New Synthesis of Benzo-*δ*-carbolines, Cryptolepines, and Their Salts: In Vitro Cytotoxic, Antiplasmodial, and Antitrypanosomal Activities of *δ*-Carbolines, Benzo-*δ*-carbolines, and Cryptolepines

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The paper describes, in its first part, a new synthesis of benzo-*δ*-carbolines, cryptolepines, and their salts. The strategy is based on the association between halogen-dance and hetero-ring cross-coupling. It is fully convergent and regioselective with interesting overall yields from 27% to 70%. A halogen-dance mechanism in quinoline series is also proposed. The formal synthesis of potential antimalarial compounds and the first total synthesis of 11-isopropylcryptolepine are also described. In the second part, cytotoxic activity against mammalian cells and activities against *Plasmodium falciparum* and *Trypanosoma cruzi* of benzo-*δ*-carbolines and *δ*-carbolines were evaluated in vitro to study the structure−activity relationships. For benzo-*δ*-carbolines, methylation at N-5 increases the cytotoxic and antiparasitic activities. A further alkylation on C-11 generally increases the cytotoxic activity but not the antiparasitic activity, cryptolepine and 11-methylcryptolepine being the most active on both parasites. Taking advantage of the fluorescence of the indoloquinoline chromophore, cryptolepine was localized by fluorescence microscopy in parasite DNA-containing structures suggesting that these compounds act through interaction with parasite DNA as proposed for cryptolepine on melanoma cells. For *δ*-carbolines, methylation at N-1 is essential for the antimalarial activity. 1-Methyl-*δ*-carboline specifically accumulates in the intracellular parasite. It has weak cytotoxic activity and can be considered as a potential antimalarial compound.

Introduction

δ-Carbolines and benzo-*δ*-carbolines[1] are very rare in nature, and the best representatives of this family are quindoline[2] (**1a**) and cryptolepine[3,4] (**2a**) (Chart 1), two indoloquinoline alkaloids isolated in 1977 and 1929, respectively, from a West African plant: *Cryptolepis sanguinolenta* (Periplocaceae). Benzo-*δ*-carbolines are also found in three other plants: *Sida acuta* (Malvaceae) from Sri Lanka,[5] *Microphilis guyanensis* (Sapotaccae), and *Genipa americana* (Rubiaceae) from Suriname.[6] Some minor indoloquinoline alkaloids are functionalized at the C-11 position. This is the case for cryptomisrine[7] (**3**), cryptolepinone[8−12] (**4**), 11-isopropylcryptolepine[13] (**2d**), and biscryptolepine[14] (**5**).

Considerable interest in this family has been shown by several teams throughout the world due to their various and important biological properties such as: antimuscarinic, antibacterial, antiviral, antiplasmodial, and antihyperglycemic activities.[15−19] Recently, two reports mentioned the cytotoxicity of cryptolepine and analogues toward B16 melanoma cells[20] and M109 Madison lung carcinoma.[6] Bonjean et al. also showed that cryptolepine interferes with topoisomerase II and

Chart 1

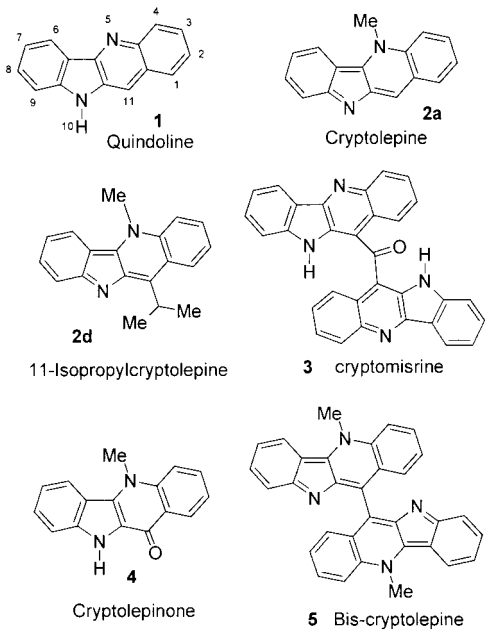

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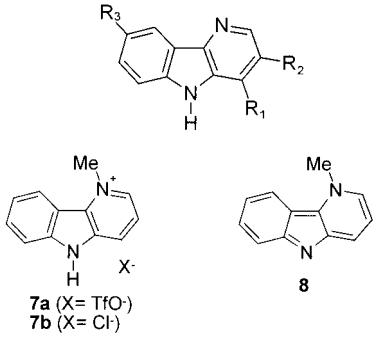
Table 1. Structures of the Tested δ-Carbolines



7a (X= TfO-)
7b (X= Cl-)

8

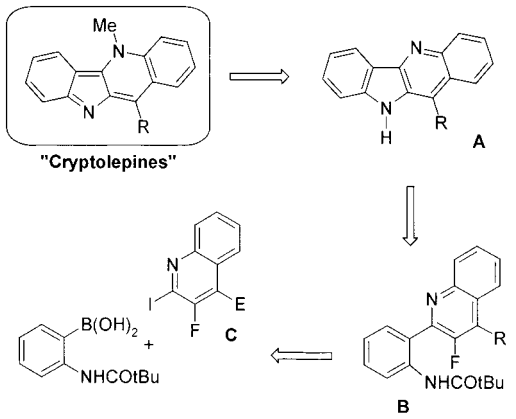
R_1	R_2	R_3	product
H	H	H	**6a**
Me	H	H	**6b**
Et	H	H	**6c**
Ph	H	H	**6d**
2-$C_6H_4NH_2$	H	H	**6e**
2-pyridyl	H	H	**6f**
2-quinolyl	H	H	**6g**
2-thienyl	H	H	**6h**
H	Ph	H	**6i**
H	2-$C_6H_4NH_2$	H	**6j**
H	2-pyridyl	H	**6k**
H	2-quinolyl	H	**6l**
H	2-thienyl	H	**6m**
Ph	Ph	H	**6n**
Me	Ph	H	**6o**
H	H	OH	**6p**

primarily inhibits DNA synthesis.[20] Moreover, some quindoline derivatives have been described as potent antitumor-active compounds.[21]

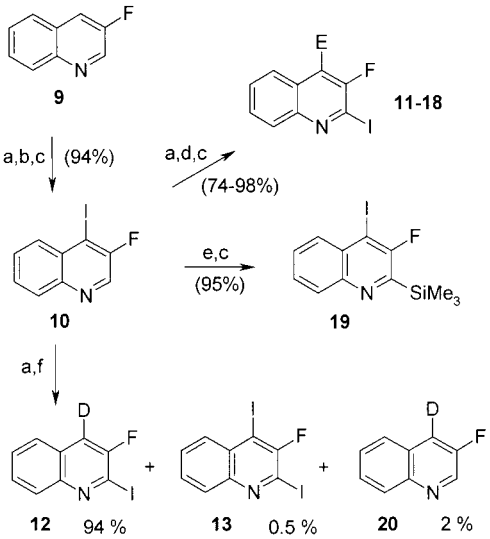
Recently, we described[22,23] a new synthesis of α-substituted, β-substituted, and α,β-disubstituted δ-carbolines (Table 1). This synthesis was based on metalation and cross-coupling reactions, starting with simple benzene and pyridine blocks. In a similar process, compound **6p** (Table 1) was obtained using a methylated boronic acid (see Experimental Section). Methylated carbolines **7**−**8** were synthesized from δ-carboline following the procedure described further under "Synthesis of Cryptolepines and Benzo-δ-carbolinium Salts".

In 1998, we reported a new and very short route[24] to quindoline (**1a**) (the benzo-δ-carboline) which involved the first halogen-dance reaction in the iodoquinoline series. One year later, using this reaction, we described the first total synthesis[25] of cryptomisrine (**3**), a bis-benzo-δ-carboline linked by a keto group. We wish to report here on an extension of this fruitful method, to the total synthesis of new C-11-substituted benzo-δ-carbolines as well as their methylated analogues, called here "cryptolepines", and their salt forms: triflates and chlorides. Cytotoxic activity toward mammalian cells and activities against the parasites *Plasmodium falciparum*, agent of malaria, and *Trypanosoma cruzi*, agent of Chagas disease, of such molecules as well as α-substituted, β-substituted, and α,β-disubstituted δ-carbolines were evaluated in order to study structure−activity relationships (SARs) (the skeleton of δ-carbolines is very close to that of benzo-δ-carboline). In addition, by taking advantage of the fluorescence of these derivatives, we used fluorescence microscopy for a subcellular localization of active compounds in parasites.

Scheme 1



Scheme 2[a]



[a] (a) 1 equiv LDA, THF, −78 °C, 2 h (**26** → **27**) or 4 h; (b) I_2, THF, -78 °C, 2 h; (c) H_2O; (d) electrophile, THF, −78 °C, 2 h; (e) 1 equiv (LDA + TMSCl), THF, −78 °C, 2 h; (f) D_2O, THF.

Chemistry

A retrosynthetic analysis (Scheme 1) suggests that cryptolepines could be prepared by methylation of the corresponding benzo-δ-carbolines **A**. These latter compounds could be obtained by cyclization of the conveniently functionalized phenylquinolines **B**, our key intermediates in this strategy. These phenylquinolines could be obtained via a cross-coupling reaction[26,27] between the required benzene and quinoline building blocks. Finally, the trisubstituted quinolines **C** could be prepared by an orthometalation−isomerization reaction on the 3-fluoro-4-iodoquinoline.

3-Fluoroquinoline (**9**) was metalated[26] with LDA at low temperature to give the 3-fluoro-4-iodoquinoline (**10**) in very good yield after reaction of iodine (Scheme 2). Treatment of **10** by LDA at −75 °C and reaction of the resulting lithio species with various electrophiles led to the corresponding 4-substituted 3-fluoro-2-iodoquinolines **11**−**18** in good to high yields (Scheme 2, Table 2).

It should be noted that the methyl group in compound **15** is the only alkyl chain which can be incorporated in such a position, probably due to the lack of reactivity of the lithio species toward alkyl iodides. Identification of compounds **11**−**18** was inferred from the ^1H and ^{13}C

Table 2. Halogen-Dance

electrophile	E	product	yield (%)
H_2O	H	**11**	95
D_2O	D	**12**	95
I_2	I	**13**	98
C_2Cl_6	Cl	**14**	74
MeI	Me	**15**	65[a]
MeCHO	MeCH(OH)	**16**	79
PhCHO	PhCH(OH)	**17**	75
HCO_2Et	CHO	**18**	95

[a] NMR integration.

