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Synthesis, characterization and anti-*Trypanosoma cruzi* evaluation of ferrocenyl and cyrhetrenyl imines derived from 5-nitrofurane

Rodrigo Arancibia [a], A. Hugo Klahn [a,*], Gonzalo E. Buono-Core [a], Enrique Gutierrez-Puebla [b], Angeles Monge [b], Manuela E. Medina [b], Claudio Olea-Azar [c], Juan D. Maya [d], Fernando Godoy [e]

[a] Instituto de Quimica, Pontificia Universidad Catolica de Valparaíso, Casilla 4059, Valparaíso, Chile
[b] Instituto de Ciencias de Materiales de Madrid, Consejo Superior de Investigaciones, Cientificas, Sor Juana Inés de la Cruz 3, 28049 Madrid, Spain
[c] Departamento de Química Inorgánica y Analítica, Facultad de Ciencias Químicas y, Farmacéuticas, Universidad de Chile, Casilla 233, Santiago, Chile
[d] Programa de Farmacología Clínica y Molecular, Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile
[e] Departamento de Química de los Materiales, Facultad de Química y Biología, Universidad de Santiago de Chile, Casilla 40, Santiago, Chile

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ABSTRACT

A series of new cyrhetrenyl and ferrocenylimines complexes derived from 5-nitrofurane were designed, synthesized and characterized. The ^{1}H and ^{13}C NMR spectra indicate that these compounds adopt an anti-(*E*) conformation in solution, and confirmed for **1b** by the X-ray crystal crystallography. The electronic effects of cyrhetrenyl (**1b**) and ferrocenyl (**1a**) bound directly to nitrogen have been correlated with the chemical shift of the iminic carbon. The trypanocidal activity (Tulahuen strain of *Trypanosoma cruzi*) of these compounds has been studied with respect to the substituent on the nitrogen atom of the 5-nitrofurylideneamino pharmacophore. Even though all the resulting derivatives were less active than Nifurtimox, the cyrhetrenyl complex (**1b**), compared with ferrocenyl (**1a**) or purely organic (**4a** and **4b**) analogues, was more efficient as antichagasic agent. This result is likely due to the enhanced lipophilic character of the molecules or from a possible synergy between the cyrhetrenyl and 5-nitrofurane groups.

1. Introduction

American Trypanosomiasis (Chagas disease) is one of the most common endemic parasitic diseases in Central and South America and is caused by the protozoa *Trypanosoma cruzi* (*T. cruzi*). The most recent data from the WHO indicate that over 24 million people, or 8% of the Latin-American population, are infected or are serologically positive for *T. cruzi* [1]. Current pharmacological treatments have been based on dated and nonspecific drugs such as Nifurtimox® (Nfx, a nitrofuran derivative, Fig. 1) and Benznidazole® (Bnz, a nitroimidazole derivative, Fig. 1).

Both drugs produce significant side effects such as peripheral neuropathy, anorexia, vomiting and allergies, as well as considerable cardiac and renal toxicity [2]. While the toxic effects and the mechanisms of action of Nfx and Bnz are not yet fully understood [3,4], a large number of new antitrypanosomal agents have been developed with derivatives structurally related to these drugs [5–8]. It has been proposed in several studies that the bioreduction of the nitro group during metabolism causes activity in these drugs [3,4]. Nfx may act by generating free radicals toxic species through a redox-cycling process, and Bnz may cause reactions with macromolecules, including the DNA, lipids and proteins of the parasite.

The nonselective bioreduction of these drugs are believed to cause the toxic side effects in the mammalian host. For these reasons, there is an urgent need for the development of new effective and nontoxic antichagasic compounds.

Different strategies have been used to search for new antitrypanosomal agents. Several organic compounds containing a nitro-aromatic system have been proposed as anti-*T. cruzi* agents, including nitroimidazole [9], nitrofurane [10] and nitroindazole [11]. Metal complexes also appear to be a promising alternative in the search for a pharmacological solution to Chagas disease [12]. Cerecetto and co-workers used an interesting approach to develop transition metal complexes by combining ligands showing antitrypanosomal activity with pharmacologically active metals. On the basis of this approach, a series of ligands derived from the 5-nitrofuryl pharmacophore (5-nitro-2-furaldehyde semicarbazone, N^4-*n*-butyl-5-nitrofuraldehyde semicarbazone, 3-(5-nitrofuryl) acroleine semicarbazone and nitrofurylthiosemicarbazones) coordinated to rhenium [13], ruthenium [14] and palladium [15,16]

* Corresponding author. Fax: +56 32 273422.
E-mail address: hklahn@ucv.cl (A.H. Klahn).

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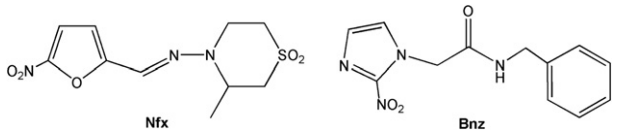


Fig. 1. Drugs commercially available for the treatment of Chagas disease: Nifurtimox (Nfx) and Benznidazole (Bnz).

centres have been prepared. Some of these complexes are more active against *T. cruzi* than the corresponding free ligands.

To the best of our knowledge, organometallic complexes bearing antitrypanosomal groups have not yet been reported. While the synthesis of 5-nitrofurfurylidenaminoferrocene has been briefly described, its potential biological activity was not studied [17]. This lack of research is in sharp contrast to the vast literature detailing biomolecules covalently bound to ferrocene and their applications [18].

In this work, we report the synthesis, characterization and biological evaluation of new bioorganometallic compounds containing the 5-nitrofuryl group attached to cyrhetrenyl and ferrocenyl fragments through conjugated and nonconjugated bridges.

