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# Antiplasmodial activity of tambjamines, dihydro- $\beta$ -agarofurans and pyrroloazepines derived from Australian plant and marine species

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## ABSTRACT

Malaria is a significant cause of morbidity and mortality, with 263 million cases and 597,000 deaths estimated in 2023. While effective drug combinations are available to prevent and treat malaria, *Plasmodium* parasite drug resistance is compromising all current options. This situation means that new drugs that act on novel *Plasmodium* drug targets are needed. Natural products, including artemisinin, derived from *Artemisia annua*, and its derivatives, have been an important source of antimalarials. In this study we investigated a panel of 43 compounds from the NatureBank natural product library for *in vitro* activity against asexual stage *P. falciparum* parasites. Four compounds isolated from Australian plant and marine samples were identified with novel antiplasmodial activity - tambjamine F (IC<sub>50</sub> 1.06  $\mu$ M) and tambjamine C (IC<sub>50</sub> 3.40  $\mu$ M) from the marine ascidian *Sigillina signifera*, bilocularin B (IC<sub>50</sub> 2.18  $\mu$ M) from the rainforest plant *Maytenus bilocularis* and hymenialdisine (IC<sub>50</sub> 2.90  $\mu$ M) from the marine sponge *Acanthella costata*.

Natural products and their derivatives are rich sources of therapeutics for human health, with >30 % of all new medicines derived from or based upon natural products between 1981 and 2019.<sup>1</sup> Natural products have been an important source of drugs for malaria, a parasitic disease caused by *Plasmodium* species. In 2023, there were 263 million clinical cases of malaria and an estimated 597,000 deaths, predominantly due to infection with *P. falciparum*.<sup>2</sup> Examples of natural product and natural product-derived antimalarial agents include quinine,<sup>3</sup> atovaquone,<sup>4</sup> and artemisinin.<sup>5,6</sup> Artemisinin combination therapies (ACTs), which contain artemisinin or one of its derivatives (e.g. dihydroartemisinin) together with a partner drug with a longer half-life and different mode of action (e.g. lumefantrine, mefloquine, or amodiaquine<sup>7,8</sup>), are recommended as first-line treatments for uncomplicated *P. falciparum* malaria. However, an ongoing challenge for malaria prevention and control is the problem of parasite drug resistance, including to ACTs (reviewed in<sup>9</sup>) which is driving the search for novel drugs. The vast chemical space occupied by natural products remains an important source of chemical diversity that may lead to therapeutic starting points for new antimalarials. In this study, we investigated the *in vitro* antiplasmodial activity of a set of 43 compounds from the NatureBank natural product library

(Griffith University, Queensland, Australia), which constituted compounds predominantly sourced from Australian marine and terrestrial biota.

*In vitro* screening of this set of 43 compounds was performed against drug-sensitive, asexual-stage *P. falciparum* 3D7 (Pf3D7) parasites in [<sup>3</sup>H]-hypoxanthine uptake assays (Supplemental Data S1).<sup>10</sup> A Z' score of 0.90 ( $\pm 0.03$ ) confirmed assay validity. Seven compounds demonstrated >90 % inhibition of parasite growth at 2.5  $\mu$ M, the "hit" criterion for further investigation (Supplemental Table S1). The control drug chloroquine inhibited the growth Pf3D7 by >90 % at 125 nM (Supplemental Table S1). Four of the seven hits (tambjamine F and tambjamine C, hymenialdisine, and bilocularin B) demonstrated no inhibitory activity in sulforhodamine-B (SRB) cytotoxicity assays (Supplemental Data S1)<sup>11</sup> against human neonatal foreskin fibroblasts (NFFs) at 2.5  $\mu$ M, and all except tambjamine F gave no inhibition at 25  $\mu$ M (Table 1; Supplemental Table S2). When tested in dose-response assays, tambjamine F, tambjamine C, bilocularin B, and hymenialdisine were found to have Pf3D7 IC<sub>50</sub> values of 1.06  $\mu$ M, 3.40  $\mu$ M, 2.18  $\mu$ M, and 2.90  $\mu$ M, and Selectivity Indices (SI; NFF IC<sub>50</sub>/Pf3D7 IC<sub>50</sub>) of >2, >7, >46 and >34 for Pf3D7 versus NFFs, respectively (Table 1). The antimalarial control

