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Synthesis and characterisation of mixed-ligand platinum(II)–sulfoxide complexes, [PtCl(DMSO)(L)], for potential use as chemotherapeutic agents (HL = *N*,*N*-dialkyl-*N*′-(3-*R*-benzoyl)thiourea)

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Abstract

A novel series of mixed-ligand platinum(II) complexes of the type [PtCl(DMSO)(L)], where HL = *N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thiourea, *N*,*N*-di(2-hydroxyethyl)-*N*′-(3-*R*-benzoyl)thiourea or *N*-morpholino-*N*′-(3-*R*-benzoyl)thiourea (R = H, Cl, NO_2, CH_3O, CH_3), have been synthesised and characterised by elemental analysis, IR spectroscopy and ^1H and ^{195}Pt NMR spectroscopy. The spectroscopic data are consistent with the complexes containing an O, S chelated ligand and an S-bonded sulfoxide ligand which is in a *cis* arrangement to that of the sulfur donor atom of the chelated ligand. Trends in the NMR spectra can be correlated with the electronic effects of the substituents on the phenyl ring of the acylthiourea ligands.

Keywords: Platinum(II); Sulfoxide; *N*,*N*-Dialkyl-*N*′-(3-*R*-benzoyl)thiourea; Acylthiourea; NMR; Chemotherapeutic agents

1. Introduction

The successful use of inorganic complexes as chemotherapeutic agents is best exemplified by cisplatin and its analogue carboplatin, which have been used clinically since 1971 and 1981, respectively [1]. Because of the beneficial clinical efficacy of cisplatin, the past 30 years have witnessed tremendous effort and progress in trying to understand the mechanism of action of this metal-based anticancer drug [1]. Moreover, the clinical success of cisplatin has sparked considerable interest and research in the search for improved metal-based drugs for the use as chemotherapeutic agents [1,2]. Several approaches have been taken over the past three decades and some of these include the synthesis of cisplatin analogues, variation of the metal ion as well as the preparation of platinum complexes that are not structurally analogous to cisplatin [1,2]. Recent reports in the literature have revealed that the latter approach has yielded some exciting and successful results and two of these complexes are currently undergoing Phase I clinical trials, such as ZD0473 (*cis*-amminedichloro(2-methylpyridine)platinum(II)) and BBR3464, a trinuclear 4+ charged platinum(II) complex, introduced by Farrell et al., the structure of which is best described as two *trans*-$[PtCl(NH_3)_2]^+$ units bridged by a non-covalent tetra-amine *trans*-$[Pt(NH_3)_2\{NH_2(CH_2)_6NH_2\}_2]^{2+}$ unit [1,2]. These results are encouraging and thus this approach continues to be a promising strategy in the design of metal-based drugs. This can be achieved by the variation of either the firmly bound non-leaving ligands or the labile leaving groups or both. The non-leaving ligands could influence both the target selection and reactivity of the metal ion. For instance, the ligands may determine whether the compound may enter a hydrophobic environment like membranes, approach charged biomolecules like DNA or fit into the ligand binding pocket of a particular protein. The leaving groups will be exchanged for more nucleophilic biomolecules and thereby infer a biological lesion. Or

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the metal complex may require an exchange of one or more of the labile ligands by water in order to become activated. These factors are also influenced by the non-leaving ligand.

