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Pyrazolyl Pd(II) complexes containing triphenylphosphine: Synthesis and antimycobacterial activity

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ABSTRACT

Complexes of the type *trans*-[$PdCl_2$(HL)(PPh_3)], where HL = pyrazole (**1**); 3,5-dimethylpyrazole (**2**); 4-nitropyrazole (**3**); 4-iodopyrazole (**4**) and PPh_3 = triphenylphosphine, were synthesized and characterized by elemental analyses, infrared and ^{1}H NMR spectroscopies. Single-crystal X-ray diffraction determination on **3**·0.9 $CHCl_3$ and **4** showed that the coordination geometry around Pd(II) is nearly square-planar, with the chloro ligands in a *trans* configuration. *In vitro* antimycobacterial evaluation demonstrated that compound **4** displayed a minimum inhibitory concentration (MIC) of 7.61 ± 2.18 μM, being superior to the values observed for some commonly used antituberculosis drugs and other metal-based complexes.

1. Introduction

Tuberculosis (TB), an airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB) and other mycobacteria, is still a major worldwide health threat [1]. The urgent need to discover new anti-TB agents is justified by many important reasons, mainly: (i) the outbreak of multidrug resistant (MDR) and extensively drug-resistant (XDR-TB) TB strains of *M. tuberculosis*; (ii) the spreading of the human immunodeficiency virus (HIV) and its deadly synergy with TB and nontubercular mycobacterial infections; (iii) the poor compliance with the complexity and toxicity of the current chemotherapeutic regimens [1–3].

In this sense, pyrazole-type heterocycles have emerged as a class of potential antimycobacterial agents [4–7]. Horrocks et al. [7] have synthesized some 3-(4-chlorophenyl)-4-substituted pyrazole derivatives which displayed not only an interesting activity against the tested strain of *M. tuberculosis* H_{37}Rv, but also exhibited remarkable antifungal activity against four pathogenic strains. Velaparthi et al. [8] have described a series of 5-tert-butyl-N-pyrazol-4-yl-4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxamide derivatives as novel potent *M. tuberculosis* pantothenate synthetase inhibitors showing cytotoxicity activity (IC_{50}) ranging from 90 nM to 7.13 μM.

The importance of pyrazole derivatives has also been accompanied by an increasing interest focused on the coordination chemistry of these heterocycles [9–11]. Particularly, metal-based compounds of pyrazoles containing phosphines as co-ligands have also received attention due to their possible use as antitumor and antimicrobial drugs [12,13]. Nomiya et al. [13] synthesized the complex [Au(HPz)(PPh_3)] (HPz = pyrazole; PPh_3 = triphenylphosphine) which showed activities against Gram-positive bacteria (*Staphylococcus aureus*) and one yeast (*Candida albicans*). Nevertheless, studies on the antimycobacterial activity towards TB involving pyrazolyl complexes bearing phosphine ligands remain scarce in literature.

For many years, our research has been focused on the synthesis of metal compounds containing N-, P- or S-based ligands and the evaluation of their activity against tumour cell lines and *M. tuberculosis* [14–19]. Ferreira et al. have obtained the organometallic compound [Pd(C-bzan)(SCN)(dppp)] {bzan = N-benzylideneaniline, dppp = 1, 3-bis(diphenylphosphino)propane} which displayed significant antimycobacterial activity (MIC_{90} = 5.15 μM) [20]. Recently, we have described the synthesis of binuclear compounds of the type [Pd(μ-L)(N_3)(PPh_3)]$_2$ {L = pyrazolate (Pz); 3,5-dimethylpyrazolate (dmPz); 4-iodopyrazolate (IPz)} [21]. *In vitro* antimycobacterial

