Novel Antimony(III) Halide Complexes with Some n-Alkyl Thioureas: Synthesis, Characterization and Study of Their Effect upon the Catalytic Oxidation of Linoleic Acid to Hydroperoxylinoleic Acid by Lipoxygenase

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Abstract: Four novel thiourea derivatives of antimony(III) compounds (SbX$_3$; X = Cl or Br) with N-methylthiourea (NMTU) and N-ethylthiourea (NETU) of formulas [SbCl$_3$(NMTU)$_3$] (**1**), [SbBr$_3$(NMTU)$_3$] (**2**),[SbCl$_3$(NETU)$_3$] (**3**), and [SbBr$_3$(NETU)$_3$] (**4**) were synthesized. These new antimony(III) halides were characterized by melting point, elemental analysis, molar conductivity, FT-Infrared spectroscopy, FT-Raman spectroscopy, UV-Vis spectrophotometry, NMR (^{1}H and ^{13}C) spectroscopy and TG-DTA analysis. The reactions of N-methylthiourea (NMTU) and N-ethylthiourea (NETU) with SbX$_3$ (X = Cl or Br) in a 2:1 ligand/metal rate but unexpected products were formed in a 3:1 ligand/metal rate. The compounds are non-electrolytes in solution and spectroscopic data of the compounds are appropriate with six coordinate octahedral geometry by three halide ions and three sulfur atoms from thiourea ligands. N-methythiourea and N-ethylthiourea ligands behave as monodentate in compounds **1**-**4** with the binding through sulfur. The influence of these compounds **1**–**4**, N-methythiourea and N-ethylthiourea upon the catalytic peroxidation of linoleic acid to hyperoxolinoleic acid by lipoxygenase was kinetically studied.

INTRODUCTION

Antimony (Sb) is a pnictogenic element and its ground state electron configuration is $5s^2 5p^3$ [1]. Antimony(III) halides, interacting with sulfur donor ligands, behave as Lewis acids, while their compounds show a range of structural motifs. One of the reasons of this geometric diversity of antimony(III) compounds is the lone pair electrons located on the antimony atom [2]. Thus, antimony(III) halide compounds with thioamide ligands contain a five coordinated metal center with a stereochemically active lone pair [3–8]. Antimony has been used as a drug for over more than 100 years. The use of antimony in medicine has been reviewed by Hadjikakou *et al*. [9]. Antimonials have been used especially for the treatment of leismaniasis (tropical disease) (*e.g.* melglumineantimoniate (Glucantime) and sodium stibogluconate (Pentostam)) [9]. The potential anticancer activity of antimony compounds is under consideration [9-22]. The last studies indicated that antimony(III) compounds are more active against carcinoma than lymphoma [17]. It is also considerable that antimony(III) compounds demonstrate strong anti-proliferative activity against human cancer cells [17]. Particularly, the antimony(III) compounds demonstrate selectivity against sarcoma and carcinoma cells [17].

Lipoxygenase is a family of iron-containing enzyme which catalyzes the oxidation of arachidonic acid to leukotrienes, in a necessary mechanism for the cell lifetime involving in inflammation mechanism [23-24]. Lipoxygenase inhibition is found to stimulate apoptosis [25], while the lipid peroxides derived from fatty acid metabolism by lipoxygenase can construct cellular proliferation [26]. So, lipoxygenase inhibitions supply a potential new target for the treatment and chemoprevention for a number of diverse cancers.

Thiourea and its derivatives have wide applications in the agricultural area, science of medicine, and analytical chemistry. The chemistry of thioureas has attracted attention owing to their potential use of reagents for the separation of metal ions and as antifungal, antiviral, and antibacterial agents [27-30]. The chemical attention of thiourea derivatives lies in the fact that they are ambidentate ligands with nitrogen and sulfur atoms susceptible for coordination and they have binding sites relevant to those in living organisms [31-32]. The coordination chemistry of thiourea derivatives with p-block elements less well studied than that of the transition metal elements and so this is still a matter of research interest [33-36].

In this work, we report the structural and spectroscopic characterization of four novel antimony (III) halide compounds with the thioureas (Scheme 1), N-methylthiourea (NMTU) and N-ethylthiourea (NETU) of formulae [SbCl$_3$(NMTU)$_3$] (**1**), [SbBr$_3$(NMTU)$_3$] (**2**), [SbCl$_3$(NETU)$_3$] (**3**) and [SbBr$_3$(NETU)$_3$] (**4**). These new compounds were used to study their influence upon the catalytic peroxidation of linoleic acid by lipoxygenase.
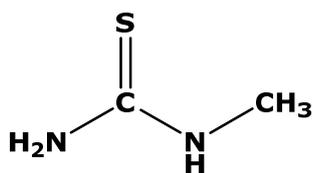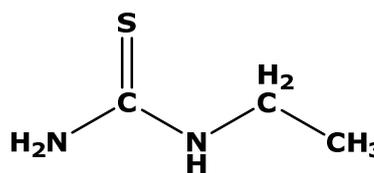
N-methythiourea (NMTU)   **N-ethylthiourea (NETU)**

Scheme 1. Formulas of the ligands used.

MATERIALS AND METHODS

Materials and Physical Measurements

All solvents used were of reagent grade; N-methylthiourea, N-ethylthiourea, and antimony(III) chloride were purchased from Sigma-Aldrich, antimony(III) bromide was purchased from Alfa Aesar. Melting points were measured using a Stuart SMP30 scientific apparatus and are uncorrected. Elemental analyses for C, H, N, and S were carried out with a Carlo Erba EA Model 1108 elemental analyzer. The molecular conductivities of compounds in DMSO were measured by means of a VWR Phenomenal conductometer CO 3000 L. FT-Raman spectra of compounds were obtained at room temperature using a low-power (~30mW) green (514.5) mm laser on a Renishaw In Via spectrometer set at 2.0 resolution. FT-Infrared spectra of compounds from 4000-400 cm^{-1} were obtained with Bruker Optics, Vertex 70 FT-Infrared spectrometer using ATR technique. The UV spectra of compounds were collected in a Shimadzu UV-2600 spectrophotometer. NMR spectra of compounds were obtained with a Varian Unity Inova 500 MHz spectrometer in DMSO-d_6 with chemical shifts given in ppm referenced to internal TMS (H). TG–DTA analysis of compounds were carried out on a Seiko SII TG/DTA 7200 apparatus under N_2 flow (50 cm^3 min^{-1}) with a heating rate of 10 °C min^{-1}.

Synthesis of [SbCl₃(NMTU)₃] (1), [SbBr₃(NMTU)₃] (2), [SbCl₃(NETU)₃] (3) and [SbBr₃(NETU)₃] (4)

1.0 mmol of N-methylthiourea (0.090 g) in benzene (10 mL) was added to a benzene (10 mL) solution of $SbCl_3$ (0.5 mmol, 0.114 g) for compound **1** and to $SbBr_3$ (0.5 mmol, 0.181 g) for compound **2**. 1.0 mmol N-ethylthiourea (0.104 g) in benzene (10 mL) was added to a benzene (10 mL) solution of $SbCl_3$ (0.5 mmol, 0.114 g) for compound **3** and to $SbBr_3$ (0,5 mmol, 0,181 g) for compound **4** and then the solutions were stirred for 30 min, then they were filtered off and then the resulting clear solutions were kept in darkness at room temperature to give compounds of the antimony(III) halide. All compounds are soluble in acetone, acetonitrile, dimethyl sulfoxide, ethanol, methanol, and tetrahydrofuran.

Result for **1:** Yellow crystals; yield 89%; mp, 114-118°C; mw, 498.56 g/mol; Found for $C_6H_{18}Cl_3N_6S_3Sb$: C: 14.38; H: 3.51; N: 16.75; S: 19.15, Calc. for C: 14.45; H: 3.64; N: 16.89; S: 19.29. UV-Vis (DMSO): λ_{max} (logε) = 257.50 (4.55). FT-IR (cm^{-1}): 3244m, 3161s, 1626s,

1551s, 1489m, 1452m, 1402m, 1338w, 1292s, 1255w, 1146w, 1122s, 972s, 773s, 715s, 633m, 598w, 544m, 482s. Λ_M = 8.8 $\Omega^{-1}.cm^2.mol^{-1}$.

Result for **2:** Yellow crystals; yield 85%; mp, 86-89°C; mw, 631.91 g/mol; found for $C_6H_{18}Br_3N_6S_3Sb$: C: 11.38; H: 2.91; N: 13.24; S:15.12, Calc. for C: 11.40; H: 2.87; N: 13.30; S: 15.22. UV-Vis (DMSO): λ_{max} (logε) = 258.00 (4.63). FT-IR (cm^{-1}): 3246m, 3161s, 1624s, 1553s, 1487m, 1452m, 1402m, 1338w, 1290s, 1257w, 1147w, 1122s, 972s, 771s, 715s, 632s, 600w, 542m, 476s. Λ_M = 23.1 $\Omega^{-1}.cm^2.mol^{-1}$.

