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Cyclopalladated complexes containing tridentate thiosemicarbazone ligands of biological significance: Synthesis, structure and antimalarial activity

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ABSTRACT

The C–H activation reaction of two aryl-derived thiosemicarbazones with $K_2[PdCl_4]$ affords tetranuclear cyclopalladated complexes (**3** and **4**) where the thiosemicarbazone ligand acts as a tridentate donor [C,N,S] coordinated to palladium via the *ortho*-carbon of the aryl ring, imine nitrogen and thiolato sulfur. The palladium–sulfur bridging coordination bonds give rise to a Pd_4S_4 core. These $Pd-S_{bridging}$ bonds were cleaved with a variety of mono- and bis-phosphines to give a series of mono, di and tetranuclear organopalladium complexes (**5**–**12**) where the phosphorus atom coordinates to palladium *trans* to the imine nitrogen. All of the complexes were fully characterized using various analytical and spectroscopic techniques. These palladium complexes along with their free ligands were evaluated as bioorganometallic antimalarial agents against two *Plasmodium falciparum* strains, 3D7 (chloroquine sensitive) and K1 (chloroquine and pyrimethamine resistant). Some of the complexes were found to be moderate inhibitors of parasite growth and were more active than the corresponding free ligand.

1. Introduction

The use of thiosemicarbazones (TSCs) as potential chemotherapeutics is an active area of research. These Schiff-base type compounds are noted for their pharmacological properties, particularly as antiparasitic [1–6], antibacterial [7–9] and antitumoral agents [10–14]. As anticancer agents, it is believed that their mechanism of action is through the inhibition of ribonucleotide reductase [15]. The thiourea moiety contains several donor atoms (Fig. 1) and is thus capable of acting as a multidentate ligand toward a metal. It is believed that the metal chelating abilities partially account for their biological activity and numerous studies on the biological activity of TSC metal complexes have been published [16–22].

The study of the coordination chemistry of thiosemicarbazones has long been of interest with the earliest review being published in 1974 [23]. Since then there have been extensive reports on the synthesis of thiosemicarbazone complexes with metals including vanadium [24,25], zinc [26], cobalt [27], gold [28], nickel [22,29], silver [30], copper [31–33] and iron [34]. Varying the substituents of the C_2 carbon of thiosemicarbazone ligands influences their bonding mode to the metal. If the substituent contains a donor atom such as nitrogen and oxygen, it is possible for the thiosemicarbazone ligand to bond to a metal in a tridentate manner. Cyclopalladated complexes with tridentate thiosemicarbazones prepared via C–H activation of an alkyl or aryl group of the C_2 carbon have also been previously described [35–38].

The antiplasmodial activity of thiosemicarbazones against *Plasmodium falciparum* strains has been reported [1,4,39–42]. These compounds are in part believed to affect processes associated with haemoglobin (Hb) digestion in the food vacuole of the parasite through several possible inhibitory mechanisms of action. As a metal chelator which can coordinate endogenous metals such as Fe(III), thiosemicarbazones can inhibit the growth of the malaria parasite by withholding it from metal dependent enzymes such as ribonucleotide reductase and enzymes in the heme biosynthetic pathway [4,42]. Alternatively, the resulting complexes could inhibit cysteine proteases which effectively would be an enhancement of the natural inhibitory effect of endogenous metals on the protease catalytic site [43]. Another possible mechanism of cysteine protease inhibition would be by nucleophilic attack of the active cysteine thiol (in the thiolate form) onto the electrophilic (thione and/or imine carbon) centres. All of the above inhibitory mechanisms would compromise the parasite's ability to degrade host haemoglobin required for (parasite) protein synthesis [44–47].

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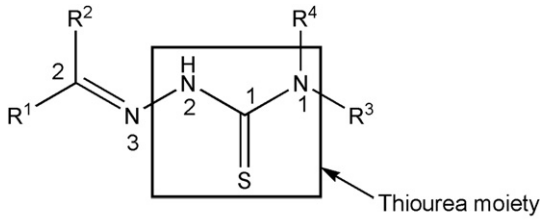


R^1 = aryl, alkyl, heterocyclic group
R^2 = H, aryl, alkyl group
R^3 = H, alkyl, aryl, heterocyclic group
R^4 = H, alkyl, aryl, heterocyclic group

Fig. 1. General structure of thiosemicarbazones.

Reports on the use of thiosemicarbazone metal complexes as antimalarial agents are sparse. Copper(II), nickel(II) and iron(II) complexes of 2-acetyl pyridine derived thiosemicarbazones have been screened for antimalarial activity [33]. The Cu(II) and Fe(II) complexes were found to exhibit modest activity compared to their free ligands while the Ni(II) complexes showed no activity. Within our group, there is ongoing investigations into the biological application of tridentate Pd(II) thiosemicarbazone complexes [48,49]. Our previous work focused on the use of [O,N,S] salicylaldiminato thiosemicarbazone palladium(II) complexes [49] and we have now turned our attention toward potentially tridentate [C,N,S] thiosemicarbazone ligands and their palladium complexes. To the best of our knowledge, ours are the first studies of cyclopalladated thiosemicarbazone complexes as antimalarial agents.

