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In vitro anticancer, antioxidant, antimicrobial, antileishmanial, enzymes inhibition and *in vivo* anti-inflammatory activities of organotin(IV) derivatives of 4-bromophenoxyacetic acid

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ABSTRACT

Organotin(IV) derivatives $\{(n\text{-C}_4\text{H}_9)_3\text{SnL}$ (1), $(\text{CH}_3)_3\text{SnL}$ (2), $(n\text{-C}_4\text{H}_9)_2\text{SnL}_2$ (3) and $(\text{CH}_3)_2\text{SnL}_2$ (4) $\}$ of 4-bromophenoxyacetic acid (HL) were synthesized and characterized by elemental, FT-IR, NMR and single crystal XRD diffraction analyses. The carboxylate ligand showed bridging/chelating bidentate coordination. The complexes 1 and 2 have adopted polymeric chain structures consisting tin atoms in distorted trigonal bipyramidal geometry.

Complex 3 has shown highest DPPH radical scavenging ($\text{IC}_{50} = 33.46 \mu\text{g/mL}$) and antileishmanial activity ($\text{IC}_{50} = 27.06 \mu\text{g/mL}$). Complex 3 was also the most efficient agent in acetylcholinesterase ($\text{IC}_{50} = 5.12 \mu\text{g/mL}$), butyrylcholinesterase ($\text{IC}_{50} = 13.79 \mu\text{g/mL}$) and Monoamine oxidase ($\text{IC}_{50} = 8.50 \mu\text{g/mL}$) inhibition assays. Complex 4 ($\text{IC}_{50} = 18.73 \mu\text{g/mL}$) was the most potent ABTS radical scavenger. Complex 1 with IC_{50} values of 27.50 and 71.32 $\mu\text{g/mL}$ was the most efficient α -glucosidase and dipeptidyl peptidase-4 enzyme inhibitor, respectively. While complex 2 was found the most potent Cyclooxygenase-2 (7.81 $\mu\text{g/mL}$) and 5-Lipoxygenase (6.69 $\mu\text{g/mL}$) inhibitor. MTT assay revealed highest inhibitory potency of complexes 4 ($\text{IC}_{50} = 8.035 \pm 0.05 \mu\text{g/mL}$), and 1 ($\text{IC}_{50} = 10.16 \pm 0.17 \mu\text{g/mL}$) towards the brain cancer cell line. The *in vivo* study performed on mice have shown potent anti-inflammatory effects of 1 and 2 comparable to the standard, indomethacin.

1. Introduction

Organotin(IV) carboxylates are in scientific discussions for a few couple of decades due to their great structural diversity and tremendous biological activities. As a result of coordination sphere expansion ability of tin due to low lying vacant d orbital and versatile coordination mode of the carboxylate ligand, organotin(IV) carboxylates with a variety of coordination numbers and geometries are reported [1,2]. The most common are complexes with coordination numbers 4–6 giving rise to tetrahedral, trigonalbipyramidal and octahedral geometries [3–5]. The nature of the tin bonded alkyl/aryl groups, steric and electronic factors

of the carboxylate ligand also have significant roles in deciding the structural behavior of these complexes in both solid and solution form [1].

Cancer, oxidative stress, inflammation, diabetes, Alzheimer's disease and microbial resistance are the challenging health issues mainly influenced by physical, chemical, environmental, and genetic factors. To combat these challenging health issues, researchers have explored extensively the drug efficacy of metal complexes. For instance, platinum based complexes were synthesized and commercialized as anticancer drugs. However, the anticancer activity of platinum complexes was questioned in different studies due to their nephrotoxicity, low

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solubility, and increased tumor resistance [6,7]. These complications diverted the interest of researchers in to non-platinum based anticancer drugs, and studies have found organotin(IV) carboxylates as the lead alternatives against a panel of human cancer cell lines [6,8,9]. Cancer cell apoptosis by organotin(IV) carboxylates is attributed to their ability to interact with DNA [6]. Furthermore, these complexes can also cause mitochondrial dysfunction and the activation of caspases, a family of protease enzymes that play an essential role in apoptosis and inflammation [7,8]. To address the increased microbial resistance issue, the antimicrobial potential of organotin(IV) carboxylates is also explored with promising results [6,10]. Furthermore, the encouraging cytotoxic [11,12] antidiabetic [13,14], antioxidant [13], enzyme inhibition [15, 16], antituberculosis [7] and anti-leishmanial activities [17,18], show the multifaceted drug potential of organotin(IV) carboxylates. The number and nature of tin bonded alkyl/aryl groups, coordination number and geometry around tin, the nature of the carboxylate ligand and its associated functional groups and the nature of the target cells/biomolecules are reported to influence the bioactivities of organotin(IV) carboxylates [19]. The alkyl/aryl groups regulates the lipophilicity and binding of the complex to the cellular proteins [20]. The carboxylate ligand with the assistance of its associated functional groups facilitates the transport of the complex to the reactive sites [7,21,22]. The coordination sphere extension ability of the tin atom, enables the complex to interact with the donor atoms of the macromolecular cellular structures [20].