Result for **3:** Light yellow crystals; yield 87%; mp, 63-65°C; mw, 540.64 g/mol; found for $C_9H_{24}Cl_3N_6S_3Sb$: C: 19.84; H: 4.42; N: 15.34; S:17.45,Calc. for C: 19.99; H: 4.47; N: 15.54; S: 17.79. UV-Vis (DMSO): λ_{max} (logε) = 257.50 (4.49). FT-IR (cm^{-1}): 3323w, 3277w, 3230w, 3147s, 2974m, 1618s, 1556w, 1541s, 1500w, 1466m, 1379m, 1344m, 1304w, 1261s, 1080w, 1032w, 1009w, 903w, 891w, 821w, 802s, 739s, 644s, 542w, 486s, 444w, 424w. Λ_M = 13.9 $\Omega^{-1}.cm^2.mol^{-1}$.

Result for **4:** Light yellow crystals; yield 89%; mp, 68-71°C; mw, 673.99 g/mol; found for $C_9H_{24}Br_3N_6S_3Sb$: C: 15.98; H: 3.52; N: 12.35; S: 14.19,Calc. for C: 16.04; H: 3.59; N: 12.47; S: 14.27. UV-Vis (DMSO): λ_{max} (logε) = 258.50 (4.73). IR (cm^{-1}): 3323w, 3277w, 3232w, 3147s, 2974m, 1618s, 1541s, 1498w, 1446w, 1379m, 1344m, 1304w, 1263s, 1171w, 1126s, 1113w, 1080w, 1032w, 1009w, 902w, 891w, 822w, 802s, 739s, 644s, 544w, 488s, 445w, 426w. Λ_M = 23.5 $\Omega^{-1}.cm^2.mol^{-1}$.

Study of lipoxygenase inhibition mechanism

Preparation of the solutions: 0.2 M borate buffer solution was used in all kinetic studies. Borate buffer solution was prepared as defined here: 6.18 g boric acid (H_3BO_3, 0.1 mol) was added to 300 mL distilled water. The pH was calibrated to 9 with 50% w/v sodium hydroxide. Lastly, the solution was diluted to 500 mL with distilled water [37]. Linoleic acid solution was prepared as defined here: 0.05 mL of linoleic acid was dissolved in 0.05 mL of ethanol (95%). 50 mL of H_2O was added in the flask. 5 mL of the prepared solution was added to 30 mL of the buffer solution. Enzyme solution: 10000 U of enzyme solution for each mL of buffer solution was prepared in ice-cold bath [38]. An amount of 500 U for every 3 mL of reaction mixture is used in every experiment. A unit of lipoxygenase causes and increases in absorption at 234 nm equal to 0.001 per minute.

Method

The activity of enzyme was observed by UV spectroscopy. The enzyme solution (0.05 mL) was added to a cell containing 2 mL of linoleic acid solution and a necessary amount of the buffer solution. The temperature of a solution of the inhibitor was preserved constant at 25 °C. No pre-incubation of the enzyme with an inhibitor solution was applied. The enzyme activity was established from an increase in the absorption intensity at 234 nm at 25°C (ε = 25 000 L mol$^-$

^{1}cm^{-1}) [39-41] caused by the oxidation of linoleic acid. Solutions of antimony(III) halide compounds **1**-**4** were prepared in dimethyl sulfoxide, concentrations of compounds being 10^{-1} and 10^{-2}mol.L^{-1}. The substrate concentration was preserved constant at a level of 0.3 mmol.L^{-1}, and the amounts of buffer and inhibitor solutions were altered according to the necessary final concentration of the inhibitor. The whole volume of the reaction mixture was 2 mL. Every experiment was repeated three times. All solutions were kept at thermostatic water bath at 25ºC, except from the enzyme solution that was kept at ice cold bath (0ºC).

RESULTS AND DISCUSSION

General Aspects

Antimony(III) halide compounds **1**-**4** were synthesized in benzene solution by reacting the thioureas with antimony(III) halide, as shown in Eq. 1. All the reactions were built in 2:1 ligand to metal rate. N-methythiourea and N-ethythiourea are coordinated to antimony through their neutral forms while no deprotonation occurred. Compounds **1**-**4** were characterized by melting point, elemental analysis, molar conductivity, FT-Infrared spectroscopy, FT-Raman spectroscopy, TG-DTA analysis, UV-Vis spectrophotometry and NMR spectroscopy. All compounds are air-stable. The melting points and elemental analyses of the compounds are given in Table 1. All compounds are neutral with octahedral (O_h) geometry with 3:1 HL/SbX$_3$ ratio (Figure 1).

$$\textbf{SbX}_3 \quad + \quad \textbf{2 HL} \xrightarrow{\textbf{Benzene}} \textbf{[SbX}_3\textbf{(HL)}_3\textbf{]} \qquad \textbf{(1)}$$
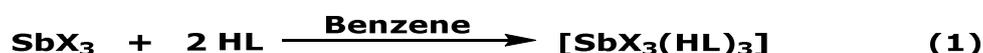
　　X: Cl or Br

　　HL : N-methythiourea (NMTU), N-ethylthiourea (NETU)

Table 1. Yields, melting points and elemental analysis of antimony(III) halide compounds.

Compounds	Yield (%)	mp (ºC)	Found (Calculated) (%)			
			C	**H**	**N**	**S**
[SbCl₃(NMTU)₃] (1)	89	114-118 °C	14.38 (14.45)	3.51 (3.64)	16.75 (16.89)	19.15 (19.29)
[SbBr₃(NMTU)₃] (2)	85	86-89 °C	11.38 (11.40)	2.91 (2.87)	13.24 (13.30)	15.12 (15.22)
[SbCl₃(NETU)₃] (3)	87	63-65 °C	19.84 (19.99)	4.42 (4.47)	15.34 (15.54)	17.45 (17.79)
[SbBr₃(NETU)₃] (4)	89	68-71 °C	15.98 (16.04)	3.52 (3.59)	12.35 (12.47)	14.19 (14.27)
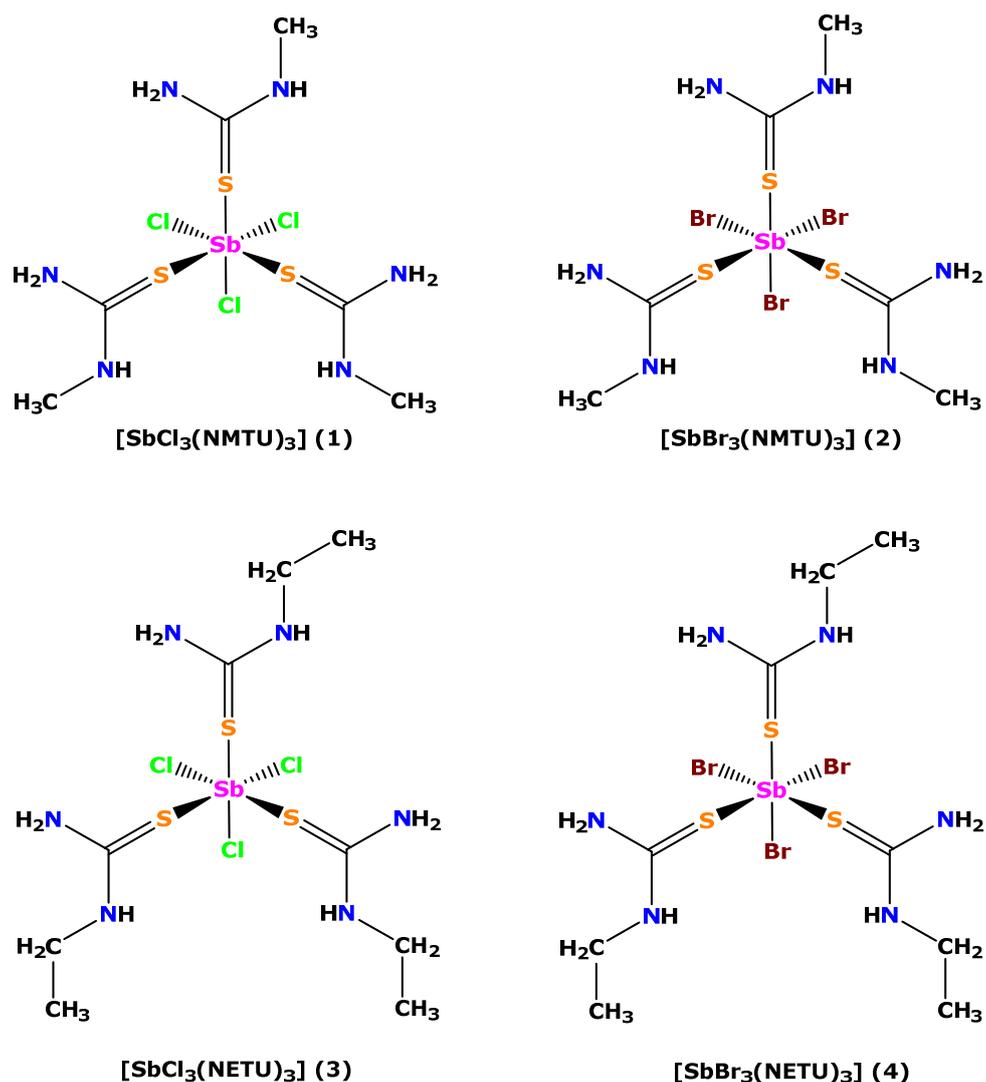
Figure 1. Proposed structures for antimony(III) halide compounds of N-methythiourea and N-ethylthiourea.

