ChemPubSoc Europe

DOI: 10.1002/chem.201404109

CHEMISTRY A European Journal Full Paper

Bismuth Chemistry

Homo- and Heteroleptic Bismuth(III/V) Thiolates from N-Heterocyclic Thiones: Synthesis, Structure and Anti-Microbial Activity

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Abstract: Homo- and heteroleptic bismuth thiolato complexes have been synthesised and characterised from biologically relevant tetrazole-, imidazole-, thiadiazole- and thiazole-based heterocyclic thiones (thiols): 1-methyl-1*H*-tetrazole-5-thiol (1-MMTZ(H)); 4-methyl-4*H*-1,2,4-triazole-3-thiol (4-MTT(H)); 1-methyl-1*H*-imidazole-2-thiol (2-MMI(H)); 5-methyl-1,3,4-thiadiazole-2-thiol (5-MMTD(H)); 1,3,4-thiadiazole-2-dithiol (2,5-DMTD(H)$_2$); and 4-(4-bromophenyl)thiazole-2-thiol (4-BrMTD(H)). Reaction of $BiPh_3$ with 1-MMTZ(H) produced the rare Bi^V thiolato complex [BiPh(1-MMTZ)$_4$], which undergoes reduction in DMSO to give [BiPh(1-MMTZ)$_2${(1-MMTZ(H)}$_2$]. Reactions with $PhBiCl_2$ or $BiPh_3$ generally produced monophenylbismuth thiolates, [BiPh(SR)$_2$]. The crystal structures of [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$], [BiPh(5-MMTD)$_2$], [BiPh{2,5-DMTD(H)}$_2$(Me$_2$C=O)] and [Bi(4-BrMTD)$_3$] were obtained. Evaluation of the bactericidal properties against *M. smegmatis, S. aureus,* MRSA, VRE, *E. faecalis and E. coli* showed complexes containing the anionic ligands 1- MMTZ, 4-MTT and 4-BrMTD to be most effective. The dithiolato dithione complexes [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] and [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] were most effective against all the bacteria: MICs 0.34 μM for [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] against VRE, and 1.33 μM for [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] against *M. smegmatis* and *S. aureus*. Tris-thiolato Bi^{III} complexes were least effective overall. All complexes showed little or no toxicity towards mammalian COS-7 cells at 20 μg mL^{-1}.

Introduction

The interest in bismuth, and its compounds, continues to attract considerable attention because of its potential as an environmentally acceptable heavy metal in chemical synthesis, materials, and medicine.[1–4] The effective biological activity of bismuth compounds towards microbes, parasites and tumour cells,[5–7] coexists with what is an apparent low systemic toxicity in humans, providing a motivation for their study and application in bio-protective surfaces,[8] therapeutics,[7,9] and molecular and cellular imaging.[10,11] While the majority of bismuth-based medicines currently available are derived from carboxylic acids (for examples bismuth subsalicylate, bismuth subcitrate) the in vivo biological targets for bismuth, with the exception of transferrin and lactoferrin, are predominantly proteins and peptides rich in S-based amino acids cysteine and methionine.[7,12,13] The Bi–S bond displays higher thermodynamic stability than Bi–O, and bismuth thiolates, unlike many carboxylates, alkoxides, and diketonates, tend to be stable towards hydrolysis. This makes the study of bismuth thiolates; their formation, structure, stability, lability, and biological activity particularly relevant.

While thermodynamically stable the Bi–S bond is still labile,[6] and so bismuth thiolates display strong bactericidal and fungicidal properties.[14–16] They have been assessed and proposed as effective agents for combating wound infection,[17] and for retarding biofilm growth on surfaces.[8,19–21] Several classes of compounds, particularly xanthates and dithiocarbamates, have shown significant in vitro anti-tumour activity.[22–25] Bismuth thiolates have also been investigated as X-ray imaging agents,[26] and more recently their decomposition to functionalised bismuth sulfide nanoparticles has given rise to a new class of contrast agent for computed tomography.[11,27–30]

Difficulties with solubility often means obtaining definitive solid and solution state structural information on bismuth thiolates is challenging, though the library is growing with a relatively small but not insignificant number complexes being structurally authenticated, particularly those based on arylthiolato ligands.[31] The paucity in the diversity of such information impacts on our knowledge of structure–activity relationships and also basic cellular mechanisms, leading Burford and coworkers more recently to explore using mass spectrometry to

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404109.

elucidate complex formation and composition with low-molecular-weight, biologically relevant thiols and thio-carboxylic acids, in which chelation plays a key role.[32–34]

Our recent interest in this area has been to study bismuth complexes built primarily around covalent Bi–S bonds; thioxoketonates, thioamides and thiobenzoates, and to compare their biological activity against *Helicobacter pylori* and the Leishmania parasite with their Bi–O analogues.[35–38] Prior to this we reported on the solvent-free and microwave-assisted synthesis of Bi^{III} complexes, $[Bi(SR)_3]$, derived from heterocyclic thiols (thiones), a family of ligands for which the bismuth chemistry has been largely neglected.[39] Recently, Dostál and co-workers developed an unusual pathway involving the oxidative addition of aromatic and heterocylic disulfides to an in situ generated N,C,N-chelated arylbismuth(I) compound, resulting in a series of heteroleptic dithiolato bismuth(III) compounds.[40] In revisiting the reaction of $BiPh_3$ with thiols, we recently uncovered an unexpected redox process in the reaction of $BiPh_3$ with 4-methyl-4*H*-1,2,4-triazole-3-thiol and 2-mercapto-1-methylimidazole (=RSH), which resulted in the formation and characterisation of the first monophenyl tetrathiolato Bi^V complexes, $[BiPh(SR)_4]$, and subsequent H_2O assisted decomposition into their Bi^{III} daughter complexes, $[BiPh(SR)_2(HSR)_2]$.[41]

This result coupled with the fact that heterocyclic thioamides are used clinically in the treatment of hyperthyroidism, for example, Methimazole, and have demonstrated broad fungicidal and antimicrobial activity,[42–44] justified a deeper and broader study of the synthesis, stability, structure and biological activity of their bismuth complexes.

In this paper we now report the synthesis, full characterisation and bactericidal activity of a series of homo- and heteroleptic bismuth complexes derived from the structurally similar heterocyclic thiols: 1-methyl-1*H*-tetrazole-5-thiol (1-MMTZ(H)), 4-methyl-4*H*-1,2,4-triazole-3-thiole (4-MTT(H)), 1-methyl-1*H*-imidazole-2-thiol (2-MM1(H)), 5-methyl-1,3,4-thiadiazole-2-thiol (5-MMTD(H)), 1,3,4-thiadiazole-2-dithiol (2,5-DMTD$(H)_2$) and 4-(4-bromophenyl)thiazole-2-thiol (4-BrMTD(H)). The structures are shown in Figure 1, including an illustration of the thione–thiol tautomerism, exemplified by 2-MMT(H), a common feature of all these N-heterocyclic compounds.[45] The complexes of various composition; $[BiPh(SR)_4]$, $[BiPh(SR)_2]$ and $[Bi(SR)_3]$, have been comprehensively characterised by multinuclear NMR and FT-IR spectroscopy, ESI-MS and elemental analysis. The oxidation state of the bismuth has been studied by electrochemistry, and four complexes have had their solid-state structures confirmed by single-crystal X-ray diffraction. Finally, their antibacterial activities have been assessed against a suite of gram-positive and antibiotic resistant bacteria; *Mycobacterium smegmatis, Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus* (MRSA), *Vancomycin Resistant Enterococcus* (VRE) and *Enterococcus faecalis,* and the gram-negative bacterium *Escherichia coli*. Mammalian cell toxicity was assessed against COS-7 cells.

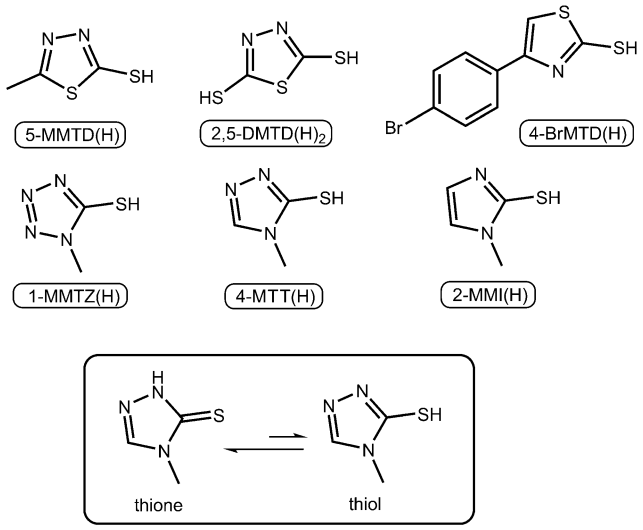


Figure 1. Six N-heterocyclic compounds used in the synthesis of Bi^V and Bi^{III} thiolate complexes: 5-MMTD(H) = 5-methyl-1,3,4-thiadiazole-2-thiol, 2,5-DMTD$(H)_2$ = 1,3,4-thiadiazole-2-dithiol, 4-BrMTD(H) = 4-(4-bromophenyl)thiazole-2-thiol, 1-MMTZ(H) = 1-methyl-1*H*-tetrazole-5-thiol, 4-MTT(H) = 4-methyl-4*H*-1,2,4-triazole-3-thiole, 2-MMI(H)] = 1-methyl-1*H*-imidazole-2-thiol. The common thiol–thione tautomerisation is shown for 4-MTT(H).

Results and Discussion

Synthesis

In targeting the most efficient and high yielding methods for the reliable and reproducible synthesis of heterocyclic thiolato bismuth complexes we have explored three different synthetic strategies; 1) the reaction of thiols with $BiPh_3$, 2) replacing $BiPh_3$ with $Bi(OtBu)_3$ as a stronger base and 3) employing salt metathesis reactions using $BiCl_3$ or $BiPhCl_2$ with sodium thiolates. These processes have been studied under standard solvent-mediated conditions and using microwave irradiation.

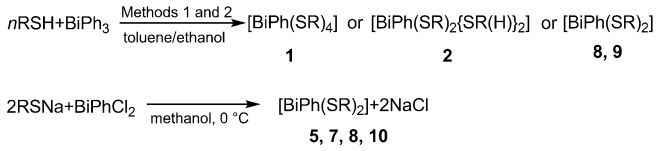
Monophenyl tris- and tetrathiolato bismuth(III/V) complexes

One surprising outcome when conducting our initial studies on the reaction of $BiPh_3$ with 4-MTT(H) and 2-MMI(H) was the formation and isolation of two unique tetrathiolato Bi^V species, $[BiPh(SR)_4]$, as confirmed by NMR spectroscopy and electrochemical analysis. These complexes proved to be stable as solids, and also initially in DMSO. However, in solution they slowly underwent hydrolysis and reduction to give crystals of the corresponding Bi^{III} complexes, $[BiPh(SR)_2(RSH)_2]$, the structures of which were determined by single-crystal X-ray diffraction.[41] This remarkable result prompted a more detailed examination of the various reaction pathways that allow for the formation of bismuth thiolates and interrogation of which ligands and which conditions support the formation and possible oxidation of the Bi^{III} complexes.

As such, the six different five-membered heterocyclic thiones (thiols) shown in Figure 1 were chosen for further study, which are based on tetrazole, triazole, imidazole, thiadiazole and thiazole.

By analogy with the reactions that resulted in the tetrathiolato Bi^{V} complexes, $BiPh_3$ was treated variously with four equivalents of 1-MMTZ(H), 5-MMTD(H), 2,5-DMTD(H)$_2$ and 4-BrMTD(H), using similar reaction conditions. Only the reaction with 1-MMTZ(H) resulted in the formation of an additional stable Bi^{V} complex, [BiPh(1-MMTZ)$_4$]. Two of the other thiols, 5-MMTD(H) and 2,5-DMTD(H)$_2$, resulted only in the disubstituted bismuth(III) thiolate complexes, [BiPh(SR)$_2$], as the single isolable products, while 4-BrMTD(H) gave a mixture of the di- and trithiolato complexes.

In addition, all six N-heterocyclic thiones and their sodium thiolato salts were successfully reacted with $BiPh_3$ or $BiPhCl_2$ respectively to give monophenylbismuth(III) thiolate complexes **1**–**10** (see Scheme 1 and ref. [41]). The outcomes of all the various reactions are summarised in Table 1, and are discussed in detail below.



Scheme 1. Summary of the synthetic methods used for the synthesis of heteroleptic monoarylbismuth thiolate complexes. Method 1: heated to reflux in the range 7–12 h. Method 2: microwave heating in the range 85–125 °C for between 5 and 25 min.

Table 1. Summary and comparison of synthetic methods and isolated yields of complexes **1**–**10**.

