Biological studies of organotin(IV) complexes with 2-mercaptopyrimidine

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The known organotin(IV) complexes with 2-mercaptopyrimidine (L) $[Me_2SnL_2]$ (**1**), $[Bu^n{}_2SnL_2]$ (**2**), $[Ph_2SnL_2]$ (**3**), and $[Ph_3SnL]$ (**4**) were synthesized using a new approach. The effect of the synthesized compounds on peroxidation of fatty acids (oleic and linoleic) was studied. Complexes **1—4** promote the peroxidation of oleic acid. Their effect on the enzymatic peroxidation of linoleic acid with lipoxygenase was compared with that of cisplatin and *in vitro* cytoxicity against sarcoma cancer cells was determined. The antiproliferative effect of complexes **2—4** was demonstrated.

Key words: bioinorganic chemistry, complexes, organotin(IV) complexes, 2-mercaptopyrimidine, lipoxygenases, antitumor activity.

Biological activity of organotin(IV) compounds has been verified many years ago.[1—3] It has been reported that a significant role in its manifestation belongs to the binding of the organotin compounds by thiol groups in biological systems.[4] Although many organotin derivatives are known to have an efficient antitumor activity,[5] its precise mechanism is still a matter of investigation.[1,2,6]

It is known that many drugs that inhibit the growth of tumor cells interact with bases and/or nucleotides of the double helix of DNA or with metalloenzymes that are necessary for the rapid growth of malignant cells.[7,8] Multinuclear 1D and 2D NMR spectroscopic studies of the interaction of the organotin(IV) compounds containing the Et_2Sn moiety with 5′-CMP, 5′-dCMP, 5′-UMP, 5′-IMP, and 5-GMP in aqueous solutions showed that at low pH values (<4) the tin atoms bind to the phosphate groups of the nucleotides.[9] At pH > 9.5 the Et_2Sn^{IV} groups react with the O(2′) and O(3′) atoms of the carbohydrate unit of the nucleotide, while no evidence for the interaction of this fragment with nucleotides was found[9] at the intermediate pH values (4.0—9.5).

These results may indicate that the anticancer activity of the organotin compounds is possibly related not to the interaction with DNA at physiological pH values.[5b] The present study is devoted to the investigation of the interaction of organotin(IV) derivatives with the enzyme lipoxygenase.[10] This enzyme catalyzes the oxidation of arachidonic acid to leukotrienes, which is essential for the cell life.[11] Prostaglandines, the final products of the metabolism of arachidonic acid, play an important role in the tumorigenesis as angiogenesis factors.[12a] Linoleic acid (found in beef and dairy products) was proven to be a potential mutagen inhibitor.[12b]

In the present study, for the four known[13] organotin(IV) complexes with 2-mercaptopyrimidine $[Me_2SnL_2]$ (**1**), $[Bu^n{}_2SnL_2]$ (**2**), $[Ph_2SnL_2]$ (**3**), and $[Ph_3SnL]$ (**4**), we found a correlation between their activity in lipoxygenase inhibition and antitumor activity. *In vitro* cytotoxicity against sarcoma cancer mesenchymal tissue from the Wistar rat, whose carcinogenesis was induced by benzo[*a*]pyrene,[14] was studied for compounds **1—4**. The antitumor activity of the complexes was studied in rela-

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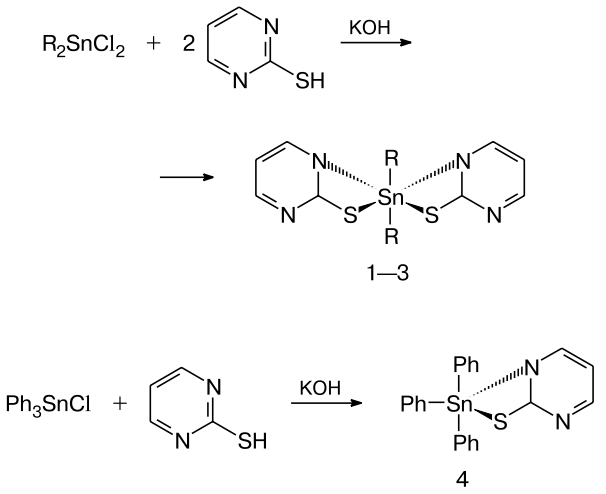
tion to the mechanism of this inhibitory activity towards linoleic acid oxidation to hydroxylinoleic acid by lipoxygenase.[11b,12a] A correlation between the antitumor activity and lipoxygenase inhibition by the studied compounds was found.