2. Experimental

2.1. Materials

Ferrocene (98%), ferrocenecarboxaldehyde (98%), 5-nitro-2-furaldehyde (99%), *p*-nitro-aniline (99%), 1,4-phenylendiamine (98%), $NH_2OH{\cdot}HCl$, $LiAlH_4$ and $NaBH_4$ were obtained from Aldrich. The solvents such as CH_2Cl_2, C_6H_6, MeOH and THF were obtained commercially and were purified using standard methods. Complexes (η^5-C_5H_4CHO)$Re(CO)_3$ [19], (η^5-$C_5H_4NH_2$)$Re(CO)_3$ [20], (η^5-C_5H_4CN)$Re(CO)_3$ [21], (η^5-$C_5H_4CH_2NH_2$)Fc [22], (η^5-$C_5H_4NH_2$)Fc [23] (Fc = Fe(η^5-C_5H_5)) were prepared according to a procedure in the literature. The infrared spectra were recorded in solution (NaCl cell) or as solid (KBr pellets) on a Perkin–Elmer FT-1605 spectrophotometer. The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution on a Bruker AVANCE 400 spectrometer. The ^1H NMR chemical shifts were referenced using the chemicals shifts of residual solvent resonances, and ^{13}C chemical shifts to solvent peaks. The mass spectra were obtained on a Thermo-Finnigan MAT 900XP, at the Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile. The elemental analyses were conducted on a Perkin–Elmer 2400 series II, CHNS/O Analyzer.

2.2. Synthesis of cyrhetrenyl and ferrocenylamines

2.2.1. Cyrhetrenylmethylamine (**5a**)

The cyanocyrhetrene [21] (170.0 mg, 0.50 mmol) was dissolved in dry THF (20.0 mL) at 0 °C, and an excess of $LiAlH_4$ (2.0 mL, 1 M in THF, 2.0 mmol) was added dropwise. The mixture was then stirred for 1 h in a nitrogen atmosphere. A mixture of benzene (10.0 mL) and CH_2Cl_2 (15.0 mL) was added with caution, and then a few drops of 5 M NaOH were added. The mixture was filtered through Celite, and the solution was evaporated under reduced pressure until it was dry. The residue was extracted with CH_2Cl_2 (5 × 10.0 mL) and washed with water and brine. After drying over $MgSO_4$, the solvent was removed in a rotary evaporator. Crystallization with CH_2Cl_2/hexane (1:5) at −18 °C gave a brown solid of **5a** (yield: 127.0 mg, 0.35 mmol, 70%). This compound was quite unstable in solution and in solid state and should be prepared immediately before use. IR (CH_2Cl_2, cm^{-1}, νCO): 2022 (s), 1924 (vs). ^1H NMR: δ 4.42 (s, 2H, CH_2); 5.32 (t, J = 2.4 Hz, 2H, C_5H_4); 5.45 (t, J = 2.4 Hz, 2H, C_5H_4). Mass spectrum (based on ^{187}Re) m/z: 365 [M^+]; 337 [M^+ − CO]; 309 [M^+ − 2CO]; 281 [M^+ − 3CO].

2.2.2. N^1-(Ferrocenylmethyl)-1,4-phenylendiamine (**5b**)

The ferrocenecarboxaldehyde (214.0 mg, 1.0 mmol) and 1,4-phenylendiamine (108.0 mg, 1.0 mmol) were dissolved in anhydrous methanol (20.0 mL). The solution was refluxed in a nitrogen atmosphere for 3 h. After this time, the solvent was removed in a vacuum, and the resulting red solid was dissolved in anhydrous THF (30.0 mL) followed by the addition of an excess of solid $LiAlH_4$ (152.0 mg, 4.0 mmol). The mixture was stirred and refluxed in a nitrogen atmosphere for 1 h. The reaction mixture was quenched with methanol (20.0 mL) and filtered, and the solvents were removed in a vacuum. The residual solid was dissolved in a minimal amount of dichloromethane and transferred to a chromatography column packed with silica gel in hexane. Elution with CH_2Cl_2/hexane (1:1) separated a red band, which was evaporated to until it was dry. A red microcrystalline solid was obtained after crystallization with a dichloromethane-hexane mixture (1:2). This compound was characterized by ^1H NMR and MS as bis-ferrocenylmethyl-phenylendiamine [24]. Elution with pure CH_2Cl_2 moved a second red band. From this band red microcrystals of **5b** were obtained after the removal of the solvent and after crystallization with CH_2Cl_2/hexane (1:5) at −18 °C (yield: 122.0 mg, 0.40 mmol, 40%). ^1H NMR: δ 3.36 (s, 3H, N<u>H</u>, N<u>H</u>$_2$); 3.90 (s, 2H, CH_2); 4.13 (t, J = 2.4 Hz, 2H, C_5H_4); 4.17 (s, 5H, $C_5\underline{H}_5$); 4.24 (t, J = 2.4 Hz, 2H, C_5H_4); 6.57 (d, 2H, J = 8.3 Hz, C_6H_4); 6.63 (d, 2H, J = 8.3 Hz, C_6H_4). Mass spectrum m/z: 306 [M^+].

