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Synthesis, Characterization, Anti-bacterial and Anti-inflammatory Activities of Bismuth(III) Complexes Based on 5-chloro-2-mercaptobenzothiazole

Ibrahim Ismet Ozturk[1] Muazzez Gurgan[2]
[1]Tekirdag Namik Kemal University, Department of Chemistry, Tekirdag, Turkey
[2]Tekirdag Namik Kemal University, Department of Biology, Tekirdag, Turkey

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***Correspondence to**: Ibrahim Ismet Ozturk, Tekirdag Namık Kemal University, Department of Chemistry, 59030, Tekirdag, Turkey.*
E-Mail: iiozturk@nku.edu.tr
Phone: +90 (282) 250 2623
Fax: +90 (282) 250 9925

ABSTRACT

Bismuth, known as a heavy metal, is excluded from this class due to its low toxicity. Due to this feature, bismuth containing compounds have always been interesting compounds in the field of medicinal chemistry. For this reason, the discovery of new bismuth compounds and the investigation of their biological properties are very important for this field. In this study, three new bismuth(III) compounds formulated as $[Bi(L)_2X_3]$ (L: 5-chloro-2-mercaptobenzothiazole (ClMBZT); X: Cl, Br, and I) were synthesized for the first time and, the molecular structure of them were elucidated by a series of spectroscopic techniques. Thermal stability and degradation steps of the title compounds were analyzed by Thermogravimetric-Differential Thermal Analysis (TG-DTA). The antibacterial study has been conducted against six strains bacteria, and the results indicated that bismuth(III) compounds generally showed more effective antibacterial activity than free ligand. The anti-inflammatory potential of bismuth(III) compounds was investigated through in vitro lipoxygenase enzyme inhibition studies. The results show that bismuth(III) compounds have higher anti-inflammatory potential than free ligand.

Keywords:
Bismuth(III) compounds; Spectroscopic techniques; Antibacterial activity; Anti-inflammatory potential.

INTRODUCTION

SkIn recent years, coordination compounds of ligands containing thioamide groups have become the focus of attention by many researchers [1–4]. The main reason for this interest is that ligands containing thioamide groups have more than one donor atom and can be coordinated to the metal ion in different ways thanks to these atoms, such as monodentate, bridging, and chelating [5]. Thus, the possibility of obtaining more than one compound with the same metal ion and ligand but with different coordination structures provides an opportunity to investigate the relationship between coordination chemistry and biological activity [6–13]. The chemistry and medical applications of transition metal compounds containing heterocyclic thioamides have been an active research area for many years [14,15], but there are very few studies in the literature on the chemistry of main group element compounds containing heterocyclic thioamides and especially their medical applications [16].

Bismuth, one of the main group elements, has been well-known for a very long time, and has an unusually low toxicity [17]. Bismuth has many medical applications due to its low toxicity. Bismuth compounds are medicinal compounds often used in the treatment of ulcer, digestive system ailments, and bacterial infections [17–19]. It is also known that bismuth compounds have a high potential effect against various cancer cells [17–20]. The coordination feature of the ligand and the geometric structure of the compound formed are one of the most important reasons for the differences in the biological properties of bismuth compounds [21]. Bismuth(III) thioamides generally form compounds with five and six coordination around the bismuth ion, although bismuth compounds can have a coordination number of 3 to 10 [22]. Bismuth(III) thioamides, which occur in four to one ligand metal stoichiometric ratios, are ionic compounds with octahedral geometry [23]. Bismuth(III) thioamides, which occur in three to one ligand metal stoichiometric ratios, are in neutral structure and have facial and meridional isomers of octahedral geometry [24]. Bismuth(III) thioamides, which occur in two to one ligand metal stoichiometric ratios, form bis-

muth compounds with a square pyramid geometric structure [25]. Square pyramid geometry is the most common geometric structure in bismuth(III) thioamide compounds.

Following our interest in the biological effects and coordination chemistry of bismuth(III) compounds [25–28], within the scope of this research, we present a series of bismuth(III) halide compounds containing 5-chloro-2-mercaptobenzothiazole (ClMBZT) (Figure 1). These bismuth(III) compounds were thoroughly analyzed by elemental (C, H, N and S) analysis, Fourier Transform Infrared (FT-IR) spectroscopy, FT-Raman spectroscopy ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, ultraviolet visible spectroscopy. The thermal stability and degradation steps of bismuth(III) compounds were investigated by Thermogravimetric-Differential Thermal Analyzer (TG-DTA). In addition, antibacterial properties and anti-inflammatory potentials of synthesized bismuth(III) compounds and free ligand were investigated.

