Eur J Med Chem (1993) 28, 347–352

Preliminary communication

Synthesis, characterization and evaluation of biological activity of palladium (II) and platinum (II) complexes with dithiocarbamic acids and their derivatives as ligands

L Marcheselli[1], C Preti[1]*, M Tagliazucchi[1], V Cherchi[2], L Sindellari[2], A Furlani[3], A Papaioannou[3], V Scarcia[3]

[1]*Department of Chemistry, University of Modena, Via G Campi 183, 41100 Modena;*
[2]*Department of Inorganic, Metallorganic and Analytical Chemistry University of Padua, Via Loredan 4, 35131 Padua;*
[3]*Institute of Pharmacology and Pharmacognosy, University of Trieste, Via A Valerio 32, 34100 Trieste, Italy*

(Received 3 August 1992; accepted 18 December 1992)

Summary — We report the preparation and characterization of new complexes of palladium (II) and platinum (II) with some heterocyclic containing dithiocarbamate ligands, such as piperidine-, morpholine-, and thiomorpholine-dithiocarbamate, their methyl esters and the corresponding thiouramdisulphides. These compounds have been studied through spectroscopic techniques, IR spectra, and electronic spectra, thermogravimetric and conductivity measurements. Thermal decomposition of the complexes takes place through a multi-step process involving pyrolysis of the organic moiety that leads to palladium oxide and platinum sponge respectively. All the complexes have been tested for cytostatic activity on KB cells and the most effective compounds also against L1210 and P388 cells.

palladium (II) complexes / platinum (II) complexes / dithiocarbamate derivative complexes / palladium (II) complexes biological activity / platinum (II) complexes biological activity

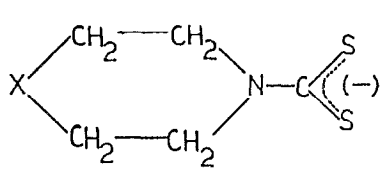
Introduction

The biological activity of sodium diethyldithiocarbamate as a detoxicant as well as an immunomodulatory drug is well known [1–3]. A combined treatment with cisplatin or other platinum complexes improves their therapeutic index, lowering the renal [4–7] and bone marrow [8–10] platinum toxicity. Moreover, diethyldithiocarbamate displays cytostatic properties [11, 12] and it has been shown that various sulphur-containing compounds exhibit different degrees of potentiation of cytotoxicity when used *in vitro* or *in vivo* in combination with some antitumor drugs [13–15].

Previous *in vitro* and *in vivo* studies of antiproliferative activity on platinum (II) and palladium (II) complexes with dithiocarbamates and their esters showed promising results. Their activity seemed to be affected by the nature of dithiocarbamate substituents [16–18].

In order to verify the effect of the substituents on the activity of metal dithiocarbamate derivatives, we extended our research to new platinum (II) and palladium (II) complexes. Moreover, in previous studies the presence of ligands with sulphur donor atoms appeared to be of particular importance in conferring antitumor properties to palladium complexes, since in aqueous media faster isomerization and hydrolysis processes occur for these compounds [17, 19].

The present study deals with the preparation and chemical characterization of a new series of platinum (II) and palladium (II) complexes with heterocyclic dithiocarbamates (Rdtc), of the type :



X=CH_2 Pipdtc

X=O Morphdtc

X=S Timdtc

their methyl esters as well as corresponding thiouramdisulphides (R_2tds).

The results of a preliminary *in vitro* cytostatic assay are also reported.

*Correspondence and reprints

Chemistry

According to the methods reported in the *Experimental protocols* we have obtained compounds of the type $M(Rdtc)_2$ working with the sodium salts of the dithiocarbamic acids; in the case of the methyl esters we have obtained complexes in the 1:1 or 1:2 metal: ligand molar ratio while in the case of the thiouramdisulphides we have always obtained complexes with 1:2 metal: ligand molar ratio.

The obtained compounds were characterized by conductivity measurements, IR and electronic spectra and thermal analyses (TG and DTG techniques); the most important IR bands in the 4000–50 cm^{-1} range are summarized in table I.

The compounds are microcrystalline, stable at room temperature, insensitive to atmospheric oxygen and moisture, and are soluble in benzene, nitrobenzene, *N,N'*-dimethylformamide, acetone, chloroform, dichloromethane and dimethylsulphoxide.

