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Synthesis and structure of highly substituted pyrazole ligands and their complexes with platinum(II) and palladium(II) metal ions

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Abstract—Reaction of 3-methoxycarbonyl-2-methyl- or 3-dimethoxyphosphoryl-2-methyl-substituted 4-oxo-4*H*-chromones **1** with *N*-methylhydrazine resulted in the formation of isomeric, highly substituted pyrazoles **4** (major products) and **5** (minor products). Intramolecular transesterification of **4** and **5** under basic conditions led, respectively, to tricyclic derivatives **7** and **8**. The structures of pyrazoles **4a** (dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate) and **4b** (methyl 4-oxo-2-methyl-4*H*-chromene-3-carboxylate) were confirmed by X-ray crystallography. Pyrazoles **4a** and **4b** were used as ligands (L) in the formation of ML_2Cl_2 complexes with platinum(II) or palladium(II) metal ions (M). Potassium tetrachloroplatinate(II), used as the metal ion reagent, gave both *trans*-[Pt(**4a**)$_2$Cl$_2$] and *cis*-[Pt(**4a**)$_2$Cl$_2$], complexes with ligand **4a**, and only *cis*-[Pt(**4b**)$_2$Cl$_2$] isomer with ligand **4b**. Palladium complexes were obtained by the reaction of bis(benzonitrile)dichloropalladium(II) with the test ligands. *trans*-[Pd(**4a**)$_2$Cl$_2$] and *trans*-[Pd(**4b**)$_2$Cl$_2$] were the exclusive products of these reactions. The structures of all the complexes were confirmed by IR, ^{1}H NMR and FAB MS spectral analysis, elemental analysis and Kurnakov tests.

1. Introduction

cis-Platin [diamminedichloroplatinum, *cis*-$PtCl_2(NH_3)_2$] is known as a DNA-modifying agent with strong anticancer potency.[1] Despite its wide application as a therapeutic agent in chemotherapy, *cis*-platin is associated with many serious side effects, such as nephrotoxicity, othotoxicity, allergy etc.[2] Thus, various platinum(II) and palladium(II) complexes with nitrogen-containing ligands are the subject of intensive biological evaluation in the search for less toxic and more selective anticancer therapeutics.[3,4] Among them, the class of pyrazole-containing complexes have been reported to possess antitumor activity comparable to that of *cis*-platin.[5] In addition, considerable interest in the pyrazole nucleus has been stimulated by promising pharmacological, agrochemical and analytical applications of pyrazole-containing derivatives.[6–9] Recently, substituted pyrazoles have been used as analytical reagents in the complexation of transition metal ions.[10–13]

Chromone (benzo-γ-pyrone) derivatives form another class of biologically important compounds.[14] These compounds exhibit a wide spectrum of biologically relevant properties including anticonvulsant,[15] antimicrobial[16] and antitumor activities.[17] New chromone derivatives containing a phosphorus atom have been considered as bioisosteric analogues of natural chromones.[18,19] For many years the synthesis of phosphonic derivatives of benzo-γ-pyrone has been a subject of interest in several laboratories.[20–23] However, the biological activity of these compounds has not been investigated.

Thus, recently our research has been focused on the synthesis and pharmacological properties of phosphonic derivatives of chromones of general formulae **1** and **2**.[24] These compounds exhibit noticeable antibacterial, cytotoxic and alkylating activity. In terms of their chemistry, we carried out a detailed investigation of the transformation of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonates **1** [R=H or CH_3, R_1=CH_3, R_2=P(O)$(OCH_3)_2$] into 2-methoxy-3-[1-(alkylamino)ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2]oxaphosphinanes **2** (R=H or CH_3, R_1=CH_3).[25,26] The reaction involves the action of various primary amines [NH_2CH_3, NH_2CH_2Ph or $NH_2(CH_2)_2OH$] on the chromone system leading to the opening of the γ-pyrone ring, followed by spontaneous cyclisation of the intermediate enamino ketones **3** [R_3=CH_3, CH_2Ph or

Keywords: Phosphonic chromone; Pyrazole; Platinum(II) complex; Palladium(II) complex; X-ray structure.
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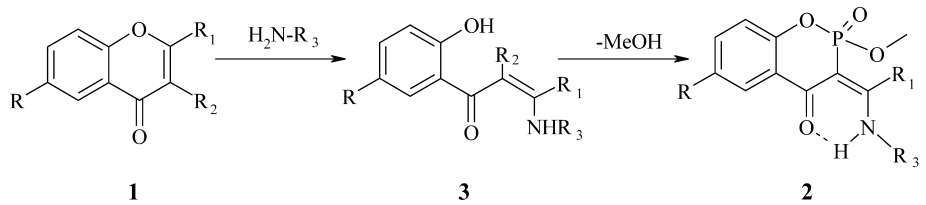
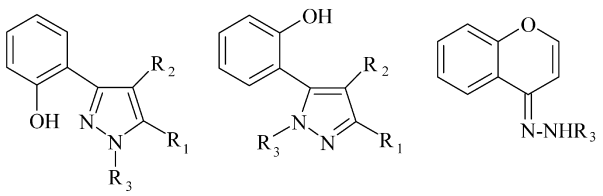


Scheme 1.

$(CH_2)_2OH$] into cyclic phosphonic isosteres of coumarin **2** (Scheme 1).

An analogous reaction of chromone itself with hydrazine hydrate led to 3- and/or 5-*o*-hydroxyphenylpyrazoles **4** or **5** (R_1, R_2 and R_3=H), and not the hydrazone **6**, as proposed in the early fifties.[27–29] Additional support comes from publications of Takagi[30] and Nawrot-Modranka and Kostka,[31,32] in which reaction of C3–Me, Ph or NO_2 substituted chromones with *N*-methylhydrazine leads to both isomeric products **4** and **5** (R_1=H, CH_3 or C_2H_5, R_2=CH_3, Ph or NO_2; R_3=CH_3). It was assumed that the molar ratio of the isomeric products **4** and **5** depends on the amount of nucleophilic reagent used.



4 **5** **6**

In the present work, we demonstrate that the reaction of phosphonic chromone **1a** [R=H, R_1=CH_3, R_2=$P(O)(OCH_3)_2$], as well as its C-3 methoxycarbonyl analogue **1b** (R_2=$COOCH_3$) with *N*-methylhydrazine leads to the substituted pyrazoles **4** and **5** and to the products of their intramolecular esterification—compounds **7** and **8**. Pyrazoles **4a** and **4b** were used as ligands (L) in the formation of ML_2Cl_2 complexes with platinum(II) or palladium(II) metal ions (M). The structures of the ligands and the resulting complexes were determined by their spectral and elemental analysis.