NMR spectra: a strong shielding of the carbon bearing the iodo atom could be observed.[27−29]

The behavior of iodoquinoline **10** toward LDA is very similar to that observed in the pyridine series.[30] Indeed, when 3-fluoro-4-iodoquinoline was treated with an equimolar mixture of LDA and TMSCl, the 2-silylated compound **19** was observed (Scheme 2), showing that the first step of this reaction is the fluoro-directed metalation of the more acidic 2-position under kinetic control. Without addition of an electrophile such as TMSCl, a fast isomerization of the 2-lithio derivative to the more stable 4-lithioquinoline occurred. This reaction seems to be very fast, since we were unable to trap the 3-fluoro-4-iodo-2-lithio derivatives by addition of electrophiles after the lithiation step. However, when 3-fluoro-4-iodoquinoline (**10**) was treated with LDA at −78 °C followed by quenching with deuterium oxide (D_2O), three products were obtained, as well as a small amount of the starting material (Scheme 2).

In all experiments, a small amount of the diiodoquinoline **13** was observed (about 0.5%) as well as the deiodinated compound **20** (about 2%). Moreover, the diiodo compound **13** seems to play a role as a catalyst in this halogen-dance reaction. Indeed, when metalation of 3-fluoro-4-iodoquinoline (**10**) was carried out with an additional 10% of diiodoquinoline **13**, the rate of the reaction was increased by 31%. In consequence of these observations and according to the literature,[31−39] we can propose the following mechanism (Scheme 3): In the first step, the 2-lithio derivative **10a** is generated by LDA (path ①) and can react with the starting material (path ②) to form the 3-fluoro-4-lithioquinoline (**20a**) and the diiodo derivative **13**. Then two pathways are made possible, with reaction of the diiodo compound **13** with either the 2-lithio species **10a** (path a) or the 4-lithioquinoline **20a** (path b), leading to the same expected 4-lithioquinoline **12a**.

Synthesis of Benzo-δ-carbolines. Palladium-catalyzed cross-coupling reaction between boronic acids **21**−**22** and iodoquinolines **11, 13**−**14** using a Suzuki procedure[26] produced the biaryls **23**−**28** in good to high yields (Scheme 4, Table 3). To synthesize other precursors (**29**−**32**) of substituted benzo-δ-carbolines, compound **23** was readily functionalized by metalation with *n*-BuLi at −78 °C followed by quenching with various electrophiles (Scheme 4, Table 4).

It can be noted that the chlorinated compound **25** is easier to obtain according to this route than the previous one, for yield and purification reasons. Metalation of compound **32** with KDA[40] followed by methylation gave the isopropyl derivatives **33** with an excellent yield (Scheme 4). This compound is a precursor of the natural alkaloid 11-isopropylcryptolepine (**2d**).

A cross-coupling reaction between phenylboronic acid and **31** led to the corresponding triaryl **34** in quantitative yield (Scheme 4). Cyclization[41,42] of the previously prepared phenylquinolines (**23, 25, 31**−**34**) to the corresponding benzo-δ-carbolines (**1a**−**f**) was best achieved by treatment with boiling pyridinium chloride at 215 °C followed by a basic workup (Scheme 5, Table 5). Compound **1a** is the natural alkaloid quindoline, and the chlorinated compound **1f** is an intermediate in the synthesis of potential antimalarial compounds.[43] It should be pointed out that 11-methylquindoline (**1b**) (Scheme 5, Table 5) had already been obtained by chemical modifications of quindoline-11-carboxylic acid.[6] Thus, our strategy allowed the formal synthesis of such compounds. Cooper et al.[10] also described this chloro compound (**1f**) as a precursor of quindoline itself (**1a**).

Synthesis of Cryptolepines and Benzo-δ-carbolinium Salts. Various cryptolepines were synthesized from the previously prepared benzo-δ-carbolines **1a**−**e** using the procedure described by Bierer et al.[44] In a first step, benzo-δ-carbolines **1a**−**e** were treated with methyl triflate in dry toluene at room temperature to give the corresponding triflate salts **35a**−**e**. Treatment of these salts by an aqueous solution of sodium carbonate in the presence of chloroform and basic alumina gave the corresponding cryptolepines **2a**−**e** in good yields (Scheme 6, Table 6). Further treatment with HCl yielded the corresponding hydrochloride compounds **36a**−**e** which were used for biological tests (see next part).

It should be noted that this general strategy of cryptolepines allowed the preparation of an analogue of ellipticine[45] (a natural alkaloid with antitumor activities[34]) and the first total synthesis of 11-isopropylcryptolepine[13] (**2d**), isolated in 1999 from the root of *C. sanguinolenta*.

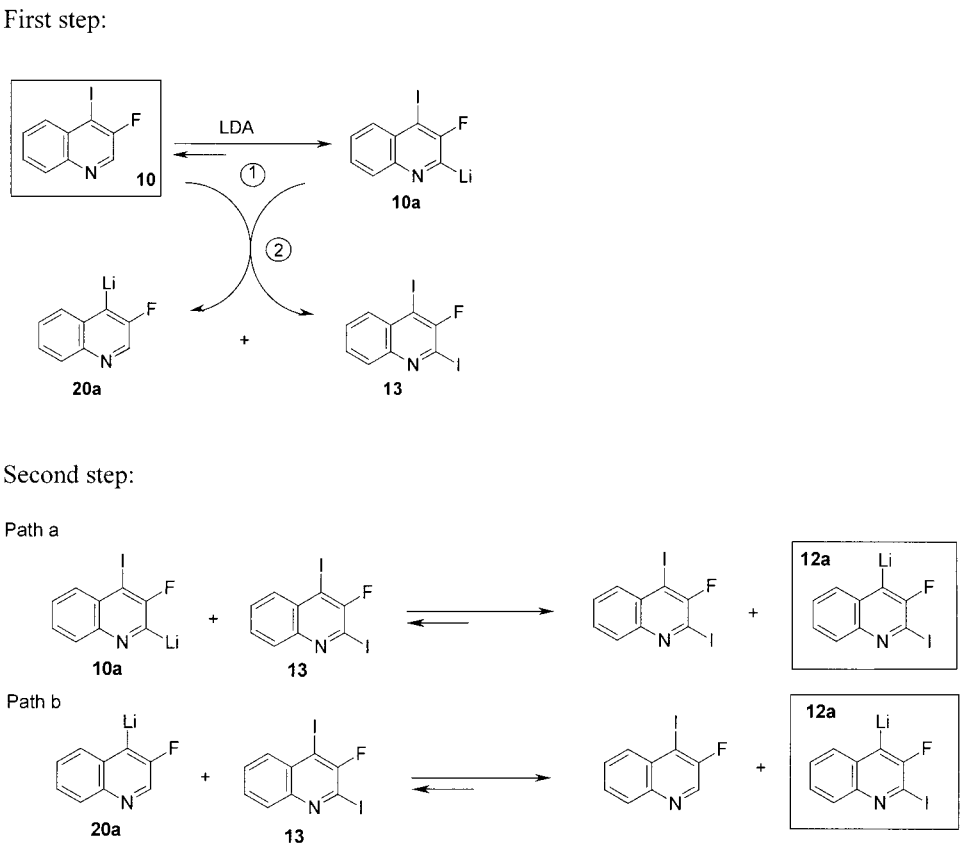
Results and Discussion

In Vitro Cytotoxicity of Benzo-δ-carbolines on KB Cells. To study the influence of the structural modifications at positions 5 and 11 toward cytotoxicity, we performed an in vitro cell survival assay on cancer KB cell lines. The results are shown in Table 7.

As noted by Kingston et al.,[6] methylation at the N-5 position led to a large increase of cytotoxicity. Quindoline (**1a**) is 30 times less cytotoxic on KB cells than cryptolepine (**2a**). In the benzo-δ-carbolines series (compounds **1b**−**e**), alkylation at the C-11 position has no effect on the activity for most of the compounds. Compounds **1b**−**d** possess similar cytotoxicity to the parent compound **1a**, but the presence of a phenyl group (compound **1e**) led to a decrease in cytotoxicity. It should be noted that this lack of cytotoxicity is not due to a lack of solubility. On the other hand, alkylation at the C-11 position in the cryptolepine series (compounds **2b**−**d**) led to a slight increase in cytotoxicity, except for 11-isopropylcryptolepine (**2d**) which is about 4 times less active than cryptolepine (**2a**). The cytotoxicity of 11-methylcryptolepine (**2b**) (IC_{50} = 0.53 μM) over cryptolepine **2a** itself made this compound a suitable candidate for further pharmacological studies.

In Vitro Antitrypanosomal and Antiplasmodial Activities of Benzo-δ-carbolines. In vitro and in vivo antiplasmodial activity of cryptolepine and related benzo-δ-carbolines has been previously reported.[6,15−19]