Conductance measurements carried out in nitrobenzene solution are indicative of 1:2 electrolytes for the thiouramdisulphide derivatives, Λ_M in the range 50–60 ohm^{-1} cm^2 mol^{-1}. All the derivatives of the dithiocarbamic acids and related methyl esters are non conductive in the above solvent; hence the

Table I. Most important IR band (cm^{-1}) for the free ligands and their palladium and platinum complexes.

Compounds	*ν (C‴N)*	*ν (C‴S)*	*ν (CS) + δ (SCS)*	*ν (M-S)*	
$PipdtcNa{\cdot}2H_2O$	1465 vs	965 vs	525 m	–	
$MorphdtcNa{\cdot}2H_2O$	1440 vs	990 s	535 m	–	
$TimdtcNa{\cdot}2H_2O$	1458 vs	995 s	490 ms	–	
$Pd(Pipdtc)_2$	1510 vs	973 m	520 m	353 m	
$Pt(Pipdtc)_2$	1515 vs	970 m	522 m	360 m	
$Pd(Morphdtc)_2$	1493 vs	985 m	520 m	346 m	
$Pt(Morphdtc)_2$	1500 vs	1005 s	515 m	345 s	
$Pd(Timdtc)_2$	1500 vs	1000 m	525 m	340 ms	
$Pt(Timdtc)_2$	1510 vs	1005 m	520 m	380 vs	
Compounds	*ν (C‴N)*	*ν (C‴S)*	*ν (M-S)*	*ν (M-Cl)*	
$PipdtcCH_3$	1470 vs	970 vs	–	–	
$MorphdtcCH_3$	1440 vs	990 s	–	–	
$TimdtcCH_3$	1455 vs	1005 s	–	–	
$Pd(PipdtcCH_3)Cl_2$	1500 vs	960 ms, 930 ms	295 mw	335 s, 320 s	
$Pt(PipdtcCH_3)_2Cl_2$	1505 vs	980 m, 960 sh, 928 m	299 mw	325 m	
$Pd(MorphdtcCH_3)Cl_2$	1490 vs	990 ms, 950 ms	290 mw	330 m, 315 s	
$Pt(MorphdtcCH_3)Cl_2$	1510 vs	1005 ms, 930 ms	285 mw	325 m, 309 s	
$Pd(TimdtcCH_3)_2Cl_2$	1500 vs	975 m, 960 m, 932 m	287 mw	330 ms	
$Pt(TimdtcCH_3)_2Cl_2$	1505 vs	977 m, 958 m, 925 m	290 mw	320 ms	
Compounds	*ν (C‴N)*	*ν (C‴S)*	*ν (C-S)*	*ν (M-S)*	*ν (S-S)*
Pip_2tds	1470 vs	960 ms	840 s	–	450 w
$Morph_2tds$	1445 vs	970 s	850 s	–	460 w
Tim_2tds	1470 vs	965 ms	845 m	–	440 w
$Pd(Pip_2tds)_2Cl_2$	1490 vs	990 s	840 m	340 ms	460 w
$Pt(Pip_2tds)_2Cl_2$	1495 s	1000 s	845 m	345 ms	450 w
$Pd(Morph_2tds)_2Cl_2$	1465 s	1005 s	860 m	350 m	430 w
$Pt(Morph_2tds)_2Cl_2$	1475 s	1010 s	850 m	355 m	435 w
$Pd(Tim_2tds)_2Cl_2$	1475 vs	1010 ms	840 m	340 m	470 w
$Pt(Tim_2tds)_2Cl_2$	1490 vs	1015 s	830 m	350 m	440 w

absence of ionic species is indicative of the covalent nature of these complexes.

Infrared spectra

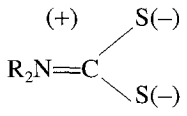
The IR spectra allow us to infer the structure of the complexes on the basis of our previous studies on the coordinating ability of the heterocyclic containing dithiocarbamates [20].

The IR spectra of the ligands, dithiocarbamato sodium salts, methyl esters, thiouramdisulphides and of the metal complexes are given in table I. The thioureide band in the range 1470–1440 cm^{-1} of free ligands indicates a considerable double-bond character of the carbon-nitrogen bond, this band being between the stretching frequencies of ν (C=N) and ν (C-N).

