Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 194–210
Bioorganic & Medicinal Chemistry

Synthesis, analytical behaviour and biological evaluation of new 4-substituted pyrrolo[1,2-*a*]quinoxalines as antileishmanial agents

Jean Guillon,[a,*] Isabelle Forfar,[a] Maria Mamani-Matsuda,[b] Vanessa Desplat,[b] Marion Saliège,[a] Denis Thiolat,[b] Stéphane Massip,[a] Anais Tabourier,[a] Jean-Michel Léger,[a] Benoit Dufaure,[a] Gilbert Haumont,[b] Christian Jarry[a] and Djavad Mossalayi[b]

[a]*EA 2962—Pharmacochimie, UFR des Sciences Pharmaceutiques, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France*
[b]*EA 3677—Bases Thérapeutiques des Inflammations et Infections, UFR des Sciences Pharmaceutiques, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France*

Received 10 July 2006; revised 19 September 2006; accepted 29 September 2006
Available online 1 October 2006

Abstract—An original series of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives, new structural analogues of *Galipea* species quinoline alkaloids, was synthesized from various substituted 2-nitroanilines via multistep heterocyclizations and tested for in vitro antiparasitic activity upon *Leishmania amazonensis* and *Leishmania infantum* strains. Structure–activity relationships enlighten the importance of the 4-substituted alkenyl side chain on the pyrrolo[1,2-*a*]quinoxaline moiety to modulate the antileishmanial activity.

1. Introduction

Protozoan parasites affect 3 billion people, with malaria and trypanosomatid parasites causing the greatest morbidity.[1,2] Leishmaniasis is a widespread parasitic disease that is caused by protozoan parasites of the genus *Leishmania* in tropical and subtropical areas in both the old and new worlds. According to recent World Health Organization reports, 88 countries are affected, comprehending 12 million infected people worldwide, with approximately 350 million people at risk. The incidence is increasing worldwide, with 1–2 million new cases registered annually, despite all efforts being made to fight the disease.[1–5] It occurs in two major forms; cutaneous/muco-cutaneous (CL) and visceral leishmaniasis (VL, or Kala-azar), depending upon parasite species. *Leishmania donovani* and *Leishmania infantum* are major causative agents of VL, while *Leishmania major*, *Leishmania tropica* and *Leishmania aethiopica*, *Leishmania braziliensis*, *Leishmania panamensis*, *Leishmania amazonensis* and *Leishmania mexicana* cause CL.[6] Therapy of patients with leishmaniasis is still a serious problem. Historically, leishmaniasis chemotherapy has been based on the use of toxic heavy metals, particularly antimony compounds. In fact, the drugs for leishmaniasis's treatment of all their clinical forms are meglumine antimonite (Glucantime®) and sodium stibogluconate (Pentostam®), despite the fact that they exhibit renal and cardiac toxicity (Fig. 1).[7,8] When this kind of treatment is not effective, alternative drugs include pentamidine (Pentostam®) and amphotericin B (Fungizone®, Ambisome®), also very toxic with serious side effects.[9] Miltefosine, a phosphocholine analogue originally developed as an anticancer agent, has been found to be highly effective against leishmaniasis in vitro and in vivo. Now, this compound is the only oral agent against cutanous[10] and visceral[11] leishmaniasis, although presenting severe gastrointestinal problems.[12] As the leishmaniasis chemotherapy is still inefficient, there is an urgent need for the development of new, efficient and safe drugs.[6,13,14] Traditional and ethnic medicine is often a good source for researchers looking for bioactive substances. Leishmaniasis is not an exception, and plants have been used for the treatment of people living far from modern medicine.[15–17] Such compounds belong to the following groups: alkaloids, terpenes,

Keywords: Pyrrolo[1,2-*a*]quinoxaline derivatives; Antileishmanial activity; Synthesis; Lipohilicity.
* Corresponding author. Fax: +33 0 5 57 57 13 52; e-mail: Jean.Guillon@chimphys.u-bordeaux2.fr

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.09.068

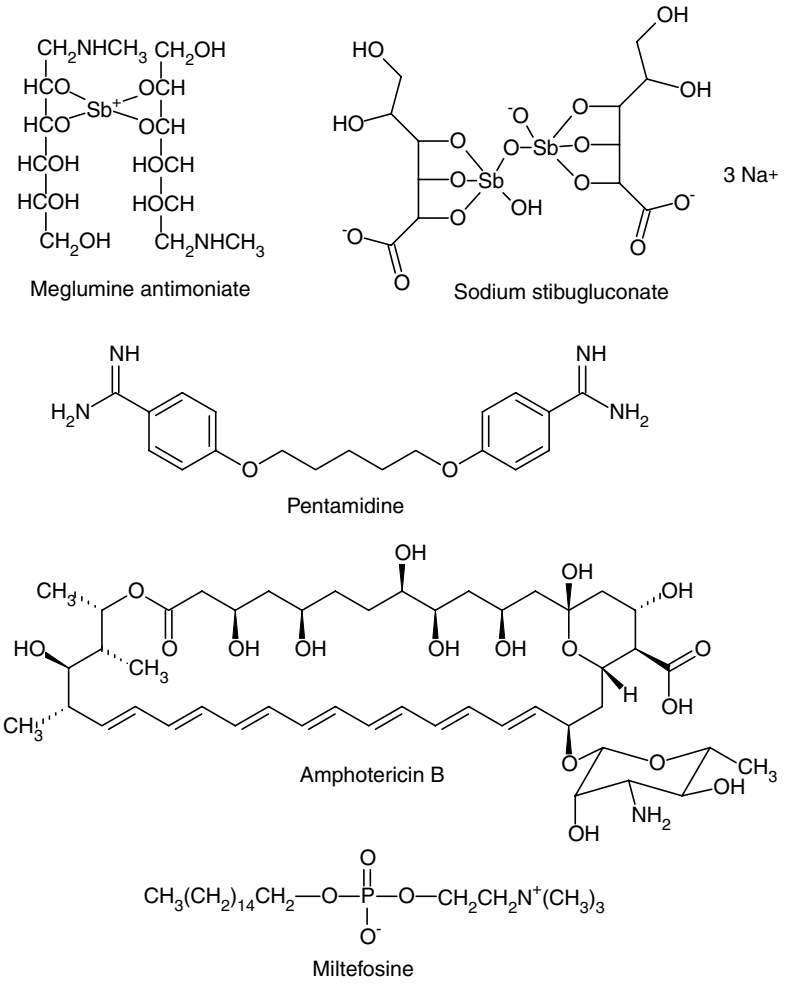


Figure 1. Structures of meglumine antimoniate (Glucantime®), sodium stibogluconate (Pentostam®), amphotericin B (Fungizone®, Ambisome®), pentamidine (Pentacarinat®) and miltefosine.

quinines, lactones, coumarins, acetogenins of annonaceae, chalcones, tetralones, lignans and saponins.[18–22] For example, some 2-substituted quinoline derivatives active against leishmaniasis were isolated from *Galipea longiflora*, through a bioactivity-guided fractionation process from an ethnopharmacological investigation in Bolivia.[17,23] The 2-substituted quinoline alkaloids 2-*n*-propylquinolines, chimanines A/B/C/D, 2-*n*-pentylquinolines, 2-phenylquinolines, 2-phenylethylquinolines and 4-methoxy-2-pentenylquinoline were extracted from the bark, root and leaves of *Galipea longiflora* Krause (Rutaceae) (Fig. 2).[23–27] *Galipea officinalis* and *Galipea bracteata* are also known to contain quinoline alkaloids such as cusparine, galipine, 2-phenylquinolines, 2-*n*-pentylquinolines and 2-pentenylquinolines (Fig. 2).[28–30] Hence, chimanine B isolated from *Galipea* species was claimed as the lead molecule useful for further pharmacomodulations.[31,32]

We previously described a novel synthetic approach to pyrrolo[1,2-*a*]quinoxaline derivatives designed as interesting bioactive analogues of quinoline derivatives.[33–36] They could be developed as new isosteres of *Galipea* species quinoline alkaloids. Hence, we reported here the synthesis and in vitro antiparasitic activity study of a series of 4-substituted pyrrolo[1,2-*a*]quinoxalines **1** upon *L. amazonensis* and *L. infantum* (Fig. 3).

As it was already noticed,[37] an often limiting factor for in vivo activity of new designed antiparasitic compounds is their lack of distribution to the intracellular target. As this property is often related to their molecular lipophilicity, we attempted a physico-chemical study of new pyrrolo[1,2-*a*]quinoxalines **1** achieved in order to define their analytical profile. $\log D$, the distribution coefficient between the aqueous and the lipid phase, was chosen as the parameter describing the accumulation of an ionizable drug in cells. Thus, we explored the behaviour of the 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives through $\log D$ HPLC determination achieved at physiological pH. On the other hand, pK_a values of the 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives were calculated through an in silico methodology.

Finally, all compounds were tested against *L. amazonenesis* and *L. infantum* protozoa with chimanine B as the reference drug. The 4-(*E*/*Z*)-propenyl and 4-(*E*)-pentenyl pyrrolo[1,2-*a*]quinoxalines were found as active as the reference providing an interesting alternative to difficult extraction procedure of quinoline alkaloids from

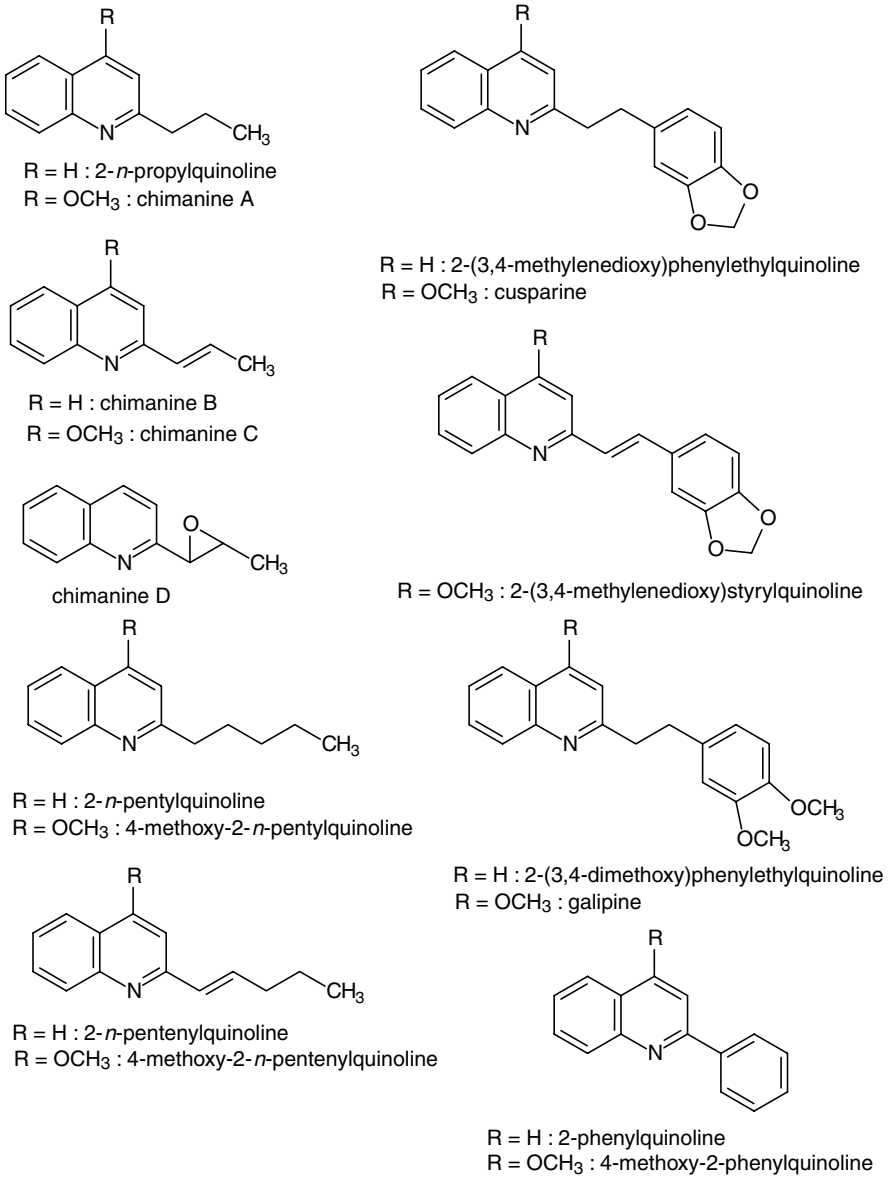


Figure 2. Structure of extracted 2-substituted quinoline alkaloids isolated from *Galipea* species.

Galipea species. These results were exploited for SAR studies that enlightened the influence of the nature of the 4-substituted alkenyl side chain on the pyrrolo[1,2-*a*]quinoxaline moiety for the modulation of antiparasitic activity. These preliminary results suggest that 4-alkenylpyrrolo[1,2-*a*]quinoxalines could be further developed as potential antileishmanial drugs.

