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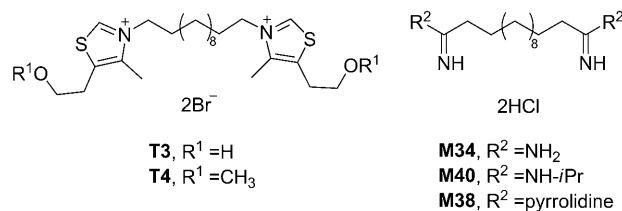
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## Synthesis and Evaluation of Hybrid Bis-cationic Salts as Antimalarial Drugs

Stéphanie Ortial,<sup>[a]</sup> Séverine Denoyelle,<sup>[a]</sup> Sharon Wein,<sup>[b]</sup> Olivier Berger,<sup>[a]</sup> Thierry Durand,<sup>[a]</sup> Roger Escale,<sup>\*,[a]</sup> Alain Pellet,<sup>[c]</sup> Henri Vial,<sup>[b]</sup> and Yen Vo-Hoang<sup>[a]</sup>

Malaria is one of the most common diseases and is caused by protozoan parasites of the genus *Plasmodium*. The World Health organization (WHO) estimates that 3 billion people live in areas where malaria transmission occurs. Indeed, it is endemic in 109 countries and territories in tropical and subtropical regions, particularly in sub-Saharan Africa. Each year, malaria affects ~300 million people worldwide and causes between 1 and 1.5 million deaths.<sup>[1–4]</sup> Moreover, this phenomenon has risen in recent years, probably due to increasing resistance to antimalarial medicine.<sup>[5–8]</sup> *Plasmodium falciparum* is responsible for the most severe form of the disease, and resistant strains have emerged to almost all currently used antimalarial agents (chloroquine, mefloquine, quinine and sulfadoxine/pyrimethamine). An exception is observed for artemisinin and its derivatives, often included in combination therapy.<sup>[9,10]</sup> However, the widespread use of artemisinin and related drugs against *P. falciparum* malaria raises concern over growing drug resistance. For many months, there have been reports from Cambodia of malaria patients showing resistance to artemisinin combination therapy (ACT). The emergence of artemisinin-resistant parasites could seriously undermine global malaria control.<sup>[11]</sup>

Consequently, the design of new antimalarial drugs that are structurally different from the existing agents should be considered a priority. To counteract chemo-resistance, another mechanism-of-action has been explored. *Plasmodium* possesses a unique phospholipid machinery, which is essential for its multiplication during the intraerythrocytic stage.<sup>[12]</sup> This phosphatidylcholine de novo biosynthesis requires the import of choline from the host and constitutes an encouraging novel target.<sup>[13,14]</sup> Choline mimics have been designed to inhibit the phospholipid metabolism.<sup>[15–19]</sup> Duplicated cationic heads have been shown to affect this biosynthetic metabolism and to possess potent antimalarial activity.<sup>[20,21]</sup> Bisquaternary ammonium salts were first synthesized,<sup>[16]</sup> and bisthiazolium salts represent the second generation of bis-cationic antimalarial agents. Bisthiazolium compounds with hydroxyethyl- (**T3**) or methoxyethyl- (**T4**) substituted thiazolium rings (Figure 1) displayed the highest potency with IC<sub>50</sub> values in the nanomolar range.<sup>[22,23]</sup>



**Figure 1.** Chemical structure of bisthiazolium salts **T3** and **T4** and bisamidines **M34**, **M40** and **M38**.

This approach has been validated by the clinical development of **T3** for therapeutic use (unpublished results).