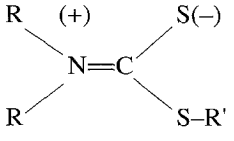
All the complexes reported herein show a band assigned to ν (C$^{\cdots}$N) in the 1515–1475 cm^{-1} range; on passing from the free ligands to the complexes, the ν (C$^{\cdots}$N) mode is shifted to higher energies and moreover the shift is greater for platinum derivatives than for palladium analogues, in accordance with the higher acceptor capacity of platinum.

		$\Delta\nu$			$\Delta\nu$			$\Delta\nu$
$Rdtc^-$	Pd	39	$RdtcCH_3$	Pd	36	R_2tds	Pd	11
	Pt	46		Pt	46		Pt	20

We can conclude that the ligands react with the contribution of the following structure :



The dithiocarbamic ester molecules form 1:1 complexes with platinum and palladium halides; few 1:2 complexes have been isolated with $PipdtcCH_3$ and with $TimdtcCH_3$. The free ligands exhibit an absorption at ≈ 1450–1500 cm^{-1} assigned to C-N bond stretching, which shifts to higher energy on coordination, indicating a predominant contribution of the form:



These act as monodentate ligands through the thiocarbonyl system, in fact the carbon–nitrogen double bond is enhanced, with a parallel ν (C$^{\cdots}$N) shift to higher frequencies with respect to the corresponding uncoordinated molecule.

For the thiouramdisulphide derivatives the greatest contribution is due to the polar structures of the resonance equilibrium as evidenced by the absence in the IR spectra of the band at some 1300 cm^{-1} due to the stretching vibration of the ν (C-N) single bond.

As regards the $M(Rdtc)_2$ derivatives, the assignment of the bands due to the CS_2 group has been matter of controversy among many authors; these bands are usually coupled and are very sensitive to the environment of this group [21] but are very useful in distinguishing between bidentate and monodentate ligands. While several authors [22, 23] ascribe these 2 bands to the ν (C-S) modes of the C=S and C-S units, others ascribe them to the antisymmetrical and symmetrical modes of the C-S moiety [21, 24, 25].

Taking into account the available crystallographic data [26–28] that indicate both for palladium and platinum and other dithiocarbamato complexes almost coincident C-S bond lengths, the second ascription should be valid, thus confirming the bidentate behaviour of the $Rdtc^-$ groups.

Furthermore, in our previous studies [29–31] we have confirmed the bidentate behaviour by XP spectra. In fact, for complexes having the same infrared spectra in the carbon–sulphur region of the complexes here reported we have observed only a band due to the S ($2p_{3/2}$) level, thus definitely confirming that both sulphur atoms within each ligand molecule should be equivalent.

Further confirmation of this behaviour comes from an analysis of the position of the ν (C$^{\cdots}$N) mode; this band undergoes blue shifts in all the complexes, while it would be shifted to lower wavelengths or remain unchanged at about the same value of the free dithiocarbamato sodium salt in the case of monodentate coordination [32].

As for the 600–500 cm^{-1} region, where the bands arise with mainly ν (CS) and δ (SCS) character, it is interesting to note that the bands in this range must entail some ring deformation involving the metal atom as demonstrated by a detailed IR isotopic study in nickel (II) and copper (II) dithiocomplexes [33].

The far IR spectra of the complexes show new bands in respect to the ligands, attributed to ν (M-S) stretching, in the range 340–380 cm^{-1} for $M(Rdtc)_2$, between 285–299 cm^{-1} in the case of the methyl ester complexes, $M(RdtcCH_3)_xCl_2$ X=1 or 2, and in the range 340–355 cm^{-1}, for the thiouramdisulphide metal derivatives, $M(Rdtc_2tds)_2Cl_2$. These bands are very close to those reported by other authors [34–38].

The far IR spectra of the methylester derivatives present bands assignable to ν (M-Cl) stretching [17, 39–41]. The 1:1 complexes show 2 metal–halogen absorptions (table I), very close to those of *cis* derivatives. So on the basis of the above-reported values, we can assign to the 1:1 derivatives a *cis* square planar geometry by chelating dithiocarbamic esters.

The 1:2 derivatives show only one ν (M-Cl) vibrational mode indicative of a *trans* square planar geometry with monodentate ligands.

No metal–halogen stretching modes have been found in the spectra of $M(Rdtc_2tds)_2Cl_2$ complexes, in accordance with their ionic nature indicated by the solution conductance measurements.

