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Synthesis, characterization and anti-leishmanial activity of neutral gold(I) complexes with *N*-heterocyclic carbene ligands bearing sulfur containing side arms.

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ABSTRACT: With an estimated annual incidence of one million cases, leishmaniasis is one of the top five vector-borne diseases. Currently available medical treatments involve side effects, including toxicity, non-specific targeting, and resistance development. Thus, new antileishmanial chemical entities are of the utmost interest to fight against this disease. We have shown in previous studies that gold(I) complexes bearing *N*-heterocyclic carbene (NHC) ligands with nitrogen or sulfur containing side arms have interesting biological activities in the field of cancer, malaria and leishmaniasis. The present study evaluates the *in vitro* antileishmania effects on *L. infantum* axenic amastigotes and their cytotoxicity for the human Thp1 cell line of a new family of 6 new imidazolium salts and their corresponding neutral (NHC)Au(I)Cl complexes. All new compounds have been characterized by classical analytical methods and five gold complexes have been evidenced by X-ray structure determination. We showed that one proligand has moderate activity (IC₅₀ = 8.24 μM) while 4 of 6 gold complexes have IC₅₀ values in the μM range (0.15-1.3 μM) including 3 with SI's between 46 and 108. These results suggest remarkable leishmanicidal activity *in vitro* for 3 new neutral (NHC)Au(I)Cl complexes making them candidate for further *in vivo* studies which are under investigation.

INTRODUCTION

INTRODUCTION

In its 2018 report WHO classified 20 Neglected Tropical Diseases (NTDs) affecting one billion people in low-income populations in 149 countries.¹ Among these NTDs, leishmaniasis threatens approximately more than one billion people¹ mostly in tropical regions (Brazil, India, East Africa) but also in wealthy countries (peculiarly around Mediterranean Sea), even if the most severe cases occur in South America (www.who.int/leishmaniasis/burden/en/). Furthermore, in a global warming context, the sandfly (vector of the illness) area is slowly extending over the Mediterranean seashore in Europe.² These infectious diseases are caused by parasites of the *Leishmania* genus, which are transmitted to a mammal host (mainly human, dog, monkey, rodent) during the bite of an infected phlebotomine sandfly (*Phlebotomus sp./Lutzomilla sp.*).³ Among several clinical forms of Leishmaniasis, visceral leishmaniasis (VL) is fatal if untreated (about 20-30000 deaths a year worldwide¹). Leishmaniasis is due to the visceralization

of the intracellular amastigote stage of the parasite, especially in liver, spleen and bone marrow, more precisely in mononuclear cells of its vertebrate host.⁴ The two main *Leishmania* species responsible for VL are *L. infantum* and *L. donovani*. In the absence of an effective human vaccine, the control of leishmaniasis is based on chemotherapy with only few efficient drugs currently available: amphotericin B, miltefosine, antimonial derivatives, pentamidine and paromomycin. These drugs are either expensive (e.g., liposomal amphotericin B), present severe side effects (e.g., the nephrotoxicity of amphotericin B, the teratogenicity of miltefosine) or show an increasing lack of efficacy due to the emergence of resistant parasites (antimony derivatives and miltefosine).^{5,6} Fexinidazole, a 5-nitroimidazole, was recently in phase II of clinical trials against VL but showed clearly a lack of efficacy and currently, there is no new chemical molecule in clinical trials at the moment.⁵

A non-classical approach concerns metallo-drugs. Some organometallic compounds have been designed as new drugs for important medical human problems including cancer, bacterial, viral and parasitic diseases.⁷ Some metal based-drugs show promising leishmanicidal activities. Cu(II), Ni(II) and Co(II) triazopyrimidine derivatives were tested *in vitro* against *L.*

braziliensis and *L. infantum* amastigotes ($IC_{50} = 17.0\text{-}40.8 \mu\text{M}$).⁸ Ni(II) thiourea and Co(II) acyl thiourea complexes showed activities *in vitro* against *L. major*, with IC_{50} in the nanomolar range.^{9,10} Cisplatin was active against murine visceral leishmaniasis alone or in association.^{11,12} The similarity between metabolic pathway of kinetoplastid parasites and tumor cells¹³ and the fact that many antiprotozoal drugs bind to DNA, has led to the use of transition metal complexes as metallointercalators in the context of leishmaniasis. In this field, iridium, ruthenium, gold, copper, platinum and rhodium complexes have shown excellent antileishmanial activities.¹⁴⁻¹⁷ Among them, Cu(II),^{18,19} Ag(I),²⁰ and Au(III)²¹ metal complexes with planar organic compounds have shown *in vitro* activities against the promastigote form of *L. braziliensis* and *L. mexicana*. Other series of Au(I) and Au(III) complexes have been studied on *L. mazonensis* and *L. braziliensis*.²²

One target for antileishmanial drugs is trypanothione reductase (TR), a crucial redox enzyme in *Leishmania*.^{23,24} TR contains active-site thiol groups so thiophilic metal-based compounds can potentially serve as selective inhibitors of TR. Gold complexes are proposed to block active site cysteine groups in thiol-dependent enzymes. The antiarthritic gold(I) drug auranofin and [AuCl(PET₃)] (PET₃: triethylphosphine) were tested *in vitro* as antileishmanial agents and induced a dose dependent antiproliferative effect on promastigotes of *L. infantum* and *L. major*.²⁵ Both auranofin and [AuCl(PET₃)] cause inhibition of TR with a K_i of 0.155 and 0.018 μM , respectively, stronger than antimony(III) compounds.²⁶ Moreover, a low-resolution crystal structure of auranofin-TR of *L. infantum* was obtained and the gold center was found to be tightly bound to two cysteine residues in the active site of the enzyme.

In this context we have shown in previous studies that gold(I) complexes bearing *N*-heterocyclic carbene (NHC) ligands with nitrogen or sulfur containing side arms have interesting biological activities in the field of cancer, malaria and leishmaniasis.²⁷⁻³⁴ In this study we present the synthesis, characterization and anti-leishmanial potency of a new family of neutral gold(I)-NHC sulfur containing systems with improved activity against *L. infantum*.