In our laboratory we have focused on preparing a series platinum(II) complexes of the type [Pt(acylthioureato)Cl(RR′SO)], in which we have varied both the non-leaving ligands and the labile leaving groups attached to the platinum(II) centre [3]. We have used the acylthiourea ligand system, $R^1C(O)NHC(S)NR^2R^2$, as the R^1 and R^2 groups can be readily varied to give a wide range of ligand systems with different physical and chemical properties, which could be used to fine-tune the biological activity of the resultant complexes. We have reported recently the synthesis and characterisation of the following [Pt(acylthioureato)Cl(RR′SO)] complexes with the acylthiourea ligands: *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea, *N*,*N*-diethyl-*N*′-benzoylthiourea and *N*,*N*-adipoylbis(*N*′,*N*′-diethylthiourea) and the sulfoxides: dimethylsulfoxide (DMSO), methylphenylsulfoxide (MPSO), *R*-methyl(*p*-tolyl)-sulfoxide (*R*-MTSO) and *S*-methyl(*p*-tolyl)sulfoxide (*S*-MTSO) [3]. We have since extended this series by preparing [Pt(acylthioureato)Cl(DMSO)] complexes using *N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thiourea, *N*,*N*-di-(2-hydroxyethyl)-*N*′-(3-*R*-benzoyl)thiourea and *N*-morpholino-*N*′-(3-*R*-benzoyl)thiourea ligands, where R = H, Cl, NO_2, OCH_3 and CH_3. Variation of the amine attached to the thiocarbonyl functionality and substitutents on the phenyl ring could influence the lipophilicity/hydrophilicity and electronic properties of the complexes and thus also affect the lability of the leaving groups which could control the reactivity and biological activity of the complexes. To this end, we herein report the synthesis and full characterisation of this novel series of platinum(II) complexes.

2. Experimental

2.1. Materials and physical methods

The potassium tetrachloroplatinate (Johnson Matthey), DMSO (Merck), 3-substituted benzoyl chlorides (Aldrich), benzoyl chloride (SaArchem) were used as supplied. The diethyl amine, morpholine and acetone were dried and distilled before use. All other solvents were commercial grade and used as received. The known complexes *cis*-[$PtCl_2(DMSO)_2$] [4], [PtCl(DMSO)(*N*,*N*-diethyl-*N*′-benzoylthioureato)] and [PtCl(DMSO)(*N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthioureato)] [3] were prepared by literature procedures. The IR spectra were recorded as KBr disks on Perkin–Elmer FT IR spectrum 2000, between 4000 and 250 cm^{-1}. ^1H NMR (1D and 2D) spectra were recorded at 400.13 MHz on a Bruker 400AMX spectrometer at 30 ± 1°C. All samples were prepared using deuterated solvents purchased from Aldrich Chemical Company, and 5 mm NMR tubes were used throughout. Chemical shifts are reported in parts per million (ppm) relative to the central line of the solvent proton resonance of known shifts relative to TMS, and coupling constants are reported in hertz (Hz). ^{195}Pt NMR spectra were recorded at 86.02 MHz on a Bruker 400AMX spectrometer at 30 ± 1°C using 70–100 KHz spectral widths and 13 μs pulses with 1 s pulse delay. Between 2048 and 16 000 transients, with a line broadening factor of 10 Hz, gave good spectra. All ^{195}Pt shifts are quoted relative to external H_2PtCl_6 (500 mg in 1 ml 30% (v/v) D_2O/1 M HCl). Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Differential scanning calorimetry (DSC) was performed on a Perkin–Elmer Delta series 7 instrument, under a nitrogen atmosphere. The temperature range for the DSC experiments was 50–250°C. Elemental analyses were carried out at the microanalytical unit at the University of Cape Town, South Africa. Thin-layer chromatography (TLC) was performed on silica sheets $60F_{254}$ (Merck, Darmstadt). Reverse phase TLC was performed on glass backed RP-$C18F_{254}S$ plates (Techware). Flash chromatography was performed on silica gel 60 (Merck, Darmstadt).

2.2. Preparation of ligands

The ligands were prepared according to the method of Douglass and Dains [5]. The synthesis of *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea (**L3a**) has been reported recently [6,7]. The preparation of *N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thioureas and *N*-morpholino-*N*′-(3-*R*-benzoyl)thioureas (**L1a**–**d**; **L2a**–**d**), where R = H, Cl, NO_2 and OCH_3, have also been described recently [8–10]. The analytical data and selected IR data for the new ligands are given below.

N,*N*-Di(2-hydroxyethyl)-*N*′-(3-nitrobenzoyl)thiourea, **L3c**: (70%), m.p. 138–141°C. *Anal.* required for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.82; N, 13.41; S, 10.23. Found: C, 46.23; H, 4.85; N, 13.48; S, 9.93%. IR (KBr pellet, cm^{-1}): *ν*(N–H) 3175 (vs, br), *ν*(C=O) 1697 (vs, sh).

