Room Temperature Synthesis and Characterization of Novel Bi(III) Complex with 2-Amino-3-Carbomethoxy-4,5,6,7-Tetrahydrobenzo[\(B\)]Thiophene as Potential Antimicrobial Agent

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Abstract

A novel bismuth(III) complex with 2-amino-3-carbomethoxy-4,5,6,7-tetrahydrobenzo[\(b\)]thiophene (ACTT) as a ligand have been synthesized. The novel complex was characterized on the basis of its IR, NMR, elemental analysis and MS spectral data. It was found that the ligand behaves as a monodentate chelating agent and bonds to the metal ion through the nitrogen atom of the amino group to form the \([\text{Bi}^{\text{III}}(\text{ACTT})_6]\)Cl3 complex. The new complex compound displayed significant antimicrobial activity (MIC = 8–32 μg/mL) against Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Shigella flexneri, Candida albicans, Candida tropicalis and Cryptococcus neoformans.

Keywords: Room temperature synthesis; antimicrobial; complexation reaction; 2-aminothiophene; bismuth

1. Introduction

Coordination chemistry is gaining more and more attention nowadays due to the increased demand of new compounds with various properties and functionalities. In fact, combining properties of metal ion like magnetic, optic, conductor, oxydoreduction, biological with the one of an organic chelate compound can lead to new hybrid coordination complexes with enhanced functionalities. Therefore, many coordination compounds with properties like antimicrobial,1–4 AND-binding,5 antiviral, anticancerous, cytotoxic,6 anti-inflammatory,7,8 analgesic,9 antioxidant,10,11 optoelectronic, superconductor, non-linear optical (NLO),12,13 light emitting device (LED),14,15 catalyst, antidiabetic,16,17 gas storage, metaloenzyme,18 nanoparticles19,20 have been reported.

Heavy metal bismuth is found in group V in the periodic table as the 83rd element. Beside its heavy metal
status, bismuth and derived compounds are relatively non-toxic and can be used as green and effective cata-
lysts in many synthetic reactions to replace toxic cata-
lysts such as compounds of mercury, lead, thallium, arse-
nic, antimony etc. Other properties of bismuth com-
ounds including antimicrobial, 23–27 cytotoxic, 25–30 anti-
"meratogenic, 31 white light emitting diode (WLEDs) 32 are also extensively reported. 2-aminitetrahydroben-
zo[b]thiophene system and their substituted derivatives have attracted a great deal of interest due to their various electronic, 33 optical, 34 dyeing, 35–37 fluorescence 38 and pharmacological properties. 39–41 On the other hand, to the best of our knowledge, the title 2-aminitetrahydro-
dervative (ACTT) used as ligand in this study has not yet been reported in any coordination reaction with bism-
uth(III) salt.

For all these reasons, we became interested on the investigation of its coordination behavior with bis-
muth(III) salts. Our expectation was that novel hybrid compounds resulting from the combination in the same molecular framework of the bismuth(III) ion coordinat-
ed to one or more 2-aminitetrahydrobenzothiophene derivative (ACTT) used as ligand in this study has not yet been reported in any coordination reaction with bism-
uth(III) salt.

2. Experimental Part

2. 1. Chemistry

All the reagents mentioned in this work were pur-
chased from Aldrich and Fluka and were used without further purification. Melting points are corrected and were determined with a STUART SCIENTIFIC Melting Point Apparatus Model SMP3 at a heating rate of 1.5 °C / min. The TLCs were carried out on Eastman Chromato-
gram Silica Gel Sheets (13181; 6060) with fluorescent in-
dicator. A mixture of ethyl acetate and methylene chlor-ide (1:1) was used as eluent and iodine was used to de-
velop the chromatograms. The IR spectra were measured with a Fourier Transform Infrared spectrometer Bruker Alpha. EIMS spectra were recorded on a double focusing mass spectrometer (Varian MAT 311A). 1HNMR spectra were recorded in DMSO-d _6_ on a Bruker DRX spectrom-
eter operating at 399 MHz with TMS used as internal reference. XRD data was collected on a STOE Stadi-p X-ray powder diffractometer (STOE & Cie GmbH, Darmstadt, Ger-
many) with Cu Kα radiation (λ = 1.54056 Å; Ge monochro-
mator; flat samples) in transmission geometry with a DECTRIS® MYTHEN 1K detector (DECTRIS, Baden-Daettwil, Switzerland). Elemental analyses were performed With a Euro Vector CHNS-O element analyz-
er (Euro EA 3000) or a vario MICRO Cube (Co. Element-
tar Analysensysteme).

