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Antibacterial Activity

The Importance of Heterolepticity in Improving the Antibacterial Activity of Bismuth(III) Thiolates

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Abstract: Five mixed thiolatobismuth(III) complexes [BiPh-(5-MMTD)$_2${4-MMT(H)}] (**1**), [Bi(1-MMTZ)$_2${(PYM)(PYM(H))$_2$}] (**2**), [Bi(MBT)$_2$(5-MMTD)] (**3**), [Bi(4-BrMTD)$_3${2-MMI(H)}] (**4**) and [Bi-(1-MMTZ)$_2${1-MMTZ(H)}(2-MMI){2-MMI(H)$_2$}] (**5**) were synthesised from imidazole-, thiazole-, thiadiazole-, triazole-, tetrazole- and pyrimidine-based heterocyclic thiones. Four of these complexes **1**–**4** were synthesized from $BiPh_3$, while complex **5** was obtained from Bi[4-(MeO)Ph]$_3$. Complexes **1**–**5** were structurally characterised by XRD. Evaluation of the antibacterial properties against *Mycobacterium smegmatis, Staphylococcus aureus*, Methicillin-resistant *S. aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), *Enterococcus faecalis* and *Escherichia coli* showed that mixed thiolato complexes containing the anionic thiazole-based ligands MBT and 4-BrMTD are most effective. The mixed thiolato complexes [Bi(MBT)$_2$(5-MMTD)] (**3**) having thiazole- and thiadiazole- and [Bi(4-BrMBT)$_3${2-MMI(H)}] (**4**) containing thiazole- and imidazole-based ligands proved to be more efficient, with low minimum inhibitory concentrations of 1.73 and 3.45 μM for **3** against VRE and *E. faecalis*, respectively, and 2.20 μM for **4** against *M. smegmatis and E. faecalis*. All complexes showed little or no toxicity towards mammalian COS-7 cell lines at 20 μg mL^{-1}.

Introduction

Recently, we have demonstrated that bismuth(III) thiolato complexes derived from a variety of five-membered N-heterocyclic thiones have powerful antibacterial properties against, among others, methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* (VRE).[1–3] The most potent complexes proved to be heteroleptic monophenyl bis-thiolato complexes, [BiPh(SR)$_2$], several of which incorporated further neutral thione ligands, [BiPh(SR)$_2$(HSR)$_2$]. These were often several orders of magnitude more active than their tris-thiolatobismuth(III) analogues [Bi(SR)$_3$]. This is well illustrated by the series of complexes derived from 4-methyl-4*H*-1,2,4-triazole-3-thione [4-MTT(H)]: [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] has a minimum inhibitory concentration (MIC) towards *S. aureus* of 3.4 μM, [BiPh(4-MTT)$_2$] 9.7 μM, and [Bi(4-MTT)$_3$] 180.1 μM.[1] From a structure–activity perspective, this suggest that either the Ph group is crucial in improving the bactericidal activity or, more generally, it is the presence of two or three different ligands on the bismuth atom which is the key to improving the bactericidal effects. To probe these effects further we have now prepared and assayed a greater diversity of heteroleptic Bi^{III} complexes, limiting the role of the Ph ligand and constructing them mostly with various thiolate/thione ligands. Thus, although the complexes are still derived from N-heterocyclic thiones, they change from being nominally [BiPh(SR)$_2$] to comprising two or three different thiolato and/or thione ligands on the same Bi atom in the same complex.

Heteroleptic, or mixed-ligand, systems are important both in the development of new metallodrugs, since they can support incremental and intrinsic changes in the chemophysical nature of metal complexes, and in understanding metal-based biological functions (e.g., metalloenzymes) and deriving biomimetic systems therefrom.[4] The majority of work has focused on heteroleptic transition metal complexes, since they include the majority of biologically essential metals and have proven to be highly adaptable in structure and function.[5] Complexes of the main group metals are less studied. The s-block metals are ubiquitous and essential but highly ionic and form labile complexes. The p-block metals are often toxic, but continue to find application in medicine, infection control and medical imaging.[6,7] Although main group metals lack some of the diversity in oxidation states of the transition metals, they often have more predictable ligand bonding modes, geometries and structures.

Our main focus is on bismuth, largely because of its apparent anomalous status as a heavy metal with good environmental credentials, and the fact it also displays good antimicrobial properties with low systemic toxicity in humans.[8–10] Due to the thiophilic nature of bismuth, biological targets are predominantly proteins and peptides rich in the S-based amino acids cysteine and methionine.[11,12] The high lability of Bi–S bonds[13] coupled with the hydrolytic and thermodynamic stability of bismuth thiolates has made them attractive targets in biological and medicinal chemistry.[14,15] In recent years they have found application as bactericidal and fungicidal agents,[16–18] and have been assessed and proposed as effective agents for combating

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wound infection,[19] as anticancer agents and for retarding biofilm growth on surfaces.[20]

Several heteroleptic thiolato complexes of bismuth have been reported previously. For example, Whitmire and co-workers reported $[Bi_6(pydc)_8(Hypdc)_2(tu)_8]$ and $[\{Bi_2(pydc)_3(tsc)_2(H_2O)_2\}]\cdot 3H_2O$ incorporating thiourea (tu), thiosemicarbazide (tsc) and 2,6-pyridinedicarboxylic acid (Hpydc) ligands,[21] and $[Bi(SC_6F_5)_3(SPPh_3)]$ and $[Bi(SC_6F_5)_3\{S=C(NHMe)_2\}_3]$ were reported by Norman et al.[22] However, only for the large number of bis(diorganodithiocarbamato) bismuth(III) complexes incorporating diorganodithiophosphate and alkylenedithiophosphate ligands developed by Chauhan and co-workers has the antimicrobial activity of such complexes been assessed. The majority of these Bi^{III} complexes showed increased inhibitory activity towards a range of bacteria compared to those of the parent dithiocarbamates and ancillary ligands.[23]

We now describe the synthesis and characterisation of five heteroleptic bismuth(III) complexes: $[BiPh(5\text{-}MMTD)_2\{4\text{-}MMT(H)\}]$ (**1**), $[Bi(1\text{-}MMTZ)_2\{(PYM)(PYM(H))_2\}_2]$ (**2**), $[Bi(MBT)_2(5\text{-}MMTD)]$ (**3**), $[Bi(4\text{-}BrMTD)_3\{2\text{-}MMI(H)\}]$ (**4**), $[Bi(1\text{-}MMTZ)_2(2\text{-}MMI)\{1\text{-}MMTZ(H)\}\{2\text{-}MMI(H)_2\}]$ (**5**), all prepared from various reactions between $BiPh_3$ and a variety of heterocyclic thiones (Figure 1): 2-MMI(H) = 1-methyl-1*H*-imidazole-2-thione, 4-MMT(H) = 4-methyl-4*H*-1,2,4-triazole-3-thione, 1-MMTZ(H) = 1-methyl-1*H*-tetrazole-5-thione, 5-MMTD(H) = 5-methyl-1,3,4-thiadiazole-2-thione, PYM(H) = pyrimidine-2-thione, MBT(H) = 4-phenylthiazole-2-thione and Br-MBT(H) = 4-(4-bromophenyl)thiazole-2-thione. The complexes were fully characterised by NMR and FTIR spectroscopy and mass spectrometry, and their solid-state structures were authenticated by single-crystal XRD. Their antibacterial activity was assayed against a range of bacteria: *Mycobacterium smegmatis*, *Staphylococcus aureus*, MRSA, VRE, *Enterococcus faecalis and Escherichia coli*, and their toxicity to mammalian cells was assessed by using COS-7 monkey liver cells.

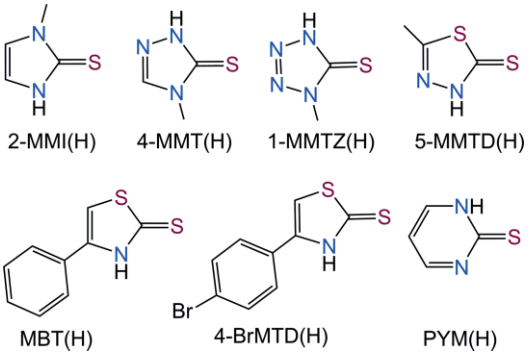
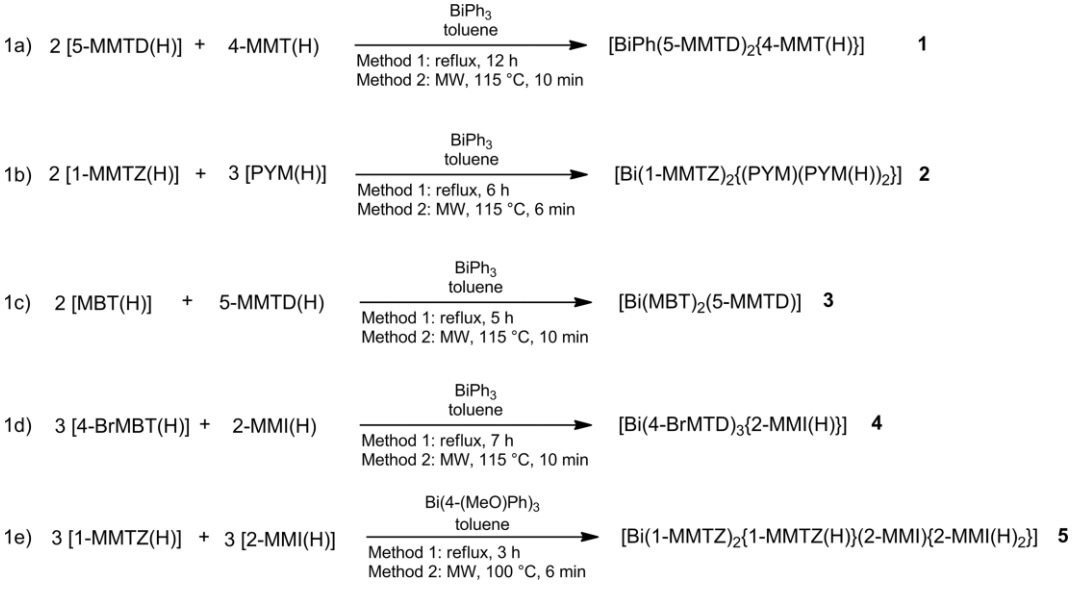


Figure 1. Heterocyclic thiones employed in the synthesis of heteroleptic bismuth(III) complexes **1**–**5**.