Molar Conductivity Studies

The molar conductance values of 10^{-3} M antimony(III) compounds **1-4** were obtained in dimethyl sulfoxide at room temperature. The measured molar conductance values of antimony(III) compounds are 8.8 $\Omega^{-1}.cm^2.mol^{-1}$ (**1**), 23.1 $\Omega^{-1}.cm^2.mol^{-1}$ (**2**),13.9 $\Omega^{-1}.cm^2.mol^{-1}$(**3**) and 23.5 $\Omega^{-1}.cm^2.mol^{-1}$ (**4**) respectively. Generally higher molar conductance values are determinative of the electrolytic nature of the metal compounds and lower values display their non-electrolytic nature [42]. The molar conductance values of antimony(III) compounds indicating that compounds **1**-**4** are non-electrolytes.

FT-Infrared and FT-Raman Spectral Studies

Characteristic infrared bands of the antimony(III) halide compounds and the free thioureas are shown in Table 2 and Figure 2. The characteristic infrared bands, responsive to molecular structure, are the strain modes for the ν(N-H), ν(C=S) and ν(C-N) bands [8,15-16]. The infrared spectra of compounds represent distinct vibration bands at 1551 cm^{-1} (**1**), 1553 cm^{-1} (**2**), 1541

cm^{-1} (**3**) and 1541cm^{-1} (**4**), respectively, which are attributed to the v(C-N) vibrations. Bands at 773 cm^{-1} (**1**), 771cm^{-1} (**2**), 802 cm^{-1} (**3**), and 802 cm^{-1} (**4**) are attributed to the v(C=S) vibrations. Amide v(N-H) vibrations were monitored in the region of 3323-3147cm^{-1} in compounds**1**-**4**. The corresponding vibrations at the free thioureas are found at 3327-3165 cm^{-1}, 1543 cm^{-1} and 775 cm^{-1} (NMTU), 3327-3147 cm^{-1}, 1541 cm^{-1} and 804 cm^{-1} (NETU). A low frequency shifts in the v(C=S) band and high frequency shifts in v(C-N) band indicate that coordination happens through sulfur atoms of the thioureas in the solid state. Since no v(S-H) vibrations are observed in the infrared spectrum of **1-4** indicating that the free ligands are coordinated through their thione forms. Sb-S and Sb-X (X: Cl or Br) vibrations are Raman-active [8,15-16]. Thus, bands at 412/406 cm^{-1} (**1**), 443 cm^{-1}(**2**), 408 cm^{-1} (**3**) and 444 cm^{-1} (**4**) in the Raman spectra of compounds **1**-**4** are owing to the Sb-S vibrations. Bands at 191/136 cm^{-1} in **1** and 199/191/133 cm^{-1} in **3** are attributed to the Sb-Cl vibrations, while band at 108/100 cm^{-1} in **2** and 105 cm^{-1} in **4** has been assigned to the Sb-Br vibrations (Figures S1-S4).

Table 2. Selected IR and Raman spectroscopic data for compounds **1**-**4** and free ligands.

Compound	Mid-IR (cm^{-1})			Raman (cm^{-1})	
	v(N-H)	v(C-N)	v(C=S)	v(Sb-S)	v(Sb-X)
NMTU	3327, 3246, 3165	1543	775	-	-
[SbCl$_3$(NMTU)$_3$] (1)	3244, 3161	1551	773	412,406	191,136
[SbBr$_3$(NMTU)$_3$] (2)	3246, 3161	1553	771	443	108,100
NETU	3327, 3232, 3147	1541	804	-	
[SbCl$_3$(NETU)$_3$] (3)	3323, 3230, 3147	1541	802	408	199,191,133
[SbBr$_3$(NETU)$_3$] (4)	3323, 3232, 3147	1541	802	444	105

(A)

(B)

(C)

(D)

(E)

(F)
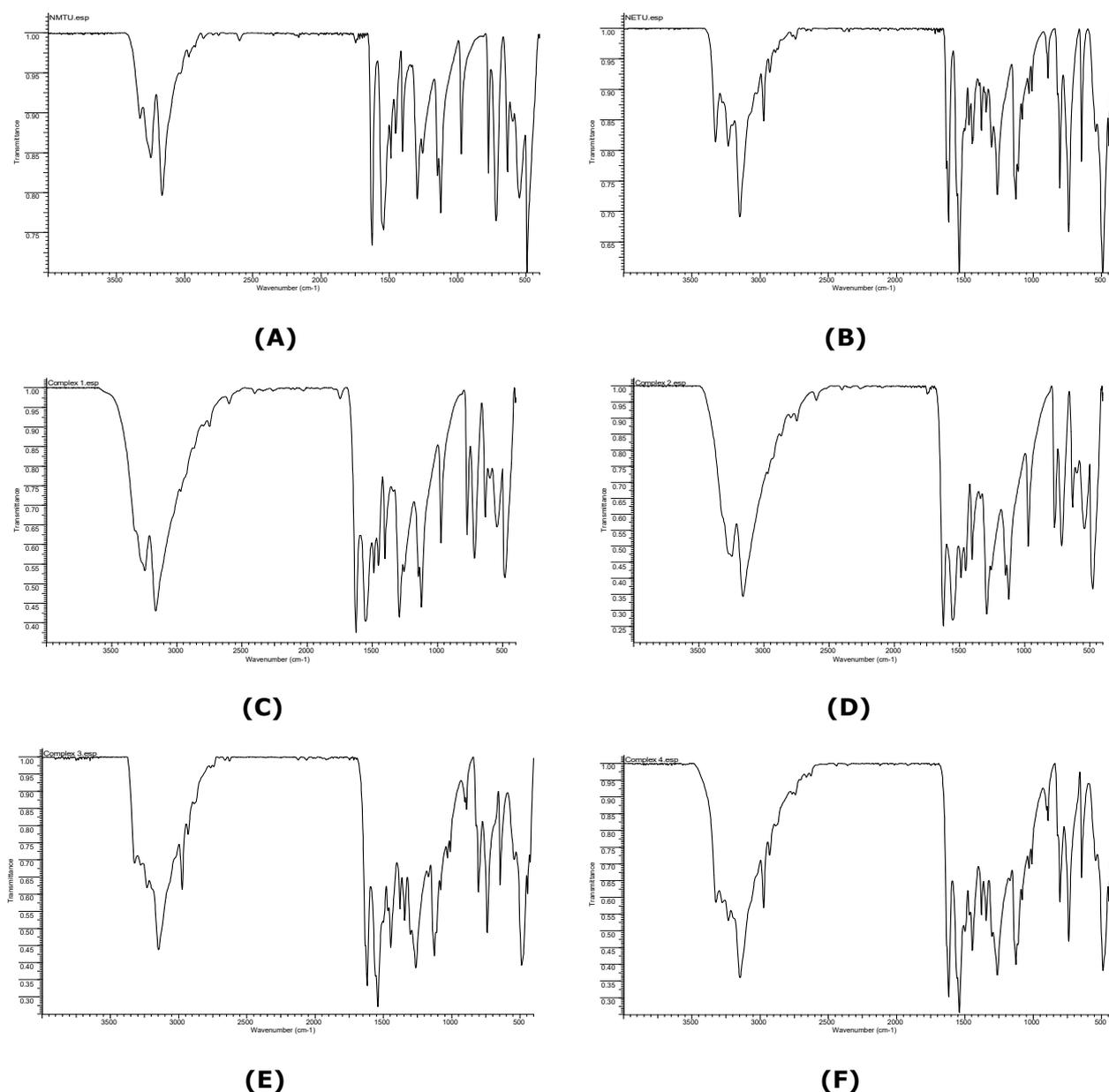
Figure 2. Infrared spectra of: (**A**) N-methylthourea, (**B**) N-ethylthiourea, (**C**) [SbCl$_3$(NMTU)$_3$] (**1**), (**D**) [SbBr$_3$(NMTU)$_3$] (**2**), (**E**) [SbCl$_3$(NETU)$_3$] (**3**) and (**F**)[SbBr$_3$(NETU)$_3$] (**4**)

Thermal Analysis

The thermal stability of antimony(III) halide compounds **1**-**4** is tested by TG-DTA analysis in an atmosphere of nitrogen in the range 25-800 °C. The data show that compounds **1**-**4** remain stable up to 149 °C (**1**), 138 °C (**2**), 146 °C (**3**), and 160 °C (**4**), respectively (Figure 2). Beyond these temperatures, compounds **1**, **2** and **4** have one decomposition step, while **3** has two decomposition steps.