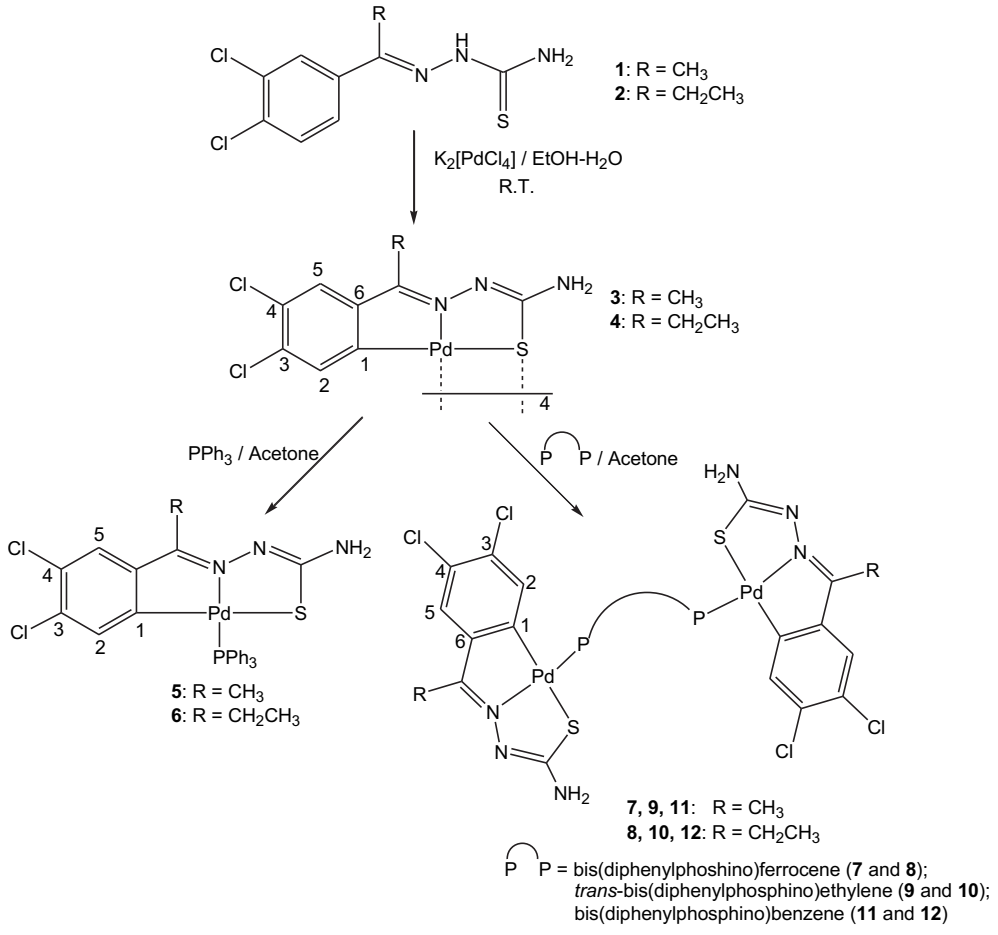
Herein, we report the synthesis, structural characterisation and antimalarial study of organometallic mono, di and tetranuclear [C,N,S] Pd(II) complexes from two thiosemicarbazone ligands which have been shown to exhibit biological activity[5,6,50–52]. The known ligands have been screened previously for activity as antivirals [51], anticonvulsants [50] and antiparasitics [5,6,52]. The objective of our study was to determine if coordination of these compounds to palladium enhances their inhibitory effects and to ascertain if the number of thiosemicarbazone Pd(II) complex moieties per molecule would increase antiplasmodial activity.

2. Results and discussion

2.1. Synthesis and characterisation of thiosemicarbazone ligands and their tridentate [C,N,S] Pd(II) complexes

The thiosemicarbazone ligands, 3,4-dichloroacetophenone thiosemicarbazone (**1**) and 3,4-dichloropropiophenone thiosemicarbazone (**2**), are known compounds and were prepared using the reported method [6]. The appropriate aryl aldehyde was condensed with thiosemicarbazide in methanol or ethanol in the presence of acetic acid as Lewis acid catalyst. Each ligand was isolated as a white solid and the spectroscopic data agreed with the reported literature [6].

Treatment of each ligand with a suspension of potassium tetrachloropalladate in deoxygenated ethanol and water gave the



Scheme 1.

tetrameric compounds **3** and **4** (Scheme 1) where the thiosemicarbazone ligand acts as a dinegative tridentate donor to palladium via the *ortho*-carbon, imine nitrogen and thiolate sulfur. Palladium–sulfur bridging bonds form a Pd_4S_4 core thus producing a tetranuclear complex. Cleavage of these bridging bonds was achieved by reaction with PPh_3 (1:4 tetramer:phosphine molar ratio) or with diphosphines (1:2 tetramer:phosphine molar ratio) in dry, deoxygenated acetone yielding mono (**5** and **6**) and dimeric (**7**–**12**) complexes respectively. Thiosemicarbazone Pd(II) complexes containing bisphosphino ligands have previously been published [53,54]. These reports however only described the synthesis of these complexes and to our knowledge this is the first report on their application as biological agents.

Each complex was isolated as an air- and moisture-stable amorphous yellow solid with high thermal stability. The ^{1}H NMR spectra for compounds **3** and **4** showed only two singlets in the aromatic region and integrated for one proton each, supporting palladation of the *ortho*-carbon upon loss of the proton. The absence of a signal corresponding to the hydrazinic proton in the proton NMR spectra for **3** and **4** corroborates coordination of sulfur to palladium in the thiolato form and formation of a new imine bond upon deprotonation of the hydrazinic nitrogen [37,55]. The amino, $-NH_2$, protons of the coordinated TSC ligand for each of the phosphine containing compounds **5**–**12** occur as a singlet in each spectrum between 6.79 and 6.99 ppm. These resonances are slightly upfield compared to their tetrameric precursors **3** and **4**, where these protons are observed as singlets at 7.17 and 7.11 ppm respectively. This slight shielding may be due to increased electron density around the metal and hence greater electron distribution over the ligand due to back-bonding between the metal and coordinated phosphorus.

The cyclopentadienyl (Cp) protons of the bis(diphenylphosphino) ferrocene (dppf) bridging ligand for compounds **7** and **8** resonate as two broad signals between 4.50 and 5.10 ppm, the downfield peak is assigned to the protons α to the carbon–phosphorus bond. For compound **9**, the alkene protons of the *trans*-bis(diphenylphosphino) ethylene (dppe) ligand are assigned to a multiplet occurring between 7.28 and 7.33 ppm. A similar shift is observed for these protons in the spectrum for compound **10**. However, this signal overlaps with the resonance assigned to H-2 of the TSC aromatic ring. The resonances of the phenyl protons of the bridging benzene ring in the bis(diphenylphoshino)benzene (dppb) ligand in compound **11** overlaps with the multiplets for the PPh_2 protons. For compound **12**, these protons are clearly observed downfield from the PPh_2 protons as a multiplet between 7.71 and 7.75 ppm.

