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Synthesis and Antileishmanial Activity of 3-Imidazolylalkylindoles. Part I

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The present study was designed to investigate conazoles as new antileishmanial agents. Several 3-imidazolylalkylindoles were prepared under mild reaction conditions and pharmacomodulation at N^1 and C^5 of the indole ring and at the level of the alkyl chain (R) was carried out starting from the corresponding 3-formylindoles 7–10. All target imidazolyl compounds 38–52 were evaluated *in vitro* against *Leishmania mexicana* promastigotes; ketoconazole, amphotericin B and meglumine antimoniate were used as references. Eight out of fifteen compounds (40, 43, 44, 47, 48, 50, 51 and 52) exerted similar activity to ketoconazole, with IC_{50} values in the range of 2.10–3.30 μg/mL. However the most potent compound, 1-(2-bromobenzyl)-3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole (38), exhibited IC_{50} value (0.011 ± 0.003 μg/mL) 270-fold lower than that of ketoconazole. Four compounds (38, 43, 50 and 52) were also tested against intracellular amastigotes of *L. mexicana*; compound 38 exhibited the highest activity with an IC_{50} value of 0.018 ± 0.004 μg/mL.

Keywords: Indoles; Azoles; *Leishmania mexicana*; Promastigotes; Amastigotes

INTRODUCTION

Leishmaniasis is an age-old parasitic disease transmitted to humans by the bite of the infected female phlebotomus sandfly. The sandfly vector is usually infected with flagellate protozoa belonging to the genus *Leishmania*. This disease has been identified as one of the six major tropical diseases and thus has been included in the special programme for research and training by the World Health Organization (WHO). The total number of infected people in the World is estimated to be 12 million, and 350 million people are at risk in about 88 countries on four continents (Africa, Asia, Europe, America). There are approximately 2 million new cases of leishmaniasis per year, of which 500,000 are visceral leishmaniases.[1,2†] In humans, the disease occurs in at least four major forms, depending on the parasite species and the cellular immune system of the patient, and are called cutaneous leishmaniasis (CL), diffuse cutaneous leishmaniasis (DCL), mucocutaneous leishmaniasis (ML) and visceral leishmaniasis (VL). Epidemics of leishmaniasis periodically flare up; for example, an epidemic of CL is ongoing in Kabul (Afghanistan) with an estimated 200,000 cases.[†]

Actually there is a lack of interest among the pharmaceutical companies to carry out research and development in leishmaniasis. However, new parameters such as the increase of international exchanges between both hemispheres, the importance of leishmaniasis encountered during Persian Gulf Wars, and the emergence of *Leishmania*/HIV co-infections have added a new economic dimension to this problem.[3,4] A further important parameter that needs to be taken into account, is that there are only a few drugs actually available on the market to treat leishmaniasis. The first antileishmanial chemotherapeutic compounds, the pentavalent antimonial agents, introduced in the 1940's, are still generally accepted as the first-line therapy for all forms of leishmaniasis. Meglumine antimoniate (MA) and sodium stibogluconate are rapidly excreted from

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[†]For general information concerning leishmaniasis, please see the WHO official website: http://www.who.int/emc/disease/leish/

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the kidneys with virtually no accumulation in the body.[5,6] However, clinical resistance and therapeutic failures in immunocompromised and immunocompetent patients have been increasingly recognized in recent years, leaving to the need for second-line drugs. Pentamidine and amphotericin B (AmB), which also have serious side effects associated with them such as renal toxicity and pancreatitis,[7–10] are used as secondary therapy. Diverse lipid formulations of AmB (AmBisome®, Abelcet®, Amphocil®) have been evaluated against leishmaniasis and are now competitive with antimonials as primary therapy for CL or VL.[11,12] Other drugs such as allopurinol, sitamaquine, paromomycin and imiquimod are known to be potent antileishmanial drugs.[13] Miltefosine, an alkylphosphocholine derivative, was reported to be an effective oral treatment for VL (Figure 1).[14] Nevertheless, the search for new, effective, less expensive and non toxic drugs has become an emergency.

