Spirotetrahydro β-carbolines (Spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria

Bryan K. S. Yeung,*† Bin Zou,‡ Matthias Rottmann,‡± Suresh B. Lakshminarayana,† Shi Hua Ang,† Seh Yong Leong,† Jocelyn Tan,† Josephine Wong,† Sonja Keller-Maerki,‡± Christoph Fischli,‡± Anne Goh,† Esther K. Schmitt,§ Philipp Krastel,§ Eric Francotte,‡ Kelli Kuhlen,‡ David Plouffe,‡ Kerstin Henson,‡ Trixie Wagner,‡ Elizabeth A. Winzeler,† Frank Petersen,§ Reto Brun,§± Veronique Dartois,† Thierry T. Diagana,† and Thomas H. Keller†

†Novartis Institute for Tropical Diseases, 10 Biopolis Road, no. 05-01 Chromos, Singapore 138670, §Swiss Tropical and Public Health Institute, Parasite Chemotherapy, Socininstrasse 57, Basel, Switzerland CH-4002, ‡Natural Products Unit, Novartis Pharma AG, Basel, Switzerland CH-4002, §Novartis Institute for Biomedical Research, Basel, Switzerland CH-4056, †Genomics Institute of the Novartis Research Foundation, 10675 John J. Hopkins Drive, San Diego, California 92121, and ‡University of Basel, Petersplatz 1, Basel, Switzerland CH-4003

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The antiplasmodial activity of a series of spirotetrahydro β-carbolines is described. Racemic spiroazepineindole (1) was identified from a phenotypic screen on wild type Plasmodium falciparum with an in vitro IC_{50} of 90 nM. Structure—activity relationships for the optimization of 1 to compound 20a (IC_{50} = 0.2 nM) including the identification of the active 1R,3S enantiomer and elimination of metabolic liabilities is presented. Improvement of the pharmacokinetic profile of the series translated to exceptional oral efficacy in the P. berghei infected malaria mouse model where full cure was achieved in four of five mice with three daily doses of 30 mg/kg.

Introduction

Malaria remains a persistent public health problem for about 40% of the global population, mainly in sub-Saharan Africa. Plasmodium falciparum, the most relevant malaria parasite, is estimated to infect 300–500 million people per year and result in over 863000 deaths in 2008 of which approximately 90% were children.1 Malaria control programs relying on disease prevention and artemisinin combination therapies (ACTs)2 have been extremely effective in reducing the disease burden. However, recent reports of increased tolerance to artemisinin derivatives in Plasmodium falciparum suggest that we may soon lose the last and only widely effective antimalarial drugs.2

In an effort to discover new antimalarial leads, a high throughput, whole cell screen based on the proliferation of P. falciparum was performed and led to the identification of racemic spiroazepineindole 1.3 The compound displayed moderate potency against both wild type (NF54) and chloroquine resistant (K1) strains of the parasite, and when tested in the Plasmodium berghei infected mouse model,4 a single 100 mg/kg dose of 1 resulted in a 96% reduction in parasitemia (activity). Encouraged by these preliminary results, an optimization effort to increase potency and in vivo activity of 1 was initiated. The structure—activity relationships (SAR) and in vivo efficacy of this new class of antimalarial is described.3

Chemistry

To reconfirm the in vitro potency of the hit, racemic 1 was prepared by reductive amination of ketone 2 followed by a Pictet–Spengler cyclization5 with 5-bromoisatin, to provide spiroazepineindole 1 in 66% yield (Scheme 1).7 The reaction conditions were expected to provide an equal mixture of four stereoisomers consisting of two pairs of the 1R,3S, 1S,3R, and 1S,3S, 1R,3R enantiomers. Instead, the reaction produced a ~9:1 diastereomeric excess favoring one pair of enantiomers.7 To determine which pair of enantiomers were formed in excess, chiral separation followed by X-ray crystallography revealed that the more favored pair consisted of the 1R,3S and 1S,3R stereoisomers (data not shown). Interestingly, when tested in vitro, the individual enantiomers displayed markedly different potencies on the parasite where 1a was greater than 250-fold more potent than 1b (Figure 1) on strain NF54.

All spiroazepineindole derivatives (1, 4, and 6) were prepared according to Scheme 1 starting from the appropriate indoleamine, while the spirotetrahydro β-carboline derivatives (17–20) were synthesized from the corresponding substituted indoles (Scheme 2).9 Briefly, Vilsmeyer–Haack formylation of the indole followed by condensation with

Scheme 1. Synthesis of Racemic 1

Reagents and conditions: (a) NaBH₃CN, NH₄OAc, rt; (b) 5-bromoisatin, p-TsOH·H₂O (cat), 110 °C.