Results and Discussion

1. General aspects. A new approach was used to synthesize organotin(IV) complexes with 2-mercaptopyrimidine **1—4** of the general formula R_nSnL_{4-n} (*cf.* Ref. 13). A solution of R_nSnCl_{4-n} in methanol was mixed with an aqueous solution of 2-mercaptopyrimidine containing an equimolar amount of potassium hydroxide (Scheme 1).

Scheme 1



R = Me (**1**), Bu^n (**2**), Ph (**3**)

The ^1H, ^{13}C, and ^{119}Sn NMR and FT-IR spectra of these compounds are identical with those reported earlier.[13] The structures of the complexes R_2SnL_2 (**1—3**)[13a,c] and Ph_3SnL (**4**) were also confirmed by the X-ray diffraction data.

The far-IR spectra of complexes **1—4** contain vibrational bands at 380—395 cm^{-1} assigned to the ν(Sn—S) stretching vibrations (see Refs 13, 15, and 16), while bands at 251—249 and 205—192 cm^{-1} are assigned to ν(Sn—N) vibrations. The vibrations of the metal—ligand bond in the Raman spectra are interpreted as follows: the bands at 212—230 cm^{-1} are due to the ν(Sn—N) stretching vibrations, and the bands at 393— 398 cm^{-1} are attributed to the ν(Sn—S) vibrations. The *cis*-N_2- and *cis*-S_2-coordination of the Sn^{4+} ion in complexes **1**, **3**, and **4** (see Refs 13a,c) is supported by the activity of the Sn—S and Sn—N bonds in both Raman and IR spectra. Thus, complex **2** has analogous *cis*-N_2- and *cis*-S_2-geometry.

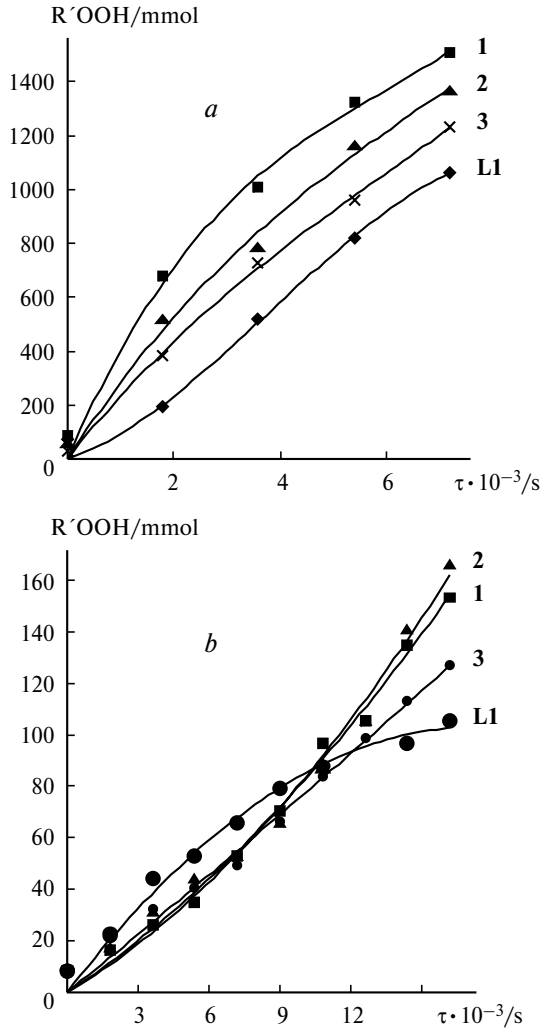


Fig. 1. Kinetic curves of R´OOH accumulation during the oxidation of oleic acid at 65 (*a*) and 37 °C (*b*) without additives (**L1**) and in the presence of additives (1 mmol L^{-1}): Me_2SnL_2 (**1**), $Bu^n{}_2SnL_2$ (**2**), and Ph_2SnL_2 (**3**).

2. Kinetic studies of the peroxidation of oleic acid. The data on the influence of organotin complexes **1—3** on the accumulation level of oleic acid hydroperoxides are presented in Fig. 1.