	Bismuth source	Reaction conditions[a]	Colour	Yield [%]
[BiPh(1-MMTZ)$_4$] (**1**)	$BiPh_3$	reflux, toluene/EtOH, 2 h	bright yellow	51
	$BiPh_3$	MW, toluene/EtOH, 100 °C, 4 min	bright yellow	57
[BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (**2**)	$BiPh_3$	reflux, toluene/EtOH, 2 h	bright yellow	53
	$BiPh_3$	MW, toluene/EtOH, 100 °C, 4 min	bright yellow	60
[BiPh(1-MMTZ)$_2$] (**5**)	$BiPhCl_2$	MeOH, 10 h	yellow	60
[PhBi(4-MTT)$_2$] (**6**)[40]	$BiPhCl_2$	MeOH, 10 h	yellow	69
[BiPh(2-MMI)$_2$] (**7**)	$BiPhCl_2$	MeOH, 7 h	yellow	77
[BiPh(5-MMTD)$_2$]$_\infty$ (**8**)	$BiPh_3$	reflux, toluene/EtOH, 16 h	pale yellow	73
	$BiPh_3$	MW, toluene/EtOH, 112 °C, 15 min	pale yellow	84
	$BiPhCl_2$	methanol, 12 h	pale yellow	83
[BiPh{2,5-DMTD(H)}$_2$]$_\infty$ (**9**)	$BiPh_3$	reflux, toluene/EtOH, 8 h	orange	73
	$BiPh_3$	MW, toluene/EtOH, 112 °C, 10 min	orange	92
[BiPh(4-BrMTD)$_2$] (**10**)	$BiPh_3$	reflux, toluene/EtOH, 6 h	orange/yellow	–
	$BiPh_3$	MW, toluene/EtOH, 115 °C, 7 min	orange/yellow	–
	$BiPhCl_2$	methanol, 16 h	yellow	78

[a] MW = microwave irradiation.

The synthesis of [BiPh(1-MMTZ)$_4$] (**1**) was achieved on treating $BiPh_3$ with four equivalents of 1-MMTZ(H) using both microwave irradiation (100 °C, 4 min) and conventional reflux using a solvent mixture of toluene and ethanol in a 2:1 ratio. Compound **1** was obtained in 51% yield by conventional reflux, while the use of microwave irradiation increased the yield marginally to 57%. The composition of the yellow product, and confirmation of the oxidation of Bi^{III} to Bi^{V}, was obtained through multinuclear NMR spectroscopy, mass spectrometry, FTIR spectroscopy and cyclic voltammetry.

Dissolution of **1** in DMSO and slow evaporation over several weeks resulted in a crop of bright yellow crystals suitable for X-ray diffraction studies. As found with the previously described complexes, [BiPh(4-MTT)$_4$] and [BiPh(2-MMI)$_4$], solid-state structure analysis of the crystals revealed the Bi^{V} complexes to have undergone slow hydrolysis and reduction in solution to give the Bi^{III} complex, [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (**2**), the structure of which is presented in Figure 3 (see later section on X-ray crystal structures). When the reaction is conducted in a 2:1 rather than 4:1 ratio of thione to $BiPh_3$, complex **1** is still obtained but in reduced yields of 30% using microwave irradiation and 23% by conventional reflux.

The dithiolato complexes, [BiPh(MMTZ)$_2$] (**5**), [BiPh(4-MTT)$_2$] (**6**) and [BiPh(2-MMI)$_2$] (**7**), were successfully synthesised using salt metathesis. Two equivalents of the appropriate sodium thiolate [NaSR] were reacted with one equivalent of $BiPhCl_2$ at 0 °C in dry methanol. Complexes **5**, **6** and **7** were isolated as yellow solids which after further washing with dry methanol gave analytically pure compounds in reasonable yields of 60, 69, and 77% respectively.

Reaction of $BiPh_3$ and 5-MMTD(H) in a toluene/ethanol (2:1) solvent mixture, either in a 1:2 or 1:4 ratio, and using either microwave irradiation (105 °C, 15 min) or conventional heating (16 h), always afforded [BiPh(5-MMTD)$_2$]$_\infty$ (**8**) as a bright yellow solid. For the 1:4 reactions, yields obtained were 85% through microwave irradiation and 72% by conventional reflux. As expected, the 1:2 reactions resulted overall in lower yields, but in a similar proportion; 73% with microwave irradiation and 66% by conventional reflux. Yellow crystals of **8** suitable for single X-ray diffraction studies were obtained on crystallising from DMSO.

Complex **8** was also synthesised through the treatment of $BiPhCl_2$ with two equivalents of [Na(5-MMTD)] in dry methanol in a 83% yield. While the yield is comparable with that of microwave synthesis the procedure is less efficient overall, though the salt metathesis route allows larger batch quantities to be synthesised.

The reaction of 2,5-DMTD(H)$_2$ with $BiPh_3$ in a toluene/ethanol (2:1) solvent mixture using microwave irradiation (112 °C, 4 min) results in the dithiolato complex [BiPh{2,5-DMTD(H)}$_2$]$_\infty$ (**9**) as an orange solid in 92% yield. Compound **9** was also synthesised under reflux in toluene/ethanol, though a maximum yield of 73% was obtained after 8 h. Single crystals of complex **9** grew over a period of a few weeks from DMSO.

The outcomes described here for 5-MMTD(H) and 2,5-DMTD(H)$_2$ are consistent with our previous observations[39] and those of Gilman and Yale,[46] that monophenylbismuth(III) thiolate complexes tend to be favoured in the thermodynamically driven protolysis reaction of thiols with $BiPh_3$. Thus, irrespective of the stoichiometries used, the reaction of $BiPh_3$ with 5-MMTD(H) or 2,5-DMTD(H)$_2$ always resulted in isolation of the monophenyl derivatives as the main product.

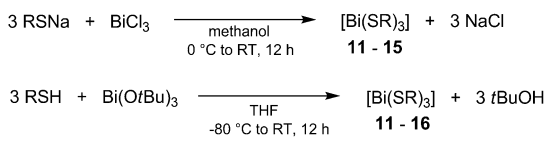
The reaction of 4-BrMTD(H) with $BiPh_3$ was problematic and the outcomes reminiscent of our previous results with 2-MMI(H).[39] Both standard reflux and microwave irradiation, in a solvent mixture of toluene and ethanol (2:1), result in a complex mixture which includes the trithiolato complex [Bi(4-BrMTD)$_3$] (39%) and the dithiolato complex [BiPh(4-BrMTD)$_2$] (13%). Attempts at a solvent-free reaction were also unsuccessful in producing a single product. In contrast, the salt metathesis route was simple and effective. Reacting two equivalents of [Na(4-BrMTD)] with one equivalent of $BiPhCl_2$ in dry methanol afforded [BiPh(4-BrMTD)$_2$] **10** as a yellow solid in 78% yield.

Tris-thiolato bismuth(III) complexes

In general, it is difficult to access trithiolato bismuth complexes [Bi(SR)$_3$] through the simple reaction of thiones (thiols) with $BiPh_3$. The thiones are generally not acidic enough. For this, the use of the stronger base Bi(O*t*Bu)$_3$ is cleaner and more effective, while the salt metathesis reaction is also effective but tends to furnish lower yields.

The trithiolato bismuth(III) complexes [Bi(1-MMTZ)$_3$] (**11**), [Bi(4-MMT)$_3$] (**12**), [Bi(2-MMI)$_3$] (**13**), [Bi(5-MMTD)$_3$] (**14**), [Bi(4-BrMTD)$_3$] (**15**) and [Bi{2,5-DMTD(H)}$_3$] (**16**) (Table 2) were all obtained by treating the appropriate thione with Bi(O*t*Bu)$_3$ (3:1) in dry THF at low temperature under inert atmosphere conditions (Scheme 2). The reaction outcomes are summarised in Table 2.

Complexes **11**–**16** are soluble in DMSO and DMF, and are partially soluble in acetone, ethanol and THF. All are insoluble in water. However, despite attempting a range of solvents, solvent mixtures, and multiple methods for recrystallisation, only complex **15** produced crystals suitable for X-ray diffraction studies.



Scheme 2. Two synthetic approaches used for the synthesis of homoleptic Bi^{III} thiolate complexes

IR spectroscopy

Heterocyclic organic compounds containing the thio-amide functional group afford four characteristic vibrational bands: ν(C–N) + δ(C–H), 1570–1390 cm^{-1}; δ(C–H) + ν(C–N) + ν(C=S), 1420–1260 cm^{-1}; ν(C–N) + ν(C=S), 1140–940 cm^{-1} and ν(C=S), 800–700 cm^{-1}. In all the parent N-heterocyclic compounds the presence of N–*H* absorption bands (absence of SH absorption bands) and the four characteristic thioamide bands in the IR spectra confirm the thione nature of the uncoordinated compounds in the solid state.

In the IR spectra of the bismuth complexes **1**–**10** the NH absorption bands for the parent thiones (3080 to 3250 cm^{-1}) are absent, supporting deprotonation and complexation to the bismuth centre. The exceptions are complexes **2** and **9** in which there remain neutral thione ligands and secondary N*H* bonds, respectively, in the thiolato ligands, as can be seen in the solid-state structures (Figures 3 and 6, in later section X-ray crystal structures). There is no evidence in the IR spectra of any S*H* bands. The presence of the phenyl group in **1**–**10** is also confirmed through the appearance of absorption bands in the range of 690–735 cm^{-1}, attributed to the C–H bending frequencies.

NMR studies

Solution NMR studies of the six N-heterocyclic compounds in [D$_6$]DMSO also reveal a structural preference for the more stable thione form.[47] On deprotonation and binding with bismuth the thione is transformed into the more stable thiolate anion resulting in a more thermodynamically stable Bi–S bond. This phenomenon is observed for all complexes **1**–**16**.

Integration of the proton signals in the ^{1}H NMR spectrum of complex **1** [BiPh(1-MMTZ)$_4$] reveals a ligand ratio of thiolate to phenyl of 4:1. This is similar to that described previously for the other two analogous Bi^V tetrathiolato complexes [BiPh(4-MTT)$_4$] and [BiPh(2-MMI)$_4$], where no proton resonances attributable to either N*H* or S*H* are observed. Unfortunately in the NMR spectrum of the thione, and of the reduced complex **2**,

Table 2. Comparison of reaction conditions and isolated yields for the trisubstituted bismuth(III) complexes **10**–**16**.>

	Bismuth source	Reaction conditions	Colour	Yield [%]
[Bi(1-MMTZ)$_3$] (**11**)	$BiCl_3$	MeOH,0 °C–RT, overnight stirring	yellow	63
	Bi(O*t*Bu)$_3$	THF,-80 °C–RT, 10 h	pale yellow	73
[Bi(4-MTT)$_3$] (**12**)	$BiCl_3$	MeOH,0 °C–RT, overnight stirring	orange	71
	Bi(O*t*Bu)$_3$	THF, −80 °C–RT, 7 h	orange	79
[Bi(2-MMI)$_3$] (**13**)	$BiCl_3$	MeOH, 0 °C–RT, overnight stirring	orange	71
	Bi(O*t*Bu)$_3$	THF, −80 °C–RT, 7 h	orange	86
[Bi(5-MMTD)$_3$] (**14**)	$BiCl_3$	MeOH, 0 °C–RT, overnight stirring	yellow	72
	Bi(O*t*Bu)$_3$	THF, −80 °C–RT, 9 h	pale yellow	81
[Bi(4-BrMTD)$_3$] (**15**)	$BiCl_3$	MeOH,0 °C–RT, overnight stirring	orange	71
	Bi(O*t*Bu)$_3$	THF, −80 °C–RT, 12 h	orange	68
[Bi{2,5-DMTD(H))$_3$] (**16**)	Bi(O*t*Bu)$_3$	THF, −80 °C–RT, 12 h	orange	78

the N*H* or S*H* resonances are also not visible making comparisons difficult.

In contrast to **1**, complexes **5**–**10** show a thiolate to phenyl integral ratio of 2:1, supporting a general formulation of $[BiPh(SR)_2]$. In all the monophenylbismuth thiolate complexes **1**–**10**, the phenyl proton signals lie in the range of 9.02-8.24 (*ortho*), 7.90-7.54 (*meta*) and 7.50-7.32 (*para*) ppm, which are all shifted to higher frequency relative to $BiPh_3$ (*ortho*, 7.76; *meta*, 7.38, and *para*, 7.31 ppm).

In complexes **7**, $[BiPh(2\text{-}MMI)_2]$, and **13**, $[Bi(2\text{-}MMI)_3]$, the C*H* signals for the imidazole ring appear at 6.71, 6.99 ppm and 6.79, 6.96 ppm respectively, a shift to higher frequency relative to the free thione, in which they resonate at 6.85 and 7.03 ppm. In addition, the resonances attributable to the CH_3 group shift to 3.44 and 3.40 ppm in complexes **7** and **13** respectively, compared with 3.42 ppm in the thione.

The singlet for the single C*H* proton on the thiazole ring in complexes **10** $[BiPh(4\text{-}BrMTD)_2]$, and **15** $[Bi(4\text{-}BrMTD)_3]$ also shift to higher frequency, 7.71 and 7.62 ppm respectively, relative to that in the thione, 7.40 ppm. In complex **12**, $[Bi(4\text{-}MTT)_3]$, the single triazole C*H* is found at 8.25 ppm and the CH_3 at 3.42 ppm, compared with 8.35 and 3.41 ppm in 4-MTT(H).

There is almost no difference between the comparative carbon resonances in the ^{13}C NMR spectra of complexes **1** and **2**. In complex **1**, which is Bi^V, the *ortho*-, *meta*- and *para*-C signals appear at 139.3, 132.9 and 127.7 ppm respectively, while in complex **2** they appear at 138.9, 132.9 and 127.4 ppm. The CH_3 signals are found at 33.5 (in **1**) and 33.2 (in **2**) ppm, which compares with 33.3 ppm in the neutral thione, 1-MMTZ(H).

In general, the signals attributable to the CH_3 groups are largely unaffected by the thione to thiolate transformation: the thiolate (neutral thione) resonances in complexes **1**, **2**, **5, 7** and **8** are observed at 33.5 (33.5), 33.2 (33.5), 33.4 (33.5), 33.5 (33.4) and 15.3 (15.8) ppm. This is also reflected in the trithiolato bismuth(III) complexes **11**, **12, 13** and **14** where the CH_3 signals appear at 33.7, 31.1, 33.4 and 15.7 ppm respectively. Full details of the multinuclear NMR spectra and chemical shifts assignments are given in Experimental Section.

