Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 38 (2003) 711–718
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Synthesis and antileishmanil activity of new imidazolidin-2-one derivatives

Jean-Michel H. Robert [a,*], Caroline Sabourin [a], Nidia Alvarez [b], Sylvie Robert-Piessard [a], Guillaume Le Baut [a], Patrice Le Pape [b]

[a] Service de Pharmacochimie, UPRES EA 1155, Faculté de Pharmacie, 1, rue Gaston Veil F-44035 Nantes, France
[b] Service de Parasitologie, UPRES EA 1155, Faculté de Pharmacie, 1, rue Gaston Veil F- 44035 Nantes, France

Received 23 December 2002; received in revised form 19 May 2003; accepted 20 May 2003

Abstract

N^3-acyl, arylsulfonyl and benzyl derivatives of N^1-(4,6-dimethylpyridin-2-yl), (5-methylthiazol-2-yl) or (3-methylisoxazol-5-yl)imidazolidin-2-ones were synthesized and evaluated as potential antileishmanial agents. Determination of their cytotoxic effect was carried out using MRC5 cells. Two compounds, 1-(4,6-dimethylpyridin-2-yl)-3-(napht-2-ylsulfonyl)imidazolidin-2-one, **18**, and 1-(3-methylisoxazol-5-yl)-3-(4-bromobenzyl)imidazo-lidin-2-one, **25**, exerted significant antileishmanial activity in promastigotes of *Leishmania (L) mexicana* and *Leishmania infantum*, with IC_{50} in the range of 8–16 μmol L^{-1}. Antiparasitical activity of the less toxic compound, **25**, was confirmed against intracellular amastigote of *L. mexicana*, the clinical relevant stage; its low IC_{50} value (2.4 μmol L^{-1}) and its favourable toxicity/activity index (11) constitute encouraging results for ongoing pharmacomodulation in the corresponding subseries.

Keywords: Imidazolidin-2-one; Antileishmanial activity; *L.mexicana*. *L infantum*; Promastigote

1. Introduction

Leishmaniasis is a protozoan disease that affects about 12 millions of persons in the world, particularly in subtropical and tropical regions, constituting a serious public health problem [1]. Parasites exist in two forms: an amastigote in the mammalian host and a flagellated promastigote in the insect vector. Clinical manifestations occur in three major forms in human: visceral, cutaneous and mucocutaneous.

The pentavalent antimonials, sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantine®), are presently the recommended first line drugs [2–4]. However they are not orally active and they require long courses of treatment. The second line drugs, pentamidine, azole derivatives (ketoconazole, itraconazole) [1,5] and amphotericin B [6], are even less acceptable because of long-term parenteral administration and toxicity. These drawbacks explain that several investigations are oriented to searching new compounds for better treatment [7].

In a first work [8], we described arylcarboxamides derived from 2-amino-4,6-dimethylpyridine (Fig. 1) exerting significant inhibition against cultured extracellular promastigotes of *L. donovani* and *L. braziliensis*, such as compounds **1** and **2**, with IC_{50} in the range of 30 μmol L^{-1}. Compound **1**, for example, led to a 75% parasite burden reduction both in the spleen imprints and in the microdilution spleen cultures in a Balb/c mice model of visceral leishmaniasis, after intraperitoneal administration of 10 mg kg^{-1} daily for 5 consecutive days.

In estimation of this work, we synthesized and evaluated some new derivatives resulting from the integration of the amino group of 2-amino-4,6-dimethylpyridine into an imidazolidin-2-one structure [9]. These compounds (Fig. 2) were evaluated against promastigote and amastigote of *Leishmania mexicana*. Two products, **3** and **4**, showed a high level of activity

* Corresponding author.
E-mail address: jmrobert@sante.univ-nantes.fr (J.-M.H. Robert).

0223-5234/03/$ - see front matter
doi:10.1016/S0223-5234(03)00119-3

Fig. 1. General structure of arylcarboxamide derivatives of 2-amino-4,6-dimethylpyridine.

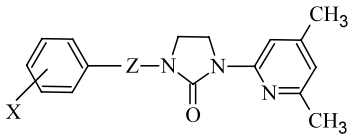


Fig. 2. General structure of imidazolidin-2-one derivatives of 2-amino-4,6-dimethylpyridine.

against the intracellular form of the parasite, with IC_{50} (μmol L^{-1}) of 13±0.5, and 7.0±3.3, respectively. Moreover, **3** and **4** were more active against the intracellular than the promastigote form of the parasite, contrary to the majority of antileishmanial drugs. These results prompted us to synthesize new derivatives possessing this imidazolidinone core. We present here the first results obtained with new N^3-acyl, arylsulfonyl or benzyl N^1-(4,6-dimethylpyridin-2-yl)imidazolidin-2-ones **11**–**19** and analogues **20**–**26** resulting from the replacement of the lutidinyl moiety by -5-methyl-2-thiazolyl or 3-methyl-5-isoxazolyl fragment (Fig. 3).