Keeping in view, the potential bioactivity and our continuous search for a class of compounds to be explored as a multifaceted drug, herein we report the synthesis, spectral characterization, *in vitro* anticancer, antioxidant, antimicrobial, antileishmanial, and enzyme inhibition potential of four new organotin(IV) derivatives of 4-bromophenoxyacetic acid. Furthermore, complexes 1 and 2 as representative compounds were also screened for *in vivo* anti-inflammatory activity. The ligand is selected for its semi-flexible nature due to the presence of the O-CH₂ moiety and the presence of polar Br group. Both of these features can assist the movement of the complex across the cell membrane to reach the target site in the cell for biological activity.

2. Experimental

2.1. Materials and physical measurements

Analytical grade tri-*n*-butyltin(IV) chloride, di-*n*-butyltin(IV) dichloride, trimethyltin(IV) chloride, dimethyltin(IV) dichloride, 4-bromophenoxyacetic acid, sodium bicarbonate, DMSO and chloroform were purchased from Sigma-Aldrich. All these chemicals were used as such without any further purification treatment. However, the solvent chloroform was dried by an earlier reported procedure [23]. Melting points of the synthesized complexes were recorded on a Gallenkamp (UK) electro thermal instrument. FT-IR spectra (4000–400 cm⁻¹) of the compounds in solid state were recorded on a Perkinelmer FT-IR spectrometer, (Model: L1600300 Spectrum Two LiTa) UK, equipped with LiTaO₃ detector. For the NMR (¹H and ¹³C) spectra taken at room temperature in CDCl₃, a Bruker Avance III HD NanoBay 400 MHz NMR spectrometer (Switzerland) was used.

2.2. Syntheses

2.2.1. Sodium-4-bromophenoxyacetate (NaL)

The ligand salt, sodium-4-bromophenoxyacetate (NaL) was prepared by the drop wise addition of an aqueous NaHCO₃ solution to an equimolar methanolic solution of 4-bromophenoxy acetic acid. The reaction mixture was stirred for an hour and the soluble sodium-4-bromophenoxy acetate salt was recovered from the solution by rotary evaporation as a white powder.

(4-bromophenoxyacetato)tri-*n*-butyltin(IV) (1)

Sodium-4-bromophenoxyacetate NaL (0.5 g, 2.45 mmol) and tri-*n*-

butyltin(IV)chloride (0.618 g, 2.45 mmol) were dissolved in 100 mL dry chloroform in a 250 mL two neck round bottom flask. The reaction mixture was refluxed for 6 h. The mixture was then cooled to room temperature and left undisturbed for one day. The insoluble byproduct (NaCl) was removed by filtration. The complex was recovered from the clear filtrate by rotary evaporation of the solvent. The complex was then recrystallized from chloroform and *n*-hexane mixture (4:1).

Chemical Composition: C₂₀H₃₃O₃BrSn. Formula Mass: 520.09. M.P: 74–75 °C. Yield: 81 %. Elemental Analysis (%): Calc (Exp): C; 46.19 (46.17), H; 6.40 (6.38). FT-IR bands (4000–400 cm⁻¹): 1603s ν(COO)_{asym}, 1411s ν(COO)_{sym}, 192 Δv, 496 ν(Sn-C), 454 ν(Sn-O), 1066v (Ar-Br). ¹H NMR (CDCl₃, ppm): 4.59 (s, 2H, 2), 6.83–6.79 (m, 2H, 4,4'), 7.41–7.37 (m, 2H, 5,5'), 1.67–1.62 (m, 6H, Hα), 1.42–1.29 (m, 6H, Hβ), 1.42–1.29 (m, 6H, Hγ), 0.93 (t, 9H, Hδ). ¹³C NMR (CDCl₃, ppm): 173.0 (C-1), 65.7(C-2), 157.1 (C-3), 116.3 (C-4,4'), 132.2 (C-5,5'), 114.5 (C-6), 27.8 (C-α), 27.1 (C-β), 27.0 (C-γ), 13.7 (C-δ).

(4-bromophenoxyacetato)trimethyltin(IV) (2)

The complex 2 was synthesized and recrystallized in the same manner as complex 1. Sodium-4-bromophenoxyacetate NaL (0.5 g, 2.45 mmol), trimethyltin(IV) chloride (0.378 g, 2.45 mmol).

Chemical Composition: C₁₁H₁₅O₃BrSn. Formula Mass: 393.85. M.P: 169–170 °C. Yield: 84 %. Elemental Analysis (%): Calc (Exp): C; 33.55 (33.53), H; 3.84 (3.82). FT-IR bands (4000–400cm⁻¹): 1578s ν(COO)_{asym}, 1381s ν(COO)_{sym}, 197 Δv, 550 ν(Sn-C), 500 ν(Sn-O), 1065v(Ar-Br). ¹H NMR (CDCl₃, ppm) [²J(¹¹⁹/¹¹⁷Sn-H) Hz]: 4.58 (s, 2H, 2), 6.83–6.79 (m, 2H, 4,4'), 7.41–7.36 (m, 2H, 5,5'), 0.63 (s, 9H, Hα) [58/56]. ¹³C NMR (CDCl₃, ppm) [¹J(¹¹⁹/¹¹⁷Sn-¹³C) Hz]: 173.3 (C-1), 65.7 (C-2), 157.1 (C-3), 116.4 (C-4,4'), 132.3 (C-5,5'), 113.5 (C-6), –2.2 (C-α) [398/366].

bis-(4-bromophenoxyacetato)di-*n*-butyltin(IV) (3)

The complex 3 was synthesized and recrystallized in the same manner as complex 1, except reactants are taken in 2:1 mole ratio. Sodium-4-bromophenoxyacetate NaL (0.5 g, 2.45 mmol), di-*n*-butyltin (IV) dichloride (0.273 g, 1.22 mmol).