Mass spectrometry

Confirmation of the change in the oxidation state of the bismuth centre from (III) to (V) in **1** is found in the ESI-MS^+ spectrum in which prominent signals are found at at *m/z* 826 (100%, $[BiPhL_4(DMSO)+H]^{+)}$, 812 (40%, $[BiPhL_4(CH_3OH)_2+H]^+$), 780 (60%, $[BiPhL_4(CH_3OH)+H]^{+)}$, 748 (32% $[BiPhL_4+H]^{+)}$, 653 (20% $[BiPhL_3(H_2O)+H]^+$), 613 (5%, $[BiPh(O)L_2(DMSO)+H]^+$), and 533 (12%, $[BiPh(O)L_2+H]^+$).

Complexes **5, 8** and **10** all display prominent peaks for the ions $[BiPhL_2+Na]^+$ at *m/z* = 540 (80%), 571 (30%) and 851 (100%), respectively. For complex **7** the ion $[BiPhL_2(DMSO)(H_2O)+H]^+$) is found at *m/z* 610 (80%), and for **9** $[BiPh(LH)_2(DMSO)_2(CH_3OH)_2+K]^+$) is seen at *m/z* 844 (100%).

The trithiolato bismuth(III) complexes **11** and **13**–**16** all show typical ions such as $[BiL_3+Na]^+$ (at *m/z* = 577 (20%) for **11**, 571 (28%) for **13** and 1045 (15%) for **15)** and $[BiL_3+H]^+$ (at *m/z* = 604 (19%) for **14**). The ESI-MS data for all the complexes is given in Experimental Section.

Electrochemistry

In our initial report on complexes $[BiPh(4\text{-}MTT)_4]$ and $[BiPh(4\text{-}MMI)_4]$ it was electrochemical studies that proved definitively that the bismuth centre was in the V oxidation state.[41] Similar studies were therefore conducted on complexes **1** and **2** to allow a comparison between the two complexes, and with the 4-MTT and 2-MMI complexes.

Generally, two steps are involved in the reduction of Bi^V compounds to elemental Bi^0 when the potential is scanned in the negative direction. In the first step Bi^V is reduced to Bi^{III}, involving a two-electron step process, and in the second step Bi^{III} reduced to elemental bismuth(0) in a three-electron step (Scheme 3).

$$Bi^V \xrightarrow{2e^-} Bi^{III} \xrightarrow{3e^-} Bi^0$$

Scheme 3. Two stage reduction of Bi^V to Bi^{III} and to bismuth metal.

While scanning the potential in the positive direction, elemental bismuth, Bi^0, deposited on the electrode surface can be stripped to give Bi^{III}. This assumption was analysed by the steady state voltammogram at a microelectrode for the reduction of complex **1** in dry DMSO under inert conditions (Figure 2a). Process A is the initial reduction step and is well defined. On scanning more negative potentials, process B is detected, which is a second more drawn out reduction process. The ratio of the limiting current for processes A and B is determined to be as 2:3. Thus, processes A and B are in excellent agreement with the $2e^-$ and $3e^-$ reduction processes depicted in Scheme 3.

While using a scan rate of 100 mVs^{-1} under transient conditions of cyclic voltammetry, in the forward scan (negative potential direction), two distinct peaks A and B along with a striping peak C on reverse scan (positive potential direction) were observed. The potential was switched after peaks A and B to establish the origin of stripping peak C. Process A at positive potentials on the reverse positive potential direction scan is still well defined (Figure 2b) and no bismuth metal is produced, as evidenced by the lack of a bismuth stripping ($Bi^0 \rightarrow Bi^{III}$) process. In contrast, the characteristic bismuth-stripping peak is now detected (process C) if the potential is switched at a value more negative than process B (Figure 2c). Furthermore, no elemental Bi^0 is detected on holding the potential at the values between the first and second process for 10 min. However, a black deposit can be seen visually on the glassy carbon electrode when the potential is held at a value slightly more negative than process B.

Voltammetry of complex **2**, tentatively assigned as a Bi^{III} compound, is very different to that described above for the Bi^V complex. This can be seen in Figure 2d. In this case, the initial process D is more drawn out than process A, but leads directly to detection of elemental bismuth (process C) when the potential is reversed. Thus, process D can be assigned to the single $3e^-$ reduction process for Bi^{III} to Bi^0. Thus, the electrochemical behaviour confirms complex **1** as a Bi^V species.

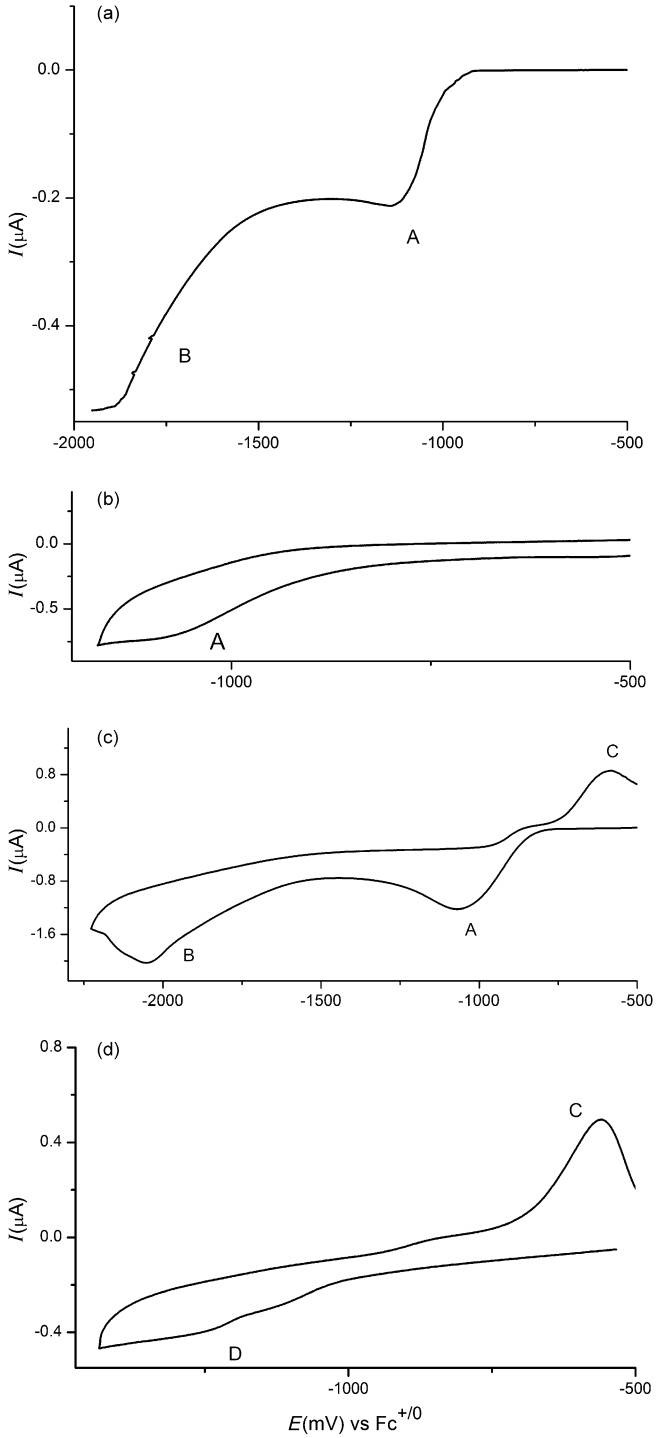


Figure 2. a) Steady state voltamogram at a carbon microelectrode for two-step reduction of Bi^{V} in $[BiPh(1\text{-}MMTZ)_4]$ **1** to Bi^{0} using scan rate (100 mV s^{-1}); b)–d) cyclic voltammetry at a glassy carbon electrode using scan rate (100 mV s^{-1}); b) potential switched after process A for complex **1**; c) potential switched after process B for complex **1**; d) potential switched after process D giving rise to reduction of Bi^{III} in $[BiPh(1\text{-}MMTZ)_2\{1\text{-}MMTZ(H)\}_2]$, **2** to Bi^{0}.

X-ray structural studies

Four complexes were successfully characterised by single-crystal X-ray diffraction. A summary of the crystallographic data for all four complexes **2**, **8**, **9** and **15** is provided in Table 3.

Complex **2** is essentially isostructural to our previously reported Bi^{III} complexes $[BiPh(4\text{-}MMT)_2\{4\text{-}MMT(H)\}_2]$ (**3**) and $[BiPh(2\text{-}MMI)_2\{2\text{-}MMI(H)\}_2]$ (**4**).[41] Adopting a distorted square-pyramidal geometry, the centrally located Bi^{III} atom in **2** is coordinated to one phenyl, two 1-MMTZ and two 1-MMTZ(H) ligands giving an overall coordination number of five to the Bi^{III} atom (Figure 3). Similar to **3** and **4**, the two hydrogen atoms

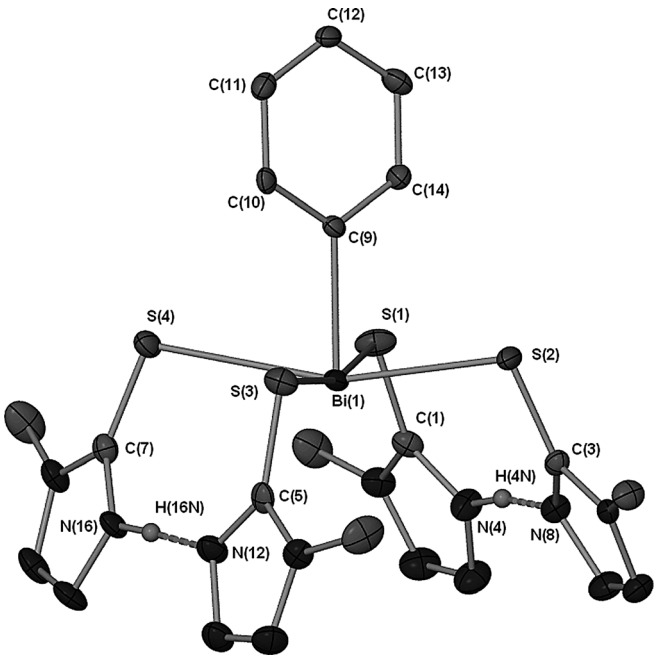


Figure 3. Molecular structure of $[BiPh(1\text{-}MMTZ)_2\{1\text{-}MMTZ(H)\}_2]$ (**2**) with thermal ellipsoids shown at 50% probability. Only one of two independent molecules is shown. Hydrogen atoms (except NH ones) have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)-C(9), 2.258(3); Bi(1)–S(1), 2.9173(12); Bi(1)–S(2), 2.7123(10); Bi(1)–S(3), 2.7355(11); Bi(1)–S(4), 2.9476(10); N(8)–H(4N), 1.08(2); N(12)–H(16N), 1.85(2); Bi(1)-S(1)-C(1), 104.38(15; Bi(1)-S(2)-C(3), 102.04(14); Bi(1)-S(3)-C(5), 95.93(14); Bi(1)-S(4)-C(7), 103.49(14); C(9)-Bi(1)-S(1), 81.14(10); C(9)-Bi(1)-S(2), 83.29(9); C(9)-Bi(1)-S(3), 88.38(10); C(9)-Bi(1)-S(4), 79.48(9); S(1)-Bi(1)-S(2), 96.28(4); S(1)-Bi(1)-S(3), 168.22(3); S(1)-Bi(1)-S(4), 82.89(3); S(2)-Bi(1)-S(3), 87.79(4); S(2)-Bi(1)-S(4), 162.68(3); S(3)-Bi(1)-S(4), 89.93(3).

H(4N) and H(16N) located on the 1-MMTZ(H) ligands in **2** make hydrogen-bond contacts to the acceptor 1-MMTZ ligands (N(4)–H(4H), 1.80(2); N16–H(16N), 1.85(2) Å) lying almost coplanar to each other, twisted by 12.04(24)° and 6.97(25)°, for the D···A (donor–acceptor) bonds N(4)–H(4N)···N(8) and N(16)–H(16N)···N(12), respectively.

The Bi–S bond lengths in **2** show distinguishable covalent (Bi(1)–S(2), 2.7123(10); Bi(1)–S(3), 2.7355(11) Å) and dative (coordinative) (Bi(1)–S(1), 2.9173(12); Bi(1)–S(4), 2.9476(10) Å) bonding modes which differs from complexes **3** and **4** in which an average Bi–S bond length of about 2.80 Å was ob-

Table 3. Summary of crystallographic data for complexes **2**, **8**, **9** and **15**.