Results and Discussion

The problem in targeting heteroleptic systems in which the ligands are anionic or neutral forms of similar classes of compound is the difficulty in controlling the reaction conditions such that the synthetic outcomes are reproducible. One possibility is simply generating from any reaction mixture a series of complexes that reflect a statistical distribution of ligands. Even when using the correct stoichiometry for any target complex, ligand lability can easily affect the outcome of this distribution. From a thermodynamic perspective, strictly controlled reaction conditions and allowing any solution to reach equilibrium become critical. To explore this we studied the impact of the bismuth reagent, solvent, reaction stoichiometry and heating method (reflux vs. microwave). To decrease the number of reaction variables, $BiPh_3$ was generally employed with toluene as the reaction medium.

From a large range of reactant permutations, several reactions generated reproducible outcomes with the composition



Scheme 1. Synthesis of heteropleptic bismuth(III) thiolato complexes **1**–**5**.

of the complex formed consistent with the applied reactant stoichiometry, sometimes independent of the ratio of reactants used. The complexes **1**–**5** reported here are those for which all analytical data were consistent with and confirmed by single-crystal XRD. These are shown in Scheme 1 and summarised below.

Synthesis

The monophenylbismuth(III) thiolato complex [BiPh(5-MMTD)$_2${4-MMT(H)}] (**1**) was prepared by treating $BiPh_3$ with 5-MMTD(H) and 4-MTT(H) in a 1:2:1 ratio in refluxing toluene for 12 h (Scheme 1, a). From the resulting solution, which was allowed to stand for 10 d at room temperature, a batch of yellow crystals appeared. Repeating the same reaction under microwave irradiation for 10 min at 115 °C improved the yield of crystalline material to 75 %. Different stoichiometries (2:1:1, 2:2:1 or 1:1:1) always resulted in complex **1**, though the yield and purity differed.

Complex [Bi(1-MMTZ)$_2${(PYM)(PYM(H))$_2$}] (**2**) was synthesised in a similar manner by the reaction of $BiPh_3$ with 3 equiv. of PYM(H) and 2 equiv. of 1-MMTZ(H). Various PYM(H):1-MMTZ(H):$BiPh_3$ ratios (2:1:1 or 2:2:1) always resulted in complex **2** as the main product (Scheme 1, b). The resulting solution was allowed to stand for 10 d at room temperature and yielded orange crystals (61 %). From the analogous reaction with microwave heating the yield of crystals was 65 %.

A 1:2:1 reaction of $BiPh_3$, MBT(H) and 5-MMTD(H) (Scheme 1, c) in toluene at reflux resulted in crystalline material, which analysed as [Bi(MBT)$_2$(5-MMTD)] (**3**). The orange crystals of **3** deposited as the hot toluene solution cooled to room temperature over 5 h in a yield of 69 %. A similar yield of 72 % was obtained by conducting the analogous reaction with microwave heating for 10 min.

Complex [Bi(4-BrMTD)$_3${2-MMI(H)}] (**4**) was synthesised by treating $BiPh_3$ with 4-BrMTD(H) and 2-MMI(H), in 1:3:1 ratio in refluxing toluene for 7 h (Scheme 1, d). The resulting solution was allowed to stand for 7 d at room temperature and yielded orange crystals in 58 % yield. From the analogous reaction with microwave heating in toluene at 115 °C for 10 min, a 65 % yield of crystals was obtained after 7 d.

In contrast to **1**–**4**, [Bi(1-MMTZ)$_2$(2-MMI){1-MMTZ(H)}{2-MMI(H)$_2$}] (**5**) was synthesised by using Bi(Ph-4-OMe)$_3$ as the aryl bismuth precursor rather than $BiPh_3$ (Scheme 1, e). Reactions of $BiPh_3$ with thiones 2-MMI(H) and 1-MMTZ(H) only resulted in mixtures with monophenyl bismuth complexes as the main constituent. The more reactive Bi[4-(MeO)Ph]$_3$ was therefore used and provided access to the target tris-thiolato species. Heating a 1:3:3 mixture of Bi[4-(MeO)Ph]$_3$/2-MMI(H)/1-MMTZ(H) in toluene to reflux or under microwave irradiation gave orange solutions from which crystals of **5** were deposited after two weeks in yields of 71 and 74 % respectively.

Characterisation

The compositions and structures of **1**–**5** were confirmed by ^{1}H and ^{13}C NMR and FTIR spectroscopy, ESI-MS, elemental analysis and single-crystal XRD, all of which were consistent with each other. NMR spectra were collected for all complexes in [D$_6$]DMSO. The discussion below focuses mainly on the diagnostic aspects of the ^{1}H NMR spectra, that is, the consistency of ligand form and quantity with the crystal structure. Full analytical details are provided in the Experimental Section. All analyses were conducted on crystalline materials.

^{1}H NMR Spectroscopy

The chemical shifts and associated integrals in the ^{1}H NMR spectrum of **1** indicates that it is composed of a residual Ph ligand, two 5-MMTD thiolato ligands and one neutral 4-MMT(H) ligand: [BiPh(5-MMTD)$_2${4-MMT(H)}]. The 4-MMT(H) and 5-MMTD ligands are identified by singlets at δ = 3.41 and 2.57 ppm, respectively, for the methyl protons. The singlet at δ = 8.38 ppm can be assigned to the proton on the triazole ring (δ = 8.32 ppm in the parent compound). The phenyl protons give peaks at 8.91 (*o*), 7.80 (*m*) and 7.41 (*p*) ppm, which are all shifted to lower frequency relative to $BiPh_3$ [δ = 7.76 (*o*), 7.38 (*m*) and 7.31 (*p*) ppm]. The disappearance of the signal of the NH proton of the thiadiazole ring at δ = 12.46 ppm indicates conversion from thione to thiolate on deprotonation and binding to the bismuth(III) centre. The neutral triazole NH signal appears at δ = 13.67 ppm.

The chemical shifts and integrals of the ligands in complex **2** indicate that its composition is [Bi(1-MMTZ)$_2${(PYM)(PYM(H))$_2$}]. The methyl protons of the 1-MMTZ tetrazole thiolato ligand appear at δ = 3.80 ppm, which is only marginally shifted downfield compared to the parent thione (δ = 3.78 ppm). The doublet at δ = 8.56 ppm and the triplet at δ = 7.27 ppm correspond to the protons of the pyrimidine ring, which are shifted downfield compared to the parent thione (8.27 and 6.83 ppm respectively).

In the ^{1}H NMR spectrum of [Bi(MBT)$_2$(5-MMTD)] (**3**) the absence of peaks for the NH protons of the parent thiones MBT(H) or 5-MMTD(H) (normally found at ca. 13.1 and 12.6 ppm, respectively) suggests that both ligands exist as thiolate anions. The relative integrals gave a 2:1 ratio for MBT/5-MMTD, which thus reflects the reaction stoichiometry. The CH_3 protons of the thiadiazole 5-MMTD ligand resonate at almost the same frequency as those in the parent thione (2.54 vs. 2.52 ppm), while the singlet corresponding to the ring proton in the MBT anion appears at δ = 7.50 ppm, shifted from 8.53 ppm in the spectrum of the thiazole thione. Only the signals of the *ortho* protons in the Ph moiety of the MBT ligand shift significantly, and move to 7.86 ppm from 7.42 ppm in MBT(H).

Complex **4** exhibits resonances for both 2-MMI(H) and 4-BrMTD, integrating in a ratio of 1:3. In the parent thiones, the chemical shifts of the NH protons in 2-MMI(H) and 4-BrMTD(H) appear at δ = 13.76 and 12.00 ppm respectively. Only the signal at δ = 12.03 ppm remains in the ^{1}H NMR spectrum of **4**, that is, the 4-BrMTD ligand is anionic and 2-MMI(H) remains neutral. Signals at 7.72 (*o*- and *m*-Ph) and 7.39 (thiazole CH) ppm are assigned to protons of 4-BrMTD, while the protons on the imidazole ring of 2-MMI(H) appear as doublets at δ = 7.04 and 6.87 ppm.

In [Bi(1-MMTZ)$_2$(2-MMI){1-MMTZ(H)}{2-MMI(H)$_2$}] (**5**), integration of the proton signals indicated an overall ratio of the tetraz-

ole to imidazole ligands of 1:1. One difficulty is that the diagnostic signal for NH in the tetrazole is not observable in the ^{1}H NMR spectrum of the parent thione 1-MMTZ(H) or in that of **5**. However, the NH signal of 2-MMI(H) is found at δ = 12.03 ppm in the spectra of the parent thione and **5**. Further, the backbone CH protons resonate at δ = 7.06 and 6.85 ppm in the neutral ligand and at δ = 7.06 and 6.88 ppm in the thiolate form. For the tetrazole ligand the shift of the CH_3 peak on changing from the neutral form to the anion is marginal (3.91 vs. 3.89 ppm). Thus, for complex **5** the composition was only really confirmed by XRD.

XRD Studies

Crystals of complex **1** grew over several weeks from DMSO solution and were analysed by single-crystal XRD and authenticated as $[BiPh(5\text{-}MMTD)_2\{4\text{-}MMT(H)\}]_2$. Complex **1** crystallises in the monoclinic space group $P2_1/n$. The molecular structure is shown in Figures 2 and 3, and selected bond lengths and angles are listed in Table 1.

