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Palladium (II) and platinum (II) complexes containing organometallic thiosemicarbazone ligands: Synthesis, characterization, X-ray structures and antitubercular evaluation

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ABSTRACT

A new series of palladium (II) and platinum (II) complexes containing ferrocenyl and cyrhetrenyl thiosemicarbazone ligands were synthesized and characterized. The two-step reaction of the organometallic thiosemicarbazones with i) K_2MCl_4 and ii) PPh_3 and their subsequent recrystallization from CH_2Cl_2/hexane yielded the binuclear complexes [M{$ML_n(\eta^5\text{-}C_5H_4)C(H)$═$NN$═$C(S)NHR$}–$(Cl)(PPh_3)$] (M′═Pd, Pt; ML_n═$Re(CO)_3$, FeCp; R═H, CH_3). The structures of the products were inferred from elemental analyses and IR, ^1H and ^{31}P NMR spectroscopies. The molecular structures of **2b** and **3d** were confirmed by single crystal X-ray analysis. All complexes were screened in vitro against *Mycobacterium tuberculosis* and exhibited only moderate activity in the low micromolar range.

Organic-thiosemicarbazones (TSCs) have been extensively studied for several decades because of their ease of substitution and their capability to act as a ligand for transition metal ions in several bonding modes [1–8]. Regarding the latter, TSCs usually act as a neutral (thione form) or anionic (thiolate form) bidentate ligand by forming five membered chelate rings with the transition metal ion [6,7]. However, there are many reports of other modes of bonding, including the formation of cyclometallated complexes [8].

In recent years, there has been a great interest in the study of not only organic-TSCs but also their corresponding metal complexes because the complexes have a broad range of biological and therapeutic applications [9–14]. Several research groups have focused their studies on the development of new transition metal TSCs-containing compounds to be used (both in vitro and in vivo) as potential antiviral [15], antitumoral [16–19], antiparasital [20,21], antifungal [22,23] and antibacterial agents [24–26].

Among the wide spectrum of bioactivities found for these types of compounds, they have also been extensively reported as inhibitors of *Mycobacterium tuberculosis*, the pathogenic agent of tuberculosis [27–31].

Transition metal complexes involving organic-TSCs have emerged as a new alternative to current therapeutic agents [32–38]. In this regard, we report the synthesis and biological evaluation of cyrhetrenyl and ferrocenyl thiosemicarbazones as potential trypanocidal and antitubercular agents [39]. We found that incorporating organometallic fragments into the thiosemicarbazone scaffold resulted in a complex that exhibited moderate activity against *Trypanosoma cruzi* and *M. tuberculosis* strains. In addition, Chibale and co-workers described the synthesis and antimalarial evaluation of palladium (II), ruthenium (II) and gold (III) complexes containing ferrocenyl thiosemicarbazones [38,40,41]. In all cases, the heterobimetallic complexes exhibited moderate activity against chloroquine-susceptible (NF54) and chloroquine-resistant (Dd2) *Plasmodium falciparum* strains.

To obtain more insight into bioorganometallic compounds with potential biological activity and as part of our ongoing interest in comparing ferrocene and cyrhetrene bioconjugates, we report here the synthesis and characterization of new palladium (II) and platinum (II) complexes containing cyrhetrenyl TSCs (**2a–d**) and ferrocenyl TSCs (**3c–d**). We have also prepared previously reported palladium complexes of ferrocenyl TSCs (**3a–b**) [36] for comparative purposes.

The organometallic thiosemicarbazone ligands [39] and Pd(II) complexes (**3a–b**) [36] were prepared as previously reported. The new palladium (II) (**2a**–**b**) and platinum (II) complexes (**2c–d**, **3c–d**)

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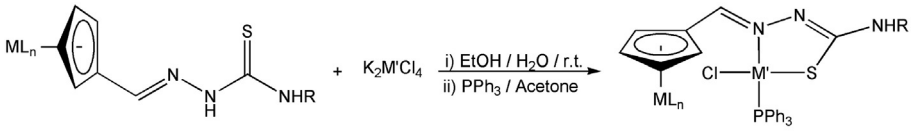

Compound	MLn	M`	R
2a	$Re(CO)_3$	Pd	H
2b	$Re(CO)_3$	Pd	CH_3
2c	$Re(CO)_3$	Pt	H
2d	$Re(CO)_3$	Pt	CH_3
3a	$Fe(\eta^5\text{-}C_5H_5)$	Pd	H
3b	$Fe(\eta^5\text{-}C_5H_5)$	Pd	CH_3
3c	$Fe(\eta^5\text{-}C_5H_5)$	Pt	H
3d	$Fe(\eta^5\text{-}C_5H_5)$	Pt	CH_3

Scheme 1. Synthesis of palladium (II) and platinum (II) complexes containing organometallic thiosemicarbazone.

were synthesized following a modification of the procedure described by Smith and co-workers [41] (Scheme 1).

