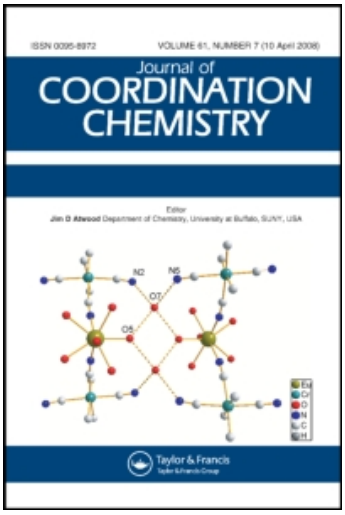

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Palladium(II) complexes containing cytokinins derived from 6-benzylaminopurine

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A series of palladium(II) complexes of general formula $[Pd(LH^+)Cl_3]$ (**1**–**12**) containing 6-benzylaminopurine derivatives has been prepared [L = 6-(2-methoxybenzylamino)purine (**1**), 6-(3-methoxybenzylamino)purine (**2**), 6-(4-methoxybenzylamino)purine (**3**), 6-(2-hydroxybenzylamino)purine (**4**), 6-(3-hydroxybenzylamino)purine (**5**), 6-(4-hydroxybenzylamino) purine (**6**), 6-(2-fluorobenzylamino)purine (**7**), 6-(3-fluorobenzylamino)purine (**8**), 6-(4-fluorobenzylamino)purine (**9**), 6-(2-chlorobenzylamino)purine (**10**), 6-(3-chlorobenzylamino) purine (**11**) and 6-(4-chlorobenzylamino)purine (**12**)]. The compounds have been characterized by elemental analysis, IR, ES+ MS and ^{1}H- and ^{13}C-NMR spectroscopy, and two of them, **6** and **12**, also by TG/DSC analyses. The complexes have been screened *in vitro* against the four human tumour cell lines G-361, HOS, K-562 and MCF7.

Keywords: Palladium(II) complexes; Cytokinin-derived compounds; Cytotoxicity; Antitumour activity

1. Introduction

Cytokinins are important plant growth regulators. Chemically, they represent adenine derivatives substituted at the N6 position with an isoprenoid or aromatic side chain [1]. They occur widely in plants, as well as in animals and bacteria, and affect a variety of important physiological processes, including cell division, differentiation and senescence. One of them, 6-benzylaminopurine (Bap), is widely used in plant biotechnology [2]. Some Bap derivatives (substituted at C2 and N9 of purine) also show potent anticancer activity. These compounds belong to a family of cyclin-dependent kinase (CDKs) inhibitors. CDKs constitute a group of serine-threonine kinases which control cycle progression in proliferating eukaryotic cells [3] and have a strong

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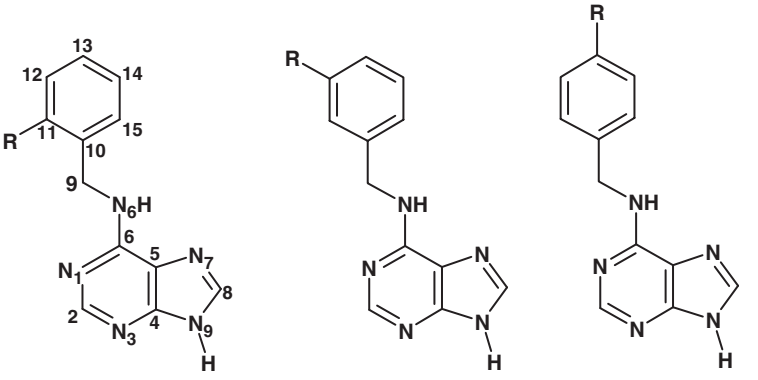
inhibitory function, with the ability to arrest cells at specific points of the cell cycle [4]. For example, *R*-roscovitine (also named as CYC202 or seliciclib) is now in Phase II clinical trials for breast and lung cancer and recently its metabolism and pharmacokinetics in the mouse were studied [5].