2. Chemistry

The general synthetic procedure used in this work is illustrated in Fig. 4. Imidazolidin-2-ones **8**–**25** (Tables 1–4) were synthesized according to the previously reported method [4]: 2-chloroethylisocyanate was condensed with the appropriate heteroarylamine to give

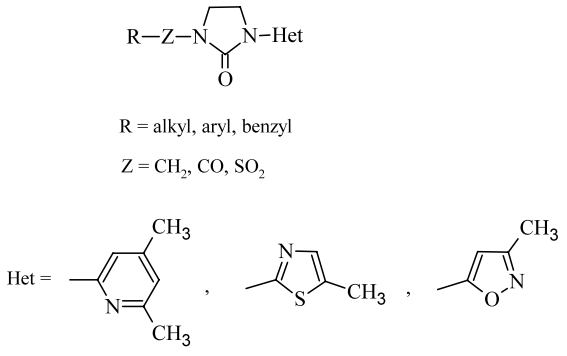
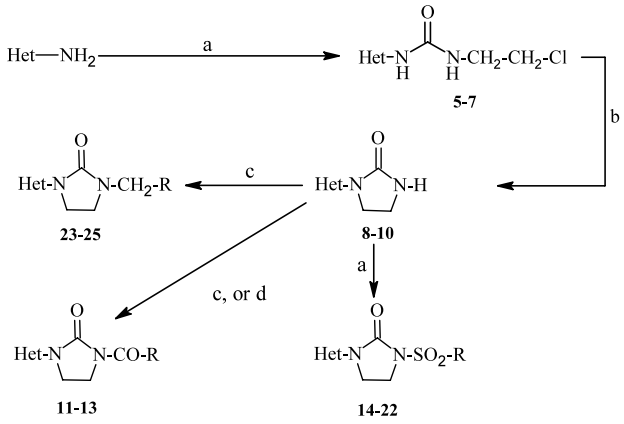


Fig. 3. General structure of new imidazolidin-2-one derivatives.



(a) Cl-CH_2-CH_2-NCO,$CHCl_3$, reflux , 3-12 h ; (b) CH_3CN , Na_2CO_3 , reflux , 16 h ; (c) TEA, 1,2-DCE , RT , 3-6 h ; (d) NaH/DMF , 0°C to RT , 1 h.

Fig. 4. Synthetic methods for the preparation of imidazolidinone derivatives **8**–**25**.

corresponding ureas **5**–**7**(method A). This condensation was followed by intramolecular alkylation, under alkaline conditions, to afford the monosubstituted imidazolidin-2-ones **8**–**10** (method B). These compounds could also be obtained, in a 'one-pot' procedure, directly from amines and isocyanate [9], but yields remained lower. N^3-acylation of **8** by acyl chlorides was carried out in 1,2-dichloroethane in presence of triethylamine (TEA), at room temperature (method C). N^3-arylsulfonylated compounds **14**–**22** were obtained by method C (compounds **14**–**19**) or in presence of the couple NaH/DMF, at 0 °C to room temperature, (method D), from the corresponding sulfonyl chlorides (compounds **20**–**22**). N^3-benzyl derivatives **23**–**25** were exclusively obtained by method D.

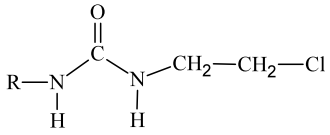
Their structure was confirmed by IR and ^{1}H-NMR spectral data and elemental analyses. Structural assignment of the imidazolidinone ring protons was carried out by C–H NMR correlation.

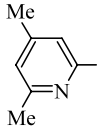
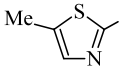
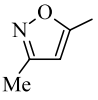
3. Parasitological results and discussion

In vitro antileishmanial activity results are gathered in Table 5. Generally speaking N^3-substitution induced a favourable effect in the three subseries. Among the 18 tested compounds, two, **18** and **25**, showed a higher activity against *L.* (*L.*) *mexicana* and *L. (L.) infantum* promastigotes with IC_{50} values of 14.4, 8.4 and 16.0, 9.5 μmol L^{-1}, respectively. Interestingly, cytotoxicity assay, carried out with MRC5 cells, brought to the fore that these two imidazolidin-2-ones possess a satisfactory toxicity/activity index: 5–11 (Table 5 and Fig. 5).

In attempt to confirm their activity against the intracellular infective stage of parasite, a *L.(L). mexicana*-infected Balb/c macrophage model was per-

Table 1
Physicochemical data of ureas **5**–**7**



N°	R	General formula, M_r	Method Yield (%)	M.p.°C/Solvent
5		$C_{10}H_{14}ClN_3O$ 227.70	A 83	116/Diethyl Ether
6		$C_7H_{10}ClN_3SO$ 219.69	A 53	154/Diisopr. Ether
7		$C_7H_{10}ClN_3O_2$ 203.63	A 89	133/Diisopr. Ether

formed. Whereas the N^3-(napht-2-ylsulfonyl)derivative **18** exerted an inhibitory activity on amastigotes comparable to that of the previously studied N^3-tolylsulfonyl congener **4** (IC_{50}: 10 and 7.3 μmol L^{-1}), **25** appeared as the most active imidazolidin-2-one ever studied against this clinical stage: IC_{50}: 2.4 μmol L^{-1}. These results showed that pharmacomodulation in the imidazolidin-2-one series allows access to more active compounds than previously stated [9].

