

Accepted Manuscript

Palladium(II)/*N,N*-disubstituted-*N'*-acylthioureas complexes as anti-*Mycobacterium tuberculosis* and anti-*Trypanosoma cruzi* Agents

Ana M. Plutín, Anislay Alvarez, Raúl Mocelo, Raúl Ramos, Eduardo E. Castellano, Monize M. da Silva, Wilmer Villarreal, Fernando R. Pavan, Cássio Santana Meira, José Simão Rodrigues Filho, Diogo Rodrigo M. Moreira, Milena Botelho P. Soares, Alzir A. Batista

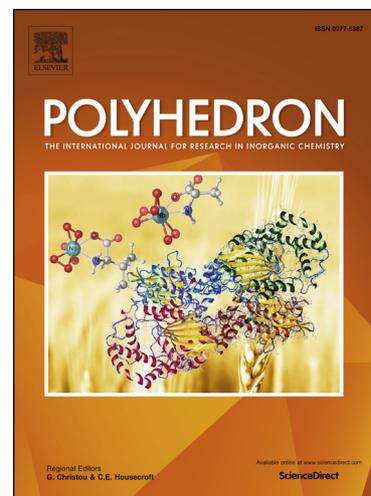
PII: S0277-5387(17)30325-X
DOI: <http://dx.doi.org/10.1016/j.poly.2017.05.003>
Reference: POLY 12616

To appear in: *Polyhedron*

Received Date: 30 January 2017
Revised Date: 22 April 2017
Accepted Date: 1 May 2017

Please cite this article as: A.M. Plutín, A. Alvarez, R. Mocelo, R. Ramos, E.E. Castellano, M.M. da Silva, W. Villarreal, F.R. Pavan, C.S. Meira, J.S.R. Filho, D.R.M. Moreira, M.B.P. Soares, A.A. Batista, Palladium(II)/*N,N*-disubstituted-*N'*-acylthioureas complexes as anti-*Mycobacterium tuberculosis* and anti-*Trypanosoma cruzi* Agents, *Polyhedron* (2017), doi: <http://dx.doi.org/10.1016/j.poly.2017.05.003>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



1 **Palladium(II)/N,N-disubstituted-N'-acylthioureas complexes as anti-**
2 ***Mycobacterium tuberculosis* and anti-*Trypanosoma cruzi* Agents**

3

4 Ana M. Plutín^{a*}, Anislay Alvarez^a, Raúl Mocoelo^a, Raúl Ramos^a, Eduardo E. Castellano^b,
5 Monize M. da Silva^c, Wilmer Villarreal^c, Fernando R. Pavan^d, Cássio Santana Meira^e,
6 José Simão Rodrigues Filho^e, Diogo Rodrigo M. Moreira^e, Milena Botelho P. Soares^{e,f}
7 Alzir A. Batista.^{c*}

8

9 ^a Laboratorio de Síntesis Orgánica, Facultad de Química, Universidad de La Habana, La
10 Habana, Cuba

11 ^b Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, SP, Brazil

12 ^c Departamento de Química, Universidade Federal de São Carlos, CEP 13.565-905, São
13 Carlos, SP, Brazil

14 ^d Faculdade de Ciências Farmacêuticas, UNESP, Araraquara, SP, Brazil

15 ^e Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, CEP 40296-750 Salvador, BA,
16 Brazil

17 ^f Centro de Biotecnologia e Terapia Celular, Hospital São Rafael, CEP 41253-190,
18 Salvador, BA, Brazil.

19

20 Corresponding Author

21 *E-mail: daab@ufscar.br (Alzir A. Batista) FAX number: 55-16-3351-8350

22

23 Keywords: metal complexes, palladium, thioureas, tuberculosis, *Trypanosoma cruzi*.

24

1 **Abstract**

2 The new complexes of Pd(II) with *N,N*-disubstituted-*N'*-acylthioureas: [(1)
3 [Pd(dppf)(*N,N*-dimethyl-*N'*-benzoylthioureato- k^2O,S)]PF₆, (2) [Pd(dppf)(*N,N*-diethyl-
4 *N'*-benzoylthioureato- k^2O,S)]PF₆, (3) [Pd(dppf)(*N,N*-dibutyl-*N'*-benzoylthioureato-
5 k^2O,S)]PF₆, (4) [Pd(dppf)(*N,N*-diphenyl-*N'*-benzoylthioureato- k^2O,S)]PF₆, (5)
6 [Pd(dppf)(*N,N*-diethyl-*N'*-furoylthioureato- k^2O,S)]PF₆, (6) [Pd(dppf)(*N,N*-diphenyl-*N'*-
7 furoylthioureato- k^2O,S)]PF₆, (7) [Pd(dppf)(*N,N*-dimethyl-*N'*- thiophenylthioureato-
8 k^2O,S)]PF₆, and (8) [Pd(dppf)(*N,N*-diphenyl-*N'*-thiophenylthioureato- k^2O,S)]PF₆, were
9 prepared and characterized by elemental analysis, and spectroscopic techniques. The
10 structures of complexes (2), (3), (5), (6) and (8) had their structures determined by X-
11 ray crystallography, confirming the coordination of the ligands with the metal through
12 sulfur and oxygen atoms, forming distorted square-planar geometries. These complexes
13 have shown antibacterial activity against Anti-*M. tuberculosis* H37Rv ATCC 27294.
14 The complexes exhibited antiparasitic activity against *T. cruzi*, while the metal-free
15 thioureas did not. The results demonstrated that the compounds described here can be
16 considered as promising anti-*M. tuberculosis* and anti-*T. cruzi* agents, since in both
17 cases their *in vitro* activity were better than reference drugs available for the treatment
18 of both diseases.

19

20

1 **1. Introduction**

2

3 The *Mycobacterium tuberculosis* (MTB), causative agent of tuberculosis, is
4 responsible for the death of around 2–3 million people, annually, and a global economic
5 toll of U\$12 billion each year [1]. The rise of multidrug resistance (MDR) in MTB has
6 complicated and prolonged the treatment. Therefore, no new drugs have been developed
7 specifically against mycobacteria since the 1960s [2]. Thus, there is a great need to
8 develop new therapeutic agents to treat tuberculosis, so as to reduce the total duration of
9 treatment and to provide more effective drugs against MDR TB and latent tuberculosis
10 infection. This involves the development of new therapeutic strategies against bacterial
11 infection, which becomes more stringent, and one reason for this is mainly due the
12 bacterial drug resistance to currently administered treatments.

13 Also, Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi* (*T.*
14 *cruzi*), affects approximately 10 million people worldwide, with a high prevalence in
15 Latin America [3]. The few drugs available, benznidazole and nifurtimox, are only
16 effective in curing when administered during the acute phase, but not effective in
17 patients that have progressed to the chronic phase [4]. Furthermore, these drugs are not
18 considered ideal, due to their severe side effects [5]. Thus, the search for new anti-*T.*
19 *cruzi* compounds is also needed.

20 One strategy for the development of antimycobacterial and antiparasitic agents
21 from the inorganic point of view is to use an organic compound, which already exhibit
22 antibacterial property, as ligand, to form metal complexes. Thus, good candidates for
23 this purpose are thiourea and their derivatives, which are known for their antiviral,
24 antibacterial and cytotoxic properties [6]. There are several works in the literature
25 demonstrating the activity of this class of compounds, against parasites such as
26 *Plasmodium falciparum*, *Trypanosoma brucei* and *T. cruzi* [7]. In recent years, a

1 number of urea, thiourea and acylthiourea derivatives containing (*R*)-2-amino-1-butanol
2 were evaluated against *Mycobacterium tuberculosis* strains H37Rv ATCC 27294,
3 showing good anti-tuberculosis effect, and the complexing capacity of thiourea
4 derivatives have been reported [8-9].

5 The biological activity of complexes containing thiourea derivatives has been
6 successfully screened for various biological processes and they exhibit a wide range of
7 biological activities, including antifungal, anticancer [9-10] and insecticidal activities
8 [11]. Therefore, in order to extend the research on potential metallodrugs aiming the
9 *M. Tuberculosis* and Chagas disease we report here on some palladium complexes
10 containing the bis(diphenylphosphine)ferrocene and *N,N*-disubstituted-*N'*-acyl thioureas
11 as ligands. Detailed descriptions of synthesis and characterization of the ligands have
12 been reported elsewhere [12]. The Pd(II)/*N,N*-disubstituted-*N'*-acyl thioureas complexes
13 described in this work were synthesized, structurally characterized and were tested for
14 their anti-*M. tuberculosis* and anti-*T. cruzi* activity, showing good results.