N,*N*-Di(2-hydroxyethyl)-*N*′-(3-methoxybenzoyl)-thiourea, **L3d**: (77%), m.p. 103–106°C. *Anal.* required for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39; S, 10.74. Found: C, 53.11; H, 6.29; N, 9.42; S, 10.40%. IR (KBr pellet, cm^{-1}): *ν*(N–H) 3232 (vs, br), *ν*(C=O) 1688 (vs, sh).

N,*N*-Di(2-hydroxyethyl)-*N*′-(3-chlorobenzoyl)-thiourea, **L3b**: (69%), m.p. 132–134°C. *Anal.* required for $C_{12}H_{15}ClN_2O_3S$: C, 47.60; H, 4.99; N, 9.25; S, 10.59. Found: C, 47.72; H, 5.09; N, 9.33; S, 10.58%. IR (KBr pellet, cm^{-1}): *ν*(N–H) 3180 (s, br), *ν*(C=O) 1693 (vs, sh).

N,*N*-Di(2-hydroxyethyl)-*N*′-(3-methylbenzoyl)-thiourea, **L3e**: (75%), m.p. 136–138°C. *Anal.* required for $C_{13}H_{18}N_2O_3S$: C, 55.29; H, 6.42; N, 9.92; S, 11.35. Found: C, 56.12; H, 6.57; N, 9.48; S, 11.36%. IR (KBr pellet, cm^{-1}): ν(N–H) 3192 (s, br), ν(C=O) 1693 (vs, sh).

N-Morpholino-*N*′-(3-methylbenzoyl)thiourea, **L2e**: (72%), m.p. 141–142°C. *Anal.* required for $C_{13}H_{16}N_2O_2S$: C, 59.06; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.12; H, 6.15; N, 10.58; S, 11.75%. IR (KBr pellet, cm^{-1}): ν(N–H) 3150 (m), ν(C=O) 1657 (vs, sh).

N,*N*-Diethyl-*N*′-(3-methylbenzoyl)thiourea, **L1e**: (55%), m.p. 96–97°C. *Anal.* required for $C_{13}H_{18}N_2OS$: C, 62.36; H, 7.25; N, 11.19; S, 12.81. Found: C, 62.37; H, 7.28; N, 11.21; S, 12.20%. IR (KBr pellet, cm^{-1}): ν(N–H) 3311 (s, sh), ν(C=O) 1646 (s, sh).

2.3. Preparation of platinum(II) sulfoxide complexes

The complexes were prepared according to the following general procedure.

A solution of *N*,*N*-dialkyl-*N*′-(3-*R*-benzoyl)thiourea (0.50 mmol) in 10 ml acetonitrile–7 ml ethanol was added dropwise to a stirred solution of *cis*-$[PtCl_2(DMSO)_2]$ (0.50 mmol) in 1.5 ml acetonitrile–2.5 ml dimethylsulfoxide. Sodium acetate (0.063 g, 0.77 mmol) in 1.5 ml water was then added. The solution was allowed to stir for 48 h. The yellow solution was concentrated to ca. 10 ml and water (40 ml) was added whereupon the solution became opaque. The opaque solution was placed in the fridge (4°C) overnight. The yellow precipitate was collected by filtration, washed with water, a little ethanol and dried in vacuo over silica gel. In some cases ,column chromatography is required in order to obtain the pure product.

3. Results and discussion

3.1. Ligand synthesis and characterisation

The ligands were prepared according to the method of Douglass and Dains [5] and were obtained in yields ranging from 55–77%. The synthesis involves the reaction of a 3-substituted benzoyl chloride with potassium thiocyanate in acetone followed by condensation of the 3-*R*-benzoylisothiocyanate with the appropriate secondary amine. The ligands were purified by recrystallisation from ethanol and characterised by elemental analysis, ^{1}H NMR and IR spectroscopy. The analytical and spectroscopic data are consistent with the proposed structures given in Fig. 1.