2.2.3. N^1-(Cyrhetrenylmethyl)-1,4-phenylendiamine (**5c**)

The 1,4-phenylendiamine 54.0 mg (0.5 mmol) was added to a solution of (η^5-C_5H_4CHO)$Re(CO)_3$ 181.0 mg (0.5 mmol) in anhydrous methanol (10.0 mL). The mixture was refluxed in a nitrogen atmosphere for 3 h. After this time, the solution was cooled, and an excess of solid $NaBH_4$ (76.0 mg, 2.0 mmol) was added in a nitrogen atmosphere and stirred for 2 h. After this time, the IR spectrum showed the presence of two new ν(CO) absorption bands that were shifted to low energy in comparison to the aldehyde precursor. The reaction was quenched with H_2O (2 drops). The pale-yellow oily solid obtained after the methanol was evaporated was chromatographed on a silica gel column that had been previously washed with hexane. The product eluted with CH_2Cl_2. Complex **5c** was isolated as a yellow oil after purification from CH_2Cl_2/hexane (1:5) at −18 °C (yield: 204.0 mg, 0.45 mmol, 90%). IR (CH_2Cl_2, cm^{-1}, νCO): 2022 (s), 1924 (vs). ^1H NMR: δ 4.1 (s, 2H, CH_2); 5.25 (t, J = 2.4 Hz, 2H, C_5H_4); 5.40 (t, J = 2.4 Hz, 2H, C_5H_4); 6.55 (d, 2H, J = 8.1 Hz, C_6H_4); 6.62 (d, 2H, J = 8.1 Hz, C_6H_4), NH (not observed).

2.3. Synthesis of ferrocenyl and cyrhetrenyl imines

The imine compounds were prepared by modifying a procedure described by Pudova et al. [23]. Equimolar amounts of the amino complexes and 5-nitrofuraldehyde were dissolved in anhydrous benzene (20.0 mL) and were heated in a water bath for 1 h, in a nitrogen atmosphere. The solvent was then removed under vacuum, and the resulting coloured solids were purified by crystallization with CH_2Cl_2/hexane (1:5) at −18 °C.

2.3.1. (5-Nitro-2-furfurylideneamino)ferrocene (**1a**)

Purple solid, yield: 90% (291.0 mg, 0.85 mmol). IR (KBr): (νC=N cm^{-1}): 1610 (w). ^1H NMR: δ 4.22 (s, 5H, $C_5\underline{H}_5$); 4.37 (t, J = 2.2 Hz, 2H, $C_5\underline{H}_4$); 4.67 (t, J = 2.2 Hz, 2H, $C_5\underline{H}_4$); 7.11 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 7.40 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 8.48 (s, 1H, C<u>H</u>=N). ^{13}C NMR: δ 63.7 ($\underline{C}_5H_4$); 69.0 ($\underline{C}_5H_4$); 70.1 ($\underline{C}_5H_5$); 102.0 ($\underline{C}_5H_{4ipso}$); 112.3 (C_4H_2O); 113.5 (C_4H_2O); 114.6 ($C_4H_2\underline{O}_{ipso}$); 143.6 (<u>C</u>H=N); 154.5 ($C_4H_2\underline{O}_{ipso}$).

Mass spectrum (m/z): 324 [M^+]. Anal.(%) Calc. for $C_{15}H_{12}N_2O_3Fe$: C, 55.56; H, 3.70 and N, 8.64; found: C, 55.60; H, 3.71 and N, 8.62.

2.3.2. (5-Nitro-2-furfurylideneamino)cyrhetrene (**1b**)

Orange crystal, yield: 90% (58.7 mg, 0.13 mmol). IR (CH_2Cl_2, cm^{-1}): 2025 (s) (νCO); 1929 (vs) (νCO); 1625 (w) (νC=N). ^{1}H NMR: δ 5.33 (t, 2H, J = 2.3 Hz, $C_5\underline{H}_4$); 5.65 (t, 2H, J = 2.3 Hz, $C_5\underline{H}_4$); 7.16 (d, 1H, J = 3.8 Hz, $C_4\underline{H}_2O$); 7.40 (d, 1H, J = 3.8 Hz, $C_4\underline{H}_2O$); 8.35 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ 78.6 ($\underline{C}_5H_4$); 82.5 ($\underline{C}_5H_4$); 112.8 (C_4H_2O); 114.6 ($\underline{C}_5H_{4ipso}$); 115.7 (C_4H_2O); 122.2 ($C_4H_2O_{ipso}$); 149.0 (CH=N); 152.1 ($C_4H_2O_{ipso}$); 193.2 (CO). Mass spectrum (based on ^{187}Re) m/z: 474 [M^+], 446 [M^+ − CO], 418 [M^+ − 2CO], 390 [M^+ − 3CO]. Anal. (%) Calc. for $C_{13}H_7N_2O_6Re$: C, 32.91; H, 1.47 and N, 5.91; found: C, 32.69; H, 1.41 and N, 5.82.

2.3.3. (5-Nitro-furfurylideneaminomethyl)ferrocene (**2a**)

The synthesis of complex **2a** was carried out similarly to that described for the general procedure, but by refluxing for 6 h using a Dean–Stark apparatus. Compound **2a** was obtained as a red solid, yield: 90% (304.0 mg, 0.9 mmol). IR (KBr): (νC=N cm^{-1}): 1628 (w). ^{1}H NMR: δ 4.17 (s, 5H, C_5H_5); 4.18 (s, 4H, C_5H_4); 4.63 (d, J = 1.5 Hz, 2H, CH_2); 6.99 (d, J = 3.8 Hz, 1H, C_4H_2O); 7.35 (d, J = 3.8 Hz, 1H, C_4H_2O); 8.07 (s, 1H, CH=N). ^{13}C NMR: δ 60.0 (CH_2); 68.4 (C_5H_4); 68.6 (C_5H_5); 68.7 (C_5H_4); 83.6 (C_5H_{4ipso}); 112.7 (C_4H_2O); 112.9 (C_4H_2O); 114.6 ($C_4H_2O_{ipso}$); 148.2 (CH=N); 153.0 ($C_4H_2O_{ipso}$). Mass spectrum m/z: 338 [M^+]. Anal. (%) Calc. for $C_{16}H_{14}N_2O_3Fe$: C, 56.80; H, 4.14 and N, 8.28; found: C, 56.70; H, 4.10 and N, 8.32.