16 2. Experimental

17 2.1. Materials and measurements

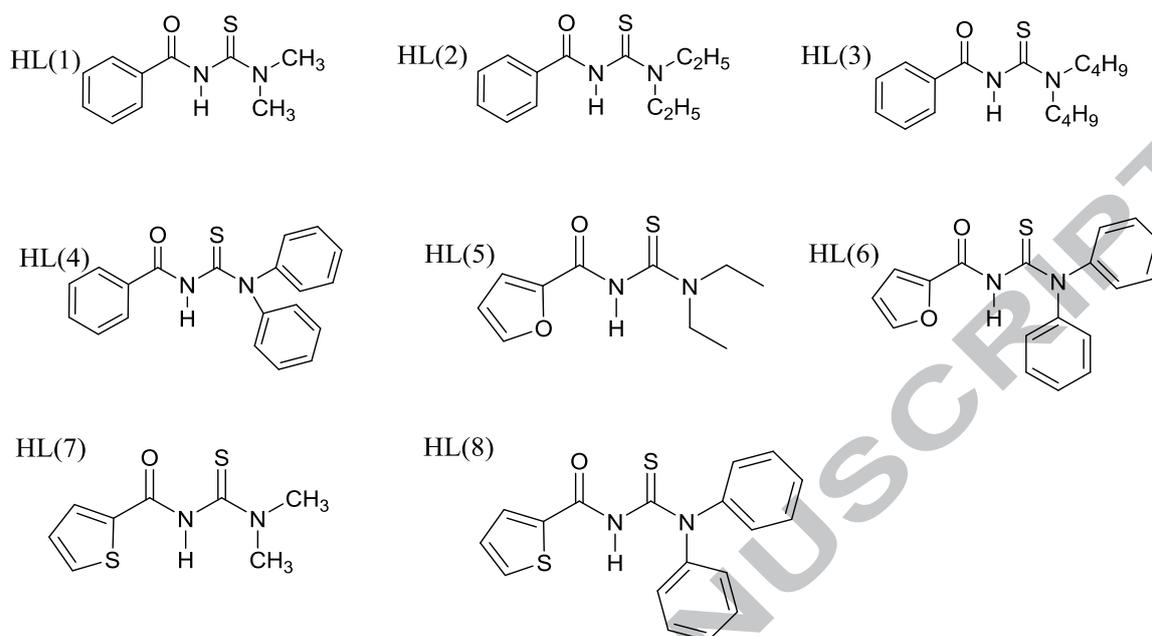
18 The dichloro[bis(diphenylphosphino)ferrocene]palladium (II) was obtained from
19 Stream. All reagents were purchased with reagent grade and used without further
20 purification. Solvents were dried and used freshly distilled, unless otherwise specifically
21 indicated. Thin layer chromatography (TLC) was performed on 0.25 mmsilic gel pre-
22 coated plastic sheets (40/80mm) (Polygram_ SIL G/UV254, Macherey& Nagel, Düren,
23 Germany) using benzene/methanol (9/1) as eluent. The IR spectra were recorded on a
24 FTIR Bomem-Michelson 102 spectrometer in the 4000–200 cm⁻¹ region using CsI
25 pellets. Conductivity values were obtained using 1.0 mmol.L⁻¹ solutions of complexes

1 in CH₂Cl₂, using a Meter Lab CDM2300 instrument. The molar conductance
2 measurements (Λ_m) were carried out in dichloromethane at 25 °C, using concentrations
3 of 1.0×10^{-3} mol.L⁻¹ for the complexes. ¹H, ³¹P{¹H} and ¹³C NMR spectra were
4 recorded on a Bruker DRX 400 MHz, internally referenced to TMS for hydrogen
5 chemical shift (δ). The ³¹P chemical shifts are reported in relation to H₃PO₄, 85%.
6 CDCl₃ was used as solvent, unless mentioned. Partial elemental analyses were carried
7 out on the Department of Chemistry of the Federal University of São Carlos, in an
8 instrument of CHNS staff EA 1108 of the FISIONS.

10 **2.2. Synthesis of *N,N*-dialkyl-*N'*-(acyl/aroyl)thioureas.**

11 The *N,N*-disubstituted-*N'*-acylthioureas HL(1–8) used in this work were
12 synthesized by the procedure previously reported in the literature [12]. A solution of an
13 appropriate acyl chloride (30 mmol) in acetone (50 mL) was added dropwise to a
14 suspension of KSCN (0.01 mol) in acetone (30 mL). The mixture was stirred until a
15 precipitate appeared (ammonium chloride), indicating the formation of the respective
16 organic isothiocyanate. The corresponding amine (40 mmol), dissolved in acetone was
17 added slowly and with constant stirring to the resulting solution. The solution was
18 cooled in an ice-water bath and the stirring was continued at room temperature during
19 2–9 h, until the reaction was completed (the reaction progress was monitored by TLC).
20 The reaction mixture was then poured into 600 mL of cold water. The solid *N,N*-
21 disubstituted-*N'*-(acyl/aroyl)thioureas were collected by filtration and finally purified by
22 recrystallization from ethanol. The compounds were obtained as crystalline solids, in
23 good yields. The identity of the products was confirmed by comparing their ¹H and ¹³C
24 NMR data with those reported in the literature [12]. The structures of the *N,N*-
25 disubstituted-*N'*-acyl thioureas used as ligands in this work are shown in Figure 1.

1

2
3

4 **Figure1.** Structures of the *N,N*-disubstituted-*N'*-acyl thioureas used as ligands in this
5 work.

6

7 2.3. Synthesis of the complexes

8 The complexes were prepared as yellow solid products by a similar method to
9 that used for [Pd(PPh₃)₂Cl₂] [9] from direct reactions with the precursor [Pd(dppf)Cl₂],
10 with the *N,N*-disubstituted-*N'*-acylthioureas, in methanol solutions. The complexes were
11 separated from the reaction mixtures as yellow crystalline solids. Filtration and further
12 washing with hot water and hot hexane were enough to afford pure and stable
13 compounds, in about 80% yields. Thus, the general procedure for the synthesis of the
14 complexes is described: A solution of [Pd(dppf)Cl₂] (1.46 g; 2.00 mmol) in 5 mL of
15 methanol, was added dropwise to a solution of corresponding *N,N*-dialkyl-*N'*-
16 (acyl/aroyl)thiourea (2.00 mmol), dissolved in 30 mL of the same solvent, and 0.368 g
17 (2.00 mmol) of KPF₆. The reaction was heated under magnetic stirring at about 80 °C,
18 for 2 h. The reaction mixture was left in the refrigerator overnight. The yellow solids

1 obtained were filtered off and washed, successively, with hot water and hot hexane (3 ×
 2 20 mL). The obtained compounds are stable in the air and in dimethylsulphoxide
 3 solutions, for at least 72 h, as showed $^{31}\text{P}\{^1\text{H}\}$ NMR experiments.

4

5 The ^1H , ^{13}C and $^{31}\text{P}\{^1\text{H}\}$ NMR, IR and the elemental analyses, melting point
 6 temperature and molar conductivity (Λ_m , 1.0×10^{-3} mol L $^{-1}$ in CH_2Cl_2) for the
 7 complexes (**1-8**) are listed below and the other data used for the characterization of the
 8 complexes will be find in the text:

9

10 **(1)** $[\text{Pd}(\text{dppf})(N,N\text{-dimethyl-}N'\text{-benzoylthioureato-}k^2\text{O,S})]\text{PF}_6$

11 ^1H NMR, δ : 7.86–7.81 (m, 5H, Ph); 7.64–7.51 (m, 5H), 7.37–7.17 (m, 10H), 3.48 (3H,
 12 s, CH_3), and 3.18 (3H, s, CH_3). NMR ^{13}C , δ : 169.7 (C=S); 161.8 (C=O); 134.5, 134.4,
 13 134.4, 134.2, 134.1, 132.7–127.7 (C-Ph), 29.7 (CH_3), 15.3 (CH_3), $^{31}\text{P}\{^1\text{H}\}$ NMR, δ ,
 14 41.12 (d); 28.06 (d); $^2J_{\text{P-P}} = 19.43$ Hz; IR, cm^{-1} : $\nu(\text{C=O})$ 1416, $\nu(\text{C=S})$ 747; $\nu(\text{C=N})$
 15 1502; Anal. (%): Found (Calc) for $\text{C}_{44}\text{H}_{39}\text{F}_6\text{FeN}_2\text{OP}_3\text{PdS}$: C, 52.26 (52.17); H, 3.90
 16 (3.88); N, 2.82 (2.77); S, 3.21 (3.17). $\Lambda_m = 48.6 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$.