Electronic spectra

The solid state electronic spectra of the dithiocarbamate derivates $M(Rdtc)_2$ reported in this study show absorption bands in the 38 000–22 500 cm^{-1} range, which can be attributed to the chromophore group NCS_2 [42]. The band at higher energy in the range 38 900–35 000 cm^{-1}, is assigned to an intramolecular charge-transfer in the ligand of the type $\pi^* \leftarrow \pi$ located on the $N^{III}C^{III}S$ group [43, 44]. The second band of 34 000–31 250 cm^{-1} is attributed to a second $\pi^* \leftarrow \pi$ transition of the $S^{III}C^{III}S$ group [45]. The third band at lower energies, *ie* 29 400–28 500 cm^{-1} may be assigned to $\pi^* \leftarrow n$ electronic transition located on the sulphur atoms [46–48]. The weakest band, 25 200–22 500 cm^{-1}, is due to a metal-ligand charge-transfer process [49], although some authors have ascribed it to a charge-transfer from the *d* orbitals of the metal to the π^* system of the ligands [21, 35].

Thermogravimetric measurements

The complexes are thermally stable up to 400°C. Above this temperature decomposition sets in and continues transforming the palladium derivatives into polysulphides which slowly yield PdO. The platinum complexes decompose with loss of the ligands producing platinum sponge as the end product.

For the chloro derivates, the decomposition process starts with the loss of ligand molecules in the 140–600°C range, and the process ends with the loss of the halide atoms giving the corresponding palladium oxide or platinum sponge as final degradation products.

Pharmacology

Cells and cytostatic assay

The cytostatic effect of new complexes was evaluated in an established cell line (KB), an epidermoid human carcinoma, and the most active compounds were also assayed against 2 murine leukemias (L1210 and P388).

The KB cells were maintained and tested as monolayers in buffered Eagle's minimal essential medium (MEM) supplemented with 10% newborn calf serum and 1% nonessential amino acids, as previously described [50]. The cell population doubling time was ≈ 24 h. L1210 and P388 cells were maintained and tested as suspension cultures in RPMI 1640 medium supplemented by 10% foetal calf serum. Under these conditions the doubling time was ≈ 12 h.

For the cytostatic assay the cells in the exponential phase of growth were seeded at 1×10^5 per Leighton tube. The compounds were added 24 h after seeding of KB cells in order to allow a cellular adhesion to substrate, whereas the L1210 and P388 cells were seeded in the presence of compounds to be tested.

The complexes were dissolved or suspended immediately before use in sterile acetone. They were not assayed as a solution in dimethylsulphoxide (DMSO), even though it appears to be a good solvent for water-insoluble compounds, since there was the possibility of interactions between the platinum and palladium complexes and DMSO with partial substitution of the ligand molecules [51]. In particular it has been demonstrated that DMSO partially or totally cleaves metal sulfur bonds in palladium and platinum adducts with thiocarbamic esters [52].

Further dilutions were performed with the growth medium to the desired drug concentration. The final solvent concentration in control and treated tubes did not exceed a predetermined noncytotoxic level (0.5% in MEM). At least 5 concentration levels were used for each compound and each concentration value was tested in triplicate. Each compound was assayed on at least 2 separate occasions.

The incubation was carried out at 37°C for 72 h (KB cells) and 48 h (L1210 and P388 cells), time intervals in which exponential growth occurs. Cell growth was estimated by counting the viable cells (Trypan blue exclusion test). The cytostatic activity was evaluated on the basis of cell growth inhibition in the treated cultures with respect to the controls. The significance of these results was evaluated by use of the Student's *t*-test ($P < 0.01$). The drug concentration at which cell proliferation was 50% of that in control cultures (IC_{50}) was determined by linear regression analysis. The IC_{50} values were expressed as molar concentration, setting the activity threshold at 10^{-4} M, since this appears to be a fairly realistic cutoff point for most compounds [53].

Results

The *in vitro* cytostatic effect of these new complexes has been evaluated as preliminary screening of their antiproliferative activity and it is expressed as molar concentration required to inhibit cell growth by 50% (table II). In general these coordination compounds showed moderate *in vitro* effects against KB cells; some of them, especially the palladium analogs, were inactive. Only 2 platinum complexes developed high cytostatic activity which was similar or slightly higher

Table II. Cytostatic activity of platinum (II) and palladium (II) complexes.