RESULTS AND DISCUSSION

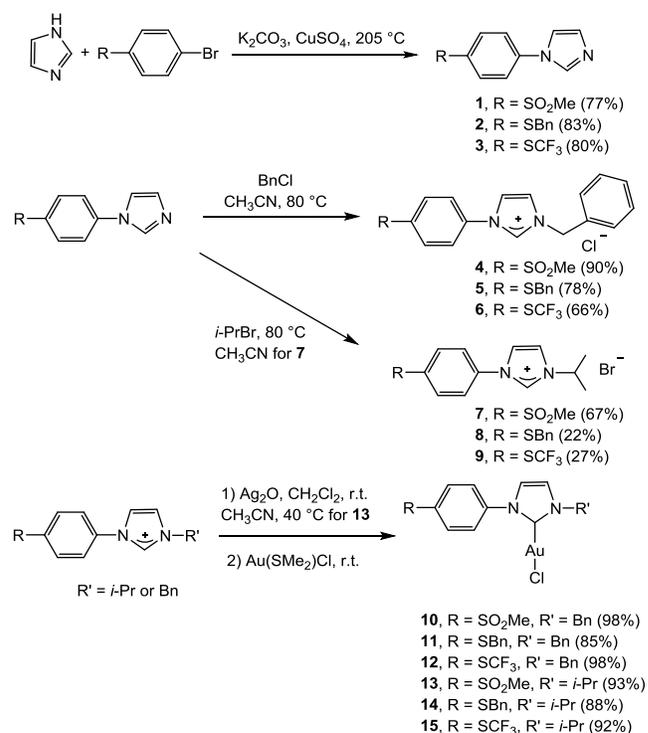
Synthesis of proligands 4 to 9 and gold(I) complexes 10 to 15:

Synthesis of substituted imidazoles **1** to **3**. The sulfur containing imidazole derivatives **1** to **3** were readily obtained by solid state reactions between imidazole and para substituted bromophenyl derivatives, namely 1-bromo-4-(methylsulfonyl)benzene, 1-bromo-4-(phenylthio)benzene and 1-bromo-4-[(trifluoromethyl)thio]benzene at 205 °C in the presence of potassium carbonate and copper sulfate. All three compounds have been characterized by ¹H and ¹³C NMR spectroscopy, high resolution mass spectrometry and elemental analysis.

Synthesis of imidazolium salts **4** to **9**. For the synthesis of **4** to **6**, benzyl chloride and **1**, **2** or **3** were dissolved in acetonitrile and heated at 80 °C. In the case of **7** to **9** a large excess of 2-bromopropane was added to the substituted imidazole derivatives **1** to **3** and heated to 80 °C, for **8** and **9** without an additional solvent and for **7** in acetonitrile. All proligands **4** to **9** have been characterized by ¹H and ¹³C NMR spectroscopy, high resolution mass spectrometry and elemental analysis. The

most characteristic features are the peaks in the ¹H-NMR spectra of the imidazolium protons H2 between 10.06 and 11.61 ppm.

Synthesis of gold(I) complexes **10** to **15**. The gold(I) NHC complexes were synthesized using the silver transmetalation route. Complexes **10** to **15** have been obtained with high yields from 85 to 98 %. All complexes have been characterized by ¹H and ¹³C NMR spectroscopy, by high resolution mass spectrometry and the purity of the complexes has been confirmed by elemental analysis. The most characteristic features are the peaks in the ¹³C NMR spectra of the carbene carbon atoms C2 between 167 and 170 ppm, typical values for mono-NHC gold(I) complexes of type NHC-Au-Cl.



Scheme 1. Synthesis of imidazolium salts **4-9** and gold(I) complexes **10-15** (yields are in brackets).

Crystal structures of complexes 10 to 13 and 15.

Crystals of **10**, **11** and **15** have been obtained by slow diffusion of diethyl ether into a saturated solution of the corresponding complex in dichloromethane. In the case of **13** pentane has been used as counter-solvent and crystals of **12** have been obtained by slow evaporation of a saturated methanol solution of **12**.

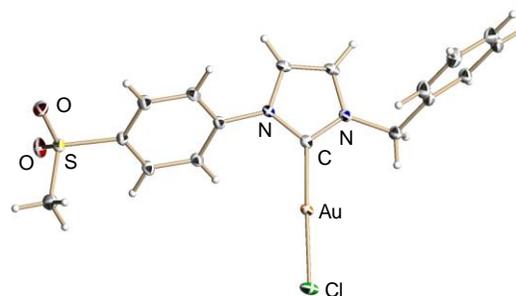


Figure 1: Structure of **10** depicted at a 50 % thermal ellipsoid level. A non-coordinating solvent molecule has been omitted for clarity. Selected bond lengths [Å] and angles [°]: Au-C 1.983(2), Au-Cl 2.282(1), C-Au-Cl 177.89(5).

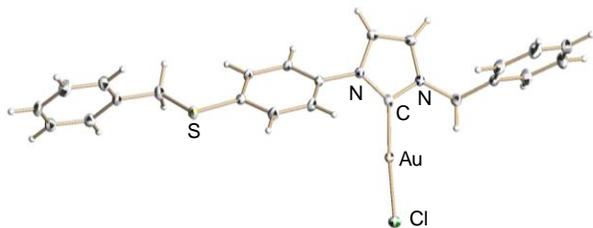


Figure 2: Structure of **11** depicted at a 50 % thermal ellipsoid level. Selected bond lengths [Å] and angles [°]: Au-C 1.982(2), Au-Cl 2.277(1), C-Au-Cl 175.37(7).

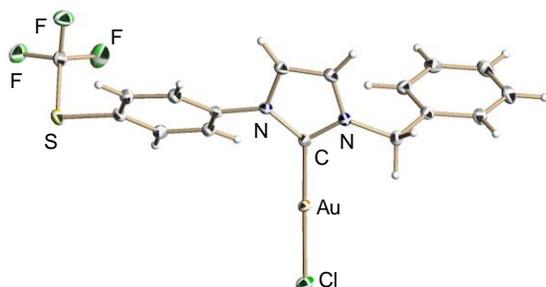


Figure 3: Structure of **12** depicted at a 50 % thermal ellipsoid level. Selected bond lengths [Å] and angles [°]: Au-C 1.976(2), Au-Cl 2.277(1), C-Au-Cl 177.55(5).