The screening of new metal complexes with antitumour activity is among our research interests. In previous work, we focussed on the preparation, characterization and cytotoxicity of selected transition metal complexes (e.g. divalent Cu, Co, Ni, Pt, Pd) with 6-benzylaminopurine derivatives [6–9]. Although a wide variety of palladium complexes with nucleic acid bases and derivatives have been studied [10–13], there are no literature data relating to Pd(II) complexes of 6-benzylaminopurine derivatives, except those that we reported formerly, $[Pd(BohH^+)Cl_3]\cdot H_2O$, $[Pd(Boh)Cl_2(H_2O)]$, $[Pd(Boh\text{-}H)Cl(H_2O)]\cdot EtOH$ and $[Pd(OloH^+)Cl_3]\cdot H_2O$ (Boh = 6-(benzylamino)-2-[(3-(hydroxypropyl)amino]-9-isopropylpurine; Olo = 6-(benzylamino)-2-[(2-(hydroxyethyl)amino]-9-methylpurine) [9]. Compounds presented here represent the first examples of Pd(II) complexes containing cytokinin derivatives. The cytokinin-derived compounds used as ligands in this study are shown above.

2. Experimental

All commercially available reagents were employed without further purification. 6-Chloropurine, 2-methoxybenzylamine, 3-methoxybenzylamine, 4-methoxybenzylamine, 2-hydroxybenzylamine, 3-hydroxybenzylamine, 4-hydroxybenzylamine, 2-fluororobenzylamine, 3-fluororobenzylamine, 4-fluororobenzylamine, 2-chlorobenzylamine, 3-chlorobenzylamine, 4-chlorobenzylamine, K_2PdCl_4 and the solvents used were purchased from Aldrich or Fluka. The 6-benzylaminopurine derivatives used as ligands in this study, 6-(2-methoxybenzylamino)purine (2MeOBap), 6-(3-methoxybenzylamino)purine (3MeOBap), 6-(4-methoxybenzylamino)purine (4MeOBap), 6-(2-hydroxybenzylamino)purine (2OHBap), 6-(3-hydroxybenzylamino)purine (3OHBap), 6-(4-hydroxybenzylamino)purine (4OHBap), 6-(2-fluorobenzylamino)purine (2FBap), 6-(3-fluorobenzylamino)purine (3FBap), 6-(4-fluorobenzylamino)purine (4FBap), 6-(2-chlorobenzylamino)purine (2ClBap), 6-(3-chloro-benzylamino)purine

(3ClBap) and 6-(4-chlorobenzylamino)purine (4ClBap), were synthesized using a slightly modified procedure described in the literature [14,15]. Properties of the ligands were in agreement with data reported [15].

2.1. *Physical techniques*

Elemental analyses (CHN) were performed on an EA1112 Flash (ThermoFinnigan) instrument. IR spectra were recorded on a NEXUS FT-IR spectrophotometer (ThermoNicolet) using polyethylene (150–600 cm^{-1}) and KBr pellets (400–4000 cm^{-1}). Conductivity measurements were made using a Cond340i/SET conductometer (WTW) (DMFA solutions at 25°C). The concentration of the complexes was 10^{-3} M. ES+ mass spectra were recorded using flow injection mode on a Waters ZMD 2000 spectrometer. The mass-monitoring interval was 30–1000 m/z. Spectra were collected using 3.0 s cyclic scans sample cone voltages of 20, 40 or 60 V, source block temperature 80°C, desolvation temperature 150°C and desolvation gas flow 200 $dm^3 h^{-1}$. The mass spectrometer was directly coupled to a MassLynx data system. All interpretations of m/z were based on ^{35}Cl and ^{106}Pd. ^1H and ^{13}C NMR spectra were measured on a Bruker Advance 300 MHz spectrometer operating at 300.13 MHz (^1H) and 75.47 MHz (^{13}C) using MeOD-d_3 and DMSO-d_6, respectively, at 300 K. Tetramethylsilane (TMS) was used as internal standard. TG/DSC measurements of 6-(4-hydroxybenzyl-amino)purine (**6**) and 6-(4-chlorobenzylamino) purine (**12**) were carried out using a TGAXP-10 thermogravimetric analyzer and a DSCXP-10 differential scanning calorimeter (Thass).

