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Synthesis and antiplasmodial activity of novel 2,4-diaminopyrimidines

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ABSTRACT

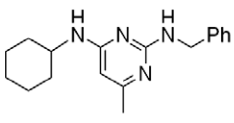
Two sets of diaminopyrimidines, totalling 45 compounds, were synthesized and assayed against *Plasmodium falciparum*. The SAR was relatively shallow, with only the presence of a 2-(pyrrolidin-1-yl)ethyl group at R^2 significantly affecting activity. A subsequent series addressed high Log *D* values by introducing more polar side groups, with the most active compounds possessing diazepine and *N*-benzyl-4-aminopiperidyl groups at R^1/R^2. A final series attempted to address high in vitro microsomal clearance by replacing the C6-Me group with CF_3, however antiplasmodial activity decreased without any improvement in clearance. The C6-CF_3 group decreased hERG inhibition, probably as a result of decreased amine basicity at C2/C4.

Malaria is a major parasitic disease in many areas of Africa, Asia and South America. The majority of cases are caused by *Plasmodium falciparum*, and its resistance to many contemporary antimalarials has compounded the problem of disease control.[1] Resistance to most available antimalarial drugs has been reported throughout Africa and parts of Asia, prompting the need to discover novel chemotherapeutic strategies.[2] To address this issue, the Broad Institute's Infectious Diseases Initiative, Genzyme and the Medicines for Malaria Venture have formed the Malaria Drug Discovery Initiative to create a pipeline capable of delivering new candidate therapeutics. Our primary means of identifying small molecule candidates utilizes a high-throughput screen to uncover scaffolds amenable to the development of novel antimalarials.[3] The structure of one of our screening positives is displayed below (**1a**, Fig. 1). This 2,4-diaminopyrimidine-based compound displayed excellent antiplasmodial activity, moderate solubility, high lipophilicity as measured by Log *D* at pH 7.4, high permeability as measured by a parallel artificial membrane permeability assay (PAMPA), low to moderate human CYP450 inhibition, and >20-fold selectivity for *P. falciparum* versus human cell lines.

The antiplasmodial activity of diaminopyrimidine-based compounds has been described on multiple occasions,[4] with pyrimethamine the most well-known example. A recent publication revealed moderate antiplasmodial activity ($\geqslant$0.9 μM) for a limited number of compounds analogous in structure to **1a**.[5] This report outlines a systematic approach towards the development of 2,4-diaminopyrimidines, alkylated at both exocyclic nitrogens, in an effort to discover a lead for our fully integrated drug development program. Novel analogs could be easily synthesized in only two steps to enable rapid SAR exploration of this compound class.

Synthesis of the initial DAP series is outlined in Scheme 1. Reaction of commercially available pyrimidine **2** with cyclohexylamine, benzylamine or *N*-methylcyclohexylamine gave **3a–c** in 71%, 63% and 68% yields respectively.[6] Intermediates **3a–c** were then reacted with the appropriate amines in dioxane under microwave irradiation[7] to afford **1b–i** (yields shown in Table 1).

The antiplasmodial activity of DAPs **1b–i** was measured by a DAPI staining-based method for determining *P. falciparum* cell



1a

Pf 3D7 EC_{50} = 0.08 μM
Pf Dd2 EC_{50} = 0.25 μM
Solubility = 26 μg/mL
LogD = 3.9
CYP450 IC_{50} (μM): 1A2 = 3.1, 2C9 >5, 2C19 >5, 2D6 = 4.2, 3A4 >5
Dermal fibroblast LC_{50} = 7.5 μM
Kidney epithelial LC_{50} = 7.5 μM

Figure 1. Structure and in vitro assay data for screening positive **1a**.

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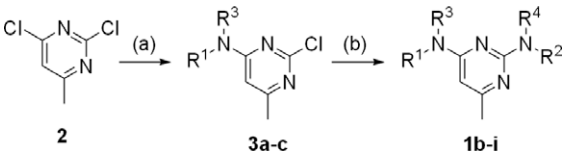


Scheme 1. Reagents and conditions: (a) EtOH, rt, 24 h and either *c*HexylNH$_2$ (**3a**, 71%), BnNH$_2$ (**3b**, 63%) or *N*-Me *c*HexylNH (**3c**, 68%). (b) **3a**, **3b** or **3c**, amine, dioxane, μwave.

