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Synthesis and Characterization of Amine-Functionalized Thiosemicarbazone Cyclopalladated Compounds †

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Abstract: Differences in the functional groups of the ligands can change the properties of the cyclometallated compounds and modify their suitability for various applications, such as catalysis and biomedicine. Herein, we report the synthesis and characterization of a new series of cyclometallated palladium compounds bearing an amine-functionalized thiosemicarbazone. The synthesis of the ligands was achieved by condensation of the thiosemicarbazide and aminoacetophenone. The reaction of the ligands with an appropriate metallating agent gave rise to the tetranuclear cyclometallated compounds. The compounds were characterized by EA, ^{1}H-NMR and IR spectroscopy.

Keywords: thiosemicarbazone; palladium; cyclometallation

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1. Introduction

Palladacycles have shown a wide variety of applications in recent years. The ubiquity of these compounds in practical approaches is proof of the versatility and effectiveness of the cyclometallated moiety. The challenges are the low solubility of the compounds in aqueous media and their dependence on the use of organic solvents, which are main contributors of waste in industry, e.g., the pharmaceutical industry, where solvent use has an environmental impact because of the energy needed for the evaporation, cooling, heating, and extraction of organic solvents [1]. This has motivated a change in the use of metal catalysts to a more sustainable chemistry [2] that can be achieved by the exploration of different organometallic compounds.

Functional groups can be included in palladacycles, modifying their properties and their suitability for these and other applications [3]. In a recently published work, we explored the effect of different substituents in the chemotherapeutic effect of thiosemicarbazone palladacycles [4].

Thiosemicarbazones show intrinsic properties in a wide variety of biological applications, including antiplasmodial [5] and antinocinoceptive [6] applications. Their cyclometallated derivatives have been studied in the past, but their potential as drugs keeps expanding in antiplasmodic [7], antiprotozoic [8], and anticancer [9,10] research.

Herein, we report the synthesis and characterization of a new series of cyclometallated palladium compounds bearing an amine-functionalized thiosemicarbazone. The synthesis of the ligands was achieved by condensation of the thiosemicarbazide and aminoacetophenone. Reaction of the ligands with an appropriate metallating agent gave rise to the tetranuclear cyclometallated compounds.

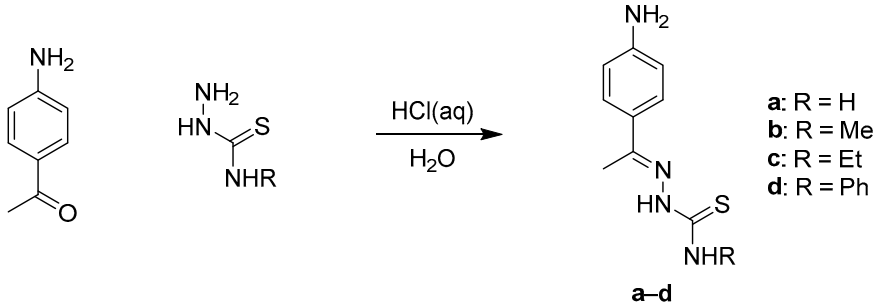
The compounds were characterized by EA, ^{1}H-NMR, and IR spectroscopy.

2. Materials and Methods

Reagents and solvents were used as received.

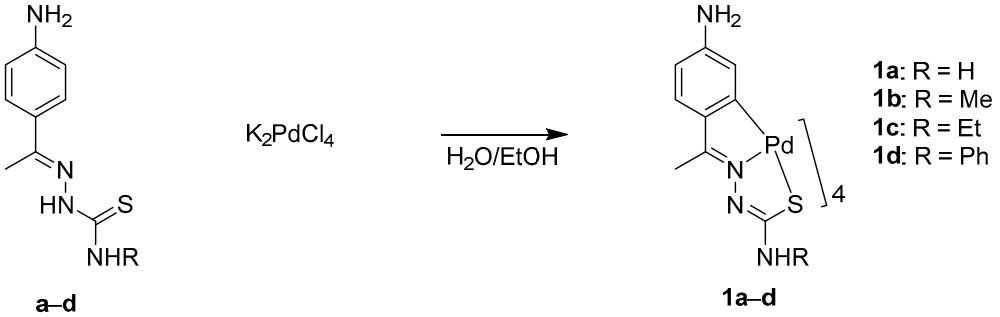
The synthesis of the ligands is achieved by the condensation reaction of *p*-aminoacetophenone and the corresponding 4-substituted thiosemicarbazide.