The permanent cationic charges in these agents prevent them from crossing the gastrointestinal barrier and consequently their oral absorption is low. To improve oral bioavailability, bisalkylamidines have been prepared as bioisosteric analogues.<sup>[24,25]</sup> Indeed, the activity of amidines against protozoal infections, such as trypanosomiasis<sup>[26]</sup> and leishmaniasis<sup>[27]</sup> and malaria is well known.<sup>[28]</sup> They are strong bases that are protonated under physiological conditions, and are able to mimic choline. Initial investigations into the bisalkylamidines gave the lead compounds **M40** (*N*-monosubstituted amidine), **M38** (*N*-disubstituted amidine) and **M34** (primary amidine), with potent antimalarial activity but insufficient oral bioavailability. In both the bisthiazolium salts and the bisalkylamidine series, the two polar heads are linked by a 12 methylene units, the optimum length required for antimalarial activity.<sup>[24]</sup> However, the high flexibility of the linker may be a significant drawback to membrane permeation.

The aim of the work presented herein was to design and synthesize a new series of hybrid bis-cationic drugs as antimalarial agents. A thiazolium salt cationic head and an amidine moiety as second polar head were combined to form asymmetrical bis-cationic drugs. The cationic heads were selected from efficient symmetrical derivatives (**T3** or **T4**; **M34**, **M40** or **M38**), in anticipation of a synergistic effect between the two different cationic heads for antimalarial activity. Notably, most of the compounds synthesized contain the **T3** moiety because the parent compound is currently under clinical development against *P. falciparum*.

To probe the structure–activity relationships of these series, the thiazolium salt and the amidine moiety were modulated and the spacer was modified. The first series possess cationic heads linked by an alkyl chain containing 8 or 12 methylene units. In the second series, a rigidification has been introduced via the insertion of an aromatic ring supporting the amidine function. This modification was incorporated because of the antimalarial potency exhibited by the well-known and intensely studied pentamidine, an aromatic bisamidine that accumu-

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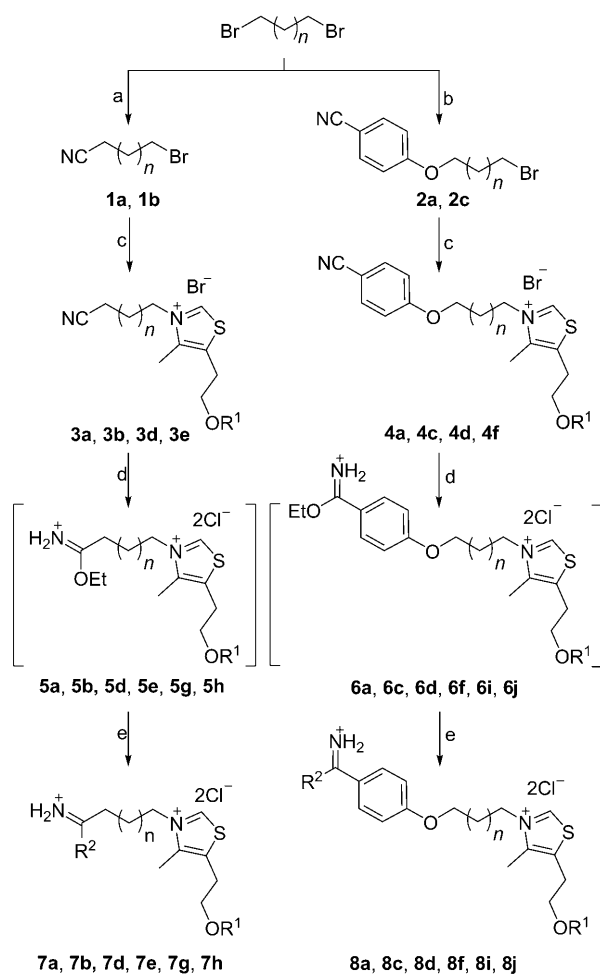
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lates at high levels within erythrocytes infected with the parasite.<sup>[29–31]</sup> In the final series, the length of the alkyl chain is 8 or 11 methylene units. Thus, the influence of flexibility on anti-malarial activity should be elucidated.

