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Synthesis of new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxalines as antileishmanial agents by Suzuki-Miyaura cross-coupling reactions

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Abstract

A series of new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxaline derivatives, structural analogues of alkaloid chimanine B, was synthesized in good yields using efficient palladium(0)-catalyzed Suzuki-Miyaura cross-coupling reactions. These new compounds were tested for *in vitro* antiparasitic activity upon *Leishmania amazonensis* and *Leishmania infantum* strains. Biological results showed activity against the promastigote forms of *L. amazonensis* and *L. infantum* with IC_{50} ranging from 0.5 to 7 μM. From a Structure-Activity Relationships point of view, these pharmacological results mainly enlightened the importance of the 4-lateral C_6, C_7 or C_8 α-unsaturated *trans*-alkenyl chain of unsubstituted pyrrolo[1,2-*a*]quinoxaline moiety.

Keywords: *4-Alkenylpyrrolo[1,2-a]quinoxaline, antileishmanial agents, leishmania amazonensis, leishmania infantum, suzuki reaction*

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Introduction

Parasitic diseases cause enormous suffering in many parts of the world. The leishmaniasis is a complex of disease syndromes caused by at least 20 species of the protozoan parasite of the genus *Leishmania* [1–2]. The disease is distributed worldwide, but mainly in the tropics and subtropics, with a prevalence of 12 million cases and an approximated incidence of 0.5 million cases of visceral (VL, or Kala-azar) and 1.5 million cases of cutaneous leishmaniasis (CL). The pentavalent antimonial compounds, sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®), which have been the first-line treatments of leishmaniases for the last 50 years, are subjects to development of resistance. Amphotericin B (Fungizone®, AmBisome®) and pentamidine (Pentacarinat®), the parenteral alternatives to antimony, cause serious and irreversible toxic effects which preclude their use [3]. Newly introduced first orally active drug miltefosine is quite effective but shows teratogenic effects and cannot be used in the pregnant women [4]. As current treatments are not ideal because they possess one or more negative attributes, including toxicity, loss of effectiveness due to resistance, expense, and inconvenience [5–8], novel therapies to combat leishmaniasis are urgently needed. Amongst new drugs, natural products [9–10] and derivatives of quinoline alkaloids such as chimanine B and some 2-substituted quinoline derivatives isolated from *Galipea longiflora* (Figure 1) have been reported to possess activity against experimental animal infections [11–13].

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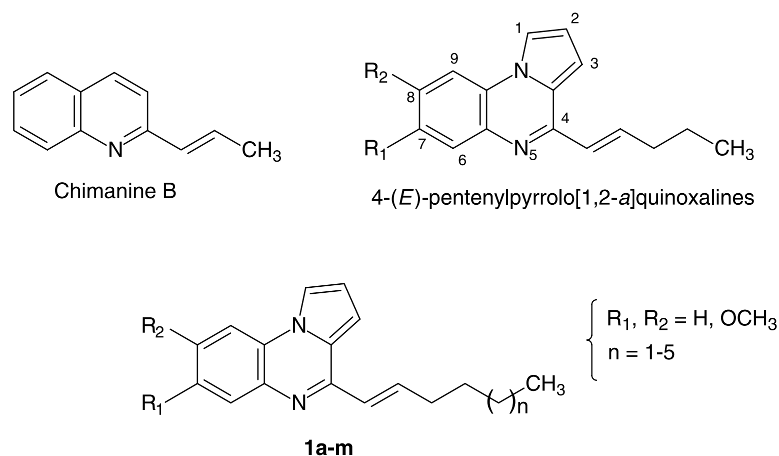

Figure 1. Structures of chimanine B, previously synthesized 4-(*E*)-pentenylpyrrolo[1,2-*a*]quinoxalines and new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxalines **1a–m**.

In the course of our work devoted to discover new compounds employed in the leishmaniasis chemotherapy, we previously identified a series of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives designed as interesting bioactive isosteres of *Galipea* species quinoline alkaloids [14]. From these preliminary results, it appeared that 4-alkenylpyrrolo[1,2-*a*]quinoxalines endowed with lipophilic unsaturated carbon chain, such as the 4-(*E*)-pentenyl derivatives (Figure 1), could initiate new valuable antileishmanial chemistry scaffolding. Thus, taking into account our experience in the field of the synthesis of new bioactive heterocyclic compounds of the type pyrrolo[1,2-*a*]quinoxaline [15–17], we designed new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxalines correlated with a particular lipophilic behavior (Figure 1). In this paper, we present preliminary results concerning the synthesis of **1a–m** via Suzuki-Miyaura cross-coupling reactions, and initial *in vitro* antileishmanial activity upon *Leishmania amazonensis* and *Leishmania infantum*.

Materials and methods

Chemistry

Instrumentation. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and reported uncorrected. NMR spectra were recorded on a BRUKER AVANCE 300 spectrometer (300 MHz). Chemical shifts refer to tetramethylsilane which was used as an internal reference. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV_{254}) with visualisation by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses were conducted by CNRS, Vernaison, France.

Synthesis of 4-[(E)-Hex-1-enyl]pyrrolo[1,2-a]quinoxalines ***1a–c***. A mixture of the 4-chloropyrrolo[1,2-*a*]quinoxaline **5a–c** [15,17] (3.4 mmol), the (*E*)-1-hexenylboronic acid pinacol ester (3.8 mmol) and $Pd(PPh_3)_4$ (0.10 mmol) in benzene (15 mL), and 4 M aqueous potassium hydroxide solution (2.4 mL) was stirred and heated under reflux under nitrogen for 5 h. It was then cooled, transferred to a separating funnel, and the reaction flask washed out with water (3 × 50 mL) and benzene (2 × 40 mL), the washings being added to the separating funnel. The organic layer was separated, washed with an aqueous saturated sodium hydrogen carbonate solution, then with a brine solution, dried over Na_2SO_4, and evaporated to dryness. Column chromatography of the residue on silica gel using diethyl ether-petroleum ether (1/3) as eluent gave the pure product **1a–c**.