In *Leishmania* species, ergosterol is a major component of their membrane structure.[15] Ergosterol biosynthesis, as in fungal cells, requires the C-14 demethylation of lanosterol. This biotransformation involves a cytochrome P450 enzyme called 14-α demethylase or CYP51. Conazole antifungals, known to interfere with the cytochrome P450 part of the 14-α demethylase, are potent candidates to treat leishmaniasis by inhibiting the sterol synthesis pathway of *Leishmania* spp. Ketoconazole (KTC) and itraconazole have been used to treat CL or VL with variable success (Figure 2).[15–19]

In a previous paper[20] we have shown that 3-(α-azolylbenzyl)indoles displayed *in vitro* activity against *L. mexicana* promastigotes (Figure 2). Compounds 1 and 2 exhibited IC_{50} values less than 0.20 μg/mL. We have pursued our investigations and prepared a new series of 3-imidazolylalkylindoles to confirm the interesting potential of azole and indole moieties for the design of antileishmanial agents. The antileishmanial activity of the synthesized compounds was evaluated against cultured extracellular promastigotes of *L. mexicana*.

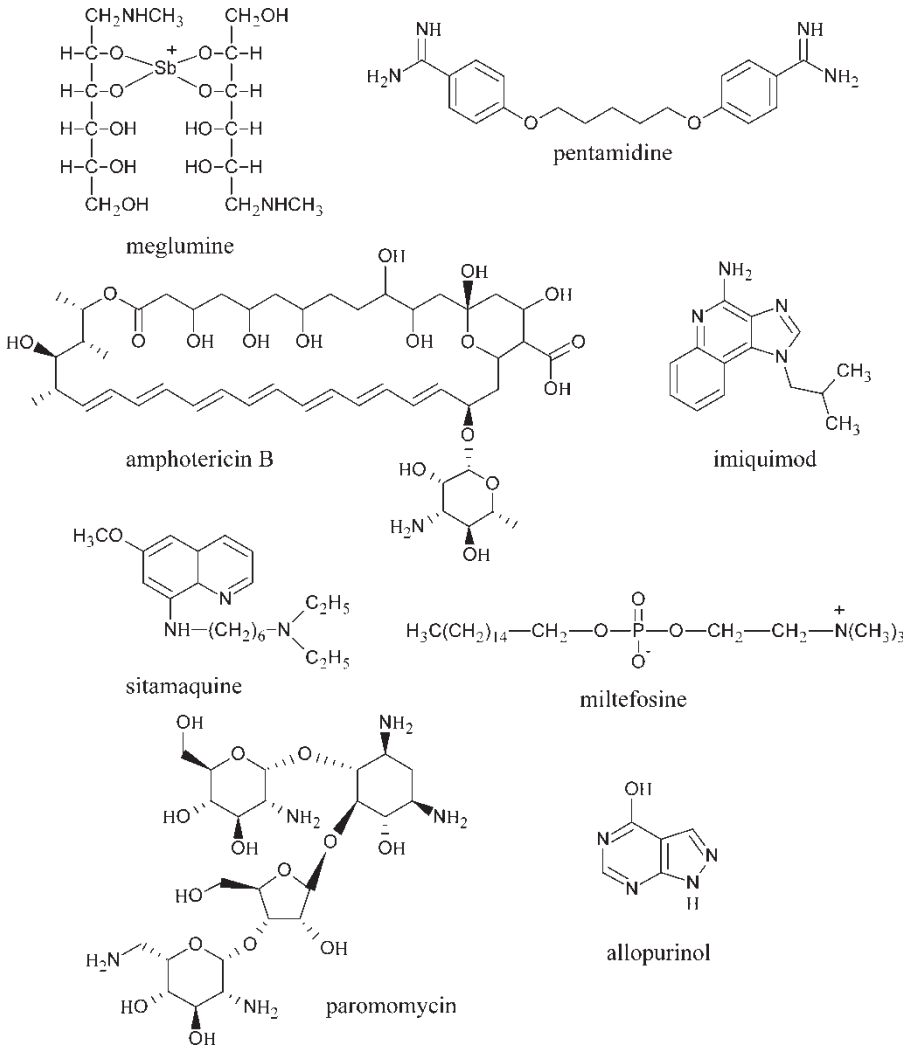


FIGURE 1 Chemical structures of antileishmanial drugs.

