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Total Synthesis of Thiaplakortone A: Derivatives as Metabolically Stable Leads for the Treatment of Malaria

Rebecca H. Pouwer,[†] Sophie M. Deydier,[†] Phuc Van Le,[†] Brett D. Schwartz,[†] Nicole C. Franken,[†] Rohan A. Davis,[†] Mark J. Coster,[†] Susan A. Charman,[‡] Michael D. Edstein,[§] Tina S. Skinner-Adams,[†] Katherine T. Andrews,[†] Ian D. Jenkins,[†] and Ronald J. Quinn*[,†]

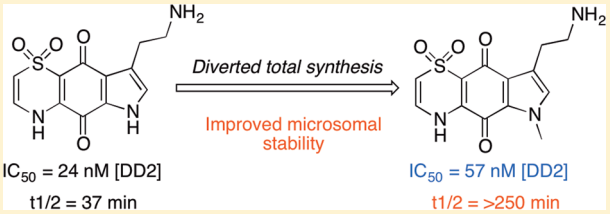
[†]Eskitis Institute for Drug Discovery, Griffith University, Brisbane, QLD 4111, Australia

[‡]Centre for Drug Candidate Optimisation, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia

[§]Australian Army Malaria Institute, Brisbane, QLD 4051, Australia

Supporting Information

ABSTRACT: Thiaplakortone A (**3a**), an antimalarial natural product, was prepared by an operationally simple and scalable synthesis. In our efforts to deliver a lead compound with improved potency, metabolic stability, and selectivity, the synthesis was diverted to access a series of analogues. Compounds **3a**–**d** showed nanomolar activity against the chloroquine-sensitive (3D7) *Plasmodium falciparum* line and were more active against the chloroquine- and mefloquine-resistant (Dd2) *P. falciparum* line. All compounds are "Rule-of-5" compliant, and we show that metabolic stability can be enhanced via modification at either the primary or pyrrole nitrogen. These promising results lay the foundation for the development of this structurally unprecedented natural product.



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Approximately 3.3 billion people, almost half the world's population, including the populations of Africa, Asia, Latin America, the Middle East, and South East Asia, are at risk of developing malaria.[1] In 2010, approximately 655,000 people died due to this disease.[1] Of these deaths, an estimated 91% occurred in sub-Saharan Africa, with children under the age of five being most at risk. The World Health Organization (WHO) recommends interventions for the prevention and treatment of malaria that include (1) the use of insecticide-treated nets; (2) drug prophylaxis in vulnerable populations; (3) rapid diagnosis; and (4) treatment with antimalarial drugs.[1] Current drug therapy for *Plasmodium falciparum* malaria, recommended by the WHO, uses artemisinin in combination with other antimalarials. The problem of parasite resistance to artemisinin-based combination therapy (ACT) is of growing and immense concern, with the presence of artemisinin resistance having been confirmed in western Cambodia and western Thailand.[2−6] In addition to the threat of parasite resistance, the poor safety profiles and undesirable side-effects associated with many of the current antimalarials are also driving the need for new small molecule therapies. New antimalarial drugs with unique mechanisms of action are urgently needed in order to combat the global problem of parasite drug resistance.[7−9]

Natural products have played a key role in antimalarial drug discovery and therapy.[10−13] Quinine and artemisinin, first isolated from the South American "quinine bark" (*Cinchona succirubra*) and the Chinese "sweet wormwood" (*Artemisia annua*), respectively,[14] are well-known natural products, which have served as a structural basis for numerous antimalarial drugs, such as artesunate, artemether, chloroquine, mefloquine, and halofantrine.[15] Many other drugs are also derived from Nature, with natural product drugs representing ∼50% of small molecule approved drugs.[13] The basis for the wide-ranging biological activity of natural products is explained by the concept of protein fold topology (PFT),[16] where molecular recognition during biosynthesis (the biosynthetic imprint) has been shown to translate to a similar binding mode with therapeutic targets. The cavity recognition points described by PFT may be unrelated to fold and sequence similarity and define a natural product's ability to interact with biological space.[17−19]

We have developed a lead-like enhanced natural product fraction screening library, in which fractions are selected for drug-like properties including logP.[20] Active natural products from our malaria drug discovery program include tsitsikammamine C (**1**) and makaluvamine G (**2**) from the marine sponge, *Zyzzya* sp.,[21] and more recently thiaplakortone A from the sponge, *Plakortis lita* (Figure 1).[22] Thiaplakortone A (**3a**) contains a unique tricyclic alkaloid skeleton that is without precedent among natural products.[22] The thiazine dioxide-fused pyrroloquinone moiety shares some structural similarity