Table 1
Yields and in vitro antiplasmodial activity for **1b–i**

No.	R^1	R^2	R^3	R^4	Yield (%)	*Pf* EC_{50} (μM)	
						3D7	Dd2
1b	*c*Hexyl	(*S*)-1-Ph-ethyl	H	H	17	0.12	0.50
1c	*c*Hexyl	(*R*)-1-Ph-ethyl	H	H	62	0.09	0.42
1d	*c*Hexyl	Bn	H	Me	72	>10	>10
1e	Bn	*c*Hexyl	H	H	63	0.43	1.26
1f	*c*Hexyl	Bn	Me	H	95	0.68	1.02
1g	*c*Hexyl	Bn	Me	Me	25	>10	>10
1h	*c*Hexyl	(*S*)-1-Ph-ethyl	Me	H	95	0.59	0.69
1i	*c*Hexyl	(*R*)-1-Ph-ethyl	Me	H	84	0.63	0.94

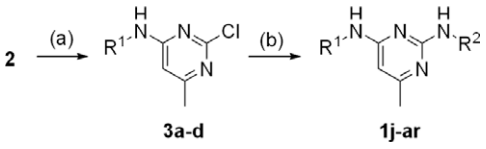
viability after exposure to the compound for 72 h (see Table 1).[3] Compounds were tested against the common laboratory strain 3D7 and the multidrug resistant southeast Asian isolate Dd2.[8] The most active compounds were **1b–c** (R^1 = cyclohexyl, R^3 = H). The presence of a methyl group at R^4 completely abrogated activity (**1d** and **1g**), and when R^3 = Me (**1f**, **1h–i**), activity also decreased significantly compared to **1a–c**. These results demonstrated that only primary amines should be reacted at both steps in the synthesis, resulting in R^3 and R^4 = H.

A second generation library was synthesized to deepen our understanding of the SAR revealed by the first series of DAPs. In addition to using intermediates **3a–b**, pyrimidine **2** was reacted with isopropylamine and aniline to afford **3c–d** in 50% and 58% yields respectively (see Scheme 2). Intermediates **3a–d** were then reacted with selected amines to yield **1j–ar**, resulting in a range of sizes, lipophilicities and hydrogen bond acceptors at R^2.[†] In contrast to Scheme 1, step (b) utilized ^{i}PrOH as the reaction solvent,[9] as this forced the reaction to completion more rapidly than dioxane.

Table 2 displays the reaction yield and antiplasmodial activity for DAPs **1j–1as**. The most noteworthy point is the significant number of compounds (18 out of 36) that were moderately potent, with EC_{50}s in the 0.20–0.75 μM range. The only SAR that could be teased out was restricted to the observation that a slight decrease in activity was seen for compounds with R^1 = ^{i}Pr (**1ab–al**), and that a 2-(pyrrolidin-1-yl)ethyl group at R^2 led to significantly less active compounds (**1m**, **1w**, **1ae** and **1ao**).

The majority of compounds in Table 2 suffered from Log *D* values >3 and rapid metabolism in an in vitro rat and human liver microsome clearance assay (data not shown). To address the high Log *D* values, three analogs were synthesized that possessed a diazepine moiety at the C2 position of the pyrimidine ring to decrease lipophilicity. Intermediate **3d** was reacted with *N*-Me and *N*-Boc diazepine to afford **4a** and **4b** in 87% and 80% yields respectively (Scheme 3). The latter compound was converted to the unprotected diazepine **4c** upon exposure to HCl/dioxane, and isolated as the free amine in 87% yield. These and subsequent compounds were tested only against the Dd2 strain, as **1j–t**, **1am–ap** and **1ar–as** did not display consistent selectivity for either 3D7 or Dd2.

[†] A limited number of these analogs have been described in the literature—**1k** and **1ab** displayed herbicidal/fungicidal activity,[10] and **1z** showed antimicrobial activity.[11]

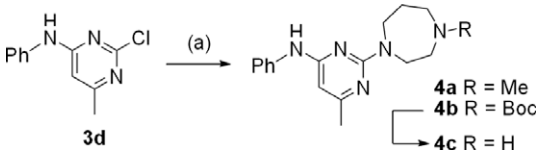


Scheme 2. Reagents and conditions: (a) EtOH, rt, 24 h and either ^{i}PrNH$_2$ (**3c**, 50%) or PhNH$_2$ (**3d**, 58%); (b) **3a**, **3b**, **3c** or **3d**, amine, ^{i}PrOH, μwave.