17

18 **(2)** $[\text{Pd}(\text{dppf})(N,N\text{-diethyl-}N'\text{-benzoylthioureato-}k^2\text{O,S})]\text{PF}_6$

19 ^1H NMR, δ : 7.87–7.82 (m, 1H), 7.61–7.48 (m, 5H), 7.36–7.31 (m, 5H), 7.15–6.99 (m,
 20 10H), 3.81 (d, $J=7.07$ Hz, 2H, CH_2), 3.58 (d, $J=7.07$ Hz, 2H, CH_2), 1.28 (t, $J = 7.02$,
 21 7.02 Hz, 3H, CH_3), 1.31 (t, $J = 7.02$, 7.02 Hz, 3H, CH_3); NMR ^{13}C , δ : 170.0 (C=S);
 22 169.6 (C=O); 135.7, 135.6, 134.6, 134.5, 134.2–127.5 (C-Ph), 47.3 (CH_2), 46.5 (CH_2),
 23 13.1 (CH_3), 12.1 (CH_3); $^{31}\text{P}\{^1\text{H}\}$, δ : 41.27 (d); 27.41 (d); $^2J_{\text{P-P}} = 21.86$ Hz; IR, cm^{-1} :
 24 $\nu(\text{C=O})$ 1414, $\nu(\text{C=S})$ 750; $\nu(\text{C=N})$ 1501; Anal. (%): Found (Calc) for
 25 $\text{C}_{46}\text{H}_{43}\text{F}_6\text{FeN}_2\text{OP}_3\text{PdS}$: C, 53.15 (53.07); H, 4.08 (4.16); N, 2.70 (2.69); S, 3.00 (3.08).

1 MP: 270-272 °C, $\Lambda_m = 44.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

2

3 **(3)** [Pd(dppf)(*N,N*-dibutyl-*N'*-benzoylthioureato- k^2 O,S)]PF₆

4 ¹H NMR, δ : 8.04-7.99(m, 1H), 7.80-7.08 (m, 34H), 4.88 (d, $J=7.08$ Hz, 2H, CH₂), 3.68
 5 (4H, q, CH₂), 2.07-1.70 (2H, m, CH₂), 0.93 (3H, t, CH₃, $J = 7.01$ Hz). NMR ¹³C, δ :
 6 170.6 (C=S), 168.5 (C=O), 135.6, 135.3, 135.2, 133.6–128.8 (C-Ph), 53.6 (CH₂), 52.4
 7 (CH₂), 20.9 (CH₂), 14.2 (CH₃); ³¹P {¹H}, δ : 41.18 (d); 27.63 (d); ²J_{P-P} = 20.26 Hz; IR,
 8 cm⁻¹: ν (C=O) 1495, ν (C=S) 747; ν (C=N) 1495; Anal. (%): Found (Calc) for
 9 C₅₀H₅₁F₆FeN₂OP₃PdS: C, 54.54 (54.74); H, 4.65 (4.68); N, 2.53 (2.55); S, 2.85 (2.92),
 10 MP: 230-232 °C, $\Lambda_m = 47.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

11

12 **(4)** [Pd(dppf)(*N,N*-diphenyl-*N'*-benzoylthioureato- k^2 O,S)]PF₆

13 ¹H NMR, δ : 7.86–7.82 (m, 1H), 7.14 (s, 1H), 6.73 (d, $J=1.60$ Hz, 1H), 6.86–6.83 (m,
 14 1H), NMR ¹³C, δ : 174.6 (C=S); 172.9 (C=O); 144.0, 143.1, 134.4, 134.3, 134.2, 134.1–
 15 127.3 (C\Ph). ³¹P {¹H}, δ : 41.25 (d), 27.58 (d) ²J_{P-P} = 20.26; IR, cm⁻¹: ν (C=O) 1430,
 16 ν (C=S) 752; ν (C=N) 1494; Anal. (%): Found (Calc) for C₅₄H₄₃F₆FeN₂OP₃PdS: C, 56.98
 17 (57.03); H, 3.90 (3.81); N, 2.37 (2.46); S, 2.78 (2.82). MP: 275-277 °C, $\Lambda_m = 48.6 \Omega^{-1}$
 18 cm² mol⁻¹.

19

20 **(5)** [Pd(dppf)(*N,N*-diethyl-*N'*-furoylthioureato- k^2 O,S)]PF₆

21 ¹H NMR, δ : 7.85–7.80 (m, 1H), 7.60–6.18 (3H, m, furoyl), 3.74 (2H, d, CH₂), 3.34 (2H,
 22 d, CH₂), 1.22 (3H, t, CH₃), 0.95 (3H, t, CH₃). NMR ¹³C, δ : 165.7 (C=S), 159.8 (C=O),
 23 145.9, 134.6, 134.5, 134.1–129.4 (C-Ph), 128.8–112.0 (C-Ph and furan ring), 47.2
 24 (CH₂), 46.5 (CH₂), 13.1 (CH₃) 11.9 (CH₃). ³¹P {¹H}, δ : 41.45 (d), 27.32 d); ²J_{P-P} =
 25 19.43, IR, cm⁻¹: ν (C=O) 1474., ν (C=S) 747; ν (C=N) 1504; Anal. (%): Found (Calc):

1 Anal. (%): Found (Calc) for $C_{44}H_{41}F_6FeN_2O_2P_3PdS$: C, 51.15 (51.26); H, 3.97 (4.00);
 2 N, 2.68 (2.72); S, 3.09 (3.11). MP: 242-244 $^{\circ}C$, $\Lambda_m = 48.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

3

4 (6) $[Pd(dppf)(N,N\text{-diphenyl-}N'\text{-furoylthioureato-}k^2O,S)]PF_6$

5 1H NMR, δ : 7.91–7.80 (m, 1H), 7.63–7.43 (m, 1H), 7.20–6.99 (m, 1H), 6.53–6.16 (m,
 6 1H), 4.98 (s, 2H, CH_2), 4.77 (s, 2H, CH_2). NMR ^{13}C , δ : 167.7 (C=S); 162.0 (C=O);
 7 149.5, 146.8, 146.1, 145.7, 145.2–112.3 (C-Ph), 53.5 (CH_2), 52.8 (CH_2). ^{31}P { 1H }, δ :
 8 41, 30 (d), 27,54 (d), $^2J_{P-P} = 19.43$; IR, cm^{-1} : $\nu(C=O)$ 1486, $\nu(C=S)$ 741; $\nu(C=N)$ 1573;

9 Anal. (%): Found (Calc) for $C_{52}H_{41}F_6FeN_2O_2P_3PdS$: C, 55.39 (55.41); H, 3.61 (3.66);
 10 N, 2.45 (2.49); S, 2.80 (2.84). MP: 264-266 $^{\circ}C$, $\Lambda_m = 52.6 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

11

12 (7) $[Pd(dppf)(N,N\text{-dimethyl-}N'\text{-thiophenylthioureato-}k^2O,S)]PF_6$

13 1H NMR, δ : 8.02 (1H, dd, $J_1 = 7.2$ Hz, $J_2 = 8.1$ Hz, thiophene CH), 7.87 (1H, dd, $J_1 =$
 14 7.59 Hz, $J_2 = 8.2$ Hz, thiophene CH), 6.70 (1H, dd, $J_1 = 6.7$ Hz, $J_2 = 8.6$ Hz, thiophene
 15 CH), 7.59–7.27 (C-Ph) 0.97 (6H, t, CH_3 , $J = 7.1$ Hz), NMR ^{13}C , δ : 166.7 (C=S); 164.1
 16 (C=O); 141.2, 134.6, 134.5, 134.5, 134.4, 132.4, 132.3, 132.2, 131.7, 128.9 - 125.6 (C-
 17 Ph); 21.8 (2 CH_3). ^{31}P { 1H }, δ : 41.58 (d), 27.97 (d), $^2J_{P-P} = 19.47$; IR, cm^{-1} : $\nu(C=O)$ 1418,
 18 $\nu(C=S)$ 745; $\nu(C=N)$ 1494; : Anal. (%): Found (Calc) for $C_{42}H_{37}F_6FeN_2OP_3PdS_2$: C,

19 49.35 (49.50); H, 3.60 (3.66); N, 2.71 (2.75); S, 6.20 (6.29). MP: 245-247 $^{\circ}C$, $\Lambda_m =$
 20 50.6 $\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$.