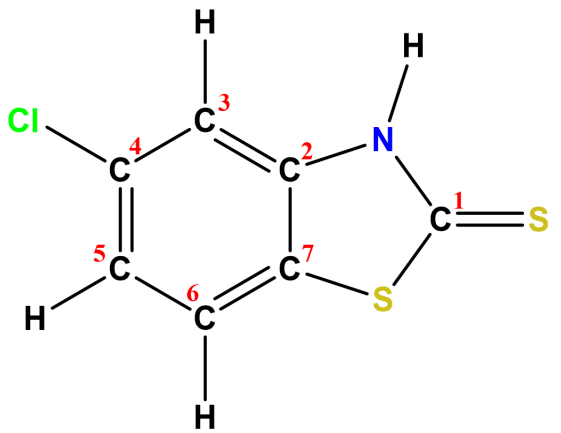

Figure 1. Structural representation of 5-chloro-2-mercaptobenzothiazole (ClMBZT)

MATERIAL AND METHODS

All bismuth(III) salts (Aldrich), 5-chloro-2-mercaptobenzothiazole (Aldrich) and all solvents (Merck) used in the experiments were purchased commercially and no purification was applied.

The STUART SMP30 scientific melting point instrument was used to appoint the melting point of synthesized compounds. Molar conductivity was measured by the VWR CO 3000 L Phenomenal conductometer. Elemental (C, H, N and S) analyses were detected via a Carlo Erba EA MODEL 1108 elemental analyzer. IR-ATR spectra were gained via a Bruker Optics, Vertex 70 FT-IR spectrometer. FT-Raman spectra were gained via a Renishaw In Via spectrometer. The thermal stability and degradation steps of the compounds were determinate on HITACHI SII 7300 EXSTAR apparatus, under inert gas (N_2) flow. The ^{1}H and ^{13}C nuclear magnetic resonance measurements were performed with an Agilent Premium Compact 600 MHz spectrometer. The ultraviolet visible spectra in DMSO solution were gained via a Shimadzu UV-2600 spectrophotometer working in the range of 190–900 nm.

Synthesis of $[BiCl_3(ClMBZT)_2]$ (1)

202 mg of 5-chloro-2-mercaptobenzothiazole (0.0010 mol) was mixed in 10 ml of acetonitrile. To this mixture, 158 mg of bismuth(III) chloride (0.0005 mol) dissolved in 10 ml of dichloromethane solution was added little by little. After addition, a yellow solution was formed. The resulting yellow clear solution was stirred at room temperature for 3 hours. After 3 hours, the resulting solution was filtered and kept at room temperature. After six days, compound **1** was obtained in yellow color and powder form. Yellow powder; yield: %87.7; melting point: 145-147°C; molecular weight: 718.70 g/mol; Anal. Calc. for $C_{14}H_8BiCl_5N_2S_4$: 23.40 (C %), 1.12 (H %), 3.90 (N %), 17.84 (S %). Exp.: 23.32 (C %), 1.14 (H %), 3.94 (N %), 17.79 (S %); Soluble in acetone, dichloromethane, ethanol, methanol, acetonitrile, chloroform, toluene, hexane, benzene, and dimethyl sulfoxide; ΛM (DMSO, $\Omega^{-1}cm^2mol^{-1}$): 12.6±0.7; IR-ATR: 3083(m), 3019(m) 2950(m), 2865(m), 1590(m), 1493(m), 1439(s), 1396(s), 1318(m), 1146(w), 1074(s), 1019(s), 910(m), 865(w), 808(m), 740(m), 682(m), 626(m), 541(m) cm^{-1}. UV–Vis (DMSO, nm): λmax (log ε): 335 (4.42), 257 (4.04). ^{1}H NMR (600 MHz, DMSO-d_6): 13.71 (s, 1H, NH), 7.71-7.63 (m, C^6H) 7.33–7.23 (m, 2H, C^3H, C^5H) ppm. ^{13}C NMR (600 MHz, DMSO-d_6): 191.27 (C^1), 142.69 (C^2), 132.23 (C^4), 128.69 (C^7), 124.50 (C^6), 123.65 (C^5), 112.41 (C^3) ppm.