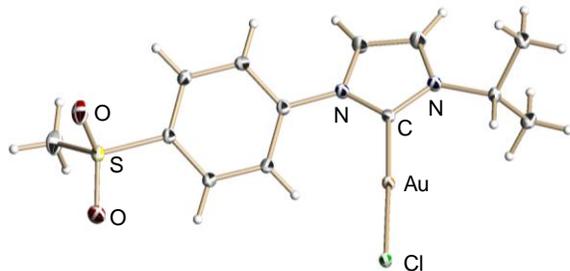


Figure 4: Structure of **13** depicted at a 50 % thermal ellipsoid level. Selected bond lengths [Å] and angles [°]: Au-C 1.988(2), Au-Cl 2.324(1), C-Au-Cl 177.93(6).

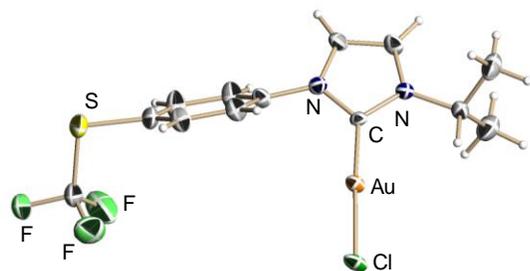


Figure 5: Structure of **15** depicted at a 50 % thermal ellipsoid level. Selected bond lengths [Å] and angles [°]: Au-C 1.981(7), Au-Cl 2.302(3), C-Au-Cl 175.8(6).

Main features of all here presented structures are very similar; the gold carbon distances range from 1.97 to 1.99 Å, the gold chlorine distances from 2.27 to 2.30 Å, and the C-Au-Cl

angles are very close to the expected linear coordination for gold(I) with values between 175 and 178°. Only complex **15** shows weak auriphilic interactions in the solid state with an Au-Au distance of 3.553 Å.

Biological results:

All imidazolium salts (**4-9**) and Au^I(NHC)Cl complexes **10-15** have been tested against the axenic amastigote form of *L. infantum*. Toxicity has been evaluated on human monocyte cell line THP1. Auranofin has been used as gold-containing control drug and amphotericin B, miltefosine and pentamidine were used as antileishmanial compounds of reference. All results are presented in Table 1.

Table 1. *In vitro* antileishmanial activity and cytotoxicity of compounds 4-15.

Compound	<i>L. infantum</i> axenic amastigotes IC ₅₀ (μM) ^a	THP1 CC ₅₀ (μM) ^a	Selectivity index CC ₅₀ / IC ₅₀
4	>143		
5	8.24±0.15	7.78±0.9	0.94
6	>134.47		
7	>144.40		
8	>128.09		
9	>135.78		
10	9.84±1.47	59.65±7.48	6.06
11	1.30±0.05	13.47±2.19	10.36
12	0.34±0.03	15.84±2.86	46.58
13	9.33±1.81	>100	>11
14	0.35±0.07	20.93±1.68	59.8
15	0.15±0.04	16.24±3.27	108.27
Auranofin^b	0.07±0.01	2.64±0.24	37.71
Amphotericin B^c	0.06±0.01	13.13±0.92	218.83
Pentamidine^c	1.36±0.31	65.87±7.49	48.43
Miltefosine^c	0.46±0.04	35.02±2.98	76.13
Doxorubicin^d	-	0.83±0.07	-

^a Mean of three independent experiments.

^b Auranofin was used as a gold-based drug of reference.

^c Amphotericin B, miltefosine and pentamidine were used as antileishmanial compounds of reference.

^d Doxorubicin was used as positive control of cytotoxicity.

As observed in previous studies, the precursors of the carbene ligands are either inactive with IC₅₀ values higher than 100 μM as in the case of **4** and **6** to **9**, or they show some non-

specific activity with selectivity indexes close to 1, as in the case of proligand **5**. In contrast to this, all here presented gold(I) complexes show moderate to good antileishmanial activity with SI's higher than 6. The crucial role of gold cations is not limited to NHC ligands, the same phenomenon has been observed in the case of neutral thiolato-gold(I) complexes and cationic gold(I) complexes coordinated by thione group containing ligands.³⁵⁻³⁷ For such sulfur-containing gold(I) complexes IC₅₀ values between 0.5 and 3.7 μM for *L. infantum* amastigotes have been found. The corresponding SI values, in relation to THP1 cells, are in the range of 2 to 6. In a previous study, we used a thioanisole substituted NHC ligand bearing either a benzyl group or a quinoline moiety, and the corresponding neutral Au(NHC)Cl complexes showed IC₅₀ values of 0.7 and 0.9 μM for axenic amastigotes of *L. infantum* with SI's around 9 for both, based on the toxicity against J774A.1 cells.³⁰ These here presented series focus on variations of sulfur-groups based on the thioanisole motif by replacing SME by SO₂Me, SBn and SCF₃. The SO₂Me group bearing complexes **10** and **13** show the lowest positive effect against *Leishmania*, with IC₅₀ values of 9.8 and 9.3 μM, respectively. This is going on with a low selectivity with SI's of 6 and 11 respectively. Complexes **10** and **13** show significantly lower activity and selectivity in comparison to all reference drugs tested in this study. Concerns the SBn group, complex **11** gives an IC₅₀ of 1.3 μM, close to the activity of pentamidine, but with low selectivity (SI = 10.4), five times lower than pentamidine. Isopropyl substituted **14** shows even better activity (IC₅₀ = 0.35 μM) than miltefosine (IC₅₀ = 0.46 μM), combined with a selectivity (SI = 60) between miltefosine and pentamidine. The best results have been obtained using the SCF₃ group (complexes **12** and **15**). While complex **12** gives IC₅₀ values (0.34 μM) and selectivity (SI = 46) very similar to complex **14**, complex **15** shows values (IC₅₀ = 0.15 μM and SI = 108) lying between the most active and selective reference drugs, namely miltefosine and amphotericin B. Concerning all here tested gold complexes, auranofin shows a lower IC₅₀ than all here tested complexes, but accompanied by a high toxicity against THP1 leading to a lower selectivity than complexes **12**, **14** and **15**. Regarding the second substituent of the NHC ligand, the isopropyl group gives better activities and selectivity than benzyl, so the best result could be obtained with complex **15** combining SCF₃ and isopropyl.