2. Results and discussion

2.1. Chemistry

All of the reported 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1a**–**n** were obtained from 1-(2-aminophenyl)pyrroles **2a**–**c**. Preparation of the latter was performed 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 **3a**–**c** were subsequently reduced into the attempted 1-(2-aminophenyl)pyrroles **2a**–**c** using a $BiCl_3$–$NaBH_4$ treatment (Scheme 1). Not commercially available 5-methoxy-2-nitroaniline was prepared according to the literature.[38,39] The reaction of various alkyl-, alkenyl-, or aryl-acid chlorides with **2a**–**d** led to the acetamides **4a**–**n**. The 4-substituted pyrrolo[1,2-*a*]quinoxalines **1a**–**n** were prepared by cyclisation of these amides **4a**–**n** in refluxing phosphorus oxychloride according to the Bischler-Napieralski reaction.[40] All the synthesized compounds were characterized by nuclear magnetic resonance (^{1}H and ^{13}C NMR). The 4-propenyl derivatives **1c**–**e** were afforded as single *E* isomers. Thus, their ^{1}H NMR spectra showed the characteristic chemical shifts of a *trans*-propenyl chain at 7.25–7.08 ppm (1H, qd, J = 16.50–15.35 and 6.80–6.70 Hz), 6.88–6.82 ppm (1H, dd, J = 16.50–15.35 and 1.70–1.25 Hz), and 2.08–2.01 ppm (3H, dd, J = 6.80–6.70 and 1.70–1.25 Hz). A

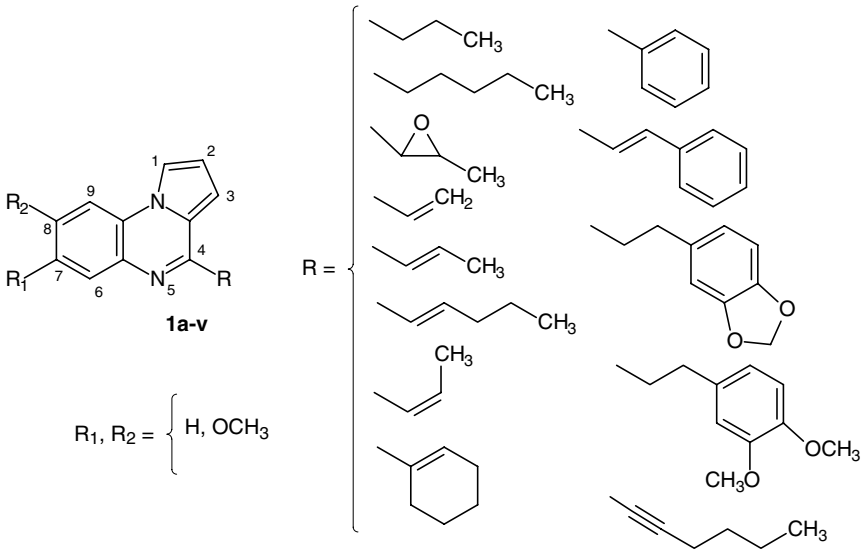


Figure 3. General structure of synthesized 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1a**–**v**.

coupling constant value of 16.50–15.35 Hz was in favor of a *trans* configuration in the double bond. Analysis of the ^{1}H NMR of compounds **1h**–**j** showed two signals in the olefinic region [δ 7.21–7.15 (ddd) and δ 6.83–6.77 (ddd)] and also revealed the presence of a *trans* substituted double bond.

The 4-(*E*)-styrylpyrrolo[1,2-*a*]quinoxalines **1o**,**p** were easily synthesized by the Perkin reaction of 4-methylpyrrolo[1,2-*a*]quinoxalines **6a**,**b**, previously obtained via the amides **5a**,**b**, with benzaldehyde in refluxing Ac_2O under conditions inspired by those of Kaslow and Stayner (Scheme 2).[41,42]

To prepare the 4-epoxypropylpyrrolo[1,2-*a*]quinoxaline **1q**, structural analogue of chimanine D, we first synthesized the pyrrolo[1,2-*a*]quinoxaline-4-carboxaldehyde **7** by oxidation of **6a** with SeO_2 in dioxane.[43] The Corey–Chaykovsky reaction of the sulfur ylide generated from triethylsulfonium tetrafluoroborate on aldehyde **7** gave the epoxides **1q**,**r** (Scheme 3), as a separable mixture of *Z* and *E* isomers (ratio: 1/4).[43–45] The stereochemistry of these epoxides was determined by studying their ^{1}H NMR spectra: measure of $J_{H2'\text{-}H3'}$ (4.35 and 1.95 Hz for *Z* and *E* isomers, respectively) and comparison with the ^{1}H NMR spectrum of the *E* antileishmanial natural epoxide.

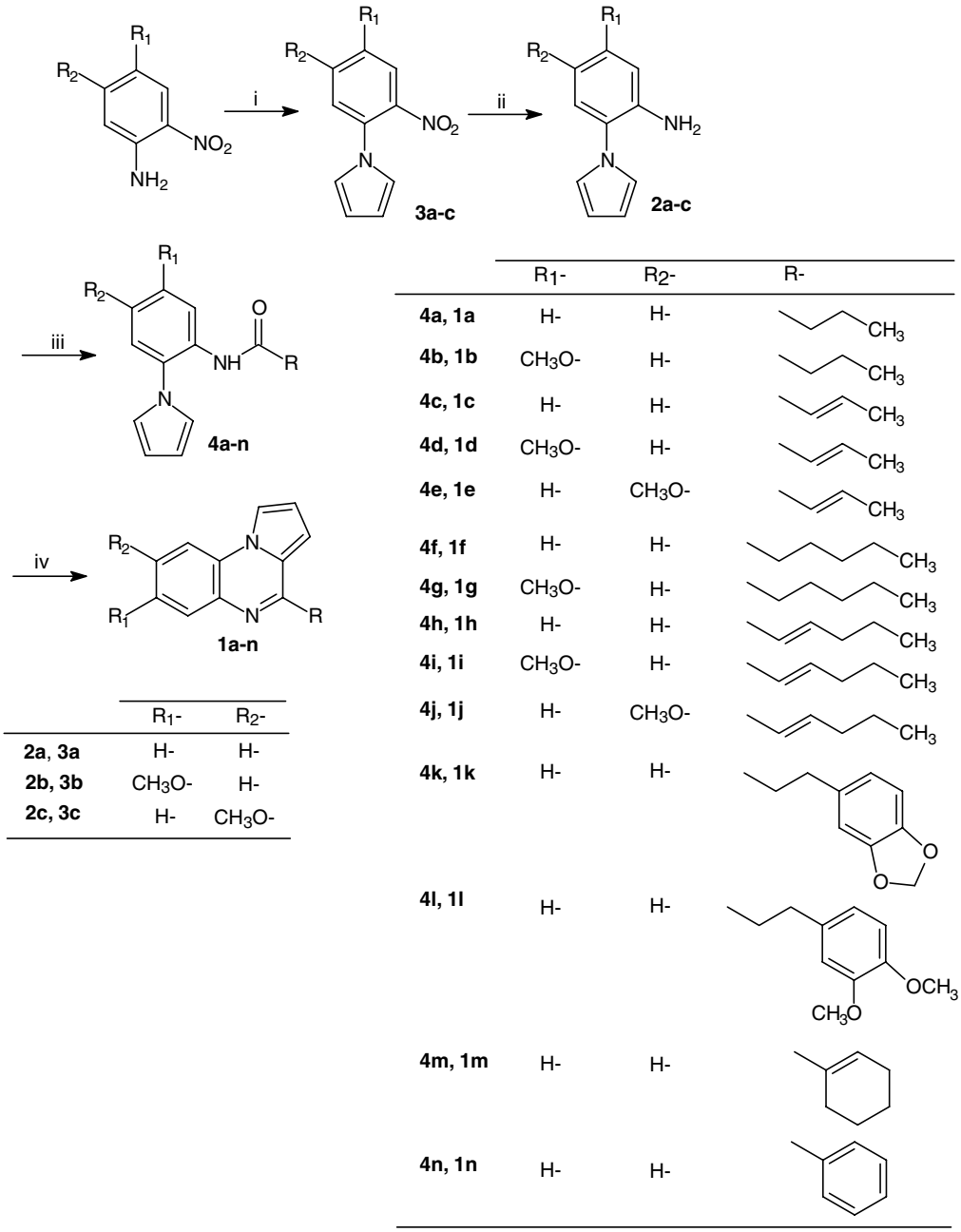
We also synthesized the 4-propenylpyrrolo[1,2-*a*]quinoxaline **1c** by Wittig olefination between the aldehyde **7** and ethyltriphenylphosphonium bromide to afford **1c** as single *E* isomer in 40% yield (Scheme 3).[43,46]

Due to the moderate yields obtained in the synthesis of the 4-alkenylpyrrolo[1,2-*a*]quinoxalines by the Bischler-Napieralski or Wittig reactions, we investigated new general methods for their preparation. Thus, 4-alkenylpyrrolo[1,2-*a*]quinoxalines **1c**,**d**, **1h**,**i**, **1n**–**p** and **1s** were easily prepared in quite good yield (51–86%) by a direct Suzuki cross-coupling reaction of 4-chloroquinoxalines **8a**,**b** with various aryl- or alkenylboronic acids in the presence of $Pd(PPh_3)_4$ as a catalyst and a 2 M aqueous solution of sodium carbonate (Scheme 4).[47–49] The *cis* configuration of **1s** was established by ^{1}H NMR study, that is, a typical pattern of the *cis* olefinic protons was observed at 6.77 and 6.30 ppm (J = 11.25 Hz). Derivative **1t** was synthesized via the palladium-catalyzed cross-coupling reaction of a vinylboronate with **8a** in the presence of potassium hydroxide used as the base.[50] The heteroaryl chlorides **8a**,**b** were previously prepared by reacting **2a**,**b** with triphosgene in toluene to give the lactams **7a**,**b**, which were subsequently chlorodehydroxylated with phosphorous oxychloride.[36] Moreover, the Sonogashira coupling reaction of 4-chloroquinoxalines **8a**,**b** with 1-hexyne in the presence of $[PdCl_2(PPh_3)_2]$/CuI, in refluxing triethylamine gave **1u**,**v** (Scheme 4).[51,52]

Compounds **1a**–**p** and **1t**–**v** were then converted into their hydrochlorides in 32–80% yields by treatment with hydrochloric acid gas in diethyl ether (Table 1). However, acidic treatment of the oily 4-(*Z*)-propenylpyrroloquinoxaline **1s** always led to the hydrochloride salt of **1c** through a *cis* to *trans* isomerization. A X-ray single crystal analysis was performed on pyrroloquinoxaline **1c** as base in order to study the lateral chain configuration (Fig. 4). The 4-propenylpyrroloquinoxaline system was found quite planar. The C(14)–C(15) propenyl double bond was noticed at 1.344(7) Å, as typically observed for the C=C double bonds. The crystalline cohesion could be ensured by a rigidification of the sequence N(7)–C(8)–C(4)–C(15) through a van der Waals contact between N(7) and H(15) observed at 2.605 Å. This contact could be necessary for the solid form cohesion and subsequent molecular stability.

2.2. Antileishmanial activity

Compounds **1a**–**v** were tested for their in vitro antileishmanial activity upon the *L. amazonensis* and *L. infantum*



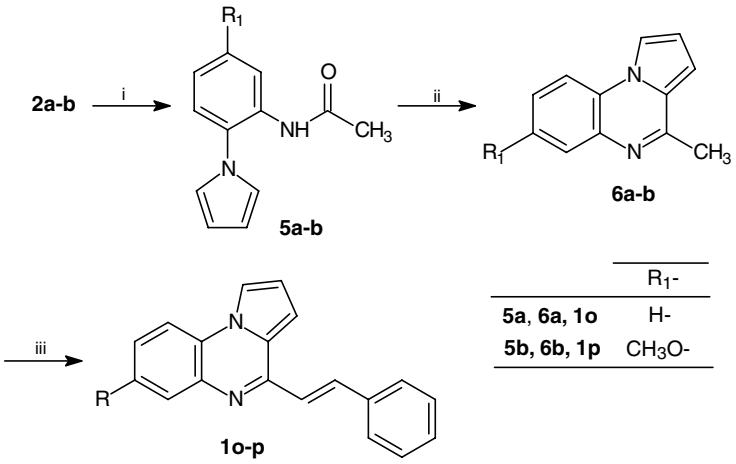
	R_1-	R_2-
2a, **3a**	H-	H-
2b, **3b**	CH_3O-	H-
2c, **3c**	H-	CH_3O-

	R_1-	R_2-	R-
4a, 1a	H-	H-	CH_3
4b, 1b	CH_3O-	H-	CH_3
4c, 1c	H-	H-	CH_3
4d, 1d	CH_3O-	H-	CH_3
4e, 1e	H-	CH_3O-	CH_3
4f, 1f	H-	H-	CH_3
4g, 1g	CH_3O-	H-	CH_3
4h, 1h	H-	H-	CH_3
4i, 1i	CH_3O-	H-	CH_3
4j, 1j	H-	CH_3O-	CH_3
4k, 1k	H-	H-	O, O
4l, 1l	H-	H-	OCH_3, CH_3O
4m, 1m	H-	H-	
4n, 1n	H-	H-	

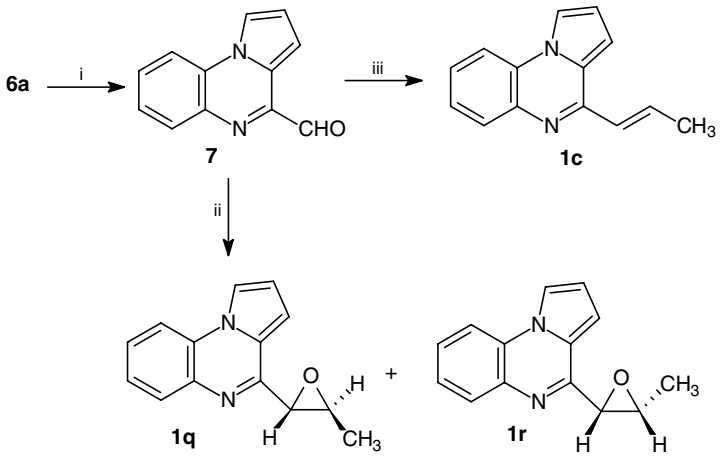
Scheme 1. Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1a**–**n**. Reagents and conditions: (i) DMTHF, AcOH, Δ; (ii) $BiCl_3$, $NaBH_4$, EtOH; (iii) RCOCl, pyridine, dioxane, Δ; (iv) 1—$POCl_3$, toluene, Δ; 2—$NaHCO_3$, H_2O, rt.

strains with chimanine B as the reference (Table 2). Amphotericin B was also used in these tests as the reference standard drug. The pyrroloquinoxalines **1c**–**e**, **1h**–**k**, **1s**,**t** and **1v** were found the most active compounds against the promastigote forms of *L. amazonensis* with IC_{50} from 0.5 to 7 μM. In particular, **1c**, designed as a chimanine B structural analogue, was found to be 10 times more active than the reference alkaloid (IC_{50} = 0.5 μM vs IC_{50} = 5 μM). The 7-methoxy and 8-methoxy-4-(*E*)-propenylpyrroloquinoxalines **1d**,**e** showed an IC_{50} of 7 and 1 μM, respectively. The introduction of a (*Z*)-propenyl or vinyl substituent on position C-4 of the pyrroloquinoxaline moiety (compounds **1s**,**t**) seems to slightly decrease the activity in comparison with compound **1c** with IC_{50} = 4 and 3 μM, respectively.