2. 1. 1. Preparation of 2-amino-3-carbomethoxy-
4,5,6,7-tetrahydrobenzo[b]thiophene (3)

A mixture of cyclohexanone (50 mmol, 4.9 g), meth-
yl cyanoacetate (50 mmol, 4.95 g) and sulphur (55 mmol, 1.76 g) in methanol (80 mL) was stirred using a magnetic plate shaker thermostated at 50–60 °C. Ammonia (5 mL) was added drop wise during the first 10 min of the reac-
tion. After 3 h of reaction, the resulting precipitate (8.66 g, 82%) was collected by filtration and crystallized from methanol to yield a yellow powder, mp: 133–135 °C (Lit. 42 127–128°C from methanol). IR ( neat) ν cm⁻¹: 3419, 3310 (–NH₂); 1649 (C=O); 1585, 1575 (C=C); 775; 734 (C–S); 1332 (C–N); 1268 (C–O). 1H-NMR (400 MHz, DMSO-d _6_ ) δH: 7.17, 3.61, 2.52, 2.46, 2.36, 1.61. 13C-NMR (101 MHz, DMSO-d _6_ ) δC: 165.85, 164.31, 131.83, 115.93, 102.90, 50.77, 26.97, 24.41, 23.34, 22.87. Elemental analysis found (calculated): C: 56.87% (56.87%); H: 6.16% (6.16%); N: 6.63% (6.64%); S: 15.17% (15.17%).

2. 1. 2. Preparation of Metal Complex 4

To a magnetically stirred solution of the ligand 3 (0.32 g; 1.5 mmol) in methanol (10 mL) a solution of BiCl₃ (0.315 g; 1 mmol) in methanol (10 mL) was gradually added. After 48 h, the product formed was collected by filtra-
tion and crystallized from a mixture water/methanol to give 0.39 g (82%) of 4 as brown precipitate; mp 112 °C. IR ( neat) ν cm⁻¹: 3480; 3333 (–NH₂); 1653 (C=O); 1576; 1526 (C=C); 1323 (C–N); 1271 (C–O). 1H-NMR (400 MHz, DMSO-d _6_ ) δH: 7.93, 7.91, 7.74, 7.72, 7.33, 7.22, 7.09, 6.96, 4.63, 3.78, 3.62, 3.59, 3.58, 3.58, 3.45, 3.44, 3.42, 3.38, 3.37, 3.35, 3.33, 1.94, 1.62, 1.19. 13C-NMR (101 MHz, DM-
SO-d _6_ ) δC: 166.65, 165.88, 165.17, 163.92, 163.74, 163.41, 132.03, 131.84, 130.31, 120.99, 116.26, 115.94, 102.06, 101.30, 51.75, 51.06, 50.95, 50.77, 27.77, 26.98, 24.57, 24.41, 24.26, 24.11, 23.34, 22.87, 18.42. Elemental analysis found (calculated): C: 45.53% (45.53%); H: 4.94% (4.93%); N: 5.31% (5.31%); S: 12.14% (12.14%).

