot spot was replaced by a methoxylpyridyl substituent leading to the identification of an equally potent (IC_{50} = 51.0 nM, K1 and NF54) but more metabolically stable (E_H = 0.26) compound, **8** (Figure 2).

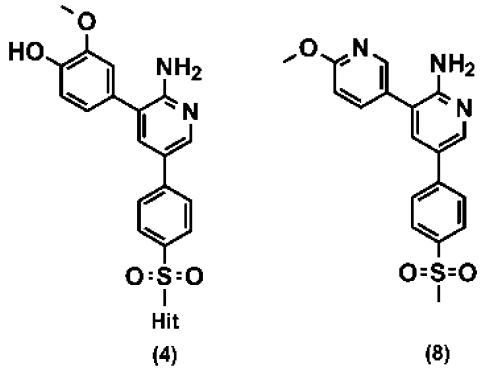

Figure 2. Structures of hit compound **4** and frontrunner **8** aminopyridine derivatives.

When administered by either oral or sc routes at a dose of 50 mg/kg in the standard 4 days Peters test, the animals treated with **8** were cured.[20] In the absence of prior art describing the antimalarial activity of 3,5-diarylaminopyridines, this exciting in vivo activity of **8** triggered a hit to lead (H2L) and lead optimization (LO) campaign aimed at exploring the potential opportunities and liabilities of this class and optimizing in vitro potency, ADME properties, and in vivo efficacy to identify a potential candidate for development.

Here, we report the synthesis and SAR studies around aryl substitution at position 3 of the 2-aminopyridine core to augment the SAR revealed from the HTS data at position 5. Extensive profiling of frontrunner compounds toward identification of a clinical candidate is also reported.

RESULTS AND DISCUSSION

Chemistry. An efficient three-step general synthetic route for obtaining the target compounds **4** and **8**−**38** (Table 1) is shown in Scheme 1. The synthesis started with commercially available 3-bromopyridin-2-amine **5**, which following iodination using iodine in DMSO at 100 °C for 4 h gave 3-bromo-5-iodopyridin-2-amine **6**.[21] A Suzuki cross-coupling reaction,[22,23] with 4-methylsulfonyl-phenyl boronic acid under standard Suzuki reaction conditions, led to a substituted 3-bromopyridin-2-amine intermediate **7**. This intermediate was subjected to a second Suzuki reaction with a range of boronic acids to furnish the target compounds **4** and **8**−**38**. All intermediates and target compounds were purified using column chromatography and fully characterized by a range of analytical and spectroscopic techniques.

In Vitro Antiplasmodial Activity. The activities of all synthesized compounds were determined in vitro against a sensitive (NF54) and drug-resistant (K1) strain of *P.*

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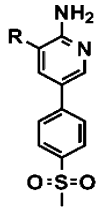
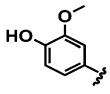
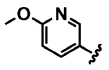
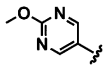
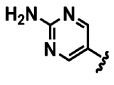
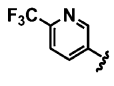
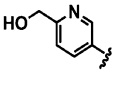
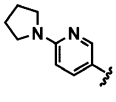
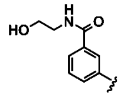
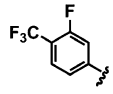
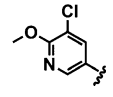
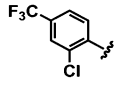
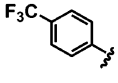
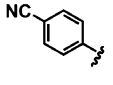
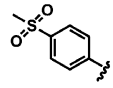
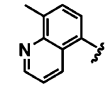
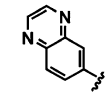
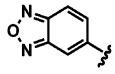
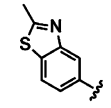
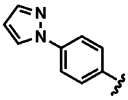
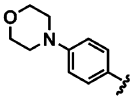
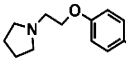
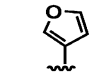
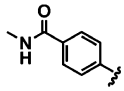
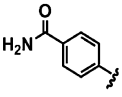
Table 1. In Vitro Antiplasmodial Activity and SAR of Compounds 4 and 8−38