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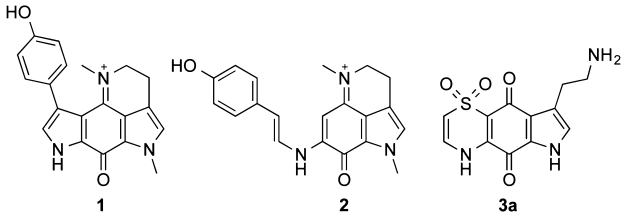


Figure 1. Antimalarial pyrroloquinone natural products.

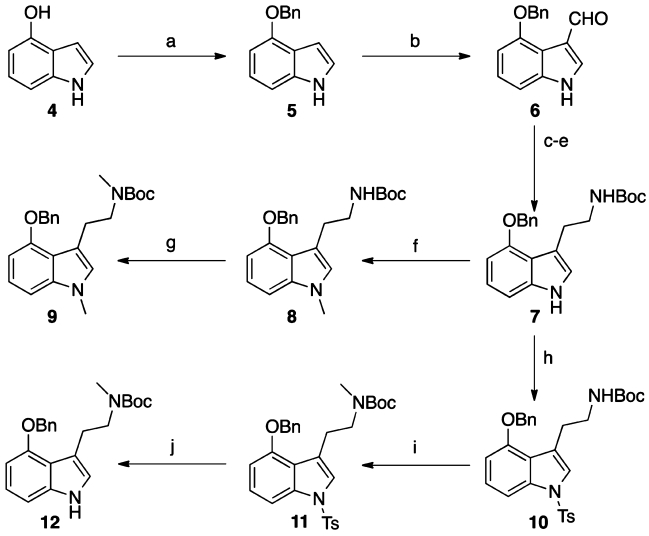
with the antimalarial natural products tsitsikammamine C (**1**) and makaluvamine G (**2**). Previous studies of the tsitsikammamine and makaluvamine series indicated that methylation affected antimalarial activity and metabolic stability. In comparing the structural features of **1**, **2**, and **3a**, the right hemisphere of **3a** has the intact pyrrolo moiety; however, the iminoquinone present in **1** and **2** is ring opened to the quinone with a free primary amine side chain in **3a**. Tsitsikammamine C (**1**) displayed potent in vitro activity (IC_{50} = 13 nM [3D7], 18 nM [Dd2]), had selectivity indices of >200, and inhibited both ring and trophozoite stages of the parasite life cycle. Makaluvamine G (**2**) (IC_{50} = 36 nM [3D7], 39 nM [Dd2]) had selectivity indices of >50 and primarily inhibited the trophozoite stage. Thiaplakortone A (**3a**) was found to have IC_{50} values of 51 and 6.6 nM against the chloroquine-sensitive 3D7 and the chloroquine- and mefloquine-resistant Dd2 *Plasmodium falciparum* lines in an imaging-based growth inhibition assay, respectively.[22] These data led us to further explore the antimalarial properties of pyrroloquinone scaffolds through a diverted total synthesis of thiaplakortone A (**3a**).

Herein we report the first total synthesis of **3a**, along with several thiaplakortone-based analogues (**3b–d**, **17**). The in vitro antimalarial activity and mammalian cell toxicity studies for all compounds is also reported as well as metabolic profiling and in vivo studies with lead compounds in mice.

In developing a synthetic strategy toward **3a** as an early lead compound for the treatment of malaria, we were mindful of expense and the need for the synthesis to be operationally simple. Furthermore, the ability to access monomethyl and dimethyl analogues (**3b–d**) for structure–activity relationship development was of central importance in our synthetic design.

Synthesis of the common intermediate **7** from commercially available 4-hydroxyindole (**4**)[23] commenced with protection of the phenol as its benzyl ether,[24] followed by Vilsmeier–Haack formylation to produce aldehyde **6** (Scheme 1). This compound was subsequently subjected to Henry reaction with nitromethane, where the resulting nitroalkene was reduced by $LiAlH_4$, and the primary amine was protected as its *t*-butylcarbamate (**7**). Thus, **7** was synthesized in five facile synthetic steps from **4**, requiring only two chromatographic separations. Selective methylation of **7** (MeI, KOH) yielded **8**, thus allowing access to derivatives of the natural product in which the pyrrole nitrogen is methylated. Compound **8**, which upon subsequent treatment with LiHMDS and MeI provided **9**, also served as a precursor to a dimethylated analogue of **3a**. To selectively access an analogue in which only the side-chain amine was alkylated, it was necessary to protect the indole nitrogen of **7**. Consequently, **7** was protected as its tosylate (**10**), and subsequent methylation (LiHMDS, MeI) and deprotection (Mg, MeOH) gave rise to the monomethylated derivative **12**. It is worth noting that **10** resembles a synthetic intermediate used in the total synthesis of tsitsikammamine

