European Journal of Medicinal Chemistry 44 (2009) 3981–3985

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, characterization, antimicrobial and antitumor screening of some diorganotin(IV) complexes of 2-[(9*H*-Purin-6-ylimino)]-phenol

Wajid Rehman [a,*], Amin Badshah [b], Salimullah Khan [c], Le Thi Anh Tuyet [d]

[a] Department of Chemistry, Hazara University, Mansehra, Pakistan
[b] Department of Chemistry, Quaid-e-Azam University, Islamabad, Pakistan
[c] Department of Pharmacy, Hazara University, Mansehra, Pakistan
[d] Institute of Pharmacy, Department of Pharmaceutical Biology, Ernst-Moritz-Arndt University, Greifswald, Greifswald D-17487, Germany

ARTICLE INFO

Article history:
Received 22 January 2009
Received in revised form
3 April 2009
Accepted 16 April 2009
Available online 22 April 2009

Keywords:
Organotin
Salicylaldehyde
Adenine
Schiff base
Antimicrobial
Antitumor

ABSTRACT

A new series of diorganotin(IV) complexes of the type R_2SnL_2 (R = Me, Et, Bu, Ph, Bz and L = 2-[(9*H*-Purin-6-ylimino)]-phenol) have been synthesized, characterized by elemental analyses and their solid state configuration has been determined by various spectroscopic (IR, ^{1}H, ^{13}C, ^{119}Sn NMR, ^{119m}Sn Mössbauer) techniques. The results obtained on the basis of these techniques are in full concurrence with the proposed 2:1 stoichiometry. The title complexes have been screened against various microorganisms, fungi and human cell line KB, the results obtained showed that the bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diphenyltin(IV) complex exhibited excellent activity against all types of bacteria and fungi used, while bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diethyltin(IV) complex was found to have promising antitumor activity.

1. Introduction

Schiff base ligands are considered as "privileged ligands" because of their easiness of preparation and their use as fluorogenic agent, pesticides, herbicidal agents [1], blocking agents, and in catalysis [2]. Schiff bases derived from salicylaldehydes are well known polydentate ligands [3]. Organotin compounds have been broadly studied for their biological activity especially antibacterial and antifungal [4]. In general, the in vitro fungicidal and antibacterial properties of organotins have indicated that the order of activity is related to the number of R groups attached to the tin atom. The order of activity has been observed to be: $RSnX_3 < R_2SnX_2$, $R_2SnL_2 < R_3SnX$, R_3SnL. The nature of the X group has relatively little influence on the biological activity of an organotin compound [5–7]. In order to expand the scope of investigations on the coordination behavior of various donor ligands including Schiff base towards organotins, we carried out the investigations and established their bioactivities [8–14]. As an extension of this research field, we are now interested in the development of the chemistry of some novel organotin compounds obtained by the interaction of a number of diorganotin(IV) halides with the 2-[(9*H*-Purin-6-ylimino)]-phenol derived from salicylaldehyde and adenine.

2. Experimental

All the diorganotin(IV) compounds except dibenzyltin dichloride were purchased from Fluka and were used as such. Dibenzyltin dichloride was synthesized through a known method [15]. Schiff base ligand was prepared according to the literature method [25]. All the reactions were carried out under anhydrous and oxygen free atmosphere. The solvents used were dried before use according to the prescribed method [16]. Melting point was measured on a Reichert thermometer of F.G. Bode Co., Austria. IR spectra were obtained in KBr using Perkin–Elmer FTIR 1605 spectrophotometer. An elemental analysis was carried out on a Yanaco MT-3 high-speed CHN analyzer with an antipyrene as a reference compound. The amount of tin was determined using an inductively coupled plasma atomic emission spectrometry (ICP-AES) on ARL 3410. The ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a multinuclear FT NMR 300 MHz of Bruker Biospin using TMS (^{1}H and ^{13}C) and Me_4Sn (^{119}Sn) as internal standard. The Mössbauer spectra were recorded at 80 K on a Cryophysics instrument equipped with a 15 mCi Ca $^{119}SnO_3$ source.