21

22 (8) $[Pd(dppf)(N,N\text{-diphenyl-}N'\text{-thiophenylthioureato-}k^2O,S)]PF_6$

23 1H NMR, δ : 8.02 (1H, dd, $J_1 = 7.2$ Hz, $J_2 = 8.1$ Hz, thiophene CH), 7.90 (1H, dd, $J_1 =$
 24 7.5 Hz, $J_2 = 8.2$ Hz, thiophene CH), 7.89 (1H, dd, $J_1 = 6.7$ Hz, $J_2 = 8.3$ Hz, thiophene
 25 CH), 7.82-7.13 (m, 10H, arom-H). NMR ^{13}C , δ : 173.7 (C=S); 166.2 (C=O); 144.1,

1 143.2, 140.8, 140.7, 134.7, 134.2, 134.1, 134.0, 133.9, 132.3, 128.5 - 127.8 (C-Ph);
2 $^{31}\text{P}\{^1\text{H}\}$, δ : 41.62 (d); 27.63 (d); $^2J_{\text{P-P}} = 19.43$ Hz; IR, cm^{-1} : $\nu(\text{C=O})$ 1420, $\nu(\text{C=S})$ 743;
3 $\nu(\text{C=N})$ 1479; Anal. (%) Found (Calc) for $\text{C}_{52}\text{H}_{41}\text{F}_6\text{FeN}_2\text{OP}_3\text{PdS}_2$: C, 54.45 (54.63); H,
4 3.49 (3.61); N, 2.41 (2.45); S, 5.54 (5.61). MP: 256-258 $^{\circ}\text{C}$., $\Lambda_{\text{M}} = 49.6 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$.

5

6 **2.4. Crystal structure determination.**

7 Single crystals suitable for X-ray diffraction were obtained by slow evaporation
8 of CHCl_3 :n-hexane (3:1) solutions of the complexes **2**, **3**, **5**, **6** and **8**. Diffraction data
9 were collected on an Enraf-Nonius Kappa-CCD diffractometer with graphite-
10 monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). The final unit cell parameters were
11 based on all reflections. Data collections were performed using the COLLECT program
12 [13]; integration and scaling of the reflections were performed with the HKL Denzo-
13 Scalepack system of programs [14]. Absorption corrections were carried out using the
14 Gaussian method [15]. The structures were solved by direct methods with SHELXS-97
15 [16]. The models were refined by full-matrix least-squares on F 2 by means of
16 SHELXL-97 [17]. The projection views of the structures were prepared using ORTEP-3
17 for Windows [18]. Hydrogen atoms were stereochemically positioned and refined with
18 the riding model. Data collections and experimental details are summarized in Table 1.
19 Relevant interatomic bond lengths and angles are listed in Table 2. Also included are
20 the CCDC deposit numbers for supplementary crystallographic data.

Table 1. Crystal data and refinement parameters for **2**, **3**, **5**, **6**, and **8** complexes.

Compound	2	3	5	6	8
Empirical formula	C ₄₆ H ₄₃ F ₆ FeN ₂ OP ₃ PdS. CH ₂ Cl ₂	C ₅₀ H ₅₁ F ₆ FeN ₂ OP ₃ PdS	C ₄₄ H ₄₁ F ₆ FeN ₂ O ₂ P ₃ PdS	C ₅₂ H ₄₁ F ₆ FeN ₂ O ₂ P ₃ PdS	C ₅₂ H ₄₁ F ₆ FeN ₂ O P ₃ PdS ₂
Formula weight	1125.97	1097.15	1031.01	1127.09	1143.15
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	P2 ₁ /c	Pc	P2 ₁ /a	P-1	P-1
Temperature (K)	293	296		296	296
a (Å)	10.5650(2)	10.6147(5)	10.8430(2)	12.5827(3)	12.5960(3)
b (Å)	27.6270(8)	14.557 (1)	28.8291(5)	13.8101(4)	13.8000(4)
c (Å)	16.8200(4)	16.325(1)	14.1096(2)	14.9739(4)	15.0780(4)
V (Å ³)	4861.2(2)	2506.2(3)	4406.77(13)	2453.78(12)	2479.3 (1)
Z	4	2	4	2	2
D. calc (mg/m ³)	1.538	1.454	1.554	1.525	1.531
Absorption coefficient (mm ⁻¹)	0.981	0.846	0.958	0.868	0.899
F(000)	2280	1120	2088	1140	1156
θ range for data collection (°)	2.555 to 25.999	2.875 to 25.997	2.565 to 25.997	2.972 to 25.999	2.84 to 26.00
Index ranges	-11 ≤ h ≤ 13 -32 ≤ k ≤ 34 -20 ≤ l ≤ 12	-12 ≤ h ≤ 13 -17 ≤ k ≤ 17 -20 ≤ l ≤ 16	-12 ≤ h ≤ 13 -35 ≤ k ≤ 35 -16 ≤ l ≤ 17	-15 ≤ h ≤ 15 -17 ≤ k ≤ 16 -18 ≤ l ≤ 18	-15 ≤ h ≤ 15 -17 ≤ k ≤ 17 -18 ≤ l ≤ 18
Reflections collected	25156	12255	38378	25632	28331
Independent reflections (R _{int})	9351 [R(int) = 0.0386]	7966 [R(int) = 0.0592]	8639 [R(int) = 0.0926]	9547 [R(int) = 0.0481]	9719 [R(int) = 0.0387]
Goodness-of-fit on F ²	1.024	1.044	1.026	1.019	1.070
Final R indices [I N 2σ (I)]	R1 = 0.0518 wR2 = 0.1345	R1 = 0.0603 wR2 = 0.1537	R1 = 0.0509 wR2 = 0.1275	R1 = 0.0479 wR2 = 0.1247	R1 = 0.0461 wR2 = 0.1314
Largest diff. peak and hole (eÅ ⁻³)	0.848 and -0.631	0.779 and -0.487	0.888 and -0.810	0.623 and -0.794	1.160 and -0.794
CCDC deposit number	1502550	1502551	1502552	1502553	1502554

2.5. Antimycobacterial activity assay

Antimycobacterial activities of each tested compound and of the standard drug ethambutol were determined in triplicate, in sterile 96-well flat bottom microplates. The tested compound concentrations ranged from 0.087-25 $\mu\text{g}/\text{mL}$, and the ethambutol from 0.015 to 1.0 $\mu\text{g}/\text{mL}$. The microplate Alamar Blue assay [19] was used to measure the minimal inhibitory concentration (MIC) for the tested compounds (minimum concentration necessary to inhibit 90 % growth of *M. tuberculosis* H₃₇Rv ATCC 27294). The development of a pink color in the wells was taken as indicating bacterial growth and the maintenance of a blue color as the contrary. The fluorescence of the dye was measured in a SPECTRAfluor Plus microplate reader (Tecan*) in bottom reading mode with excitation at 530 nm and emission at 590 nm.

