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RESEARCH ARTICLE

Design and synthesis of simplified speciophylline analogues and β-carbolines as active molecules against *Plasmodium falciparum*

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Abstract

A structure–activity relationship study of active molecules against chloroquine-resistant *Plasmodium falciparum* K1 strain is reported. Structurally simplified analogues of antiplasmodial active alkaloids presented similar levels of activity as their corresponding natural products extracted from *Guiera senegalensis* and *Mitragyna inermis* with IC_{50} values on chloroquine-resistant *P. falciparum* K1 strain of up to 10.6 μM for spirooxindoles and 13.8 μM for β-carbolines. The identification of such simpler and cheaper structural analogues is crucial to efficiently study these natural products' action mode as well as developing new cures against malaria.

KEYWORDS

antimalarial activity, speciophylline, spirooxindoles, β-carbolines

1 | INTRODUCTION

Malaria remains a major public health problem around the world. In 2016, there were an estimated 216 million malaria cases causing 445 hundred deaths, primarily children under the age of 5 in Africa (World Health Organization, 2017a, 2017b). Among the six species of malaria parasites that infect humans, *Plasmodium falciparum* is the most virulent with high mortality and morbidity rate (Krungkrai & Krungkrai, 2016). Antimalarial drug resistance of *P. falciparum* is one of the greatest challenges confronting malaria control. Artemisinin-based combination therapies (ACTs) which combine an artemisinin derivative with a partner drug are the most effective antimalarial medicines available today. Currently, three ACTs are used as the first-line treatment for *falciparum* malaria in most endemic countries: artemether–lumefantrine, artesunate–mefloquine, and dihydroartemisinin–piperaquine (World Health Organization, 2015). However, a decline in ACT efficacy has been recently seen in Southeast Asia (World Health Organization, 2017a, 2017b). This represents a major concern for global public health especially as very few new compounds are currently in the development pipeline (Phyo & Nosten, 2018). Therefore,

Abbreviations: IC_{50}, half-maximal inhibitory concentration; HRP2-ELISA, histidine-rich protein 2 enzyme-linked immuno-sorbent assay; 5-FU, 5-fluorouracil; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; dr, diastereomeric ratio; CBz, carboxybenzyl; Ts, tosyl; Bn, benzyl; rt, room temperature; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; DMAP, dimethylaminopyridine; DMF, dimethylformamide; Boc_2O, di-*tert*-butyl dicarbonate.

the study of alternative action mechanisms would enable the development of new and complementary curative agents against *P. falciparum*. One major approach for the discovery of new drugs relies on the exploration of Nature as a source of novel active molecules and scaffolds. Based on this observation and considering that about 80% of the African population used traditional medicine to treat malaria, work has been carried out jointly by the faculties of pharmacy of Marseille and Bamako on the antiplasmodial activity of various prepared herbal remedies (Ancolio et al., 2002; Traore-Keita et al., 2000). Several active plants have been identified including *Mitragyna inermis*, an endemic plant in tropical Africa. Among the various tetracyclic and oxindolic tetracyclic and pentacyclic indole alkaloids isolated from *Mitragyna inermis*, speciophylline featuring a spiro[pyrrolidin-3,3′-oxindole] core, showed encouraging in vitro antiplasmodial activity on the chloroquine-resistant strain W2 (IC_{50} = 42 μM, Figure 1) and was retained for further optimization (Fiot et al., 2005). Although its IC_{50} is high relative to artemisinin or chloroquine, this concentration of interest should be put into perspective with its lifetime in the body (Sinou et al., 2010).

A preliminary study has demonstrated hepatic cellular activity induced by speciophylline with no hepatotoxic effect (Toure, Balansard, Pauli, & Scotto, 1996). Cytotoxicity studies have also been conducted on mixtures of alkaloids containing, among others, speciophylline. The toxicity of speciophylline in the rodent has been studied and shows a good tolerance, which suggests that it could be used as a treatment in humans (Monjanel-Mouterde et al., 2006). Its mode of action is however unknown; and it seems possible that this molecule operates via an original mechanism. Indeed, although not all known pharmacological targets have yet been tested, no specific interaction could be detected with chloroquine and no significant effect could be found either on the crystallization of heme of hemoglobin or on the production of free radicals.

