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Bismuth(III) Complexes Derived from *α*-Amino Acids: The Impact of Hydrolysis and Oxido-Cluster Formation on their Activity against *Helicobacter pylori*

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Abstract

Eight bismuth(III) complexes derived from a variety of *α*-amino acids covering a range of physico-chemical properties (L-phenylalanine (Phe), L-proline (Pro), L-methionine (Met), L-cysteine (Cys), D,L-serine (Ser), L-tyrosine (Tyr), L-aspartic acid (Asp) and L-glutamic acid (Glu)) have been synthesised, characterised, and evaluated for their activity against *Helicobacter pylori.* The optimal synthetic procedure utilises $[Bi(O^tBu)_3]$, giving the complexes $[BiL_3]$ (L = Phe **1**, Pro **2**, Met **3**, Ser **5**, Tyr **6**) and $[Bi_2L_3]$ (L = Cys **4**, Asp **7**, Glu **8**) cleanly and in good yield. However, the synthesis is sensitive to both temperature and moisture. The solubility and stability of the bismuth(III) complexes was investigated using ESI-MS. Almost all compounds (except for $[Bi(Phe)_3]$ and $[Bi(Pro)_3]$) were found to be partially or completely soluble in aqueous solution giving a pH 2.5 - 5.0, indicating the presence of free *α*-amino acid and hydrolysis of the bismuth(III) complexes to polynuclear bismuth oxido clusters. The results of the bactericidal studies against *Helicobacter pylori* demonstrate that this hydrolysis process impacts significantly on the observed Minimum Inhibitory Concentration (MICs) which are increased substantially, often by many orders of magnitude, when the complexes are initially prepared in water rather than DMSO.

Introduction

Bismuth(III) compounds which are used routinely as over-the-counter medications, for example in the treatment of travellers diarrhoea, and clinically, for the treatment of *Helicobacter pylori* infection,[1-4] are derived primarily from carboxylic acids; salicylic acid, citric acid, and gallic acid. Thus, our understanding of the synthetic and biological chemistry of bismuth(III) carboxylates is generally more advanced than that for other ligand families.[5] Bismuth(III) carboxylates are also known to undergo hydrolysis to give large oxido-clusters of varying nuclearity, indicated by the use of the *sub* prefix in the compound names of the common medications: bismuth *sub*salicylate (Pepto-Bismol), colloidal bismuth *sub*citrate (De-Nol), and bismuth *sub*gallate (Devrom). The complex nature and structure of these and related polynuclear ligand encapsulated oxido-clusters have been explored and described in detail in the recent past. The carboxylate cages whose structures have been authenticated are: $[Bi_{38}O_{44}(HSal)_{26}(Me_2C{=}O)_{16}(H_2O)_2]$,(6) $[Bi_9O_7(HSal)_{13}(Me_2C{=}O)_5]$,[6] $[Bi_{38}O_{45}(OH)_2(HSal)_{22}(DMSO)_{16.5}](DMSO)(H_2O)$ (HSal = salicylate),[7] $[Bi_{38}O_{45}$(HSal-4-Me$)_{24}(DMSO)_{14}(H_2O)_2](H_2O)_4$,[8] $[Bi_{38}O_{45}(HSal)_{22}(OMc)_2(DMSO)_{15}(H_2O)](DMSO)(H_2O)_2$ (HSal-4-Me = 4-methylsalicylate, OMc = methacrylate),[9] $(NH_4)_6[Bi_6O_4OH(cit)_3(H_2O)_3](H_2O)_2$,[10] $(NH_4)_{12}[Bi_{12}O_8(cit)_8](H_2O)_{10}$ (cit = citrate),[11] $[Bi_{38}O_{45}(OMc)_{24}(DMSO)_9](DMSO)_2(H_2O)_7$,[12] $[Bi_{10}O_8\{2\text{-}(NO_2)C_6H_4CO_2\}_{14}(EtOH)_3]$,[13] $[Bi_{38}O_{45}(OH)_4\{3,5\text{-}(NO_2)_2C_6H_3CO_2\}_{20}(DMSO)_{16}](DMSO)_4(H_2O)_{11}$,[14] $[Bi_{38}O_{45}(OH)_2\{3,5\text{-}(NO_2)_2C_6H_3CO_2\}_{20}(CH_3CO_2)_2(DMF)_{10}](DMF)_{15}(H_2O)_{20}$;[14] $[\{Bi_{38}O_{45}(NO_3)_{20}(OBz)_4(DMSO)_{24}\}(DMSO)_4][\{Bi_{38}O_{45}(NO_3)_{24}(DMSO)_{26}\}(DMSO)_4]$ (OBz = benzoate).[15]

Detailed studies have demonstrated that *in vivo* it is peptides and proteins rich in cysteine and methionine that are the primary biological targets for Bi^{3+}, alongside lactoferrin and transferrin.[4,16-20] This results from a high affinity of bismuth, as a borderline metal, for sulfur (mostly in the form of thiolate).[21] Thus, there have been several studies on bismuth(III) complexes derived from or involving the α-amino acids cysteine[22-25] and methionine.[26-27] Beyond this, however, reports on the synthetic and structural chemistry of bismuth(III) with α-amino acids is scarce. The only other studies involve the determination of stability constants of bismuth(III) complexes with L-lysine[28] and serine.[29] With α-amino acids being formally carboxylic acids the crossover between the known chemistry of bismuth(III)

carboxylates with their biological and bactericidal properties could provide important insights into their efficacy and mode of action.

Recently, the crystal structure of the bismuth(III) cysteine complex [$Bi(Cys)_3$] was published by Wang and Xu.[30] Noteworthy is the binding of bismuth(III) to three deprotonated thiolate groups of cysteine residues with an average Bi-S bond length of ~2.54 Å, which is in good agreement with other reported Bi-S bond lengths in bismuth(III) thiolates.[23,25,31] Surprisingly, no involvement of the carboxylate or amino functionalities in binding to the bismuth(III) atom was observed. This result confirmed the findings of Napoli[25] and Alonzo et *al.*[22] and demonstrates the preference of bismuth(III) for thiolate ions. However, a second solid-state structure published by Briand *et al.,*[23] [$Bi(cys)(NO_3)(phen)(H_2O)]NO_3$, shows chelation of bismuth(III) by the thiolate and carboxylate functionalities, revealing the pH dependency of the structural outcomes.

In this paper we describe a variety of different synthetic approaches to the formation of bismuth(III) complexes derived from a range of *α*-amino acids with differing chemical and physical features, explore the composition and solubility of these compounds, and describe their hydrolytic stability in aqueous solutions. Furthermore, the bactericidal activity of the complexes against *H. pylori* is described and is shown to be highly sensitive to the solvent used and the rate and extent of hydrolysis of the complexes.

Results and Discussion

Eight *α*-amino acids were targeted in this study and are shown in Figure 1: (*S*)-2-amino-3-phenylpropanoic acid [L-phenylalanine (Phe)], (*S*)-pyrrolidine-2-carboxylic acid [L-proline (Pro)], (*S*)-2-amino-4-(methylthio)butanoic acid [L-methionine (Met)], (*S*)-2-amino-3-sulfidopropanoic acid [L-cysteine (Cys)], 2-amino-3-hydroxypropanoic acid [D,L-serine (Ser)], (*S*)-2-amino-3-(4-hydroxyphenyl)propanoic acid [L-tyrosine (Tyr)], (*S*)-2-amino-butanedionic acid [L-aspartic acid (Asp)], and (*S*)-2-amino-pentanedionic acid [L-glutamic acid (Glu)]. The following key factors were considered important when choosing the range of *α*-amino acids: (i) non-polar and polar, (ii) neutral and acidic, (iii) aromatic and aliphatic side arms, (iv) endocyclic and exocyclic amino functionalities and (v) the acids would be zwitterionic in nature.

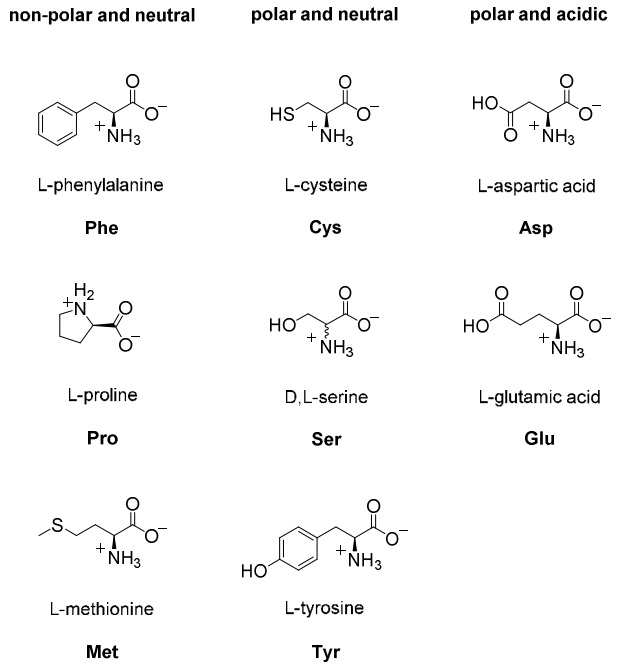


Figure 1. Structures of the *α*-amino acids applied in the synthesis of the *tris*-substituted Bi(III) complexes.

Synthesis

Since α-amino acids are formally carboxylic acids the synthesis of the bismuth(III) carboxylate (and thiolato) complexes derived from *α*-amino acids was initially investigated using both solvent-free (SF) and solvent-mediated (SM) methods. Both these methods have proved useful and successful in synthesising bismuth(III) carboxylates and thiolates cleanly and in good yield.[5,32]

Table 1 lists the pK_a values of the carboxylic proton of the *α*-amino acids under study. Normally carboxylic acids with pK_a values ≤ 5.0 allow access to the bismuth carboxylates on reaction with $BiPh_3$ under solvent free conditions.[5] Since the pK_a values of the carboxylic acid group lie in the range 1.50 to 2.20, both the SF and SM methods should be thermodynamically feasible.

However, both methods proved unsuccessful, with only starting materials being recovered from the reaction mixture. Analysis of the SF reaction using differential scanning calorimetry (DSC) supported the lack of reaction observed in the batch processes. Rather than displaying typical exothermic peaks reflecting protolysis of $BiPh_3$ and subsequent loss of nPhH (n = 1 – 3), the DSC traces showed only separate endothermic peaks relating to the melting of $BiPh_3$ and of the *α*-amino acid (see Figure S1).