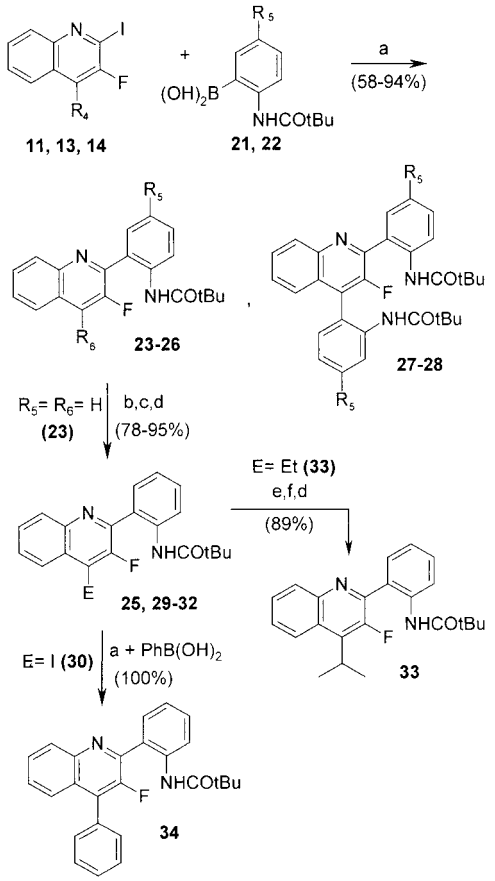
Scheme 3



However, their activity against *T. cruzi*, especially against the intracellular multiplication of the amastigote stage, has only been investigated a little. We therefore studied the influence of the structural modifications of cryptolepine at N-5 and C-11 positions on the activity against the *T. cruzi* Tulahuen strain and the chloroquine-resistant K1 strain of *P. falciparum*. Results are reported in Table 8. Methylation at position 5 is essential for the activity since quindoline (**1a**) was about 100 times less active against both parasites than cryptolepine **35a**. Cryptomisrine (**3**) showed higher activity than quindoline, but its index of selectivity (IS) stayed in a similar range. The IS for *T. cruzi* was defined as the ratio between the IC_{50} value on the L6 cells and the IC_{50} value on the intracellular multiplication of the amastigote forms. The IS for *P. falciparum* was defined as the ratio between the IC_{50} value on the L6 cells and the IC_{50} value against *P. falciparum*. Compounds that demonstrate a higher selectivity (greater IS number) should offer the potential of more safer therapy. In the quindoline series, alkylation at the C-11 position (compounds **1b,c**) had no significant effect on the activity against both parasites, except that 11-ethylquindoline (**1c**) showed activity about 10 times higher on the *T. cruzi* trypomastigote forms than quindoline. In the cryptolepine series, alkylation at the C-11 position (compounds **35b**−**d**) reduced the activity against *P. falciparum*, except for 11-methylcryptolepine **35b** which was about 5 times more active than cryptolepine **35a**. However, as observed for cancer KB cells, C-11 methylation also increased cytotoxicity toward the L6 cells and the IS value was similar to that of cryptolepine (IS of 22−24). Benzo-*δ*-carbolines were generally more active against *P. falciparum* when used under salt form. As for *P. falciparum*, the C-11 alkylation also reduced the activity against the intracellular multiplication of the *T. cruzi* amastigote forms, except for 11-methylcryptolepine **35b** which is slightly more active than cryptolepine **35a**. Benzo-*δ*-carbolines seem to be about one-half as active against amastigotes when used under their salt forms. With an IS of about 65, cryptolepine **35a** is the most promising antitrypanosomal compound, which will require further investigations.

In Vitro Antitrypanosomal and Antiplasmodial Activities of *δ*-Carbolines. Table 9 summaries the activities of *δ*-carboline derivatives against *T. cruzi*, *P. falciparum*, and the murin L6 cells. Compound **6a** was found to be the most efficient of the *δ*-carbolines to inhibit the dividing forms of *T. cruzi* (epimastigotes and amastigotes) with IC_{50}s of around 20 μM, which are about 10 times lower than the IC_{50} measured on the L6 cells (around 230 μM). Compound **6a** was however not very effective against the trypomastigote, the infective but nondividing form of *T. cruzi* (no effect for concentrations of up to 100 μM). Modifications to increase the hydrophilic character (hydroxylation at the 8 position, compound **7a**) or the hydrophobic character (modifications at the 3 and/or 4 position, e.g. compounds **6d,e**,**j**) of *δ*-carboline **6a**, as well as methylation at the 1 position (compounds **7**−**8**), did not result in an increase of the IS compared to compound **6a**. On *P. falciparum*, compound **6a** showed weak activity with an IS of 2.2. Increase of hydrophilic or hydrophobic character of derivatives generally decreased the IS values, except for compound **6k** (IS = 9.8). In contrast, methylation at the 1 position (compounds **7**−**8**) considerably increased the activity against *P. falciparum* with IC_{50} values in the low micromolar range (1.5−2.2 μM). As these com-

Scheme 4[a]



[a] (a) cat. $Pd(PPh_3)_4$, 2 M K_2CO_3, EtOH, toluene, reflux under argon, 48 h; (b) 2.8 equiv *n*-BuLi, THF, −78 °C, 3 h; (c) electrophile, THF, −78 °C, 2 h; (d) H_2O; (e) 3.5 equiv KDA, THF, −50 °C, 45 min; (f) CH_3I, THF, −78 °C, 1 h.

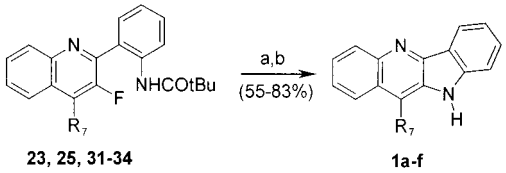
Table 3. Cross-Coupling

R_5 (boronic)	R_4 (iodo)	R_6 (product)	product	yield (%)
H (**21**)	H (**11**)	H	**23**	94
OMe (**22**)	H (**11**)	H	**24**	83
H	Cl (**14**)	Cl	**25**	58
OMe	Cl (**14**)	Cl	**26**	58
H	I (**12**)	R_5 = H	**27**	79
OMe	I (**12**)	R_5 = OMe	**28**	54

Table 4. Metalation of **40**

electrophile	E	product	yield (%)
D_2O	D	**29**	95
I_2	I	**30**	94
C_2Cl_6	Cl	**25**	80
MeI	Me	**31**	85
EtI	Et	**32**	78

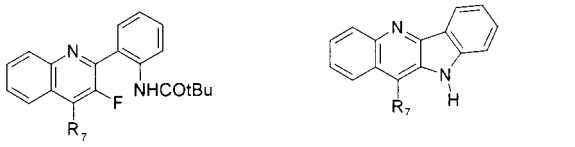
Scheme 5[a]



[a] (a) Pyridinium chloride, 215 °C, 30 min; (b) NH_3/H_2O.

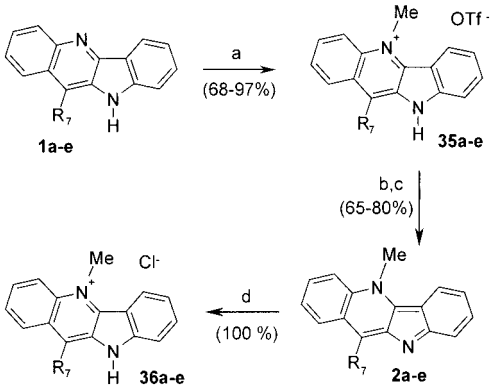
pounds have weak cytotoxic activities against the L6 cells (IC_{50}s > 200 μM), they can be considered as potential antimalarial compounds (IS > 100) and required further pharmacological studies.

Table 5. Benzo-δ-carbolines



starting material	R_7	benzo-δ-carboline	yield (%)
23	H	**1a**	83
31	Me	**1b**	75
32	Et	**1c**	74
33	*i*Pr	**1d**	80
34	Ph	**1e**	85
25	Cl	**1f**	55

Scheme 6[a]

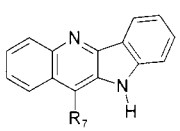
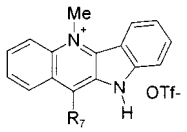
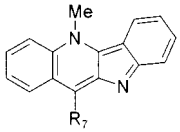
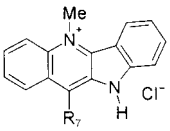


[a] (a) MeOTf, toluene, 20 °C, 24 h; (b) 5% Na_2CO_3; (c) $CHCl_3$, basic alumina; (d) 1 M HCl/Et_2O.

Intracellular Localization of Cryptolepine and 1-Methyl-δ-carboline. Taking advantage of the fluorescence of the indoloquinoline chromophore, fluorescence microscopy was used to localize cryptolepine **35a** inside the human fetal fibroblasts infected by *T. cruzi* amastigotes and the red blood cells (RBC) infected by *P. falciparum*. In *T. cruzi*-infected cells, cryptolepine accumulated mainly in the intracellular amastigotes (Figure 1). Cytoplasm of fibroblasts was not labeled, and a weak fluorescence was associated with the host cell nucleus. In amastigotes, cryptolepine strongly accumulated into barlike structures whose staining corresponds to a typical staining of kinetoplast DNA. Round structures were also stained that could indicate accumulation into the parasite nuclei. For *P. falciparum*, cryptolepine also accumulated into specific parasite structures that could correspond to the parasite nuclei (Figure 2a,b). No labeling of the cytoplasm of infected RBC or noninfected RBC was observed. Previous studies have shown the specific accumulation of cryptolepine into the nucleus of the melanoma cells[20] and the DNA-intercalating properties of cryptolepine.[46] These data associated with the typical staining of the kinetoplast DNA strongly suggest that cryptolepine acts through interactions with parasite DNA. As proposed by Dassonneville et al.,[46] stimulation of topoisomerase-mediated DNA cleavage by the DNA-intercalating properties of cryptolepine may then be its mechanism of action.

Fluorescence of 1-methyl-δ-carboline (**7b**), one of the most active δ-carboline derivatives tested against *P. falciparum*, also allowed to visualize its accumulation inside the *P. falciparum*-infected RBC (Figure 2c,d). Fluorescence was specifically localized in a parasite

Table 6. Benzo-*δ*-carbolines, Cryptolepines, and Their Salts

R_7	benzo-*δ*-carboline	triflate salt	cryptolepine	yield (%)[a]	chloride salt
H	**1a**	**35a**	**2a**	78	**36a**
Me	**1b**	**35b**	**2b**	59	**36b**
Et	**1c**	**35c**	**2c**	82	**36c**
*i*Pr	**1d**	**35d**	**2d**	69	**36d**
Ph	**1e**	**35e**	**2e**	51	**36e**

[a] Global yields (2 steps) for pure compounds.

Table 7. KB Cytotoxicity of Benzo-*δ*-carbolines and Cryptolepines[a]

compd	IC_{50} (μM)	compd	IC_{50} (μM)
1a	45 ± 10	**2d**	6.5 ± 0.5
1b	40 ± 5	**2e**	0.75 ± 0.05
1c	40 ± 10	**35b**	0.57 ± 0.35
1d	57 ± 3	**35d**	6.4 ± 1.6
1e	>100	**36a**	1.75 ± 0.75
2a	1.5 ± 0.5	**36b**	0.42 ± 0.08
2b	0.53 ± 0.07	**36c**	1.5 ± 0.5
2c	0.7 ± 0.1	**36d**	9.25 ± 0.75

[a] IC_{50} values are the means ± standard deviation of 3 independent experiments.

structure that could correspond to the parasite nucleus. However, whether 1-methyl-*δ*-carboline (**7b**) possesses DNA-interacting properties still must be demonstrated. No labeling of the cytoplasm of infected and noninfected RBC was observed. Surprisingly, 1-methyl-*δ*-carboline accumulation seems to be dependent on the parasite development. Accumulation was restricted to the young stage (ring and trophozoite stage); no labeling was observed for the dividing stage (schizont stage) suggesting either stage-specific targets or stage-specific permeability.