The assignments of the ^{1}H NMR spectra of the *N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thiourea, *N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthiourea and *N*-morpholino-*N*′-(3-*R*-benzoyl)-thiourea ligands were in general straightforward, except for the assignments of the H_4 and H_6 protons which were confirmed by 2D [^{1}H, ^{13}C] HMBC experiments. The chemical shift data are given in Table 1. The data for the ligands that have been reported already are included for comparison. The numbering scheme for the thioamide protons are as given in Tables 3–5.

A notable feature of the ^{1}H NMR spectra of the ligands is the observation of separate resonances for the methylene protons (H_α) attached to the nitrogen of the respective thioamides. The magnetic inequivalence of these methylene protons can be ascribed to the restricted rotation around the C–N bond between the thiocarbonyl and the amine nitrogen due to the partial double bond character of this bond.

The ^{1}H NMR spectra of the *N*,*N*-di(2-hydroxyethyl)-*N*′-(3-*R*-benzoyl)thiourea ligands in DMSO-d_6 show inequivalent proton resonances for the hydroxyl protons. The lower field signal is broad and unresolved, while the higher field signal is a well-resolved triplet. This inequivalence of the hydroxyl protons is due to the presence of an intramolecular hydrogen bond between one hydroxyl moiety and the amide N–H [6].

The proton resonances for the phenyl ring and N–H protons are significantly affected by the presence of electron-withdrawing and electron-releasing substituents on the benzoyl moiety. As shown in Table 1, on increasing the electron withdrawing ability of the *R*-group there is a downfield shift of the proton resonances, the most pronounced shifts being observed for the ligands **L1c**, **L2c** and **L3c** which contain the nitro substituent.

3.2. Synthesis of [PtCl(DMSO)(L)] complexes

The complexes were prepared according to the general method described by Eqs. (1) and (2), where HL represents an acylthiourea ligand. The structural formulae for the complexes are given in Fig. 1.

$$K_2PtCl_4 + 3DMSO \rightarrow cis\text{-}[PtCl_2(DMSO)_2] \quad (1)$$

$$cis\text{-}[PtCl_2(DMSO)_2] + HL \xrightarrow{Base} [PtCl(DMSO)(L)] + cis\text{-}[Pt(L)_2] \quad (2)$$

As indicated by Eq. (2), it was found, for ligands **L1a**–**e** and **L2a**–**e**, that in addition to the formation of the desired complex, [PtCl(DMSO)(L)], the corresponding neutral *cis*-$[Pt(L)_2]$ complex was also formed as a minor product. This was evident from both the TLC and the ^{1}H NMR spectra. Integration of the proton resonances indicated that the *cis*-$[Pt(L)_2]$ was present as the minor product (ca. 5–15%). The *cis*-$[Pt(L)_2]$ complexes have a higher mobility on silica gel (R_f ca. 0.8) compared to the [PtCl(DMSO)(L)] complexes (R_f 0.5–0.6) and consequently the complexes were readily separated using flash column chromatography. The

platinum complexes containing the *N*,*N*-di(2-hydroxyethyl)-*N*′-(3-*R*-benzoyl)thiourea ligands were isolated by filtration free of the *cis*-[Pt(L)$_2$] complex. This is most likely due to the *cis*-[Pt(L)$_2$] complex being more hydrophilic than the [PtCl(DMSO)(L)] complex.

The analytical data, ^{195}Pt NMR chemical shifts and relevant IR data for the [PtCl(DMSO)(L)] complexes are given in Table 2. The ^{1}H NMR data for all the platinum complexes are given in Tables 3–5.

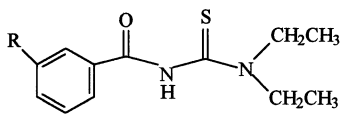
3.3. Characterisation of [PtCl(DMSO)(L)] complexes

3.3.1. Infrared spectra

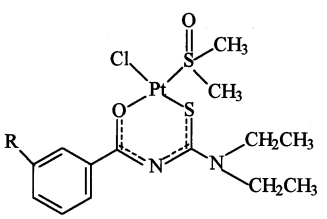
The IR spectra of the platinum(II) sulfoxide complexes are very similar. Notable features of the infrared spectra of the platinum complexes are the disappearance of the N–H stretching vibrations and shifts of the ν(C=O) peaks to higher frequencies upon complexation of the acylthiourea ligands. A shift to a higher frequency would also be expected for the C=S stretch vibration, but this vibration could not be assigned unambiguously. The strong IR band in the region of 1130–1150 cm^{-1} is assigned to the ν(SO) stretching frequency. The ν(SO) peak is shifted to a higher frequency upon complexation, relative to the uncoordinated dimethylsulfoxide, which is indicative of a sulfoxide bonded through the sulfur atom [4,11].