The spirooxindole subunit constitutes an important pharmacophore found in many natural products (Trost & Brennan, 2009) displaying important biological activities (Antonchick et al., 2010; Galliford & Scheidt, 2007; Santos, 2014; Ye, Chen, Wold, Shi, & Zhou, 2016; Yu, Yu, & Liu, 2015) and has been the center of many synthetic efforts (Cheng, Ishihara, Tan, & Barbas III, 2014; Liang & Wang, 2013). Danishefsky and coworkers showed that structurally simpler analogues of the alkaloid spirotryprostatin A, displaying only the 3,3′-pyrrolidinyl-spirooxindole core, were more active than the parent natural product as cell cycle inhibitors (Edmondson, Danishefsky, Sepp-Lorenzino, & Rosen, 1999). Interestingly, the configuration of the spirooxindole's stereogenic center (*C*3) appeared unimportant in this specific case, with similar biological activity for both epimers. Based on this observation, we decided to develop a simple and robust synthetic platform of different simplified speciophylline analogues having a spiro[pyrrolidin-3,3′-oxindole] core, and test their antiplasmodial activity as well as their toxicity to shed light on the possible nature of the active pharmacophore.

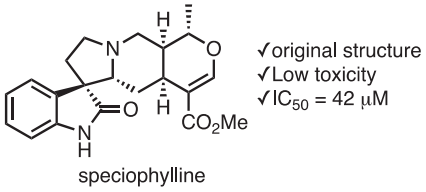


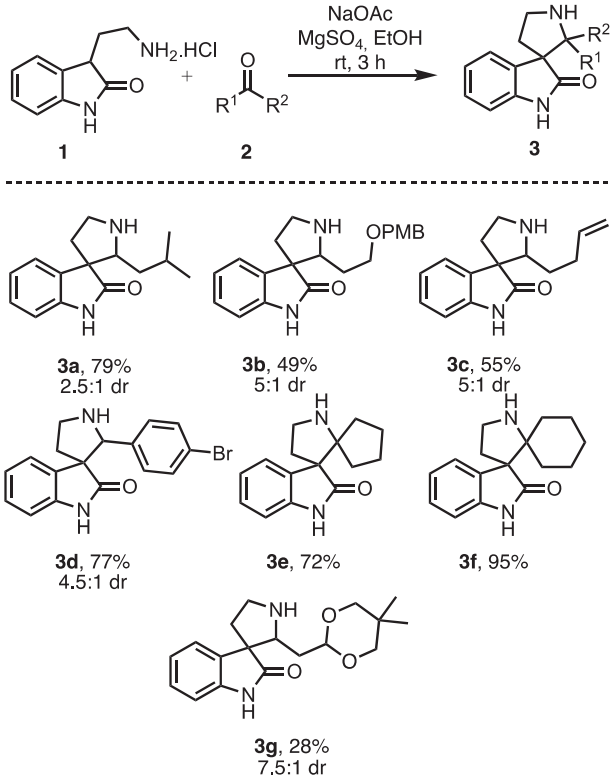
FIGURE 1 Structure of speciophylline

2 | RESULTS AND DISCUSSION

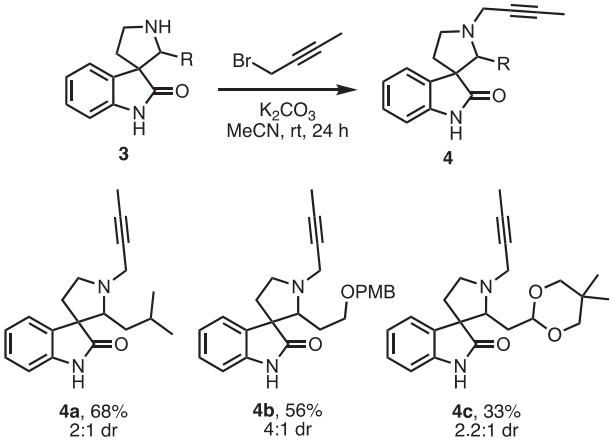
Our strategy relies on the versatility of an intramolecular Mannich reaction of commercially available 2-oxotryptamine hydrochloride (**1**) (Dörnyei, Incze, Kajtár-Peredy, & Szántay, 2002; Harley-Mason & Ingleby, 1958; Incze, Dörnyei, Kajtár-Peredy, & Szántay, 1999; Jansen & Richards, 1965; Oishi, Nagai, & Ban, 1968) with simple carbonyl compounds **2** (aldehydes or ketones) (Scheme 1). After optimization of the reaction conditions the combination of sodium acetate with magnesium sulfate was found efficient and reproducible and the desired spirooxindoles **3a-f** were obtained in moderate to good yields and low to moderate diastereoselectivities.

