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FULL PAPER

Synthesis, characterization and antileishmanial studies of some bioactive heteroleptic pentavalent antimonials

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In pursuit of safe drug candidates for the treatment of parasitic diseases like leishmaniasis, a series of heteroleptic pentavalent antimonials of the type $[R_3Sb(O_2CR')_2]$ (**1–9**) have been synthesized and characterized using elemental analysis (CHN), Fourier transform infrared spectroscopy and multinuclear (^1H and ^{13}C) NMR spectroscopy. The carboxylates studied are predominantly substituted benzoates with some complexes having acetato or nicotinato ligands. The crystal structures of $[Sb(C_6H_5)_3(o\text{-}NH_2C_6H_4COO)_2]$ (**1**) and $[Sb(C_6H_5)_3(3,5\text{-}Cl_2C_6H_3COO)_2]$ (**4**) were determined as essentially monomeric with an Sb(V) centre and shown to adopt geometries intermediate between trigonal bipyramidal and square pyramidal. The antileishmanial activity was assessed against *Leishmania tropica* KWH23, and also human macrophages were used to measure the cytotoxicity of these complexes. The IC_{50} of the antimonials **1–9** indicates their efficaciousness as compared with the standard antimonial drug used. The significant activity of complex **1** assumes that greater multitude of interactions is the cause of enhanced antileishmanial activity. Cytotoxicity results showed that these antimonials are highly active even at low concentrations and are biocompatible with human macrophages, making them promising drug candidates for further investigations in this field.

KEYWORDS

carboxylato pentavalent antimonials, cytotoxicity, *Leishmania tropica* KWH23, leishmanicidal

1 | INTRODUCTION

The medicinal chemistry of carboxylic acids has been a subject of investigations in life sciences, particularly for their antipyretic, anti-inflammatory and *in vitro* anti-carcinoma properties.[1–3] Metal–organic assemblies with such types of biologically active ligands are of increased interest for inorganic, pharmaceutical and medicinal chemists, as an approach to the development of highly effective metal-based drugs.[4] In the past few years, various gold(III), palladium (II) and rhenium(V) cyclometallated complexes have been investigated as potential inhibitors of different cysteine proteases in the search for metal-based drugs suitable not only for American trypanosomiasis but also for leishmaniasis.[5,6] Protein crystallographic studies of *Leishmania* trypanothione reductase have disclosed the actual mechanism of enzyme inhibition by antimonials. It was shown that trivalent antimony binds to the protein active site with high affinity, strongly inhibiting enzyme activity.[7] The metal binds directly to Cys52, Cys57, Thr335 and His461, thereby blocking hydride transfer and trypanothione reduction. The observed Sb–protein interaction is consistent with the usual modalities of cysteine binding of thiophilic metals such as As(III), Sb(III) and Bi(III). Such metal-dependent inhibition of thiol reductases opens the way to combined metal therapy of leishmaniasis. It is very likely that this enzyme is similarly inhibited by other classes of metal complexes that are soft Lewis acids.

Over the past few decades, the use of antimony compounds in medicine has attracted much attention of inorganic biochemists as anti-protozoal drugs. The major clinical uses of antimony compounds are for treatment of leishmaniasis.[8–11] The pentavalent antimonials like sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime) are clinically used against leishmaniasis, although it is found that antimony(V) is reduced to antimony(III) *in vivo*.[12–14] The exact mode of action of these drugs is yet to be explored comprehensively. There have been speculations as to whether Indian *Leshmania donovani* has become truly resistant to Sb(V); studies reveal that this is true to some extent in some areas of South Asia due to inadequate regimens followed by unqualified local practitioners.[15,16]

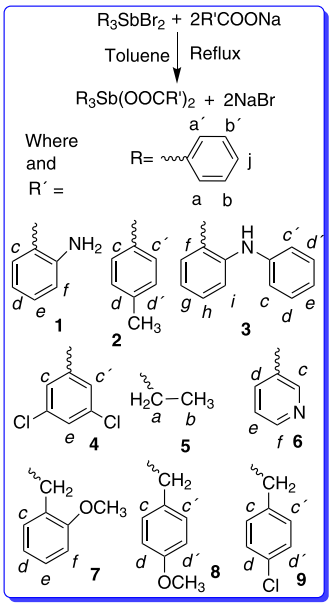
The needs for new antileishmanial drugs have been highlighted in recent decades by the expression of acquired resistance to the pentavalent antimonial drugs, still first-line antileishmanial agents worldwide. Besides post-clinical issues, the inherent problems associated with the existing pentavalent antimonials are degree of purity, exact structure and shelf-life reliability. The synthesis of antimony(V) organometallics of the types R_3SbX_2 and $R_3Sb(O_2R')_2$ and their screening for leishmanicidal properties are a part of our ongoing project for the development of tri/pentavalent antimonial drugs for leishmaniasis therapies.[17–19] The versatile bonding pattern around the Sb(V) centre and the load of pharmacophore substituents may lead to a different mode of action and enhanced efficacy as compared to the existing metal–organic pentavalent antimonials.

2 | RESULTS AND DISCUSSION

2.1 | Synthesis and spectroscopic characterization

The preparation of triorganoantimony(V) carboxylates has been realized using a variety of synthetic methods as reported in the literature.[20,21] The most used methods are the reaction of triorganoantimony(V) halides with two equivalents of carboxylic acids and triethylamine or with carboxylate salts of alkali metals (Na^+/K^+) or silver (Ag^+).[17,22] The synthesis of dicarboxylato complexes of Sb(V) (**1–9**) was achieved using a salt metathesis reaction in which triorganoantimony(V) bromide was treated with the sodium salt of a carboxylic acid in toluene (Scheme 1).