2. Results

2.1. Chemistry

2.1.1. Synthesis of ligands. An NMR scale reaction of **1a** with an equimolar amount of *N*-methylhydrazine was carried out in methanol. The progress of the conversion of **1a** was monitored by ^{31}P NMR spectroscopy and by thin layer chromatography (TLC). In the ^{31}P NMR spectrum (Fig. 1a), obtained within the first 15 min of the reaction, the signals of two new products at 19.57 (**4a**) and 18.34 ppm

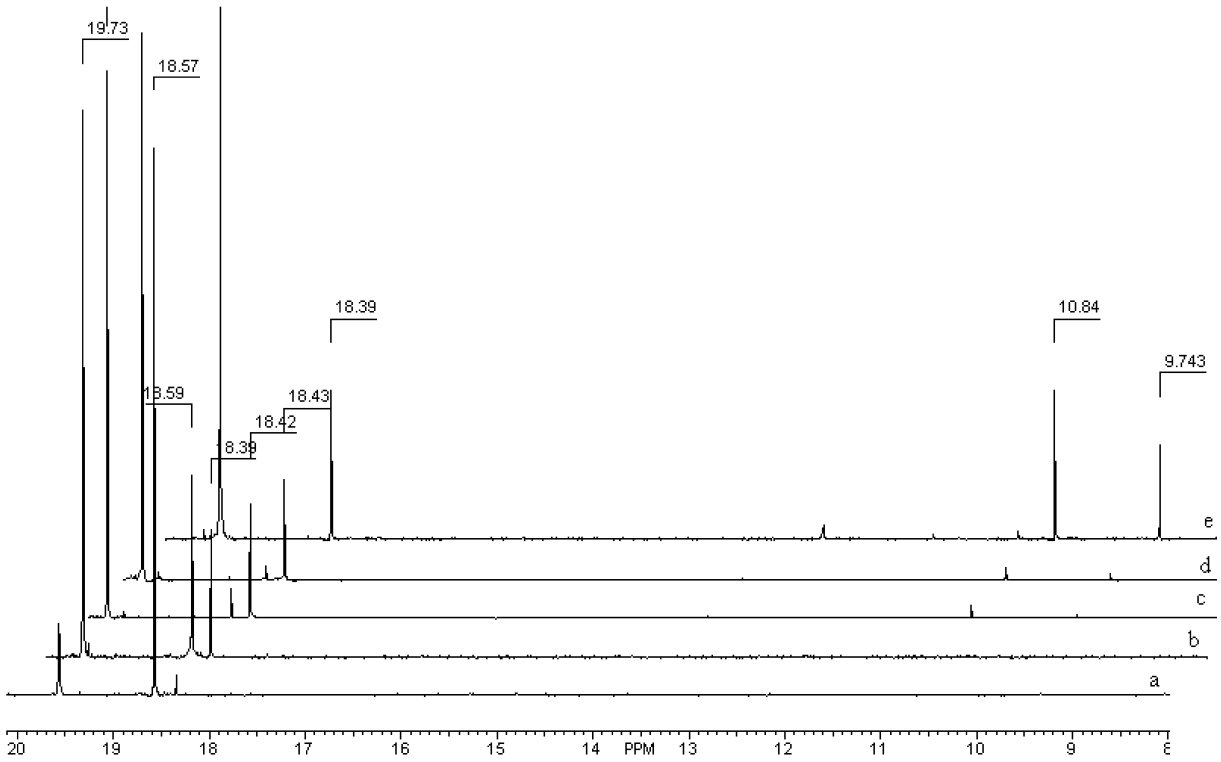


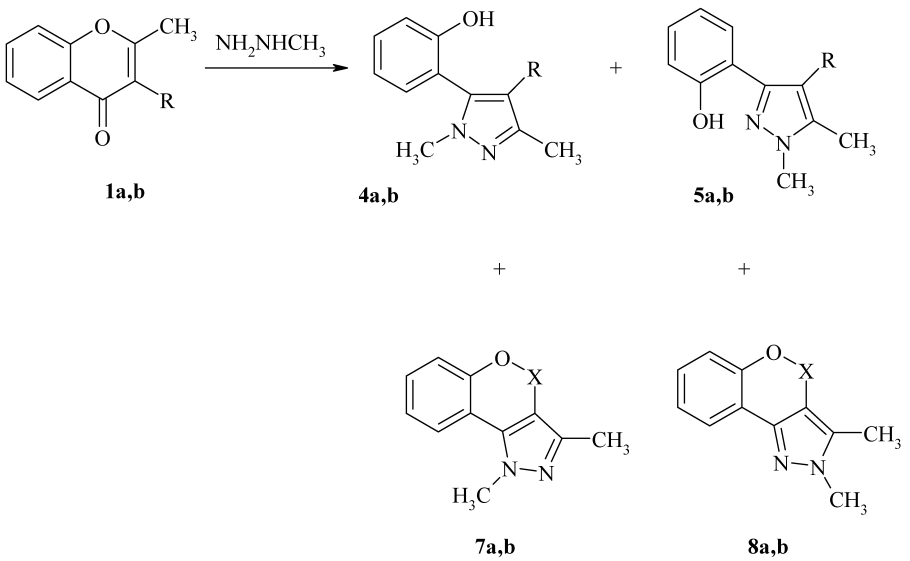
Figure 1. ^{31}P NMR analysis of the reaction products of chromone **1a** with 1 equiv. of *N*-methylhydrazine in methanol. The spectra were measured after 0.25 (a), 2 (b), 24 (c) and 48 h (d) of reaction time. Spectrum e was collected 24 h after addition of a second equivalent of *N*-methylhydrazine to the reaction mixture represented by spectrum d.

(**5a**) were observed, in addition to the signal of the substrate **1a** at 18.57 ppm. The intensity of these signals gradually increased until only traces of substrate were left (48 h, Fig. 1d). The ratio of the products was 4:1, with the major reaction product associated with the downfield resonance. Interestingly, after 24 h two additional minute signals could be seen in NMR spectrum (Fig. 1c). The ratio of these additional signals at 10.92 and 9.81 ppm was also 4:1. Careful chromatographic analysis allowed us to relate the mobility of these four products and their chemical shifts in the ^{31}P NMR spectra. No significant increase in the content of the two minor products was observed in the next 24 h (Fig. 1d); while addition of a second equivalent of *N*-methylhydrazine to the reaction mixture dramatically improved the yield of these products, giving rise to a higher intensity of the upfield signals. All four products were present after 15 min when the reaction was carried out in the absence of solvent or when a twofold molar excess of *N*-methylhydrazine in methanol was used. Similar ratios of both pairs of signals (ca. 4:1) were observed throughout these experiments (as in Fig. 1e).

The reaction of chromone **1a** with an equimolar amount of *N*-methylhydrazine, performed on a larger scale without any solvent, gave three isolated products. The major product (64% yield, δ 19.57 ppm) was isolated from the reaction mixture by addition of acetone, while the two other products, giving rise to signals at 10.92 and 9.81 ppm, respectively, were separated chromatographically from the remaining mixture. The major reaction product was shown to be the 5-(2-hydroxyphenyl)-1,3-dimethyl-4-phosphonyl-substituted pyrazole **4a** (Scheme 2). Unexpectedly, no isomeric 3-(2-hydroxyphenyl)-1,5-dimethyl-4-phosphonyl-substituted pyrazole **5a** (giving ^{31}P NMR signal at 18.34 ppm) was obtained. Instead, compound **8a** was isolated in 20% yield. Probably **5a**, formed in the first step of the reaction, was unstable under the chromatographic conditions and underwent intramolecular cyclisation giving rise to **8a**. The third reaction product, identified as **7a** and originating from an analogous cyclisation of **4a**, was obtained in the lowest yield (16%). The ratio of isolated products **8a** to **7a** (5:4) was much higher than present in ^{31}P NMR spectrum (1:4, Fig. 1e).

A multimilligram reaction of **1b** with one equivalent of *N*-methylhydrazine gave a similar mixture of products **4b** (64%), **7b** (16%) and **8b** (20%). No isomeric product **5b** was isolated, although it was seen during TLC analysis of the crude reaction mixture. Compounds **7b** and **8b** were previously obtained by Collota et al.[33] as by-products of the reaction of 3-acetyl-4-hydroxycoumarin with *N*-methylhydrazine in the presence of acetic acid but were not fully characterised. The reported melting points (194–196 and 210–212 °C) are in agreement with those obtained for our compounds **7b** and **8b** (192–194 and 208–209 °C, respectively).