2.6 Antiparasitic activity

Y strain trypomastigotes of *T. cruzi* collected from the LLC-MK2 cell supernatant were dispensed into 96-well plates at a cell density of 2.0×10^6 cells/mL in 200 μL of RPMI medium. Compounds were tested at eight concentrations from (10-0.01 μM), in triplicate. The plate was incubated for 24 h at 37 °C and 5 % CO₂. Aliquots from each well were collected and the number of viable parasites, based on parasite viability, was assessed in a Neubauer chamber and compared to untreated parasite culture. This experiment was performed three times. Inhibitory concentration for 50 % (IC₅₀) was calculated using data-points gathered from three independent experiments. Benznidazole was used as a positive control.

2.7 Cytotoxicity in murine cells

J774 cells (murine macrophages cell line, established from a tumor that arose in female BALB/c mouse) were placed on 96-well plates at a cell density of 5×10^4 cells/ML in 200 μL

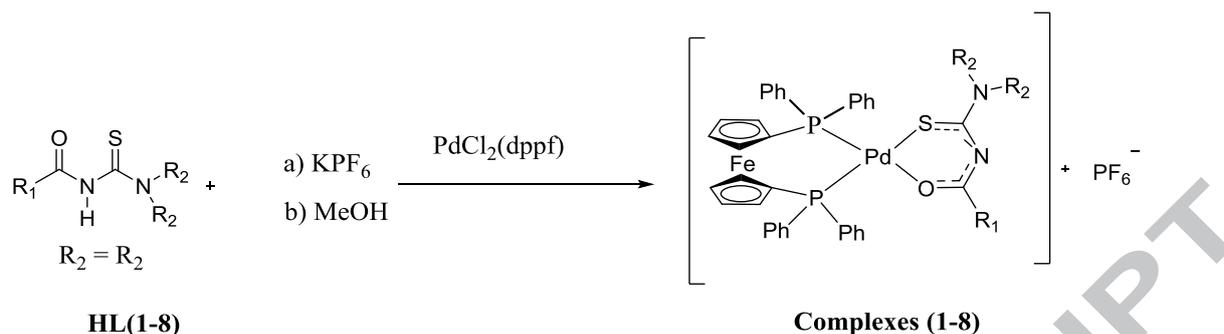
of RPMI-1640 medium (no phenol red) and supplemented with 10 % FBS and 50 µg/mL of gentamycin and incubated for 24 h at 37°C and 5 % CO₂. Compounds were added in a series of eight concentrations, in triplicate, and incubated for 72 h. Then, 20 µL/well of AlamarBlue (Invitrogen, Carlsbad, USA) was added to all wells and incubated during 6 h. Colorimetric readings were performed at 570 and 600 nm. Cytotoxic concentration for 50 % (CC₅₀) was calculated using data-points gathered from three independent experiments. Gentian violet was used as a positive control.

2.8 Propidium iodide (PI) and annexin V staining

T. cruzi trypomastigotes from Y strain (1×10^7) were incubated for 24 h at 37 °C in the absence or presence of **1** (0.61 or 1.22 µM) or **4** (1.91 or 3.82 µM). After incubation, the parasites were labeled for PI and FITC-annexin V using the annexin V-FITC apoptosis detection kit (Sigma-Aldrich), according to the manufacturer's instructions. Acquisition and analyses was performed using a FACS Calibur flow cytometer (Becton Dickinson, San Diego, CA), with FlowJo software (Tree Star, Ashland, OR). A total of 10.000 events were acquired in the region previously established as that corresponding to trypomastigotes.

3. Results and discussion

The ligands were prepared following the procedures previously reported in the literature [12] and were obtained in yields ranging from 79–91%. The complexes of the type [Pd(dppf)(L)] were obtained by the reactions between [Pd(dppf)Cl₂] and the ligands (see Scheme 1). The synthesized complexes were yellowish crystals and their elemental analyses, melting point temperatures, and molar conductivities are listed in the experimental section. Complexes **2**, **3**, **5**, **6** and **8** were also characterized by single crystal X-ray diffraction.



Scheme I: Route for the syntheses of $[\text{Pd}(\text{dppf})(N,N\text{-disubstituted-}N'\text{-acylthiourea})]\text{PF}_6$ complexes

The IR spectra of the complexes were compared with those of the free ligands. The N-H stretching vibrations which exist in the ligands disappear. A broad peak ascribed to the C-N bond appears around $1580\text{--}1600\text{ cm}^{-1}$, indicating deprotonation of the acylthioureido group of the ligands during the complexes formation and therefore their coordination through the oxygen and sulfur atoms [20-22]. The bands observed around $471\text{--}490\text{ cm}^{-1}$ were assigned to M-O [23, 24]. Assignment of the Pd-S stretching vibration bands at about 360 cm^{-1} are in accordance to the reported literature [25,26]. The bands in the $551\text{--}556\text{ cm}^{-1}$ range are assigned to M-N (imino nitrogen) [20]. Strong bands in the region of about 1500 cm^{-1} , are shown by the IR spectra of the complexes which may reasonably be assigned to the coordinated C-O groups. The absorption bands at $815\text{--}878\text{ cm}^{-1}$ in the spectra of free *N,N*-disubstituted-*N'*-acylthioureas, attributed to the $\nu(\text{C-S})$ stretching vibrations, shift to the $837\text{--}845\text{ cm}^{-1}$ range in the complexes spectra, corresponding to the weakening of the C-S double bond character [21].

In the ^1H NMR spectra (CDCl_3) of the ligands HL(1-8), the NH proton appears at 8.79-8.45 ppm as broad singlets. This signal is absent in the ^1H NMR spectra of the corresponding palladium complexes, in the same solvent, as a consequence of the deprotonation of the nitrogen atom. Similarly, the IR spectra of the ligands HL(1-8) show NH stretching vibrations in the range $3150\text{--}3260\text{ cm}^{-1}$, but these signals are absent in the

spectra of the corresponding metal complexes. In the ^{13}C NMR spectra, the carbon atom of the thiocarbonyl group appears at $\delta = 165.67\text{--}173.67$ in the metal complexes, as mentioned in the experimental section.

The $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the precursor $[\text{Pd}(\text{dppf})\text{Cl}_2]$, in CH_2Cl_2 solution, shows a singlet peak for phosphorus atoms at $\delta = 35.12$. For all complexes two doublets arise, at about $\delta = 41.34$ and 27.64 , indicating the presence of two magnetically different phosphorus atoms coordinated to the palladium(II) ion. Also in the region of $\delta = -138\text{--}158$ a multiple signal of the PF_6^- , functioning as outer-sphere anions for the complexes is observed, in accordance to the molar conductivity measurements for these complexes (see experimental section). These data are consistent with those obtained for some thiosemicarbazones and *N,N*-disubstituted-*N'*-acyl thioureas complexes [10, 21,27].

The molecular structures of **2**, $[\text{Pd}(\text{dppf})(\text{N,N}\text{-diethyl-}\text{N}'\text{-benzoylthioureato-}\text{k}^2\text{O,S})]\text{PF}_6$, **3**, $[\text{Pd}(\text{dppf})(\text{N,N}\text{-dibutyl-}\text{N}'\text{-benzoylthioureato-}\text{k}^2\text{O,S})]\text{PF}_6$, **5**, $[\text{Pd}(\text{dppf})(\text{N,N}\text{-diethyl-}\text{N}'\text{-furoylthioureato-}\text{k}^2\text{O,S})]\text{PF}_6$, **6**, $[\text{Pd}(\text{dppf})(\text{N,N}\text{-diphenyl-}\text{N}'\text{-furoylthioureato-}\text{k}^2\text{O,S})]\text{PF}_6$, and **8**, $[\text{Pd}(\text{dppf})(\text{N,N}\text{-diphenyl-}\text{N}'\text{-thiophenylthioureato-}\text{k}^2\text{O,S})]\text{PF}_6$, are shown in Fig. 2, and selected bond lengths and angles ($^\circ$) for these structures are listed in Table 2.