2.2. *Synthesis of [Pd(LH$^+$)Cl$_3$] (1–12)*

The complexes were prepared according to a general procedure from K_2PdCl_4 and the corresponding cytokinin-derived compound (1 : 1 mol ratio) in 2 M HCl with *ca* 75–85% yields.

K_2PdCl_4 (0.16 g, 0.5 mmol) was dissolved in warm 2 M HCl (30 cm^3) and added to a solution of the corresponding ligand, L, (0.5 mmol) in 30 cm^3 of warm 2 M HCl. The mixture was heated at 90°C with stirring for *ca* 5 h. The yellow precipitate that formed was filtered off, washed with 2 M HCl (2×5 cm^3) and H_2O (10 cm^3) and dried under an IR lamp at 40°C.

2.3. In vitro *biological activity*

Cytotoxic activity of the complexes [general formula [Pd(LH^+)Cl_3], L = 6-(2-methoxybenzylamino)purine (**1**), 6-(3-methoxybenzylamino)purine (**2**), 6-(4-methoxybenzylamino)purine (**3**), 6-(2-hydroxy-benzylamino)purine (**4**), 6-(3-hydroxybenzylamino) purine (**5**), 6-(4-hydroxybenzyl-amino)purine (**6**), 6-(2-fluorobenzylamino)purine (**7**), 6-(3-fluorobenzylamino)purine (**8**), 6-(4-fluorobenzylamino)purine (**9**), 6-(2-chlorobenzylamino)purine (**10**), 6-(3-chlorobenzyl-amino)purine (**11**) and 6-(4-chlorobenzylamino)purine (**12**)] was assessed by a Calcein acetoxymethyl (AM) assay, as described previously [6–9]. The human tumour cell lines malignant melanoma (*G-361*), chronic myelogenous erythroleukemia (*K-562*), osteogenic sarcoma (*HOS*) and breast adenocarcinoma (*MCF7*) were used. After 12 h preincubation (37°C, 5% CO_2, 100% humidity), the compounds in six concentrations covering the range 0.69–166 μM

Table 1. Colour, analytical and conductivity data for the complexes.

Complex	Colour	Found (calcd) (%)			λ_M ($S\,cm^2\,mol^{-1}$)
		C	H	N	
(**1**) $[Pd(2MeOBapH^+)Cl_3]$	Yellow	33.2 (33.3)	3.1 (3.0)	15.1 (14.9)	35.0
(**2**) $[Pd(3MeOBapH^+)Cl_3]$	Yellow	33.3 (33.3)	2.9 (3.0)	15.1 (14.9)	29.3
(**3**) $[Pd(4MeOBapH^+)Cl_3]$	Yellow	33.4 (33.3)	3.0 (3.0)	15.0 (14.9)	34.5
(**4**) $[Pd(2OHBapH^+)Cl_3]$	Yellow	32.0 (31.7)	2.7 (2.7)	15.6 (15.4)	23.7
(**5**) $[Pd(3OHBapH^+)Cl_3]$	Yellow	32.4 (31.7)	2.7 (2.7)	15.6 (15.4)	25.4
(**6**) $[Pd(4OHBapH^+)Cl_3]\cdot H_2O$	Yellow	30.3 (30.5)	2.9 (3.0)	15.1 (14.8)	22.1
(**7**) $[Pd(2FbapH^+)Cl_3]$	Yellow	31.7 (31.5)	2.4 (2.4)	15.1 (15.3)	33.0
(**8**) $[Pd(3FbapH^+)Cl_3]$	Yellow	31.9 (31.5)	2.5 (2.4)	15.4 (15.3)	33.5
(**9**) $[Pd(4FbapH^+)Cl_3]$	Yellow	31.3 (31.5)	2.7 (2.4)	15.7 (15.3)	30.4
(**10**) $[Pd(2ClBapH^+)Cl_3]$	Yellow	30.4 (30.4)	2.4 (2.3)	14.7 (14.8)	25.6
(**11**) $[Pd(3ClBapH^+)Cl_3]$	Yellow	30.3 (30.4)	2.4 (2.3)	14.6 (14.8)	27.8
(**12**) $[Pd(4ClBapH^+)Cl_3]$	Yellow	30.5 (30.4)	2.4 (2.3)	15.0 (14.8)	24.3

