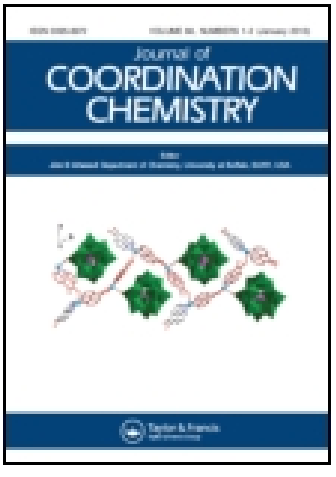

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Synthesis, characterization, and antitumor activities of new palladium(II) complexes with 1-(alkyldithiocarbonyl)-imidazoles

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Synthesis, characterization, and antitumor activities of new palladium(II) complexes with 1-(alkyldithiocarbonyl)-imidazoles

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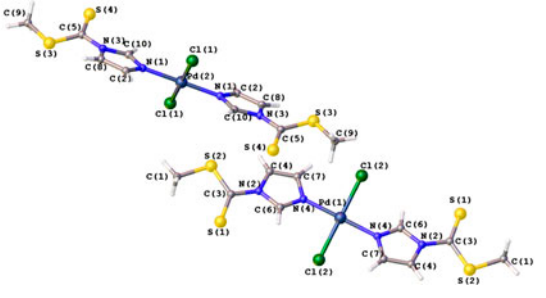

Pd(II) complexes with imidazole linked to dithiocarbamate derivatives were synthesized by reacting 1-(alkyldithiocarbonyl)-imidazoles with $PdCl_2$ in a 2 : 1 molar ratio. The complexes were characterized by elemental analyses, FT-IR, and ^{1}H NMR. The single crystal structure of **4** shows that the ligand is chelated by nitrogens in imidazole, instead of sulfur, to palladium. All synthesized compounds were tested for *in vitro* anticancer activities. Compound **5** had better activities in the HL-60 cell line and twofold better activities in the HeLa cell line than that of cisplatin.

Keywords: Dithiocarbamate; Palladium; Imidazole; Antitumor activity

1. Introduction

Following the discovery of cisplatin and the understanding of its potent anticancer properties in the late 1960s [1], there has been explosive designing of new metal complexes that show anticancer activities equivalent or better than the clinically used ones [2]. Since the most important side effect of cisplatin is high nephrotoxicity, many efforts have been made to reduce the toxicity of the platinum-based anticancer drugs. Renal adverse effects are related to platinum binding and inactivation of thiol-containing enzymes [3]. Using

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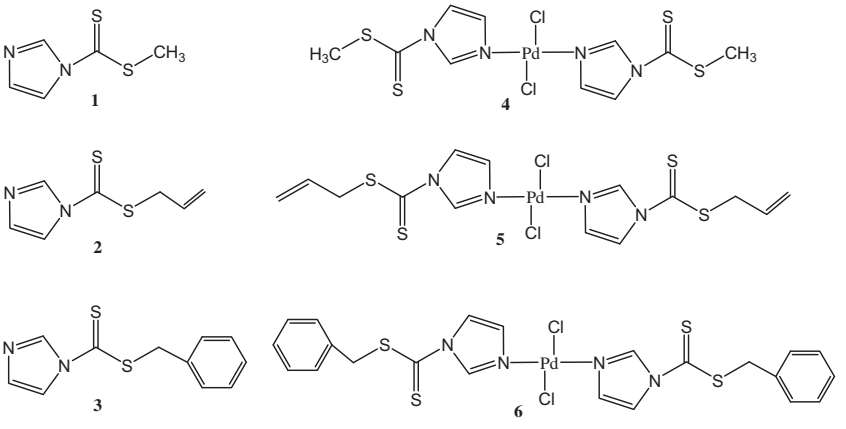

Figure 1. The structures of **1–6**.

sulfur-containing compounds [4], especially dithiocarbamate, is one of the most efficient methods to prevent or at least limit the reaction with other sulfur-containing renal proteins [5].

Dithiocarbamate is widely used in industry, agriculture, medicine, and chemistry as flotation agents, pesticides, antifungal agents, and to chelate with heavy metals [6]. After extraction from broccoli and cauliflower, dithiocarbamates have been reported to have chempreventive and anticancer activities [7]. Dithiocarbamate complexes of palladium(II) and platinum(II) have attracted attention due to their better antitumor properties and lower toxicity than cisplatin [8], and the complexes show cytotoxic activities against most of the usual tumor cells, such as hepatic, cervical, gastric, breast cancer, and leukemic cells. [9].