Conclusion

The link between metalation and cross-coupling provides a new convenient and general way to synthesize benzo-*δ*-carbolines, as well as cryptolepine and its substituted analogues. The overall strategy relies on such key steps such as metalation, halogen-dance, and hetero-ring cross-coupling. It is fully convergent and regioselective. Substituted benzo-*δ*-carbolines **1a**−**f** were obtained in 4−6 steps from 3-fluoroquinoline (**9**) with interesting 37−70% overall yields and cryptolepines **2a**−**e** in 6−8 steps from the same fluorinated compound in 27−58% overall yields. We also described a formal synthesis of potential antimalarial compounds and the first total synthesis of 11-isopropylcryptolepine (**2d**), isolated last year. Biological evaluation of benzo-*δ*-carbolines showed that methylation at the N-5 position (cryptolepine series) led to a large increase of their cytotoxic activity toward mammalian cells, as well as their antiplasmodial and antitrypanosomal activities. Alkylation at the C-11 position in the cryptolepine series generally increased the cytotoxic activity, 11-methylcryptolepine being the most active among the compounds tested. In contrast, except for 11-methylcryptolepine, alkylation at C-11 did not increase the antiplasmodial and antitrypanosomal activities. The subcellular localization of cryptolepine in parasite DNA-containing structures (nucleus, kinetoplast) strongly suggests that compounds of the cryptolepine series act on the parasite through interaction with DNA, by a mechanism that could be similar to the one proposed by Dassonneville et al.[47] for cryptolepine on melanoma cells: stimulation of topoisomerase-mediated DNA cleavage by the DNA-intercalating properties. Study of the SAR of *δ*-carboline derivatives pointed to the importance of methylation at N-1 for their antimalarial activity. 1-Methyl-*δ*-carboline specifically accumulates in intracellular parasites and has weak cytotoxic activity. It can be considered as a potentiel antimalarial compound that warrants further investigation. This synthetic strategy is currently being extended to the preparation of new alkaloids in these structural families.

Experimental Section

1. Chemistry. General Data. The ^1H, ^{19}F and ^{13}C NMR were obtained from a Brucker Advance 300 (300 MHz frequency for ^1H) spectrometer; *J* values are given in Hz. The IR spectra were run on a Perkin-Elmer Paragon 500 FT-IR spectrometer, main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Mass spectra were obtained from a JEOL D700 instrument. Elemental analyses were performed on a CE instrument apparatus EA 1110 CHNS-O. Tetrahydrofuran was distilled from sodium/benzophenone. The water content of the solvent was estimated to be lower than 25 ppm by the Karl Fischer method.[47] Commercial diisopropylamine was distilled from calcium hydride under a dry nitrogen atmosphere. Commercial 2.5 M solution of *n*-butyllithium in hexane used and all reactions involving organometallic compounds were carried out under a dry nitrogen atmosphere. 3-Fluoroquinoline (**9**) was prepared by the Roe and Hawkins[27] method starting from 3-aminoquinoline. 3-Fluoro-4-iodoquinoline (**10**), cryptomisrine (**3**) and compounds **6a**−**o** were described in previous papers[22−23,25] Boronic acids **21**−**22** were also described in a previous paper.[48]

General Procedure A: Metalation−Isomerization of 3-Fluoro-4-iodoquinoline (10). *n*-Butyllithium in hexane (10.0 mmol, 4.0 mL, 2.5 M) was added to diisopropylamine (10.0 mmol, 1.4 mL) in THF (40.0 mL) at −78 °C. After 20 min, a solution of 3-fluoro-4-iodoquinoline (**10**; 10.0 mmol, 2.73 g) in 8.0 mL of THF was slowly added to the previous solution (LDA). The resulting solution was stirred for 2 h at −78 °C and the electrophile (10.0 mmol) in 10.0 mL of THF was slowly added. Stirring was continued for 2 h at −78 °C before hydrolysis at 0 °C by 10.0 mL of THF/H_2O (9/1). Extraction with ethyl acetate, drying with $MgSO_4$, filtration and solvent removal gave a crude product which was purified by flash chromatography on silica gel.

3-Fluoro-2-iodoquinoline (11). General procedure A, using water as the electrophile, gave 2.60 g (95%) of **11**: mp 87 °C; ^1H NMR ($CDCl_3$) δ 8.10 (dd, 1H, H8, J = 1.0, 8.0), 7.81 (dd, 1H, H5, J = 1.5, 8.0), 7.75−7.58 (m, 3H, H4, H6 and H7);

Table 8. In Vitro Cytotoxicity and Antitrypanosomial and Antiplasmodial Activities of Benzo-δ-carbolines and Cryptolepines[a]

	L6 cells	*T. cruzi*				*P. falciparum*	
compd	IC_{50} (μM)	epimastigotes IC_{50} (μM)	amastigotes IC_{50} (μM)	trypomastigotes (μM)[b]	IS[c]	K1 strain IC_{50} (μM)	IS[d]
1a	48.6 ± 19.7 (3)	8.7 ± 2.3 (3)	14.2 ± 2.3 (4)	50	3.4	36.2 ± 3.2 (3)	1.3
1b	18.9 ± 9.1 (3)	3.9 ± 0.4 (3)	4.7 ± 1.7 (3)	25	4.0	74.6 ± 3.0 (3)	0.25
1c	21.5 ± 10.6 (3)	2.8 ± 0.4 (3)	5.7 ± 2.0 (5)	6.25	3.8	30.9 ± 7.7 (3)	0.7
1f	43.2 ± 11.5 (5)	6.3 ± 1.2 (3)	6.7 ± 2.4 (3)	50	6.4	74.6 ± 12.7 (4)	1.7
2b	3.7 ± 0.6 (3)	ND	ND	ND	ND	0.101 ± 0.03 (3)	41.9
2c	5.9 ± 3.8 (4)	3.2 ± 0.6 (3)	0.18 ± 0.13 (3)	6.25	33	1.1 ± 0.4 (6)	5.5
2d	23.8 ± 2.8 (3)	ND	ND	ND	ND	2.2 ± 0.9 (6)	10.6
2e	5.5 ± 3.1 (4)	0.23 ± 0.03 (3)	0.34 ± 0.13 (5)	1.5	16.6	1.1 ± 0.3 (8)	5.5
3	15.2 ± 5.9 (3)	>200	5.7 ± 2.6 (3)	100	2.7	6.4 ± 2.8 (3)	2.4
35a	8.1 ± 2.3 (3)	1.3 ± 0.2 (3)	0.125 ± 0.008 (4)	50	64.8	0.33 ± 0.05 (5)	24.5
35b	1.4 ± 0.9 (3)	0.30 ± 0.05 (3)	0.074 ± 0.009 (4)	12.5	18.9	0.062 ± 0.023 (4)	22.5
35c	6.8 ± 3.2 (3)	0.34 ± 0.17 (3)	0.39 ± 0.09 (5)	50	17.4	0.48 ± 0.09 (6)	14.1
35d	15.1 ± 3.8 (3)	0.73 ± 0.07 (3)	3.3 ± 1.1 (6)	12.5	4.6	1.3 ± 0.4 (8)	12.6
35e	6.8 ± 0.4 (3)	0.54 ± 0.32 (3)	0.88 ± 0.17 (5)	12.5	7.7	1.1 ± 0.2 (8)	6.2

[a] IC_{50} values are the means ± standard deviation of several independent experiments whose numbers are indicated in parentheses. ND: not determined. [b] Concentration of drug tested with no detectable effects by microscopy on the trypomastigote motility (mean of 2 independent experiments). [c] Index of selectivity (IS) defined by the ratio IC_{50} on L6 cells/IC_{50} on the intracellular amastigote proliferation. [d] Index of selectivity (IS) defined by the ratio IC_{50} on L6 cells/IC_{50} on *P. falciparum*.

Table 9. In Vitro Cytotoxicity and Antitrypanosomial and Antiplasmodial Activities of δ-Carbolines[a]

	L6 cells	*T. cruzi*				*P. falciparum*	
compd	IC_{50} (μM)	epimastigotes IC_{50} (μM)	amastigotes IC_{50} (μM)	trypomastigotes (μM)[b]	IS[c]	K1 strain IC_{50} (μM)	IS[d]
6a	229 ± 97 (3)	23.2 ± 4.8 (3)	23.5 ± 7.7 (4)	100	9.7	104 ± 17 (3)	2.2
6b	82.4 ± 38.5 (3)	6.6 ± 0.8 (3)	10.4 ± 4.4 (4)	100	7.9	45.6 ± 7.7 (3)	1.8
6c	44.9 ± 5.6 (3)	21.4 ± 4.3 (3)	12.2 ± 5.1 (3)	50	3.7	66.8 ± 17.8 (3)	0.7
6d	14.3 ± 3.7 (3)	11.1 ± 1.6 (3)	11.9 ± 7.4 (3)	25	1.2	38.5 ± 6.9 (3)	0.4
6e	16.2 ± 8.5 (3)	34.4 ± 9.1 (3)	18.9 ± 11.1 (3)	50	0.9	23.9 ± 8.1 (3)	0.7
6f	75.1 ± 47.3 (3)	58.4 ± 10.6 (3)	18.8 ± 8.9 (5)	25	4	33.1 ± 3.3 (3)	2.3
6g	41.6 ± 7.5 (3)	26.4 ± 5.4 (3)	6.4 ± 3.1 (3)	100	6.5	16.3 ± 3.7 (3)	2.6
6h	1.8 ± 0.5 (3)	11.2 ± 4.4 (3)	1.8 ± 0.2 (3)	200	1	14.8 ± 2.4 (3)	0.12
6i	37.2 ± 7.8 (3)	ND	8.6 ± 6.1 (5)	200	4.3	129 ± 16 (4)	0.3
6j	14.3 ± 5.1 (3)	10.4 ± 0.6 (3)	11.2 ± 3.1 (3)	50	1.3	29.3 ± 1.9 (3)	0.5
6k	204 (2)	49.8 ± 5.3 (3)	20.8 ± 6.5 (4)	50	9.8	22.1 ± 4.1 (3)	9.2
6l	22.7 ± 9.5 (3)	18.6 ± 7.8 (3)	3.3 ± 1.4 (3)	100	6.9	14.2 ± 1.7 (3)	1.6
6m	54.0 ± 16.8 (4)	6.8 ± 1.6 (3)	8.4 ± 4.4 (3)	200	6.4	16.8 ± 2.4 (3)	3.2
6n	>156 (3)	>312 (3)	108.4 ± 56.8 (3)	100	>1.5	259 ± 22 (3)	>0.6
6o	21.3 ± 12.1 (3)	2.3 ± 0.8 (3)	1.9 ± 0.9 (5)	6.25	11.2	23.6 ± 1.9 (3)	0.9
6p	235 ± 37 (3)	129 ± 40 (3)	122 ± 54 (4)	200	1.9	56.5 ± 9.8 (3)	4.2
7a	>150 (5)	>300 (3)	199 ± 63 (3)	100	>1	1.5 ± 0.6 (4)	>100
7b	>230 (5)	428 ± 38 (3)	192 ± 91 (3)	200	>1	1.6 ± 0.7 (4)	>138
8	>220 (5)	>550 (3)	258 ± 137 (3)	200	>1	2.2 ± 0.6 (4)	>100

[a] IC_{50} values are the means ± standard deviation of several independent experiments whose numbers are indicated between brackets. ND: not determined. [b] Concentration of drug tested with no detectable effects by microscopy on the trypomastigote motility (mean of 2 independent experiments). [c] Index of selectivity (IS) defined by the ratio IC_{50} on L6 cells/IC_{50} on the intracellular amastigote proliferation. [d] Index of selectivity (IS) defined by the ratio IC_{50} on L6 cells/IC_{50} on *P. falciparum*.