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In general, the minor pair of diastereomers was not isolated from the reaction mixture except in a few cases. For example, in the case of 9, also prepared according to Scheme 2, all four stereoisomers were isolated and tested individually for potency. The minor 1S,3S and 1R,3R pair of stereoisomers were found to be less potent than the corresponding active 1R,3S stereoisomer (Figure 2). This trend was found to be consistent across the class and in all cases where all four stereoisomers were isolated. From these results, we concluded that the 1R,3S configuration was the required stereochemistry for activity on \textit{P. falciparum}.

Diastereoselectivity in the Pictet–Spengler reaction is well documented and has been studied by several groups.\textsuperscript{10} We sought to take advantage of the high degree of diastereoselectivity observed in our system by using enantiopure \textit{S}-\textit{\&}\textit{R}-methyl indoleamines instead of the racemic mixtures. This would directly provide the corresponding 1R,3S enantiomer and obviate the need for chiral resolution, as only a single pair of diastereomers would be formed.\textsuperscript{11}

Enantiopure 9\textit{\textit{a}} and 9\textit{\textit{b}} were obtained from the corresponding \textit{S}- and \textit{R}-\textit{\&}\textit{R}-methyl indoleamines respectively. \textit{(S)}-2-(1\textit{H}-Indol-3-yl)-1-methyl-ethylamine (22) was prepared from \textit{\&}-tryptophanol after complete reduction of the hydroxymethyl nitroethane provided the corresponding nitroalkene. Next, reduction of the nitroalkene with lithium aluminum hydride, followed by condensation with 5-chloroisatin provided racemic 17\textendash{}20 with a high degree of diastereoselectivity. The individual 1R,3S and 1S,3R enantiomers were then resolved by chiral chromatography and could be readily identified and differentiated by optical rotation.

**Scheme 2.** Racemic Route to the Spirotetrahydro \textit{\&}-Carbolines Series

Reagents and conditions: (a) POCl\textsubscript{3}, DMF; (b) nitroethane, ammonium acetate, reflux; (c) LiAlH\textsubscript{4}, THF, reflux; (d) 5-chloroisatin, \textit{p}-TsOH–H\textsubscript{2}O (cat), 110 °C.

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**Figure 1.** In vitro activity of spiroindolone 1 and the readily accessible stereoisomers.

**Figure 2.** In vitro activity of spiroindolone 9 and its four stereoisomers.

**Figure 3.** Crystal structure of the active 1R,3S enantiomer of 9\textit{\textit{a}} (only one of the two independent molecules is shown). Atomic displacement ellipsoids are drawn at the 50\% probability level, hydrogen atoms drawn as spheres of arbitrary radius. For clarity only the stereogenic centers are labeled (C9\textit{\textit{R}}, C11\textit{\textit{S}}).
Scheme 3. Synthesis of the Active Enantiomer of 9a from d-Tryptophanol

Reagents and conditions: (a) (1) CbzCl, Na₂CO₃, rt; (2) p-TsCl, TEA, rt; (b) H₂, Pd(OH)₂, rt; (c) 5-chloroisatin, p-TsOH·H₂O (cat), 110 °C.

Table 1. In Vitro Antimalarial Activity and Structure–Activity Relationships of the Spiroindolones

| compound | structure | activity on P. falciparum strains | comment |
|----------|-----------|----------------------------------|---------|
|          |           | NF54 IC₅₀ (nM) | K1 IC₅₀ (nM) |         |
| 4        |           | 84                | n.d.      | racemic-1R,3S and 1S,3R |
| 5        |           | > 5000            | > 5000    | racemate |
| 6        |           | 86                | 83        | racemate |
| 7        |           | 126               | 104       | racemate |
| 8        |           | 857               | 819       | racemate |
| 9        |           | 27                | 21        | racemate-1R,3S and 1S,3R |

Table 2. Key Physicochemical Properties of the Spiroindolones

| compd  | solubility (pH 6.8) (μg/mL) | logP | clogD₂₄ | pKᵣ⁻¹/pKᵣ⁺² |
|--------|-----------------------------|------|---------|-------------|
| 1a     | 79                          | 3.9  | 4.0     | 5.2/nd      |
| 9a     | 194                         | 3.4  | 3.5     | 5.1/10.4    |
| 17a    | 140                         | 3.6  | 3.8     | 4.8/nd      |
| 18a    | 8                           | 4.8  | 4.4     | 5.2/10.6    |
| 20a    | 170                         | 4.0  | 3.9     | 4.9/nd      |

a Data were experimentally determined except clogD₂₄; nd, not determined.

Results and Discussion

Structure–Activity Relationships. On the basis of the difference in potencies between the enantiomers, we surmised that the spirocenter was an essential feature of the scaffold, and indeed its removal lead to an almost complete loss of activity for the series (see Supporting Information). Hence to readily access the spirocenter, we incorporated the oxindole moiety via isatins in all of the derivatives described.