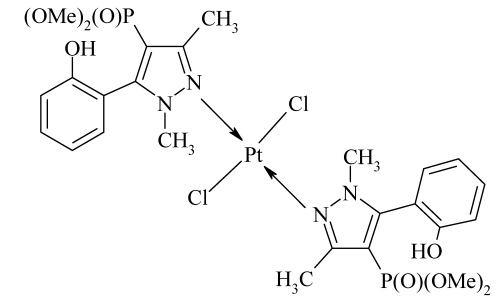
As expected, compound **4b** was readily transformed into tricyclic product **7b** on treatment with an equimolar amount of *N*-methylhydrazine. Thus, we conclude that both pairs of parent products **4a**,**5a** and **4b**,**5b** undergo intramolecular transesterification in the presence of *N*-methylhydrazine to give two pairs of products **7a**,**8a** and **7b**,**8b**, respectively. Moreover, products **5a** and **5b** are unstable under the isolation acidic conditions (silica gel) and are easily transformed into the stable tricyclic products **8a** and **8b**, respectively.



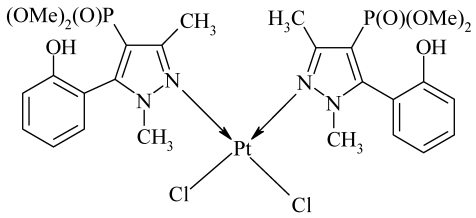
a: R= -P(O)(OCH$_3$)$_2$ X= >P(O)(OCH$_3$)

b: R= -COOCH$_3$ X= >C=O

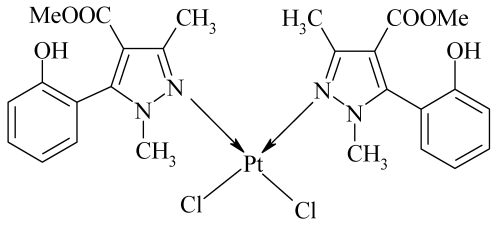
Scheme 2. Reaction of the phosphonic chromone **1a** and its C-3 methoxycarbonyl analogue **1b** with *N*-methylhydrazine.



9a



10a



10b

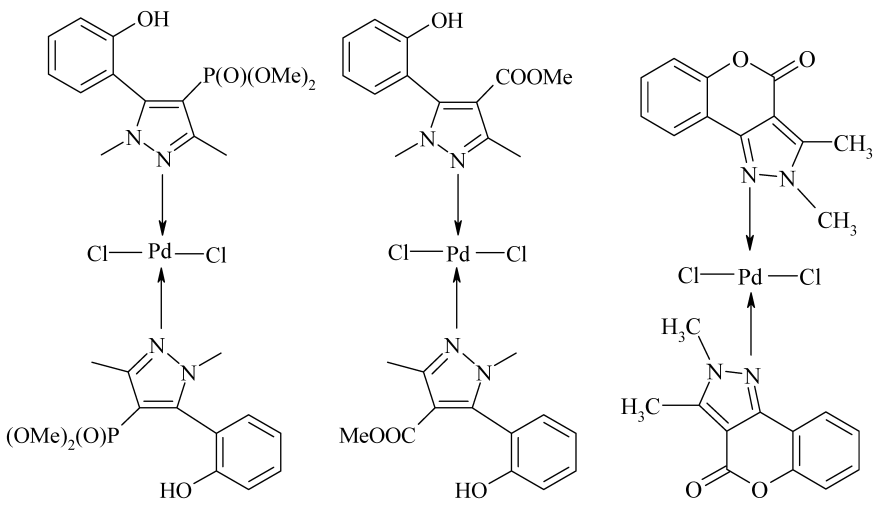
Figure 2. The structures of the platinum(II) complexes of the highly substituted pyrazoles **4a** and **4b**.

2.1.2. Synthesis of Pt(II) and Pd(II) complexes. Potassium tetrachloroplatinate(II) and bis(benzonitrile)dichloropalladium(II) were used as metal ion reagents. Synthesis of the platinum complexes of ligand **4a** was carried out in aqueous acetone at 60 °C for 6 h. Cooling the reaction mixture to ambient temperature, followed by slow removal of part of the solvent afforded a dark-brown precipitate which was filtered off. The remaining yellow solution was cooled in an ice bath and left for 24 h in −12 °C. The resulting yellow solid was filtered off. Both complexes were analysed by their IR spectra and a Kurnakov test.[34] The first compound, which has a melting point above 350 °C was identified as *trans*-[Pt(**4a**)$_2$Cl$_2$] **9a** and the remaining solid, with mp 153–156 °C, was identified as the *cis*-[Pt(**4a**)$_2$Cl$_2$] isomer **10a** (Fig. 2).

An analogous synthesis of the platinum complexes of ligand **4b** was carried out in aqueous ethanol for 72 h at room temperature. In this reaction only one complex was obtained. It was identified as *cis*-[Pt(**4b**)$_2$Cl$_2$] **10b**.

Palladium complexes of ligands **4a** and **4b** were synthesized by addition of a dichloromethane solution of ligand to a solution of bis(benzonitrile)dichloropalladium(II) in the same solvent at RT in 24 h. Only one complex was isolated from each reaction. Spectral analysis of the resulting complexes showed that exclusively the *trans* isomers, **11a** and **11b** were formed (Fig. 3).

We also tested the most available chromone analogue ligand **8b** for its potential to form a palladium complex. Thus an analogous reaction with bis(benzonitrile)dichloropalladium(II) in dichloromethane was performed with this ligand. The resulting solid, mp 334 °C, was identified by FAB MS spectrometry and elemental analysis as the complex [Pd(**8b**)$_2$Cl$_2$]. Its poor solubility in most of the suitable solvents did not allow us to obtain ^{1}H NMR spectrum. However, careful infrared data analysis enabled us to deduce that it is the *trans*-isomer **12b**, since palladium(II) metal ion form predominantly *trans*-complexes,



11a **11b** **12b**

Figure 3. The structures of the palladium(II) complexes of the highly substituted pyrazoles **4a**, **4b** and **8b**.

Table 1. Selected geometric parameters of the crystal structures of **4a** and **4b**

Environment of P atom		Geometric parameters for pyrazole ring			
4a	(Å)	**4a**	(Å)	**4b**	(Å)
P1–O1	1.464(2)	N1–N2	1.356(2)	N1–N2	1.358(2)
P1–O2	1.567(2)	N2–C3	1.321(2)	N2–C3	1.327(3)
P1–O3	1.556(1)	C3–C4	1.420(2)	C3–C4	1.416(3)
P1–C4	1.757(2)	C4–C5	1.393(2)	C4–C5	1.394(3)
O1–P1–O3	114.7(1)	C5–N1	1.347(2)	C5–N1	1.351(2)
O1–P1–O2	107.5(1)	N1–N2–C3	105.5(1)	N1–N2–C3	106.2(2)
O3–P1–O2	107.6(1)	N2–C3–C4	110.8(2)	N2–C3–C4	110.0(2)
O1–P1–C4	115.6(1)	C3–C4–C5	104.9(2)	C3–C4–C5	105.8(2)
O3–P1–C4	103.1(1)	C4–C5–N1	106.0(2)	C4–C5–N1	105.8(2)
O2–P1–C4	108.0(1)	C5–N1–N2	112.8(1)	C5–N1–N2	112.3(2)