Chemical Composition: C₂₄H₃₀O₆Br₂Sn. Formula Mass: 693.01. M.P: 102–103 °C. Yield: 83 %. Elemental Analysis (%): Calc (Exp): C; 41.59 (41.57), H; 4.36 (4.34). FT-IR bands (4000–400 cm⁻¹): 1601s ν(COO)_{asym}, 1487s ν(COO)_{sym}, 114 Δv, 526 ν(Sn-C), 480 ν(Sn-O), 1063v (Ar-Br). ¹H NMR (CDCl₃, ppm): 4.70 (s, 4H, 2), 6.81 (d, 2H, 4,4'), 7.45–7.40 (m, 2H, 5,5'), 1.83–1.62 (m, 4H, Hα), 1.47–1.35 (m, 4H, Hβ), 1.47–1.35 (m, 4H, Hγ), 0.96 (t, 6H, Hδ). ¹³C NMR (CDCl₃, ppm): 175.5 (C-1), 64.8 (C-2), 156.4 (C-3), 116.5 (C-4,4'), 132.7 (C-5,5'), 114.5 (C-6), 27.3 (C-α), 26.6 (C-β), 26.4 (C-γ), 13.6 (C-δ).

bis-(4-bromophenoxyacetato)dimethyltin(IV) (4)

The complex 4 was synthesized and recrystallized in the same manner as complex 1, except reactants are taken in 2:1 mole ratio. Sodium-4-bromophenoxyacetate NaL (0.5 g, 2.45 mmol), di-*n*-methyltin(IV) dichloride (0.197 g, 1.22 mmol).

Chemical Composition: C₁₈H₁₈O₆Br₂Sn. Formula Mass: 608.85. M.P: 202–203 °C. Yield: 79 %. Elemental Analysis (%): Calc (Exp): C; 35.51 (35.49), H; 2.98 (2.96). FT-IR bands (4000–400cm⁻¹): 1548s ν(COO)_{asym}, 1412s ν(COO)_{sym}, 136 Δv, 549 ν(Sn-C), 501 ν(Sn-O), 1065v(Ar-Br). ¹H NMR (CDCl₃, ppm): 4.69 (s, 4H, 2), 6.81 (bs, 2H, 4,4'), 7.43 (bs, 2H, 5,5'), 1.10 (Hα). ¹³C NMR (CDCl₃, ppm): 176.6 (C-1), 65.1 (C-2), 156.6 (C-3), 116.3(C-4,4'), 132.5 (C-5,5'), 114.5 (C-6), 4.9 (C-α).

2.3. X-ray single crystal analysis

The diffraction data were collected by the ω-scan technique, at 100 (1) K, on Rigaku XCalibur four-circle diffractometer with Eos CCD detector, equipped with graphite-monochromatized MoKα radiation source (λ = 0.71073 Å). The data were corrected for Lorentz-polarization as well as for absorption effects [24]. The structures were solved with SHELXT [25] and refined with the full-matrix least-squares procedure on F2 by SHELXL-2013 [26]. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in idealized

positions and refined as 'riding model' with isotropic displacement parameters set at 1.2 (1.5 for methyl groups) times Ueq of appropriate carrier atoms.

2.4. Hirshfeld surface analysis

The Hirshfeld surfaces and 2D fingerprint plots were generated using Crystal Explorer 17.50 [27]. The X-ray single-crystal crystallographic information files were used as input files. The default setting used for Hirshfeld Surface/fingerprint generation in Crystal Explorer is as follows:

property: none; resolution: High (standard). For fingerprint generation (di vs. de plot) we used: range: standard; filter: by elements and fingerprint filter options is both inside-outside elements including reciprocal contacts. The interactions with normalized contact distance in crystal structure shorter than the sum of the corresponding van der Waals radii of the atoms are highlighted by red spots and the longer contacts with the positive d_{norm} value are represented in blue color.

2.5. Biological assays

2.5.1. Anticancer activity

The cell lines utilized in this study were Human Embryonic Kidney HEK293 and U87-Malignant Glioma (ATCC-HTB-14™), both of which were acquired from the cell culture bank at the Atta-Ur-Rahman School of Applied Biosciences, National University of Science and Technology (NUST), Islamabad, Pakistan. The cells were cultured in a humidified incubator set at 37 °C with 5 % carbon dioxide in Dulbecco's modified Eagle's medium (DMEM) (Gibco, Thermo Fisher Scientific, USA) containing 4.5 g/L glucose, supplemented with 10 % fetal bovine serum (FBS) (Gibco, Thermo Fisher Scientific, USA), and 1 % penicillin and streptomycin (Gibco, Thermo Fisher Scientific, USA). The free ligand acid HL and synthesized complexes 1–4 were added to the 96-well culture plate at a density of 1×10^3 cells per well, which was maintained in a humidified incubator containing 5 % CO₂ at 37 °C. After 24 h of incubation of plating, and the cells had become adhered, variable concentrations of each testing compound (10, 20, 40, 80, 100, 150, and 200 µg/mL) were added to 100 µL of the cells. The cells were then incubated at 37 °C for 48 h. Cytotoxicity was assessed 48 h after the introduction of the test compounds. This was accomplished by incubating each well for 3 h in 5 mg/mL MTT solution (Phytotech Laboratories, USA) dissolved in 15 µL of phosphate-buffered saline (PBS) (Bio basic Canada inc.). In addition, the supernatant was discarded, and 100 µL of DMSO was added to each well to dissolve the formazan crystals;