After stirring at room temperature under dry nitrogen atmosphere for 10–12 h, all solids were removed by filtration and the product was collected through removal of the solvent from the filtrate under reduced pressure. The products were recrystallized from toluene–dichloromethane (1:1). The final complexes $[SbR_3(O_2CR')_2]$ were confirmed through ^1H NMR, ^{13}C NMR and Fourier transform infrared (FT-IR) spectroscopies and elemental analysis. Full analytical details for each of **1–9** are provided in Section 4. The FT-IR spectra of the acids show the stretch for the carboxyl group ranging



SCHEME 1 Synthesis of complexes 1–9

from 1670 to 1700 cm^{-1}. The lowering of the wavenumber by 35–45 cm^{-1} for the symmetric and asymmetric carboxylate stretching bands on formation of the antimony(V) carboxylato complexes indicates the metal–carboxylate linkage. The characteristic absorptions observed in the lower wavenumber region at 584–545 and 486–480 cm^{-1} correspond to Sb−C deformations and the Sb−O stretching mode, respectively, both of which are consistent with literature reports.[17,23–25]

The γ(CH) band at 725–735 cm^{-1} indicates the presence of the aryl group. The value of $\Delta\nu$ ($\nu CO_{2(asymm)} - \nu CO_{2(symm)}$) is less than 200 cm^{-1} for all the complexes. This is indicative of the carboxylato ligands adopting a unidentate binding mode[26] in all of the synthesized complexes and is consistent with the crystal structures obtained for **1** and **4**. The NMR spectra of the complexes were recorded in $CDCl_3$ at room temperature. All the complexes show a high frequency shift in the H and C resonances for the carboxylate ligands relative to those observed in the NMR spectra of the free acids. In addition, the NMR spectra of the antimony(V) complexes show resonances for the aromatic protons in the expected range of 6.86–8.23 ppm.[27,28]

2.2 | Structural characterizations

The antimony(V) complexes **1** and **4** are five-coordinate with geometries intermediate between trigonal bipyramidal and square pyramidal. In the trigonal bipyramidal configuration, the monodentate carboxylate ligands occupy axial position with a *syn* conformation and the phenyl moieties rest at equatorial positions, while in the square pyramidal configuration the C7–C12 (for **1**) or C13a–C18a (for **4**) phenyl group is apical. The molecular structure of complex **1** is presented in Figure 1 and of complex **4** in Figure 2.

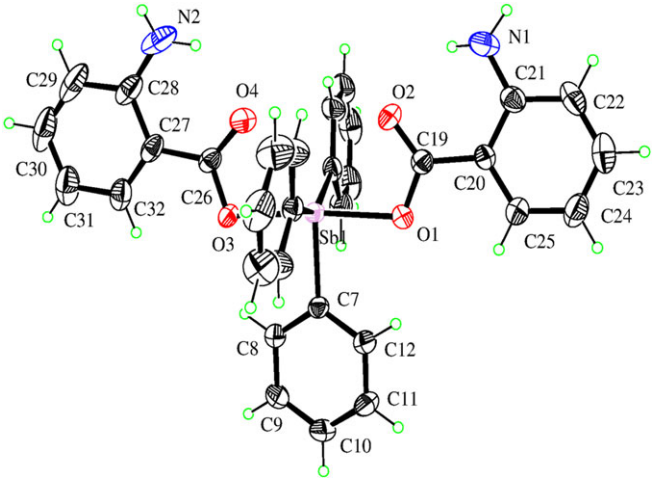


FIGURE 1 Molecular structure of 1 with labels for the core atoms only. Hydrogen atoms are drawn as circles of arbitrary radii.

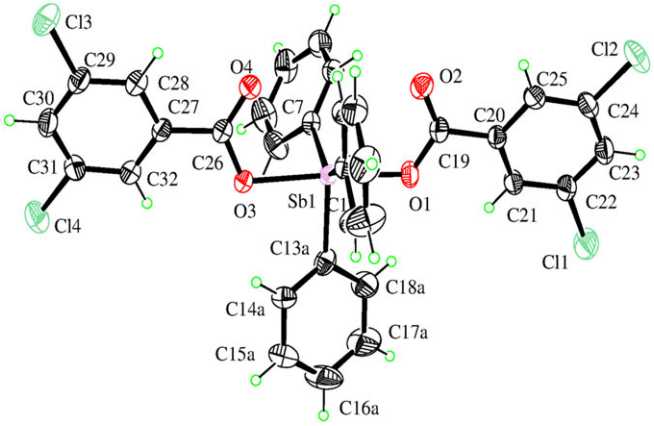


FIGURE 2 Molecular structure of 4 with labels for the core atoms only. Hydrogen atoms are drawn as circles of arbitrary radii.

The geometries in these complexes closely conform to those typically found for complexes with essentially *syn* monodentate carboxylate ligands in approximately 53 similar compounds listed in the Cambridge Structural Database (four additional compounds listed in the database are with carboxylate ligands serving as bidentate and monodentate as well). The 2-aminobenzoato (**1**) and 3,5-dichlorobenzoato (**4**) ligands show average C−O bond lengths of 1.271(3) and 1.261(3) Å, respectively. The Sb−O bond lengths for these complexes cluster at comparatively larger values of 2.1286 (18) and 2.1134(15) Å. The non-ligating Sb···O contacts, involving oxygen atoms, are in the range 2.726–3.010 Å, a contact range that has been most frequently found for similar complexes.[17] Details of the data collection and structure refinement parameters are summarized in Table 1.