Table 2. Hydrogen bonding geometry for structure **4a** and **4b**

	D–H (Å)	H···A (Å)	D···A (Å)	<D–H···A (deg)
Structure **4a**				
O52–H52···O1^{i}	0.82(4)	1.87(4)	2.688(2)	175(3)
Structure **4b**				
O51–H51···N2^{ii}	0.98(2)	1.80(2)	2.763(2)	167(2)

Symmetry code: (i) $x-1$, y, z; (ii) $x+\frac{1}{2}$, $-y+\frac{1}{2}+1$, $-z$.

characterised by a sharp Pd–Cl band in the range of ca. 350 cm^{-1}. In contrast, *cis*-complexes exhibit broad or double IR band in the range of ca. 330 cm^{-1}.[35]

2.2. Structural studies

2.2.1. X-ray crystallographic study of ligands 4a and 4b. X-ray structure investigations were undertaken for the two major ligands **4a** and **4b**. The structure of **4a** shows the pyrazole ring substituted by methyl groups at positions 1 and 3, a dimethyl phosphonate moiety at C-4 and a hydroxyphenyl group at position 5. The pyrazole and phenyl rings are planar. The geometry around the P atom is best described as between a distorted tetrahedron and a trigonal pyramid with a P1–C4 elongated bond (Table 1). An intermolecular hydrogen bond between O52–H52 and O1^{i} [symmetry code: (i) $x-1$, y, z] is observed (Table 2).

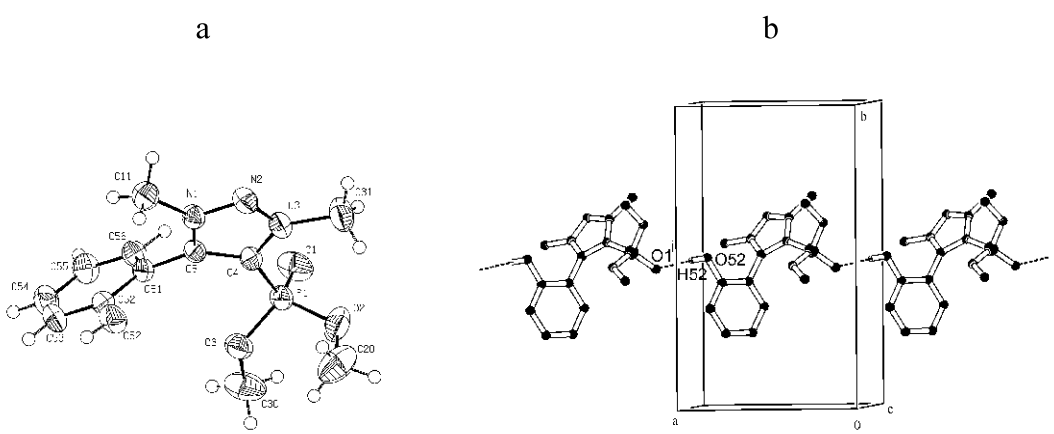


Figure 4. X-ray structure of **4a** (a) single molecule and (b) crystal lattice.

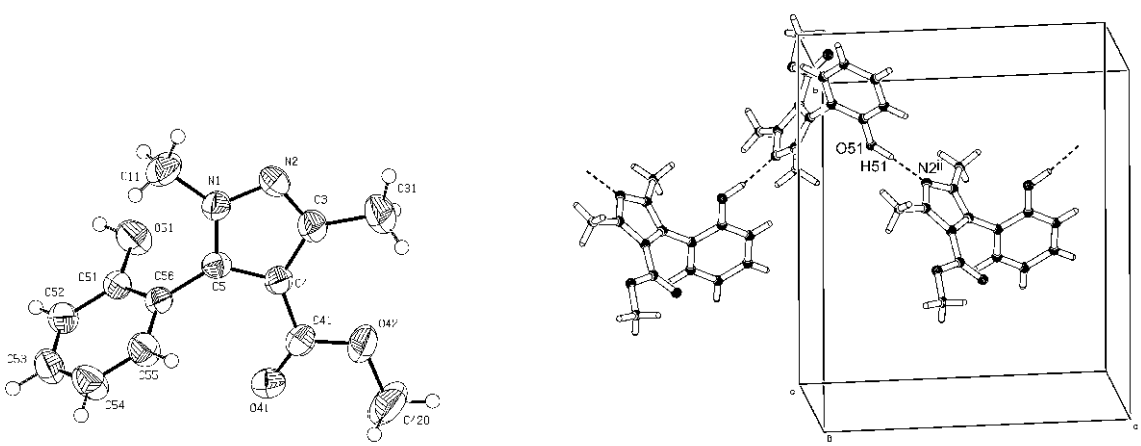


Figure 5. X-ray structure of **4b** (a) single molecule and (b) crystal lattice.

Thus the molecules form chains running along the *a* axis (Fig. 4b).

The structure of molecule **4b** (Fig. 5a) shows a pyrazole ring substituted with methyl groups at positions 1 and 5, a methoxycarbonyl group at C-4 and a hydroxyphenyl group at position 3. The pyrazole and phenyl rings are planar. The dihedral angle between the pyrazole ring and the phenyl ring is 69.07(7)°. In the crystal lattice the molecules are linked by an intermolecular hydrogen bond O51–H51···N2^{ii} [symmetry code: (ii) $x+\frac{1}{2}, -y+\frac{1}{2}+1, -z$] (Table 2 and Fig. 5b).

All intra-molecular bond distances and angles are in a good agreement with expected values.[36]

2.2.2. Spectral characteristics of Pt(II) and Pd(II) complexes. The assignments of the most important IR spectra bands for the ligands **4a** and **4b** and the platinum(II) and palladium(II) complexes **9**–**12** are listed in Tables 3 and 4.

The IR spectrum of ligand **4a** (Table 3) shows a large number of absorption bands in the range 1700–1000 cm^{-1} assigned to different vibration modes of the pyrazole ring and phosphonate function. The band at 1600 cm^{-1}, assigned to the C=N vibration, shifts to higher energy in the IR spectra of complexes **9a**–**11a**, giving rise to the bands at 1614 and 1618 cm^{-1} for the Pt and Pd complexes, respectively. The same tendency in the shift of C=N vibration to higher energy is seen for complexes **10b**–**12b** (Table 4). This phenomenon indicates that the nitrogen atom participates in the coordination of the metal ion.[37] The other characteristic bands of the pyrazole ring of the free ligand shift to higher frequencies upon complexation confirming coordination of the heterocyclic N atoms.

The two new bands at about 400 cm^{-1} in both Pt and Pd complexes may correspond to the metal-nitrogen vibrations involving the N-atoms of the pyrazole ring.[38] The absorption observed in the low-energy region at 310–350 cm^{-1} is assigned to the M−Cl stretching vibration.[39]

Table 3. IR frequencies for pyrazole derivative **4a** and for complexes **9a**, **10a** and **11a**

ν (cm^{-1})	OH	–N=C–	P=O	P–O–C	M–N–	M–Cl
4a	3131	1594	1213	1049	—	—
9a	3449	1637	1228	1038	422	326
10a	3475	1614	1223	1036	487	332
11a	3443	1618	1238	1044	421	354

Table 4. IR frequencies for pyrazole derivatives **4b** and **8b** and for their complexes **10b**–**12b**

1	OH	–C=O	–N=C–	C–O–C	M–N–	M–Cl
4b	3081	1721	1611	1097	—	—
10b	3478	1722	1615	1098	480	330
11b	3342	1714	1614	1124	414	354
8b	—	1737	1592	—	—	—
12b	—	1755	1619	—	420	354