4. Conclusion

Altogether these results demonstrate the in vitro antileishmanial activity of new N^1-azaaryl-imidazolidin-2-ones. These compounds, and especially **25**, could represent new attractive drug candidates for extended pharmacomodulation studies and putative drugs for treatment of cutaneous and visceral leishmaniasis. In vivo antileishmanial activity evaluation of **25**, in a Balb/c mice model, is now in progress.

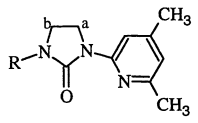
In attempt to elucidate the molecular target of these new antileishmanial compounds, we had demonstrated that the first imidazolidin-2-one derivatives inhibit parasite phospholipase A_2 (PLA_2). This inhibition leads to a reduced capacity of parasite to invade macrophages [9]. Because PLA_2 is activated after phosphorylation by protein kinase C (PKC), the interference of imidazolidin-2-one derivatives with PKC must be investigated.

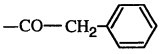
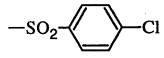
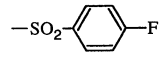
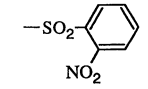
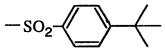
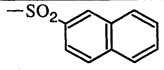
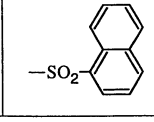
5. Experimental

5.1. Chemistry

Melting points were determined on a Tottoli–Büchi apparatus (Büchi, Flawil, Switzerland) and are uncorrected. Structures of the described products were supported by IR, ^{1}H-NMR and microanalytical data. IR spectra were run with KBr pellets with a Perkin–Elmer FT-IR Paragon 1000 grating infrared spectrophotometer (Perkin–Elmer, St Quentin-en-Yvelines, France). ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz) (Bruker, Wissembourg, France), using $CDCl_3$ as solvent; chemical shifts (δ) are reported in parts per million (ppm) from internal Me_4Si. Deuterated solvents were purchased from S.D.S. (Peypin, France). Microanalysis were performed on a Perkin–Elmer CHN 240 apparatus. Analytical TLC was performed on precoated silica gel aluminum plates (1.2 mm, GF 254, E. Merck, Darmstadt, Germany). Spots were located by UV-illumination. Evaporations were made under vacuum (rotating evaporator). Anhydrous sodium sulfate was always used as the drying agent. Purifications of synthesized compounds were made through columns of silica gel (silica gel 60, 70–230 mesh, E. Merck) with an appropriate solvent (generally diethyl oxide). Chemicals were purchased from Sigma–Aldrich-Fluka (St Quentin Fallavier, France), Lancaster Synthesis (Bischheim, France) or Avocado (La Tour du Pin, France).

Table 2
Physicochemical data of 1-(4,6-dimethylpyridin-2-yl)imidazolidin-2-ones **8** and **11**–**19**



N°	R	General formula M_r	Method Yield (%)	M.p. (°C) solvent
8	H	$C_{10}H_{13}N_3O$ 191.24	B 61	67/Diisopr. Ether
11		$C_{14}H_{17}N_3O_2$ 259.31	C 22	87/Diisopr. Ether
12		$C_{17}H_{15}F_2N_3O_2$ 331.32	C 47	128/Diisopr. Ether
13		$C_{18}H_{19}N_3O_2$ 309.37	C 51	77/Diethyl Ether
14		$C_{16}H_{16}ClN_3SO_3$ 365.84	C 60	130/Diisopr. Ether
15		$C_{16}H_{16}FN_3SO_3$ 349.38	C 62	150/Diisopr. Ether
16		$C_{16}H_{16}N_4SO_5$ 376.39	C 44	145/Diethyl Ether
17		$C_{20}H_{25}N_3SO_3$ 387.50	C 33	141/Diethyl Ether
18		$C_{20}H_{19}N_3SO_3$ 381.46	C 53	146-(dec.) Diethyl Ether
19		$C_{20}H_{19}N_3SO_3$ 381.46	C 61	132/Diethyl Ether

Yields and physical data of compounds **8**–**25** are given in Tables 1–4.

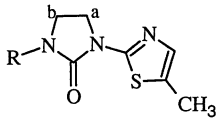
*5.1.1. General procedure for the preparation of ureas **5**–**7** (method A)*

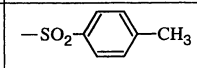
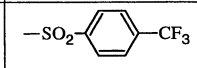
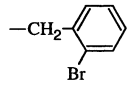
*5.1.1.1. 1-(2-Chloroethyl)-3-(4,6-dimethylpyridin-2-yl)urea (**5**).* To a solution of 2-amino-4,6-dimethylpyridine (7.06 g, 58 mmol) in chloroform (500 mL) was added 2-chloroethyl isocyanate (5 mL, 58 mmol), and the resulting mixture was refluxed for 3 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was chromatographed on a silicagel (EtOEt); 10.96 g of urea **5** were isolated as white crystals. Yield = 83%; IR (KBr) (cm^{-1}): 3350, 3210 (νNH); 2920, 2870 (ν aliph.CH); 1680 (νC=O); ^{1}H-NMR ($CDCl_3$) δ: 2.25 (s, 3H, 4-CH_3); 2.42 (s, 3H, 6-CH_3); 3.73–3.76 (m, 4H, CH_2–CH_2); 6.38 (s, 1H, pyr H5); 6.57 (s, 1H, pyr H^3); 8.25 (t, 1H, CO–N*H*–CH_2, $J = 5.6$ Hz); 10.26 (s; 1H; pyr–NH–CO). Anal. $C_{10}H_{14}ClN_3O$ (C, H, N).