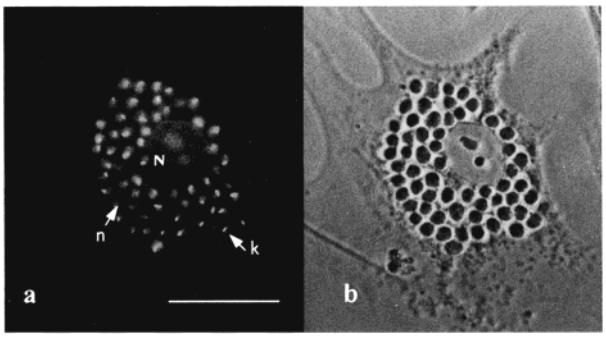


Figure 1. Intracellular localization of cryptolepine into *T. cruzi*-infected human fetal fibroblasts. Cells infected by amastigote stages were incubated for 1 h at 37 °C with 5 μM cryptolepine **35a** and were immediately observed after washes by epifluorescence using UV filters. Nucleus (N) of fibroblast is weakly labeled. Strong staining is associated with a parasite barlike structure that corresponds to kinetoplast (k). Round parasite structure is also stained that could correspond to the parasite nucleus (n). Bar scale: 50 μm.

^{13}C NMR ($CDCl_3$) δ 154.5 (d, 1C, C3, J = 258.3), 146.69 (s, 1C, C1a), 129.31 (d, 1C, CHquino, J = 2.7), 128.79 (d, 1C, CHquino, J = 0.9), 128.11 (d, 1C, CHquino, J = 0.8), 127.95 (s, 1C, CHquino), 127.87 (s, 1C, Cquino), 127.10 (d, 1C, C4, J = 5.0), 110.50 (d, 1C, C2, J = 31.3); ^{19}F NMR ($CDCl_3$) δ −105.14 (d, 1F, J = 8.0); IR (KBr) 1594, 1491, 1396, 1330, 1204, 1170, 1023, 912, 774, 755, 711, 609. Anal. (C_9H_5FIN) C, H, N.

4-Deutero-3-fluoro-2-iodoquinoline (12). General procedure A, using deuterium oxide as the electrophile, gave 95% (NMR integration) of **12**. This product was not isolated: ^1H NMR ($CDCl_3$) δ 8.10 (dd, 1H, H8, J = 1.0, 8.0), 7.81 (dd, 1H, H5, J = 1.5, 8.0), 7.75−7.58 (m, 2H, H6 and H7); ^{19}F NMR ($CDCl_3$) δ −105.38 (s, 1F).

2,4-Diiodo-3-fluoroquinoline (13). General procedure A, using iodide as the electrophile, gave 3.91 g (98%) of **13**: mp 162 °C; ^1H NMR ($CDCl_3$) δ 8.07−7.96 (m, 2H, H5 and H8), 7.75−7.63 (m, 2H, H6 and H7); ^{13}C NMR ($CDCl_3$) δ 154.71 (d, 1C, C3, J = 254.0), 146.40 (d, 1C, C1a, J = 2.7), 130.94 (d, 1C, Cquino, J = 5.3), 130.20 (s, 1C, CHquino), 129.85 (d, 1C, CHquino, J = 3.0), 129.43 (s, 1C, CHquino), 129.19 (d, 1C, CHquino, J = 1.2), 107.83 (d, 1C, C2, J = 35.2), 93.70 (d, 1C, C4, J = 25.8); ^{19}F NMR ($CDCl_3$) δ −79.91 (s, 1F); IR (KBr) 1557, 1371, 1360, 1324, 1307, 1290, 1217, 1146, 756, 734, 641. Anal. ($C_9H_4FI_2N$) C, H, N.

4-Chloro-3-fluoro-2-iodoquinoline (14). General procedure A, using hexachloroethane as the electrophile, gave 2.28 g (74%) of **14**: mp 91 °C; ^1H NMR ($CDCl_3$) δ 8.10−7.97 (m, 2H, H5 and H8), 7.93−7.59 (m, 2H, H6 and H7); ^{13}C NMR

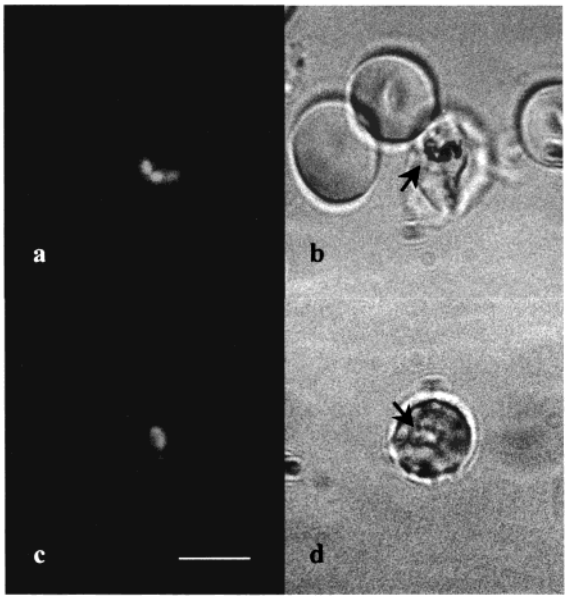


Figure 2. Intracellular localization of cryptolepine **35a** and 1-methyl-*δ*-carboline **7b** into *P. falciparum*-infected erythrocytes. Cells were incubated for 1 h at 37 °C with 5 μM cryptolepine (a, b) or 100 μM 1-methyl-*δ*-carboline (c, d) and immediately observed after washes using an epifluorescence microscope fitted with UV filters. (a, b) Schizont-infected erythrocyte (arrow) labeled with cryptolepine and corresponding phase contrast image, respectively. (c, d) Ring-infected erythrocyte (arrow) labeled with 1-methyl-*δ*-carboline and corresponding phase contrast image, respectively. Bar scale: 5 μm.

($CDCl_3$) δ 150.42 (d, 1C, C3, J = 257.9), 148.86 (s, 1C, C1a), 146.31 (d, 1C, C4, J = 13.2), 130.00 (d, 1C, CHquino, J = 2.5), 129.21 (s, 1C, CHquino), 128.81 (s, 1C, CHquino), 126.35 (s, 1C, Carom), 123.73 (d, 1C, CHarom, J = 5.6), 109.12 (d, 1C, C2, J = 21.3); ^{19}F NMR ($CDCl_3$) δ −104.00 (s, 1F); IR (KBr) 1578, 1486, 1383, 1331, 1302, 1145, 942, 833, 764, 668. Anal. (C_9H_4ClFIN) C, H, N.

3-Fluoro-2-iodo-4-methylquinoline (15). General procedure A, using iodomethane as the electrophile, gave 65% (NMR integration) of **15**. This product was not isolated.

3-Fluoro-4-(1-hydroxyethyl)-2-iodoquinoline (16). General procedure A, using acetaldehyde as the electrophile, gave 2.51 g (79%) of **16**: mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (comp, 1H, H8 or H5), 7.91 (comp, 1H, H5 or H8), 7.62−7.49 (m, 2H, H6 and H7), 5.65 (q, 1H, CH, J = 6.7), 4.17 (s, 1H, OH), 1.64 (s, 3H, Me, J = 6.7); ^{13}C NMR ($CDCl_3$) δ 150.64 (d, 1C, C3, J = 255.0), 147.04 (d, 1C, C1a, J = 3.0), 132.83 (d, 1C, C4, J = 11.0), 129.25 (d, 1C, Cquino, J = 1.1), 128.94 (d, 1C, CHquino, J = 2.6), 127.60 (s, 1C, CHquino), 125.79 (s, 1C, C4a, J = 1.5), 125.08 (d, 1C, CHquino, J = 5.6), 110.63 (d, 1C, C2, J = 34.3), 64.00 (d, 1C, CH(OH), J = 3.7), 23.12 (d, 1C, Me, J = 1.2); ^{19}F NMR ($CDCl_3$) δ −108.57 (s, 1F); IR (KBr) 3439, 3333, 2984, 2928, 1579, 1550, 1392, 1365, 1326, 1165, 1037, 762, 684, 636, 579. Anal. ($C_{11}H_9FINO$) C, H, N.

3-Fluoro-4-(1-hydroxybenzyl)-2-iodoquinoline (17). General procedure A, using benzaldehyde as the electrophile, gave 2.85 g (75%) of **17**: mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (comp, 1H, Hquino), 8.07 (comp, 1H, Hquino), 7.63 (comp, 1H, Hquino), 7.54−7.30 (m, 6H, Harom), 6.75 (s, 1C, CH(OH)), 3.51 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 151.5 (d, 1C, C3, J = 255.4), 147.41 (d, 1C, C1a, J = 3.3), 140.74 (s, 1C, Carom), 131.10 (d, 1C, C4, J = 11.1), 129.31 (s, 1C, CHarom), 129.30 (d, 1C, Carom, J = 2.2), 128.62 (s, 2C, CHph), 127.80 (d, 1C, CHarom, J = 3.9), 125.82 (d, 1C, CHarom, J = 5.0), 125.80 (s, 1C, CHarom), 125.54 (s, 1C, CHph), 125.52 (s, 2C, CHph), 110.42 (d, 1C, C2, J = 34.3), 68.42 (d, 1C, CH(OH), J = 3.3); ^{19}F NMR ($CDCl_3$) δ −108.95 (s, 1F); IR (KBr) 3307, 1579, 1497, 1450, 1324, 1160, 1046, 768, 705, 658. Anal. ($C_{16}H_{11}FINO$) C, H, N.