The effect of compounds **1—3** is manifested as an increase in the content of hydroperoxide R´OOH in the initial period (see Fig. 1, curves *1—3*). The data presented demonstrate the effect of the nature of the organic group on the activity of the corresponding complexes R_2SnL_2. The initial rate constants for R´OOH formation at 65 °C are $3.7 \cdot 10^{-4}$ s^{-1} and $7.1 \cdot 10^{-4}$, $6.4 \cdot 10^{-4}$, and $5.9 \cdot 10^{-4}$ s^{-1} for oleic acid without additives and with addition of complexes **1**, **2**, and **3**, respectively. Analogous values at 37 °C are lower because of a decrease in the rate of peroxidation of the substrate, being $1.9 \cdot 10^{-4}$, $2.1 \cdot 10^{-4}$, $2.0 \cdot 10^{-4}$, and $1.6 \cdot 10^{-4}$ s^{-1} for oleic acid without additives and with addition of complexes **1**, **2**, and **3**, respectively.

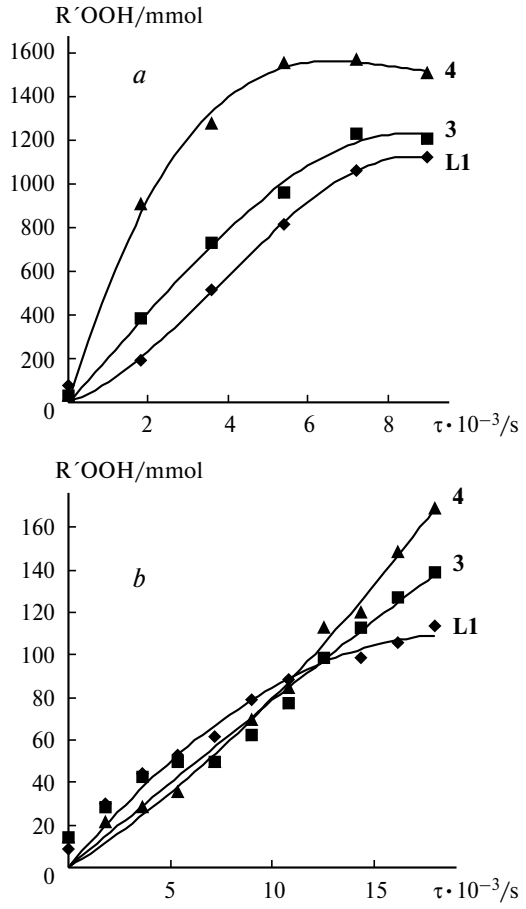


Fig. 2. Kinetic curves of R´OOH accumulation during the oxidation of oleic acid at 65 (*a*) and 37 °C (*b*) without additives (**L1**) and in the presence of additives (1 mmol L^{-1}): Ph_2SnL_2 (**3**) and Ph_3SnL_2 (**4**).

The number of organic substituents R in compounds R_nSnL_{4-n} also affects the effectiveness of the complexes as promoters of oxidation, which was observed in the case of the phenyl-containing derivatives (Fig. 2). Complex **4** exhibits a higher activity at 65 °C ($k = 6.9 \cdot 10^{-4}$ s^{-1}) in the initiation of peroxidation compared to its diphenyl analog. However, the difference in the k values for a similar pair of the complexes at 37 °C is lower, being $1.6 \cdot 10^{-4}$ and $1.7 \cdot 10^{-4}$ s^{-1} for Ph_2SnL_2 and Ph_3SnL, respectively.

The comparative data for the total content of R´OOH in the oxidation of oleic acid in the presence of R_nSnL_{4-n} are presented in Fig. 3. A considerable increase in the R´OOH content is observed as compared to autooxidation of oleic acid.