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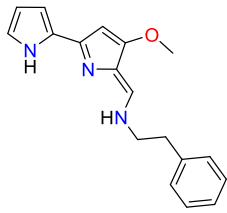
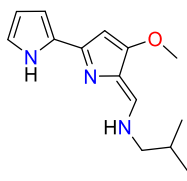
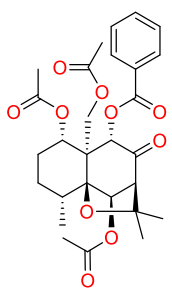
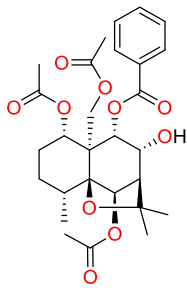
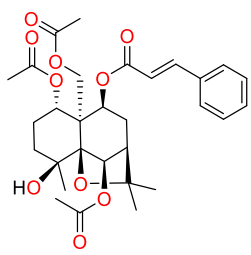
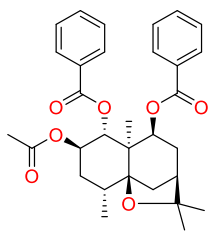
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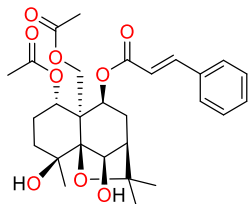
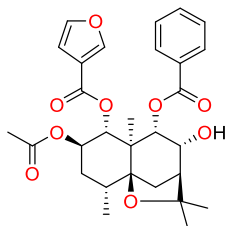
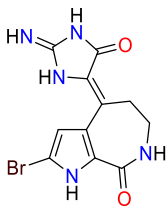
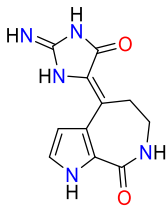
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**Table 1**  
Antiplasmodial activity of natural products.

| Name                         | Structure                                                                           | CLogP <sup>a</sup> | <i>Pf</i> 3D7<br>IC <sub>50</sub> (μM) <sup>b</sup> | NFF<br>IC <sub>50</sub> (μM) <sup>c</sup> | SI <sup>d</sup> |
|------------------------------|-------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------|-------------------------------------------|-----------------|
| <b>Bipyrroles</b>            |                                                                                     |                    |                                                     |                                           |                 |
| Tambjamine F                 |    | 3.43               | 1.06 (±0.34)                                        | >2.5*                                     | >2              |
| Tambjamine C                 |    | 2.79               | 3.40 (±2.96)                                        | >25*                                      | >7              |
| <b>Dihydro-β-agarofurans</b> |                                                                                     |                    |                                                     |                                           |                 |
| Bilocularin B                |   | 4.22               | 2.18 (±0.45)                                        | >100                                      | >46             |
| Bilocularin A                |  | 5.89               | >12.5                                               | >100                                      | >8              |
| Denhaminol A                 |  | 5.55               | 18.12 (±9.39)                                       | >25                                       | >1              |
| Celastrofuran B              |  | 6.78               | 20.24 (±5.25)                                       | >25                                       | >1              |

(continued on next page)

Table 1 (continued)

| Name                    | Structure                                                                          | CLogP <sup>a</sup> | <i>Pf</i> 3D7<br>IC <sub>50</sub> (μM) <sup>b</sup> | NFF<br>IC <sub>50</sub> (μM) <sup>c</sup> | SI <sup>d</sup> |
|-------------------------|------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------|-------------------------------------------|-----------------|
| Denhaminol C            |   | 5.33               | >25                                                 | >25                                       | >1              |
| Celastrofuran E         |   | 4.95               | >25                                                 | >25                                       | >1              |
| <b>Pyrroloazepines</b>  |                                                                                    |                    |                                                     |                                           |                 |
| Hymenialdisine          |   | −1.58              | 2.90 (±0.58)                                        | >100                                      | >34             |
| Debromo-hymenialdisine  |  | −1.70              | 4.57 (±1.18)                                        | >100                                      | >22             |
| <b>Positive Control</b> |                                                                                    |                    |                                                     |                                           |                 |
| Chloroquine             |                                                                                    | 5.06               | 0.01 (±0.02)                                        | 44.8 (±17.9)                              | 4480            |

<sup>a</sup> CLogP = calculated logarithm of the partition coefficient [calculated using ChemDraw version 23.1.1.3 (Revvity, USA)].

