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Potent 4-aminopiperidine based antimalarial agents

Kristin M. Brinner,[a,†] Mary Ann Powles,[b] Dennis M. Schmatz[b] and Jonathan A. Ellman[a,*]

[a]*Center for New Directions in Organic Synthesis, Chemistry Department, University of California, Berkeley, CA 94720, USA*
[b]*Merck and Co., Rahway, NJ 07065, USA*

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Abstract—A series of compounds with potent activity against a multi-drug-resistant strain of *Plasmodium falciparum*, the causative agent of the deadliest strain of malaria, is described. These compounds were also tested for cytotoxicity in human foreskin fibroblast assays, evaluated to determine their log *D*, and assayed for metabolism by human and murine hepatocytes. This work resulted in the development of compounds **9e** and **10d**, which showed good potency (IC_{50} = 75 nM and <60 nM, respectively, against Dd2), acceptable log *D* values, and reasonable metabolic stability.

Malaria is a disease of worldwide implications. It is estimated that 40% of the world's population resides in malaria-endemic regions of the world. Over 300 million cases are reported annually, resulting in 1–3 million deaths.[1] The clinical symptoms and the majority of deaths caused by malaria occur during the intra-erythrocytic phase of the parasite's complex life cycle within its human host. While the parasites develop within human red blood cells, fever, chills, anemia, and more severe clinical complications are all observed.[2] During this phase of the parasite's life cycle, hemoglobin is consumed as a primary source of amino acids to fuel the explosive growth of the parasite. Upon catabolism of hemoglobin, heme is released, which would be cytotoxic to the parasite in its soluble form. However, *Plasmodium* have evolved a unique heme detoxification pathway, where free heme is dimerized whereupon hydrogen bonding between heme dimers results in polymeric non-toxic hemozoin formation.[3] There is considerable evidence that the aminoquinoline based antimalarials, including chloroquine, quinine, and mefloquine, act through inhibiting this heme detoxification pathway.[4] Unfortunately, increasing drug resistance to these agents complicates the treatment of malaria. Additionally, resistance to these common antimalarial medications cannot be overcome by increasing their dosages, as they have extremely narrow therapeutic windows.

We previously reported the synthesis and evaluation of a novel series of amino-piperidine based compounds that showed promising activity against both chloroquine-sensitive (3D7) and resistant (W2) strains of *P. falciparum*, the deadliest strain of the malarial parasite.[5] While the mechanism of action of these compounds was not known, there was evidence that they acted by inhibiting heme polymerization. When comparing the structure of the best compound from this series to that of chloroquine, we observed that the basic nitrogens are arrayed in a similar fashion (Fig. 1).

By combining structural features of both compound **1** and chloroquine, we hoped to further improve the activity of the compounds. This would allow us not only to capitalize on a drug intervention pathway already well established by the aminoquinoline based drugs, but also to bypass established mechanisms of resistance development by avoiding the aminoquinoline scaffold itself. Upon synthesis and evaluation of compound **2**, we observed that the compound maintained potent activity against a chloroquine sensitive strain of *P. falciparum*, but had significantly less activity against a multi-drug-resistant strain of the parasite (Dd2). However, we were encouraged to optimize the activity of additional compounds of this structural type, because **2** had low levels of toxicity.

Here we report the synthesis of analogs of compound **2**, their activity against a multi-drug-resistant strain of

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* Corresponding author. Tel.: +1 510 642 4488; fax: +1 510 642 8369; e-mail: ellman@cchem.berkeley.edu
† Present address: Chiron Corporation, Emeryville, CA 94608, USA.

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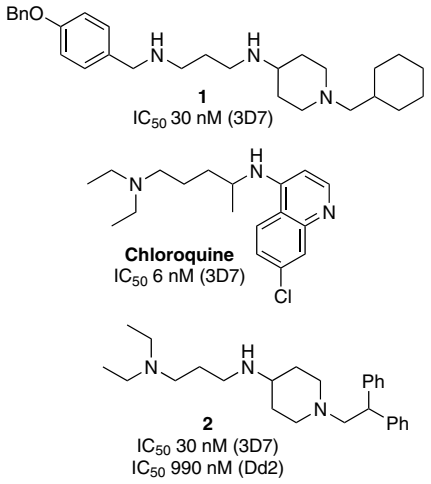
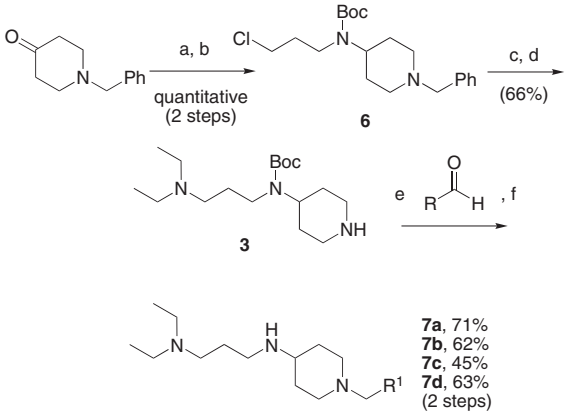


Figure 1. Merging of structures of lead compounds and chloroquine.