	2	**8**	**9**	**15**
formula	$C_{24}H_{22}Bi_2N_8S_8$	$C_{13}H_{13}BiN_4OS_6$	$C_{14}H_{19}BiN_{16}S_4$	$C_{27}H_{15}BiBr_3N_3S_6$
M_r	1096.4	642.61	748.67	1022.49
crystal system	monoclinic	monoclinic	triclinic	triclinic
a [Å]	11.2611(3)	10.420(3)	11.8411(7)	10.262(2)
b [Å]	15.0043(5)	10.781(4)	12.4586(5)	12.642(3)
c [Å]	19.4828(6)	17.833(8)	20.2080(10)	13.497(3)
α [°]	90.00	90.00	89.050(4)	69.50(3)
β [°]	93.387(3)	91.849(7)	83.516(4)	85.78(3)
γ [°]	90.00	90.00	63.576(5)	68.71(3)
V [Å^3]	3826.16(17)	2002.3(13)	2650.7(2)	1525.2(5)
T [K]	123(2)	173 (2)	173(2)	173(2)
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
Z	4	4	4	2
reflns measured	33989	38549	28435	32758
independent reflns	10546	3434	16815	8639
R_{int}	0.0450	0.0994	0.0363	0.0467
final R_1 values [$I > 2\sigma(I)$]	0.0375	0.0290	0.0654	0.1211
final $wR(F^2)$ values [$I > 2\sigma(I)$]	0.0554	0.0691	0.0596	0.0564
final R_1 values (all data)	0.0594	0.0295	0.0742	0.1364
final $wR(F^2)$ values (all data)	0.0633	0.0695	0.1566	0.1800

served. Complex **2** has significantly different Bi-S-C angles; three obtuse angles (104.38(15), 102.04(14) and 103.49(14)°) lying close to the expected bond angle of around 109° seen in other similar Bi-S-C bonded complexes;[48] while one is more acute in nature (95.93(14)°) lying close to the Bi-S-C angles found in both complexes **3** and **4** (Bi-S-C average 93.50°). On searching the literature and the Cambridge Crystallographic Database (CCDB), **2** can best be compared to the recently reported Bi^{III} tetrazole complex $[(o,o\text{-}C_6H_3(CH_2NMe_2)_2Bi(SAr)_2]$[40] (in which Ar = 1-phenyltetrazol-5-yl) which contains slightly elongated Bi–S covalent bonds (Bi(1)–S(1), 2.796(2); Bi(1)-S(2), 2.784(2) Å), compared to complex **2**, due to additional intermolecular N donor coordination.

The asymmetric unit of complex **8** is shown in Figure 4 and reveals a dimeric system in which two $[BiPh(5\text{-}MMTD)_2]$ units combine through relatively short intermolecular Bi–N bonds. Each Bi^{III} centre adopts a distorted pentagonal bipyramidal geometry composed of two deprotonated thiadiazole ligands and one phenyl group. The thiadiazole ligands chelate to the Bi^{III} centres by means of short Bi–S bonds (average 2.64 Å), while the Bi–N bonds form an asymmetric coordination with one short (Bi(1)–N(1), 2.865(3); Bi(2)–N(8), 2.882(4) Å) and one long bond (Bi(1)–N(3), 2.959(4); Bi(2)–N(5), 3.059(4) Å), highlighting the thiophilicity of the Bi^{III} centres. Dimerisation of this unit raises the coordination number of the two Bi^{III} centres to six through the formation of longer dative Bi–N bonds (Bi(1)–N(7), 3.087(3); Bi(2)–N(4), 3.044(3) Å) to form an almost planar (±0.11 Å) central six-atom Bi_2N_4 ring. Finally the dimer polymerises through a series of long electrostatic interactions; Bi(2) interacts with the delocalised electron density around the diazole moiety, centered on N(7) (Bi(2)–N(7)′, 3.551(4); Bi(2)–N(8)′, 3.640(4); Bi(2)–C(17)′, 3.614(5) Å), while Bi(1) connects with S(3)′ (3.865(14) Å) and S(5)′ (3.8160(12) Å) to form a final zigzag polymeric chain (Figure 5).

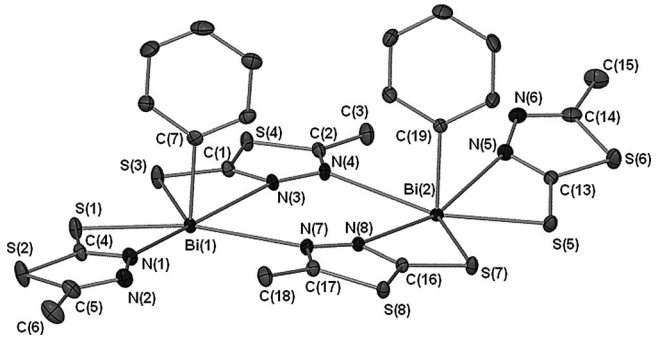


Figure 4. Molecular structure of $[Bi_2(5\text{-}MMTD)_4]_\infty$ (**8**) with thermal ellipsoids shown at 50% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)–C(7), 2.260(5); Bi(1)–S(1), 2.6520(11); Bi(1)–S(3), 2.6323(11); Bi(1)–N(7), 3.087(3); Bi(1)–N(1), 2.865(3); Bi(1)–N(3), 2.959(4); Bi(2)–C(19), 2.239(5); Bi(2)–S(5), 2.6571(11), Bi(2)–S(7), 2.6181(11); Bi(2)–N(5), 3.059(4); Bi(2)–N(8), 2.882(4); S(3)-Bi(1)-S(1), 76.69(4); C(7)-Bi(1)-S(1), 92.82(12); C(7)-Bi(1)-S(3), 91.36(11); C(7)-Bi(1)-N(7), 83.76(13); S(3)-Bi(1)-N(3), 56.92(7); S(1)-Bi(1)-N(1), 57.73(7); N(1)-Bi(1)-N(3), 166.25(10); S(5)-Bi(2)-S(7), 76.66(3); C(19)-Bi(2)-S(5), 95.08(110); C(19)-Bi(2)-S(7), 93.82(10); S(5)-Bi(2)-N(5), 55.29(7); S(7)-Bi(2)-N(8), 57.87(7); N(5)-Bi(2)-N(8), 164.91(10).

Switching to 1,3,4-thiadiazole-2-dithiol 2,5-$DMTD(H)_2$, crystallisation from acetone solution reveals formation of the deprotonated complex **9** (Figure 6). Polymeric **9** contains a C2 axis along C(4), C(1) and Bi(1) adopting an overall distorted square-pyramidal geometry reminiscent of the Bi^{III} thiolate complexes **3** and **4** recently reported by our research group.[41]

In the asymmetric unit (Figure 6) the Bi^{III} atom is three coordinate, bonded to two dithiolate ligands, through short Bi–S bonds (Bi(1)–S(1), 2.8690(14); Bi(1)–S(4), 2.7284(14) Å), and one phenyl group (Bi(1)–C(1), 2.239(5) Å). The two monodeprotonated 2,5-DMTD(H) ligands have hydrogen atoms located on N(2) and N(4), which were located by residual density in the

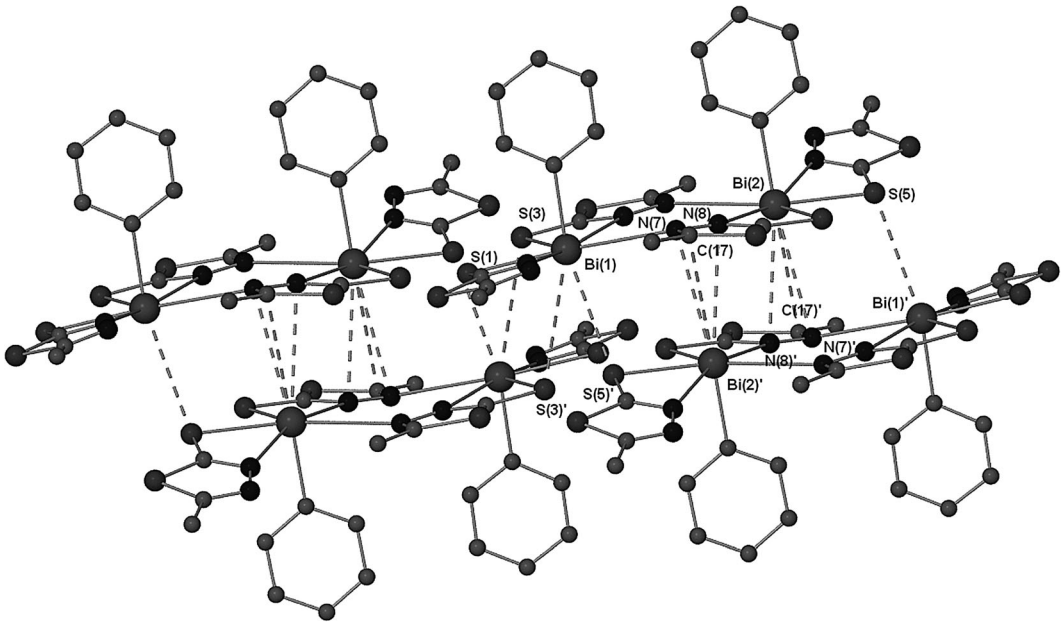


Figure 5. Extended zigzag chain arrangement of **8** with selected atom labelling. Hydrogen atoms have been omitted for clarity. Symmetry operator ′: 1−*x*, 1−*y*, −*z*. Selected bond lengths (Å): Bi(1)–S(3)′ 3.865(14); Bi(1)–S(5)′, 3.8160(12); Bi(2)–N(7)′, 3.551(4); Bi(2)–N(8)′, 3.640(4); Bi(2)–C(17)′, 3.614(5).

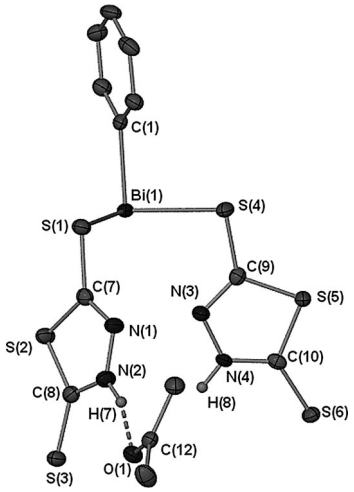


Figure 6. Asymmetric unit of [BiPh{2,5-DMTD(H)}-κ-S(Me_2C=O)]$_\infty$ (**9**) with thermal ellipsoids shown at 50% probability. Hydrogen atoms (except NH) have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)–S(1), 2.6890(14), Bi(1)–S(4), 2.7284(14); Bi(1)–C(1), 2.239(5); H(7)–O(1), 1.91(3); C(1)-Bi(1)-S(1), 88.01(13); C(1)-Bi(1)-S(4), 88.17(13); Bi(1)-S(1)-C(7), 98.10(17); Bi(1)-S(4)-C(9), 93.34(17).

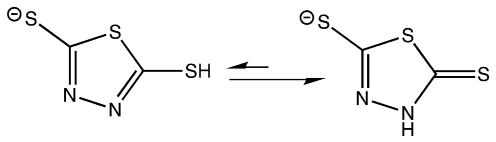


Figure 7. Thiol–thione tautomerisation of the monoanionic 2,5-DMTD(H) ligand.

electron difference maps and placed in calculated positions. This suggests a 1,2 hydride shift of the deprotonated ligand to form the thione complex (Figure 7) once monodeprotonated by Bi^{III}. The long (S(1)–C(7), 1.732(5); S(4)–C(9); 1.729(5) Å) and short (S(3)–C(8), 1.679(5); S(6)–C(10), 1.683(5) Å) S–C bond lengths in **2** support the tautomerisation to the thione form once deprotonated.

Unlike in complexes **3** and **4**, in which hydrogen bonding aligns the triazole–thione and imidazole–thione ligands to be almost co-planar with each other,[41] in **9** the 2,5-DMTD(H) rings systems are orthogonal, twisted by 56.56(13)° with the H(7) atom preferring to hydrogen bond to a molecule of acetone (H(7)–O(1), 1.91(3) Å) rather than its neighbouring ligand.

The complex then extends into a polymeric zigzag chain (Figure 8) through the second thiol (thione) group of the 2,5-DMTD(H) ligand making the overall coordination number of the central Bi^{III} atom five. The Bi–S bonds that propagate the polymeric chain (Bi(1)′–S(3), 3.0407(15); Bi(1)′–S(6), 2.9146(15) Å) are significantly longer than those in the asymmetric unit being more indicative of a coordinative dative Bi–S bond length (approximately 3.0 Å)[49] supporting the presence of the thione form of the ligand.