However, all these complexes are metal-dithiocarbamate derivatives in which the metals are coordinated to sulfur of dithiocarbamate. Although dithiocarbamate derivatives containing N-heterocycles have been reported to have anticancer activities [10], few studies have been reported on the antitumor activities of the metal complexes of this kind of derivatives in which the metals are coordinated to nitrogen. Since there are several published articles showing that palladium complexes containing N-heterocycles have good antitumor or antibacterial activities [11], we focus our research on imidazole. Imidazole has a ring system which is present in biological building blocks. Imidazole can also serve both as a base and as a weak acid. Many drugs contain an imidazole ring, such as the antifungal drug Fhconazob and anticancer drug Levamisole. In this article, we report the synthesis, characterization, and anticancer activities of three palladium(II) complexes of 1-(alkyldithiocarbonyl)-imidazoles which are Pd-imidazole derivatives (**4–6**, figure 1).

2. Experimental

2.1. *Materials and methods*

Reagents and solvents are of commercial quality and used without purification. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a VARIAN INOVA-400 spectrometer using DMSO-d_6 as solvent and

TMS as an internal standard. FT-IR spectra were recorded in solid KBr on a BIO-RAD FTS165 spectrophotometer from 400 to 4000 cm^{-1}. Elemental analyses were determined with a PE-2400 elemental analyzer. Single-crystal X-ray diffraction experiments were performed on a R-AXIS-SPIDER diffractometer.

2.2. *Synthesis of the 1-(alkyldithiocarbonyl)-imidazoles*

The 1-(alkyldithiocarbonyl)-imidazoles were synthesized according to a literature method [12]. Typically, a mixture of imidazole (1 mM) and dehydrated K_3PO_4 (1 mM) in acetone (5 mL) was stirred for 10 min in an ice bath, and then carbon disulfide (3 mM) was added. The reaction mixture was stirred for an additional 30 min and then halide (1 mM) was added. Stirring was continued at room temperature until the reaction was complete, which can be monitored by thin layer chromatography (TLC). The precipitate was filtered and washed with acetone. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on a silica gel column (petroleum ether/EtOAc = 5 : 1) to give the desired 1-(alkyldithiocarbonyl)imidazoles **1–3**.

2.2.1. Methyl 1H-imidazole-1-carbodithioate (1). Yellow viscous oil; yield 94%; IR (cm^{-1}): 1466 (C–N), 1054, 1006 (C–S), 834 (SCS), 1275, 1222 (imidazole); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.81 (s, 3H), 7.10 (d, J = 1.8 Hz, 1H, ArH), 7.83 (d, J = 1.8 Hz, 1H, ArH), and 8.49 (s, 1H, ArH).

2.2.2. Allyl 1H-imidazole-1-carbodithioate (2). Yellow viscous oil; yield 91%; IR (cm^{-1}): 1467 (C–N), 1053, 1005 (C–S), 833 (SCS), 1273, 1222 (imidazole); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.14 (d, J = 6.8 Hz, 2H, =CH_2), 5.28 (dd, J = 1.2 Hz, 10.2 Hz, 1H, =CH_2), 5.31 (dd, J = 1.4 Hz, 17.2 Hz, 1H, =CH_2), 5.91–5.99 (m, 1H, =CH), 7.18 (d, J = 0.8 Hz, 1H, ArH), 8.02 (t, J = 1.6 Hz, 1H, ArH), and 8.64 (s, 1H, ArH).

2.2.3. Benzyl 1H-imidazole-1-carbodithioate (3). Yellow viscous oil; yield 90%; IR (cm^{-1}): 1478 (C–N), 1069, 1003 (C–S), 823 (SCS), 1260, 1225 (imidazole); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.62 (s, 2H, CH_2), 7.11 (d, J = 1.2 Hz, 1H, ArH), 7.27–7.41 (m, 5H, ArH), 7.77 (d, 1H, J = 1.2 Hz, ArH), 8.48 (s, 1H, ArH).

2.3. *Synthesis of the complexes*

To a suspension of $PdCl_2$ in dichloromethane, 1-(alkyldithiocarbonyl)-imidazoles were slowly added in a 2 : 1 ligand : metal molar ratio. The mixture was kept in the dark and stirred at room temperature for 24 h. The initial deep red suspension yielded an almost clear orange solution. The solution thus obtained was carefully filtered and the filtrate was kept at room temperature to get the desired products. Results from the chemical analysis for all the synthesized complexes are summarized as follows.