Synthesis of $[BiBr_3(ClMBZT)_2]$ (2)

202 mg of 5-chloro-2-mercaptobenzothiazole (0.0010 mol) was mixed in 10 ml of acetonitrile. To this mixture, 224 mg of bismuth(III) chloride (0.0005 mol) dissolved in 10 ml of dichloromethane solution was added little by little. After addition, a yellow solution was formed. The resulting yellow clear solution was stirred at room temperature for 3 hours. After 3 hours, the resulting solution was filtered and kept at room temperature. After six days, compound 2 was obtained in orange color and powder form.

Orange powder; yield: %86.2; melting point: 169-171°C; molecular weight: 852.06 g/mol; Anal. Calc. for C14H8BiBr3Cl2N2S4: 19.73 (C %), 0.95 (H %), 3.29 (N %), 15.05 (S %). Exp.: 19.79 (C %), 1.01 (H %), 3.32 (N %), 15.11 (S %). Soluble in acetone, dichloromethane, ethanol, methanol, acetonitrile, chloroform, toluene, hexane, benzene, and dimethyl sulfoxide; ΛM (DMSO, Ω-1cm2mol-1): 18.5±0.3. IR-ATR: 3081(m), 3021(m) 2951(w), 2864(m), 1589(m),

1489(m), 1440(s), 1392(s), 1315(m), 1301(m), 1145(w), 1072(s), 1018(s), 909(m), 853(w), 808(m), 733(m), 680(m), 625(m) cm^{-1}. UV–Vis (DMSO, nm): λmax (log ε): 335 (4.46), 257 (4.10). ^1H NMR (600 MHz, DMSO-d_6): 13.76 (s, 1H, NH), 7.65 (d, J=8.52 Hz, 1H, C^6H) 7.28–7.23 (m, 2H, C^3H, C^5H) ppm. ^{13}C NMR (600 MHz, DMSO-d_6): 191.25 (C^1), 142.69 (C^2), 132.23 (C^4), 128.69 (C^7), 124.46 (C^6), 123.58 (C^5), 112.42 (C^3) ppm.

Synthesis of [BiI_3(ClMBZT)] (3)

101 mg of 5-chloro-2-mercaptobenzothiazole (0.0005 mol) was mixed in 10 ml of acetonitrile. To this mixture, 147 mg of bismuth(III) iodide (0.00025 mol) dissolved in 10 ml of acetone solution was added slowly. After addition, a red solution was formed. The red resulting solution was stirred and refluxed for 3 h and cooled to room temperature. The solution was then filtered and kept at room temperature. After six days, compound 3 was obtained in red color and powder form.

Red powder; yield: %75.4; melting point: 256-258°C; molecular weight: 993.07 g/mol; Anal. Calc. for $C_{14}H_{18}BiI_3Cl_2N_2S_4$: 16.93 (C %), 0.81 (H %), 2.82 (N %), 12.91 (S %). Exp.: C, 16.98 (C %), 0.88 (H %), 2.80 (N %), 12.94 (S %). Soluble in acetone, dichloromethane, ethanol, methanol, acetonitrile, chloroform, toluene, hexane, benzene, and dimethyl sulfoxide; ΛM (DMSO, $\Omega^{-1}cm^2mol^{-1}$): 16.9±0.4. IR-ATR: 3080(m), 3027(m) 2945(m), 2864(m), 1585(m), 1488(m), 1440(s), 1388(s), 1303(m), 1253(m), 1142(s), 1071(m), 1022(s), 908(m), 839(w), 802(m), 725(w), 676(m), 622(m), 532(m), 435(m) cm^{-1}. UV–Vis (DMSO, nm): λmax (log ε): 335 (4.48), 257 (4.10). ^1H NMR (600 MHz, DMSO-d_6): 13.77 (s, 1H, NH), 7.68-7.65 (m, C^6H), 7.31–7.24 (m, 2H, C^3H, C^5H) ppm. ^{13}C NMR (600 MHz, DMSO-d_6): 191.29 (C^1), 142.69 (C^2), 132.23 (C^4), 128.69 (C^7), 124.48 (C^6), 123.61 (C^5), 112.43 (C^3) ppm.

Antimicrobial tests

The bismuth(III) compounds (1-3) and the 5-chloro-2-mercaptobenzothiazole were tested for their antibacterial activity one by one against Gram-positive bacteria which they are Klebsiella pneumonia (ATCC 700603), Escherichia coli (ATCC 25922) and Pseudomonas aeruginosa (ATCC 27853), and Gram-negative bacteria which they are Staphylococcus aureus (ATCC 29213), Streptococcus mutans (ATCC 25175) and, Enterococcus faecalis (ATCC 29212). All bacteria used in the experimental study were obtained from Middle East Technical University, Ankara, Turkey and from the Republic of Turkey, General Directorate of Public Health, Ankara, Turkey. Experimental studies were carried out as stated in the literature [24].