Three of these spirooxindoles were alkylated to have closer structures to the one of speciophylline and to evaluate the effect of *N*-alkylation on biological activity (Scheme 2). Hence, three spirooxindoles **3a**, **3b**, and **3g** (R^1 = H, R^2 = (5,5-dimethyl-1,3-dioxan-2-yl) methyl) were reacted with but-2-yne bromide in the presence of potassium carbonate. The products **4a-c** were obtained with lower diastereomeric ratio, which can be explained by an increased rate of the retro-Mannich reaction, leading to partial epimerization, once the amine function is tertiarized (Seaton, Nair, Edwards, & Marion, 1960; Wenkert, Udelhofen, & Bhattacharyya, 1959).

A previous study reported antiplasmodial activity for total alkaloids of *Guiera senegalensis* leaves and roots. Among the alkaloids identified in this plant, the β-carbolines, harman, and tetrahydroharman showed significative activity. A synergistic association between alkaloids from *Guiera senegalensis* and those of *Mitragyna inermis* has been found, and might explain the combination of both plants in traditional remedies to treat malaria (Fiot et al., 2006). An additive combination between β-carbolines isolated from *Guiera senegalensis* and speciophylline isolated from *Mitragyna inermis* has been observed. Other naturally occurring β-carboline has been found to possess antimalarial properties (Ashok, Ganguly, & Murugesan, 2013; Chan, Pearce, Page, Kaiser, & Copp, 2011). In addition, Yeung and coworkers have reported antiplasmodial activity for a series of spirotetrahydro-β-carbolines (Yeung et al., 2010), while Kara's team described in vivo antimalarial activity of the β-carboline alkaloid manzamine A (Ang, Holmes, Higa, Hamann, & Kara, 2000). Moreover, it is known that spirooxindole natural products originate from the corresponding β-carboline precursors by oxidative processes, which supports the biological evaluation of these two families of compounds (Wang & Ganesan, 2000; Yu, Guo, Jian, Chen, & Xu, 2018; Zinnes & Shavel Jr, 1966). We started our investigation by synthesizing a series of β-carbolines (Scheme 3). Compound **7** was prepared by a Pictet-Spengler reaction between tryptamine hydrochloride (**5**) and carbethoxypyruvic acid (**6**). The amino group was then protected by either a carbobenzyloxy or a tosyl group (**8a** and **8b**, respectively). Alternatively, the amine was converted to the corresponding amide **8c** by coupling with (*E*)-but-2-enoic acid. In addition, alkylation of the amine was undertaken using



SCHEME 1 Synthesis of spirocyclic oxindoles **3a-g** via intramolecular Mannich reaction

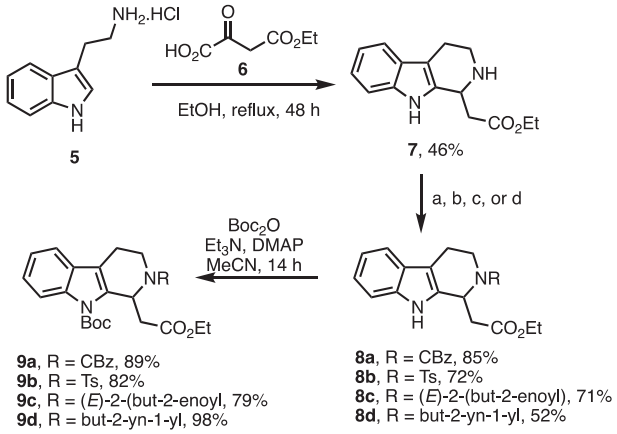


SCHEME 2 Alkylation of spirooxindoles **3a-c**

the same reaction conditions than before (Scheme 2) and the desired β-carboline **8d** was obtained in 52% yield. Finally, the indole nitrogen atom of **8a-8d** was protected as a *tert*-butoxycarbonyl group and the corresponding products **9a-9d** were obtained in good to excellent yields.