The zwitterionic nature of the *α*-amino acids, highlighted in Figure 1, seems to be the key structural factor that suppresses the SF, and presumably SM, reaction. Therefore, the pK_a value of interest is the ammonium proton which is known to lie in the range 9 - 11.[33] Due to these more basic pK_a values for the ammonium proton, it appears the SF and SM methods using $BiPh_3$ as bismuth(III) source are not feasible.

Table 1. Summary of some properties (polarity, pK_a and melting point) of the *α*-amino acids used to synthesise the corresponding Bi(III) complexes.

α-amino acid	properties	pK_a (25 °C)(26)			M.p. [°C](27)
		COO***H***	COO***H***	NH_2	
Phe	non-polar, neutral	2.20	-	9.31	270-275
Pro	non-polar, neutral	1.95	-	10.64	228 (Dec.)
Met	non-polar, neutral	2.13	-	9.27	>284 (Dec)
Cys	slightly polar, neutral	1.50	8.7 (S***H***)	10.20	220 (Dec)
Ser	polar, neutral	2.19	-	9.21	222 (Dec)
Tyr	polar, neutral	2.20	-	9.11	>300 (Dec)
Asp	polar, acidic	1.99	3.90	9.90	>300 (Dec)
Glu	polar, acidic	2.13	4.31	9.67	205 (Dec)

This problem of dealing with zwitterionic salts is challenging but not new, and was central to our recent report on the synthesis of a series bismuth(III) amino-arenesulfonates.[35] These complexes were ultimately accessible in high yield through either a metathesis reaction of the silver(I) amino-arenesulfonates with $BiCl_3$, or through direct reaction of the amino-arenesulfonic acids with $[Bi(O^tBu)_3]$.

Our initial experiments concentrated on L-phenylalanine since the silver(I) complex has been previously reported.[36] When freshly prepared Ag_2O was used in targeting the Ag(I) complex, a silver mirror deposited on the wall of the flask. This phenomenon was observed repeatedly on applying the same synthetic method to other *α*-amino acids; L-proline, L-tyrosine, *D,*L-serine and L-cysteine. All reactions were accompanied by the release of CO_2 and NH_3, and the formation of various aldehydes dependent on the amino acid used.

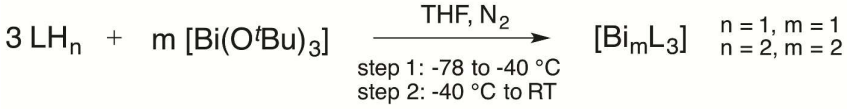
Other possible sources of silver(I) such as $AgNO_3$ or $Ag(O_2CCH_3)$ are not ideal due to the *in situ* formation of relatively strong acids, *i.e.* HNO_3 or CH_3CO_2H, and the consequent

formation of unwanted bismuth(III) compounds; $[Bi(O_2CCH_3)_3]$ or bismuth(III) nitrates. On this basis the use of Ag(I) salts in metathesis reactions does not represent an optimal synthetic pathway to the targeted Bi(III) salts. It should also be noted that the use of the Na and K salts led to solubility and separation issues, with evidence of inclusion of these metals in the final product(s).

Bismuth *tert*-butoxide, $[Bi(O^tBu)_3]$, is a stronger base than $BiPh_3$ and is useful for the deprotonation of weakly acidic protons within a pK_a range of 10 – 15. Unlike $BiPh_3$, however, it is air and moisture sensitive and is not so easily handled. In addition to having been effective in the formation of bismuth(III) amino-arenesulfonates, it has also been used successfully for the synthesis of a variety of bismuth(III) compounds such as silanolates,[37-40] amine*tris*(phenoxides),[41] calixarenes,[42-44] allyloxides,[45] and sulfabenzimides.[46]

Initial experiments involved treatment of the target α-amino acid with freshly prepared $[Bi(O^tBu)_3]$[37] in dry THF, at room temperature, and under a nitrogen atmosphere. Unfortunately, under these conditions the reaction mixture turned completely black shortly after addition of the dry THF solution of $[Bi(O^tBu)_3]$, with simultaneous formation of a gas being observed. The black precipitate results from the reduction of Bi(III) to Bi(0), which occurs upon the facile decarboxylation of the newly formed bismuth(III) carboxylate. This mirrors the outcomes observed on attempting to access the Ag(I) salts with Ag_2O.

The target compounds **1** to **8** were finally synthesised when the initial reaction temperature was reduced to -78 °C. However, warming the reaction mixture too quickly can again result in the rapid unwanted reduction of Bi(III) to Bi(0) and oxidation of the *α*-amino acid derived carboxylato ligand. The best result is achieved when $[Bi(O^tBu)_3]$ is added at -78 °C and the reaction temperature allowed to rise slowly to -40 °C, where it is maintained for at least three hours. It is then allowed to slowly warm to room temperature (Scheme 2). Table 2 summarises the yields obtained for all compounds **1** to **8**.



Scheme 1. Reaction scheme for the synthesis of bismuth(III) complexes derived from *α*-amino acids using $[Bi(O^tBu)_3$

Table 2. Summary of isolated yields and products obtained for compounds **1** to **8** applying the [Bi(O^tBu)$_3$]-method.

	α-amino acid	$[Bi_mL_n]$		yield [%]	appearance
		m	n		
1	Phe	1	3	79	beige
2	Pro	1	3	89	yellow
3	Met	1	3	95	pale yellow
4	Cys	2	3	85	yellow
5	Ser	1	3	86	colourless
6	Tyr	1	3	82	colourless
7	Asp	2	3	80	colourless
8	Glu	2	3	90	beige

Characterisation

All eight Bi(III) complexes were fully characterised by means of NMR, ESI-MS, ATR and elemental analysis. These data are provided in full in the experimental section for each compound. Crystallisation was attempted through the use of diffusion, layering and H-tube methods, but proved ultimately, and disappointingly, unsuccessful in the formation of single crystals suitable for X-ray diffraction studies.

On investigating the solubility of bismuth(III) complexes **1** to **8,** it was found that **3** - **8** dissolved either completely or partially in water (Table 3), while **1** is only soluble in DMSO and DMF, and **2** dissolves completely in methanol and ethanol. All water-soluble Bi(III) complexes displayed at least a concentration of 2.0 mg mL^{-1}. This concentration was the minimum required for the biological assays. The best water solubility was achieved with complex **8** which was found to have a maximal concentration of 33.85 mM (26.25 g L^{-1}) and the relative solubilities observed to be **8** > **7** > **4** > **3** > **5** > **6**.

Of note is the pH of the aqueous solutions which were measured to be in the pH range 2.5 - 5.0. Over a 24 h period this slowly lowers for each complex by a factor of ΔpH = -0.5 (Table 3), suggesting an increasing presence of free α-amino acid and concomitant hydrolysis of the bismuth(III) complexes. In fact this lowering the pH slightly most likely acts to support further hydrolysis and oxido-cluster formation since Bi-O cage formation is more favoured at low pH values.

Table 3. Solubility in water and pH measurements of compounds **1** to **8**.

	α-amino acid	properties	solubility in H_2O	pH	
				0 hr	24 hr
1	Phe	non-polar, neutral	-	-	-
2	Pro	non-polar, neutral	-	-	-
3	Met	non-polar, neutral	H_2O (partially)	5.0	4.5
4	Cys	slightly polar,	H_2O (completely)	4.0	3.5
5	Ser	polar, neutral	H_2O (partially)	5.0	4.5
6	Tyr	polar, neutral	H_2O (partially)	5.0	4.5
7	Asp	polar, acidic	H_2O (completely)	3.0	2.5
8	Glu	polar, acidic	H_2O (completely)	3.0	2.5

Further evidence for this apparent hydrolytic instability of the bismuth(III) complexes was given by the positive ion ESI-MS spectra obtained on **1** to **8**. Complexes **1** and **2** were investigated applying the solvent-mixture DMSO/MeOH (1:5) while complexes **3** to **8** were studied using the solvent-mixture H_2O/MeOH (1:5). It is important to note that the DMSO/MeOH solvent mixture was not dried and contained entrained H_2O. Importantly, with a pK_a for H_2O in DMSO of 32 it is significantly more basic than pure H_2O.

The positive ion ESI-MS spectra did not display ions indicative of the expected simple mononuclear and binuclear species such as $[BiL_3+M(Sol)]^+$, $[BiL_2(Sol)]^+$ or $[BiLR(Sol)]^+$ (Sol = solvent) (see Table S1). Instead many more peaks were present. No signals were observed in the negative ion ESI-MS, suggesting the formation of bismuth(III)-oxido/hydroxido clusters in solution. Full details of the analysis of the positive ESI-MS spectra for the compounds **1** to **8** are given in the experimental section and Table S2.

All positive ion ESI-MS spectra showed similar bismuth(III) oxido/hydroxido cluster fragmentation ions such as $[Bi_9O_7L_4(OH)_5(Sol)]^{4+}$, $[Bi_8O_6L_4(OH)_4(Sol)]^{4+}$, $[Bi_6O_4L_4(OH)_2(Sol)]^{4+}$ and $[Bi_4O_2L_4(Sol)]^{4+}$ for the complexes derived from a monoprotic *α*-amino acid **1**-**3**, **5** and **6**, and $[Bi_{10}O_8L_4(OH)_2(Sol)]^{4+}$, $[Bi_9O_7L_4(OH)(Sol)]^{4+}$, $[Bi_8O_6L_4(Sol)]^{4+}$, $[Bi_6O_4L_2(OH)_2(Sol)]^{4+}$ and $[Bi_4O_2L_2(Sol)]^{4+}$ for the complexes derived from a diprotic *α*-amino acid **4**, **7** and **8**.

This is not unexpected since in a series of recent papers Mehring and co-workers have used ESI-MS to great effect in identifying and describing the composition of various inorganic and metal-organic bismuth oxido-clusters.[8, 47, 48] In addition to the recent salicylato cluster

$[Bi_{38}O_{45}(HSal\text{-}4\text{-}Me)_{24}(DMSO)_{14}(H_2O)_2](H_2O)_4$,[8] these studies also have included the BOC (= *t*-butyl carbamate) protected amino acid derivatives $[Bi_{38}O_{45}(OH)_2(BOC\text{-}PheO)_{22}]$ and $[Bi_{38}O_{45}(OH)_2(BOC\text{-}ValO)_{22}]$,[49] supporting our observations on cluster formation with the unprotected amino acid derivatives.