UV-Vis Spectral Studies

The UV-Vis spectra of the free N-methylthiourea, N-ethylthiourea, and their antimony(III) compounds in dimethyl sulfoxide is described in Figures 3 and 4. Free thioureas and their antimony(III) halide compounds exhibit one major absorption band in the UV region. Compounds **1-4** exhibit at 257.50 nm (**1**), 258.00 nm (**2**), 257.50 nm (**3**) and 258.50 (**4**), respectively,

which are assigned to the n-π* transitions. The corresponding absorption band at the free ligands is found at 256.50 nm (NMTU and NETU). The absorption bands shift to lower energy from chloro to bromo Sb(III) compounds.
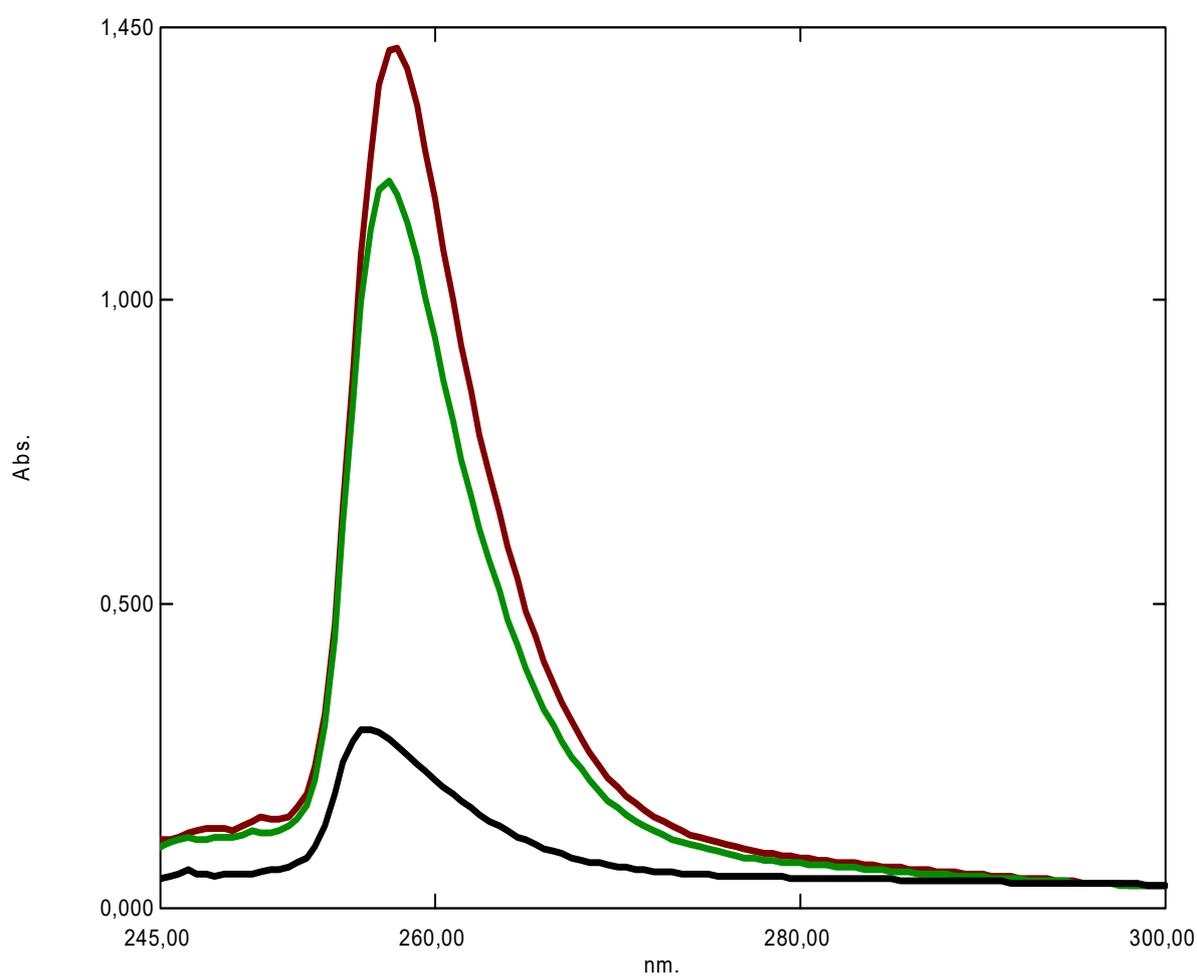
Figure 4. Uv-Vis absorption spectra of N-methylthiourea (━), $[SbCl_3(NMTU)_3]$ (**1**) (━) and $[SbBr_3(NMTU)_3]$ (**2**) (━)

(A)

(B)

(C)