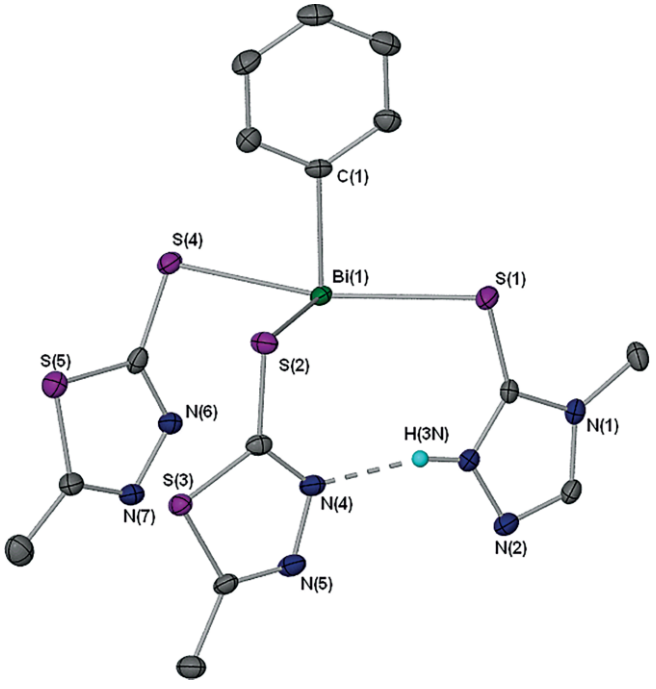


Figure 2. Molecular structure of **1** with thermal ellipsoids shown at 50 % probability. Hydrogen atoms (except NH) have been omitted for clarity.

Complex **1** is a dimeric, homometallic complex containing two deprotonated molecules of 5-MMTD, a neutral 4-MTT(H) molecule and one phenyl group (Figure 2). The Bi–S bond lengths [Bi(1)–S(1) 2.8507(16), Bi(1)–S(2) 2.6763(17) and Bi(1)–S(4) 2.7772(16) Å] are comparable to those of the complex $[BiPh(4\text{-}MMT)_2\{4\text{-}MMT(H)\}_2]$[24] containing triazole moieties (av. 2.8055 Å) and longer than those of thiadiazole-containing complex $[Bi_2(5\text{-}MMTD)_4]_\infty$ (av. 2.642 Å).[1] The molecular structure reveals a trigonal-pyramidal geometry in which the phenyl group lies perpendicular to the BiS_3 plane. The structure is stabilised by intramolecular hydrogen bonds between H(3N) of the 4-MTT(H) and N(4) of the 5-MMTD ligand [H(3N)–N(4), 1.93(3) Å]. The Bi–S–C angles [Bi(1)–S(1)–C(7) 97.65(19)°, Bi(1)–S(2)–C(10) 96.02(2) and Bi(1)–S(4)–C(13), 93.7(2)°] are comparable to those of previously synthesized complexes (av. 96.13°).[1]

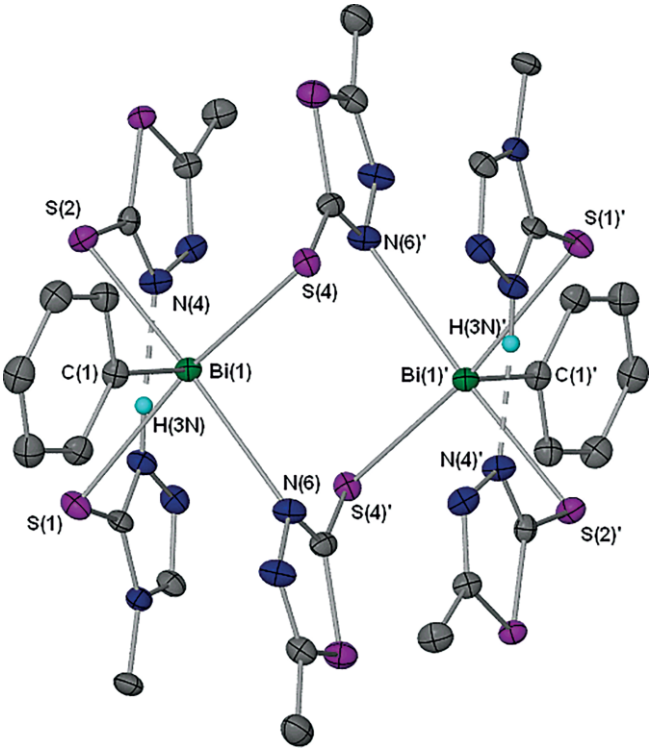


Figure 3. Dimeric structure of **1** with thermal ellipsoids shown at 50 % probability. Hydrogen atoms (except NH) have been omitted for clarity. Symmetry operator ′ = 2 – *x*, –*y*, –*z*.

Table 1. Selected bond lengths [Å] and angles [°] for **1**.

Bi(1)–C(1)	2.267(6)	C(1)–Bi(1)–S(4)	86.42(16)
Bi(1)–S(1)	2.8507(16)	C(1)–Bi(1)–S(1)	88.303(4)
Bi(1)–S(4)	2.7772(16)	S(2)–Bi(1)–S(4)	93.81(5)
Bi(1)–S(2)	2.6763(17)	S(2)–Bi(1)–S(1)	96.39(5)
S(1)–C(7)	1.709(6)	S(4)–Bi(1)–S(1)	167.16(5)
S(2)–C(10)	1.741(6)	C(7)–S(1)–Bi(1)	97.65(19)
S(4)–C(13)	1.717(6)	C(10)–S(2)–Bi(1)	96.0(2)
Bi(1)–N(6)′1	2.777(5)	C(13)–S(4)–Bi(1)	93.7(2)
N(6)–Bi(1)′	2.777(5)	C(1)–Bi(1)–N(6)′	91.92(19)
C(1)–Bi(1)–S(2)	86.66(16)	N(6)′-Bi(1)–S(1)	80.78(12)
C(10)–S(3)–C(11)	87.4(3)	S(2)–Bi(1)–N(6)′	176.92(12)

Dimerisation of two monomeric units takes place through a bismuth–bridging nitrogen interaction (Bi(1)–N(6)′ 2.77(5) Å; Figure 3), which increases the coordination number of the bismuth(III) centre to five and results in an overall distorted square-based pyramidal coordination geometry and formation of a central eight-membered $Bi_2S_2N_2C_2$ ring.

Orange needle crystals suitable for X-ray diffraction studies were obtained from a toluene solution of **2** after 7 d. The complex crystallizes in the triclinic space group $P\bar{1}$. The asymmetric unit is shown in Figure 4, and selected bond lengths and angles are listed in Table 2. The geometry around the bismuth(III) centre is distorted pentagonal-bipyramidal with a coordination number of seven. The tetrazole-containing ligand binds primarily through its S^- centre, which confirms the predominance of

the thiol form. This is in contrast to pyrimidine-based ligands, which mainly exist in the thione form.

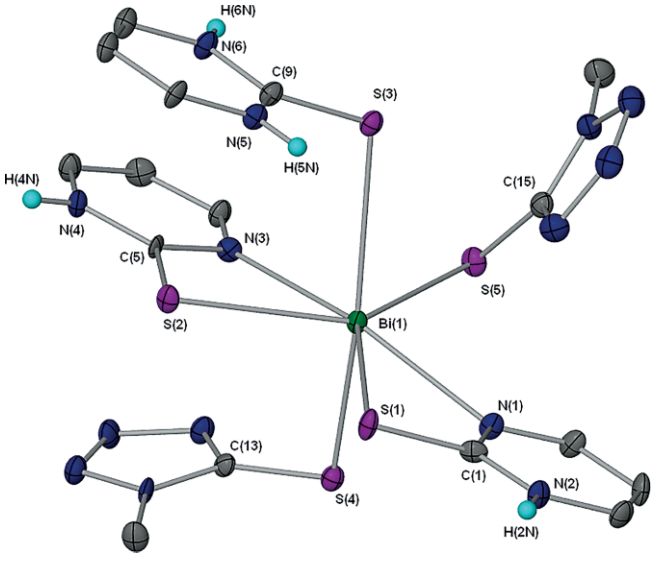


Figure 4. Molecular structure of **2** with thermal ellipsoids shown at 50 % probability. Four hydrogen atoms are shown, but each has only 0.5 occupancy, so in total they only contribute +2 to balancing the overall charge on the bismuth(III) centre.

Table 2. Selected bond lengths [Å] and angles [°] for **2**.

Bi(1)–N(1)	2.542(5)	N(1)–Bi(1)–S(1)	57.10(10)
Bi(1)–N(3)	2.621(5)	N(1)–Bi(1)–S(2)	136.96(10)
Bi(1)–S(1)	2.9123(17)	N(1)–Bi(1)–S(4)	72.26(12)
Bi(1)–S(2)	2.9029 (16)	N(1)–Bi(1)–S(5)	83.48(10)
Bi(1)–S(3)	3.0472(15)	N(3)–Bi(1)–S(1)	137.75(10)
Bi(1)–S(4)	2.6472(15)	N(3)–Bi(1)–S(2)	56.65(10)
Bi(1)–S(5)	2.8223(15)	N(3)–Bi(1)–S(4)	88.51(11)
S(1)–C(1)	1.708(6)	N(3)–Bi(1)–S(5)	83.30(11)
S(2)–C(5)	1.715(5)	C(1)–S(1)–Bi(1)	81.21(18)
S(3)–C(9)	1.687(6)	C(5)–S(2)–Bi(1)	83.57(19)
S(4)–C(13)	1.722(6)	C(9)–S(3)–Bi(1)	108.22(19)
S(5)–C(15)	1.734(6)	C(13)–S(4)–Bi(1)	102.51(18)
N(3)–C(5)	1.364(7)	C(15)–S(5)–Bi(1)	90.17(18)
N(5)–C(9)	1.360(7)	S(1)–Bi(1)–S(3)	103.19(5)
N(1)–C(1)	1.358(6)	S(2)–Bi(1)–S(3)	82.26(5)

The Bi–S bond lengths of the deprotonated tetrazole thiolates [Bi(1)–S(4) 2.647(15), Bi(1)–S(5), 2.822(15) Å] are comparable to those of tetrazole-containing complex [BiPh(1-MMTZ)$_2$-{1-MMTZ(H)}] (av. 2.72 Å).[24] The C–S [S(4)–C(13) 1.722(3), S(5)–C(15) 1.734(6) Å] and C–N bond lengths [N(7)–C(13) 1.347(7), N(11)–C(15),1.330(7) Å] show single-bond character. Two of the three pyrimidine-containing ligands chelate the Bi centre through their N and S atoms with formation of two four-membered metallacyclic, rings while the third pyrimidine molecule binds to the bismuth(III) centre in a monodentate mode involving only the S atom. The C(9)–S(3)–Bi(1) bond angle [108.22(19)°] of the S-bonded pyrimidine-containing ligand is larger than the C(1)–S(1)–Bi(1) [81.21(18)°] and C(5)–S(2)–Bi(1) [83.57(19)°] bond angles of the chelating ligands. Thus, the binding mode of the pyrimidine-2-thione can be judged by comparing these C–S–Bi bond angles. The Bi–S and Bi–N bond lengths are in the range of 2.902(16)–3.047(15) and 2.542(5)–2.621(5) Å, respectively. Four hydrogen atoms on N(2), N(4), N(5) and N(6) were located by residual density in the electron-density difference maps and placed in calculated positions. Each hydrogen atom has half-occupancy due to disorder, so in total they only contribute +2 to balancing the overall charge on the bismuth centre.