In the $^{13}C\{^1H\}$ NMR spectra for the tetrameric compounds (**3** and **4**), coordination of the imine nitrogen to palladium is further supported by the assignment of the imine carbon to a peak between 166.0 and 168.0 ppm, a downfield shift relative to the free ligands (**1** and **2**) where the *C*=N carbon peak occurs between 140.0 and 149.0 ppm. This is in accordance with resonances observed for similar complexes [37,56]. An upfield shift of approximately 10 ppm of the *C*–S carbon in the complex compared to the thione carbon of the free ligand confirms coordination of sulfur in the thiolato form [56]. For complexes **3** and **4**, the *ortho*-carbon shows a large shift from approximately 128.0 ppm in the free ligand to 165.0 ppm. This extreme deshielding of the carbon nucleus is characteristic of palladation of the *ortho*-carbon and substantiates formation of the cyclopalladated complexes **3** and **4** [56,57]. Compared to **3** and **4**, similar resonances are observed for the imine carbon of compounds **7**–**12** and a downfield shift is observed for the *C*–S carbon resonance from between 166.0 and 168.0 ppm for **3** and **4** to between 175.0 and 179.0 ppm for **7**–**12**.

For all complexes (**5**–**12**), a singlet was observed in the $^{31}P\{^1H\}$ NMR spectra. The mononuclear compounds **5** and **6** exhibit a resonance at 38.75 and 38.55 ppm respectively; the phosphorus nuclei for compounds **11** and **12** show a similar resonance to that of **5** and **6** owing to the similarity of their phosphine ligands. For compounds **7** and **8**, the phosphorus nuclei of the dppf ligand resonate at a lower chemical shift, 29.19 and 29.12 ppm respectively, due to the ferrocenyl moiety and the phosphorus singlet of the *trans*-dppe ligand for compounds **10** and **11** occurs between 33.00 and 34.20 ppm. All of these resonances are consistent with those of similar complexes and further support coordination of phosphorus *trans* to the imine nitrogen [35,37,58–61].

Only two absorption bands are observed in the N–H region of the infrared spectrum for all complexes (**5**–**12**), indicating that there are only two amine bonds in the complexes compared to that of the free ligands. The formation of the second imine bond is supported by the observation of two absorption bands between 1525 and 1620 cm^{-1}. The lower frequency band is assigned to the palladium coordinated imine. A shift to lower frequency compared to the free ligand is attributed to the loss of double bond character upon coordination of the nitrogen to the metal. The higher absorption band is hence assigned to the stretching vibration of the newly formed C=N and points to the existence of the metal coordinated to sulfur in the thiolate form.

ESI-mass spectrometry was used to further characterise the complexes (**3**–**12**) prepared. All of the compounds exhibit molecular ion peaks corresponding to each compound in its protonated form.

2.2. X-ray diffraction study of complex 6

Single crystals were grown by slow evaporation of DMSO from the NMR sample for complex **6**. The molecular structure was elucidated using single crystal X-ray diffraction and validates the spectroscopic and analytical characterization of the mononuclear cyclopalladated (**5** and **6**) thiosemicarbazone palladium(II) complexes. The molecular structure of **6** is shown in Fig. 2 and Table 1 lists the crystallographic data. Selected bond lengths and angles are given in Table 2.

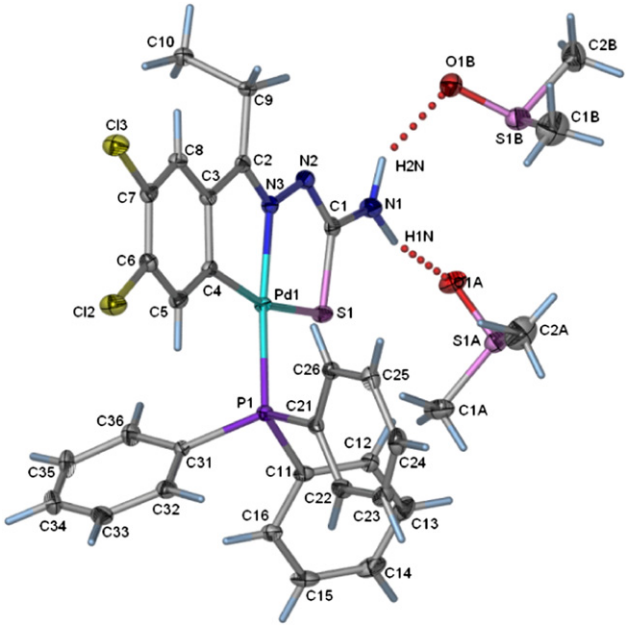


Fig. 2. Molecular structure of **6** with ellipsoidal model of probability level = 40%. The hydrogen bonds are shown as dotted lines.

Table 1
Crystal data and structure refinement data for complex **6**·2DMSO.

Empirical formula	$C_{32}H_{36}Cl_2N_3O_2PPdS_3$
Empirical weight	799.09
Temperature (K)	173(2) K
Wavelength (Å)	0.71073 Å
Crystal system	Orthorhombic
Space group	$Pca2_1$
Unit cell dimensions	
a (Å)	15.6030(6) Å
b (Å)	9.6129(2) Å
c (Å)	23.0082(4) Å
Volume (Å^3)	3451.00(16) Å^3
Z	4
D_{calc} (mg/m^3)	1.538 mg/m^3
Absorption coefficient mm^{-1}	0.955 mm^{-1}
F(000)	1632
Crystal size (mm^3)	0.16 × 0.14 × 0.11
θ range for data collection (°)	2.49–26.02
Limiting indices	$-19 \le h \le 19$, $-11 \le k \le 11$, $-28 \le l \le 27$
Reflections collected	67208
Independent reflections	6788 [*R*(int) = 0.0703]
Completeness to $\theta = 26.02$	99.9%
Maximum and minimum transmission	0.9023 and 0.8622
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6788/3/406
Goodness-of-fit on F^2	1.072
Final *R* indices [$I > 2\theta(I)$]	$R_1 = 0.0306$, $wR_2 = 0.0635$
R indices (all data)	$R_1 = 0.0417$, $wR_2 = 0.0677$
Absolute structure parameter	−0.03 (2)
Extinction coefficient	0.00070 (15)
Largest diff. peak and hole (e Å^3)	0.803 and −0.516

Complex **6** crystallizes with two DMSO solvent molecules per complex in an orthorhombic system and space group $Pca2_1$. In the crystal system, the terminal amine of one complex molecule intermolecularly hydrogen bonds to the oxygen of two solvent molecules.