Finally the only trisubstituted bismuth(III) complex amenable to X-ray diffraction studies was **15**, which gave orange crystals from DMSO. The asymmetric unit, seen in Figure 9, is composed of three chelating 4-BrMTD ligands bonded covalently to the Bi^{III} atom through the deprotonated thiol group and datively through the N atom in the thiazole ring. The Bi–S bonds (Bi(1)–S(1), 2.5930(18); Bi(1)–S(3), 2.6041(16); Bi(1)–S(5), 2.6133(13) Å) lie in the typical covalent bond range Σ_{cov}(Bi, S) = 2.54,[50] while the intramolecular coordinative (dative) Bi–N bonds show three significantly different lengths; short (Bi(1)–N(3), 2.776(4) Å), medium (Bi(1)–N(1), 2.828(4) Å) and long (Bi(1)–N(2), 3.028(5) Å). The asymmetric unit has a six-coordinate Bi^{III} centre, which owing to the small bite angles of the

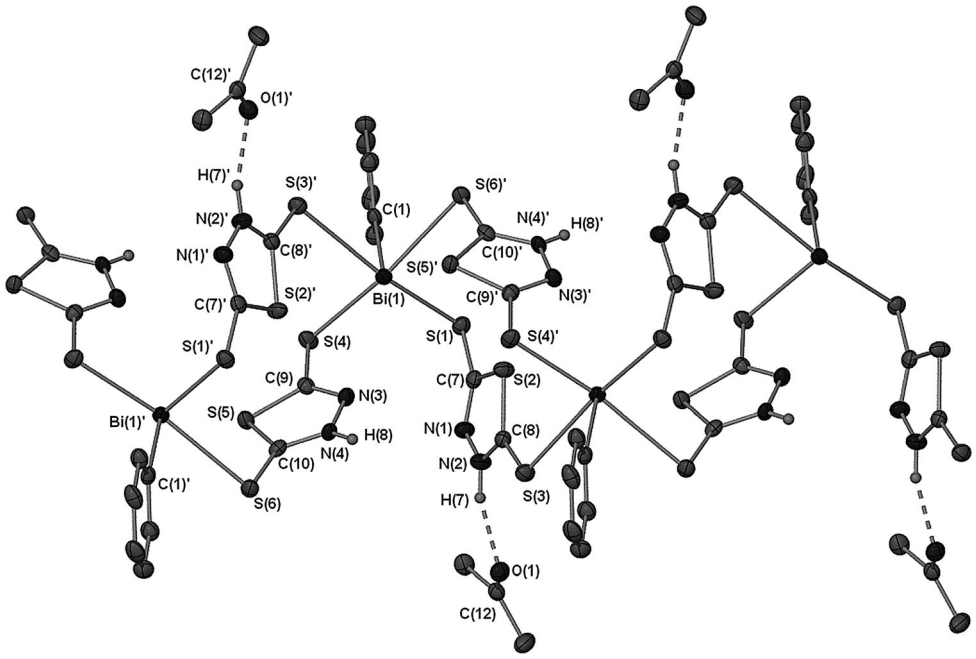


Figure 8. Extended zigzag chain arrangement of [BiPh{2,5-DMTD(H)}-κ-S(Me_2C=O)]$_\infty$ (**9**). Symmetry operator ′: $-x$, $^1/_2+y$, $^1/_2-z$. Additional selected bond lengths (Å) and angles (°): Bi(1)–S(3)′, 3.0407(15); Bi(1)–S(6)′ 2.9146(15); C(1)-Bi(1)-S(3)′, 82.69(13); C(1)-Bi(1)-S(6)′, 81.61(13); Bi(1)-S(3)′-C(8)′, 106.77(18); Bi(1)-S(6)′-C(10)′, 95.72(17).

common hexagonal geometry. However, dimerisation of two monomeric units through a long electrostatic interaction with the deprotonated thiol group (Bi(1)–S(5)′, 3.2208(18) Å; Figure 10), increases the coordination of the Bi^{III} centre to seven, giving an overall distorted pentagonal pyramidal coordination geometry and formation of a central planar four-membered Bi_2S_2 ring.

Complex **10** can best be compared to the recently reported Bi^{III} methylthiazole complex [(*o*,*o*-$C_6H_3(CH_2NMe_2)_2Bi(SAr)_2$][40] (in which Ar = 4-methylthiazol), which has a significantly longer Bi–S bond length of 2.8017(11) Å compared to complex **10** (average Bi–S bong length = 2.6034 Å) due to internal coordination of two N donor arms on the ligand.

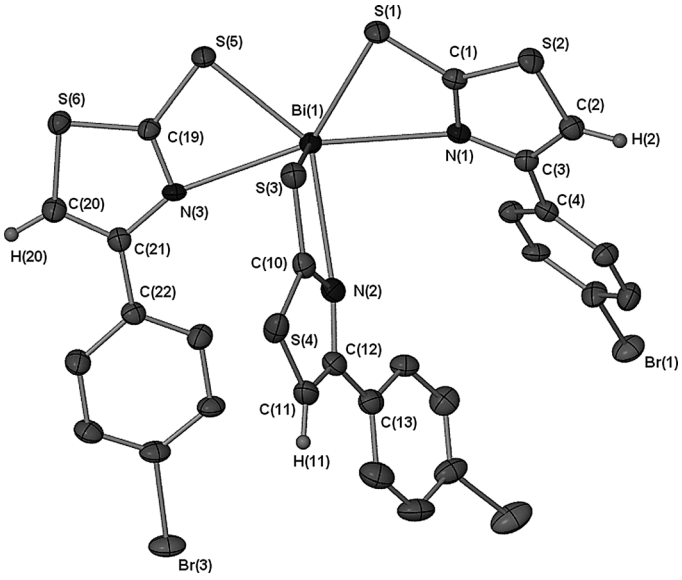


Figure 9. Asymmetric unit of [Bi(4-BrMTD)$_3$]$_2$ (**15**) with thermal ellipsoids shown at 50% probability. Hydrogen atoms (except C–H ones) have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)–S(1), 2.5930(18); Bi(1)–S(3), 2.6041(16); Bi(1)–S(5), 2.6133(13); Bi(1)–N(1), 2.828(4); Bi(1)–N(2), 3.028(5); Bi(1)–N(3), 2.776(4); S(1)-Bi(1)-N(1), 59.12(9); S(1)-Bi(1)-N(2), 124.24(9); S(1)-Bi(1)-S(3), 86.54(5); S(1)-Bi(1)-N(3), 140.35(9); S(1)-Bi(1)-S(5), 81.14(5); N(1)-Bi(1)-N(2), 87.05(13); N(1)-Bi(1)-S(3), 102.26(10); N(1)-Bi(1)-N(3), 159.90(11); N(1)-Bi(1)-S(5), 137.46(10); N(2)-Bi(1)-S(3), 56.77(9); N(2)-Bi(1)-N(3), 82.64(12); N(2)-Bi(1)-S(5), 131.24(9); S(3)-Bi(1)-N(3), 86.44(10); S(3)-Bi(1)-S(5), 88.83(5); N(3)-Bi(1)-S(5), 59.74(9).

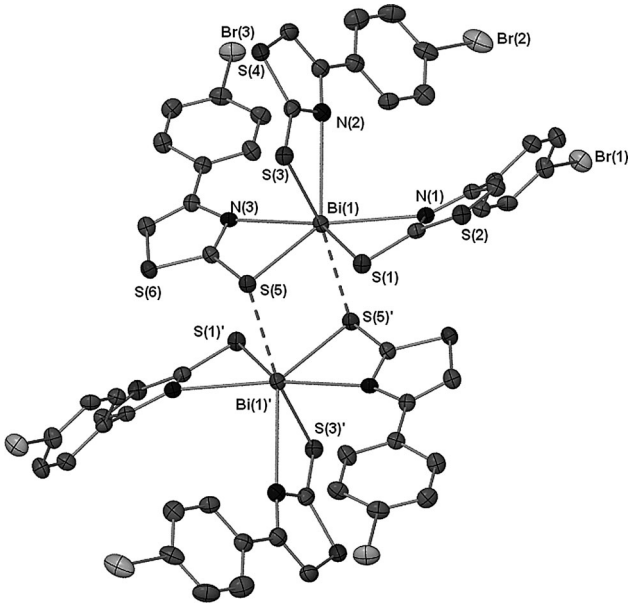


Figure 10. Dimer formation for [Bi(4-BrMTD)$_3$]$_2$ (**15**). Symmetry operator ′: $-x$, $1-y$, $1-z$. Bi(1)–S(5)′ bond length 3.2206(18).

chelating N and S atoms of the 4-(4-bromophenyl)thiazole-2-thiol ligand (S-Bi-N: 59.74(9), 59.12(9) and 56.77(9)°) has no

Anti-bacterial activity

The in vitro antibacterial activity of all the homo- and heteroleptic bismuth(III) compounds, including the previously described complexes [BiPh(4-MTT)$_2${4-MTT(H)}$_2$], [BiPh(2-MMI)$_2${2-MMI(H)}$_2$] and [BiPh(4-MTT)$_2$], was assessed against six different strains of bacteria; *M. smegmatis, S. aureus,* MRSA, VRE*, E. coli and E. faecalis*. For comparison the activity of the five heterocy-

clic thiols and $BiPh_3$ was also assessed. The solvent used for the preparation of sample solution of required concentration was DMSO. Isoniazid (isonicotinohydrazide), a first-line drug for the treatment of tuberculosis, was used as a control.

The in vitro activity of the bismuth(III) thiolate complexes, free thiols (thiones), and Isoniazid were initially compared using drug-diffusion assays in which filter-paper discs containing the drug were placed onto the surface of agar plates spread with the bacterial culture. Following incubation overnight, the presence of a zone of inhibition of bacterial growth around the disc indicated some level of antibacterial activity. Compounds that were positive in this initial screen were then used in minimum inhibitory concentration (MIC) assays to quantify their level of antibacterial activity. The MICs are expressed as $\mu g\,mL^{-1}$ (and calculated as μM), as the minimal concentration of the drug that still completely inhibited bacterial growth in culture. The results are summarised in Table 4. The activities of the compounds against each individual bacterium are provided as Supplementary Information.

General observations

The experiments show that the thiones (thiols) and $BiPh_3$ are relatively poor anti-microbial agents and displayed no bactericidal activity at the maximum concentration measured ($100\ \mu g\,mL^{-1}$). The comparison, shown in Table 4, of the inhibitory activities of the various bismuth(III) thiolate complexes demonstrates some marked differences based on ligand type and substitution pattern, with the monophenylbismuth(III) complexes being generally more potent than the trithiolatobismuth(III) complexes. Thus, replacement of two Ph ligands on $BiPh_3$ by two thiolate ligands has a profound effect on the bactericidal activity. This enhancement of biological activity following ligand substitution has also been demonstrated for phenylbismuth sulfonates[51] and thioamides,[38] reflecting the observed low toxicity of $BiPh_3$.

The five coordinate dithiolato dithione complexes [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] and [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] complexes show by far the greatest activities against all bacteria tested with MIC values as low as $0.25\ \mu g\,mL^{-1}$ ($0.34\ \mu M$) for [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] against VRE and of $1.0\ \mu g\,mL^{-1}$ ($1.33\ \mu M$) for [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] against *M. smegmatis* and *S. aureus*. The simple structural feature, extrapolated from the solid-state X-ray study, which may explain this is that these five-coordinate complexes are all monomeric, whereas the others are either oligomers or polymers. Of key importance is that fact that these complexes, with such a specific composition and structure, are only accessible thus far through reduction of the Bi^V tetrathiolato complexes, for example, [BiPh(1-MMTZ)$_4$].[40]

That the dithiolato complexes are in general more active than their trithiolato counterparts appears to support the assertion of Kotani[52] that lipophilicity of bismuth complexes is of key importance in their antibacterial action. The *clogP* values (see Supporting Information) for the dithiolato complexes are mostly, but not in every case, higher (range 0.79 for **2** to 7.67 for **8**) than the related trithiolato complexes (range −1.5 for **10** to 8.82 for **11**). The most active monomeric dithiolato dithione complexes have the largest *clogP* values for their family of complexes containing a particular ligand; 2.12 for [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] (cf. 0.79 for [BiPh(4-MTT)$_2$]), 6.31 for [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (cf. 2.93 for [BiPh(2-MMI)$_2$]) and 3.89 for BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (cf. 2.54 for [BiPh(1-MMTZ)$_2$]). That *clogP* values may also be a poor predictor of in-

Table 4. Anti-bacterial activities of monophenylbismuth(III) thiolate complexes and trithiolato bismuth(III) complexes, free thiols and Isoniazid against *M. smegmatis*, *S. aureus*, MRSA, VRE, *E. faecalis and E. coli.*

	MIC [$\mu g\,mL^{-1}$] ([μM])					
	M. smegmatis	*S. aureus*	MRSA	VRE	*E. faecalis*	*E. coli*
isoniazid	1 (7.29)	100 (729.18)	100 (729.19)	100 (729.19)	100 (729.19)	100 (729.19)
4-MTT(H)			>100			
2-MMI(H)			>100			
1-MMTZ(H)			>100			
5-MMTD(H)			>100			
2,5-DMTD(H)$_2$			>100			
BrMBT(H)			>100			
[BiPh(4-MTT)$_2${4-MTT(H)}$_2$]	0.5 (0.67)	2.5 (3.4)	5.0 (0.67)	0.25 (0.34)	5.0 (6.70)	10 (13.40)
[BiPh(2-MMI)$_2${2-MMI(H)}$_2$]	10 (13.50)	100 (134.50)	100 (134.50)	100 (134.50)	10 (13.50)	100 (134.50)
[BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] (**2**)	1.0 (1.33)	1.0 (1.33)	2.5 (3.34)	2.5 (3.34)	2.0 (2.67)	10 (10.33)
[BiPh(1-MMTZ)$_2$] (**5**)	2.5 (4.84)	5.0 (9.68)	5.0 (9.68)	2.5 (4.84)	2.5 (4.84)	10 (19.36)
[BiPh(4-MTT)$_2$] (**6**)	10 (19.44)	5.0 (9.72)	5.0 (9.72)	10 (19.44)	5.0 (9.72)	10 (19.44)
[BiPh(2-MMI)$_2$] (**7**)	10 (19.51)	100 (190.51)	100 (190.51)	100 (190.51)	5.0 (19.51)	100 (190.51)
[BiPh(5-MMTD)$_2]_\infty$ (**8**)	2.5 (4.56)	10 (18.23)	100 (180.23)	100 (180.23	1.5 (2.73)	20 (36.46)
[BiPh{2,5-DMTD(H)}$_2]_\infty$ (**9**)	20 (34.21)	100 (171.07)	100 (171.07)	100 (171.07)	100 (171.07)	100 (171.07)
[BiPh(4-BrMTD)$_2$] (**10**)	20 (24.25)	1.0 (1.21)	5.0 (6.06)	5.0 (6.06)	20 (24.25)	40 48.52
[Bi(1-MMTZ)$_3$] (**11**)	5.0 (9.01)	100 (180.37)	100 (180.37)	100 (180.37)	40 (72.15)	100 (180.37)
[Bi(4-MTT)$_3$] (**12**)	5.0 (9.07)	10 (18.13)	100 (180.13)	100 (180.13)	10 (18.13)	100 (180.13)
[Bi(2-MMI)$_3$] (**13**)	20 (36.47)	100 (182.33)	100 (182.33)	100 (182.33)	100 (182.33)	100 (182.33)
[Bi(5-MMTD)$_3$] (**14**)	100 (165.56)	40 (66.23)	40 (66.23)	40 (66.23)	100 (165.56)	100 (165.56)
[Bi(4-BrMTD)$_3$] (**15**)	40 (39.14)	10 (9.78)	100 (90.78)	40 (39.14)	40 (39.14)	40 (39.14)
[Bi{2,5-DMTD(H)}$_3$] (**16**)	100 (152.44)	40 (60.98)	40 (60.98)	40 (60.98)	100 (152.44)	100 (152.44)

hibitory activity is seen in those complexes containing the 2-MMI ligand, which apart from *M. smegmatis* provide the lowest activities of all complexes across all other bacteria studied.