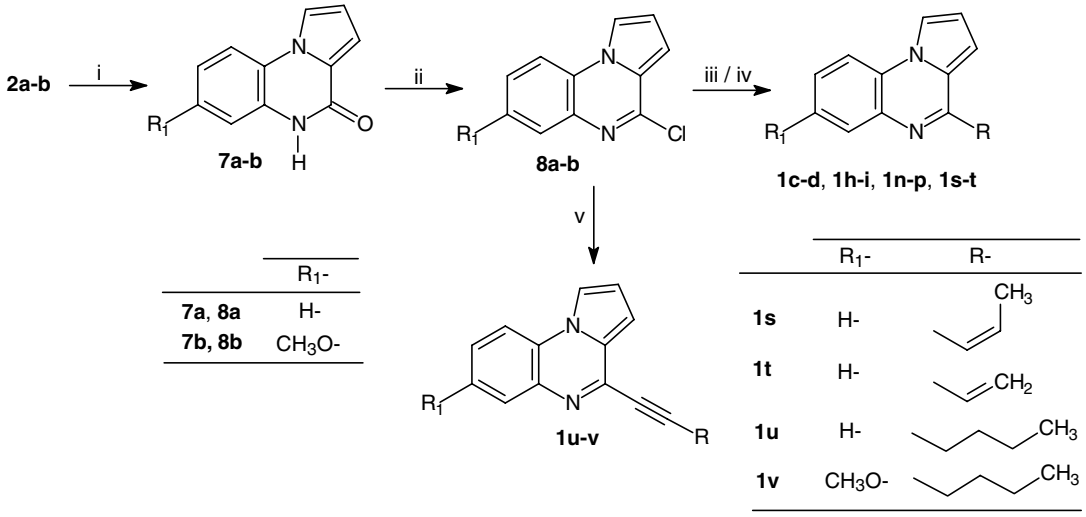
With respect to **1c**, the alkenyl chain replacement by a styryl one in compounds **1o**,**p** induced an activity loss, that is, IC_{50} = 35 and 36 μM for **1o**,**p**, respectively, whereas the increase of the carbon alkenyl chain length in **1h**–**j** gave slightly less potent compounds (IC_{50} =4–6 μM). If the alkenyl function is found in a restricted configuration as observed in the cyclohexenyl ring (**1m**), this compound was found inactive until 50 μM. On the other hand, the replacement of a pentenyl chain by an hexynyl one in compounds **1u**,**v** did not increase the antileishmanial activity for **1u** (IC_{50} = 18 μM), but is less detrimental for **1v**



Scheme 2. Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1o**,**p**. Reagents and conditions: (i) CH_3COCl, pyridine, dioxane, Δ; (ii) 1—$POCl_3$, toluene, Δ; 2—$NaHCO_3$, H_2O, rt; (iii) C_6H_5–CHO, Ac_2O, Δ.



Scheme 3. Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1c** and **1q**,**r**. Reagents and conditions: (i) SeO_2, dioxane, Δ; (ii) Et_3SBF_4, KOH, $MeCN/H_2O$; (iii) $Et(C_6H_5)_3PBr$, *t*-BuOK, toluene, 0 °C then Δ.



Scheme 4. Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1c**,**d**, **1h**,**i**, **1n**–**p**, **1s**,**t** and **1u**,**v**. Reagents and conditions: (i) $CO(OCCl_3)_2$, toluene, Δ; (ii) $POCl_3$, Δ; (iii) R–$B(OH)_2$, $Pd[P(C_6H_5)_3]_4$, Na_2CO_3, C_6H_6, Δ.; (iv) $H_2C{=}CH$–$B(O\text{-}n\text{-}Bu)_2$, KOH; $Pd[P(C_6H_5)_3]_4$, C_6H_6, Δ; (v) $PdCl_2[P(C_6H_5)_3]_2$, HC≡C–R, CuI, TEA, Δ.

Table 1. Physical properties of the final amines **1**

Compound	pK_a	log $D_{7.4}$	Salt[a]	Mp (°C) of the salts or bases	% yield
1a	9.19	3.35	HCl	132	91
1b	9.45	3.40	HCl	139	82
1c	9.59	3.44	HCl	170	89
1d	9.84	3.47	HCl	90	63
1e	9.72	3.48	HCl	156	77
1f	9.12	4.04	HCl	124	94
1g	9.37	4.38	HCl	101	68
1h	9.63	4.44	HCl	121	52
1i	9.88	4.52	HCl	155	56
1j	9.49	4.30	HCl	71	84
1k	9.25	3.84	HCl	157	92
1l	9.17	2.97	HCl	124	90
1m	9.08	4.12	HCl	88	85
1n	9.86	3.60	HCl	123	75
1o	9.51	4.84	HCl	157	70
1p	9.76	5.34	HCl	119	90
1q	10.98	2.61	—[b]	62	40
1r	10.98	2.55	—[b]	—	13
1s	9.47	3.30	—[b]	—	51
1t	9.52	3.08	HCl	>300	65
1u	9.28	4.36	HCl	91	80
1v	9.53	4.35	HCl	100	60
Chimanine B	4.67	2.23	HCl	129	89

[a] The 4-substituted pyrrolo[1,2-*a*]quinoxalines **1** were dissolved in 25 mL of Et_2O and treated with hydrochloric acid gas. The hydrochloride salts which precipitated were collected by filtration and were washed with Et_2O.
[b] Compound tested as a free base.

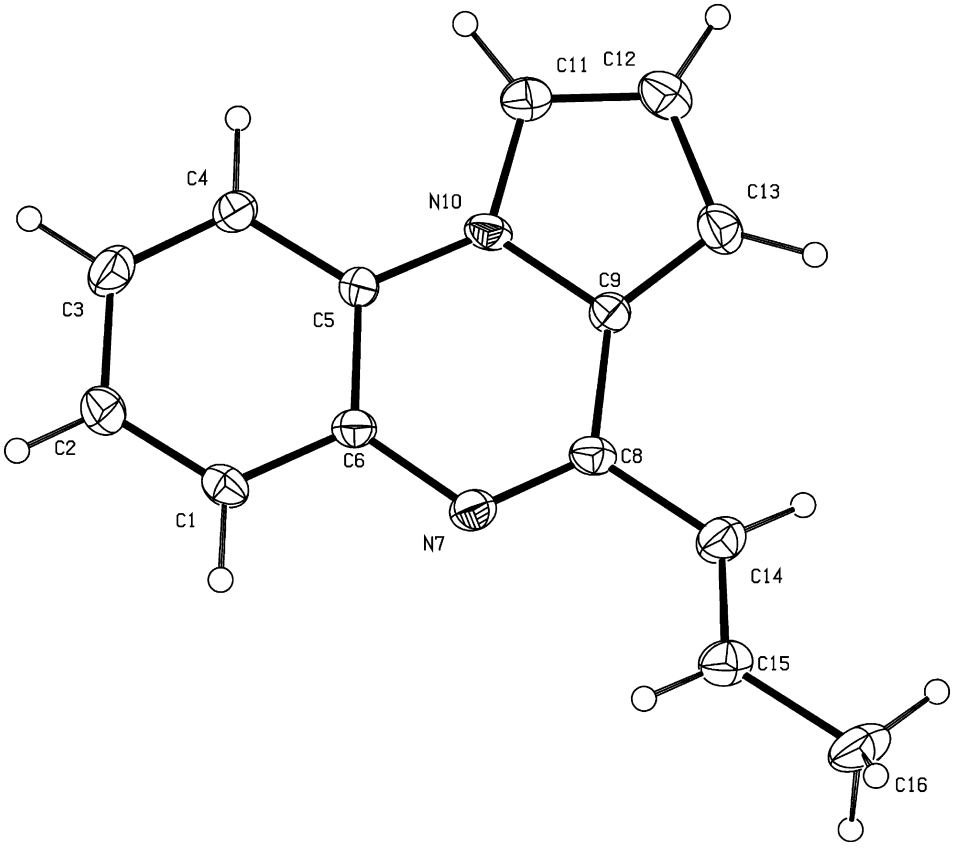


Figure 4. The ORTEP drawing of 4-[(*E*)-prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline **1c** with thermal ellipsoids at 30% level.

Table 2. In vitro sensitivity of *Leishmania amazonensis* and *L infantum* strains, and cytotoxicity on human peripheral blood mononuclear cells PNMC + PHA

Compound	IC_{50} values (μM)[a]				Index of selectivity[b]	
	Leishmania strains		Cytotoxicity on human peripheral blood mononuclear cells (PMNC)		*L. amazonensis*	*L. infantum*
	L. amazonensis promastigotes	*L. infantum* promastigotes	PMNC	PMNC + PHA		
Amphotericin B	1 ± 0.2	0.9 ± 0.1	>100	96 ± 10	96	106.6
Chimanine B	5 ± 1	7 ± 2	43 ± 3	42 ± 4	8.4	6
1a	>50	>50	>100	100 ± 6		
1b	>50	>50	>100	90 ± 10		
1c	0.5 ± 0.1	0.7 ± 0.1	6 ± 0.3	5 ± 0.4	10	7.1
1d	7 ± 1	2 ± 0.3	5 ± 1	5 ± 0.5	0.7	2.5
1e	1 ± 0.1	0.5 ± 0.1	7 ± 0.8	5 ± 0.3	5	10
1f	>50	>50	>100	30 ± 3	<1	<1
1g	>50	>50	66 ± 4	45 ± 5	<1	<1
1h	5 ± 0.2	7 ± 0.6	70 ± 12	52 ± 3	10.4	7.4
1i	6 ± 1	1 ± 0.1	60 ± 5	40 ± 4	6.7	40
1j	4 ± 0.2	2.5 ± 0.4	55 ± 5	30 ± 4	7.5	12
1k	7 ± 0.8	>50	>100	65 ± 5	9.3	
1l	30 ± 6	>50	>100	>100	>3.3	
1m	>50	>50	>100	>100		
1n	>50	>50	>100	>100		
1o	35 ± 10	>50	>100	>100	>2.9	
1p	36 ± 9	5 ± 0.6	>100	>100	>2.8	>20
1q	>50	>50	>100	>100		
1r	>50	>50	>100	>100		
1s	4 ± 0.3	0.8 ± 0.1	8 ± 0.9	6 ± 0.9	1.5	7.5
1t	3 ± 0.3	0.5 ± 0.1	3 ± 0.2	1 ± 0.2	0.3	2
1u	18 ± 6	25 ± 6	50 ± 6	25 ± 3	1.4	1
1v	3 ± 0.1	7 ± 1	6 ± 0.3	5 ± 0.3	1.7	0.7

[a] IC_{50} values were measured on the promastigotes of the *Leishmania amazonensis* (MHOM/BR/1987/BA) and *L. infantum* (clone MCAN/GR/82/LEM497) strains. The IC_{50} (μM) values correspond to means ± SD from three independent experiments.

[b] Index of selectivity (I.S.) was defined as the ratio between the IC_{50} value on the PMNC + PHA cells and the IC_{50} value against the *L. amazonensis* and *L. infantum* strain.

(3 μM). A total loss of activity was observed for compounds **1a**,**b** and **1f**,**g** possessing a three- or five-carbon saturated side chain (IC_{50} > 50 μM).

With the galipine as a model we designed then compounds **1k**,**l** with a phenethyl-substituted C-4 chain. Whereas the substituted 4-(3,4-dimethoxyphenylethyl) compound **1l** was found with a moderate activity (IC_{50} = 30 μM), surprisingly the 4-(3,4-methylenedioxyphenylethyl)pyrrolo[1,2-*a*]quinoxaline **1k** exhibited a potent anti*L. amazonensis* activity with a 7 μM IC_{50} value. Moreover, the *trans* epoxide **1q**, a structural analogue of chimanine D, was found inactive until 50 μM against *L. amazonensis*, as its *cis* epoxide homologue **1r**. Finally, compound **1n**, with a phenyl group in position 4, did not show any antileishmanial activity.