Further functionalizations of **8a** were conducted on the ester function (Scheme 4). Hence, conversion of the ester into the Weinreb amide was accomplished and the compound **10** was obtained in 83% yield. Instead, the alcohol **11** was synthesized in moderate yield (48%) from **8a** by reduction using diisobutylaluminum hydride.

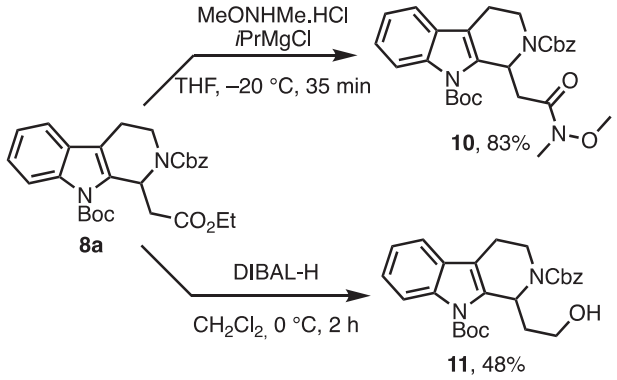
The antimalarial effect of the listed molecules in Table 1 was tested against the chloroquine-resistant K1 *P. falciparum* strain, using synchronized cultures. They were screened for their ability to inhibit



SCHEME 3 Synthesis of β-carbolines. Reaction conditions: (a) BnCOCl, Et_3N, DMPA, CH_2Cl_2, rt, 12 hr. (b) TsCl, Et_3N, CH_2Cl_2, rt, 24 hr. (c) (*E*)-but-2-enoic acid, EDCI, DMAP, CH_2Cl_2, rt, 3 hr. (d) but-2-yne bromide, K_2CO_3, DMF, rt, 16 hr

the growth of parasite activity, which was determined by a home-made HRP2-ELISA based assay. The first analysis revealed that compound **3b** possessing a *p*-methoxybenzyl group at 11-position was the most active among the screened spirooxindoles. This compound (IC_{50} of 10.6 μM) was slightly more potent than speciophylline (IC_{50} of 42.1 ± 7.7 μM). The other spirooxindoles (**3a**, **3c-f**) showed no or only moderate activity (>50 μM). In the next step, three *N-alkylated* spirooxindole derivatives (**4a-4c**) were tested for their in vitro *antimalarial* activity. The two separated and independently tested diastereomeric forms of **4a**, **4b**, and **4c** had similar IC_{50} values for K1 strain. These were generally slightly lower than those obtained with the similarly *secondary amine analogues (compare compound **4a** with **3a**), comparable* to the activity of speciophylline. Finally, β-carboline derivatives were tested in vitro for antimalarial activity. The compounds **9a**, **9c-d**, **10**, and **11** into which a BOC protecting group was introduced at the indole nitrogen atom had the greatest activity with IC_{50} ranging between 13.8 μM and 29.8 μM for K1 strain. The most promising β-carboline compounds **9a**, **9c**, and **10** were about 3-fold more active than speciophylline.

Next, nine compounds were screened for their in vitro cytotoxicity against HT29 colon adenocarcinoma cancer cell line using MTT colorimetric method with 5-FU as positive control (Table 2). Among all



SCHEME 4 Further functionalizations of β-carbolines

TABLE 1 In vitro activity of chloroquine, speciophylline, and several derivatives against chloroquine-resistant K1 *Plasmodium falciparum* strain

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
Chloroquine[a]	0.21 ± 0.01		
Speciophylline[a]	42.1 ± 7.7		
3a	>100	**4c** (dia 1)	35.4
3b	10.6	**4c** (dia 2)	55.3
3c	>100	**8b**	37.1
3d	55.1	**8c**	35.0
3e	63.8	**8d**	>125
3f	>100	**9a**	15.5
4a (dia 1)	29.4	**9c**	15.0
4a (dia 2)	17.3	**9d**	29.8
4b (dia 1)	11.2	**10**	13.8
4b (dia 2)	13.9	**11**	21.4

[a]Results expressed as mean ± *SD*.