2.3.1. Pd(II) methyl 1H-imidazole-1-carbodithioate dichloride (4). Orange–yellow solid; m.p. 162–164 °C; yield 90%; Anal. Calcd for $C_{10}H_{12}Cl_2N_4PdS_4$: C, 24.32; H, 2.45;

N, 11.35; Found: C, 24.11; H, 2.02; N, 11.00. IR (cm^{-1}): 1475 (C–N), 1065, 1015 (C–S), 831 (SCS); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84 (s, 6H, 2 × CH_3), 7.21 (s, 2H, ArH), 8.04 (s, 2H, ArH), and 8.69 (s, 2H, ArH).

2.3.2. Pd(II) allyl 1H-imidazole-1-carbodithioate dichloride (5). Orange–yellow solid; m.p. 111–113 °C; yield 87%; Anal. Calcd for $C_{14}H_{16}Cl_2N_4PdS_4$: C, 30.80; H, 2.95; N, 10.26; Found: C, 30.48; H, 2.89; N, 10.35. IR (cm^{-1}): 1478 (C–N), 1069, 1003 (C–S), 823 (SCS); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.17 (d, J = 6.2 Hz, 4H, 2 × CH_2), 5.28 (d, J = 8.0 Hz, 2H, =CH_2), 5.45 (d, d, J = 1.4 Hz, 17.0 Hz, 2H, =CH_2), 5.91–5.97 (m, 2H, =CH), 7.45 (s, 2H, ArH), 8.13 (t, J = 1.6 Hz, 2H, ArH), and 8.98 (s, 2H, ArH).

2.3.3. Pd(II) benzyl 1H-imidazole-1-carbodithioate dichloride (6). Orange–yellow solid; 140–142 °C; yield 83%; Anal. Calcd for $C_{22}H_{20}Cl_2N_4PdS_4$: C, 40.90; H, 3.12; N, 8.67; Found: C, 41.18; H, 2.85; N, 8.66. IR (cm^{-1}): 1474 (C–N), 1067, 1013 (C–S), 835 (SCS); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.59 (s, 4H, 2 × CH_2), 7.35–7.38 (m, 10H, ArH), 7.53 (q, J = 1.2 Hz, 2H, ArH), 7.70 (t, J = 1.8 Hz, 2H, ArH), and 8.98 (q, J = 1.2 Hz, 2H, ArH).

2.4. *X-ray data collection and structure determination of 4*

An orange–yellow and transparent crystal of **4** with dimensions 0.82 × 0.27 × 0.18 mm^3 was chosen for structure determination. Unit cell parameters were derived from a least-squares analysis of 8313 reflections in the range 3.05° < θ < 27.48°. Intensity data were collected on a Rigaku R-AXIS Spider using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and integrated with the SAINT-Plus program [13a]. All calculations were performed with the SHELXTL-97 crystallographic software package [13b]. The crystal structure was solved in space group P-1. Final least-squares refinement on F_0^2 with data having $F_0^2 \geq 2\sigma$ (F_0^2) includes anisotropic displacement parameters for non-H atoms. The final difference Fourier synthesis showed maximum and minimum peaks at 1.250 and –1.101 e $Å^{-3}$, respectively.

The structure was checked for missing symmetry elements with PLATON [14]. Crystal data and structure refinement information are summarized in table 1. Final atomic coordinates and equivalent isotropic displacement parameters of the title compound are listed in table S1 in the Supplementary material (see online supplemental material at http://dx.doi.org/10.1080/00958972.2013.890717). Selected interatomic distances and angles are given in table S2 in the Supplementary material.

2.5. *Anticancer activity*

RPMI1640 and DMEM culture materials were purchased from Invitrogen Corporation (Gaithersberg, MD, USA). DMSO and methylthiazolyldiphenyl-tetrazolium bromide (MTT) were purchased from Sigma–Aldrich (St. Louis, MO, USA). The test and reference compounds were dissolved in DMSO as a 2 mM stock solution (stored at −20 °C) and were further diluted to the desired concentration in the culturing medium. The human cancer cells examined in the present study were human gastric carcinoma cell line (BGC-823), human colon carcinoma cell line (SW480), human hepatocellular carcinoma cell line (HepG2), human cervical carcinoma cell line (HeLa), and human breast carcinoma cell line (MCF-7). BGC-823 and SW480 were maintained in RPMI-1640 and the others were maintained in

Table 1. Crystal data and structure refinement for **4**.