4-[(E)-Hex-1-enyl]pyrrolo[1,2-a]quinoxaline ***(1a)***. Yield: 76%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.96 (dd, *J* 8.80 and 2.20 Hz, 1H, H-9), 7.93 (dd, *J* 2.90 and 1.25 Hz, 1H, H-1), 7.83 (dd, *J* 8.80 and 2.20 Hz, 1H, H-6), 7.46 (m, 2H, H-7 and H-8), 7.24 (ddd, *J* 15.50 and 7.05 Hz, 1H, =CH), 7.02 (dd, *J* 3.95 and 1.25 Hz, 1H, H-3), 6.88 (dd, *J* 3.95 and 2.90 Hz, 1H, H-2), 6.85 (ddd, *J* 15.50 and 1.50 Hz, 1H, HC=), 2.41 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 0.98 (t, *J* 7.20 Hz, 3H, CH_3). Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.31; H, 7.39; N, 11.28%.

4-[(E)-Hex-1-enyl]-7-methoxypyrrolo[1,2-a]quinoxaline ***(1b)***. Yield: 72%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.85 (dd, *J* 2.60 and 1.20 Hz, 1H, H-1), 7.73 (d, *J* 8.95 Hz, 1H, H-9), 7.43 (d, *J* 2.75 Hz, 1H, H-6), 7.22 (ddd, *J* 15.50 and 7.05 Hz, 1H, =CH), 7.06 (dd, *J* 8.95 and 2.75 Hz, 1H, H-8), 6.98 (dd, *J* 4.05 and 1.20 Hz, 1H, H-3), 6.86 (dd, *J* 4.05 and 2.60 Hz, 1H, H-2), 6.82 (ddd, *J* 15.50 and 1.55 Hz, 1H, HC=), 3.93 (s, 3H, CH_3O), 2.39

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(m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 0.98 (t, *J* 7.25 Hz, 3H, CH_3). Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.94; H, 7.03; N, 10.06%.

*4-[(E)-Hex-1-enyl]-8-methoxypyrrolo[1,2-a]quinoxaline (**1c**)*. Yield: 63%, pale-yellow crystals, mp = 28°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.87 (d, *J* 8.90 Hz, 1H, H-6), 7.81 (dd, *J* 2.75 and 1.25 Hz, 1H, H-1), 7.27 (d, *J* 2.65 Hz, 1H, H-9), 7.15 (ddd, *J* 15.60 and 7.00 Hz, 1H, =CH), 7.02 (dd, *J* 8.90 and 2.65 Hz, 1H, H-7), 6.97 (dd, *J* 3.95 and 1.25 Hz, 1H, H-3), 6.87 (dd, *J* 3.95 and 2.75 Hz, 1H, H-2), 6.82 (ddd, *J* 15.60 and 1.50 Hz, 1H, HC=), 3.95 (s, 3H, CH_3O), 2.39 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 0.98 (t, *J* 7.20 Hz, 3H, CH_3). Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.19; H, 7.35; N, 10.14%.

*Synthesis of 4-[(E)-Hept-1-enyl]pyrrolo[1,2-a]quinoxalines **1d-f**, 4-[(E)-Oct-1-enyl]pyrrolo[1,2-a]quinoxalines **1g–i** and 4-[(E)-Non-1-enyl]pyrrolo[1,2-a] quinoxaline **1j–k***. A mixture of the 4-chloropyrrolo[1,2-*a*]quinoxaline **5a–c** [15,17] (5 mmol), the alkenylboronic acid (5.5 mmol) and $Pd(PPh_3)_4$ (0.15 mmol) in benzene (25 mL), ethanol (1.6 mL) and 2 M aqueous sodium carbonate solution (5.4 mL) was stirred and heated under reflux under nitrogen for 24 h. It was then cooled, transferred to a separating funnel, and the reaction flask washed out with water (3 × 50 mL) and dichloromethane (3 × 90 mL), the washings being added to the separating funnel. The organic layer was separated and the aqueous phase extracted with dichloromethane (2 × 100 mL). The combined organic extracts were then washed with water (3 × 130 mL), dried over Na_2SO_4, filtered and the filtrate evaporated under reduced pressure. Column chromatography of the residue on silica gel using diethyl ether-petroleum ether (1/3) as eluent gave the pure product **1d–k**.

*4-[(E)-Hept-1-enyl]pyrrolo[1,2-a]quinoxaline (**1d**)*. Yield: 66%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.95 (dd, *J* 8.85 and 2.15 Hz, 1H, H-9), 7.93 (dd, *J* 2.90 and 1.15 Hz, 1H, H-1), 7.83 (dd, *J* 8.85 and 2.15 Hz, 1H, H-6), 7.45 (m, 2H, H-7 and H-8), 7.26 (ddd, *J* 15.35 and 7.05 Hz, 1H, =CH), 7.02 (dd, *J* 3.95 and 1.15 Hz, 1H, H-3), 6.86 (dd, *J* 3.95 and 2.90 Hz, 1H, H-2), 6.86 (ddd, *J* 15.35 and 1.40 Hz, 1H, HC=), 2.40 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.42 (m, 4H, $2CH_2$), 0.94 (t, *J* 7.20 Hz, 3H, CH_3). Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.62; N, 10.60. Found: C, 81.95; H, 7.55; N, 10.63%.