From a SAR point of view, these pharmacological results enlighten the importance of the nature of the 4-lateral chain on the pyrrolo[1,2-*a*]quinoxaline moiety, in our series. Hence, an α-unsaturated (*trans*- or *cis*-alkenyl or alkynyl) lateral chain induces a notable increase in the activity. On the other hand, the substitution at position 7 or 8 of the pyrrolo[1,2-*a*]quinoxaline heterocycle by one methoxy group is not crucial as illustrated by results for compounds **1b**, **1d**,**e**, **1g** and **1i**,**j** in comparison with those of their unsubstituted homologues (compounds **1a**, **1c**, **1f** and **1h**). Only the 7-methoxysubstituted 4-alkynyl derivative **1v** was more potent than its unsubstituted analogue **1u** (IC_{50} = 3 compared with 18 μM for **1u**).

A second evaluation was achieved against the promastigote forms of *L. infantum* in an experimental visceral leishmaniasis model, with chimanine B as the reference (Table 2). Compounds **1d**, **1h–j**, **1p** and **1v** showed almost the same level of activity with IC_{50} ranging from 1 to 7 μM. It must be noticed that four compounds **1c**, **1e**, **1s** and **1t** showed an IC_{50} < 1 μM, more potent than the reference (IC_{50} = 7 μM). Hence, the introduction of a methoxy substituent in position C-7 or C-8 of the 4-alkenyl or 4-alkynylpyrrolo[1,2-*a*]quinoxaline moiety resulted in the increase of the antileishmanial activity in comparison with their respective unsubstituted 4-alkenyl or 4-alkynylpyrrolo[1,2-*a*]quinoxaline homologues (i.e., **1e** compared to **1c**, **1i**,**j** to **1h**, **1p** to **1o** and **1v** to **1u**).

In summary, except for **1p** and **1k**, all compounds showed almost the same level of activity on *L. amazonensis* and on *L. infantum* promastigotes. The mechanism by which these new 4-substituted pyrrolo[1,2-*a*]quinoxalines are active against *Leishmania* parasites is unknown. Further pharmacological studies should now be investigated to determine the target of action.

2.3. Cytotoxicity

All compounds **1a**–**v** were tested on activated (PBMC + PHA) and not activated (PBMC) human peripheral blood mononuclear cells (Table 2). Not activated cells were considered as control measurements. As expected, most of the already inactive pyrrolo[1,2-*a*]quinoxalines showed a low cytotoxicity against monocytes (IC_{50} > 100 μM), whereas cytotoxicity was noticed for most active ones. However, among these last compounds, the most active (*E*)-propenylpyrroloquinoxaline **1c** on *L. amazonensis* strain exhibited a higher level of cytotoxicity against host cells (IC_{50} = 5 μM). Such an observation was also noticed for the active (*Z*)-propenyl and vinyl compounds **1s**,**t** (IC_{50} of 6 and 1 μM, respectively). Moreover, the (*E*)-propenylpyrrolo[1,2-*a*]quinoxalines **1d**,**e**, both substituted by a methoxy function in position 7 or 8, also showed high cytotoxicity (IC_{50} = 5 μM, both), while their (*E*)-pentenyl analogues **1i**,**j** displayed IC_{50} values of 40 and 30 μM, respectively. Otherwise, the unsubstituted pentenylpyrroloquinoxaline **1h** was also found less toxic than its methoxy substituted analogues **1i**,**j** (IC_{50} = 52 μM). Data also indicated that the introduction of hexynyl group in **1u**,**v** increased the toxicity (IC_{50} = 25 and 5 μM, respectively). The other different substitutions on the pyrrolo[1,2-*a*]quinoxaline moiety seem to have less influence on the PBMC + 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 led to the identification of compound **1p** with IS > 20 on *L. infantum*. On the other hand, the (*E*)-pentenylpyrrolo[1,2-*a*]quinoxalines **1h**–**j** are remarkable with IS = between 7 and 40, on both strains. These four molecules would constitute suitable pharmacophores for the design of new candidates in forthcoming pharmacological investigations.

2.4. Lipophilicity

The activity of an ionizable drug is determined by two major parameters: the partition coefficient log *P* between the aqueous and the lipid phases and its modification by the ionization constant pK_a of the drug. For partially ionized compounds, the partition coefficient between two phases at any fixed pH is called the distribution coefficient *D*, usually expressed as log *D*.[53] Here, for all new synthesized compounds, log *D* was determined by an HPLC method at pH 7.4, considered as the biological medium pH[54] and the acidity constant pK_a calculated using Pallas® program (Table 1).[55] This allowed us to calculate the partial ionization percentage according to the Henderson–Hasselbach equation[56] at pH 7.4, always found inferior than 2% except for chimanine B (>99%).

log *D* values were found between 2.23 for the reference chimanine B and 5.34 for **1p**. As expected the highest lipophilic pyrroloquinoxalines **1** (log *D* > 4.0) present a substituent in position 4 of the heterocyclic moiety that is either a 5- or 6-carbon atom chain (**1f**–**j** and **1u**,**v**) or a bulky group (**1l**–**p**).

A plot of antileishmanial IC_{50} versus log *D* values is presented in Figure 5, permitting to classify compounds in various subsets. The two more lipophilic (**1o**,**p**) and the three less lipophilic (**1r**, **1q** and **1l**) are almost inactive while the following **1t** and **1s** are active. log *D* values of compounds **1a**,**b** substituted by a three carbon saturated linear chain and of their homologues **1c**–**e** substituted by a three-carbon unsaturated chain are in the same range (3.35–3.48), but not their activity. The four compounds (**1n**, **1k**, **1f** and **1m**) with log *D* between 3.60 and 4.12 are inactive. An heterogeneous behaviour was found for compounds with log *D* between 4.30 and 4.52 as **1j**, **1v**, **1u**, **1h** and **1i** are active while **1g** is devoid of appreciable potency.

These results clearly indicated that the choice and the introduction of an α-unsaturation in position 4 of the pyrrolo[1,2-*a*]quinoxaline moiety correlated with a particular lipophilic behaviour seem to be fundamental

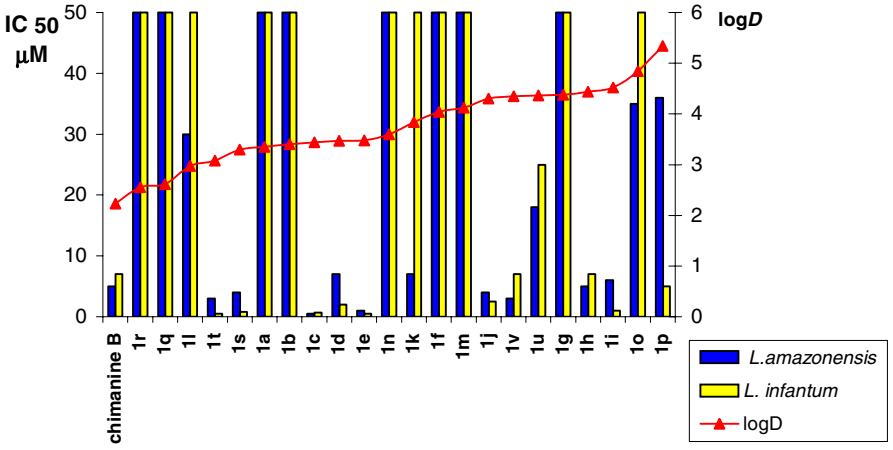


Figure 5. log *D*/activity relationship for pyrrolo[1,2-*a*]quinoxalines **1a**–**v**.

for the antileishmanial activity observed for this new series.

3. Conclusion

In conclusion, new 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives were designed as new structural analogues of *Galipea* species quinoline alkaloids. They were synthesized via Bischler-Napieralski, Perkin, Corey-Chaykovsky, Wittig, Suzuki or Sonogashira reactions, and tested for their *in vitro* antiparasitic activity on two strains: *L. amazonensis* and *L. infantum*. The use of the palladium-catalyzed Suzuki cross-coupling reactions enabled one to access easily to new substituted 4-alkenylpyrrolo[1,2-*a*]quinoxaline derivatives, more difficultly obtained through a classical 4-substituted pyrrolo[1,2-*a*]quinoxaline synthetic pathway.

The biological results obtained with chimanine B as the reference highlighted the crucial role of C-4 substitution introduced on the pyrrolo[1,2-*a*]quinoxaline nucleus, on the antileishmanial activity modulation. Hence, an α-unsaturated (*trans*- or *cis*-alkenyl or alkynyl) lateral chain induces a notable increase in the antiparasitic activity on both strains. On the other hand, the advantage of the substitution at position 7 or 8 of the pyrrolo[1,2-*a*]quinoxaline heterocycle by one methoxy group depends on the studied strain, that is, it is only beneficial for the visceral *L. infantum* strain.

The physico-chemical profile of new 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives was studied through log *D* HPLC determination achieved at physiological pH and pK_a calculation through an in silico methodology. These results have been discussed in terms of lipophilic behaviour for a preliminary SAR study. Although antiparasitic activity is generally related to the distribution of studied compounds to the intracellular target it was not possible to establish pertinent and definitive correlation. Nevertheless, it appeared that pyrrolo[1,2-*a*]quinoxalines endowed with lipophilic unsaturated carbon chain could open the way to new valuable antileishmanial chemistry scaffolding. This will be the target of further investigations.

4. Experimental

4.1. Chemistry

Commercial reagents were used as received without additional purification. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra were recorded on a BRUKER IFS-25 spectrophotometer. NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AVANCE 300 spectrometer (^{1}H, ^{13}C, 2D-COSY). Splitting patterns have been designated as follows: s, singlet; br s, broad singlet; d, doublet; dd, double doublet; qd, quadruple doublet; t, triplet; q, quartet; qt, quintuplet; sex, sextuplet; m, multiplet. 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 (C, H, N) for new compounds were performed by CNRS (Vernaison-France) and agreed with the proposed structures within ±0.3% of the theoretical values. Chimanine B was synthesized in analogy to described procedure.[45]

4.1.1. General procedure for 1-(2-alkanoyl- or 2-alkenoyl- or 2-benzoylaminophenyl)pyrrole (4a–n). To a solution of 1-(2-aminophenyl)pyrrole **2a**–**c** (0.02 mol) in dioxane (80 mL) were added pyridine (0.022 mol) then propanoyl chloride (0.02 mol). The reaction mixture was refluxed for 4 h and the solvent then removed under reduced pressure. The residue was triturated with water and extracted with diethyl ether (2 × 80 mL). The organic layers were collected, washed with an aqueous sodium hydrogen carbonate solution (100 mL) then with water (100 mL), dried over Na_2SO_4 and evaporated to dryness. The precipitate was crystallized from petroleum ether to afford **4a**–**n**.

4.1.1.1. 1-(2-Propanoylaminophenyl)pyrrole (4a). White crystals (60%); mp 48 °C; IR (KBr) 3200 (NH), 1650 (*C*═O); ^{1}H NMR ($CDCl_3$) δ: 8.38 (d, 1H, J = 7.75 Hz, H-3), 7.40 (t, 1H, J = 7.75 Hz, H-4), 7.32 (d, 1H, J = 7.75 Hz, H-6), 7.16 (t, 1H, J = 7.75 Hz, H-5), 6.94 (br s, 1H, NH), 6.76 (dd, 2H, J = 1.95 and 1.95 Hz, H-α), 6.39 (dd, 2H, J = 1.95 and 1.95 Hz, H-β), 2.17 (t, 2 H, J = 7.35 Hz, CH_2), 1.59 (sex, 2H, J = 7.35 Hz, CH_2), 0.92 (t, 3H, J = 7.35 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 171.2 (C═O), 133.9 (C-1), 130.5 (C-2), 128.7 (C-6), 126.7 (C-3), 123.9 (C-5), 121.9 (C-α), 121.4 (C-4), 110.4 (C-β), 39.7 (CH_2), 18.7 (CH_2), 13.6 (CH_3). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.69; H, 6.91; N, 12.36.

4.1.1.2. 1-(4-Methoxy-2-propanoylaminophenyl)pyrrole (4b). Pale-yellow crystals (78%); mp 51 °C; IR (KBr) 3240 (NH), 1655 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.10 (d, 1H, J = 2.75 Hz, H-3), 7.16 (d, 1H, J = 8.70 Hz, H-6), 6.89 (br s, 1H, NH), 6.71 (dd, 2H, J = 2.05 and 2.05 Hz, H-α), 6.65 (dd, 1H, J = 8.70 and 2.75 Hz, H-5), 6.36 (dd, 2H, J = 2.05 and 2.05 Hz, H-β), 3.84 (s, 3H, CH_3O), 2.16 (t, 2H, J = 7.35 Hz, CH_2), 1.60 (sex, 2H, J = 7.35 Hz, CH_2), 0.91 (t, 3H, J = 7.35 Hz, CH_3). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.65; H, 6.85; N, 10.98.

4.1.1.3. 1-(2-*trans*-Crotonylaminophenyl)pyrrole (4c). White crystals (59%); mp 58 °C; IR (KBr) 3240 (NH), 1655 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.47 (d, 1H, J = 8.25 Hz, H-3), 7.36 (t, 1H, J = 8.25 Hz, H-4), 7.25 (d, 1H, J = 8.25 Hz, H-6), 7.12 (t, 1H, J = 8.25 Hz, H-5), 6.99 (br s, 1H, NH), 6.89 (qd, 1H, J = 15.15 and 6.90 Hz, =CH), 6.81 (dd, 2H, J = 2.10 and 2.10 Hz, H-α), 6.39 (dd, 2H, J = 2.10 and 2.10 Hz, H-β), 5.70 (dd, 1H, J = 15.15 and 1.65 Hz, HC═), 1.84 (dd, 3H, J = 6.90 and 1.65 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 163.9 (CO), 141.8 (═CH), 134.1 (C-1), 130.7 (C-2), 128.8 (HC═), 126.9 (C-6), 125.6 (C-3), 124.1 (C-5),

122.1 (C-α), 121.6 (C-4), 110.6 (C-β), 17.9 (CH_3). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.38. Found: C, 74.41; H, 6.28; N, 12.47.