3.3.2. NMR spectra

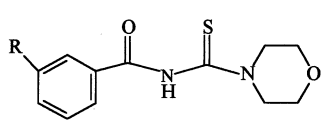
In accordance with the IR spectra, the N–H signal, observed for the ligands in the 8–11 ppm region, disappears upon complexation. A downfield shift is



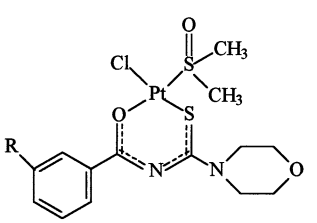
L1a: R = H
L1b: R = Cl
L1c: R = NO$_2$
L1d: R = OCH$_3$
L1e: R = CH$_3$



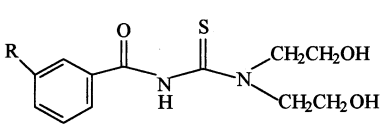
1a: R = H
1b: R = Cl
1c: R = NO$_2$
1d: R = OCH$_3$
1e: R = CH$_3$



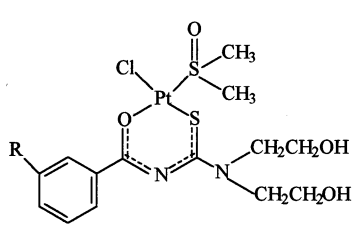
L2a: R = H
L2b: R = Cl
L2c: R = NO$_2$
L2d: R = OCH$_3$
L2e: R = CH$_3$



2a: R = H
2b: R = Cl
2c: R = NO$_2$
2d: R = OCH$_3$
2e: R = CH$_3$



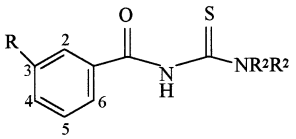
L3a: R = H
L3b: R = Cl
L3c: R = NO$_2$
L3d: R = OCH$_3$
L3e: R = CH$_3$



3a: R = H
3b: R = Cl
3c: R = NO$_2$
3d: R = OCH$_3$
3e: R = CH$_3$

Fig. 1. The structural formulae of the ligands and their corresponding platinum(II) sulfoxide complexes.

Table 1
^{1}H NMR data for the acylthiourea ligands



Ligand	R-group	δH_2	δH_3	δH_4	δH_5	δH_6	δH_α	δH_β	δH_γ	δH_R	δH_{NH}
L1a	H	7.823	7.461	7.563	7.461	7.823	4.018 3.606	1.322			8.238
L1b	Cl	7.816		7.539	7.410	7.692	4.016 3.594	1.222			8.165
L1c	NO_2	8.654		8.170	7.662	8.418	3.987 3.595	1.322			8.774
L1d	OCH_3	7.324		7.065	7.324	7.324	3.993 3.580	1.300		3.815	8.428
L1e	CH_3	7.639		7.355	7.355	7.608	4.026 3.605	1.328		2.403	8.176
L2a	H	7.832	7.488	7.594	7.488	7.832	4.230 3.663	3.838			8.410
L2b	Cl	7.828		7.565	7.431	7.696	4.228 3.644	3.835			8.361
L2c	NO_2	8.681		8.181	7.712	8.443	4.232 3.659	3.844			8.577
L2d	OCH_3	7.375		7.119	7.375	7.375	4.226 3.670	3.853		3.853	8.386
L2e	CH_3	7.642		7.395	7.363	7.610	4.226 3.656	3.837		2.413	8.380
L3a [a]	H [b]	7.85	7.50	7.59	7.50	7.85	3.97 3.73	3.75 3.69	5.60 4.85		10.86
L3b [a]	Cl	7.882		7.671	7.540	7.811	3.990 3.726	3.726	5.516 4.843		10.818
L3c [a]	NO_2	8.659		8.279	7.792	8.435	4.007 3.735	3.735	5.538 4.857		11.129
L3d [a]	OCH_3	7.438		7.162	7.438	7.438	3.985 3.742	3.742	5.624 4.840	3.814	10.829
L3e [a]	CH_3	7.685		7.413	7.382	7.650	3.981 3.742	3.742	5.621 4.840	2.368	10.813