*4-[(E)-Hept-1-enyl]-7-methoxypyrrolo[1,2-a]quinoxaline (**1e**)*. Yield: 55%, pale-yellow crystals, mp = 41°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.85 (dd, *J* 2.65 and 1.25 Hz, 1H, H-1), 7.72 (d, *J* 9.00 Hz, 1H, H-9), 7.43 (d, *J* 2.80 Hz, 1H, H-6), 7.22 (ddd, *J* 15.55 and 7.05 Hz, 1H, =CH), 7.07 (dd, *J* 9.00 and 2.80 Hz, 1H, H-8), 6.99 (dd, *J* 4.05 and 1.25 Hz, 1H, H-3), 6.85 (dd, *J* 4.05 and 2.65 Hz, 1H, H-2), 6.84 (ddd, *J* 15.55 and 1.50 Hz, 1H, HC=), 3.93 (s, 3H, CH_3O), 2.41 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.42 (m, 4H, $2CH_2$), 0.94 (t, *J* 7.20 Hz, 3H, CH_3). Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.72; H, 7.78; N, 9.49%.

*4-[(E)-Hept-1-enyl]-8-methoxypyrrolo[1,2-a]quinoxaline (**1f**)*. Yield: 59%, pale-yellow crystals, mp = 51°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.87 (d, *J* 8.95 Hz, 1H, H-6), 7.81 (dd, *J* 2.70 and 1.30 Hz, 1H, H-1), 7.23 (d, *J* 2.65 Hz, 1H, H-9), 7.15 (ddd, *J* 15.55 and 7.00 Hz, 1H, =CH), 7.03 (dd, *J* 8.95 and 2.65 Hz, 1H, H-7), 6.98 (dd, *J* 4.00 and 1.30 Hz, 1H, H-3), 6.87 (dd, *J* 4.00 and 2.70 Hz, 1H, H-2), 6.82 (ddd, *J* 15.55 and 1.50 Hz, 1H, HC=), 3.95 (s, 3H, CH_3O), 2.38 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.40 (m, 4H, $2CH_2$), 0.94 (t, *J* 7.25 Hz, 3H, CH_3). Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.61; H, 7.70; N, 9.42%.

*4-[(E)-Oct-1-enyl]pyrrolo[1,2-a]quinoxaline (**1g**)*. Yield: 52%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.97 (dd, *J* 8.90 and 2.20 Hz, 1H, H-9), 7.93 (dd, *J* 2.70 and 1.30 Hz, 1H, H-1), 7.83 (dd, *J* 8.90 and 2.20 Hz, 1H, H-6), 7.45 (m, 2H, H-7 and H-8), 7.24 (ddd, *J* 15.50 and 7.00 Hz, 1H, =CH), 7.02 (dd, *J* 4.00 and 1.30 Hz, 1H, H-3), 6.88 (dd, *J* 4.00 and 2.70 Hz, 1H, H-2), 6.86 (ddd, *J* 15.50 and 1.50 Hz, 1H, HC=), 2.41 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 1.37 (m, 4H, $2CH_2$), 0.93 (t, *J* 6.85 Hz, 3H, CH_3). Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.96; N, 10.08. Found: C, 82.17; H, 8.05; N, 10.13%.

*7-Methoxy-4-[(E)-oct-1-enyl]pyrrolo[1,2-a]quinoxaline (**1h**)*. Yield: 42%, pale-yellow crystals, mp = 72°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.86 (dd, *J* 2.60 and 1.20 Hz, 1H, H-1), 7.73 (d, *J* 8.95 Hz, 1H, H-9), 7.43 (d, *J* 2.80 Hz, 1H, H-6), 7.22 (ddd, *J* 15.50 and 7.05 Hz, 1H, =CH), 7.08 (dd, *J* 8.95 and 2.80 Hz, 1H, H-8), 6.99 (dd, *J* 4.05 and 1.20 Hz, 1H, H-3), 6.85 (dd, *J* 4.05 and 2.60 Hz, 1H, H-2), 6.84 (ddd, *J* 15.50 and 1.45 Hz, 1H, HC=), 3.93 (s, 3H, CH_3O), 2.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.35 (m, 4H, $2CH_2$), 0.93 (t, *J* 6.80 Hz, 3H, CH_3). Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.97; H, 7.68; N, 9.22%.

*8-Methoxy-4-[(E)-oct-1-enyl]pyrrolo[1,2-a]quinoxaline (**1i**)*. Yield: 57%, pale-yellow crystals, mp = 52°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.88 (d, *J* 8.95 Hz, 1H, H-6), 7.82 (dd, *J* 2.75 and 1.20 Hz, 1H, H-1), 7.25 (d, *J* 2.65 Hz, 1H, H-9), 7.15 (ddd, *J* 15.55 and 7.00 Hz, 1H, =CH), 7.04 (dd, *J* 8.95 and 2.65 Hz, 1H, H-7), 6.98 (dd, *J* 3.95 and 1.20 Hz, 1H, H-3),

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6.88 (dd, *J* 3.95 and 2.75 Hz, 1H, H-2), 6.82 (ddd, *J* 15.55 and 1.40 Hz, 1H, HC=), 3.96 (s, 3H, CH_3O), 2.38 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.46 (m, 2H, CH_2), 1.38 (m, 4H, $2CH_2$), 0.93 (t, *J* 6.75 Hz, 3H, CH_3). Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.80; H, 7.94; N, 9.14%.