Table 5. ^{1}H and ^{31}P NMR (DMSO-d_6) characteristics of pyrazole **4a** and **4b** and their complexes with Pt(II) and Pd(II) metal ions (chemical shifts are given in ppm). $\Delta\delta$ corresponds to the difference in chemical shifts of protons in the ligands and in the corresponding complexes

	C–CH$_3$	OCH$_3$	O–CH$_3$	N–CH$_3$	OH	^{31}P NMR
4a	2.283	3.363	3.436	3.494	9.986	19.57
9a	2.425	3.523	3.701	3.889	10.145	17.89
$\Delta\delta$	0.142	0.160	0.238	0.395	0.159	1.68
10a	2.385	3.465	3.537	3.780	12.04	18.07
$\Delta\delta$	0.102	0.102	0.101	0.286	2.100	1.50
11a	2.210	3.461	3.513	3.682	10.210	18.30
$\Delta\delta$	0.073	0.098	0.077	0.186	0.224	1.27
4b	2.352	—	3.508	3.355	9.821	—
10b	2.368	—	3.612	3.394	9.954	—
$\Delta\delta$	0.016	—	0.104	0.039	0.133	—
11b	2.348	—	3.504	3.366	9.802	—
$\Delta\delta$	0.004	—	0.004	0.009	0.019	—

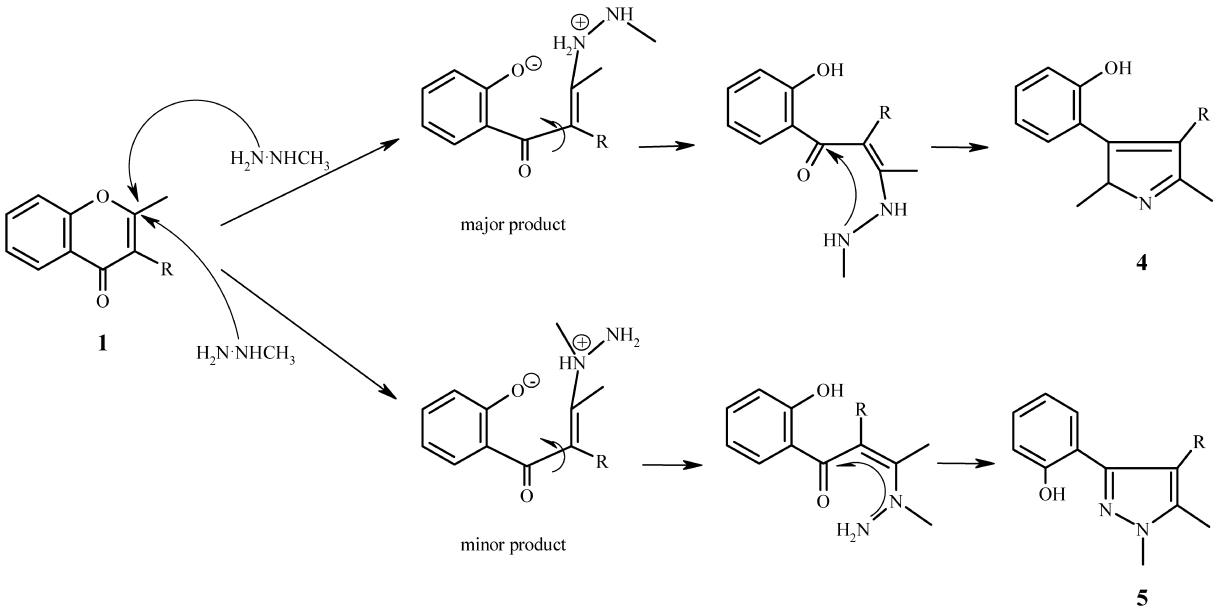
The selected chemical shifts assigned in the ^{1}H NMR spectra of pyrazole **4a** and **4b** and their P(II) and Pd(II) complexes **10** and **11** are shown in Table 5. The spectra are quite similar, however, in the metal complexes, all the signals are shifted downfield.[8] The differences between the chemical shifts of protons in the ligands and in the corresponding complexes are shown as $\Delta\delta$ (in ppm).

Apart from the remarkable values of $\Delta\delta$ for the OH groups the biggest differences in the chemical shifts of complexes **9a**, **10a**, **11a** and **11b** and their parent ligands are observed for the methyl group attached to the nitrogen atom adjacent to the coordinating center. In the spectrum of complex **10b** the most significant shift is observed for the methyl ester group.

3. Discussion

In the present work we describe the synthesis of several novel, highly substituted pyrazole derivatives as well as their complexes with Pt(II) and Pd(II) metal ions. Isomeric pyrazoles **4a**,**b** and **5a**,**b**, containing phosphonic or carboxylic acid residues, were obtained by means of the reaction of phosphonic chromone **1a** or its C-3 methoxycarbonyl analogue **1b**, with *N*-methylhydrazine (Scheme 2). The reaction proceeded according to the general mechanism described for the reaction of chromones with nitrogen nucleophiles,[40,41] including hydrazines.[31,32,42,43] Attack of a nitrogen nucleophile at C-2 of the chromone led to the opening of the γ-pyrone ring. When an alkylamine was used as the nucleophilic agent an enamino ketone derivative (as e.g., **3**) was formed.[25] Further reactions could occur when the initial product contained other reactive groups (as for example reaction of **1a** with methylamine which resulted in the formation of the cyclic phosphonic isostere **2** (R_1, R_3=CH_3) of coumarin). An analogous reaction of chromone **1** (R, R_1, R_2=H) with *N*-methylhydrazine led to both isomeric products **4** and **5** (R_1, R_2=H and R_3=CH_3) and not to the hydrazone **6**, as initially proposed.[27–29] It was also suggested that the molar ratio of the isomeric products **4** and **5** (R_1, R_2=H and R_3=CH_3) depends on the amount of nucleophilic reagent used such a reaction.[31]

In our experiments, the progress of the reaction of chromone derivative **1a** with *N*-methylhydrazine (1:1 molar ratio) in



Scheme 3. Proposed mechanism of the formation of isomeric pyrazoles **4** and **5**.

methanol was monitored by ^{31}P NMR spectroscopy. The ^{31}P NMR spectra monitored after 0.25, 2, 24 and 48 h of the reaction showed the presence of the signals of the two new products identified as **4a** and **5a** (Fig. 1a–d, respectively). Both products were formed in a ratio of 4:1, independently of the reaction time. Thus, according to the general mechanism, we assume that, in the first step, C-2 of the chromone is attacked by the nitrogen nucleophile resulting in opening of the γ-pyrone ring. Both nitrogen atoms of *N*-methylhydrazine may be considered as nucleophiles. Their participation in this reaction is governed by their relative nucleophilicity and their steric accessibility. No pKa value for N-1 of *N*-methylhydrazine has been reported while the value for N-2 was determined as 7.87.[44] It seems that N-1 should be a better nucleophile due to the presence of the electron donating adjacent methyl group. On the other hand, the presence of the methyl group causes steric hindrance which makes N-1 a less effective nucleophile. Thus, two opening products are formed - a major product, resulting from nucleophilic attack of the sterically more accessible N-2, and a minor product, arising from participation of the less sterically accessible although the more basic N-1 (Scheme 3). Both intermediate hydrazines undergo subsequent spontaneous cyclisation with the carbonyl group of the opened γ-pyrone system leading to the major product **4b** and minor product **5b**, respectively. As determined by integration of ^{31}P NMR spectra the ratio of products **4b** to **5b** is 4:1, and is similar to the ratio of products obtained in the reaction carried out without any solvent. Two other products, **7a** and **8a**, are the products of intramolecular transesterification of the parent pyrazoles **4a** and **5a**, respectively.