The thiosemicarbazone ligand bonds to the palladium(II) atom in the expected [C,N,S] fashion forming two five-membered chelate rings [37,61]. The fourth coordination site on the metal is occupied by a triphenylphosphine ligand. Inspection of the angles formed between the metal and the coordinated atoms shows that the metal is contained within a slightly distorted square-planar environment. The angles N(3)–Pd(1)–S(1) 82.48(8) and N(3)–Pd(1)–C(4) 81.30 (12) formed between the thiosemicarbazone ligand and the metal are less than 90°. The angles P(1)–Pd(1)–S(1) 99.85(3) and P(1)–Pd(1)–C(4) 96.55(10) are therefore greater than 90°. Collectively the bite angles observed in the molecular structure compare favourably with those of analogous cyclopalladated triphenylphosphine complexes [37,61].

The bond lengths between palladium and the donor atoms are within the range of 2.03–2.33 Å, with the shorter bond distances occurring between the metal and the N(3) and C(4) atoms. The strong *trans* influence of the phosphorus atom is reflected in the Pd (1)–N(3) bond distance which is slightly longer than the expected length calculated from the covalent radii of palladium and nitrogen (2.01 Å) [37,61,62]. A C(1)–S(1) bond length of 1.762(4) is consistent with single bond character and confirms that sulfur bonds to the metal in the thiolate form, additionally the C(1)–N(2) bond length substantiates the formation of a double bond upon deprotonation of the hydrazinic nitrogen [37,61].

Table 2
Selected bond lengths and angles for complex **6** 2DMSO.

Pd(1)–S(1)	2.3324(9) Å
Pd(1)–P(1)	2.2614(9) Å
Pd(1)–N(3)	2.036(3) Å
Pd(1)–C(4)	2.038(4) Å
C(1)–S(1)	1.762(4) Å
C(1)–N(2)	1.324(5) Å
C(2)–N(3)	1.299(4) Å
N(3)–Pd(1)–S(1)	82.48(8)°
N(3)–Pd(1)–C(4)	81.30(12) °
P(1)–Pd(1)–S(1)	99.85(3)°
P(1)–Pd(1)–C(4)	96.55(10)°

2.3. Antimalarial activity of compounds **1**–**12**

All of the cyclopalladated complexes prepared (**3**–**12**) were screened for antiplasmodial activity along with the corresponding free ligands (**1** and **2**) against two *P. falciparum* strains, the 3D7 (drug sensitive) and K1 (chloroquine and pyrimethamine resistant). Table 3 summarises the IC_{50} values ascertained for all the compounds. Chloroquine (CQ), Artesunate (ASN) and Podophyllotoxin (POD) were used as reference drugs. Against both strains, complexes **4** and **9**–**12** did not display inhibitory effects at the highest concentration (20 μg/ml) tested. The ligands, 3,4-dichloroacetophenone thiosemicarbazone (**1**) and 3,4-dichloropropiophenone thiosemicarbazone (**2**), were not active at the highest concentration (20 μg/ml) tested for the K1 strain but exhibited IC_{50} values of 25.48 and 47.68 μM respectively against the 3D7 strain. The mononuclear complexes **5** and **6** and the bis (diphenylphosphinoferrocene) bridged complex **7** displayed moderate IC_{50} values that were comparable to each other, between *ca* 2.27 and 4.71 μM against the 3D7 strain. The propiophenone analogue (**8**) of complex **7** also showed moderate inhibitory activity ($IC_{50} = 5.10$ μM) against this strain.

The tetrapalladated complex **3** displayed a better IC_{50} value (3.19 μM) against K1, while complex **5** was approximately 3.5 times less active compared to the 3D7 strain. Complex **6** displayed an inhibitory effect of 4.81 μM in the K1 strain; comparable to its activity against the 3D7 strain. The bis(diphenylphosphinoferrocene) bridged complexes **7** and **8** both exhibited IC_{50} values less than 7.2 μM against K1 but these values were still higher than those observed for the 3D7 strain. The other bis(diphenylphosphino) bridged complexes (**9**–**12**) did not exhibit significant activity against either *P. falciparum* strain suggesting that the presence of iron enhances the inhibitory effects of the bridged complexes

Table 3
In vitro antimalarial activity against two strains of *P. falciparum* in the 48 h 3H-hypoxanthine incorporation assay.

Compound	IC_{50} (μg/ml)			
	3D7[a]		K1[b]	
	Average [c]	SD	Average [c]	SD
1	6.68 (25.48)	–	>20	–
2	13.17 (47.68)	8.87 (32.12)	>20	–
3	5.90 (4.02)	3.02 (2.060)	4.68 (3.19)	1.96 (1.34)
4	>20	–	>20	–
5	2.43 (3.86)	0.27 (0.429)	8.83 (14.04)	0.52 (0.82)
6	3.03 (4.71)	1.58 (2.46)	3.09 (4.81)	0.32 (0.49)
7	2.94 (2.27)	–	4.36 (3.37)	1 (0.77)
8	6.86 (5.10)	–	9.65 (7.18)	4.57 (3.40)
9	>20	–	>20	–
10	>20	–	>20	–
11	>20	–	>20	–
12	>20	–	19.44 (16.10)	–
ASN	0.002 (0.0052)	0.001 (0.0026)	0.002 (0.0052)	0.001 (0.0026)
CQ	0.0065 (0.020)	0.005 (0.0156)	0.4 (1.25)	0.23 (0.72)
POD	–	–	–	–

[a] *P. falciparum* drug sensitive strain.
[b] *P. falciparum* chloroquine and pyrimethamine resistant strain.
[c] IC_{50} values reported in μM are given in parentheses.

within the parasite. Overall, the mononuclear (**5** and **6**), tetranuclear (**3** and **4**) and dppf bridged (**7** and **8**) complexes were found to be moderate inhibitors against both strains and their IC_{50} values were better than those of their free ligands illustrating that coordination to palladium enhances the inhibitory effects of their thiosemicarbazones. On average, out of all the complexes found active, complex **6** was the best inhibitor showing almost identical IC_{50} values (4.71/4.81 μM) against both strains. Overall, these preliminary results suggest that the number of metal centres do not directly influence the antiplasmodial activity as the tetranuclear complex **4** was found inactive while complex **3** showed appreciable activity. Further investigations into the factors responsible for this observation are currently underway.