An X-ray crystal structure of 9a unambiguously assign the 1R,3S configuration to the active enantiomer (Figure 3) and showed that both potency and the corresponding stereochemistry of the spirotetrahydro β-carboline series was consistent with that of the spiroazepineindole series (1a).

The only drawback of this potentially ideal route is the limited availability of chiral, substituted α-methyl indoleamines or d-tryptophan derivatives. Because of this, we chose the racemic route to compounds 17–20 utilizing a chiral resolution step as the preferred synthesis to explore SAR. Upon identifying biologically active racemates in vitro, the potency of a particular compound could always be improved by isolation or synthesis of the corresponding 1R,3S enantiomer.

to the corresponding methyl group (Scheme 3). Subsequent cyclization with 5-chloroisatin in the presence of catalytic acid provided enantiopure 9a after purification. The reduction of the tosyl group could also be achieved with lithium aluminum hydride with no observable racemization of the stereogenic center. The opposite, 1S,3R enantiomer (9b) was obtained from l-tryptophanol using the same procedure.

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Replacement of the 5′-bromide of 1 with other halogens had negative effects except for the 5′-chloro derivative (4). Although a number of additional mono- and disubstituted oxindole derivatives were prepared, only the monosubstituted, 5′-chloro derivatives had the optimum balance between potency, favorable pharmacokinetics, and synthetic accessibility.

Simplifying the structure by removing the C3 stereogenic center and increasing the size of the central ring azepine ring...
by one carbon lead to an inactive compound (5: IC₅₀ > 5000 nM); however, azepineindole (6) and tetrahydro-β-carboline (7) derivatives retained moderate potency (Table 1). Interestingly for the azepineindoles, the similar potency between 4 and 6 suggests that the C3 methyl is not essential in this series. In contrast, the C3 methyl enhances potency in the tetrahydro β-carboline series, where an almost five-fold increase in activity is observed with the methyl group present (7 vs 9). Substitutions at C3 were found to be extremely limited. Only methyl or trifluoromethyl was tolerated because increasing the steric bulk to gem-dimethyl (8), hydroxymethyl, n-propyl, or methyl ester significantly decreased activity even with the required stereochemistry (see Supporting Information).

### Optimizing the Pharmacokinetic Profile

The spiroindolones as a class proved to be an exceptionally high quality scaffold from a medicinal chemistry perspective (Table 2). Most derivatives prepared displayed favorable in vitro solubility and permeability (PAMPA and Caco-2). Derivatives generally did not show cytotoxicity across several human cell lines nor was there significant binding in a panel of human receptors, kinases, and ion channels (IC₅₀ > 10 μM). Moreover the spiroindolones display low cardiotoxicity potential (hERG), and genotoxicity potential (miniaturized Ames test and high content micronucleus), hence no effort to improve these properties was required. In addition to in vitro potency, significant differences between pairs of enantiomers were observed with respect to metabolic stability and CYP450 inhibition. Compounds 9a and 9b proved to be representative of the types of trends we observed for most analogues in Table 3. More specifically, the less active, or 1S,3R, enantiomers displayed superior metabolic stability in the presence of liver microsomes, had low to medium in vivo clearance, and showed little or no propensity for drug-drug interactions (CYP450 liabilities). In contrast, the biologically active 1R,3S enantiomers often displayed high clearance with poor microsomal stability and were found to inhibit CYP 2C9 preferentially although were generally inactive against CYP 3A4 and CYP 2D6 isoforms (Table 3).

### Table 3. Comparison of the Pharmacokinetic Profile of the Spirotetrahydro β-Carbolines

| compound | structure | hepatic CLₐₐₜₐ a mouse | human | CYP 2C9 inhibition (μM) | in vivo CL b (mL/min/kg) | NF54 IC₅₀ (nM) |
|----------|-----------|---------------------|-------|-----------------|-----------------------|-----------------|
| 9a       | ![Structure](image) | high | high | 1.51 | 49.66 | 9 |
| 9b       | ![Structure](image) | low | low | > 10.00 | n.d. | > 5000 |
| 17a      | ![Structure](image) | high | med | 1.72 | 24.01 | 3 |
| 17b      | ![Structure](image) | med | low | > 10.00 | n.d. | 182 |
| 18a      | ![Structure](image) | low | low | 4.11 | 60.08 | 4 |
| 18b      | ![Structure](image) | low | low | > 10.00 | n.d. | 116 |
| 19a      | ![Structure](image) | low | low | 5.42 | 9.75 | 0.9 |
| 19b      | ![Structure](image) | low | low | > 10.00 | 2.58 | 77 |
| 20a      | ![Structure](image) | low | low | 7.35 | 8.53 | 0.2 |
| 20b      | ![Structure](image) | low | low | > 10.00 | 4.14 | 83 |

a intrinsic clearance in liver microsomes, where high clearance corresponds to poor stability in the presence of liver enzymes. b Measured in mice at a single 5 mg/kg iv dose. nd, not determined.
To address the metabolic stability of 9a and to reduce its CYP 2C9 liabilities, we identified susceptible sites on the molecule which could be modified or blocked by chemical means and translate into a longer half-life.