The bismuth complexes demonstrate a better range of antimicrobial activities against the gram positive bacteria than against the single gram negative bacterium tested (*E. coli*). This observation again supports earlier studies by Kotani[52] and Domenico[53] on cyclic organobismuth(III) compounds and bismuth(III) thiol chelators respectively. Gram-negative bacteria possess a double membrane that forms a permeability barrier restricting the penetration of some antimicrobial agents and not allowing the multi-drug resistance pumps to extrude toxins across this barrier.[54] Difficulty in permeating the outer membrane has been touted as the reason for the low activity of bismuth(III) thiolates against *E. coli*.[8]

M. smegmatis, a relatively fast-growing and non-pathogenic mycobacterium, is frequently used as a model for *M. tuberculosis*.[55] The best performing complexes, with exceptional activities of $\leq 5.0\ \mu g\,mL^{-1}$, are those based on the triazole 4-MTT ligand; $[BiPh(4\text{-}MTT)_2\{4\text{-}MTT(H)\}_2]$ $0.5\ \mu g\,mL^{-1}$ (0.67 μM), $[Bi(4\text{-}MTT)_3]$ $5.0\ \mu g\,mL^{-1}$ (9.07 μM), and on the tetrazole 1-MMTZ ligand; $[BiPh(1\text{-}MMTZ)_2\{1\text{-}MMTZ(H)\}_2]$ $1.0\ \mu g\,mL^{-1}$ (1.33 μM), $[BiPh(1\text{-}MMTZ)_2]$ $1.0\ \mu g\,mL^{-1}$ (4.84 μM) and $[Bi(1\text{-}MMTZ)_3]$ $5.0\ \mu g\,mL^{-1}$ (9.01 μM).

In fact, this pattern is carried through into the level of activities observed against the other bacteria; *S. aureus,* MRSA, VRE, *E. faecalis and E. coli*. The monophenylbismuth(III) dithiolate derivatives, and in particular the monomeric dithione-containing complexes of the 1-MMTZ and 4-MTT ligands, invariably provide the lowest MIC values. With the sole exception of an MIC of $10\ \mu g\,mL^{-1}$ for $[BiPh(4\text{-}MTT)_2]$ against VRE, the MIC values are all $\leq 5.0\ \mu g\,mL^{-1}$. Outside of these tetrazole and triazole based ligands the best inhibitory activity is observed with the monophenyl complex $[BiP(4\text{-}BrMTD)_2]$, which contains the anionic thiazole-based ligand 4-BrMTD; MIC $1.0\ \mu g\,mL^{-1}$ (1.21 μM) for *S. aureus*, and $5.0\ \mu g\,mL^{-1}$ (6.06 μM) for MRSA and VRE. It is less active against *E. faecalis* ($20.0\ \mu g\,mL^{-1}$) and *E. coli* ($40\ \mu g\,mL^{-1}$). For comparison, observed MIC values for vancomycin towards MRSA are in the range 1–2 $\mu g\,mL^{-1}$.[56]

The trithiolato bismuth(III), $[Bi(SR)_3]$, complexes rarely gave MIC values below $40\ \mu g\,mL^{-1}$ and regularly showed inhibitory concentrations of $100\ \mu g\,mL^{-1}$. Again, the exceptions were for 4-MTT and 1-MMTZ complexes against *M. smegmatis* with MIC values of $5.0\ \mu g\,mL^{-1}$ (9.07 and 9.01 μM, respectively), and for 4-MTT and 4-BrMTD complexes against *S. aureus* with MIC values of $10\ \mu g\,mL^{-1}$ (18.13 and 9.78 μM, respectively).

Cytotoxicity studies towards mammalian cells (COS-7)

Although a strong anti-bacterial activity is essential for potential new therapeutic agents, the compound must have low toxicity towards human or animal cells. Toxicity assays of these complexes performed against cultured COS-7 cell lines revealed that the complexes were largely non-toxic to mammalian cells at $20\ \mu g\,mL^{-1}$ providing a good therapeutic index relative to the best performing bismuth(III) complexes. The single exception was $[BiPh(4\text{-}MTT)_2]$, which killed 25% of cells at $10\ \mu g\,mL^{-1}$. The activity of the bismuth(III) complexes against a range of bacteria, including drug resistant strains, combined with their low host cell toxicity strongly suggests that they are worthy of further investigation and development as antimicrobial agents. This is particularly significant given the continuing appearance of drug resistance in bacteria of medical importance.

Conclusion

Heteroleptic monophenylbismuth thiolato complexes derived from N-heterocyclic thiones (thiols) have been prepared through either protolysis with $BiPh_3$ or more efficiently using salt metathesis with $BiPhCl_2$ and the sodium thiolates. The rare Bi^V complex, $[BiPh(1\text{-}MMTZ)_4]$, is formed with 1-methyl-1*H*-tetrazole-5-thiol, being only the third example of a bismuth(V) thiolato complex, and follows similar recent results with 4-methyl-4*H*-1,2,4-triazole-3-thiole, 4-MTT(H), and 1-methyl-1*H*-imidazole-2-thiol, 2-MMI(H). This complex undergoes slow hydrolytic reduction in DMSO to give the Bi^{III} complex $[BiPh(1\text{-}MMTZ)_2\{(1\text{-}MMTZ(H)\}_2]$. Almost all other thiones studied on treatment with $BiPh_3$ produce the Bi^{III} thiolato complexes $[BiPh(SR)_2]$, irrespective of the stoichiometries used. The exception is 4-(4-bromophenyl)thiazole-2-thiol, which always gave a mixture of substituted products. Using microwave heating over standard reflux conditions delivers overall better yields in a fraction of the time. In contrast, the salt metathesis route gives access to all the monophenylbismuth(III) thiolato derivatives of all the thiones efficiently and in good yield. Crystals of three complexes were obtained; $[BiPh(1\text{-}MMTZ)_2\{1\text{-}MMTZ(H)\}_2]$ and $[BiPh(5\text{-}MMTD)_2]$ from DMSO and $[BiPh\{2,5\text{-}DMTD(H)\}_2\text{-}(Me_2C{=}O)]$ from acetone, allowing their solid-state structures to be determined by single-crystal X-ray diffraction. $[BiPh(1\text{-}MMTZ)_2\{1\text{-}MMTZ(H)\}_2]$ derives from the Bi^V parent complex and retains a distorted square pyramidal geometry with close hydrogen-bonding between the ligands. $[BiPh(5\text{-}MMTD)_2]_\infty$ adopts distorted pentagonal bipyramidal geometry at the Bi^{III} centre as it extends out into a polymer through long intramolecular Bi–N and Bi–S bonds. Intramolecular Bi–S bonds also establish a distorted square pyramidal geometry at the Bi^{III} centre in polymeric $[BiPh\{2,5\text{-}DMTD(H)\}_2(Me_2C{=}O)]_\infty$. The acetone molecules engage in hydrogen-bonding with the ligands rather than with the metal centres.

The homoleptic trithiolato Bi^{III}, $[Bi(SR)_3]$, complexes are not accessible through reaction with $BiPh_3$. Instead a good yields and clean products from the thiones are obtained using a salt metathesis route with $BiCl_3$ and an acid-base route with $Bi(OtBu)_3$. The only exception was to this was complex **16** $[Bi\{2,5\text{-}DMTD(H)\}_3]$, which could only be obtained with high purity through the reaction with $Bi(OtBu)_3$. In general better yields are obtained using the butoxide rather than the chloride. Crystals of $[\{Bi(4\text{-}BrMTD)_3\}_2]$ were obtained from DMSO, providing a rare solid-state structure of a homoleptic bismuth(III) thiolate. All three ligands chelate to the Bi^{III} centre and with a longer intramolecular Bi–S bond included the metal attains a coordination number of seven with a distorted pentagonal pyramidal geometry. Overall the synthetic methods describe herein provide for

the clean and efficient preparation of stable and biologically relevant bismuth thiolates from N-heterocyclic thiones.

The anti-bacterial activities of the Bi^{III} thiolato complexes against *M. smegmatis, S. aureus,* MRSA, VRE, *E. faecalis and E. coli* showed that those containing the anionic ligands 1-MMTZ, 4-MTT and 4-BrMTD are the most effective, with the monophenyl dithiolato complexes giving MIC values of $\leq 5.0\ \mu g\,mL^{-1}$. In particular, the five-coordinate dithiolato dithione complexes [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] and [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] proved to be most effective against the range of bacteria, with MIC values as low as $0.25\ \mu g\,mL^{-1}$ (0.34 μM) for [BiPh(4-MTT)$_2${4-MTT(H)}$_2$] against VRE and of $1.0\ \mu g\,mL^{-1}$ (1.33 μM) for [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$] against *M. smegmatis* and *S. aureus*. The trithiolato Bi^{III} complexes were least effective overall. All complexes showed little or no toxicity towards mammalian COS-7 cells at $20\ \mu g\,mL^{-1}$.

Experimental Section

$BiPh_3$ was synthesised through a standard Grignard metathesis reaction from the treatment of $BiCl_3$ with MgPhBr in dried diethyl ether at 0 °C, and subsequently recrystallised from ethanol. Ph_2BiCl was synthesised by mixing $BiPh_3$ and $BiCl_3$ in a 2:1 ratio in dried diethyl ether, and $Bi(OtBu)_3$ was synthesised according to literature procedures.[57] Ethanol, DMSO and toluene were used as solvents for recrystallization. Diethyl ether and THF were dried prior to use by M-Braun-SPS-800 solvent purification system and molecular sieves (4 Å) were used to store. All moisture sensitive reactions were conducted with oven dried glassware under an atmosphere of dry nitrogen using a vacuum/nitrogen line and Schlenk techniques. The heterocyclic compounds were purchased from Sigma–Aldrich and used as supplied. Microwave irradiation was carried out in a CEM Discoverer Microwave oven with maximum power 0–300W, model number 9080, maximum current 6.38 A with 50/60 MHz frequency. NMR spectra of complexes were recorded on a Brucker DPX 400 spectrometer in [D_6]DMSO with TMS as internal standard at room temperature. Elemental analysis (C, H and N) were performed by the Campbell Microanalytical lab, department of chemistry, University of Otago, Dunedin, New Zealand. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus. Mass spectra were recorded on a micromass platform electrospray mass spectrometer.

All voltammetric experiments were carried out at (25 ± 2) °C on Potentiostat BAS 100W electrochemical workstation using a three electrode electrochemical cell configuration. The glassy carbon (GC) disc electrode ($d = 1.0$ mm) for cyclic voltammetry was polished consecutively with 0.05 μm and 0.3 μm alumina (Buehler, Lake Bluff, IL) on a clean polishing cloth then rinsed with water, sonicated for 20 s and again rinsed with water and dried under nitrogen. For steady-state studies, a glassy carbon microelectrode ($d =$ 11 μm) was polished with 0.05 μm alumina in the similar way. Indium tin oxide slides (ITO) were used as working electrode during bulk electrolysis of tetrathiolatobismuth(V) complex to deposit bismuth metal. ITO was cleaned by sonicating in isopropanol for 15–25 min. A platinum wire was used as the quasi-reference electrode and another platinum wire was used as the auxiliary electrode.

Electrochemical behaviour of a 1 mM solution of [BiPh(1-MMTZ)$_4$] (**1**) and 1-methyl-1*H*-tetrazole-5-thiol 1-MMTZ(H) was studied in DMSO containing 0.1 M tetrabutylammoniumhexaflurophosphate (Bu_4NPF_6) as the supporting electrolyte. As quasi-reference electrode was used, potentials were calibrated versus ferrocene by the addition of 1.0 mM ferrocene. XRD spectra were collected on a Philips PW1140 diffractometer from 2–60° (2θ) at 4° min^{-1} with a step size of 0.02° using a $Cu_{K\alpha}$ source ($\lambda = 1.54$ nm). A 1° divergence slit, 1° receiving slit and 0.2° scatter aperture were used. Samples were prepared by bulk electrolysis on Indium tin oxide slides.