Complexes	*IC_{50} x 10^{-6} M*		
	KB cells	*L1210 cells*	*P388 cells*
$Pd(Pipdtc)_2$	Inactive		
$Pt(Pipdtc)_2$	15.94		
$Pd(Morphdtc)_2$	19.51		
$Pt(Morphdtc)_2$	16.63		
$Pd(Timdtc)_2$	19.52		
$Pt(Timdtc)_2$	Inactive		
$Pd(PipdtcCH_3)Cl_2$	18.04		
$Pt(PipdtcCH_3)_2Cl_2$	5.63		
$Pd(MorphdtcCH_3)Cl_2$	6.12		
$Pt(MorphdtcCH_3)Cl_2$	8.89		
$Pd(TimdtcCH_3)_2Cl_2$	8.22		
$Pt(TimdtcCH_3)_2Cl_2$	3.32	3.09	0.86
$Pd(Pip_2tds)_2Cl_2$	29.53		
$Pt(Pip_2tds)_2Cl_2$	0.22	0.17	0.08
$Pd(Morph_2tds)_2Cl_2$	35.83		
$Pt(Morph_2tds)_2Cl_2$	9.61		
$Pd(Tim_2tds)_2Cl_2$	15.17		
$Pt(Tim_2tds)_2Cl_2$	0.11	0.08	0.06

than that obtained by us with CDDP under the same experimental conditions (IC_{50} 0.34 x 10^{-6} M). Both the complexes contain thiouramdisulphides as ligand, Pip_2tds and Tim_2tds (IC_{50} 0.2 x 10^{-6} M and 0.1 x 10^{-6} M respectively). Instead, the *in vitro* effect appeared to fall considerably by use of $Morph_2tds$ as ligand.

The 3 most effective complexes were also *in vitro* tested against 2 established murine leukaemias. It should be noted that, whereas there were no significant differences in response between KB and L1210 cell lines, the P388 leukaemia appeared to be more responsive.

The ligands were also tested using the same *in vitro* procedure but only at concentrations present in the IC_{50} value of the respective complex in order to determine whether the cytostatic effect of compounds could be ascribed to the ligand itself. In fact it should be noted that the relative compound, sodium diethyldithiocarbamate, is an effective *in vitro* cytotoxic agent as it can inhibit the synthesis of cellular DNA [11]. The obtained results excluded this possibility since no cytotoxicity was observed at doses assayed in our study.

Experimental protocols

Preparation of the ligands

The dithiocarbamate sodium salts were obtained by treating piperidine, morpholine and thiomorpholine in dry diethylether with CS_2 and adding NaOH with vigorous stirring over 4 h using molar ratios of amine CS_2 NaOH = 1:1:1. The crude products were recrystallized from isopropyl alcohol.

The dithiocarbamic methyl esters were prepared by reacting the dithiocarbamate sodium salts dissolved in water with NaOH and dimethylsulphate $(CH_3)_2SO_4$ in the molar ratios RdtcNa NaOH $(CH_3)_2SO_4$ = 1:2:1.2 under vigorous stirring for 1 h. The crude solid products obtained were washed many times with water and recrystallized from *n*-pentane.

The thiouramdisulphides were prepared by treating an aqueous solution of the corresponding sodium dithiocarbamate with a slight excess of potassium esacyanoferrate (III), $K_3[Fe(CN)_6]$, at 0–5°C. The precipitates so formed were filtered, washed several times with cold water and dried over P_4O_{10}.

Preparation of the complexes

The dithiocarbamato and thiouramdisulphide metal complexes were prepared by reaction of an aqueous solution of K_2PtCl_4 or K_2PdCl_4 with the dithiocarbamate sodium salts or the thiuramdisulphides dissolved in a water–methanol mixture, in a 1:2 molar ratio, at room temperature under vigorous stirring for ≈ 30 min.

The complexes, which precipitated spontaneously, were filtered off and washed with methanol and diethyl ether and dried over P_4O_{10}.

The methylester derivatives were prepared by reaction of $PtCl_2$ and $PdCl_2$ and the ligands in water–methanol, or acetone or CH_2Cl_2 in a 1:2 molar ratio, under stirring for 8–10 h.

The complexes, which precipitated spontaneously, were filtered off and washed with methanol and diethyl ether and dried over P_4O_{10}.

Repeated syntheses and elemental analysis gave reproducible results.