First, the thiosemicarbazide (3.7 mmol, 1 equiv.) was dissolved in acidified water. Then, the *p*-aminoacetophenone (500 mg, 3.7 mmol.) was added with stirring, at which point it was possible to observe the precipitation of a white solid. The reaction mixture was stirred overnight, and the precipitate was filtered off and washed with cold water, dried under vacuum, and stored.



The metalating agent of choice is potassium tetrachloropalladate.

Potassium tetrachloropalladate (75 mg, 0.23 mmol) was dissolved in a small amount of water (*ca.* 2 cm^3). The solution was added dropwise to stirred ethanol, forming a suspension. Then, the thiosemicarbazone ligand (0.23 mmol, 1 equiv.) was added to the suspension. The reaction mixture was stirred for 24 h, at which point water was added and a solid is formed. The solid was separated by centrifugation and then washed with cold water.



Ligands **a**–**d** and compounds **1a**–**d** were characterized by EA, IR, and ^{1}H-NMR. NMR spectra were recorded in deuterated DMSO.

3. Discussion

3.1. NMR

The NMR spectra of the ligands show signals characteristic for the thiosemicarbazone moiety (e.g., Figure 1). The hydrazinic proton is assigned to the down field signal *ca.* 10 ppm, which is a singlet. The AA′XX′ system appears as a pair of apparent doublets in the aromatic region of the spectra, as expected. The NHR proton resonance can change its shift depending on the substituent. For the phenyl group, the signal appears deshielded *ca.* 10 ppm, in close proximity to the hydrazinic proton, whereas the alkyl substituents change field and the multiplet appears *ca.* 8 ppm. In the case of the amide, there are two signals for the non-equivalent protons.

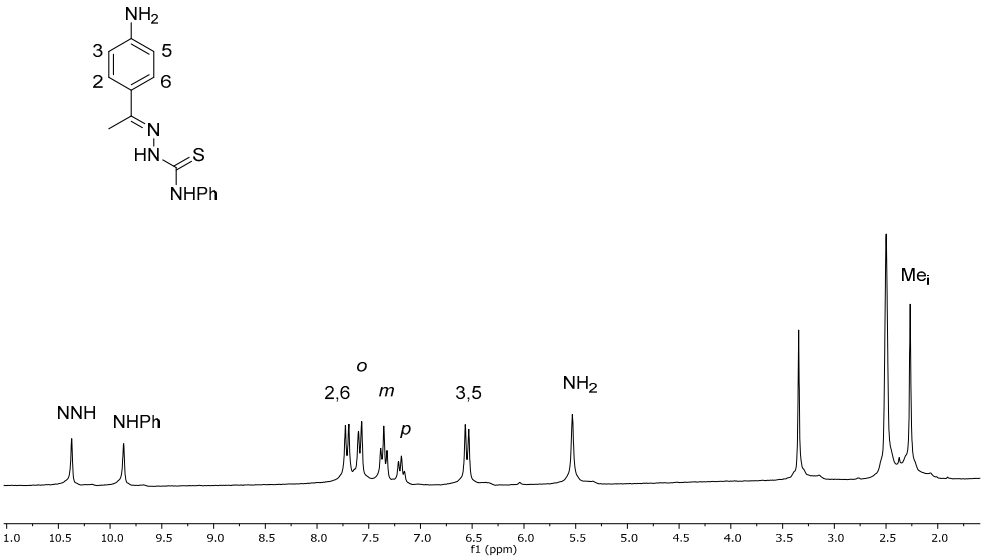


Figure 1. ^{1}H-NMR spectrum of compound **d** in DMSO.

The signals for the remaining thiosemicarbazone ligands are assigned in Table 1.