(for organic ligands) and 0.41–100 μM (for the complexes) were added to the cells (20 μL per well). Concentration ranges were chosen for reasons of limited solubility. Incubation was performed for 72 h (above conditions). Subsequently, the cells were treated with Calcein AM (1 h) and fluorescence of live cells was measured at 485/538 nm (excitation/emission) with a Fluoroskan Ascent (Labsystem) instrument. IC_{50} values were estimated.

3. Results and discussion

Reaction of K_2PdCl_4 and the corresponding cytokinin-derived compound (L) in 2 M HCl afforded the square-planar complexes $[Pd(LH^+)Cl_3]$ (**1**–**12**). The constitution of the complexes follows from elemental analyses, IR, ES+ MS and ^1H and ^{13}C NMR data (see tables 1–3). Molar conductance values in DMFA vary from 22.1 to 35.0 $S\,cm^2\,mol^{-1}$, revealing the non-electrolytic nature of the complexes [16], albeit their somewhat higher values can be connected with partial dissociation.

3.1. *Infrared spectra*

Far-IR spectra of the complexes displayed sharp bands at 341–347 and 459–490 cm^{-1} associated with ν(Pd–Cl) and ν(Pd–N), respectively [17]. Bands at 1641–1656 and 1572–1590 cm^{-1} may be assigned to ν(C=N) and ν(C=C), respectively. Complexes containing hydroxy and methoxy groups showed peaks at 1212–1266 cm^{-1} due to $\nu(C_{ar}–O)$ and bands at 1222–1250 and 1049–1079 cm^{-1} are probably due to $\nu(C_{ar}–F)$ and $\nu(C_{ar}–Cl)$, respectively. IR spectra show characteristic bands at 3250 and 3050 cm^{-1} assigned to ν(N–H) and $\nu(C_{ar}–H)$, respectively [18,19]. Comparison of the IR spectra of ligands and complexes in the C=N and C=C stretching region of the purine ring (1400–1700 cm^{-1}) shows that bands in the complexes are shifted to higher frequencies by some 20–30 cm^{-1}. This supports the conclusion that the ligands coordinate palladium via one of the four purine nitrogens.

Table 2. Selected IR and ES+ MS data for the complexes.

	IR spectral data (cm^{-1})					ES+ MS (m/z)	
Compound	$\nu(C_{ar}–X)$[a]	ν(C=C)	ν(C=N)	ν(Pd–N)	ν(Pd–Cl)	$[L+H]^{+}$[b]	$[M+H]^{+}$
(**1**) $[Pd(2MeOBapH^{+})Cl_3]$	1248vs	1585s 1463s	1641vs	464m	344s	256	468
(**2**) $[Pd(3MeOBapH^{+})Cl_3]$	1266s	1585s 1460s	1651vs	461m	345s	256	
(**3**) $[Pd(4MeOBapH^{+})Cl_3]$	1249s	1588s 1460s	1651vs	462m	345s	256	468
(**4**) $[Pd(2OHBapH^{+})Cl_3]$	1237s	1580s 1459s	1656vs	460m	347s	242	
(**5**) $[Pd(3OHBapH^{+})Cl_3]$	1215s	1585s 1459s	1654vs	494m	345s	242	454
(**6**) $[Pd(4OHBapH^{+})Cl_3]\cdot H_2O$	1217s	1580m 1449s	1652vs	474m	346s	242	454
(**7**) $[Pd(2FbapH^{+})Cl_3]$	1231s	1588s 1454s	1653vs	494m	343s	244	457
(**8**) $[Pd(3FbapH^{+})Cl_3]$	1250s	1591s 1450s	1655vs	459m	344s	244	457
(**9**) $[Pd(4FbapH^{+})Cl_3]$	1222vs	1590s 1452s	1642vs	303w	343s	244	
(**10**) $[Pd(2ClBapH^{+})Cl_3]$	1052s	1572s 1443s	1654vs	460m	341s	260	
(**11**) $[Pd(3ClBapH^{+})Cl_3]$	1079s	1577s 1451s	1656vs	450m	343m	260	
(**12**) $[Pd(4ClBapH^{+})Cl_3]$	1049s	1572s 1447s	1652vs	490s	342s	260	