4-[(E)-Non-1-enyl]pyrrolo[1,2-a]quinoxaline ***(1j)***. Yield: 71%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.95 (dd, *J* 8.90 and 2.25 Hz, 1H, H-9), 7.93 (dd, *J* 2.75 and 1.30 Hz, 1H, H-1), 7.83 (dd, *J* 8.90 and 2.25 Hz, 1H, H-6), 7.45 (m, 2H, H-7 and H-8), 7.23 (ddd, *J* 15.50 and 7.00 Hz, 1H, =CH), 7.02 (dd, *J* 4.00 and 1.30 Hz, 1H, H-3), 6.88 (dd, *J* 4.00 and 2.75 Hz, 1H, H-2), 6.85 (ddd, *J* 15.50 and 1.55 Hz, 1H, HC=), 2.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 1.37 (m, 6H, $3CH_2$), 0.93 (t, *J* 6.85 Hz, 3H, CH_3). Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.32; H, 8.23; N, 9.67%.

7-Methoxy-4-[(E)-non-1-enyl]pyrrolo[1,2-a]quinoxaline ***(1k)***. Yield: 56%, yellow oil; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.85 (dd, *J* 2.65 and 1.25 Hz, 1H, H-1), 7.72 (d, *J* 8.95 Hz, 1H, H-9), 7.42 (d, *J* 2.75 Hz, 1H, H-6), 7.22 (ddd, *J* 15.50 and 7.05 Hz, 1H, =CH), 7.07 (dd, *J* 8.95 and 2.75 Hz, 1H, H-8), 6.99 (dd, *J* 4.05 and 1.25 Hz, 1H, H-3), 6.85 (dd, *J* 4.05 and 2.65 Hz, 1H, H-2), 6.84 (ddd, *J* 15.50 and 1.45 Hz, 1H, HC=), 3.92 (s, 3H, CH_3O), 2.41 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.36 (m, 6H, $3CH_2$), 0.90 (t, *J* 6.85 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.45; H, 7.96; N, 8.77%.

Synthesis of 4-[(E)-dec-1-enyl]pyrrolo[1,2-a]quinoxaline ***(1l)*** *and 4-[(E)-dec-1-enyl]-7-methoxypyrrolo[1,2-a]quinoxaline* ***(1m)***. To a suspension of potassium (*E*)-decenyltrifluoroborate (1.5 mmol), cesium carbonate (4.5 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.15 mmol), and 4-chloropyrrolo[1,2-*a*]quinoxaline **5a–b** [15,17] (1.65 mmol), in THF (15 mL) was added water (1.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at reflux temperature for 18 h, then cooled to room temperature, diluted with water (25 mL), and extracted with diethyl ether. The combined organic extracts were washed with brine and then dried over Na_2SO_4, filtered and the filtrate evaporated under reduced pressure. Column chromatography of the residue on silica gel using diethyl ether-petroleum ether (1/3) as eluent gave the pure product **1l–m**.

4-[(E)-Dec-1-enyl]pyrrolo[1,2-a]quinoxaline ***(1l)***. Yield: 66%, pale-yellow crystals, mp = 30°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.96 (dd, *J* 8.85 and 2.20 Hz, 1H, H-9), 7.93 (dd, *J* 2.70 and 1.25 Hz, 1H, H-1), 7.84 (dd, *J* 8.85 and 2.20 Hz, 1H, H-6), 7.45 (m, 2H, H-7 and H-8), 7.23 (ddd, *J* 15.50 and 7.00 Hz, 1H, =CH), 7.02 (dd, *J* 4.05 and 1.25 Hz, 1H, H-3), 6.89 (dd, *J* 4.05 and 2.70 Hz, 1H, H-2), 6.85 (ddd, *J* 15.50 and 1.45 Hz, 1H, HC=), 2.41 (m, 2H, CH_2), 1.59 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.36 (m, 8H, $4CH_2$), 0.91 (t, *J* 6.75 Hz, 3H, CH_3). Anal. Calcd. for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.17; H, 8.63; N, 9.07%.

4-[(E)-Dec-1-enyl]-7-methoxypyrrolo[1,2-a]quinoxaline ***(1m)***. Yield: 69%, pale-yellow crystals, mp = 49°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.86 (dd, *J* 2.70 and 1.25 Hz, 1H, H-1), 7.74 (d, *J* 8.95 Hz, 1H, H-9), 7.44 (d, *J* 2.75 Hz, 1H, H-6), 7.21 (ddd, *J* 15.50 and 7.05 Hz, 1H, =CH), 7.08 (dd, *J* 8.95 and 2.75 Hz, 1H, H-8), 6.99 (dd, *J* 4.00 and 1.25 Hz, 1H, H-3), 6.85 (dd, *J* 4.00 and 2.70 Hz, 1H, H-2), 6.84 (ddd, *J* 15.50 and 1.45 Hz, 1H, HC=), 3.93 (s, 3H, CH_3O), 2.40 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.34 (m, 8H, $4CH_2$), 0.89 (t, *J* 6.85 Hz, 3H, CH_3). Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.32. Found: C, 78.58; H, 8.54; N, 8.22%.