NMR spectroscopy (^1H and ^{13}C) confirmed the formation of the bismuth(III) complexes with spectra obtained immediately after sample preparation in the best solvent for solubilisation. The chemical shifts for each complex are reported in the experimental section. Proton resonances generally moved to a lower frequency on deprotonation and complexation with bismuth(III), for examples a notable shift is seen in the Cys complex **4** where the dianionic nature of the ligand causes a significant shift from 3.10 to 1.23 ppm for the CH_2S protons. The ^{13}C signals generally follow a similar trend with the carboxylate (*C*=O) resonances shifting to lower frequency by *ca.* Δ2.0 ppm on complexation with Bi(III). Unfortunately, the NMR spectra did not provide unambiguous evidence of hydrolysis and cluster formation, most likely because of signal averaging at the temperature of data collection, 30 °C.

The main features observed in ATR-IR spectroscopy also support complexation to bismuth(III) and are summarised in Table 4. The ATR-IR spectra display stretching vibrations of the carboxylate functionality with the $\tilde{\upsilon}_{as}$(COO) absorption bands between 1687 and 1506 cm^{-1} and the $\tilde{\upsilon}_{s}$(COO) absorption bands between 1435 and 1297 cm^{-1} indicating a high degree of covalent character in the Bi-O(carboxylate) bonds.[50] The amino functionality shows broad and unresolved stretching vibration absorption bands in the region of 3400 – 3000 cm^{-1}, which suggests involvement of the amino groups in hydrogen bonding.[27,30] The ATR-IR spectra give no evidence of a $\tilde{\upsilon}$(Bi-N) absorption band and display only small to no shifts for the other amino absorption bands, and therefore, a dative bonding between the bismuth metal and the amino functionality is not likely. The absence of the $\tilde{\upsilon}$(SH) stretching vibration absorption band at 2540 cm^{-1} for the bismuth(III) complex of L-cysteine **4** supports binding to bismuth(III) through the thiolate functionality.[22,23,25,30] The bismuth(III) complexes of D,L-serine, **5** and L-tyrosine, **6**, display the δ(OH) bending absorption band at 1246 - 1181 cm^{-1} and 1266 - 1213 cm^{-1}, respectively, suggesting that the hydroxyl group retains the proton.

Table 4. Comparison of the absorption bands obtained for the Bi(III) complexes **1** to **8**. ATR-IR absorption bands are reported in cm^{-1}.

	α-amino acid	$\tilde{\upsilon}_{as}$(COO)	$\tilde{\upsilon}_{s}$(COO)	δ(OH)
1	Phe	1622-1556	1334-1305	-
2	Pro	1611-1552	1374-1318	-
3	Met	1560-1508	1351-1315	-
4	Cys	1579-1543	1391-1346	-
5	Ser	1573-1506	1351-1311	1246-1181
6	Tyr	1583-1511	1361-1328	1266-1213
7	Asp	1687-1509	1420-1297	-
8	Glu	1638-1509	1435-1309	-

Evidence for the formation of the bismuth(III) complexes with general formula of $[BiL_3]$ (L = Phe **1**, Pro **2**, Met **3**, Ser **5**, Tyr **6**) or $[Bi_2L_3]$ (L = Cys **4**, Asp **7**, Glu **8**) was provided by elemental analysis and a summary table is given in the supporting information (Table S3).

Antimicrobial Properties – Activity against *H.pylori*

Biological Testing

As described in the introduction, the bismuth compounds used to treat *H. pylori* infection are all carboxylates and tend to exist in the hydrolysed *sub* form, comprising large poynuclear oxido species. They display minimum inhibitory concentrations (MIC) of 12.5 μg mL^{-1} for bismuth *sub*salicylate (BSS) and colloidal bismuth *sub*citrate (CBS), and 8 μg mL^{-1} for ranitidine bismuth citrate (RBC).[51-53] In treating *H. pylori* they are used in conjunction with other antibiotics such as amoxicillin and metronidazole. We have recently shown that pure *tris*-carboxylato bismuth(III) compounds, including those derived from non-steroidal anti-inflammatory drugs (NSAIDs), provide significantly lower MIC values, typically 6.25 μg mL-1.[54-56] Since *α*-amino acids give rise to bismuth(III) carboxylates of form $[BiL_3]$ and $[Bi_2L_3]$, and are of negligible toxicity, it is of interest to determine their activity against *H. pylori*.

Several features of the *α*-amino acids were of importance in studying and comparing the impact of various structural features: (i) the change in polarity from non-polar to polar *α*-amino acids, (ii) monoprotic *vs* polyprotic *α*-amino acids, (iii) aromatic *vs* aliphatic *α*-amino acids, and (iv) inclusion of the nitrogen atom in a heterocycle as comparator with exocyclic amines. The bismuth complexes **1** - **8** were then assessed alongside each of the free *α*-amino acids for their activity against three laboratory strains of *H. pylori* (251, B128 and 26695) using the agar diffusion method.

As described earlier, mass spectrometry suggests that the bismuth(III) complexes **1** – **8** undergo hydrolysis in aqueous solutions, and with this process protonation and release of the free *α*-amino acid(s) occurs. Therefore, the toxicological effect of the free *α*-amino acids needs to be considered when forming and assessing any metallo-drugs.

Toxicity studies on *α*-amino acids that are considered important in our diet have been reported.[57-64] In general, the *α*-amino acids showed no mutagenic activity, no toxicological relevant effects, and no observed deaths. The *α*-amino acid L-histidine demonstrates a low systematic toxicity (LD_{50} oral dose of in rats is 4.8 g kg^{-1}) and was not carcinogenic.[57] Recently, a review of the safety of L-glutamine was published by Shao and Hathcock showing that up to 14 g of L-glutamine per day can be tolerated by humans,[65] and the World Health Organisation (WHO) reports it is non-genotoxic.[66] Although most of the *α*-amino acids tested within this work were not toxicologically investigated, a general overview from the published data in the literature would suggest, that *α*-amino acids are suitable acids for medicinal and therapeutic applications in humans. All *α*-amino acids were tested under the same conditions as their corresponding bismuth(III) compounds to assure that no effect originated from the *α*-amino acid itself.

Solubility and stability

Complexes **1** and **2** are insoluble in water and in 1.0 M aqueous HCl solution, and there was no evidence of dissolution or decomposition of the complexes after stirring for 12 hours at 22 °C. However, complexes **3** - **8** are soluble in water in the pH range 2 - 5. Equimolar ESI-MS studies on **1** - **8** in DMSO/MeOH (1:5) and/or H_2O/MeOH (1:5) indicates hydrolysis occurs and acid formation may play a role in enhancing the liberation of free Bi^{3+} ions.

Activity against *H. pylori*

The *in-vitro* anti-bacterial activity of bismuth compounds **1** - **8**, was assessed against three laboratory strains of *H. pylori*: B128, 251 and 26695. B128 is a gastric ulcer strain which can easily colonise the stomach of mice and Mongolian gerbils.[67] Strain 251 is a human clinical isolate from non-ulcer dyspepsia,[68] while strain 26695 was originally isolated from a patient with gastritis.[69] For comparison, the activity of the corresponding free α-amino acids was also assessed.

DMSO was used as the control in each case since it has no activity against these strains of *H. pylori*. The MIC of each compound was established using the agar dilution method

(described in the Experimental section) and are presented in Table 5. The MIC values relating to the molecular mass of the initial complex, as $[BiL_3]$ or $[Bi_2L_3]$, is provided in the Supporting Information (see Table S4). Table 5 illustrates both the diversity in activities across and within particular strains, and highlights the impact of the choice of solvent for solubilisation of the compound.

Table 5. Summary of the biological test results – MIC (in $\mu g \cdot mL^{-1}$) determination of the bismuth compounds **1** to **8**.

Compound	Aqueous Solubility		Activity MIC (µg/mL)		
	pH 7	pH 2	251	B128	26695
$[Bi(Phe)_3]$ – **1** (tested in DMSO)	***insol***	***insol***	**12.5**	**0.049**	**3.125**
$[Bi(Pro)_3]$ – **2** (tested in DMSO)	***insol***	***insol***	**1.563**	**12.5**	**50**
$[Bi(Met)_3]$ – **3** (tested in DMSO)	***sol***	***sol***	**3.125**	**12.5**	**25**
$[Bi(Met)_3]$ – **3** (tested in water)	***sol***	***sol***	**6.25**	**25**	**25**
$[Bi_2(Cys)_3]$ – **4** (tested in DMSO)	***sol***	***sol***	**0.195**	**0.049**	**0.195**
$[Bi_2(Cys)_3]$ – **4** (tested in water)	***sol***	***sol***	**25**	**0.049**	**100**
$[Bi(Ser)_3]$ – **5** (tested in DMSO)	***sol***	***sol***	**0.098**	**0.049**	**50**
$[Bi(Ser)_3]$ – **5** (tested in water)	***sol***	***sol***	**100**	**100**	**50**
$[Bi(Tyr)_3]$ – **6** (tested in DMSO)	***sol***	***sol***	**3.125**	**6.25**	**25**
$[Bi_2(Asp)_3]$ – **7** (tested in DMSO)	***sol***	***sol***	**3.125**	**25**	**25**
$[Bi_2(Glu)_3]$ – **8** (tested in DMSO)	***sol***	***sol***	**12.5**	**0.049**	**0.195**
$[Bi_2(Glu)_3]$ – **8** (tested in water)	***sol***	***sol***	**25**	**12.5**	**0.781**

General Observations

All eight *α*-amino acids proved to be inactive against all strains at the maximum concentration tested (100 μg mL^{-1}). The bactericidal activity is enhanced significantly through deprotonation and complexation with bismuth(III).

For strain 251 the bismuth(III) complexes of the polar *α*-amino acids **4** to **8** were more active compared to those of the non-polar *α*-amino acids **1** to **3**. The MIC values for the bismuth(III) compounds of the neutral *α*-amino acids **4** to **6** were significantly lower than that of the acidic *α*-amino acids **7** and **8**, with MIC values as low as 0.098 μg mL^{-1} for **5**.