All compounds were obtained in moderate yields (45–55%). The compounds were air-stable and soluble in most common organic solvents. Spectroscopic techniques, such as FT-IR and NMR, and elemental analyses were used to verify the nature of the compounds (Supplementary material).

The FT-IR spectra of the complexes indicated a shift of the ν(C═N) band to a lower wavenumber than that of the ν(C═N) band in the free ligand [39]. In addition, the absence of both the ν(C═S) stretching vibration and the ν(N–H) vibrations in the spectra of compounds 3a–d confirmed the coordination of organometallic thiosemicarbazone to the metal atom [42]. For all compounds, the ^{1}H NMR spectra indicated the presence of a single compound. In the case of the Pd(II) and Pt(II) complexes containing cyrhetrenyl thiosemicarbazone ligands (**2a–d**), the two triplets observed at 6.2–6.3 ppm were assigned to the hydrogen nuclei of the substituted ring. For the complexes (**3a–d**), the typical pattern of the ferrocenyl group was observed: a singlet at 4.0–4.2 ppm and two triplets at 4.4–5.1 ppm. These peaks were assigned to the C_5H_5 and C_5H_4 rings, respectively [36,38].

It is important to note that the resonances of the imine groups (8.25–8.66 ppm) in the complexes **3a–d** were shifted downfield compared with the signals of the corresponding organometallic TSC free ligand ($\Delta\delta = 0.8$). This observation is in agreement with previously reports [36,38] and indicates the coordination of imine nitrogen atom to the metal centre. In addition, the imine resonances were observed as a doublet ($^4J_{HP}$ ~ 3.90 Hz) as a consequence of phosphorus–proton coupling (due to the *trans* stereochemistry of the phosphine and imine nitrogen in a square planar geometry). This phenomenon is consistent with the "transphobic effect" [43]. As expected in all cases, the ^{31}P–{^{1}H} NMR spectra exhibited a single resonance for the phosphorus nuclei, attesting to the purity of these complexes. According to literature reports, the absence of the resonance for the N–NH–C═S moiety (expected to occur at approximately 9.0 ppm) is further proof that the organometallic TSCs are coordinated under the anionic thiolate form [36–38].

Suitable crystals of **2b** and **3d** were obtained by slowly diffusing hexane into dichloromethane. A full description of the crystal data, data collection and refinement parameters are given in the Supplementary material. Figs. 1 and 2 show the ORTEP view of the structure of each compound, including some selected bond distances and angles. The crystal structures were comparable to those characterized by Vila for **3a** and **3b** [36]. In both cases, the molecular structures for **2b** and **3d** display a distorted square planar geometry with the palladium (II) or platinum (II) centre. The metal centre is coordinated to an iminic nitrogen atom, a thioamide sulphur atom of the deprotonated thiosemicarbazone ligand, a chlorine atom (*trans* to S), and a phosphorus atom from the triphenylphosphine ligand. The bond angles between adjacent coordinated atoms are approximately 90°: the values range between 82.30(4) and 96.40(4)°. The S–C and C–N bond lengths in the chelate ring [S(1)–C(10) 1.780(3); N(2)–C(10) 1.310(3) Å, **2b**; S(1)–C(12) 1.747(10); N(1)–C(12)

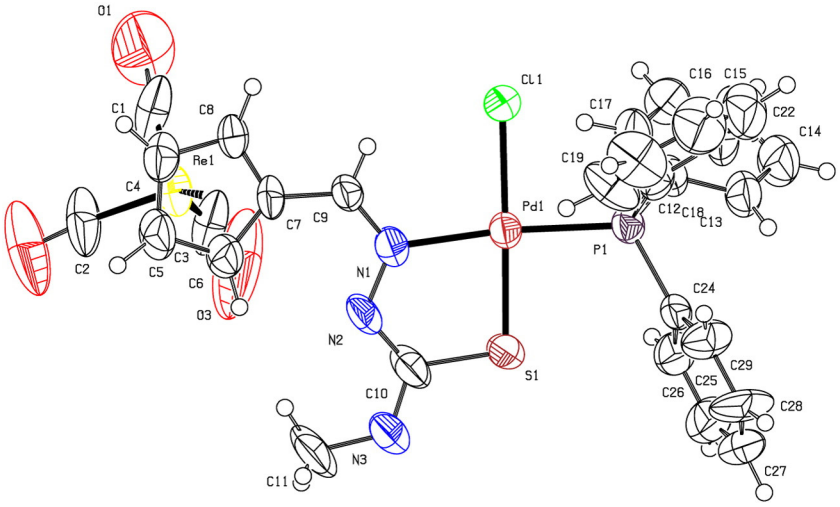

Fig. 1. Molecular structure of **2b**. Selected bond lengths (Å) and bond angles (°): Pd(1)–N(1) 2.115(14); Pd(1)–Cl(1) 2.341(5); Pd(1)–P(1) 2.260(5); Pd(1)–S(1) 2.237(5); S(1)–C(10) 1.780(3); N(2)–C(10) 1.310(3); N(1)–C(9) 1.312(19); N(1)–Pd(1)–Cl(1) 96.40(4); N(1)–Pd(1)–S(1) 82.30(4); N(1)–Pd(1)–P(1) 172.20(5); P(1)–Pd(1)–S(1) 92.42(18); Cl(1)–Pd(1)–S(1) 178.54(19); Cl(1)–Pd(1)–P(1) 88.89(17).