Pharmacology

In vitro L. amazonensis and L. infantum Culture and Drug Assays. Promastigotes of the *L. infantum* (clone MCAN/GR/82/LEM497) and *L. amazonensis* (MHOM/BR/1987/BA) were maintained at 26°C in RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum (FCS), 200 U/mL penicillin, 100 μg/mL streptomycin, sodium bicarbonate and non-essential amino acids (all from Gibco, Peisley, UK). At stationary growth phase parasites (10^6/mL) were harvested, washed and incubated in culture media with our molecules. The viability of promastigotes was checked using the MTS tetrazolium colorimetric assay CellTiter 96 Aqueous (Promega, USA). The MTS cell proliferation assay is a colorimetric assay system, which measures the reduction of a tetrazolium component (MTS) into formazan produced by the mitochondria of viable cells. Cells were plated in triplicate into microtiter-plate wells in 100 μM culture media with our various compound at increasing concentration (0, 1, 5, 10 and 25 μM). After 3 h of incubation with 20 μL MTS/well, the samples were read using an ELISA plate reader at 490 nm wavelength. The amount of colour produced was directly proportional to the number of viable cells. The results are expressed as the concentrations inhibiting parasite growth by 50% (IC_{50}) after a 1-2 day incubation period.

Cytotoxicity test upon human cells. The toxicity of various molecules was evaluated on non-activated, freshly isolated normal human peripheral blood

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mononuclear cells (PBMNC), as well as phytohemagglutinin (PHA)-induced cells. PBMNC from healthy volunteers were obtained following centrifugation on Ficoll gradient. Cells were then incubated in medium alone or induced to enter cell cycle by the addition of PHA (5 μg/mL, Murex Biotech Limited, Dartford, UK). Our molecules were added as described under results. Following cell cultures during 3–4 days, cells were harvested, washed, and counted with trypan blue exclusion. In some experiments, the proliferation of PBMNC was checked using the MTS dye colorimetric method as described previously. The 50% inhibitory concentrations (IC_{50}) were determined by linear regression analysis, expressed in μM ± SD and the maximum tolerated concentration expressed in μM was evaluated for each compound.

Partition coefficients-Log D (pH 7.4). In this study, the relative log *D* (pH 7.4) were assessed at pH 7.4 by the micro-HPLC method [14]. Determinations were performed with a chromatographic apparatus (Spectra Series, San Jose, USA) equipped with a model P1000XR pump and a model SCM 1000 vacuum membrane degasser, a model UV 150 ultraviolet detector (203 nm ≤ λ_{max} ≤ 253 nm) and a ChromJet data module integrator (ThermoFinnigan, San Jose, USA). The reversed phase column used, was an Equisorb (C.I.L. Cluzeau) C_8 (4.6 × 150 mm; 5 μm particle size) with a mobile phase consisting of acetonitrile – potassium dihydrogenophosphate (6.24 × 10^{-2} M; pH = 3.5 adjusted with orthophosphoric acid) (65: 35, v/v). The compounds were partitioned between *n*-octanol (HPLC grade) and phosphate buffer (pH = 7.4). Octanol was presatured with the adequate phosphate buffer (2%), and conversely. An amount of 1 mg of each compound was dissolved in an adequate volume of methanol in order to achieve 1 mg/mL stock solutions. Then, an appropriate aliquot of these methanolic solutions was dissolved in buffer to obtain final concentration of 50 μg/mL. Under the above-described chromatographic conditions, 50 μL of aqueous phase was injected into the chromatograph, leading to the determination of a peak area before partitioning (W_0). In screw-capped tubes, 4000 μL of the aqueous phase (V_{aq}) was then added to 10 μL of *n*-octanol (V_{oct}). The mixture was shaken by mechanical rotation during 30 min, followed by centrifugation achieved at 3000 rpm during 15 min. An amount of 50 μL of the lower phase was injected into the chromatograph column. This led to the determination of a peak area after partitioning (W_1). For each compound, the log *D* value was calculated using the formula: $\log D = \log [(W_0 - W_1)V_{aq}/W_1 V_{oct}]$.

Results and discussion

Chemistry

All reported 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxaline derivatives **1a–m** were obtained from 1-(2-nitrophenyl)pyrroles **2a–c** [15,17] (Scheme 1), prepared in acetic acid according to the Clauson-Kaas reaction, starting from 2-nitroanilines and 2,5-dimethoxytetrahydrofuran (DMTHF).

The resulting 1-(2-nitrophenyl)pyrroles intermediates **2a–c** were subsequently reduced into the attempted 1-(2-aminophenyl)pyrroles **3a–c** [15,17] using a sodium borohydride-copper(II) sulfate in ethanol at room temperature according to the conditions described by Yoo and Lee [18]. This $NaBH_4$-$CuSO_4$ system was found to be quite powerful in reducing the aromatic nitro groups with excellent yields (85–94%). Not commercialy available 5-methoxy-2-nitroaniline was prepared according to the literature [19–20]. The reaction of **3a–c** with triphosgene in toluene gave the lactams **4a–c**, which were subsequently chlorodehydroxylated with phosphorous oxychloride, leading to the 4-chloroquinoxalines **5a–c** [15,17]. 4-(*E*)-Hex-1-enylpyrrolo[1,2-*a*]quinoxalines **1a–c** were easily prepared in quite good yields (63–76%) by a direct Suzuki-Miyaura cross-coupling reaction of 4-chloropyrroloquinoxalines **5a–c** with (*E*)-1-hexenylboronic acid pinacol ester performed in the presence of $Pd(PPh_3)_4$ as a catalyst and a 4 M aqueous solution of potassium hydroxide solution [21–22]. Then, the 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxalines **1d–k** were synthesized *via* the palladium-catalyzed cross-coupling reaction of various (*E*)-alkenylboronic acids with **5a–c** in the presence of sodium carbonate used as the base [14,23–24]. The Suzuki-Miyaura-type reaction was then expanded to the use of potassium (*E*)-decenyltrifluoroborate and 4-chloropyrrolo[1,2-*a*]quinoxaline **5a–b** as coupling partner by using $PdCl_2$ (dppf)·CH_2Cl_2 as the catalyst, cesium carbonate as the base, and THF-H_2O as the solvent system [25–27]. Thus, this new palladium-catalyzed cross-coupling reaction led to the expected 4-[(*E*)-dec-1-enyl]pyrrolo[1,2-*a*]quinoxalines **1l–m** with an 66–69% yield (Table I). From NMR assignations, it appeared that 4-alkenyl derivatives **1a–m** were afforded as single *E* isomers. Thus, their ^{1}H NMR spectra showed two characteristic chemical shifts of a (*E*)-alkenyl chain in the olefinic region [δ 7.26–7.15 ppm (1H, ddd, *J* = 15.60–15.35 and 7.05–7.00 Hz), and 6.86–6.82 ppm (1H, ddd, *J* = 15.60–15.35 and 1.55–1.40 Hz)]. A coupling constant value of 15.60–15.35 Hz was in favor of a (*E*)-configuration in the double bond.

