Dalton Transactions

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Journal:	*Dalton Transactions*
Manuscript ID:	DT-ART-04-2014-000957.R1
Article Type:	Paper
Date Submitted by the Author:	11-Jun-2014

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Stability and Toxicity of Heteroleptic Organometallic Bi(V) Complexes towards *Leishmania major*

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Abstract

Eleven heteroleptic Bi(V) complexes of the form $[BiPh_3(O_2CR)_2]$ have been synthesised and fully characterised. The carboxylate ligands are derived from a series of simple substituted benzoic acids, four of which are common non-steroidal anti-inflammatories (NSAIDs). The solid-state structures of eight of the complexes were determined by single crystal X-ray diffraction, and all were shown to adopt a typical trigonal bipyramidal geometry with chelating carboxylate ligands. Nine of the complexes were assessed for their anti-parasitic activity against *Leishmania major* promastigotes and their cytotoxicity towards human fibroblasts. The assays indicated that while the complexes showed good anti-leishmanial activity with IC_{50} values ranging from 0.6 to 2.5 μM they were also non-selectively toxic towards the fibroblasts at similar or slightly higher concentrations. Using ^1H NMR, the stability of one of the complexes, $[Bi(C_6H_5)_3(O_2CC_6H_3(m\text{-}OH)_2)_2]$ was studied in water, DMSO and in the DMEM culture medium. This showed that while the Bi(V) complex was stable in D_2O and DMSO, the complex slowly decomposed in the culture medium undergoing reduction to give $BiPh_3$ and the free acid. Since the acids and $BiPh_3$ were not toxic to either the parasites or fibroblasts at the concentrations studied, the implication is that the Bi(V) complexes are stable enough for long enough to have significant *in vitro* anti-parasitic activity.

Introduction

Leishmaniasis, a disease caused by the *Leishmania* parasite, is transmitted to humans through the bite of sandflies. It is endemic in developing countries, and currently it is estimated that around 12 million people in 88 countries suffer from the disease, with an annual infection rate of 1 - 1.5 million people and mortality rate of 30,000. It is regarded by the World Health Organisation as being one of the world's most serious neglected tropical diseases.[1] The most devastating form of the disease, visceral leishmaniasis, which targets the internal organs, is normally fatal within two years if left untreated.[2]

The frontline treatment for Leishmaniasis has changed little in 70 years and remains a daily injection over several weeks of a pentavalent antimony compound; either sodium stibogluconate or meglumine antimoniate. For clinical administration, these Sb(V) compounds are less toxic than their Sb(III) analogues, though they are considered pro-drugs since Sb(V) is reduced to Sb(III) inside the macrophage-bound amastigote through interaction with the cysteine-rich peptide trypanothione (TS) and with trypanothione reductase (TR) at a cellular pH of 5.[3] TR is inhibited by Sb(III), disrupting the redox potential of the cell.[3, 4]

There are additional drawbacks associated with the compounds over and above the high toxicity of Sb(III). Since the drugs are hydrophilic, they cannot cross the intestinal lipid bilayer and so cannot be delivered orally leading to incidences of non-compliance,[4] and drug resistance is now established, particularly in the Bihar region of India.[5] Alternative treatments exist, for example liposomal Amphotericin B,[6] but are significantly more expensive, and are often not an option in developing countries. The only orally administered drug, Miltefosine, harbours problems with teratogenicity, has a narrow therapeutic window and is a risk for resistance since it remains in the bloodstream for up to five months after treatment.[7]

In recent years we have begun to investigate two areas in which we think incremental but significant advances can be made on the current metallodrugs used in *Leishmania* treatment. Firstly, we have demonstrated that organometallic Sb(V) dicarboxylato complexes of the form $[SbAr_3(O_2CR)_2]$ can have excellent activity towards both promastigotes and amastigotes at very low concentrations (0.5 – 3.5 μM) while being non-toxic towards human fibroblasts at levels < 25 μM.[8] Thus, these compounds have real potential for further drug development, noting that the current Sb(V) drugs are mainly only active against the amastigote form of the parasite.[8] Secondly, in seeking to exploit the periodic relationship of antimony and bismuth and to exploit the apparent low systemic toxicity in humans of bismuth, we demonstrated that Bi(III) carboxylato compounds can be highly toxic towards promastigotes, though the toxicity to human fibroblast cells is often not insignificant and is ligand dependant.[9, 10] In the first of the only two studies on the anti-leishmanial activity of Bi(V) compounds, Soares and co-workers demonstrated reasonable activity against *L. amazonensis* of $[BiPh_3Cl_2]$ and the lapachol (LpH) derivative $[BiPh_3(Lp)]_2O$ with the former being more active (IC_{50} 5.40 ± 0.16 μg/mL) than the latter (IC_{50} 29.05 ± 18.45 μg/mL), with the lapachol Bi(V) complex being less toxic than lapachol (LpH) itself. Both complexes were toxic to murine macrophages.[11] Very recently, Demicheli *et al* tested and compared three Bi(V) compounds: $[BiPh_3CO_3]$, $[BiPh_3(L^1)_2]$ and $[BiPh_3(L^2)_2]$ (L^1H = aspirin; L^2H = 3-acetoxybenzoic acid) against *L. infantum and L. amazonesis* promastigates.[12] $BiPh_3CO_3$ proved to be the most active compound of the three with IC_{50} values of 1.1 (±0.37) and 2.7 (±0.34) μM for *L. infantum and L. amazonesis* respectively.

To establish a more direct and comprehensive comparison with the promising organometallic Sb(V) compounds, we turned our attention to the analogous, but more unstable and more highly oxidizing form of bismuth, and targeted the synthesis, characterisation, and *in vitro* anti-leishmanial activity of a series of organometallic Bi(V) dicarboxylato complexes of the form $[BiPh_3(O_2CR)_2]$. The carboxylic acids used in the study

are shown in Figure 1. Eleven Bi(V) complexes **1B** **11B,** have been prepared from $BiPh_3$ and common benzoic acids, **1** **11**, some of which are classed as non-steroidal anti-inflammatory drugs (NSAIDs). We now report on the chemistry of these compounds, and their toxicity towards both *Leishmania major* parasites (promastigotes) and human fibroblast cells.

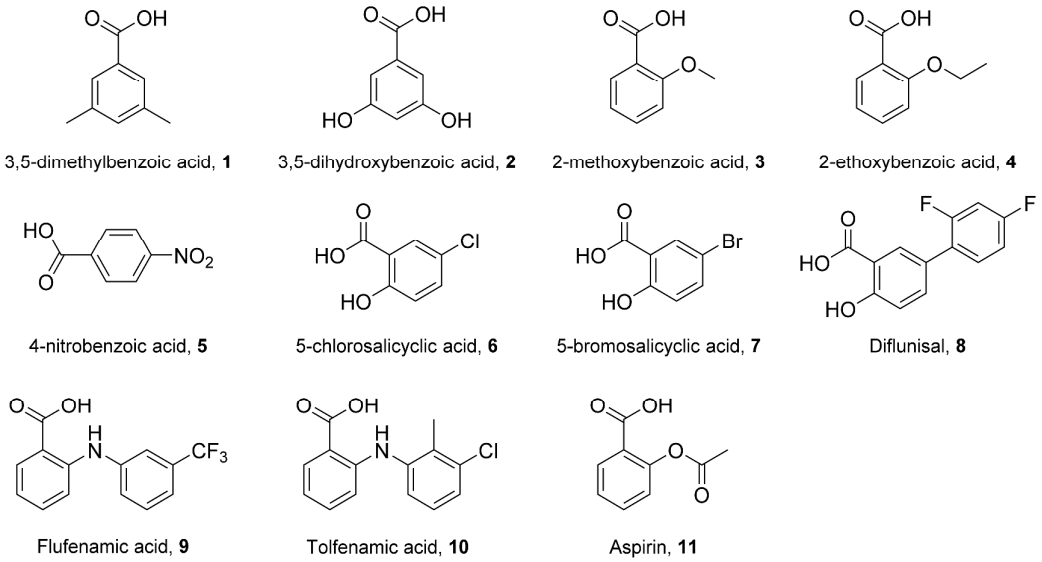

Figure 1. Various substituted benzoic acids (**1**-**11**) used in the formation of Bi(V) complexes $[BiPh_3(O_2CR)_2]$, **1B**-**11B**

Results and Discussion

The synthesis of the target Bi(V) complexes, **1B – 11B**, was achieved using an oxidative addition reaction in which $BiPh_3$ and the benzoic acid were mixed in the presence of hydrogen peroxide in a 1: 2 : 1 stoichiometric ratio (Scheme 1).[13]

$$BiPh_3 + 2\,RCO_2H \xrightarrow[-\,H_2O]{H_2O_2} [BiPh_3(O_2CR)_2]$$

Scheme 1. Reaction of triphenylbismuth with carboxylic acid in the presence of 30 % hydrogen peroxide

Using this approach a pure crystalline product could be isolated from each reaction in good yield after a short reaction time (*ca*. 15 min.) and with little work-up. Hydrogen peroxide acts as the oxidising agent taking Bi(III) to Bi(V), subsequently allowing the condensation reaction of newly formed $[BiPh_3(OH)_2]$ with two equivalents of the chosen benzoic acid. This results in the facile elimination of water and formation of $[BiPh_3(O_2CR)_2]$. After the initial reaction period and allowing the solution to stand overnight at room temperature, the crystalline product can be collected by filtration and washed with diethyl ether to remove unreacted acid and $BiPh_3$.[13] In comparison, acid-base reactions using $BiPh_3Cl_2$ and two equivalents of RCO_2H in the presence of NEt_3,[14] and a salt metathesis route using $BiPh_3Cl_2$ and 2 RCO_2M (M = Na or Ag),[15] proved to be less effective, requiring greater purification steps and giving overall lower yields.

The composition of complexes **1B** – **11B**, shown in Table 1, was confirmed through ^{1}H and ^{13}C NMR spectroscopy, melting point, FT-IR spectroscopy, and elemental analysis. In addition, complexes **1B**, **3B** – **8B** and **10B** were characterised by single crystal X-ray diffraction. Full analytical details for all compounds are provided in the Experimental section.