Empirical formula	$C_{10}H_{12}Cl_2N_4PdS_4$
Formula weight	493.78
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	a = 8.1793(16) Å α = 78.80(3)° b = 9.6888(19) Å β = 76.83(3)° c = 11.427(2) Å γ = 76.23(3)°
Volume	847.0(3) Å^3
Z	2
Density (calculated)	1.936 mg m^{-3}
Absorption coefficient	1.900 mm
F(0 0 0)	488
Crystal size	0.82 mm × 0.27 mm × 0.18 mm
Theta range for data collection	3.05°–27.48°
Limiting indices	$-10 \le h \le 9$, $-12 \le k \le 12$, $-14 \le l \le 14$
Reflections collected/unique	8313/3818 [R(int) = 0.0293]
Completeness to theta = 30.49	98.1%
Max. and min. transmission	0.7261 and 0.3042
Refinement method	Full-matrix least-squares on F_0^2
Data/restraints/parameters	3818/0/194
Goodness-of-fit on F_0^2	1.137
Final R indices [$F_0^2 > 2\sigma(F_0^2)$][a]	R_1 = 0.0275, wR_2 = 0.0813
R indices (all data)[a]	R_1 = 0.0289, wR_2 = 0.0826
Extinction coefficient	0.0075(10)
Largest diff. peak and hole	1.250 and −1.101 e Å^{-3}

[a]$R_1 = \Sigma||F_0| - |F_c||/\Sigma|F_0|$ and $wR_2 = [\Sigma w(F_0^2 - F_c^2)^2/\Sigma w\ F_0^4]^{1/2}$ for $F_0^2 > 2\sigma(F_0^2)$ and $w^{-1} = \sigma^2(F_0^2) + (0.0472P)^2 + 0.4252P$, where $P = (F_0^2 + 2F_c^2)/3$.

Dulbecco's modified Eagle's medium. Culture medium was supplemented with 10% heat-inactivated fetal bovine serum (Hyclone), penicillin (100 U/mL), and streptomycin (100 µg/mL). The cells were grown at 37 °C in air with 5% CO_2. All experiments were performed on exponentially growing cancer cells.

Cell viability was determined using the conversion of MTT to formazan via mitochondrial oxidation. Briefly, cancer cells (5000 cells/well) were allowed to adhere in 96-well culture plates overnight. Cells were exposed to various concentrations (30, 20, 10, and 1 µM) of compounds or the same amount of DMSO as vehicle control for 48 h. Cisplatin was evaluated under the same experimental conditions as reference. Then, MTT solution (10 mg/mL in PBS) was added to each well at a final concentration of 1 mg/mL per well and the plates were incubated at 37 °C for another 2 h. After incubation, 200 µl DMSO was added to each well to dissolve the formazan and the absorbance was read at 570 nm using a spectrophotometric microplate reader (SpectraMax M5, USA).

3. Results and discussion

3.1. *Chemistry*

The dithiocarbamates can be prepared by the literature method almost in quantitative yields. Although only one product was detected by TLC, the reaction mixture should be carefully treated to remove any unconverted imidazole in order to decrease the side reactions in the next step. All dithiocarbamate derivatives of imidazole are light yellow oils and should be stored under 0 °C to prevent their decomposition.

In this study, palladium chloride was used. Synthesis of the palladium complexes of the ligands were carried out in dichloromethane at room temperature in the dark. After 24 h, the initial red-dark suspension changed to an almost clear orange solution. The reaction mixture was carefully filtered and the filtrate was left at room temperature to obtain the target compounds. Three solvents were tested in the synthesis of the complex: dichloromethane, methanol, and acetone. Dichloromethane is the most suitable solvent for this reaction and resulted in an almost clear reaction mixture with the presence of only a little solid material when the reaction was over. The other two solvents gave only solid products suspended in the solution which were difficult to be purified. This is because once the products formed as solids, it was difficult to dissolve them again even at elevated temperature. In dichloromethane, the reaction mixture can be filtered and the solvent slowly evaporate to obtain the pure product through recrystallization. The poor solubility of the products in most solvents only allowed us to do NMR measurements and biological studies in DMSO. The products are stable at room temperature and can be stored.