CONCLUSION

A family of six new imidazolium salts and their corresponding neutral Au^I(NHC)Cl complexes has been synthesized and characterized. Five of the six gold complexes have been crystallized and analyzed by X-ray structure determination. All twelve new compounds have been studied on *L. infantum* axenic amastigotes for their antileishmanial properties and three of the gold complexes revealed good to very good anti-amastigote activity combined with high selectivity in the same range as the reference drugs. Complexes **12**, **14** and **15** could be promising candidates for the development of a new class of antileishmanial drugs and further mechanistical and *in vivo* studies are under investigation.

EXPERIMENTAL SECTION

General Information:

All complexation reactions were performed under an inert atmosphere of dry nitrogen by using standard vacuum line and Schlenk tube techniques. All reagents were used as received from commercial

suppliers. Reactions involving silver compounds were performed with the exclusion of light. ¹H (300 or 400 MHz), ¹³C (75 or 101 MHz) and ¹⁹F (282 or 376 MHz) NMR spectra were recorded at 298 K on Bruker AV300 or Bruker AV400 spectrometers in CDCl₃, CD₃CN and DMSO-*d*₆ as solvents. Elemental analyses were carried out by the "Service de Microanalyse du Laboratoire de Chimie de Coordination (Toulouse)". HRMS were performed with a Thermo Finnigan MAT 95 XL spectrometer using electrospray ionization (ESI) by the "Service de Spectrométrie de Masse de Chimie UPS-CNRS" (Toulouse).

1-[4-(Methylsulfonyl)phenyl]-1*H*-imidazole (**1**)

In a pressure flask, imidazole (867.75 mg, 12.75 mmol), 1-bromo-4-(methylsulfonyl)benzene (1.5 mg, 6.37 mmol), K₂CO₃ (881.02 mg, 6.37 mmol) and a catalytic amount of CuSO₄ were stirred at 205 °C for 48 h. After cooling to room temperature, the crude product was extracted with MeOH, filtered and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel with a mixture of CH₂Cl₂ and MeOH (90/10) as eluent to give a yellow solid (1.09 g, 77%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.45 (dd, *J* = 1.4, 0.8 Hz, 1H, H2), 8.09–8.03 (m, 2H, H8), 8.00–7.95 (m, 2H, H7), 7.92 (dd, *J* = 1.4 Hz, 1H, H5), 7.17 (dd, *J* = 1.4, 0.8 Hz, 1H, H4), 3.28 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 141.4 (1C, C2), 139.2 (1C, C9), 135.4 (1C, C6), 131.6 (1C, C4), 129.7 (2C, C8), 121.4 (2C, C7), 117.7 (1C, C5), 44.6 (1C, CH₃). HMRS (ES⁺): Calc. For C₁₀H₁₁N₂O₂ 223.0541 found 223.0546 [M+H⁺].

1-[4-(Benzylsulfonyl)phenyl]-1*H*-imidazole (**2**)

In a pressure flask, imidazole (229.25 mg, 3.36 mmol), 1-bromo-4-(benzylsulfonyl)benzene (470.1 mg, 1.68 mmol), K₂CO₃ (232.25 mg, 1.68 mmol) and a catalytic amount of CuSO₄ were stirred at 205 °C for 48 h. After cooling to room temperature, the crude product was extracted with MeOH, filtered and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel with a mixture of CH₂Cl₂ and MeOH (90/10) as eluent to give a brown solid (370.9 mg, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, *J* = 1.5 Hz, 1H, H2), 7.39 – 7.20 (m, 11H, H4, H5, H7, H8, H12, H13, H14), 4.15 (s, 2H, CH₂). ¹³C NMR (75 MHz, CDCl₃) δ 137.0 (1C, C11), 135.8 (1C, C2), 135.6 (1C, C6), 135.5 (1C, C9), 131.1 (2C, C13), 130.5 (1C, C4), 128.8 (2C, C12), 128.6 (2C, C8), 127.4 (1C, C14), 121.7 (2C, C7), 118.1 (1C, C5), 39.1 (1C, C10). HMRS (ES⁺): Calc. For C₁₆H₁₅N₂S 267.0956 found 267.0963 [M+H⁺].

1-[4-(Trifluoromethyl)sulfonyl]phenyl]-1*H*-imidazole (**3**)

In a pressure flask, imidazole (264.15 mg, 3.88 mmol), 1-bromo-4-(trifluoromethylsulfonyl)benzene (500 mg, 1.94 mmol), K₂CO₃ (268.11 mg, 1.94 mmol) and a catalytic amount of CuSO₄ were stirred at 180 °C for 48 h. After cooling to room temperature, the crude product was extracted with MeOH, filtered and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel with a mixture of CH₂Cl₂ and MeOH (90/10) as eluent to give a yellow solid (382.8 mg, 80% yield). ¹H NMR (400 MHz, CD₃CN) δ 8.08–7.99 (m, 1H, H2), 7.86–7.75 (m, 2H, H8), 7.67–7.57 (m, 2H, H7), 7.55–7.45 (m, 1H, H5), 7.21–7.12 (m, 1H, H4). ¹³C NMR (101 MHz, CD₃CN) δ 139.6 (1C, C2), 138.0 (2C, C8), 135.7 (1C, C9), 130.5 (1C, C6), 129.8 (1C, CF₃, *q*, *J* = 307.1 Hz), 121.8 (1C, C4), 121.6 (2C, C7), 117.3 (1C, C5). ¹⁹F NMR (376 MHz, CDCl₃) δ -42.70 (3F, CF₃). HMRS (ES⁺): Calc. For C₁₀H₈F₃N₂S 245.0360 found 245.0361 [M+H⁺].

3-Benzyl-1-[4-(methylsulfonyl)phenyl]-1*H*-imidazol-3-ium chloride (**4**)

Under nitrogen atmosphere, **1** (250 mg, 1.12 mmol) and benzyl chloride (0.14 mL, 1.22 mmol) were dissolved in dry CH₃CN (10 mL) and stirred at 80 °C for 5 days. The solvent was evaporated under reduced pressure, the residue was washed with ether and dried under vacuum to give a white solid (351 mg, 90% yield). Anal. Calcd. For C₁₇H₁₇ClN₂O₂S: C, 58.53; H, 4.91; N, 8.03; Found: C, 58.72, H, 4.83, N, 7.98. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (d, *J* = 1.7 Hz, 1H, H2), 8.53 (t, *J* = 1.9 Hz, 1H, H5), 8.25–8.10 (m, 5H, H12, H13, H14),

7.64–7.56 (m, 2H, H8), 7.49–7.36 (m, 3H, H4, H7), 5.60 (s, 2H, H10), 3.34 (s, 3H, CH₃). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 142.0 (1C, C6), 138.8 (1C, C2), 136.9 (1C, C9), 134.9 (1C, C11), 129.4 (2C, C13), 129.4 (2C, C12), 129.3 (1C, C14), 129.1 (2C, C8), 123.9 (1C, C4), 123.2 (2C, C7), 122.0 (1C, C5), 52.8 (1C, C10), 43.7 (1C, CH₃). HMRS (ES⁺): Calc. For C₁₇H₁₇N₂O₂S 313.1011 found 313.1014 [M-Cl].