Crystallographic data

Crystallographic data of compounds **9** and **15** were collected at the MX1 beamline at the Australian Synchrotron, Melbourne, Victoria (Australia) with the wavelength set at 0.7107 Å (17.4 keV) using an open flow of N_2 cryostream. The software used for data collection and reduction of the data were BluIce[58] and XDS.[59] Crystallographic data for compounds **2** and **8** were obtained on an OXFORD Gemini Ultra equipped with an OXFORD Cryosystems 700 Cryostream and cooled to 123(1) K. Data was collected with monochromatic (graphite) $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and processed using the CrysAlisProv 1.171.34.36[60] software; Lorentz, polarization and absorption corrections (multi-scan) were applied. The structures were solved and refined with SHELX-97.[61] All non-hydrogen atoms were refined with anisotropic thermal parameters unless otherwise indicated and hydrogen atoms were placed in calculated positions using a riding model with C–H = 0.95–0.98 Å and $U_{iso}(H) = xU_{iso}(C)$, $x = 1.2$ or 1.5 unless otherwise indicated. CCDC-1007779 (**9**), CCDC-1007780 (**2**), CCDC-1007781 (**8**) and CCDC-1007782 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Antimicrobial activity

Mycobacterium smegmatis was cultured in Middlebrook 7H9/7H10 medium (Difco) for 3 days at 37 °C. *Escherichia coli* was cultured overnight at 37 °C in LB (Luria-Bertani) medium. *Staphylococcus aureus*, MRSA (methicillin-resistant *S. aureus*), *Enterococcus faecalis* and VRE (vancomycin-resistant *E. faecalis*) were cultured in BHI (brain heart infusion) medium (Oxoid) overnight at 37 °C.

In initial activity screens, filter paper discs were soaked with 2 μL of $5\ mg\,mL^{-1}$ compound, 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, while minimum inhibitory concentration (MIC) assays were performed for all positive compounds.

To determine MICs, liquid cultures of bacteria were prepared containing serial dilutions of the compounds, from $80\ \mu g\,mL^{-1}$ to $0.25\ \mu g\,mL^{-1}$. 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 anti-mycobacterial drugs isoniazid and ethambutol was included as controls.

Cell toxicity assays

Toxicities against eukaryotic cells were assayed using the in vitro toxicology assay kit MTT-based (Sigma–Aldrich; cat. no. TOX1–1 KT), according to the manufacturer's instructions. Compounds were added to cultured COS-7 (monkey kidney-derived) cells at 10 and $20\ \mu g\,mL^{-1}$ for 1 h prior to addition of the tetrazolium dye MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reagent. 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.

Synthesis and Characterisation

[BiPh(1-MMTZ)$_4$] (1)—1:4 reaction of BiPh$_3$ with 1-MMTZ(H)

Conventional method: A solution of triphenyl bismuth (0.22 g, 0.50 mmol) in toluene (20.0 mL) was added to a hot solution of 1-methyl-1*H*-tetrazole-5-thiol (0.23 g, 2.0 mmol) in ethanol (10.0 mL) and the reaction mixture stirred and then refluxed for 2 h. The bright yellow product thus obtained was washed several times with acetone and ethanol. Yield: 0.18 g (51%).

Microwave-assisted synthesis: A mixture of 1-methyl-1*H*-tetrazole-5-thiol (0.12 g, 1.0 mmol) in ethanol (2.0 mL) and triphenylbismuth (0.11 g, 0.25 mmol) in toluene (4.0 mL) was stirred and then irradiated at 100 °C for 4 min. The resultant bright yellow precipitate was filtered by suction and washed with acetone. Yield: 0.10 g (57%); m.p. 210 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 8.97$ (d, $J = 6.0$ Hz, 2H; *o*-Ph), 7.87 (t, 2H; *m*-Ph), 7.44 (t, 1H; *p*-Ph), 3.76 ppm (s, 12H; tetrazole CH$_3$); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 156.2$ (tetrazole CS), 139.3 (*o*-Ph), 132.9 (*m*-Ph), 127.7 (*p*-Ph), 33.5 ppm (tetrazole CH$_3$); FT-IR: $\tilde{\nu} = 1628$ (s), 1472 (m), 1375 (m), 1276 (s), 1174 (s), 1035 (m), 723 (m), 701 cm^{-1} (s); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z*: 826 [BiPhL$_4$(DMSO)+H]$^+$, 812 [BiPhL$_4$(CH$_3$OH)$_2$+H]$^+$, 780 [BiPhL$_4$(CH$_3$OH)+H]$^+$, 748 [BiPhL$_4$+H]$^+$, 653 [BiPhL$_3$(H$_2$O)+H]$^+$, 613 [BiPh(O)L$_2$(DMSO)+H]$^+$, 533 [BiPh(O)L$_2$+H]$^+$; elemental analysis calcd (%) for $BiC_{14}H_{17}N_{16}S_4$: C 22.52, H 2.29, N 30.02; found: C 22.78, H 2.59, N 30.03.

[BiPh(1-MMTZ)$_2${1-MTTZ(H)}$_2$] (2): Complex **1** (0.20 g, 0.27 mmol) was dissolved in hot DMSO (2.0 mL) and deep yellow crystals of **2** suitable for single-crystal X-ray diffraction studies were obtained after eight weeks. Yield 0.09 g (49%); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 8.96$ (d, $J = 17$ Hz, 2H; *o*-Ph), 7.87 (t, $J = 10$ Hz, 2H; *m*-Ph), 7.46 (t, $J = 9$ Hz, 1H; *p*-Ph), 3.77 ppm (s, 12H; tetrazole CH$_3$); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 138.9$ (*o*-Ph), 132.9 (*m*-Ph), 127.4 (*p*-Ph), 33.2 ppm (tetrazole CH$_3$); FT-IR: $\tilde{\nu} = 3045$ (b), 1552 (s), 1429 (m), 1372 (s), 1280 (m), 1169 (s), 1033 (m), 733 (s), 703 cm^{-1} (m); elemental analysis calcd (%) for $BiC_{14}H_{19}N_{16}S_4$: C 22.46, H 2.56, N 29.93; found: C 22.64, H 2.78, N 29.95.

[BiPh(1-MMTZ)$_2$] (5)—1:2 reaction of BiPhCl$_2$ with [Na(1-MMTZ)]

Salt metathesis method: All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 1-methyl-1*H*-tetrazole-5-thiol (0.2 g, 1.43 mmol) was dissolved in dry methanol (20 mL). The resultant solution was cooled below 0 °C before the addition of phenyl bismuth dichloride (0.25 g, 0.71 mmol). The reaction mixture was stirred for 10 h and resultant light yellow precipitate was filtered and washed with methanol and diethyl ether. Yield: 0.17 g (60%); m.p. 259 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 9.01$ (d, $J = 14$ Hz, 2H; *o*-Ph), 7.90 (t, 2H; *m*-Ph), 7.49 (t, $J = 10$ Hz, 1H; *p*-Ph), 3.80 ppm (s, 6H; tetrazole CH$_3$); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 139.4$ (*o*-Ph), 132.9 (*m*-Ph), 128.1 (*p*-Ph), 33.4 ppm (tetrazole CH$_3$). FT-IR: $\tilde{\nu} = 1548$ (s), 1415 (m), 1171 (s), 1027 (m), 703 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 575 (50) [BiPhL$_2$(H$_2$O)$_2$+Na]$^+$, 540 (80) [BiPhL$_2$+Na]$^+$, 517 (10) [BiPhL$_2$+H]$^+$, 501 (40) [BiPhL(CH$_3$OH)$_2$(H$_2$O)$_2$]$^+$; elemental analysis calcd (%) for $BiC_{10}H_{11}N_8S_2$: C 23.26, H 2.16, N 21.70; found: C 24.05, H 2.76, N 21.75.

[BiPh(2-MMI)$_2$] (7)—1:2 reaction of BiPhCl$_2$ with [Na(2-MMI)]

Salt metathesis method: All the manipulations were carried out under nitrogen atmosphere. The sodium salt of methyl-1*H*-imidazole-2-thiol (0.25 g, 1.84 mmol) was dissolved in dry methanol (20 mL). The resultant yellow brown solution was cooled below 0 °C before the addition of phenyl bismuth dichloride (0.33 g, 0.92 mmol). The reaction mixture was stirred for 7 h and resultant yellow precipitate was filtered and washed with methanol and ethanol. Yield: 0.20 g (77%); m.p. 178 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 8.22$ (d, $J = 9.0$ Hz, 2H; *o*-Ph), 7.54 (t, $J = 7.0$ Hz, 2H; *m*-Ph), 7.33 (t, 1H; *p*-Ph), 6.99 (s, 2H; imidazole CH), 6.71 (s, 2H; imidazole CH), 3.44 ppm (s 6H; imidazole CH$_3$). ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 137.7$ (*o*-Ph), 130.9 (*m*-Ph), 127.3 (*p*-Ph), 33.5 ppm (imidazole CH$_3$); FT-IR: $\tilde{\nu} = 1653$ (m), 1525 (m), 1467 (s), 1389 (s), 1309 (s), 1197 (m), 830 (s), 742 (s), 691 (s), 639 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 610 (15) [BiPhL$_2$(DMSO)(H$_2$O)+H]$^+$, 596 (60) [PhBiL$_2$(CH$_3$OH)$_2$(H$_2$O)+H]$^+$; elemental analysis calcd (%) for $BiC_{14}H_{15}N_4S_2$: C 32.82, H 2.95, N 10.93; found: C 32.61, H 3.47, N 10.55.

[BiPh(5-MMTD)$_2$]$_\infty$ (8)—1:2 reaction of BiPh$_3$ with 5-MMTD(H)

Conventional reflux method: Triphenyl bismuth (0.2 g, 0.45 mmol) in toluene (20.0 mL) was added to a hot solution of 5-methyl-1,3,4-thiadiazole-2-thiol (0.24 g, 1.80 mmol) in ethanol (10.0 mL) and the reaction mixture was refluxed for 16 h. Excess solvent was removed under reduced pressure. The pale yellow product thus obtained was washed several times with acetone. Yield: 0.12 g (73%).

Microwave-assisted synthesis: The mixture of 5-methyl-1,3,4-thiadiazole-2-thiol (0.24 g, 1.80 mmol) in ethanol (2.0 mL) and triphenyl bismuth (0.2 g, 0.45 mmol) in toluene (4 mL) was irradiated at 112 °C for 15 min. The resultant pale yellow precipitate was filtered and washed with diethyl ether in order to remove unreacted materials. Yield: 0.14 g (84%).

[BiPh(5-MMTD)$_2$]$_\infty$ (8)—1:2 reaction of BiPhCl$_2$ with [Na(5-MMTD)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 5-methyl-1,3,4-thiadiazole-2-thiol (0.15 g, 1 mmol) was dissolved in dry methanol (20 mL). The resultant light yellow solution was cooled below 0 °C before the addition of phenyl bismuth dichloride (0.18 g, 0.5 mmol). The reaction mixture was stirred overnight and resultant pale yellow precipitate was filtered and washed with methanol and diethyl ether. Yield: 0.20 g (83%); m.p. 218–220 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 9.02$ (d, $J = 8.0$ Hz, 2H; *o*-Ph), 7.73 (t, 2H; *m*-Ph), 7.40 (t, 1H; *p*-Ph), 2.46 ppm (s, 6H; thiadiazole CH$_3$); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 137.9$ (*o*-Ph), 131.2 (*m*-Ph), 127.7 (*p*-Ph), 15.3 ppm (thiadiazole CH$_3$); FT-IR: $\tilde{\nu} = 1637$ (m), 1429 (br), 1364 (s), 1037 (s), 979 (m), 727 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 571 (30) [BiPhL$_2$+Na]$^+$, 417 (28) [BiPhL]$^+$, 285 (100) [L$_2$+Na]$^+$; elemental analysis calcd (%) for $BiC_{12}H_{11}N_4S_4$: C 26.28, H 2.02, N 10.21; found: C 27.11, H 1.89, N 10.73. Single crystals of **8** were obtained on recrystallization of the bulk solid form DMSO solution over a period of eight weeks. Analysis of the crystals as [BiPh(5-MMTD)$_2$] was consistent with the bulk solid.

[BiPh{2,5-DMTD(H)}$_2$]$_\infty$ (9)—1:2 reaction of BiPh$_3$ with 2,5-DMTD(H)$_2$

Conventional method: Triphenyl bismuth (0.15 g, 0.34 mmol) in toluene (20 mL) was added to a hot solution of 1,3,4-thiadiazole-2,5-dithiol (0.1 g, 0.67 mmol) in ethanol (10 mL) and the reaction mixture was refluxed for 8 h. The resulting orange precipitate was washed with diethyl ether. Yield: 0.15 g (73%).

Microwave-assisted synthesis: The mixture of 1,3,4-thiadiazole-2,5-dithiol (0.1 g, 0.67 mmol) in ethanol (2.0 mL) and triphenyl bismuth (0.146 g, 0.34 mmol) in toluene (4 mL) was irradiated at 112 °C for 10 min. Resultant orange precipitate was filtered and washed with acetone and diethyl ether in order to remove unreacted materials. Yield: 0.17 g (92%); m.p. 248–250 °C (decomp); ^{1}H NMR (400 MHz,

[D_6]DMSO, 30 °C): $\delta = 8.84$ (d, $J = 9.0$ Hz, 2H; *o*-Ph), 7.87 (t, 2H; *m*-Ph), 7.44 ppm (t, $J = 11$ Hz, 1H; *p*-Ph); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 139.5$ (*o*-Ph), 133.5 (*m*-Ph), 128.3 ppm (*p*-Ph); FT-IR: $\tilde{\nu} = 1546$ (m), 1467 (s), 1044 (s), 719 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 844 (100) $[PhBi(LH)_2(DMSO)_2\text{-}(CH_3OH)_2 + K]^+$, 436 (33) $[BiPhLH]^+$, 171 (10) $[LH + Na]^+$; elemental analysis calcd (%) for $BiC_{10}H_7N_4S_6$: C 20.55, H 1.21, N 9.58; found: C 19.83, H 0.92, N 10.93. Single crystals of **9** were obtained on recrystallization of the bulk solid form DMSO solution over a period of ten to twelve weeks. Analysis of the crystals as [BiPh{2,5-DMTD(H)}$_2$] was consistent with the bulk solid.