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assays demonstrated that compound $[Pd(\mu\text{-}Pz)(N_3)(PPh_3)]_2$ exhibited a MIC of 8.16 μM. This findings have prompted us to evaluate the anti-TB activity of other Pd(II) compounds bearing phosphine ligands. Inspired by the promising biological results obtained for mononuclear compounds of the type [Au(pyrazoles)(PPh_3)] [12,13] and as a part of our ongoing studies on coordination chemistry of pyrazolyl ligands [22–24], we prepared analogous Pd(II) derivatives with general formulae *trans*-$[PdCl_2(HL)(PPh_3)]$, where PPh_3 = triphenylphosphine and HL are ligands of type pyrazole (HPz); 3,5-dimethylpyrazole (HdmPz); 4-nitropyrazole (HNO_2Pz) and 4-iodopyrazole (HIPz), and investigated their antimycobacterial activity against *M. tuberculosis*. The crystallographic structures of the compounds **3**·0.9 $CHCl_3$ and **4** are also described in this work.

2. Material and methods

2.1. General methods

Synthesis were performed at ambient temperature. The precursor $[PdCl_2(MeCN)_2]$ was prepared as previously described [25]. Pyrazolyl ligands and triphenylphosphine were purchased from Sigma Aldrich or Merck. Reagents and solvents were employed without further purification.

2.2. Synthesis

Compounds $[PdCl_2(HPz)(PPh_3)]$ (**1**), $[PdCl_2(HdmPz)(PPh_3)]$ (**2**), $[PdCl_2(HNO_2Pz)(PPh_3)]$ (**3**) and $[PdCl_2(HIPz)(PPh_3)]$ (**4**) were prepared by adding a mixture containing 1.17 mmol of the appropriated pyrazolyl ligand {79.6 mg of HPz (**1**), 112 mg of HdmPz (**2**), 132 mg of HNO_2Pz (**3**) or 227 mg of HIPz (**4**)} and triphenylphosphine (307 mg; 1.17 mmol) in 5 mL of $CHCl_3$ to an orange solution of $[PdCl_2(CH_3CN)_2]$ (301 mg; 1.16 mmol) in 15 mL of $CHCl_3$. The mixtures were stirred magnetically for 2 h, and then the solutions were concentrated to 2 mL under reduced pressure. The addition of pentane (30 mL) resulted in the precipitation of the products **1**–**4**, which were filtered and dried under vacuum. Yield 79–90%.

2.3. Physical measurements

C, H and N analyses were performed on a Perkin Elmer 2400. Conductivities were measured with a Digimed-DM-31 conductometer using 1×10^{-3} mol L^{-1} DMSO solutions. Infrared spectra were recorded as KBr pellets on a Nicolet FTIR-Impact 400 spectrophotometer in the spectral range 4000–400 cm^{-1} with resolution of 2 cm^{-1}. The ^1H NMR spectra were obtained using $CDCl_3$ solutions, on a Varian INOVA 500 spectrometer.

2.4. Single-crystal X-ray diffraction studies

Single crystals for X-ray crystallography of **3** and **4** were obtained by slow diffusion of pentane into a solution of the complexes in chloroform. X-ray diffraction data for **3**·0.9 $CHCl_3$ and **4** were collected on a Bruker X8 Kappa APEX II with a charge-coupled device (CCD) area-detector diffractometer (Mo Kα graphite-monochromated radiation, λ = 0.71073 Å) controlled by the APEX2 software package [26], and equipped with an Oxford Cryosystems Series 700 cryostream monitored remotely using the software interface Cryopad [27]. Images were processed using the software package SAINT+ [28], and data were corrected for absorption by the multi-scan semi-empirical method implemented in SADABS [29]. The crystal structures of **3**·0.9 $CHCl_3$ and **4** were solved using the Patterson synthesis algorithm implemented in SHELXS-97 [30], which allowed the immediate location of the crystallographically independent Pd^{2+} centers and the most of the heaviest atoms. All remaining non-hydrogen atoms were located from difference Fourier maps calculated from successive full-matrix least squares refinement cycles on F^2 using SHELXL-2014 [31,32], and refined using anisotropic displacement parameters. Refinement of solvent occupancy of the chloroform molecule in **3** converged at 0.892(2), however this was fixed at 0.9.