Scheme 1[a]

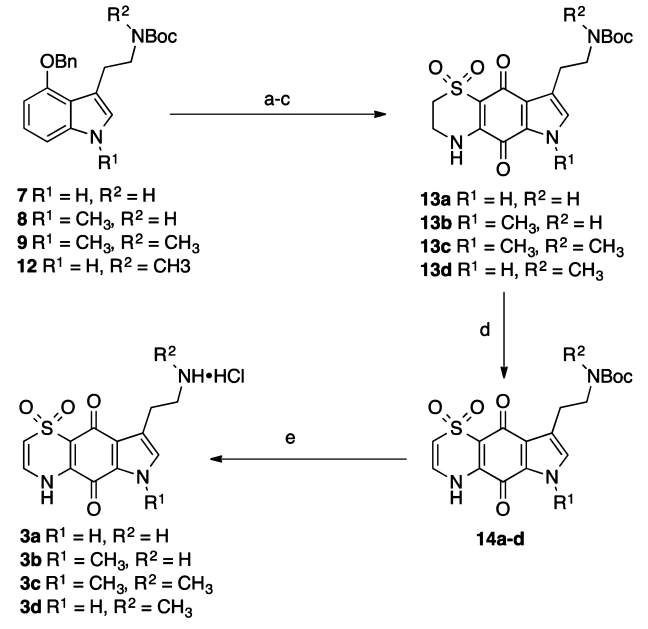


[a]Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux, 36 h; (b) $POCl_3$, DMF, rt, 1 h, then KOH, H_2O, reflux, 3 h; (c) CH_3NO_2, NH_4OAc, reflux, 1 h; (d) $LiAlH_4$, THF, reflux, 6 h; (e) Boc_2O, Et_3N, THF, rt, 16 h; (f) MeI, KOH, DMSO, rt, 19 h; (g) MeI, LiHMDS, THF, rt, 2 h; (h) TsCl, Bu_4NHSO_4, KOH, toluene, H_2O, rt, 24 h; (i) MeI, LiHMDS, THF, rt, 2 h; (j) Mg, MeOH, sonicate, 30 min.

A,[25,26] and it is anticipated that our synthetic strategy would equally serve to access compounds of type **1** and **2**.

The tryptamine derivatives **7–9** and **12** were then subjected to a general procedure for the synthesis of the thiazine dioxide pyrroloquinones (Scheme 2). Initial hydrogenolysis of the benzyl protecting group was followed by immediate oxidation of the unstable intermediate with Fremy's salt. The resulting

Scheme 2[a]



[a]Reagents and conditions: (a) H_2, Pd/C, MeOH, rt, 24 h; (b) Fremy's salt, NaH_2PO_4, CH_3CN, H_2O, rt, 4 h; (c) 2-aminoethanesulfinic acid, EtOH, CH_3CN, H_2O, rt, 16 h; (d) O_2, KOH, MeOH, H_2O, 60 °C; (e) HCl, MeOH, H_2O, rt, 18 h, or HCl 1,4-dioxane, rt, 30 min.

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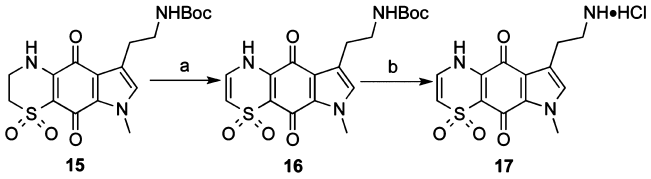
quinones participated in a double conjugate addition/oxidation sequence upon treatment with 2-aminoethanesulfinic acid to yield dihydrothiazine dioxides **13a–d** as separable mixtures with their corresponding regioisomers. Dihydrothiazine dioxides **13a–d** were then oxidized (O_2, KOH) and deprotected under acidic conditions to produce the natural product **3a** and thiazine dioxides **3b–d** as their hydrochloride salts. Compound **15**, the regioisomer of **13b**, was subjected to an equivalent sequence to deliver **17** (Scheme 3). From tryptamine