Table 2
Yields and in vitro antiplasmodial activity for **1j–3as**

No.	R^1	R^2	Yield (%)	*Pf* EC_{50} (μM)	
				3D7	Dd2
1j	*c*Hexyl	^{i}Pr	95	ND[a]	0.74
1k	*c*Hexyl	*c*Hexyl	69	ND	0.21
1l	*c*Hexyl	Heptyl	86	ND	0.21
1m	*c*Hexyl	2-(Pyrrolidin-1-yl)ethyl	45	ND	2.75
1n	*c*Hexyl	1-(Adamantyl)methyl	45	ND	0.37
1o	*c*Hexyl	*N*-Benzylpiperidin-4-yl	30	ND	0.25
1p	*c*Hexyl	Ph	73	ND	0.23
1q	*c*Hexyl	3,4,5-Trimethoxybenzyl	55	ND	0.26
1r	*c*Hexyl	(Piperon-5-yl)methyl	84	ND	0.20
1s	*c*Hexyl	(*N*-Methylindol-5-yl)methyl	18	ND	0.24
1t	*c*Hexyl	Pyridin-2-yl	5	>1	>2
1u	Bn	^{i}Pr	77	1.43	1.05
1v	Bn	*c*Hexyl	91	0.47	0.46
1w	Bn	2-(Pyrrolidin-1-yl)ethyl	60	1.08	1.45
1x	Bn	1-(Adamantyl)methyl	96	0.41	0.40
1y	Bn	*N*-Benzylpiperidin-4-yl	84	0.16	0.16
1z	Bn	Ph	96	0.85	1.02
1aa	Bn	3,4,5-Trimethoxybenzyl	80	0.78	0.93
1ab	^{i}Pr	^{i}Pr	45	ND	4.27
1ac	^{i}Pr	*c*Hexyl	82	ND	0.39
1ad	^{i}Pr	Heptyl	99	ND	0.31
1ae	^{i}Pr	2-(Pyrrolidin-1-yl)ethyl	28	ND	>5
1af	^{i}Pr	1-(Adamantyl)methyl	93	ND	0.27
1ag	^{i}Pr	Bn	86	ND	0.35
1ah	^{i}Pr	*N*-Benzylpiperidin-4-yl	67	ND	0.81
1ai	^{i}Pr	Ph	97	ND	1.50
1aj	^{i}Pr	3,4,5-Trimethoxybenzyl	93	ND	1.92
1ak	^{i}Pr	(Piperon-5-yl)methyl	72	ND	0.84
1al	^{i}Pr	(*N*-Methylindol-5-yl)methyl	37	ND	1.22
1am	Ph	^{i}Pr	85	0.28	0.75
1an	Ph	Heptyl	50	0.09	0.09
1ao	Ph	2-(Pyrrolidin-1-yl)ethyl	80	1.46	1.24
1ap	Ph	Bn	84	0.12	0.09
1aq	Ph	(Pyridin-2-yl)methyl	72	ND	2.14
1ar	Ph	(Piperon-5-yl)methyl	83	0.11	0.36
1as	Ph	(*N*-Methylindol-5-yl)methyl	16	0.35	0.59

[a] ND = not determined.



Scheme 3. Reagents and conditions: (a) ^{i}PrOH, μwave and either *N*-Me diazepine (**4a**, 87%) or *N*-Boc diazepine (**4b**, 80%); (b) 4 M HCl/dioxane (87%).

Table 3
In vitro antiplasmodial activity and Log *D* values for **4a–c**

No.	*Pf* EC_{50} Dd2 (μM)	Log *D*
4a	3.52	1.70
4b	1.87	3.95
4c	1.96	0.51

DAPs **4a–c** displayed relatively poor antiplasmodial activity (Table 3), in agreement with the lack of activity displayed by **1d** and **1g**, both of which had a dialkylated nitrogen attached at the C2 position of the pyrimidine ring. However, both **4a** and **4c** had lower Log *D* values compared to the majority of compounds in Table 2, and **4a** was in our preferred range for compound development (between 1 and 3). This finding validated the use of heteroatom-containing auxiliary groups as a strategy to lower Log *D* values.