The binding of the organotin moieties to the sulfur atom of 2-mercaptopyrimidine prevents possible interaction of the tin atoms with the free SH groups of the proteins. However, the complexes R_nSnL_{4-n} containing the Sn—C σ-bond are reactive with respect to peroxyl radicals R´OO• formed from oleic acid.[17a]

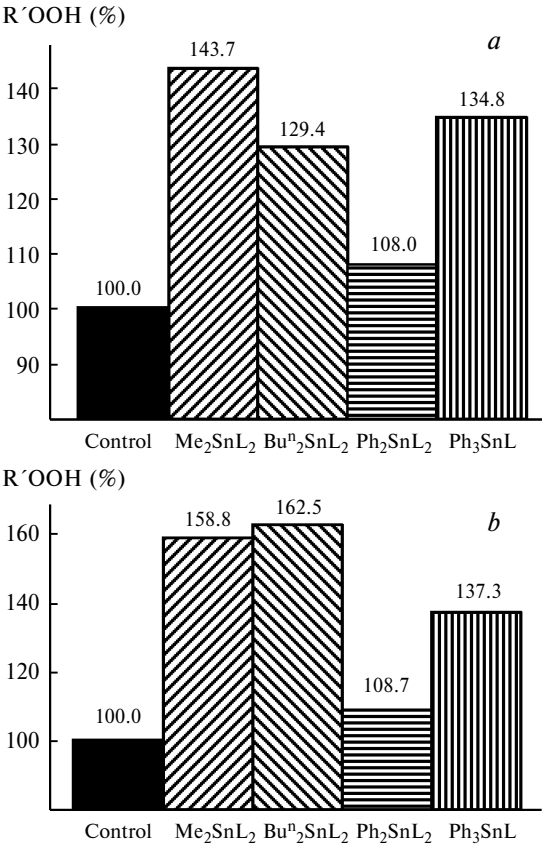


Fig. 3. Relative content of R´OOH in oleic acid (% relative to standard) in the presence of 1 *M* Me_2SnL_2, $Bu^n_2SnL_2$, Ph_2SnL_2, and Ph_3SnL at 65 (*a*) and 37 °C (*b*) after storage for 2.5 (*a*) and 5 h (*b*).

The formation of the radicals R• and/or $[R´OOR_nSnL_{4-n}]$• can be a reason for the initiation of the radical-chain process of substrate oxidation.[17b] The half-life period of the radicals formed can affect the degree of promotion,[10] *i.e.*, the more stable the C-centered radicals formed in an oxidative medium ($Me• < MeCH_2CH_2CH_2• < Ph•$),[17b] the more efficient promoters of oxidation the corresponding complexes.[10] It has previously been shown[10] that an analogous effect is observed in the case of organotin complexes with 5-chloro-2-mercaptobenzothiazole where the Ph_2Sn derivatives were more active than the corresponding Me_2Sn complex. However, this effect is not observed for compounds **1—4**: complex **1** is more active than compound **3**. These results demonstrate the influence of the half-life period of the radicals R• and $[R´OOR_nSnL_{4-n}]$• on the activity of the compounds studied.

3. Study of the peroxidation of linoleic acid with the enzyme lipoxygenase in the presence of complexes 1—4. The influence of complexes **1—4** on the oxidation of linoleic acid by lipoxygenase was studied in a wide concentration interval. The activity of the enzyme (*A*, %) in the

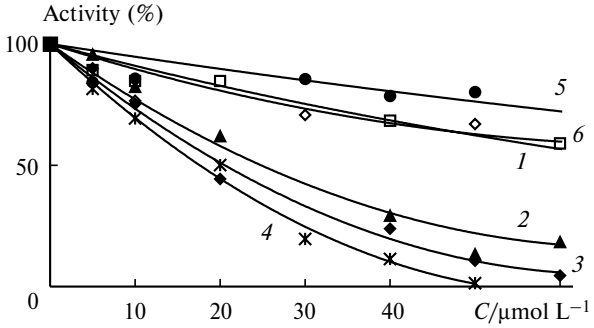


Fig. 4. Activity of the enzyme during the oxidation of linoleic acid in the presence of 2-mercaptopyrimidine and complexes **1—4** (*1—4*), cisplatin (*5*), and LH (*6*).

presence of the complexes was calculated using a known procedure.[18a] The results characterizing the inhibitory effect of complexes **1—4** at various concentrations are shown in Fig. 4. The catalytic activity of lipoxygenase is shown to decrease noticeably at low concentrations of complexes **2—4** (5—75 μmol L^{-1}), whereas no significant decrease in activity was observed for cisplatin or the free ligand 2-mercaptopyrimidine.

The concentrations at which the enzymatic activity is inhibited by 50% (IC_{50}) for complexes **1—4** are 61.3, 26.2, 20.5, and 16.9 μmol L^{-1}, respectively, indicating a higher inhibitory activity of complex **4** compared to those of complexes **1—3**. Complex **4** also exhibits a higher inhibitory activity than compound **2**, whereas complex **1** demonstrates a much lower activity. Thus, the inhibitory activity of complexes **1—4** depends on both the number and the nature of substituents bound to the tin(IV) atom.