Scheme 3[a]



[a]Reagents and conditions: (a) O_2, KOH, MeOH, H_2O, 60 °C; (b) HCl, MeOH, H_2O, rt, 18 h.

derivatives **7–9** and **12**, this synthetic sequence required only one chromatographic separation and was used to rapidly produce the thiazinedioxides on multigram scale. The NMR spectroscopic data for synthetic **3a** (HCl salt) was essentially identical to that previously reported for the natural product, thiaplakortone A, which was isolated as a TFA salt.[22]

Compounds were evaluated for in vitro antimalarial activity using the [^{3}H]-hypoxanthine incorporation assay[27,28] against the chloroquine-sensitive 3D7 and the chloroquine- and mefloquine-resistant Dd2 *Plasmodium falciparum* lines. To compare the selectivity of the compounds for malaria parasites versus normal mammalian cells, cytotoxicity tests were carried out using human neonatal foreskin fibroblast (NFF) cells. All biological data, including selectivity indices and calculated physicochemical properties, are detailed in Table 1.

The synthetic natural product **3a** had an IC_{50} of 104 nM against the 3D7 *P. falciparum* line and was found to be 4.3-fold more potent against the multidrug resistant *P. falciparum* line Dd2 (IC_{50} = 24 nM). This interesting observation held true for analogues **3b–d**, with selectivity for the *P. falciparum* line Dd2 ranging between 1.7- to 3.4-fold. This effect was not observed for compounds **1** and **2** and is in fact opposite to that for chloroquine, which has more than 8-fold less potency against the Dd2 *P. falciparum* line. For the makaluvamine series (e.g., **2**), we previously reported that the presence of an *N*-methyl iminium moiety increased antimalarial activity by ∼10- to 30-fold compared to a secondary imine skeleton, while methylation of the pyrrole nitrogen appears not to affect the bioactivity.[21] With respect to the thiaplakortone scaffold, our results demonstrate that alkylation of both the pyrrole and side-chain nitrogens is well tolerated, with analogues **3b–d** demonstrating low nM potency in both the 3D7 (**3b** IC_{50} = 128 nM, **3c** IC_{50} = 137 nM, **3d** IC_{50} = 160 nM) and Dd2 (**3b** IC_{50} = 57 nM, **3c** IC_{50} = 79 nM, **3d** IC_{50} = 47 nM) *P. falciparum* lines. When compared with **3b**, regioisomer **17** showed decreased activity against both malaria parasite lines (IC_{50} = 416 nM [3D7], 162 nM [Dd2]), suggesting that the orientation of the thiazine dioxide moiety plays an important role in biological activity. These observations open avenues for the further manipulation of these moieties in future structure–activity relationship investigations.

Selectivity between host and parasite is of paramount concern, as quinones have been associated with toxic effects.[30] All compounds were found to have greater than 9-fold selectivity for the 3D7 *P. falciparum* line over NFF cells, providing a reasonable therapeutic window for the development of an early lead compound. Interestingly, regioisomer **17** showed the highest levels of selectivity (32-fold in 3D7 and 81-fold in Dd2), demonstrating that minor manipulation of the core may result in an improved toxicity profile.

All compounds complied with Lipinski's rule-of-five[31] (logP < 5, hydrogen bond acceptors (HBA) < 10, hydrogen bond donors (HBD) < 5, MW < 500), and Hann–Oprea's guidelines for lead-likeness[32] (logP < 4, HBA < 9, HBD < 5, MW < 460, rotatable bonds < 10). Compounds **3a–d** displayed good solubility in phosphate buffered saline under both neutral and acidic conditions. These physicochemical properties support the drug-likeness of compounds **3a–d**.

In vitro studies in hepatic microsomes were conducted to assess the extent of metabolic degradation (Table 2).

Table 2. In Vitro Metabolism of Compounds 3a–d in Human and Mouse Liver Microsomes

compd	species	half-life (min)	in vitro CL_{int} (μL/min/mg protein)	E_H[a]
3a	human	37	46	0.64
	mouse	25	68	0.75
3b	human	>250	<7	<0.23
	mouse	>250	<7	<0.23
3c	human	>250	<7	<0.23
	mouse	>250	<7	<0.23
3d	human	100	17	0.40
	mouse	151	11	0.33

[a]E_H: predicted in vivo hepatic extraction ratio, calculated according to published methods.