Drugs were synthesized as described in Scheme 1. First, asymmetrical compounds **1a** and **1b** were prepared by reaction of the appropriate dibromoalkane and potassium cyanide. The bromine substitution was conducted in a mixture EtOH/Water 85/15 (v/v) to promote the solubility of starting materials. Optimal results for this monosubstitution were obtained using dibromoalkane/KCN in a two to one molar ratio. To prepare the cyano derivatives **2a** and **2c** from the 4-hydroxybenzonitrile and the corresponding dibromoalkane, two methodologies were evaluated. In classical conditions of phenol alkyla-

tion in the presence of sodium hydride in THF,<sup>[32]</sup> monosubstitution occurred but a significant amount of disubstituted product was also isolated. Disubstitution was minimized by using milder conditions; a phase transfer catalysis, tetrabutylammonium bromide, in a mixture CH<sub>2</sub>Cl<sub>2</sub>/NaOH (2 N).<sup>[33]</sup> Addition of the thiazole derivative was achieved under microwave conditions for 3–4 h or in refluxing acetonitrile over three days.<sup>[23]</sup> These last conditions afforded **3a**, **3b**, **3d**, **3e**, **4a**, **4c**, **4d** and **4f** in significantly higher yields. Treatment of these cyano derivatives under Pinner's conditions (gaseous HCl in EtOH) converted them to the unstable ethyl imidates **5a**, **5b**, **5d**, **5e**, **5g**, **5h**, **6a**, **6c**, **6d**, **6f**, **6i**, **6j**, which were immediately reacted with excess ammonia, isopropylamine or pyrrolidine in methanol to provide the amidine derivatives **7a**, **7b**, **7d**, **7e**, **7g**, **7h**, **8a**, **8c**, **8d**, **8f**, **8i**, **8j**. All drugs were isolated as the HCl salt after purification by reverse-phase chromatography.

The in vitro antimalarial activities (Table 1) were evaluated against a chloroquine-sensitive strain of *P. falciparum* (Nigerian strain).<sup>[34]</sup> All compounds exhibited a potent antimalarial activity in the very low nanomolar range, except compounds **7a**



**Scheme 1.** Synthesis of hybrid bis-cationic drugs. *Reagents and conditions:* a) KCN, EtOH/H<sub>2</sub>O, 60 °C, 12 h (72%); b) Hydroxybenzonitrile, TBABr, NaOH 2 N, CH<sub>2</sub>Cl<sub>2</sub>, RT, 72 h (69–73%); c) 4-methyl-5-thiazolethanol or 4-methyl-5-(2-methoxyethyl)thiazole, anhyd CH<sub>3</sub>CN, reflux, 72 h (76–96%); d) HCl<sub>(g)</sub>, anhyd EtOH, RT, 12 h; e) 2 N NH<sub>3</sub>, isopropylamine or pyrrolidine in anhyd CH<sub>3</sub>OH, RT, 12 h (44–71%).