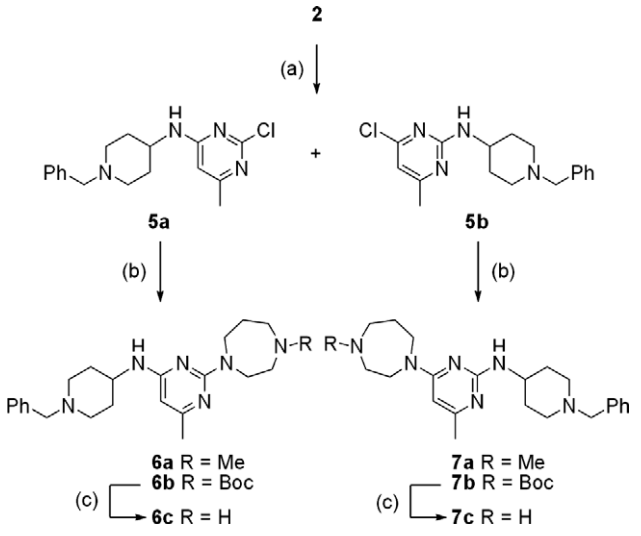
Further exploration of the Log *D* properties of this compound class was undertaken by incorporating heteroatoms in both groups attached to the pyrimidine core. To this end, **2** was reacted with *N*-benzyl-4-aminopiperidine to give regioisomers **5a** and **5b** in 46% and 23% yields respectively after chromatographic separation (Scheme 4). Analogous to Scheme 3, both regioisomers were reacted with *N*-Me and *N*-Boc diazepine to yield **6a–b** and **7a–b**. The *N*-Boc analogs **6b** and **7b** were deprotected to afford **6c** and **7c** as the free amines in 32% and 53% yields respectively.

Pyrimidines **6a–c** and **7a–c** displayed greater antiplasmodial activity than **4a–c**, especially **7a–c**, which all had a monoalkylated nitrogen at the C2 position (Table 4). The strategy of incorporating heteroatoms and C2 and C4 brought the Log *D* values for **6a–b** and **7a–b** into our preferred range, however **6c** and **7c** displayed a preference for partitioning into the aqueous layer in the Log *D* assay.

To address the high microsomal clearance, we initially wanted to prevent metabolism occurring at the C6-Me group (cf metabolism of toluene to benzyl alcohol by CYP450 enzymes[12]) by replacement with CF_3, and by introducing a heteroatom into the aromatic group at C2. The CF_3 group was introduced by reaction of **8** with aniline to yield **9** in 40% yield (Scheme 5). Intermediate **9** was then reacted with four aromatic methylamines to afford **10a–d**, with **10b–c** possessing pyridyl groups.

Table 5 reveals that the C6-CF_3 group led to a significant decrease in antiplasmodial activity compared to the C6-Me analogs. Additionally, it decreased solubility to the extent that microsomal clearance could not be determined (**10a**, **10d**), or increased clearance compared to the C6-Me analog (**10b**). The pyridyl groups had no effect on clearance (**10b–c**).

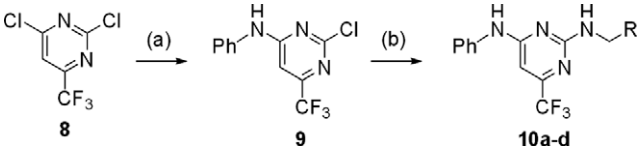
We also utilized the CF_3 group to address the potential inhibition of hERG, a cardiac ion channel that plays an important role in ventricular repolarization. hERG inhibition is an undesirable property in many drug development programs due to the potential for heart arrhythmias in patients.[13] Inhibition of hERG has been widely described for pyrimidine-based compounds,[14] and the scaffold used in this study fits the model for hERG inhibitors as it features a basic nitrogen flanked by aromatic or hydrophobic groups.[15] Introduction of an electron-withdrawing CF_3 group at C6 would reduce the pK_a of the nitrogens at C2/C4, an approach that has been used to lower hERG inhibition.[16] Two pairs of compounds were tested in an in vitro hERG inhibition assay, with the compounds in a pair differentiated by either Me or CF_3 at C6 (Table 6). In both cases, the CF_3 compound displayed less inhibitory



Scheme 4. Reagents and conditions: (a) *N*-Benzyl-4-aminopiperidine, EtOH, rt, 24 h (**5a**, 46%), (**5b**, 23%); (b) ^{i}PrOH, μwave and either *N*-Me diazepine (**6a**, 75%), (**7a**, 40%), or *N*-Boc diazepine (**6b**, 73%), (**7b**, 69%); (c) 4 M HCl/dioxane (**6c**, 32%), (**7c**, 53%).