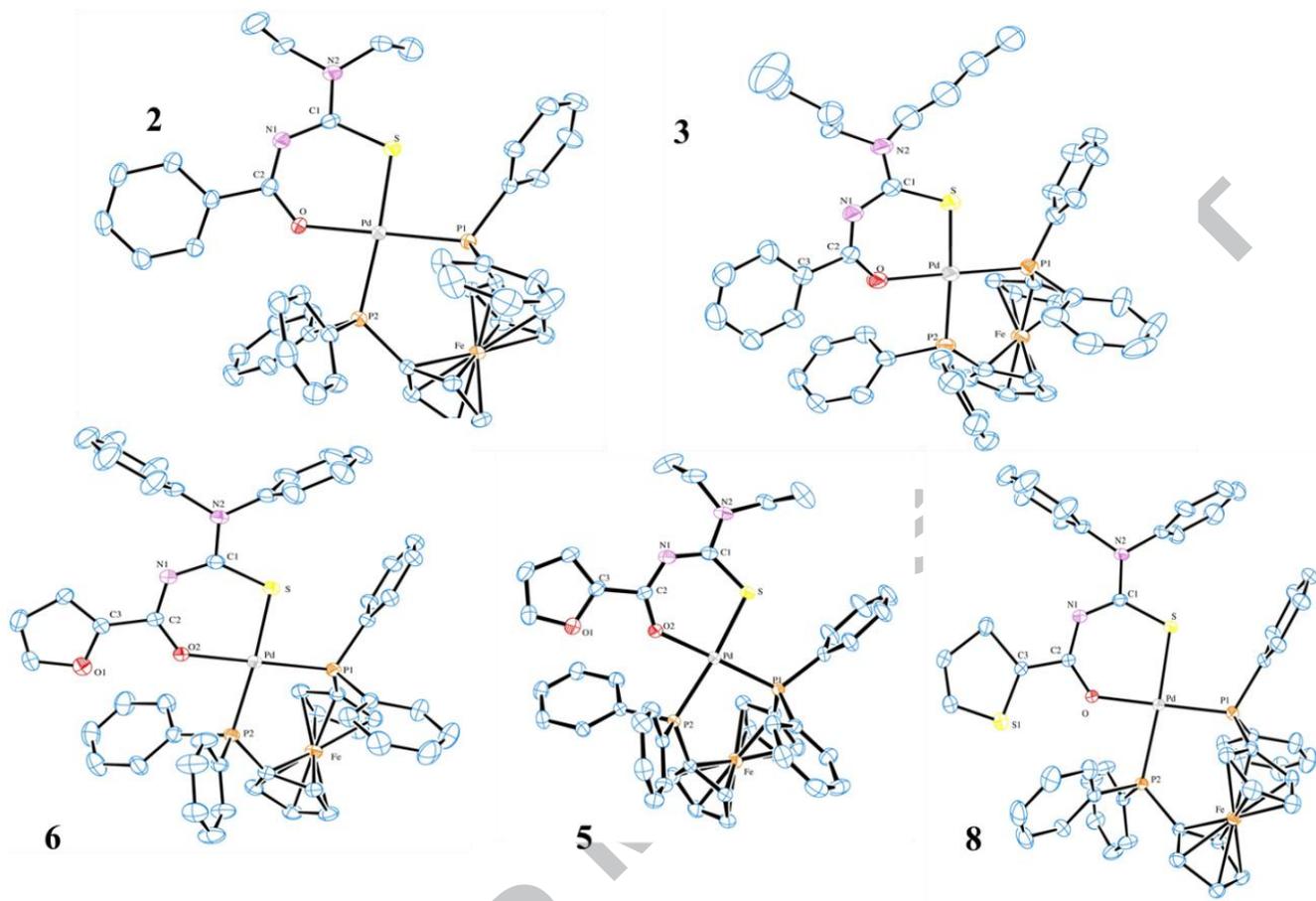


Figure 2. ORTEP view of complexes **2**, **3**, **5**, **6** and **8** showing 50% probability ellipsoids. The $(\text{PF}_6)^-$ anion and some labels of the ligands are omitted for clarity. For complex **2** there is a CH_2Cl_2 solvated molecule, which was also omitted.

In all complexes the Pd(II) ion is nearly planar, in a fourfold environment. The thione C-S bond in the coordinated anionic ligands becomes formally a single bond making it longer (average = 1.734 Å) than the C=S bond of the neutral moieties [27, 28] (Fig. 2, Table 2). Thus the metal is coordinated to the negatively charged organic molecules, which act as bidentate ligands, through oxygen (average distance Pd-O = 2.0494 Å) and sulfur (average distance Pd-S = 2.2964 Å) atoms. The Pd-S average distance is close to the ones found for other palladium(II) thiosemicarbazones complexes [21]. The remaining binding sites are occupied by biphosphines (dppf) (average distance Pd-P1 = 2.2604 Å and Pd-P2 =

2.3531 Å). The distances for the C-S and C-O bonds in the chelate rings, listed in Table 2, are the characteristic of single and double bond lengths, respectively [9, 21, 27]. The N1-C1 and N2-N1 bond distances (average 1.3402 Å and 1.307 Å, respectively) present typical bond lengths of double bond character, suggesting an electron delocalization in the acylthiourea moiety [21-27]. The C-O bond distances are slightly sensitive to the coordination of the ligand to the metal. In previously work it was reported, on the bis-triphenylphosphine-N,N-diethyl-N'-furoylthioureato-k₂O,S, that the C-O distance for the free ligand is 1.226(3) Å (average for two independent molecules per asymmetric unit), and 1.266(9) Å (average), after its coordination to the metal [28].

Table 2. Selected bond lengths (Å) and angles (°) for **2**, **3**, **5**, **6** and **8** complexes.

Bond lengths (Å)	2	3	5	6	8
Pd-O	2.046(3)	2.067(7)	2.032(3)	2.049(2)	2.053(2)
Pd-P(1)	2.261 (1)	2.266(2)	2.255 (1)	2.2578(9)	2.2620(8)
Pd-P(2)	2.356 (1)	2.359(2)	2.35(1)	2.3478(9)	2.3527(8)
Pd-S	2.290 (1)	2.295(2)	2.300 (1)	2.2979(9)	2.2991(9)
S-C1	1.740(4)	1.73 (1)	1.748(5)	1.721(4)	1.731(4)
O-C2	1.274(5)	1.26 (1)	1.259(5)	1.267(4)	1.270(4)
C1-N1	1.335(6)	1.37(1)	1.333(6)	1.334(5)	1.329(5)
C2-N1	1.297(6)	1.29(1)	1.309(6)	1.317(5)	1.322(4)
Angles (°)					
O-Pd-S	91.88(9)	92.2(2)	90.9 (1)	91.94(7)	92.16(7)
O-Pd-P(1)	178.8 (1)	178.8(2)	176.0 (1)	179.41(8)	178.67(9)
O-Pd-P(2)	84.53(9)	84.6(2)	84.1(1)	83.25(7)	83.86(7)
P(2)-Pd-S	175.94(4)	176.8(1)	174.41(4)	174.64(3)	174.29(3)
P(1)-Pd-S	88.43(4)	88.24(9)	90.42(4)	88.14(3)	87.58(3)
P(2)-Pd-P(1)	95.12(4)	94.99(8)	94.74(4)	96.70(3)	96.49(3)

After structural characterization, the metal-free *N,N*-disubstituted-*N'*-acylthioureas and metal complexes were investigated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv strain and antiparasitic activity against Y strain *T. cruzi* trypomastigotes. The results are displayed in Table 3.

Table 3. Antimycobacterial, antiparasitic and cytotoxicity activity of ligands and complexes

1-8.