(D)
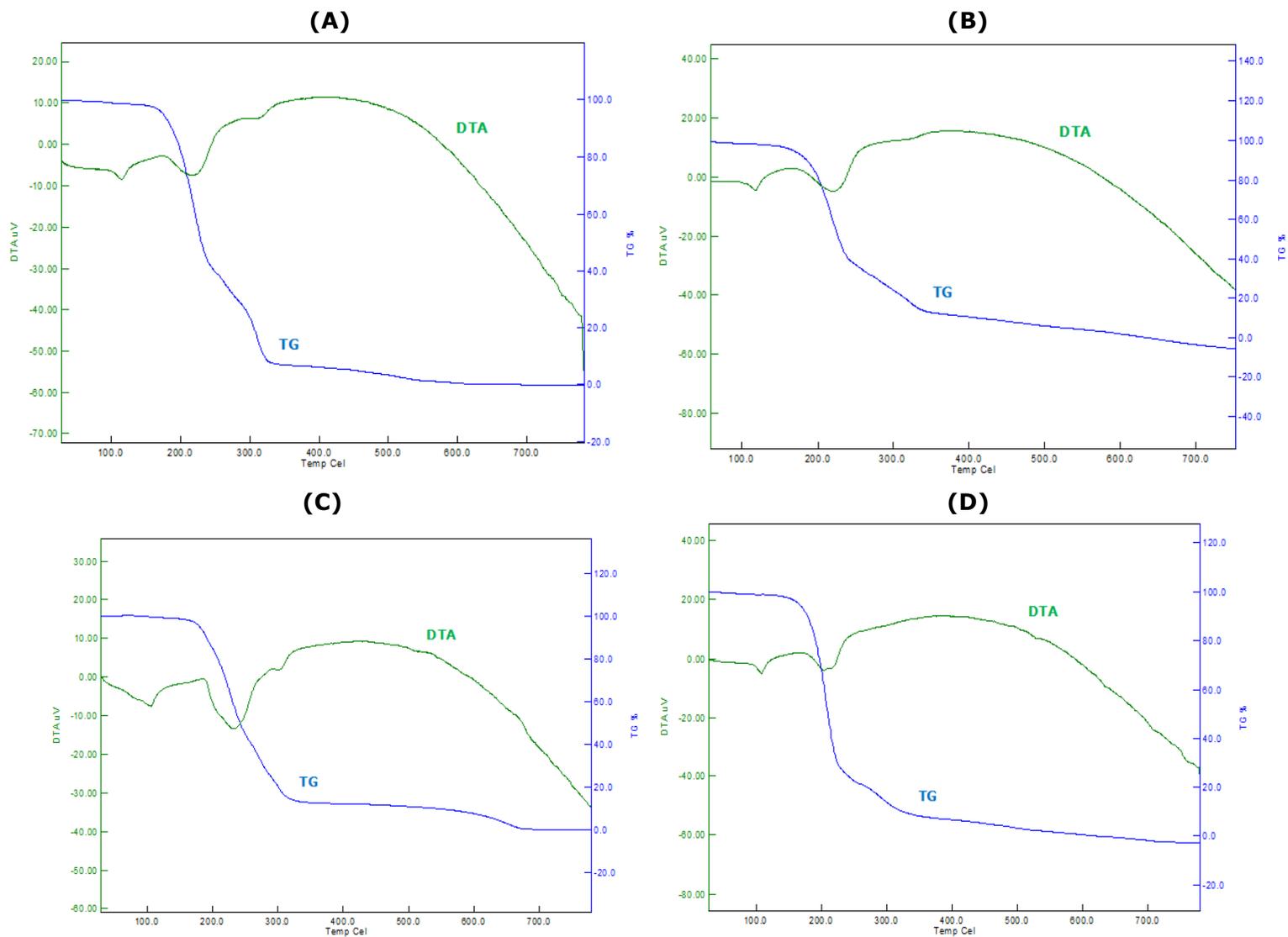
Figure 3. TG and DTA curves for compounds (A) [SbCl$_3$(NMTU)$_3$] (**1**),(B) [SbBr$_3$(NMTU)$_3$] (**2**), (C) [SbCl$_3$(NETU)$_3$] (**3**) and (D) [SbBr$_3$(NETU)$_3$] (**4**)
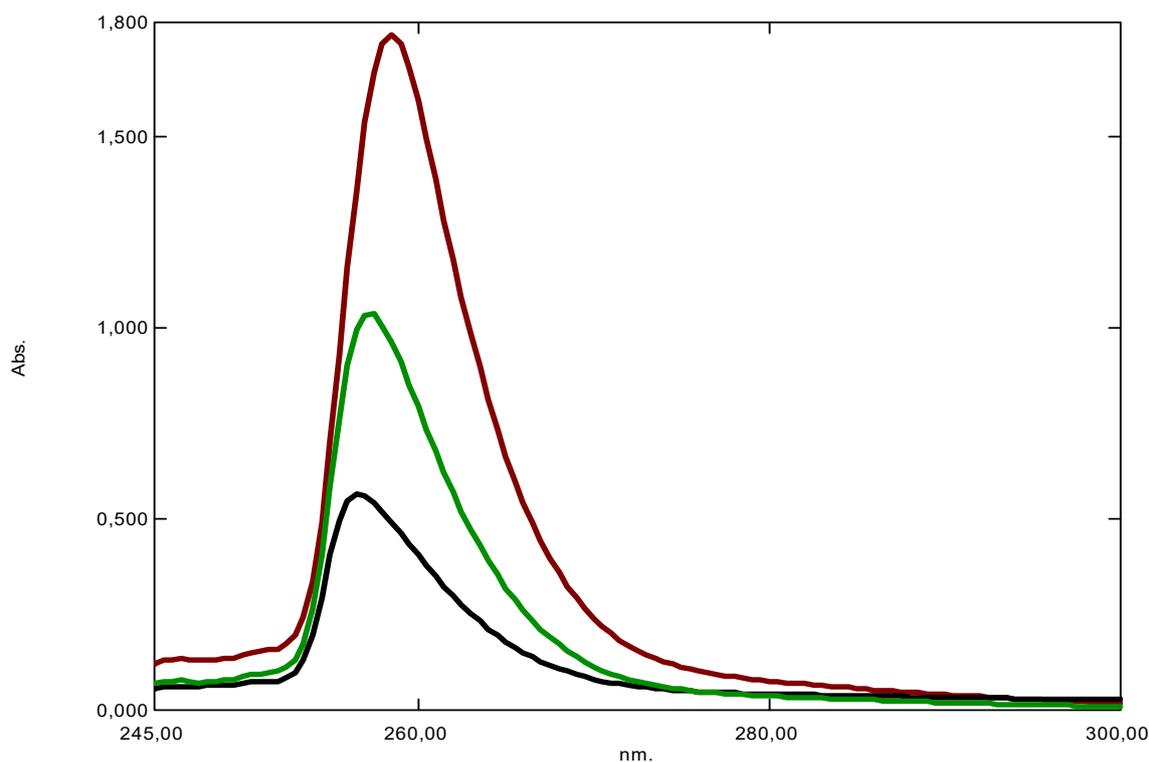
Figure 5. UV-Vis absorption spectra of N-ethylthiourea (━), [SbCl$_3$(NETU)$_3$] (**3**) (━) and

[SbBr$_3$(NETU)$_3$] (**4**) (━).

NMR Spectral Studies

The ^{1}H and ^{13}C NMR chemical shifts of N-methylthiourea, N-ethylthiourea and those of the antimony(III) halide compounds **1**–**4** in DMSO-d_6 are summarized in Table 3 (Figures S5–S14). In the ^{1}H NMR spectra of the compounds, the N–H signal of thiourea ligands became less intense upon coordination and shifted downfield from their positions in the free ligands. The deshielding is related to an increase in π-electron density in the C–N bond upon coordination [27, 29, 30, 34]. The appearance of the N–H signal shows that the N-methylthiourea and N-ethylthiourea are coordinated to antimony(III) via the thione group. Table 3 shows that the N–H protons of NMTU and NETU are nonequivalent (NH$_2$ appears as a doublet) and also after coordination N-H protons of compounds **1**-**4** are nonequivalent. It should be noted that NMTU and NETU in ^{13}C NMR gives two signals for >C=S, -CH$_2$- and -CH$_3$ carbons for showing that the compounds exist in two isomeric forms [43]. The new signal observed at 3.49 (**1**), 3.60 (**2**), 3.49 (**3**) and 3.62 (**4**) ppm, respectively in the ^{1}H NMR spectra. These new signals are attributed to the halogen-hydrogen interaction. All other resonance signals of the thioureas remain un-shifted in the spectra of the compounds. However, such narrow shifts were also monitored for antimony(III) halide compounds with thione ligands [17-20].

Table 3. Chemical shifts (ppm) of the resonance signals observed in ^1H and ^{13}C NMR spectra of free thioureas and their antimony(III) compounds **1**−**4** in *DMSO-d^6.*

Compounds	^1H NMR chemical shifts (ppm)	^{13}C NMR chemical shifts (ppm)
N-methylthiourea (NMTU)	7.64, 7.47, 6.93 (N-H) 2.84, 2.64 (-CH$_3$)	184.94, 181.87 (>C=S) 31.97, 30.80 (-CH$_3$)
[SbCl$_3$(NMTU)$_3$] (**1**)	7.68, 7.50, 6.98 (N-H) 2.84, 2.64 (-CH$_3$) 3.49 (Cl···H)	184.95, 181.83 (>C=S) 31.92, 30.76 (-CH$_3$)
[SbBr$_3$(NMTU)$_3$] (**2**)	7.73, 7.51, 7.16 (N-H) 2.84, 2.65 (-CH$_3$) 3.60 (Br···H)	184.91, 181.26 (>C=S) 31.96, 30.84 (-CH$_3$)
N-ethylthiourea (NETU)	7.53, 7.23, 6.88 (N-H) 3.41, 3.07 (-CH$_2$-) 1.05-1.08, t (-CH$_3$)	183.83, 180.95 (>C=S) 39.66, 38.60 (-CH$_2$-) 15.45, 14.88 (-CH$_3$)
[SbCl$_3$(NETU)$_3$] (**3**)	7.68, 7.55, 6.90 (N-H) 3.38, 3.06 (-CH$_2$-) 1.05-1.08, t (-CH$_3$) 3.49 (Cl···H)	183,83 180.79 (>C=S) 39.66, 38.59 (-CH$_2$-) 15.48, 14.85 (-CH$_3$)
[SbBr$_3$(NETU)$_3$] (**4**)	7.73, 7.56, 6.90 (N-H) 3.38, 3.07 (-CH$_2$-) 1.05-1.08, t (-CH$_3$) 3.62 (Br···H)	183.80, 180.37 (>C=S) 38.63, 38.63 (-CH$_2$-) 15.45, 14.83 (-CH$_3$)

Kinetic study of the peroxidation of linoleic acid by lipoxygenase in the presence of antimony(III) compounds 1−4 and free thioureas