3-Benzyl-1-[4-(benzylsulfanyl)phenyl]-1H-imidazol-3-ium chloride (5)

Under nitrogen atmosphere, **2** (100 mg, 0.37 mmol) and benzyl chloride (0.05 mL, 0.44 mmol) were dissolved in dry CH₃CN (10 mL) and stirred at 80 °C for 5 days. The solvent was evaporated under reduced pressure, the residue was washed with ether and dried under vacuum to give a yellow solid (113.5 mg, 78% yield). Anal. Calcd. For C₂₃H₂₁ClN₂S: C, 70.30; H, 5.39; N, 7.13; Found: C, 71.02, H, 5.14, N, 7.21. ¹H NMR (300 MHz, CDCl₃) δ 11.37 (t, *J* = 1.5 Hz, 1H, H2), 7.85 (t, *J* = 1.8 Hz, 1H, H4), 7.69–7.54 (m, 5H, H5, H7, H8), 7.34–7.12 (m, 10H, H12, H13, H14, H17, H18, H19), 5.71 (s, 2H, H15), 4.07 (s, 2H, H10). ¹³C NMR (75 MHz, CDCl₃) δ 140.0 (1C, C6), 136.2 (1C, C11), 135.8 (1C, C2), 133.2 (1C, C9), 132.0 (1C, C16), 129.8 (2C, C13), 129.4 (1C, C19), 129.4 (2C, C18), 129.3 (2C, C12), 128.8 (2C, C17), 128.7 (2C, C8), 127.5 (1C, C14), 122.8 (1C, C5), 121.9 (2C, C7), 120.6 (1C, C4), 53.5 (1C, C15), 37.9 (1C, C10). HMRS (ES⁺): Calc. For C₂₃H₂₁N₂S 357.1425 found 357.1428 [M-Cl].

3-Benzyl-1-[4-[(trifluoromethyl)sulfanyl]phenyl]-1H-imidazol-3-ium chloride (6)

Under nitrogen atmosphere, **3** (130 mg, 0.53 mmol) and benzyl chloride (0.07 mL, 0.61 mmol) were dissolved in dry CH₃CN (10 mL) and stirred at 80 °C for 5 days. The solvent was evaporated under reduced pressure, the residue was washed with ether and dried under vacuum to give a white solid (130.3 mg, 66% yield). Anal. Calcd. For C₁₇H₁₄ClF₃N₂S: C, 55.06; H, 3.81; N, 7.55; Found: C, 54.98, H, 3.88, N, 7.51. ¹H NMR (400 MHz, CDCl₃) δ 11.61 (t, *J* = 1.6 Hz, 1H, H2), 8.24 (t, *J* = 1.9 Hz, 1H, H5), 8.04–7.92 (m, 2H, H7), 7.73 (t, *J* = 1.8 Hz, 1H, H4), 7.72–7.64 (m, 2H, H8), 7.61–7.46 (m, 2H, H12), 7.27–7.15 (m, 3H, H13, H14), 5.68 (s, 2H, H10). ¹³C NMR (101 MHz, CDCl₃) δ 137.9 (2C, C8), 136.3 (1C, C2), 136.1 (1C, C9), 133.0 (1C, C6), 129.5 (1C, C11), 129.3 (2C, C7), 129.1 (2C, C13), 129.0 (1C, CF₃), *q*, *J* = 308.7 Hz), 126.6 (1C, C4), 123.3 (1C, C5), 122.4 (2C, C12), 121.1 (1C, C14), 120.6 (1C, C10). ¹⁹F NMR (376 MHz, CDCl₃) δ -42.17 (3F, CF₃). HMRS (ES⁺): Calc. For C₁₇H₁₄N₂F₃S 335.0830 found 335.0838 [M-Cl].

3-Isopropyl-1-(4-(methylsulfonyl)phenyl)-1H-imidazol-3-ium bromide (7)

In a pressure flask, **1** (200 mg, 0.90 mmol) and 2-bromopropane (3 mL, 32 mmol) were dissolved in CH₃CN (5 mL) and stirred at 80 °C for one week. The solvent was evaporated under reduced pressure, the residue was washed with DCM and dried under vacuum to give a white solid (207.7 mg, 67% yield). Anal. Calcd. For C₁₃H₁₇BrN₂O₂S: C, 45.22; H, 4.96; N, 8.11; Found: C, 45.15, H, 5.01, N, 8.25. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.06 (s, 1H, H2), 8.49 (s, 1H, H4), 8.32–8.08 (m, 5H, H5, H7, H8), 4.76 (qq, *J* = 6.6 Hz, 1H, H10), 3.34 (s, 3H, H12), 1.58 (d, *J* = 6.6 Hz, 6H, H11). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 141.9 (1C, C6), 138.9 (1C, C9), 135.4 (1C, C2), 129.4 (2C, C8), 123.2 (2C, C7), 122.3 (1C, C5), 121.6 (1C, C4), 53.7 (1C, C10), 43.7 (1C, C12), 22.7 (2C, C11). HMRS (ES⁺): Calc. For C₁₃H₁₇N₂O₂S 265.1011 found 265.1008 [M-Br].