Compound	<i>M. tuberculosis</i> H ₃₇ Rv MIC (μM) ^(a)	<i>T. cruzi</i> IC ₅₀ ±S.E.M.(μM) ^(b)	Cytotoxicity CC ₅₀ ±S.D.(μM) ^(c)	SI ^(d)
HL (1)	>119.6	> 10	> 30	-
HL (2)	>100.3	> 10	> 30	-
HL (3)	>85.6	> 10	> 30	-
HL (4)	>75.3	> 10	> 30	-
HL (5)	>110.6	> 10	> 30	-
HL (6)	>75.3	> 10	> 30	-
HL (7)	>116.8	> 10	> 30	-
HL (8)	>73.9	> 10	> 30	-
1	2.58 ± 0.38	0.61 ± 0.27	2.63 ± 1.25	4.3
2	2.82 ± 0.04	0.53 ± 0.21	1.53 ± 0.50	2.9
3	5.24 ± 0.33	1.47 ± 0.47	4.14 ± 1.35	2.8
4	17.32 ± 0.20	1.91 ± 0.50	8.83 ± 1.60	4.6
5	2.98 ± 0.02	0.76 ± 0.20	2.27 ± 0.64	3.0
6	6.36 ± 0.16	1.91 ± 0.70	3.86 ± 0.35	2.0
7	2.88 ± 0.07	0.55 ± 0.07	1.85 ± 0.48	3.3
8	9.71 ± 1.12	1.59 ± 0.04	5.83 ± 0.72	3.7
Ethambutol	5.62	-	-	-
Benznidazole	-	10.61 ± 0.87	> 30	>2.8
Gentian Violet	-	-	0.82 ± 0.12	-

^(a) Determined after 7 days incubation time with the drugs. ^(b) Determined in trypomastigotes after 24 h incubation. ^(c) Determined in J774 macrophages after 72 h incubation. ^(d) SI = selectivity index for antiparasitic activity, determined as CC₅₀(cytotoxicity)/IC₅₀ (trypomastigotes).

None the metal-free ligands presented antimycobacterial activity in concentration below 70 μM, while the palladium complexes presented activity in the same micromolar range as observed under Ethambutol treatment. Therefore, the presence of palladium is essential to improve the antimycobacterial activity of the free ligands. Regarding structure-activity relationships, the main difference between most and less active Pd(II) complexes is the presence of a linear and alkyl side chain attached at R2 in the ligand structure. This may be the reason for the decreased the antimycobacterial activity of complexes **4**, **6** and **8** in comparison to **1**, **2**, **3**, **5** and **7**.

Next, the antiparasitic activity was analyzed and the results were compared to the reference drug benznidazole, which displayed an IC_{50} value of $10.61 \pm 0.87 \mu\text{M}$. None the metal-free ligands displayed antiparasitic activity, while the Pd(II) complexes exhibit antiparasitic activity. In general, the metal complexes were more potent antiparasitic agents than benznidazole, however, they presented lower selectivity indexes than benznidazole. After observing that palladium complexes exhibit antiparasitic activity, it was investigated how the complexes can cause parasite cell death. To this end, trypomastigotes were treated with the IC_{50} or IC_{99} concentration of complexes **1** and **4** for 24 h and then stained with PI/annexin (Figure 3).

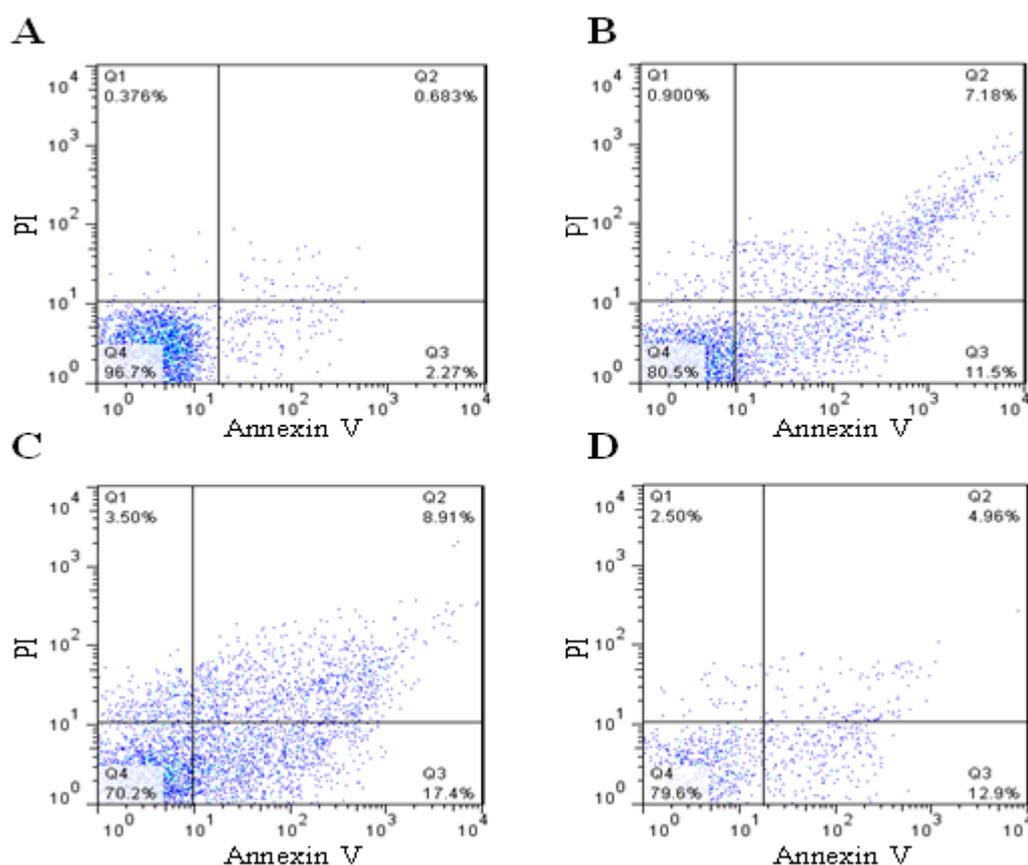


Figure 3. Flow cytometry analysis of trypanomastigotes (Ystrain) treated with **1** or **4** for 24 h and stained with PI and annexin V. (A) Representative untreated trypanomastigotes; (B)

trypomastigotes treated with **1** ($0.61 \mu\text{mol L}^{-1}$); (C) trypomastigotes treated with **1** ($1.22 \mu\text{M}$); (D) trypomastigotes treated with **4** ($1.91 \mu\text{M}$). Three independent experiments were performed, here on representative experiment is shown.

In comparison to untreated parasites, treatment with complex **1** at IC_{50} concentration increased from 2.2 to 11.5 % cells positively stained for annexin. When the complex **1** was added at IC_{99} concentration, the % of annexin-stained cells changed from 11.5 to 17.4, indicating that complex acts in a concentration-dependent manner. It was also observed that complex **1** treatment increased the double staining for PI/annexin. A similar cell death was also observed when complex **4** was evaluated. The single and double staining observed here for these complexes are indicative that parasite cell death occurs through an apoptosis process. Antiparasitic properties of palladium complexes have been observed as causing apoptotic cell death [29], while other metal transition complexes usually cause a necrotic death [30].

4. Conclusions

A novel series of Pd(II)/*N,N*-disubstituted-*N'*-acyl thioureas is here reported. The IR and NMR data suggest the coordination of the ligands to the metal center occurs bidentately, through the oxygen and sulfur atoms, which was confirmed by X-ray crystallographic characterization for complexes **2**, **3**, **5**, **6** and **8**. *In vitro* screening of complexes against *M. tuberculosis* and *T. cruzi* revealed that metal-free ligands were inactive, while complexes were activity. Structure-activity relationship indicated that their activity are dependent of the R2 group present in the amine nitrogen, while the nature of R1, attached in the acyl group, was less important for activity. The findings observed here reinforce that palladium are valuable antiparasitic agents.

Acknowledgments

This work was supported by CAPES (Project Oficio/CSS/CGCI/ 23038009487/2011-25/DRI/CAPES, AUX CAPES-MES-Cuba, 339/2011), CNPq, FAPESP (Processo 2014/13691-4) and FAPESB.