Infrared measurements

The IR spectra were recorded in the region 4000–50 cm^{-1} with a Bruker 113v FT-IR spectrophotometer of the CIGS (Centro Interdipartimentale Grandi Strumenti) of Modena University. The spectra were measured as KBr discs in the 4000–400 cm^{-1} range and in polyethylene discs in the 400–50 cm^{-1} range. Atmospheric water was removed by flushing with dry nitrogen.

Electronic spectra

The electronic spectra were recorded with Shimadzu MPS-50L spectrophotometer in the solid state in the range 5000–45 000 cm^{-1}, the method of Venanzi *et al* being used [54].

Thermal analyses

Thermogravimetric studies (tg and dtg) were performed in air on a Mettler TG50 thermobalance equipped with a Mettler TC 10TA processor. A scan rate of 10°C min^{-1} was used.

Conductivity measurements

These measurements were carried out with a WTW LBR type conductivity bridge for freshly prepared 10^{-3} M solutions in nitrobenzene at 25°C.

Analyses

Carbon, hydrogen, nitrogen and sulphur were determined by using a Carlo–Erba 1106 elemental analyser.

Acknowledgments

We thank G Goldoni and G Pistoni for elemental analyses, L Ravalico, Institute of Pharmacology and Pharmacognosy, for technical assistance, the Centro Interdipartimentale Grandi Strumenti (CIGS) of Modena University for the availability of the Bruker 113v FT-IR spectrophotometer, and the Consiglio Nazionale delle Ricerche (CNR) of Italy for financial support. LM was supported by a grant from Hospal Dasco SpA and VC received a grant from Boehringer–Mannheim Italia SpA.