Table 1. Summary of reactions attempted with the series of benzoic acids **1-11** with triphenylbismuth, and details of their corresponding complexes **1B-11B.**

Complex	Benzoic Acid	MPt (°C)	Crystal Appearance	% Yield
1B	3,5-dimethylbenzoic acid	179-181	Pale green	24
2B	3,5-dihydroxybenzoic acid	118-120 (Decomp.)	Brown	31
3B	2-methoxybenzoic acid	152-154	Brown	56
4B	2-ethoxybenzoic acid	167-170	White	76
5B	4-nitrobenzoic acid	188-191[a]	Orange	30
6B	5-chlorosalicyclic acid	196-197	White	77
7B	5-bromosalicyclic acid	194-195	White	27
8B	Diflunisal	195-197 (Decomp.)	Yellow	58
9B	Flufenamic acid	164-166	Yellow	52

10B	Tolfenamic acid	176-178	Orange	57
11B	Aspirin	161-164[b]	Yellow	85

[a] literature value of 181 °C.[14]

[b] literature value of 161 °C (decomp).[13]

Depending on compound solubility, ^{1}H and ^{13}C NMR spectra for **1B** – **11B** were recorded in D_6-DMSO (**1B** – **4B**, **8B**, **9B**, **11B**) or $CDCl_3$ (**5B** – **7B**, **10B**). All complexes showed a general high frequency shift for the *o*-, *m*- and *p*- Ph proton signals in comparison to those in $BiPh_3$, increasing by 0.32 (**2B**) – 0.58 (**10B**) ppm for the *ortho* signals, 0.27 (**3B**) – 0.42 (**8B**) ppm for the *meta* signals, and 0.21 (**1B**) – 0.33 (**8B**) ppm for the *para* signals. Furthermore, the loss of the signal attributable to the acidic -CO_2H proton, observed between 11.61 (**8**) – 13.67 (**5**) ppm in the parent acids, indicates deprotonation and subsequent complexation of the carboxylate ligands to the Bi(V) centre.

Compared with the parent benzoic acids **1** – **11**, all of which have their acid carbonyl absorbance in the normal range 1650 – 1700 cm^{-1}, all the complexes **1B** – **11B** show a shift to lower wavenumber for their carboxylate asymmetric and symmetric stretches to 1540-1650 cm^{-1} and 1300-1420 cm^{-1} respectively. This confirms deprotonation of the CO_2H group in each acid to form the Bi(V) bound carboxylates. The difference between the asymmetric and symmetric shifts $\Delta\nu$, where $\Delta\nu = \nu CO_2^-{}_{(asymm)} - \nu CO_2^-{}_{(symm)}$, is less than 200 cm^{-1} for each complex. According to Deacon and Philips,[16] this indicates that the carboxylate ligands adopt a bidentate chelating mode, observed and confirmed in the solid-state structures of **1B**, **3B** – **8B** and **10B**.

Stability studies

To assess the stability of the complexes to atmospheric oxygen and moisture, all complexes were exposed to air and screened by melting point analysis over a period of four months.

There was no difference in the observed melting point of each compound over that time indicating they have a high degree of stability in the solid state.

The stability of the complexes in solution was studied by comparing the ^{1}H NMR spectra of each complex, obtained in either D_6-DMSO or $CDCl_3$, at times t = 0 hours and t = 48 hours. The spectrum for each complex with the exception of **10B** was unchanged. The changes in the chemical shifts in the NMR spectrum **10B** represent electronic and structural changes rather than decomposition since crystals of the complex obtained from DMSO solution were unchanged after 8 months, as evidenced by unit cell comparisons. As **5B** and **10B** were not completely soluble in D_6-DMSO, they were not considered for biological testing.

^{1}H NMR spectra of complex **6B** (Figure 2) in D_6-DMSO were obtained from sampling a single solid product, initially on formation (t = 0) and secondly after a period of 6 months (t = 6 months). The two spectra presented differences in the proton signals associated with the benzoate ligands, which split in two while maintaining the same integration values relative to the *Ph* protons. Over the six month period the melting point of the solid sample did not change. Therefore, rather than decomposition, the differences in the two spectra are most likely indicative of a thermodynamically favoured interconversion in the solid-state from trigonal bipyramidal geometry to square pyramidal.[17]

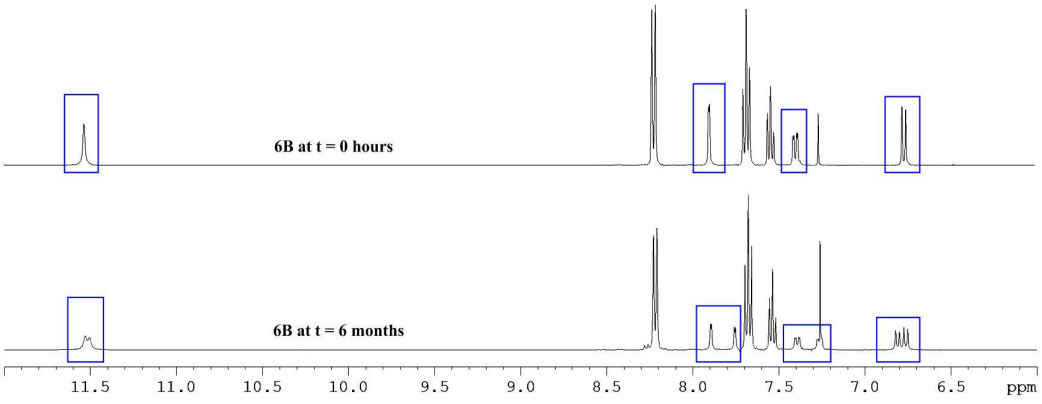

Figure 2. ^{1}H NMR spectrum of complex [Bi(C_6H_5)$_3$($O_2CC_6H_3$-2-OH-5-Cl)$_2$] **6B** in $CDCl_3$ at 25°C at t = 0 h and t = 6 months.

To gain some understanding of the stability of the bismuth(V) complexes in cell culture medium, ^{1}H NMR spectral data on complex **2B**, as a representative example, was collected and analysed at t = 0 and t = 48 h, replicating as closely as possible the conditions used in the biological testing. Unfortunately the signal-to-noise ratio even for the highest concentration used in the *in-vitro* biological assay (100 μM) was too low to provide any meaningful data. Therefore, a sample concentration of 1.0 mM was used. To minimise the effects of the H_2O signal the culture medium was freeze-dried and reconstituted using D_2O.

It was observed that integrations and chemical shifts changed over 24 h, with the first significant changes observable after 6 h in the form of the appearance of a doublet at 7.98 ppm (Figure 3). This became greater over time, while the broad signal at 7.85 ppm continued to decrease in intensity. By 24 hours, an additional triplet has developed at 7.51 ppm, with reduction in intensity of the triplet at 7.57 ppm.

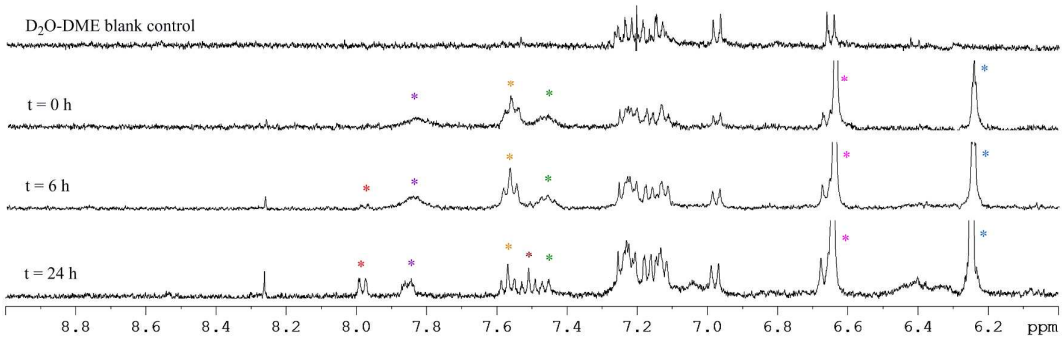

Figure 3. Comparison of **2B** in D_2O-DME culture media at t = 0 h, t = 6 h and t = 48 h with ^{1}H NMR at 25°C.

Furthermore, in the NMR tubes of all three samples studied a white precipitate forms over time. On isolation this white precipitate proved to be soluble in D_6-DMSO and D_6-acetone, forming a clear solution. In the ^{1}H NMR spectrum the phenyl proton signals shift to lower frequency: from 8.16 (*o*-), 7.74 (*m*-) and 7.55 (*p*-) ppm in the complex to 7.72 (*o*-), 7.38 (*m*-) ppm and 7.30 (*p*-) ppm respectively, and in fact resonate at the same frequencies as observed for $BiPh_3$ (Figure 4). In order to confirm the identity of the decomposition product, the experiment was conducted on a larger scale (5ml of 10 mM **2B** in 50 ml of DMEM cell culture media). The dark pink precipitate that appears over 48 hours was extracted using centrifugation three times, washing consecutively with distilled water and acetone. The cream coloured solid that appeared overnight from the final acetone filtrate was washed finally with hexane and shown by ^{1}H NMR spectroscopy and by duplicate melting point analysis (77 °C) to be $BiPh_3$.

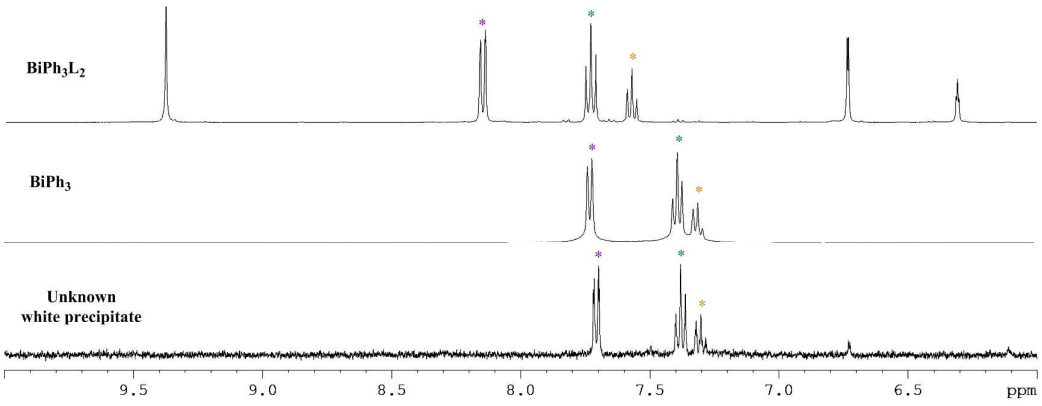

Figure 4. ^{1}H NMR spectra of **2B**, $BiPh_3$ and unknown white precipitate in d_6-DMSO at 25°C.

The NMR data suggests that hydrolysis or other ligand exchange reactions are occurring and that the benzoate ligands are protonated to give the soluble free benzoic acids. If the sole process is hydrolysis then the co-product should be $BiPh_3O$, though this appears to be precluded by differences in melting point: freshly prepared $BiPh_3O$ was measured to melt at 148-152 °C (*lit.* [$BiPh_3O$], 155 °C; [$BiPh_3Cl_2$], 158-160 °C).[18] In addition, the chemical shifts for

the *o*, *m* and *p* protons in [$BiPh_3O$] in the ^1H NMR spectrum recorded in d_6-DMSO are observed at higher frequencies (8.36, 7.76 and 7.61 ppm) than for $BiPh_3$ (7.70, 7.38 and 7.30 ppm) as presented in Figure 5. Also presented, simply for comparison, is the spectra of $BiPh_3$ and the starting Bi(V) material [$BiPh_3Cl_2$] . Based on this the possibility that $BiPh_3O$ was the unknown precipitate was eliminated.