Focusing on the western part of the molecule, positions C6 and C7 stood out as susceptible metabolic sites prone to oxidation and thus high clearance. The racemic 6-fluoro derivative (17) showed a moderate improvement in metabolic stability, however, upon separation of the two enantiomers (17a and 17b), only the less active 1S,3R enantiomer displayed the desired stability profile in vitro (Table 2). Moreover, the 6-fluoro substitution had no effect on decreasing CYP 2C9 inhibition although potency of the active enantiomer (17a) had improved slightly. Interestingly, despite the high clearance and low stability predicted from in vitro assays, 17a showed a nearly two-fold improvement in clearance over 9a in vivo.

In contrast to 17, when the individual enantiomers of 18 were profiled, the active 1R,3S enantiomer (18a) showed improved microsomal stability that was similar to 18b. In addition a three-fold improvement in potency on the parasite and lower CYP 2C9 inhibition was achieved over 9a (Table 2). Combining both C6 and C7 substitutions had an additive affect on potency and further improved the pharmacokinetic properties. Compounds 19a and 20a now displayed subnanomolar potency on the parasite with the desired in vitro stability and decreased CYP 2C9 liabilities. Thus C7 substitutions were critical in increasing metabolic stability, minimizing drug–drug interaction, and increasing in vitro potency. In Vivo Pharmacokinetic Profile of 9a and 20a. The marked difference in the in vitro PK profile of unsubstituted (9a) and substituted (20a) spiroindolones translated well in vivo (Figure 4 and Table 4). Following intravenous administration, 9a displayed a moderate total systemic clearance (55% hepatic blood flow), moderate volume of distribution (0.91 L/kg or 1.2 times the total volume of body water), and short half-life of 0.42 h. The relatively low oral exposure of 9a (3.88 μM·h) resulted in modest oral bioavailability (13%). In contrast, after intravenous administration, 20a displayed a higher volume of distribution, 2.7 times the total body water (1.60 L/kg). Similar to the low in vitro clearance observed in liver microsomes, the total systemic clearance was lower (~10% hepatic blood flow) and the compound had a markedly longer half-life than 9a. Although the oral absorption (Tmax) of 20a was significantly slower than 9a, the compound reached both higher peak plasma concentrations and 18-fold greater exposure (AUC0→∞) than 9a. The increased exposure translated to an apparent bioavailability of 53%. Moreover, the Cmax of 20a in mice is about 40000-fold above the Plasmodium falciparum IC50 suggesting lower doses for efficacy and decreased potential for adverse toxicity.

![Figure 4](image)

**Figure 4.** In vivo PK profile of 9a and 20a showing a plot of plasma concentration vs time for 9a (Δ) and 20a (□) administered orally (A) and intravenously (B) to mice. Plasma concentrations are indicated in ng/mL ± standard deviation (n = 3).

**Table 4.** Pharmacokinetic Parameters for 9a and 20a Following Oral Dosing at 25 mg/kg and iv Dosing at 5 mg/kg in Mice

| compd | Cmax (μM) | Tmax (h) | AUC∞ (μM·h) | T½ (h) | F (%) | Vss (L/kg) | CL (mL/min/kg) | T½ (h) |
|-------|-----------|----------|-------------|--------|-------|------------|----------------|--------|
| 9a    | 3.58      | 0.25     | 3.88        | 0.66   | 13    | 0.91       | 49.66          | 0.42   |
| 20a   | 8.32      | 2.00     | 71.44       | 3.18   | 53    | 1.60       | 8.53           | 2.94   |

*p* Cmax maximum concentration of drug in plasma; Tmax, time to maximum concentration of drug in plasma; AUC∞, area under the curve extrapolated to infinity; Vss, volume of distribution at steady state; CL, clearance; T½, half-life; F, oral bioavailability.
Collectively, the data suggests that the excellent in vitro potency, good bioavailability, long oral exposure, and half-life (3 h) of 20a is amenable to a single or low dose oral treatment for malaria. To evaluate the oral efficacy of 9a and 20a, the compounds were tested in the *P. berghei* infected malaria mouse model.