Compound	R	IC50 (μM)[a] K1	IC50 (μM)[a] NF54
Chloroquine[b]		0.194	0.016
Artesunate[b]		0.003	0.004
(4)		0.049	0.049
(8)		0.051	0.051
(9)		0.818	0.575
(10)		1.106	1.227
(11)		0.28	0.26
(12)		0.120	0.12
(13)		0.029	0.028
(14)		0.50	0.64
(15)		0.025	0.028
(16)		0.169	0.171
(17)		0.540	0.456
(18)		0.155	0.181
(19)		0.18	0.19
(20)		0.09	0.11
(21)		0.634	0.603
(22)		0.019	0.021
(23)		0.058	0.078
(24)		2.132	2.234
(25)		0.818	.806
(26)		0.020	0.019
(27)		0.15	0.16
(28)		0.080	0.080
(29)		0.033	0.036
(30)		0.59	0.62
(31)		0.52	0.47
(32)		0.33	0.39
(33)		0.22	0.23
(34)		2.40	2.46
(35)		2.16	2.07
(36)		1.12	1.13
(37)		0.071	0.079
(38)		0.030	0.030

[a]Mean from *n* values of ≥2 independent experiments. [b]Data from González Cabrera et al.[27]

falciparum[7] and selected compounds for cytotoxicity against the mammalian L-6 cell line. CQ and artesunate were used as the reference drugs in all of the experiments. The data are shown in Table 1. Generally speaking, in comparison to CQ [IC_{50} = 194.0 nM (K1) and 16.0 nM (NF54)], this series produced compounds that were either superior (17) or comparable (15) in activity. A wide range of para substituents were tolerated as were substituents in the meta position. However, substitution in the ortho position, for example, **25**, significantly reduced the activity unless it formed part of a bicyclic ring. For the lead **8**, either removal of the para methoxy substituent or its replacement with ortho and/or meta methoxy substituents decreased activity as in **9** [IC_{50} = 818.0 nM (K1); 575.0 nM (NF54)] and **10** (IC_{50} = 1106 nM). The most notable analogues from this series include **13** [IC_{50} = 28.0 nM), **26** (IC_{50} = 20.0 nM), **15** (IC_{50} 25.0 nM), **22** (IC_{50} = 19.0 nM),

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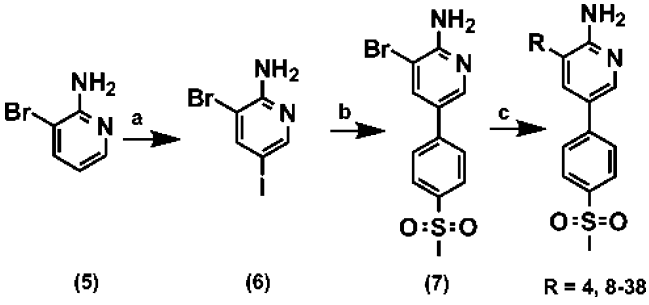
Scheme 1. General Synthetic Approach for Synthesized Compounds 4 and 8−38[a]



[a]Conditions: (a) I_2, DMSO, 100 °C, 4 h, (79%); (b) 4-methanesulfonyl boronic acid, 1,4-dioxane, K_2CO_3 (aq., 1 M), $Pd(PPh_3)_2Cl_2$ (5 mol %), 110 °C, 16 h, (58%); (c) boronic acid, 1,4-dioxane, K_2CO_3 (aq., 1 M), $Pd(PPh_3)_2Cl_2$ (7 mol %), 110 °C, 16 h, (45−65%).

and **38** (IC_{50} = 30.0 nM). All compounds were generally equipotent against the two strains.

In Vitro ADME Profiling. The most promising compounds based on in vitro antiplasmodial activity were evaluated for their physicochemical properties and in vitro metabolic stability using human liver microsomes (Table 2). The physicochemical properties were evaluated through a combination of in silico and experimental techniques.[24−26] The partition coefficient values were generally moderate, with Log $D_{7.4}$ values ranging from 1.5 to 3.6. The compounds showed varied kinetic solubility at pH 6.5, with **22**, **23**, **26**, and **27** demonstrating poor solubility and the remaining 11 compounds showing moderate solubility. In addition, the compounds demonstrated a broad range of plasma protein binding properties (determined initially using a chromatographic screening assay) ranging from 74.4 to 96.9% bound, which generally correlated with Log *D*. Most compounds were designed with metabolically deactivating groups on the 3-aryl ring, and minimal degradation in a microsomal assay was observed for most analogues, suggesting they would have low hepatic clearance in vivo. Only compounds **4**, **22**, **23**, and **29** exhibited moderate to high rates of in vitro degradation in liver microsomes and would be expected to have intermediate to high hepatic metabolic clearance in vivo. Generally, most of the aminopyridine derivates showed comparable levels of metabolic stability across human, rat, and mouse liver microsomes.