<sup>b</sup> Compounds were tested in dose response using [<sup>3</sup>H]-hypoxanthine uptake assays over 72 h.<sup>10</sup> Mean IC<sub>50</sub> (±SD) is shown for two independent assays, each performed in triplicate wells.

<sup>c</sup> Compounds were assessed for cytotoxicity at 2.5 μM and 25 μM concentrations against human NFFs using SRB assays<sup>11</sup> in two independent assays (\*single assay due to limited compound availability), each performed in duplicate wells.

<sup>d</sup> Indicative SI calculated as NFF IC<sub>50</sub>/*Pf*3D7 IC<sub>50</sub>.

chloroquine displayed a *Pf*3D7 IC<sub>50</sub> of 0.01 μM and SI of 4480, in line with previously reported data.<sup>10</sup>

The most potent compound identified in this study was tambjamine F (*Pf*3D7 IC<sub>50</sub> 1.06 μM; SI >2), with tambjamine C being ~3-fold less potent (*Pf*3D7 IC<sub>50</sub> 3.40 μM; SI >7; Table 1). Both compounds were isolated from *Sigillina signifera*, an ascidian collected from the Great Barrier Reef, Far North Queensland.<sup>12</sup> The first reports of these compounds were from *Sigillina* specimens collected from the Caribbean Sea<sup>13</sup> and various nudibranch species.<sup>14</sup> Tambjamines are used by ascidians to deter carnivorous fish<sup>15</sup> and have a broad range of biological activities including antibacterial, antifungal, antiprotozoal, immunosuppressive, anion-transport and anticancer activity.<sup>16–21</sup> While the antiparasmodial activity of tambjamines F and C has not previously been reported, other tambjamine and tambjamine-like analogues (which have various alkyl/arylamines in the place of ring-C and the OMe group at the C4-position on the ring-B) have been shown to have activity against *P. falciparum* drug-sensitive (*Pf*D6) and drug-resistant (*Pf*Dd2) parasites. Some of those compounds (e.g. KAR425) have IC<sub>50</sub>'s < 250 nM against *P. falciparum* parasites,<sup>18</sup> more than 4-fold more potent than the level of activity observed in this study for tambjamine F and tambjamine C

(*Pf*3D7 IC<sub>50</sub> > 1 μM). Furthermore, tambjamine-like analogues (e.g. KAR425, KAR457, KAR458 and KAR790) have activity against *P. berghei* exoerythrocytic liver-stage parasites (IC<sub>50</sub> 0.017–0.11 μM) and *P. falciparum* stage V gametocytes (IC<sub>50</sub> 1.41–2.55 μM), *in vivo* efficacy in *P. yoelii* infected mice and in a humanized *P. falciparum* mouse model, as well as *ex vivo* activity against Ugandan clinical isolates.<sup>21</sup>

Bilocularin B (*Pf*3D7 IC<sub>50</sub> 2.18 μM; SI >46; Table 1), a dihydro-β-agarofuran that was isolated from the Australian rainforest plant species *Maytenus bilocularis*,<sup>22</sup> has not been previously reported to have antiparasmodial activity. Bilocularin B and analogues have been shown to inhibit leucine uptake in the human prostate cancer cell line LNCaP (lymph node carcinoma of the prostate) but did not impact the viability of these cells.<sup>23</sup> In addition, several analogues inhibited human P-glycoprotein, reversing MDR1-mediated drug-resistance to daunomycin and vinblastine in murine fibroblasts, with some analogues exhibiting a similar potency to the reference drug verapamil.<sup>22</sup> Interestingly, bilocularin A, which has a hydroxyl group at position C8 of the agarofuran scaffold, was found in this study to be inactive against *P. falciparum* (*Pf*3D7 IC<sub>50</sub> > 12.5 μM; Table 1; Supplementary Table S1). In addition, the related dihydro-β-agarofurans, denhaminols A and C,<sup>24</sup> and