$$\text{Cell viability (\%)} = \frac{\text{mean OD of the sample} - \text{mean OD of the positive control}}{\text{mean OD of the negative control} - \text{mean OD of the positive control}} \times 100$$

the mixture was then incubated for an additional 30 min. The optical density was quantified utilizing a microplate reader (Bio-Rad PR4100) at a wavelength of 550 nm. Using the absorbance data obtained, the percentage of viable cells was computed utilizing the subsequent equation [28,29].

$$\% \text{ cell viability} = \frac{(A_{\text{sample}} - A_{\text{blank}})}{A_{\text{control}} - A_{\text{blank}}} \times 100$$

2.5.2. Antioxidant activity

The *in vitro* antioxidant potential of the free ligand acid (HL) and synthesized complexes 1–4 was assessed by DPPH and ABTS free radicals scavenging assays.

For the DPPH free radical scavenging activity, a reported procedure

concentrations (500, 250, 125, 62.5, 31.25 µg/mL) were mixed with 1000 µL of 255 µM DPPH solution made in ethanol. The mixture solutions were shaken and incubated in dark for half an hour at ambient temperature. The absorbance of the solutions was noted at 518 nm using UV-VIS spectrophotometer. Ascorbic acid was used as a positive control and experiments were performed in triplicate. %inhibition of the test compounds was evaluated by using the formula:

$$\% \text{Scavenging} = \left(\frac{A_c - A_s}{A_c} \right) \times 100$$

Where A_c and A_s are the observed absorbance values of the control and the test compound, respectively.

For the *in vitro* ABTS assay, solutions of K₂SO₄ (2.45 mM) and ABTS (7 mM) were mixed. The mixture was kept in the dark for approximately 16 h. The phosphate buffer (0.01 M, pH 7.4) was used to dilute the ABTS cation solution, and the absorbance value (0.70) was set at 734 nm. The test compounds of different concentrations (500, 250, 125, 62.25, 31.25 µg/mL) were mixed with 3.0 mL of ABTS solution. The decrease in absorption at 734 nm was monitored after one minute for six minutes. The ascorbic acid was used as a positive control. The experiments were performed in triplicates and the IC₅₀ values and %inhibitions were calculated [31].

2.5.3. Antileishmanial activity

In vitro, antileishmanial assay was performed on promastigotes form of *Leishmania tropica*, cultivated in a medium (RPMI-1640), supplemented with 1 % antibiotics and 10 % fetal bovine serum (HIFBS) inactivated by heating and incubated at 25 ± 1 °C. Test compounds stock solutions (10 mg/mL) were made in DMSO.

For the assay a slightly modified reported procedure was used [32]. *Leishmania tropica* promastigotes (1×10^5 parasites/well) and samples (1000, 500 and 250 µg/mL) were kept in a flat-bottom 96-well microtiter plate. Amphotericin-B (AmB) and plan media with DMSO were employed as positive control and blank, respectively. The plates were kept at 25 ± 1 °C for 72 hrs. After this, 100 µL of 3-(4,5-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution was poured to the wells. The plate was again placed for four hours at 31 °C. A 40 µL of DMSO was poured in to wells to solubilize the formazan crystals of MTT. The plates were stirred slowly for 15 min. A microplate reader (Bio Tek™ ELx800) was used to find the absorbance of these plates at 570 nm. %age inhibition was then found by using the equation:

with slight modification was used [30]. Test compounds of different

$$\% \text{ inhibition} = (100 - \text{viability})$$

2.5.4. Antimicrobial activity

For the *in vitro* antibacterial activity of the free ligand acid **HL** and synthesized complexes **1–4**, disc diffusion method was used [33]. Freshly prepared inoculum of bacterial strains (*S. aureus* (ATCC# 6538), *B. subtilis* (ATCC# 6633), *E. coli* (ATCC# 25,922) and *P. aeruginosa* (ATCC#15,442) containing almost 10^4 to 10^6 (CFU)/mL were spread on the surface of nutrient agar plates with the help of a sterile cotton swab. The turbidity of the inoculum was adjusted using a 0.5 McFarland scale by following Clinical and Laboratory Standards Institute (CLSI) guidelines [33]. Cefixime was used as positive control and DMSO was used as negative control. Test samples 20 µg/disc (5 µL) along with controls

were loaded into complete sterile discs (6 mm in diameter). After 24 h of incubation at 37 °C, the diameter of the sample inhibition zone and standards were measured. The experiment was performed in triplicates.

Similarly disc diffusion assay method was used for *in vitro* antifungal activity against two *Candida* strains (*Candida albicans* ATCC 9002 and *Candida parapsilosis* ATCC 22,019). These strains were used to prepare fresh culture before performing anticandidal activity using CLSI standard protocol [33,34]. Freshly prepared inoculum of fungal strains was used for the preparation of plates of Sabouraud dextrose agar. Clotrimazole was used as positive control and DMSO was used as negative control. Test samples 20 µg/disc (5 µL) along with controls were loaded into complete sterile discs (6 mm in diameter). Plates were incubated at 30 °C for 48 h and the zone of inhibition around the disc was measured in mm. The experiments were performed in triplicates.