[a]X = O, F or Cl.
[b]L = the corresponding organic ligand.

Table 3. Differences [$\Delta = \delta$(complex) – δ(ligand)] in ^{13}C NMR chemical shifts of purine carbon atoms in the complexes and free ligands.

Complex	C(2)	C(4)	C(5)	C(6)	C(8)
(**1**) $[Pd(2MeOBapH^{+})Cl_3]$	3.28	−1.87	−6.36	−1.51	6.60
(**2**) $[Pd(3MeOBapH^{+})Cl_3]$	3.28	−2.12	−6.83	−2.22	4.87
(**3**) $[Pd(4MeOBapH^{+})Cl_3]$	2.75	−3.43	−6.55	−3.07	5.09
(**4**) $[Pd(2OHBapH^{+})Cl_3]$	2.02	−2.60	−6.02	−2.38	4.02
(**5**) $[Pd(3OHBapH^{+})Cl_3]$	2.75	−3.45	−6.87	−3.80	4.58
(**6**) $[Pd(4OHBapH^{+})Cl_3]\cdot H_2O$	3.17	−2.84	−7.03	−3.75	4.95
(**7**) $[Pd(2FbapH^{+})Cl_3]$	3.01	−2.44	−6.10	−2.55	4.71
(**8**) $[Pd(3FbapH^{+})Cl_3]$	3.75	−2.13	−5.58	−2.20	5.24
(**9**) $[Pd(4FbapH^{+})Cl_3]$	3.20	−2.59	−6.08	−2.81	4.73
(**10**) $[Pd(2ClBapH^{+})Cl_3]$	3.31	−3.30	−7.06	−3.36	4.40
(**11**) $[Pd(3ClBapH^{+})Cl_3]$	3.20	−2.75	−5.90	−2.58	4.34
(**12**) $[Pd(4ClBapH^{+})Cl_3]$	3.02	−2.50	−5.82	−2.62	3.06

3.2. *NMR data*

^{1}H and ^{13}C NMR spectra were recorded to confirm not only the presence of coordinated cytokinin derivatives in the complexes, but also the manner of their coordination to Pd(II). Multiplets observed in the ^{1}H NMR spectra of the free organic ligands and the complexes in the δ 6.7–7.4 ppm region can be assigned to aromatic protons. Singlets at *ca* δ 8.2 and 8.0 ppm correspond to protons attached to the C(8)

and C(2) atoms of the purine ring, respectively. Both signals are shifted downfield in ^{1}H NMR spectra of the complexes [$\Delta = \delta$(complex) $-$ δ(ligand); average $\Delta = 0.41$ ppm ppm for H(8), $\Delta = 0.29$ ppm for H(2)]. Another singlet at 12.2–12.8 ppm can be assigned to N*H*, while the presence of hydroxy and methoxy groups is evident from singlets at *ca* δ 10.2 and 3.7 ppm, respectively.