Table 1. Assignation of the NMR signals of compounds **a**–**d**.

	a	**b**	**c**	**d**
NNH	10.06 (s, 1H)	9.99 (s, 1H)	9.89 (s, 1H)	9.87 (s, 1H)
NHR	8.16 (s, 1H)	8.30 (s, 1H)	8.32 (t, *J* = 6.0 Hz, 1H)	10.37 (s, 1H)
NH_2	5.52 (s, 2H)	5.50(s, 2H)	5.48 (s, 2H)	5.53 (s, 2H)
H2/H6	7.72 (d, *J* = 8.3 Hz, 2H)	7.68 (d, *J* = 8.4 Hz, 2H)	7.63 (d, *J* = 8.3 Hz, 2H)	7.71 (d, *J* = 8.3 Hz, 2H)
H3/H5	6.70 (d, *J* = 8.2 Hz, 2H)	6.63 (d, *J* = 8.4 Hz, 2H)	6.54 (d, *J* = 8.4 Hz, 2H)	6.55 (d, *J* = 8.4 Hz, 2H)
R	7.79 (s, 1H)	3.01 (s, 3H)	3.59 (p, *J* = 6.9 Hz, 2H) 1.13 (t, *J* = 7.0 Hz, 3H)	7.58 (d, *J* = 7.8 Hz, 2H) 7.35 (t, *J* = 7.6 Hz, 2H) 7.18 (t, *J* = 7.3 Hz, 1H)
Me	2.20 (s, 3H)	2.18 (s, 3H)	2.18 (s, 3H)	2.27 (s, 3H).

Cyclometallation is evidenced in the NMR spectra of the products **1a**–**d** by the changes in the signals in the aromatic region (e.g., Figure 2). The aromatic AA′XX′ system of the ligands disappears due to the metallation in the 6 position, changing the multiplicity and shift of the remaining protons. The H5 signal appears as a singlet or as a small *J* doublet while those for H2 and H3 change to a pair of coupled doublets, as can be seen in Table 2.

Table 2. Assignation of the NMR signals of compounds **1a**–**d**.

	1a	**1b**	**1c**	**1d**
NHR	6.37 (s, 2H)	6.64 (s, 1H)	6.66 (s, 1H)	9.04 (s, 1H)
NH_2	5.43 (s, 2H)	5.44 (s, 2H)	5.41 (s, 2H)	5.62 (s, 2H)
H2	6.82 (d, *J* = 8.1 Hz, 1H)	6.84 (d, *J* = 8.2 Hz, 1H)	6.84 (d, *J* = 8.1 Hz, 1H)	6.95 (d, *J* = 8.2 Hz, 1H)
H3	6.14 (d, *J* = 8.1 Hz, 1H)	6.15 (d, *J* = 8.2 Hz, 1H)	6.16 (dd, *J* = 8.2, 2.1 Hz 1H)	6.18 (dd, *J* = 8.2, 2.1 Hz 1H)
H5	6.76 (s, 1H)	6.78 (s, 1H)	6.79 (d, *J* = 2.0 Hz, 1H)	6.81 (d, *J* = 2.1 Hz, 1H)
R	-	2.74 (s, 3H)	3.19 (p, *J* = 6.9 Hz, 2H) 1.07 (t, *J* = 7.1 Hz, 3H)	7.65 (d, *J* = 8.1 Hz, 2H) 7.23 (t, *J* = 7.7 Hz, 2H) 6.88 (t, *J* = 7.3 Hz, 1H)
Me	2.12 (s, 3H)	2.17 (s, 3H)	2.17 (s, 3H)	2.30 (s, 3H)