2.3.4. (5-Nitro-furfurylideneaminomethyl)cyrhetrene (**2b**)

The synthesis of complex **2b** was carried out similarly to that described for **2a**. Complex **2b** was obtained as brown solid, yield: 60% (78.0 mg, 0.16 mmol). IR (CH_2Cl_2, cm^{-1}): 2022 (s) (νCO); 1926 (s) (νCO); 1622 (w) (νC=N). ^{1}H NMR: δ 4.60 (s, 2H, $C\underline{H}_2$); 5.32 (t, 2H, J = 2.3 Hz, $C_5\underline{H}_4$); 5.45 (t, 2H, J = 2.3 Hz, $C_5\underline{H}_4$); 7.07 (d, 1H, J = 3.8 Hz, $C_4\underline{H}_2O$); 7.40 (d, 1H, J = 3.8 Hz, $C_4\underline{H}_2O$); 8.17 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ 41.4 ($C\underline{H}_2$); 83.5 ($\underline{C}_5H_4$); 83.7 ($\underline{C}_5H_4$); 112.8 (C_4H_2O); 114.6 (C_5H_{4ipso}); 115.7 (C_4H_2O); 122.2 ($C_4H_2O_{ipso}$); 147.1 (CH=N); 152.1 ($C_4H_2O_{ipso}$); 193.2 (CO). Mass spectrum (based on ^{187}Re) m/z: 488 [M^+]; 460 [M^+ − CO]; 432 [M^+ − 2CO]; 404 [M^+ − 3CO]. Anal. (%) Calc. for $C_{14}H_9N_2O_6Re$: C, 34.43; H, 2.87 and N, 5.74; found: C, 34.60; H, 2.91 and N, 5.80.

2.3.5. (N^1-(Ferrocenylmethyl)-N^2-(5-nitrofuran-2-yl)methylen)-1,4-phenylendiamine (**3a**)

Complex **3a** was isolated as red solid, yield: 90% (128.7 mg, 0.3 mmol). IR (KBr): (νC=N cm^{-1}): 1625 (w). ^{1}H NMR: δ 4.00 (s, 2H, CH_2); 4.17 (t, J = 2.4 Hz, 2H, C_5H_4); 4.20 (s, 5H, C_5H_5); 4.25 (t, J = 2.4 Hz, 2H, C_5H_4); 6.67 (d, J = 8.2 Hz, 2H, C_6H_4); 7.11 (d, J = 3.1 Hz, 1H, $C_4\underline{H}_2O$); 7.31 (d, J = 8.2 Hz, 2H, C_6H_4); 7.41 (d, J = 3.1 Hz, 1H, $C_4\underline{H}_2O$); 8.42 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ 43.2 (CH_2); 68.0 ($\underline{C}_5H_4$); 68.1 ($\underline{C}_5H_5$); 68.5 ($\underline{C}_5H_4$); 85.6 ($\underline{C}_5H_{4ipso}$); 112.6 ($\underline{C}_4H_2O$); 112.8 ($\underline{C}_4H_2O$); 113.0 ($\underline{C}_4H_2O_{ipso}$); 123.5 ($C_6H_4$); 139.0 ($C_6H_4$); 140.2 ($\underline{C}_6H_4$); 148.7 ($\underline{C}$H=N); 154.0 ($\underline{C}_4H_2O_{ipso}$). Mass spectrum m/z: 429 [M^+], 200 [M^+ − $C_{11}H_8N_3O_3$]. Anal. (%) Calc. for $C_{22}H_{19}N_3O_3Fe$: C, 61.54; H, 4.43 and N, 9.79; found: C, 61.30; H, 4.20 and N, 9.72.

2.3.6. (N^1-(Cyrhetrenylmethyl)-N^2-(5-nitrofuran-2-yl)methylen)-1,4-phenylendiamine (**3b**)

Complex **3b** was isolated as red crystals, yield: 90% (114.4 mg, 0.2 mmol). IR (CH_2Cl_2, cm^{-1}): 2022 (s) (νCO); 1924 (s) (νCO); 1630 (w) (νC=N). ^{1}H NMR: δ 4.20 (s, 2H, CH_2); 5.31 (t, J = 2.1 Hz, 2H, C_5H_4); 5.45 (t, J = 2.1 Hz, 2H, C_5H_4); 6.69 (d, J = 8.5 Hz, 2H, C_6H_4); 7.11 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 7.30 (d, J = 8.5 Hz, 2H, C_6H_4); 7.41 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 8.41 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ: 41.2 (CH_2); 83.6 (C_5H_4); 83.8 (C_5H_4); 107.7 ($C_5\underline{H}_{4ipso}$); 112.9 (C_4H_2O); 113.3 (C_6H_4); 113.8 (C_4H_2O); 123.0 (C_6H_4); 140.0 (C_6H_4); 141.2 ($C_4H_2O_{ipso}$); 147.3 (C$\underline{H}$=N); 154.5 ($C_4H_2O_{ipso}$); 193 (CO). Mass spectrum (based on ^{187}Re) m/z: 579 [M^+]; 349 [M^+ − $C_{11}H_8N_3O_3$]; 321 [M^+ − $C_{11}H_8N_3O_3$ − CO]; 293 [M^+ − $C_{11}H_8N_3O_3$ − 2CO]; 265 [M^+ − $C_{11}H_8N_3O_3$ − 3CO]. Anal. (%) Calc. for $C_{20}H_{14}N_3O_6Re$: C, 41.45; H, 2.42 and N, 7.25; found: C, 40.98; H, 2.40 and N, 7.30.