2.5.5. Enzyme inhibition assays

2.5.5.1. α -glucosidase assay. The α -glucosidase inhibition potential of the free ligand acid and synthesized complexes was assessed by a modified reported procedure against acarbose as a standard drug [35]. α -glucosidase solution (0.5 units/mL) was made in 0.1 M phosphate buffer (pH 6.90). *p*-Nitrophenyl- α -D-glucopyranoside was used as a substrate solution. Sample compound solutions of varying concentrations (500, 250, 125, 62.5, 31.25 µg/mL) were prepared. The sample solutions were mixed with the enzyme solutions, and the mixtures were incubated at 37 °C for 15 min. Subsequently, the substrate solutions were mixed with these solutions and the mixtures were again incubated followed by addition of 80 µL sodium carbonate (0.2 M) solution. The mixture solution without α -glucosidase was used as a blank solution. The absorption of the solution was measured at 405 nm. The experiments were performed in triplicate. The%inhibitions and IC₅₀ values were calculated.

2.5.5.2. Dipeptidyl peptidase-4 assay. The inhibitory effect of the synthesized complexes on the Dipeptidyl peptidase-4 (DPP-4) enzyme was evaluated using fluorescent probe based *in vitro* test [36]. DPP-4 (recombinant human) and tetraphenylethene-lys-Phe-Pro-Glu (TPE-KFPE) in buffer (HEPES) were treated with the sample compounds at 37 °C for 30 min. The 96-well Microplate Reader was used for the assay. The sample inhibition potential was assessed at different concentrations (500, 250, 125, 62.5, 31.25 µg/mL). The experiments were performed in triplicate. Urosolic acid was used as standard drug. The%inhibition and IC₅₀ values were calculated to have an insight about the enzyme inhibition potential of the test compounds.

2.5.5.3. Acetyl and butyrylcholinesterase assays. The synthesized complexes were tested for the acetyl and butyrylcholinesterase inhibition activities in comparison to galantamine reference. Different concentrations (500, 250, 125, 62.25, 31.25 µg/ml) of the test samples were made. The enzyme dilutions were made in phosphate buffer (pH 8). The 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), acetyl and butyrylthiocholine iodide solutions (0.05 mM each) were made in distilled water and kept at 8 °C for 15 min. The enzyme solution (5 µL), samples (205 µL) and DNTB (5 µL) solutions were mixed and incubated for 15 min at 30 °C. The absorption of the mixture was measured at 412 nm. All the solutions without test compounds served as the negative control, and galantamine served as the positive control. The experiments were performed in triplicate. The% inhibitions and IC₅₀ values were calculated [31,37].

2.5.5.4. Monoamine oxidase (MAO-B) assay. The microplate assay, as described earlier [38] was used some modifications to determine MAO-B inhibition potential of the free ligand acid and synthesized complexes. In a 96-well microplate, 40 µL of the test compound was added to 30 µL potassium phosphate buffer (0.2 M, pH 7.6) and serially diluted. Following this, 40 µL chromogenic solution (1 mM vanillic acid and 2.5

mM 4-aminoantipyrine in 0.2 M potassium phosphate buffer, pH 7.2 and 4 U/ml peroxidase) and 120 µL 2.5 mM pyramine in 0.2 M potassium phosphate buffer (pH 7.2) was added to each well. Absorbance was then read once at 490 nm using an Opsys MR micro-plate reader. Subsequently, 40 µL of the recombinant human monoamine oxidase B (MAO-B 8 U/mL) was added to each well of the microplate. The absorbance of the reaction mixture was read at 490 nm seven times every 5 min. Safinamide was used as a standard. Experiments were performed in triplicates. MAO inhibition was calculated by comparing the rates of enzyme reaction of the test compounds with that of a blank containing potassium phosphate buffer according to the following equation:

$$\% \text{Inhibition} = 1 - \frac{\text{RR}_{\text{sample}}}{\text{RR}_{\text{control}}} \times 100$$

Where RR_{sample} is the rate of enzyme reaction of the test compounds and RR_{control} is that of the blank.

2.5.5.5. Anticyclooxygenase-2 assay (COX-2). The synthesized organotin(IV) complexes were tested against COX-2 enzyme. The COX-2 (300 units/mL) was activated on ice for 5 min. A 50 µL co-factor containing glutathione, hematin, 1.0 mM and TMPD in a Tris-HCl buffer (pH 8) was added to the activated solution. The mixtures containing test compound solution (20 µL) and activated enzyme solution (60 µL) were maintained at room temperature for 5 min. The addition of 20 µL of arachidonic acid started the enzyme inhibition reaction. The reaction was incubated for 5 min, and absorbance was measured at 570 nm. The experiments were repeated three times. The%inhibitions and IC₅₀ values were compared with the standard celecoxib [31].