3-Fluoro-2-iodo-4-quinolinecarboxaldehyde (18). General procedure A, using ethyl formate as the electrophile, gave 2.85 g (95%) of **18**: mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 10.79 (s, 1H, CHO), 8.98 (comp, 1H, H5 or H8), 8.14 (comp, 1H, H8 or H5), 7.77 (m, 2H, H6 and H7); ^{13}C NMR ($CDCl_3$) δ 188.15 (d, 1C, CHO, J = 9.4), 157.20 (d, 1C, C3, J = 271.4), 147.56 (d, 1C, C8a, J = 3.9), 130.83 (s, 1Carom), 129.95 (d, 1Carom, J = 2.2), 129.32 (s, 1Carom), 125.14 (d, 1Carom, J = 5.5), 123.14 (s, 1Carom), 120.28 (d, 1Carom, J = 5.5), 110.70 (d, 1C, C2, J = 32.5); ^{19}F NMR ($CDCl_3$) δ −111.95 (s, 1F); IR (KBr) 2925, 1693, 1542, 1494, 1396, 1315, 1181, 1071, 765, 706; MS (electron impact) m/z 301 (M^+, 100%). Anal. ($C_{10}H_5FINO$) C, H, N.

3-Fluoro-4-iodo-2-trimethylsilylquinoline (19). General procedure A, using trimethylsilyl chloride as the electrophile (simultaneously introduced with the starting material), gave 95% (^{1}H NMR integration) of **19**. This product was not isolated: ^{1}H NMR ($CDCl_3$) δ 8.12−8.03 (m, 2H, H5 and H8), 7.69−7.58 (m, 2H, H6 and H7), 0.61 (s, 9H, $SiMe_3$).

General procedure A, using deuterium oxide as electrophile, gave 94% (NMR) of **12**, 2% (NMR) of **20** and 0.5% (NMR) of **13**. These products were not isolated.

General Procedure D: Cyclization. Anhydrous pyridinium chloride (χ g) at its boiling point (215 °C) was added to the corresponding phenylquinoline (χ/5 mmol) and the mixture was refluxed for 30 min. The resulting hot solution was poured onto a mixture of ice (χ g) and concentrated ammonia (χ mL). Extraction of the aqueous layer with ethyl acetate, drying with magnesium sulfate, solvent removal and flash chromatography on silica (light petroleum/ethyl acetate: 7/3) gave a pure product.

11-Methyl-10*H*-indolo[3,2-*b*]quinoline (1b). General procedure D (χ = 5.0), using **33**, gave 175 mg (75%) of **1b** as a white powder: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H, NH), 8.38 (d, 1H, H6, J = 7.9), 8.23 (m, 2H, Harom), 7.71−7.59 (m, 4H, Harom), 7.31 (t, 1H, Harom, J = 7.5), 2.92 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 144.82 (s, 1C, Carom), 143.94 (s, 1C, Carom), 143.61 (s, 1C, Carom), 131.87 (s, 1C, Carom), 129.53 (s, 1C, CHarom), 129.33 (s, 1C, CHarom), 125.98 (s, 1C, Carom), 125.76 (s, 1C, CHarom), 124.60 (s, 1C, CHarom), 123.35 (s, 1C, CHarom), 121.47 (s, 1C, Carom), 121.40 (s, 1C, CHarom), 121.25 (s, 1C, Carom), 119.25 (s, 1C, CHarom), 111.46 (s, 1C, CHarom), 12.43 (s, 1C, Me); IR (KBr) 3161, 3072, 1633, 1617, 1560, 1494, 1460, 1395, 1373, 1341, 1224, 1142, 744, 719; MS (electron impact) m/z 232 (M^+, 100%), 204 (8%). Anal. ($C_{16}H_{12}N_2 \cdot 0.25H_2O$) C, H, N.

11-Ethyl-10*H*-indolo[3,2-*b*]quinoline (1c). General procedure D (χ = 5.0), using **32**, gave 182 mg (74%) of **1c** as a pale yellow solid: mp 238 °C; ^{1}H NMR (DMSO-d_6) δ 11.42 (s, 1H, NH), 8.33 (d, 1H, H6, J = 8,0), 8.20−8.18 (m, 2H, Harom), 7.66−7.54 (m, 4H, Harom), 7.26 (ddd, 1H, H7, J = 1.4, 6.2, 8.0), 3.39 (q, 2H, CH_2 (Et), J = 7.3), 1.34 (t, 3H, Me (Et), J = 7.3); ^{13}C NMR (DMSO-d_6) δ 144.97 (s, 1C, Carom), 143.94 (1C, Carom), 143.85 (s, 1C, Carom), 130.93 (s, 1C, Carom), 129.58 (s, 1C, CHarom), 129.50 (s, 1C, CHarom), 127.31 (s, 1C, Carom), 125.77 (s, 1C, CHarom), 124.84 (s, 1C, Carom), 124.77 (s, 1C, CHarom), 123.00 (s, 1C, CHarom), 121.42 (s, 1C, Carom), 121.37 (s, 1C, CHarom), 119.27 (s, 1C, CHarom), 111.52 (s, 1C, CHarom), 19.65 (s, 1C, CH_2 (Et)), 14.35 (s, 1C, Me (Et)); IR (KBr) 3064, 2967, 2869, 1615, 1565, 1492, 1450, 1397, 1340, 1243, 1220, 1141, 748; MS (electron impact) m/z 246 (M^+, 100%), 231 (91%). Anal. ($C_{17}H_{14}N_2$) C, H, N.

11-Isopropyl-10*H*-indolo[3,2-*b*]quinoline (1d). General procedure D (χ = 2.5), using **33**, gave 129 mg (85%) of **33** as an orange solid: mp 216 °C; ^{1}H NMR (DMSO-d_6) δ 11.04 (s, 1H, NH), 8.39 (d, 1H, H4, J = 8,4), 8.31 (d, 1H, H6, J = 7.7), 8.18 (d, 1H, H1, J = 8,4), 7.65−7.53 (m, 4H, Harom), 7.25 (td, 1H, Harom, J = 2.2, 7.7), 4.16 (ht, 1H, CH (*i*Pr), J = 7.1), 1.61 (d, 6H, Me (*i*Pr), J = 7.1); ^{13}C NMR (DMSO-d_6) δ 145.35 (s, 1C, Carom), 144.21 (s, 2C, Carom), 143.76 (s, 2C, Carom), 132.21 (s, 1C, Carom), 130.17 (s, 1C, CHarom), 129.38 (s, 1C, CHarom), 126.34 (s, 1C, CHarom), 125.15 (s, 1C, CHarom), 124.70 (s, 1C, Carom), 123.80 (s, 1C, CHarom), 121.65 (s, 1C, CHarom), 120.79 (s, 1C, Carom), 119.77 (s, 1C, CHarom),

112.07 (s, 1C, CHarom), 27.17 (s, 1C, CH (*i*Pr)), 27.05 (s, 2C, Me (*i*Pr)); IR (KBr) 3154, 3068, 2966, 1624, 1613, 1562, 1492, 1367, 1337, 1217, 769, 745; MS (chemical ionization) *m/z* 261 (MH^+, 100%). Anal. ($C_{18}H_{16}N_2$) C, H, N.

11-Phenyl-10*H*-indolo[3,2-*b*]quinoline (1e). General procedure D ($\chi = 5.0$), using **34**, gave 235 mg (80%) of **34** as a pale yellow solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1H, NH), 8.36 (d, 1H, H6, $J = 7.7$), 8.25 (dd, 1H, H1, $J = 0.8, 8.4$), 7.76 (dd, 1H, H4, $J = 0.7, 8.4$), 7.72−7.62 (m, 6H, Harom and H2), 7.59−7.48 (m, 2H, H8 and H3), 7.28 (ddd, 1H, H7, $J = 1.5/6.5/7.5$); IR (KBr) 3050, 2958, 2872, 2756, 2670, 1613, 1566, 1489, 1472, 1400, 1382, 1338, 1220, 1141, 745, 697; MS (electron impact) *m/z* 294 (M^+, 100%), 147 (16%). Anal. ($C_{21}H_{14}N_2$) C, H, N.

11-Chloro-10*H*-indolo[3,2-*b*]quinoline (1f). General procedure D ($\chi = 2.5$), using **25**, gave 147 mg (55%) of **1f** as a pale green solid: mp 221 °C; ^{1}H NMR (DMSO-d_6) δ 11.83 (s, 1H, NH), 8.35 (d, 1H, H6, $J = 7.8$), 8.31−8.25 (m, 2H, Harom), 7.80−7.60 (m, 4H, Harom), 7.34 (ddd, 1H, H7, $J = 1.8, 6.4, 7.1$); ^{13}C NMR (DMSO-d_6) δ 146.40 (s, 1C, Carom), 144.49 (s, 1C, Carom), 144.17 (s, 1C, Carom), 130.73 (s, 1C, Carom), 130.45 (s, 1C, CHarom), 129.63 (s, 1C, Carom), 127.19 (s, 1C, Carom), 126.72 (s, 1C, Carom), 123.96 (s, 1C, CHarom), 122.47 (s, 1C, CHarom), 122.06 (s, 1C, CHarom), 121.53 (s, 1C, Carom), 120.58 (s, 1C, CHarom), 118.30 (s, 1C, CHarom), 112.38 (s, 1C, CHarom); IR (KBr) 3161, 3057, 1614, 1551, 1489, 1459, 1392, 1372, 1338, 1225, 1144, 1108, 1047, 885, 845, 820, 745, 713; MS (electron impact) *m/z* 252 (M^+, 100%), 216 (15%), 190 (10%), 126 (15%). Anal. ($C_{15}H_9ClN_2$) C, H, N.

General Procedure E: Triflate Salts. To deoxygenated and freshly distilled toluene (3 mL) were added 0.5 mmol of the corresponding carboline and 0.95 mmol of methyl triflate. The resulting solution was stirred for 24 h at room temperature, filtered and the salt washed with diethyl ether and dried.