In Vivo Efficacy Study. Compounds characterized by good in vitro antiplasmodial activity and metabolic stability were selected for in vivo evaluation in *Plasmodium berghei*-infected mice.[7] The in vivo activity of compounds was evaluated following oral (po) administration of 4 × 50 mg/kg doses using a 70/30 Tween 80/ethanol formulation vehicle. Most of the compounds showed >99.0% suppression of parasitemia at this dose level (Table 3). Notably, toxicity symptoms (impaired coordination following the third application) were observed only for **26** using the 4 × 50 mg/kg dose regimen. Compounds **8**, **15**, **27**, and **37** administered at a single oral dose of 100 mg/kg displayed 98.0−99.5% inhibition of *P. berghei*, and these four compounds also provided a cure in mice following administration of 4 × 50 mg/kg oral doses. Compound **15** also cured mice following single doses of either 30 or 100 mg/kg. This result is noteworthy in view of the fact that clinically used drugs such as CQ, mefloquine, and the artemisinins do not achieve a single oral dose cure in this *P. berghei* model. Artesunate and CQ both require four daily oral doses of 100 mg/kg, while mefloquine requires four daily oral doses of 30 mg/kg to achieve a cure in this *P. berghei* model.[7] Interestingly, **26** showed high inhibition [97.3%, mean survival time (MSD) 15 days] at 30 mg/kg, and no toxicity symptoms were observed. Compounds **8** and **26** also showed high (99%) inhibition of parasitemia at 30 mg/kg albeit with reduced MSD times of 8.0 and 10 days, respectively. While a full in vivo pharmacokinetic study of each of these compounds was not conducted in mice, analysis of selected plasma samples from a satellite group of noninfected animals administered with a single 30 mg/kg oral dose of **15** or **26** suggested that the systemic exposure for each of these compounds was high and sustained, with concentrations remaining 200−300-fold above the respective in vitro IC_{50} values for greater than 24 h postdose. In contrast, plasma concentrations of **37** and **38** were more moderate and below the respective in vitro IC_{50} values at 24 h postdose, consistent

Table 2. In Vitro ADME Profiling of Selected Analogues

	Log *D*[a]	solubility	metabolism in human liver microsomes			protein binding
compd	pH 7.4	pH 6.5 (μg/mL)	$t_{1/2}$ (min)	CLint (μL/min/mg)	E_H[b]	cPPB[c] (%)
4	1.9	6.3−12.5	103	17	0.48	82.8
8	2.2	121	>99	<28	0.26	90
13	1.8	50−100	>350	<5.0	<0.20	74.4
14	1.1	25−50	247	<7.0	<0.28	56.9
15	2.6	6.3−12.5	>500	<1.4	<0.07	86.1
16	1.2	25−50	>250	<7.0	<0.28	45.9
20	3.3	3.1−6.3	>250	<7.0	<0.28	94.1
22	3.6	1.6−3.1	75	23.0	0.56	96.9
23	3.1	1.6−3.1	123	14	0.44	94.8
26	3.4	<1.60	>250	<7.0	<0.28	96.2
27	2.4	1.6−3.1	>350	<5.0	<0.20	*d*
28	2.0	6.3−12.5	>350	<5.0	<0.20	*d*
29	2.6	6.3−12.5	106	16.0	0.48	94.4
37	1.7	25−50	>350	<5.0	<0.20	81.8
38	1.5	25−50	>350	<5.0	<0.20	78.4

[a]Log $D_{pH7.4}$ values were determined using a chromatographic estimation method. [b]Predicted E_H based on in vitro intrinsic clearance. [c]Values measured using a chromatographic PPB technique. [d]Value was not measured.

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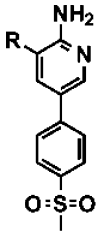
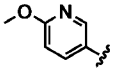
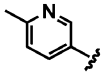
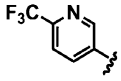
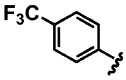
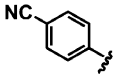
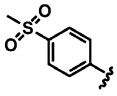
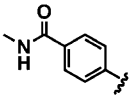
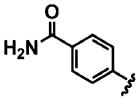
Table 3. Antimalarial Efficacy Using Single- and Multidose of Compounds 8, 13, 15, 26−28, 37, and 38 in *P. berghei*-Infected Mice*