Anti-inflammatory activity

Experimental studies were carried out as stated in the literature [28].

RESULTS AND DISCUSSION

Synthesis

Bismuth(III) compounds with a square pyramid geometric structure were synthesized as shown in Figure 2 as a result of the reaction of 5-chloro-2-mercaptobenzothiazole with bismuth(III) halide (BiX_3; X: Cl, Br and I) in 2:1 molar stoichiometric ratios. The synthesized bismuth(III) compounds were obtained in a yield range of 75% to 86%. The bismuth(III) compounds are soluble in common solvents (acetone, dichloromethane, ethanol, methanol, acetonitrile, chloroform, toluene, hexane, benzene, and dimethyl sulfoxide). The synthesized bismuth compounds are solid at room temperature and are stable to air. The melting temperature range of the compounds is in the range of 145 to 258°C. C, H, N and S percentages obtained for all bismuth(III) compounds were found to be in good agreement with the calculated values of the predicted geometric structures. Elemental analysis and molar conductivity values suggest that, the synthesized compounds are neutral $[Bi(L)_2X_3]$ compounds with square pyramid geometry (Figure 3). The analytical data and physical properties of the synthesized bismuth(III) compounds are reported in Table 1.

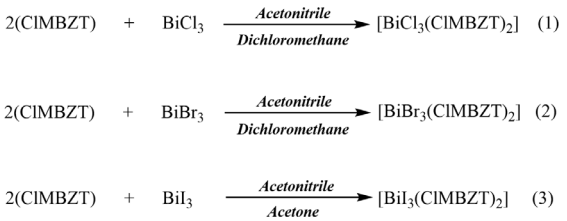

Figure 2. Reaction scheme for the synthesis of bismuth(III) halide complexes.

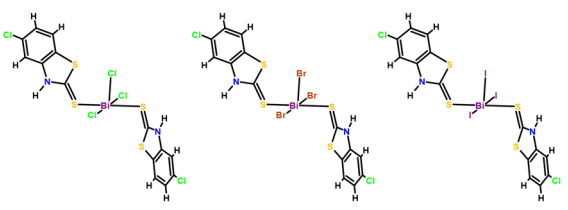

Figure 3. Proposed structures of bismuth(III) halide complexes (1-3).

Molar conductivity

Molar conductivity measurements of the synthesized

Table 1. Physical and analytical data of new bismuth(III) halide complexes (1-3).

Compounds	Color	M.p. (°C)	Yield (%)	ΛM mol Ω^{-1} cm^2mol^{-1}	Elemental Analysis found (calcd.)			
					C	H	N	S
1	Yellow	145-147	85.7	12.6±0.7	23.32 (23.40)	1.14 (1.12)	3.94 (3.90)	17.79 (17.84)
2	Orange	169-171	86.2	18.5±0.3	19.79 (19.73)	1.01 (0.95)	3.32 (3.29)	15.11 (15.05)
3	Red	256-258	75.4	16.9±0.4	16.98 (16.93)	0.88 (0.81)	2.80 (2.82)	12.94 (12.91)

bismuth(III) compounds were carried out in 10^{-3} M dimethyl sulfoxide solution at 25°C. (Table 1). The molar conductivity values of the compounds (1-3) in dimethyl sulfoxide were in the non-electrolytic range (< 50 $\Omega^{-1}cm^2mol^{-1}$) [29], (4.8±0.2 (1), 14.2±0.5 (2) and 18.9±0.4 $\Omega^{-1}cm^2mol^{-1}$ (3)) and thus their conductivity measurements indicate their non-electrolytic nature. These values are proof that the synthesized bismuth(III) compounds are in neutral form in solution and do not dissociate into ions.

Stability

Molar conductivity measurements and ultraviolet visible spectra of the bismuth(III) compounds (1–3) were analyzed at different time (0–48 h). A period of 48 hours was chosen for stability testing of the complexes. Because common biological studies require an incubation period of 48 hours. No significant change was observed in the molar conductivity measurements of the complexes at the end of 0 hours, 24 hours and 48 hours (Table 2). Also, no new absorption peaks appeared in the UV spectra of the complexes and no significant shifts in the existing absorption peaks occurred (Figure 4). These results show that the solutions of the complexes in dimethyl sulfoxide did not decompose for 48 hours and the complexes remained stable in solution.

Table 2. Molar conductivity values of the bismuth(III) complexes 1-3 for 0 h, 24 h and 48 h.