* Corresponding author. Tel.: +92 997 414136; fax: +92 997 530046.
E-mail address: sono_waj@yahoo.com (W. Rehman).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.04.027

2.1. Preparation of tin(IV) complexes

To a hot solution of Schiff base ligand (20 mmol) in toluene, triethylamine(20 mmol) was added dropwise with constant stirring, then dimethyltin, diethyltin, dibutyltin, diphenyltin or dibenzyltin dichloride (10 mmol) was added and this mixture was refluxed for 7–8 h under nitrogen. The solid formed (triethyl ammonium chloride) during the reaction was centrifuged and filtered. Excess of solvent was then removed under reduced pressure. White solid obtained was recrystallized in mixture of ethanol and petroleum ether (1:2(v/v)) having boiling point 40–60 °C.

2.2. Antibacterial studies

The antibacterial activities were investigated using agar well diffusion method [17]. The activity was performed on *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi* (as gram negative bacteria). Two milligrams of the complexes were dissolved in 1 mL of DMSO. Centrifuged pellets of bacteria from a 24-h-old culture containing approximately 10^4–10^6 colony forming unit (CFU) per mL were spread on the surface of Muller Hinton Agar (MHA) plates. Wells were created in medium with the help of a sterile metallic borer and nutrients agar medium were prepared by suspending nutrient agar (Merck) 20 g in 1000 mL of distilled water (pH 7.0), autoclaved and cooled down to 45 °C. Then it was seeded with 10 mL of prepared inocula to have 10^6 CFU/mL. Petri plates were prepared by pouring 75 mL of seeded nutrient agar. The activity was determined by measuring the diameter of the inhibition zone (in mm). Growth inhibition was calculated according to reference [17].

2.3. Antifungal activity

The dilution plate method [18] was used for isolation of fungi. Selected and isolated fungi were maintained on potato dextrose agar plates at 40 °C for further experimental work. The antifungal activities of the ligands, mixed-ligand complexes, fungicides (Bavistin and Emcarb), and the control DMSO (dimethylsulfoxide) were screened using the plate poison technique [19]. Solution of desired concentration (500 μg/mL) was obtained by dissolving 50 mg of each compound in DMSO and added to potato dextrose agar (PDA) medium in 90-mm sterile Petri dishes replicated thrice for each treatment. Seven-day old cultures of *Aspergillus niger*, *Fusarium oxysporum*, and *Aspergillus flavus* were used as test organisms. The sterilized medium with the added sample solution was poured into 90 mm sterile Petri plates and allowed to solidify. They were inoculated with a 5 mm actively growing mycelial disc and incubated at 27 °C for 72 h. After 72 h of inoculation, the percent reduction in the radial growth diameter over the control was calculated. The growth was compared with dimethylsulfoxide as the control. Each experiment was performed three times, and the data were averaged.

2.4. Antitumor activity

Antitumor activity was assayed against the established cell line KB, which derives from a human oral epidermoid carcinoma. Stock cultures were grown in 25 cm^3 flasks containing 10 mL of buffered Eagle's minimum essential medium (MEM) supplemented with glutamine, non-essential amino acids (1%) and new born calf serum (10%), according the literature [20]. The cell population doubling time was approximately 24 h. The cells were dissociated with 0.05% trypsin solution, plated at density of 5×10^5 cells per well in 24-well cell culture clusters (Costar) containing 1.0 mL of MEM per well, and pre-incubated for 24 h to allow adhesion to the substrate. Subsequently, the compounds to be tested were dissolved immediately before use in DMSO and these solutions were diluted with the growth medium to the desired concentrations before addition to the wells. At least five concentrations of each compound were used, with eight cell culture wells for each concentration. Each compound was assayed on at least three separate occasions. Each assay included a blank containing complete medium without cells. The cells were incubated with the compounds to be tested at 37 °C in an atmosphere that was 5% CO_2 and had a relative humidity of 100%. The incubation time was 72 h, during which period the control cells showed exponential growth. Cells growth was terminated by in situ fixation and followed by staining with the protein-binding dye sulforhodamine B (SRB) [19]. Specifically, adherent cell cultures were fixed in situ by the addition of 250 μL of cold 50% (w/v) trichloroacetic acid (TCA) and were kept for 60 min at 4 °C. The supernatant was then discarded and the plates were washed three times with deionised water and dried. SRB solution (500 μL, 0.4% (w/v) in 1% AcOH) was added to each well, and the cells were allowed to stain for 20–30 min at room temperature. Unbound SRB was removed by washing three times with 1% AcOH, and the plates were then air dried while bound stain was solubilized with unbuffered tris base [tris(hydoxymethyl)aminomethane]. Optical densities at 565 nm were read on a Perkin–Elmer 550 SE spectrophotometer. Antitumor activity was evaluated from the inhibition of cell growth in the treated cultures with respect to the controls. IC_{50}, the concentration of the test compound at which cell proliferation was 50% of that observed in control cultures, was determined by linear regression analysis. The statistical significance of these results was estimated by means of Student's *t*-test ($P < 0.01$).