Hydrogen atoms bound to carbon were placed at their idealized positions using appropriate *HFIX* instructions in SHELXL: 13 for the –CH from chloroform and 43 for the CH groups of the aromatic rings. These atoms were included in subsequent refinement cycles in riding motion approximation with isotropic thermal displacements parameters (U_{iso}) fixed at 1.2 × U_{eq} of the parent carbon atoms. In opposition, H atoms bonded to nitrogen were located from difference Fourier maps and the N–H distance and isotropic thermal displacements parameters (U_{iso}) fixed at 0.88 Å and 1.5 × U_{eq} of the nitrogen atoms, respectively.

For compound **3**·0.9 $CHCl_3$, the last difference Fourier map synthesis showed the highest peak (0.89 $eÅ^{-3}$) located at 1.02 Å from Cl4, and the deepest hole (−1.12 $eÅ^{-3}$) at 0.76 Å from Pd1. For compound **4**, the last difference Fourier map synthesis showed the highest peak (2.59 $eÅ^{-3}$), and the deepest hole (−3.22 $eÅ^{-3}$), located at 0.44 and 1.06 Å from I1, respectively. Details of the crystal data and structure refinement parameters for **3**·0.9 $CHCl_3$ and **4** are summarized in Table 1.

2.5. Antimycobacterial assays

The anti-*M. tuberculosis* activity was determined by the Resazurin Microtiter Assay (REMA) [33,34]. Stock solutions of the test compounds were prepared in DMSO and diluted in

Table 1
Crystal and structure refinement data for $[PdCl_2(HNO_2Pz)(PPh_3)]$·0.9 $CHCl_3$ (**3**·0.9 $CHCl_3$) and $[PdCl_2(HIPz)(PPh_3)]$ (**4**).

	(**3**·0.9 $CHCl_3$)	(**4**)
Formula	$C_{21}H_{18}Cl_2N_3O_2PPd$·0.9($CHCl_3$)	$C_{21}H_{18}Cl_2IN_2PPd$
Formula weight	660.09	633.54
Crystal system	monoclinic	triclinic
Space group	$P2_1/n$	$P\bar{1}$
T (K)	150	150
a (Å)	15.0018(8)	10.2246(5)
b (Å)	9.4988(5)	10.5312(5)
c (Å)	18.6528(10)	12.0140(5)
α (°)	90	102.004(2)
β (°)	103.784(3)	96.708(2)
γ (°)	90	116.699(2)
V ($Å^3$)	2581.5(2)	1097.22(19)
Z	4	2
D_{calc} (g cm^{-3})	1.698	1.918
θ range (°)	3.6–33.1	2.3–25.4
μ (Mo Kα) (mm^{-1})	1.29	2.58
Crystal type	Yellow block	Orange block
Crystal size (mm)	0.15 × 0.12 × 0.08	0.15 × 0.12 × 0.08
Index ranges	$-23 \leqslant h \leqslant 17$, $-14 \leqslant k \leqslant 14$, $-27 \leqslant l \leqslant 28$	$-12 \leqslant h \leqslant 12$, $-12 \leqslant k \leqslant 12$, $-14 \leqslant l \leqslant 14$
Reflections collected	32371	52973
Independent reflections	9819 [R_{int} = 0.062]	4014 [R_{int} = 0.0648]
Completeness	99.7% (to θ = 30.0)	100% (to θ = 25.4)
Final R indices [$I > 2\sigma(I)$][a,b]	R_1 = 0.047, wR_2 = 0.112	R_1 = 0.040, wR_2 = 0.089
Weighting scheme[c]	m = 0.0446 n = 0	m = 0.183 n = 6.1607
Largest diff. peak and hole (e $Å^{-3}$)	0.89 and −1.12	2.59 and −3.22

[a] $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$.

[b] $wR_2 = \sqrt{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]}$.

[c] $w = 1/[\sigma^2(F_o^2) + (mP)^2 + nP]$ where $P = (F_o^2 + 2F_c^2)/3$.