2. 2. Biology

2. 2. 1. Microorganisms

A total of six bacteria and three yeasts strains were tested for their susceptibility to the studied compounds. The studied microorganisms include Staphylococcus aureus ATCC25923, Escherichia coli S2(1), Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa ATCC27853, Shigella flexneri SDINT, Candida albicans ATCC10231, Candida tropicalis PK233, Cryptococcus neo-
formans H99. These microorganisms were taken from our laboratory collection. The bacterial and fungal species were maintained on agar slant at +4°C and subcultured at 37°C on nutrient agar (NA, Conda, Madrid, Spain) and Sabouraud Dextrose Agar (SDA, Conda) slants respecti-
vely, prior to any antimicrobial test.
2.2.2. Determination of Minimum Inhibitory Concentration (MIC) and Minimum Microbicidal Concentration (MMC)

MIC values were determined by a broth micro-dilution method as described earlier. Each test sample was dissolved in dimethyl sulfoxide (DMSO) and the solution was then added to Mueller Hinton Broth (MHB) for bacteria or Sabouraud Dextrose Broth (SDB) for yeasts to give a final concentration of 1024 μg/mL. This was serially diluted twofold to obtain a concentration range of 0.25–512 μg/mL. Then, 100 μL of each concentration were added in each well (96-well microplate) containing 95 μL of MHB or SDB and 5 μL of inoculum for final concentrations varying from 0.125–256 μg/mL. Then, 100 μL of each concentration were added in each well (96-well microplate) containing 95 μL of MHB or SDB and 5 μL of inoculum for final concentrations ranging from 0.125–256 μg/mL. The inoculum was standardized at 1.5 x 10^6 colony-forming units (CFU)/mL for bacteria and 2 x 10^5 spores/mL for yeasts using a spectrophotometer (Jenway™ 6305 UV/Visible Spectrophotometer, Fisher scientific, UK). The negative control well consisted of 195 μL of MHB or SDB and 5 μL of the standard inoculum. The MICs were assessed visually and were taken as the lowest compound concentration at which there was no growth or virtually no growth. The lowest concentration that yielded no growth after the sub-culturing was considered as the minimum microbicidal concentrations (MMCs). Ciprofloxacin (Sigma-Aldrich, Steinheim, Germany) and nystatin (Merck, Darmstadt, Germany) were used as positive controls for bacteria and yeasts, respectively. All the tests were performed in triplicate.

3. Results and Discussion

3.1. Chemistry

The thiophene compound 2-amino-3-carbomethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene (ACTT) was prepared by applying one-pot procedure of the second version of the Gewald technique, whereby cyclohexanone (1), methyl cyanoacetate (2) and elemental sulfur were condensed in methanol in the presence of catalytic amount of ammonia (Scheme 1).

The structure of the ligand substrate 3 (ACTT = CH₂O₂C-Ar-NH₂) was confirmed with its physical and spectroscopic data which are in full agreement with those previously reported.

The reaction of compound 3 with bismuth(III) chloride in methanol with constant stirring at room temperature for 48 hours gave the compound 4 (Scheme 2).

3.1.1. IR spectrum of the Bismuth Complex 4

The IR bands of the complex 4 were assigned by comparison with the IR spectrum of the starting 2-aminothiophene ligand 3. The elongation frequencies υ(NH₂) of the aromatic amine which were found in the ligand at 3419 cm⁻¹ (more intense) and 3310 cm⁻¹ (more intense) in the ligand, respectively, are shifted to higher frequencies at 3480 cm⁻¹ (shoulder), 3333 cm⁻¹ (shoulder), respectively, in the complex. The presence of these two bands of the amino group in the IR spectrum of the ligand is a clear indication that the complexation occurred without deprotonation of the primary aromatic amine. The modification observed in the shapes of these bands (shoulder) in addition to their important shift (Δυ = 61 and 23 cm⁻¹) to higher frequencies may be due to the involvement of the corresponding nitrogen atom to the coordination process.

One can also notice that the strong absorption band of the carbonyl function of the carbomethoxy group which appears at 1649 cm⁻¹ in the ligand undergoes a Δυ = 4 cm⁻¹ shift to higher frequencies and is shown at 1653 cm⁻¹ in the complex. This observation indicates that the oxygen atoms of the carbonyl function of the ester groups of the coordinated 2-aminothiophene ligands are involved in various hydrogen bonds interactions with –NH₂ groups.