1*N*-Methyl-*δ*-carbolinium Triflate (7a). General procedure E, using the *δ*-carboline, gave 84 mg (97%) of **7a** as a white solid: mp 230 °C; ^{1}H NMR (DMSO-d_6) δ 12.77 (s, 1H, NH), 8.83 (d, 1H, H2, $J = 5.8$), 8.64 (d, 1H, H4, $J = 8.4$), 8.45 (d, 1H, H6, $J = 8.1$), 7.97 (dd, 1H, H3, $J = 8.4, 5.8$), 7.78−7.76 (m, 2H, H8 and H9), 7.45 (td, 1H, H7, $J = 1.9, 8.1$), 4.78 (s, 3H, NMe); ^{13}C NMR (DMSO-d_6) δ 141.74 (s, 1C, Carom), 137.79 (s, 1C, Carom), 135.73 (s, 1C, CHarom), 131.04 (s, 1C, Carom), 131.24 (s, 1C, CHarom), 126.49 (s, 1C, CHarom), 123.99 (s, 1C, CHarom), 121.64 (s, 1C, CHarom), 121.35 (s, 1C, CHarom), 120.74 (q, 1C, CF_3, $J = 322.3$), 114.33 (s, 1C, Carom), 113.17 (s, 1C, CHarom), 46.12 (s, 1C, NMe); ^{19}F NMR (DMSO-d_6) δ −73.29 (s, 3F, CF_3); IR (KBr) 3185, 3102, 1638, 1462, 1254, 1224, 1162, 725, 63. Anal. ($C_{13}H_{11}F_3N_2O_3S$) C, H, N, S.

5*N*-Methylbenzo-*δ*-carbolinium Triflate (35a). General procedure E, using **1a**, gave 162 mg (97%) of **35a** as an orange solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H, NH), 9.30 (s, 1H, H11), 8.84−8.75 (m, 2H, Harom), 8.58 (d, 1H, H6 or H9, $J = 7.6$), 8.17 (t, 1H, Harom, $J = 8.0$), 7.98−7.84 (m, 3H, Harom), 7.52 (t, 1H, Harom, $J = 7.5$), 5.04 (s, 3H, NMe); ^{13}C NMR (DMSO-d_6) δ 142.21 (s, 1C, Carom), 139.48 (s, 1C, Carom), 138.84 (s, 1C, Carom), 132.75 (s, 1C, Carom), 129.99 (s, 1C, CHarom), 127.16 (s, 1C, CHarom), 126.79 (s, 1C, Carom), 125.36 (s, 1C, CHarom), 124.30 (s, 1C, CHarom), 123.34 (s, 1C, CHarom), 123.04 (s, 1C, CHarom), 121.31 (s, 1C, CHarom), 121.23 (q, 1C, CF_3, $J = 322.3$), 119.87 (s, 1C, CHarom), 119.47 (s, 1C, Carom), 112.79 (s, 1C, CHarom), 51.05 (s, 1C, NMe); ^{19}F NMR (DMSO-d_6) δ −73.31 (s, 3F, CF_3); IR (KBr) 3175, 3119, 3036, 1508, 1273, 1223, 1155, 1031, 753, 745, 633. Anal. ($C_{17}H_{13}F_3N_2O_3S$) C, H, N, S.

5*N*,11-Dimethylbenzo-*δ*-carbolinium Triflate (35b). General procedure E, using **1b**, gave 182 mg (92%) of **35b** as a yellow solid: mp >260 °C; ^{1}H NMR (DMSO-d_6) δ 12.84 (s, 1H, NH), 8.79−8.74 (m, 2H, Harom), 8.65 (d, 1H, Harom, $J = 8.4$), 8.20 (t, 1H, Harom, $J = 7.3$), 8.00−7.91 (m, 2H, Harom), 7.84 (d, 1H, Harom, $J = 8.0$), 7.51 (t, 1H, Harom, $J = 7.7$), 5.00 (s, 3H, NMe), 3.23 (s, 3H, Me (C11)); ^{13}C NMR (DMSO-d_6) δ 145.17 (s, 1C, Carom), 136.39 (s, 1C, Carom), 135.76 (s, 1C, Carom), 135.14 (s, 1C, Carom), 133.61 (s, 1C, CHarom), 132.67 (s, 1C, Carom), 132.13 (s, 1C, CHarom), 126.84 (s, 1C, CHarom), 126.09 (s, 1C, CHarom), 125.88 (s, 1C, CHarom), 125.18 (s, 1C, Carom), 121.34 (s, 1C, CHarom), 121.03 (q, 1C, CF_3, $J = 321,7$), 118.12 (s, 1C, CHarom), 114,03 (s, 1C, Carom), 112.95 (s, 1C, CHarom), 39.85 (s, 1C, NMe), 14.26 (s, 1C, Me (C11)); ^{19}F NMR (DMSO-d_6) δ −73.31 (s, 3F, CF_3); IR (KBr) 3206, 1638, 1616, 1587, 1371, 1302, 1283, 1241, 1160, 1027, 755, 638. Anal. ($C_{18}H_{15}F_3N_2O_3S$) C, H, N, S.

11-Ethyl-5*N*-methylbenzo-*δ*-carbolinium Triflate (35c). General procedure E, using **1c**, gave 201 mg (98%) of **35c** as a yellow solid: mp 234 °C; ^{1}H NMR (DMSO-d_6) δ 12.86 (s, 1H, NH), 8.79 (d, 1H, Harom, $J = 8.4$), 8.76 (d, 1H, Harom, $J = 7.2$), 8.70 (d, 1H, H1, $J = 8.7$), 8.18 (t, 1H, Harom, $J = 7.0$), 8.00−7.91 (m, 2H, Harom), 7.85 (d, 1H, Harom, $J = 8.0$), 7.51 (t, 1H, Harom, $J = 8.0$), 4.99 (s, 3H, NMe), 3.68 (q, 2H, CH_2 (Et), $J = 7.7$), 1.42 (t, 3H, Me (Et), $J = 7.7$); ^{13}C NMR (DMSO-d_6) δ 145.35 (s, 1C, Carom), 140.82 (s, 1C, Carom), 137.00 (s, 1C, Carom), 135.61 (s, 1C, Carom), 133.71 (s, 1C, CHarom), 132.10 (s, 1C, Carom), 127.07 (s, 1C, Carom), 126.26 (s, 1C, CHarom), 125.56 (s, 1C, CHarom), 125.56 (s, 1C, Carom), 124.29 (s, 1C, CHarom), 121.52 (q, 1C, CF_3, $J = 321.5$), 121.38 (s, 1C, CHarom), 118.51 (s, 1C, CHarom), 114.32 (s, 1C, CHarom), 113.15 (s, 1C, CHarom), 60.12 (s, 1C, NMe), 21.01 (s, 1C, CH_2 (Et)), 14.50 (s, 1C, Me (Et)); ^{19}F NMR (DMSO-d_6) δ −73.11 (s, 3F, CF_3); IR (KBr) 3161, 3111, 2975, 1634, 1506, 1294, 1237, 1216, 1143, 1029, 754, 630. Anal. ($C_{19}H_{17}F_3N_2O_3S$) C, H, N, S.

11-Isopropyl-5*N*-methylbenzo-*δ*-carbolinium Triflate (35d). General procedure E, using **1d**, gave 98 mg (92%) of **35d** as a yellow solid: mp 224 °C; ^{1}H NMR (DMSO-d_6) δ 12.42 (s, 1H, NH), 8.85 (d, 1H, H4, $J = 8.3$), 8.76 (d, 1H, Harom, $J = 8.2$), 8.75 (d, 1H, Harom, $J = 8.8$), 8.16 (t, 1H, Harom, $J = 7.5$), 7.97−7.88 (m, 3H, Harom), 7.51 (t, 1H, Harom, $J = 7.3$), 4.99 (s, 3H, NMe), 4.12 (ht, 1H, CH (*i*Pr), $J = 7.2$), 1.71 (d, 6H, Me (*i*Pr), $J = 7.2$); ^{13}C NMR (DMSO-d_6) δ 145.41 (s, 1C, Carom), 144.18 (s, 1C, Carom), 137.83 (s, 1C, Carom), 135.80 (s, 1C, Carom), 133.86 (s, 1C, CHarom), 132.05 (s, 1C, CHarom), 131.41 (s, 1C, CHarom), 126.97 (s, 1C, CHarom), 126.27 (s, 1C, CHarom), 126.02 (s, 1C, CHarom), 124.24 (s, 1C, Carom), 121.69 (q, 1C, CF_3, $J = 321.5$), 121.54 (s, 1C, CHarom), 118.69 (s, 1C, CHarom), 114.00 (s, 1C, Carom), 113.36 (s, 1C, CHarom), 40.38 (s, 1C, NMe), 28.41 (s, 1C, CH (*i*Pr)), 20.75 (s, 2C, Me (*i*Pr)); ^{19}F NMR (DMSO-d_6) δ −73.33 (s, 3F, CF_3); IR (KBr) 3503, 3063, 2979, 2884, 1630, 1508, 1283, 1254, 1226, 1160, 1032, 752, 637. Anal. ($C_{20}H_{19}F_3N_2O_3S$) C, H, N, S.

5*N*-Methyl-11-phenylbenzo-*δ*-carbolinium Triflate (35e). General procedure E, using **1e**, gave 156 mg (68%) of **35e** as a yellow solid: mp 210 °C; ^{1}H NMR (DMSO-d_6) δ 12.31 (s, 1H, NH), 8.86−8.83 (m, 2H, Harom), 8.19−7.53 (m, 11H, Harom), 5.09 (s, 3H, NMe); ^{13}C NMR (DMSO-d_6) δ 146.26 (s, 1C, Carom), 138.03 (s, 1C, Carom), 136.74 (s, 1C, Carom), 135.84 (s, 1C, Carom), 133.97 (s, 1C, CHarom), 132.19 (s, 1C, CHarom), 132.09 (s, 1C, Carom), 131.59 (s, 1C, Carom), 130.29 (s, 1C, CHarom), 130.11 (s, 2C, CHph), 129.57 (s, 2C, CHph), 127.44 (s, 1C, CHarom), 127.00 (s, 1C, CHarom), 126.34 (s, 1C, CHarom), 124.96 (s, 1C, Carom), 122.35 (q, 1C, CF_3, $J = 324.5$), 121.64 (s, 1C, Carom), 118.33 (s, 1C, CHarom), 114.17 (s, 1C, Carom), 113.50 (s, 1C, CHarom), 40.41 (s, 1C, NMe); ^{19}F NMR (DMSO-d_6) δ −73.32 (s, 3F, CF_3); IR (KBr) 3226, 3065, 1625, 1585, 1506, 1294, 1239, 1160, 1028, 761, 636. Anal. ($C_{23}H_{17}F_3N_2O_3S$) H, N, S; C: calcd, 60.26; found, 58.22.

General Procedure F: Synthesis of Cryptolepines. To an aqueous solution of sodium carbonate (5 mL, 5%) was added 0.25 mmol of the corresponding triflate. The resulting solution was stirred for 15 min before adding 10 mL of distilled chloroform. Extraction of the aqueous layer with chloroform, drying with magnesium sulfate and solvent removal gave a crude product which was purified by flash chromatography on alumina (chloroform then chloroform/methanol: 9/1).