The benzoato ligands are almost coplanar in both complexes (angle between mean plane normals of 10.50 (5)° and 3.77(5)° for **1** and **4**, respectively). O–Sb–C(7) (for **1**) or O–Sb–C(13a) (for **4**) angles <90° between the apical phenyl and basal carboxylate ligands indicate that the carboxylate ligands are distorted above the basal plane. Similar distortions are found for related complexes in the Cambridge Structural Database. Sb−C bond lengths average 2.122(3) and 2.134(3) Å for structures **1** and **4**, respectively. The average Sb−C bond lengths for these two structures fall within the range 2.089–2.130 Å, most frequently observed for similar complexes.[17] Selected geometrical parameters are presented in Tables 2 and 3.

TABLE 1 Crystallographic data for **1** and **4**

	1	**4**
Formula	$C_{32}H_{27}N_2O_4Sb$	$C_{32}H_{21}Cl_4O_4Sb$
Formula weight	625.30	733.04
Crystal system	Orthorhombic	Triclinic
Space group	*Pccn*	$P\bar{1}$
a (Å)	19.9860(4)	11.8863(4)
b (Å)	16.5608(3)	12.1976(5)
c (Å)	16.9796(4)	13.4850(8)
α, *β*, *γ* (°)	90 90 90	106.764(2) 100.831(2) 117.6370(10)
V (Å^3), *Z*	5620.0(2), 8	1534.53(12), 2
T (K)	296(2)	296(2)
D_C (Mg m^{-3}), μ (mm^{-1})	1.478, 1.021	1.586, 1.283
F(000)	2528	728
Crystal size (mm^3)	0.30 × 0.28 × 0.24	0.38 × 0.28 × 0.26
θ range (°)	1.997 to 27.000	1.704 to 27.000
Index ranges	$-17 \le h \le 25$ $-12 \le k \le 21$ $-20 \le l \le 21$	$-14 \le h \le 15$ $-15 \le k \le 13$ $-17 \le l \le 16$
Reflections collected	24 886	22 464
Independent reflections [*R*(int)]	6093, 0.0286	6615, 0.0271
Completeness to *θ* (%)	99.7	98.7
Max. and min. Transmission	0.738 and 0.771	0.645 and 0.733
Data/restraints/parameters	9310/0/519	6615/0/401
Goodness-of-fit on F^2	1.012	1.060
R_1 [$I > 2\sigma(I)$], wR_2 [all data]	0.0281, 0.0746	0.0249, 0.0642
Largest peak, hole (e Å^{-3})	0.320, −0.491	0.353, −0.594

The crystal packing in **1** (orthorhombic P*ccn*) compared to **4** (triclinic $P\bar{1}$) has a more complicated unit cell packing in which double layers of Sb(V) complexes are stacked along *c* (Figure 3).

In the crystal structure of **1**, molecules are connected through C−H···N and N−H···O intermolecular and N−H···O and C−H···O intramolecular interactions forming a three-dimensional network extending throughout the crystal system (Figure 4). Molecular structures with greater multitude of interactions are considered to be very potent regarding biological activities as evident from **1** and **3**. The crystal structure of **4** is stabilized via C−H···Cl and Cl···Cl interactions along *c*-axis forming $R_4^4(32)$ type motifs (Figure 5).

TABLE 2 Selected bond lengths (Å) and angles (°) for **1**and **4**

1			
Sb(1)–C(1)	2.117(3)	C(1)–Sb(1)–C(1)	90.94(8)
Sb(1)–C(13)	2.121(3)	C(1)–Sb(1)–C(13)	149.91(12)
Sb(1)–C(7)	2.130(3)	C(1)–Sb(1)–C(7)	103.81(10)
Sb(1)–O(1)	2.1195(18)	C(13)–Sb(1)–O(1)	90.77(8)
Sb(1)–O(3)	2.1377(18)	C(7)–Sb(1)–O(11)	87.67(9)
O(1)–C(19)	1.299(3)	C(1)–Sb(1)–O(3)	90.57(8)
4			
Sb(1)–C(1)	2.108(2)	C(15)–C(8)–Sb(1)	118.70(14)
Sb(1)–C(7)	2.106(2)	C(7)–Sb(1)–C(1)	139.05(9)
Sb(1)–O(1)	2.1021(15)	Sb(1)–O(1)–C(19)	118.70(14)
Sb(1)–O(3)	2.1246(14)	Sb(1)–O(3)–C(26)	111.62(13)
O(2)–C(19)	1.211(3)	C(7)–Sb(1)–O(1)	90.73(7)
O(1)–C(19)	1.309(3)	C(1)–Sb(1)–O(3)	91.62(7)

TABLE 3 Intermolecular and intramolecular hydrogen bonds for **1** (hydrogen bond geometry: distance, Å; angle, °)

D–H···A	D–H	H···A	D···A	D–H···A
N(1)–H(1B)···O(2)	0.85(4)	2.13(4)	2.703(4)	124(3)
N(2)–H(2 A)···O(2)^{i}	0.79(4)	2.46(4)	3.175(4)	152(4)
N(2)–H(2B)···O(4)	0.95(4)	1.99(4)	2.676(4)	127(4)
Symmetry codes: (i) $-x + 1/2, -y + 3/2, z$ (**1**)				

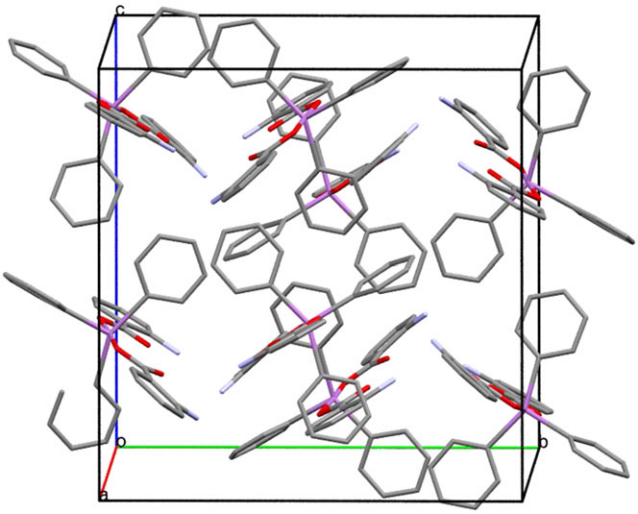


FIGURE 3 Unit cell packing for 1 in which double layers of Sb(V) complexes are stacked along c.