To determine the inhibition type, we used the steady-state kinetic method at various substrate concentrations (0.01—0.1 mmol L^{-1}) in the absence and in the presence (15 μmol L^{-1}) of the complexes. The experimental data were processed by the graphical method in the Lineweaver—Burk coordinates (double reciprocal method). The Michaelis constant (K_M) for the enzyme was 0.035 mmol L^{-1} at the V_{max} of 27.5 mmol L^{-1} s^{-1} (see Ref. 18a), whereas K_M was 0.025 and V_{max} = 24.3 mmol L^{-1} s^{-1} in the presence of 9 μL of DMSO. For complexes **1—4**, the apparent K_M values are 0.054, 0.038, 0.049, and 0.130 mol L^{-1} with V_{max} = 25.7, 19.1, 24.7, and 22.1 mmol L^{-1} s^{-1}, respectively. Thus, the compounds studied are characterized by a mixed type of enzyme inhibition.[18b] This agrees with the known[18a] type of inhibition for the complexes $Ph_2SnCl(L)$ (L is 2-mercaptonicotinic acid), Ph_2SnL_2 (L is 2-mercaptobenzothiazole), and Ph_3SnL (L is 2-mercaptobenzothiazole, 5-chloro-2-mercaptobenzothiazole, and 2-mercaptobenzoxazole).[10] According to this mechanism, enzyme—inhibitor (**EI**) and enzyme—substrate—inhibitor (**ESI**) complexes are formed.[18b] This occurs when the inhibitor binds at the enzyme site away from the substrate binding site, resulting in a decrease in the rate of the enzymatic reaction.

4. Docking study. In order to investigate the interaction of the complexes with the protein, we performed computational molecular docking studies. The binding energy (E) of linoleic acid as substrate **S** to its binding site of the enzyme lipoxygenase (**E**) when complex **ES** is formed is −7.89 kcal mol^{-1} (see Ref. 18a). The corresponding binding energies of the complexes as inhibitors (**I**) in **ESI** are calculated to be −6.2 (**1**), −7.9 (**3**), and −9.8 kcal mol^{-1} (**4**), respectively, whereas the binding energies of **EI** are −6.3 (**1**), −7.8 (**3**), and −8.3 kcal mol^{-1} (**4**). Thus, the E values for **ES**, **EI**, and **ESI** suggest that complexes **ESI** and **EI** can be formed in the case of inhibitors **3** and **4**, whereas for complex **1** the energies of the complexes **ESI** and **EI** are lower than those o **ES**. These results can explain the low inhibitory activity of complex **1** found.

It is known that the substrate-binding site in complex **ES** is away from the active site of lipoxygenase (d(Fe—C) = 19.7 Å, d(Fe—C) = 21.4 Å) and is located in the region Ala76, Arg533, Asp760, Glu761, Leu249, Lys110, Met15, Phe108, Ser759, and Val762 (see Ref. 18a). The docked conformations of inhibitors **1**, **3**, and **4** in complexes **EI** are located away from the active site of lipoxygenase. The calculated distances between the tin(IV) atom in the inhibitor and the iron ion in the active site of lipoxygenase in complexes **EI** are 18.9 (**1**), 26.7 (**3**), and 20.6 Å (**4**), respectively. The distances d(Fe—Sn) for complexes **ESI** are 30.0 (**1**), 26.4 (**3**), and 23.8 Å (**4**), respectively. The distance between the tin atom of the inhibitor and the C(8) atom of linoleic acid are 39.4 (**1**), 40.3 (**3**), and 5.2 Å (**4**), respectively. The CPK presentation of lipoxygenase is shown in Fig. 5, where the amino acids of the binding site are represented with space filling mode, while complexes **1** (Fig. 5, *a*) and **4** (Fig. 5, *b*) docked into the binding site of the enzyme lipoxygenase in the case of **ESI** are shown with balls and sticks. It is shown that complex **1** is docked away from the binding site of linoleic acid, whereas complex **4** is docked near to it. The binding site of complex **4** is in the binding pocket calculated for the inhibitors of lipoxygenase.[10]

5. Biological tests. Compounds **1—4** were tested for antitumor activity against sarcoma cells (mesenchymal tissue) from the Wistar rat induced by benzo[*a*]pyrene. The inhibitory IC_{50} concentrations found for the tumor cell after treatment with complexes **1—4** for 24 h are 20—60 (**1**), 0.65 (**2**), 1.0—2.0 (**3**), and 0.1 μmol L^{-1} (**4**), respectively. These results demonstrate the antiproliferative effect of complexes **2—4** and agree with the data on the low inhibitory activity of complex **1** and high activity of complex **4** towards lipoxygenase.