The bismuth(III) complexes derived from aliphatic *α*-amino acids performed, in general, better than the relevant aromatic *α*-amino acids. For the strain B128 the same trends are observed as for 251, however, MIC values as low as 0.049 μg mL^{-1} (**1**, **4**, **5** and **8**) are obtained for some bismuth(III) compounds.

In general, a significant increase in the MIC values, and therefore, decrease in activity was obtained for the strain 26695 (MIC values up to 50 μg mL^{-1} were observed). The inclusion of the nitrogen atom in the heterocycle showed no effects, as the *tris*-substituted bismuth(III) derived from L-proline, **2**, displayed results that were comparable with exocyclic bismuth(III) compounds. The most consistent results were obtained with the bismuth(III) complex of L-cysteine, **4**, which showed MIC values of 0.195 μg mL^{-1} for the strains 251 and 26695, and 0.049 μg mL^{-1} for the strain B128. These activity results are comparable with the bismuth(III) sulfonate[70] and amino arenesulfonate[35] complexes. Generally, the obtained results showed a great diversity in the MIC values obtained for the different strains and different bismuth(III) compounds, which ranged from MIC values of 0.049 μg mL^{-1} to 50 μg mL^{-1}.

When water was used to dissolve compounds **3 – 5** and **8** the MIC values for some strains dramatically increased, and at least doubled (see $[Bi(Met)_3]$, **3**). Only on a few occasions does the level of activity remain comparable with that when the compound is initially dissolved in DMSO, for example $[Bi_2(Cys)_3]$, **4**, towards strain B128. The bismuth(III) compound derived from L-serine became essentially inactive with MIC values of 100 μg mL^{-1} (comparable with MIC value of $BiPh_3$ (> 64 μg mL^{-1}) which is considered inactive).

Although the solvents themselves showed no activity against *H. pylori*, the solvent in which the compounds are initially dissolved clearly impacts on the bactericidal properties of the bismuth(III) complexes. This is linked to ligand lability and the rate of hydrolysis of the

compounds in generating polynuclear oxido clusters. The acidity of water in DMSO is lowered substantially (to have a pK_a of 32) and most likely slows the hydrolysis process substantially relative to water only. It is known that the formation of oxido clusters is favoured in highly acidic conditions, *e.g.* with nitrate and sulfonic acids. The culture medium is buffered by PBS at a pH of 7.4 and most likely inhibits, or at least slows substantially, both cluster growth and new cluster formation. Thus, whether DMSO or water is used to prepare the initial stock solution of water-soluble bismuth compound leads to differing outcomes in bacterial *in-vitro* tests.

Conclusions

The synthesis of bismuth(III) complexes derived from *α*-amino acids was investigated by three different methods: using $BiPh_3$ under SF and SM conditions; metathesis with Ag(I) salts of the α-amino acids, and with $[Bi(O^tBu)_3]$. Reactions with $BiPh_3$ were unsuccessful because of the low acidity of the ammonium protons in the zwitterion form of the amino acids, while the Ag(I) salts undergo facile decomposition. As such these synthetic routes are not viable approaches to bismuth(III) derivatives. The target carboxylato compounds are successfully made using $[Bi(O^tBu)_3]$ with careful maintenance of low temperatures to avoid decomposition. Thus, four new bismuth(III) complexes derived from monoprotic *α*-amino acids with general formula $[BiL_3]$ {L = Phe (**1**), Pro (**2**), Ser (**5**) and Tyr (**6**)}. Further analytical data was provided for the bismuth(III) complex of L-methionine $[Bi(Met)_3]$, (**3**), as only IR data was previously reported. The polyprotic *α*-amino acids resulted in three new bismuth(III) compounds of the general formula $[Bi_2L_3]$ {L = Cys (**4**), Asp (**7**) and Glu (**8**)}. All Bi(III) complexes were synthesised and characterised (^{1}H and ^{13}C NMR, ATR-IR, ESI-MS$^+$ and elemental analysis).

Complexes **4**, **7** and **8** dissolved well in water while those of **3**, **5** and **6** are partially water-soluble. The acidic pH values of the aqueous solutions provided evidence of the presence of free *α*-amino acid(s) indicating hydrolysis. Mass spectrometry studies using positive ESI-MS provided further evidence for hydrolysis and showed the formation of bismuth(III)-oxido/hydroxido species in aqueous solutions.

Since *α*-amino acids are generally considered to have no toxicological relevant effects, the bismuth(III) complexes **1** to **8** were assessed for their activity against *H. pylori*. The obtained

results showed a great diversity in the MIC values obtained for the different strains and different bismuth(III) compounds, which ranged from MIC values of 0.049 μg mL^{-1} to 50 μg mL^{-1}, while all eight *α*-amino acids proved to be essentially inactive (>100 μg mL^{-1}). However, general trends showed that bismuth(III) complexes of polar, neutral and aliphatic *α*-amino acids gave lower MIC values compared to the bismuth(III) complexes of non-polar, acidic and aromatic *α*-amino acids. The bismuth(III) complex of L-cysteine, **4**, showed the most consistent results between different solvents with MIC values of 0.195 μg mL^{-1} for the strains 251 and 26695, and 0.049 μg·mL^{-1} for the strain B128. A general decrease in activity was obtained for the strain 26695 (MIC values up to 50 μg mL^{-1} were observed). The inclusion of the nitrogen atom in the heterocycle showed no effect on the bactericidal properties when compared to the exocyclic compounds. The MIC values dramatically increased (reduced toxicity) when water was used as solvent instead of DMSO and the bismuth(III) compound of the *α*-amino acid L-serine, **5**, became essentially inactive with MIC values of 100 μg mL^{-1}. Although the solvents themselves (DMSO and water) showed no activity against *H. pylori*, the bactericidal properties of the bismuth(III) compounds are clearly influenced by the solvent used in sample preparation.

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Experimental

General: All laboratory reagents and chemicals were purchased from Sigma Aldrich. $[Bi(O^tBu)_3]$ was synthesised and purified according to an established procedure.[37] Horse blood agar (HBA) and brain heart infusion broth (BHI) were obtained from Oxoid Australia Pty. Fetal calf serum (FCS) was purchased from Invitrogen. Polymyxin B, Vancomycin, Trimethoprim and Amphotericin B were purchased from Sigma, MO, USA. All ATR spectra were recorded on an ATR-IR Spectrometer, Bruker IFS 55 Equinox. NMR spectra were obtained with Bruker AV300 spectrometer with chemical shifts referenced to C_6D_6 ($[Bi(O^tBu)_3]$), D_6-DMSO (**1** and **6**), D_6-EtOH (**2**) and D_2O (**3**-**5**, **7** and **8**). Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer with an electrospray

source and a cone voltage of 35eV using a DMSO or DMSO/MeOH or DMSO/EtOH solution as the mobile phase. Elemental analysis was carried out by The Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, New Zealand. Differential Scanning Colorimetry (DSC) was carried out using a DSC Q100 Thermogravimetric Analyzer. The starting materials were dried a minimum of 4 h in vacuum prior to use. The dried materials were grinded together and the mixed sample (5 mg to 10 mg) was placed in an aluminium pan and heated from 30 °C to 300 °C using a 10 °C/min heating modus. Solvents were purified as follows. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use and stored over 4Å molecular sieves (MS) under N_2. Benzene and D_6-DMSO were distilled from calcium hydride (CaH_2) prior to use and stored over 4Å or 3Å MS under N_2. All MS were dried at 120 °C and allowed to cool under vacuum before use. ^{1}H-NMR spectra were taken to check purity of all starting materials. Solid reagents were all dried under high vacuum for a minimum of 4 h prior to use. All reactions requiring anhydrous conditions were conducted with oven dried glassware under an atmosphere of dry nitrogen using a vacuum/nitrogen line and Schlenk techniques. All glassware was dried at 120 °C for approximately 24 h prior to use and allowed to cool under vacuum to minimize moisture content. Filtering of solutions was carried out through rubber seals using an oven dried/nitrogen purged cannula equipped with glass fibre microfilters (GF/A, circles ø 42.5 cm, Whatman®) fixed with Teflon tape. All analytical samples of air-sensitive compounds were prepared using a high purity nitrogen recirculating dry box.

Solubility of the complexes in water was tested by means of dissolving the Bi(III) complexes **1** - **8** in distilled water without heating until the solution reached a minimum of 2.0 mg mL-1, the concentration necessary for the biological assays. Otherwise the compounds were tested in DMSO only. As a reference point the maximal concentration was only accurately calculated for the most soluble compound [$Bi_2(Glu)_3$].

Bacterial strains and culture conditions: *H. pylori* strains 251, B128 and 26695[71] were routinely cultured on horse blood agar (HBA) or in brain heart infusion broth (BHI), supplemented with either 7.5% (v/v) fresh horse blood or 10% (v/v) FCS, respectively.[72] Culture media were further supplemented with 155 mg L^{-1} polymyxin B, 6.25 mg L^{-1} vancomycin, 3.125 mg L^{-1} trimethoprim, 1.25 mg L^{-1} Amphotericin B.

Determination of the Minimum Inhibitory Concentration (MIC): The MICs of bismuth(III) complexes **1** to **8** were determined by the agar dilution technique. All bismuth(III) complexes were dissolved in DMSO or H_2O to give clear, colourless solutions of known concentration. *H. pylori* cultures were incubated in BHI for 18 h shaking at 140 rpm at 37 °C under micro-aerobic conditions. Bacteria were pelleted, washed in plain BHI and then resuspended in plain BHI. Each suspension was adjusted to give an approximate density of 10^6 bacteria per mL^{-1}. Aliquots (10 µL) of these suspensions were then streaked onto HBA plates containing serial dilutions of the different concentrations of bismuth compounds, ranging in concentration from 6.25–25 µg mL^{-1}. Each compound was tested alongside the free α-amino acids to exclude any effect on the activity against *H. pylori.* The MICs of the different compounds were determined by examination of the plates after incubation for 48 h at 37 °C.