3. Results and discussion

Reaction of Schiff base ligand with R_2SnCl_2 and triethylamine in 2:1 molar ratios respectively, led to the formation of complexes according to Equation (1). These reactions were found to be quite facile and were completed within 7–8 h of refluxing. The resulting solid complexes were obtained in excellent yields (71–82%). The solid complexes were soluble in methanol, chloroform, DMSO and DMF. Elemental analyses obtained (Table 1) are in good agreement with the suggested chemical formulae of the compounds. Structural proposals are based on FT-IR, ^1H NMR, ^{13}C NMR, and ^{119m}Sn Mössbauer studies. The results obtained through these techniques are in agreement with the proposed 2:1 stoichiometry between the organotin moiety and Schiff base ligand.

$$R_2SnCl_2 + 2L + 2Et_3N \rightarrow R_2SnL_2 + 2Et_3N{\cdot}HCl \quad (1)$$

R = methyl, ethyl, phenyl and benzyl.

3.1. Infrared spectroscopy

IR spectroscopy is useful tool in structural determination of coordination compounds [22,23]. The υ(C=N) band at 1590 cm^{-1} found in the spectrum of free ligand is shifted to 1576, 1580, 1585 in complexes, showing that the azomethinic nitrogen coordinates with the central tin atom [21–23]. The strong peak appearing at 574–588 cm^{-1} in the respective spectra of the complexes (absent in the spectrum of ligand) was assigned to Sn–O bond [24]. Compared with the ligand peaks appeared at 475–495 cm^{-1} and 540–575 cm^{-1} were assigned to Sn ← N and Sn–C, (Table 2) which confirmed the existence of Sn ← N and Sn–C bonds for all the five complexes [25–27].

Table 1
Analytical data of the organotin(IV) complexes.

Compound	Molecular formula	Molecular weight	m.p. (°C)	Yield (%)	Elemental analysis found (calc.)			
					C	H	N	Sn
Ligand	$C_{12}H_9N_5O$	239	184	82	60.19(60.25)	3.69(3.77)	29.20(29.27)	–
*1	$C_{26}H_{24}N_{10}O_2Sn$	628	122	71	49.61(49.68)	3.77(3.82)	22.24(22.29)	18.96(19.10)
2	$C_{28}H_{28}N_{10}O_2Sn$	656	115	77	51.18(51.22)	4.21(4.27)	21.28(21.34)	18.22(18.29)
3	$C_{32}H_{36}N_{10}O_2Sn$	712	167	82	53.88(53.93)	4.97(5.05)	19.61(19.67	16.80(16.85)
4	$C_{36}H_{28}N_{10}O_2Sn$	752	194	73	57.39(57.45)	3.69(3.72)	18.55(18.61)	15.89(15.96)
5	$C_{38}H_{32}N_{10}O_2Sn$	780	161	71	58.40(58.46)	3.97(4.10)	17.90(17.95)	15.30(15.38)

Ligand = 2-[(9*H*-Purin-6-ylimino)]-phenol (Schiff base); *1 = bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) dimethyltin; **2** = bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diethyltin; **3** = bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) dibutyltin; **4** = bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diphenyltin; **5** = bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) dibenzyltin.

Table 2
IR and ^{119}Sn spectral results of diorganotin(IV) complexes.

Compound	C–H	C=N	Sn–C	Sn–O	Sn–N	IS	QS
Ligand	3135	1590	–	–	–	–	–
1	3140	1590	542	568	477	1.21 ± 01	3.70 ± 0.04
2	3140	1582	545	580	498	1.20 ± 01	3.75 ± 0.04
3	3155	1578	545	580	495	1.27 ± 01	3.80 ± 0.04
4	3155	1588	555	588	497	1.33 ± 01	3.94 ± 0.04
5	3140	1580	542	574	479	1.30 ± 01	3.90 ± 0.04

3.2. ^{119m}Sn Mössbauer

The ^{119m}Sn Mössbauer parameters (IS and QS) have been utilized as an analytical tool for proposing the structure that a particular complex can adopt. The spectra of the complexes display a characteristic doublet absorption indicating a single tin site. The R_2Sn derivatives show isomer shift (IS) and the quadrupole splitting (QS) values in the range of 1.20–1.33 and 3.70–3.94 mms^{-1}, (Table 2) suggesting octahedral geometry [25].