Compound	Structure	4x50mg/kg %Reduction Parasitemia (MSD)	1x100mg/kg %Reduction Parasitemia (MSD)	1x30mg/kg %Reduction Parasitemia (MSD)	1x10mg/kg %Reduction Parasitemia (MSD)	1x3mg/kg %Reduction Parasitemia (MSD)
(8)		99.8% (>30)[b,c]	99.3% (21)	99.0% (8)	82% (7)	<40 (3)[a]
(13)		99.8% (>30)[b]	ND	99.2% (8)	ND	<40 (3)[a]
(15)		99.7% (>30)[b]	99.5% (>30)[b]	99.3% (>30)[b,c]	98%(13)[c]	98% (8)[c]
(26)		Tox.	ND	97.3% (15)	98% (9)	ND
(27)		99.7% (>30)[b]	99.4% (14)	99.1% (10)	ND	ND
(28)		99.6%(15)	ND	ND	ND	ND
(37)		99.7% (9)	98% (6)	77.0% (7)	ND	ND
(38)		66% (7)	64% (7)	<40 (3)[a]	ND	ND
Chloroquine		99.9% (24)[d]	99.9% (12)	99.7% (9)	99.5% (7)	83% (7)

*MSD (in days). ND, not determined. Test compounds were formulated in 70/30 Tween 80/ethanol and diluted 10× with water before oral administration (≥3 mice per group). [a]Mice were euthanized on day 3, to prevent death otherwise occurring at ∼day 6. [b]No detectable parasites at day 30 postinfection. [c]Average of two independent experiments. [d]4× 30 mg/kg po.

Table 4. Pharmacokinetic Parameters for Compounds 8, 15, and 26 Following iv and Oral Administration to Male Sprague Dawley Rats[a]

	8			15		26	
parameter	iv[b]	oral[b]	oral[b]	iv[b]	oral[b]	iv[b]	oral[b]
nominal dose (mg/kg)	4.7	5.0	22.3	3.2	20.2	4.7	21.7
apparent $t_{1/2}$ (h)	8.0	6.7	6.5	7.3	8.5	11.3	6.0[c]
plasma CL_{total} (mL/min/kg)	16.7	–	–	6.5	–	29.0	–
blood CL_{total} (mL/min/kg)	18.3	–	–	–	–	–	–
blood/plasma	0.91	–	–	–	–	–	–
V_{ss} (L/kg)	4.3	–	–	2.7	–	8.0	–
C_{max} (μM)	–	5.4	21.0	–	8.0	–	1.0
T_{max} (min)	–	15	105	–	150	–	195
$AUC_{0\text{-inf}}$ (μM min)	789	705	6880	1402	4453	419	496[c]
bioavailability (%)	–	83	>100	–	51	–	26[c]

[a]Empty cells indicate that the value was not measured or was not relevant. [b]Values are the mean of two animals. [c]The profile was not well-defined, and the value is likely to underestimate the actual value.

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with the lower in vivo activity observed for these two compounds. Compound **15** remained the most active compound showing 98.0 (MSD 13 days) and 98.0% (MSD 8 days) inhibition at 10 and 3 mg/kg single oral doses, respectively, while at a single oral dose of 10 mg/kg, compounds **8** and **26** displayed 82.0 and 98% inhibition, respectively.

The effective oral dose for the most promising compounds was determined using a single dose response study where 50 (ED_{50}) and 90% (ED_{90}) reduction in parasitaemia was measured. Compound **8** showed ED_{50} and ED_{90} values of 4.7 and 17 mg/kg, while **15** showed ED_{50} and ED_{90} values of 0.83 and 1.7 mg/kg, respectively.

In Vivo Pharmacokinetic Studies. The in vivo pharmacokinetics of **8**, **15**, and **26** were assessed following administration at dose levels of 5 mg/kg intravenously and 5 or 20 mg/kg orally (in an aqueous suspension vehicle) to male Sprague–Dawley rats (Table 4 and Figure 3).

Compound **8** showed good oral bioavailability in rats (~83% at 5 mg/kg) and a relatively long half-life (~8 h). This compound displayed some dose-dependent pharmacokinetics (PK) in the rat with a 10-fold increase in area under the curve (AUC) for a 4-fold increase in dose (5–20 mg/kg). There was more rapid absorption at the lower dose but similar half-lives at both oral doses and after iv administration. The in vivo clearance in rats after iv dosing was low, and the volume of distribution was high. Compound **26** also had a lower oral bioavailability (26%) that is likely to be in part due to first-pass metabolism. In addition, **26** had lower aqueous solubility at intestinal pH (<1.6 μg/mL at pH 6.5, see Table 2) and showed a high volume of distribution and moderate plasma clearance following iv administration. On the other hand, PK studies with **15** in the rat indicated that this compound has good oral bioavailability (51% at 20 mg/kg), with a long half-life ($t_{1/2}$ = 7–8 h). The in vivo clearance was low (6.5 mL/min/kg), consistent with the in vitro predictions, while the volume of distribution was moderate (2.7 L/kg), and there was no evidence of instability in blood and plasma.