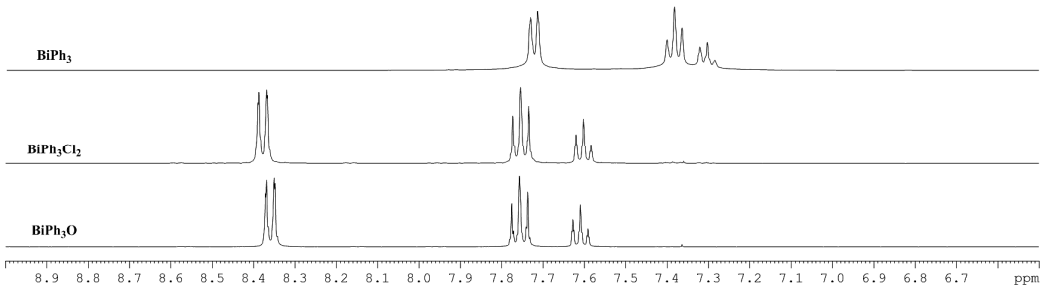

Figure 5. Comparison of the ^1H NMR spectra of [$BiPh_3O$], $BiPh_3$ and starting material [$BiPh_3Cl_2$] in d_6-DMSO at 25°C.

The identity of the solid was further investigated using mass spectrometry. The ESI(+)-MS spectra displayed *m/z* ions that were characteristic of $BiPh_3$. Two main species, $[BiPh_2 + 6H_2O]^+$ for *m/z* 471.1 and $[BiPh_2 + 2MeOH + 4H_2O]^+$ for *m/z* 499.1, were of particular interest, as they had the highest relative abundances among the other main peaks: [Bi] at *m/z* 209.0, $[BiPhH]^+$ at *m/z* 285.9, $[BiPh_2]^+$ at *m/z* 363.0 and $[BiPh_2 + MeOH]^+$ at *m/z* 395.0. As such, we can conclude that the unknown precipitate resulting from the interaction of cell culture media with **2B** in DMSO is $BiPh_3$.

Toxicity testing, described below, indicates that $BiPh_3$ is benign toward the parasites at the highest concentration studied (100 μM), yet significant toxicity for **2B** in observed in the assay. This, supported by the NMR data, suggests the compound decomposes slowly to $BiPh_3$ upon interaction with the culture medium, and that **2B**, or a Bi(V) derivative thereof, remains toxic to the parasite.

A comparison with **2B** in D_2O in the absence of cell culture medium indicated that the complex is stable, suggesting one of the components in the cell culture medium is responsible for decomposition. Cell culture contains a number of acids including amino acids and vitamins, which are constituted as their hydrochloride salt. Interaction with these ions could results in decomposition of **2B**. In order to test this hypothesis, a D_2O solution of DL-lysine.HCl and **2B** in final concentrations of 8.0 mM (the highest concentration in the culture medium) and 1.0 mM respectively was prepared and the ^{1}H NMR spectrum recorded at t = 0 h and t = 20 h. This was compared with spectra recorded on each of the individual components. No change was observed in either the chemical shift values or in the signal integrations over the 20 h period, and the proton signals remained consistent with those observed in the individual spectra. This indicates that there is no observable reaction between the amino acid salt and that of the pentavalent bismuth, suggesting this to be an unlikely decomposition pathway.

One other possible exchange is that of phosphate for carboxylate through the presence in DMEM media of sodium phosphate monobasic, NaH_2PO_4 at a concentration of *ca.* 1.0 mM. To determine the stability of the Bi(V) complexes in the presence of phosphate ions, 50 µL of a 10 mM solution of each complex in D_6-DMSO was added to 1.0 ml of the DMEM cell culture medium. For each complex an emulsion formed with no visible signs of precipitation. Since complexes **5B** and **10B** are largely insoluble in DMSO they were excluded from the test. The control was 50 µL of D_6-DMSO in 1.0 ml of DMEM. For comparison, sodium phosphate monobasic, dissolved in distilled water, was added to D_6-DMSO and the spectrum recorded. There are no examples of soluble bismuth phosphate complexes available for direct comparison, though recently a soluble large polynuclear metal-organic bismuth(III) phosphate cage, $[\{(ArO)_{10}\{(ArO)PO_2OH\}_2(Bi_{14}O_{10})]$ (Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$), has been described in which the P centres resonate in δ −7.67 and −13.40 in the ^{31}P spectrum in $CDCl_3$.[19]

The ^{31}P NMR shift observed for this compound is also included to provide a comparison. For each of these solutions, decoupled ^{31}P NMR spectra were obtained and the chemical shifts compared. These are noted in Table 2 below.

Table 2. ^{31}P NMR chemical shifts of controls and complexes **1B – 11B** in D_6-DMSO

Description	Chemical Shift
NaH_2PO_4	-0.19
DMEM	2.34
1B	2.41
2B	2.40
3B	2.35
4B	2.39
6B	2.36
7B	2.37
8B	2.40
9B	2.34
11B	2.34
Bi(III) cage[19]	-7.67, -13.40

From the chemical shifts observed, the ^{31}P decoupled NMR signals for the complexes remain in the range of 2.3 - 2.4 ppm. This is similar to that of the culture media control ^{31}P NMR shift of 2.34 ppm. Hence, we can conclude that our complexes tested are stable to phosphate exchange.

X-ray crystallography

Crystallisation of complexes **1B**, **3B** - **8B** and **10B** from either DMSO, diethyl ether, THF or hexane/diethyl ether solutions provided crystals suitable for X-ray diffraction studies. Complexes **3B**, **6B** and **10B** can be seen in Figures 5, 6 and 7 respectively with selected bond lengths and angles provided in the accompanying figure captions. The remaining complexes **1B**, **4B - 5B** and **7B** - **8B**, along with their pertinent bond lengths and angles, can be found in the Supporting Information.

All of the complexes **1B**, **3B** - **8B** and **10B** are essentially isostructural adopting a distorted trigonal bipyramidal geometry about the Bi(V) metal centre with the axial positions occupied by the oxygen atoms of the deprotonated carboxylate functionality, while the phenyl groups,

orientated in a propeller-like fashion, occupy the equatorial positions. In all eight complexes the deprotonated benzoic acid ligands are coordinated to the Bi(V) centre in a bidentate chelating mode, commonly seen for other Bi(V) complexes,[13, 20, 21] increasing the coordination number of the Bi(V) centre to seven giving an overall pentagonal bipyramidal geometry.

The Bi-C bonds of the phenyl groups range from 2.177(4) Å – 2.210(6) Å with an average bond length of 2.1957 Å which lies in the range of other reported heteroleptic pentavalent triarylbismuth complexes $[BiPh_3(O_2CC_6H_5)_2]$ (2.20(1) Å),[20] $[BiPh_3(O_2CC_6H_2\text{-}3,4,5\text{-}F)_2]$ (2.193(6) Å)[20] and $[BiPh_3(O_2CC_6F_5)_2]$ (2.196(6) Å).[21] As expected for a bidentate chelating carboxylic acid the Bi-O bonds are non symmetrical with one short (average 2.281 Å) covalent and one longer (average 2.870 Å) dative bound oxygen atoms. Interestingly, the presence of a *ortho* – OH functional group on the phenyl ring of the benzoic acid, in complexes **6B**, **7B** and **8B** (Figures 4 – 6) results in elongation of the dative Bi···(O=C) bond (2.924(2) Å- 3.041(7) Å for **6B** – **8B** *c.f.* average 2.789 Å for **1B**, **3B** – **5B** and **10B**) which can be attributed to the strong hydrogen-bond donating ability of the hydroxy functionality resulting in the weakening of the Bi···(O=C) interaction.[22]

All the deprotonated benzoic acids are coordinated to the Bi(V) centre in a bi-dentate chelating manner with O–Bi–O bite angles ranging from 46.22(7)° – 51.47(16)°. Again, the presence of the 2-hydroxy functional group on the phenyl ring of complexes **6B** – **8B** results in a more acute O–Bi–O bite angle of 46.22(7)°, 47.44(9)° and 46.30(29)° respectively, when compared to the other complexes without (Table 3).

Table 3. List of bonds lengths (Å) for complexes **1B**, **3B**-**8B** and **10B**

Complex	Ligand	Bi–C(Ph)	Bi–O(C=O)	Bi···(O=C)	O–Bi–O
1B	3,5-dimethylbenzoate	2.191(3)	2.282(3)	2.7737(19)	50.95(6)
		2.191(3)			
		2.206(3)			

3B	2-methoxybenzoate	2.201(3)	2.283(2)	2.728(2)	51.38(7)
4B	2-ethoxybenzoate	2.198(3)	2.270(2)	2.8666(18)	49.63(6)
		2.198(3)			
		2.204(3)			
5B	4-nitrobenzoate	2.180(4)	2.280(3)	2.902(3)	49.05(9)
		2.180(4)			
		2.198(6)			
6B	5-chlorosalicylate	2.186(3)	2.284(2)	2.924(2)	48.71(7)
		2.187(3)		3.080(2)	46.22(7)
		2.194(3)			
7B	5-bromosalicylate	2.177(4)	2.282(3)	3.002(3)	47.44(9)
		2.184(4)			
		2.188(4)			
8B	2',4'-difluoro-4-hydroxybiphenyl-3-carboxylate[a]	2.204(8)	2.253(6)	3.041(7)	46.30(19)
		2.204(8)			
		2.217(12)			
10B	2-[(3-chloro-2-methylphenyl)amino]benzoate[b]	2.199(7)	2.260(5)	2.745(5)	51.47(16)
		2.198(7)	2.310(5)	2.803(4)	
		2.210(6)			
11B	acetylsalicylate[c]	2.211(2)	2.306(2)	2.702(2)	51.09(5)
		2.226(2)			
Average		2.197	2.281	2.870	49.22

[a] from diflunisal; [b] from tolfenamic acid; [c] from aspirin[13]

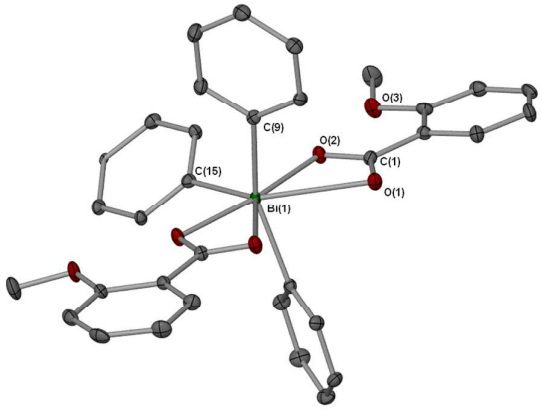

Figure 6. Molecular structure of $[Bi(C_6H_5)_3(O_2CC_6H_4\text{-}o\text{-}OCH_3)_2]$ **3B** showing thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity. Symmetry operator, -x, y, 3/2-z. Selected bond lengths (Å) and angles (°): Bi(1)-O(1), 2.728(2); Bi(1)-O(2), 2.283(2); Bi(1)-C(9), 2.201(3); Bi(1)-C(15), 2.201(3); O(1)-Bi(1)-O(2), 51.38(7); C(9)'-Bi(1)-C(9), 151.94(14); C(9)-Bi(1)-C(15), 104.03(7).