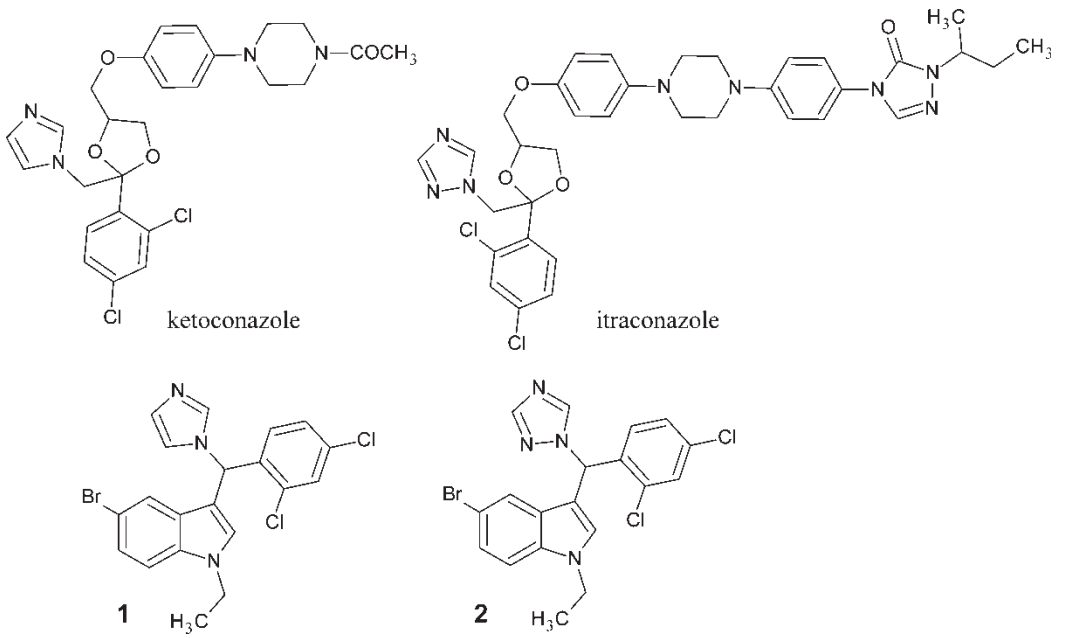


FIGURE 2 Chemical structures of antifungal azoles and 3-(α-azolylbenzyl)indoles **1** and **2**.

MATERIALS AND METHODS

Chemistry

All common chemicals and solvents utilized were reagent grade and purchased from Sigma-Aldrich (Saint Quentin, France). Melting points were determined on a Electrothermal IA9300 melting point digital apparatus and reported uncorrected. Infrared (IR) spectra were obtained in KBr pellets or neat liquid films with a Perkin-Elmer Paragon FTIR 1000 PC spectrometer. ^{1}H-NMR spectra were obtained using a Bruker AC 250 apparatus operating at 250 MHz with d_6-DMSO as solvent. Chemical shifts are expressed as δ values (ppm) relative to Me_4Si as internal standard. All reactions were monitored by TLC, using 0.25 mm-thick precoated silica gel plates (E. Merck) eluted with dichloromethane or dichloromethane/absolute ethanol gradients. Compounds were purified by CC using silica gel 60 as stationnary phase and eluted with dichloromethane or dichloromethane/absolute ethanol gradients. The synthesis of 3-formylindole **7** and 5-bromo-3-formylindole **8** have been previously described.[21] The access of precursors **16**, **19**, **20**, **28**, **31**, **32**, **35**, **36**, **37** and target imidazolyl compounds **43**, **46**, **47**, **50**, **51** and **52** have been previously reported by us.[22]

General Procedure for the Synthesis of 3-formylindoles 7–10

A solution of 1*H*-indole (**3**–**6**, 7.62 mmol) in 5 mL of *N*,*N*-dimethylformamide was added at 5–10°C over 60 min to a solution of phosphorus oxychloride (0.79 mL, 8.46 mmol) in *N*,*N*-dimethylformamide (2.6 mL). The orange solution was stirred at room temperature for 60 min. Ice (12 g) was added, followed by addition of a solution of potassium hydroxide (3.38 g, 84.5 mmol) in water (30 mL). The mixture was heated at 93°C for 30 min, and then stored at room temperature overnight. The precipitate was collected, washed with water, and dried over anhydrous Na_2SO_4 to give the corresponding 3-formylindole **7**–**10**.