**In Vivo Efficacy in the *P. berghei* Malaria Mouse Model.** Average mouse survival results using two different oral dosing regimens of 9a and 20a are presented along with chloroquine (CQ) and artesunate (AS) as comparisons (Table 5). The spiroindolones show excellent in vivo activity. A single oral dose of 9a (30 mg/kg) reduced parasitemia on day three by more than 99% and prolonged average mouse survival to 10.7 days. Increasing the dose to 100 mg/kg had only a marginal effect on mouse survival (14.3 days) and may be attributed to the high clearance of the compound. At single doses, the increased absorption (high C_{max}) and greater exposure (AUC) of 20a did not lead to a significant improvement in efficacy. A single oral dose of 30 mg/kg reduced parasitemia by more than 99% and prolonged mouse survival for 12 days while increasing the dose to 100 mg/kg lead to essentially no change in mouse survival. However, under these conditions, both spiroindolones were comparable to CQ (99.6%, 12.5 days) and outperformed AS (98.0% and 7.3 days) in terms of average mouse survival.

In a multiple oral dosing regimen, differences between 9a and 20a became more apparent where, 20a proved to be superior to 9a, CQ, and AS (Table 6). Three oral daily doses of 10 mg/kg resulted in 17.2 days average mouse survival while 29.4 days survival was achieved with 3 × 30 mg/kg oral doses (full cure in four out of five mice). In addition, neither toxicity nor behavioral changes after drug administration was observed in any of the animals treated with 9a and 20a at any dosing regimen. The in vivo efficacy data suggests that despite the high clearance and short half-life, 9a is a highly efficacious antimalarial when administered orally and comparable to CQ and AS (Table 5). Spiroindolones show excellent in vivo activity. A single oral dose of 9a (30 mg/kg) reduced parasitemia on day three by more than 99% and prolonged average mouse survival to 10.7 days. Increasing the dose to 100 mg/kg had only a marginal effect on mouse survival (14.3 days) and may be attributed to the high clearance of the compound. At single doses, the increased absorption (high C_{max}) and greater exposure (AUC) of 20a did not lead to a significant improvement in efficacy. A single oral dose of 30 mg/kg reduced parasitemia by more than 99% and prolonged mouse survival for 12 days while increasing the dose to 100 mg/kg lead to essentially no change in mouse survival. However, under these conditions, both spiroindolones were comparable to CQ (99.6%, 12.5 days) and outperformed AS (98.0% and 7.3 days) in terms of average mouse survival.

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The spiroindolones represent a promising new antimalarial chemotype, displaying exceptional in vitro activity and parasitemia reduction at low doses in the *P. berghei* mouse model. Although the mechanism of action (MoA) and molecular target is currently unknown, preliminary evidence suggests that the spiroindolone function by a different mechanism than the heme detoxification pathway of 4-aminoquinolines and instead may act by inhibiting protein synthesis within the parasite. Furthermore, the observation that only the R,S,3S enantiomer is biologically active implies the presence of a discrete molecular target. Further preclinical evaluation of this series of compounds is currently ongoing.

**Experimental Section**

**General Methods.** Reagents and solvents were purchased from Aldrich, Acros, or other commercial sources and used without further purification. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from Merck. Compounds were visualized under UV light, ninhydrin, or phosphomolybdic acid (PMA) stain. NMR spectra were obtained on a Varian 300 MHz Mercury NMR or Bruker 500 MHz Ultrashield spectrometer using CDCl$_3$, DMSO-d$_6$, or MeOD-d$_4$ as solvents. Preparative chiral separation was performed on a Chiralcel OD-H column (2 cm × 25 cm) with 90:10 hexanes-methanol as the mobile phase. Analytical chiral chromatography was carried out on a Chiralcel AD-H column and all single enantiomers reported were greater than 98% e.e. Compound purity was determined by LC/MS and HPLC and carried out on an Agilent LC110 HPLC equipped with a Waters Symmetry Shield RP18, 3.5 μm, 4.6 mm × 150 mm column using a gradient (13 min) of 95.5 H$_2$O (0.1% formic acid):CH$_3$CN to 5.95 H$_2$O (0.1% formic acid):CH$_3$CN. The purity of all compounds reported were >95% measured at 254 nm. The specific rotation reported for all compounds was measured on a Jasco P-1020 polarimeter at 25 °C with sample concentration and solvent noted where appropriate.

**X-ray Structure Determination.** Intensity data collection for 9a was performed on the PX II beamline at the Swiss Light Source in Villigen at a wavelength of 0.71073 Å, which corresponds to Mo Kα radiation. The structure was solved by dual-space recycling methods and refined by full-matrix least-squares on *F*² using the SHELXTL program suite. The asymmetric unit contains two independent molecules. Non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were calculated in idealized positions and refined using a riding model. The crystals are twinned (twist law −1 0 0 0: −1 0 0 0 1). CCDC 758814 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
$J = 12.0, 8.1, 4.5$ Hz, 1H), 2.86 (ddd, $d = 12.9, 8.7, 4.2$ Hz, 1H), 2.79 (d, $J = 5.7$ Hz, 1H), 2.07 (m, 1H), 1.65 (ddd, $d = 12.2, 8.4, 3.9$ Hz, 1H), 1.05 (d, $J = 6.6$ Hz, 3H). MS (ESI) $m/z$ 397.0 (M + H)$^+$. The racemate (1) was separated into its enantiomers by chiral chromatography under the conditions described in General Methods. The absolute configuration was determined by X-ray crystal analysis and characterized below.