3. Conclusions

Cyclopalladated complexes have been synthesized from aryl-derived thiosemicarbazones which act as tridentate [C,N,S] donors to palladium forming two five-membered rings with the metal. These complexes were fully characterized and the molecular structure of complex **6** confirmed palladation of the *ortho*-carbon. Antiplasmodial studies against two *P. falciparum* strains showed that a selection of these complexes is moderate inhibitors of the parasite with the mononuclear complexes (**5** and **6**) displaying the best activities against the chloroquine sensitive strain. All of the active complexes were found to be more active than their corresponding free, uncomplexed thiosemicarbazone ligand. Further studies into the mechanism of action of the synthesised complexes, as well as why only certain complexes are active, are ongoing.

4. Experimental

4.1. General remarks

All complexation reactions were performed under a nitrogen or argon atmosphere using a dual vacuum/nitrogen line and standard Schlenk-line techniques unless otherwise stated. All reaction solvents were dried by refluxing under an inert atmosphere over the appropriate drying agent and all samples were dried under vacuum. Reagents and solvents were purchased from commercial suppliers and used without further purification. $PdCl_2$ was kindly donated by Johnson-Matthey Inc. The thiosemicarbazone ligands **1** and **2** [6] and $K_2[PdCl_4]$ [63] were synthesized according to previously published methods. Nuclear Magnetic Resonance (NMR) Spectra were recorded on a Varian Unity XR400 MHz (^{1}H at 399.95 MHz, ^{13}C at 100.58 MHz, ^{31}P at 161.90 MHz) or Varian Mercury XR300 (^{1}H at 300.08 MHz, ^{13}C at 75.46 MHz, ^{31}P at 121.47 MHz) MHz spectrometer at ambient temperature. Chemical shifts for ^{1}H and ^{13}C{^{1}H} NMR shifts are reported using tetramethylsilane (TMS) as the internal standard and ^{31}P{^{1}H} spectra were measured relative to H_3PO_4 as the external standard. Infrared absorptions (IR) were measured on a Perkin–Elmer Spectrum One FT-IR Spectrometer as KBr pellets. Microanalyses for C, H, N and S were carried out using a Thermo Flash 1112 Series CHNS–O Analyser and melting points were determined using a Kofler hot stage microscope (Reichert Thermovar). Mass Spectrometry determinations were carried out on all new compounds using electron spray ionisation on a Waters API Quattro Micro instrument in the positive or negative mode.

4.2. Synthesis of [Pd(3,4-dichloroacetophenone thiosemicarbazone)]$_4$ (**3**)

Potassium tetrachloropalladate (0.402 g, 1.230 mmol) was dissolved in deionised water (5 cm^3). Ethanol (40 cm^3) was added and 3,4-dichloroacetophenone thiosemicarbazone (**1**) (0.355 g, 1.356 mmol) was added to the resulting yellow suspension. The reaction mixture was stirred at room temperature for 48 h. The product was collected as a yellow solid via filtration, washed with ethanol (3 × 10 cm^3) and dried under vacuum. Yield: 0.326 g, 73%. M.p.: decomposition without melting 307–309 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) = 7.36 (s, 1H, H2), 7.17 (s, 2H, NH_2), 6.71 (s, 1H, H5), 1.99 (s, 3H, CH_3). ^{13}C NMR (75.46 MHz, DMSO): δ (ppm) = 167.7 (*C*=S), 166.1 (*C*=N), 165.1 (C1), 150.7 (C6), 133.9 (C3), 129.9 (C4), 126.8 (C5), 126.6 (C2), 14.3 (*C*H$_3$). IR (KBr, cm^{-1}) υ = 3442 (m, N–H), 3369 (m, N–H), 1597 (s, C=N), 1560 (m, C=N), 1524 (s, C=C aromatics). Elemental Analysis for $C_{36}H_{28}Cl_8N_{12}Pd_4S_4$: found C 29.1, H 2.4, N 10.9, S 8.6%; calculated C 29.4, H 1.9, N 11.5, S 8.8%. ESI-MS: *m*/*z* 1468 ([M + 2H]$^+$, 20%), 368 ([M/4 + H]$^+$, 100%).

4.3. Synthesis of [Pd(3,4-dichloropropiophenone thiosemicarbazone)]$_4$ (**4**)

Compound **4** was synthesised using the same procedure as for compound **3**. Potassium tetrachloropalladate (0.231 g, 0.709 mmol) was reacted with 3,4-dichloropropiophenone thiosemicarbazone (0.201 g, 0.773 mmol). The product was isolated as a yellow solid by filtration. Product yield: 0.166 g, 61%. M.p.: decomposition without melting 309–311 °C. ^{1}H NMR (300.08 MHz, DMSO): δ (ppm) = 7.36 (s, 1H, H2), 7.11 (s, 2H, NH_2), 6.68 (s, 1H, H5), 2.48 (dt, *J* = 1.88, 3.74 Hz, 2H, CH_3), 0.925 (t, *J* = 7.52 Hz, 3H, CH_2). ^{13}C NMR (100.58 MHz, DMSO): δ (ppm) = 170.8 (*C*–S), 168.1 (*C*=N), 165.5 (C1), 149.4 (C6), 134.2 (C3), 130.3 (C4), 126.9 (C5), 126.3 (C2), 21.1 (*C*H$_2$), 12.0 (*C*H$_3$). IR (KBr, cm^{-1}) υ = 3459 (m, N–H), 3376 (m, N–H), 1595 (s, C=N), 1561 (m, C=N), 1525 (s, C=C aromatics). Elemental Analysis for $C_{40}H_{36}Cl_8N_{12}Pd_4S_4$: found C 31.4, H 2.6, N 10.1, S 10.1%; calculated C 31.6, H 2.4, N 11.0, S 8.4%. ESI-MS: *m*/*z* 1522 ([M]$^+$, 20%), 382 ([M/4]$^+$, 100%).