Pharmacology

Antileishmanial activity. Compounds **1a–m** were tested for their *in vitro* antileishmanial activity upon

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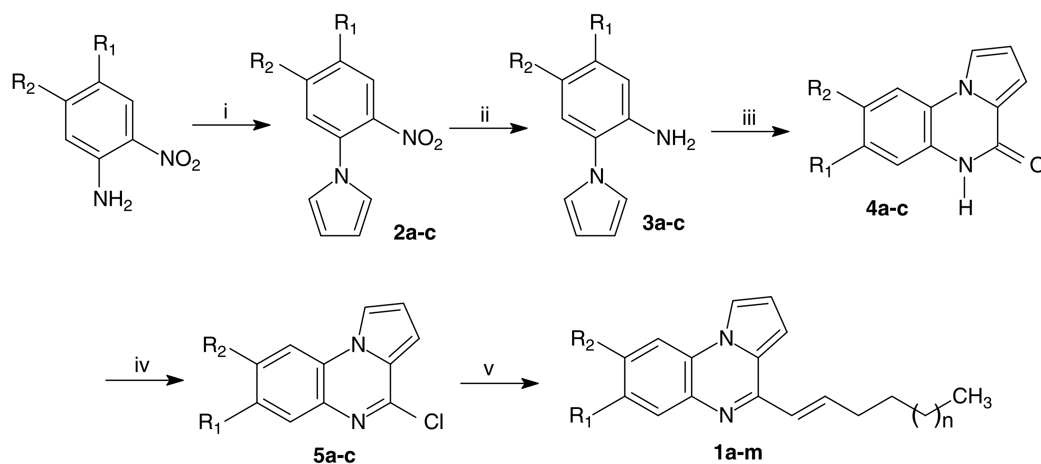

	R_1-	R_2-
2-5a	H-	H-
2-5b	CH_3O-	H-
2-5c	H-	CH_3O-

	R_1-	R_2-	n	Method
1a	H-	H-	1	A
1b	CH_3O-	H-	1	A
1c	H-	CH_3O-	1	A
1d	H-	H-	2	B
1e	CH_3O-	H-	2	B
1f	H-	CH_3O-	2	B
1g	H-	H-	3	B
1h	CH_3O-	H-	3	B
1i	H-	CH_3O-	3	B
1j	H-	H-	4	B
1k	CH_3O-	H-	4	B
1l	H-	H-	5	C
1m	CH_3O-	H-	5	C

Scheme 1. Synthesis of 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxaline derivatives **1a–m**. Reagents and conditions: (i) DMTHF, AcOH, Δ; (ii) $CuSO_4$, $NaBH_4$, EtOH, RT; (iii) $CO(OCCl_3)_2$, toluene, Δ; (iv) $POCl_3$, Δ; (v) *Method A*: $CH_3(CH_2)_3CH{=}CH\text{-}B(O\text{-}C(CH_3)_2\text{-})_2$, KOH; $Pd[P(C_6H_5)_3]_4$, C_6H_6, Δ; *Method B*: $CH_3(CH_2)_{4-6}CH{=}CH\text{-}B(OH)_2$, $Pd[P(C_6H_5)_3]_4$, Na_2CO_3, C_6H_6, EtOH, Δ.; *Method C*: $CH_3(CH_2)_7CH{=}CH\text{-}BF_3K$, $PdCl_2(dppf)\cdot CH_2Cl_2$, Cs_2CO_3, $THF\text{-}H_2O$, Δ.

the *L. amazonensis* and *L. infantum* strains [28–29] with chimanine B as the reference and Amphotericin B as the reference standard drug (Table II). All the 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxaline **1a–m** were found active against the promastigote forms of *L. amazonensis* with IC_{50} ranging from 0.5 to 7 μM. The pyrrolo[1,2-*a*]quinoxalines **1a**, **1d** and **1g**, substituted at the 4-position with a (*E*)-hexenyl, a (*E*)-heptenyl or a (*E*)-octenyl chain, respectively presented the best activities of all investigated compounds against *L. amazonensis* with IC_{50} of 0.5, 1 and 0.5 μM, respectively. In these same series, comparison of **1a, 1d** and **1g** with their corresponding 7-methoxy substituted derivatives **1b, 1e** and **1h** respectively, showed that the 7-methoxy substitution led to a slight decrease in the antileishmanial activity ($IC_{50} = 2$ μM). On the other hand, the substitution at position 8 of the C_6, C_7 or C_8 4-alkenylpyrrolo[1,2-*a*]quinoxaline heterocycle by one methoxy group (compounds **1c**, **1f** and **1i**) decreased once more the antiparasitic activity upon the *L. amazonensis* strain with IC_{50} values of 2.5 to 7 μM. Surprisingly, the 7-methoxysubstituted 4-(*E*)-nonenyl **1k** and 4-(*E*)-decenyl derivatives **1m** were more potent than their unsubstituted analogues **1j** and **1l** ($IC_{50} = 2$ and 1 compared with 3 and 4 μM for **1j** and **1l**).