In Vitro Toxicology. Frontrunner compounds **8** and **15** were further profiled for potential cardiovascular (hERG) and drug–drug interaction (CYP450 inhibition) risks as shown in Table 5 as well as for genetic toxicity (Ames test). Both compounds exhibited low potential to inhibit all five major CYP450 isoforms. Within the context of genetic toxicity testing, the two compounds were negative in the Ames assay. In addition, they exhibited comparable moderate hERG activity (**8**, IC_{50} = 5.5 μM; **15**, IC_{50} = 4.7–11 μM). Toward hERG derisking, **15** was further evaluated in an in vitro rabbit ventricular wedge assay at a concentration of 2 μM due to solubility constraints at higher concentration (10 μM). No change in QT, TP-e, and ORS was observed.

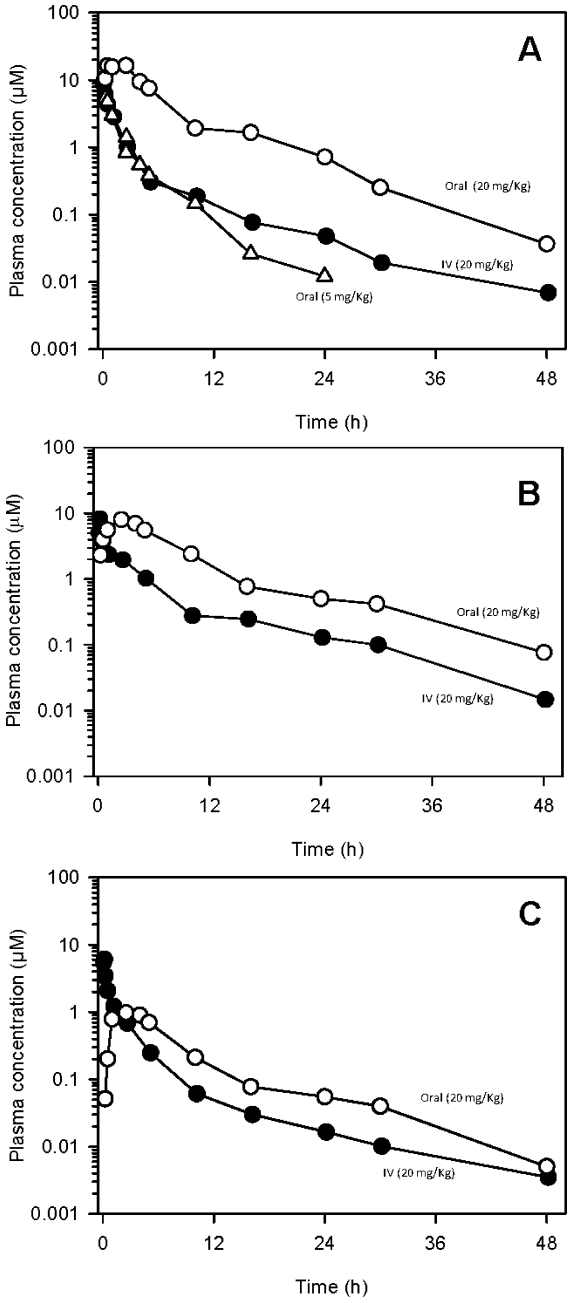

Figure 3. In vivo plasma concentration vs time profiles (mean of n = 2 animals) for **8**, **15**, and **26** administrated orally and intravenously to male Sprague–Dawley rats. Intravenous data are represented by the filled symbols, and oral data are represented by the open symbols. Compound **8** was administered at 5 (triangles) and 20 mg/kg (circles) orally, while **15** and **26** were administered only at 20 mg/kg orally. (A) Compound **8**, (B) compound **15**, and (C) compound **26**.

CONCLUSIONS

In the search for new antimalarials, a novel class of orally active 3,5-diarylaminopyridine series, which combines good in vitro activity against *P. falciparum* with efficacy in a *P. berghei* mouse model following administration of single oral doses, was identified. A single oral dose of 30 mg/kg of **15** was completely curative, an outstanding result worth noting in view of the fact that clinically used drugs such as CQ, mefloquine, and the artemisinins do not achieve a single oral dose cure in this *P. berghei* model. Furthermore, the frontrunner compound shows clinical candidate potential. Further work is needed to identify compounds that have the potential for an improved hERG profile. Furthermore, although the molecular target of these antimalarial aminopyridines in the malaria parasite is unknown, a useful starting point toward target identification would be profiling against available panels of human and *P. falciparum* kinases. This is in view of the reported inhibition of kinases by 2-aminopyridines.