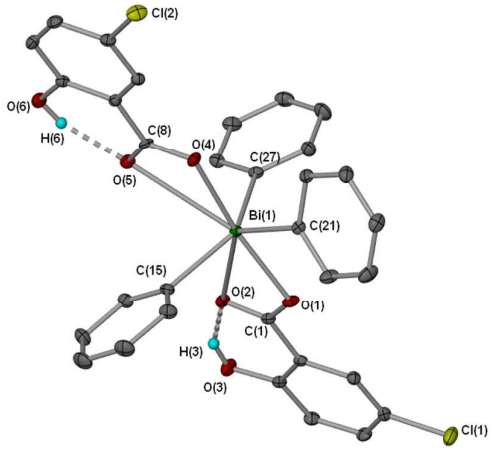

Figure 7. Molecular strucutre of $[Bi(C_6H_5)_3(O_2CC_6H_3\text{-}2\text{-}OH\text{-}5\text{-}Cl)_2]$ **6B** showing thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)-O(1), 2.284(2); Bi(1)-O(2), 2.924(2); Bi(1)-O(4), 2.279(2); Bi(1)-O(4), 2.279(2); Bi(1)-O(5), 3.080(2); Bi(1)-C(15), 2.187(3); Bi(1)-C(21), 2.194(3); Bi(1)-C(27), 2.186(3); O(4)-Bi(1)-O(5), 46.22(7); O(1)-Bi(1)-O(2), 48.71(7); C(27)-Bi(1)-C(15), 136.09(11); C(27)-Bi(1)-C(21), 112.11(11); C(15)-Bi(1)-C(21), 111.70(11).

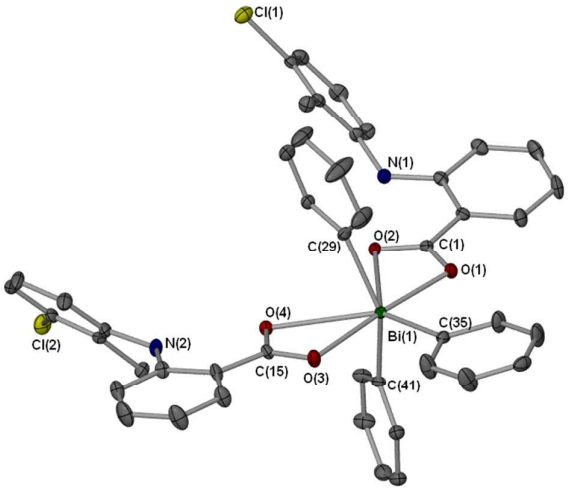

Figure 8. Molecular structure of **[**$Bi(C_6H_5)_3(O_2CC_6H_4\text{-}2\text{-}NH\text{-}(C_6H_3\text{-}2\text{-}CH_3,3\text{-}Cl))_2$] **10B** showing thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Bi(1)-O(1), 2.260(5); BI(1)-O(2), 2.745; Bi(1)-O(3), 2.310(5); Bi(1)-O(4), 2.803(4); Bi(1)-C(29), 2.198(7); Bi(1)-C(35), 2.210(6); Bi(1)-C(41), 2.199(7); O(1)-Bi-O(2), 51.47(16); O(3)-Bi(1)-O(4), 50.24(15); C(41)-Bi(1)-C(29), 148.8(2); C(14)-Bi(1)-C(35), 105.6(2); C(29)-Bi(1)-C(35), 105.4(2).

Biological activity

Complexes **1B** – **11B** and their parent acids were tested for their activity against *Leishmania major* promastigotes and human fibroblasts. Amphotericin B is the reference anti-Leishmanial agent. Complexes **5B** and **10B** were not tested as they showed poor solubility in DMSO.

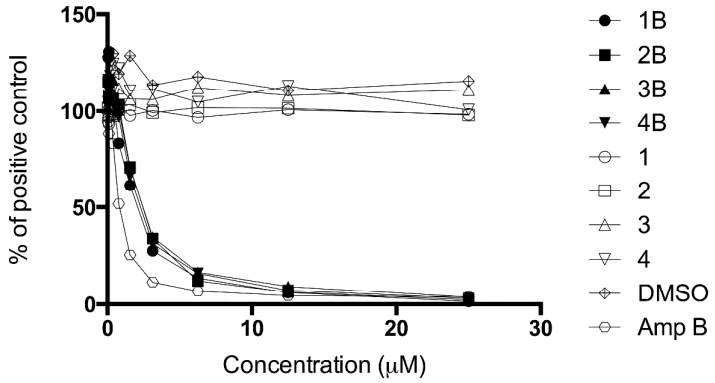

Figure 9. Activity of the non-NSAID benzoic acids and their bismuth derived complexes against *Leishmania major* promastigotes after 48 hours exposure.

After 48 hours, all of the parent acids showed little or no toxicity towards the parasites (Figure 9). In contrast, the bismuth complexes are highly toxic, with complete eradication at a concentrations > 25 μM. Compared to Amphotericin B, which gave 4 % viability at 25 μM, the complexes eliminated the parasites to slightly lower percentage viabilities (3.7 - 1.4 %) at the same concentration. This suggests that the bismuth complexes **1B** – **4B** are marginally more potent *in-vitro* than Amphotericin B.

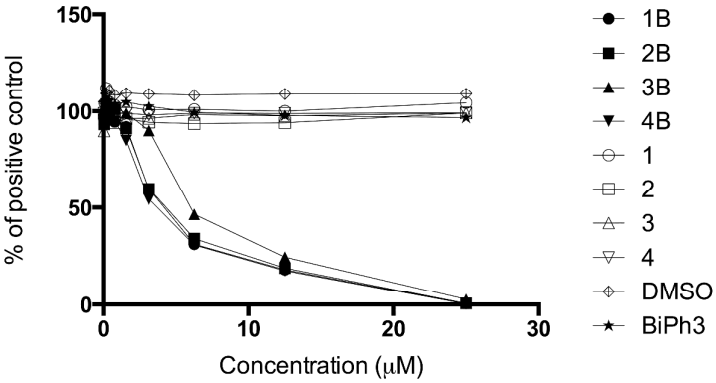

Figure 10. Activity of the non-NSAID benzoic acids and their bismuth derived complexes against human fibroblasts after 48 hours exposure.

The remaining benzoic acids, their bismuth derivatives and $BiPh_3$ were then tested on human fibroblast cells (Figure 10). The acids proved to be essentially non-toxic to the cells and $BiPh_3$ showed only marginal toxicity, killing 20% of the cells at 100 μM. In contrast, all the bismuth complexes were highly toxic to the cells, mirroring the concentrations observed with the parasites. Thus, the Bi(V) complexes demonstrate general toxicity and show little or no discrimination between the parasites and mammalian cells. Complex **3B**, incorporating 2-methoxybenzoate, is marginally less toxic towards the fibroblasts when compared with the other complexes, supporting 90 % cell viability compared with 54 – 60 % at a complex concentration of 3.125 μM. However, at concentrations > 12.5 μM, all complexes showed the same degree of toxicity.

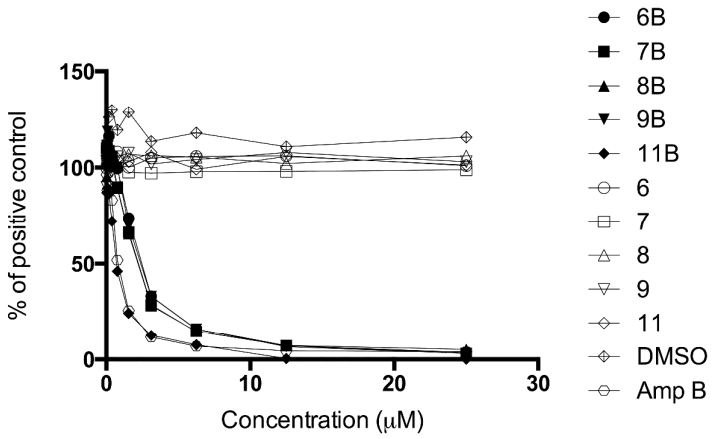

Figure 11. Activity of the NSAID benzoic acids and their bismuth derived complexes against *Leishmania major* promastigotes after 48 hours exposure.

In general, the NSAID derived complexes exhibit the same general pattern of toxicity as shown by the benzoate complexes. The NSAID acids show no toxicity towards the parasites, while their Bi(V) derivatives show strong toxicity in a quantitative nature at lower concentrations in the range 12.5 - 1.56 μM (Figure 11). Complex **11B** though does differ slightly to the other complexes in that its parasite viability falls to zero at 12.5 μM compared

with 50 μM for the other complexes **6B – 9B**. The *Leishmania major* IC_{50} for **11B** was found to be 0.6 (±0.03) μM as opposed to an average of 2.3 μM for **1B – 9B**. (Table 4). Demicheli and coworkers recently reported IC_{50} levels for the Bi(V) aspirinate complex towards *L. infantum and L. amazonesis* of 8.6 (±1.36) and 8.5 (±0.56) μM12 respectively suggesting the complex is more potent against *L. major.*[12]

Table 4. IC_{50} of the complexes **1B**-**11B** and control against *Leishmania major* promastigotes and human fibroblasts at t = 48 h

Bi(V) complex	Parent acid	IC_{50} (± SEM) (μM)	
		Leishmania major	**Human fibroblasts**
1B	3,5-dimethylbenzoic acid	2.00 (0.07)	4.21 (0.03)
2B	3,5-dihydroxybenzoic acid	2.42 (0.04)	4.38 (0.02)
3B	2-methoxybenzoic acid	2.50 (0.05)	6.58 (0.02)
4B	2-ethoxybenzoic acid	2.29 (0.04)	3.84 (0.03)
6B	5-chlorosalicyclic acid	2.48 (0.03)	5.45 (0.03)
7B	5-bromosalicyclic acid	2.18 (0.03)	5.85 (0.03)
8B	Diflunisal	2.15 (0.04)	6.07 (0.02)
9B	Flufenamic acid	2.40 (0.04)	5.67 (0.03)
11B	Aspirin	0.71 (0.03)	2.95 (0.03)
AmpB	Control	0.88 (0.03)	-
$BiPh_3$	Control	45.84 (0.10)	157.5 (1.99)

11B also has the lowest IC_{50} for the fibroblasts as compared to the rest of the complexes, indicating a higher toxicity to the fibroblasts as compared to the other complexes. Conversely, **3B** has the highest IC_{50} of 6.58 (±0.02) μM, indicating that it is the least toxic complex and has some degree of selectivity as compared to the rest. Amphotericin B has no IC_{50} for the fibroblasts since Amphotericin B is non-toxic towards the fibroblasts, maintaining 100% viability even at 100 μM.