Needle-like crystals of **3** were obtained after two weeks by slow evaporation of a toluene solution. Single-crystal analysis revealed the formula to be [Bi(MBT)$_2$(5-MMTD)]. The complex crystallizes in the monoclinic space group $P2_1/c$. The asymmetric unit is shown in Figure 5 with selected bond lengths and angles listed in Table 3. In the asymmetric unit the mixed thiolato complex **3** is composed of one 5-MMTD and two MBT chelating ligands bonded covalently to the bismuth(III) centre through the deprotonated thiol groups and datively through the N atoms in the thiazole and thiadiazole moieties. The Bi–S bond lengths [Bi(1)–S(1) 2.599(14), Bi(1)–S(3) 2.630(15) and Bi(1)–S(5) 2.581(16) Å] are similar to those of the tris-thiolatobismuth(III) complex [Bi(MBT)$_3$] (av. 2.591 Å),[2] the thiadiazole-containing complex [Bi$_2$(5-MMTD)$_4$]$_\infty$ (av. 2.642 Å)[1] and [Bi(SC$_6$F$_5$)$_3$(SPPh$_3$)] (av. 2.581 Å). The C–S [S(1)–C(1) 1.726(6), S(5)–C(19) 1.728(6) and S(3)–C(9) 1.687(6) Å] and C–N bond lengths [N(1)–C(1) 1.310(7), N(2)–C(10) 1.315(7) and N(3)–C(19) 1.301(8) Å] have single-bond character and are comparable with the reported values [S–C 1.699(14) and C–N 1.309(12) Å].[25] All the ligands form four-membered metallacyclic rings due to chelation through the N and S donor atoms with small bite angles [S(1)–Bi(1)–N(1) 59.35(10), S(3)–Bi(1)–N(2) 58.37(10) and S(5)–Bi(1)–N(3) 58.70(12)°].

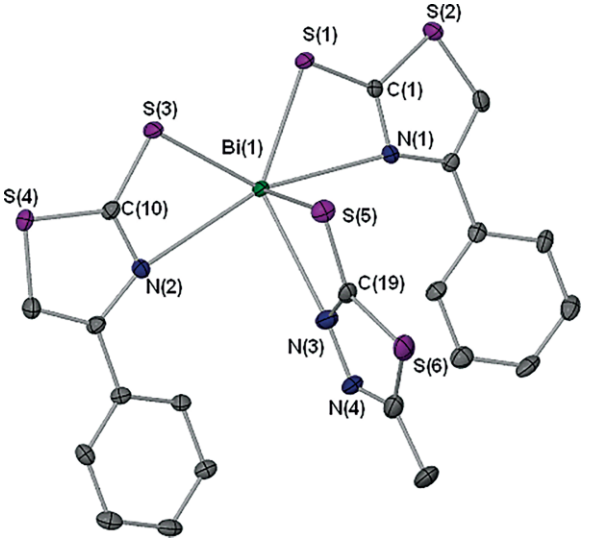


Figure 5. Asymmetric unit of [Bi(MBT)$_2$(5-MMTD)] **3** with thermal ellipsoids shown at 50 % probability. Hydrogen atoms have been omitted for clarity.

Dimerisation of two monomeric units of **3** occurs through a long interaction between the bismuth centre and π electrons of an adjacent aromatic ring of MBT (Figure 6). This increases the coordination number of the bismuth(III) centre to seven and gives an overall distorted pentagonal-bipyramidal coordination geometry.

Table 3. Selected bond lengths [Å] and angles [°] for **3**.

Bi(1)–N(1)	2.804(5)	N(3)–C(19)	1.301(8)
Bi(1)–N(2)	2.879(5)	N(4)–C(20)	1.304(9)
Bi(1)–N(3)	2.864(5)	S(1)–Bi(1)–N(1)	59.35(10)
Bi(2)–N(4)	7.089(6)	S(3)–Bi(1)–N(2)	58.37(10)
Bi(2)–N(5)	2.957(5)	S(5)–Bi(1)–N(3)	58.70(12)
Bi(2)–N(6)	2.847(5)	S(7)–Bi(2)–N(5)	57.84(10)
Bi(2)–N(7)	2.881(5)	S(9)–Bi(2)–N(6)	59.06(10)
Bi(1)–S(1)	2.5994(14)	S(11)–Bi(2)–N(7)	58.55(11)
Bi(1)–S(3)	2.6303(15)	C(1)–S(1)–Bi(1)	87.66(19)
Bi(1)–S(5)	2.5814(16)	C(10)–S(3)Bi(1)	89.27(18)
Bi(2)–S(11)	2.5771(15)	C(19)–S(5)–Bi(1)	89.6(2)
Bi(2)–S(9)	2.5975(15)	C(22)–S(7)–Bi(2)	91.13(19)
Bi(2)–S(7)	2.6008(15)	C(31)–S(9)–Bi(2)	88.65(19)
S(1)–C(1)	1.726(6)	C(40)–S(11)–Bi(2)	89.59(19)

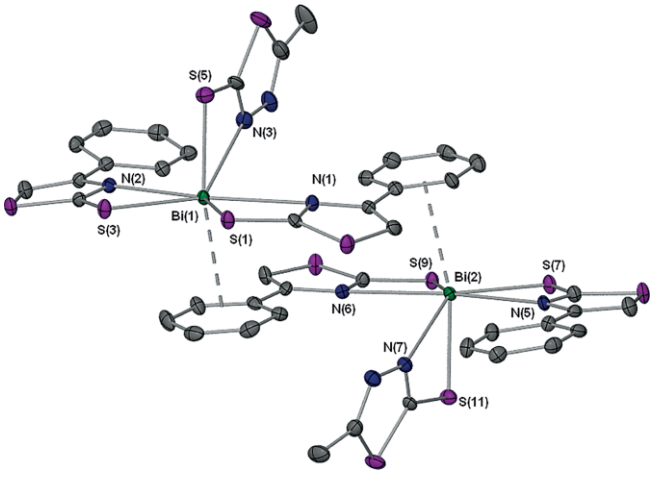


Figure 6. Dimeric $[Bi(MBT)_2(5\text{-MMTD})]_2$ **3** with thermal ellipsoids shown at 50 % probability. Hydrogen atoms have been omitted for clarity.

Single crystals of complex **4** grew over a few weeks from toluene solution and were authenticated as [Bi(4-BrMBT)$_3${2-MMI(H)}]. The molecular structure of complex **4** is shown in Figure 7 with selected bond lengths and angles listed in Table 4. The complex crystallises in the triclinic space group $P\bar{1}$ with a four-coordinate trigonal-pyramidal geometry. Complex **4** has one neutral 2-MMI(H) and three deprotonated 4-BrMTD ligands. The binding of the 4-BrMTD ligand is primarily through its S^- centre. The Bi–S bond lengths of the 4-BrMTD ligand lie in the range of 2.589(10)–2.669(11) Å and are comparable with those of the tris-thiolato complex [Bi(4-BrMBT)$_3$] (av. 2.601 Å)[2] and [Bi(2-$SC_5H_3NSiMe)_3$] (av. 2.626 Å).[26] The C–S bond lengths of 4-BrMTD range from 1.734(5) to 1.739(4) Å, which are longer than the thionic C–S bond length of 1.720(5) Å in 2-MMI(H). The C–N bond lengths of the 4-BrMBT ligands [N(1)–C(1) 1.306(5), N(2)–C(10) 1.319(5) and N(3)–C(19) 1.314(5) Å] are shorter than those of neutral 2-MMI(H) [N(4)–C(28) 1.335(5) Å]. The Bi–S bond length of 2-MMI(H) [Bi(1)–S(7) 3.0227(13) Å] is comparable to the reported values for coordinate dative Bi←S bonds (ca. 3.0 Å) and is longer than those of 4-BrMBT (Table 4). These somewhat different Bi–S, C–S and C–N bond lengths support the different coordination modes of 4-BrMBT and 2-MMI(H) in the complexes.

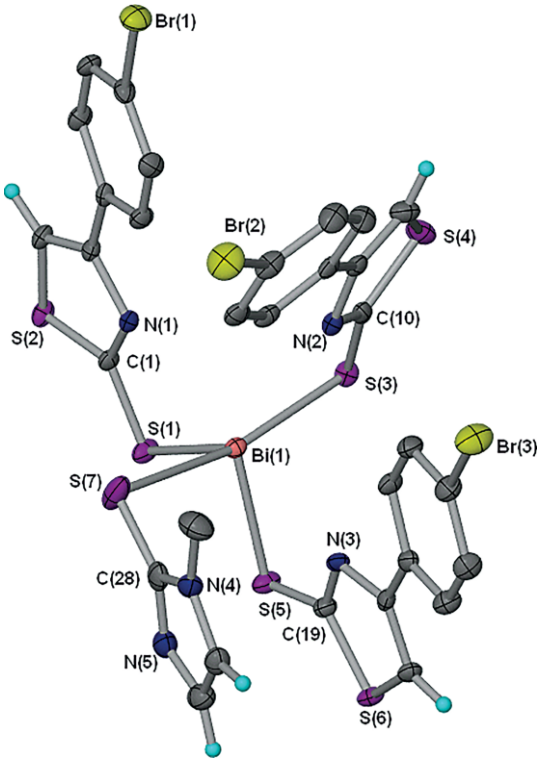


Figure 7. Molecular structure of **4** with thermal ellipsoids show at 50 % probability. Selected hydrogen atoms removed for clarity.