EXPERIMENTAL SECTION

General Comments on Experimental Data. All other reagents were purchased from commercial sources and used without further

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Table 5. In Vitro Mammalian Cytotoxicity, Cytochrome P450, and hERG Inhibition of 8 and 15

	cytochrome P450 inhibition (μM)						
compd	1A2	2C9	2C19	2D6	3A4/5(testosterone)	hERG (μM)	cytotox (L6) (μM)
8	>30	>30	>30	>30	>30	3.0	>146
15	>20	>20	>20	>20	>20	4.7	251.4

purification. Column chromatography was carried out using silica gel 60 (Fluka), particle size 0.063−0.2 mm (70−230 mesh ASTM), as the stationary phase. Analytical thin-layer chromatography (TLC) was performed on silica on TLC aluminum foils, H × W 20 cm × 20 cm, with fluorescent indicator (200 μm thick, Fluka), and visualized under UV light. Melting points were determined on a Reichert-Jung Thermovar hotstage microscope and are uncorrected. Routine ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Mercury-300 (^{1}H = 300.13, ^{13}C = 75.5 MHz) or 400 MHz on a Bruker AV 400 (^{1}H = 300.13, ^{13}C = 75.5 MHz) instrument. Spectra were recorded at ambient temperature, unless otherwise stated. Chemical shifts (δ) are reported in parts per million from low to high field and referenced to residual solvent. Standard abbreviations indicating multiplicity are used as follows: br s = broad, d = doublet, m = multiplet, q = quartet, quint. = quintet, s = singlet, and t = triplet. In many cases, DMSO-d_6 was used as a solvent, and the ^{1}H was referenced to 2.500 ppm for the quintuplet downfield methyl signal. ^{13}C was reference to the methyl carbon septuplet at 39.52 ppm. Atmospheric pressure chemical ionization (APCI) mass spectrometry was carried out by the services at the Centre for Drug Candidate Optimisation and Syngene. All final compounds were purified to ≥95% purity as determined by LC using Phenomenex-Luna C18 (250 mm × 4.6 mm) 5u column; 2.0 μL injection volume; flow, 0.7 mL/min; gradient: 30−100% B in 15 min (hold 2 min) (mobile phase A, 10 nM NH_4OAc in H_2O, and mobile phase B, acetonitrile) with a Thermo Separation Products (TSP), Spectra SERIES P200 pump UV100 detector set at 254 nm.

3-Bromo-5-iodopyridin-2-amine (6). Iodine (8.81 g, 34.7 mmol) was added to a solution of 3-bromopyridin-2-amine (5.00 g, 28.9 mmol) in DMSO (30 mL), and the resulting mixture was stirred at 100 °C for 4 h. The reaction mixture was poured onto a saturated $Na_2S_2O_5$ aqueous solution (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (50% hexane/EtOAc) providing 3-bromo-5-iodopyridin-2-amine 7 (6.83 g, 79%) as a yellow solid; mp 109−112 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (1H, d, J = 2.0 Hz), 7.97 (1H, d, J = 2.0 Hz), 6.37 (2H, br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.0, 152.7, 146.6, 104.8, 75.0.

General Procedure for the Cross-Coupling Reactions To Afford Compounds 4, 7, and 8−40. To solution of aryl halid **6** or **7** (1.0 equiv) in 1,4-dioxan, the boronic acid (1.1 equiv) was added. The mixture was thoroughly degassed with nitrogen for 15 min. $Pd(PPh)_3Cl_2$ (5−7 mol %) was added to the degassed solution under a nitrogen atmosphere, followed by aqueous K_2CO_3 (1 M, 3.0 equiv). The reaction mixture was stirred at 110 °C for 16 h, poured into H_2O, and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel Hexane/EtOAc to give the product as solid.

3-Bromo-5-[4-(methylsulfonyl)phenyl]pyridin-2-amine (7). Yield, 58%; mp 197−201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (1H, d, J = 2.5 Hz), 8.14 (1H, d, J = 2.5 Hz), 7.88 (4H, m), 6.50 (2H, br s), 3.19 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9, 146.2, 142.0, 138.8, 128.7, 128.1 (2 × C), 126.7 (2 × C), 124.5, 104.0, 44.2. Anal. RP-high pressure liquid chromatography (HPLC) t_R = 7.26 min (method 5F, purity 99.6%). LRMS (APCI): m/z = 328.0 [(M + H)$^+$] (anal. calcd for $C_{12}H_{11}BrN_2O_2S^+$: m/z = 327.20).