Synthesis and Characterisation

General Procedure using example of *tris*-(*(S)*-2-amino-3-phenylpropanoato) bismuth(III), [Bi(Phe)$_3$] (1):

All reagents were dried *in vacuo* at least 4 h prior to use. To a suspension of *(S)*-2-amino-3-phenylpropanoic acid (*L*-phenylalanine = Phe) (1.5 mmol, 3 eq) in abs. THF (10 ml) at -78 °C (ethanol-liquid nitrogen bath), a solution of [Bi(O^{t}Bu)$_3$] (0.5 mmol, 1 eq) in abs. THF (5 ml) was added very slowly. The reaction mixture was allowed to warm to -40 °C and this temperature maintained for *ca*. 3 h before warming to RT overnight. The solvent was removed by filtration with a filter cannula and the resulting precipitate washed with ether (3 x 10 ml). The residue was dried *in vacuo* to yield the *tris*-substituted bismuth(III) product as a beige coloured powder **1**. Yield 277 mg (79 %). M.pt. 176 C° (decomp.). ^{1}H NMR (300 MHz, D_6-DMSO, 30°C): δ = 7.32-7.19 (5H, m, H^5 to H^9), 4.58 (2H, bs, NH_2), 3.74 (1H, dd, ^3J = 3.00, 6.00 Hz, H^2), 3.13 (1H, dd, ^2J = 6.00 Hz, ^3J = 12.00 Hz, H^{3a}), 2.80 (1H, dd, ^2J = 9.00 Hz, ^3J = 15.00 Hz, H^{3b}). ^{13}C NMR (75 MHz, D_6-DMSO, 30°C): δ = 177.0 (C^1), 138.6 (C^4), 129.3 (C^5, C^9), 128.3 (C^6, C^8), 126.2 (C^7), 55.9 (C^2), 40.4 (C^3). ATR-IR (cm^{-1}): ũ = 3003(m), 2961(m), 1622(m), 1556(s), 1493(s), 1456(m), 1445(m), 1408(s), 1334(m), 1320(m), 1305(s), 1292(m), 1223(m), 1152(m), 1129(m), 1074(w), 1024(w), 1002(w), 949(w), 913(w), 848(m), 777(m), 744(s), 697(s), 681(m). ESI-MS$^+$ (solvent: DMSO/MeOH): *m/z* = 909 (15%,

$[Bi_9O_7L_7(OH)_2(MeOH)_{10}(H_2O)_8]^{4+}$), 837 (5%, $[Bi_9O_7L_6(OH)_3(MeOH)_{10}]^{4+}$), 826 (7%, $[Bi_9O_7L_6(OH)_3(MeOH)_6(H_2O)_3]^{4+}$), 755 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_3(DMSO)_2]^{4+}$), 744 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_7(H_2O)]^{4+}$), 727 (5%, $[Bi_9O_7L_4(OH)_5(DMSO)_2(H_2O)]^{4+}$), 705 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)(H_2O)_3]^{4+}$), 683 (15%, $[Bi_8O_6L_4(OH)_4(DMSO)(H_2O)_9]^{4+}$), 661 (20%, $[Bi_8O_6L_2(OH)_6(MeOH)_{10}(H_2O)_7]^{4+}$), 590 (15%, $[Bi_8O_6L_2(OH)_6(H_2O)_9]^{4+}$), 584 (5%, $[Bi_6O_4L_4(MeOH)_4(DMSO)_3]^{4+}$), 562 (15%, $[Bi_8O_6L_2(OH)_6(MeOH)(H_2O)]^{4+}$), 540 (5%, $[Bi_6O_6L_2(MeOH)_{10}(H_2O)_9]^{4+}$), 534 (20%, $[Bi_6O_6L_2(MeOH)_7(DMSO)_3]^{4+}$), 518 (15%, $[Bi_6O_6L_2(MeOH)_5(DMSO)_3]^{4+}$), 496 (10%, $[Bi_6O_6L_2(MeOH)_9(H_2O)]^{4+}$), 375 (5%, $[Bi_4O_2L_2(OH)_2(MeOH)_6(DMSO)]^{4+}$), 369 (10%, $[Bi_4O_2L_2(OH)_2(MeOH)_6(H_2O)_3]^{4+}$), 366 (10%, $[Bi_4O_2L_2(OH)_2(DMSO)_3]^{4+}$), 353 (100%, $[Bi_4O_2L_2(OH)_2(MeOH)_4(H_2O)_3]^{4+}$), 210 (10%, $[LNa+Na]^+$), 188 (30%, $[LH+Na]^+$), 166 (20%, $[LH+H]^+$), 120 (100%, $[L\text{-}CO_2]^+$). Elemental Analysis: $BiC_{27}H_{30}O_6N_3{\cdot}H_2O$ (719.52): calc. C 45.07, H 4.48, N 5.84; found: C 44.80, H 4.50, N 5.65 %.

***Tris*-(*(S)*-pyrrolidine-2-carboxylato) bismuth(III), [Bi(Pro)$_3$] (2):**

The general procedure was followed applying *(S)*-pyrrolidine-2-carboxylic acid (*L*-proline = Pro) to give the compound **2** as a yellow coloured powder. Yield 245 mg (89 %). M.pt. 163 C° (decomp.) ^{1}H NMR (300 MHz, D_6-EtOH, 30°C): δ = 3.82 (1H, t, ^3J = 6.00 Hz, H^2), 3.09-3.06 (2H, m, H^5), 2.13-1.98 (2H, m, H^3), 1.30 - 1.76 (2H, m, H^4). ^{13}C NMR (75 MHz, D_6-EtOH, 30°C): δ = 60.9 (C^2), 45.6 (C^5), 29.00 (C^3), 24.0 (C^4). ATR-IR (cm^{-1}): ũ = 3045(m), 2981(s), 2776(m), 1611(s), 1552(s), 1473(m), 1448(sh), 1374(s), 1318(m), 1289(m), 1254(m), 1168(w), 1084(w), 1033(m), 981(w), 946(w), 913(w), 847(m), 786(m), 639(m). ESI-MS$^+$ (solvent: DMSO/MeOH): *m/z* = 749 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_6(H_2O)_{15}]^{4+}$), 713 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_6(H_2O)_7]^{4+}$), 691 (10%, $[Bi_9O_7L_2(OH)_7(MeOH)_2(H_2O)_{20}]^{4+}$), 657 (5%, $[Bi_9O_7L_2(OH)_7(MeOH)_9]^{4+}$), 619 (5%, $[Bi_9O_7L_2(OH)_7(MeOH)_2(H_2O)_4]^{4+}$), 613 (20%, $[Bi_8O_6L_4(OH)_4(MeOH)_5]^{4+}$), 585 (5%, $[Bi_8O_6L_2(OH)_6(MeOH)_7(H_2O)]^{4+}$), 576 (20%, $[Bi_8O_6L_2(OH)_6(MeOH)_4(DMSO)]^{4+}$), 569 (20%, $[Bi_8O_6L_2(OH)_6(MeOH)_5(H_2O)]^{4+}$), 563 (5%, $[Bi_8O_6L_2(OH)_6(MeOH)_2(H_2O)_5]^{4+}$), 541 (10%, $[Bi_6O_4L_4(MeOH)_6(H_2O)_{11}]^{4+}$), 527 (5%, $[Bi_6O_4L_4(MeOH)_8(DMSO)]^{4+}$), 525 (30%, $[Bi_6O_4L_4(MeOH)_4(H_2O)_{11}]^{4+}$), 505 (5%, $[Bi_6O_4L_4(MeOH)_6(H_2O)_3]^{4+}$), 499 (20%, $[Bi_6O_4L_4(MeOH)_3(H_2O)_7]^{4+}$), 483 (20%, $[Bi_6O_4L_4(MeOH)(H_2O)_7]^{4+}$), 481 (40%, $[Bi_6O_4L_4(MeOH)_3(H_2O)_3]^{4+}$), 461 (50%, $[Bi_6O_4L_2(OH)_2(MeOH)_9(H_2O)_2]^{4+}$), 448 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_3(H_2O)_{10}]^{4+}$), 437 (45%, $[Bi_6O_4L_2(OH)_2(MeOH)_3(H_2O)_4]^{4+}$), 426 (5%,

$[Bi_4O_2L_4(MeOH)_4(H_2O)_{14}]^{4+}$), 415 (5%, $[Bi_4O_2L_4(DMSO)_2(H_2O)_{10}]^{4+}$), 412 (15%, $[Bi_4O_2L_4(MeOH)_9(H_2O)_2]^{4+}$), 403 (15%, $[Bi_4O_2L_4(MeOH)_9]^{4+}$), 393 (55%, $[Bi_4O_2L_4(MeOH)(H_2O)_{12}]^{4+}$), 390 (10%, $[Bi_4O_2L_4(MeOH)_4(H_2O)_6]^{4+}$), 368 (15%, $[Bi_4O_2L_2(OH)_2(MeOH)_9(H_2O)_3]^{4+}$), 346 (90%, $[Bi_4O_2L_2(OH)_2(MeOH)_4(H_2O)_7]^{4+}$), 327 (15%, $[Bi_4O_2L_2(OH)_2(MeOH)_5(H_2O)]^{4+}$), 316 (5%, $[Bi_3OL(OH)_3(MeOH)(H_2O)_6]^{3+}$), 309 (100%, $[Bi_3OL(OH)_3(DMSO)(H_2O)_2]^{3+}$), 305 (15%, $[Bi_2L(MeOH)_9(H_2O)_5]^{3+}$), 275 (5%, $[Bi_2L(MeOH)_9]^{3+}$), 268 (10%, $[BiL(MeOH)_2(H_2O)_8]^{2+}$), 263 (20%, $[Bi_2L(MeOH)_3(DMSO)_2]^{4+}$), 253 (10%, $[2LH+Na]^+$), 231 (50%, $[2LH+H]^+$), 192 (10%, $[LH(H_2O)_3+Na]^+$), 154 (10%, $[LH+K]^+$), 138 (100%, $[LH+Na]^+$), 138 (100%, $[LH+H]^+$). Elemental Analysis: $BiC_{15}H_{24}O_6N_3{\cdot}H_2O$ (569.352): calc. C 31.64, H 4.60, N 7.38; found: C 31.52, H 4.79, N 7.28 %.