Table 4. Selected bond lengths [Å] and angles [°] for **4**.

Bi(1)–S(1)	2.5899(10)	C(1)–S(1)–Bi(1)	90.88(14)
Bi(1)–S(3)	2.6692(11)	C(10)–S(3)–Bi(1)	90.07(15)
Bi(1)–S(5)	2.5890(11)	C(19)–S(5)–Bi(1)	92.01(15)
Bi(1)–S(7)	3.0227(13)	C(28)–S(7)–Bi(1)	99.50(15)
S(1)–C(1)	1.739(4)	S(1)–Bi(1)–S(3)	92.15(4)
S(3)–C(10)	1.735(4)	S(1)–Bi(1)–S(7)	97.75(4)
S(5)–C(19)	1.734(4)	S(5)–Bi(1)–S(1)	77.91(4)
S(7)–C(28)	1.720(5)	S(5)–Bi(1)–S(3)	94.94(4)
N(1)–C(1)	1.306(5)	S(5)–Bi(1)–S(7)	100.20(4)
N(2)–C(10)	1.319(5)	N(2)–C(10)–S(3)	124.7(4)
N(3)–C(19)	1.314(5)	N(1)–C(1)–S(1)	123.5(3)
N(4)–C(28)	1.335(6)	N(3)–C(19)–S(6)	115.2(3)
Br(1)–C(7)	1.908(4)	N(5)–C(28)–S(7)	127.6(4)

Orange crystals suitable for X-ray diffraction studies were obtained from a toluene solution of **5** after 6–7 d. The complex crystallizes in the triclinic space group $P\bar{1}$. The molecular structure was established by X-ray crystallography and with the help of NMR spectroscopy; hydrogen atoms were located by residual electron density and placed in calculated positions (Figure 8). Selected interatomic parameters are summarised in Table 5. Complex **5** contains one neutral and two tetrazole thiolate and two neutral and one imidazole thiolate ligands. The geometry around the bismuth(III) centre is a distorted octahedron with a coordination number of six. The binding of two 1-MMTZ and one 2-MMI ligand is primarily through the deprotonated sulfur atom of the thiol group, while the remaining ligands bind in a neutral fashion. The Bi–S bond lengths for the three thiolato ligands [Bi(1)–S(2) 2.775(2), Bi(1)–S(6) 2.711(2) and Bi(1)–S(5) 2.791(2) Å] are comparable with those of [BiPh(1-MMTZ)$_2${1-

MMTZ(H)}$_2$] (av. 2.724 Å) but slightly shorter than those of [BiPh(2-MMI)$_2${2-MMI(H)}$_2$] (av. 2.812 Å).[24] In the neutral 2-MMI(H) ligands, the Bi–S bond lengths of 2.969(2) and 3.015(2) Å are significantly longer than those in **5**, which are in the range of 2.9173(12)–2.9476(10) Å. In the neutral 1-MMTZ(H) ligand, the Bi–S bond length is slightly shorter than that in [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (av. 2.934 Å).[24] Thus, they constitute an average between typical covalent Bi–S (ca. 2.6 Å)[27,28] and coordinate dative Bi←S (ca. 3.0 Å) bonding modes.[29,30] This may be due to averaging of the six bonds throughout the crystal owing to the possibility of the three calculated NH protons on the neutral ligands being located on any three of the heterocyclic ligands at any one time. The structure is stabilised by intramolecular hydrogen bonding [H(9N)–N(13) 1.93(11), H(11N)–N(5) 1.99(12) and H(4N)–N(17) 2.01(11) Å, which lie in the range of typical hydrogen bonds].

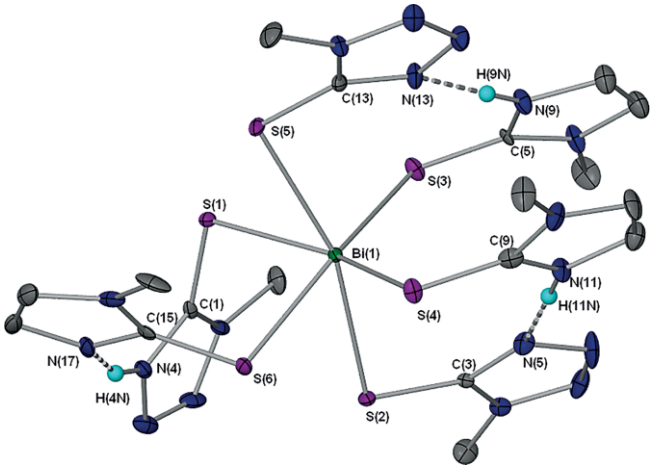


Figure 8. Molecular structure of **5** with thermal ellipsoids shown at 50 % probability. Hydrogen atoms (except NH) have been omitted for clarity.

Table 5. Selected bond lengths [Å] and angles [°] for **5**.

Bi(1)–S(1)	2.693(2)	N(9)–C(5)	1.351(12)
Bi(1)–S(2)	2.775(2)	N(13)–C(13)	1.335(13)
Bi(1)–S(3)	3.015(2)	N(11)–C(9)	1.332(13)
Bi(1)–S(5)	2.791(2)	N(17)–C(15)	1.336(13)
Bi(1)–S(4)	2.969(2)	C(1)–S(1)–Bi(1)	103.2(3)
Bi(1)–S(6)	2.711(2)	C(3)–S(2)–Bi(1)	99.0(3)
S(1)–C(1)	1.743(10)	C(5)–S(3)–Bi(1)	105.6(3)
S(2)–C(3)	1.718(10)	C(9)–S(3)–Bi(1)	108.2(19)
S(3)–C(5)	1.698(9)	C(13)–S(5)–Bi(1)	98.8(3)
S(4)–C(9)	1.708(12)	C(15)–S(6)–Bi(1)	110.3(3)
S(5)–C(13)	1.714(10)	S(1)–Bi(1)–S(6)	2.693(2)
S(6)–C(15)	1.704(10)	S(1)–Bi(1)–S(2)	93.04(8)
N(4)–C(1)	1.305(11)	S(6)–Bi(1)–S(2)	75.94(8)

Antibacterial Studies

All the parent thiones and their Bi^{III} complexes were tested against six different strains of bacteria: *M. smegmatis*, *S. aureus*, MRSA, VRE, *E. faecalis* and *E. coli*. For comparison, the activity of $BiPh_3$ was also assessed. The solvent used for the preparation of sample solutions of required concentration was DMSO. Isoniazid (isonicotinyl hydrazide), a first-line drug for the treatment of tuberculosis, and vancomycin (clinical MIC = 2 μg/mL, 1.38 μM) were used as controls.[31–34]

The MIC is the minimal concentration of a drug that still completely inhibits bacterial growth in culture. The in vitro activities of all the compounds are listed in Table 6. Most of these heterocyclic, mixed thiolatobismuth complexes demonstrated significant antimicrobial activity against gram-positive bacteria, that is *M. smegmatis*, *S. aureus*, MRSA, VRE and *E. faecalis*.

Complexes **1**–**4** proved to be highly active against of all the gram-positive bacteria tested. Bismuth compounds[35–38] tend to be less effective against gram-negative bacteria such as *E. coli*, presumably because of difficulties caused by the double membrane. However, some complexes do show good activity, and in this study complexes **1**, **3** and **4** showed activity at relatively low MICs.

Complex **1** contains one phenyl, two anionic thiadiazole thiolato ligands and one neutral triazole thione ligand, and shows good activity towards all the gram-positive bacteria with MIC ≤ 7.49 μM. It also shows good activity towards *E. coli* with an MIC of 13.4 μM. The most closely related complexes with which to judge the impact of the various ligands are our previously described bis- and tris-thiolato complexes [BiPh(5-MMTD)$_2$] and [Bi(5-MMTD)$_3$].[1] Notably, [Bi(5-MMTD)$_3$] performs poorly with an MIC of 66.23 μM for *S. aureus*, MRSA and VRE and 165.56 μM for *M. segamatis*, *E. faecilis* and *E. coli*. Surprisingly, the heteroleptic complex [BiPh(5-MMTD)$_2$] is even more ineffective towards MRSA and VRE (180.23 μM) but shows better activity

Table 6. Antibacterial activities of mixed-ligand bismuth(III) thiolate complexes **1**–**5** against *M. smegmatis*, *S. aureus*, MRSA, VRE, *E. coli and E. faecalis*.