In summary, we studied the interaction of organotin(IV) complexes with the metalloenzyme necessary for the rapid growth of malignant cells. Organotin(IV)

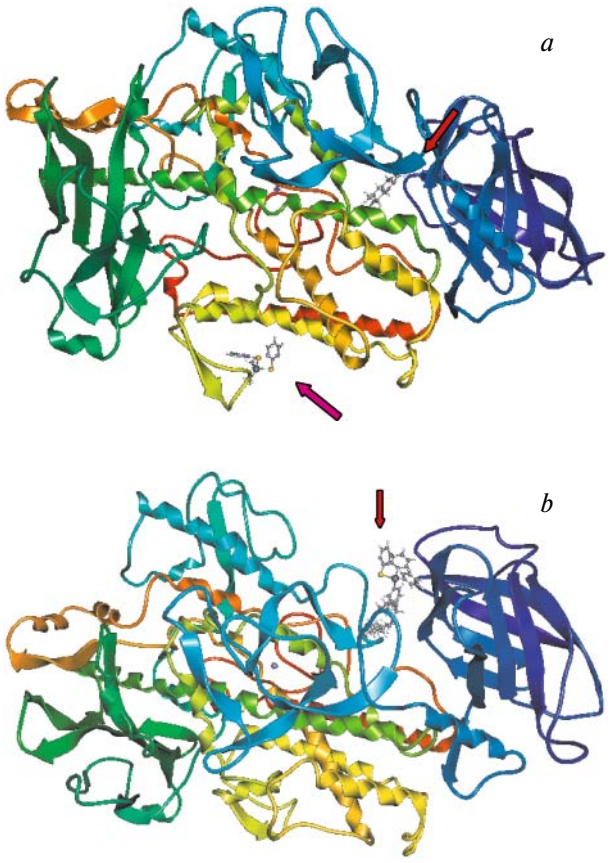


Fig. 5. Binding sites of inhibitors **1** and **4** in lipoxygenase.
Note. Fig. 5 is available in full color in the on-line version of the journal (http://www.springerlink.com/issn/1573-9171/current) and on the web-site of the journal (http://russchembull.ru).

complexes **1—4** inhibit the peroxidation of linoleic acid with the enzyme lipoxygenase. The antiproliferative activity of the complexes studied corresponds to the regularity of inhibition of the lipoxygenase activity. Complex **3** demonstrates the highest activity, and complex **4** (pentacoordinate tin) exhibits the high cytotoxic activity exceeding that of cisplatin. These results can be compared with the earlier[10] obtained data for the complexes Ph_3SnL (L is 2-mercaptobenzothiazole (**5**), 5-chloro-2-mercaptobenzothiazole (**6**), and 2-mercaptobenzoxazole (**7**)) and R_2SnL_2 (L is 2-mercaptobenzothiazole, R = Ph (**8**), Bu^n (**9**), and Me (**10**)).[10] Complex **9** demonstrates the highest antitumor activity and the highest inhibitory activity against lipoxygenase. The results of the present study confirm the correlation earlier found[10] between the antitumor (antiproliferative) and inhibitory activities of the organotin complexes with thioamides. The correlation is independent of the geometry or the number and type of the aryl and alkyl substituents at the tin(IV) ion but is determined to a great extent by the ligand nature. Complexes **8—10** were found to inhibit the lipoxygenase activity with the same rate as that of promotion of the non-enzymatic peroxidation of oleic acid.[10] The observed regularity is not fulfilled in the case of complexes **1—4**; in this series, compound **1** promotes the non-enzymatic peroxidation of oleic acid but is a less pronounced inhibitor of lipoxygenase.