Compounds	0 h	24 h	48 h
1	4.8±0.2	5.1±0.4	5.3±0.4
2	14.2±0.5	14.3±0.3	14.5±0.5
3	18.9±0.2	19.1±0.4	19.3±0.2

Spectroscopic characterization

The important characteristic vibration bands observed in

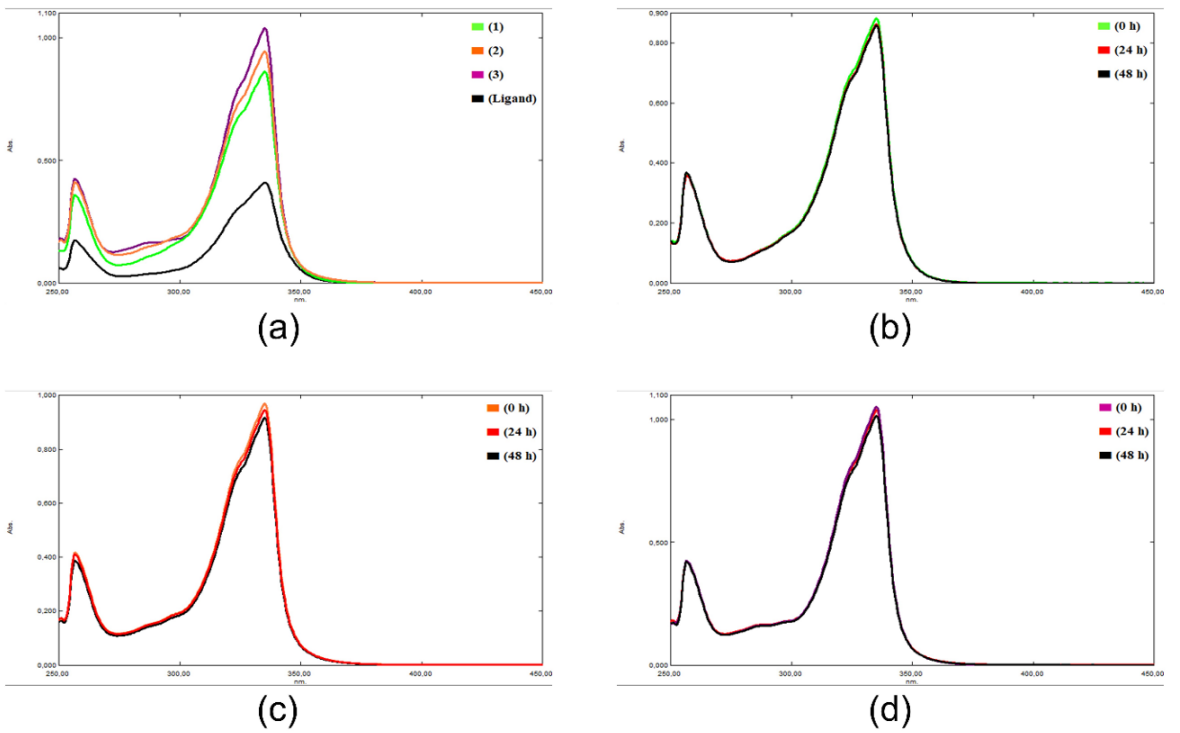

Figure 4. **(a)** UV-Vis spectra of bismuth(III) halide complexes and the free ligand in DMSO (10-3 M). **(b)** UV-Vis spectra of 1 for 0 h, 24 h and 48 h; **(c)** UV-Vis spectra of 2 for 0 h, 24 h and 48 h; **(d)** UV-Vis spectra of 3 for 0 h, 24 h and 48 h.