**Table 1.** In vitro and in vivo evaluation of the antimalarial activity of asymmetric compounds **7a–8j**.

Compd	R <sup>1</sup>	R <sup>2</sup>	TS <sup>[a]</sup>	Linker (CH <sub>2</sub> ) <sub>n</sub>	Ar	IC <sub>50</sub> <sup>[b]</sup> [nM]	ED <sub>50</sub> <sup>[c,d]</sup> [mg kg <sup>-1</sup> ]	ip	po
<b>M34</b> <sup>[25]</sup>	–	NH <sub>2</sub>	–	12	–	0.3	>10	>100	
<b>M40</b> <sup>[25]</sup>	–	NH <i>i</i> Pr	–	12	–	31	4.1	>100	
<b>M38</b> <sup>[25]</sup>	–	Pyrrolidine	–	12	–	1.4	1.3	>100	
<b>T3</b> <sup>[23]</sup>	H	–	–	12	–	2.25	0.2	>10	
<b>T4</b> <sup>[23]</sup>	CH <sub>3</sub>	–	–	12	–	0.65	0.14	n.d.	
<b>7a</b>	H	NH <sub>2</sub>	<b>T3</b>	8	–	430	>20	>180	
<b>7b</b>	H	NH <sub>2</sub>	<b>T3</b>	12	–	2.2	2.3	110	
<b>7d</b>	CH <sub>3</sub>	NH <sub>2</sub>	<b>T4</b>	8	–	440	n.d.	n.d.	
<b>7e</b>	CH <sub>3</sub>	NH <sub>2</sub>	<b>T4</b>	12	–	6.15	1.2	60	
<b>7g</b>	H	NH <i>i</i> Pr	<b>T3</b>	12	–	4.5	1.2	70	
<b>7h</b>	H	pyrrolidine	<b>T3</b>	12	–	4.5	0.9	57	
<b>8a</b>	H	NH <sub>2</sub>	<b>T3</b>	8	Phenyl-O	9.3	3	110	
<b>8c</b>	H	NH <sub>2</sub>	<b>T3</b>	11	Phenyl-O	22.5	5	>90	
<b>8d</b>	CH <sub>3</sub>	NH <sub>2</sub>	<b>T4</b>	8	Phenyl-O	10.2	0.93	50	
<b>8f</b>	CH <sub>3</sub>	NH <sub>2</sub>	<b>T4</b>	11	Phenyl-O	26	>2	>90	
<b>8i</b>	H	NH <i>i</i> Pr	<b>T3</b>	8	Phenyl-O	12.5	0.31	23	
<b>8j</b>	H	pyrrolidine	<b>T3</b>	8	Phenyl-O	10.6	0.31	17	

[a] TS, thiazolium salt; (CH<sub>2</sub>)<sub>n</sub>, number of methylene units in the linker; Ar, aromatic ring. [b] IC<sub>50</sub> values—measured against *P. falciparum*—are given as the mean of at least two independent experiments conducted in duplicate. [c] Antimalarial activities (ED<sub>50</sub>)—against *P. vinckeii*—were determined after intraperitoneal (ip) or oral (po) administration of the compounds once daily for 4 days to infected mice. [d] n.d., not determined.

and **7d**. This result clearly shows that a shorter chain (8 methylene units) has a detrimental effect on the biological activity. Conversely, compounds **8c** and **8f** displayed weaker activity indicating that a linker too long in length between the cationic heads also decreases the antimalarial activity. According to the preliminary results obtained in the symmetrical series,<sup>[20]</sup> the alkyl chain containing 12 methylene units is necessary for optimal in vitro/in vivo antimalarial activity. Since the linkers composed of 12 or 8 methylene units and a phenoxy group led to

similar antimalarial activities, the distance between the two cationic heads prevail over its nature. Synergistic effects arising due to the two cationic heads is not clearly indicated by these in vitro results since almost all agents displayed very potent in vitro antimalarial activities with  $IC_{50}$  values between 2 and 12.5 nM similar to the parent bithiazolium salts or bisalkylamidines.

The in vivo antimalarial activities were measured against the *P. vinckei petteri* strain (279BY) in female Swiss mice.<sup>[35]</sup> The mice were treated with compounds by intraperitoneal (ip) or orally (po) administration once daily for four consecutive days (days 1–4 post infection). After ip administration, hybrid derivatives displayed a potent antimalarial activity, except molecules **7a** and **7d**. Indeed, compound **7a** was not able to reduce parasitemia at 20 mg kg<sup>-1</sup>, which may be due to the linker length (8 methylene units), whose effect was underlined earlier. Hence, no in vivo experiments were realized for compound **7d**, because of its weak in vitro activity. The benzamidine derivative **8c**, with a linker containing 11 methylene units, displayed a slightly weaker antimalarial activity compared to **8a**. Asymmetrical compounds **7b**, **7e**, **7g**, **7h**, **8a**, **8d**, **8i** and **8j** exhibited good potency, with  $ED_{50}$  (ip) values lower than 5 mg kg<sup>-1</sup>. Notably, changing the N-substituents of the amidine polar heads for the same **T3** thiazolium moiety led to hybrid drugs that exhibit very close  $ED_{50}$  (ip) values.