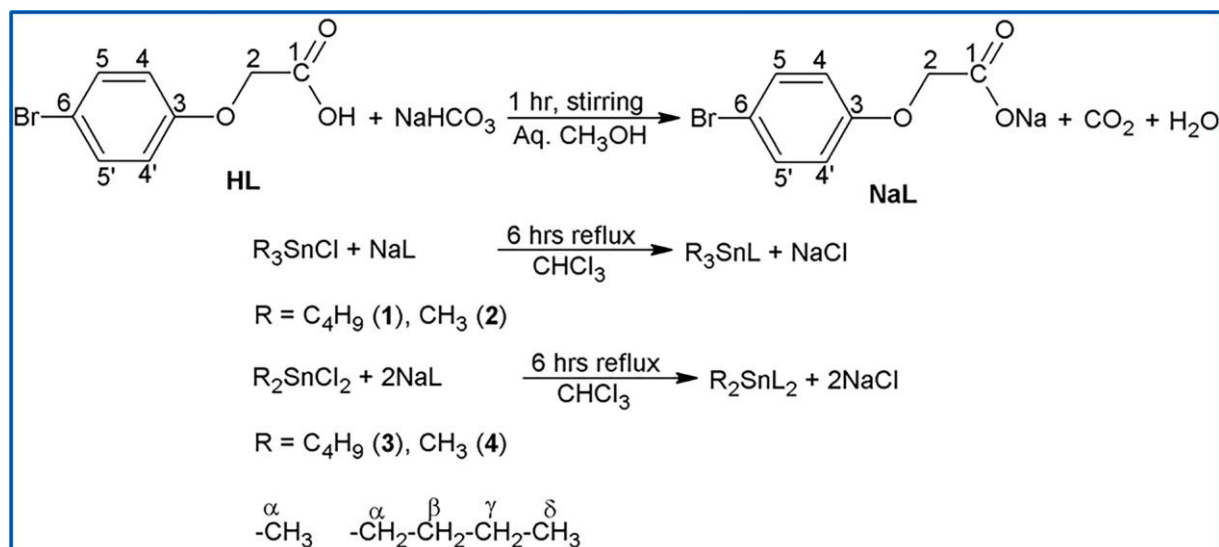
2.5.5.6. 5-Lipoxygenase assay (5-LOX). This assay with some modification was performed against Montelukast as a standard and linoleic acid was used as a substrate [31]. The test compounds were dissolved in phosphate buffer (pH 6.3) followed by the addition of enzyme solution (10,000 unit/µL). The mixture was incubated for 5 min at room temperature followed by the addition of linoleic acid. The mixture was left for 5 min and absorbance was measured at 234 nm. The experiments were performed in triplicate and the%inhibitions and IC₅₀ values were calculated.

2.6. Carrageenan induced *in vivo* inflammation

Carrageenan was used for the preliminary *in vivo* anti-inflammatory assay of complexes 1 and 2 on mice of either sexes (25–30 g). Total forty albino mice were arbitrarily divided into five groups. Randomly divided, with eight animals in each group. Group-I, with 1 % DMSO (10 mL/kg body weight) was negative control. The Group-II, with 50 mg/kg body weight of indomethacin was the positive control. Groups-III, IV and V were given 125, 250 and 500 mg/kg, respective doses of complexes 1 and 2. With a 60 min interval, 1% w/v of freshly prepared saline solution (0.05 ml) of carrageenan was given in the sub-planter surface of each mouse. After the administration of the carrageenan, the paw edema volume was immediately deliberated via plethysmometer (LE 7500 plan lab S.L) at 1–5 h intervals. Paw edema of tested complexes and standard drug were calculated at different time intervals and were compared with negative control group. The following formula was used for the percent inhibitions of the inflammation;

$$\% \text{inhibition} = EC - \frac{ET}{EC} \times 100$$

Where “EC” is the average edema of control and “ET” is the edema of tested group.



Scheme 1. Synthetic and atomic numbering scheme of complexes 1–4.

3. Results and discussion

3.1. Synthesis

Organotin(IV) derivatives; (*n*-C₄H₉)₃SnL (1), (CH₃)₃SnL (2), (*n*-C₄H₉)₂SnL₂ (3) and (CH₃)₂SnL₂ (4) of 4-bromophenoxyacetic acid (**HL**) were prepared by the condensation reaction of organotin(IV) chlorides with sodium-4-bromophenoxyacetate (NaL) in suitable mole ratio in dry chloroform under 6 hrs reflux condition as shown in Scheme 1. The complexes were obtained in good yields (84–79 %). All the complexes were obtained as white solids showing air stability and solubility in DMSO and chloroform at room temperature. The complexes recrystallization was done in chloroform and *n*-hexane mixture (4:1). The elemental analysis confirmed the expected composition and thus purity of the synthesized complexes.

3.2. FT-IR spectroscopy

The preliminary solid state structural elucidation of the synthesized complexes 1–4 was made by FT-IR spectra in the range 4000–400 cm^{−1} as shown in Figs. S1–S4, respectively. The spectral comparison of the free ligand acid **HL** and complexes 1–4 has shown some prominent differences and thus reflected the formation of the complexes. For