1*N*-Methyl-*δ*-carboline (8). General procedure F, using **7a**, gave 30 mg (65%) of **8** as an orange solid: mp 202−206 °C dec; ^{1}H NMR ($CDCl_3$) 8.37 (d, 1H, H2, $J = 8.3$), 8.07 (d, 1H, H6 ou H9, $J = 8.3$), 7.91 (d, 1H, H9 or H6, $J = 8.7$), 7.70 (d,

1H, H4, J = 5.6), 7.55 (td, 1H, H7 or H8, J = 1.0, 7.9), 7.34 (dd, 1H, H3, J = 5.6, 8.3), 7.14 (td, 1H, H8 or H7, J = 1.0, 8.3), 4,58 (s, 3H, NMe); ^{13}C NMR ($CDCl_3$ − 100 MHz − Cr-(acac)) δ 155.21 (s, 1C, Carom), 146.27 (s, 1C, CHaom), 129.06 (s, 1C, Carom), 128.94 (s, 1C, CHarom), 128.40 (s, 1C, Carom), 121.89 (s, 1C, CHarom), 119.52 (s, 1C, CHarom), 118.34 (s, 1C, CHarom), 116.30 (s, 1C, CHarom), 114.87 (s, 1C, CHarom), 45.49 (s, 1C, NMe); IR (KBr) 3340, 3080, 1624, 1589, 1475, 1434, 1382, 1333, 1315, 1272, 1258, 784, 748, 720; MS (electron impact) m/z 182 (M^+, 100%), 167 (10%). Anal. ($C_{12}H_{10}N_2$) C, H, N.

5*N*,11-Dimethylindolo[3,2-*b*]quinoline or 11-Methylcryptolepine (2b). General procedure F, using **35b**, gave 48 mg (64%) of **2b** as a dark purple solid: mp 232 °C; ^{1}H NMR ($CDCl_3$) δ 8.40 (dd, 1H, Harom, J = 1.1, 8.4), 8.20 (d, 1H, Harom, J = 8.4), 8.10 (d, 1H, Harom, J = 8.7), 7.91 (d, 1H, Harom, J = 8.4), 7.81 (ddd, 1H, Harom, J = 1.5, 7.0, 8.4), 7.63 (td, 1H, Harom, J = 1.1, 8.4), 7.53 (ddd, 1H, Harom, J = 1.0, 6.6, 7.5), 4.76 (s, 3H, NMe), 3.27 (s, 3H, Me); IR (KBr) 3045, 1619, 1488, 1459, 1368, 1341, 1300, 1268, 1239, 1128, 741; MS (chemical ionization) m/z 247 (MH^+, 100%), 233 (55%). Anal. ($C_{17}H_{14}N_2$·2.8H_2O) C, H, N.

11-Ethyl-5*N*-methylindolo[3,2-*b*]quinoline or 11-Ethylcryptolepine (2c). General procedure F, using **35c**, gave 48 mg (64%) of **2c** as a purple solid: mp 200 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (dd, 1H, H1 or H4, J = 1.1, 8.4), 8.04 (dd, 1H, H4 or H1, J = 1.1, 8.4), 8.00 (d, 1H, H9 or H6, J = 8.8), 7.85 (d, 1H, H6 or H9, J = 8.7), 7.73 (ddd, 1H, Harom, J = 1.4, 6.6, 7.8), 7.56 (ddd, 1H, Harom, J = 1.1, 6.6, 7.7), 7.42 (ddd, 1H, Harom, J = 1.1, 6.6, 7.5), 6.89 (ddd, 1H, Harom, J = 1.1, 6.6, 7.5), 4.61 (s, 3H, Me), 4.61 (q, 2H, CH_2 (Et), J = 7.7), 1.45 (t, 3H, Me (Et), J = 7.7); ^{13}C NMR ($CDCl_3$ − 100 MHz − Cr(acac)) δ 159.92 (s, 1C, Carom), 143.93 (s, 1C, Carom), 142.90 (s, 1C, CHarom), 137.65 (s, 1C, Carom), 133.22 (s, 1C, Carom), 130.38 (s, 1C, C arom), 128.47 (s, 1C, CHarom), 125.88 (s, 1C, CHarom), 123.66 (s, 1C, CHarom), 123.36 (s, 1C, CHarom), 122.77 (s, 1C, Carom), 120,37 (s, 1C, CHarom), 117.11 (s, 1C, CHarom), 115.57 (s, 1C, CHarom), 114.36 (s, 1C, CHarom), 38.16 (s, 1C, NMe), 21.41 (s, 1C, CH_2 (Et)), 15.24 (s, 1C, Me (Et)); IR (KBr) 3240, 2965, 1621, 1585, 1488, 1461, 1367, 1345, 1242, 759, 739; MS (FAB$^+$) 261 (MH^+, 85%). Anal. ($C_{18}H_{16}N_2$·1.5H_2O) C, H, N.

General Procedure G: Chloride Salts of Cryptolepines. The corresponding cryptolepine (0.25 mmol) was treated with a 1 M HCl solution in diethyl ether (5 mL). The resulting yellow salt was filtered and dried at 50 °C. The yield is quantitative (mp >260 °C).

2. Biological Evaluation. Cytotoxicity Assay. KB cells, a mouth epidermoid carcinoma,[49] were originally obtained from the American type culture collection. The KB cells were serially cultured in MEM (minimal essential medium with Earle's salt solution) containing 10% fetal calf serum, 2 mM L-glutamine, 60 μg/mL penicillin G and streptomycin sulfate and 40 μg/mL gentamycin. For the assay, KB cells were grown as monolayers in NUNC 24-well plastic plates (25 000 cells/well in 1 mL medium). Serial dilutions of the stock solutions of the compounds under test were made in DMSO (compounds **1a**−**e, 2a**−**e**) or in water (salts **36a**−**d**) and added to the cultures under a volume of 10 μL/well, immediately after plating the cells. All cultures were incubated at 37 °C in a 95% air−5% CO_2 humidified incubator. After 3 days of incubation, cell viability was determined by a further 8−16 h of incubation following addition to each well of 100 μL of a 0.02% solution in a medium of the vital dye neutral red, followed by washing the cell monolayers with phosphate-buffred saline, lysis of the cells with a 1% solution of sodium lauryl-dodecyl sulfate and photometric quantification of the extracted dye at 540 nm, using a Uniskan-II microplate reader, as originally described by Borenfreund and Puerner.[50]

In Vitro Activity Against *P. falciparum*. The chloroquine-resistant strain K1/Thailand of *P. falciparum* was maintained in continuous culture on human erythrocytes as described by Trager and Jensen.[51] In vitro antimalarial activity was determined using a modification of the semiautomated microdilution technique of Desjardins et al.[52] Stock solutions of compounds were prepared in DMSO. Drug solutions were serially diluted with culture medium and added to asynchronous parasite cultures (1% parasitemia and 1% final hematocrit) in 96-well plates for 24 h, at 37 °C, prior to the addition of 0.5 μCi of [^{3}H]hypoxanthine (1−5 Ci/mmol; Amersham, Les Ulis, France) per well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated in the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50% inhibition of parasite growth (IC_{50}) was obtained from the drug concentration−response curve, and the results were expressed as the mean ± standard deviation determined from several independent experiments. The DMSO concentration never exceeded 0.2% and did not inhibit the parasite growth.

Cytotoxicity Test on Murine Myoblast-Derived L6 Cells. L6 cells were maintained in DMEM culture medium supplemented with 25 mM HEPES, pH 7.5, 10% fetal calf serum, 100 μg/mL penicillin and streptomycin, at 37 °C, under an atmosphere of 5% CO_2. For the cytotoxicity test, L6 cells were collected and seeded in 96-well microplates at 5 × 10^3 cells/well. After 24 h, the cells were washed and 2-fold dilutions of the drug were added in 200 μL culture medium. Untreated cultures were included as controls. The final DMSO concentration in the culture remained below 0.5%. Cells were maintained for 5 days in culture and cell proliferation was determined using the XTT-based colorimetric assay (cell proliferation kit II, Boehringer Mannheim S.A., Meylan, France). Growth inhibition was determined from the percentage of reduction of absorption at 540 nm of treated cultures versus untreated control cultures. IC_{50} value was calculated from dose−response curves from several independent experiments.

In Vitro Activity Against *T. cruzi*. Experiments were performed with the β-galactosidase-expressing parasite Tulahuen LacZ clone 4 kindly provided by W. Van Voorhis.[53] Epimastigote forms were grown in liver infusion tryptose medium containing 10% fetal calf serum, at 28 °C.[54] In vitro activity against epimastigote forms was evaluated in a 96-well plate (1 × 10^4 parasite/well) over 5 days in the presence of 2-fold dilutions of the drug. Trypomastigote forms were obtained from infected culture of murine muscle L6 cells.[55] Effects of 2-fold dilutions of the drug (from 200 to 1.5 μM) on trypomastigotes were scored microscopically by evaluation of their motility after 48 h of incubation. For the in vitro activity against the intracellular amasitogte form, L6 cells were seeded in a 96-well plate at 5 × 10^3 cells/well. After 24 h, 10^5 trypomastigotes were added/well for 6 h. Cells were washed twice to remove extracellular trypomastigotes and incubated with 2-fold dilutions of the drug, at 37 °C, under a 5% CO_2 atmosphere for 5 days. In all these experiments, controls were constituted by untreated parasite cultures. Growth inhibition was quantified by measuring β-galactosidase activity using chlorophenol red β-D-galactopyranoside as the substrate according to Buckner et al.[54] IC_{50} value was calculated from dose−response curves from several independent experiments.

Cellular Localization by Fluorescence Microscopy. Human fetal fibroblasts were maintained in 8-well Lab-Tek culture slides (Nunc, Inc., Naperville, IL) in DMEM supplemented with 10% fetal calf serum. Five days after culture infection by *T. cruzi* trypomastigotes, cells were washed twice with culture medium and incubated for 1 h with the drug in culture medium. After three washes, slides were immediately observed. *P. falciparum*-infected red blood cells were incubated for 1 h with the drug in culture medium, washed twice with culture medium and immediately observed. Cellular localization was realized using a Nikon Eclipse 600 inverted epifluorescence microscope fitted with a UV filter.

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Supporting Information Available: Experimental procedures (B and C) and characterization data for compounds **1a, 2a,d,e** and **23**−**34**; table listing the elemental analyses of compounds **1a**−**f, 2a**−**e, 6p, 7a, 8, 11, 13**−**14, 16**−**18, 23**−**28, 30**−**34, 35a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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