4.4. Synthesis of [Pd(3,4-dichloroacetophenone thiosemicarbazone)(PPh$_3$)] (**5**)

Compound **3** (0.100 g, 0.069 mmol) was suspended in dry acetone (15 cm^3). Triphenylphosphine (0.073 g, 0.275 mmol) was added and the reaction was stirred under argon gas for 4 h. The product was collected as a bright yellow solid by filtration, washed with acetone (2 × 5 cm^3) and dried under vacuum. Yield: 0.129 g, 75%. M.p.: decomposition without melting 290–291 °C ^{1}H NMR (300.08 MHz, DMSO): δ (ppm) = 7.42–7.64 (m, 15H, PPh$_3$), 7.20 (s, 1H, H2), 6.79 (s, 2H, NH_2), 6.10 (s,1H, H5), 2.76 (s, 3H, CH_3). ^{13}C NMR (75.46 MHz, DMSO): δ (ppm) = 176.6 (*C*–S), 163.6 (*C*=N), 152.7 (C1), 136.1 (C6), 133.8 (C4), 133.7 (C3), 128.5–131.1 (PPh$_3$), 126.2 (C5), 126.1 (C2), 13.0 (*C*H$_3$). ^{31}P NMR (121.47 MHz, DMSO): δ (ppm) = 38.75 (PPh$_3$). IR (KBr, cm^{-1}) υ = 3474 (m, N–H), 3332 (s, N–H), 1601 (s, C=N), 1579 (m, C=N), 1496 (s, C=C aromatics). Elemental Analysis for $C_{27}H_{22}Cl_2N_3PPdS$: found C 51.4, H 3.5, N 6.3, S 4.8%; calculated C 51.6, H 3.5, N 6.7, S 5.1%. ESI-MS: *m*/*z* 630 ([M + H]$^+$, 100%).

Compounds **6**–**12** were synthesised using the same procedure as for compound **5**.

4.5. Synthesis of [Pd(3,4-dichloropropiophenone thiosemicarbazone)(PPh$_3$)] (**6**)

Triphenylphosphine (0.089 g, 0.338 mmol) was reacted with compound **4** (0.106 g, 0.0700 mmol). The product was isolated as a yellow solid. Yield: 0.129 g, 72%. M.p.: 280–283 °C. ^{1}H NMR (300.08 MHz, DMSO): δ (ppm) = 7.40–7.74 (m, 15H, PPh$_3$), 7.21 (s, 1H, H2), 6.88 (s, 2H, NH_2), 6.34 (s, 1H, H5), 2.82 (q, *J* = 7.32, 7.29 Hz, 2H, CH_2), 1.11 (t, *J* = 7.22 Hz, 3H, CH_3). ^{13}C NMR (75.46 MHz, DMSO):

δ (ppm) = 176.9 (*C*–S), 168.2 (*C*=N), 164.1 (C1), 151.5 (C6), 136.5 (C4), 133.9–128.6 (C3 and PPh_3), 126.3 (C5), 125.9 (C2), 19.5 (CH_2), 10.9 (CH_3). ^{31}P NMR (121.47 MHz, DMSO): δ (ppm) = 38.55 (PPh_3). IR (KBr, cm^{-1}) υ = 3466 (m, N–H), 3289 (s, N–H), 1618 (s, C=N), 1577 (m, C=N), 1481 (s, C=C aromatics). Elemental Analysis for $C_{28}H_{24}Cl_2N_3PPdS$: found C 52.2, H 3.9, N 5.9, S 4.6%; calculated C 52.3, H 3.8, N 6.5, S 5.0%. ESI-MS: *m*/*z* 644 ($[M + H]^+$, 100%).

4.6. Synthesis of [Pd_2(3,4-dichloroacetophenone thiosemicarbazone)$_2$(dppf)] (**7**)

Bis(diphenylphosphinoferrocene) (0.0786 g, 0.142 mmol) was reacted with compound **3** (0.105 g, 0.0717 mmol). The product was isolated as a yellow solid. Yield: 0.127 g, 90%. M.p.: decomposition without melting 204–206 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) = 7.40–7.58 (m, 20H, PPh_2), 7.25 (s, 2H, H2), 6.96 (s, 4H, NH_2), 6.08 (s, 2H, H5), 5.07 (br, 4H, Cp-*H*), 4.27 (br, 4H, Cp-*H*), 2.31 (s, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 178.6 (*C*–S), 163.8 (*C*=N), 152.7 (C1), 136.14 (C6), 133.0–133.2 (PPh_2), 131.1 (C4), 129.4 (C3), 128.4–128.5 (PPh_2), 126.4 (C5), 126.3 (C2), 75.4–74.2 (Cp), 13.3 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 29.19 (PPh_3). IR (KBr, cm^{-1}) υ = 3479 (m, N–H), 3383 (m, N–H), 1595 (s, C=N), 1574 (s, C=N), 1491 (s, C=C aromatics). Elemental Analysis for $C_{52}H_{42}Cl_4FeN_6P_2Pd_2S_2$: found C 49.0, H 3.5, N 6.2, S 4.1%; calculated C 48.5, H 3.3, N 6.5, S 5.0%. ESI-MS: *m*/*z* 1288.87 ($[M + H]^+$, 50%), 644.94 ($[M/2 + 2H]^{2+}$, 100%).