P. falciparum, and their cytotoxicity. These compounds showed promising activity as well as low levels of toxicity, and were further characterized for their drug-like properties and metabolic lability.

Three regions of compound **2** could easily be modified to rapidly assess structure–activity relationships (SAR) (Fig. 2). The R^1 substitution could be varied through reductive alkylation of amino piperidine **3**. Additionally, R^2 and R^3 could be varied through alkylation of a variety of primary and secondary amines with alkyl chloride **4**. Finally, R^2 could be varied while holding R^3 as an ethyl substituent, by reductive alkylation of secondary amine **5** with a series of aldehydes. As these synthetic sequences were efficient and generated sufficient material for biological testing, they were not further optimized. All compounds were purified by standard silica gel chromatography, and converted to the HCl salts for biological testing.

Diversity at the R^1 position was investigated through derivatization of **3** (Scheme 1). *N*-Benzyl-4-piperidone was reductively alkylated with 3-chloroaminopropane, and the resultant amine was Boc protected. Primary alkyl chloride **6** was then reacted with ethylamine, and the benzyl group was subsequently removed under transfer hydrogenation conditions to afford **3**. The free piperidine **3** was then reductively alkylated with a series of four aldehydes, followed by acidic deprotection, to afford compounds **7a**–**d**.



Scheme 1. Reagents and conditions: (a) $NaBH(OAc)_3$, AcOH, Et_3N, 3-chloroaminopropane; (b) Boc_2O, THF; (c) Et_2NH, NaI, DMF, 70 °C; (d) NH_4HCO_2, Pd/C, MeOH, EtOAc; (e) $NaBH(OAc)_3$; (f) HCl, dioxane.

Diversity at the R^2 and R^3 positions was investigated through reaction of a variety of primary and secondary amines with compound **4** (Scheme 2). 4-Piperidone monohydrate hydrochloride was reductively alkylated with 1,1-diphenylacetaldehyde to afford amino piperidone **8**. This was then subjected to reductive amination with 3-chloroaminopropane, and the resultant secondary amine was Boc protected to afford **4**. Primary alkyl chloride **4** was reacted with a series of five amines, followed by cleavage of the Boc group under acidic conditions to afford compounds **9a**–**e**.

Finally, R^3 was varied while holding R^2 constant (Scheme 3). Primary alkyl chloride **4** was reacted with

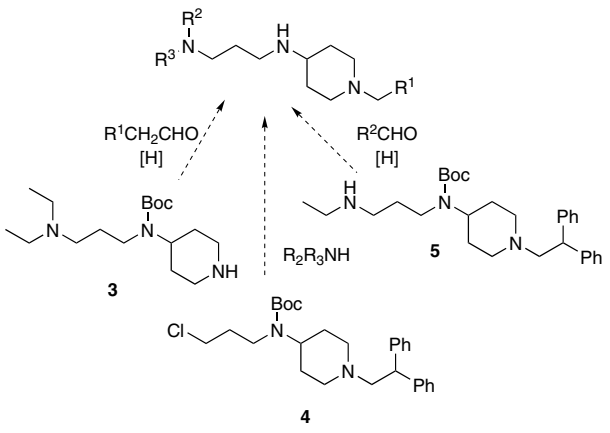
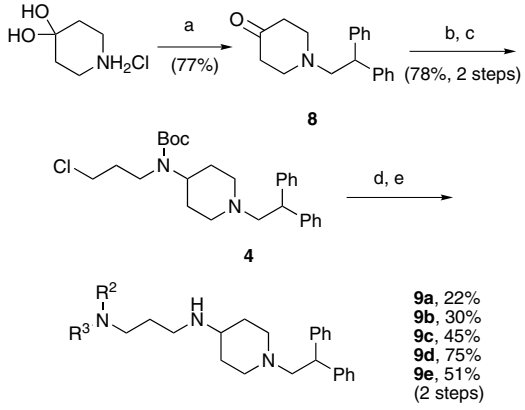


Figure 2. Modification of **2** to assess SAR.



Scheme 2. Reagents and conditions: (a) 1,1-diphenylacetaldehyde, $NaBH(OAc)_3$, Et_3N, AcOH, MeOH; (b) $NaBH(OAc)_3$, Et_3N, AcOH, CH_3CN, 3-chloroaminopropane; (c) Boc_2O, THF; (d) NaI, DMF, 70 °C; (e) HCl, dioxane.