celastrolfurans B and E,<sup>25</sup> were also found to lack activity against *P. falciparum* parasites in this study (>12.5  $\mu\text{M}$ ; Table 1). While the different antiparasmodial activity profiles of these compounds suggest that medicinal chemistry optimisation may prove useful in identifying compounds with improved biological activities, bilocularin B may also be of interest as a tool to investigate whether these compounds act on a novel druggable target within the parasite. For example, related dihydro- $\beta$ -agarofuran compounds have been shown to possess anti-inflammatory activity by inhibiting nitric oxide production in macrophage-like cells.<sup>26</sup> This may be of interest for future studies as there is an association between *Plasmodium* infection and nitric oxide levels.<sup>27</sup> Related dihydro- $\beta$ -agarofuran compounds also demonstrate inhibitory activity of acetylcholinesterase and COX enzymes.<sup>28</sup>

Hymenialdisine (Pf3D7 IC<sub>50</sub> 2.90  $\mu\text{M}$ ; SI > 34; Table 1), a pyrroloazepine alkaloid that in this study was isolated from the Great Barrier Reef marine sponge *Acanthella costata*, has no prior reports of antiplasmodial activity. Hymenialdisine has been isolated from *Acanthella*, *Axinella*, *Stylissa*, *Hymeniacidon*, and *Pseudaxinyssa* sponges in other studies.<sup>29,30</sup> An analogue of this compound available in NatureBank, debromohymenialdisine, which lacks a bromine on the pyrrole moiety, was also tested here and was found to be ~2 fold less potent than hymenialdisine (Pf3D7 IC<sub>50</sub> 4.57  $\mu\text{M}$ ; SI > 22; Table 1). Both hymenialdisine (CLogP -1.58) and debromohymenialdisine (CLogP -1.70) are polar compounds and thus modifications to improve permeability and absorption may be warranted for further antiparasmodial studies if this structural class were to be considered as a candidate drug lead for malaria. Both compounds have been shown to be inhibitors of human protein kinases (CDKs, MEK1, GSK3 $\beta$ , CK1, and CHK1), and have anti-inflammatory effects in human cancer cells and rheumatoid synovial fibroblasts, inhibiting NF- $\kappa\text{B}$  nuclear binding and decreasing the generation of various proinflammatory cytokines such as IL-8, IL-2, IL-6, IL-1, and TNF- $\alpha$ .<sup>31–33</sup> Hymenialdisine can also inhibit RANKL-induced osteoclast formation and promote osteoblast differentiation, two factors favourable in the treatment of osteolytic diseases,<sup>34</sup> and is cytotoxic against cisplatin-sensitive ovarian cancer cell lines.<sup>35</sup> While therapeutically targeting the *Plasmodium* kinome is of interest,<sup>36,37</sup> the selectivity for *Plasmodium* kinases over human kinases must be considered.<sup>38</sup>

In summary, this work has identified four natural compounds from Australian plant and marine biota with novel *in vitro* activity against asexual-stage *P. falciparum* parasites. Our findings expand data on the tambjamine chemotype with two additional analogues (tambjamine F and C) and provide the first report of antiparasmodial activity for the bilocularin and hymenialdisine chemotypes. While bilocularin B and hymenialdisine displayed modest antiparasmodial activity and selectivity (Pf3D7 IC<sub>50</sub> 2.18  $\mu\text{M}$  and 2.90  $\mu\text{M}$ ; SI >46 and >34, respectively), and subsequent studies on available analogues did not identify compounds with improved activity (Table 1), future medicinal chemistry studies may lead to improvements in antiparasmodial potency and/or selectivity. Given the novel chemistry of these compounds relative to current anti-malarial drugs, further studies examining their antiparasitic activities may also be worth pursuing as a mechanism to identify new druggable parasite targets.

#### CRediT authorship contribution statement

**Jacinta R. Macdonald:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation. **Gillian M. Fisher:** Writing – review & editing, Supervision, Methodology. **Sasha Hayes:** Writing – review & editing, Resources, Data curation. **Tina S. Skinner-Adams:** Writing – review & editing, Supervision, Conceptualization. **Rohan A. Davis:** Writing – review & editing, Visualization, Resources, Methodology, Conceptualization, Data curation, Supervision. **Katherine T. Andrews:** Writing – review & editing, Supervision, Methodology, Conceptualization, Resources.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmcl.2025.130369>.

#### Data availability

Data will be made available on request.

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