Table I. Physical properties of 4-(*E*)-alkenylpyrrolo[1,2-*a*] quinoxalines **1a–m**.

Compound	log $D_{7.4}$	mp (°C)	% Yield
1a	4.47	–	76
1b	4.70	–	72
1c	4.73	28	63
1d	4.90	–	66
1e	5.05	41	55
1f	5.10	51	59
1g	5.05	–	52
1h	4.77	72	42
1i	5.12	52	57
1j	5.05	–	71
1k	4.83	–	56
1l	5.09	30	66
1m	4.98	49	69

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Table II. In vitro sensitivity of compounds 1a–m on L. amazonensis and L infantum strains, and cytotoxicity on human peripheral blood mononuclear cells PBMNC + PHA.

Compound	IC_{50} values (μM)[a]			Index of selectivity[b]	
	Leishmania strains		*Cytotoxicity on activated human peripheral blood mononuclear cells (PBMNC)*		
	L. amazonensis promastigotes	*L. infantum* promastigotes	PBMNC + PHA	*L. amazonensis*	*L. infantum*
Amphotericin B	1 ± 0.2	0.9 ± 0.1	96 ± 10	96	106.6
Chimanine B	5 ± 1	7 ± 2	42 ± 4	8.4	6
1a	0.5 ± 0.1	0.6 ± 0.1	7 ± 0.5	14	11.7
1b	2 ± 0.1	2.5 ± 0.1	5 ± 0.5	2.5	2
1c	2.5 ± 0.1	2.5 ± 0.1	5 ± 0.5	2	2
1d	1 ± 0.1	1.5 ± 0.2	7 ± 0.4	7	4.7
1e	2 ± 0.1	0.5 ± 0.1	5 ± 0.4	2.5	10
1f	2.5 ± 0.1	5 ± 0.2	10 ± 1	4	2
1 g	0.5 ± 0.1	0.6 ± 0.1	8 ± 0.5	16	13.3
1 h	2 ± 0.3	1.2 ± 0.1	8 ± 0.6	4	6.7
1i	7 ± 0.1	5 ± 0.1	20 ± 3	2.8	4
1j	3 ± 0.1	3 ± 0.1	7 ± 0.5	2.3	2.3
1k	2 ± 0.2	4 ± 0.1	5 ± 0.6	2.5	1.25
1 l	4 ± 0.4	3 ± 0.2	7 ± 0.4	1.75	2.3
1m	1 ± 0.2	4 ± 1	5 ± 0.4	5	1.25

[a] IC_{50} values were measured on the promastigotes of the *Leishmania amazonensis* (MHOM/BR/1987/BA) and *Leishmania infantum* (clone MCAN/GR/82/LEM497) strains. The IC_{50} (μM) values correspond to the mean +/− standard deviation from 3 independent experiments; [b] Index of selectivity (I.S.) was defined as the ratio between the IC_{50} value on the PBMNC + PHA cells and the IC_{50} value against the *Leishmania amazonensis* and *Leishmania infantum* strains.

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In the 7-methoxy substituted 4-alkenylpyrrolo[1,2-*a*]quinoxaline derivative series, the length of the *trans* α-unsaturated lateral chain at position 4 of the pyrroloquinoxaline moiety seemed not to be crucial as illustrated by results obtained for compounds **1b**, **1e**, **1h**, **1k** and **1m** ($IC_{50} = 1$–$2\,\mu M$) in comparison with those of their unsubstituted homologues **1a**, **1d**, **1g**, **1j** and **1l**. From a SAR point of view, these preliminary pharmacological results mainly enlightened the importance of the 4-lateral C_6, C_7 or C_8 α-unsaturated *trans*-alkenyl chain in the unsubstituted pyrrolo[1,2-*a*]quinoxaline moiety, in our series.

A second pharmacological evaluation was achieved against the promastigote forms of *L. infantum* in an experimental visceral leishmaniasis model, with chimanine B as the reference (Table II). All tested compounds **1a–m** showed almost the same level of activity as those observed upon the *L. amazonensis* strain with IC_{50} ranging from 0.5 to $5\,\mu M$. It must be noticed that all these new 4-(*E*)-alkenyl pyrroloquinoxaline derivatives **1a–m** were found more potent than chimanine B, the reference alkaloid ($IC_{50} = 7\,\mu M$). Moreover, three compounds **1a**, **1e** and **1g** showed an $IC_{50} < 1\,\mu M$. As a general rule, the introduction of a methoxy substituent in position C-7 or C-8 of the 4-alkenyl pyrrolo[1,2-*a*]quinoxaline skeleton seemed to slightly decrease the antileishmanial activity in comparison with their respective unsubstituted 4-alkenyl pyrrolo[1,2-*a*]quinoxaline homologues (i.e., **1a** compared to **1b** and **1c**, **1d** to **1f**, **1g** to **1h** and **1i**, **1j** to **1k**, and **1l** to **1m**), with the exception of **1e**, which showed a better antileishmanial activity than its unsubstituted analogue **1d** ($IC_{50} = 0.5\,\mu M$ versus 1.5 μM for **1d**).