4.1.1.4. 1-[2-(*trans*-Crotonylamino)-4-methoxyphenyl]pyrrole (4d). White crystals (71%); mp 71 °C; IR (KBr) 3240 (NH), 1665 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.18 (d, 1H, J = 2.75 Hz, H-3), 7.16 (d, 1H, J = 8.70 Hz, H-6), 6.92 (br s, 1H, NH), 6.84 (qd, 1H, J = 15.15 and 6.85 Hz, ═CH), 6.72 (dd, 2H, J = 1.95 and 1.95 Hz, H-α), 6.65 (dd, 1H, J = 8.70 and 2.75 Hz, H-5), 6.38 (dd, 2H, J = 1.95 and 1.95 Hz, H-β), 5.65 (dd, 1H, J = 15.15 and 1.50 Hz, HC═), 3.84 (s, 3H, CH_3O), 1.83 (dd, 3H, J = 6.85 and 1.50 Hz, CH_3). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.23; H, 6.20; N, 10.99.

4.1.1.5. 1-[2-(*trans*-Crotonylamino)-5-methoxyphenyl]pyrrole (4e). Pale-yellow crystals (60%); mp 127 °C; IR (KBr) 3230 (NH), 1650 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.38 (d, 1H, J = 8.15 Hz, H-3), 6.94–6.76 (m, 6H, H-4, H-6, NH, ═CH and H-α), 6.37 (dd, 2H, J = 1.90 and 1.90 Hz, H-β), 5.71 (dd, 1H, J = 15.15 and 1.35 Hz, HC═), 3.79 (s, 3H, CH_3O), 1.84 (dd, 3H, J = 6.85 and 1.35 Hz, CH_3). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.36; H, 6.45; N, 11.14.

4.1.1.6. 1-(2-Hexanoylaminophenyl)pyrrole (4f). White crystals (71%); mp 40 °C; IR (KBr) 3220 (NH), 1645 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.37 (d, 1H, J = 7.70 Hz, H-3), 7.36 (t, 1H, J = 7.70 Hz, H-4), 7.25 (d, 1H, J = 7.70 Hz, H-6), 7.13 (t, 1H, J = 7.70 Hz, H-5), 7.00 (br s, 1H, NH), 6.77 (dd, 2H, J = 1.80 and 1.80 Hz, H-α), 6.38 (dd, 2H, J = 1.80 and 1.80 Hz, H-β), 2.19 (t, 2H, J = 7.00 Hz, CH_2), 1.57 (m, 4H, CH_2), 1.27 (m, 4H, CH_2), 0.87 (t, 3H, J = 7.00 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 172.1 (CO), 134.4 (C-1), 131.1 (C-2), 129.3 (C-6), 127.3 (C-3), 124.6 (C-5), 122.6 (C-α), 122.0 (C-4), 110.9 (C-β), 38.4 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 22.9 (CH_2), 14.5 (CH_3). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.06; H, 7.95; N, 11.12.

4.1.1.7. 1-(2-Hexanoylamino-4-methoxyphenyl)pyrrole (4g). Pale-yellow crystals (74%); mp 44 °C; IR (KBr) 3220 (NH), 1645 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.09 (d, 1H, J = 2.70 Hz, H-3), 7.16 (d, 1H, J = 8.65 Hz, H-6), 6.90 (s, 1H, NH), 6.71 (dd, 2H, J = 1.85 and 1.85 Hz, H-α), 6.64 (dd, 1H, J = 8.65 and 2.70 Hz, H-5), 6.36 (dd, 2H, J = 1.85 and 1.85 Hz, H-β), 3.83 (s, 3H, CH_3O), 2.15 (t, 2H, J = 6.80 Hz, CH_2), 1.55 (m, 2H, CH_2), 1.26 (m, 4H, CH_2), 0.86 (t, 3H, J = 6.80 Hz, CH_3). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.42; H, 7.96; N, 10.03.

4.1.1.8. 1-(2-*trans*-Hexenoylaminophenyl)pyrrole (4h). White crystals (72%); mp 46 °C; IR (KBr) 3210 (NH), 1640 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.48 (d, 1H, J = 7.75 Hz, H-3), 7.37 (t, 1H, J = 7.75 Hz, H-4), 7.26 (d, 1H, J = 7.75 Hz, H-6), 7.13 (t, 1H, J = 7.75 Hz, H-5), 7.01 (br s, 1H, NH), 6.83 (m, 1H, ═CH), 6.78 (dd, 2H, J = 2.15 and 2.15 Hz, H-α), 6.40 (dd, 2H, J = 2.15 and 2.15 Hz, H-β), 5.66 (dd, 1H, J = 15.45 and 1.15 Hz, HC═), 2.14 (m, 2H, CH_2), 1.45 (sex, 2H, J = 7.35 Hz, CH_2), 0.91 (t, 3 H, J = 7.35 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 163.9 (CO), 146.6 (═CH), 133.9 (C-1), 130.4 (C-2), 128.7 (C-6), 126.7 (HC═), 123.9 (C-3), 123.8 (C-5), 122.0 (C-α), 121.3 (C-4), 110.4 (C-β), 34.0 (CH_2), 21.4 (CH_2), 13.6 (CH_3). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.52; H, 7.21; N, 10.93.

4.1.1.9. 1-[2-(*trans*-Hexenoylamino)-4-methoxyphenyl]pyrrole (4i). Pale-yellow crystals (61%); mp 51 °C; IR (KBr) 3215 (NH), 1640 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.19 (d, 1H, J = 2.80 Hz, H-3), 7.16 (d, 1H, J = 8.65 Hz, H-6), 6.94 (br s, 1H, NH), 6.81 (m, 1H, ═CH), 6.73 (dd, 2H, J = 1.90 and 1.90 Hz, H-α), 6.68 (dd, 1H, J = 8.65 and 2.80 Hz, H-5), 6.37 (dd, 2H, J = 1.90 and 1.90 Hz, H-β), 5.63 (d, 1H, J = 15.25 Hz, HC═), 3.84 (s, 3H, CH_3O), 2.15 (m, 2H, CH_2), 1.44 (sex, 2H, J = 7.40 Hz, CH_2), 0.90 (t, 3H, J = 7.40 Hz, CH_3). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.84; H, 7.18; N, 9.77.

4.1.1.10. 1-[2-(*trans*-Hexenoylamino)-5-methoxyphenyl]pyrrole (4j). White crystals (60%); mp 82 °C; IR (KBr) 3200 (NH), 1645 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.28 (d, 1H, J = 8.75 Hz, H-3), 6.95 (m, 2H, H-4 and H-6), 6.87 (m, 2H, ═CH and NH), 6.83 (dd, 2H, J = 1.95 and 1.95 Hz, H-α), 6.40 (dd, 2H, J = 1.95 and 1.95 Hz, H-β), 5.71 (d, 1H, J = 15.25 Hz, HC═), 3.82 (s, 3H, CH_3O), 2.16 (m, 2H, CH_2), 1.47 (sex, 2H, J = 7.35 Hz, CH_2), 0.93 (t, 3H, J = 7.35 Hz, CH_3). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.95; H, 7.02; N, 9.97.

4.1.1.11. 1-[2-(3,4-Methylenedioxy)phenylethanoylaminophenyl]pyrrole (4k). White crystals (74%); mp 85 °C; IR (KBr) 3220 (NH), 1640 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.34 (d, 1H, J = 7.90 Hz, H-3), 7.38 (t, 1H, J = 7.90 Hz, H-4), 7.22 (d, 1H, J = 7.90 Hz, H-6), 7.13 (t, 1H, J = 7.90 Hz, H-5), 6.90 (br s, 1H, NH), 6.64 (m, 5H, H-2′, H-5′, H-6′ and H-α), 6.35 (dd, 2H, J = 2.00 and 2.00 Hz, H-β), 5.89 (s, 2H, OCH_2O), 2.86 (t, 2H, J = 7.45 Hz, CH_2), 2.45 (t, 2H, J = 7.45 Hz, CH_2). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.42; N, 8.38. Found: C, 72.02; H, 5.56; N, 8.52.

4.1.1.12. 1-[2-(3,4-Dimethoxy)phenylethanoylaminophenyl]pyrrole (4l). White crystals (63%); mp 91 °C; IR (KBr) 3210 (NH), 1645 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.35 (d, 1H, J = 7.85 Hz, H-3), 7.38 (t, 1H, J = 7.85 Hz, H-4), 7.24 (d, 1H, J = 7.85 Hz, H-6), 7.14 (t, 1H, J = 7.85 Hz, H-5), 6.89 (br s, 1H, NH), 6.75 (m, 2H, H-5′ and H-6′), 6.67 (d, 1H, J = 1.15 Hz, H-2′), 6.61 (dd, 2H, J = 1.90 and 1.90 Hz, H-α), 6.32 (dd, 2H, J = 1.90 and 1.90 Hz, H-β), 3.85 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 2.88 (t, 2H, J = 7.45 Hz, CH_2), 2.47 (t, 2H, J = 7.45 Hz, CH_2). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.11; H, 6.27; N, 8.21.

4.1.1.13. 1-[2-(Cyclohex-1-enecarbonyl)aminophenyl]pyrrole (4m). White crystals (79%); mp 119 °C; IR (KBr) 3210 (NH), 1645 (C=O); ^{1}H NMR ($CDCl_3$) δ: 8.55 (d, 1H, J = 7.85 Hz, H-3), 7.42 (t, 1H, J = 7.85 Hz, H-4), 7.33 (br s, 1H, NH), 7.31 (d, 1H, J = 7.85 Hz, H-6), 7.16 (t, 1H, J = 7.85 Hz, H-5), 6.81 (dd, 2H, J = 2.10 and 2.10 Hz, H-α), 6.60 (m, 1H, =CH), 6.43 (dd, 2H, J = 2.10 and 2.10 Hz, H-β), 2.17 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 1.69–1.56 (m, 4 H, CH_2). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.81; H, 6.82; N, 10.49.

4.1.1.14. 1-(2-Benzamidophenyl)pyrrole (4n). White crystals (71%).[32]

4.1.2. General procedure for 4-alkyl- or 4-alkenyl- or 4-arylpyrrolo[1,2-*a*]quinoxaline (1a–n). A solution of acetamide **4a**–**n** (0.02 mol) and phosphorous oxychloride (0.1 mol) in toluene (100 mL) was heated under reflux for 4 h. After cooling, the precipitate was filtered and dissolved in water (80 mL). The solution was then made alkaline with sodium hydrogen carbonate and extracted with methylene chloride (150 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/petroleum ether = 20:80) to give **1a**–**n**.

4.1.2.1. 4-Propylpyrrolo[1,2-*a*]quinoxaline (1a). White crystals (78%); mp 33 °C ; IR (KBr) 1620 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.89 (d, 1H, J = 7.95 Hz, H-9), 7.85 (dd, 1H, J = 2.60 and 1.25 Hz, H-1), 7.77 (d, 1H, J = 7.95 Hz, H-6), 7.41 (m, 2H, H-7 and H-8), 6.88 (dd, 1H, J = 3.90 and 1.25 Hz, H-3), 6.81 (dd, 1H, J = 3.90 and 2.60 Hz, H-2), 2.98 (t, 2H, J = 7.45 Hz, CH_2), 1.91 (sex, 2H, J = 7.45 Hz, CH_2), 1.07 (t, 3H, J = 7.45 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 157.9 (C-4), 136.6 (C-9a), 129.9 (C-5a), 127.8 (C-3a), 127.3 (C-8), 126.6 (C-7), 125.5 (C-6), 114.5 (C-9), 114.0 (C-1), 113.8 (C-3), 106.7 (C-2), 38.3 (CH_2), 22.4 (CH_2), 14.8 (CH_3). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.08; H, 6.73; N, 13.43.

4.1.2.2. 7-[(Methoxy-4-propylpyrrolo[1,2-*a*]quinoxaline (1b). Beige crystals (50%); mp 45 °C; IR (KBr) 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.82 (dd, 1H, J = 2.55 and 1.15 Hz, H-1), 7.71 (d, 1H, J = 8.95 Hz, H-9), 7.38 (d, 1H, J = 2.75 Hz, H-6), 7.06 (dd, 1H, J = 8.95 and 2.75 Hz, H-8), 6.86 (dd, 1H, J = 3.95 and 1.15 Hz, H-3), 6791 (dd, 1H, J = 3.95 and 2.55 Hz, H-2), 3.89 (s, 3H, CH_3O), 2.96 (t, 2 H, J = 7.40 Hz, CH_2), 1.89 (sex, 2H, J = 7.40 Hz, CH_2), 1.06 (t, 3H, J = 7.40 Hz, CH_3). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.06; H, 6.54; N, 11.78.

4.1.2.3. 4-[(*E*)-prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1c). Pale-yellow crystals (23%); mp 89 °C; IR (KBr) 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.98 (dd, 1H, J = 7.60 and 2.00 Hz, H-9), 7.94 (dd, 1 H, J = 2.70 and 1.15 Hz, H-1), 7.85 (dd, 1H, J = 7.60 and 2.00 Hz, H-6), 7.51–7.41 (m, 2H, H-7 and H-8), 7.25 (qd, 1H, J = 15.40 and 6.80 Hz, =CH), 7.01 (dd, 1H, J = 3.95 and 1.15 Hz, H-3), 6.89 (dd, 1H, J = 3.95 and 2.70 Hz, H-2), 6.88 (dd, 1H, J = 15.40 and 1.70 Hz, HC=), 2.08 (dd, 3H, J = 6.80 and 1.70 Hz, CH_3). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.80; H, 5.97; N, 13.54.