3.1.2. ¹H NMR-Spectrum of Complex 4

Similarly, the ¹H NMR signals of compound 4 was assigned by comparison with the ¹H NMR spectrum of the ligand 3. In Table 1 the chemical shifts of both compounds are recapitulated. One can also notice here that each signal
of individual hydrogen or groups of chemically and magnetically equivalent hydrogen atoms in the starting free 2-aminothiophene ligand 3 is splitted into a number of corresponding signals attributed to the six 2-aminothiophene ligands coordinated to the central bismuth(III) ion.

3.1.3. 13C NMR-Spectrum of Complex 4

The assignments of the 13C NMR signals of compound 4 were made by comparison with the 13C NMR spectrum of the ligand 3. As recapitulated in Table 1, each signal of individual carbon atoms in the starting free 2-aminothiophene ligand 3 is splitted in a number of corresponding signals attributed to the six ligands coordinated to the bismuth(III) ion in the complex compound 4.

3.1.4. 2D NMR Data of Complex 4 and Ligand 3

The important interactions found in the 1H, 1H-COSY; 1H, 13C-HSQC, 1H, 13C-HMBC and 1H, 1H-NOESY experiments for compounds 3 and 4 are recapitulated in Table 2.

The HSQC spectrum (Figure 1) of the ligand shows five correlation spots corresponding to the five carbon atoms bearing protons. Correlation spots are also observed between methoxyl proton at 3.61 ppm and the corresponding carbon at 50.8 ppm. The assignment of the –NH2 protons at 7.18 ppm could be rationalized based on the fact that this signal doesn’t correlate with any carbon atom. Similar assignments could be done for the complex by comparison (Table 2).

The HMBC experiment shows different correlations’ spots that were helpful for the accurate assignments of the

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**Table 1.** Comparison of the 1H and 13C NMR (DMSO-d6) chemical shifts of the ligand 3 with those of the complex 4.

<table>
<thead>
<tr>
<th>N° C/H</th>
<th>δH in ppm</th>
<th>δC in ppm</th>
<th>δH in ppm</th>
<th>δC in ppm</th>
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<tbody>
<tr>
<td>2</td>
<td>–</td>
<td>102.91</td>
<td>–</td>
<td>102.89, 102.06, 101.30</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>131.83</td>
<td>–</td>
<td>132.03, 131.84, 130.31</td>
</tr>
<tr>
<td>3a</td>
<td>–</td>
<td>115.93</td>
<td>–</td>
<td>120.99, 116.26, 115.94</td>
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<tr>
<td>4</td>
<td>1.62</td>
<td>22.87</td>
<td>1.60, 1.66, 22.87, 18.42</td>
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</tr>
<tr>
<td>5</td>
<td>2.52</td>
<td>26.97</td>
<td>2.55</td>
<td>27.77, 27.76, 26.98</td>
</tr>
<tr>
<td>6</td>
<td>2.35</td>
<td>24.41</td>
<td>2.46</td>
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</tr>
<tr>
<td>7</td>
<td>1.62</td>
<td>23.34</td>
<td>1.60, 1.66</td>
<td>24.11, 23.34</td>
</tr>
<tr>
<td>7a</td>
<td>–</td>
<td>163.41</td>
<td>–</td>
<td>163.92, 163.74, 163.41</td>
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<tr>
<td>C=O</td>
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<td>165.88</td>
<td>–</td>
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<tr>
<td>–OCH3</td>
<td>3.62</td>
<td>50.76</td>
<td>4.61, 3.78, 3.73, 51.75, 50.95, 50.77,</td>
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<td></td>
<td>3.62, 3.59, 3.44</td>
<td>50.88, 50.86, 50.68</td>
</tr>
<tr>
<td>–NH2</td>
<td>7.18</td>
<td>–</td>
<td>7.73, 7.22</td>
<td>–</td>
</tr>
</tbody>
</table>

**Figure 1.** HSQC spectrum of complex with some correlations
For instance, a correlation between the methoxyl proton appearing at 3.61 ppm and the carbonyl carbon function at 165.9 ppm have been found. Correlations between these methoxyl protons and some carbon atoms of the thiophenic ring at 102.9 ppm have also been observed. A number of these analogous correlations have been found in the HMBC spectrum of compound 4 but their individual assignments to each coordinated ligand could not be conclusive due to high complexity of the overlapping signals caused by the homologous proton systems of the six coordinated ligands.