3.2. *Structural studies*

X-ray structure investigation was undertaken for **4**. The structure (figure 2) of **4** shows that one nitrogen in imidazole was substituted by the dithiocarbamate group and the other nitrogen attached to palladium. The two nitrogens and two chlorides attached to palladium are in the same plane with palladium, while the two imidazole rings are a little distorted. All intramolecular bond distances and angles are in agreement with the expected values.

3.3. *Spectral characteristics of the synthesized complex*

Studies in the near IR region (4000–400 cm^{-1}) allowed us to identify the characteristic absorptions of free ligands and complexes. The ν(C–N) is at 1467 cm^{-1} in the free ligands but 1474–1478 cm^{-1} in the complexes, shifted to higher frequency by only about 10 cm^{-1}.

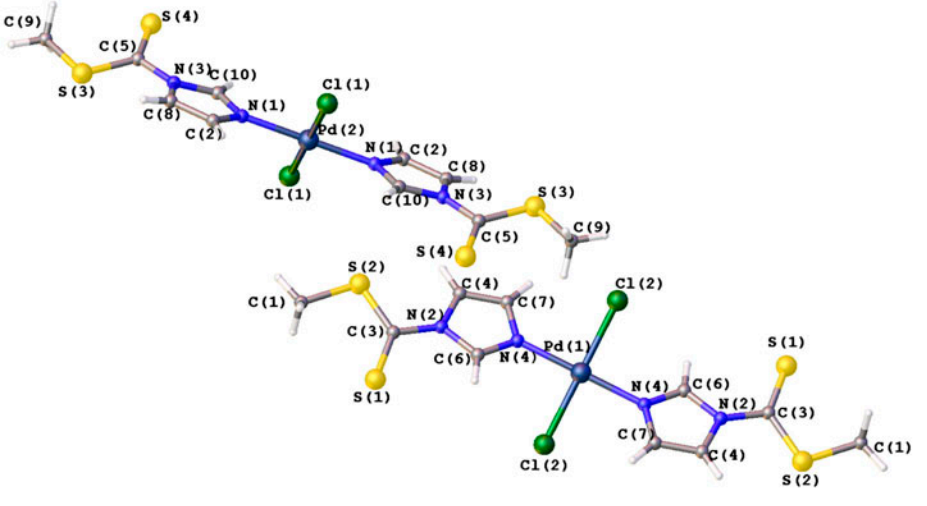

Figure 2. X-ray structure of **4**.

The 940–1060 cm^{-1} region is associated with (C–S) vibrations [15] and this bond undergoes a blue shift when the 1-(alkyldithiocarbonyl)-imidazoles are coordinated. In this case, the shifts are approximately 10–20 cm^{-1}. Compared to the other complexes in which the dithiocarbamate is a bidentate chelating ligand through two sulfurs (50–100 cm^{-1}), the shifts are smaller. There is no obvious change in the frequencies for ν(SCS). The stretching frequencies for the ring imidazole are shifted to higher frequency by about 10–20 cm^{-1}. Thus, the IR absorption shows no significant differences before and after coordination, and the coordination is between nitrogen in imidazole and palladium.

^{1}H NMR spectra of the dithiocarbamates (**1–3**) and their Pd(II) complexes (**4–6**) were quite similar. However, almost all the signals in the metal complexes are shifted downfield [16]. In the spectrum, the most significant shift differences between the chemical shifts of protons in the ligands and in the corresponding complexes are observed for protons on the imidazole rings (about 0.2 ppm), while the group adjacent to imidazole which is far from palladium showed little chemical shift difference. For example, in **2** and **5**, there is only 0.029 ppm difference in the chemical shift of CH_3 between the ligand and the complex. For the chemical shift of ArH in imidazole, the difference is about 0.2 ppm because of the influence of palladium.

3.4. *Anticancer activity*

All the compounds were screened for preliminary *in vitro* anticancer activity against six different cell lines: human promyelocyticfina leukemic cell line (HL-60), human cervical carcinoma cell line (HeLa), human hepatocellular carcinoma cell line (HepG2), human gastric carcinoma cell line (BGC-823), human colon carcinoma cell line (SW480), and human breast carcinoma cell line (MCF-7), for three times at four different concentrations. Because most of the compounds showed inhibition only on HL-60, HeLa, and HepG2 cells (IC50 < 50 μM), we herein merely list the biological results of these three cell lines and used cisplatin as the reference compound.