4-(2-Amino-5-(4-(methylsulfonyl)phenyl)pyridin-3-yl)-2-methoxyphenol (4). Yield, 57%; mp 204−207 °C. ^{1}H NMR (400 MHz, DMSO-d_6): ^{1}H NMR (300 MHz, DMSO-d_6): 9.02 (1H, br s), 8.37 (1H, d, J = 2.5 Hz), 7.92 (4H, m), 7.69 (1H, d, J = 2.5 Hz), 7.06 (1H, d, J = 2.0 Hz), 6.92 (1H, d, J = 2.0 Hz), 6.89 (1H, m), 5.82 (2H, br s), 3.83 (3H, s), 3.21 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.4, 147.6, 146.1, 144.8, 142.7, 138.2, 135.2, 128.3, 127.3 (2 × C), 125.8 (2 × C), 123.0, 120.9, 120.7, 115.8, 112.7, 55.6, 43.7. Anal. RP-HPLC t_R = 13.36 min (purity 96.5%). LRMS (APCI): m/z = 371.1 [(M + H)$^+$] (anal. calcd for $C_{19}H_{18}N_2O_4S^+$: m/z = 370.10).

3-(6-Methoxypyridin-3-yl)-5-(4-methylsulfonylphenyl)-pyridin-2-amine (8). Yield, 65%; mp 225−227 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (1H, d, J = 2.5 Hz), 8.27 (1H, d, J = 2.5 Hz), 7.91 (4H, m), 7.84 (1H, dd, J = 2.5, 8.5 Hz), 7.46 (1H, d, J = 2.5 Hz), 6.90 (1H, d, J = 8.5 Hz), 6.02 (2H, br s), 3.89 (3H, s), 3.20 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 157.9, 147.1, 146.5, 143.3, 140.1, 139.0, 136.7, 128.1 (2 × C), 127.4, 126.6 (2 × C), 123.7, 117.8, 111.1, 53.7, 44.2. Anal. RP-HPLC t_R = 6.13 min (purity 98.7%). LRMS (APCI): m/z = 356.0 [(M + H)$^+$] (anal. calcd for $C_{18}H_{17}N_3O_3S^+$: m/z = 355.10).

3-(2-Methylpyridin-5-yl)-5-[4-(methylsulfonyl)phenyl]-pyridin-2-amine (13). Yield, 60%; mp 185−187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (1H, d, J = 2.5 Hz), 8.40 (1H, d, J = 2.5 Hz), 7.97−7.91 (4H, m), 7.84 (1H, dd, J = 2.5 Hz, 8.5 Hz), 7.76 (1H, d, J = 2.5 Hz), 7.37 (1H, d, J = 8.5 Hz), 6.13 (2H, br s), 3.24 (3H, s), 2.53 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 156.5, 149.2, 146.9, 143.7, 139.2, 137.0, 136.7, 130.5, 128.4 (2 × C), 127.1 (2 × C), 126.1, 123.7, 118.7, 44.9, 24.5. Anal. RP-HPLC t_R = 15.35 min (purity 97.4%). LRMS (APCI): m/z = 340.0 [(M + H)$^+$] (anal. calcd for $C_{18}H_{17}N_3O_2S^+$: m/z = 339.10).

3-[2-(Trifluoromethyl)pyridin-5-yl]-5-[4-(methylsulfonyl)-phenyl]pyridin-2-amine (15). Yield, 65%; mp 224−225 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (1H, d, J = 2.3 Hz), 8.47 (1H, d, J = 2.3 Hz), 8.21 (1H, dd, J = 2.3, 8.1 Hz), 7.95 (1H, d, J = 8.1 Hz), 7.93−7.89 (4H, m), 7.86 (1H, d, J = 2.3 Hz), 6.27 (2H, br s), 3.26 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.6, 150.6, 147.7, 143.0, 139.1, 138.9, 137.8, 137.4, 128.1 (2 × C), 126.6 (2 × C), 123.7, 121.3, 116.3, 44.2. Anal. RP-HPLC t_R = 8.97 min (purity 98.0%). LRMS (APCI): m/z = 394.0 [(M + H)$^+$] (anal. calcd for $C_{18}H_{14}F_3N_3O_2S^+$: m/z = 394.08).

3-[4-(Trifluoromethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-pyridin-2-amine (26). Yield, 63%; mp 247−249 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (1H, d, J = 2.5 Hz), 7.97−7.91 (4H, m), 7.85−7.77 (5H, m), 6.12 (2H, br s), 3.23 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.2, 147.0, 142.8, 139.0, 136.8, 132.2, 130.1 (2 × C), 129.3, 128.0 (2 × C), 126.6 (2 × C), 126.3 (2 × C), 126.2, 123.7, 119.4, 44.1. Anal. RP-HPLC t_R = 11.16 min (purity 96.4%). LRMS (APCI): m/z = 393.0 [(M + H)$^+$] (anal. calcd for $C_{19}H_{15}F_3N_2O_2S^+$: m/z = 392.08).