With the aim of determining the coordination site of the cytokinin derivatives, ^{13}C NMR spectra of the free ligands and Pd(II) complexes were recorded. Selected ^{13}C NMR data are given in table 3. From a general point of view, each of the Bap derivatives contains five nitrogen atoms as possible coordination sites. To date, 10 molecular structures of Pd(II) complexes of adenine derivatives have been deposited at the Cambridge Crystallographic Data Centre database [20]. It is evident that N9 or N3 or μ_2-N3,N9 positions are preferred for adenine (AdeH) coordination as found for [Pd(Ade-*N9*)$_2${P(*n*-Bu)$_3$}$_2$]$\cdot$MeOH [21], [Pd(AdeH-*N3*)(L$_1$)]BF$_4$, [Pd(AdeH-*N3*)(L$_2$)]BF$_4$ [L$_1$ = 11(1,4),15(1,3),19(1,4)-tribenzena-1,4,7,10-tetra-oxa-13, 17-dithianonadecaphane; L$_2$ = 11,15,19-tribenzena(1,3)-1,4,7,10-tetra-oxa-13, 17-dithianonadecaphane] [22] and [Pd$_2$(μ_2-Ade-*N3,N9*)(L$_3$)$_2$](NO$_3$)$\cdot$3H$_2$O [L$_3$ = (4-methyl-2-(1,10-phenanthrolin-2-yl)phenyl-C,N,N′)] [23]. In the case that N9 of adenine is blocked by a substituent, coordination occurs via N3 as it was found in [PdCl(L$_4$)]BF$_4$, [PdCl(L$_5$)]Cl$\cdot$H$_2$O [L$_4$ = 7-(ethylenediamino)ethyladenine; L$_5$ = 7-(ethylenediamino)propyladenine] [24], [PdCl(L$_6$)]SiF$_6\cdot$9H$_2$O [L$_6$ = 1-(3-(2-(2-(9-adenyl)ethylthio)ethylthio)propyl)thymine] [25], [PdCl(L$_7$)]BF$_4\cdot$1/2H$_2$O [L$_7$ = 1-(adenin-9-yl)-3,6-dithiaheptane] [26] and [Pd(deta)(L$_8$)](ClO$_4$)$_2$ [deta = diethylenetriamine, L$_8$ = 6′,6′,9′-trimethyladenine] [13].

Coordination of the ligands to palladium in (**1**–**12**) as well as protonation sites are apparent from the fact that significant changes in chemical shifts were observed in ^{13}C NMR spectra for all carbon atoms of purine (see table 3). Based on the fact that signals belonging to C(8) and C(2) in the complexes are shifted downfield [$\Delta = \delta$(complex) $-$ δ(ligand)] while signals of C(4), C(5) and C(6) are shifted upfield as compared to the free ligands, we assume that coordination of the Bap derivatives involves N(9). The coordinated ligand is protonated at N1 and N7. The proposed structure of the complexes is represented by that of [Pd(2FbapH$^+$)Cl$_3$] (**7**), as shown in figure 1. Geometry was optimized at the B3LYP/lanl2dz level of theory using the Gaussian03 program [27].

3.3. *ES+ mass spectra*

Electrospray mass spectra in the positive ion mode (ES+) were measured for all complexes and selected results are given in table 2. The spectra support the mononuclear nature of the complexes. Although molecular ion peaks corresponding to the monomer are absent in some cases, peaks due to the fragments [{M–Cl} + H]$^+$, [{M–Cl$_2$} + H]$^+$ and [{M–Cl$_3$} + H]$^+$ were observed at 433 for **3**, 386 for **8**, and 367 *m*/*z* for **10**–**12**, respectively. Dominant peaks at 256, 242, 244 and 260 *m*/*z* in the spectra of **1**–**12** provide evidence for the presence of the organic ligands, i.e. [L + H]$^+$, in the complexes. Consequently, fragmentation of ligands is evident from peaks observed at 136, 126, 121, 109, 108 and 107 *m*/*z*. These are connected with fragments of adenine, [C$_6$H$_4$(Cl)–CH$_2$ + H]$^+$, and purine, [C$_6$H$_4$(F)–CH$_2$ + H]$^+$, [C$_6$H$_4$(OCH$_3$) + H]$^+$ and [C$_6$H$_4$(OH)–CH$_2$ + H$^+$], respectively.