	MIC [μg/mL (μM)]					
	M. smegmatis	*S. aureus*	MRSA	VRE	*E. faecalis*	*E. coli*
Isoniazid	1 (7.29)	>100	>100	>100	>100	>100
4-MMT(H)			>100			
5-MMTD(H)			>100			
1-MMTZ(H)			>100			
PYM(H)			>100			
MBT(H)			>100			
4-BrMTD(H)			>100			
1	2.5 (3.74)	5.0 (7.49)	5.0 (7.49)	2.5 (3.74)	2.5 (3.74)	10 (15.0)
2	2.5 (3.25)	5.0 (6.50)	10 (13.0)	5.0 (6.50)	5.0 (6.50)	>100 (>130)
3	>100 (>138)	5.0 (6.90)	5.0 (6.90)	1.25 (1.73)	2.5 (3.45)	20 (27.6)
4	2.5 (2.20)	5.0 (4.40)	5.0 (4.40)	5.0 (4.40)	2.5 (2.20)	10 (8.81)
5	10 (13.5)	>100 (>135)	>100 (>135)	>100 (>135)	10 (13.5)	>100 (>135)

towards *S. aureus* (18.23 μM), *M. smegamatis* (4.56 μM), *E. faecilis* (2.73 μM) and *E. coli* (36.46) μM. This suggests that the 5-MMTD ligand alone is not particularly good at facilitating antimicrobial activity and that heteroleptic complexes generally perform better. The introduction of the thione ligand 4-MMT(H) both maintains and increases the bactericidal activity towards the gram-positive bacteria and *E. coli*. The complex [BiPh(4-MMT)$_2${4-MMT(H)}$_2$], which also contains the triazole in its neutral form, is highly active against all the bacteria tested, with MIC ranging from 0.34 μM for VRE to 13.40 μM for *E. coli*. Related complexes with the ligand in its anionic form, 4-MMT$^-$, follow the typical pattern of losing effectiveness as the number of this ligand increases. As such, the MICs for [BiPh(4-MMT)$_2$] range from 9.72 μM (MRSA, *S. aureus*, *E. faecalis*) to 19.44 μM (*E. coli*, VRE, *M. smegmatis*), and they become significantly worse for [Bi(4-MMT)$_3$] (180.13 μM for MRSA, VRE, *E. coli* and 18.13 μM for *S. aureus, E. faecalis*), except towards *M. smegmatis* (9.07 μM).

Complex **2** contains two thiolato anions (1-MMTZ) derived from 1-methyl-1*H*-tetrazole-5-thione, and also incorporates one anionic (PYM) and two neutral ligands of pyrimidine-2-thione [PYM(H)] in its thione form. The complex demonstrates good activity towards *S. aureus*, VRE and *E. facealis* at 6.50 μM and moderately good activity towards MRSA at 13.0 μM. This is consistent with our previous study that demonstrated that the heteroleptic bis-tetrazole thiolato complexes [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] and [BiPh(1-MMTZ)$_2$] are significantly more active towards all the bacteria (ranges of 1.33–3.34 μM and 4.84–9.68 μM, respectively, for gram-positive bacteria) than the homoleptic tris-thiolato complex [Bi(1-MMTZ)$_3$], which shows very little activity towards *S. aureus*, MRSA, VRE and *E. coli* (all 180 μM).[1] However, all three complexes are highly active towards *M. smegmatis* (1.33–9.07 μM), which is largely consistent with **2** (3.13 μM).

While many metal complexes containing the neutral PYM(H) ligand have been structurally characterised, only one complex containing the anionic PYM ligand has been characterised.[37] The only antibacterial studies associated with metal complexes of this ligand in any form were performed on a series of Cu and Ag complexes of form [M(PPh$_3$)$_n${PYM(H)}$_m$]X (M = Cu; X = BF$_4$; n = 3, m = 1; n = m = 2M = Ag; X = NO$_3$; n = 3, m = 1; n = 2, m = 1).[39] The Ag complexes were more active towards *S. aureus* than the Cu complexes (8.0 vs. 24 μg/mL), and their activities were similar to that of complex **2** (5.0 μg/mL). The Ag complexes are also active towards *E. coli* (7.5 μg/mL), but **2** and the Cu complexes are not, and this suggests that PYM(H) is not the determining factor in this.

Complex **3**, having thiazole and thiadiazole moieties, shows excellent activity towards *S. aureus*, MRSA, VRE *and E. faecalis* with MICs of 6.90, 6.90, 1.73 and 3.45 μM, respectively. These MICs align closely with those observed for the two analogous thiazole-based complexes studied previously, [Bi(MBT)$_3$] and [BiPh(MBT)$_2$].[2] The sole exception is the activity of [Bi(MBT)$_3$] towards VRE, for which the MIC was significantly higher (59.6 μM). Considering the role of the 5-MMTD ligand, it is interesting that the previously described complex [BiPh(5-MMTD)$_2$] showed good activity towards *M. smegmatis* (4.56 μM) and *E. faecalis* (2.73 μM) but was largely ineffective against MRSA and VRE (both 171.07 μM). The activity of the complex towards *E. coli* (27.6 μM) is almost certainly predicated on the 5-MMTD ligand, as the MICs for [BiPh(MBT)$_2$] and [Bi(MBT)$_3$] are 127.3 and 149.1 μM respectively.

Similarly, complex **4**, containing thiazole- and imidazole-based ligands, also shows excellent activity with MIC values of 4.40 μM towards *S. aureus*, MRSA and VRE, and 2.20 μM towards *E. faecalis*. This level of activity towards *S. aureus* and MRSA is comparable with that of vancomycin (1.38 μM).[31] In comparison with the tris-thiolato parent complex [Bi(4-BrMTD)$_3$] the effect of introducing the neutral 2-MMI(H) ligand on the Bi atom is significant. The MIC for [Bi(4-BrMTD)$_3$] against *S. aureus* is 9.78 μM, and that against MRSA is ten times higher (97.8 μM). Against the other four bacteria the MIC is 39.14 μM. The monophenyl bis-thiolato complex [BiPh(4-BrMTD)] is significantly more active towards all the bacteria tested than [Bi(4-BrMTD)$_3$], though not as potent as **4**, except in the case of *S. aureus* (1.21 μM).[1] For comparison, the MIC for [BiPh(4-BrMTD)] towards both MRSA and VRE was 6.06 μM.[2] Interestingly, complexes containing the imidazole ligand as an anion, [BiPh(2-MMI)$_2$] and [Bi(2-MMI)$_3$], and also in its neutral form, [BiPh(2-MMI)$_2${2-MMI(H)}$_2$], are poor antibacterial agents.[1] None of the complexes are particularly active towards *S. aureus*, MRSA, VRE and *E. coli*, and all three complexes have MICs greater than 100 μg mL^{-1} for each of these bacteria. Thus, the dominant ligand in **4** is the thiazole 4-BrMTD, and this further supported by comparing the activity of **4**, [BiPh(4-BrMTD)] and [Bi(4-BrMTD)$_3$] towards *E. coli*, for which they have MICs of 8.81, 48.5 and 39.14 μM, respectively.

Complex **5** is the most ineffective of the five complexes. Structurally it is similar to **2** in that it contains two thiolato anions (1-MMTZ) derived from 1-methyl-1*H*-tetrazole-5-thione. However, the only similarities are in the activity of the two complexes towards *M. smegmatis* (3.13 and 13.5 μM, respectively), *E. faecelis* (6.25 and 13.5 μM, respectively) and their inactivity towards *E. coli* (> 130 μM). Surprisingly, unlike **1**–**4** it shows no activity towards *S. aureus*, MRSA or VRE at the upper concentration tested (MIC > 135 μM). This suggests the coligands, one anionic (2-MMI) and two neutral ligands [2-MMI(H)] of 1-methyl-1*H*-imidazole-2-thione, have a dramatic effect. Previous Bi^{III} complexes we have studied containing either of these ligands have demonstrated generally poor antibacterial properties (MIC ≥ 135 μM), irrespective of whether they are heteroleptic or homoleptic.[1] The exceptions were towards *M. smegmatis* (13.5 and 19.5 μM for {BiPh(2-MMI)$_2$[2-MMI(H)]$_2$} and [BiPh(2-MMI)$_2$], respectively) and *E. faecalis* (13.5 and 9.75 μM for {BiPh(2-MMI)$_2$[2-MMI(H)]$_2$} and [BiPh(2-MMI)$_2$], respectively). Therefore, this may contribute to the effectiveness of **5** towards *M. smegmatis* and *E. faecalis* (both 13.5 μM).

Mammalian Cell Toxicity

Although a strong antibacterial activity is essential for potential new therapeutic agents, the compound must have low toxicity towards human or animal eukaryotic cells. Toxicity assays of all the complexes were conducted on cultured COS-7 cell lines. These revealed the complexes to be non-toxic to mammalian cells at 20 μg/mL (Figure 9).

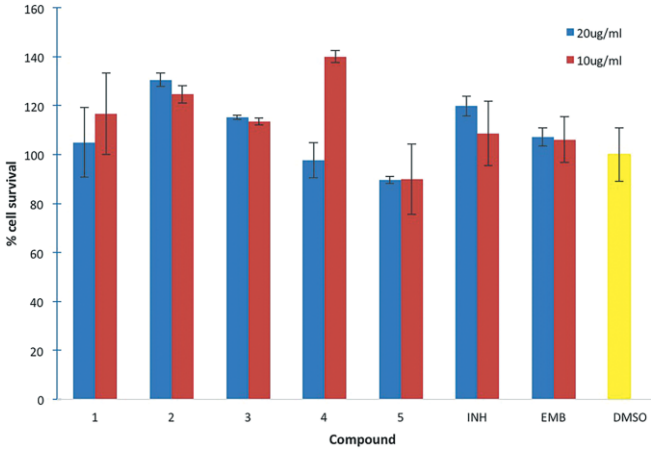


Figure 9. Toxicity assays of compounds **1**–**5**, isoniazid (INH) and ethambutol (EMB) against cultured COS-7 cell lines.

Conclusions

Five new heteroleptic bismuth(III) thiolato complexes **1**–**5** were synthesised and fully characterised. Crystals were grown from DMSO (**1**) or toluene solution (**2**–**5**), and allowed their solid-state structures to be characterised by single-crystal XRD. Complexes **2**, **4** and **5** are monomeric, and the geometries around the central bismuth atom are distorted pentagonal-bipyramidal, trigonal-pyramidal and distorted octahedral, respectively. In contrast, complex **1** adopts a trigonal-pyramidal geometry at the bismuth atom and extends into a dimeric structure through long intermolecular Bi–N and Bi–S interactions. Dimerisation of two monomeric units of **3** occurs through a long interaction between the bismuth centre and π electrons of an adjacent aromatic ring to give an overall distorted pentagonal-pyramidal coordination geometry. Both NMR studies and the crystallographic data reveal the different binding modes of the ligands.