5-Fluoro-3-Formyl-1*H*-Indole (**10**)

As a yellow powder, yield: 80%, m.p.: 162–163°C (ethanol). IR (KBr), cm^{-1}: 3366 (νN-H), 1655 (νC = O). ^{1}H-NMR (d_6-DMSO), δ (ppm): 7.15 (ddd, 1H, $^3J_{HF}$ = 9.30 Hz, $^3J_{HH}$ = 8.85 Hz, $^4J_{HH}$ = 2.60 Hz, H^6), 7.56 (dd, 1H, $^3J_{HH}$ = 8.85 Hz, $^4J_{HF}$ = 4.35 Hz, H^7), 7.79 (dd, 1H, $^3J_{HF}$ = 8.80 Hz, $^4J_{HH}$ = 2.60 Hz, H^4), 8.39 (s, 1H, H^2), 9.96 (s, 1H, CHO), 12.29 (s, 1H, NH).

General Procedure for the Synthesis of 1-benzyl-3-formylindoles 11–22

Sodium hydride (37.8 mmol) as a suspension (60%) in mineral oil was added to a stirred solution of 3-formylindole (**7**–**10**, 34.4 mmol) in anhydrous dimethylsulfoxide (200 mL), and the mixture was stirred for 60 min at room temperature. Then benzyl chloride (41.3 mmol) was added to the solution and the mixture was stirred at room temperature for 2 h. After addition of water (100 mL), the mixture was extracted with dichloromethane (50 mL × 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography

(dichloromethane/*n*-hexane: 1/1) to afford the required 1-benzyl-3-formylindole **11**–**22**.

1-(2-Bromobenzyl)-3-Formyl-1*H*-Indole (**11**)

As a red powder, yield: 95%, m.p.: 115–117°C (diisopropyl ether). IR (KBr), cm^{-1}: 3390 (νN–H), 1654 (νC=O). ^{1}H-NMR (d_6-DMSO), δ (ppm): 5.64 (s, 2H, CH_2), 6.88 (dd, 1H, $J = 7.30$ Hz, $J = 2.30$ Hz, $H^{6'}$), 7.28–7.38 (m, 4H, H^5, H^6, $H^{4'}$, $H^{5'}$), 7.52–7.58 (m, 1H, H^7), 7.75 (dd, 1H, $^3J = 7.55$ Hz, $^4J = 2.00$ Hz, $H^{3'}$), 8.17–8.22 (m, 1H, H^4), 8.38 (s, 1H, H^2), 9.99 (s, 1H, CHO).

General Procedure for the Synthesis of 1-benzyl-3-hydroxymethylindoles 23–34

To a solution of 1-benzyl-3-formylindole (**11**–**22**, 3,25 mmol) in anhydrous tetrahydrofuran (15 mL), lithium aluminum hydride (1.1 eq) was slowly added with vigorous stirring under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 30 min and then quenched with water. The mixture was extracted with dichloromethane (20 mL × 2) and the combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was purified by recrystallization from dichloromethane–ethanol (19:1, v/v) to give pure 1-benzyl-3-hydroxymethylindole **23**–**34**.

1-(2-Bromobenzyl)-3-Hydroxymethyl-1*H*-Indole (**23**)

As a yellow crystals, yield: 83%, m.p.: 102–105°C (diisopropyl ether). IR (KBr), cm^{-1}: 3208 (νO–H). ^{1}H-NMR (d_6-DMSO), δ (ppm): 4.70 (d, 2H, $^3J = 5.40$ Hz, CH_2), 4.91 (t, 1H, $^3J = 5.40$ Hz, OH), 5.47 (s, 2H, CH_2), 6.64 (dd, 1H, $^3J = 6.20$ Hz, $^4J = 2.95$ Hz, $H^{6'}$), 7.05–7.18 (m, 2H, H^5, H^6), 7.23–7.35 (m, 3H, $H^{4'}$, $H^{5'}$, H^7), 7.37 (s, 1H, H^2), 7.68–7.74 (m, 2H, $H^{3'}$, H^4).