*5.1.1.2. 1-(2-Chloroethyl)-3-(5-methylthiazol-2-yl) urea (**6**).* Compound **6** was prepared as described above for **5**. Yield = 53%; IR (KBr) (cm^{-1}): 3371 (νNH); 1683 (νC=O); ^{1}H-NMR($CDCl_3$) δ: 2.30 (s, 3H, 5-CH_3); 3.54–3.71 (m, 4H, CH_2CH_2); 6.93 (s, 1H, H^4); 7.49 (bs, 1H, CO–N*H*–CH_2). 9.12 (s, 1H, Thiaz-2-NH–CO). Anal. $C_7H_{10}ClN_3SO$ (C, H, N).

5.1.1.3. 1-(2-Chloroethyl)-5-(3-methylisoxazol-5-yl) urea (7). Compound **7** was obtained as described for compound **5**. Yield = 89%; IR (KBr) (cm^{-1}): 3370 (νNH); 1680 (νC=O); ^{1}H-NMR($CDCl_3$) δ: 2.37 (s,

Table 3
Physicochemical data of 1-(5-methylthiazol-2-yl)imidazolidin-2-ones **9** and **21**–**23**



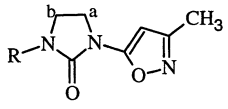
N°	R	General formula M_r	Method Yeld (%)	M.p. (°C) solvent
9	**H**	$C_7H_9N_3SO$ 183.23	B 82	219/Diethyl Ether
20		$C_{14}H_{15}N_3S_2O_3$ 337.42	D 52	248/Diethyl Ether
21		$C_{14}H_{12}F_3N_3S_2O_3$ 391.39	D 25	260/Diethyl Ether
23		$C_{14}H_{14}BrN_3SO$ 352.26	D 83	249/Diethyl Ether

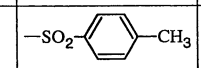
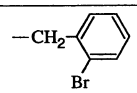
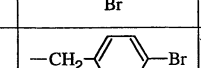
3H, 5-CH_3), 3.64–3.68 (m, 4H; CH_2CH_2); 5.98 (s, 1H, H^4); 7.25 (bs, 1H, CON*H*CH_2); 9.39 (s, 1H, Isox-5-NH–CO). Anal. $C_7H_{10}ClN_3O_2$ (C, H, N).

*5.1.2. General procedure for the synthesis of N^1-substituted imidazolidin-2-ones **8**–**10** (method B)*

*5.1.2.1. 1-(4,6-Dimethylpyridin-2-yl)imidazolidin-2-one (**8**).* To a solution of urea **5** (4.5 g, 19.8 mmol) in acetonitrile (80 mL) was added sodium carbonate (3g, 28.3 mmol) and the mixture was refluxed during 16 h. After cooling and filtration, the resulting filtrate was concentrated under reduced pressure. The resulting brown-colored oil was dissolved in dichloromethane (80 mL) and purified with activated charcoal. The mixture was filtered and after concentration of the filtrate under vacuum, crystallization of the isolated colorless oil from diisopropyl ether afforded 2.41 g of the imidazolidin-2-one **8**. Yield 64%; IR (KBr) (cm^{-1}): 3210 (νNH); 1670 (νNCON); 1615 (νC=N); ^{1}H-NMR ($CDCl_3$) δ: 2.20 (s, 3H, 4-CH_3); 2.36 (s, 3H, 6-CH_3); 3.70 (t, 2H, H^b, $J_{H^aH^b}$ = 7.9 Hz); 4.35 (t, 2H, H^a); 6.51

Table 4
Physicochemical data of 1-(3-methylisoxazol-5-yl)imidazolidin-2-ones **10** and **22**–**25**



N°	R	General formula M_r	Method Yield (%)	M.p. (°C) solvent
10	**H**	$C_7H_9N_3O_2$ 167.17	B 72	182/Diethyl Ether
22		$C_{14}H_{15}N_3SO_4$ 321.36	D 51	199/Diethyl Ether
24		$C_{14}H_{14}BrN_3O_2$ 336.20	D 59	119/Diethyl Ether
25		$C_{14}H_{14}BrN_3O_2$ 336.20	D 61	130/Diethyl Ether

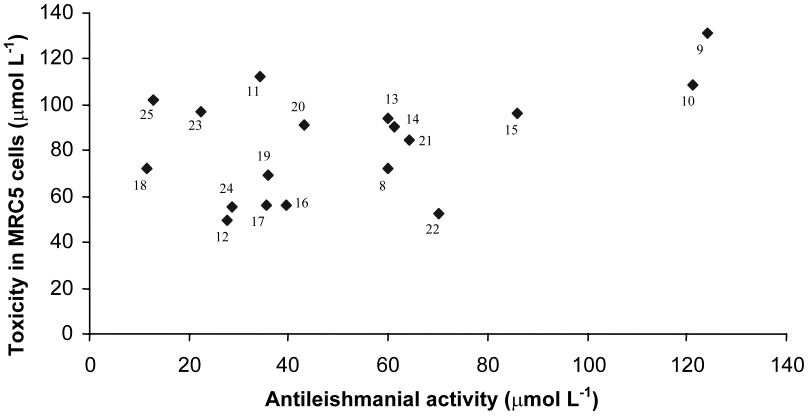


Fig. 5. Toxicity/activity relationship for imidazolidin-2-ones **8**–**25**.