Analysis of the antibacterial activity of the complexes against *M. smegmatis, S. aureus*, MRSA, VRE, *E. faecalis and E. coli* demonstrated that heteroleptic Bi^{III} complexes are almost always more effective than their homoleptic analogues. From our study the thiadiazole (5-MMTD) and thiazole ligands (MBT and 4-BrMTD) appear to be particularly effective, while the tetrazole ligand 1-MMTZ results in more modest activity. The imidazole [2-MMI, 2-MMI(H)] and pyrimidine ligands [PYM, PYM(H)] appear to be the least effective. All the complexes showed poor activity towards the gram-negative bacterium *E. coli* but, more promisingly, showed little or no toxicity towards mammalian COS-7 cell lines at 20 μg mL^{-1}.

This all suggests that future endeavours should focus on developing and assaying a broader range of heteroleptic thiadiazole- and thiazole-based Bi^{III} complexes as the most promising targets for this class of complex.

Experimental Section

$BiPh_3$ was synthesised by a standard Grignard metathesis reaction in which $BiCl_3$ was treated with MgPhBr in dried diethyl ether at 0 °C, and subsequently recrystallised from ethanol. $PhBiCl_2$ was synthesised by mixing $BiPh_3$ and $BiCl_3$ in a 2:1 ratio in dried diethyl ether. Ethanol, DMSO and toluene were used as solvents for recrystallisation. Diethyl ether and THF were dried prior to use with an M-Braun-SPS-800 solvent purification system and stored over molecular sieves (4 Å). Microwave irradiation was carried out in a CEM Discoverer Microwave oven with 0–300 W power, model number 9080, maximum current 6.38 A with 50/60 MHz frequency. NMR spectra of complexes were recorded with a Bruker DPX 400 spectrometer in [D_6]DMSO with TMS as internal standard at room temperature. Elemental analysis (C, H and N) was performed by the Campbell Microanalytical lab, Department of Chemistry, University of Otago, Dunedin, New Zealand. Melting points were determined with a Stuart Scientific SMP3 melting point apparatus. Mass spectra were recorded with Micromass Platform Electrospray Mass Spectrometer. The atom-labelling scheme used for NMR chemical shift assignments is shown in Figure 10.

Crystallographic Data: Crystallographic data of compounds **1**–**3** was collected at the MX1 beamline comprising a Φ goniostat with an ADSC Quantum 210r detector at the Australian Synchrotron, Melbourne, Victoria, Australia. All data were collected at 100 K, maintained by using an open flow of nitrogen. The software used for collection and reduction of the data was BlueIce,[40] and data were processed with XDS.[41] Crystallographic data of compounds **4** and **5** were collected with an Oxford Gemini Ultra equipped with an Oxford Cryosystems 700 Cryostream [123(1) K]. Data were collected with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and processed with the CrysAlisPro 1.171.34.3 software;[42] Lorentzian, polarisation and absorption corrections (multi-scan) were applied. All compounds **1**–**5** were solved and refined with SHELX-97.[43] All non-hydrogen atoms were refined with anisotropic thermal parameters, unless otherwise indicated. Hydrogen atoms were placed in calculated positions by using a riding model with d(C–H) = 0.95–0.98 Å and U_{iso}(H) = xU_{iso}(C), x = 1.2 or 1.5, unless otherwise indicated. For compound **5** the data were modelled as a merohedral twin and solved by using the twin data processing in CrysAlis*i*Pro, and the final structure was refined by using HKLF 5 format.
CCDC 1436829 (for **1**), 1436830 (for **2**), 1436831 (for **3**), 1436832 (for **4**), and 1436833 (for **5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Antimicrobial Activity: *Mycobacterium smegmatis* was cultured in Middlebrook 7H9/7H10 medium (Difco) for 3 d at 37 °C. *Escherichia coli* was cultured overnight at 37 °C in Luria–Bertani medium. *Staphylococcus aureus*, MRSA, *Enterococcus faecalis* and VRE were cultured in brain–heart infusion medium (Oxoid) overnight at 37 °C.

In initial activity screens, filter paper discs were soaked with 2 μL of 5 mg/mL compound, and then placed on the surface of agar plates that had been pre-spread with a culture of the bacterial strain of interest. Following incubation, the plates were examined for the presence of zones of inhibition of bacterial growth around the discs. Compounds that were negative in this assay were not examined further, and MIC assays were performed for all positive compounds.

To determine MICs, liquid cultures of bacteria were prepared containing serial dilutions of the compounds, from 80 to 0.25 μg/mL. After incubation, the cultures were examined to determine the minimum concentration of compound that caused total inhibition of growth; this value was recorded as the MIC. The antimycobacterial drugs isoniazid and ethambutol were included as controls.

Cell Toxicity Assays: Toxicities against eukaryotic cells were assayed by using an MTT-based in vitro toxicology assay kit (Sigma-

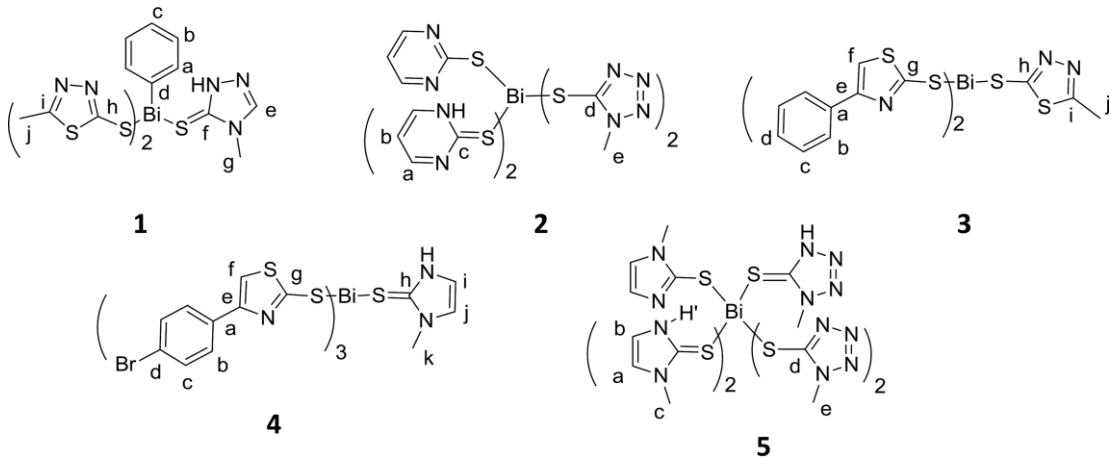


Figure 10. Complexes **1**–**5** with labelling corresponding to NMR chemical shift assignments.

Aldrich; cat. no. TOX1-1KT), according to the manufacturer's instructions. Compounds were added to cultured COS-7 (monkey kidney derived) cells at 10 and 20 µg/mL for 2 h prior to addition of the tetrazolium dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]. OD_{690} measurements were expressed as a percentage the DMSO-only negative controls. All assays were performed in triplicate. Isoniazid- and ethambutol-treated COS-7 cells were included as controls.

General Procedures (GP)

GP1: Microwave heating: All reactions were conducted with one equivalent of $BiPh_3$ plus one and/or two equivalents of the chosen thione(s). Crystalline $BiPh_3$ was ground together with the thione(s) and placed in an Emery microwave vial followed by the addition of toluene. The sample was then heated in the microwave reactor. On completion, all volatile substancess were removed and the solid product obtained was washed with a small amount of cold toluene, ethanol, diethyl ether or acetone to remove unconverted $BiPh_3$ and thiones(s). The solid was then taken up in DMSO or toluene and allowed to crystallise over 7–14 d. All reactions were carried out 300 W.

GP2: Synthesis by Conventional Reflux: Crystalline $BiPh_3$ and the chosen thione(s) were placed in a small round-bottomed flask with toluene (25 mL) as solvent and the mixture heated to reflux for 4–15 h. The toluene was removed in vacuo and the remaining solid washed with a small amount of toluene, ethanol, diethyl ether or acetone to remove unconverted $BiPh_3$ and/or thione(s) prior to drying in air. The solid was then taken up in DMSO or toluene and allowed to crystallise over 7–14 d.

Heteroleptic Thiolato Bismuth(III) Complexes

Synthesis of [BiPh(5-MMTD)$_2${4-MMT(H)}] (1)

Microwave-Assisted Synthesis: A mixture of 5-methyl-1,3,4-thiadiazole-2-thione (0.10 g, 0.75 mmol) and triphenylbismuth (0.17 g, 0.37 mmol) in toluene (4 mL) was stirred constantly at room temperature for five minutes according to **GP1**. The yellow solution obtained was then mixed with a solution of 4-methyl-4*H*-1,2,4-triazole-3-thione (0.043 g, 0.37 mmol) in toluene (2 mL) and was irradiated at 115 °C for 10 min. The yellow crystals of **1** thus obtained were washed with acetone and diethyl ether, yield 0.12 g (75 %).

Conventional Method: The general procedure **GP2** with triphenylbismuth (0.17 g, 0.37 mmol), 5-methyl-1,3,4-thiadiazole-2-thione (0.10 g, 0.75 mmol), and 4-methyl-4*H*-1,2,4-triazole-3-thione (0.043 g, 0.37 mmol) in toluene (12 h reflux) afforded yellow crystals of **1** (0.10 g, 62 %), m.p. 232–234 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.67. (s, 1 H, NH), 8.90 (d, 2 H, H^a), 8.38 (s, 1 H, H^e), 7.80 (t, 2 H, H^b), 7.41 (t, 1 H, H^c), 3.43 (s, 3 H, H^g), 2.57 (s, 6 H, H^j) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.7 (Ci), 143.0 (C^e), 139.3 (C^a), 132.8 (C^b), 127.7 (C^c), 31.2 (C^g), 15.4 (C^j) ppm. FTIR: $\tilde{\nu}$ = 3096 (b), 1567 (s), 1505 (s), 1473 (s), 1425 (m), 1348 (m), 1197 (s), 1155 (m), 1052 (m), 1031 (s), 766 (s), 722 (m), 691 (s), 679 (m) cm^{-1}. ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* = 741 (20) [BiPhL$_2$(L'H)-(H$_2$O)$_3$(Na)]$^+$, 687 (70) [BiPhL$_2$(L'H)(Na)]$^+$, 571 (7) [BiPhL$_2$(Na)]$^+$. ESI-MS$^-$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%) = 777 (10) [BiPhL$_2$(L'H)-(DMSO)(Cl)]$^-$, 681 (45) [BiPhL$_2$(L'H)(OH)]$^-$. (L = 5-MMTD and L' = 4-MMT). $BiC_{15}H_{16}N_7S_5$ (663.6): calcd. C 27.15, H 2.58, N 15.86; found C 27.45, H 2.31, N 15.55.