2.3.7. N-[(5-Nitrofuran-2-yl)methylen]-benzene-1,4-diamine (**4a**)

Purple crystals, yield: 90% (208.0 mg, 0.9 mmol). IR (KBr): (νC=N cm^{-1}): 1628 (w). ^{1}H NMR: δ 6.70 (d, J = 8.2 Hz, 2H, C_6H_4); 7.11 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 7.20 (d, J = 8.2 Hz, 2H, C_6H_4); 7.41 (d, J = 3.8 Hz, 1H, $C_4\underline{H}_2O$); 8.50 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ: 112.6 (C_4H_2O); 114.1 (C_4H_2O); 123.5 (C_6H_4); 139.0 (C_6H_4); 147.3 (CH=N); 154.5 ($C_4H_2O_{ipso}$). Mass spectrum m/z: 231 [M^+]. Anal. (%) Calc. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.90 and N, 18.18; found: C, 57.14; H, 3.89 and N, 18.20.

2.3.8. 4-Nitro-N-((5-nitrofuran-2-yl)methylene)benzenamine (**4b**)

Yellow crystals, yield: 90% (235.0 mg, 0.9 mmol). IR (KBr): (νC=N cm^{-1}): 1632 (w). ^{1}H NMR: δ 7.28 (d, J = 3.9 Hz, 1H, $C_4\underline{H}_2O$); 7.34 (d, J = 8.8 Hz, 2H, C_6H_4); 7.41 (d, J = 3.9 Hz, 1H, $C_4\underline{H}_2O$); 8.30 (d, J = 8.8 Hz, 2H, C_6H_4); 8.37 (s, 1H, C$\underline{H}$=N). ^{13}C NMR: δ 112.5 (C_4H_2O); 116.3 (C_4H_2O); 121.5 (C_6H_4); 125.2 (C_6H_4); 148.9 (CH=N); 152.1 ($C_4H_2O_{ipso}$); 155.5 ($C_4H_2O_{ipso}$). Mass spectrum m/z: 261 [M^+]. Anal. (%) Calc. for $C_{11}H_7N_3O_5$: C, 50.57; H, 2.68 and N, 16.09; found: C, 50.58; H, 2.69 and N, 16.02.

2.4. Biological assays

A suspension of 3×10^6 epimastigotes of the Tulahuen strain of *T. cruzi* was cultured at 28 °C in monophasic Diamond's culture medium and was supplemented with 4 μM haemin and inactivated bovine calf serum at a final concentration of 4%. Drugs dissolved in DMSO (final concentration of 1%) were added to the culture media to give 0.5–150 μM final concentrations. The parasite growth was followed by nephelometry for 7–10 days. The nephelometry readings were directly proportional to the concentration of parasites. No toxic effect of the DMSO alone was observed [24]. The growth culture constant (k) for each drug concentration employed was calculated using an exponential epimastigote growth curve (regression coefficient > 0:97, P < 0:05). The slope resulting from plotting the natural logarithm (Ln) of the nephelometry reading versus time (hours) corresponds to k (hr^{-1}). The IC_{50} is defined as the drug concentration needed to diminish k by 50%. It is calculated by a linear regression analysis from the k values and the tested concentrations. Reported values are the means of three independent experiments.

2.5. Crystal structure determination

A summary of the fundamental crystal and refinement data for **1b** are given in Table 2. Crystals of **1b** were selected under a polarizing optical microscope and were glued on a glass fibre for a single-

Table 1
^{13}C NMR shifts for Schiff bases.

Compound	^{13}C NMR[a] (C$\underline{H}$=N)
1a	143.6
1b	149.0
2a	148.2
2b	147.1
3a	148.7
3b	147.3
4a	147.3
4b	148.9

[a] ppm, $CDCl_3$.

Table 2
Crystal data and structure refinement for **1b**.

Empirical formula	$C_{13}H_7N_2O_6Re$
Formula weight	473.41
Temperature	296(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2(1)/c$
Unit cell dimensions	$a = 6.5287(11)$ Å $\alpha = 90°$.
	$b = 20.005(3)$ Å $\beta = 106.85°$.
	$c = 11.263(2)$ Å $\gamma = 90°$.
Volume	1407.9(4) Å^3
Z	4
Density (calculated)	2.233 Mg/m^3
Absorption coefficient	17.201 mm^{-1}
$F(000)$	888
Theta range for data collection	4.66–54.02°
Index ranges	$-5 \le h \le 6$, $-21 \le k \le 20$, $-10 \le l \le 11$
Reflections collected	3986
Independent reflections	1586 [R(int) = 0.1187]
Completeness to $\theta = 54.02°$	93.3%
Max. and min. Transmission	0.2781 and 0.1303
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1586/0/200
Goodness-of-fit on F^2	1.062
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0835$, $wR_2 = 0.1956$
R indices (all data)	$R_1 = 0.0855$, $wR_2 = 0.1981$

crystal X-ray diffraction experiment. X-ray intensity data were collected in a Bruker SMART CCD diffractometer equipped with a normal focus, 2.4 kW sealed tube X-ray source (MoK_α radiation = 0.71073 Å). The data were collected at room temperature in a hemisphere of the reciprocal space by a combination of three sets of exposures. Each exposure of 20 s covered 0.3° in ω. The crystal to detector distance was 5.08 cm.

The unit cell dimensions were determined by a least-squares fit of reflections collected with $I > 2\sigma(I)$. The first 100 frames were recollected at the end of the data acquisition to monitor crystal decay. Data were integrated and scaled using the SAINTplus program [25]. A semi-empirical absorption and scale correction based on the equivalent reflection was carried out using SADABS [26]. Space group determinations were determined using XPREP [27]. Calculations were performed with the SMART software for data collection and data reduction and SHELXTL [27]. The structures were solved by direct methods. The final cycles of refinement were carried out by full-matrix least-squares analyses with anisotropic thermal parameters for all nonhydrogen atoms. The hydrogen atoms of the organic ligands were situated at their calculated positions. Weighted R factors (Rw) and all goodness-of-fit (S) are based on F^2. Conventional R factors (R) are based on F.