Asymmetrical compounds **7g** (isopropyl) and **7h** (pyrrolidinyl) exhibited  $ED_{50}$  (ip) values of 0.9 and 1.2 mg kg<sup>-1</sup>, respectively, close to those of symmetrical **M38** (pyrrolidinyl) and **M40** (isopropyl). Drug **7b** (amino) also displayed a potent antimalarial effect (2.3 mg kg<sup>-1</sup>), while symmetrical **M34** (amino) exhibited no antiplasmodial activity when administered ip. In the benzamidine series, isopropyl (**8i**) and pyrrolidinyl (**8j**) derivatives are tenfold more efficient than amino-bearing compound **8a**. For the same primary amidine polar head, the substitution of thiazolium **T3** by **T4** drastically enhanced antimalarial activity;  $ED_{50}$  (ip) values of compounds **7e** and **8d** are two- to threefold lower than those of compounds **7b** and **8a**. Such a difference was not observed for the symmetrical parent molecules **T3** and **T4**, which presented nearly the same  $ED_{50}$  (ip) values.

No antimalarial activity could be detected after po administration of 100 mg kg<sup>-1</sup> of symmetrical alkylamidines **M34**, **M38** or **M40**; the same observation was made for **7a** and **7d**, which do not possess the optimum distance between the two cationic heads. The longer alkyl chain (11 methylene units) with the phenoxy group is likely to have also hampered oral bioavailability since no effect could be detected at a 90 mg kg<sup>-1</sup> dose. On the other hand, hybrid drugs **7e**, **7g**, **7h**, **8d**, **8i** and **8j** exhibited a significant antimalarial activity after their oral administration to mice. With respect to the amidine N-substituents, antimalarial potency was improved for **7g** ( $ED_{50}$  (po) = 70 mg kg<sup>-1</sup>) and **7h** ( $ED_{50}$  (po) = 57 mg kg<sup>-1</sup>) derivatives containing isopropyl and pyrrolidinyl moieties, respectively, when compared to **7b** ( $ED_{50}$  (po) = 110 mg kg<sup>-1</sup>) with an amino residue. This difference is drastically enhanced in the benzamidine asymmetrical series since compounds **8i** and **8j** presented low  $ED_{50}$  (po) values (23 and 17 mg kg<sup>-1</sup>, respectively). As discussed

for ip administration, the presence of the thiazole moiety **T4** increases antimalarial activity with  $ED_{50}$  (po) values from 1.8- to 2.2-times lower than those obtained with the analogous **T3** derivative. Oral absorptions (estimated through ip/po index: 1.6–2.7%) of hybrid compounds **7b**, **7e**, **7g**, **7h**, **8a**, **8d** and **8i**, **8j** are still weak, and considered to be insufficient for the purpose of oral antimalarial agents.

In conclusion, we synthesized a new series of hybrid bis-cationic molecules with potent antimalarial activities. While we did not observe any synergy between amidine and thiazolium cationic heads, orally potent drugs emerged from the study compared to previously reported symmetrical amidines. The length of the linker plays a critical role in antimalarial activity. On the other hand, the introduction of an aromatic ring supporting the amidine function slightly affects the in vitro antimalarial activity, but readily increases the in vivo efficiency of the pyrrolidinyl- and isopropyl-containing hybrid drugs.

## Experimental Section

### Synthesis

The general procedure for the preparation of the most active hybrid compound **8j** is reported herein. The synthesis of all the bis-cations and their intermediates are described in the Supporting Information with their relative spectroscopic data.