The proposed earlier mechanism of nucleophilic opening of chromone ring, by which **4a** can be formed exclusively, while its isomer, compound **5a** can be obtained by the reaction of the intermediate major enamine ketone with an additional *N*-methylhydrazine followed by cyclisation of the respective hydrazone,[31] does not explain our data. Our proposed mechanism for the formation of the isomeric pyrazoles is outlined in Scheme 3. An analogous mechanism is proposed for the formation of isomeric pyrazoles **4b** and **5b** and their intramolecular transesterification products **7b** and **8b**.

The structures of the **9a**, **10a**,**b** and **11a**,**b** metal complexes were confirmed by spectral (IR, ^{1}H NMR and FAB MS) and elemental analysis. DMSO-d_6 was the solvent of choice in proton NMR experiments because of the very limited solubility of all complexes in other solvents. For complex **12b** it was impossible to obtain good ^{1}H NMR spectrum due to its very poor solubility, even in DMSO. We should point out that DMSO replaces chlorine atoms in *cis*-and *trans*-platin[45,46] and thus the data obtained in our measurements may not be unequivocally attributed to structures **9**, **10** and **11** but possibly to their DMSO analogues.

4. Conclusions

Several highly substituted pyrazole ligands were obtained by the reaction of dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate and 2-methyl-4-oxo-4*H*-chromene-3-carboxylic acid methyl ester with *N*-methylhydrazine. Selected compounds were used as ligands for the synthesis of novel ML_2Cl_2 type platinum(II) and palladium(II) complexes. The structures of the ligands and the metal complexes were confirmed by spectral and elemental analyses. The structures of ligands **4a** and **4b** were confirmed by X-ray analysis. The biological activities of the palladium(II) and platinum(II) complexes will be reported in due course.

5. Experimental

5.1. General

The melting points were determined using an Electrothermal 1A9100 apparatus and they are uncorrected. The IR spectra were recorded on a Pey-Unicam 200G

Spectrophotometer in KBr or CsI. The ^{1}H NMR spectra were registered at 300 MHz on a Varian Mercury spectrometer. ^{31}P NMR spectra were recorded on a Varian 75 MHz spectrometer. Positive chemical shift values are assigned to compounds resonating downfield of phosphoric acid. The MS data were obtained on a LKB 2091 mass spectrometer (70 eV ionisation energy) and the MS-FAB data were determined on Finnigan Matt 95 mass spectrometer (NBA, Cs^+ gun operating at 13 keV). Satisfactory elemental analyses (±0.3% of the calculated values) were obtained for the new compounds in the Microanalytical Laboratory of the Department of Bioorganic Chemistry (Medical University, Lodz) using a Perkin Elmer PE 2400 CHNS analyser or in the Institute for Physical Chemistry, University of Vienna, Austria. Dimethyl 2-methyl-4-oxo-4*H*-chromen-3-yl-phosphonate (**1a**), was prepared according to literature,[20] methyl 2-methyl-4-oxo-4*H*-chromene-3-carboxylate (**1b**) was prepared according to literature.[47]

5.2. Synthesis of compounds 4a, 7a and 8a

To the solution of chromone **1a** 268 mg (1.0 mmol) in methanol (5 mL) *N*-methylhydrazine, 9.2 mg (2.0 mmol) solution in methanol (0.5 mL) was added. The mixture was left overnight at room temperature. The mixture was concentrated to dryness and then dry acetone was added. Crude solid **4a** was filtered off, dried, and recrystallized from acetone. The remaining solution was evaporated to dryness and chromatographed on a silica gel column. Pure **4a** was eluted from the column with chloroform–acetone 5:1, v/v.

5.2.1. Dimethyl [5-(2-hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazol-4-yl]-phosphonate (4a). Yield: 189.6 mg (64%, acetone), mp 176.9–179.2 °C, R_f=0.19 (chloroform–acetone, 5:1). IR (KBr): ν=3131 (OH); 1594 (N=C); 1213 (P=O); 1049 (P–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.41 (s, 3H, CH_3); 3.51 (d, 3H, OCH_3, $^3J_{PH}$=11.7 Hz); 3.59 (s, 3H, N–CH_3); 3.70 (d, 3H, OCH_3, $^3J_{PH}$=11.7 Hz); 7.08–7.31 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$) δ=13.89 (C–CH_3); 36.91 (N–CH_3); 52.57 (P–O–CH_3, $^2J_{PC}$=5.73 Hz); 102.85 (C–P, $^1J_{PC}$=221.6 Hz); 116.49; 117.16; 119.46; 131.2; 146.84; 151.1; 155.42. ^{31}P NMR ($CDCl_3$) δ=19.57. MS (70 eV) *m*/*z* (%): 296 (100, M$^+$), 279 (18.37), 233 (10.38), 201 (9.98), 187 (10.59), 115 (5.25). Anal. found: C, 52.78; H, 5.84; N, 9.58; P, 10.61. Calcd for $C_{13}H_{17}N_2O_4P$ (296.26): C, 52.7; H, 5.78; N, 9.46; P, 10.45%.

5.2.2. 4-Methoxy-1,3-dimethyl-1,4-dihydro[1,2]benzoxaphosphinino[4,3-c]pyrazole-4-oxide (7a). Yield: 42.3 mg (16%), mp 103.0–104.7 °C, R_f=0.38 (chloroform–acetone, 5: 1). IR (KBr): ν=3360 (OH); 1250 (P=O); 1028 (P–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.48 (d, 3H, C–CH_3, J_{PC}=1.19 Hz); 3.80 (d, 3H, OCH_3, $^3J_{PC}$=11.9 Hz); 4.22 (s, 3H, N–CH_3); 7.30–7.86 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ 13.2 (C–CH_3); 37.3 (N–CH_3); 53.0 (P–O–CH_3, $^2J_{PC}$=6.6 Hz); 104.0 (P–C, $^1J_{PC}$=212.7 Hz); 115.9; 121.21; 126.92; 148.73; 149.9; 150.6. ^{31} P NMR ($CDCl_3$): δ 10.86. MS (70 eV) *m*/*z* (%): 264(100, M$^+$); 233(29); 132(8.7); 56(13.19). Anal. found: C, 54.46; H, 5.14; N, 10.53; P, 11.97. Calcd for $C_{12}H_{13}N_2O_3P$ (264.21): C, 54.50; H, 4.96; N, 10.60; P, 11.72%.

5.2.3. 4-Methoxy-2,3-dimethyl-2,4-dihydro[1,2]benzoxaphospinono[4,3-c]pyrazole-4-oxide (8a). Yield: 52.8 mg (20%), mp 147.5–149.0 °C, R_f=0.24 (chloroform–acetone 5:1). IR (KBr): ν=3375 (OH); 1259 (P=O); 1031 (P–O–C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.53 (s, 3H, C–CH_3, J_{PC}=3.9 Hz); 3.74 (d, 3H, OCH_3, $^3J_{PC}$=12.0 Hz); 3.89 (s, 3H, N–CH_3); 7.13–7.98 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=11.68 (C–CH_3); 36.82 (N–CH_3); 53.20 (P–O–CH_3, $^2J_{PC}$=6.58 Hz); 100.42 (P–C, $^1J_{PC}$=212.71 Hz); 117.46; 119.21; 124.21; 130.02; 143.33; 149.09; 151.02. ^{31}P NMR ($CDCl_3$): δ=9.64. MS (70 eV) *m*/*z* (%): 264(100, M$^+$); 249(11); 233(21.52); 132(5.07); 56(13.19). Anal. found: C, 54.56; H, 5.24; N, 10.43; P, 11.54. Calcd for $C_{12}H_{13}N_2O_3P$ (264.21): C, 54.55; H, 4.96; N, 10.60; P, 11.72%.