the infrared spectra of the synthesized bismuth(III) compounds in the range of 4000-400 cm^{-1} and in the Raman spectra in the range of 500-100 cm^{-1} are given in Table 3. There are four characteristic vibrational bands that should be considered in the infrared spectra of ligands containing thioamide group and metal compounds containing these ligands. These characteristic vibrations are those caused by the nitrogen and sulfur atoms forming the thioamide group. These four characteristic vibration bands are called thioamide I, thioamide II, thioamide III and thioamide IV. The thioamide I vibration band includes δ(N-H), δ(C-H) and ν(C=N) vibrations. The thioamide II vibration band includes ν(C-N), δ(N-H), δ(C-H) and ν(C=S) vibrations. The thioamide III vibration band includes ν(C-N) and ν(C=S) vibrations and thioamide IV vibration band includes only ν(C=S) vibration. The thioamide I vibrational bands of the synthesized bismuth(III) compounds are attributed to vibrations in the range of 1493-1489 cm-1. The thioamide II vibration bands of the synthesized bismuth(III) compounds are ascribed to vibrations of the order of 1317-1304 cm^{-1}. In line with these results, it was observed that there was no significant shift in the thioamide I and II vibration bands of the synthesized bismuth compounds compared to the thioamide I (1493 cm^{-1}) and II (1303 cm^{-1}) vibration bands of the ligand. Symmetrical and asymmetrical N-H vibrational bands of the synthesized bismuth(III) compounds are observed in the range of 3082-3020 cm^{-1}, while the symmetrical and asymmetrical N-H vibrational bands of the free ligand are observed in the range of 3088-3025 cm^{-1}. The presence of N-H vibrations in the synthesized bismuth(III) compounds shows that the ligands in the compounds are not deprotonated and the ligands are not bonded to the bismuth ion via the nitrogen atom. The thioamide III vibrational bands of the synthesized bismuth(III) compounds are attributed to vibrations in the range of 1022-1018 cm^{-1}. The thioamide IV vibration bands of the synthesized bismuth(III) compounds are ascribed to vibrations of the order of 740-725 cm^{-1}. It is observed that a more shift occurs in the thioamide III and thioamide IV bands of the synthesized bismuth(III) compounds when compared to the thioamide III (1029 cm^{-1}) and thioamide IV (708 cm^{-1}) bands of the free ligand. This shows that in all compounds, the free ligand binds to the bismuth ion only via the sulfur atom and monodentately.

Raman spectroscopy is a very useful spectroscopic method used to detect the vibrational bands of the bonds formed between the ligand and the metal ion. The Bi-N, Bi-S, and Bi-X (X: Cl, Br or I) vibrations are Raman active vibrations, so Raman spectroscopy provides detailed information on the binding pattern of the thioamide ligand and the coordination chemistry of the bismuth ion. The characteristic Raman vibration bands of bismuth(III) compounds are presented in Table 3. When the Raman spectra of the synthesized bismuth(III) compounds are examined in the 600-100 cm^{-1} range, Bi-S vibrational bands in the 400-350 cm^{-1} range and Bi-X (X: Cl, Br or I) vibrational bands in the 300-100 cm^{-1} range are encountered. But, Bi-N vibrations, which should be seen in the range of 600-500 cm^{-1}, are not encountered. This explains that in the synthesized bismuth(III) compounds, the ligand is monodentately bonded to the bismuth ion via the sulfur donor atom and there are halogen atoms attached to the bismuth ion.

UV-Vis absorption spectra of 5-chloro-2-mercaptobenzothiazole and bismuth(III) compounds have been registered in DMSO solution (Figure 4a). When the electronic spectra of the ligand and all the synthesized bismuth(III) compounds are examined, it is seen that they all have an absorption band at the same wavelength and in the same ultraviolet region. These electronic absorption bands correspond to electronic transitions n, $\pi \rightarrow \pi^*$ within the ligand orbitals.

The NMR spectra of the bismuth(III) compounds (1-3) were recorded in DMSO-d_6. When the ^{1}H-NMR spectra of all compounds are examined, the presence of N-H signal in the range of 13-14 ppm is observed. The presence of the N-H signal indicates that the ligand molecules that coordi-

Table 3. Selected Mid-IR and Raman spectroscopic data (cm-1) for bismuth(III) halide complexes (1-3).

Compounds	Infrared Data					
	ν(N-H)	ν(S-H)	Thioamide I	Thioamide II	Thioamide III	Thioamide IV
Ligand	3088-3025		1493	1303	1029	708
1 (X: Cl)	3083-3019	-	1493	1318	1019	740
2 (X: Br)	3081-3021	-	1489	1315	1018	733
3 (X: I)	3080-3027	-	1488	1303	1022	725
	Raman Data					
	ν(Bi-S)			ν(Bi-X)		
1 (X: Cl)	395			274, 216, 195		
2 (X: Br)	396			217, 182, 145		
3 (X: I)	399			154, 114		

nate to the bismuth ion are not deprotonated and that the ligand molecule cannot coordinate to the bismuth ion via the nitrogen atom. In addition, multiplets in the range of 7.2-7.7 ppm are observed in the ^{1}H-NMR spectra of all synthesized bismuth(III) compounds, which are attributed to the aromatic protons in the benzene ring in the ligand molecule. In the ^{13}C-NMR spectra of the synthesized bismuth compounds, a signal of ^{1}C carbon atom (C=S) is observed around 191 ppm. Small shifts in this signal indicate that the ligand molecule is coordinated to the bismuth ion via the sulfur donor atom. The absence of a shift in the signals of other carbon atoms in the ligand molecules coordinating to the bismuth ion may be due to the absence of a remarkable change in the chemical environment of the molecule.