4.1.2.4. 7-Methoxy-4-[(*E*)-prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1d). *Method A:* yellow crystals (16%); mp 80 °C; IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.83 (dd, 1H, J = 2.55 and 1.15 Hz, H-1), 7.69 (d, 1H, J = 8.95 Hz, H-9), 7.38 (d, 1H, J = 2.75 Hz, H-6), 7.20 (qd, 1H, J = 15.35 and 6.75 Hz, =CH), 7.07 (dd, 1H, J = 8.95 and 2.75 Hz, H-8), 6.94 (dd, 1H, J = 3.90 and 1.15 Hz, H-3), 6.87 (dd, 1H, J = 15.35 and 1.55 Hz, HC=), 6.82 (dd, 1H, J = 3.90 and 2.55 Hz, H-2), 3.89 (s, 3H, CH_3O), 2.03 (dd, 3H, J = 6.75 and 1.55 Hz, CH_3). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.55; H, 6.08; N, 11.64.

4.1.2.5. 8-Methoxy-4-[(*E*)-prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1e). Yellow crystals (22%); mp 45 °C; IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.82 (d, 1H, J = 8.95 Hz, H-6), 7.78 (m, 1H, H-1), 7.19 (d, 1H, J = 2.40 Hz, H-9), 7.08 (qd, 1H, J = 16.50 and 6.70 Hz, =CH), 6.97 (dd, 1H, J = 8.95 and 2.40 Hz, H-7), 6.93 (m, 1H, H-3), 6.85 (m, 1H, H-2), 6.82 (dd, 1H, J = 16.50 and 1.25 Hz, HC=), 3.96 (s, 3H, CH_3O), 2.01 (dd, 3H, J = 6.70 and 1.25 Hz, CH_3). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.72; H, 6.03; N, 11.89.

4.1.2.6. 4-Pentylpyrrolo[1,2-*a*]quinoxaline (1f). Colorless oil (61%); IR (KBr) 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.90 (dd, 1H, J = 7.90 Hz, H-9), 7.81 (dd, 1H, J = 2.65 and 1.10 Hz, H-1), 7.72 (d, 1H, J = 7.90 Hz, H-6), 7.38 (m, 2H, H-7 and H-8), 6.86 (dd, 1H, J = 3.90 and 1.10 Hz, H-3), 6.78 (dd, 1H, J = 3.90 and 2.65 Hz, H-2), 2.98 (t, 2H, J = 7.00 Hz, CH_2), 1.89 (m, 2H, CH_2), 1.44 (m, 4H, CH_2), 0.90 (t, 3H, J = 7.00 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ: 158.1 (C-4), 136.5 (C-9a), 129.9 (C-5a), 127.8 (C-3a), 127.3 (C-8), 126.5 (C-7), 125.5 (C-6), 114.6 (C-9), 114.1 (C-1), 113.9 (C-3), 106.7 (C-2), 36.5 (CH_2), 32.6 (CH_2), 28.9 (CH_2), 23.1 (CH_2), 14.6 (CH_3). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.57; H, 7.72; N, 11.82.

4.1.2.7. 7-Methoxy-4-pentylpyrrolo[1,2-*a*]quinoxaline (1g). Yellow oil (93%); IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.75 (m, 1H, H-1), 7.64 (d, 1H, J = 8.90 Hz, H-9), 7.36 (d, 1H, J = 1.70 Hz, H-6), 7.01 (dd, 1H, J = 8.90 and 1.70 Hz, H-8), 6.83 (m, 1H, H-3), 6.76 (m, 1H, H-2), 3.86 (s, 3H, CH_3O), 2.96 (t, 2H, J = 7.15 Hz, CH_2), 1.87 (m, 2H, CH_2), 1.40 (m, 4H, CH_2), 0.89 (t, 3H, J = 7.15 Hz, CH_3). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.89; H, 7.42; N, 10.38.

4.1.2.8. 4-[(*E*)-Pent-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1h). Yellow oil (54%); IR (KBr) 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.92 (dd, 1H, J = 7.85 and 2.05 Hz, H-9), 7.84 (dd, 1H, J = 2.85 and 1.20 Hz, H-1), 7.73 (dd, 1H, J = 7.85 and 2.05 Hz, H-6), 7.37 (m, 2H, H-7 and H-8), 7.21 (m, 1H, =CH), 6.97 (dd, 1H, J = 4.00

and 1.20 Hz, H-3), 6.85 (dd, 1H, J = 4.00 and 2.85 Hz, H-2), 6.83 (dd, 1H, J = 15.40 and 1.25 Hz, HC═), 2.37 (m, 2H, CH_2), 1.63 (sex, 2H, J = 7.30 Hz, CH_2), 1.01 (t, 3H, J = 7.30 Hz, CH_3). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.86. Found: C, 81.29; H, 6.98; N, 11.85.

4.1.2.9. 7-Methoxy-4-[(*E*)-pent-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1i). Yellow oil (37%); IR (KBr) 1610 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.84 (dd, 1H, J = 2.90 and 1.25 Hz, H-1), 7.71 (d, 1H, J = 8.95 Hz, H-9), 7.40 (d, 1H, J = 2.80 Hz, H-6), 7.15 (m, 1H, ═CH), 7.06 (dd, 1H, J = 8.95 and 2.80 Hz, H-8), 6.97 (dd, 1H, J = 3.90 and 1.25 Hz, H-3), 6.83 (dd, 1H, J = 3.90 and 2.90 Hz, H-2), 6.77 (dd, 1H, J = 15.30 and 1.15 Hz, HC═), 3.90 (s, 3H, CH_3O), 2.36 (m, 2H, CH_2), 1.62 (sex, 2H, J = 7.35 Hz, CH_2), 0.97 (t, 3H, J = 7.35 Hz, CH_3). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.51; H, 6.75; N, 10.56.

4.1.2.10. 8-Methoxy-4-[(*E*)-pent-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1j). Yellow oil (26%); IR (KBr) 1610 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.88 (d, 1H, J = 8.95 Hz, H-6), 7.82 (dd, 1H, J = 2.75 and 1.30 Hz, H-1), 7.24 (d, 1H, J = 2.65 Hz, H-9), 7.15 (ddd, 1H, J = 15.60 and 6.95 Hz, =CH), 7.03 (dd, 1H, J = 8.95 and 2.65 Hz, H-7), 6.98 (dd, 1H, J = 4.00 and 1.30 Hz, H-3), 6.87 (dd, 1H, J = 4.00 and 2.75 Hz, H-2), 6.82 (ddd, 1H, J = 15.60 and 1.50 Hz, HC═), 3.95 (s, 3H, CH_3O), 2.38 (m, 2H, CH_2), 1.63 (sex, 2H, J = 7.40 Hz, CH_2), 1.04 (t, 3H, J = 7.40 Hz, CH_3). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.44; H, 6.73; N, 10.68.

4.1.2.11. 4-(3,4-Methylenedioxyphenethyl)pyrrolo[1,2-*a*]quinoxaline (1k). White crystals (77%); mp 69 °C; IR (KBr) 1615 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.94 (d, 1H, J = 8.00 Hz, H-9), 7.88 (m, 1H, H-1), 7.82 (d, 1H, J = 8.00 Hz, H-6), 7.43 (m, 2H, H-7 and H-8), 6.87–6.74 (m, 5H, H-2, H-3, H-2′, H-5′ and H-6′), 5.90 (s, 2H, OCH_2O), 3.28 (m, 2H, CH_2), 3.15 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 156.2 (C-4), 147.8 (C-3′), 145.9 (C-4′), 135.7 (C-1′), 129.7 (C-9a), 127.4 (C-5a), 127.1 (C-3a), 126.1 (C-8), 125.2 (C-7), 121.4 (C-6′), 114.3 (C-9), 113.8 (C-6), 113.6 (C-3), 109.1 (C-1), 108.4 (C-5′), 106.2 (C-2 and C-2′), 100.9 (OCH_2O), 37.8 (CH_2), 33.9 (CH_2). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 76.11; H, 5.13; N, 8.74.

4.1.2.12. 4-(3,4-Dimethoxyphenethyl)pyrrolo[1,2-*a*]-quinoxaline (1l). White crystals (70%); mp 174 °C; IR (KBr) 1615 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.89 (d, 1H, J = 7.90 Hz, H-9), 7.83 (dd, 1H, J = 2.65 and 1.15 Hz, H-1), 7.78 (d, 1H, J = 7.90 Hz, H-6), 7.43 (m, 2H, H-7 and H-8), 6.88–6.81 (m, 5H, H-2, H-3, H-2′, H-5′ and H-6′), 3.84 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 3.30 (m, 2H, CH_2), 3.17 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ: 156.2 (C-4), 148.9 (C-3′), 147.4 (C-4′), 135.9 (C-1′), 134.4 (C-9a), 129.4 (C-5a), 127.2 (C-3a), 126.9 (C-8), 125.7 (C-7), 125.1 (C-6′), 120.2 (C-6), 114.2 (C-9), 113.6 (C-3), 113.5 (C-1), 112.0 (C-2′), 111.4 (C-5′), 106.1 (C-2), 55.9 (CH_3O), 55.8 (CH_3O), 37.7 (CH_2), 33.7 (CH_2). Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 76.07; H, 6.30; N, 8.57.

4.1.2.13. 4-(Cyclohex-1-enyl)pyrrolo[1,2-*a*]quinoxaline (1m). Yellow oil (48%); IR (KBr) 1615 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.96 (d, 1H, J = 8.00 Hz, H-9), 7.93 (dd, 1H, J = 2.75 and 1.30 Hz, H-1), 7.82 (d, 1H, J = 8.00 Hz, H-6), 7.47 (t, 1H, J = 8.00 Hz, H-8), 7.42 (t, 1H, J = 8.00 Hz, H-7), 6.98 (dd, 1H, J = 4.00 and 1.30 Hz, H-3), 6.85 (dd, 1H, J = 4.00 and 2.75 Hz, H-2), 6.59 (m, 1H, ═CH), 2.69 (m, 2H, CH_2), 2.33 (m, 2H, CH_2), 1.93–1.77 (m, 4H, CH_2). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.10; H, 6.45; N, 11.13.

4.1.2.14. 4-Phenylpyrrolo[1,2-*a*]quinoxaline (1n). White crystals (53%).[34]

4.1.3. General procedure for 1-(2-acetylaminophenyl)pyrrole (5a,b). To a solution of 1-(2-aminophenyl)pyrrole **2a**,**b** (0.02 mol) in dioxane (80 mL) were added pyridine (0.022 mol) then acetyl chloride (0.02 mol). The reaction mixture was refluxed for 4 h and the solvent then removed under reduced pressure. The residue was triturated with water and extracted with diethyl ether (2× 80 mL) The organic layers were collected, washed with an aqueous sodium hydrogen carbonate solution (100 mL) then with water (100 mL), dried over Na_2SO_4 and evaporated to dryness. The precipitate was crystallized from petroleum ether to afford **5a**,**b**.

4.1.3.1. 1-(2-Acetylaminophenyl)pyrrole (5a). White crystals (67%).[34]

4.1.3.2. 1-(2-Acetylamino-4-methoxyphenyl)pyrrole (5b). Pale-yellow crystals (62%); mp 73 °C; IR (KBr) 3200 (NH), 1650 (C═O); ^{1}H NMR ($CDCl_3$) δ: 8.04 (d, 1H, J = 2.50 Hz, H-3), 7.15 (d, 1H, J = 8.55 Hz, H-6), 6.90 (s, 1H, NH), 6.72 (dd, 2H, J = 1.95 and 1.95 Hz, H-α), 6.64 (dd, 1H, J = 8.55 and 2.50 Hz, H-5), 6.35 (dd, 2H, J = 1.95 and 1.95 Hz, H-β), 3.83 (s, 3H, CH_3O), 2.00 (s, 3H, CH_3). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.75; H, 6.03; N, 12.22.

4.1.4. General procedure for 4-methylpyrrolo[1,2-*a*]quinoxaline (6a,b). A solution of 1-(2-propanoylaminophenyl)pyrrole **5a**,**b** (0.02 mol) and phosphorous oxychloride (0.1 mol) in toluene (100 mL) was heated under reflux for 4 h. After cooling, the precipitate was filtered and dissolved in water (80 mL). The solution was then made alkaline with sodium hydrogen carbonate and extracted with methylene chloride (150 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give **6a**,**b**.

4.1.4.1. 4-Methylpyrrolo[1,2-*a*]quinoxaline (6a). White crystals (67%).[34]

4.1.4.2. 7-Methoxy-4-methylpyrrolo[1,2-*a*]quinoxaline (6b). Pale-orange crystals (58%); mp 50 °C; IR (KBr) 1620 (C═N); ^{1}H NMR ($CDCl_3$) δ: 7.82 (dd, 1H,

J = 2.75 and 1.15 Hz, H-1), 7.71 (d, 1H, J = 8.95 Hz, H-9), 7.37 (d, 1H, J = 2.75 Hz, H-6), 7.07 (dd, 1H, J = 8.95 and 2.75 Hz, H-8), 6.85 (dd, 1H, J = 3.90 and 1.15 Hz, H-3), 6.80 (dd, 1H, J = 3.90 and 2.75 Hz, H-2), 3.89 (s, 3H, CH_3O), 2.70 (s, 3H, CH_3). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.65; H, 5.78; N, 13.15.