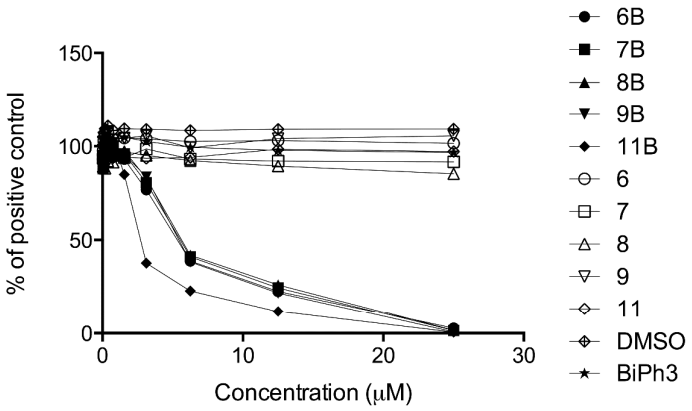

Figure 12. Activity of the NSAID benzoic acids and their bismuth derived complexes against human fibroblasts after 48 hours exposure.

Figure 12 shows the NSAID derived Bi(V) complexes are again highly toxic to the fibroblast cells, while the parent acids are relatively benign, showing almost no toxicity even at 100 μM. The only complex to show some level of selectivity is the aspirin derived complex **11B**.

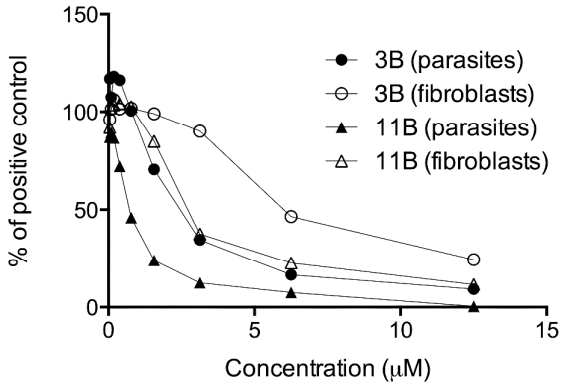

Figure 13. Selectivity of **3B** and **11B** on *Leishmania major* promastigotes and fibroblasts at concentrations below 12.5 μM.

Figure 13 provides a closer look at **3B** and **11B** by setting them with their activities on the same plot. These two complexes were selected because they had high fibroblast viabilities with considerably lower parasite viability at selected concentrations, which was not immediately evident based only on the IC_{50} values in the case of the aspirin derived **11B**. At 3.125 μM, **3B** affected only 10 % of fibroblasts while eliminating parasites to < 35%. For **11B**,

at 1.56 μM, 85% of the fibroblast remained viable while killing all but 24 % of parasites. **3B** has an IC_{50} of 2.5 μM, which is comparable to all other complexes with the exception of **11B**. **11B** has an exceptionally low IC_{50} of 0.71 (± 0.03) μM and shows a greater level of selectivity between the parasites and fibroblasts at a concentration of 1.56 μM (ratio 4.16).

Our recent study on the anti-leishmanial activity of organometallic Sb(V) compounds $[SbAr_3(O_2CR')]$ demonstrated that they have selective toxicity towards the parasites and human fibroblasts.[8] The *m*- or *p*- tolyl substituted complexes were exceptionally active against both *L. major* promastigotes and amastigotes at concentrations of 0.5 – 3.5 μM while being non-toxic towards the fibroblasts below 25 μM.[8] The *tris*-Ph complexes, while not as toxic to the parasites, showed a similar pattern of behaviour. The Bi(V) complexes in this study (all *tris*-Ph) are also active against the promastigotes at a similarly low concentration (3.125 μM) but unlike the Sb(V) complexes show significant toxicity towards the fibroblasts below 25 μM indicating different behaviour. As stated in the introduction Bi(V) is strongly oxidising and the reduction potential for Bi(V)/Bi(III) is 2.03 V [23] while that of Sb(V)/Sb(III) is 0.6 V. [24] It is possible that the non-selective toxicity of the Bi(V) complexes is primarily because of its oxidising power. However, to establish this without ambiguity will take further studies with other complex families, and is the focus of our current studies.

Conclusions

A series of eleven organometallic heteroleptic Bi(V) dibenzoates $[BiPh_3(O_2CR)_2]$ have been synthesised, fully characterised, and assessed for their anti-parasitic activity against *L. major* promastigotes and for cytotoxicity against human fibroblasts. The solid-state structures of eight complexes were determined by single crystal X-ray diffraction, showing a consistent distorted trigonal bipyramidal motif, as observed for other similar known complexes. The complexes are monomeric in the solid state with a seven coordinate Bi(V) centre and with the carboxylate ligands adopting a bidentate binding mode at the Bi(V) centre.

Nine of the eleven complexes were screened in the biological assays. While these demonstrated toxicity towards the *L. major* promastigotes at low concentrations (3.125 M) they were also unselectively toxic against the fibroblasts as similar concentrations, with the greatest degree of discrimination observed for $[Bi(C_6H_5)_3(O_2CC_6H_4\text{-}o\text{-}OCH_3)_2]$ (**3B**) and the aspirin derivative $[Bi(C_6H_5)_3(O_2CC_6H_4\text{-}o\text{-}OCOCH_3)_2]$ (**11B**). The parent acids, $BiPh_3$, and solvent DMSO showed little or no toxic effects.

As an illustrative example, complex **2B**, $[Bi(C_6H_5)_3(O_2CC_6H_3(m\text{-}OH)_2)_2]$, was studied for its stability in DMSO, water and the parasite culture medium (DMEM). ^{1}H NMR studies indicated that the complex is stable in both DMSO and D_2O. However, it decomposes slowly in the culture medium (reconstituted in D_2O), precipitating $BiPh_3$ (as evidenced by ESI-MS) and liberating the free carboxylic acid. That neither of these constituents are toxic to the promastigotes or fibroblasts at the studied concentrations suggests that the concentration of the Bi(V) complexes remains high enough for a long enough period of time to be toxic to both. Visible evidence of decomposition in the ^{1}H NMR spectrum occurred after 6 h and continued to increase slowly thereafter. It is not yet known if the observed toxicity results simply from the strong oxidising nature of Bi(V), and hence uncontrolled cellular damage, or through definable pathways and processes. This is the subject of our on-going investigations.

Acknowledgements

The authors thank the Australian Research Council, Monash University and the Walter and Eliza Institute of Medical Research for financial support, and Dr. Chris Tonkin (WEHI) for the supply of human primary fibroblast cells.

Experimental Section

All solvents used were purchased from Merck. For synthesis of $BiPh_3$, solvents were dried prior to use via the MBraun-SPS-800 and stored over molecular sieves (4Å) in a Schlenk flask

under N_2. All other required chemicals were purchased from Sigma-Aldrich and used as received. NMR spectra were recorded on a Bruker Avance DRX400 spectrometer (400 MHz) with chemical shifts referenced to the appropriate deuterated solvents. Infrared spectra were recorded on an Agilent Technologies Cary 360 FTIR spectrometer in the range 4000-500 cm^{-1}. Melting points were determined in soda glass tubes on a digital Stuart Scientific melting point apparatus SMP10. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer with an electrospray source and a cone voltage of 35 eV. CHN elemental analysis was performed by The Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago in Dunedin, New Zealand.

Biological Assays

Cell viability assay: The Celltiter Blue Cell Viability Assay (Promega, Madison, WI, USA) was used for screening for anti-leishmanial activity and toxicity. Compounds were dissolved in DMSO at 10 mmol/L working stock and diluted out in appropriate culture media. The assay was set up in duplicates in 96-well plates according to the manufacturer's instructions.10^6 promastigotes/mL and 10^5/mL primary human fibroblasts were used. Cell viability was assessed by measuring fluorescence at 550 nm excitation and 590 nm emission as per manufacturers' instructions.[25] The Celltiter Blue dye was added to samples at the time of setting up the assay and the negative control (no cells) value was subtracted from all subsequent readings as a background value. The mean was calculated from duplicate readings. All readings were compared to the no-drug control and the percentage growth inhibition was calculated. DMSO controls were included. All plates were assessed microscopically. The graphs shown in this paper give the percentage of positive control versus concentration.

Cell culture: *Leishmania major* virulent clone V121 was derived from the *L. major* isolate LRC-L137 and maintained at 26˚C in M199 medium supplemented with 10% (v/v) heat

inactivated FBS (Trace Biosciences, NSW, Australia).[26] The human primary fibroblast were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Life Technologies) supplemented with 10 % HI-FBS at 37 °C in 5 % CO_2.

Data analysis: Statistical analysis IC50 values were calculated in Graphpad Prism by non-linear regression (curve fit), dose-response inhibition, log(inhibitor) *vs* normalised response, variable slope

Crystallography

Crystallographic data of compounds **3B, 6B, 8B** and **10B** were collected at the MX1 beamline and compounds **4B** and **7B** were collected on the MX2 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[27] and XDS.[28] Crystallographic data for compound **5B** was collected on an OXFORD Gemini Ultra equipped with an OXFORD Cryosystems 700 Cryostream and cooled to 173 (2) K. Data was collected with monochromatic (graphite) MoK_α radiation (λ = 0.71073 Å) and processed using the CrysAlisProv 1.171.34.36 software;[29] Lorentz, polarization and absorption corrections (multi-scan) were applied. Crystallographic data for compound **1B** was obtained on a Bruker X8 APEXII CCD diffractometer equipped with an OXFORD Cryosystems 700 Cryostream and cooled to 123(2) K. Data was collected with monochromatic (graphite) MoK_α radiation (λ = 0.71073 Å) and processed using the Bruker Apex2 v2012.2.0 software;[30] Lorentz, polarization and absorption corrections (multi-scan – SADABS)[31] were applied. All compounds were solved and refined with SHELX-97.[32] 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. Selected

crystallographic data for compounds **1B**, **3B**-**8B** and **10B** are given in Table 5. CCDC numbers for compounds **1B**, **3B**-**8B** and **10B** are 978095-978102 respectively.

Table 5. Summary of crystallographic data for complexes **1B**, **3B**-**8B** and **10B**.