Thermal analysis

The degradation steps and thermal stability of the synthesized bismuth(III) compounds were investigated by TG-DTA analysis. The mass recording that could occur in the compounds was analyzed in the range of 25 to 850°C, in an atmosphere of nitrogen and at an increase of 5°C min-1. The bismuth(III) compounds are thermally stable up to 145°C (1), 160°C (2), and 230°C (3), respectively. The fact that the compounds are stable up to high temperature and that no mass loss occurs up to this temperature shows that solvent molecules are not included in the chemical structures of the synthesized compounds. All compounds have a single degradation step. When the TG-DTA analysis result of compound 1 is examined, a mass loss of % 70.83 (calc. % 70.92) occurred in the range of 145-350°C, and when the TG-DTA analysis result of compound 2 was examined, a mass loss of % 74.02 (calc. % 75.47) was observed in the range of 160-350°C. When the TG-DTA analysis result of compound 3 is examined, it is seen that a mass loss of % 78.69 (calc. % 78.96) occurs in the range of 230-460°C. These mass losses occurring in a single step in all compounds correspond to the evolution of two ligand molecules and three halide atoms. All complexes show a similar decomposition step (Figure 5).

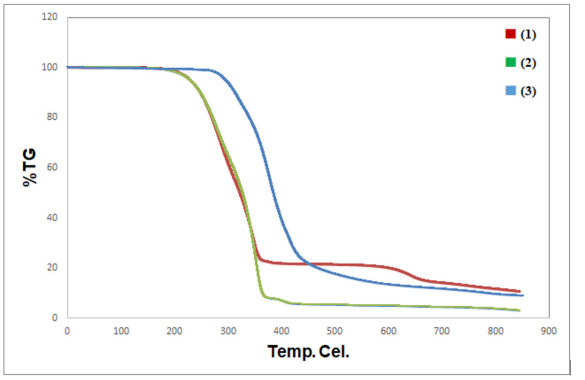

Figure 5. Proposed structures of bismuth(III) halide complexes (1-3).

Antimicrobial activity

The newly synthesized bismuth(III) halide compounds and the 5-chloro-2-mercaptobenzothiazole were examined for their antimicrobial activities on three Gram-negative (*E. coli*, *P. aeruginosa* and *K. pneumonia*) and three Gram-positive (*S. aureus*, *S. mutans* and *E. faecalis*) bacteria. The tested bacteria are normal flora members and may cause serious nosocomial infections which in turn result in many health and economic problems [30–32]. The concentrations of the complexes and free ligand that exert antimicrobial activity are given in Table 4. The negative control dimethyl sulfoxide could not inhibit any bacterial growth [33]. It was determined that the synthesized bismuth(III) compounds showed higher activity against all tested Gram positive and Gram negative strains than 5-chloro-2-mercaptobenzothiazole. Tweedy's chelation theory can explain why complexed have more antibacterial activity than the free ligand [34]. In general, it was determined that the synthesized bismuth(III) compounds were more effective against gram positive bacteria than gram negative bacteria. Compounds 1 and 3 show 4 times more activity than Gentamicin and 16 times more than 5-chloro-2-mercaptobenzothiazole against *E. faecalis*. The same compounds show 8 times more activity than the 5-chloro-2-mercaptobenzothiazole against *S. mutans*. As a result, it was observed that

Table 4. Concentration of the compound showing significant inhibition compared to Gentamicin

	Concentration (mg/mL)					
	Gram-negative bacteria			Gram-positive bacteria		
Compounds	E. coli	P. aeruginosa	K. pneumonia	S. aureus	S. mutans	E. faecalis
1	32	2	128	<2	2	16
2	32	8	128	<2	8	32
3	32	2	128	<2	2	16
ClMBZT	32	4	>256	<2	16	>256
Gentamicin	≤2	≤8	≤2	≤2	≤1	≤64

[Bi(ClMBZT)$_2$Cl$_3$] (1) and [Bi(ClMBZT)$_2$I$_3$] (3) were more effective compounds than [Bi(ClMBZT)$_2$Br$_3$] (2) and 5-chloro-2-mercaptobenzothiazole against selected gram positive bacteria.