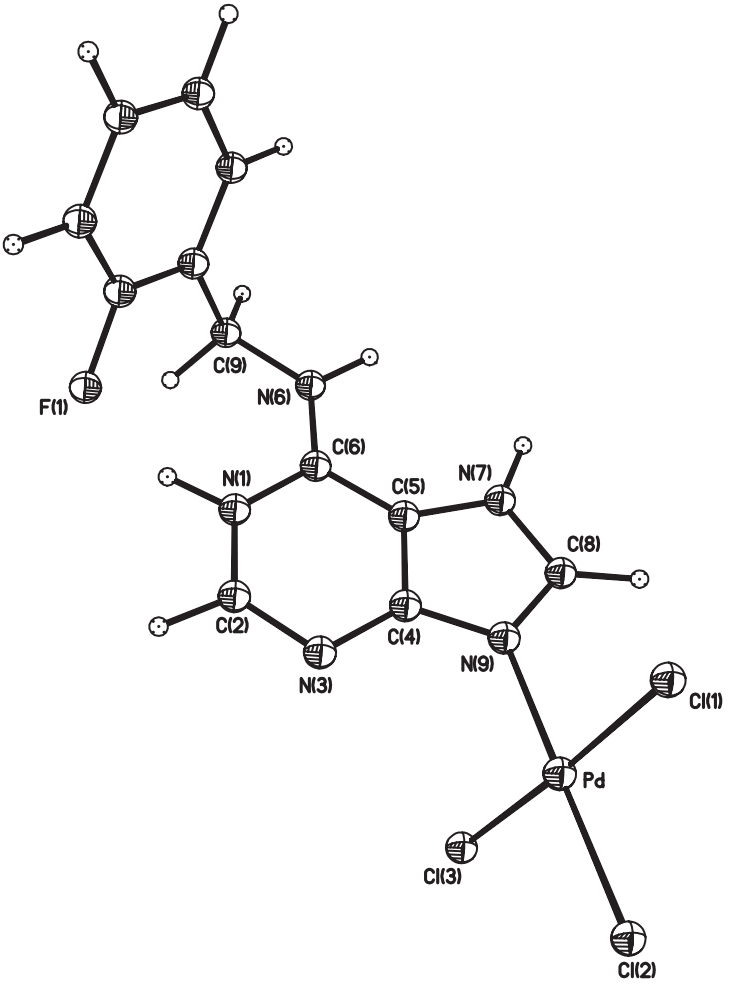


Figure 1. Geometry of **7** optimized at the B3LYP/lan2dz level of theory using the Gaussian03 program.

3.4. *Thermal analysis*

Thermal decomposition of **6** and **12** was studied in the temperature interval 20–560°C in air, while their DSC curves were recorded between 20 and 400°C; thermolyses of both complexes are very similar. Thermolysis of **6** starts at 35°C and the complex eliminates one uncoordinated water molecule (found/calcd: 3.4/3.6%). This step is accompanied by an endo-effect with the minimum at 52°C. Further decomposition proceeds in two steps. The first occurs between 180 and 330°C, while the second at 340–460°C. A broad endo-effect is observed with the minimum at 268°C. This is probably connected with the melting of the corresponding organic ligand, 6-(4-hydroxybenzylamino)purine. The melting point of the free ligand is 271–273°C. A plateau in the TG curve between 460 and 560°C is observed. The final product is a mixture of Pd and PdO as revealed by X-ray powder diffraction [28].

3.5. In vitro *cytotoxic activity*

The cytotoxicity of the complexes against malignant melanoma *G-361*, osteogenic sarcoma *HOS*, chronic myelogenous leukemia *K-562* and breast adenocarcinoma cell line *MCF7* was estimated. No complex showed significant cytotoxicity, with all IC_{50} values above 100 μM. There is no marked difference in relative cytotoxicity between the complexes and the free ligands. The highest IC_{50}, 56.6 μM, was found for 6-(2-chlorobenzylamino)purine, (2ClBap), in the case of the *G-361* cell line. IC_{50} values for the remaining free ligands are higher than 167 μM in the majority of cases, as described in the literature [15].

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