Compound	**1B**	**3B**	**4B**	**5B**	**6B**	**7B**	**8B**	**10B**
Chemical formula	$C_{36}H_{33}BiO_4$	$C_{36}H_{58}Bi_2O_{12}$	$C_{36}H_{33}BiO_6$	$C_{64}H_{46}Bi_2N_4O_{16}$	$C_{36}H_{31}BiCl_2O_7$	$C_{36}H_{33}BiBr_2O_7$	$C_{44}H_{29}BiF_4O_6$	$C_{48}H_{41}BiCl_2N_2O_5S$
Formula Mass	738.60	1485.10	770.60	1545.01	855.49	946.42	938.65	1037.77
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Triclinic	Triclinic	Monoclinic	Triclinic
a/Å	20.8600(11)	15.413(3)	19.838(4)	13.4495(7)	9.1640(18)	8.7860(18)	11.139(2)	11.180(3)
b/Å	9.7446(4)	9.4312(19)	9.6450(19)	19.5188(13)	11.027(2)	11.096(2)	9.972(2)	12.750(3)
c/Å	15.9050(6)	19.920(4)	15.899(3)	21.4053(13)	17.058(3)	18.289(4)	16.079(3)	16.190(3)
α/°	90.00	90.00	90	90	103.21(3)	103.99(3)	90	79.78(3)
β/°	91.932(3)	91.62(3)	90.27(3)	90	90.76(3)	96.10(3)	96.81(3)	71.76(3)
γ/°	90.00	90.00	90	90	100.90(3)	98.63(3)	90	84.42(3)
V/Å^3	3231.2(2)	2894.6(10)	3042.1(11)	5619.3(6)	1645.5(6)	1691.5(6)	1773.4(6)	2154.9(7)
Space group	*C2/c*	*C2/c*	*C2/c*	*Fddd*	*P-1*	*P-1*	*P2/c*	*P-1*
Z	4	2	4	4	2	2	2	2
Reflections collected	37741	22123	29667	3813	27775	32646	30400	42087
Ind. reflns	3335	3205	4067	2377	7377	8514	4442	9486
R_{int}	0.0248	0.0702	0.0501	0.0228	0.0297	0.0475	0.0331	0.1895
Final R_1 values[a]	0.0375	0.0228	0.0255	0.0196	0.0229	0.0305	0.0583	0.0542
Final $wR(F^2)$ values[a]	0.0491	0.0572	0.0708	0.0488	0.0554	0.0766	0.1633	0.1411
Final R_1 values[b]	0.0192	0.0229	0.0271	0.0235	0.0232	0.0318	0.0593	0.1098
Final $wR(F^2)$ values[b]	0.0688	0.0573	0.0737	0.0511	0.0556	0.0774	0.1660	0.1772

[a]($I > 2\sigma(I)$); [b] all data

Syntheses and Characterisation

General Synthetic Procedure (GP): Stoichiometric amounts of $BiPh_3$ and benzoic acid (1:2) were each dissolved in 5 ml of warm solvent and combined. This was followed by the addition of one equivalent of 30 % H_2O_2. The mixture was stirred for 10 minutes and filtered. Crystals were subsequently obtained on allowing the filtrate to stand at room temperature overnight.

Synthesis of triphenylbismuth bis(3,5-dimethylbenzoate), 1B

$BiPh_3$ (0.125 g, 0.28 mmol), 3, 5-dimethylbenzoic acid (0.085 g, 0.57 mmol) and 30 % H_2O_2 (0.025 ml, 0.032 mmol) were reacted in diethyl ether according to GP. Storage over 18 hours furnished a crop of pale green crystalline product. Yield (single crystal) = 23.9 % (0.05 g, 0.07 mmol); MP: 179-181 °C; Solubility: DCM, chloroform, hot acetone; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 8.18 (6H, d, ^3J = 7.3, *o*-C*H*), 7.73 (6H, t, ^4J = 7.6, *m*-CH_{ar}), 7.56 (3H, t, ^3J = 7.4, *p*-CH_{ar}), 7.48 (4H, s, CH_{ar}), 7.13 (2H, s, CH_{ar}), 2.26 (12H, s, CH_3); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ =172.0 (*C*OO), 160.7 (Bi*C*), 137.4 (*C*CH_3), 133.5 (*C*COO), 133.3 (*o*-*C*H_{ar}), 132.0 (*C*H_{ar}), 131.7 (*m*-*C*H_{ar}), 131.1 (*p*-*C*H_{ar}), 127.3 (*C*H_{ar}), 20.6 (*C*H_3); MS (ESI)$^+$ *m/z* = 457.0 $[BiPh_2 + Na + 4H_2O]^+$, 471.1 $[BiPh_2 + 6H_2O]^+$, 589.1 $[BiPh_3L]^+$, 761.2 $[BiPh_3L_2 + Na]^+$; (ESI)$^-$ *m/z* = 149.0 $[L]^-$, 661.2 $[BiPh_2L_2]^-$; IR[cm^{-1}]: 3452 (w), 3006 (w), 2918 (w), 2862 (w), 1557 (s), 1585 (s), 1387 (sh), 1471 (sh), 1438 (sh), 1352 (s), 1262 (sh), 1182 (w), 1164 (w), 1050 (w), 1013 (w), 985 (sh), 788 (sh), 752 (s), 732 (sh), 773 (sh), 680 (sh); $C_{36}H_{33}BiO_4$ (738.22): Calculated (Found) %C 58.54 (58.63), %H 4.50 (4.45).

Synthesis of triphenylbismuth bis(3,5-dihydroxybenzoate), 2B

$BiPh_3$ (0.25 g, 0.56 mmol), 3, 5-dihydroxybenzoic acid (0.175 g, 1.13 mmol) and 30% H_2O_2 (0.05 ml) were reacted in diethyl ether according to GP. Vapour diffusion against *n*-hexane over 18 hours furnished a crop of pale brown crystals. Yield (single crystal) = 30.6 % (0.130 g, 0.17 mmol) ; MP: 118-120 °C (phase change); Solubility: Methanol, DMSO; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 9.40 (4H, s, O*H*). 8.14 (6H, d, ^3J = 7.8, *o*-CH_{ar}), 7.73 (6H, t, ^3J = 7.6, *m*-CH_{ar}), 7.58 (3H, t, ^3J = 7.3, *p*-CH_{ar}), 6.73 (4H, d, ^4J = 1.6, $(O_2C)CCHC(OH)$), 6.30 (2H, s, $(OH)CCHC(OH)$); ^{13}C {^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ = 171.9 (*C*OO), 160.5 (Bi*CCH*), 158.1 (*C*OH), 134.01(*C*COO), 133.3 (*o*-*C*H_{ar}), 131.6 (*m*-*C*H_{ar}), 131.1 (*p*-*C*H_{ar}), 107.6 (*C*H_{ar}), 106.1(*C*H_{ar}); MS (ESI)$^+$ *m/z* = 363.1 $[BiPh_2]^+$, 593.2 $[BiPhL_2]$; (ESI)$^-$ *m/z* = 229.1 $[PhL]^-$, 363.1 $[BiLH]^-$, 590.9 $[BiPhL_2]^-$, 669.0 $[BiPh_2L_2]^-$, 745.0 $[BiPh_3L_2]^-$; IR[cm^{-1}]: 3188 (s), 1603 (w), 1583

(w), 1544 (s), 1469 (sh), 1438 (sh), 1348 (s), 1298 (s), 1208 (w), 1158 (sh), 1005 (sh), 985 (sh), 862 (sh), 851 (sh), 778 (sh), 730 (sh), 678 (sh); $C_{32}H_{25}BiO_8$. $3H_2O$ (800.56): Calculated (Found) %C 48.01 (48.30), %H, 3.90 (3.91).

Synthesis of triphenylbismuth bis(2-methoxybenozate), 3B

$BiPh_3$ (0.50 g, 1.13 mmol) and 2-methoxybenzoic acid (0.346 g, 2.27 mmol) and 30% H_2O_2 (0.1 ml) were reacted in diethyl ether according to GP. Storage over 18 hours furnished a clear crystalline product. Yield (single crystal) = 55.7 % (0.47 g, 0.63 mmol); MP: 152-154 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 8.24 (6H, d, ^3J = 7.4, *o*-CH_{ar}), 7.74 (6H, t, ^3J = 7.7, *m*-CH_{ar}), 7.57 (3H, t, ^3J = 7.3, *p*-CH_{ar}), 7.39 (4H, m, CH_{ar}), 7.03 (2H, d, ^3J = 8.2, CH_{ar}), 6.90 (2H, t, ^3J = 7.4, CH_{ar}), 3.77 (6H, s, OCH_3); ^{13}C {^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ = 172.2 (*C*OO), 160.0 (Bi*C*), 157.7 (*C*OCH$_3$), 133.5 (*C*H$_{ar}$), 131.9 (*o*-*C*H$_{ar}$), 131.6 (*C*H$_{ar}$), 131.1 (*m*-*C*H$_{ar}$), 130.2 (*p*-*C*H$_{ar}$), 123.5 (*C*H$_{ar}$), 119.9 (*C*COO), 112.5 (*C*H$_{ar}$), 55.8 (O*C*H$_3$); MS (ESI)$^+$ *m/z* = 363.1 [$BiPh_2$]$^+$, 471.2 [$BiPh_2$ + $6H_2O$]$^+$, 591.2 [$BiPh_3L$]$^+$, 765.1 [$BiPh_3L_2$ + MeOH]; (ESI)$^-$ *m/z* = 165.2 [LMe]$^-$; IR[cm^{-1}]: 3075 (w), 3043 (w), 3008 (w), 2965 (w), 2935 (w), 2836 (w), 1601 (m), 1588 (m), 1555 (m), 1486 (m), 1469 (m), 1434 (m), 1344 (m), 1274 (sh), 1248 (s), 1181 (m), 1162 (m), 1147 (m), 1095 (m), 1052 (m), 1000 (w), 983 (sh), 924 (w), 858 (sh), 808 (w), 735 (sh), 696 (sh), 681 (sh), 663 (sh); $C_{34}H_{29}BiO_6$ (742.18): Calculated (Found) %C 54.99 (54.95), %H 3.94 (4.07).

Synthesis of triphenylbismuth bis(2-ethoxybenozate), 4B

$BiPh_3$ (0.50 g, 1.13 mmol), 2-ethoxybenzoic acid (0.342 ml, 2.27 mmol) and 30% H_2O_2 (0.1 ml) were reacted in diethyl ether according to GP. Upon standing, crystalline product was observed after 18 hours. Yield (single crystal) = 76 % (0.66 g, 0.63 mmol); MP: 167-170 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 8.25 (6H, d, ^3J = 7.3, *o*-CH_{ar}), 7.72 (6H, t, ^3J = 7.7, *m*-CH_{ar}), 7.57 (3H, t, ^3J = 7.3, *p*-CH_{ar}), 7.36 (4H, m, CH_{ar}), 7.01 (2H, d, ^3J = 8.6, CH_{ar}), 6.84 (2H, t, ^3J = 7.4, CH_{ar}), 4.00 (4H, q, ^3J = 6.9, OCH_2CH$_3$), 1.30 (6H, t, ^3J = 6.9, OCH$_2$CH_3); ^{13}C {^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ = 172.5 (*C*OO), 160.4 (Bi*C*), 157.0 (*i*-*C*$_{ar}$), 133.4 (*C*H$_{ar}$), 131.8 (*o*-*C*H$_{ar}$), 131.5 (*C*H$_{ar}$), 131.1 (*m*-*C*H$_{ar}$), 130.2 (*p*-*C*H$_{ar}$), 123.7 (*C*H$_{ar}$), 119.9 (*C*COO), 113.4 (*C*H$_{ar}$), 63.9 (O*C*H$_2$CH$_3$), 14.7 (OCH$_2$*C*H$_3$); MS (ESI)$^+$ *m/z* = 189.1 [L + Na]$^+$, 242.3 [PhL]$^+$, 363.1 [$BiPh_2$]$^+$, 605.2 [$BiPh_3L$]$^+$, 793.2 [$BiPh_3L_2$ + Na]$^+$; (ESI)$^-$ *m/z* = 665.1 [$BiPh_2L_2$ −H]$^-$; IR[cm^{-1}]: 3080 (w), 3043 (w), 2983 (w), 2933 (w), 2885 (w), 1601 (sh), 1585 (sh), 1553 (m), 1471 (m), 1452 (m), 1438 (m), 1352 (s), 1300 (w), 1268 (sh), 1249 (sh), 1164 (sh), 1151 (sh), 1117 (sh), 1097 (w),

1151 (sh),1013 (sh), 985 (sh), 927 (sh), 855 (sh), 838 (w), 806 (w), 752 (sh), 732 (sh), 704 (sh), 670 (sh) ; $C_{36}H_{33}BiO_6$ (770.62): Calculated (Found) %C 56.11 (55.81), %H 4.32 (4.37).