General Procedure for the Synthesis of 1-benzyl-3-(1-hydroxyalkyl)indoles 35–37

Under an atmosphere of nitrogen, a solution of 1-benzyl-3-formylindole (**19**, 1,1 mmol) in tetrahydrofuran (15 mL) was cooled at −40°C and then the appropriate alkylmagnesium bromide or chloride (1.2 eq) was added dropwise over a period of 15 min to the solution and the mixture was stirred at room temperature for 60 min. After addition of a saturated aqueous solution of NH_4Cl (100 mL), the mixture was extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with brine (50 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give 1-benzyl-3-(1-hydroxyalkyl)indole **35**–**37**.

1-(4-Chlorobenzyl)-3-(1-Hydroxy-2-Methylprop-1-Yl)-1*H*-Indole (**35**)

As a yellow oil, yield: 97%. IR (NaCl), cm^{-1}: 3250 (νO–H), 1237 (νC–N), 1075 (νC–Cl). ^{1}H-NMR (d_6-DMSO), δ (ppm): 0.81 (d, 6H, $^3J = 6.60$ Hz, CH_3), 1.77–1.82 (m, 1H, CH), 4.88–4.91 (m, 1H, CH), 4.97–5.00 (m, 1H, OH), 5.39 (s, 2H, CH_2), 7.00–7.12 (m, 2H, H^5, H^6), 7.25 (d, 2H, $^3J = 8.35$ Hz, $H^{2'}$, $H^{6'}$), 7.40 (d, 2H, $^3J = 8.35$ Hz, $H^{3'}$, $H^{5'}$), 7.43–7.47 (m, 2H, H^4, H^7), 7.76 (s, 1H, H^2).

General Procedure for the Synthesis of 3-(1-imidazolylalkyl)indoles 38–52

1,1′-Carbonydiimidazole (1.2 eq) was added to a solution of alcohol (**23**–**37**, 4.5 mmol) in anhydrous tetrahydrofuran (20 mL) and the reaction mixture heated to reflux for 5 h. After addition of water (60 mL), the mixture was extracted with dichloromethane (30 mL × 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane/ethanol: 20/1) to afford 3-(1-imidazolylalkyl)indole **38**–**52**.

1-(2-Bromobenzyl)-3-(1*H*-Imidazol-1-Ylmethyl)-1-*H*-Indole (**38**)

As a light brown powder, yield: 37%, m.p.: 98–100°C (diisopropyl ether). IR (KBr), cm^{-1}: 1575, 1498 (νC=C and νC=N). ^{1}H-NMR (d_6-DMSO), δ (ppm): 5.37 (s, 2H, CH_2), 5.49 (s, 2H, CH_2), 6.68 (d, 1H, $^3J = 7.30$ Hz, $H^{6'}$), 6.88 (s, 1H, azole CH), 7.05–7.28 (m, 4H, $H^{4'}$, $H^{5'}$, H^5, H^6), 7.21 (s, 1H, azole CH), 7.40 (d, 1H, $^3J = 8.00$ Hz, H^7), 7.57 (s, 1H, H^2), 7.61 (d, 1H, $^3J = 5.40$ Hz, H^4), 7.72 (d, 1H, $^3J = 7.50$ Hz, $H^{3'}$), 7.80 (s, 1H, azole CH).

Biological Tests

Leishmania (*L.*) *mexicana* promastigotes (MHOM/MEX/96/UPN5) were maintained in Schneider's insect medium (Sigma Chemical Co., St. Louis, MO, USA), plus 10% heat-inactivated foetal calf serum (FCS) (Sigma), penicillin and streptomycin, at 26°C, by passage every 7 days.

In Vitro Antileishmanial Activity

L. mexicana promastigotes were inoculated into 96-well plates (Nunc Inc., Naperville, IL, USA). The cultures were exposed for 96 h at 26°C to the studied 3-imidazolylalkylindoles **38**–**52** with a triplicate culture for each concentration (100, 10 and 1 μmol). The antiproliferative effect was determined by a colorimetric method based on the conversion of MTT into a blue formazan product, by mitochondrial

dehydrogenases. Absorbance was monitored at 570 nm.[23,24]

The activity against the intracellular stage of the parasite (amastigote) was determined in a Balb/c mouse peritoneal macrophage model (Centre d'élevage R. Janvier, Le Genest, France) as previously described.[25] Briefly, peritoneal cells were placed into a 24-well plate (Nunc Inc.) and infected with stationary phase promastigotes. After a 24-hour incubation time, the culture was washed and exposed to drugs. Cytotoxicity was determined after exposure to the target imidazolylindoles for 96 h. IC_{50s} were calculated using the values of number of amastigotes per macrophage.