**5-(2-Hydroxyethyl)-3-(8-{4-[imino(pyrrolidin-1-yl)methyl]phenoxy}octyl)-4-methyl-1,3-thiazol-3-ium dichloride (**8j**):** 4-Hydroxybenzotrile (1 equiv) and TBABr (0.1 equiv) were added to a 2 N aqueous solution of NaOH (5 equiv). Separately, a solution of 1,8-dibromooctane (2.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> was prepared and added to the aqueous solution. The mixture was vigorously stirred for 3 d. The two layers were separated and the organic layer was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. Purification by flash chromatography (EtOAc/cyclohexane; 5:95) gave compound **2a** as a white powder. A solution of **2a** (1 equiv) and 4-methyl-5-thiazoethanol (1.5 equiv) in anhyd CH<sub>3</sub>CN was refluxed for 3 d. The reaction was then concentrated in vacuo and purified by chromatography on alumina gel (CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH; 98:2) to give **4a** as a white powder. HCl(g) was bubbled through a solution of **4a** in anhyd EtOH under N<sub>2</sub> for 20 h. After completion, the reaction was concentrated in vacuo for 12 h. The crude was redissolved in anhyd CH<sub>3</sub>OH and treated dropwise with pyrrolidine (1.5 equiv). The mixture was stirred at RT for 24 h. Purification of the crude oil by reverse phase chromatography (C18, 100% H<sub>2</sub>O) afforded **8j** as a colorless oil (42%, three steps):  $R_f$  = 0.32 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 8:2; alumina gel); <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 10.20 (1H, s), 9.22 (1H, m), 8.83 (1H, m), 7.58 (2H, d,  $J$  = 8.8 Hz), 7.10 (2H, d,  $J$  = 8.8 Hz), 4.48 (2H, t,  $J$  = 7.6 Hz), 4.05 (2H, t,  $J$  = 6.4 Hz), 3.63 (2H, t,  $J$  = 5.6 Hz), 3.56 (2H, t,  $J$  = 6.8 Hz), 3.44 (2H, t,  $J$  = 6.8 Hz), 3.03 (2H, t,  $J$  = 5.6 Hz), 2.47 (3H, s), 2.04 (2H, m), 1.87–1.70 (6H, m), 1.33 ppm (8H, m); <sup>13</sup>C NMR (75.47 MHz, CD<sub>3</sub>OD):  $\delta$  = 162.8, 162.2 (C), 155.1 (CH), 142.0, 136.0 (C), 129.4 (CH), 121.5 (C), 114.6 (CH), 68.0, 59.9, 53.3, 51.8, 29.4, 29.0, 28.7, 28.6, 28.5, 25.7, 25.5, 25.1, 24.4 (CH<sub>2</sub>), 10.3 (CH<sub>3</sub>). IR (cm<sup>-1</sup>)  $\nu$  3393, 2937, 2883, 1671, 1609, 1464, 1050, 1023, 1003, 760 ppm; MS (ESI+):  $m/z$  (%): 222.7 (100%) [ $M+H$ ]<sup>+</sup>/2, 223.2 (43%) [ $M+2H$ ]<sup>+</sup>/2, 223.7 (15%) [ $M+3H$ ]<sup>+</sup>/2, 444.4 (12%) [ $M$ ]<sup>+</sup>, 445.4 (4%) [ $M+H$ ]<sup>+</sup>; HRMS:  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>25</sub>H<sub>38</sub>N<sub>3</sub>O<sub>2</sub>S<sup>+</sup>: 444.2685, found: 444.2686.

## Biological assays

In vitro antimalarial activities were determined against a chloroquine-sensitive strain of *P. falciparum* (Nigerian strain). Growth of *P. falciparum* cultures (0.6% initial parasitemia and 1.5% hematocrit) was measured in microtiter plates by [<sup>3</sup>H]hypoxanthine incorporation after 48 h of incubation with the compounds to determine the 50% inhibition concentration (IC<sub>50</sub>) value, according to Desjardins et al.<sup>[34]</sup> Compounds were dissolved in RPMI 1640 or DMSO (final concentration < 0.1 %).

All biological experiments were done in accordance with the French law and the local ethical committee guidelines for animal research.