The COSY experiment of the ligand clearly exhibited the correlation spots between the protons of the cyclohexane ring (Table 2). For the complex (Figure 3), besides the homologous correlations displayed in the COSY experiment, a correlation was observed between the methoxyl protons at 4.62 ppm and the amino protons 7.73 ppm.

The spatial proximity between the methoxyl group and the amino group is confirmed by the NOESY experiment for the ligand and for the complex as well.

### 3.1.5. Mass Spectrum of Complex 4

The mass spectrum of compound 4 exhibited characteristic ion fragments such as [Bi(C_{10}H_{13}NSO_{2})_{2}]^{3+} (m/z = 630), [Bi(C_{10}H_{13}NSO_{2})]^{3+} (m/z = 419), Bi (isotope) or (C_{10}H_{13}NSO_{2})^{+} (m/z = 210), in agreement with the suggested structure.

Furthermore, one can notice the absence of ion fragments such as [BiCl]^{+} or [BiCl{2}]^{+} proving that chlorine
atoms are not directly coordinated to the central metal ion in the complex.\textsuperscript{45}

### 3. 1. 7. Powder XRD Study of Compound 4

X-ray diffraction analysis performed on complex 4 shows a good crystalline structure of the complex formed with well-organized particles (Figure 4). Compound 4 has therefore a stable structure in which there is a good cohesion between atoms.

From the above data and based on various literature reports,\textsuperscript{21,24,46,47} we suggest that in compound [Bi(ACTT)\textsubscript{6}]\textsubscript{Cl\textsubscript{3}} (4), the bismuth atom exhibits a six-fold coordination to the 2-aminothiophene ligands in a tetragonal bipyramidal geometry. Around the central Bi atom, four N atoms occupy the equatorial positions and two N atoms occupy the axial ones. In this representation, the free rotation of the -Ar–CO\textsubscript{2}CH\textsubscript{3} fragment of each N-coordinated 2-aminothiophene moiety around the C\textsubscript{sp\textsuperscript{2}}–N bond enables the formation of various hydrogen bonds between the six oxygen atoms of the carbonyl functions of the six carbomethoxy groups and the hydrogen atoms of the –NH\textsubscript{2} group. These interactions are clearly exhibited in the 3D view of the complex shown in Figure 6.

![Figure 4. Powder XRD patterns of complex 4.](image)

### 3. 2. Antimicrobial Activity

Antimicrobial activity of the ligand, 2-amino-3-carbomethoxy-4,5,6,7-tetrahydrobenzo[b]thiophene (3) and its bismuth complex 4 was examined \textit{in vitro} against bacterial...
Figure 5. Structural representation of complex 4

Figure 6. 3D view of the coordination sphere of complex 4 drawn with ACD/Labs 3D viewer (freeware)

Table 4. Antimicrobial activity (MIC, MBC and MFC in µg/mL) of compound complex against bacterial and yeast species

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Inhibition</th>
<th>Compound 4 parameters</th>
<th>Reference drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> ATCC25923</td>
<td>MIC 16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC 16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC/MIC 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>Bacillus subtilis</em></td>
<td>MIC 8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC 8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC/MIC 1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>MIC 16</td>
<td>4</td>
<td></td>
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<tr>
<td></td>
<td>MBC 16</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC/MIC 1</td>
<td>1</td>
<td></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em> ATCC27853</td>
<td>MIC 16</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>MBC 32</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MBC/MIC 2</td>
<td>1</td>
<td></td>
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<tr>
<td><em>Escherichia coli</em> S2(1)</td>
<td>MIC 8</td>
<td>4</td>
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<tr>
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<td>MBC 8</td>
<td>4</td>
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</tr>
<tr>
<td></td>
<td>MBC/MIC 1</td>
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<tr>
<td><em>Shigella flexneri</em> SDINT</td>
<td>MIC 32</td>
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<tr>
<td></td>
<td>MBC 64</td>
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<td>MBC/MIC 2</td>
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<tr>
<td><em>Candida albicans</em> ATCC10231</td>
<td>MIC 32</td>
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<td></td>
<td>MFC 32</td>
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<tr>
<td></td>
<td>MFC/MIC 1</td>
<td>1</td>
<td></td>
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<tr>
<td><em>Candida tropicalis</em> PK233</td>
<td>MIC 32</td>
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<tr>
<td></td>
<td>MFC 32</td>
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<td><em>Cryptococcus neoformans</em> H99</td>
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<tr>
<td></td>
<td>MFC/MIC 2</td>
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</table>