Cytotoxicity

Cytotoxicity of compound **38** was studied with human fibroblasts (MRC5). After incubation for 96 h with **38**, the cytotoxic effect was measured with an Alamar blue® fluorochrome reagent (Interchim, Montluçon, France).[26]

RESULTS AND DISCUSSION

Chemistry

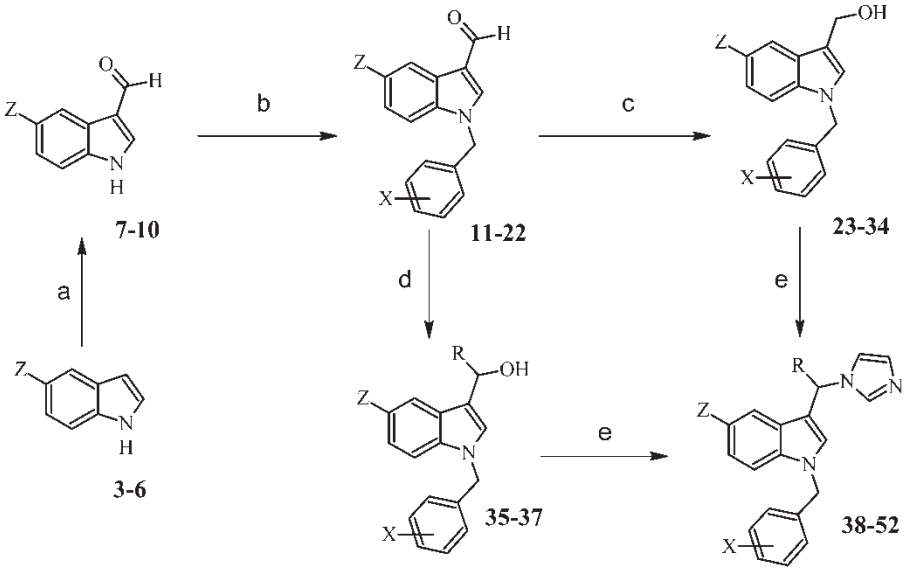
Preparation of the target 1-benzyl-3-(1-imidazolylalkyl)indoles **38**–**52** (Scheme 1) was carried out by two pathways: (i) reduction of 1-benzyl-3-formylindoles **11**–**22** using lithium aluminium hydride in methanol afforded the intermediate alcohols **23**–**34** which were condensed with 1,1′-carbonyldimidazole (CDI) in THF[27], leading to carbamates which underwent in situ decarboxylation to afford the expected compounds; (ii) an alternative route consisted in synthesizing the alcohols **35**–**37** by a Grignard reaction starting from 1-benzyl-3-formylindole **16**.[22]

N-alkylation of 3-formyl-1*H*-indoles **7**–**10** with benzyl chlorides, using sodium hydride in anhydrous dimethylsulfoxide, afforded the *N*-substituted indole derivatives **11**–**22**. The key intermediates **7**–**10** were obtained under Vilsmeier-Haack conditions involving dimethylformamide and phosphorus oxychloride.[22] Chemical structures of the target 3-imidazolylalkylindoles **38**–**52** and their precursors **7**–**37** are presented in Figure 3.

Biological Results

All the target 1-benzyl-3-imidazolylalkylindole derivatives **38**–**52** were tested for antileishmanial activity against *L. mexicana* promastigotes as described in "Materials and Methods". KTC, AMB and MA were used as positive controls. The IC_{50} values are shown in Table I. Pharmacomodulation aimed at evaluating the influence of, (i) the nature and position of the halogen group X positioned at the benzyl unit, (ii) the steric bulk and the lipophilicity resulting from alkyl substitution at R and (iii) a halogen atom at C^5 of indole.