In summary, all compounds showed almost the same level of activity on *L. amazonensis* and on *L. infantum* promastigotes. Further pharmacological studies should be investigated to determine the intracellular target(s) of these new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxalines, and to clarify their action mechanism against *Leishmania* parasites.

Cytotoxicity. All compounds **1a–m** were tested on activated (PBMNC + PHA) human peripheral blood mononuclear cells (Table II) [30]. As expected, most of the active pyrrolo[1,2-*a*]quinoxalines **1a–m** showed significant level of cytotoxicity against monocytes ($IC_{50} = 5$–$20\,\mu M$). The different substituents introduced on the pyrrolo[1,2-*a*]quinoxaline moiety seemed to have less influence on the PBMNC + PHA IC_{50} values than those observed for the antileishmanial activity. Index of selectivity (IS) was defined as the ratio of the IC_{50} value on the human mononuclear cells to the IC_{50} value on the *L. amazonensis* or *L. infantum* strains (promastigotes). This IS led to the identification of compound **1g** with IS of 16 on *L. amazonensis*, and 13.3 on *L. infantum*. On the other hand, the 4-(*E*)-hexenylpyrrolo[1,2-*a*]quinoxaline **1a** is also remarkable with IS = 14 and 11.7, on both strains respectively. These two molecules would constitute suitable pharmacophores for the design of new candidates in forthcoming pharmacological investigations.

Lipophilicity. Preliminary pharmacological results could be discussed in terms of physicochemical behaviour through the partitioning theory, determined here by the distribution coefficient *D*, usually expressed as log *D*. Consequently, HPLC determination of log *D* at pH = 7.4, considered as the biological medium pH, for the thirteen bispyrrolo[1,2-*a*]quinoxalines **1a–m** was achieved. All compounds were found very lipophilic with Log *D* values between 4.47 for **1a** and 5.12 for **1i**. A plot of antileishmanial IC_{50} versus log *D* values was presented in Figure 2, permitting to classify compounds in various subsets. The less lipophilic compound (**1a**) is the most active ($IC_{50} = 0.5$–$0.6\,\mu M$) while the four more lipophilic ones (**1j**, **1l**, **1f** and **1i**) are found slightly less active ($IC_{50} = 2.5$–$7\,\mu M$) on both *L. amazonensis* or *L. infantum* strains. A more heterogenous behaviour was found for compounds with log *D* between 4.90 and 5.05, as for **1d**, **1m** and

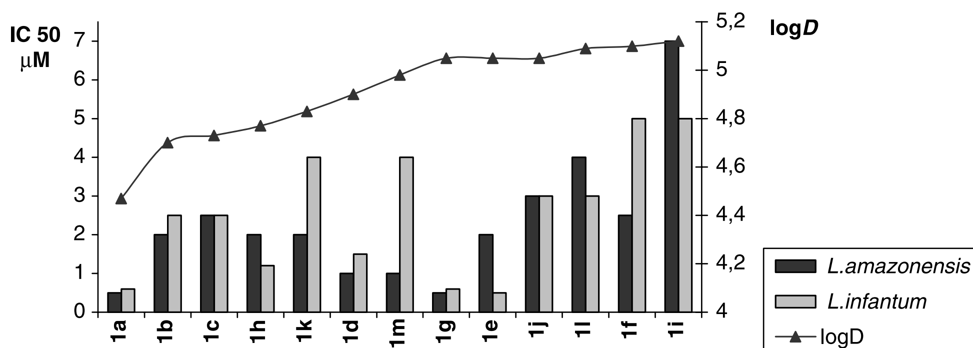

Figure 2. Log *D* / activity relationship for pyrrolo[1,2-*a*]quinoxalines **1a–m** *L. amazonensis* and *L. infantum* strains.

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1 g compounds which were are active on *L. amazonensis*. Such an observation could be noticed for **1 g** and **1e** with log *D* values of 5.05 from results observed on the *L. infantum* strain.

These results indicated that the choice and the length of the α-unsaturated *trans*-alkenyl chain in position 4 of the pyrrolo[1,2-*a*]quinoxaline moiety could be correlated with a particular lipophilic behaviour for the antileishmanial activity observed for this new series.

Conclusion

In the present report, we described the synthesis of new 4-(*E*)-alkenyl pyrrolo[1,2-*a*]quinoxaline derivatives *via* Suzuki cross-coupling reactions and presented their leishmanial activity. The physicochemical profile of new 4-(*E*)-alkenylpyrrolo[1,2-*a*]quinoxaline derivatives was studied through log *D* HPLC determination, achieved at physiological pH. These results have been discussed in terms of lipophilic behaviour in a preliminary SAR study. Nevertheless, as antiparasitic activity is generally related to the distribution of studied compounds to the intracellular target, it is not possible to establish pertinent and definitive correlation. These preliminary pharmacological results mainly enlightened the importance of the 4-lateral C_6, C_7 or C_8 α-unsaturated *trans*-alkenyl chain in the unsubstituted pyrrolo[1,2-*a*]quinoxaline moiety. Finally, with respect to our previously described 4-(*E*)-pentenyl-pyrrolo[1,2-*a*]quinoxalines, that showed IC_{50} ranging from 2 to 7 μM on both *L. amazonensis* and *L. infantum* strains [14], these new pyrrolo[1,2-*a*]quinoxalines **1a–m** endowed with a more lipophilic unsaturated carbon chain presented, in general, better antiparasitic activities, and could be further developed as potential antileishmanial drugs.

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