***Tris*-(*(S)*-2-amino-4-(methylthio)butanato) bismuth(III), [Bi(Met)$_3$] (3):**

The general procedure was carried out using *(S)*-2-amino-4-(methylthio)butanoic acid (*L*-methionine = Met) to yield compound **3** as a pale yellow powder. Yield 310 mg (95 %). M.pt. 175 C° (decomp.). ^{1}H NMR (300 MHz, D_2O, 30°C): δ = 3.92 (1H, dd, ^3J = 6.00 Hz, 9.00 Hz, H^2), 2.71 (2H, t, ^3J = 9.00 Hz, H^4), 2.32-2.22 (2H, m, H^3), 2.20 (3H, s, H^5). ^{13}C NMR (75 MHz, D_2O, 30°C): δ = 174.6 (C^1), 54.2 (C^2), 30.0 (C^3), 29.1 (C^4), 14.2 (Me). ATR-IR (cm^{-1}): $\tilde{u}$ = 2914(s), 2570(m), 1580(s), 1560(s), 1508(s), 1447(m), 1405(s), 1351(m), 1315(m), 1275(w), 1242(m), 1184(m), 1150(w), 1118(w), 1069(w), 980(w), 951(w), 873(w), 804(w), 765(w), 750(w), 680(w), 643(w). ESI-MS$^+$ (solvent: DMSO/MeOH): *m/z* = 779 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_{10}(H_2O)_7]^{4+}$), 727 (25%, $[Bi_9O_7L_4(OH)_5(MeOH)_5(DMSO)]^{4+}$), 707 (10%, $[Bi_9O_7L_2(OH)_7(MeOH)_{12}(H_2O)_2]^{4+}$), 686 (5%, $[Bi_9O_7L_2(OH)_7(MeOH)_6(H_2O)_8]^{4+}$), 670 (35%, $[Bi_9O_7L_2(OH)_7(MeOH)_4(H_2O)_8]^{4+}$), 664 (10%, $[Bi_9O_7L_2(OH)_7(MeOH)(H_2O)_{12}]^{4+}$), 663 (35%, $[Bi_9O_7L_2(OH)_7(MeOH)_2(H_2O)_{10}]^{4+}$), 652 (30%, $[Bi_8O_6L_4(OH)_4(H_2O)_{10}]^{4+}$), 641 (100%, $[Bi_9O_7L_2(OH)_7(DMSO)]^{4+}$), 630 (30%, $[Bi_8O_6L_2(OH)_6(MeOH)_9(H_2O)_6]^{4+}$), 619 (5%, $[Bi_8O_6L_2(OH)_6(MeOH)_8(H_2O)_3]^{4+}$), 597 (5%, $[Bi_8O_6L_2(OH)_6(MeOH)_3(H_2O)_7]^{4+}$), 589 (30%, $[Bi_8O_6L_2(OH)_6(MeOH)_2(H_2O)_7]^{4+}$), 578 (55%, $[Bi_8O_6L_2(OH)_6(MeOH)_4(H_2O)]^{4+}$), 566.5 (40%, $[Bi_8O_6L_2(OH)_6(MeOH)_2(H_2O)_2]^{4+}$), 556 (40%, $[Bi_6O_4L_4(MeOH)_7(H_2O)_5]^{4+}$), 545 (45%, $[Bi_6O_4L_4(MeOH)_6(DMSO)]^{4+}$), 536 (85%, $[Bi_6O_4L_4(DMSO)_3]^{4+}$), 514 (20%, $[Bi_6O_4L_4(MeOH)_4(H_2O)]^{4+}$), 492 (25%, $[Bi_6O_4L_2(OH)_2(MeOH)_{10}]^{4+}$), 470 (15%, $[Bi_6O_6L_2(DMSO)_3]^{4+}$), 448 (5%, $[Bi_6O_6L_2(MeOH)_4(H_2O)]^{4+}$), 365 (5%, $[Bi_4O_2L_4]^{4+}$), 350 (15%, $[Bi_3OL(OH)_3(MeOH)_2(H_2O)_8]^{3+}$), 343 (15%, $[Bi_4O_2L_2(OH)_2(MeOH)_3(DMSO)]^{4+}$), 337 (15%,

$[Bi_4O_2L_2(OH)_2(MeOH)_3(H_2O)_3]^{4+}$), 321 (30%, $[Bi_4O_2L_2(OH)(MeoH)(H_2O)_3]^{4+}$), 194 (30%, $[LNa+Na]^+$), 172 (100%, $[LH+Na]^+$), 150 (45%, $[LH+H]^+$). Elemental Analysis: $BiC_{15}H_{30}O_6N_3S_3$ (653.583): calc. C 27.56, H 4.63, N 6.43; found: C 27.44, H 4.49, N 6.70 %.

Tris-((S)-2-amino-3-sulfidopropanato) bismuth(III), $[Bi_2(Cys)_3]$ (4):

The general procedure was applied using *(S)*-2-amino-3-sulfidopropanoic acid (*L*-cysteine = Cys) to yield compound **4** as a yellow powder. Yield 165 mg (85 %). M.pt. 180 C° (decomp.). ^{1}H NMR (300 MHz, D_2O, 30°C): δ = 3.73-3.66 (1H, m, H^2), 1.25-1.20 (2H, m, H^3). ^{13}C NMR (75 MHz, D_2O, 30°C): δ = 172.7 (C^1), 56.1 (C^2), 25.1 (C^3). ATR-IR (cm^{-1}): ũ = 2959(m), 2550(w), 1579(s), 1543(m), 1421(m), 1391(m), 1346(m), 1296(m), 1239(m), 1156(m), 1063(m), 942(m), 866(w), 823(m), 805(w), 692(w), 636(w). ESI-MS^+ (solvent: DMSO/MeOH): *m/z* = 963 (10%, $[Bi_{14}O_{10}L_2(OH)_{14}(MeOH)_9(H_2O)_2]^{4+}$), 874 (5%, $[Bi_{10}O_8L_4(OH)_2(DMSO)_8(H_2O)_8]^{4+}$), 820 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_6(H_2O)_{20}]^{4+}$), 809 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_8(H_2O)_{14}]^{4+}$), 798 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_{10}(H_2O)_8]^{4+}$), 787 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_{12}(H_2O)_2]^{4+}$), 776 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_5(H_2O)_{12}]^{4+}$), 636 (5%, $[Bi_9O_7L_2(OH)_5(MeOH)_6(H_2O)_2]^{4+}$), 612 (5%, $[Bi_9O_7L_2(OH)_5(MeOH)_3(H_2O)_2]^{4+}$), 590 (10%, $[Bi_8O_6L_2(OH)_4(MeOH)_5(H_2O)_7]^{4+}$), 568 (10%, $[Bi_8O_6L_2(OH)_4(H_2O)_{11}]^{4+}$), 547 (10%, $[Bi_8O_6L_2(OH)_4(MeOH)_3(H_2O)]^{4+}$), 525 (25%, $[Bi_6O_4L_2(OH)_2(MeOH)_{12}(H_2O)_7]^{4+}$), 519 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_9(H_2O)_{11}]^{4+}$), 515 (15%, $[Bi_6O_4L_2(OH)_2(MeOH)_{16}(H_2O)_3]^{4+}$), 493 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_7(H_2O)_8]^{4+}$), 485 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_7(H_2O)_7]^{4+}$), 481 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_2(H_2O)_{15}]^{4+}$), 471 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_3(H_2O)_{11}]^{4+}$), 449 (100%, $[Bi_6O_4L_2(OH)_2(MeOH)_4(DMSO)]^{4+}$), 402 (5%, $[Bi_6O_4L_2(OH)_2(H_2O)]^{4+}$), 364 (10%, $[Bi_4O_2L_2(MeOH)_7(H_2O)_7]^{4+}$), 350 (10%, $[Bi_4O_2L_2(MeOH)_3(H_2O)_{11}]^{4+}$), 328 (15%, $[Bi_4O_2\ L_2(MeOH)_4(DMSO)]^{3+}$), 307 (10%, $[Bi_4O_2L_2(MeOH)(H_2O)_5]^{4+}$), 184 (30%, $[LHNa(H_2O)+Na]^+$), 166 (10%, $[LHNa+Na]^+$), 144 (15%, $[LH_2+Na]^+$), 122 (100%, $[LH_2+H]^+$). Elemental Analysis: $Bi_2C_9H_{15}O_6N_3S_3$ (775.383): calc. C 13.94, H 1.95, N 5.42; found: C 13.86, H 2.10, N 5.25 %.

***Tris*-(2-amino-3-hydroxypropanoato) bismuth(III), $[Bi(Ser)_3]$ (5):**

2-Amino-3-hydroxypropanoic acid (*D,L*-serine = Ser) was used in the general procedure to produce compound **5** as colourless powder. Yield 232 mg (86 %). M.pt. 183 C° (decomp.). ^{1}H NMR (300 MHz, D_2O, 30°C): δ = 5.85 (2H, bs, NH_2), 3.91 (1H, m, H^{3a}), 3.74 (1H, m, H^2), 3.29