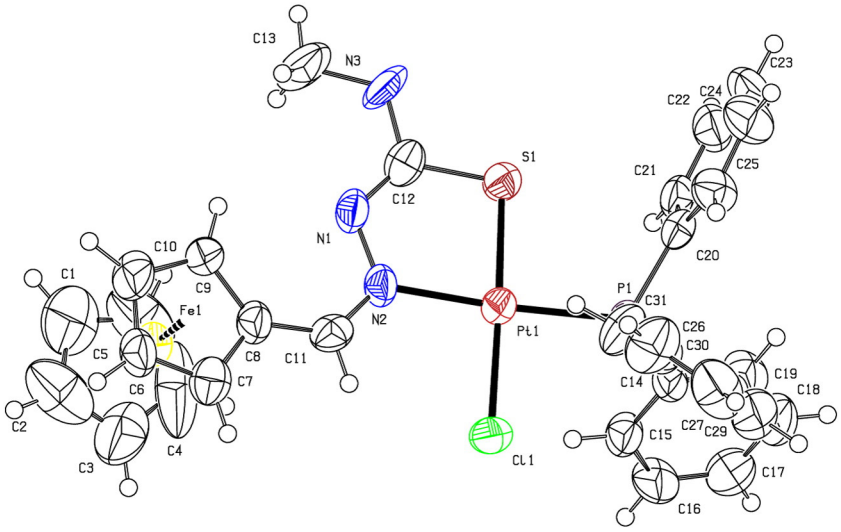

Fig. 2. Molecular structure of **3d**. Selected bond lengths (Å) and bond angles (°): Pt(1)–N(2) 2.104(7); Pt(1)–Cl(1) 2.339(2); Pt(1)–P(1) 2.237(3); Pt(1)–S(1) 2.248(2); N(2)–C(11) 1.263(11); S(1)–C(12) 1.747(10); N(1)–C(12) 1.292(12); N(2)–Pt(1)–Cl(1) 94.40(2); N(2)–Pt(1)–S(1) 83.80(2); N(2)–Pt(1)–P(1) 173.10(2); P(1)–Pt(1)–S(1) 93.97(10); Cl(1)–Pt(1)–S(1) 178.08(10); Cl(1)–Pt(1)–P(1) 87.89(10).

1.292(12) Å, **3d**] are consistent with an increased single and double bond character, respectively. Based on these bond lengths, the chelation of organometallic-TSCs in the thiolate form was confirmed.

Finally, the synthesized derivatives were evaluated against *M. tuberculosis* using the mc^{2}7000 strain (Supplementary material). Table 1 shows the minimal inhibitory concentrations (MIC_{99}). Isoniazid was used as the control drug in this study. All compounds presented MIC_{99} values in the micromolar range (Table 1). The palladium (II) complexes **2a–b** and **3a–b** (MIC = 6.0–29.0 μM) had higher activities than did their platinum (II) analogues **2c–d** and **3c–d** (MIC = 11.0–32.0 μM). In addition, complexes containing cyrhetrenyl-TSC ligands (**2a–d**) are more potent than are the complexes with ferrocenyl-TSCs (**3a–d**). This behaviour can be associated with the electron withdrawing properties and better lipophilicity of the cyrhetrenyl moiety present in **2a–d** compared with the analogous ferrocenyl moieties in compounds **3a–d**. We previously reported similar conclusions in quinoline, nitrofurane, chalcone and benzimidazole series containing these groups [44–47]. However, none of the complexes proved to be more potent than that of the front-line drug isoniazid.

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Appendix A. Supplementary material

Electronic Supplementary Information (ESI) available: Synthesis, characterization data, in vitro anti-tubercular evaluation and X-ray crystal structure determinations. CIF files containing tables of crystallographic parameters, bond distances, bond angles, as well as a list of structure factors have been deposited in the Cambridge Crystallographic Data Centre (CCDC nos. 1043655 and 1043654 for **2b** and **3d**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html; from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or via e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.inoche.2015.03.036.

Table 1
In vitro activity against *M. tuberculosis* strain mc^{2}7000.

Compound	MIC_{99} (in μM)
2a	6–24
2b	6–23
2c	11–27
2d	11–27
3a	7–29
3b	7–28
3c	13–32
3d	13–32
Isoniazid	0.4

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