Anti-inflammatory activity

Lipoxygenase (LOX) enzymes are non-heme iron dioxygenases that catalyze the oxygenation of polyunsaturated fatty acids (e.g., arachidonic acid and linoleic acid) containing one or several cis,cis-pentadiene systems (e.g., linoleic acid) [35]. In addition, this enzyme produces metabolites that react with polyunsaturated fatty acids and play a role in many important human diseases such as cancer [36]. Given the role of LOX in the progression of some cancers, the discovery of LOX inhibitors could potentially lead to the development of new cancer therapeutics [37].

The degree of LOX activity (A, %) of compounds 1-3 and 5-chloro-2-mercaptobenzothiazole was calculated according to the method described in previous studies [8]. The half-maximum inhibitory concentration (IC_{50}) values of the synthesized bismuth compounds and 5-chloro-2-mercaptobenzothiazole were calculated as 10.62±3.24 µM (1), 10.42±4.32 µM (2), 8.75±3.12 µM (3) and 49.55±3.29 µM (5-chloro-2-mercaptobenzothiazole), respectively (Figure 6). From these results, it was determined that all synthesized bismuth compounds showed 4 to 5 times higher anti-inflammatory effects than 5-chloro-2-mercaptobenzothiazole. Among the synthesized bismuth compounds, it is seen that the compound with the highest anti-inflammatory effect is [Bi(ClMBZT)2I3] (3) . Also all compounds show higher anti-inflammatory activity than cis-platin (IC50: 65.9 µM) and nimesulide (IC_{50}: >30 µM) [38].

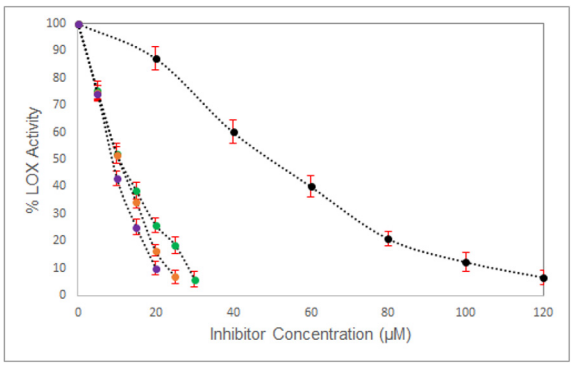

Figure 6. The inhibitory effects of the bismuth(III) halide complexes (1 (●), 2 (●) and 3 (●) and the free ligand (ClMBZT (●)).

CONCLUSION

In this study, three new bismuth(III) halide complexes containing 5-chloro-2-mercaptobenzothiazole ([Bi(ClMBZT)$_2$X$_3$], X: Cl (1), Br (2) and I (3)) were synthesized and characterized by various spectroscopic methods. By this work, we perform further expansion of the series of bismuth(III) halide complexes containing thioamides. Structural studies on the synthesized bismuth(III) halide compounds have shown that these compounds exhibit a 2:1 ligand/bismuth(III) halide stoichiometric ratio. In addition, these studies showed that the 5-chloro-2-mercaptobenzothiazole is coordinated to the bismuth ion only through the sulfur atom and not deprotonated through the nitrogen atom. These results show that square pyramid geometry occurs around the bismuth atom in all compounds (1-3). Bismuth(III) halide compounds (1-3) are more active against Gram positive (*S. aureus*, *S. mutans* and *E. faecalis*) than Gram negative (*E. coli*, *P. aeruginosa* and *K. pneumonia*) strains. According to the antibacterial activity results, it was observed that compounds [Bi(ClMBZT)$_2$Cl$_3$] (1) and [Bi(ClMBZT)$_2$I$_3$] (3), are more effective compounds against selected bacteria. The compounds 1-3 showed much stronger anti-inflammatory activity than 5-chloro-2-mercaptobenzothiazole and the compound [Bi(ClMBZT)$_2$I$_3$] (3) showed higher anti-inflammatory activity than compounds [Bi(ClMBZT)$_2$Cl$_3$] (1) and [Bi(ClMBZT)$_2$Br$_3$] (2). In line with this study, it is seen that the bismuth(III) compounds of ligands containing thion groups show remarkable results in terms of antibacterial and anti-inflammatory effects. In future studies, the relationship between geometric structure and biological effect can be determined by synthesizing types of such compounds with different geometric structures. In addition, in future studies, the presence of substituted groups on the ligand molecule with a high tendency to gain electrons may allow to obtain new compounds that are more biologically effective.

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CONFLICT OF INTEREST

The author deny any conflict of interest.

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