2.3 | Antileishmanial activity

The potential of the pentavalent antimonials **1–9** to inhibit *Leishmania* growth was evaluated using the *Leishmania tropica* KWH23 strain promastigotes. All the compounds show good to significant antileishmanial activity. On the basis of significant IC_{50} values (Table S1 in the supporting information), the compounds are categorized in the following order: **1 > 3 > 5 > 6 > 4 > 2 > 7 > 9 > 8** (Figure 6) as compared with the standard Glucantime (5.21 ± 1.29 μg ml^{-1}). Concentration-dependent anti-

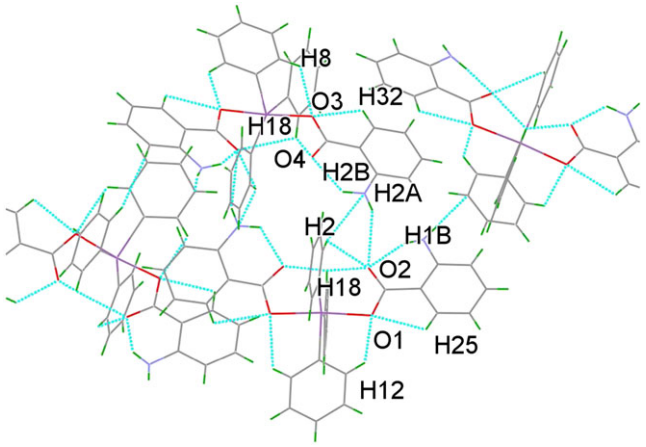


FIGURE 4 Supramolecular structure of complex 1 showing three-dimensional network of short contacts and hydrogen bonds stabilizing the crystal structure.

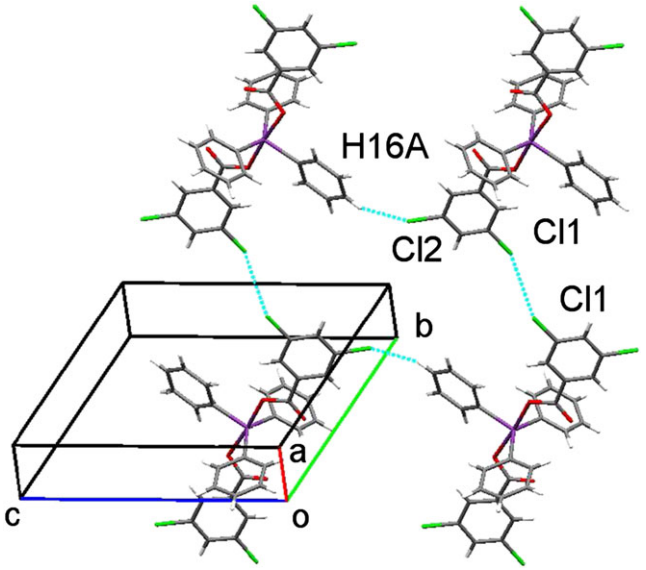


FIGURE 5 One-dimensional view of 4 along c-axis forming type motifs stabilized by alternate Cl·Cl and C−H·Cl short contacts.

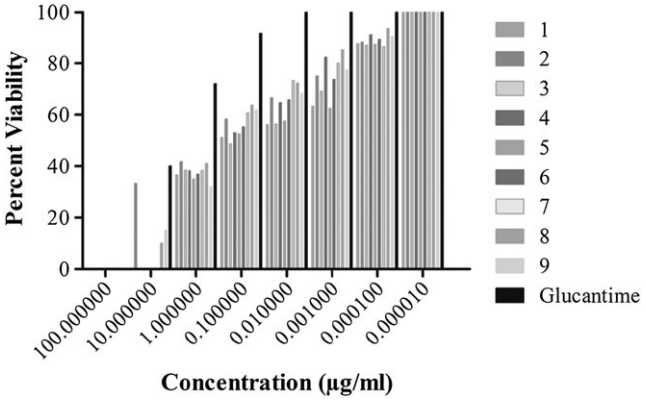


FIGURE 6 Concentration-dependent activity of synthesized antimonials 1–9.

TABLE 4 Cytotoxicity (LD_{50} μg ml^{-1}) of the synthesized antimonials **1–9**

Sample	Cytotoxicity					
	Triplicate LD_{50} values			Average LD_{50}	Standard error (±SE)	*C*log *P*
1	21.0	19.15	21.20	20.45	0.652	6.909
2	24.9	25.22	27.7	25.94	0.884	10.361
3	10.3	10.99	12.4	11.23	0.617	12.339
4	22.39	18.92	21.28	20.86	1.023	12.215
5	19.1	18.1	20.10	19.10	0.577	7.551
6	35.9	35.1	36.8	35.93	0.491	6.369
7	20.8	21.39	22.6	21.59	0.529	9.867
8	17.9	19.02	17.8	18.24	0.391	9.867
9	19.80	22.39	20.6	20.93	0.765	11.455

promastigotes assay shows that these synthetic antimonials directly annihilate *Leishmania tropica* parasites and hence show leishmanicidal behaviour. It is found that all the complexes are more potent against promastigotes. Among them, complexes **1** and **3** exhibit excellent IC_{50} against promastigotes. The significant activity of complex **1** assumes that the presence of inter- and intramolecular interactions makes the carboxylate ligands more interactive and thereby increases the hydrophilic character of the metal complex which also favours its absorption in biological fluids.