3.3. NMR spectroscopy

In ^{1}H NMR chemical shift assignments of the diorganotin(IV) moiety are straightforward from the multiplicity pattern and/or resonance intensities; whereas the ligand skeleton was assigned by multiplicity patterns and/or resonance intensities (Table 3). In the spectra of ligand, single resonance is observed at 12.2 ppm (H-18), which is absent in the spectra of all the five complexes, indicating the replacement of phenolic proton by organotin moiety [26]. The azomethinic protons are in the range of 9.0–9.6 ppm like in other similar compounds [26].

The ^{2}J (^{119}Sn–^{1}H) values are informative in assigning geometries to the coordination complexes, for five coordinated complexes ^{2}J (^{119}Sn–^{1}H) values are 65–80 Hz, for six coordinated 85–110 Hz, the ^{2}J (^{119}Sn–^{1}H) values obtained for all the complexes are consistence with the literature [27]. The characteristic signals for all the magnetically non-equivalent alkyl- or phenyl-protons of the organotin moieties have also been assigned, which are in good agreement with reported values [28].

The characteristic resonance peaks in ^{13}C NMR spectra of the complexes were recorded in $CDCl_3$. The ^{13}C NMR spectra of the complexes show a considerable up field shift of all carbon resonance, compared with the ligand acid. The shift is an outcome of an electron density transfer from the ligand to the acceptor [14]. Coordination of the tin atom in organotins has been related to the ^{1}J (^{119}Sn–^{13}C) coupling constants. The ^{1}J (^{119}Sn–^{13}C) coupling constants for the synthesized compounds ranged from 755 to 850 Hz (Table 4), which is indicative of six-coordinated compounds [29–31].

3.4. ^{119}Sn NMR

^{119}Sn NMR spectra can be used as an indicator of the coordination number of the tin atom. According to Holeĉek and coworkers, for the range of +200 to −60, −90 to −190, −210 to −400, −440 to −540 ppm, the coordinate number of the tin is four, five, six and seven [32,33]. The diorganotin complexes under investigation exhibited the ^{119}Sn spectra under the range of −210 to −440 ppm (Table 4), indicating that the tin atom is six-coordinate in all the studied complexes.

3.5. Antibacterial activity

The activity of the ligand and its tin(IV) complexes was tested against bacteria while Imipenem ($C_{12}H_{17}N_3O_4S$) is used as a standard drug for comparison. The microorganisms used in the present

Table 3
^{1}H NMR spectral data of the diorganotin(IV) complexes.

Proton	Ligand	**1**	**2**	**3**	**4**	**5**
1	12.2s	12.2s	12.2s	12.4s	12.4s	12.1s
2	8.1s	8.3s	8.1s	8.0s	8.2s	8.0s
7	8.8m	8.9m	8.8m	8.7m	8.8m	8.7m
11a	9.0s	9.2s	9.5s	9.5s	9.6s	9.1s
14	6.8m	6.8m	6.7m	6.6m	6.9m	6.6m
15	7.1m	7.3m	7.1m	7.2m	7.3m	7.0m
16	6.7m	6.9m	6.9m	7.1m	6.8m	6.7m
17	7.5m	7.4m	7.7m	7.5m	7.9m	7.7m
18	12.2s	A	A	A	A	A
α	–	0.5s [^{2}J ^{119}Sn–^{1}H = 67 Hz]	1.6t [^{2}J ^{119}Sn–^{1}H = 72 Hz]	0.8t [^{2}J ^{119}Sn–^{1}H = 77 Hz]	7.0m [^{2}J ^{119}Sn–^{1}H = 85 Hz]	1.8s [^{2}J ^{119}Sn–^{1}H = 68 Hz]
β		–	2.1q	1.3se	7.1m	7.0m
γ	–	–	–	1.5q	7.0m	7.3m
δ	–	–	–	1.5t	7.5m	7.5m
ω	–	–	–	–	–	7.7m

s = singlet; t = triplet; q = quintet; m = multiplet; A = absent.

Table 4
^{13}C and ^{119}Sn spectral data for diorganotin(IV) complexes.