[a] Spectra were recorded in DMSO-d_6.
[b] Ref. [6].

observed for the H_2 and H_6 aromatic protons and an upfield shift for the H_3, H_4 and H_5 proton resonances relative to that of the free ligand, with the exception of the H_4 proton resonances for complexes **1c**, **2c** and **3a**–**d** which undergo downfield shifts.

The ^{1}H NMR chemical shift for the methyl protons of the coordinated dimethylsulfoxide are shifted 1 ppm downfield relative to free dimethylsulfoxide, which is typical for sulfur bonded sulfoxides [3,4]. The assignment of the mode of coordination of the dimethylsulfoxide was further supported by the presence of platinum satellites due to vicinal coupling of the methyl protons of the dimethylsulfoxide with the platinum centre, ^{195}Pt (33.7%, $I = 1/2$). The $^3J(^{195}Pt–^1H)$ coupling constants were approximately 23 Hz, which is the same order of magnitude found for sulfur bonded sulfoxides [4]. The data are consistent with that reported for the [PtCl(L)(RR′SO)] complexes with *N*,*N*-dialkyl-*N*′-benzoylthiourea ligands, which were confirmed by the crystal structure of the [PtCl(*N*,*N*-diethyl-*N*′-benzoylthioureato)(MPSO)] complex [3]. The methylphenyl sulfoxide (MPSO) is sulfur bonded to the platinum and *cis* to the sulfur of the *N*,*N*-diethyl-*N*′-benzoylthiourea ligand. Variation of the electronic properties of the benzoyl moieties appears to have little affect on the ^{1}H NMR chemical shift position of the methyl protons of the coordinated sulfoxide.

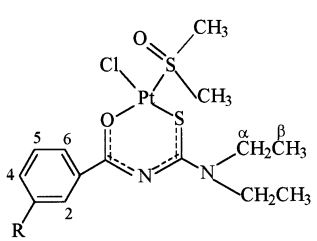
All the [Pt(acylthioureato)Cl(DMSO)] complexes show ^{195}Pt chemical shifts in the -3200 to -3300 ppm region. This chemical shift range is characteristic of complexes with the coordination sphere [PtSOSCl] [3]. The 3-substitution of the benzoyl moiety of these complexes results in a small but significant difference in the ^{195}Pt chemical shifts for the [Pt(acylthioureato)Cl(DMSO)] complexes, demonstrating the sensitivity of the ^{195}Pt nucleus to subtle electronic changes on

Table 2
Analytical and selected spectroscopic data for the platinum(II) sulfoxide complexes