Because lipoxygenase inhibition is found to induce apoptosis [25] the effect of compounds **1**−**4** and free ligands on the oxidation of linoleic acid by lipoxygenase were studied in a vast concentration area. The degree of lipoxygenase activity (A, %) in the presence of these compounds was calculated according to the process described previously [38]. Figures 6 and 7 compares the inhibitory effect of **1**−**4** in different concentrations. The IC$_{50}$ values which were found for antimony(III) compounds are 44.22 μM (**1**), 39.63 μM (**2**),45.05 μM (**3**) and 53.55 μM (**4**), N-methylthiourea (NMTU) 221.66 μM and for N-ethylthiourea (NETU) 217.65 μM, respectively. Thus, all four compounds show higher inhibitory activity of lipoxygenase than free thioureas (N-methylthiourea (NMTU) and N-ethylthiourea (NETU)) and moreover, antimony(III) halide compounds of N-methylthiourea (**1** and **2**) show higher inhibitory activity of lipoxygenase than antimony(III) halide compounds of N-ethylthiourea (**3** and **4**).
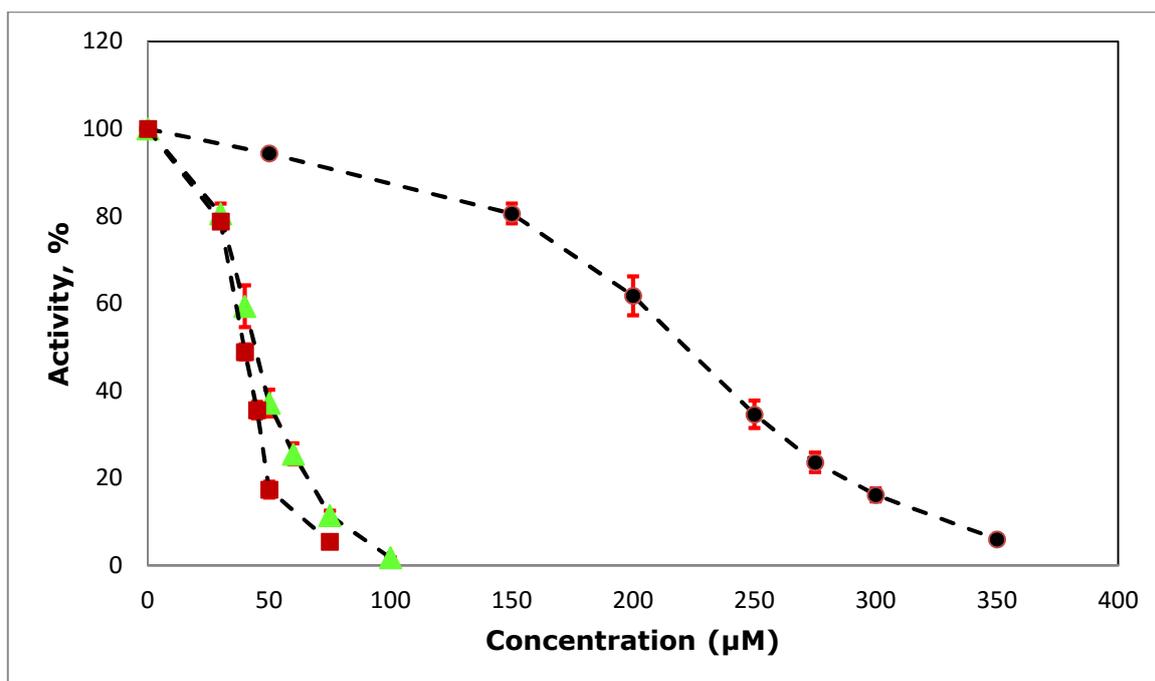
Figure 6. The inhibitory effect against lipoxygenase caused by (▲)[SbCl₃(NMTU)₃] (1), (■)[SbBr₃(NMTU)₃] (**2**),and (●) N-methythiourea in various concentrations.
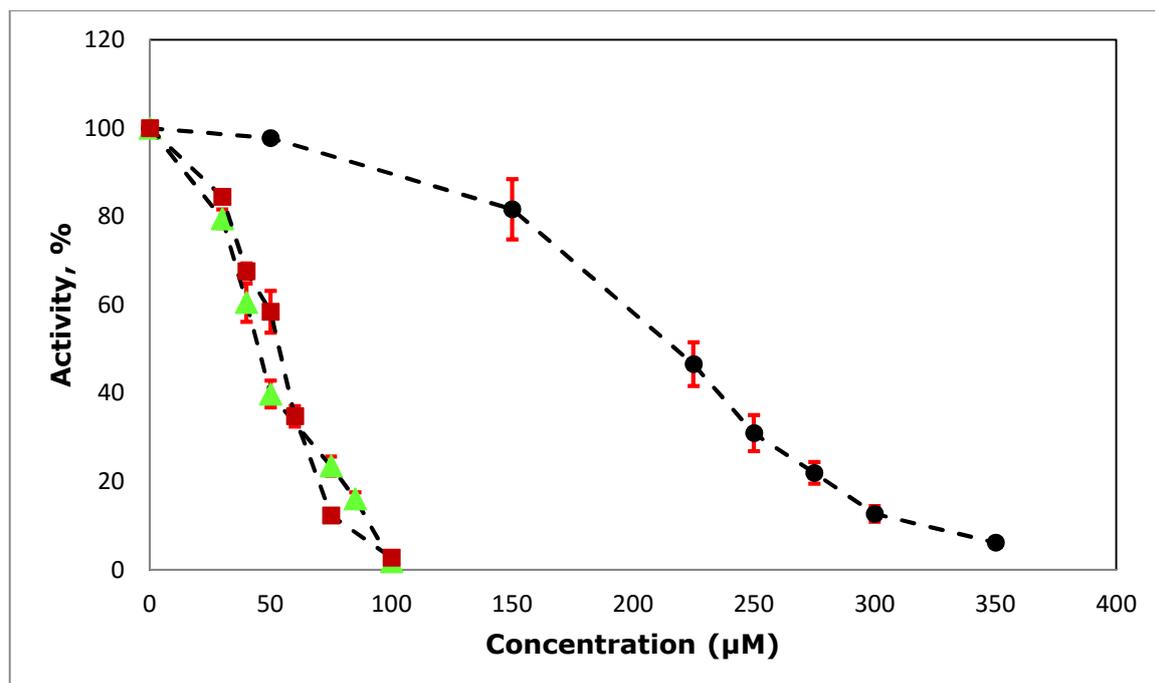
Figure 7. The inhibitory effect against lipoxygenase caused by (▲)[SbCl₃(NETU)₃] (3), (■)[SbBr₃(NETU)₃] (**4**), and (●) N-ethythiourea in various concentrations.

CONCLUSIONS

N-alkyl thioureas, namely N-methylthiourea (NMTU) and N-ethylthiourea (NETU) react with antimony(III) halides (halide: Cl or Br) to form compounds of formulas $[SbCl_3(NMTU)_3]$ (**1**), $[SbBr_3(NMTU)_3]$ (**2**),$[SbCl_3(NETU)_3]$ (**3**) and $[SbBr_3(NETU)_3]$ (**4**). The reactions of N-methylthiourea (NMTU) and N-ethylthiourea (NETU) with SbX_3 (X = Cl or Br) in a 2:1 HL/SbX_3 rate, but unexpected compounds were formed in a 3:1HL/SbX_3rate. All antimony(III) halide compounds are neutral with octahedral (O_h) geometry. All four compounds show higher inhibitory activity of lipoxygenase than free thioureas (N-methylthiourea (NMTU) and N-ethylthiourea (NETU)) and moreover, antimony(III) compounds of N-methylthiourea (**1**-**2**) show higher inhibitory activity of lipoxygenase than antimony(III) compounds of N-ethylthiourea (**3**-**4**). On the other hand, while antimony(III) halide compounds **1**-**4** display similar lipoxygenase inhibition with other antimony (III) compounds, they display lower lipoxygenase inhibition than the tin compounds in the literature [14, 38].

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REFERENCES

1. Norman NC, Editor. Chemistry of Arsenic, Antimony and Bismuth. Blackie Academic and Professional; 1998. ISBN: 978-0-7514-0389-3.

2. Sun H, Editor. Biological Chemistry of Arsenic, Antimony and Bismuth. Wiley. 2010. ISBN: 978-0-470-71390-7.

3. Parrilha GL, Dias RP, Rocha WR, Mendes IC, Benítez D, Varela J, Cerecetto H, M. González M, Melo CML, Neves JKAL, Pereira VRA, Beraldo H. 2-Acetylpyridine and 2-benzoylpyridine-derived thiosemicarbazones and their antimony(III) complexes exhibit high anti-trypanosomal activity. Polyhedron, 2012; 31; 614-21.DOI:10.1016/j.poly.2011.10.018.

4. Ajaz H, Hussain S, Altaf M, Stoeckli-Evans H, Isab AA, Mahmood R, Altaf S, Ahmad S. Synthesis and Characterization of Antimony(III) Complexes of Thioamides, and Crystal Structure of {[Sb(Imt)_2Cl_2]_2((_2-Imt)}Cl_2(Imt=Imidazolidine-2-thione). Chinese Journal of Chemistry, 2011; 29; 254-58. DOI: 10.1002/cjoc.201190074.