Carbon	Ligand	1	2	3	4	5
2	155.0	157.0	156	156.5	156.5	155.5
4	117.0	116.0	116.5	117.4	117.4	117.0
5	148.0	150.0	149.5	150.1	150.1	150.8
7	150.5	152.5	151.0	151.9	151.9	151.0
9	151.0	151.5	150.5	151.0	151.0	150.9
11	166.5	167.5	167.0	16.7	17.5	16.5
12	118.5	119.0	120.0	118.9	118.9	119.3
13	158.9	165.7	164.3	163.7	170.3	164.0
14	120.0	122.5	121.8	120.9	122.0	121.3
15	135.2	135.9	135.2	134.8	135.2	135.2
16	121.5	125.5	124.3	125.0	125.4	125.6
17	132.5	133.7	133.1	133.4	133.8	134.4
α	–	2.1 ^{1}J ($^{119}Sn–^{13}C$) = 758 Hz	2.5 ^{1}J ($^{119}Sn–^{13}C$) = 765 Hz	25.9 ^{1}J ($^{119}Sn–^{13}C$) = 790 Hz	125.2 ^{1}J ($^{119}Sn–^{13}C$) = 830 Hz	27.6 ^{1}J ($^{119}Sn–^{13}C$) = 755 Hz
β	–	–	22.4 ^{2}J ($^{119}Sn–^{13}C$) = 29 Hz	28.5 ^{2}J ($^{119}Sn–^{13}C$) = 25 Hz	130.2 ^{2}J ($^{119}Sn–^{13}C$) = 30 Hz	124.7 ^{2}J ($^{119}Sn–^{13}C$) = 28 Hz
γ	–	–	–	24.5	127.5 ^{3}J ($^{119}Sn–^{13}C$) = 64 Hz	120.7 ^{3}J ($^{119}Sn–^{13}C$) = 65 Hz
δ	–	–	–	12.8	124.7	121.5
ω	–	–	–	–	–	123.2
^{119}Sn	–	−315	−303	−290	−222	−280

investigations included *S. aureus* and *B. subtilis* (as Gram positive bacteria) and *P. aeruginosa*, *E. coli* and *S. typhi* (as Gram negative bacteria). The diffusion agar technique was used to evaluate the antibacterial activity of the synthesized mixed-ligand complexes [34]. The results of the bactericidal study of the synthesized compounds are displayed in Table 5. From the bactericidal activity, it is apparent that the complexes were more toxic towards Gram positive strains than Gram negative strains. The reason is the difference in the structures of the cell walls. The walls of Gram negative cells are more complex than those of Gram positive cells. The zone of inhibition (ZOI) values obtained indicates that the ligand has moderate activity against *S. aureus*, *E. coli* and less active in comparison with *P. aeruginosa*. Ligand also shows a moderate activity towards *B. subtilis*. Antibacterial activity of all complexes towards gram positive and negative bacteria is quite significant. Further to it, the ligand showed low, and the complexes moderate to high activities as compared to standard drug towards all the organisms.

3.6. Minimum inhibitory concentration (MIC)

The MIC values for ligand against *B. subtilis*, *S. aureus*, *E. coli*, *S. typhi* and *P. aeruginosa* were 128, 128, 64, 64 and 64 μg/mL for ligand, 64, 64, 32, 32 and 32 μg/mL for Me_2SnL_2, 32, 64, 32, 32 and 32 μg/mL for Et_2SnL_2, 16, 16, 32, 32 and 16 μg/mL, for Bu_2SnL_2 8, 8, 16, 8 and 8 μg/mL for Ph_2SnL_2, 32, 16, 16, 16 and 32 μg/mL for Bz_2SnL_2 respectively (Table 6). The values of MIC showed that the Ph_2SnL_2 complex was found more potent as compared to the other studied complexes.

Table 5
Bactericidal screening data of the ligand and their corresponding organotin(IV) complexes (inhibition zone in mm).

Microorganisms	Ligand	1	2	3	4	5	Standard drug
Gram-positive							
Bacillus subtilis	++	++	++	++	++++	++	++++
Staphylococcus aureus	n.c	+	++	++	++++	++	++++
Gram-negative							
Escherichia coli	+	+	++	+	+++	++	++++
Salmonella typhi	+	n.a	n.a	++	+++	+	++++
Pseudomonas aeruginosa	n.c	+	++	+	+++	++	++++

++++ = Excellent activity (100% inhibition), +++ = good activity (60–70% inhibition), ++ = significant activity (30–50% inhibition), + = negligible activity (10–20% inhibition), n.a = no activity, n.c = not checked, Size of well: 6 mm (diameter), Standard drug = Imipenem ($C_{12}H_{17}N_3O_4S$).