4.1.5. General procedure for 4-styrylpyrrolo[1,2-*a*]quinoxaline (1o,p). 4-Methylpyrrolo[1,2-*a*]quinoxaline **6a**,**b** (3.3 mmol), benzaldehyde (3.3 mmol) and Ac_2O (5 mL) were refluxed for 5 h. The solvent was then evaporated under reduced pressure. The residue was triturated in water and extracted with dichloromethane. The organic layer was washed with an aqueous saturated sodium hydrogen carbonate solution, dried over Na_2SO_4 and evaporated and then chromatographed over Si gel. Elution with hexane/AcOEt (8:2) afforded the pure compound **1o**,**p**.

4.1.5.1. 4-Styrylpyrrolo[1,2-*a*]quinoxaline (1o). Yellow crystals (41%).[34]

4.1.5.2. 7-Methoxy-4-styrylpyrrolo[1,2-*a*]quinoxaline (1p). Pale-yellow crystals (30%); mp 156 °C; IR (KBr) 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ: 8.04 (d, 1H, J = 15.95 Hz, HC=), 7.86 (dd, 1H, J = 2.65 and 1.25 Hz, H-1), 7.73 (d, 1H, J = 9.15 Hz, H-9), 7.66 (m, 2H, Ar′-H), 7.49 (d, 1H, J = 15.95 Hz, =CH), 7.44 (d, 1H, J = 2.65 Hz, H-6), 7.39 (m, 3H, Ar′-H), 7.07 (m, 2H, H-8 and H-3), 6.87 (dd, 1H, J = 3.90 and 2.65 Hz, H-2), 3.92 (s, 3H, CH_3O). Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.33. Found: C, 80.13; H, 5.27; N, 9.36.

4.1.6. [Pyrrolo [1,2-*a*]quinoxaline-4-carboxaldehyde (7). 4-Methylpyrrolo[1,2-*a*]quinoxaline **6a** (2.3 mmol) and SeO_2 (3.45 mmol) were stirred in dioxane (10 mL) under reflux for 4 h. After cooling and filtration, the solution was concentrated and the residue was purified on silica gel. Elution with CH_2Cl_2 gave **7** as orange crystals (59%); mp 162 °C; IR (KBr) 1680 (C=O); ^{1}H NMR ($CDCl_3$) δ: 10.12 (s, 1H, CHO), 8.13 (d, 1H, J = 8.05 Hz, H-9), 8.02 (dd, 1H, J = 2.75 and 1.20 Hz, H-1), 7.92 (d, 1H, J = 8.05 Hz, H-6), 7.69 (dd, 1H, J = 4.05 and 1.20 Hz, H-3), 7.67 (t, 1H, J = 8.05 Hz, H-8), 7.54 (t, 1H, J = 8.05 Hz, H-7), 7.03 (dd, 1H, J = 4.05 and 2.75 Hz, H-2). Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.54; H, 4.31; N, 14.39.

4.1.7. 4-[(*E*)-Prop-1-enyl]pyrrolo[1,2-*a*] quinoxaline (1c). Method B: To a suspension of ethyltriphenylphosphonium bromide (2.44 mmol) in 6 mL of anhydrous toluene at 0 °C was added potassium *tert*-butoxide (2.94 mmol). After 20 min of stirring at 0 °C, a solution of aldehyde **7** (1.22 mmol) in 8 mL of anhydrous tetrahydrofuran was added to the reaction mixture. The mixture reaction was then heated at 70 °C for 1.5 h. After cooling, the mixture was hydrolysed by adding 7 mL of water. The aqueous layer was then extracted with AcOEt, the resultant organic extracts were washed with an aqueous saturated sodium hydrogen carbonate, then with a brine solution, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel with dichloromethane/hexane (4:1) as eluent to give **1c** as yellow crystals (29%). IR and ^{1}H NMR data were in accordance with those of Method A.

4.1.8. General procedure for trans-4-(2-methyloxirane)pyrrolo[1,2-*a*]quinoxaline (1q) and *cis*-4-(2-methyloxirane)pyrrolo[1,2-*a*]quinoxaline (1r). A mixture of triethylsulfonium tetrafluoroborate (2.24 mmol), potassium hydroxide pellets (15.7 mmol), 8 mL of acetonitrile and 0.1 mL of water was warmed at 60 °C for 15 min in the absence of light. A solution of pyrrolo[1,2-*a*]quinoxaline-4-carboxaldehyde **7** (2.24 mmol) in 8 mL of acetonitrile was then added dropwise and the mixture was stirred at 60 °C for 2 h. The mixture was filtered and the solid was extracted with acetonitrile then with dichloromethane. The organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel with hexane/AcOEt (8:2) as eluent. The first eluted product (R_f = 0.38) was the *trans* epoxide **1q**, followed by the *cis* epoxide **1r** (R_f = 0.20).

4.1.8.1. *Trans*-4-(2-methyloxirane)pyrrolo[1,2-a]quinoxaline (1q). Yellow crystals (40%); mp 62 °C; IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.93 (d, 1H, J = 7.85 Hz, H-9), 7.89 (dd, 1H, J = 2.55 and 1.30 Hz, H-1), 7.78 (d, 1H, J = 7.85 Hz, H-6), 7.47 (t, 1H, J = 7.85 Hz, H-8), 7.39 (t, 1H, J = 7.85 Hz, H-7), 7.12 (dd, 1H, J = 3.90 and 1.30 Hz, H-3), 6.83 (dd, 1H, J = 3.90 and 2.55 Hz, H-2), 3.99 (d, 1H, J = 2.00 Hz, H-1′), 3.59 (qd, 1H, J = 5.15 and 2.00 Hz, H-2′), 1.54 (d, 3H, J = 5.15 Hz, CH_3). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.15; H, 5.56; N, 12.50.

4.1.8.2. *Cis*-4-(2-methyloxirane)pyrrolo[1,2-*a*]quinoxaline (1r). Yellow oil (13%); IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 8.01 (d, 1H, J = 7.80 Hz, H-9), 7.94 (dd, 1H, J = 2.65 and 1.10 Hz, H-1), 7.83 (d, 1H, J = 7.80 Hz, H-6), 7.50 (t, 1H, J = 7.80 Hz, H-8), 7.41 (t, 1H, J = 7.80 Hz, H-7), 7.15 (dd, 1H, J = 4.00 and 1.10 Hz, H-3), 6.86 (dd, 1H, J = 4.00 and 2.65 Hz, H-2), 4.33 (d, 1H, J = 4.35 Hz, H-1′), 3.54 (qd, 1H, J = 5.30 and 4.35 Hz, H-2′), 1.25 (d, 3H, J = 5.30 Hz, CH_3). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.06; H, 5.21; N, 12.38.

4.1.9. General procedure for 4-alkenyl- or 4-arylpyrrolo [1,2-*a*]quinoxaline (1c,d), (1h,i), (1n–p), and (1s). Method C: A mixture of the 4-chloropyrrolo[1,2-*a*]quinoxaline **8a**[34] or **8b**[36] (5 mmol), the alkenylboronic acid (5.5 mmol) and $Pd(PPh_3)_4$ (0.15 mmol) in benzene (21 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 **1c**,**d**, **1h**,**i**, **1n**–**p**, or **1s**.

4.1.9.1. 4-[(*E*)-Prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1c). Pale-yellow crystals (77%); IR and ^{1}H NMR data were in accordance with those of Methods A and B.

4.1.9.2. 7-Methoxy-4-[(*E*)-prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1d). Yellow crystals (65%); IR and ^{1}H NMR data were in accordance with those of Method A.

4.1.9.3. 4-[(*E*)-Pent-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1h). Yellow crystals (61%); IR and ^{1}H NMR data were in accordance with those of Method A.

4.1.9.4. 7-Methoxy-4-[(*E*)-pent-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1i). Yellow crystals (56%); IR and ^{1}H NMR data were in accordance with those of Method A.

4.1.9.5. 4-Phenylpyrrolo[1,2-*a*]quinoxaline (1n). White crystals (85%); IR and ^{1}H NMR data were in accordance with those of Method A.[34]

4.1.9.6. 4-Styrylpyrrolo[1,2-*a*]quinoxaline (1o). Yellow crystals (86%); IR and ^{1}H NMR data were in accordance with those described above.

4.1.9.7. 7-Methoxy-4-styrylpyrrolo[1,2-*a*]quinoxaline (1p). Yellow crystals (75%); IR and ^{1}H NMR data were in accordance with those described above.

4.1.9.8. 4-[(*Z*)-Prop-1-enyl]pyrrolo[1,2-*a*]quinoxaline (1s). Yellow oil (51%); IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.99 (dd, 1H, J = 7.90 and 1.65 Hz, H-9), 7.92 (dd, 1H, J = 2.65 and 1.35 Hz, H-1), 7.84 (dd, 1H, J = 7.90 and 1.65 Hz, H-6), 7.49 (ddd, 1H, J = 7.90, 7.25 and 1.65 Hz, H-8), 7.43 (ddd, 1H, J = 7.90, 7.25 and 1.65 Hz, H-7), 6.89 (dd, 1H, J = 3.95 and 1.35 Hz, H-3), 6.86 (dd, 1H, J = 3.95 and 2.65 Hz, H-2), 6.77 (qd, 1H, J = 11.65 and 1.80 Hz, HC=), 6.30 (qd, 1H, J = 11.65 and 7.20 Hz, =CH), 2.26 (dd, 3H, J = 7.20 and 1.80 Hz, CH_3). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.60; H, 5.94; N, 13.59.

4.1.10. 4-(Eth-1-enyl)pyrrolo[1,2-*a*]quinoxaline (1t). A mixture of the 4-chloropyrrolo[1,2-*a*]quinoxaline **8a** (3.4 mmol), the vinylboronic acid di-*n*-butyl 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, 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 **1t** as yellow crystals (30%); mp 76 °C; IR (KBr) 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ: 7.99 (d, 1H, J = 8.05 Hz, H-9), 7.96 (dd, 1H, J = 2.75 and 1.20 Hz, H-1), 7.86 (d, 1H, J = 8.05 Hz, H-6), 7.51 (t, 1H, J = 8.05 Hz, H-8), 7.45 (t, 1H, J = 8.05 Hz, H-7), 7.18 (dd, 1H, J = 17.30 and 10.85 Hz, HC=), 7.04 (dd, 1H, J = 4.05 and 1.20 Hz, H-3), 6.91 (dd, 1H, J = 4.05 and 2.75 Hz, H-2), 6.65 (dd, 1H, J = 17.30 and 1.65 Hz, =CH_2), 5.79 (dd, 1H, J = 10.85 and 1.65 Hz, =CH_2). Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.31; H, 5.34; N, 14.49.

4.1.11. General procedure for 4-(hex-1-ynyl)pyrrolo[1,2-*a*]quinoxaline (1u,v). A mixture of CuI (0.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol), anhydrous triethylamine (10 mL), 4-chloropyrrolo[1,2-*a*]quinoxaline **8a**,**b** (2.5 mmol) and 1-hexyne (3.75 mmol) was stirred and heated at 80 °C for 24 h. The reaction mixture was cooled to rt and filtered. The solid residue was washed thoroughly with hexane, combined filtrates were evaporated under reduced pressure, and the residue was purified over a column of silica gel with hexane/AcOEt (10:1) as eluent to give **1u**,**v**.

4.1.11.1. 4-(Hex-1-ynyl)pyrrolo[1,2-*a*]quinoxaline (1u). Yellow oil (29%); IR (KBr) 2210 (C≡C); ^{1}H NMR ($CDCl_3$) δ: 7.93 (d, 1H, J = 8.00 Hz, H-9), 7.89 (dd, 1H, J = 2.70 and 1.20 Hz, H-1), 7.80 (d, 1H, J = 8.00 Hz, H-6), 7.48 (t, 1H, J = 8.00 Hz, H-8), 7.41 (t, 1H, J = 8.00 Hz, H-7), 7.00 (dd, 1H, J = 3.95 and 1.20 Hz, H-3), 6.86 (dd, 1H, J = 3.95 and 2.70 Hz, H-2), 2.55 (t, 2H, J = 7.10 Hz, CH_2), 1.69 (qt, 2H, J = 7.10 Hz, CH_2), 1.52 (sex, 2H, J = 7.10 Hz, CH_2), 0.96 (t, 2H, J = 7.10 Hz, CH_3). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.36; H, 6.34; N, 11.35.

4.1.11.2. 4-(Hex-1-ynyl)-7-methoxypyrrolo[1,2-*a*]quinoxaline (1v). Yellow oil (42%) ; IR (KBr) 2210 (C≡C); ^{1}H NMR ($CDCl_3$) δ: 7.85 (dd, 1H, J = 2.65 and 1.35 Hz, H-1), 7.76 (d, 1H, J = 9.00 Hz, H-9), 7.45 (d, 1H, J = 2.80 Hz, H-6), 7.13 (dd, 1H, J = 9.00 and 2.80 Hz, H-8), 7.02 (dd, 1H, J = 4.00 and 1.35 Hz, H-3), 6.87 (dd, 1H, J = 4.00 and 2.65 Hz, H-2), 3.91 (s, 3H, CH_3O), 2.59 (t, 2H, J = 7.15 Hz, CH_2), 1.73 (qt, 2H, J = 7.15 Hz, CH_2), 1.59 (sex, 2H, J = 7.15 Hz, CH_2), 1.00 (t, 3H, J = 7.15 Hz, CH_3). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.75; H, 6.44; N, 9.86.