(s, 1H, pyr H^5); 6.63 (s, 1H, pyr H^3); 9.64 (s, 1H, NH). Anal. $C_{10}H_{13}N_3O$ (C, H, N).

*5.1.2.2. 1-(5-Methylthiazol-2-yl) imidazolidin-2-one (**9**).* IR (KBr) (cm^{-1}): 1713 (νNCON); 1613 (νC=N); ^{1}H-NMR ($CDCl_3$) δ: 2.33 (d, 3H, 5-CH_3, $J^4_{HMeH} = 1.3$ Hz); 3.51 (t, 2H, H^b, $J_{H^aH^b} = 8.6$ Hz); 4.00 (t, 2H, H^a); 7.04 (d, 1H, H^4); 7.53 (s, 1H, NH). Anal. $C_7H_9N_3SO$ (C, H, N).

*5.1.2.3. 1-(3-Methylisoxazol-5-yl)imidazolidin-2-one (**10**).* IR (KBr) (cm^{-1}): 1670 ν(NCON); 1613 ν(C=N); ^{1}H-NMR($CDCl_3$) δ: 2.38 (d, 3H, 5-CH_3, $J^4_{HMeH} = 0.8$ Hz); 3.63 (t; 2H, H^b, $J_{H^aH^b} = 8.4$ Hz); 3.99 (t, 2H, H^a): 5.34 (s, 1H, NH); 6.69 (d, 1H, H^4). Anal. $C_7H_9N_3O_2$ (C, H, N).

*5.1.3. Acylation and sulfonylation of imidazolidin-2-one **8** (method C)*

*5.1.3.1. 3-(3,5-Difluorobenzoyl)-1-(4,6-dimethylpyridin-2-yl)imidazolidin-2-one (**12**).* To a solution of **8** (3 g, 15.69 mmol) and TEA (3 mL) in 1,2-dichloroethane (50 mL), was added dropwise a solution of 3,5-difluoroben-

Table 6
IR and ^{1}H-NMR data of 3-substituted derivatives of 1-(4,6-dimethylpyridin-2-yl)imidazolidin-2-one **8**