TABLE 2 Cytotoxicity of compounds 1–9 against HT29 human cancer cell line

Compound	IC_{50} (μM)[a]
3a	>100
3b	67.7 ± 12.2
3c	>100
3d	>100
3e	>100
3f	>100
4a	65.9 ± 9.6
4c	85.8 ± 10.9
4b	79.4 ± 4.6
5-FU[b]	>100

[a]Each value is expressed as mean ± *SD* of three independent determinations.
[b]Positive control.

tested samples, only four compounds (**3b**, **4a-4c**, Table 2) exhibited moderate cytotoxic activity against HT29 cell line (Table 2). The protected alcohol **3b** and its alkylated analog **4b** exhibit cytotoxicity which may be partly responsible for its activity. Moreover, the introduction of the alkyne chain on the nitrogen atom leads to increased cytotoxicity and can explain the increase antiplasmodial activity.

3 | CONCLUSIONS

In conclusion, we have shown that simplified and easily accessible analogues of speciophylline had similar ranges of antiplasmodial activity as the natural product. It seems that the spirooxindole moiety could be responsible for this biological activity. Moreover, we found that simple β-carboline analogues presented comparable activities to the best spirooxindoles derivatives in this study. These results pave the way for further studies towards the understanding of speciophylline's mode of action and the synergy between the alkaloids from *Guiera senegalensis* and *Mitragyna inermis*.

4 | EXPERIMENTAL SECTION

4.1 | Evaluation of in vitro antimalarial activity

The chloroquine-resistant *P. falciparum* K1 strain (BEI Resources, MR4/ATCC, Manassas, VA) was cultured in complete medium consisting of RPMI 1640 medium (Gibco) supplemented with 50 mg/L hypoxanthine (Sigma), 25 mM $NaHCO_3$ (Sigma), 20 mg/L gentamycin (Sigma), and 10% human serum, at 37 °C and under an atmosphere containing 5% CO_2, 10% O_2, and 85% N_2 (Trager & Jensen, 1976). Cultures were synchronized by sorbitol treatments (Lambros & Vanderberg, 1979). Stock solutions of compounds were prepared in sterile DMSO and later dilutions were made in serum-free culture medium. Ring stage parasite cultures (1.5% hematocrit, 0.5% parasitemia) were exposed to increasing concentrations of compounds in 96-well plates. Chloroquine and speciophylline were used as reference drugs. DMSO alone (without compound) at a concentration equal to that in drug-treated cell samples was used as control. The plates were incubated 72 hr, at 37 °C in an atmosphere of 5% CO_2, 10% O_2, and 85% N_2 and then frozen at −80 °C. The revelation of parasite growth was realized using a homemade HRP2-based ELISA assay (Nakweti, Sinou, Luyindula, Sabot, & Franche, 2018). Briefly, 1 μg/mL of anti-HRP2 IgG (MPFM-55A, Immunology Consultants Laboratories, Inc., Portland, OR) in PBS was immobilized overnight in a 96-well plate, which was then blocked with 5% skimmed milk in PBS for 2 hr. Samples were then diluted in PBS with 1% Tween 20 and 5% skimmed milk and added to the plate for 1 hr. Finally, mouse peroxidase conjugated detection antibody (MPFG-55P, IgG, Immunology Consultants Laboratories) diluted in PBS with 1% Tween 20 and 5% skimmed milk was added for 1 hr. Signal was visualized with a commercially available 3,3′,5,5′-tetramethylbenzidine (TMB) substrate (TMB Chromogen Solution Single, Zymed Laboratories, Inc., South San Francisco, CA, and stopped with 1 M sulfuric acid after 10 min. Absorbance was read at 450 nm with a Safire spectrophotometer (Tecan, Austria) using the Magellan data analysis software (Tecan, Austria). The 50% inhibitory concentrations (IC_{50}) were calculated by nonlinear regression analysis from the dose response relationship as fitted by software ICEstimator 1.2 (http://www.antimalaria-icestimator.net) (Le Nagard, Vincent, Mentré, & Le Bras, 2011).

4.2 | Synthesis of spirooxindoles and β-carbolines

Experimental procedures and spectral data for new compounds are detailed in the Supporting Information which is available online.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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