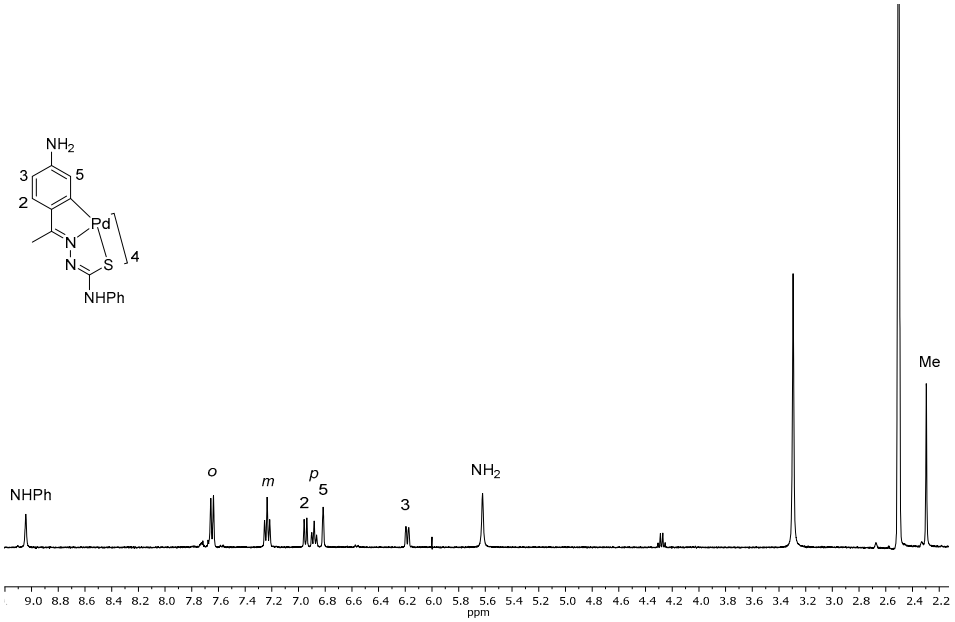


Figure 2. ^{1}H-NMR spectrum of compound **1d** in DMSO.

3.2. IR Spectroscopy

The IR spectroscopic data for the ligands and their corresponding cyclometallated compounds show a shift in the position of the ν(C=N) band corresponding to the iminic group (Table 3). The magnitude of this shift confirms coordination through the nitrogen lone pair. Moreover, the ν(C=S) band is missing in the palladacycles due to coordination in thiol form. Bands assignable to the N-H stretch can also be observed around 3300–3000 cm^{-1}.

Table 3. Summary of the main bands that experience changes due to the metalation.

	ν(C=N)	Δ(ν(C=N))	ν(C=S)
a	1596	-	829
b	1594	-	830
c	1597	-	831
d	1591	-	830
1a	1572	24	-
1b	1571	23	-
1c	1576	21	-
1d	1567	24	-

4. Results

The main results of the study are summarized in Table 4.

Table 4. Summary of the experimental data.

Compound	Yield%	IR/cm^{-1}	EA Found (Calcd)	RMN
a	93	3304, 3210, 2971, 2950, 2932 ν(N-H) 1596 ν(C=N) 829 ν(C=S)	C, 52.0; H, 5.7; N, 26.8; S, 15.2 (C, 51.9; H, 5.8; N, 26.9; S, 15.4)	^{1}H NMR (250 MHz, DMSO-d_6) δ 10.06 (s, 1H, NN*H*), 8.16 (s, 1H, NH_2), 7.79 (s, 1H, NH_2), 7.72 (d, *J* = 8.3 Hz, 2H, H2/H6), 6.70 (d, *J* = 8.2 Hz, 2H, H3/H5), 2.20 (s, 3H, Me)
b	95	3302, 3207, 2945 ν(N-H) 1594 ν(C=N) 830 ν(C=S)	C, 53.8; H, 6.6; N, 25.1; S, 14.3 (C, 54.0; H, 6.4; N, 25.2; S, 14.4)	^{1}H NMR (250 MHz, DMSO-d_6) δ 9.99 (s, 1H, NNH), 8.30 (s, 1H, NHMe), 7.68 (d, *J* = 8.4 Hz, 2H, H2/H6), 6.63 (d, *J* = 8.4 Hz, 2H, H3/H5), 3.01 (s, 3H, NHMe), 2.18 (s, 3H, Me)