(1R,3S)-5-Bromo-3-methyl-3,4,5,10-tetrahydro-2H-furo[azepino-[3,4-b]indole-1,3-indol]-2(1H)-one (1a). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.43 (s, 1H), 9.96 (s, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 1H), 7.26 (d, $J = 1.8$ Hz, 1H), 7.16 (dd, $J = 7.0, 1.2$ Hz, 1H), 6.98 (td, $J = 6.9, 1.5$ Hz, 1H), 6.94 (td, $J = 6.9, 1.2$ Hz, 1H), 6.86 (d, $J = 8.43$ Hz, 1H), 3.88 (m, 1H), 3.11 (ddd, $d = 12.0, 7.8, 4.2$ Hz, 1H), 2.87 (d, $J = 12.9, 8.7, 3.9$ Hz, 1H), 2.79 (d, $J = 6.0$ Hz, 1H), 2.07 (m, 1H), 1.64 (ddd, $d = 12.9, 8.7, 4.2$ Hz, 1H), 1.04 (d, $J = 6.6$ Hz, 3H). MS (ESI) $m/z$ 397.0 (M + H)$^+$. $^{13}C$ NMR $\delta$ 192.3, 147.3, 146.4, 134.7, 133.6, 129.7, 125.8, 121.6, 118.2, 117.1, 110.9, 53.0, 35.9, 33.7, 30.7. In vacuo. The residue was dissolved in ethyl acetate and then dried over $\text{Na}_2\text{SO}_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to provide 7 as an orange solid (65.9% yield).

5-Chloro-3,3-dimethyl-2,3,4,9-tetrahydrospiro[carboline-1,1'-indol]-2(1H)-one (8). Sodium hydroxide (2.88 g, 72.0 mmol) was added to a solution of LiBr (12.0 g, 69.0 mmol) in 2-nitropropane (44 mL, 490 mmol) and heated to reflux. After 18 h, the solution was cooled to room temperature and 10% aqueous acetic acid (60 mL) added. After stirring for an additional hour, the mixture was diluted with water and extracted with diethyl ether. The organic phase was separated and washed with water then dried over $\text{MgSO}_4$ to provide 3-(2-methyl-2-nitropropyl)-1H-indole as a dark-brown oil (16.5 g, quantitative), which was used in the next step without further purification.

A solution of hydrate hydrate (5.68 g, 114 mmol) in 95% ethanol (6.5 mL) was added to a well-stirred suspension of 3-(2-methyl-2-nitropropyl)-1H-indole (8.5 g, 39.0 mmol) and Raney Ni in 95% ethanol (57 mL) and heated to reflux. After 12 h, the reaction was filtered through celite and concentrated in vacuo. The residue was recrystallized from isopropanol to provide 1-(1H-indol-3-yl)-2-methylpropan-2-amine (2.8 g, 38%). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.55 (s, 1H), 10.51 (s, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.28 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.17 (d, $J = 8.1$ Hz, 1H), 7.00 (m, 3H), 6.90 (d, $J = 8.4$ Hz, 1H), 2.76 (d, $J = 14.7$ Hz, 1H), 2.67 (d, $J = 14.7$ Hz, 1H), 1.84 (s, 1H), 1.30 (s, 3H), 1.29 (s, 3H). MS (ESI) $m/z$ 320.0 (M + H)$^+$. $p$-Toluenesulfonic acid (0.022 g, 0.117 mmol) was added to solution of 1-(1H-indol-3-yl)-2-methylpropan-2-amine (0.110 g, 0.59 mmol) and 5-chloroisatin (0.106 g, 0.59 mmol) in absolute ethanol (6 mL) and heated to 130 °C in a sealed tube. After 16 h, the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography to provide 8 (98 mg, 43%). $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.58 (s, 1H), 11.53 (s, 1H), 9.72 (m, 2H), 3.32 (m, 2H), 2.18 (t, $J = 8.4$ Hz, 2H), 1.69 (m, 2H), 1.34 (s, 3H), 1.24 (s, 3H). MS (ESI) $m/z$ 320.0 (M + H)$^+$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.55 (s, 1H), 10.51 (s, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.28 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.17 (d, $J = 8.1$ Hz, 1H), 7.00 (m, 3H), 6.90 (d, $J = 8.4$ Hz, 1H), 2.76 (d, $J = 14.7$ Hz, 1H), 2.67 (d, $J = 14.7$ Hz, 1H), 1.84 (s, 1H), 1.30 (s, 3H), 1.29 (s, 3H). MS (ESI) $m/z$ 320.0 (M + H)$^+$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.55 (s, 1H), 10.51 (s, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.28 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.17 (d, $J = 8.1$ Hz, 1H), 7.00 (m, 3H), 6.90 (d, $J = 8.4$ Hz, 1H), 2.76 (d, $J = 14.7$ Hz, 1H), 2.67 (d, $J = 14.7$ Hz, 1H), 1.84 (s, 1H), 1.30 (s, 3H), 1.29 (s, 3H). MS (ESI) $m/z$ 320.0 (M + H)$^+$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 10.45 (s, 1H), 10.42 (s, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.31 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.16 (d, $J = 7.2$ Hz, 1H), 7.03 (d, $J = 2.4$ Hz, 1H), 6.99 (m, 1H), 6.92 (d, $J = 8.4$ Hz, 2H), 3.93 (m, 1H), 3.05 (d, $J = 6.3$ Hz, 1H), 2.79 (dd, $J = 15.0, 3.6$ Hz, 1H), 2.41 (dd, $J = 15.0, 10.5$ Hz, 1H), 1.18 (d, $J = 6.3$ Hz, 3H). MS (ESI) $m/z$ 338.0 (M + H)$^+$. Preparation of 9a from 9-Tryptophan. Benzyl chloroformate (0.374 mL, 2.72 mmol) was added dropwise to a suspension of sodium carbonate (482 mg, 3.92 mmol) and 9-Tryptophan (500 mg, 2.27 mmol) in a 1:1 solution of water and acetonitrile (22 mL) at 0 °C. After addition, the solution was carefully acidified to pH 2 with concentrated HCl and diluted with water. The aqueous layer was washed with ethyl acetate and the combined
organic phases separated and dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to give the corresponding tosylate (580 mg, 100%).