Synthesis of [Bi(1-MTTZ)$_2${(PYM)(PYM(H)$_2$)}] (2)

Microwave-Assisted Synthesis: A mixture of pyrimidine-2-thione (0.12 g, 1.06 mmol) and triphenylbismuth (0.15 g, 0.33 mmol) in toluene (4 mL) was stirred constantly at room temperature for about 5 min according to **GP1**. The colourless solution obtained was than mixed with the solution of 1-methyl-1*H*-tetrazole-5-thione (0.06 g, 0.53 mmol) in toluene (2 mL) and irradiated at 100 °C for 8 min. The resulting solution was allowed to stand for 10 d at room temperature. The orange crystals obtained were filtered off, washed with toluene and acetone and air-dried. These were identified as **2**, yield 0.15 g (65 %).

Conventional Method: The general procedure **GP2** with triphenylbismuth (0.15 g, 0.33 mmol), pyrimidine-2-thione (0.12 g, 1.06 mmol), and 1-methyl-1*H*-tetrazole-5-thione (0.06 g, 0.53 mmol) in toluene (6 h reflux) afforded orange crystals of **2** (0.12 g, 61 %), m.p. 201 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.56 (d, ^3J = 6.20 Hz, 6 H, H^a), 7.27 (t, ^3J = 6.20 Hz, 3 H, H^b), 3.80 (s, 6 H, H^e) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 156.5 (C^a), 32.2 (C^e) ppm. FTIR: $\tilde{\nu}$ = 3064 (m), 1597 (m), 1537 (m), 1464 (s), 1417 (s), 1373 (s), 1316 (s), 1267 (s), 1207 (m), 1035 (s), 979 (s), 756 (s), 735 (s), 700 (m), 655 (m) cm^{-1}. ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%) = 737 (20), [Bi(L)$_2$(L'$_3$H$_2$)(H$_2$O)$_3$(Na)]$^+$ (L = 1-MTTZ and L' = PYM). $BiC_{14}H_{14}N_{10}S_4$ (659.6): calcd. C 24.81, H 2.21, N 22.31; found C 24.26, H 2.31, N 22.23.

Synthesis of [Bi(MBT)$_2$(5-MMTD)] (3)

Microwave-Assisted Synthesis: A mixture of 4-phenylthiazole-2-thione (0.14 g, 0.72 mmol) and triphenylbismuth (0.15 g, 0.36 mmol) in toluene (4 mL) was stirred constantly at room temperature for

about 5 min. The solution obtained was than mixed with a solution of 5-methyl-1,3,4-thiadiazole-2-thione (0.05 g, 0.36 mmol) in toluene (2 mL) and irradiated at 112 °C for 10 min. The yellow crystals thus obtained were washed with toluene and diethyl ether and identified as **3**, yield 0.09 g (72 %).

Conventional Method: The general procedure **GP2** with triphenylbismuth (0.15 g, 0.36 mmol), 4-phenylthiazole-2-thione (0.14 g, 0.72 mmol) and 5-methyl-1,3,4-thiadiazole-2-thione (0.05 g, 0.36 mmol) in toluene yielded yellow crystals of **3** (0.08 g, 69 %).

M.p. 170 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.72 (d, 4 H, H^b), 7.55 (s, 2 H, H^f), 7.25 (m, 6 H, H^{c,d}), 2.54 (s, 3 H, H^j) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 152.2 (C^e), 141.9 (C^h), 133.4 (C^a), 128.6 (C^c), 127.9 (C^d), 126.1 (C^b), 113.6 (C^f), 15.9 (C^j) ppm. FT-IR: $\tilde{\nu}$ = 2943 (s), 1632 (s), 1458 (s), 1270 (m), 953 (m), 762 (s) cm^{-1}. ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%) = 860 (10) [PhBiL$_2$-(L′)(DMSO)(H$_2$O)(K)]$^+$, 842 (18) [BiL$_2$(L′)(DMSO)(K)]$^+$, 762 (18) [BiL$_2$-(L′)(H$_2$O)$_2$(H)]$^+$ (L = 5-MMTD and L′ = MBT). ESI-MS$^-$ (solvent: DMSO/MeOH, 35 eV): *m/z* 995 (10) [BiL$_2$(L′)(DMSO)$_3$(Cl)]$^-$, 892 (20) [BiL$_2$-(L′)(DMSO)(H$_2$O)$_3$(Cl)]$^-$. $BiC_{21}H_{15}N_4S_6$ (724.7): calcd. C 34.80, H 2.09, N 7.73; found C 34.25, H 2.31, N 7.65.

Synthesis of [Bi(4-BrMTD)$_3${2-MMI(H)}] (4)

Microwave-Assisted Synthesis: A mixture of triphenylbismuth (0.08 g, 0.17 mmol) and 4-(4-bromophenyl)thiazole-2-thione (0.14 g, 0.51 mmol) in toluene (4 mL) was stirred at room temperature for 5 min according to **GP1**. The solution obtained was than mixed with the solution of 1-methyl-1*H*-imidazole-2-thione (0.02 g, 0.17 mmol) in toluene (2 mL) and irradiated at 115 °C for 10 min. The orange crystals of **4** that precipitated were collected by filtration, washed with toluene and diethyl ether and dried in air, yield 0.13 g (65 %).

Conventional Method: The general procedure **GP2** with triphenylbismuth (0.08 g, 0.17 mmol), 4-(4-bromophenyl)thiazole-2-thione (0.14 g, 0.51 mmol) and 1-methyl-1*H*-imidazole-2-thione (0.02 g, 0.17 mmol) in toluene (7 h reflux) afforded **4** as orange crystals (0.12 g, 60 %).

M.p. 145 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.03 (s, 1 H, NH), 7.72 (m, 12 H, H^{bc}), 7.39 (s, 3 H, H^f), 7.04 (d, 1 H, H^j), 6.87 (d, 1 H, H^i), 3.41 (s, 3 H, H^k) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.2 (C^g), 150.9 (C^e), 131.4 (C^c), 127.4 (C^b), 120.6 (Ci), 114.4 (C^j), 113.4 (C^f) ppm. FTIR: $\tilde{\nu}$ = 3059 (m), 1651 (s), 1595 (s), 1473 (m), 1441 (m), 1272 (s), 1180, 1072 (s), 1051 (s), 774 (m), 718 (s), 686 (m), 667 (m) cm^{-1}. ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%) = 1156 (27) [Bi(L)$_3$(L′H)(H$_2$O)(H)]$^+$(^{79}Br isotope), 1158 (25) [Bi(L)$_3$(L′H)-(H$_2$O)(H)]$^+$(^{81}Br isotope). ESI-MS$^-$ (solvent: DMSO/MeOH, 35 eV): *m/z* 1172 (50) [Bi(L)$_3$(L′H)(H$_2$O)(OH)] – (^{79}Br isotope), (L = 4-BrMBT and L′ = 2-MMI). $BiC_{31}H_{21}Br_3N_5S_7$ (1136.6): calcd. C 32.76, H 1.86, N 6.16; found C 32.51, H 1.89, N 5.93.

Synthesis of [Bi(1-MMTZ)$_2${1-MMTZ(H)}{2-MMI}{2-MMI(H)$_2$}] 5

Microwave-Assisted Synthesis: A mixture of tris-(2-methoxyphenyl)bismuth (0.22 g, 0.43 mmol) and 1-methyl-1*H*-l-tetrazole-5-thione (0.15 g, 1.29 mmol) in toluene (4 mL) was stirred constantly at room temperature for about 5 min. The colourless solution obtained was than mixed with a solution of 1-methyl-1*H*-imidazole-2-thione (0.14 g, 1.29 mmol) in toluene (2 mL) and irradiated at 100 °C for 6 min. The resulting solution was allowed to stand for two weeks at room temperature. The orange crystals of **5** which formed were collected by filtration, washed with toluene and dried in air, yield 0.13 g (74 %).

Conventional Method: The general procedure **GP2** with tris(2-methoxyphenyl)bismuth (0.22 g, 0.43 mmol), 1-methyl-1*H*-l-tetrazole-5-thione (0.15 g, 1.29 mmol) and 1-methyl-1*H*-imidazole-2-thione (0.14 g, 1.29 mmol) in toluene (4 h reflux) afforded 5 as orange crystals (0.12 g, 71 %).

M.p. 125 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.03 (s, 2 H, NH′), 7.04 (d, 3 H, H^a), 6.85 (d, 3 H, H^b), 3.89 (s, 9 H, H^e), 3.43 (s, 9 H, H^c) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 120.3 (C^b), 114.5 (C^a), 33.4 (C^e), 33.3 (C^c) ppm. FTIR: $\tilde{\nu}$ = 3102 (m), 3058 (m), 1571 (s), 1505 (m), 1437 (s), 1417 (s), 1372 (s), 1306 (s), 1269 (s), 1073 (s), 1032 (m), 973 (s), 776 (s), 737 (s), 703 (m), 690 (m), 670 (m) cm^{-1}. ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%) = 934 (50) [Bi(L$_3$H)(L′$_3$H$_2$)(H$_2$O)$_2$(H)]$^+$, 209 (20) [Bi]$^+$ (L = 1-MMTZ and L′ = 2-MMI). $BiC_{18}H_{27}N_{18}S_6$ (896.9): calcd. C 24.10, H 3.03, N 28.11; found C 24.15, H 3.21, N 28.43.

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Keywords: Bismuth · S ligands · Heteroleptic complexes · Drug design · Medicinal chemistry · Antibiotics

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