Experimental

Materials and instruments. Commercial solvents, 2-mercaptopyrimidine, and organotin chlorides (Aldrich, Merck) were used as received. Elemental analysis was carried out on a Carlo Erba EA MODEL 1108 microanalyzer. IR spectra were recorded on a Perkin—Elmer Spectrum GX FT-IR spectrometer in ranges of 370—4000 cm^{-1} (KBr pellets) and 700—30 cm^{-1} (polyethylene discs). Micro FT-Raman spectra were obtained in the near-IR laser radiation (Nd^{3+} : YAG, 1064.1 nm) with a resolution of 2.6 cm^{-1} on a Bruker IFS-88 FT-IR/FRA-105 Raman module fitted with a Ge proprietary detector and coupled *via* two photooptic cables (1.0 m) to a Nikon Optiphot-II optical microscope equipped with a Nikon 20X super-long-range objective. Near-IR laser radiation was directed onto the sample through the objective and collected along the same optical pathway in a 180° back scattering mode. Samples were measured as solid powders dispersed on a glass slide. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 250 NMR instrument in DMSO-d_6 solutions. Mass spectra (electrospray ionization) of solutions of the complexes in methanol were recorded on an Agilent 1100 ESI-LC-MS spectrometer.

Influence of complexes 1—4 *on the peroxidation of oleic acid*

Oleic acid (Sigma, 99%) was used. The monitoring of the level of peroxidation of oleic acid as the substrate (R´H) was performed by the determination of the total content of isomeric hydroperoxides R´OOH using iodometric titration. Oleic acid was oxidized using a temperature-controlled cell (65 and 37 °C) with an air flow with a constant rate of 2—4 mL min^{-1}. Before the addition of complexes, air was passed for 2 h. The concentrations of compounds **1—4** were 1 mmol L^{-1}, which is comparable with the initial concentrations of hydroperoxides. The approximation coefficients of the kinetic curves were 0.965—0.984, and their shape for substrate oxidation in the presence of complexes **1—4** follows the exponential law. It turned out that the initial rate of hydroperoxide accumulation obeys the pseudo-first-order equation.

Study of the mechanism of lipoxygenase inhibition

Preparation of solutions. A 0.2 *M* borate buffer (pH 9) was used.[10,18a] A solution of linoleic acid was prepared as follows: linoleic acid (0.05 mL, Merck) was dissolved in 95% ethanol (0.05 mL), and water was added to a volume of 50 mL. The solution prepared (5 mL) was added to the borate buffer (30 mL). Lipoxygenase from soybean Type I-B as a lyophilized powder (48 000 units mg^{-1}, Aldrich) was used: a solution of 10 000 units of enzyme for each cm^3 of the borate buffer was prepared in an ice bath.[10,18a] The enzyme was used in experiment in an amount of 500 units per 3 mL of the reaction mixture. A lipoxygenase unit induces an increase in the absorption at 234 nm by 0.001 per 1 min.

Determination of the lipoxygenase activity. The enzyme activity was monitored by UV spectroscopy. A solution of the enzyme (0.05 mL) was added to a cell containing 2 mL of a solution of linoleic acid and a necessary amount of the buffer. The temperature of a solution of the inhibitor was maintained constant at 25 °C. No preincubation of the enzyme with an inhibitor solution was carried out. The enzyme activity was determined from an increase in the intensity of the absorption at 234 nm at 25 °C ($\varepsilon = 25\,000$ L mol^{-1} cm^{-1})[10,18a] caused by the oxidation of linoleic acid. Solutions of compounds **1—4** were prepared in DMSO, their concentrations being 10^{-2}, $5 \cdot 10^{-3}$, $2.5 \cdot 10^{-3}$, and 10^{-3} mol L^{-1}. The substrate concentration was maintained constant at a level of 0.3 mmol L^{-1}, and the amounts of solutions of the buffer and inhibitor were varied according to the necessary final concentration of the inhibitor (5—60 μmol L^{-1} or 9—18 μL). The total volume of the reaction mixture was 2 mL.

Three series of experiments were carried out to determine the K_M and V_{max} values. The inhibitor concentration was constant (15 μmol L^{-1} in DMSO). The substrate concentrations were 0.01, 0.025, 0.05, 0.075, and 0.1 mmol L^{-1}.