3.7. Antifungal activity

The results of the antifungal studies are presented in Table 7, the results obtained showed that the mixed-ligand complexes are more toxic than their parent ligand against the same microorganisms. The increase in the antifungal activity of the mixed-ligand complexes may be due to the effect of the metal ion on the normal cell processes. A possible mode for the toxicity increase may be considered in light of Tweede's chelation theory [18]. Chelation considerably reduced the polarity of the metal ion because of the partial sharing of its positive charge with the donor groups and the pi-electron delocalization over the whole chelate ring. Such chelation could enhance the lipophilic character of the central metal atom, which subsequently favours its permeation through the lipid layer of the cell membrane. Among the synthesized compounds the bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diphenyltin complex showed excellent activity against all fungi used [19].

3.8. Antitumor activity

The efficiency of all the complexes as potential antitumor drug has been tested in vitro on the KB cell line, derived from a human epidermoid carcinoma by using dimethylsulfoxide to solubilize the complexes prior to use in biological experiments. The results expressed as the concentration of the complex required to inhibit the tumor cell growth by 50% (IC_{50}), are summarized in Table 8. All the studied complexes were found to have a certain inhibitory effect, the bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diethyltin (IV) and bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) dibutyltin(IV) complexes are the most potent with mean IC_{50} values across the cell line The bis(2-[(9*H*-Purin-6-ylimino)]-phenolate) diethyltin(IV) complex showed the most promising cytotoxic results against the

Table 6
Minimum Inhibitory Concentration (MIC) values for the ligand and their corresponding tin(IV)complexes.

MIC (μg/mL)						
Microorganisms	Ligand	1	2	3	4	5
Bacillus subtilis	128	64	32	16	8	32
Staphylococcus aureus	128	64	64	16	8	16
Escherichia coli	64	32	32	32	16	32
Salmonella typhi	64	32	32	32	8	32
Pseudomonas aeruginosa	64	32	32	16	8	32

Table 7
Fungicidal screening data of the ligand and their corresponding tin(IV)complexes.

Compounds	% Inhibition (growth diameter in mm)		
	Aspergillus niger	*Fusarium oxysporum*	*Aspergillus flavus*
[a]Bavistin	(00)100	(00)100	(00)100
[a]Emcarb	(00)100	(00)100	(00)100
DMSO(Control)	(21)29	(27)33	(31)40
Ligand	(06)08	(10)12	(08)10
1	(12)14	(12)14	(11)15
2	(10)12	(10)13	(12)14
3	(16)19	(20)22	(20)22
4	(24)22	(26)25	(24)27
5	(20)21	(18)21	(21)24

[a] Conventional fungicides.

Table 8
Results of in vitro antitumor activity using human cell line KB for the ligand and their corresponding tin(IV)complexes.

Compound	IC_{50} ($\mu g\,mL^{-1}$ medium)	IC_{50} (μM)
Ligand	0.11	0.17
1	0.23	0.67
2	2.57	5.15
3	0.36	0.62
4	0.17	0.33
5	0.20	0.38
Standard drug cis-$[PtCl_2(NH_3)_2]$	0.11	0.37

cell line which is even better than the cisplatin under the same experimental conditions. From the antitumor results one can conclude that the present complexes are more cytotoxic, which is in accordance with the assumptions that complexes of ligands containing N-bond hydrogen suitable for hydrogen bond formation are more active than those derived from the heterocyclic N-donor ligands [35].

Acknowledgments

One of the authors, Dr Wajid Rehman, is highly thankful to Professor A. Christofides (University of Thessalonki, Greece) for providing useful research material. Mr Isfahan Tauseef Department of Microbiology Hazara University, Mansehra is highly acknowledged for useful discussion.