3. Results and discussion

Our initial goal in preparing organometallic derivatives of nitrofurane was to compare the electronic effects of ferrocenyl and cyrhetrenyl groups in the biological activity of these systems against *T. cruzi*. For that purpose, we designed the following two types of compounds: i) those connected electronically between the two groups through a simple imine (**1a** and **1b**) and 1,4-phenyldimine bridge and ii) those containing nitrofurylimine without any electronic communication with the organometallic fragment (**2a** and **2b**).

In the first case, we succeed with the synthesis of **1a** and **1b**; however, attempts to form the corresponding 1,4-phenyldimine were unsuccessful because of the instability of such compounds, which have precedent in the literature [28]. For that reason, we also included compounds **3a** and **3b**, which can be considered to be type ii compounds.

3.1. Synthesis

To prepare some of the Schiff bases described below, it was necessary to synthesize the organometallic amine precursors (η^5-$C_5H_4CH_2NH_2$)$Re(CO)_3$ (**5a**), (η^5-$C_5H_4CH_2$–NH–1,4-$C_6H_4NH_2$)M, M = Fc (**5b**), and $Re(CO)_3$ (**5c**) (Scheme 1). The unreported **5a** was obtained by the reduction of cyanocyrhetrene [21] with $LiAlH_4$. This compound is quite unstable and should be prepared immediately prior to use. The compounds **5b** and **5c** were prepared by first condensing the organometallic aldehyde with 1,4-phenyldiamine (1:1 ratio), followed by an *in situ* reduction with $LiAlH_4$. These complexes were characterized only by spectroscopy (see Experimental section).

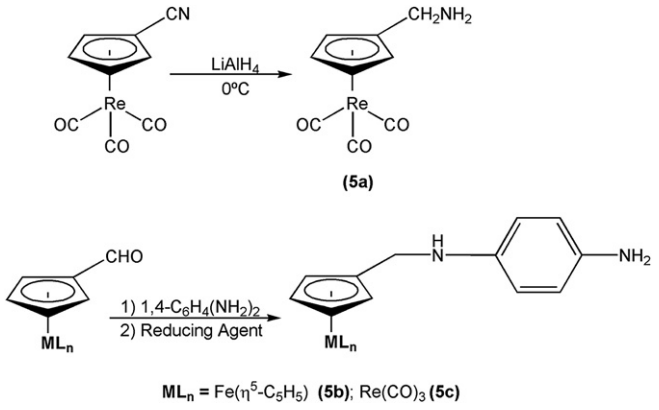
The imine complexes were synthesized following the same procedure as described for analogous ferrocenylimines [29] and cyrhetrenyl imines [30], that is, by the condensation of equimolar amounts of the corresponding organometallic–amine complex with 5-nitro-furaldehyde (Scheme 2) [31].

In all cases, the products were isolated as solids after crystallization with the CH_2Cl_2/hexane mixture. They are air-stable and are soluble in most organic solvents.

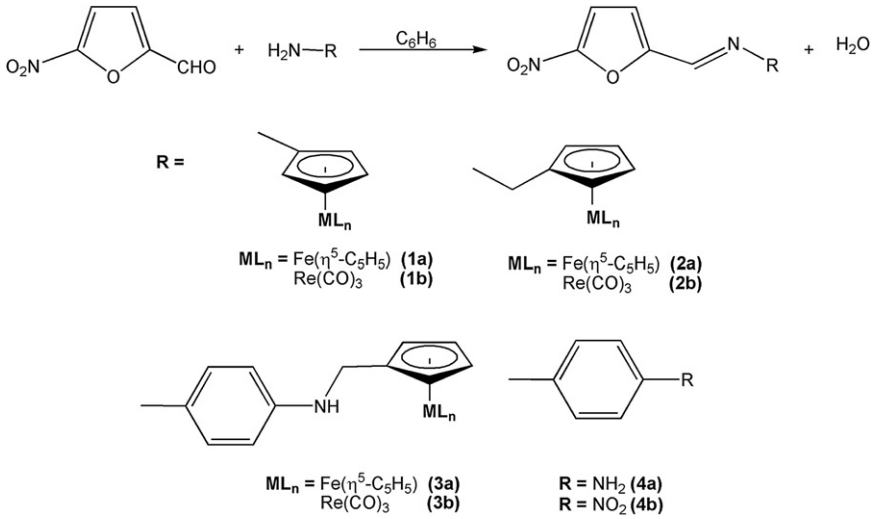
The IR spectra of these compounds showed the expected absorption band for the νC=N stretch in the range of 1610–1630 cm^{-1} in CH_2Cl_2 solution or KBr disc. Similar νC=N frequency values have been reported for Schiff bases derived from formylferrocene [29] and formylcyrhetrene [30]. The stoichiometry of the complexes was established by elemental analysis and mass spectrometry. Each of the imine complexes showed a strong molecular ion in their mass spectra. For the cyrhetrenyl derivatives, the successive losses of CO ligands were also present in the spectra.

For all complexes, the ^{1}H NMR spectra showed the presence of a single compound. A sharp singlet near 8.00–8.50 ppm was assigned to the iminic proton, and the two doublets at δ 7.11–7.42 were assigned to the hydrogen atoms of the furfuryl ring. For the ferrocene derivatives **1a**, **2a** and **3a**, the resonances assigned to the protons of unsubstituted cyclopentadienyl appeared as a singlet in the region δ 4.0–4.2. The two triplets observed at 4.27 ppm and 4.62–4.65 ppm are assigned to the hydrogen nuclei of the substituted ring. These results are in agreement with the values reported for several analogous iminoferrocene complexes [29,32]. Similarly, complexes **1b**, **2b** and **3b** showed two set of resonances around 5.31–5.65 ppm for cyrhetrenyl group.