1-(4-(Benzylthio)phenyl)-3-isopropyl-1H-imidazol-3-ium bromide (8)

In a pressure flask, **2** (100 mg, 0.37 mmol) was dissolved in 2-bromopropane (3 mL, 32 mmol) and stirred at 80 °C for one week. The solvent was evaporated under reduced pressure, the residue was washed with ether and dried under vacuum to give a yellow solid (32.3 mg, 22% yield). Anal. Calcd. For C₁₉H₂₁BrN₂S: C, 58.61; H, 5.44; N, 7.19; Found: C, 58.59, H, 5.39, N, 7.22. ¹H NMR (300 MHz, CDCl₃) δ 11.13 (s, 1H, H2), 7.91–7.63 (m, 4H, H4, H5, H8), 7.45–7.36 (m, 2H, H7), 7.33–7.22 (m, 5H, C12, C13, C14), 5.27 (qq, *J* =

6.7 Hz, 1H, H15), 4.17 (s, 2H, H10), 1.69 (d, *J* = 6.7 Hz, 6H, H16). ¹³C NMR (75 MHz, CDCl₃) δ 140.1 (1C, C6), 136.2 (1C, C11), 134.8 (1C, C2), 132.0 (1C, C9), 129.9 (2C, C13), 128.8 (2C, C12), 128.7 (2C, C8), 127.6 (1C, C14), 122.1 (2C, C7), 120.8 (1C, C4), 120.6 (1C, C5), 53.9 (1C, C15), 38.0 (1C, C10), 23.2 (2C, C16). HMRS (ES⁺): Calc. For C₁₉H₂₁N₂S 309.1425 found 309.1431 [M-Br].

3-Isopropyl-1-(4-((trifluoromethyl)thio)phenyl)-1H-imidazol-3-ium bromide (9)

In a pressure flask, **3** (125 mg, 0.59 mmol), were dissolved in 2-bromopropane (3 mL) and stirred at 80 °C one week, the solvent was evaporated under reduced pressure, and the solid washed with diethyl ether, and dried to have a yellow solid (58.2 mg, 27 % yield). Anal. Calcd. For C₁₃H₁₄BrF₃N₂S: C, 42.52; H, 3.84; N, 7.63; Found: C, 42.41, H, 3.79, N, 7.68. ¹H NMR (300 MHz, CD₃CN) δ 10.32 (dt, *J* = 1.8, 0.9 Hz, 1H, H2), 8.13–8.01 (m, 3H, H4, H7), 7.98–7.91 (m, 2H, H8), 7.88 (t, *J* = 1.9 Hz, 1H, H5), 4.89 (qq, *J* = 6.7 Hz, 1H, H10), 1.65 (d, *J* = 6.7 Hz, 6H, H11). ¹³C NMR (75 MHz, CD₃CN) δ 137.8 (2C, C8), 137.2 (1C, C2), 134.9 (1C, C6), 129.6 (q, *J* = 307.2 Hz, 1C, CF₃), 125.6 (1C, C9), 123.4 (2C, C7), 121.6 (1C, C4), 121.2 (1C, C5), 53.9 (1C, C10), 22.0 (2C, C11). ¹⁹F NMR (282 MHz, CD₃CN) δ -43.38 (3F, CF₃). HMRS (ES⁺): Calc. For C₁₃H₁₄F₃N₂S 287.0830 found 287.0830 [M-Br].

Complex 10

Under nitrogen atmosphere, (100 mg, 0.28 mmol) of **4** and (33.15 mg, 0.14 mmol) of Ag₂O were dissolved in dry CH₂Cl₂, and stirred at r.t. for 18h. (90.72 mg, 0.31 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a white solid (150.5 mg, 98 % yield). Anal. Calcd. For C₁₇H₁₆AuClN₂O₂S: C, 37.41; H, 3.14; N, 5.13; Found: C, 37.74, H, 3.18, N, 5.17. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.20–8.12 (m, 2H, H8), 8.12–8.05 (m, 2H, H7), 7.96 (d, *J* = 2.0 Hz, 1H, H5), 7.88 (d, *J* = 2.0 Hz, 1H, H4), 7.52–7.33 (m, 5H, H12, H13, H14), 5.51 (s, 2H, H10), 3.35 (s, 3H, CH₃). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 169.3 (1C, C2), 143.1 (1C, C6), 141.5 (1C, C9), 136.7 (1C, C11), 129.3 (2C, C13), 128.9 (2C, C12), 128.8 (1C, C14), 128.3 (2C, C8), 126.4 (2C, C7), 123.6 (1C, C4), 123.5 (1C, C5), 54.8 (1C, C10), 43.7 (1C, CH₃). HMRS (ES⁺): Calc. For C₁₉H₁₉AuN₃O₂S 550.0863 found 550.0873 [M-Cl+CH₃CN].

Complex 11

Under nitrogen atmosphere, **5** (70 mg, 0.18 mmol) and (20.58 mg, 0.09 mmol) of Ag₂O were dissolved in dry CH₂Cl₂, and stirred at r.t. for 18 h. (57.67 mg, 0.19 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a white solid (88.9 mg, 85% yield). Anal. Calcd. For C₂₃H₂₀AuClN₂S: C, 46.91; H, 3.42; N, 4.76; Found: C, 46.92, H, 3.31, N, 4.72. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.83–7.77 (m, 2H, H4, H5), 7.70–7.64 (m, 2H, H7), 7.53–7.48 (m, 2H, H8), 7.45–7.20 (m, 10H, H12, H13, H14, H17, H18, H19), 5.46 (s, 2H, H10), 4.35 (s, 2H, H15). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 168.9 (1C, C2), 138.2 (1C, C6), 137.4 (1C, C9), 136.8 (1C, C11), 136.8 (1C, C16), 129.3 (2C, C7), 129.3 (2C, C18), 128.9 (2C, C17), 128.7 (1C, C19), 128.6 (2C, C13), 128.2 (2C, C8), 127.7 (1C, C14), 125.9 (2C, C12), 123.5 (1C, C4), 123.0 (1C, C5), 54.6 (1C, C10), 36.5 (1C, C15). HMRS (ES⁺): Calc. For C₂₃H₂₀AuN₂S 553.1013 found 553.1014 [M-Cl].