5.6.5 Synthesis of triphenylbismuth bis(4-nitrobenzoate), 5B

$BiPh_3$ (0.255 g, 0.58 mmol), 4-nitrobenzoic acid (0.193 g, 1.15 mmol) and 30% H_2O_2 (0.1 ml) were reacted in THF according to GP. Vapour diffusion with *n*-hexane over three days furnished a crop of orange crystals. Yield (single crystal) = 30.3 % (0.135 g, 0.18 mmol); MP: 188-191 °C (lit. MP 181 °C [14]); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.28 (6H, d, ^3J = 7.2, *o*-CH_{ar}), 8.13 (8H, br. dd, ^3J = 7.4, CH_{ar}), 7.65 (6H, t, ^3J = 6.9, *m*-CH_{ar}), 7.51 (3H, t, ^3J = 6.6, *p*-CH_{ar}); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.5 (*C*OO), 159.6 (Bi*C*), 150.0 (*C*NO_2), 139.0 (*C*COO), 134.2 (*o*-*C*H_{ar}), 131.7 (*m*-*C*H_{ar}), 131.5 (*p*-*CH*$_{ar}$), 131.1 (*CH*$_{ar}$), 123.3 (*CH*$_{ar}$); MS (ESI)$^+$ *m/z* = 471.1 [$BiPh_2$ + 6H_2O], 606.1 [$BiPh_3L$]$^+$; (ESI)$^-$ *m/z* = 166.0 [L]$^-$, 705.4 [$BiPh_2L_2$]$^-$; IR: 3086 (w), 3065 (w), 3051 (w), 1752 (sh), 1628 (w), 1594 (sh), 1560(sh), 1544 (sh), 1523(sh), 1473 (sh), 1456 (sh), 1439 (s), 1339 (s), 1320 (s), 1225 (sh), 1199 (m), 1190 (m), 1104 (w), 1095 (w), 1015 (m), 987 (sh), 927 (sh), 879 (w), 834 (sh), 795 (w), 741 (sh), 722 (sh), 683 (sh); $C_{32}H_{23}BiN_2O_8$ (772.51): Calculated (Found) %C 49.75 (49.79), %H 3.00 (2.96), %N 3.63 (3.62).

Synthesis of triphenylbismuth bis(5-chlorosalicyclate), 6B

$BiPh_3$ (0.5 g, 1.13 mmol), 5-chlorosalicyclic acid (0.392 g, 2.27 mmol) and 30% H_2O_2 (0.1 ml) were reacted in warm diethyl ether according to GP. Vapour diffusion with *n*-hexane over 17 hours furnished a crop of clear crystalline blocks and this was left for 2 days to obtain maximal yield. Yield (single crystal) = 76.8% (0.68 g, 0.87 mmol); MP: 196-197 °C; Solubility: Chloroform, hot DCM, hot DMSO (partial); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 11.53 (2H, s, O*H*), 8.21 (6H, d, ^3J = 8.l, *o*-CH_{ar}), 7.89 (2H, d, ^4J = 2.2, (O_2C)CC*H*C(Cl)), 7.68 (2H, t, ^3J = 7.7, *m*-CH_{ar}), 7.54 (3H, t, ^3J = 7.2, *p*-CH_{ar}), 7.39 (2H, dd, ^3J = 8.8, ^4J = 2.2, (Cl)CC*H*CHC(OH)), 6.76 (2H, d, ^3J = 8.8, (Cl)CCHC*H*C(OH)); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.0 (*C*OO), 160.6 (*C*OH), 159.1 (Bi*C*), 137.4 (*C*H_{ar}), 134.1 (*o*-*C*H_{ar}), 133.4 (*C*H_{ar}), 132.0 (*m*-*C*H_{ar}), 131.7 (*p*-*C*H_{ar}), 119.1 (*C*H_{ar}), 116.7 (*i*-*C*$_{ar}$), 110.2 (*C*COO); MS (ESI)$^+$ *m/z* = 363.1 [$BiPh_2$]$^+$, 457.3 [BiPhL]$^+$, 471.3 [$BiPh_2$ + 6H_2O], 611.4 [$BiPh_3L$]$^+$; (ESI)$^-$ *m/z* = 365.2 [L_2 + Na]$^-$, 705.4 [$BiPh_2L_2$] ; IR[cm^{-1}]: 3054 (w), 1626 (sh), 1587 (s), 1560 (s), 1467 (sh), 1439 (sh), 1328 (s), 1365 (s), 1348 (s), 1328 (s), 1292 (sh), 11242 (sh), 1227 (s), 1214 (s), 1102 (w), 1056 (w), 1015 (sh), 989 (sh), 899 (w), 883 (w), 815 (sh), 808 (sh), 678 (sh), 700 (sh), 725 (sh); $C_{32}H_{33}BiCl_2O_8$ (783.41): Calculated (Found) %C, 49.06 (49.99), %H, 2.96 (3.44).

5.6.7 Synthesis of triphenylbismuth bis(5-bromosalicyclate), 7B

$BiPh_3$ (0.5 g, 1.13 mmol), 5-bromosalicyclic acid (0.392 g, 2.27 mmol) and 30% H_2O_2 (0.1 ml) were reacted in warm diethyl ether according to GP. Upon standing, pure crystalline product was observed after 18 hours and this was left for 2 days to obtain maximal yield. Yield (single crystal) = 26.8 % (0.26 g, 0.30 mmol); MP: 194-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.53 (2H, s, O*H*), 8.22 (6H, dd, ^3J = 8.3, ^4J = 1.0, *o*-CH_{ar}), 7.90 (2H, d, ^4J = 2.5, (O_2C)CC*H*C(Br)), 7.68 (2H, t, ^3J = 7.7, *m*-CH_{ar}), 7.53 (3H, t, ^3J = 7.4, *p*-CH_{ar}), 7.39 (2H, dd, ^3J = 8.8, ^4J = 2.5, (Br)CC*H*CHC(OH)), 6.76 (2H, d, ^3J = 8.8, (Br)CCHC*H*C(OH)); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.0 (*C*OO), 160.6 (*C*OH), 159.1 (Bi*C*), 137.4 (*C*H$_{ar}$), 134.1 (*o*-*C*H$_{ar}$), 133.4 (*C*H$_{ar}$), 132.0 (*m*-*C*H$_{ar}$), 131.7 (*p*-*C*H$_{ar}$), 119.1 (*C*H$_{ar}$), 116.7 (*C*Br), 110.2 (*C*COO); MS (ESI)$^+$ *m/z* = 363.2 [$BiPh_2$]$^+$, 457.3 [$BiPh_2$ + Na + 4H_2O]$^+$, 471.3 [$BiPh_2$ + 6H_2O]$^+$, 657.3 [$BiPh_3$L]$^+$; (ESI)$^-$ *m/z* = 215.1 [L]$^-$, 455.1 [BiL + MeOH]$^-$, 795.3 [$BiPh_2L_2$]; IR[cm^{-1}]: 3060 (br), 2972 (br), 2924 (br), 1655 (w), 1620 (sh), 1585 (m), 1560 (m), 1544 (sh), 1467 (sh), 1421 (s), 1439 (s), 1365 (s), 1350 (s), 1292 (sh), 1225 (s), 1240 (s), 1212 (s), 1151 (sh), 1100 (sh), 1050 (w), 989 (s), 892 (s), 825 (s), 827 (s), 726 (w), 696 (s), 678 (sh); $C_{32}H_{23}BiBr_2O_6$ (872.31): Calculated (Found) %C 44.06 (44.56), %H 2.66 (2.81).

5.6.8 Synthesis of triphenylbismuth bis(2',4'-difluoro-4-hydroxybiphenyl-3-carboxylate), 8B

$BiPh_3$ (0.176 g, 0.4 mmol), diflunisal (0.20 g, 0.8 mmol) and 30% H_2O_2 (0.025 ml) were reacted in diethyl ether according to GP. Vapour diffusion against n-hexane over 17 hours furnished pale yellow crystals. Yield (single crystal) = 58.4 % (0.22 g, 0.23 mmol); MP: 195-197 °C (Decomp.); ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 11.64 (2H, s, O*H*), 8.24 (6H, d, ^3J = 7.7, o-CH_{ar}), 7.89 (2H, s, CH_{ar}), 7.80 (6H, t, ^3J = 7.6, *m*-CH_{ar}), 7.63 (3H, t, ^3J = 7.4, *p*-CH_{ar}), 7.55 (4H, m, CH_{ar}), 7.33 (2H, td, ^3J = 10.2, ^4J = 2.5, CH_{ar}), 7.15 (2H, td, ^3J = 8.4, ^4J = 2.2, CH_{ar}), 6.94 (2H, d, ^3J = 8.6, CH_{ar}); ^{13}C {^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ = 173.5 (*C*OO), 162.7 (Bi*C*), 160.3 (*C*F), 157.8 (*C*F), 136.7 (*C*H$_{ar}$), 135.1 (*C*COO), 133.7 (*o*-*C*H$_{ar}$), 132.2 (*m*-*C*H$_{ar}$), 131.9 (*p*-*C*H$_{ar}$), 131.4 (*C*H$_{ar}$), 130.8 (*C*H$_{ar}$), 124.8 (*i*-*C*$_{ar}$), 124.0 (*i*-*C*$_{ar}$), 117.18 (*C*H$_{ar}$), 115.0 (*C*OH), 112.0 (*C*H$_{ar}$), 104.5 (*C*H$_{ar}$); MS (ESI)$^+$ *m/z* = 363.2 [$BiPh_2$]$^+$, 457.3 [$BiPh_2$ + Na + 4H_2O]$^+$, 471.3 [$BiPh_2$ + 6H_2O)]$^+$, 689.4 [$BiPh_3$L]$^+$; (ESI)$^-$ *m/z* = 249.2 [L]$^-$, 805.4 [$BiPhL_2$ + Na]$^-$, 861.6 [$BiPh_2L_2$]$^-$, 937.6 [$BiPh_3L_2$]; IR[cm^{-1}]: 3078 (br), 3054 (br), 1635 (sh), 1596 (sh), 1559 (sh), 1471 (sh), 1436 (sh), 1510 (w), 1378 (s), 1298 (sh), 1285 (sh), 1261 (s), 1249 (s), 1225(w), 1162 (w), 1145 (sh), 1108 (sh), 1035 (w), 985 (sh), 970 (sh), 848 (w), 804 (sh), 680 (sh), 670 (sh), 732 (s); $C_{44}H_{29}BiF_4O_6$ (938.67): Calculated (Found) %C 56.30 (56.93), %H 3.11 (3.09).