2.4 | Cytotoxicity

Cytotoxicity of the synthesized antimonials **1–9** was analysed using macrophages isolated from human peripheral blood by the ficollgastrografin method.[29,30] *Leishmania* has the capability of attacking and proliferating in macrophages; thus these cells were used for cytotoxicity analysis. The percentage mortality for all the compounds was calculated. It is found that the survival percentage is concentration dependent. The results are in correlation with the drug concentrations: more macrophages are viable at lower concentrations and mortality rate is higher upon increasing the dose. LD_{50} shows that all compounds **1–9** are biologically active and less toxic or non-toxic upon comparison with IC_{50} of *Leishmania* (Table 4).

Comparison of the LD_{50} of the compounds against macrophages and *Leishmania* shows a clear difference, such that these compounds can be further investigated for their use as antileishmanial drugs.

3 | CONCLUSIONS

The synthesis of compounds **1–9** is highly repeatable. The activity of the compounds against *Leishmania* parasite and the toxicity against human macrophage cells were evaluated. For the leishmanicidal activity of compounds **1–9**, the differences reached values close to 100-fold between macrophages and the host cell for *Leishmania*. Thus, owing to their anti-leishmanial efficacy and low cytotoxicity, these compounds are a better choice for further investigations as antileishmanial therapeutic agents than the traditionally used antimonials for the treatment of leishmaniasis. There is no clear pattern yet about which features of the carboxylate ligands make them more selective, and this is the focus of our future studies to assess the antileishmanial activity, biocompatibility and bio-safety of such compounds *in vivo*. However, the activity and selectivity pattern of compounds **1** and **3** reveal that the carboxylate ligands with greater interactions show very good antileishmanial activity. In our recent publication,[15] we have calculated the *C*log *P* values for about 25 pentavalent antimonials. The Sb(V) species Sb(p-$CH_3C_6H_4)_3Br_2$ (**a**), Sb(m-$CH_3C_6H_4)_3Br_2$ (**b**), Sb(o-$CH_3C_6H_4)_3Br_2$ (**c**) and $SbPh_3Br_2$ (**d**) have *C*log *P* values of 6.5, 6.5, 6.5 and 5.0, respectively. With the incorporation of carboxylate ligands the *C*log *P* values increase (about 1.5–2.0 times) which is an indicator of increase in lipophilicity. The *C*log *P* values for carboxylic acids are between the ranges of high hydrophilicity, i.e. 1 to 2. The antileishmanial results for the carboxylate derivatives of Sb(V) species **a–d** reveal that the substitution of $-CH_3$ group at *o*-, *m*- and *p*-positions on the phenyl ring proved to be highly effective against the parasite amastigotes at concentrations of 0.5–3.5 μM, although these organometallic antimony(V) dicarboxylates have presented high values of *C*log *P* (6.9–13.8). The studies show that the antileishmanial activities of these compounds are not very much dependent on the *C*log *P* factor. There is no clear mechanism yet as to which features of the carboxylate ligands and the core Sb (V) moieties make them more selective, and this is the focus of future investigations. In future, the main focus of our studies is to explore the effect of lipophilicity by introducing long-chain aliphatic groups and the active species produced during dissolution process. Also, the compounds are non-toxic towards mammalian cells at levels below 25 μM, making them highly promising drug candidates.

4 | EXPERIMENTAL

4.1 | General remarks

All reactions were conducted under a nitrogen atmosphere using standard Schlenk glassware techniques. The solvents were distilled prior to use and stored under nitrogen over activated molecular sieves. All manipulations were carried out under the specified conditions of temperature. Solvents were distilled from drying agents and degassed before use using the ultrasonication technique.

NMR spectra were recorded with a Bruker ARX spectrometer. ^1H NMR (300 MHz): internal standard solvent, $CDCl_3$ (7.28 ppm from TMS); internal standard, TMS. ^{13}C NMR (75.47 MHz): internal standard solvent, $CDCl_3$ (77.0 ppm from TMS); internal standard, TMS. The splitting

of proton resonances in the reported ^{1}H NMR data are defined as s = singlet, d = doublet, t = triplet, q = quartet and m = complex pattern; coupling constants are reported in Hz. FT-IR spectra were recorded as KBr pellets with a Bio-Rad Excalibur FT-IR model FTS 3000 MX (400–4000 cm^{-1}) and with attenuated total reflectance using a PerkinElmer System 2000 (200–500 cm^{-1}). Elemental analyses were performed using a LECO-932 CHNS analyser. The *C*log *P* values (*n*-octanol–water partition coefficient) were calculated using ChemBioDraw Ultra 2010 (PerkinElmer).

4.2 | General procedure for syntheses

All reactions were conducted using 0.005 mol of triphenylantimony(V) dibromide precursor and 0.01 mol of potassium or sodium salt of the respective carboxylic acid. The reactants were placed in a Schlenk flask and dried *in vacuo* prior to use. About 50 ml of dry toluene was then added and the reaction mixture stirred at room temperature for 12 h. The salt(s) formed were filtered off and the resulting clear solution was removed under reduced pressure to yield a solid residue. Synthesis and manipulation of all the compounds were performed using a vacuum/argon line following Schlenk techniques.[17,18] Toluene was distilled over sodium benzophenone ketyl and further stored over activated molecular sieves (4 Å) under nitrogen atmosphere.