Table 4. *Cont.*

Compound	Yield%	IR/cm^{-1}	EA Found (Calcd)	RMN
c	94	3300, 3205, 2969, 2944, 2928 ν(N-H) 1597 ν(C=N) 831 ν(C=S)	C, 55.6; H, 6.9; N, 23.5; S, 13.4 (C, 55.9; H, 6.8; N, 23.7; S, 13.6)	^{1}H NMR (250 MHz, DMSO-d_6) δ 9.89 (s, 1H, NN*H*), 8.32 (t, *J* = 6.0 Hz, 1H, N*H*Et), 7.63 (d, *J* = 8.3 Hz, 2H, H2/H6), 6.54 (d, *J* = 8.4 Hz, 2H, H3/H5), 5.48 (s, 2H, NH_2), 3.59 (p, *J* = 6.9 Hz, 2H, CH_2), 2.18 (s, 3H, Me), 1.13 (t, *J* = 7.0 Hz, 3H, CH_3).
d	98	3355, 3279, 3182 ν(N-H) 1591 ν(C=N) 830 ν(C=S)	C, 63.1; H, 5.6; N, 19.6; S, 11.2 (C, 63.4; H, 5.7; N, 19.7; S, 11.3)	^{1}H NMR (250 MHz, DMSO-d_6) δ 10.37 (s, 1H, N*H*Ph), 9.87 (s, 1H, NN*H*), 7.71 (d, *J* = 8.3 Hz, 2H/H6, H2), 7.58 (d, *J* = 7.8 Hz, 2H, *o*-Ar), 7.35 (t, *J* = 7.6 Hz, 2H, *m*-Ar), 7.18 (t, *J* = 7.3 Hz, 1H, *p*-Ar), 6.55 (d, *J* = 8.4 Hz, 2H, H3/H5), 5.53 (s, 2H, NH_2), 2.27 (s, 3H, Me).
1a	89	3324, 3162, 2912 ν(N-H) 1572 ν(C=N)	C, 34.8; H, 3.3; N, 18.0; S, 10.4 (C, 34.6; H, 3.2; N, 17.9; S, 10.3)	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (d, *J* = 8.1 Hz, 1H, H2), 6.76 (s, 1H, H5), 6.37 (s, 2H, NH_2), 6.14 (d, *J* = 8.1 Hz, 1H, H3), 5.43 (s, 2H, NH_2), 2.12 (s, 3H, Me).
1b	91	3334, 3176, 2912 ν(N-H) 1571 ν(C=N)	C, 36.5; H, 3.5; N, 17.1; S, 9.6 (C, 36.8; H, 3.7; N, 17.2; S, 9.8)	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, *J* = 8.2 Hz, 1H, H2), 6.78 (s, 1H, H5), 6.64 (s, 1H, N*H*R), 6.15 (d, *J* = 8.2 Hz, 1H, H3), 5.44 (s, 2H, NH_2), 2.74 (s, 3H, CH_3), 2.17 (s, 3H, Me)
1c	86	3307, 3150, 2914 ν(N-H) 1576 ν(C=N)	C, 38.7; H, 4.0; N, 16.2; S, 9.2 (C, 38.8; H, 4.1; N, 16.4; S, 9.4)	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, *J* = 8.1 Hz, 1H, H2), 6.79 (d, *J* = 2.0 Hz, 1H, H5), 6.66 (s, 1H, N*H*Et), 6.16 (dd, *J* = 8.2, 2.1 Hz 1H, H3), 5.41 (s, 2H, N*H*$_2$), 3.19 (p, *J* = 6.9 Hz, 2H, CH_2), 2.17 (s, 3H, Me), 1.07 (t, *J* = 7.1 Hz, 3H, CH_3).
1d	94	3360, 3200, 3022, 2914 ν(N-H) 1567 ν(C=N)	C, 46.5; H, 3.5; N, 14.3; S, 8.1 (C, 46.3; H, 3.6; N, 14.4; S, 8.3)	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H, N*H*Ph), 7.65 (d, *J* = 8.1 Hz, 2H, *o*-Ar), 7.23 (t, *J* = 7.7 Hz, 2H, *m*-Ar), 6.95 (d, *J* = 8.2 Hz, 1H, H2), 6.88 (t, *J* = 7.3 Hz, 1H, *p*-Ar), 6.81 (d, *J* = 2.1 Hz, 1H, H5), 6.18 (dd, *J* = 8.2, 2.1 Hz 1H, H3), 5.62 (s, 2H, NH_2), 2.30 (s, 3H, Me).