Computational methods — docking study. The docking program was ArgusLab.[19a] This program was also applied for visualization and molecular modeling of the compounds. The three-dimensional coordinates of lipoxygenase was obtained through the Internet at the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank.[19b] The coordinates of the complexes were obtained by X-ray diffraction analysis.[13] The ArgusLab program implements an efficient grid-based docking algorithm, which approximates an exhaustive search within the free volume of the binding site cavity. The conformational space was explored by the geometry optimization of the flexible ligand (rings are treated as rigid) in combination with the incremental construction of the ligand torsions. Thus, docking occurs between the flexible ligands and a rigid protein. The ligand orientation is determined by a shape scoring function based on the enhanced modification of the XScore(HP) method,[19c] and the final positions are ranked by lowest interaction energy values. Prior to docking, the ground state was optimized using the structures of the complexes determined by X-ray diffraction and using the PM3 parametrization[19d] implemented in the ArgusLab program package to confirm no significant divergence in the conformations of the complexes due to crystal packing effects.

Biological tests. Determination of *in vitro* cell toxicity as the cell proliferation/survival (%) was measured at intervals of 24 and 48 h. Cell lines were maintained at 37 °C in Dulbecco´s modified Eagle´s medium (DMEM) containing 10% fetal calf serum (FCS) (incubated at 37 °C, 5% CO_2). The initial concentrations of the tested compounds were 1 μmol L^{-1}. Exponentially growing cancer cells were seeded in six culture plates at 50 000 mL^{-1}, stored for 24 h, and treated with solutions (100 μL) of the tested compounds. After 24 and 48 h, the cells were washed with a buffer solution, detached from the support with trypsin—EDTA, and counted in a Bauer Slide hemocytometer.[10]

***Synthesis of complexes* 1—4.** A 1 *M* solution of KOH (3 mL (3 mmol) for **1—3** and 1.5 mL (1.5 mmol) for **4**) was added to a suspension of 2-mercaptopyrimidine (0.224 g (2 mmol) to obtain **1—3** and 0.112 g (1 mmol) for **4**) in water (8 mL) as transparent solutions. Then a solution of an organotin compound (Me_2SnCl_2, 0.220 g (1 mmol) for **1**, $Bu^n_2SnCl_2$, 0.304 g (1 mmol) for **2**, Ph_2SnCl_2, 0.334 g (1 mmol) for **3**, and Ph_3SnCl, 0.385 g (1 mmol) for **4**) in methanol (3 mL) was added. The mixture was stirred for 1 h and the precipitate that formed was filtered off, washed with cold water (2—3 mL), and dried *in vacuo* over silica gel.

Bis(pyrimidine-2-thiolato)dimethyltin(IV) (1). The yield was 50%; m.p. 257—260 °C. Found (%): C, 32.56; H, 3.86; N, 15.87; S, 17.12. $C_{10}H_{12}N_4S_2Sn$. Calculated (%): C, 32.37; H, 3.26; N, 15.10; S, 17.28. MS (ESI), *m/z*: 394 ($[C_{10}H_{12}N_2S_2SnNa]^+$ 394).

Bis(pyrimidine-2-thiolato)di-*n*-butyltin(IV) (2). The yield was 61%; m.p. 159—163 °C. Found (%): C, 42.31; H, 5.62; N, 12.55; S, 14.57. $C_{16}H_{24}N_4S_2Sn$. Calculated (%): C, 42.2; H, 5.3; N, 12.3; S, 14.1. MS (ESI), *m/z*: 479 ($[C_{16}H_{24}N_4S_2SnNa]^+$ 480).

Bis(pyrimidine-2-thiolato)diphenyltin(IV) (3). The yield was 42%; m.p. 217—222 °C. Found (%): C, 48.36; H, 3.29; N, 11.31; S, 12.78. $C_{20}H_{16}N_4S_2Sn$. Calculated (%): C, 48.50; H, 3.25; N, 11.31; S, 12.95. MS (ESI), *m/z*: 519 ($[C_{22}H_{18}N_4S_2SnNa]^+$ 520).

(Pyrimidine-2-thiolato)triphenyltin(IV) (4). The yield was 38%; m.p. 225—226 °C. Found (%): C, 57.43; H, 3.90; N, 6.20; S, 6.00. $C_{22}H_{18}N_2SSn$. Calculated (%): C, 57.3; H, 3.9; N, 6.1; S, 6.9. MS (ESI), *m/z*: 485 ($[C_{21}H_{17}N_2SSnNa]^+$ 484).

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