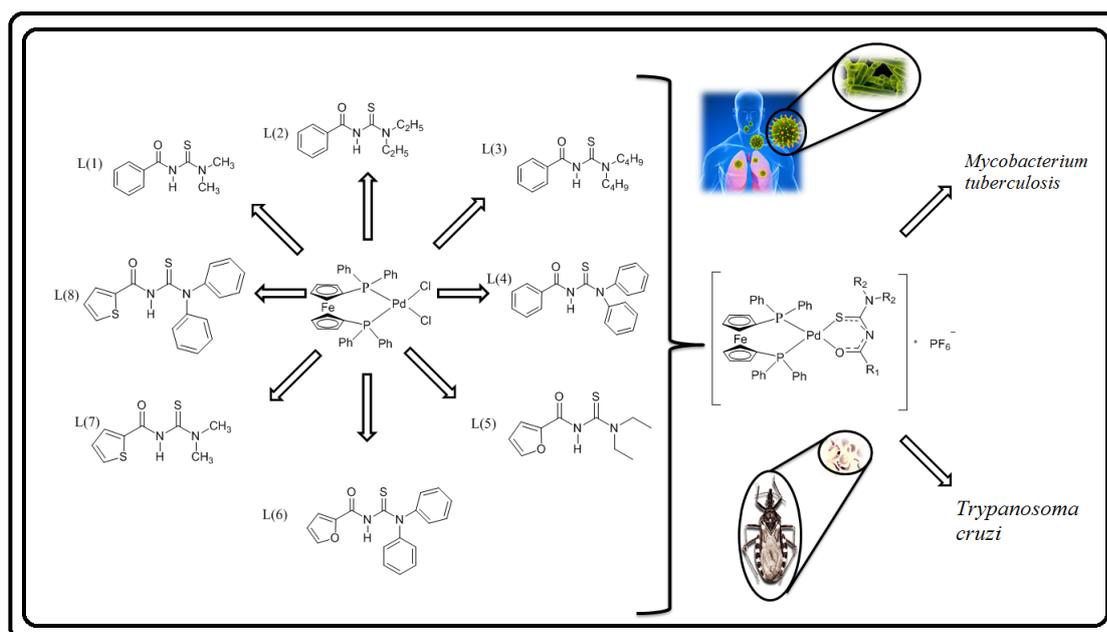
Appendix A. Supplementary data Supplementary crystallographic data for complexes 2, 3, 5, 6 and 8 (CCDC 1502550, 1502551, 1502552, 1502553 and 1502554, respectively) can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.

References.

1. Global Alliance for TB Drug Development. www.tballiance.org [accessed 01.06.2016].
2. T.D. Primm, S.G. Franzblau, *Curr. Bioact. Compd.*, 6 (2007) 201–208.
3. C. J. Schofield CJ, Jannin J, R. Salvatella, *Trends Parasitol.*, 12 (2006) 583–588.
4. S. Antinori, R. Grande, R. Bianco, L. Traversi, C. Cogliati, D. Torzillo, E. Repetto, M. Corbellino, L. Milazzo, M. Galli, and L. Galimberti, *Clinic. Infect. Dis.*, 60 (2015) 1873-1875.
5. J. A. Urbina, *Acta Trop.*, 115 (2010) 55–68.
6. H. Pervze, H. P. Iqbal, M. Y. Tahir, F. H. Nasim, M. I. Choudhary, K. M. Khan, *J. Enzym. Inhib. Med. Chem.*, 23 (2008) 848-854.

7. D. C. Greenbaum, Z. Mackey, E. Hansell, P. Doyle, J. Gut, C. R. Caffrey, J. Lehrman, P. J. Rosenthal, J. H. Mckerrow, K. Chibale, *J. Med. Chem.* 47 (2004) 3212-3219.
8. G. M. Dobrikov, V. Valcheva, Y. Nikolova, I. Ugrinova, E. Pasheva, V. Dimitrov, *Eur. J. Med. Chem.* 63 (2013) 468-473.
9. A. M. Plutín, R. Mocelo, A. Alvarez, R. Ramos, E. E. Castellano, Marcia R. Cominetti, A. E. Graminha, A. G. Ferreira, A. A. Batista, *J. Inorg. Biochem.*, 134 (2014) 76-82
10. R. S. Correa, K. M. de Oliveira, F. G. Delolo, A. Alvarez, R. Mocelo, A. M. Plutin, M. R. Cominetti, E. E. Castellano, A. A. Batista, *J. Inorg. Biochem.*, 150 (2015) 63-71
11. H. Arslan, N. Duran, G. Borekci, C. K. Ozer, C. Akbay, *Molecules*, 14 (2009) 519-527.
12. A. Plutin, H. Márquez, M. Morales, M. Sosa, L. Morán, Y. Rodríguez, M. Suárez, C. Seoane, N. Martín, *Tetrahedron*, 56 (2000) 1533-1539.
13. Enraf-Nonius, Collect, Nonius BV, Delft, The Netherlands, 1997-2000.
14. Z. Otwinowski, W. Minor, Processing of X-ray diffraction data collected in oscillation mode, *Macromol. Crystallogr.*, (1997) A 276.
15. R.H. Blessing, *Acta Crystallogr. Sect.*, A 51 (1995) 33-38.
16. G.M. Sheldrick, ShelXS-97 Program for Crystal Structure Resolution, University of Göttingen, Göttingen, Germany, 1997.
17. G.M. Sheldrick, ShelXL-97, Program for Crystal Structures Analysis, University of Göttingen, Göttingen, Germany, 1997.
18. L.J. Farrugia, *J. Appl. Crystallogr.*, 30 (1997) 565-566.
19. L. A. Collins, S. G. Franzblan. *Antimicrob. Agents Chemother.*, 41 (1997), 1004-1009.
20. A.E. Graminha, C. Rodrigues, A.A. Batista, L.R. Teixeira, E.S. Fagundes, H. Beraldo, *Spectrochim. Acta A*, 69 (2008) 1073-1076.

21. P. I.da S. Maia, A.E. Graminha, F.R. Pavan, C.Q.F. Leite, A.A. Batista, D.F. Back, E.S. Lang,J. Ellena, S. de S. Lemos, H.S. Salistre-de-Araujo, V.M. Deflon, J. Braz. Chem. Soc., 21 (2010) 1177–1186.
22. A.P. Rebolledo, M. Vieites, D. Gambino, O.E. Piro, E.E. Castellano, C.L. Zani, E.M. Souza-Fagundes, L.R. Teixeira, A.A. Batista, H. Beraldo, *J. Inorg. Biochem.*, 99 (2005) 698–706.
23. K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, fourth ed. Wiley, New York, 1986.
24. A. Pérez-Rebolledo, O.E. Piro, E.E. Castellano, L.R. Teixeira, A.A. Batista, H. Beraldo, *J. Mol. Struct.*, 794 (2006) 18–23.
25. B. H. Abdullah, Y. M. Salh, *Oriental Journal of Chemistry*, 26 (2010) 763-773 .
- 26.M. N. Patel, C. R. Patel, H. N. Joshi, P. A. Vekariya, *Appl Biochem Biotechnol*, 172 (2014) 1846–1858.
27. A. M. Plutin, A. Alvarez, R. Mocelo, R. Ramos, E. E. Castellano, M. M. da Silva, L. Colina-Vegas, Fernando R. Pavan, A. A. Batista, *Inorg. Chem. Com.*, 63 (2016) 74-80.
28. B. O'Reilly, A.M. Plutín, H. Pérez, O. Calderón, R. Ramos, R. Martínez, R.A. Toscano, J. Duque, H. Rodríguez-Solla, R.Martínez-Alvarez,M. Suárez, N. Martín, *Polyhedron*, 36 (2010) 133–140.
29. A. L. Matsuo, L. S. Silva, A. C. Torrecilhas, B. S. Pascoalino, T. C. Ramos, E. G. Rodrigues, S. Schenkman, A. C. Caires, L. R. Travassos, *Antimicrob Agents Chemother*, 54 (2010) 3318-3325.
30. T. M. Bastos, M. I. Barbosa, M. M. da Silva, J. W. da C. Júnior, C. S. Meira, E. T. Guimaraes, J. Ellena, D. R. Moreira, A. A. Batista, M. B. Soares, *Antimicrob Agents Chemother*, 58 (2014) 6044-6055.



Synopsis

New complexes of Pd(II) with *N,N*-disubstituted-*N'*-acylthioureas, with general formula $[Pd(dppf)(N,N\text{-disubstituted-}N'\text{-acylthioureaato-}k^2O,S)]PF_6$, (dppf = 1,1-bis(diphenylphosphine) ferrocene) were prepared and characterized by elemental analysis, spectroscopic techniques, and by X-ray crystallography. The structures of complexes show that the ligands are coordinated to the metal through sulfur and oxygen atoms, forming distorted square-planar geometries. The complexes have shown antibacterial activity against Anti-*M. tuberculosis* H37Rv ATCC 27294. Also, the complexes exhibited good antiparasitic activity against *T. cruzi*, while the metal-free thiourea did not.