References

[1] P.J. Smith, A.J. Crow, R. Hill, Publication no. 559, International Tin Research Institute, London, 1979.
[2] C.J. Evans, R.J. Hill, Oil Color Chem. Assoc. 64 (1981) 215.
[3] R. Sylvain, J.L. Bernier, M.J. Waring, J. Org. Chem. 61 (1996) 2326.
[4] A.G. Davies, Organotin Chemistry, VCH, Weinheim, Germany, 2004.
[5] M. Gielen, An overview of forty years organotin chemistry developed at the Free Universities of Brussels ULB and VUB, J. Braz. Chem. Soc. 14 (2003) 1.
[6] Marianna N. Xanthopoulou, Sotiris K. Hadjikakou, Nick Hadjiliadis, et al., Eur. J. Med. Chem. 43 (2008) 327–335.
[7] Marianna N. Xanthopoulou, Sotiris K. Hadjikakou, Nick Hadjiliadis, et al., Inorg. Chem. 46 (2007) 1187–1195.
[8] W. Rehman, M.K. Baloch, A. Badshah, et al., J. Chin. Chem. Soc. 52 (2005) 231–236.
[9] W. Rehman, A. Badshah, M.K. Baloch, et al., J. Chin. Chem. Soc. 51 (2004) 929–934.
[10] W. Rehman, M.K. Baloch, B. Muhammad, et al., Chin. Sci. Bull. 49 (2004) 119–122.
[11] W. Rehman, M.K. Baloch, A. Badshah, et al., Spectrochim. Acta A 65 (2006) 689–694.
[12] W. Rehman, M.K. Baloch, A. Badshah, J. Braz. Chem. Soc. 16 (2005) 827–834.
[13] W. Rehman, M.K. Baloch, A. Badshah, et al., Russ. J. Coord. Chem. 31 (2005) 856–860.
[14] W. Rehman, B. Muhammad, F. Ali, et al., Chin. J. Struct. Chem. 27 (2008) 846–852.
[15] K. Sisido, Y. Takeda, Z. Kinugawa, J. Am. Chem. Soc. 83 (1961) 538–541.
[16] D.D. Perrin, W.L.F. Armengo, Purification of Laboratory Chemicals, Pergamon, Oxford, 1988.
[17] A. Rahman, M.I. Choudhary, W.J. Thomsen, Bioassay Techniques for Drug Development, Harwood Academic Publishers, The Netherlands, 2001, pp. 16.
[18] B.G. Tweedy, Elemental sulfur, in: D.C. Torgeson (Ed.), Fungicides. An Advanced Treatise, Chemistry and Physiology, vol. II, Academic Press, London, UK, 1969, p. 119.
[19] C. Rossi, A. Ambrogi, C.G. Grandolini, et al., J. Pharm. Sci. 75 (1986) 784–786.
[20] P. Skehan, R. Storeng, D. Scudiero, J. Natl. Cancer Inst. 82 (1990) 1107.
[21] D.H. Whiffen, J. Chem. Soc. (1956) 1350.
[22] W. Rehman, M.K. Baloch, A. Badshah, et al., Russ. J Coord. Chem 34 (2008) 256–258.
[23] C.L. Ma, Q. Jiang, R.F. Zhang, Can. J. Chem. 81 (2003) 825.
[24] C.L. Ma, Q. Jiang, R.F. Zhang, Appl. Organomet. Chem. 17 (2003) 623.
[25] W. Rehman, M.K. Baloch, A. Badshah, Eur. J. Med. Chem. 43 (2008) 2380–2385.
[26] R. Barbieri, F. Huber, L. Pellerito, et al., ^{119m}Sn Mössbauer studies on tin compounds, in: P.J. Smith (Ed.), Chemistry of Tin, Blackie Academic and Professional, London, 1998, p. 496.
[27] J.J. Bonire, S.P. Fricker, J. Inorg. Biochem. 83 (2001) 217.
[28] G.L. Sandhu, R. Hundal, E.R.T. Tiekink, J. Organomet. Chem. 430 (1992) 15.
[29] T.P. Lockhart, W.F. Manders, E.M. Holt, J. Am. Chem. Soc. 108 (1986) 6611.
[30] H.D. Yin, Q.B. Wang, S.C. Xue, J. Organomet. Chem. 690 (2005) 435.
[31] M. Nath, S. Pokharia, X. Song, et al., Appl. Organomet. Chem. 17 (2003) 305.
[32] J. Holeček, A. Lycka, Inorg. Chim. Acta 118 (1986) L15–L17.
[33] J. Holeček, M. Nadvornik, K. Handlir, et al., J. Organomet. Chem. 241 (1983) 177–184.
[34] M.B. Ferrari, S. Capacchi, G. Pelosi, et al., Inorg. Chim. Acta 286 (1999) 134–141.
[35] C.G.V. Kralingen, J. Reedijk, A.L. Spek, Inorg. Chem. 19 (1980) 481.