All the compounds **38**–**52** showed high inhibitory activities ($IC_{50} < 26\,\mu g/mL$) compared to MA (IC_{50}: 4,300 μg/mL). Substitution on the benzyl moiety by 2-chloro (compound **41**), 3-chloro (compound **42**), 3-fluoro (compound **45**) and 4-fluoro (compound **46**) induced a decrease in activity; IC_{50} values were superior to 9 μg/mL for these chloro and fluoro derivatives and equal to 3 μg/mL for KTC. Based on a comparison of compounds **41**–**46**



SCHEME 1 Synthesis of compounds **7**–**52**. Reagents and conditions: (a) $POCl_3$, DMF, 5°C to r.t.; (b) NaH, DMSO, benzyl chloride, r.t.; (c) $LiAlH_4$, THF, r.t.; (d) RMgX, THF, −40°C to r.t.; (e) CDI, THF, reflux.

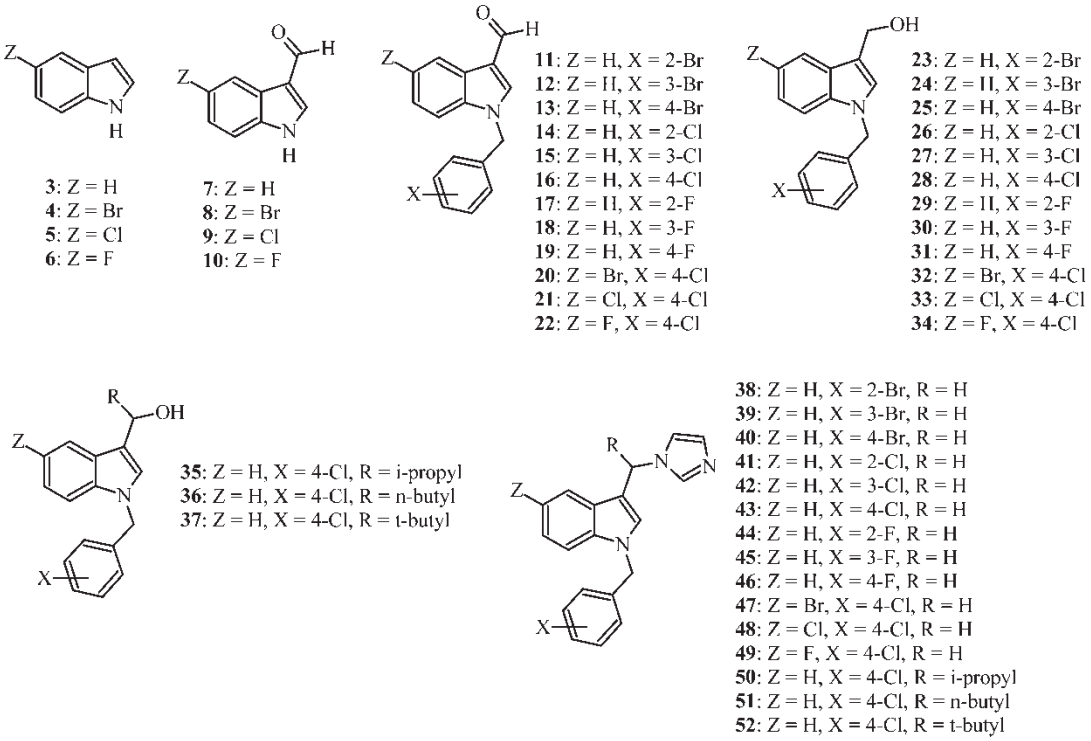


FIGURE 3 Chemical structures of 3-imidazolylalkylindoles **38**–**52** and their precursors **7**–**37**.