Compound	R-group	M.p. (°C) [a]	Yield (%)	Analytical data (% C/H/N/S) [b]	ν(S=O) (cm^{-1})	^{195}Pt NMR (ppm)
1a	H	139–141	72	31.84; 3.93; 5.19; 11.69 (30.91; 3.89; 5.15; 11.79)	1139	−3256 −3229 [c]
1b	Cl	160–162	67	29.48; 3.51; 4.78; 11.07 (29.07; 3.48; 4.84; 11.08)	1144	−3250
1c	NO_2	187–190	60	28.56; 3.34; 6.88; 10.68 (28.55; 3.42; 7.14; 10.89)	1153	−3242
1d	OCH_3	138–140	80	31.52; 4.06; 4.93; 11.13 (31.38; 4.04; 4.88; 11.17)	1137	−3256
1e	CH_3	109–111	45	32.57; 4.20; 4.94; 11.18 (32.28; 4.15; 5.02; 11.49)	1137	−3257
2a	H	197–dec [a]	51	30.92; 3.54; 4.80; 10.82 (30.13; 3.43; 5.02; 11.49)	1147	−3231 [c]
2b	Cl	165–dec [a]	89	28.52; 3.04; 4.77; 11.13 (28.38; 3.06; 4.73; 10.82)	1148	−3224 [c]
2c	NO_2	208–dec [a]	94	28.39; 3.12; 6.87; 10.65 (27.88; 3.01; 6.97; 10.63)	1145	−3219 [c]
2d	OCH_3	189–dec [a]	49	31.00; 3.58; 4.74; 10.92 (30.64; 3.60; 4.76; 10.90)	1150	−3230 [c]
2e	CH_3	187–dec [a]	86	31.63; 3.65; 4.98; 11.28 (31.49; 3.70; 4.90; 11.21)	1147	−3232 [c]
3a	H	139–140	75	29.17; 3.66; 4.81; 11.05 (29.19; 3.67; 4.86; 11.13)	1146	−3229 [c]
3b	Cl	130–132	77	28.20; 3.34; 4.79; 10.41 (27.54; 3.30; 4.59; 10.50)	1138	−3223 [c]
3c	NO_2	152–154	68	27.44; 3.26; 6.84; 10.19 (27.08; 3.25; 6.77; 10.32)	1146	−3219 [c]
3d	OCH_3	145–147	69	30.14; 4.00; 4.87; 10.40 (29.73; 3.82; 4.62; 10.58)	1148	−3228 [c]
3e	CH_3	127–129	35	30.73; 3.86; 4.84; 10.79 (30.53; 3.93; 4.75; 10.87)	1149	−3231 [c]

[a] Melting points were determined by DSC.
[b] Calculated values are given in parentheses.
[c] Spectra recorded in DMSO-d_6.

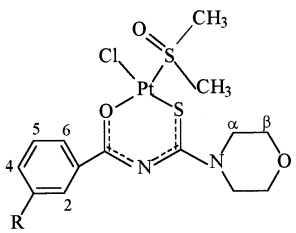
Table 3
^{1}H NMR data for *N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thiourea platinum(II) sulfoxide complexes [a]



R-group	δH_2	δH_3	δH_4	δH_5	δH_6	δH_α	δH_β	δH_{Sme}	δH_R
H	8.181	7.370	7.484	7.370	8.181	1.357 1.296	3.829	3.595	
Cl	8.116		7.455	7.312	8.070	1.361 1.301	3.825	3.598	
NO_2	8.968		8.336	7.580	8.522	1.362	3.843	3.608	
OCH_3	7.739		7.038	7.279	7.789	1.355 1.299	3.822	3.594	3.833
CH_3	7.911		7.238	7.192	7.911	1.276 1.212	3.749	3.596	2.313

[a] The spectra were recorded in $CDCl_3$ at 303 K.

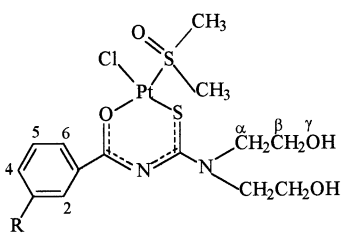
Table 4
^{1}H NMR data for *N*-morpholino-*N*′-(3-*R*-benzoyl)thiourea platinum(II) sulfoxide complexes [a]



R-group	δH_2	δH_3	δH_4	δH_5	δH_6	δH_α	δH_β	δH_{Sme}	δH_R
H	8.164	7.376	7.503	7.376	8.164	4.205 4.093	3.799	3.602	
Cl	8.089		7.472	7.318	8.056	4.183 4.096	3.809	3.604	
NO_2	8.917		8.352	7.587	8.507	4.228 4.118	3.833	3.614	
OCH_3	7.705		7.054	7.285	7.765	4.197 4.090	3.789	3.600	3.837
CH_3	7.959		7.313	7.254	7.959	4.200 4.092	3.803	3.601	2.384

[a] The spectra were recorded in $CDCl_3$ at 303 K.