Complex 12

Under nitrogen atmosphere, **6** (80 mg, 0.22 mmol) and (27.04 mg, 0.12 mmol) of Ag₂O were dissolved in dry CH₂Cl₂, and stirred at r.t. for 18 h. (69.8 mg, 0.24 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a white solid (119.8 mg, 98% yield). Anal. Calcd. For C₁₇H₁₃AuClF₃N₂S: C, 35.96; H, 2.49; N, 4.93; Found: C, 36.05, H, 2.41, N, 4.92. ¹H NMR (400 MHz, CD₃CN) δ 7.88 (s, 4H, H7, H8), 7.54–7.27 (m, 7H, H4, H5, H12, H13, H14), 5.48 (s, 2H, H10). ¹³C NMR (101 MHz, CD₃CN) δ 170.3 (1C, C2), 141.6 (1C, C6), 137.3 (2C, C13), 136.0 (1C, C11), 129.7 (q, *J* = 307.1 Hz, 1C, CF₃), 128.9 (2C, C8), 128.5 (1C, C9), 127.9 (2C, C12), 126.4 (2C, C7), 124.7 (1C, C14), 122.5 (1C, C5),

122.3 (1C, C4), 54.6 (1C, C10). ¹⁹F NMR (376 MHz, CD₃CN) δ -43.37 (3F, CF₃). HMRS (ES⁺): Calc. For C₁₉H₁₆AuF₃N₃S 572.0683 found 572.0682 [M-Cl⁻+CH₃CN].

Complex 13

Under nitrogen atmosphere, **7** (50 mg, 0.14 mmol) and (16.64 mg, 0.07 mmol) of Ag₂O were dissolved in dry CH₃CN, and stirred at 40 °C for 18 h. (46.83 mg, 0.16 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a grey solid (67.3 mg, 93% yield). Anal. Calcd. For C₁₃H₁₆AuClN₂O₂S: C, 31.37; H, 3.44; N, 5.63; Found: C, 31.47, H, 3.48, N, 5.65. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.18–8.11 (m, 2H, H8), 8.11–8.02 (m, 2H, H7), 7.96 (m, 2H, H4, H5), 5.02 (qq, *J* = 6.7 Hz, 1H, H10), 3.35 (s, 3H, SCH₃), 1.53 (d, *J* = 6.7 Hz, 6H, H11). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 167.7 (1C, C2), 143.3 (1C, C6), 141.4 (1C, C9), 128.9 (2C, C8), 126.3 (2C, C7), 123.4 (1C, C5), 120.0 (1C, C4), 54.7 (1C, C10), 43.7 (1C, SCH₃), 23.1 (2C, C11). HMRS (ES⁺): Calc. For C₁₅H₁₉AuN₃O₂S 502.0863 found 502.0866 [M-Cl⁻+CH₃CN].

Complex 14

Under nitrogen atmosphere, **8** (34.6 mg, 0.09 mmol) and (11.58 mg, 0.05 mmol) of Ag₂O were dissolved in dry CH₂Cl₂, and stirred at r.t. for 18 h. (32.4 mg, 0.11 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a white solid (43 mg, 88% yield). Anal. Calcd. For C₁₉H₂₀AuClN₂S: C, 42.12; H, 3.91; N, 5.17; Found: C, 42.03, H, 3.83, N, 5.21. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89–7.83 (m, 1H, H5), 7.80 (d, *J* = 2.1 Hz, 1H, H4), 7.70–7.60 (m, 2H, H7), 7.56–7.46 (m, 2H, H8), 7.43–7.39 (m, 2H, H12), 7.33 (m, 2H, H13), 7.28–7.23 (m, 1H, H14), 4.97 (qq, *J* = 6.9 Hz, 1H, H15), 4.35 (d, *J* = 3.2 Hz, 2H, H10), 1.51 (d, *J* = 6.9 Hz, 6H, H16). ¹³C NMR (101 MHz, DMSO) δ 167.3 (1C, C2), 138.1 (1C, C11), 137.4 (1C, C9), 137.1 (1C, C6), 129.3 (2C, C13), 128.9 (2C, C12), 128.6 (2C, C8), 127.7 (1C, C14), 125.9 (2C, C7), 123.4 (1C, C5), 119.4 (1C, C4), 54.3 (1C, C15), 36.6 (1C, C10), 23.2 (2C, C16). HMRS (ES⁺): Calc. For C₁₉H₂₀AuN₂S 505.1013 found 505.1013 [M-Cl⁻].

Complex 15

Under nitrogen atmosphere, **9** (47.7 mg, 0.13 mmol) and (14.79 mg, 0.064 mmol) of Ag₂O were dissolved in dry CH₂Cl₂, and stirred at r.t. for 18 h. (41.53 mg, 0.14 mmol) of Au(SMe₂)Cl were added and stirred for 2 h. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to give a white solid (61.9 mg, 92% yield). Anal. Calcd. For C₁₃H₁₃AuClF₃N₂S: C, 30.04; H, 2.72; N, 5.39; Found: C, 30.17, H, 2.42, N, 5.45. ¹H NMR (400 MHz, CDCl₃) δ 7.94–7.66 (m, 4H, H7, H8), 7.27 (d, *J* = 2.1 Hz, 1H, H5), 7.23 (d, *J* = 2.1 Hz, 1H, H4), 5.26 (qq, *J* = 6.8 Hz, 1H, H10), 1.57 (d, *J* = 6.8 Hz, 6H, H11). ¹³C NMR (101 MHz, CDCl₃) δ 169.5 (1C, C2), 141.2 (1C, C9), 137.4 (2C, C8), 129.2 (q, *J* = 308.4 Hz, 1C, CF₃), 125.7 (2C, C7), 125.6 (1C, C6), 121.7 (1C, C5), 117.8 (1C, C4), 54.5 (1C, C10), 23.3 (2C, C11). ¹⁹F NMR (376 MHz, CDCl₃) δ -42.11 (3F, CF₃). HMRS (ES⁺): Calc. For C₁₅H₁₆AuF₃N₃S 524.0683 found 524.0679 [M-Cl⁻+CH₃CN].

Crystal data of 10 to 13 and 15:

All data were collected at low temperature (100(2) K) using an oil-coated shock-cooled crystal on a Bruker-AXS APEX II diffractometer with MoK α radiation (λ = 0.71073 Å). The structure was solved by direct methods³⁸ and all non-hydrogen atoms were refined anisotropically using the least-squares method on F².³⁹ The absolute structure of **15** has been refined.⁴⁰

10: C_{17.5}H₁₇AuCl₂N₂O₂S, Mr = 587.26, crystal size = 0.40 x 0.30 x 0.30 mm³, triclinic, space group *P* $\bar{1}$, *a* = 9.537(1) Å, *b* = 9.696(1) Å, *c* = 12.554(2) Å, α = 83.399(3)°, β = 73.612(2)°, γ = 61.558(2)°, *V* = 979.0(2) Å³, *Z* = 2, 28538 reflections collected, 6772 unique reflections (Rint = 0.0290), R1 = 0.0161, wR2 = 0.0350 [*I*>2 σ (*I*)], R1 = 0.0182, wR2 = 0.0356 (all data) residual electron density = 1.132 e Å⁻³.