4.7. Synthesis of [Pd_2(3,4-dichloropropiophenone thiosemicarbazone)$_2$(dppf)] (**8**)

Bis(diphenylphosphinoferrocene) (0.0518 g, 0.0934 mmol) was reacted with compound **4** (0.0713 g, 0.0468 mmol). The product was isolated as a yellow solid. Yield: 0.0552 g, 89%. M.p.: decomposition without melting 196–198 °C. ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) = 7.45–7.56 (m, 20H, PPh_2), 7.26 (s, 2H, H2), 6.98 (s, 4H, NH_2), 6.10 (s, 2H, H5), 5.03 (br, 4H, Cp-*H*), 4.27 (br, 4H, Cp-*H*), 2.79 (q, *J* = 7.00, 6.92 Hz, 2H, CH_2), 1.11 (t, *J* = 7.46 Hz, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 176.8 (*C*–S), 168.3 (*C*=N), 151.4 (C1), 136.2 (C6), 133.1–132.9 (PPh_2), 130.8 (C_d), 129.3 (C_c), 128.3–128.2 (PPh_2), 126.4 (C_e), 125.8 (C_b), 74.6–75.1 (Cp), 19.6 (CH_2), 10.8 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 29.12 (PPh_2). IR (KBr, cm^{-1}) υ = 3467 (m, N–H), 3387 (m, N–H), 1591 (s, C=N), 1567 (m, C=N), 1491 (s, C=C aromatics). Elemental Analysis for $C_{54}H_{46}Cl_4FeN_6P_2Pd_2S_2$: found C 49.0, H 3.5, N 6.9, S 4.3%; calculated C 49.3, H 3.5, N 6.4, S 4.9%. ESI-MS: *m*/*z* 1316.89 ($[M + H]^+$, 50%), 658.95 ($[M/2 + 2H]^{2+}$, 100%).

4.8. Synthesis of [Pd_2(3,4-dichloroacetophenone thiosemicarbazone)$_2$(trans-dppe)] (**9**)

Bis(diphenylphosphinoethylene) (0.0592 g, 0.149 mmol) was reacted with compound **3** (0.105 g, 0.0719 mmol). The product was isolated as a yellow solid. Yield: 0.134 g, 79%. M.p.: 211–213 °C (decomp.). ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) = 7.52–7.57 (m, 20H, PPh_2), 7.28–7.33 (m, 2H, $PPh_2CH{=}CHPPh_2$), 7.21 (s, 2H, H2), 6.95 (s, 4H, NH_2), 6.23 (s, 2H, H5), 2.28 (s, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 176.6 (*C*–S), 164.0 (*C*=N), 163.3 (C1), 152.6 (C6), 135.7 (C4), 133.1–133.2 (PPh_2), 131.4 ($PPh_2CH{=}CHPPh_2$), 131.1 (C3), 128.9–129.0 (PPh_2), 126.6 (C5), 125.3 (C2), 13.1 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 34.18 (PPh_2). IR (KBr, cm^{-1}) υ = 3455 (m, N–H), 3317 (s, N–H), 1623 (m, C=N), 1605 (s, C=N), 1483 (s, C=C aromatics). Elemental Analysis for $C_{44}H_{36}Cl_4N_6P_2Pd_2S_2$: found C 46.8, H 3.2, N 7.3, S 5.7%; calculated C 46.8, H 3.2, N 7.4, S 5.7%. ESI-MS: *m*/*z* 1130.88 ($[M + H]^+$, 50%), 565.95 ($[M/2 + 2H]^{2+}$, 100%).

4.9. Synthesis of [Pd_2(3,4-dichloropropiophenone thiosemicarbazone)$_2$(trans-dppe)] (**10**)

Bis(diphenylphosphinoethylene) (0.0460 g, 0.116 mmol) was reacted with compound **4** (0.0884 g, 0.0581 mmol). The product was isolated as a yellow solid. Yield: 0.0615 g, 91%. M.p.: 216–218 °C (decomp.). ^{1}H NMR (399.95 MHz, DMSO): δ (ppm) = 7.52–7.58 (m, 20H, PPh_2), 7.17–7.26 (m, 4H, H2, $PPh_2CH{=}CHPPh_2$), 6.99 (s, 4H, NH_2), 6.22 (s, 2H, H5), 2.77 (q, *J* = 7.24, 7.23 Hz, 4H, CH_2), 1.13 (t, *J* = 7.50 Hz, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 176.6 (*C*–S), 168.4 (*C*=N), 163.7 (C1), 151.3 (C6), 140.9 (C4), 135.8 (C3), 132.9–133.2 (PPh_2), 131.4 ($PPh_2CH{=}CHPPh_2$), 128.6–128.9 (PPh_2), 126.5 (C5), 125.9 (C2), 19.6 (CH_2), 10.8 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 33.71 (PPh_2). IR (KBr, cm^{-1}) υ = 3496 (m, N–H), 3386 (s, N–H), 1594 (s, C=N), 1573 (m, C=N), 1486 (s, C=C aromatics). Elemental Analysis for $C_{46}H_{40}Cl_4N_6P_2Pd_2S_2$: found C 47.2, H 3.6, N 7.9, S 5.7%; calculated C 47.8, H 3.5, N 7.3, S 5.5%. ESI-MS: *m*/*z* 1158.91 ($[M + H]^+$, 25%), 579.96 ($[M/2 + 2H]^{2+}$, 100%).

4.10. Synthesis of [Pd_2(3,4-dichloroacetophenone thiosemicarbazone)$_2$(dppb)] (**11**)

Bis(diphenylphosphinobenzene) (0.0631 g, 0.149 mmol) was reacted with compound **3** (0.0947 g, 0.0646 mmol). The product was isolated as a yellow solid. Yield: 0.0686 g, 90%. M.p.: 142–143 °C (decomp.). ^{1}H NMR (300.07 MHz, DMSO): δ (ppm) = 7.48–7.76 (m, 24H, PPh_2, P–C_6H_4–P), 7.23 (s, 2H, H2), 6.95 (s, 4H, NH_2), 6.08 (s, 2H, H5), 2.27 (s, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 165.1 (*C*–S), 163.9 (*C*=N), 153.2 (C1), 136.8 (C6), 128.8–134.7 (PPh_2, P–C_6H_4–P, C3, C4), 126.7 (C5), 126.3 (C2), 13.8 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 38.96 (PPh_2). IR (KBr, cm^{-1}) υ = 3396 (m, N–H), 3055 (m, N–H), 1610 (s, C=N), 1561 (s, C=N), 1482 (s, C=C aromatics), 1436 (C=C, aromatics). Elemental Analysis for $C_{48}H_{38}Cl_4N_6P_2Pd_2S_2$: found C 48.3, H 3.2, N 7.1, S 5.5%; calculated C 48.9, H 3.2, N 7.1, S 5.4%. ESI-MS: *m*/*z* 1180.89 ($[M + H]^+$, 30%), 590.95 ($[M/2 + 2H]^{2+}$, 100%).