*Ciprofloxacin for bacteria and nystatin for yeasts; MIC: Minimum Inhibitory Concentration; MBC: Minimum Bactericidal Concentration; MFC: Minimum Fungicidal Concentration.
and fungal species (Table 4). No activity was noticed for the 2-aminothiophene ligand against all the tested microorganisms (results not shown). However, the bismuth(III) complex showed different degrees of antimicrobial activities against the tested fungal and bacterial species (Table 4).

The bismuth complex showed antibacterial activities against all the tested microorganisms (MIC = 8–32 µg/mL). The lowest MIC value for this compound (8 µg/mL) corresponding to the best antimicrobial activity was obtained on B. subtilis and E. coli. Interestingly, the antibacterial activity of the complex (MIC = 8 µg/mL) on B. subtilis was found to be equal to that of ciprofloxacin (MIC = 8 µg/mL) used as reference drugs; highlighting its good antibacterial potency. The least sensitive microorganism was Shigella flexneri and MBC (64 µg/mL) values recorded.

The complex compound was more active against bacterial species (MIC = 8–32 µg/mL) than against yeast strains (MIC = 32 µg/mL). The findings of the present study showed that the antimicrobial activities varied with the bacterial and fungal strains. These variations may be due to genetic differences between the microorganisms.

The MBC and MFC values obtained were fourfold less than their corresponding MIC values; indicating that this compound has microbicidal effect against the tested microorganisms.48 The antimicrobial activity of compound 4 is in agreement with recent findings by Nur Amirah Jamaluddin et al. and Latika Dawara et al. respectively, who reported the antimicrobial activities of some bismuth(III) complex derivatives against a wide range of microorganisms including Staphylococcus aureus, Bacillus subtilis, Escherichia coli.

3. 3. Effects of Chelation to the Activity of Compounds Complex

Biological screenings’ results show that the 2-aminothiophene ligand which was initially non-active yielded a compound with much better biological profile after the complexation with the bismuth. Chelation is certainly responsible of these new properties. Obviously, the polarity of the metal ion will be reduced to greater extent on chelation, due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups.49 The complexation further increases the delocalization of π-electrons over the whole chelating ring which may facilitate the penetration of the complexes into lipid membranes and the blocking of the metal binding sites in the enzymes of microorganisms.44 It may be hypothesized that there are other factors such as solubility, conductivity and bond length between the metal and ligand which also increase the activity.50

4. Conclusion

In summary, we have synthesized and characterized a coordination complex containing Bi(III) with 2-ami-no-3-carbomethoxy-4,5,6,7-tetrahydrobenzo[b]thio-

References


Povzetek

Sintetizirali smo nov bizmutov(III) kompleks z 2-amino-3-karbometoksi-4,5,6,7-tetrahidrobenzo[b]tiofenom (ACTT) kot ligandom. Spojina je bila okarakterizirana na podlagi IR, NMR, elementne analize in MS. Ligand je enovezno koordiniran na kovinski ion preko dušikovega atoma ter vodi do nastanka kompleksa [Bi(III)(ACTT)₆][Cl₃]. Spojina izkazuje izrazito protimikrobno aktivnost (MIC = 8–32 μg/mL) proti Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Shigella flexneri, Candida albicans, Candida tropicalis in Cryptococcus neoformans.

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