11: C₂₃H₂₀AuClN₂S, Mr = 588.89, crystal size = 0.40 x 0.20 x 0.05 mm³, monoclinic, space group *P*2₁/*c*, *a* = 10.188(1) Å, *b* = 17.565(2) Å, *c* = 11.151(1) Å, β = 91.497(2)°, *V* = 1994.8(3) Å³, *Z* = 4, 33832 reflections collected, 6328 unique reflections (Rint = 0.0430), R1 = 0.0228, wR2 = 0.0502 [*I*>2 σ (*I*)], R1 = 0.0247, wR2 = 0.0510 (all data), residual electron density = 1.340 e Å⁻³.

12: C₁₇H₁₃AuClF₃N₂S, Mr = 566.77, crystal size = 0.40 x 0.30 x 0.30 mm³, triclinic, space group *P* $\bar{1}$, *a* = 9.141(1) Å, *b* = 9.444(1) Å, *c* = 10.147(1) Å, α = 92.716(2)°, β = 96.584(2)°, γ = 90.674(2)°, *V* = 869.0(1) Å³, *Z* = 2, 29741 reflections collected, 5512 unique reflections (Rint = 0.0388), R1 = 0.0151, wR2 = 0.0380 [*I*>2 σ (*I*)], R1 = 0.0153, wR2 = 0.0381 (all data), residual electron density = 1.524 e Å⁻³.

13: C₁₃H₁₆AuClN₂O₂S, Mr = 496.75, crystal size = 0.40 x 0.30 x 0.30 mm³, monoclinic, space group *P*2₁/*c*, *a* = 11.876(1) Å, *b* = 16.723(2) Å, *c* = 7.803(1) Å, β = 104.151(2)°, *V* = 1502.5(2) Å³, *Z* = 4, 28890 reflections collected, 5369 unique reflections (Rint = 0.0392), R1 = 0.0205, wR2 = 0.0544 [*I*>2 σ (*I*)], R1 = 0.0227, wR2 = 0.0556 (all data), residual electron density = 2.740 e Å⁻³.

15: C₁₃H₁₃AuClF₃N₂S, Mr = 518.73, crystal size = 0.40 x 0.10 x 0.10 mm³, monoclinic, space group *P*2₁, *a* = 9.601(11) Å, *b* = 6.852(8) Å, *c* = 12.235(14) Å, β = 101.395(16)°, *V* = 788.9(15) Å³, *Z* = 2, 9402 reflections collected, 4619 unique reflections (Rint = 0.0390), R1 = 0.0311, wR2 = 0.0708 [*I*>2 σ (*I*)], R1 = 0.0361, wR2 = 0.0733 (all data), absolute structure factor *x* = -0.186(14), residual electron density = 1.494 e Å⁻³.

CCDC 2063045-2063049 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Antileishmanial evaluation

Leishmania species used in this study were *Leishmania infantum* strain MHOM/MA/67/ITMAP-263 (CNR *Leishmania*, Montpellier, France) expressing luciferase activity.⁴¹

Antileishmanial activity on axenic amastigotes

L. infantum promastigotes in logarithmic phase were centrifuged at 900 g for 10 min, the supernatant was removed and replaced by the same volume of RPMI 1640 complete medium at pH 5.4 and incubated for 24 h at 24 °C. Acidified promastigotes were then incubated for 24 h at 37 °C in a ventilated flask in humidified incubator with 5% CO₂. Promastigotes were thus transformed into amastigotes in axenic conditions.⁴² The effects of the tested compounds on the growth of *L. infantum* axenic amastigotes were then assessed as follows. *L. infantum* amastigotes were incubated at a density of 2.10⁶ parasites/mL in sterile 96-well plates with various concentrations of compounds dissolved in DMSO (final concentration less than 0.5% v/v), in duplicate. Appropriate controls DMSO, amphotericin B, miltefosine and pentamidine were added to each set of experiments. To estimate the luciferase activity of axenic amastigotes, 80 μ l of each well are transferred to white 96-well plates, Steady Glow® reagent (Promega) was added according to manufacturer's instructions, and plates were incubated for 2 min. The luminescence was measured in Microbeta Luminescence Counter (PerkinElmer). Inhibitory concentration 50% (IC₅₀) was defined as the concentration of drug required to inhibit by 50% the metabolic activity of *L. infantum* amastigotes compared to control. IC₅₀ values were calculated by non-linear regression analysis processed on dose–response curves, using TableCurve 2D V5 software. IC₅₀ values represent the mean value calculated from three independent experiments.

Cytotoxicity evaluation

The evaluation of the compound cytotoxicity by MTT assay was done on THP-1 cell line (human monocyte). Briefly, cells (0.77.10⁵ cells/mL) in 200 μ l of complete medium [RPMI 1640 supplemented with 10% fetal calf serum (FCS), 2 mM L-glutamine and antibiotics (100 UI/mL penicillin and 100 μ g/mL streptomycin)] + PMA (50

ng/ml) were seeded into each well of 96-well plates and incubated at 37 °C in a humidified 5% CO₂ with 95% air atmosphere. After a 96h incubation, plates were rinse 3 times with medium and 100 µl of medium were added. One hundred µL of medium with various compounds concentrations and appropriate controls were then added and the plates were incubated for 72 h at 37 °C. The medium was then aspirated from the wells. MTT solution (100 µL of 0.5 mg/mL in RPMI) were then added to each well. Cells were incubated for 2 h at 37 °C. MTT solution was then removed and DMSO (100 µL) was added to dissolve the resulting formazan crystals. Plates were shaken vigorously (300 rpm) for 5 min. The absorbance was measured at 570 nm with a microplate spectrophotometer (BIO-TEK ELx808 Absorbance Microplate Reader). DMSO was used as blank and doxorubicin (Sigma Aldrich) as positive control. CC₅₀ were calculated by non-linear regression analysis processed on dose-response curves, using TableCurve 2D V5 software.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

The supporting information contains the ¹H, ¹³C and ¹⁹F NMR spectra related to compounds **4** to **15** as PDF file.

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Notes

The authors declare no competing financial interests.

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