4.11. Synthesis of [Pd_2(3,4-dichloropropiophenone thiosemicarbazone)$_2$(dppb)] (**12**)

Bis(diphenylphosphinobenzene) (0.0562 g, 0.133 mmol) was reacted with compound **4** (0.0967 g, 0.0635 mmol). The product was isolated as a yellow solid. Yield: 0.0727 g, 95%. M.p.: 268–270 °C (decomp.). ^{1}H NMR (300.07 MHz, DMSO): δ (ppm) = 7.71–7.75 (m, 4H, P–C_6H_4–P), 7.48–7.51 (m, 20H, PPh2), 7.21 (s, 2H, H2), 6.84 (s, 4H, NH_2), 6.10 (s, 2H, H5), 2.73 (q, *J* = 7.43, 7.34 Hz, 4H, CH_2), 1.09(t, *J* = 7.40 Hz, 6H, CH_3). ^{13}C NMR (100.57 MHz, DMSO): δ (ppm) = 177.4 (*C*–S), 169.1 (*C*=N), 164.7 (C1), 152.1 (C6), 137.0 (C4), 134.4–134.6 (PPh_2), 131.9 ($PPh_2CH{=}CHPPh_2$), 130.8 (C3), 129.3–129.4 (PPh_2), 127.1 (C5), 126.6 (C2), 20.2 (CH_2), 11.48 (CH_3). ^{31}P NMR (161.90 MHz, DMSO): δ (ppm) = 38.80 (PPh_2). IR (KBr, cm^{-1}) υ = 3511 (m, N–H), 3403 (s, N–H), 1617 (m, C=N), 1591 (s, C=N), 1525 (C=C, aromatics), 1482 (s, C=C aromatics). Elemental Analysis for $C_{50}H_{42}Cl_4N_6P_2Pd_2S_2$: found C 49.3, H 3.6, N 4.8, S 5.4%; calculated C 49.7, H 3.5, N 5.0, S 5.3%. ESI-MS: *m*/*z* 1206.94 ($[M + H]^+$, 50%), 604.97 ($[M/2 + 2H]^{2+}$, 100%).

4.12. X-ray crystallography

For complex **6**, X-ray single crystal intensity data were collected on a Nonius Kappa-CCD diffractometer using graphite monochromated MoKα radiation. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). The strategy

for the data collections was evaluated using the Bruker Nonius "Collect" program. Data were scaled and reduced using DENZO-SMN software [64]. Intensity data were corrected for absorption using the program SADABS [65].

The structure was solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97 [66] refining on F^2. Packing diagrams were produced using the program PovRay and graphic interface X-seed [67]. All non-H atoms were refined anisotropically. All the hydrogen atoms except the amino hydrogens were fixed in geometrically calculated positions with U_{iso} set at 1.2 or 1.5 times those of the parent atoms. The amino hydrogens H1N and H2N were located in the difference electron density maps and refined with simple bond length constraints.

4.13. Plasmodium falciparum in vitro culture and parasite growth inhibition assays

All parasite clones, isolates and strains were acquired from MR4 (Malaria Research and Reference Reagent Resource Center, Manassas, Virginia, USA). Strains/isolates used in this study were: the drug sensitive 3D7 clone of the NF54 isolate (unknown origin); and the chloroquine, pyrimethamine and cycloguanyl resistant K1 strain (Thailand). *In vitro* culture of *P. falciparum* was carried out following standard methods [68] with modifications as described [69]. In vitro parasite growth inhibition was assessed by the incorporation of [^{3}H] hypoxanthine based on the method used by Desjardins [70] and modified as described [71]. Briefly, stock drug solutions were dissolved in 100% dimethylsulfoxide (Sigma, Dorset, UK) and 90 μL of a 10-fold dilution series (20.0, 2.00, 0.20, 0.02, 0.002, and 0.0002 μg/mL) of the drugs prepared in assay medium (RPMI 1640 supplemented with 0.5% Albumax II (Invitrogen), 0.2% w/v glucose, 0.03% L-glutamine, and 5 μM hypoxanthine) added to each well of 96-well plates in triplicate. Ninety microlitres of asynchronous (65–75% ring stage) *P. falciparum* culture (0.5% parasitemia) or uninfected erythrocytes (blank) were added to each well reaching a final volume of 180 μL per well, a final hematocrit of 2.5% and final dimethylsulfoxide concentrations ≤0.01%. Plates were incubated at 37 °C in 5% CO_2/95% air mixture for 24 h, at which point 20 μL (0.2 μCi/well) of [^{3}H]hypoxanthine (Perkin–Elmer, Hounslow, UK), was added to each well. After an additional 24 h incubation period, the experiment was terminated by placing the plates in a −80 °C freezer. Plates were thawed and harvested onto glass fibre filter mats using a 96-well cell harvester (Harvester 96, Tomtec, Oxon, UK) and left to dry. After the addition of MeltiLex solid scintillant (Perkin–Elmer, Hounslow, UK) the incorporated radioactivity was counted using a Wallac 1450 Betalux scintillation counter (Wallac).

Data acquired by the Wallac BetaLux scintillation counter were exported into an MS*xl*spreadsheet (Microsoft), and the IC_{50} values of each drug were calculated by using MS*xl*fit line fitting software (ID Business Solutions, UK). Chloroquine diphosphate, as a standard drug, and control wells with untreated infected and uninfected erythrocytes were included in all assays.

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Appendix A. Supplementary material

CCDC 719357 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

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