In vivo antimalarial activities were determined against the *P. vinckei petteri* (279BY) strain in female Swiss mice according to a modified version of the 4 day suppressive test of Peters et al.<sup>[21]</sup> Briefly, drugs and prodrugs were injected in 100 μL of 0.9% NaCl or DMSO via ip or po administration. Parasitemia levels were monitored using Giemsa-stained blood smears, and blood samples were collected for parasite determination on a fluorescence-activated cell sorter.<sup>[35]</sup>

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**Keywords:** biological activity · hybrid bis-cations · malaria · phospholipid metabolism · structure–activity relationships

- [1] *World Malaria Report 2008* (WHO/HTM/GMP/2008.1), World Health Organization, Geneva (Switzerland), **2008**; <http://apps.who.int/malaria/wmr2008/> (Last accessed: November 18, 2009).
- [2] S. I. Hay, C. A. Guerra, A. J. Tatem, A. M. Noor, R. W. Snow, *Lancet Infect. Dis.* **2004**, *4*, 327.
- [3] J. G. Breman, A. Egan, G. T. Keusch, *Am. J. Trop. Med. Hyg.* **2001**, *64*, iv.
- [4] *Malaria and Children: Progress in Intervention Coverage*, United Nations Children's Fund, **2007**; [www.unicef.fr](http://www.unicef.fr).
- [5] *The Global Malaria Action Plan for a Malaria-Free World*, World Health Organization, Geneva (Switzerland), **2008**; <http://www.rollbackmalaria.org/gmap/index.html>.
- [6] E. H. Ekland, D. A. Fidock, *Curr. Opin. Microbiol.* **2007**, *10*, 363.
- [7] E. H. Ekland, D. A. Fidock, *Int. J. Parasitol.* **2008**, *38*, 743.
- [8] C. Wongsrichanalai, A. L. Pickard, W. H. Wernsdorfer, S. R. Meshnick, *Lancet Infect. Dis.* **2002**, *2*, 209.
- [9] J. J. Walsh, D. Coughlan, N. Heneghan, C. Gaynor, A. Bell, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3599.
- [10] P. E. Duffy, T. K. Mutabingwa, *The Lancet* **2006**, *367*, 2037.
- [11] H. Noedl, Y. Se, K. Schaecher, B. L. Smith, D. Socheat, M. M. Fukuda, *N. Engl. J. Med.* **2008**, *359*, 2619.
- [12] H. Vial, C. B. Mamoun, in *Plasmodium Lipids: Metabolism and Function; Molecular Approach to Malaria*, (Ed.: I. W. Sherman), ASM Press, Washington DC, **2005**, pp. 327–352.
- [13] H. Vial, M. Calas, in *Antimalarial Chemotherapy, Mechanisms of Action, Modes of Resistance, and New Directions in Drug Development*, (Ed.: P. Rosenthal), Humana Press, Totowa, **2001**, pp. 347–365.
- [14] X. J. Salom-Roig, A. Hamze, M. Calas, H. J. Vial, *J. Comb. Chem. High Throughput Screening* **2005**, *8*, 49.
- [15] H. J. Vial, P. Eldin, A. G. M. Tielens, J. J. Van Hellemond, *Mol. Biochem. Parasitol.* **2003**, *126*, 143.
- [16] M. Calas, G. Cordina, J. Bompert, M. B. Bari, T. Jei, M. L. Ancelin, H. J. Vial, *J. Med. Chem.* **1997**, *40*, 3557.
- [17] M. Calas, M. L. Ancelin, G. Cordina, P. Portefaix, G. Piquet, V. Vidal-Sailhan, H. J. Vial, *J. Med. Chem.* **2000**, *43*, 505.