5. Barnes NA, Godfrey SM, Pritchard RG, Ratcliffe S. The reactions of SbX_3 (X = Cl, Br, I) with N-methylbenzothiazole-2-thione (mbtt) and N-methylbenzothiazole-2-selone (mbts). Formation of the mixed mer/fac-complex $[mer-SbBr_3(mbts)_2(\mu-mbts)fac-SbBr_3(mbts)_2]\cdot CH_2Cl_2$. Polyhedron, 2010; 29; 1822-32. DOI:10.1016/j.poly.2010.02.029.

6. Bukvetskii BV, Sedakova TV, Mirochnik AG. Crystal structure and luminescence of antimony(III) bromide with aniline. Journal of Structural Chemistry. 2009; 50; 322-27. DOI:10.1007/s10947-009-0044-9.

7. Barnes NA, Godfrey SM, Pritchard RG, Ratcliffe S. The reaction of N,N '-Di-tert-butylthiourea (dtbtu) with antimony(III) halides—formation of the triply bridged [(dtbtu)SbX2(mu-X)(2)(mu-

dtbtu)SbX2(dtbtu)] (X = Cl, Br) dimers. European Journal of Inorganic Chemistry.2008; 3661–67. DOI: 10.1002/ejic.200800252.

8. Yin HD, Zhai J, Sun YY, Wang DQ. Synthesis, characterizations and crystal structures of new antimony (III) complexes with dithiocarbamate ligands. Polyhedron. 2008; 27; 663-70. DOI:10.1016/j.poly.2007.10.019.

9. Hadjikakou SK, Ozturk II, Banti CN, Kourkoumelis N, Hadjiliadis N. Recent advances on antimony(III/V) compounds with potential activity against tumor cells. Journal of Inorganic Biochemistry. 2015; 153; 293-305. DOI:10.1016/j.jinorgbio.2015.06.006.

10. Hadjikakou SK, Antoniadis CD, Hadjiliadis N, Kubicki M, Binolis J, Karkabounas S, Charalabopoulos K. (2005) Synthesis and characterization of new water stable antimony(III) complex with pyrimidine-2-thione and in vitro biological study. Inorganica Chimica Acta. 2005; 358; 2861–66. DOI:10.1016/j.ica.2004.06.028.

11. Ozturk II, Hadjikakou SK, Hadjiliadis N, Kourkoumelis N, Kubicki M, Baril M, Butler IS, Balzarini J. Synthesis, structural characterization, and biological studies of new antimony(III) complexes with thiones. The influence of the solvent on the geometry of the complexes. Inorganic Chemistry. 2007; 46; 8652–61. DOI: 10.1021/ic700756e.

12. Ozturk II, Hadjikakou SK, Hadjiliadis N, Kourkoumelis N, Kubicki M, Tasiopoulos AJ, Scleiman H, Barsan MM, Butler IS, Balzarini J. New antimony(III) bromide complexes with thioamides: synthesis, characterization, and cytostatic properties. Inorganic Chemistry. 2009; 48; 2233–45. DOI: 10.1021/ic8019205.

13. Hadjikakou SK, Ozturk II, Xanthopoulou MN, Zachariadis PC, Zartilas S, Karkabounas S and Hadjiliadis N. Synthesis, structural characterization and biological study of new organotin(IV), silver(I) and antimony(III) complexes with thioamides. Journal of Inorganic Biochemistry. 2008; 102; 1007-15. DOI: 10.1016/j.jinorgbio.2007.12.027.

14. Ozturk I, Filimonova S, Hadjikakou SK, Kourkoumelis N, Dokorou V, Manos MJ, Tasiopoulos AJ, Barsan MM, Butler IS, Milaeva ER, Balzarini J, Hadjiliadis N. Structural motifs and biological studies of new antimony(III) iodide complexes with thiones. Inorganic Chemistry. 2010; 49; 488–501. DOI: 10.1021/ic901442e.

15. Ozturk II, Metsios AK, Filimonova-Orlova S, Kourkoumelis N, Hadjikakou SK, Manos E, Tasiopoulos AJ, Karkabounas S, Milaeva ER and Hadjiliadis N. Study on single crystal structure of the antimony(III) bromide complex with 3-methyl-2-mercaptobenzothiazole and biological activity of some antimony(III) bromide complexes with thioamides. Medicinal Chemistry Research. 2012; 21; 3523-31. DOI 10.1007/s00044-011-9905-9.

16. Ozturk II, Kourkoumelis N, Hadjikakou SK, Manos MJ, Tasiopoulos AJ, Butler IS, Balzarini J and Hadjiliadis N. Interaction of antimony(III) chloride with thiourea, 2-mercapto-5-methyl-benzimidazole, 3-methyl-2-mercaptobenzothiazole, 2-mercaptopyrimidine, and 2-mercaptopyridine. Journal of Coordination Chemistry. 2011; 64; 3859-71. DOI: 10.1080/00958972.2011.633603.

17. Ozturk II, Banti CN, Manos MJ, Tasiopoulos AJ, Kourkoumelis N, Charalabopoulos K and Hadjikakou SK. Synthesis, characterization and biological studies of new antimony(III) halide complexes with ω-thiocaprolactam. Journal of Inorganic Biochemistry. 2012; 109; 57-65. DOI: 10.1016/j.jinorgbio.2012.01.014.

18. Ozturk II, Urgut OS, Banti CN, Kourkoumelis N, Owczarzak AM, Kubicki M, Charalabopoulos K and Hadjikakou SK. Synthesis, structural characterization and cytotoxicity of the antimony(III) chloride complex with N,N-dicyclohexyldithiooxamide Polyhedron. 2013; 52; 1403-10. DOI: 10.1016/j.poly.2012.04.038.

19. Ozturk II, Urgut OS, Banti CN, Kourkoumelis N, Owczarzak AM, Kubicki M and Hadjikakou SK. Synthesis, structural characterization and cytostatic properties of N,N-dicyclohexyldithiooxamide complexes of antimony(III) halides (SbX3, X: Br or I). Polyhedron. 2014; 70; 172-79. DOI: 10.1016/j.poly.2013.12.025.

20. Han A, Ozturk II, Banti CN, Kourkoumelis N, Manoli M, Tasiopoulos AJ, Owczarzak AM, Kubicki M and Hadjikakou SK. Antimony(III) halide compounds of thioureas: Structures and biological activity. Polyhedron. 2014; 79; 151-60. DOI: 10.1016/j.poly.2014.05.014.

21. Urgut OS, Ozturk II, Banti CN, Kourkoumelis N, Manoli M, Tasiopoulos AJ and Hadjikakou SK. New antimony(III) halide complexes with dithiocarbamate ligands derived from thiuram degradation: The effect of the molecule's close contacts on in vitro cytotoxic activity. Materials Science and Engineering C. 2016; 58; 396–408. DOI: 10.1016/j.msec.2015.08.030.

22. Urgut OS, Ozturk II, Banti CN, Kourkoumelis N, Manoli M, Tasiopoulos AJ and Hadjikakou SK. Addition of tetraethylthiuram disulfide to antimony(III) iodide; synthesis, characterization and biological activity.InorganicaChimicaActa. 2016; 443; 141-150. DOI: 10.1016/j.ica.2015.12.028.

23. Samuelsson B, Dahlen SE, Lindgren J, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science. 1987; 237; 1171-76. DOI: 10.1126/science.2820055

24. Knapp MJ, Klinman JP. Kinetic Studies of Oxygen Reactivity in Soybean Lipoxygenase-1. Biochemistry. 2003; 42; 11466-75. DOI: 10.1021/bi0300884.

25. Ding XZ, Kuszynski CA, El-Metwally TH, Adrian TE. Lipoxygenase Inhibition Induced Apoptosis, Morphological Changes, and Carbonic Anhydrase Expression in Human Pancreatic Cancer Cells. Biochemical and Biophysical Research Communications. 1999; 266; 392-99. DOI: 10.1006/bbrc.1999.1824.

26. Pidgeon GP, Lysaght J, Krishnamoorthy S, Reynolds JV, O'Byrne K, Nie D, Honn KV. Lipoxygenase metabolism: roles in tumor progression and survival. Cancer Metastasis Reviews. 2007; 26; 26 (2007) 503-24. DOI: 10.1007/s10555-007-9098-3.