4.3 | Synthesis and characterization data for 1–9

4.3.1 | Bis(2-aminobenzoato)(triphenyl)antimony(V) (1)

Quantities used were 1.59 g (0.01 mol) of sodium salt of 2-aminobenzoic acid and 2.51 g (0.005 mol) of tris(phenyl) antimony(V) dibromide in toluene. Yield 83%; colourless solid; m.p. 210–211°C. FT-IR (powder, cm^{-1}): 3094 (C−$H_{aromatic}$), 3455, 3345 (C−NH_2), 1663 (C=O), 562 (Sb−C), 463 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 5.61 (s_{broad}, 4H, −NH_2), 6.58 (d, 2H^f, J = 8.1 Hz), 6.64 (t, dds appeared as t, 2H^d, ^3J = 7.2 Hz), 7.22 (td, dds appeared as td, 2H^e, ^3J = 8.4 Hz, ^4J = 1.5 Hz), 7.49–7.55 (m, 9H$^{b,b',j}$), 7.94 (dd, 4H^c, ^3J = 7.8 Hz, ^4J = 1.5 Hz), 8.13 (dd, 6H$^{a,a'}$, ^3J = 7.2 Hz, ^4J = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 113.2 (2C, *C*−C=O), 115.9 (2C^f), 116.4 (2C^d), 129.4 (6C$^{b,b'}$), 130.9 (3C^j), 132.3 (2C^c), 133.4 (2C^e), 133.7 (6C$^{a,a'}$), 139.2 (3C, *ipso-C*), 150.4 (2C, *C*−NH_2), 172.4 (2C, *C*=O). Anal. Calcd for $C_{32}H_{27}N_2O_4Sb$ (%): C, 61.46; H, 4.35; N, 4.48. Found (%): C, 61.40; H, 4.33; N, 4.51.

4.3.2 | Bis(4-methylbenzoato)(triphenyl)antimony(V) (2)

Quantities used were 1.58 g (0.01 mol) of sodium salt of 4-methylbenzoic acid and 2.51 g (0.005 mol) of tris(phenyl) antimony(V) dibromide in toluene. Yield 84%; colourless solid; m.p. 233–235°C. FT-IR (powder, cm^{-1}): 3054 (C−$H_{aromatic}$), 2920 (C−$H_{aliphatic}$), 1611 (C=O), 550 (Sb−C), 457 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.39 (s, 6H, −CH_3), 7.18 (d, 4H$^{d,d'}$, ^3J = 7.8 Hz), 7.49–7.54 (m, 9H$^{b,b',j}$), 7.88 (d, 4H$^{c,c'}$, ^3J = 8.1 Hz), 8.16 (dd, 6H$^{a,a'}$, ^3J = 7.5 Hz, ^4J = 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 21.6 (2C, −CH_3), 128.8 (4C$^{d,d'}$), 129.4 (6C$^{b,b'}$), 129.9 (2C, *C*−C=O), 130.0 (4C$^{c,c'}$), 131.1 (3C^j), 133.9 (6C$^{a,a'}$), 138.5 (3C, *ipso-C*), 142.6 (2C, *C*−CH_3), 170.3 (2C, *C*=O). Anal. Calcd for $C_{34}H_{29}O_4Sb$ (%): C, 65.51; H, 4.69. Found (%): C, 65.46; H, 4.65.

4.3.3 | Bis[2-(phenylamino)benzoato](triphenyl)antimony(V) (3)

Quantities used were 2.35 g (0.01 mol) of sodium salt of 2-(phenylamino)benzoic acid and 2.51 g (0.005 mol) of tris (phenyl)antimony(V) dibromide in toluene. Yield 85%; colourless solid; m.p. 155–156°C. FT-IR (powder, cm^{-1}): 3265 (−NH),3026 (C−$H_{aromatic}$), 1629 (C=O), 564 (Sb−C), 448 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.74 (td, 2H^e, ^3J = 7.2 Hz, ^4J = 1.8 Hz), 7.07 (t, dds appeared as t, 2H^h, ^3J = 7.2 Hz), 7.16–7.18 (m, 4H^{g,f}), 7.23–7.35 (m, 8H$^{c,c',d,d'}$), 7.51–7.54 (m, 9H$^{b,b',j}$), 8.04 (d, 2H^i, ^3J = 8.1 Hz), 8.16 (dd, 6H$^{a,a'}$, ^3J = 7.2 Hz, ^4J = 2.4 Hz), 9.54 (s, 2H, −NH−). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 113.7 (2C, *C*−C=O), 114.7 (4C$^{c,c'}$), 116.8 (2C^g), 122.2 (6C$^{b,b'}$), 122.9 (2C^e), 129.2 (4C$^{d,d'}$), 129.6 (6C$^{a,a'}$), 131.3 (2C^i), 132.7 (2C^f), 133.4 (2C^h), 133.8 (3C^j), 138.5 (2C, *ipso-C*), 141.2 (2C, C_6H_4−NH−*C*), 147.5 (3C, *C*−NH−C_6H_6), 172.3 (2C, *C*=O). Anal. Calcd for $C_{44}H_{35}N_2O_4Sb$ (%): C, 67.97; H, 4.54; N, 3.60. Found (%): C, 67.95; H, 4.49; N, 3.64.