4-{2-Amino-5-[4-(methylsulfonyl)phenyl]pyridin-3-yl}-benzonitrile (27). Yield, 57%; mp 236−237 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (1H, d, J = 2.5 Hz), 7.95−7.89 (6H, m), 7.77 (1H, d, J = 2.5 Hz), 7.74 (2H, d, J = 8.5 Hz), 6.14 (2H, br s), 3.21 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 147.3, 143.3, 143.1, 139.1, 136.8, 133.3 (2 × C), 130.3 (2 × C), 128.1(2 × C), 126.6 (2 × C), 123.7, 119.4, 119.3, 110.6, 44.2. Anal. RP-HPLC t_R = 22.21 min (purity 98.5%). LRMS (APCI): m/z = 350.2 [(M + H)$^+$] (anal. calcd for $C_{19}H_{15}N_3O_2S^+$: m/z = 349.09.

3,5-Di-[4-(methylsulfonyl)phenyl]pyridin-2-amine (28). Yield, 63%; mp 273−275 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (1H, d, J = 2.5 Hz), 8.03 (2H, m), 7.97 (2H, d, J = 9.2 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.84 (2H, m), 7.81 (1H, d, J = 2.5 Hz), 6.17 (2H, br s), 3.27 (3H, s), 3.23 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 147.2, 143.6, 143.1, 140.1, 139.0, 136.8, 130.2 (2 × C), 128.0 (2 × C), 128.0 (2 × C), 126.6 (2 × C), 123.7, 119.2, 44.1 (2 × C). Anal. RP-HPLC t_R = 5.30 min (purity 98.8%). LRMS (APCI): m/z = 403.0 [(M + H)$^+$] (anal. calcd for $C_{19}H_{18}N_2O_4S_2^+$: m/z = 402.07).

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4-{2-Amino-5-[4-(methylsulfonyl)phenyl]pyridin-3-yl}-*N*-methylbenzamide (37). Yield, 53%; mp 199−201 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (2H, m), 7.94 (6H, m), 7.77 (1H, d, J = 2.5 Hz), 7.64 (1H, d, J = 8.5 Hz), 5.98 (2H, br s), 3.25 (1H, br s), 3.18 (3H, s), 2.77 (3H, d, J = 4.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.6, 157.2, 146.6, 143.2, 140.9, 138.9, 136.5, 133.9, 129.0 (2 × C), 128.1 (2 × C), 128.0 (2 × C), 126.6 (2 × C), 123.7, 120.1, 44.2, 26.8. Anal. RP-HPLC t_R = 5.32 min (purity 97.2%). LRMS (APCI): m/z = 382.0 [(M + H)$^+$] (anal. calcd for $C_{20}H_{19}N_3O_3S^+$: m/z = 381.11).

4-{2-Amino-5-[4-(methylsulfonyl)phenyl]pyridin-3-yl}-benzamide (38). Yield, 47%; mp 284−286 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (1H, d, J = 2.5 Hz), 8.00 (2H, d, J = 8.3 Hz), 7.97−9.72 (4H, m), 7.78 (1H, d, J = 2.5 Hz), 7.64 (2H, d, J = 8.3 Hz), 7.37 (2H, br s), 6.04 (2H, br s), 3.24 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 157.2, 146.7, 143.2, 141.1, 138.9, 136.5, 133.7, 129.0 (2 × C), 128.6 (2 × C), 128.0 (2 × C), 126.6 (2 × C), 123.7,120.2, 44.1. Anal. RP-HPLC t_R = 8.3 min (purity 96.1%). LRMS (APCI): m/z = 368.0 [(M + H)$^+$] (anal. calcd for $C_{19}H_{17}N_3O_3S^+$: m/z = 367.10).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional details of the characterization of selected compounds and the procedures used for the in vitro and in vivo antimalarial studies as well as metabolism and PK studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ADME, absorption, distribution, metabolism, and excretion; AUC, area under the curve; CQ, chloroquine; E_H, hepatic extraction ratio; GPCR, G protein-coupled receptor; GSK, GlaxoSmithKline; TCAMS, Tres Cantos Antimalarial Set; HPLC, high-pressure liquid chromatography; HTS, high-throughput screening; H2L, hit to lead; ip, intraperitoneal injection; LO, lead optimization; MMV, Medicines for Malaria Venture; MSD, mean survival time; po, oral administration; SAR, structure−activity relationship; sc, subcutaneous; PK, pharmacokinetics; TLC, thin-layer chromatography

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