(1H, m, H^{3b}). ^{13}C NMR (75 MHz, D_2O, 30°C): δ = 172.6 (C^1), 60.4 (C^3), 56.7 (C^2). ATR-IR (cm^{-1}): ũ = 2940(s), 2645(m), 1656(m), 1635(m), 1573(s), 1506(s), 1431(s), 1351(s), 1311(s), 1246(m), 1181(w), 1149(m), 1094(m), 1029(s), 982(m), 900(m), 849(w), 815(w), 727(m), 617(m). ESI-MS^+ (solvent: DMSO/MeOH): *m/z* = 996 (15%, $[Bi_{14}O_{16}L_6(MeOH)_5(H_2O)]^{4+}$), 927 (5%, $[Bi_{12}O_{10}L_6(OH)_4(MeOH)_3(H_2O)_{14}]^{4+}$), 906 (5%, $[Bi_{12}O_{10}L_8(OH)_2(H_2O)_5]^{4+}$), 863 (5%, $[Bi_{12}O_{10}L_4(OH)_6(MeOH)(H_2O)_{13}]^{4+}$), 821.5 (10%, $[Bi_{12}O_{10}L_4(OH)_6(MeOH)_2(H_2O)_2]^{4+}$), 758 (10%, $[Bi_9O_7L_8(OH)(MeOH)_2(H_2O)_7]^{4+}$), 728 (5%, $[Bi_9O_7L_6(OH)_3(MeOH)_2(H_2O)_{10}]^{4+}$), 675 (10%, $[Bi_9O_7L_6(OH)_3(MeOH)]^{4+}$), 664 (5%, $[Bi_8O_6L_4(OH)_4(MeOH)_7(H_2O)_{10}]^{4+}$), 658 (5%, $[Bi_9O_7L_2(OH)_7(MeOH)_3(H_2O)_{12}]^{4+}$), 653 (10%, $[Bi_9O_7L_4(OH)_5(MeOH)_2(H_2O)_3]^{4+}$), 623 (5%, $[Bi_9O_7L_2(OH)_7(MeOH)_2(H_2O)_6]^{4+}$), 612 (10%, $[Bi_9O_7L_2(OH)_7(MeOH)_4]^{4+}$), 589 (5%, $[Bi_9O_7L_2(OH)_7(H_2O)_2]^{4+}$), 570 (15%, $[Bi_6O_4L_4(MeOH)_{12}(H_2O)_9]^{4+}$), 548 (25%, $[Bi_6O_4L_4(MeOH)_7(H_2O)_{13}]^{4+}$), 531 (15%, $[Bi_6O_4L_4(MeOH)_6(H_2O)_{11}]^{4+}$), 507 (15%, $[Bi_6O_4L_4(MeOH)_3(H_2O)_{11}]^{4+}$), 465 (20%, $[Bi_6O_4L_4(H_2O)_7]^{4+}$), 462 (5%, $[Bi_6O_4L_4(MeOH)_3(H_2O)]^{4+}$), 443 (25%, $[Bi_6O_4L_2(OH)_2(MeOH)(H_2O)_{10}]^{4+}$), 404 (10%, $[Bi_4O_2L_2(MeOH)_7(H_2O)_6]^{4+}$), 382 (5%, $[Bi_4O_2L_4(MeOH)_2(H_2O)_{10}]^{4+}$), 360 (25%, $[Bi_4O_2L_2(OH)_2(MeOH)_3(H_2O)_{13}]^{4+}$), 354 (5%, $[Bi_4O_2L_4(MeOH)_3(H_2O)_2]^{4+}$), 338 (5%, $[Bi_4O_2L_4(MeOH)(H_2O)_2]^{4+}$), 328 (20%, $[Bi_3OL(OH)_3(MeOH)_3(H_2O)_5]^{4+}$), 316 (10%, $[Bi_4O_2L_2(OH)_2(MeOH)_2(H_2O)_5]^{4+}$), 309 (100%, $[Bi_4OL_2(OH)_4(H_2O)_6]^{4+}$), 306 (5%, $[Bi_2L(MeOH)_9(H_2O)_6]^{3+}$), 304 (10%, $[Bi_2L(MeOH)_6(H_2O)_{11}]^{3+}$), 293 (30%, $[Bi_4O_3L_2(H_2O)_2]^{4+}$), 277 (5%, $[Bi_3OL_2(OH)_2(H_2O)_3]^{3+}$), 249 (10%, $[Bi_3OL_2(OH)(MeOH)_4]^{4+}$), 233 (5%, $[Bi_3OL_2(OH)(MeOH)_2]^{4+}$]; 204 (25%, $[LNa(H_2O)_3+Na]^+$), 188 (15%, $[LH(MeOH)_2(H_2O)+H]^+$), 150 (30%, $[LNa+Na]^+$), 128 (30%, $[LH+Na]^+$). Elemental Analysis: $BiC_9H_{18}O_9N_3 \cdot H_2O$ (539.24): calc. C 20.04, H 3.74, N 7.79; found: C 19.91 , H 3.83, N 7.68 %.

***Tris*-(*(S)*-2-amino-3-(4-hydroxyphenyl)propanoato) bismuth(III), [Bi(Tyr)$_3$] (6):**

(S)-2-amino-3-(4-hydroxyphenyl)propanoic acid (*L*-tyrosine = Tyr) was used in the general procedure and produced compound **6** as a colourless powder. Yield 307 mg (82 %). M.pt. 256 C° (decomp.). ^1H NMR (300 MHz, D_6-DMSO, 30°C): δ = 7.03-6.99 (2H, m, H^5 & H^9), 6.68 (2H, d, ^3J = 6.00 Hz, H^6 & H^8), 3.54 (1H, m, H^2), 3.29 (1H, m, H^{3a}), 2.97 (1H, m, H^{3b}). ATR-IR (cm^{-1}): ũ = 3198(m), 3101(w), 3040(sh), 2929(m), 2878(m), 2738(m), 2646(m), 2596(m), 1606(m), 1583(s), 1511(s), 1451(m), 1434(m), 1416(m), 1361(s), 1328(s), 1266(w), 1242(s), 1213(m), 1174(m), 1154(m), 1111(m), 1098(m), 1042(m), 984(m), 939(w), 896(w), 877(w),

839(m), 792(m), 738(m), 712(m), 647(m). ESI-MS^+ (solvent: DMSO/MeOH): *m/z* = 906 (35%, $[Bi_9O_7L_6(OH)_3(MeOH)_{10}(H_2O)_{10}]^{4+}$), 835 (5%, $[Bi_9O_7L_4(OH)_5(MeOH)_{13}(H_2O)_7]^{4+}$), 816 (30%, $[Bi_9O_7L_4(OH)_5(MeOH)_{14}(H_2O)]^{4+}$), 791 (10%, $[Bi_9O_7L_4(OH)_5(MeOH)_3(H_2O)_{15}]^{4+}$), 769 (10%, $[Bi_9O_7L_4(OH)_5(MeOH)_7(H_2O)_3]^{4+}$), 763 (10%, $[Bi_9O_7L_4(OH)_5(MeOH)_4(H_2O)_7]^{4+}$), 725 (50%, $[Bi_9O_7L_2(OH)_7(MeOH)_{10}(H_2O)_6]^{4+}$), 640 (10%, $[Bi_8O_6L_2(OH)_6(MeOH)_3(H_2O)_{13}]^{4+}$), 632 (15%, $[Bi_8O_6L_2(OH)_6(MeOH)_2(H_2O)_{13}]^{4+}$), 610 (20%, $[Bi_8O_6L_2(OH)_6(MeOH)_6(H_2O)]^{4+}$), 602 (15%, $[Bi_8O_6L_2(OH)_6(MeOH)_5(H_2O)]^{4+}$), 596 (25%, $[Bi_8O_6L_2(OH)_6(MeOH)_2(H_2O)_5]^{4+}$), 588 (10%, $[Bi_8O_6L_2(OH)_6(MeOH)(H_2O)_5]^{4+}$), 582 (65%, $[Bi_6O_4L_4(OH)_2(MeOH)_8]^{4+}$), 566 (20%, $[Bi_6O_4L_4(OH)_4(MeOH)_6]^{4+}$), 544 (100%, $[Bi_6O_4L_2(OH)_4(MeOH)_5(H_2O)_{15}]^{4+}$), 524 (10%, $[Bi_6O_4L_2(OH)_4(MeOH)_7(H_2O)_7]^{4+}$), 501 (5%, $[Bi_6O_4L_2(OH)_4(MeOH)_3(H_2O)_9]^{4+}$), 429 (5%, $[Bi_4O_2L_4(MeOH)_4]^{4+}$), 420 (15%, $[Bi_4O_2L_2(OH)_2(MeOH)_8(H_2O)_9]^{4+}$), 415 (25%, $[Bi_4O_2L_2(OH)_2(MeOH)_4(H_2O)_{15}]^{4+}$), 407 (10%, $[Bi_4O_2L_2(OH)_2(MeOH)_3(H_2O)_{15}]^{4+}$), 401 (25%, $[Bi_4O_2L_2(OH)_2(MeOH)_9(H_2O)_3]^{4+}$), 385 (95%, $[Bi_4O_2L_2(OH)_2(MeOH)_7(H_2O)_3]^{4+}$), 382 (75%, $[Bi_4O_2L_2(OH)_2(MeOH)(H_2O)_{13}]^{4+}$), 363 (15%, $[Bi_4O_2L_2(OH)_2(MeOH)_2(H_2O)_7]^{4+}$), 309 (15%, $[Bi_3OL_2(OH)(H_2O)_{12}]^{4+}$), 226 (45%, $[LNa+Na]^+$), 204 (55%, $[LH+Na]^+$), 182 (30%, $[LH+H]^+$), 120 (100%, $[L\text{-}CO_2]^+$). Elemental Analysis: $BiC_{27}H_{30}O_9N_3$ (749.502): calc. C 43.26, H 4.03, N 5.61; found: C 43.35, H 4.00, N 5.42 %.

Tris-((S)-2-amino-butanedionato) bismuth(III), $[Bi_2(Asp)_3]$ (7):

(S)-2-amino-butanedionic acid (*L*-aspartic acid = Asp) was used according to the general procedure and compound **7** was obtained as a colourless powder. Yield 162 mg (80 %). M.pt. 226 C° (decomp.) ^{1}H NMR (300 MHz, D_2O, 30°C): δ = 4.23-4.19 (1H, m, H^2), 2.96-2.90 (2H, m, H^3). ^{13}C NMR (75 MHz, D_2O, 30°C): δ = 173.3 (C^1), 170.9 (C^4), 49.5 (C^2), 33.9 (C^3). ATR-IR (cm^{-1}): ũ = 2953(m), 2731(w), 2655(w), 2507(w), 1886(w), 1687(m), 1642(m), 1597(m), 1509(s), 1420(s), 1358(w), 1297(s), 1247(s), 1151(s), 1119(s), 1081(w), 1042(s), 989(s), 936(w), 898(m), 873(m), 777(w), 753(m), 654(m). ESI-MS^+ (solvent: DMSO/MeOH): *m/z* = 932 (5%, $[Bi_{12}O_{10}L_4(OH)_4(MeOH)_{10}(H_2O)_{15}]^{4+}$), 887 (5%, $[Bi_{12}O_{10}L_4(OH)_4(MeOH)_{10}(H_2O)_5]^{4+}$), 799 (5%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_7(H_2O)_{14}]^{4+}$), 733 (10%, $[Bi_{10}O_8L_4(OH)_2(MeOH)(H_2O)_{10}]^{4+}$), 697 (15%, $[Bi_{10}O_8L_4(OH)_2(MeOH)(H_2O)_2]^{4+}$), 666 (25%, $[Bi_{10}O_8L_2(OH)_6(MeOH)(DMSO)]^{4+}$), 638 (5%, $[Bi_9O_7L_2(OH)_5(MeOH)_3(H_2O)_8]^{4+}$), 615 (10%, $[Bi_8O_6L_4(MeOH)_7]^{4+}$), 600 (10%, $[Bi_8O_6L_4(MeOH)_4(H_2O)_2]^{4+}$), 571 (5%, $[Bi_8O_6L_2(OH)_2(MeOH)_5(H_2O)_3]^{4+}$), 533 (20%, $[Bi_6O_4L_2(OH)_2(MeOH)_{12}(H_2O)_9]^{4+}$), 532 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_{13}(H_2O)_7]^{4+}$), 510 (10%,