References

1 Renoux G (1982) *J Pharmacol (Paris)* 13, 95–134
2 Topping RJ, Jones MM (1988) *Med Hypotheses* 27, 55–57
3 Bachelet M, Charbonnier C, Coquet B, Musset M (1988) *Advances in Immunomodulations* (Bizzini B, Bonmassar E, eds) Pythagora Press, Rome, 77–96
4 Gale GR, Atkins LM, Walker EM (1982) *Ann Clin Lab Sci* 12, 345–355
5 Jones MM, Basinger MA, Mitchell WM, Bradley CA (1986) *Cancer Chemother Pharmacol* 17, 38–42
6 Bodenner DL, Dedon PC, Keng PC, Katz JC, Borch RF (1986) *Cancer Res* 46, 2751–2755
7 Basinger MA, Jones MM, Gilbreath SG, Walker EM, Fody EP, Mayhue MA (1989) *Toxicol Appl Pharmacol* 97, 279–288
8 Evans RG, Wheatley C, Engel C, Nielsen J, Ciborowski LJ (1984) *Cancer Res* 44, 3686–3690
9 Gringeri A, Keng PC, Borck RF (1989) *Cancer Res* 48, 5708–5712
10 Schmalbach TK, Borch RF (1989) *Cancer Res* 49, 6629–6633
11 Tempel K, Schmerold I, Goette A (1985) *Arzneim-Forsch/Drug Res* 35, 1052–1054
12 Spath A, Tempel K (1987) *Chem–Biol Interactions* 64, 151–166
13 Valeriote F, Grates HE (1986) *Int J Radiat Oncol Biol Phys* 12, 1165–1169
14 Valeriote F, Grates HE (1989) *Cancer Res* 49, 6658–6661
15 Ujjani B, Lyman S, Winkelmann D, Antholine W, Petering DH, Jones MM (1990) *J Inorg Biochem* 38, 81–93
16 Furlani A, Scarcia V, Faraglia G, Sindellari L, Zarli B (1982) *Inorg Chim Acta* 67, L41–L45
17 Furlani A, Scarcia V, Faraglia G, Sindellari L, Trincia L, Nicolini M (1986) *Eur J Med Chem* 21, 261–265
18 Sindellari L, Trincia L, Nicolini M, Carrara M, Cima L, Zampiron S (1987) *Inorg Chim Acta* 137, 109–113
19 Afcharian A, Butour JL, Castan P, Wimmers S (1990) *Metal Ions in Biology and Medicine* (Collery P, Porier LA, Manfait M, Etienne JC, eds) John Libbey Eurotext, Paris, 514–516
20 Forghieri F, Preti C, Tassi L, Tosi G (1988) *Polyhedron* 7, 1231–1237
21 Hadjikostas CC, Katsoulos GA, Shakhaetreh SK (1987) *Inorg Chim Acta* 133, 129–132
22 Srivastava TN, Kumar V, Rastogi RB (1978) *J Inorg Nucl Chem* 40, 399–401
23 Best SA, Brant P, Feltaem RD, Raushfauss JS, Roudhili DM, Walton RA (1977) *Inorg Chem* 16, 1976–1979
24 Granozzi G, Vittadini A, Sindellari L, Ajo D (1984) *Inorg Chem* 23, 702–706
25 Clemente DA, Faraglia G, Sindellari L, Trincia L (1987) *J Chem Soc Dalton Trans* 1823–1826
26 Crass JK, Emett MT, Kleckin P, Baker AT (1989) *Symp Metal Complexes in the Detection and Treatment of Cancer*. July 10–14, Marysville, Victoria, Australia, abstr P5
27 Benedetti A, Fabretti AC, Preti C (1988) *J Cryst Spectr Res* 18, 685–692
28 Benedetti A, Fabretti AC, Preti C (1989) *J Cryst Spectr Res* 19, 957–966
29 Furlani A, Polzonetti G, Preti C, Tosi G (1983) *Inorg Chim Acta* 73, 105–111
30 Furlani A, Polzonetti G, Preti C, Tosi G (1983) *Gazz Chim Ital* 113, 609–613
31 Polzonetti G, Preti C, Tosi G (1986) *Polyhedron* 5, 1969–1974
32 O'Connor C, Gilbert JD, Wilkinson G (1969) *J Chem Soc (A)* 84–87
33 Desseyn HO, Fabretti AC, Forghieri F, Preti C (1985) *Spectrochim Acta* 41A, 1105–1108
34 Nakamoto N, Fujita J, Contrate RA, Morimoto Y (1963) *J Chem Phys* 39, 423–427
35 Franchini GC, Giusti A, Preti C, Tassi L, Zannini P (1985) *Polyhedron* 4, 1553–1558
36 Criado JJ, Fernandez I, Macias B, Salas JM, Medarde M (1990) *Inorg Chim Acta* 174, 67–75
37 Sindellari L, Faraglia G, Zarli B, Cavoli P (1980) *Inorg Chim Acta* 46, 57–62
38 Faraglia G, Sindellari L, Chiavegato L, Sitran S (1983) *Inorg Chim Acta* 76, L103–L107
39 Faraglia G, Sindellari L, Trincia L, Furlani A, Scarcia V (1985) *Inorg Chim Acta* 106, 31–35
40 Adams DM (1967) *Metal–Ligand and Related Vibrations*. E Arnold, London
41 Ferraro JR (1971) *Low Frequency Vibrations of Inorganic and Coordination Compounds*. Plenum Press, New York
42 Jorgensen CK (1963) *Inorganic Complexes*. Academic Press, London
43 Jorgensen CK (1962) *J Inorg Nucl Chem* 24, 1571–1585
44 Takami F, Wakahara S, Maeda T (1971) *Tetrahedron Lett* 28, 2645–2648
45 Janssen MJ (1960) *Recl Trav Chim Pays-Bas* 79, 1066–1075
46 Janssen MJ (1960) *Recl Trav Chim Pays-Bas* 79, 454–463
47 Shankaranarayana ML, Patel CC (1965) *Acta Chem Scand* 19, 1113–1119
48 Bradley DC, Gitlitz MH (1969) *J Chem Soc (A)* 1152–1156
49 Clark RJH, Turtle PC (1977) *J Chem Soc Dalton Trans* 2142–2148
50 Barbetti P, Fardella G, Chiappini I, Scarcia V, Furlani A (1989) *Eur J Med Chem* 24, 299–305
51 Braddock PD, Connors TA, Jones M, Khokhar AR, Melzack DH, Tobe ML (1975) *Chem–Biol Interactions* 11, 145–161
52 Faraglia G, Sindellari L, Zarli B, Agnoletti I (1982) *Inorg Chim Acta* 58, 13–20
53 Hakala MT, Rustum JM (1979) *Method in Cancer Research* (De Vita VT Jr, Busch H, eds) Academic Press, New York, 16, 247–287
54 Dyer G, Hartley JG, Venanzi LM (1965) *J Chem Soc (A)* 1293–1297