H NMR (300 MHz, DMSO-d₆): δ 10.81 (s, 1 H), 7.71 (d, J = 8.1 Hz, 1H), 7.50–7.25 (m, 10H), 7.08 (m, 2H), 6.95 (s, J = 7.2 Hz, 1H), 4.95 (s, 2H), 4.00 (m, 2H), 3.89 (m, 1H). MS (ESI) m/z 252.0 (M + H)⁺.

p-Toluensulfonyl) chloride (199 mg, 1.05 mmol) was added to a solution of N-Chz-o-tosylphenol (320 mg, 0.988 mmol) and triethylamine (267 μL, 1.93 mmol) in dry dichloromethane (2.8 mL) at 0 °C and allowed to warm to room temperature. After 18 h, the reaction was concentrated in vacuo and the residue was purified by flash chromatography to give the corresponding tosylate (580 mg, 100%).

H NMR (300 MHz, DMSO-d₆): δ 10.81 (s, 1 H), 7.71 (d, J = 8.1 Hz, 1H), 7.50–7.25 (m, 10H), 7.08 (m, 2H), 6.95 (s, J = 7.2 Hz, 1H), 4.95 (s, 2H), 4.00 (m, 2H), 3.89 (m, 1H). MS (ESI) m/z 252.0 (M + H)⁺.

The resulting precipitate was washed with 10% ethyl acetate in petroleum ether to give 14d (180 g, 76%) as a pale-yellow solid.

H NMR (500 MHz, CDCl₃): δ 12.26 (bs, 1H), 9.92 (s, 1H), 8.36 (s, 1H), 7.94 (dd, J = 8.2, 2.8 Hz, 1H), 7.57 (dd, J = 6.4, 4.4 Hz, 1H). MS (ESI) m/z 180.0 (M − H)⁻.

5,6-Difluoro-3-(2-nitro-propenyl)-1H-indole (15d). A solution of 5,6-difluoro-1H-indole-3-carbaldelyde (200 g, 1.11 mol) in nitroethane (2 L) was refluxed with ammonium acetate (72.4 g, 0.94 mol). After 2 h, the reaction mixture was concentrated in vacuo to remove nitroethane, diluted with ethyl acetate, and washed with water and brine then dried over anhydrous Na₂SO₄. The organic layer was concentrated in vacuo and precipitated from 10% ethyl acetate in petroleum ether to provide 15d (172 g, 65%) as a yellow solid.

H NMR (500 MHz, CDCl₃): δ 12.29 (bs, 1H), 8.39 (s, 1H), 8.05 (s, 1H), 7.99 (dd, J = 8.2, 3.6 Hz, 1H), 7.52 (dd, J = 6.8, 4.0 Hz, 1H), 2.47 (s, 3H). MS (ESI) m/z 237.0 (M − H)⁻.