instance, the broad band due to OH of the COOH group of the **HL** in the range 3600–2600 cm^{−1} was absent in the spectra of all the synthesized complexes [39]. This observation reflected the presence of deprotonated carboxylate ligand in the complexes [39]. The coordination of deprotonated carboxylate ligand was further supported by the presence of weak/medium intensity bands in the range 501–480 cm^{−1} due to Sn–O bond vibrations [40]. The coordination has also significantly changed the bands at 1700 and 1226 due to C=O and C–O bond vibrations, respectively of the free carboxylic acid [41]. These two bands were replaced by a set of two new bands in the range 1603–1548 cm^{−1} and 1487–1382 cm^{−1} due to asymmetric and symmetric vibration of the coordinated COO moiety, respectively in the complexes [41]. The difference of these two vibrations ($\Delta\nu = \text{COO}_{\text{asym}} - \text{COO}_{\text{sym}}$) gave an indication about the bonding mode of the carboxylate ligand in the synthesized complexes 1–4. The $\Delta\nu$ values were 192, 197, 114 and 136 cm^{−1} for complexes 1–4, respectively thus suggesting bridging bidentate coordination of the ligand in triorganotin(IV) complexes (1 and 2) and chelating bidentate coordination of the ligand in diorganotin(IV) complexes (3 and 4) [42]. The Sn–C bond vibrations appeared in the range 550–496 cm^{−1} as weak/medium bands in the synthesized complexes

Table 1

Crystallographic data of complexes 1 and 2.

Compound	1	2
Empirical formula	C ₂₀ H ₃₃ BrO ₃ Sn	C ₁₁ H ₁₅ BrO ₃ Sn
Formula weight	520.06	393.83
Temperature [K]	100(1)	284(1)
Wavelength [Å]	0.71073	0.71073
crystal system	Monoclinic	Monoclinic
space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> [Å]	25.1732(6)	10.9272(3)
<i>b</i> [Å]	17.8699(5)	10.4571(3)
<i>c</i> [Å]	10.2249(3)	12.4800(4)
<i>a</i> [Å]	90	90
<i>b</i> [Å]	100.685(2)	97.208(3)
<i>g</i> [Å]	90	90
Volume [Å ³]	4519.8(2)	1414.78(7)
<i>Z</i>	8	4
Calculated density (Mg/m ³)	1.529	1.849
Absorption coefficient (mm ^{−1})	2.913	4.621
<i>F</i> (000)	2096	760
Crystal size (mm ³)	0.25×0.1×0.1	0.3×0.15×0.15
Reflections collected	25,579	5323
Independent reflection	8833	2722
<i>R</i> (int)	0.0479	0.0172
Parameters	457	149
Goodness-of-fit on <i>F</i> ²	1.154	1.033
<i>R</i> ₁ (<i>I</i> > 2σ(<i>I</i>))	0.0589	0.0263
w <i>R</i> ₂ (<i>I</i> > 2σ(<i>I</i>))	0.1635	0.0587
Extinction coefficient	n/a	0.0022(2)
Largest diff. peak and hole (e.Å ^{−3})	2.361 and −1.557	0.461 and −0.471
CCDC NO.	2,307,864	2,307,863

1–4 [42].

3.3. Single crystal analysis

The recrystallization of complexes from chloroform and *n*-hexane mixture (4:1) afforded single crystals of complexes 1 and 2, suitable for XRD analysis. The Crystal data and structure refinement parameters of complexes 1 and 2 are presented in Table 1.

The crystal structure of complex 1 is monoclinic, *P*2₁/*c* and has an asymmetric unit containing two independent components, each comprising a tin atom coordinated by one (4-bromo-phenoxy) acetate and three butyl groups (Fig. 1a). The tin atom coordination is distorted trigonal bipyramidal. The Sn–C bond lengths are about 2.128(7) Å to 2.144(7) Å (Table 2) for both Sn1A and Sn1B, whereas the Sn–O bond