4.3.4 | Bis(3,5-dichlorobenzoato)(triphenyl)antimony(V) (4)

Quantities used were 2.13 g (0.01 mol) of sodium salt of 3, 5-dichlorobenzoic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 84%; colourless solid; m.p. 145–146°C. FT-IR (powder, cm^{-1}): 3068 (C−$H_{aromatic}$), 1647 (C=O), 739 (C−Cl), 583 (Sb−C), 444 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.44 (st, 3H^e, ^4J = 2.1 Hz), 7.56–7.59 (m, 9H$^{b,b',j}$), 7.80 (sd, 4H$^{c,c'}$, ^4J = 2.1 Hz), 8.12 (dd, 6H$^{a,a'}$, ^3J = 7.2 Hz, ^4J = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 128.3 (4C$^{c,c'}$), 129.7 (6C$^{b,b'}$), 131.6 (3C^j), 131.8 (2C, *C*−C=O), 133.7 (6C$^{a,a'}$), 134.8 (4C, *C*−Cl), 135.5 (2C^e), 136.9 (3C, *ipso-C*), 167.5 (2C, *C*=O). Anal. Calcd for $C_{32}H_{21}C_{l4}O_4Sb$ (%): C, 52.43; H, 2.89. Found (%): C, 52.40; H, 2.85.

4.3.5 | Bis(propanoato)(triphenyl)antimony(V) (5)

Quantities used were 0.96 g (0.01 mol) of sodium salt of propanoic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 85%; colourless solid; m.p. 121–123°C. FT-IR (powder, cm^{-1}): 3057 (C−$H_{aromatic}$), 2974–2937 (C−$H_{aliphatic}$), 1647 (C=O), 555 (Sb−C), 458 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.93 (t, 6H^b, $CH_3{}^b$−$CH_2{}^a$−, ^3J = 7.5 Hz), 2.13 (q, 4H^a, $CH_3{}^b$−$CH_2{}^a$−, ^3J = 7.5 Hz), 7.48–7.52 (m, 9H$^{b,b',j}$), 8.03

(dd, 6H$^{a,a'}$, ^3J = 6.0 Hz, ^4J = 2.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 9.7 (2C, $-CH_3$), 28.9 (2C, $-CH_2-$), 129.1 (6C$^{a,a'}$), 130.8 (3C^j), 133.8 (6C$^{b,b'}$), 139.0 (3C, *ipso-C*), 178.8 (2C, *C*=O). Anal. Calcd for $C_{24}H_{25}O_4Sb$ (%): C, 57.74; H, 5.05. Found (%): C, 57.70; H, 5.01.

4.3.6 | Bis(nicotinato)(triphenyl)antimony(V) (6)

Quantities used were 1.45 g (0.01 mol) of sodium salt of nicotinic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 82%; colourless solid; m.p. 180–182°C. FT-IR (powder, cm^{-1}): 3054 (C−H$_{aromatic}$), 1654 (C=O), 1587 (C−N), 562 (Sb−C), 447 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.28–7.32 (m, 2H^e), 7.50–7.56 (m, 9H$^{b,b',j}$), 8.12–8.18 (m, 8H$^{a,a',d}$), 8.68 (dd, 2H^f, ^3J = 4.8 Hz, ^4J = 1.5 Hz), 9.15 (sd, 2H^c, ^4J = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 123.1 (2C^e), 128.3 (2C, *C*−C=O), 129.7 (6C$^{b,b'}$), 131.6 (4C^j), 133.8 (6C$^{a,a'}$), 136.9 (3C, *ipso-C*), 137.4 (2C^d), 151.2 (2C^c), 152.4 (2C^f), 168.3 (2C, *C*=O). Anal. Calcd for $C_{30}H_{23}N_2O_4Sb$ (%): C, 60.33; H, 3.88; N, 4.69. Found (%): C, 60.29; H, 3.85; N, 4.72.

4.3.7 | Bis(2-methoxyphenylacetato)(triphenyl)antimony(V) (7)

Quantities used were 1.88 g (0.01 mol) of sodium salt of 2-methoxyphenylacetic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 85%; colourless solid; m.p. 168–170°C. FT-IR (powder, cm^{-1}): 3018 (C−H$_{aromatic}$), 2926 (C−H$_{aliphatic}$), 1657 (C=O), 582 (Sb−C), 484 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.39 (s, 4H, $-CH_2-$), 3.88 (s, 6H, $-OCH_3$), 6.75 (d, 2H^f, ^3J = 8.1 Hz), 6.84 (t, 2H^d, ^3J = 7.2 Hz), 7.24 (td, dds appeared as td, 2H^e, ^3J = 7.2 Hz, ^4J = 1.5 Hz), 7.42–7.52 (m, 9H$^{b,b',j}$), 7.91 (d, 4H^c,^3J = 7.8 Hz), 8.11 (dd, 6H$^{a,a'}$, ^3J = 8.1 Hz, ^4J = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 45.0 (2C, $-CH_2-$), 55.2 (2C, $-OCH_3$), 110.2 (2C, *C*−CH_2-), 120.6 (2C^f), 123.3 (2C^d), 128.2 (6C$^{b,b'}$), 129.6 (3C^j), 129.8 (2C^c), 131.1 (6C$^{a,a'}$), 135.0 (2C^e), 136.1 (3C, *ipso-C*), 157.4 (2C, *C*−OCH_3), 177.3 (2C, *C*=O). Anal. Calcd for $C_{36}H_{33}O_6Sb$ (%): C, 63.27; H, 4.87. Found (%): C, 63.24; H, 4.83.