Table 5
^{1}H NMR data for *N*,*N*-di(2-hydroxyethyl)-*N*′-(3-*R*-benzoyl)thiourea platinum(II) sulfoxide complexes [a]



R-group	δH_2	δH_3	δH_4	δH_5	δH_6	δH_α	δH_β	δH_γ	δH_R
H	8.069	7.441	7.602	7.441	8.069	4.008 3.921	3.772 3.696	5.052 4.936	
Cl	7.985		7.678	7.526	8.014	4.005 3.924	3.780 3.689	5.060 4.944	
NO_2	8.759		8.445	7.794	8.445	4.042 3.939	3.789 3.717	5.077 4.957	
OCH_3	7.594		7.176	7.397	7.651	3.993 3.913	3.785 3.709	5.052 4.932	3.792
CH_3	7.870		7.416	7.361	7.870	4.001 3.917	3.775 3.694	5.048 4.930	2.366

[a] The spectra were recorded in DMSO-d_6 at 303 K.

the benzoyl moiety [11]. The electron-withdrawing affect of the nitro- and chloro- substituents results in notable downfield shifts of the ^{195}Pt signal: NO_2 ($\Delta\delta$: 10–14 ppm) > Cl ($\Delta\delta$: 6–7 ppm) > $OCH_3 \approx H \approx CH_3$, which is consistent with the mesomeric/inductive effects expected for a 3-substituted benzoyl group and parallels the trend observed for the ^{1}H NMR data. No significant effect was observed with variation of the thioamide moiety.

The sensitivity of the ^{195}Pt NMR signal to changes in the benzoyl substituent indicates that these groups influence the electron density at the platinum centre and are therefore expected to have an influence on the substitution reaction kinetics of these complexes. Since the rate of substitution of the dimethylsulfoxide and chloride ligands is of utmost importance in gaining insight into the reactivity and mode of binding of these complexes to DNA detailed studies are underway cur-

rently to evaluate the substitution kinetics of these complexes. In the meanwhile, preliminary substitution reaction kinetic studies of [PtCl(DMSO)(*N*,*N*-diethyl-*N*′-(3-*R*-benzoyl)thioureato)] and the anionic nucleophile azide have revealed that the rate of substitution of the chloride leaving group is influenced by the electronic properties of the R group on the phenyl ring. The rate of substitution decreases in the order of $NO_2 > Cl > OCH_3 \approx H \approx CH_3$. These results are in agreement with the ^{195}Pt NMR results, which provide evidence that the electron-withdrawing substituents on the phenyl ring results in a decrease in the electron density at the Pt centre thereby making it more susceptible to nucleophilic attack. The substitution of the chloride-leaving group was established from the ^{1}H NMR spectrum of the complex. In the presence of the azide anion a significant upfield shift was observed for the protons of the coordinated DMSO and there was no significant appearance of free DMSO at 2.5 ppm.

It is also noteworthy to mention that preliminary in vitro cytotoxicity studies against a HeLa cell line have shown that both the benzoyl substituent and the thioamide moiety play an important role in determining whether the complexes exhibit any anticancer activity. The [PtCl(DMSO)(*N*,*N*-diethyl-*N*′-benzoylthioureato)], and [PtCl(DMSO)(*N*,*N*-di(2-hydroxyethyl)-*N*′-benzoylthioureato)] complexes did not exhibit any cytotoxic behaviour, whereas a notable concentration-dependent anti-proliferative effect was observed for the HeLa cell line treated with the [Pt(acylthioureato)Cl(DMSO)] complexes containing the *N*,*N*-diethyl-*N*′-(3-nitrobenzoyl)thiourea, *N*-morpholino-*N*′-(3-nitrobenzoyl)thiourea or *N*-morpholino-*N*′-(3-methoxybenzoyl)thiourea ligands [12]. These preliminary results are most encouraging in that they support our hypothesis that the acylthiourea ligand could play an important role in the biological activity of this series of complexes and can thus be used to fine-tune their anti-tumour behaviour. Detailed studies are thus currently underway to investigate the biological activity of this series of complexes and to try and establish a structure–activity relationship.

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