The ^{13}C NMR data also indicate the existence of a single compound. Despite that these type of compounds could adopt two different forms (*E*- or *Z*-), their ^{1}H and ^{13}C NMR spectra agreed with those reported for related ferrocenyl and cyrhetrenyl Schiff bases [29,30,32]; this finding indicates that only one isomer (*E*-form) was



Scheme 1. Synthesis of organometallic amine precursors.



Scheme 2. Synthesis of cyrhetrenyl and ferrocenylimines complexes.

present in the solution. Further proof was provided by an X-ray crystal structure determination of **1b** (see below). The most important feature of these spectra is the presence of a low field resonance (δ 143–148) assigned to the iminyl carbon. This resonance occurs at almost the same δ as those reported for other Schiff bases mentioned above. These assignments were confirmed by $^{1}H–^{13}C$ NMR HMBC. It is worth nothing that both the ^{1}H and ^{13}C NMR spectra of derivatives **2** and **3** showed the presence of a methylene group and C_6H_4 and CH_2 groups, respectively.

The ^{13}C shifts of the iminyl carbons of **1a** and **1b** show clear dependence on the presence of ferrocenyl or cyrhetrenyl bound to the nitrogen atom. This phenomenon is not observed in compounds **2** and **3** for which the electronic communication is impeded by a methylene group (Table 1).

The upfield shift observed for the ferrocenyl derivative (**1a**) compared with **1b** ($\Delta\delta$ = 5.4 ppm) can be related to the opposite electronic effects of these organometallic fragments [33]. Thus, the known electron-acceptor properties of cyrhetrenyl group [34] are therefore better than ferrocenyl at stabilizing any positive charge built up on the iminyl carbon and producing a marked deshielding of the carbon resonance. Similar results have been reported by Houlton for a series of ferrocenylimines of the type ((η^5-C_5H_4CHNAr)Fc, Ar = Ph, C_6H_4X-p, X = H, F, Cl, CN, NO_2, OMe) [35]. Furthermore, the dependence of the electronic effects on the aryl ring substituent in purely organic compounds **4a** and **4b** are also in agreement with the above observation (see Table 1).

With the aim of comparing structural parameters of these compounds with the crystallographic data reported for several ferrocenyl and cyrhetrenyl imines [30], we undertook a crystallographic study of complex **1b**. Fig. 2 shows an Ortep view of **1b** and the most relevant bond length and angles. Table 2 reports the crystal structure and refinement data. The structure confirms the *E* configuration assigned tentatively by NMR.

Taking into account the internal C–C distances of the cyclopentadienyl ring, a η^2-η^3-coordination mode can be considered for **1b** because it possesses three short and two long C–C distances: C(1)–C(2) 1.380 Å; C(1)–C(5) 1.380 Å; C(4)–C(3) 1.380 Å; C(2)–C(3) 1.410 Å; and C(4)–C(5) 1.430 Å. The dihedral angle between the C_5 ring plane and the iminyl group plane is 6.30°. Thus, the imine moiety is nearly coplanar with the ring plane. Nevertheless, there is no appreciable delocalization within these two fragments, as indicated by the remarkable single bond character of C(1)–N(2) (1.449(16) Å). Alternatively, the iminic double bond N(1)–C(6) (1.266 Å) is markedly localized and resembles those measured for several organometallic imines [29–31]. It is slightly shorter than those reported for the other compound possessing the 5-nitrofurane group bound to iminyl carbon [36–38]. The C(6)–C(7) distance (1.439(19) Å) is within the range found in O_2N–5-C_4H_2O–2-CH=N–R: R = OH (1.441 Å) [36], R = $C_{11}H_{11}N_2O$ (1.438 Å) [37] and R = $N_3C_2H_2$ (1.430 Å) [38]. However, the internal C–C (C(7)–C(8), 1.361 Å; C(8)–C(9), 1.38(2) Å and C(9)–C(10),

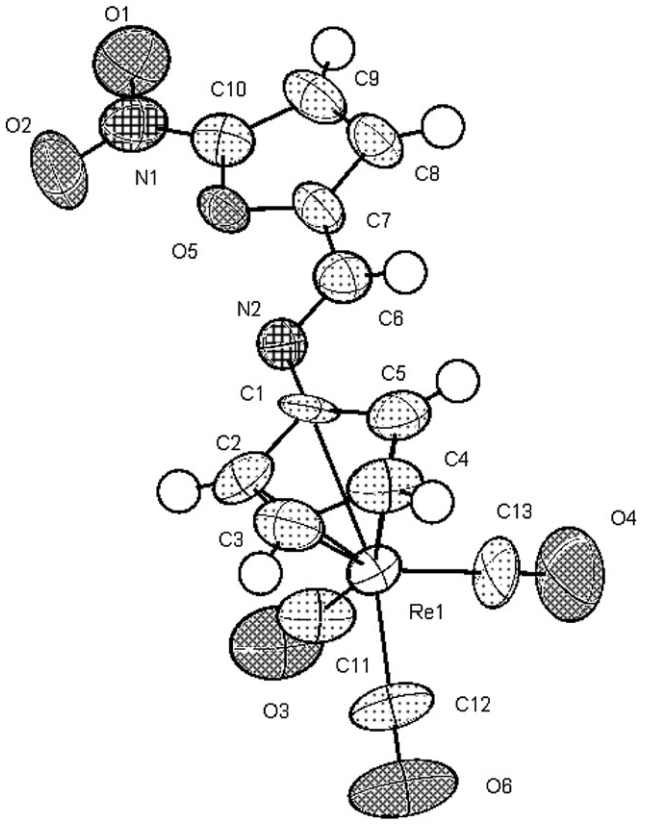


Fig. 2. Ortep plot of the asymmetrical unit of **1b**. Relevant bond length (Å): C(1)–N(2) 1.449(16); N(2)–C(6) 1.266(15); C(6)–C(7) 1.439(19); Cp(centroid)–Re(1) 1.961(6) and angles (°): N(2)–C(6)–C(7) 122.8(12); C(6)–N(2)–C(5) 120.1(11).