4.2. X-ray data

Pale-yellow single crystal ($0.15 \times 0.01 \times 0.01$ mm^3) of **1c** was obtained by slow evaporation from methanol/chloroform (20:80) solution: orthorhombic, space group P n a 21, a = 13.079(6) Å, b = 19.592(9) Å, c = 4.289(4) Å, α = 90°, β = 90°, γ = 90°, V = 1099.08(12) Å^3, Z = 4, δ(calcd) = 1.259 Mg m^{-3}, FW = 208.26 for $C_{14}H_{12}N_2$, F(000) = 440. The unit cell dimensions were determined using the least-squares fit from 25 reflections ($25° < \theta < 35°$). Intensities were collected with an En-

raf-Nonius CAD-4 diffactometer using the CuKα radiation and a graphite monochromator up to $\theta = 55°$. No intensity variation of two standard reflections monitored every 90 min was observed. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC-297422), UK, as Supplementary material.[57] The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[58] The structure was solved by direct methods Shelx 86 [59] and refined using Shelx 93[60] suite of programs.

4.3. Partition coefficients log *D* (pH 7.4)

The relative log *D* (pH 7.4) in this study was assessed by the micro-HPLC method.[61] These 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 ($203 \text{ nm} \leqslant \lambda_{max} \leqslant 253$ nm) and a ChromJet data module integrator (ThermoFinnigan, San Jose, USA). A reversed phase column was used: a Waters SunFire™ C_{18} (3.0×150 mm; 5 μm particle size) with a mobile phase consisting of acetonitrile – phosphate buffer (pH 4.5) (65:35, v/v (**1g**, **1i**–**m**, **1o**,**p** and **1u**,**v**); 60:40, v/v (**1f**, **1h**, **1n**, **1s**, and chimanine B); 55:45, v/v (**1e**); 50:50, v/v (**1a**–**d**); 40:60, v/v (**1q**,**r**). The compounds were partitioned between 1-octanol (HPLC grade) and phosphate buffer (pH 7.4). Octanol was presaturated 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 100 μg/mL. Under the above-described chromatographic conditions, 100 μL of this aqueous phase was injected into the chromatograph, leading to the determination of a peak area before partitioning (W_0). In screw-capped tubes, 2000 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. Then the centrifugation was achieved at 3000 rpm in 15 min. An amount of 100 μL of the lower phase was injected into the chromatograph column. This led to the determination of a peak area after partitioning (W_1). The log *D* value was determined by the formula: $\log D = \log [(W_0 - W_1)V_{aq}/W_1 V_{oct}]$.

4.4. Biological assays

4.4.1. In vitro *L. amazonensis* and *L. infantum* culture and drug assays.[62,63] 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 foetal calf serum (FCS), 200 U/ml penicillin, 100 μg/ml streptomycin, sodium bicarbonate end non-essential amino acids (all from Gibco, Paisley, UK). At stationary growth phase parasites (10^6/ml) were harvested, washed and incubated in culture media with various molecules. The viability of promastigotes was checked using the tetrazolium-dye (MTT) colorimetric method (Promega, USA). The MTT cell proliferation assay is a colorimetric assay system, which measures the reduction of a tetrazolium component (MTT) into an insoluble formazan product by the mitochondria of viable cells. After incubation of the cells with the MTT reagent, a detergent solution was added to lyse the cells and solubilize the coloured crystals. The samples were read using an ELISA plate reader at a wavelength of 570 nm. The amount of colour produced was directly proportional to the number of viable cells. In some experiments, parasites were diluted in culture medium and directly counted under microscope. Each concentration was screened in triplicate. The results are expressed as the concentrations inhibiting parasite growth by 50% (IC_{50}) after a 1–2 day incubation period.

4.4.2. Cytotoxicity test upon cells.[64] The toxicity of various molecules was evaluated on non-activated, freshly isolated normal human peripheral blood mononuclear cells (PBMC), as well as phytohaemagglutinin (PHA)-induced cells. PBMC 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). Various 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 PBMC was checked using the MTT 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.

References and notes

1. Tropical Disease Research: Progress 1999–2000; World Health Organization: Geneva, **2001**.
2. Gelb, M. H.; Hol, W. G. J. *Science* **2002**, *297*, 343.
3. Davies, C. R.; Kaye, R. P.; Croft, S. L.; Sundar, S. *Br. Med. J.* **2003**, *15*, 377.
4. Desjeux, P. *World Health Stat. Q* **1992**, *45*, 267.
5. Trouiller, P.; Torreele, E.; Olliaro, P.; White, N.; Foster, S.; Wirth, D.; Pécoul, B. *Trop. Med. Int. Health* **2001**, *6*, 945.
6. Croft, S. L.; Coombs, G. H. *Trends Parasitol.* **2003**, *19*, 502.
7. Raht, S.; Trivellin, A.; Imbrunito, T. R.; Tomazela, D. M.; Jesus, M. N.; Marzal, P. C.; Junior, H. F. A.; Tempone, A. G. *Quim. Nova* **2003**, *26*, 550.
8. Roberts, W. L.; McMurray, W. J.; Rainey, P. M. *Antimicrob. Agents Chemother.* **1998**, *42*, 1076.
9. Mcgregor, A. *Lancet* **1998**, *351*, 575.
10. Soto, J.; Arana, B. A.; Toledo, J.; Rizzo, N.; Vbega, J. C.; Diaz, A.; Luz, M.; Gutierre-Arboleda, M.; Berman, J. D.; Junge, K.; Engel, J.; Sindermann, H. *Clin. Infect. Dis.* **2004**, *38*, 1266.
11. Prasad, R.; Kumar, R.; Jaiswal, B. P.; Singh, U. K. *Indian J. Pediatr.* **2004**, *71*, 143.
12. Sangraula, H.; Sharma, K. K.; Rijal, S.; Dwivedi, S.; Koirala, S. *J. Assoc. Physicians India* **2003**, *51*, 686.
13. Ouellette, M.; Drummelsmith, J.; Papadopoulou, B. *Drug Resist. Updat.* **2004**, *7*, 257.

14. Davis, A. J.; Kedzierski, L. *Curr. Opin. Investig. Drugs* **2005**, *6*, 163.
15. Kirby, G. C. *Trans. R. Soc. Trop. Med. Hyg.* **1996**, *90*, 605.
16. Franca, F.; Lago, E. L.; Marsden, P. D. *Brazil. Rev. Soc. Bras. Med. Trop* **1996**, *29*, 229.
17. Fournet, A.; Barrios, A. A.; Munoz, V. *J. Ethnopharmacol.* **1994**, *41*, 19.
18. Akendengue, B.; Ngou-Milama, E.; Laurens, A.; Hocquemiller, R. *Parasite* **1999**, *6*, 3.
19. De Carvalho, P. B.; Ferreira, E. I. *Fitoterapia* **2001**, *72*, 599.
20. Chan-Bacab, M. J.; Pena-Rodriguez, L. M. *Nat. Prod. Rep.* **2001**, *18*, 674.
21. Fournet, A.; Munoz, V. *Curr. Top. Med. Chem.* **2002**, *2*, 1215.
22. Kayser, O.; Kiderlen, A. F.; Croft, S. L. *Parasitol. Res.* **2003**, *90*, S55.
23. Fournet, A.; Vagneur, B.; Richomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116.
24. Fournet, A.; Hocquemiller, R.; Roblot, F.; Cavé, A.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **1993**, *56*, 1547.
25. Fournet, A.; Barrios, A. A.; Munoz, V.; Hocquemiller, R.; Cavé, A.; Bruneton, J. *Antimicrob. Agents Chemother.* **1993**, *37*, 859.
26. Fournet, A.; Barrios, A. A.; Munoz, V.; Hocquemiller, R.; Roblot, F.; Cavé, A.; Richomme, P.; Bruneton, J. *Phytother. Res.* **1994**, *8*, 174.
27. Fournet, A.; Ferreira, M.; Rojas de Arias, A.; Torres de Ortiz, S.; Fuentes, S.; Nakayama, H.; Schinini, A.; Hocquemiller, R. *Antimicrob. Agents Chemother.* **1996**, *40*, 2447.
28. Viera, P. C.; Kubo, I. *Phytochem.* **1990**, *29*, 813.
29. Houghton, P. J.; Woldemariam, T. Z.; Watanabe, Y.; Yates, M. *Planta Med.* **1999**, *65*, 250.
30. Jacquemond-Collet, I.; Bessière, J.-M.; Hannedouche, S.; Bertrand, C.; Fourasté, I.; Moulis, C. *Phytochem. Anal.* **2001**, *12*, 312.
31. Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J.-F.; Franck, X.; Hocquemiller, R.; Figadère, B. *Bioorg. Med. Chem.* **2003**, *11*, 5013.
32. Nakayama, H.; Loiseau, P. M.; Bories, C.; Torres de Ortiz, S.; Schinini, A.; Serna, E.; Rojas de Arias, A.; Fakhfakh, M. A.; Franck, X.; Figadère, B.; Hocquemiller, R.; Fournet, A. *Antimicrob. Agents Chemother.* **2005**, *49*, 4950.
33. Guillon, J.; Dumoulin, H.; Dallemagne, P.; Reynolds, R.; Rault, S. *Pharm. Pharmacol. Commun.* **1998**, *4*, 33.
34. Guillon, J.; Dallemagne, P.; Pfeiffer, B.; Renard, P.; Manechez, D.; Kervran, A.; Rault, S. *Eur. J. Med. Chem.* **1998**, *33*, 293.
35. Guillon, J.; Boulouard, M.; Lisowski, V.; Stiebing, S.; Lelong, V.; Dallemagne, P.; Rault, S. *J. Pharm. Pharmacol.* **2000**, *52*, 1369.
36. Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Léger, J.-M.; Déprez-Poulain, R.; Forfar-Bares, I.; Dallemagne, P.; Lemaıtre, N.; Péhourcq, F.; Rochette, J.; Sergheraert, C.; Jarry, C. *J. Med. Chem.* **2004**, *47*, 1997.
37. Mäntyla, A.; Garnier, T.; Rautio, J.; Nevalainen, T.; Vepsälainen, J.; Koskinen, A.; Croft, S. L.; Järvinen, T. *J. Med. Chem.* **2004**, *47*, 188.
38. Kauffman, J. M.; Litak, P. T.; Boyko, W. J. *J. Heterocycl. Chem.* **1995**, *32*, 1541.
39. Zhang, Z.; Tillekeratne, L. M. V.; Hudson, R. A. *Synthesis* **1996**, *3*, 377.
40. Bischler, A. B. *Ber* **1893**, *26*, 1903.
41. Kaslow, C. E.; Stayner, R. D. *J. Am. Chem. Soc.* **1945**, *67*, 1716.
42. Caron, S.; Desfossés, S.; Dionne, R.; Théberge, N.; Burnell, R. H. *J. Nat. Prod.* **1993**, *56*, 138.
43. Dade, J.; Provot, O.; Moskowitz, H.; Mayrargue, J.; Prina, E. *Chem. Pharm. Bull.* **2001**, *49*, 480.
44. Corey, E. J.; Chaychovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
45. Munos, M.-H.; Mayrargue, J.; Fournet, A.; Gantier, J.-C.; Hocquemiller, R.; Moskowitz, H. *Chem. Pharm. Bull.* **1994**, *42*, 1914.
46. Fakhfakh, M. A.; Franck, X.; Fournet, A.; Hocquemiller, R.; Figadère, B. *Synth. Commun.* **2002**, *32*, 2863.
47. Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.
48. Ciufolini, M. A.; Mitchell, J. W.; Roschangar, F. *Tetrahedron Lett.* **1996**, *37*, 8281.
49. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
50. Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.
51. Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.
52. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467.
53. Warhust, D. W.; Craig, J. C.; Agadu, I. S.; Meyer, D. J.; Lee, S. Y. *Malar. J.* **2003**, *2*, 26.
54. Glaser, T. A.; Baatz, J. E.; Kreishman, G. P.; Mukkada, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7602.
55. Pallas 3.0, Compu-Drug Chemistry Ltd, San Francisco CA, USA.
56. Hill, J. W.; Petrucci, R. H.; McCreary, T. W.; Perry, S. S. *General Chemistry*; 4th ed.; International edition, Pearson Education International: Upper Saddle River, 2005; pp 649–651.
57. Supplementary X-ray crystallographic data: Cambridge Crystallographic Data Centre, University Chemical Lab, Lensfield Road, Cambridge, CB2 1EW, UK; E-mail: deposit@chemcrys.cam.ac.uk.
58. North, A. C. T.; Phillips, D. C.; Mathews, F. S. *Acta Crystallogr.* **1968**, *A24*, 351.
59. Sheldrick, G. M.; Kröger, C.; Goddard, R. *SHELX 86 in Crystallographic Computing 3*; Oxford University Press: New York, 1985, p 175.
60. Sheldrick, G. M. *SHELX 93, Program for the Refinement of the Crystal Structures*; University of Göttingen: Germany, 1993.
61. Pehourcq, F.; Thomas, J.; Jarry, C. *J. Liq. Chromatogr. Related Technol.* **2000**, *23*, 443.
62. Vouldoukis, I.; Becherel, P. A.; Riveros-Moreno, V.; Arock, M.; da Silva, O.; Debre, P.; Mazier, D.; Mossalayi, M. D. *Eur. J. Immunol.* **1997**, *27*, 860.
63. Vouldoukis, I.; Riveros-Moreno, V.; Dugas, B.; Ouaaz, F.; Becherel, P.; Debre, P.; Moncada, S.; Mossalayi, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 7804.
64. Ferry-Dumazet, H.; Garnier, O.; Mamani-Matsuda, M.; Vercauteren, J.; Belloc, F.; Billiard, C.; Dupouy, M.; Thiolat, D.; Kolb, J. P.; Marit, G.; Reiffers, J.; Mossalayi, M. D. *Carcinogenesis* **2002**, *23*, 1327.