As seen in table 2, all of the free dithiocarbamates were ineffective for the tumor cell lines, whereas their palladium complexes showed very good activities, even better than that of cisplatin in some of the cell lines. N-heterocycles and Pd chelated complexes were expected to exhibit more antitumor and antibacterial activities [17]. In the HL-60 cell line, all three complexes showed antitumor activities: **5** exhibited better activity than cisplatin and **4** and **6** displayed less activity than cisplatin. For the cell lines HeLa and HepG2, only **5** showed twofold better activities than cisplatin in the HeLa cell line and no significant anticancer activity against the HepG2 cell line. As a result, **5** was the most potent derivative with IC50 values comparable to that of cisplatin.

Table 2. IC_{50} (μM) values of **1–6** and cisplatin.

Compound	HL-60	Hela	HepG2
1	–	–	–
2	–	–	–
3	–	–	–
4	9.4	–	–
5	3.6	8.2	>30
6	24.8	–	–
Cisplatin	4.6	16.7	22.4

Note: –, no anticancer activity ($IC_{50} > 100$).
>30, no significant anticancer activity.

4. Conclusion

We synthesized three palladium complexes of different dithiocarbamates and the structure of one of them was resolved by single-crystal X-ray experiments. The results provide information about the bonding of Pd(II) complexes in which nitrogen in imidazole is the donor instead of sulfur. All of the synthesized compounds were tested for *in vitro* anticancer activities. Compound **5** showed a little better activity in the HL-60 cell line and twofold better activity in HeLa cell line than the reference compound cisplatin. The results provide promising information for further development of potent tumor inhibitors.

Supplementary material

CSD 422089 contains the supplementary crystallographic data for **4**. These data can be obtained free of charge via http://www.fiz-karlsruhe.de/icsd.html, or Email: crysdata@fiz-karlsruhe.de. Supporting information associated with this article can be found in the online version.