1.360(19)) and C–N(NO_2) (1.380(18) Å) bond distances of the nitrofurane group are much shorter than those reported for the above compounds and may suggest some delocalization of electron density over the furane–CH=N moiety. Within the cyrhetrenyl group, the average Re–C(O) distance and the Re–C–O angle are concordant with related tricarbonyl cyclopentadienyl rhenium(I) complexes [39].

3.2. Biological assays

To study the influence of the ferrocene and cyrhetrene incorporation in 5-nitrofurfuryl antitrypanosomal compounds, **1a**,**b**, **3a**,**b** and **4a**,**b** were measured against the Tulahuen strain of *T. cruzi* (epimastigote). Table 3 shows the IC_{50} values found for the new compounds. For comparison, we include the values for the drugs that are in clinical use.

From the analysis of Table 3, it can be observed that the activity of the compounds that possess electronic communication between nitrofurane and the organometallic groups, the cyrhetrenyl derivative **1b** was considerably better than the ferrocenyl analogue **1a**, suggesting that the electron-withdrawing and bulky carbonyl ligands stabilize a large electron density on the metal in comparison to **1a**. If these electronic changes are efficiently transferred through resonance or polarization [40] to the furane group, then the reduction of NO_2 group should proceed to more easily to form the radical $NO_2^{\bullet -}$ and therefore improve its antitrypanosomal activity [2].

To confirm this hypothesis, the IC_{50} of the closely related organic derivatives **4a** (containing an electron-donor aminophenyl) and **4b** (containing an electron-withdrawing nitrophenyl) were measured under the same experimental conditions. Unfortunately, both compounds showed remarkably less activity than their organometallic analogues because their IC_{50} values (>150 μM) were higher than the limit of the drug concentration.

For type ii compounds (**2** and **3**), the IC_{50} values appear to be independent of the presence of the organometallic fragment because comparable antitrypanosomal activity is observed within each series. However, clear differences are observed when the IC_{50} of the two series are compared (**2a**,**b** vs **3a**,**b**). The lower values found for the compounds **3a** and **3b** that possess an aryl bridge between the imine and methylcyclopentadienyl metal fragment can be explained by the increase of the electronic delocalization between the furane and the aryl ring through the imine bridge.

Considering the IC_{50} values shown in Table 3, an obvious question emerges—why do the purely organic derivatives (**4a** and **4b**) show a remarkably lower activity than **3a** and **3b**? The literature reports dealing with the lipophilic enhancement observed in some drugs by incorporating an organometallic fragment offer insight [41,42]. On this respect, we have recently demonstrated that the introduction of the cyrhetrenyl moiety at the end of the lateral chain of a 4-aminoquinoline scaffold dramatically increased lipophilicity when compared with their pure organic analogues [43].

Table 3
In vitro susceptibilities of *T. cruzi*.

Compound	IC_{50} (μM)
1a	100.2 ± 3.8
1b	43.6 ± 0.9
2a	76.4 ± 6.1
2b	84.1 ± 3.2
3a	45.5 ± 4.9
3b	47.3 ± 8.1
4a	>150
4b	>150
Nfx	10.4 ± 0.3
Bnz	12.8 ± 1.1

Accordingly, we believe that the substantial improvement in the cytotoxicity of 5-nitrofurfuryl group bearing organometallic moieties compared with their purely organic analogues could proceed from two sources: the increase in the lipophilic character of the drug by incorporating the organometallic entity or by possible synergism between the two moieties.

4. Conclusion

Ferrocenyl and cyrhetrenyl Schiff bases containing 5-nitrofurane pharmacophore were successfully synthesized. Like many other organometallic imine derivatives, these complexes adopt an *anti* configuration for the iminyl moiety, which was confirmed by NMR data and X-ray crystallography. The electron-donor (ferrocene and aminophenyl) and electron-withdrawing (cyrhetrene and nitrophenyl) capability of the substituents on the iminyl nitrogen correlate properly with the ^{13}C shift of the carbon nuclei of the C=N bridging group. The results of an *in vitro* antitrypanosomal assay of the compounds against strains of *T. cruzi* indicate that they are less active than Nifurtimox. However, some interesting observations can be reported. Compounds possessing electronic communication between the organometallic and 5-nitrofurane groups, such as the cyrhetrenyl derivative, show a better antichagasic activity. This result is likely due to its electron-withdrawing effects that are efficiently transferred to the furane group facilitating the reduction of NO_2 to $NO_2^{\bullet -}$. This situation contrasts the higher IC_{50} values found for the ferrocene analogue. Therefore, the electronic effects should be considered an influencing factor in designing new molecules with potential antitrypanosomal activity. When compared with their purely organic derivatives, the presence of the organometallic moieties dramatically enhanced the cytotoxicity, probably by increasing the lipophilic character or by a possible synergism between the organometallic and 5-nitrofurfuryl groups.

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Appendix A. Supplementary material

CCDC 781523 contains the supplementary crystallographic data for complex **1b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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