- [18] M. L. Ancelin, M. Calas, J. Bompert, G. Cordina, D. Martin, M. B. Bari, T. Jei, P. Druilhe, H. J. Vial, *Blood* **1998**, *91*, 1426.
- [19] M. L. Ancelin, M. Calas, V. Vidal-Sailhan, S. Herbute, P. Ringwald, H. J. Vial, *Antimicrob. Agents Chemother.* **2003**, *47*, 2590.
- [20] K. Wengelnik, V. Vidal, M. L. Ancelin, A. M. Cathiard, J. L. Morgat, C. Kocken, M. Calas, S. Herrera, A. Thomas, H. Vial, *Science* **2002**, *295*, 1311.
- [21] M. L. Ancelin, M. Calas, A. Bonhoure, S. Herbute, H. J. Vial, *Antimicrob. Agents Chemother.* **2003**, *47*, 2598.
- [22] H. J. Vial, S. Wein, C. Farenc, C. Kocken, O. Nicolas, M. L. Ancelin, F. Bressole, A. Thomas, M. Calas, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 15458.
- [23] A. Hamzé, E. Rubi, P. Arnal, M. Boisbrun, C. Carcel, X. Salom-Roig, M. Maynadier, S. Wein, H. Vial, M. Calas, *J. Med. Chem.* **2005**, *48*, 3639.
- [24] M. Calas, M. Ouattara, G. Piquet, Z. Ziora, Y. Bordat, M. L. Ancelin, R. Escalé, H. J. Vial, *J. Med. Chem.* **2007**, *50*, 6307.
- [25] H. Vial, M. Calas, M. L. Ancelin, R. Escalé, V. Vidal, F. Bressolle, WO Patent WO 04/009068, **2004**.
- [26] E. M. Lourie, W. Yorke, *Ann. Trop. Med. Parasitol.* **1939**, *33*, 289.
- [27] R. Kirk, M. H. Sati, *Ann. Trop. Med. Parasitol.* **1940**, *34*, 181.
- [28] B. M. Das Gupta, L. B. Siddons, *Indian Med. Gaz.* **1944**, *79*, 527.
- [29] A. M. W. Stead, P. G. Bray, I. G. Edwards, H. P. Dekoning, B. C. Elford, P. A. Stocks, S. A. Ward, *Mol. Pharmacol.* **2001**, *59*, 1298.
- [30] C. A. Bell, J. E. Hall, D. E. Kyle, M. Grogil, K. A. Ohemeng, M. A. Allen, R. R. Tidwell, *Antimicrob. Agents Chemother.* **1990**, *34*, 1381.
- [31] For recent work on pentamidine and its derivatives, see Tidwell and co-workers articles: a) S. A. Bakunov, S. M. Bakunova, A. S. Bridges, T. Wenzler, T. Barszcz, K. A. Werbovetz, R. Brun, R. R. Tidwell, *J. Med. Chem.* **2009**, *52*, 5763; b) S. M. Bakunova, S. A. Bakunov, T. Wenzler, T. Barszcz, K. A. Werbovetz, R. Brun, R. R. Tidwell, *J. Med. Chem.* **2009**, *52*, 4657; c) S. M. Bakunova, S. A. Bakunov, D. A. Patrick, E. V. K. S. Kumar, K. A. Ohemeng, A. S. Bridges, T. Wenzler, T. Barszcz, S. Kilgore Jones, K. A. Werbovetz, R. Brun, R. R. Tidwell, *J. Med. Chem.* **2009**, *52*, 2016; d) S. M. Bakunova, S. A. Bakunov, T. Wenzler, T. Barszcz, K. A. Werbovetz, R. Brun, E. D. Hall, R. R. Tidwell, *J. Med. Chem.* **2007**, *50*, 5807.
- [32] X. Bao, I. Isaacsohn, A. F. Drew, D. B. Smithrud, *J. Org. Chem.* **2007**, *72*, 3988.
- [33] T. A. Spencer, T. J. Onofrey, R. O. Cann, J. S. Russel, L. E. Lee, D. E. Blanchard, A. Castro, P. Gu, G. Jiang, I. Shechter, *J. Org. Chem.* **1999**, *64*, 807.
- [34] R. E. Desjardins, C. J. Canfield, J. D. Haynes, J. D. Chulay, *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
- [35] D. Barkan, H. Ginsburg, J. Golenser, *Int. J. Parasitol.* **2000**, *30*, 649.

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