2-(5,6-Difluoro-1H-indol-3-yl)-1-methyl-ethylamine (16d). A solution of 15d (170 g, 0.714 mol) in dry THF (2 L) was added dropwise to a suspension of lithium aluminum hydride (95 g, 2.5 mol) in THF (1 L) at 0 °C then heated to reflux. After two hours, the reaction mixture was cooled to 0 °C and quenched by slow addition of brine then diluted with ethyl acetate and filtered through celite. The filtrate was dried over anhydrous Na₂SO₄ and concentrated to give 16d (150 g crude) as a viscous brown syrup. The residue was used in the next step without further purification.

H NMR (500 MHz, CDCl₃): δ 8.18 (bs, 1H), 7.3 (dd, J = 10.0, 4.0 Hz, 1H), 7.12 (dd, J = 8.6, 5.2 Hz, 1H), 7.05 (s, 1H), 3.25 (m, 1H), 2.8 (dd, J = 7.2, 11.6 Hz, 1H), 2.61 (dd, J = 10.6, 8.4 Hz, 1H), 1.16 (d, J = 8.0 Hz, 3H). MS (ESI) m/z 211.0 (M + H)⁺.

5-Chloro-6,7-difluoro-3-methyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3-indol]-2'(1H)-one (17d). p-Toluensulfonic acid (13.6 g, 0.071 mol) was added to a mixture of 16d (150 g, 0.714 mol) and 5-chloroisatin (90.8 g, 0.5 mol) in absolute ethanol (1.5 L) and heated to reflux. After 20 h, the reaction was cooled to room temperature and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with 2N HCl. The organic phase was separated and washed sequentially with saturated aqueous NaOH, water, and brine. The organic layer was separated and dried over anhydrous Na₂SO₄ and concentrated to provide a brown residue, which was triturated with dichloromethane to provide racemic 20 (110 g, 41%) as a light-yellow solid.

H NMR (500 MHz, DMSO-d₆): δ 10.65 (s, 1H), 10.48 (s, 1H), 7.43 (dd, J = 10.8, 4.0 Hz, 1H), 7.32 (dd, J = 8.8, 2.6 Hz, 1H), 7.1 (dd, J = 9.2, 6.0 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 10.8, 1.8 Hz, 1H), 3.08 (d, J = 8.1 Hz, 1H), 2.76 (m, 1H), 2.33 (m, 1H), 1.16 (d, J = 8.8 Hz, 3H). MS (ESI) m/z 374.0 (M + H)⁺. The racemate (20) was separated into its enantiomers by chiral chromatography under the conditions described in General Methods.
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Supporting Information Available: Additional experimental details for in vitro and in vivo pharmacokinetic studies, antimarial assays, and P. berghei mouse efficacy studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1R,3S)-5-Chloro-6-fluoro-3-methyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3-indol]-2(1'H)-one (17a). 1H NMR (300 MHz, DMSO-d6): δ 10.55 (s, 1H), 10.51 (s, 1H), 7.87 (d, J = 8.4, 2.4 Hz, 1H), 7.18 (d, J = 8.2, 1.4 Hz, 1H), 7.14 (d, J = 8.8, 4.5 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 9.3, 2.4 Hz, 1H), 3.93 (m, 1H), 3.36 (bs, 1H), 2.76 (dd, J = 15.0, 3.6 Hz, 1H) 2.39 (dd, J = 15.2, 10.5 Hz, 1H). 1.17 (d, J = 6.3 Hz, 3H). MS (ESI) m/z 357.0 (M + H)+; [α]D = 204.4º (c = 0.113 g/ml, methanol).

5,7-Dichloro-3-methyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3-indol]-2(1'H)-one (18). 1H NMR (300 MHz, CDCl3): δ 7.64 (bs, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.34 (bs, 1H), 7.29 (dd, J = 8.1, 2.4 Hz, 1H), 7.18 (d, J = 1.6 Hz, 1H), 1.75 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.4, 1.7 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 4.20 (m, 1H), 2.95 (dd, J = 15.4, 3.8 Hz, 1H), 2.53 (dd, J = 15.4, 10.4 Hz, 1H), 1.31 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.2 Hz, 1H). MS (ESI) m/z 372.1 (M)+; [α]D = 285.4º (c = 0.101 g/ml, methanol).

5,7-Dichloro-6-fluoro-3-methyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3-indol]-2(1'H)-one (19). 1H NMR (300 MHz, DMSO-d6): δ 10.69 (s, 1H), 10.51 (s, 1H), 7.43 (d, J = 10.0 Hz, 1H), 7.32 (bd, J = 8.3 Hz, 1H), 7.26 (d, J = 6.5 Hz, 1H), 7.04 (bs, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.91 (m, 1H), 3.12 (bd, J = 5.5 Hz, 1H), 2.77 (bd, J = 14.2 Hz, 1H) 1.28 (bd, J = 14.2, 10.9 Hz, 1H), 1.16 (d, J = 6.5 Hz, 1H). MS (ESI) m/z 390.0 (M)+.

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