Table 1. Physicochemical Parameters and Biological Profiles of Compounds 3a–d and 17

	physicochemical parameters[a]				IC_{50} ± SD (nM)[b]			SI[c]	
compd	MW	cLogP	HBA	HBD	3D7	Dd2	NFF	3D7	Dd2
3a	293	−2.06	6	3	104 ± 22	24 ± 2	1500 ± 500	14	60
3b	307	−1.84	6	2	128 ± 20	57 ± 14	2309 ± 1037	18	40
3c	321	−1.40	6	2	137 ± 29	79 ± 0.2	2309 ± 1229	17	29
3d	307	−1.77	6	3	160 ± 11	47 ± 10	1477 ± 607	9	31
17	307	−1.84	6	2	416 ± 90	162 ± 87	13197 ± 3236	32	81
chloroquine	319	3.93	4	1	15 ± 4	130 ± 22	45900 ± 19300	3060	353

[a]In silico calculations performed using Instant JChem software.[29] MW = molecular weight (Da) of free base, HBA = H-bond acceptors, and HBD = H-bond donors. [b]50% inhibitory concentration in vitro against *P. falciparum* chloroquine-sensitive (3D7) and drug-resistant (Dd2) lines, and human neonatal foreskin fibroblast cells (NFF). [c]SI = mammalian cell IC_{50}/*P. falciparum* IC_{50}.

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Compounds **3a**–**d** were found to be stable in the microsomal matrix in the absence of cofactors, suggesting that there was no major contribution of cofactor-independent metabolism to the rate of metabolism. In the presence of NADPH in both human and mouse liver microsomes, the synthetic natural product **3a** was rapidly degraded, with half-lives of 37 and 25 min, respectively. Analogues **3b** and **3c**, which both feature a methylated pyrrole, were minimally degraded in both species, and were found to have significantly increased half-lives (>250 min) and low predicted hepatic extraction ratios (<0.23) in comparison to **3a** and **3d** (Table 2). Monomethylation of the primary amine side-chain (i.e., **3d**) resulted in an increased half-life of 100 min in human microsomes. These results highlight an opportunity to improve metabolic stability through a simple modification of either the primary or pyrrole nitrogen of the natural product.

The tolerability of **3a**–**c** was assessed in healthy mice. A slight whole body tremor lasting about 1–2 h after each dose and slightly ruffled coat were observed in mice administered **3a** at a daily dose of 8 mg/kg for 4 d. However, at 16 mg/kg the mice exhibited marked whole body tremors, lethargy, and ruffled coat within 2 h after the first dose. Mice administered **3b** at a dose of 4 and 8 mg/kg exhibited panting and whole body tremors within 10 to 15 min of the first dose, with adverse events more noticeable with the higher dose. Compound **3c**, at a dose of 8 mg/kg, led to marked physical distress in all animals, with whole body tremors, difficulty in moving about, orange urine, and swollen conjunctiva of the eyes. Overall, **3a**–**c** were not well tolerated in mice at relatively low doses of compound. Investigations to address in vivo tolerability of this compound series are underway.

In conclusion, from **3a**, an antimalarial natural product, we have developed potent antimalarial compounds with favorable physicochemical and ADME properties. We have designed and completed the rapid and operationally simple total synthesis of **3a** and have diverted this synthesis to access analogues **3b**–**d**. Methylation of the thiaplakortone scaffold was well tolerated, and analogues **3b**–**d** showed low nM in vitro activity against drug-sensitive and drug-resistant *P. falciparum* lines. Methylation of the pyrrole nitrogen was found to dramatically increase the metabolic stability of analogues, without significant loss of antimalarial activity. These studies pave the way for the development of structurally unprecedented lead compounds for the treatment of malaria.

■ ASSOCIATED CONTENT

Supporting Information

Details regarding compound synthesis and characterization and biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(R.J.Q.) Tel: +61-7-3735-6000. Fax: +61-7-3735-6001. E-mail: r.quinn@griffith.edu.au.

Author Contributions

All authors have given approval to the final version of the manuscript.

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Notes

The opinions expressed herein are those of the authors and do not necessarily reflect those of the Australian Defence Force, Joint Health Command or any extant policy.

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PFT, protein fold topology; ACT, artemisinin-based combination therapy; NFF, neonatal foreskin fibroblast cells; 3D7, chloroquine-sensitive *P. falciparum* line; Dd2, chloroquine-resistant *P. falciparum* line

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