5.6.9 Synthesis of triphenylbismuth bis[2-((3-(trifluoromethyl) phenyl) amino) benzoate], 9B

$BiPh_3$ (0.5 g, 1.13 mmol), flufenamic acid (0.638 g, 2.27 mmol) and 30% H_2O_2 (0.1 ml) were reacted in diethyl ether/acetone/THF according to GP. Vapour diffusion against *n*-hexane over three days furnished a crop of yellow crystals. Yield (single crystal) = 52.2 % (0.59 g, 0.59 mmol); MP: 164-166 °C, Solubility: THF, warm chloroform, DMSO (partial); ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 25 °C): δ = 9.63 (2H, s, N*H*), 8.23 (6H, d, ^3J = 7.5, *o*-CH_{ar}), 7.91 (2H, d, ^3J = 7.4, CH_{ar}), 7.70 (6H, t, ^3J = 7.6, *m*-CH_{ar}), 7.54 (3H, t, ^3J = 7.4, *p*-CH_{ar}), 7.50 (2H, t, ^3J = 7.8, CH_{ar}), 7.38 (6H, m, CH_{ar}), 7.28 (2H, d, ^3J = 7.6, CH_{ar}), 7.24 (2H, d, ^3J = 8.1, CH_{ar}), 6.84 (2H, t, ^3J = 7.5, CH_{ar}); ^{13}C {^{1}H} NMR (100 MHz, $(CD_3)_2SO$, 25 °C): δ = 172.90 (*C*OO), 159.64 (Bi*C*), 144.39 *C*(NH)), 142.22 *C*(NH)), 133.52 (*C*H_{ar}), 133.42 (*C*H_{ar}), 132.61 (*C*H_{ar}), 131.84 (*C*H_{ar}), 131.36 (*C*H_{ar}), 130.36 (*C*(CF_3)), 130.26 (C^{14}), 130.04 (*C*H_{ar}), 128.11 (*i*-*C*$_{ar}$), 125.41 (*i*-*C*$_{ar}$), 122.81 (*C*H_{ar}), 122.70 (*i*-*C*$_{ar}$), 119.05 (*C*H_{ar}), 118.01 (*C*H_{ar}), 115.51 (*C*H_{ar}), 114.99 (*C*COO); MS (ESI)$^+$ *m/z* = 363.2 $[BiPh_2]^+$, 457.3 $[BiPh_2 + Na + 4H_2O]^+$, 471.3 $[BiPh_2 + 6H_2O]^+$, 643.4 $[BiPh_2L]^+$, 720.4 $[BiPh_3L]^+$, 769.5 $[BiL_2]^+$, 1023.6 $[BiPh_3L_2 + Na]^+$; (ESI)$^-$ *m/z* = 280.2 $[L]^-$, 583.4 $[BiPhL(OH)]^-$, 923.7 $[BiPh_2L_2]$; IR[cm^{-1}]: 3270 (m), 3065 (w), 1613 (w), 1587 (sh), 1562 (sh), 1520 (sh), 1466 (sh), 1439 (sh), 1361 (sh), 1343 (sh), 1328 (sh), 1292 (sh), 1276 (sh), 1242 (m), 1154 (s), 1113 (sh), 1069 (m), 987 (sh), 935 (sh), 896 (w), 840 (w), 812 (sh), 799 (sh), 760 (sh), 724 (s), 698 (s), 676 (s), 663 (s); $C_{46}H_{33}BiF_6N_2O_4$ (1000.74) Calculated (Found): %C 55.21 (55.60), %H 3.32 (3.32), %N 2.80 (2.86).

5.6.10 Synthesis of triphenylbismuth bis[2-((3-chloro-2-methylphenyl)amino)benzoate], 10B

Triphenylbismuth (0.25 g, 0.57 mmol), tolfenamic acid (0.297 g, 1.14 mmol) and 30% H_2O_2 (0.05 ml) were reacted in diethyl ether/acetone/THF/DMSO according to GP. With diethyl ether/acetone/THF, vapour diffusion against *n*-hexane gives a dark orange crystalline product after a period of three days. With evaporation of DMSO, a yellow crystalline product was formed. Yield (single crystal) = 57.0 % (0.31 g, 0.32 mmol); MP: 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.58 (2H, s, N*H*), 8.30 (6H, dd, ^3J = 7.3, ^4J = 7.4, *o*-CH_{ar}), 7.99 (2H, dd, ^3J = 7.9, ^4J = 1.6, CH_{ar}), 7.59 (6H, t, ^3J = 7.4, *m*-CH_{ar}), 7.46 (3H, t, ^3J = 7.4, *p*-CH_{ar}), 7.18 (6H, m, CH_{ar}), 7.08 (2H, t, ^3J = 7.9, CH_{ar}), 6.81 (2H, d, ^3J = 7.7, CH_{ar}), 6.67 (2H, t, ^3J = 7.5, CH_{ar}), 2.24 (6H, s, CH_{ar}); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.6 (*C*OO), 161.2 (Bi*C*), 147.8 (*i*-*C*$_{ar}$), 141.4 (*i*-*C*$_{ar}$), 135.5 (*i*-*C*$_{ar}$), 134.1 (*o*-*C*H_{ar}), 133.2 (*C*H_{ar}), 133.0 (*C*H_{ar}), 131.4 (*m*-*C*H_{ar}), 131.0 (*p*-

*C*H$_{ar}$), 130.9 (*i*-*C*$_{ar}$), 126.8 (*C*H$_{ar}$), 124.9 (*C*H$_{ar}$), 122.2 (*C*H$_{ar}$), 116.9 (*C*H$_{ar}$), 115.1 (*C*COO), 113.5 (*C*H$_{ar}$), 15.1 (*C*H$_3$); MS (ESI)$^+$ *m/z* = 457.3 [BiPh$_2$ + Na + 4H$_2$O]$^+$, 623.4 [BiPh$_2$L]$^+$, 700.4 [BiPh$_3$L]$^+$, 915.5 [BiPh$_2$L$_2$ + MeOH]$^+$; (ESI)$^-$ *m/z* = 260.2 [L]$^-$, 883.6 [BiPh$_2$L$_2$]; IR [cm^{-1}]: 3248 (m), 3058 (br), 1713 (sh), 1615 (sh), 1581 (sh), 1562 (sh), 1495 (m), 1473 (sh), 1460 (sh), 1439 (sh), 1419 (w), 1326 (w), 1365 (s), 1270 (s), 1156 (m), 1089 (w), 1013 (sh), 987 (sh), 910 (m), 853 (sh), 814 (sh), 776 (m), 748 (sh), 726 (sh), 706 (m), 672 (sh), 691 (m); $C_{46}H_{37}BiCl_2N_2O_4$ (961.68) Calculated (Found) % 57.45 (57.67) %H 3.88 (3.99) %N 2.91 (3.01).

5.6.5 Synthesis of triphenylbismuth bis(2-acetoxybenzoate), 11B[c]

BiPh$_3$ (0.50 g, 1.14 mmol), acetosalicylic acid (0.41 g, 2.27 mmol) and 30 % H$_2$O$_2$ (0.1 ml) were reacted in diethyl ether according to GP. Standing overnight furnished a crop of pale yellow crystals. Yield (single crystal)= 85% (0.77g, 0.96 mmol); MP: 161-164 °C; ^{1}H NMR (400 MHz, (CD$_3$)$_2$SO, 25 °C): δ = 8.11, (6H, d, ^{3}J = 7.8), 7.74 (8H, m, *o*-C*H*$_{ar}$ & (O2C)CC*H*), 7.58 (3H, t, ^{3}*J* = 7.3, *p*-C*H*$_{ar}$), 7.51 (2H, td, ^{3}*J* = 7.7, ^{4}*J* = 1.6, (O$_2$C)CCHC*H*), 7.27 (2H, td, ^{3}*J* = 7.5, ^{4}*J* = 0.8, (O$_2$C)CCHCHC*H*), 7.07 (2H, d, ^{3}*J* = 8.0, *H*CC(OC(CH$_3$)), 1.99 (6H, s, 2 × C*H*$_3$); ^{13}C {^{1}H} NMR (100 MHz, (CD$_3$)$_2$SO, 25 °C): δ = 170.3 (*C*OO), 168.9 (Bi*C*), 159.6 (*i*-*C*$_{ar}$), 149.6 (*i*-*C*$_{ar}$), 133.3 (*C*H$_{ar}$), 132.8 (*C*H$_{ar}$), 131.7 (*C*H$_{ar}$), 131.4 (*C*H$_{ar}$), 131.3 (*C*H$_{ar}$), 126.2 (*i*-*C*H$_{ar}$), 123.5 (*C*H$_{ar}$), 20.7 (*C*H$_3$); MS (ESI)$^+$ *m/z* = 457.3 [BiPh$_2$ + Na + 4H$_2$O]$^+$, 471.1 [BiPh$_2$ + 6H$_2$O]$^+$, 821.1 [BiPh$_3$L$_2$ + 3H$_2$O]; (ESI)$^-$ *m/z* = 721.1 [BiPh$_2$L$_2$ + MeOH]; IR [cm^{-1}]: 3077 (w), 3062 (w), 3043 (w), 2989 (w), 1752 (sh), 1607 (m), 1590 (m), 1544 (m), 1473 (m), 1454 (m), 1439 (m), 1367 (s), 1223 (s), 1199 (s), 1095 (m), 1046 (w), 1013 (m), 987 (m), 925 (m), 883 (w), 758 (m), 741 (sh), 711 (m), 683 (sh), 674 (sh); $C_{36}H_{29}BiO_8$ (798.60). This analytical data is largely consistent with that described recently by Demicheli.[12]

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Table of Contents

A series of organometallic bismuth(V) dicarboxylates, $[BiPh_3(O_2CR')_2]$, were synthesised, characterised and evaluated for their anti-leishmanial activity. The Bi(V) complexes are highly effective against parasite promastigotes (0.6 - 2.5 μM), but also undergo slow reductive decomposition to $BiPh_3$ and the parent acid in the culture medium.