$[Bi_6O_4L_2(OH)_2(MeOH)_8(H_2O)_{11}]^{4+}$), 491 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_9(H_2O)_5]^{4+}$), 482 (10%, $[Bi_6O_4L_2(OH)_2(MeOH)_9(H_2O)_3]^{4+}$), 476 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_6(H_2O)_7]^{4+}$), 438 (30%, $[Bi_4O_2L_2(MeOH)_{13}(DMSO)_3]^{4+}$), 437 (10%, $[Bi_6O_4L_2(OH)_2(H_2O)_9]^{4+}$), 431 (5%, $[Bi_4O_2L_2(MeOH)_{17}(DMSO)]^{4+}$), 400 (85%, $[Bi_4O_2L_2(MeOH)_{15}(H_2O)]^{4+}$), 377 (15%, $[Bi_4O_2L_2(MeOH)_{11}(H_2O)_3]^{4+}$), 355 (20%, $[Bi_4O_2L_2(MeOH)_6(H_2O)_7]^{4+}$), 333 (50%, $[Bi_4O_2L_2(MeOH)(H_2O)_{11}]^{4+}$), 329 (5%, $[Bi_4O_2\ L_2(MeOH)_5(H_2O)_3]^{4+}$), 327 (100%, $[Bi_4O_2L_4(MeOH)_4(DMSO)]^{4+}$), 309 (20%, $[Bi_3L_2(OH)(MeOH)_5(H_2O)_{11}]^{4+}$), 304 (10%, $[Bi_3L_2(OH)(MeOH)_{10}(H_2O)]^{4+}$), 267 (5%, $[Bi_3L_2(OH)(MeOH)_2(H_2O)_7]^{4+}$), 254 (10%, $[LHNa(H_2O)_5+Na]^{+}$), 200 (65%, $[LHNa(H_2O)_2+Na]^{+}$), 178 (55%, $[LH_2(H_2O)_2+Na]^{+}$). Elemental Analysis: $Bi_2C_{12}H_{15}O_{12}N_3$ (811.209): calc. C 17.77, H 1.86, N 5.18; found: C 17.70 , H 1.72, N 5.31 %.

Tris-((S)-2-amino-pentanedionato) bismuth(III), $[Bi_2(Glu)_3]$ (8):

The general procedure was carried out using *(S)*-2-amino-pentanedionic acid (*L*-glutamic acid = Glu) to yield compound **8** as biege coloured powder. Yield 192 mg (90 %). M.pt. 187 - 188 C°. ^{1}H NMR (300 MHz, D_2O, 30°C): δ = 3.87 (1H, t, ^3J = 6.00 Hz, H^2), 2.58 (2H, t, ^3J = 6.00 Hz, H^4), 2.58 (2H, q, ^3J = 6.00, 12.00 Hz, H^3). ^{13}C NMR (75 MHz, D_2O, 30°C): δ = 179.7 (C^1), 174.8 (C^5), 54.5 (C^2), 31.8 (C^3), 23.3 (C^4). ATR-IR (cm^{-1}): ũ = 3030(m), 2961(m), 2739(w), 2652(w), 1831(w), 1638(s), 1614(m), 1509(s), 1435(w), 1419(m), 1349(s), 1309(s), 1254(s), 1230(s), 1211(s), 1150(m), 1124(s), 1074(s), 1053(s), 945(m), 912(w), 866(m), 805(s), 712(m), 702(m), 671(m). ESI-MS^+ (solvent: DMSO/MeOH): *m/z* = 982 (15%, $[Bi_{14}O_{10}L_2(OH)_{14}(MeOH)_7(H_2O)_5]^{4+}$), 894 (15%, $[Bi_{12}O_{10}L_3(OH)_6(MeOH)_6(H_2O)_{10}]^{4+}$), 883 (30%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_{14}(H_2O)_{14}]^{4+}$), 854 (10%, $[Bi_{12}O_{10}L_4(OH)_4(MeOH)_2(H_2O)_2]^{4+}$), 824 (20%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_{10}(H_2O)_8]^{4+}$), 810 (25%, $[Bi_{12}O_{10}L_4(OH)_4(H_2O)_2]^{4+}$), 787 (10%, $[Bi_{10}O_8L_5(MeOH)_3(H_2O)_6]^{4+}$), 780 (20%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_9]^{4+}$), 765 (15%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_6(H_2O)_2]^{4+}$), 758 (30%, $[Bi_{10}O_8L_4(OH)_2(MeOH)_4(H_2O)_4]^{4+}$), 747 (15%, $[Bi_{10}O_8L_3(OH)_4(MeOH)_5(H_2O)_6]^{4+}$), 743 (10%, $[Bi_{10}O_8L_3(OH)_4(MeOH)_5(H_2O)_5]^{4+}$), 736 (35%, $[Bi_9O_7L_3(OH)_3(MeOH)_{14}(H_2O)]^{4+}$), 721 (5%, $[Bi_9O_7L_4(OH)(MeOH)_3(H_2O)_{11}]^{4+}$), 708 (5%, $[Bi_9O_7L_2(OH)_5(MeOH)_{10}(H_2O)_8]^{4+}$), 699 (10%, $[Bi_9O_7L_2(OH)_5(MeOH)_{10}(H_2O)_6]^{4+}$), 695 (15%, $[Bi_9O_7L_4(OH)(MeOH)_6]^{4+}$), 685 (5%, $[Bi_9O_7L_3(OH)_3(MeOH)_7(H_2O)_2]^{4+}$), 677 (25%, $[Bi_9O_7L_2(OH)_5(MeOH)_5(H_2O)_{10}]^{4+}$), 655 (30%, $[Bi_9O_7L_2(OH)_5(H_2O)_{14}]^{4+}$), 633 (25%, $[Bi_9O_7L_3(OH)_3(H_2O)_3]^{4+}$), 615 (10%, $[Bi_8O_6L_3(OH)_2(MeOH)_7]^{4+}$), 611 (65%, $[Bi_8O_6L_4(MeOH)_3]^{4+}$),

596 (15%, $[Bi_8O_6L_3(OH)_2(MeOH)_4(H_2O)]^{4+}$), 589 (50%, $[Bi_8O_6L_2(OH)_4(MeOH)(H_2O)_{11}]^{4+}$), 574 (45%, $[Bi_8O_6L(OH)_6(MeOH)_2(H_2O)_{12}]^{4+}$), 568 (30%, $[Bi_8O_6L_2(OH)_4(MeOH)_4(H_2O)]^{4+}$), 552 (45%, $[Bi_6O_4L_2(OH)_2(MeOH)_{16}(H_2O)_3]^{4+}$), 530 (65%, $[Bi_6O_4\ L_2(OH)_2(MeOH)_{11}(H_2O)_7]^{4+}$), 518 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_5(H_2O)_{15}]^{4+}$), 508 (85%, $[Bi_6O_4L_2(OH)_2(MeOH)_6(H_2O)_{11}]^{4+}$), 502 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_3(H_2O)_{15}]^{4+}$), 486 (100%, $[Bi_6O_4L_2(OH)_2(MeOH)(H_2O)_{15}]^{4+}$), 480 (5%, $[Bi_6O_4L_2(OH)_2(MeOH)_7(H_2O)_3]^{4+}$), 464 (65%, $[Bi_6O_3L_2(OH)_3(MeOH)_5(H_2O)_3]^{4+}$), 442 (95%, $[Bi_6O_3L_2(OH)_3(H_2O)_7]^{4+}$), 437 (15%, $[Bi_6O_4L_2(OH)_2(H_2O)_6]^{4+}$), 405 (35%, $[Bi_4O_2L_2(MeOH)_6(H_2O)_{15}]^{4+}$), 383 (90%, $[Bi_4O_2L_2(MeOH)_{10}(H_2O)_3]^{4+}$), 361 (100%, $[Bi_4O_2L_2(MeOH)_5(H_2O)_7]^{4+}$), 348 (90%, $[Bi_4O_2L_2(H_2O)_{13}]^{4+}$), 339 (30%, $[Bi_4O_2L_2(H_2O)_{11}]^{4+}$), 333 (25%, $[Bi_3L_2(OH)(MeOH)_4(H_2O)_{15}]^{4+}$), 317 (50%, $[Bi_4O_2L(OH)_2(MeOH)_3(H_2O)_7]^{4+}$), 295 (65%, $[Bi_3OL(OH)(MeOH)_5(H_2O)_{12}]^{4+}$), 264 (5%, $[Bi_3L_2(OH)(MeOH)(H_2O)_5]^{4+}$), 214 (10%, $[LNa_2+Na]^+$), 204 (5%, $[LH_2(H_2O)+K]^+$), 192 (10%, $[LHNa+Na]^+$), 184 (5%, $[LH_2(H_2O)_2+H]^+$), 170 (5%, $[LH_2+Na]^+$), 148 (50%, $[LH_2+H]^+$). Elemental Analysis: $Bi_2C_{15}H_{21}O_{12}N_3$ (853.28): calc. C 21.11, H 2.48, N 4.92; found: C 21.01, H 2.46, N 5.03 %.

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Table of Contents

Bismuth(III) complexes derived from α-amino acids (LH) have been synthesized and characterized, and are formulated as either $[BiL_3]$ or $[Bi_2L_3]$. Water solubility leads to hydrolysis and oxido cluster formation, which is shown to impact significantly on their activity towards *Helicobacter pylori*.