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References

[1] B. Rosenberg, L. VanCamp, J.E. Trosko, V.H. Mansour. *Nature*, **222**, 385 (1969).
[2] (a) S.M. Sbovata, F. Bettio, M. Mozzon, R. Bertani, A. Venzo, F. Benetollo, R.-A. Michelin, V. Gandin, C. Marzano. *J. Med. Chem.*, **50**, 4775 (2007); (b) D. Bouvet, A. Michalowicz, S. Crauste-Manciet, D. Brossard, K. Provost. *Inorg. Chem.*, **45**, 3393 (2006); (c) L.L. Li, J.C. Zhang, L.L. Ma, Z.L. Zhang, S.X. Wang, S.H. Li, G.Q. Zhou. *J. Coord. Chem.*, **66**, 638 (2013).
[3] D.L. Bodenner, P.C. Dedon, P.C. Keng, R. Borch. *Cancer Res.*, **46**, 2745 (1986).
[4] (a) J.C. Zhang, L.L. Ma, F.F. Zhang, Z.L. Zhang, L.W. Li, S.X. Wang. *J. Coord. Chem.*, **65**, 239 (2012); (b) L.L. Ma, J.C. Zhang, F.F. Zhang, C. Chen, L.W. Li, S.X. Wang, S.H. Li. *J. Coord. Chem.*, **65**, 3160 (2012).
[5] S. Hidaka, M. Tsuruoka, T. Funakoshi, H. Shimada, M. Kiyozumi, S. Kojima. *Ren. Fail.*, **16**, 337 (1994).
[6] (a) A.M. Bond, R.L. Martin. *Coord. Chem. Rev.*, **54**, 23 (1984); (b) K. Hiroaki, T. Yuriko, Y. Yoshihiro. *Anal. Chim. Acta*, **494**, 49 (2003); (c) S. Hidaka, T. Funakoshi, H. Shimada, M. Tsuruoka, S. Kojima. *J. Appl. Toxicol.*, **15**, 267 (1995); (d) F.R.G. Bergamini, C. Abbehausen, A. Magalhães, W.R. Lustri, A.F. Gomes, F.C. Gozzo, P.P. Corbi. *J. Coord. Chem.*, **64**, 3092 (2011).
[7] (a) Y. Zhang, P. Talalay, C.G. Cho, G.H. Posner. *Proc. Natl. Acad. Sci.*, **89**, 2399 (1992); (b) R.G. Mehta, J. Liu, A. Constantinou, C.F. Thomas, M. Hawthorne, C. Gerhäuser, J.M. Pezzuto, R.C. Moon, R.M. Moriarty. *Carcinogenesis (Lond.)*, **16**, 399 (1995); (c) W.H. Hirschelman, L.S. Song, E.J. Park, Y. Tan, R. Yu, M. Hawthorne, R.G. Mehta, C.J. Grubbs, R.A. Lubet, R.M. Moriarty, J.M. Pezzuto. Cancer chemopreventive activity of oxomate, a monofunctional inducer of phase II detoxification enzymes. In *224th ACS National Meeting: Division of Medicinal Chemistry*, Boston, MA, p. 98 (2002); (d) D.H.S. Lee, J.P. Macintyre, G.R. Taylor, E. Wang, R.K. Plante, S.S.C. Tam, B.L. Pope, C.Y. Lau. *J. Pharmacol. Exp. Ther.*, **289**, 1465 (1999).
[8] (a) L. Giovagnini, L. Ronconi, D. Aldinucci, D. Lorenzon, S. Sitran, D. Fregona. *J. Med. Chem.*, **48**, 1588 (2005); (b) F. Shaheen, A. Badshah, M. Gielen, C. Gieck, D. Vos. *Appl. Organomet. Chem.*, **21**, 633 (2007); (c) F. Shaheen, A. Badshah, M. Gielen, M. Dusek, K. Fejfarova, D. Vos, B. Mirza. *J. Organomet. Chem.*, **692**, 3019 (2007); (d) H. Mansouri-Torshizi, M. I-Moghaddam, A. Divsalar, A.-A. Saboury. *Bioorg. Med. Chem.*, **16**, 9616 (2008); (e) C. Marzano, A. Trevisan, L. Giovagnini, D. Fregona. *Toxicol. in Vitro*, **16**, 413 (2002).
[9] (a) B. Cvek, V. Milacic, J. Taraba, Q.-P. Dou. *J. Med. Chem.*, **51**, 6256 (2008); (b) R. Edward, T. Tiekink. *Appl. Organomet. Chem.*, **22**, 533 (2008); (c) L. Marcheselli, C. Preti, M. Tagliazucchi, V. Cherchi, L. Sindellari, A. Furlani, A. Papaioannou, V. Scarcia. *Eur. J. Med. Chem.*, **28**, 347 (1993).

[10] X.L. Hou, Z.M. Ge, T.M. Wang, W. Guo, J.R. Cui, T.M. Cheng, C.S. Lai, R.T. Li. *Bioorg. Med. Chem. Lett.*, **16**, 4214 (2006).
[11] (a) A.C. Moro, A.C. Urbaczek, E.T. De Almeida, F.R. Pavan, C.Q.F. Leite, A.V.G. Netto, A.E. Mauro. *J. Coord. Chem.*, **65**, 1434 (2012); (b) M.A. Carvalho, B.C. Souza, R.E.F. Paiva, F.R.G. Bergamini, A.F. Gomes, F.C. Gozzo, W.R. Lustri, A.L.B. Formiga, G. Rigatto, P.P. Corbi. *J. Coord. Chem.*, **65**, 1700 (2012); (c) M.N. Patel, P.A. Dosi, B.S. Bhatt. *J. Coord. Chem.*, **65**, 3833 (2012).
[12] Y.Q. Wang, Z.M. Ge, X.L. Hou, T.M. Cheng, R.T. Li. *Synthesis*, **5**, 675 (2004).
[13] (a) *SAINT-Plus, (Version 6.02A)*, Bruker Analytical X-ray Instruments Inc., Madison, Wiskonsin (2000); (b) G.M., Sheldrick. *SHELXTL, (Version 6.14)*, Bruker Analytical X-ray Instruments Inc., Madison, Wiskonsin (2003).
[14] A.L. Spek. *J. Appl. Crystallogr.*, **36**, 7 (2003).
[15] D.A. Brown, W.K. Glass, M.A. Burke. *Spectrochim. Acta, Part A*, **32A**, 137 (1976).
[16] G.B. Onoa, V. Moreno, M. Font-Bardia, X. Solans, J.M. Pérez, C. Alonso. *J. Inorg. Biochem.*, **75**, 205 (1999).
[17] A.A. El-Sherif. *J. Coord. Chem.*, **64**, 2035 (2011).