5.3. Reaction of 3-carboxylic derivatives of chromones with *N*-methylhydrazine

To a solution of **1b** (218.2 mg, 1.0 mmol) in methanol (5 mL) a solution of *N*-methylhydrazine (9.2 mg, 2.0 mmol) in methanol (0.5 mL) was added. The mixture was stirred at room temperature and after 2 h the product **8b** precipitated. The solid was filtered off and than recrystallized from methanol. The filtrate was left at room temperature overnight. After this time the product **4b** was filtered off, and recrystallized from acetone. The filtrate was evaporated to dryness and the residual solid was recrystallized from methanol to give **7b** as a crystalline white solid.

5.3.1. 5-(2-Hydroxyphenyl)-1,3-dimethyl-1*H*-pyrazole-4-carboxylic acid methyl ester (4b). Yield: 169.1 mg (64%), mp 182.5–183.5 °C, R_f=0.29 (chloroform–acetone, 5:1). IR (KBr): ν=3133 (OH); 1721 (C=O); 1611 (N=C); 1097 (C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.47 (s, 3H, CH_3); 3.62 (s, 3H, N–CH_3); 3.72 (s, 3H, OCH_3); 7.01–7.38 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=14.40 (C–CH_3); 37.23 (N–CH_3); 51.71 (O–CH_3); 111.18; 111.67; 118.16; 120.46; 131.29; 143.62; 150.50; 154.54; 165.55. MS (70 eV) *m*/*z* (%): 247(100, M$^+$); 215 (6.0). Anal. found: C, 63.48; H, 5.81; N, 11.43. Calcd for $C_{13}H_{14}N_2O_3$ (246.26): C, 63.40; H, 5.73; N, 11.38%.

5.3.2. 1,3-Dimethyl-1*H*-chromeno[4,3-*c*]pyrazol-4-one (7b). Yield: 34.3 mg (16%), mp 192.5–193.9 °C, R_f=0.38 (chloroform–acetone, 5:1). IR (KBr): ν=1731 (C=O); 1612 (–N=C–); 1018 (C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.60 (s, 3H, CH_3); 4.27 (s, 3H, N–CH_3); 7.35–7.94 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=13.11 (C–CH_3); 39.89 (N–CH_3); 112.62; 118.57; 122.28; 124.44; 130.97; 149.54; 158.25 (C=O). MS (70 eV) *m*/*z* (%): 215 (100, M+H$^+$); 203 (14.0); 117 (6.0); 93 (5.25). Anal. found: C, 67.33; H, 4.77; N, 13.35. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.70; N, 13.08%.

5.3.3. 1,5-Dimethyl-1*H*-chromeno[4,3-c]pyrazol-4-one (8b). Yield: 42.8 mg (20%) mp 208–209 °C, R_f=0.27 (chloroform–acetone, 5:1). IR (KBr): ν=1737 (C=O); 1592 (–N=C–) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.69 (s, 3H, CH_3); 3.96 (s, 3H, N–CH_3); 7.25–8.01 (m, 4H, arom.). ^{13}C NMR ($CDCl_3$): δ=11.02 (C–CH_3); 37.12 (N–CH_3); 115.22; 117.69; 118.16; 122.46; 124.42; 130.13; 162.30 (C=O). MS (70 eV) *m*/*z* (%): 215 (100, M$^+$+H$^+$), 203

(14.0); 117 (6.0); 93 (5.25). Anal. found: C, 67.13; H, 4.76; N, 13.21. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.70; N, 13.08%.

5.4. Syntheses of complexes *trans*-[Pt(4a)$_2$Cl$_2$] (9a) and *cis*-[Pt(4a)$_2$Cl$_2$] (10a)

$K_2[PtCl_4]$ (83.4 mg, 0.20 mmol) was dissolved in 3 mL of acetone–water (1:1) mixture and the solution was slowly added to solution of pyrazole **4a** (118.5 mg, 0.40 mmol) in acetone (5 mL). A pink solid started to precipitate at the end of the addition. The suspension was heated to reflux at 115 °C with good stirring. After 6 h at reflux, a brown powder precipitated was filtered off and dried to give complex **9a**. The remaining yellow solution was cooled down in an ice bath and left for 24 h in the freezer (−12 °C). The yellow powder was filtered off, washed with cold water and then with diethyl ether, to afford **10a**.

5.4.1. *trans*-[Pt(4a)$_2$Cl$_2$] (9a). Yield: 12.0 mg (7%), mp>350 °C. IR (CsI): ν=3449 (OH); 1637 (N=C); 1228 (P=O); 1038 (P–O–C); 422 (M−N); 326 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.43 (s, 3H, CH_3); 3.52 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.70 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.89 (s, 3H, N–CH_3); 7.00–8.16 (m, 4H, arom.), 10.15 (s, 1H, OH). ^{31}P NMR (DMSO): δ=17.89. MS-FAB *m/z*: 857. Anal. found: C, 36.66; H, 4.06; N, 6.39. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pt$ (858.51): C, 36.37; H, 3.99; N, 6.53%.

5.4.2. *cis*-[Pt(4a)$_2$Cl$_2$] (10a). Yield: 138.0 mg (80%), mp 153–156 °C. IR (CsI): ν=3461 (OH); 1218.5 (P=O); 1038.4 (P–O–C); 585 (Pt–N); 426.8; 343 (Pt–Cl) cm^{-1}.^{1}H NMR (DMSO): δ=2.39 (s, 3H, CH_3); 3.47 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.54 (d, 3H, O–CH_3, $^3J_{PH}$=11.9 Hz); 3.78 (s, 3H, N–CH_3); 6.96–7.84 (m, 4H, arom.), 12.04 (s, 1H, OH). ^{31}P NMR (DMSO): δ=18.07. ^{13}C NMR (DMSO-d_6): δ=14.07 (C–CH_3); 37.09 (N–CH_3); 52.75 (d, P–O–CH_3, $^2J_{PC}$=5.73 Hz); 103.05 (C–P, $^1J_{PC}$=221.6 Hz); 117.09; 117.36; 119.86; 131.43; 147.14; 151.61; 155.96. MS-FAB *m/z*: 857. Anal. Found: C, 36.61; H, 4.11; N, 6.47. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pt$ (858.51): C, 36.37; H 3.99; N 6.53%.

5.5. Syntheses of *cis*-[Pt(4b)$_2$Cl$_2$] complex 10b

$K_2[PtCl_4]$ (41.5 mg, 0.10 mmol) was dissolved in water (5 mL) and ligand **4b** (49.25 mg, 0.2 mmol), dissolved in methanol (15 mL), added slowly dropwise. The mixture was stirred for 48 h at room temperature, and then half of the volume of methanol was removed under reduced pressure at room temperature. A yellow solid started to precipitate at the end of concentration. The solid was filtered off, washed with water and then with diethyl ether and dried in vacuo to give complex **10b**.

5.5.1. *cis*-[Pt(4b)$_2$Cl$_2$] complex 10b. Yield: 25.8 mg (34%)) mp 263 °C dec. IR (CsI): ν=3342 (OH); 1722 (C=O); 1615 (N=C); 1098 (C–O–C); 480 (M−N); 330 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.37 (s, 3H, C–CH_3); 3.39 (s, 3H, N–CH_3); 3.61 (d, 3H, OCH_3); 7.18–7.74 (m, 4H, arom.); 9.95 (s, 1H, OH). MS-FAB *m/z*: 758.0. Anal. found: C, 41.40; H, 3.96; N, 7.43. Calcd for $C_{26}H_{28}N_4O_6Cl_2Pt$ (758.49): C, 41.2; H, 3.72; N, 7.38%.