No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
11	1706 ν(C=O) 1672 ν(N *CO*N) 1608 ν(C=N)	0.94–1.15 (m, 4H, CH_2CH_2 cycloprop.); 2.28 (s, 3H, pyr 4-CH_3); 2.47 (s, 3H, pyr 6-CH_3); 3.71 (m, 1H, cycloprop.H[1]); 4.05 (t, 2H, H^b, $J_{H^aH^b} = 7.8$ Hz); 4.35 (t, 2H, H^a); 6.58 (s, 1H, pyr H^5); 6.71 (s, 1H, pyr H^3)
13	1718 ν(C=O) 1670 ν(N *CO*N) 1608 ν(C=N)	2.29 (s, 3H, pyr 4-CH_3); 2.48 (s, 3H, pyr 6-CH_3); 4.05 (t, 2H, H^b, $J_{H^aH^b} = 7.8$ Hz); 4.33 (t, 2H, H^a); 4.54 (s, 2H, benz.CH_2); 6.51 (s, 1H, pyr H^5); 6.72 (s, 1H, pyr H^3); 7.26–7.33 (m, 5 arom H)
14	1695 ν(N *CO*N) 1605 ν(C=N) 1363, 1176 ν as. and s. (SO_2)	2.33 (s, 3H, pyr 4-CH_3); 2.40 (s, 3H, pyr 6-CH_3); 4.05 (t, 2H, H^b, $J_{H^aH^b} = 7.2$ Hz); 4.36 (t, 2H, H^a); 6.44 (s, 1H, pyr H^5); 6.67 (s, 1H, pyr H^3); 7.52 (d, 2H, $H^{3'}H^{5'}$, $J_{H^{3'}H^{5'}} = J_{H^{2'}H^{6'}} = 8.7$ Hz); 8.10 (d, 2H, $H^{2'}H^{6'}$)
15	1692 ν(N *CO*N) 1605 ν(C=N) 1362, 1172 ν as. and s. (SO_2)	2.23 (s, 3H, pyr 4-CH_3); 2.40 (s, 3H, pyr 6-CH_3); 4.05 (t, 2H, H^b, $J_{H^aH^b} = 7.3$ Hz); 4.36 (t, 2H, H^a); 6.44 (s, 1H, pyr H^5); 6.67 (s, 1H, pyr H^3); 7.17–7.27 (m, 2 arom.H, $H^{3'}H^{5'}$); 8.15–8.23 (m, 2 arom H, $H^{2'}H^{6'}$)
16	1720 ν(N *CO*N) 1605 ν(C=N) 1378, 1184 ν as. and s. (SO_2)	2.23 (s, 3H, pyr 4-CH_3); 2.41 (s, 3H, pyr 6-CH_3); 4.12 (t, 2H, H^b, $J_{H^aH^b} = 7.2$ Hz); 4.53 (t, 2H, H^a); 6.38 (s, 1H, pyr H^5); 6.67 (s, 1H, pyr H^3); 7.71–7.79 (m, 3H, $H^{4'}H^{5'}H^{6'}$); 8.58 (m, 1H, $H^{3'}$)
17	1698 ν(N *CO*N) 1606 ν(C=N) 1370, 1170 ν as. and s. (SO_2)	1.35 (s, 9H, $C(CH_3)_3$; 2.23 (s, 3H, pyr 4-CH_3); 2.41 (s, 3H, pyr 6-CH_3); 4.06 (t, 2H, H^b, $J_{H^aH^b} = 7.2$ Hz); 4.35 (t, 2H, H^a); 6.46 (s, 1H, pyr H^5); 6.66 (s, 1H, pyr H^3); 7.56 (d, 2H, $H^3H^{5'}$, $J_{H^{3'}H^{5'}} = J_{H^{2'}H^{6'}} = 6.8$ Hz); 8.07 (d, 2H, $H^{2'}H^{6'}$)
18	1714 ν(N *CO*N) 1605 ν(C=N) 1372, 1169 ν as. and s. (SO_2)	2.19 (s, 3H, pyr 4-CH_3); 2.39 (s, 3H, pyr 6-CH_3); 4.12 (t, 2H, H^b, $J_{H^aH^b} = 7.0$ Hz); 4.35 (t, 2H, H^a); 6.39 (s, 1H, pyr H^5); 6.64 (s, 1H, pyr H^3); 7.58 (dd, 1H, $H^{8'}$); 7.64 (d, 1H, $H^{5'}$); 7.89 (dd, 1H, $H^{7'}$); 7.97 (dd, 1H, $H^{4'}$); 8.00 (dd, 1H, $H^{6'}$); 8.14 (dd, 1H, $H^{3'}$); 8.78 (d, 1H, $H^{1'}$, $J_{H^{1'}H^{3'}} = 1.8$ Hz; $J_{H^{3'}H^{4'}} = 8.7$ Hz; $J_{H^{5'}H^{6'}} = 7.0$ Hz; $J_{H^{6'}H^{7'}} = 7.0$ Hz; $J_{H^{5'}H^{7'}} = 1.5$ Hz; $J_{H^{7'}H^{8'}} = 7.1$ Hz; $J_{H^{8'}H^{6'}} = 1.5$ Hz)
19	1702 ν(N *CO*N) 1608 ν(C=N) 1345, 1167 ν as. and s. (SO_2)	2.19 (s, 3H, pyr 4-CH_3); 2.37 (s, 3H, pyr 6-CH_3); 4.27 (t, 2H, H^b, $J_{H^aH^b} = 7.3$ Hz); 4.45 (t, 2H, H^a); 6.24 (s, 1H, pyr H^5); 6.61 (s, 1H, pyr H^3); 7.72 (dd, 1H, $H^{5'}$); 7.56–7.72 (m, 3H, $H^{3'}H^{6'}H^{7'}$); 8.13 (dd, 1H, $H^{4'}$); 8.60 (dd, 1H, $H^{8'}$); 8.76 (dd, 1H, $H^{2'}$); $J_{H^{2'}H^{3'}} = 8.5$ Hz; $J_{H^{2'}H^{4'}} = 0.8$ Hz; $J_{H^{3'}H^{4'}} = 8.5$ Hz; $J_{H^{5'}H^{6'}} = J_{H^{7'}H^{8'}} = 7.5$ Hz; $J_{H^{5'}H^{7'}} = 1.1$ Hz; $J_{H^{6'}H^{8'}} = 1.0$ Hz

Table 7
IR and ^{1}H-NMR data of 3-substituted derivatives of 1-thiazolyl and 1-isoxazolylimidazolidin-2-ones **9** and **10**.