(with chlorine and fluorine substituents), with analogues **38**–**40** (possessing bromine substituents), it is suggested that bromine atom plays a major role in the increase in antileishmanial activity. The 3-bromobenzyl analogue **39** (IC_{50}: 5.50 μg/mL) and the 4-bromobenzyl analogue **40** (IC_{50}: 3.07 μg/mL) presented similar antileishmanial potencies to that of KTC. On the other hand, compound **38**, with a 2-bromobenzyl substituent, was 273- and 2.7-fold more potent against *L. mexicana* promastigotes than KTC and AMB, respectively. C^5 substitution in compound **43** (with a 4-chlorobenzyl group) did not alter antileishmanial activity. Compounds **47** (C^5: bromine atom) and **48** (C^5: chlorine atom) showed potencies very close to those of compound **43** and KTC: IC_{50} values were 3, 3.3, 2.1 and 3 μg/mL, respectively. In addition, replacing hydrogen in compound **43** by an alkyl group (R) maintained a similar level of activity among compounds **50**–**52**. These three compounds were found to be as active as KTC with IC_{50} values in the range 2.10–2.60 μg/mL, indicating that higher lipophilicity did not prevent activity.

The protozoan parasite *L. mexicana* survives and multiplies within mammalian macrophages as the amastigote form. It is therefore of interest to evaluate the efficacy of active 1-benzyl-3-imidazolylalkylindoles on the clinically relevant stage. Four compounds (**38**, **43**, **50** and **52**) were selected for further evaluation against *L. mexicana* amastigotes using KTC, AmB and MA as references (see Table II).

TABLE I *In vitro* activities of 3-imidazolylalkylindoles **38**–**52** against promastigotes of a strain of *L. mexicana*

Compound	IC_{50} (μg/mL)[a] promastigotes
38	00.011 ± 0.003
39	05.50 ± 1.40
40	03.07 ± 0.10
41	11.20 ± 1.00
42	18.40 ± 2.90
43	02.10 ± 0.06
44	03.00 ± 0.50
45	09.20 ± 0.70
46	25.15 ± 3.40
47	03.00 ± 0.50
48	03.30 ± 0.08
49	05.40 ± 1.60
50	02.10 ± 0.03
51	02.60 ± 0.03
52	02.20 ± 0.03
KTC	03.00 ± 0.50
AMB	00.03 ± 0.03
MA	>100 (4,300 ± 50)

[a] Mean from at least three determinations.

TABLE II *In vitro* activities of 3-imidazolylalkylindoles **38**, **43**, **50**, **52** against intracellular amastigotes of a strain of *L. mexicana*

Compound	IC_{50} (μg/mL)[a] amastigotes
38	00.018 ± 0.004
43	01.40 ± 0.09
50	01.80 ± 0.08
52	01.60 ± 0.05
KTC	01.30 ± 0.20
AMB	00.47 ± 0.05
MA	48.70 ± 8.40

[a] Mean from at least three determinations.

TABLE III *In vitro* cytotoxicity of compound **38** on MRC5 cells

IC_{50} (μg/mL) promastigotes	IC_{50} (μg/mL) amastigotes	IC_{50} (μg/mL) MRC5 cells	Index of selectivity P[a]	Index of selectivity A[b]
0.011	00.018	29.12	2647	1618

[a] Index of selectivity P is defined as the ratio of the IC_{50} value on MRC5 cells to the IC_{50} value against *L. mexicana* promastigotes. [b] Index of selectivity A: IC_{50} (MRC5)/IC_{50} (amastigotes).

Compound **43** and its two analogues **50** and **52** (*i*-Pr and *t*-Bu, respectively) displayed an interesting antileishmanial profile (IC_{50} range 1.4–1.8 μg/mL). Their activity can be compared to KTC (IC_{50}: 1.3 μg/mL). Compound **38** showed higher activity: it was 72- and 26-fold more potent on *L. mexicana* amastigotes than KTC and AMB, respectively. This suggest that 1-(2-bromobenzyl)-3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole (**38**) could represent a good candidate for *in vivo* evaluation.

Furthermore, its cytotoxicity on a MRC5 cell line was determined (see Table III). It showed cytotoxicity in the micromolar range (IC_{50}: 29.12 μg/mL). Index of selectivity (P and A) was defined as the ratio of the IC_{50} value on the MRC5 cells to the IC_{50} value on the *L. mexicana* strain (promastigotes or amastigotes). Compound **38** demonstrated a very high selectivity (P: 2647 and A: 1618) and should offer the potential of safer therapy.

Taken together these preliminary results prompted us to select compound **38** as a new lead for further pharmacomodulation in the series of indole-based derivatives. New chemical and biological investigations are currently underway in our laboratories.

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