5. Conclusions

A new family of thiosemicarbazone cyclometallated compounds bearing the amine functional group has been satisfactorily synthesized and characterized.

The amine group is not affected by metallation and does not hinder the synthesis of the cyclometallated compounds.

The IR analysis confirms the thione form in solid state of the thiosemicarbazone ligand and the coordination to the palladium center in thiolic form, while the NMR analysis confirms the *ortho*-metalation of the phenyl ring, confirming the proposed structure of the compounds.

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References

1. Clarke, C.J.; Tu, W.C.; Levers, O.; Bröhl, A.; Hallett, J.P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* **2018**, *118*, 747–800. [CrossRef]
2. Hayler, J.D.; Leahy, D.K.; Simmons, E.M. A Pharmaceutical Industry Perspective on Sustainable Metal Catalysis. *Organometallics* **2019**, *38*, 36–46. [CrossRef]
3. Vila, J.M.; Pereira, M.T.; Lucio-Martínez, F.; Reigosa, F. Palladacycles as Efficient Precatalysts for Suzuki-Miyaura Cross-Coupling Reactions. In *Palladacycles*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 1–20. [CrossRef]
4. Reigosa-Chamorro, F.; Raposo, L.R.; Munín-Cruz, P.; Pereira, M.T.; Roma-Rodrigues, C.; Baptista, P.V.; Fernandes, A.R.; Vila, J.M. In Vitro and in Vivo Effect of Palladacycles: Targeting A2780 Ovarian Carcinoma Cells and Modulation of Angiogenesis. *Inorg. Chem.* **2021**, *60*, 3939–3951. [CrossRef] [PubMed]
5. Khanye, S.D.; Gut, J.; Rosenthal, P.J.; Chibale, K.; Smith, G.S. Ferrocenylthiosemicarbazones conjugated to a poly(propyleneimine) dendrimer scaffold: Synthesis and in vitro antimalarial activity. *J. Organomet. Chem.* **2011**, *696*, 3296–3300. [CrossRef]
6. Moreira, D.R.M.; Santos, D.S.; do Espírito Santo, R.F.; dos Santos, F.E.; de Oliveira Filho, G.B.; Leite, A.C.L.; Soares, M.B.P.; Villarreal, C.F. Structural improvement of new thiazolidinones compounds with antinociceptive activity in experimental chemotherapy-induced painful neuropathy. *Chem. Biol. Drug Des.* **2017**, *90*, 297–307. [CrossRef]
7. Adams, M.; Barnard, L.; de Kock, C.; Smith, P.J.; Wiesner, L.; Chibale, K.; Smith, G.S. Cyclopalladated organosilane-tethered thiosemicarbazones: Novel strategies for improving antiplasmodial activity. *Dalt. Trans.* **2016**, *45*, 5514–5520. [CrossRef] [PubMed]
8. Cipriani, M.; Toloza, J.; Bradford, L.; Putzu, E.; Vieites, M.; Curbelo, E.; Tomaz, A.I.; Garat, B.; Guerrero, J.; Gancheff, J.S.; et al. Effect of the metal ion on the anti T. cruzi activity and mechanism of action of 5-nitrofuryl-containing thiosemicarbazone metal complexes. *Eur. J. Inorg. Chem.* **2014**, *2014*, 4677–4689. [CrossRef]
9. Kovala-Demertzi, D.; Galani, A.; Miller, J.R.; Frampton, C.S.; Demertzis, M.A. Synthesis, structure, spectroscopic studies and cytotoxic effect of novel palladium(II) complexes with 2-formylpyridine-4-Nethyl-thiosemicarbazone: Potential antitumour agents. *Polyhedron* **2013**, *52*, 1096–1102. [CrossRef]
10. Matesanz, A.I.; Hernández, C.; Rodríguez, A.; Souza, P. 3,5-Diacetyl-1,2,4-triazol bis(4N-substituted thiosemicarbazone) palladium(II) complexes: Synthesis, structure, antiproliferative activity and low toxicity on normal kidney cells. *J. Inorg. Biochem.* **2011**, *105*, 1613–1622. [CrossRef] [PubMed]