No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
21	1736 ν(N *CO*N) 1614 ν(C=N)	2.38 (d, 3H, 5-CH_3, $J_{H}^{Me}{}_{H}^{4}$ = 1.3 Hz); 4.13 (m, 4H, H^a and H^b); 7.04 (d, 1H, H^4); 7.85 (d, 2H, H$^{3'}$ and H$^{5'}$, $J_{H}^{2'}{}_{H}^{3'}$ = $J_{H}^{5'}{}_{H}^{6'}$ = 8.3 Hz); 8.26 (d, 2H, H$^{2'}$ and H$^{6'}$)
22	1738 ν(N *CO*N) 1610 ν(C=N)	2.35 (d, 3H, 5-CH_3, $J_{H}^{Me}{}_{H}^{4}$ = 0.7 Hz); 2.45 (s, 3H, 4-CH_3); 3.90 (t, 2H, H^b, $J_{H}^{a}{}_{H}^{b}$ = 8.3Hz); 4.04 (t,2H, H^a); 6.60 (d, 1H, H^4); 7.35 (d, 2H, H$^{3'}$ and H$^{5'}$,$J_{H}^{2'}{}_{H}^{3'}$ = $J_{H}^{5'}{}_{H}^{6'}$ = 8.3 Hz); 7.95 (d, 2H, H$^{2'}$ and H$^{6'}$)
23	1715 ν(N *CO*N)	2.37 (d, 3H, 5-CH_3, $J_{H}^{Me}{}_{H}^{4}$ = 1.3 Hz); 3.52 (t, 2H, H^b, $J_{H}^{a}{}_{H}^{b}$ = 7.9 Hz); 4.09 (t, 2H, H^a); 4.64 (s, 2H, CH_2); 7.00 (d, 1H, H^4); 7.17 (ddd, 1H, H$^{4'}$); 7.31(ddd, 1H, H$^{5'}$); 7.39 (dd, 1H, H$^{6'}$); 7.57 (dd, 1H, H$^{3'}$); $J_{H}^{5'}{}_{H}^{6'}$ = 7.2 Hz; $J_{H}^{3'}{}_{H}^{4'}$ = 7.9 Hz; $J_{H}^{4'}{}_{H}^{5'}$ = 8.0 Hz; $J_{H}^{3'}{}_{H}^{5'}$ = 1.2 Hz; $J_{H}^{4'}{}_{H}^{6'}$ = 1.9 Hz
24	1736 ν(N *CO*N) 1613 ν(C=N)	2.39 (d, 3H, 5-CH_3, $J_{H}^{Me}{}_{H}^{4}$ = 0.6 Hz); 3.51 (t, 2H, H^b, $J_{H}^{a}{}_{H}^{b}$ = 8.0 Hz); 3.88 (t, 2H, H^a); 4.63 (s, 2H, CH_2); 6.75 (d, 1H, H^4); 7.18 (ddd, 1H, H$^{4'}$); 7.28–7.38 (m, 2H, H$^{6'}$and H$^{5'}$); 7.58 (dd, 1H, H$^{3'}$); $J_{H}^{3'}{}_{H}^{4'}$ = 7.8 Hz; $J_{H}^{4'}{}_{H}^{5'}$ = 7.8 Hz; $J_{H}^{4'}{}_{H}^{6'}$ = 2.2 Hz; $J_{H}^{3'}{}_{H}^{5'}$ = 1.8 Hz
25	1690 ν(N *CO*N) 1613 ν(C=N)	2.38 (d, 3H, 5-CH_3, $J_{H}^{Me}{}_{H}^{4}$ = 0.7 Hz); 3.40 (t, 2H, H^b, $J_{H}^{a}{}_{H}^{b}$ = 7.6 Hz); 3.85 (t, 2H, H^a); 4.41 (s, 2H, CH_2); 6.73 (d, 1H, H^4) 7.17 (d, 2H, H$^{3'}$ and H$^{5'}$, $J_{H}^{2'}{}_{H}^{3'}$ = $J_{H}^{5'}{}_{H}^{6'}$ = 8.3 Hz); 7.95 (d, 2H, H$^{2'}$ and H$^{6'}$)

zoyl chloride (3.0 g, 17 mmol) in the same solvent (10 mL). The mixture was stirred at room temperature for 2 h. Then, after filtration and concentration under reduced pressure, the residue was chromatographed on a silica gel column with diethyl ether as eluent, to afford **12** (2.42 g) as a white crystalline powder. Yield = 47%; IR (KBr) (cm^{-1}): 1720 (νC=O); 1672 (νNCON); 1609 (νC=N); ^{1}H-NMR($CDCl_3$) δ: 2.22 (s, 3H; 4-CH_3); 2.40 (s, 3H, 6-CH_3); 4.15 (t, 2H, H^b, $J_{H}^{a}{}_{H}^{b}$ = 7.5 Hz); 4.50 (t, 2H, H^a); 6.25 (s, 1H, pyr H^5); 6.65 (s, 1H, pyr H^3); 6.68–6.72 (m, 1H, H^4); 7.22–7.27 (m, 2H, H^{2}and H^6). Anal. $C_{17}H_{15}F_2N_3O_2$ (C, H, N).

N^3-acyl compounds **11**, **13** and N^3-arylsulfonyl compounds **14**–**19** (Table 2) were synthesized according to this general procedure.

Table 5
In vitro antileishmanial activity of imidazolidin-2-ones **8**–**25**

Compounds	Antileishmanial activity in promastigotes (μmol L^{-1})		Cytotoxicity (μmol L^{-1})
	L. mexicana	*L. infantum*	MRC5
8	67.9	51.8	72.1
9	84.6	> 163.8	131.6
10	62.8	> 179.4	108.3
11	35.0	33.2	112.0
12	35.1	20.1	49.8
13	22.9	> 97.0	93.7
14	> 82.0	40.7	90.5
15	> 85.9	> 85.9	96.5
16	29.2	50.0	55.8
17	52.2	18.9	55.8
18	14.4	8.4	72.0
19	58.0	14.0	69.0
20	69.0	17.0	91.0
21	52.1	> 76.6	84.6
22	46.7	> 93.3	52.3
23	> 24.1	20.4	96.8
24	23.5	33.9	55.3
25	16.0	9.5	102.0