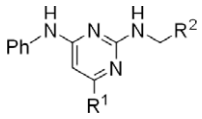
Table 4
In vitro antiplasmodial activity and Log *D* values for **6a–c** and **7a–c**

No.	*Pf* EC_{50} Dd2 (μM)	Log *D*
6a	0.30	1.00
6b	0.57	2.77
6c	0.30	−0.17
7a	0.16	1.00
7b	0.20	2.70
7c	0.16	−0.15



Scheme 5. Reagents and conditions: (a) Aniline, EtOH, rt, 24 h (40%); (b) ^{i}PrOH, μwave and either $BnNH_2$ (**10a**, 79%), 2-(pyridyl)CH_2NH_2 (**10b**, 92%), 4-(pyridyl)CH_2NH_2 (**10c**, 37%) or 5-(piperonyl)CH_2NH_2 (**10d**, 96%).

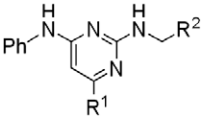
Table 5
In vitro antiplasmodial activity and microsomal clearance of **10a–d** (live–dead EC_{50} and microsomal clearance values for the C6-Me analogs **1ap**, **1aq** and **1ar** are also displayed)



No.	R^1	R^2	*Pf* EC_{50} Dd2 (μM)	Cl_{int} (μL/min/mg prot.)	
				Rat	Human
10a	CF_3	Ph	5.00	ND[a]	ND[a]
1ap	Me	Ph	0.09	>119	55.2
10b	CF_3	Pyridin-2-yl	7.09	>119	>99
1aq	Me	Pyridin-2-yl	2.14	114	70.0
10c	CF_3	Pyridin-4-yl	7.19	>119	56.2
10d	CF_3	Piperon-5-yl	10.1	ND[a]	ND[a]
1ar	Me	Piperon-5-yl	0.36	>119	31.3

[a] ND = not determined because of low solubility (<0.1 μg/mL).

Table 6
hERG channel inhibitory activity of **1aq**, **1ar**, **10a** and **10d**[a]



No.	R^1	R^2	hERG IC_{50} (μM)
1aq	Me	Pyridin-2-yl	15.8
1ar	Me	Piperon-5-yl	9.50
10b	CF_3	Pyridin-2-yl	40.1
10d	CF_3	Piperon-5-yl	135

[a] Cisapride was used as a positive control (IC_{50} = 35 nM).

activity, with a 2.5-fold difference between **1ap** and **10b**, and a 14-fold difference between **1aq** and **10d**.

In summary, two sets of 2,4-diaminopyrimidines (DAPs) totalling 45 compounds were synthesized and assayed against *P. falciparum*. The SAR revealed relatively few major changes in activity that could be attributed to the presence or absence of specific group(s) at R^1 or R^2. The two major observations were a slight decrease in activity when $R^1 = {}^i$Pr, and a significant decrease in activity when R^2 = 2-(pyrrolidin-1-yl)ethyl. A subsequent series of nine compounds addressed high Log *D* values by the introduction of more polar side groups at R^1/R^2. The most active compounds in this series (**7a**–**c**), while 2–2.5-fold less active than **1an**, had more favorable Log *D* values. A final series attempted to address high in vitro microsomal clearance by replacing the C6-Me group with CF_3, however antiplasmodial activity decreased without any improvement in clearance. The C6-CF_3 group decreased hERG inhibition, probably as a result of the lower basicity of the nitrogens at C2/C4.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.10.133.

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6. A stirred solution of 2,4-dichloro-6-methylpyrimidine (**1**, ~1 g) in dry EtOH (6 mL) under an inert atmosphere was cooled to 0 °C, after which the amine (2 equiv) was added dropwise. The reaction mixture was warmed to rt over 24 h, then evaporated to dryness. CH_2Cl_2 (20 mL) was added, washed with water (2 × 20 mL), dried ($MgSO_4$), evaporated to dryness, and the crude material was purified by flash chromatography.
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