27. Bourne S, Koch KR. Intramolecular hydrogen-bond controlled unidentate co-ordination of potentially chelating N-acyl-N'-alkylthioureas: crystal structure of cis-bis(N-benzoyl-N'-propylthiourea) dichloroplatinum(II). Journal of the Chemical Society, Dalton Transactions. 1993; 13; 2071–72. DOI: 10.1039/DT9930002071.

28. Kucukguzel I, Kucukguzel SG, Rollas S, Kiras M. Some 3-Thioxo/alkylthio-1,2,4-triazoles with a substituted thiourea moiety as possible antimycobacterials. Bioorganic Medicinal Chemistry Letters. 2001; 11; 1703–07. DOI: 10.1016/S0960-894X(01)00283-9.

29. Venkatachalam TK, Sudbeck EA, Uckun FM. Regiospecific synthesis, X-ray crystal structure and biological activities of 5-bromothiophenethyl thioureas. Tetrahedron Letters. 2001; 42; 6629–32. DOI: 10.1016/S0040-4039(01)01290-4.

30. Campo RD, Criado JJ, Gheorghe R, Gonzalez FJ, Hermosa MR, Sanz F, Manzano JL, Monte E, Rodrıguez-Fernandez E. N-benzoyl-N′-alkylthioureas and their complexes with Ni(II), Co(III) and Pt(II) – crystal structure of 3-benzoyl-1-butyl-1-methyl-thiourea: activity against fungi and yeast. Journal of Inorganic Biochemistry. 2004; 98; 1307–14. DOI: 10.1016/j.jinorgbio.2004.03.019.

31. Ahmad S, Isab AA, Ahmad S. ^{1}H, ^{13}C, ^{15}N NMR and IR Spectroscopic Studies of a Rh(II) Complex of Thiourea. Journal of Coordination Chemistry. 2003; 56; 1587-95.DOI: 10.1080/00958970310001641688.

32. Rodríguez-Fernández E, Manzano JL, Benito JJ, Hermosa R, Monte E, Criado JJ. Thiourea, triazole and thiadiazine compounds and their metal complexes as antifungal agents. Journal of Inorganic Biochemistry. 2005; 99; 1558-72. DOI: 10.1016/j.jinorgbio.2005.05.004.

33. Plutín AM, Alvarez A, Mocelo R, Ramos R, Castellano EE, da Silva MM, Colina-Vegas L, Pavan FR, Batista AA. Anti-Mycobacterium tuberculosis activity of platinum(II)/N,N-disubstituted-N'-acyl thiourea complexes. Inorganic Chemistry Communications. 2016; 63; 74–80. DOI: 10.1016/j.inoche.2015.11.020.

34. Schwade VD, Kirsten L, Hagenbach A, Lang ES, Abram U. Indium(III), lead(II), gold(I) and copper(II) complexes with isophthaloylbis(thiourea) ligands. Polyhedron. 2013; 55; 155–61. DOI: 10.1016/j.poly.2013.03.008.

35. Bowmaker GA, Pakawatchai C, Saithong S, Skelton BW, White AH, Structural and spectroscopic studies of some adducts of silver(I) halides withthiourea and N-ethyl substituted thioureas. Dalton Transactions. 2010; 39; 4391–4404. DOI: 10.1039/C001398F.

36. Hough E, Nicholson DG. Stereochemical role of lone pairs in main-group elements. Part 2. Structure and bonding in trichloro(tetramethylthiourea)antimony(III) studied by means of X-ray crystallography and antimony-121 Mössbauer spectroscopy. Journal of the Chemical Society, Dalton Transactions. 1981; 10; 2083-87. DOI: 10.1039/DT9810002083.

37. Xanthopoulou MN, Hadjikakou SK, Hadjiliadis N, Milaeva ER, Gracheva YA, Tyurin VY, Kourkoumelis N, Christoforidis KC, Metsios AK, Karkabounas S, and Charalabopoulos K. Biological studies of new organotin(IV) complexes of thioamide ligands.European Journal of Medicinal Chemistry. 2008; 43; 327-35. DOI: 10.1016/j.ejmech.2007.03.028.

38. Xanthopoulou MN, Hadjikakou SK, Hadjiliadis N, Kubicki M, Karkabounas S, Charalabopoulos K, Kourkoumelis N, and Bakas T. Synthesis and characterization of a new chloro-di-phenyltin(IV) complex with 2-mercapto-nicotinic acid: Study of its influence upon the catalytic oxidation of linoleic acid to hydroperoxylinoleic acid by the enzyme lipoxygenase. Journal of Organometallic Chemistry. 2006; 691; 1780-89. DOI: 10.1016/j.jorganchem.2005.11.073.

39. Glick D, Editor. Methods of Biochemical Analysis, Volume 2. Interscience Publishers. 1955. ISBN: 9780471304593.

40. Lopez-Nicolas JM, Bru R, Sanchez-Ferrer A, Carcia-Carmona A. An Octaethylene Glycol Monododecyl Ether-Based Mixed Micellar Assay for Lipoxygenase Acting at Neutral pH. Analytical Biochemistry. 1994; 221; 410-15. DOI: 10.1006/abio.1994.1435.

41. Axelrod B, Cheesbrough TM, Laakso S. [53] Lipoxygenase from soybeans: EC 1.13.11.12 Linoleate: oxygen oxidoreductase. Methods Enzymology. 1981; 71; 441-451. DOI:10.1016/0076-6879(81)71055-3.

42. Refat MS, Killa HMA, Fetooh H. Spectroscopic and thermal characterization of Cu(II), Co(II), Ni(II) and Mn(II) complexes of fluorescent dye 4-N,N-dimethyl-ethanolamine-N-allyl-1,8-naphthalimide (4DMEAN). Journal of Molecular Structure. 2010; 983; 122–132. DOI:10.1016/j.molstruc.2010.08.041.

43. Nadeem S, Rauf MK, Ahmad S, Ebihara M, Tirmizi SA, Bashir SA, Badshah A. Synthesis and characterization of palladium(II) complexes of thioureas. X-ray structures of [Pd(N,N'-dimethylthiourea)$_4$]Cl$_2$.2H$_2$O and [Pd(tetramethylthiourea)$_4$]Cl$_2$. Transition Metal Chemistry. 2009; 34; 197–202. DOI: 10.1007/s11243-008-9177-5.

Türkçe Öz ve Anahtar Kelimeler

Bazı n-Alkil Tiyoüreler İçeren Yeni Antimon(III) Halojenür Kompleksleri: Sentez, Karakterizasyon ve Linoleik Asidin Hidroperoksilinoleik Aside Lipoksijenaz ile Katalitik Yükseltgenmesindeki Etkilerinin İncelenmesi

Ibrahim Ismet Ozturk

Öz: Dört yeni tiyoüre-antimon(III) bileşiği (SbX$_3$; X=Cl veya Br) sentezlenmiştir. Kullanılan üre türevleri N-metiltiyoüre (NMTU) ve N-etiltiyoüre (NETU) olup oluşan komplekslerin kapalı formülleri [SbCl$_3$(NMTU)$_3$] (**1**), [SbBr$_3$(NMTU)$_3$] (**2**),[SbCl$_3$(NETU)$_3$] (**3**) ve [SbBr$_3$(NETU)$_3$] (**4**) olarak belirlenmiştir. Bu yeni antimon(III) halojenürler erime noktası, elementel analiz, molar iletkenlik, FT-Kızılötesi spektroskopisi, FT-Raman spektroskopisi, UV-Vis spektrofotometrisi NMR (^{1}H ve ^{13}C) spektroskopisi ve TG-DTA analizi ile karakterize edilmiştir. N-Metiltiyoüre (NMTU) ve N-etiltiyoüre (NETU) ile SbX$_3$ (X = Cl veya Br) arasındaki 2:1 ligand/metal oranındaki tepkimeden 3:1 ligand metal oranına sahip beklenmeyen ürünler elde edilmiştir. Bileşikler çözeltide non-elektrolit olarak bulunur ve bileşiklerin spektroskopik verileri altı koordinasyonlu oktahedral geometri ile uyumludur, bu komplekslerde üç halojenür iyonu ve üç tiyoüre kükürt atomu bulunmaktadır. N-Metiltiyoüre ve N-etiltiyoüre ligandları **1-4** bileşiklerinde kükürt üzerinden bağlanan monodentat bir karaktere sahiptir. **1-4** bileşiklerinin, N-metiltiyoüre ve N-etiltiyoürenin, linoleik asidin hidroperoksilinoleik aside lipoksijenaz ile katalitik peroksidasyonu ile dönüşmesi kinetik olarak çalışılmıştır.

Anahtar kelimeler: Antimon(III) halojenürler; N-alkil tiyoüreler; spektroskopik karakterizasyon; lipoksijenaz.
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