[BiPh(4-BRMTD)] (10)—1:2 reaction of $BiPhCl_2$ with [Na(4-BRMTD)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 4-(4-bromophenyl)thiazole-2-thiol (0.16 g, 0.54 mmol) was dissolved in dry methanol (25 mL). The resultant light yellow solution was cooled below 0 °C before the addition of phenyl bismuth dichloride (0.1 g, 0.27 mmol). The reaction mixture was stirred overnight and resultant yellow precipitate was filtered and washed with methanol and acetone. Yield: 0.17 g (78%); m.p. 282–284 °C (decomp); ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): $\delta = 8.94$ (d. $J = 10$ Hz, 2H; *o*-Ph), 7.82 (t, $J = 10$ Hz, 2H; *m*-Ph), 7.74 (d, $J = 12$ Hz, 6H; Br-Ph), 7.71 (s, 2H; thiazole CH), 7.42 (t, $J = 2.0$ Hz, 1H; *p*-Ph), 7.35 ppm (d, 4H; Br-Ph). ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta =$ 137.4 (*o*-Ph), 132.9 (*Br*-Ph) 131.8 (*Br*-Ph), 130.3 (*m*-Ph), 128.0 (*Br*-Ph), 127.5 (*o*-Ph), 122.4 (*Br*-Ph), 110.6 ppm (thiazole CH); FT-IR: $\tilde{\nu} = 1596$ (s), 1579 (m), 1474 (s), 1443 (m), 1320 w, 1273 (m), 1038 (s), 724 (s), 686 cm^{-1} (s); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 851 (100) $[BiPhL_2 + Na]^+$, 830 (10) $[BiPhL_2 + H]^+$, 558 (45) $[BiPhL]^+$; elemental analysis calcd (%) for $BiC_{24}H_{15}Br_2N_2S_4$: C 34.80, H 1.83, N 3.38; found: C 34.91, H 1.89, N 3.63.

[Bi(1-MMTZ)$_3$] (11)—1:3 reaction of $BiCl_3$ with [Na(1-MMTZ)]

Salt metathesis method: All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 1-methyl-1*H*-tetrazole-5-thiol (0.25 g, 1.8 mmol) was dissolved in dry methanol (20 mL). The resultant solution was cooled below 0 °C before the addition of bismuth chloride (0.19 g, 0.60 mmol). The reaction mixture was stirred overnight and resultant light yellow precipitate was filtered and washed with methanol and diethyl ether. Yield: 0.21 g (63%).

[Bi(1-MMTZ)$_3$] (11)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 1-MMTZ(H)

All the manipulations were carried out under nitrogen atmosphere. Bismuth *tert*-butoxide (0.31 g, 0.73 mmol) was dissolved in dry tetrahydrofuran (10 mL) followed by addition of 1-methyl-*1H*-tetrazole-5-thiol (0.25 g, 2.16 mmol) at −70 °C. The reaction mixture was stirred for 10 h and resultant pale yellow precipitate was filtered and washed with dry THF. Yield: 0.29 g (73%); m.p. 198 °C (decomp); ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): $\delta = 3.90$ ppm (s, 9H; tetrazole CH_3); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 155.8$ (tetrazole CS), 33.7 ppm (tetrazole CH_3); FT-IR: $\tilde{\nu} = 1472$ (br), 1375 (s), 1276 (m), 1174 (s), 971 (m), 701 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 577 (20) $[BiL_3 + Na]^+$, 503 (60) $[BiL_2\text{-}(CH_3OH)_2]^+$, 402 (7), $[BiL(DMSO)]^+$; elemental analysis calcd (%) for $BiC_6H_9N_{12}S_3$: C 13.00, H 1.64, N 30.32; found: C 13.55, H 2.13, N 30.34.

[Bi(4-MTT)$_3$] (12)—1:3 reaction of $BiCl_3$ with [Na(4-MTT)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 4-methyl-4*H*-1,2,4-triazole-3-thiol (0.23 g, 1.68 mmol) was dissolved in dry methanol (20 mL). The resultant solution was cooled below 0 °C and bismuth chloride (0.18 g, 0.56 mmol) added as a solid. The reaction mixture was stirred overnight and resultant yellow precipitate was filtered and washed with methanol and ethanol. Yield: 0.22 g (71%).

[Bi(4-MTT)$_3$] (12)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 4-MTT(H)

All the manipulations were carried out under nitrogen atmosphere. Bismuth *tert*-butoxide (0.3 g, 0.72 mmol) was dissolved in dry tetrahydrofuran (10 mL) followed by addition of 4-methyl-4*H*-1,2,4-triazole-3-thiol (0.25 g, 2.17 mmol) at −70 °C. The reaction mixture was stirred for 7 h and resultant orange precipitate was filtered and washed with dry diethyl ether. Yield: 0.31 g (79%); m.p. 291 °C (decomp); ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): $\delta = 8.25$ (s, 3H; triazole CH), 3.42 ppm (s, 9H; triazole CH_3); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 143.9$ (triazole CH), 31.1 ppm (triazole CH_3); FT-IR: $\tilde{\nu} = 1558$ (s), 1464 (m), 1200 (m), 1005 (s), 692 cm^{-1} (m); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 620 (8) $[BiL_3(CH_3OH)\text{-}(H2O)_2]^+$, 574 (5) $[BiL_3 + Na]^+$, 395 (100) $[BiL(H_2O)_4]^+$, 283 (80) $[LL\text{-}(CH_3OH) + Na]^+$, 227 (30) $[Bi(H_2O)]^+$, 169 (15) $[L(CH_3OH) + Na]^+$; elemental analysis calcd (%) for $BiC_9H_{12}N_9S_3$: C 19.60, H 2.19, N 22.86; found: C 20.11, H 2.59, N 23.11.

[Bi(2-MMI)$_3$] (13)—1:3 reaction of $BiCl_3$ with [Na(2-MMI)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of methyl-1*H*-imidazole-2-thiol (0.25 g, 1.83 mmol) was dissolved in dry methanol (20 mL). The resultant yellow solution was cooled below 0 °C before the addition of bismuth chloride (0.19 g, 0.61 mmol). The reaction mixture was stirred overnight and resultant yellow precipitate was filtered and washed with methanol and ethanol. Yield: 0.22 g (71%).

[Bi(2-MMI)$_3$] (13)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 2-MMI(H)

All the manipulations were carried out under nitrogen atmosphere. Bismuth *tert*-butoxide (0.14 g, 0.33 mmol) was dissolved in dry tetrahydrofuran (10 mL) followed by addition of methyl-1*H*-imidazole-2-thiol (0.11 g, 1 mmol) at −70 °C. The reaction mixture was stirred for 7 h and resultant precipitate was filtered and washed with dry diethyl ether. Yield: 0.15 (86%); m.p. 285 °C (decomp); ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): $\delta = 6.96$ (d, 2H; imidazole CH), 6.79 (d, 2H; imidazole CH), 3.40 ppm (s, 9H; imidazole CH_3); ^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 119.6$ (imidazole CH), 114.2 (imidazole CH), 33.3 ppm (imidazole CH_3); FT-IR: $\tilde{\nu} = 1574$ (m), 1518 (m), 1445 (s), 1359 (s), 1316 (s), 1278 (m), 1057 (br), 861 (s), 738 (s), 685 cm^{-1} (s); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 571 (28) $[BiL_3 + Na]^+$, 435 (25) $[BiL_2]^+$, 249 (100) $[L_2 + Na]^+$), 136 (80), $[L + Na]^+$; elemental analysis calcd (%) for $BiC_{12}H_{15}N_6S_3$: C 26.28, H 2.76, N 15.32; found: C 26.44, H 2.89, N 15.43.

[Bi(5-MMTD)$_3$] (14)—1:3 reaction of $BiCl_3$ with [Na(5-MMTD)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 5-methyl-1,3,4-thiadiazole-2-thiol (0.30 g, 1.9 mmol) was dissolved in dry methanol (20 mL). The resultant light yellow solution was cooled below 0 °C before the addition of bismuth chloride (0.20 g, 0.65 mmol). The reaction mixture was stirred overnight and resultant pale yellow precipitate was filtered and washed with methanol and diethyl ether. Yield: 0.27 g (72%).

[Bi(5-MMTD)$_3$] (14)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 5-MMTD(H)

All the manipulations were carried out under nitrogen atmosphere. Bismuth *tert*-butoxide (0.16 g, 0.38 mmol) was dissolved in dry tetrahydrofuran (10 mL) followed by addition of 5-methyl-1,3,4-thiadiazole-2-thiol (0.15 g, 1.2 mmol) at −70 °C. The reaction mixture was stirred for 9 h and resultant pale yellow precipitate was filtered and washed with dry diethyl ether. Yield: 0.18 g (81%); m.p. 265–267 °C (decomp); ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): $\delta =$ 2.46 ppm (s, 9H; thiadiazole CH_3).^{13}C NMR (100 MHz, [D_6]DMSO): $\delta = 15.7$ ppm (thiadiazole CH_3); FT-IR: $\tilde{\nu} = 1482$ (br), 1425 (br), 1258 (s), 1031 (br), 795 cm^{-1} (s); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 604 (19) $[BiL_3 + H]^+$, 503 (20) $[BiL_2(CH_3OH)]^+$, 440 (50) [BiL-

$(CH_3OH)_2(H_2O)_2]^+$, 285 (100) $[L_2+Na]^+$); elemental analysis calcd (%) for $BiC_9H_9N_6S_6$: C 17.94, H 1.51, N 13.95; found: C 18.40, H 2.2, N 14.19.

[Bi(4-BrMTD)$_3$] (15)—1:3 reaction of BiCl$_3$ with [Na(4-BrMTD)]

All the manipulations were carried out under nitrogen atmosphere. The sodium salt of 4-(4-bromophenyl)thiazole-2-thiol (0.20 g, 0.68 mmol) was dissolved in dry methanol (20 mL). The resultant solution was cooled below 0 °C before the addition of bismuth chloride (0.07 g, 0.23 mmol). The reaction mixture was stirred overnight and resultant pale yellow precipitate was filtered and washed with methanol and diethyl ether. Yield: 0.20 g (71 %).

[Bi(4-BrMTD)$_3$] (15)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 4-BrMTD(H)

All the manipulations were carried out under nitrogen atmosphere. Bismuth *tert*-butoxide (0.12 g, 0.28 mmol) was dissolved in dry tetrahydrofuran (10 mL) followed by addition of 4-(4-bromophenyl)thiazole-2-thiol (0.23 g, 0.84 mmol) at −70 °C. The reaction mixture was stirred for 12 h and resultant orange precipitate was filtered and washed with dry diethyl ether. Yield: 0.19 g (68 %); m.p. 217 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 7.76$ (d, $J =$ 12 Hz, 6H; Br-Ph), 7.62 (s, 3H; thiazole CH), 7.29 ppm (d, $J = 11$ Hz, 6H; Br-Ph); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 167.7$ (thiazole CS), 132.6 (Br-Ph), 131.4 (Br-Ph), 128.0 (Br-Ph), 121.0 (Br-Ph), 114.9 ppm (thiazole CH). FT-IR: $\tilde{\nu} = 1513$ (m), 1465 (s), 1382 (m), 1007 (s), 825 (s), 735 (s), 661 cm^{-1} (s); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 1045 (15) $[BiL_3+Na]^+$, 751 (40) $[BiL_2]^+$, 480 (15), $[BiL]^+$; elemental analysis calcd (%) for $BiC_{27}H_{15}Br_3N_3S_6$: C 31.71, H 1.48, N 4.11; found: C 32.12, H 1.63, N 4.37. Single crystals of **15** were obtained on recrystallization of the bulk solid form DMSO solution over a period of ten weeks. Analysis of the crystals as [Bi(4-BrMTD)$_3$] was consistent with the bulk solid.

[Bi{2,5-DMTD(H)}$_3$] (16)—1:3 reaction of [Bi(O*t*Bu)$_3$] with 2,5-DMTD(H)$_2$

Bismuth *tert*-butoxide (0.19 g, 0.44 mmol) was dissolved in dry tetrahydrofuran (10.0 mL) followed by addition of 1,3,4-thiadiazole-2,5-dithiol (0.20 g, 1.32 mmol) at −70 °C. The reaction mixture was stirred for 6 h and the resultant red precipitate was filtered and washed with dry diethyl ether. Yield: 0.22 g (78 %); m.p. 202 °C (decomp); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): $\delta = 14.03$ ppm (s, 3H; NH); ESI-MS$^+$ (solvent: DMSO/MeOH, 35 eV): *m/z* (%): 758 (70) $[Bi(LH)_3(DMSO)+Na]^+$, 640 (96) $[Bi(LH)_2(DMSO)(H_2O)_3]^+$; elemental analysis calcd (%) for $BiC_6H_3N_6S_9$: C 10.97, H 0.46, N 12.80; found: C 11.27, H 0.70, N 12.08.

Acknowledgements

We thank Monash University and the Australian Research Council (DP110103812) for financial support. We also wish to thank Associate Professor Benjamin Howden (Austin Health) for supplying the MRSA and VRE strains for antimicrobial activity testing.

Keywords: bacteria · bismuth · structure elucidation · synthesis · thiolate

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Received: June 24, 2014
Published online on September 15, 2014