5.1.4. N^3-Sulfonylation and benzylation of imidazolidin-2-ones **9** and **10** (method D)

*5.1.4.1. 1-(5-Methylthiazol-2-yl)-3-(p-toluenesulfonyl)imidazolidin-2-one (**20**).* To a solution of **9** (1 g, 5.46 mmol.) in dry DMF (10 mL) was added NaH (0.34 g, 16 mmol); the resulting suspension was placed under stirring at 0 °C for 20 min. Then, *p*-toluene-sulfonyl chloride (3.24 g, 17 mmol) was added and the mixture stirred for 2 h at room temperature. At the end of this time, the reaction was stopped by water addition (50 mL), and the mixture was extracted by dichloromethane (3 × 100 mL). The organic fraction was collected, dried over Na_2SO_4 and concentrated under reduced pressure. The oily residue was purified by column chromatography on silica gel, using diethyl ether as eluent. The isolated compound **20** was crystallized from diethyl ether to afford 0.96 g of a white product. Yield = 52%; IR (KBr) (cm^{-1}): 1724 (νN CON); 1610 (νC=N); ^{1}H-NMR($CDCl_3$) δ: 2.36 (d, 3H, 5-CH_3, J^4_{HMeH} = 1.2 Hz); 2.45 (s, 3H, 4′-CH_3); 4.05–4.10 (m, 4H, H^a and H^b) 7.01 (d, 1H, H^4); 7.36 (d, 2H, H$^{3'}$H$^{5'}$, $J_{H}^{2'}{}_{H}^{3'}$ = $J_{H}^{2'}{}_{H}^{6'}$ = 8.4 Hz); 7.98 (d, 2H, H$^{2'}$H$^{6'}$). Anal. $C_{14}H_{15}N_3S_2O_3$ (C, H, N).

All N^3-arylsulfonyl and benzyl derivatives of imidazolidinones **9** and **10** (Tables 3 and 4) were synthesized according to this procedure. IR and NMR data of the corresponding compounds are gathered in Tables 6 and 7.

5.2. Parasitological assays

5.2.1. Parasites

L.(L). infantum (MHOM/FR/91/LEM2259), and *L.(L). mexicana* (MHOM/MX/95/NAN1) strains were cultured at 26 °C in Schneider's insect media (Sigma Chemical Co., St. Louis, MO), supplemented with 15% of fetal calf serum (Sigma), penicillin (100 UI mL^{-1}) and streptomycin (100 μg mL^{-1}).

5.2.2. In vitro antileishmanial activity

L.(L). infantum and *L.(L). mexicana* promastigotes (2×10^6 mL^{-1}) in the exponential stage were inoculated into 96-well plates and exposed to triplicate concentrations of imidazolidinone derivatives. Cultures were incubated for 96 h at 26 °C. The anti-proliferative effect was determined by MTT method based on the tetrazolium salt reduction by mitochondrial dehydrogenases. Absorbance was determined at 570 nm [10] and IC_{50} was calculated. *L.(L). mexicana*-Balb/c-infected macrophage model was developed in order to determine the anti-*Leishmania* activity against intracellular amastigotes. Peritoneal macrophages were adjusted to 10^6 cells mL^{-1} of RPMI 1640+15% FBS into 24 well plates. Cultures were then challenged for 24 h with stationary promastigotes at 37 °C and 5% CO_2. After a contact period of 96 h with the studied compounds, anti-*Leishmania* activity was expressed as the reduction of parasite loads in comparison to controls (IC_{50}).

5.2.3. Cytotoxicity

Cytotoxicity was studied after 96 h-incubation of human diploid fibroblasts (MRC5) with imidazolidin-2-one derivatives. Cytotoxic effect was measured using an Alamarblue fluorochrome-modified method (Interchim, Montluçon, France) [11].

Acknowledgements

This work was supported by funds provided by Project No. CF99S03 (ECOS Nord-French and Colombian Cooperative programme) ECOS/ICFEX/COL-CIENCIAS/ICETEX. We thank M. Biron, C. Picot and M. Ravily for technical assistance.

References

[1] J.D. Berman, Clin. Infect. Dis. 24 (1997) 684–703.
[2] J.D. Berman, M. Grolg, Exp. Parasitol. 67 (1988) 96–103.
[3] M.L. Chance, Ann. Trop. Med. Parasitol. 89 (1995) 37–43.
[4] B. Hentzer, T. Kobayasi, Ann. Trop. Med. Parasit. 71 (1977) 157–166.
[5] R. Kubba, Y. Al-Gindan, A.M. El-Hassan, A.H. Omer, Saudi. Med. J. 7 (1986) 596–604.
[6] C.P. Thakur, Trans. R. Soc. Trop. Med. Hyg. 88 (1994) 698–699.
[7] B.L. Herwaldt, Lancet 354 (1999) 1191–1199.
[8] P. Le Pape, H. Adala, F. Pagniez, J.M. Robert, G. Le Baut, Acta Parasitologica. 44 (1999) 156–159.
[9] H. Abdala, J.M. Robert, P. Le Pape, G. Wielgosz, S. Robert-Piessard, G. Le Baut, Arzneim Forsch./Drug Res. 50 (2000) 479–484.
[10] P. Le Pape, M. Zidane, H. Abdala, M.T. Moré, Cell Biol. Int. 24 (2000) 51–56.
[11] B. Pagé, M. Pagé, C. Noel, Int. J. Oncol. 3 (1993) 473–476.