4.3.8 | Bis(4-methoxyphenylacetato)(triphenyl)antimony(V) (8)

Quantities used were 1.88 g (0.01 mol) of sodium salt of 4-methoxyphenylacetic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 84%; colourless solid; m.p. 171–172°C. FT-IR (powder, cm^{-1}): 2936 (C−H$_{aromatic}$), 2840 (C−H$_{aliphatic}$), 1652 (C=O), 548 (Sb−C), 484 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.37 (s, 4H, $-CH_2-$), 3.81 (s, 6H, $-OCH_3$), 6.75 (d$_{(skewed)}$, 4H$^{c,c'}$, ^3J = 8.7 Hz), 6.95 (d$_{(skewed)}$, 4H$^{d,d'}$, ^3J = 8.4 Hz), 7.39 (t$_{(skewed)}$, 6H$^{b,b'}$, ^3J = 7.5 Hz), 7.47 (tt$_{(skewed)}$, 3H^j, ^3J = 7.5 Hz, ^4J = 1.2 Hz), 7.79 (dd, 6H$^{a,a'}$, ^3J = 8.1 Hz, ^4J = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 42.3 (2C, $-CH_2-$), 55.3 (2C, $-OCH_3$), 113.6 (4C$^{d,d'}$), 127.7 (2C, C−CH_2-), 129.1 (6C$^{b,b'}$), 130.2 (4C$^{c,c'}$), 130.9 (3C^j), 133.8 (6C$^{a,a'}$), 137.4 (3C, *ipso-C*), 158.2 (2C, *C*−OCH_3), 175.1 (2C, *C*=O). Anal. Calcd for $C_{36}H_{33}O_6Sb$ (%): C, 63.27; H, 4.87. Found (%): C, 63.24; H, 4.84.

4.3.9 | Bis(4-chlorophenylacetato)tri(phenyl)antimony(V) (9)

Quantities used were 1.93 g (0.01 mol) of sodium salt of 4-chlorophenylacetic acid and 2.51 g (0.005 mol) of tris(phenyl)antimony(V) dibromide in toluene. Yield 83%; white crystalline solid; m.p. 144–145°C. FT-IR (powder, cm^{-1}): 3048 (C−H$_{aromatic}$), 2928 (C−H$_{aliphatic}$), 1641 (COO$_{asym}$), 739 (C−Cl), 563 (Sb−C), 452 (Sb−O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.39 (s, 4H, $-CH_2-$), 6.82 (d$_{(skewed)}$, 4H$^{c,c'}$,^3J = 8.7 Hz), 7.12 (d$_{(skewed)}$, 4H$^{d,d'}$, ^3J = 8.4 Hz), 7.36 (t$_{(skewed)}$, 6H$^{b,b'}$, ^3J = 7.5 Hz), 7.43 (tt$_{(skewed)}$, 3H^j, ^3J = 7.5 Hz, ^4J = 1.2 Hz), 7.72 (dd, 6H$^{a,a'}$, ^3J = 8.1 Hz, ^4J = 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 42.5 (2C, $-CH_2-$), 113.8 (4C$^{d,d'}$), 127.8 (2C, *C*−CH_2-), 129.7 (6C$^{b,b'}$), 131.2 (4C$^{c,c'}$), 132.5 (3C^j), 133.7 (6C$^{a,a'}$), 138.9 (3C, *ipso-C*), 156.8 (2C, *C*-Cl), 175.6 (2C, *C*=O). Anal. Calcd for $C_{34}H_{27}Cl_2O_4Sb$ (%): C, 58.99; H, 3.93. Found (%): C, 58.91; H, 3.92.

4.4 | Single-crystal x-ray diffraction analysis

Single crystals of **1** and **4** were mounted on a Bruker kappa APEXII CCD diffractometer equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) and intensity data were collected at ambient temperature. Details of the crystal data, and data collection and structure determination conditions and parameters are summarized in Table 1. Structure solution by direct methods and least squares refinement of all structures were routine, with all non-hydrogen atoms refined with anisotropic thermal parameters and almost all hydrogen atoms visible on later electron density difference maps. Aromatic hydrogen atom positional and isotropic thermal parameters were freely refined in both structures (U_{iso} ranges from 0.070 to 0.115 Å^2), but were constrained in the ambient temperature structures to a riding model with an idealized geometry (C−H fixed at 0.93 Å) and with U_{iso} fixed at 1.2U_{iso} of the parent carbon atom. The 1.0 mm collimator used for data collection for the structures of **1** and **4** resulted in several low-angle reflections partially or completely obscured by the beam catcher. Data were also corrected for Lorentz and polarization effects. The structures were solved using SHELXS-97. Final refinement on F^2 was carried out by full-matrix least-squares techniques using SHELXL-97.[31]

4.5 | Antileishmanial assays

Stock solutions for antileishmanial assays were prepared by dissolving 1 mg ml^{-1} of each of samples **1–9** under assay in 1 ml of dimethylsulfoxide (DMSO). Stock solutions were

further diluted serially (100, 10, 1, 0.1, 0.01, 0.001, 0.0001 and 0.00001 μg ml^{-1}) using DMSO in the wells of a 96-well plate (Table S1 in the supporting information). *Leishmania tropica* KWH23 promastigotes were grown in M199 medium with 10% foetal bovine serum, streptomycin, HEPES buffer (25 mM) and penicillin. Log phase promastigotes at 1×10^6 ml^{-1} were used for the entire assay. About 180 μl of M199, 100 μl of *Leishmania tropica* KWH23 log phase culture and 20 μl of each compound were dispensed to different wells of a microtitre plate. Here, DMSO was used as a negative control with Glucantime as positive control. Afterwards, 96-well plate was incubated at 24°C for 72 h. After incubation, about 15 μl of each dilution was pipetted on a Neubauer chamber and was counted under a microscope. The IC_{50} values were calculated using Graphpad Prism 5.[30]

4.6 | Cytotoxicity

Human macrophage cells were used to assess the cytotoxicity of the synthesized compounds **1–9**. Macrophages were isolated and cytotoxicity assay was carried out using the method of Nadhman *et al.*[30]

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