5.5.2. Syntheses of the complex *trans*-[Pd(4a)$_2$Cl$_2$] (11a). Compound **4a** (118.5 mg, 0.4 mmol) dissolved in dichloromethane (5 mL) was added to a solution of [Pd(C_6H_5CN)$_2$-Cl_2] (76.7 mg, 0.2 mmol) in the same solvent (5 mL). The reaction mixture was left with stirring at room temperature. After 2 h a yellow powder precipitated from the reaction mixture. The stirring was continued for the next 24 h. The resulting solid was filtered off, washed with water and then with diethyl ether and dried overnight in vacuo.

Yield: 124.7 mg (81%) mp 223 °C dec. IR (CsI): ν=3373 (OH); 1205 (P=O); 1020 (P–O–C); 573 (Pd–N); 382 (Pd–Cl) cm^{-1}. ^{1}H NMR (DMSO): δ=2.98 (s, 3H, CH_3); 3.43 (d, 3H, P–OCH_3, $^3J_{PH}$=11.7 Hz); 3.59 (s, 3H, N–CH_3); 3.68 (d, 3H, $POCH_3$, $^3J_{PH}$=11.7 Hz); 7.21–7.78 (m, 4H, arom.); 10.21 (s_{broad}, 1H, OH). ^{31}P NMR (DMSO): δ=18.3. MS-FAB *m/z*: 769.0. Anal. found: C, 40.34; H, 4.47; N, 7.41; P, 8.31. Calcd for $C_{26}H_{34}N_4O_8P_2Cl_2Pd$ (769.93): C, 40.56; H, 4.45; N, 7.2; P, 8.04%.

5.5.3. Synthesis of Pd(II) complex *trans*-[Pd(4b)$_2$Cl$_2$] (11b). Compound **4b** (123.1 mg, 0.5 mmol) dissolved in dichloromethane (5 mL) was added to the solution of [Pd(C_6H_5CN)$_2$Cl$_2$] (95.9 mg, 0.25 mmol) in the same solvent (5 mL). The mixture was left with stirring at room temperature. After 2 h, a yellow powder precipitated. The stirring was continued for 24 h. The resulting precipitate was filtered off, washed with water and then with diethyl ether, and dried overnight in vacuo.

Yield: 138 mg (83%) mp 336 °C dec. IR (CsI): ν=3342 (OH); 1714 (C=O); 1614 (N=C); 1124 (C–O–C); 414 (M−N); 354 (M−Cl) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ=2.35 (s, 3H, C–CH_3); 3.37 (s, 3H, N–CH_3); 3.50 (d, 3H, OCH_3); 7.21–7.78 (m, 4H, arom.); 9.8 (s, 1H, OH). MS-FAB *m/z*: 669.0. Anal. found: C, 46.47; H, 4.97; N, 8.23. Calcd for $C_{26}H_{28}N_4O_6Cl_2Pd$ (669.84): C, 46.61; H, 4.21; N, 8.36%.

5.5.4. Synthesis of Pd(II) complex 12b. Compound **8b** (150 mg, 0.7 mmol) dissolved in dichloromethane (5 mL) was added to the solution of [Pd(C_6H_5CN)$_2$Cl$_2$] (134 mg, 0.35 mmol) in the same solvent (5 mL). The mixture was left with stirring at room temperature. After 10 min a yellow powder precipitated. The stirring was continued for 24 h. The resulting precipitate was filtered off, washed with water and then with ethyl ether, and dried overnight in vacuo.

Yield: 125 mg (59%), mp 334 °C dec. IR (CsI): ν=1755 (–C=O); 1619(–N=C–); 420 (Pd–N); 354 (Pd–Cl) cm^{-1}. MS-FAB *m/z* (%): 604.5. Anal. found: C, 47.58; H, 3.57; N, 9.02. Calcd for $C_{24}H_{20}N_4O_4Cl_2Pd$ (605.75): C, 47.58; H, 3.32; N, 9.25%.

5.5.5. Crystal data for compound 4a,[48] (Fig. 4). $C_{13}H_{17}N_2O_4P$, Mr=296.26, monoclinic, space group $P2_1/n$, a=8.555(1) b=14.270(1) c=12.242(1) Å β=103.01(1)°, V=1456.1(2) Å^3, Z=4, D_x=1.351 Mg m^{-3}, $F(000)$=624, T=293 K μ(Cu Kα)=1.819 mm^{-1}, colorless crystal of dimensions 0.2×0.3×0.4 mm, cell dimension from 80 reflections in the range θ=39.85–39.97°. The intensities

were collected on a KUMA KM4 diffractometer using graphite-monochromatic Cu Kα radiation, λ=1.54178 Å, ω scans. The intensities were corrected for absorption[49] effect with T_{min}=0.51 and T_{max}=0.69 and Lorentz and polarization effect. Intensities of 3 standard reflections checked every 150 reflections: no decay, θ range 4.83–67.12°, 5250 measured reflections of which 2519 were unique (R_{int}=0.015). The structure was solved by direct methods using SHELXS8650, which revealed the positions of non-H atoms. All H-atoms were located in a difference Fourier map. The structure was refined on F^2 by full-matrix least-squares methods using SHELX9751 none-H atoms refined anisotropically, H-atoms fixed in calculated positions excluding H52. The refinement was carried out on 212 parameters using 2413 observed reflections with $I>2\sigma(I)$ gave $R1$=0.044 $wR2$=0.120 ($w=1/[\sigma^2(F_o^2)+(0.0742P)^2]$, where $P=(F_o^2+2F_c^2)/3$, S=1.0068, max and min residual electron density 0.511, −0.317 e Å^{-3}.

5.5.6. Crystal data for compound 4b,[48] (Fig. 5). $C_{13}H_{14}N_2O_3$, Mr=246.26, orthorhombic, space group $P2_12_12_1$, a=12.456(4) b=14.4589(2) c=7.084(5) Å, V=1287.2(10) Å^3, Z=4, D_x=1.271 Mg m^{-3}, $F(000)$=520, T=293 K, μ(Cu Kα)=0.76 $^{-1}$, colorless crystal of dimensions 0.5×0.1×0.1 mm, AFC5S Rigaku four-circle diffractometer, graphite-monochromatic Cu Kα radiation, λ=1.54178 Å, ω scans, cell constants from 25 reflections in the range θ=22.51–28.78°, intensities of 3 standard reflections: 3 2 0, 2 −1 −1, 2 0 −1 checked every 150 reflections, no decay, θ range 4.67–67.48°, 4866 measured reflections of which 2268 were unique (R_{int}=0.029). The intensities were corrected for absorption[49] effect with T_{min}=0.737 and T_{max}=0.936. Structure solution by direct methods using SHELXS86,[50] and refined 170 parameters on F^2 by full-matrix least-square methods using SHELX97,[51] none-H atoms refined anisotropically, H-atoms fixed in calculated positions and refined using a riding model except H51. Final $R1$=0.0328 and $wR2$=0.0756 (w=exp(3s^2)/$[\sigma^2(F_o^2)+(0.0381P)^2]$), where $P=(F_o^2+2F_c^2)/3$, S=0.854, max and min residual electron density 0.12, −0.15 e Å^{-3}.

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