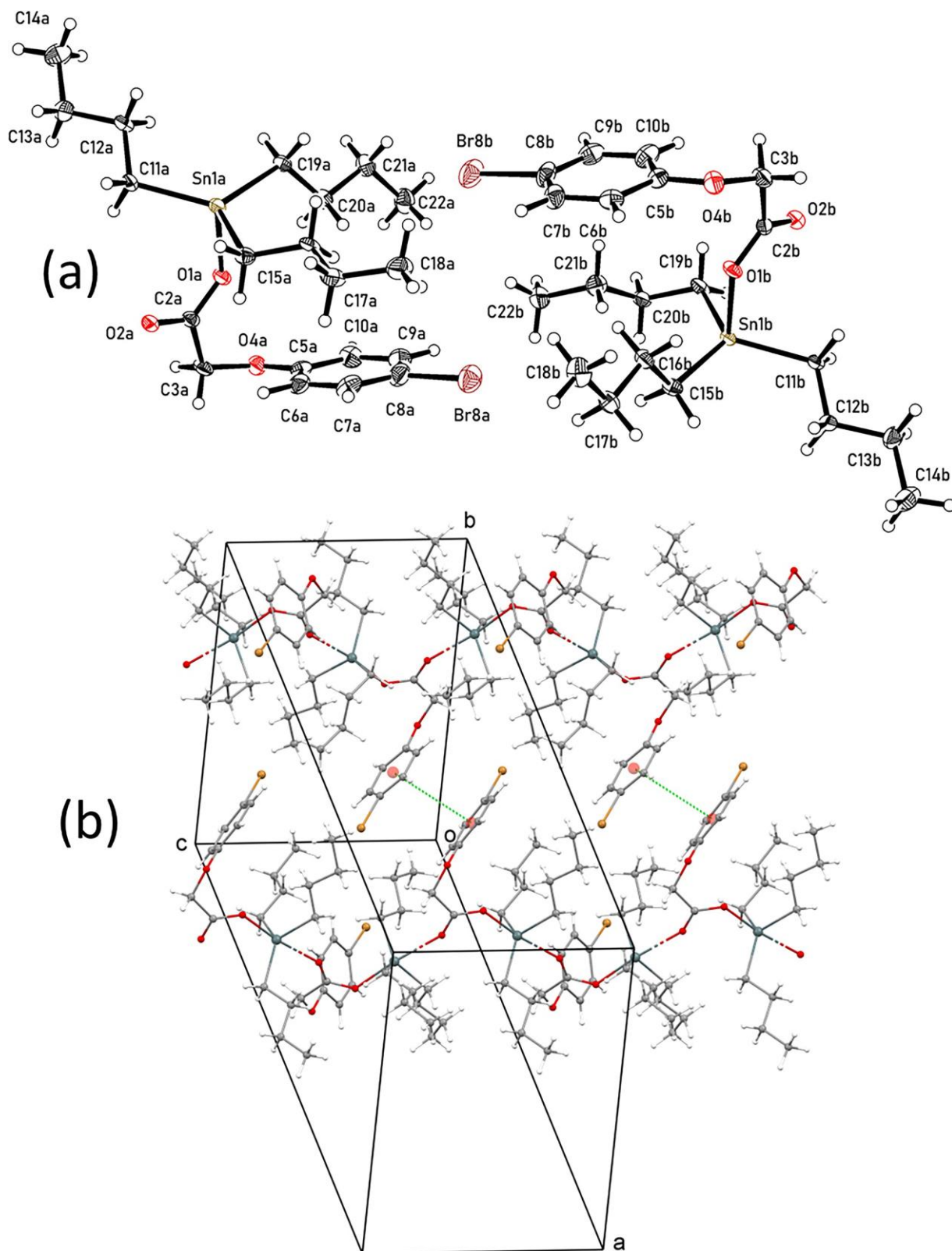


Fig. 1. Complex 1 (a) The asymmetric unit and (b) a segment showing two adjacent polymer chains with the shorted phenyl centroid-to-centroid distances shown as green dotted lines.

lengths are about 2.2 Å (for Sn(1A)-O(1A) and Sn(1B)-O(1B)) and 2.4 Å (for Sn(1A)-O(2A) and (Sn(1B)-O(2B)). The Sn atoms are slightly displaced from the plane of the coordinating C atoms (by ca. 0.2 Å). The C-Sn-C angles range from 115.9(3)° – 124.0(3)° in the structure. For the

oxygen atoms located on either side of the carbon-tin plane, C-Sn-O angles are in the range 80.7(2)°– 98.2(2)°. Both O-Sn-O bonds are ca. 172° and thus deviate from linear geometry. The butyl groups are all in trans conformation. The conformations of the two (4-bromophenoxy)

Table 2Selected bond lengths [Å] and angles [°] for **1** (#1 x, -y + 1/2, z-1/2 #2 x, -y + 3/2, z + 1/2).

Sn(1A)-C(11A)	2.137(6)	Sn(1B)-C(11B)	2.131(6)
Sn(1A)-C(19A)	2.137(6)	Sn(1B)-C(15B)	2.128(7)
Sn(1A)-C(15A)	2.135(6)	Sn(1B)-C(19B)	2.144(7)
Sn(1A)-O(1A)	2.193(4)	Sn(1B)-O(1B)	2.184(4)
Sn(1A)-O(2A)#1	2.403(4)	Sn(1B)-O(2B)#2	2.409(5)
C(11A)-Sn(1A)-C(19A)	118.5(3)	C(11B)-Sn(1B)-C(15B)	116.0(3)
C(11A)-Sn(1A)-C(15A)	123.8(3)	C(11B)-Sn(1B)-C(19B)	117.6(3)
C(19A)-Sn(1A)-C(15A)	115.9(3)	C(15B)-Sn(1B)-C(19B)	124.0(3)
C(11A)-Sn(1A)-O(1A)	97.7(2)	C(11B)-Sn(1B)-O(1B)	98.2(2)
C(19A)-Sn(1A)-O(1A)	90.6(2)	C(15B)-Sn(1B)-O(1B)	90.8(2)
C(15A)-Sn(1A)-O(1A)	94.4(2)	C(19B)-Sn(1B)-O(1B)	96.8(2)
C(11A)-Sn(1A)-O(2A)#1	86.9(2)	C(11B)-Sn(1B)-O(2B)#2	87.0(2)
C(19A)-Sn(1A)-O(2A)#1	82.0(2)	C(15B)-Sn(1B)-O(2B)#2	80.7(2)
C(15A)-Sn(1A)-O(2A)#1	87.7(2)	C(19B)-Sn(1B)-O(2B)#2	86.8(2)
O(1A)-Sn(1A)-O(2A)#1	172.56 (16)	O(1B)-Sn(1B)-O(2B)#2	171.32 (16)
O(1A)-C(2A)-C(3A)-O (4A)	20.0(8)	O(1B)-C(2B)-C(3B)-O (4B)	-14.1(9)
C(2A)-C(3A)-O(4A)-C (5A)	61.8(8)	C(2B)-C(3B)-O(4B)-C (5B)	-63.7(8)

acetate groups are similar, with O(1A)-C(2A)-C(3A)-O(4A) and O(1B)-C(2B)-C(3B)-O(4B) being approximately eclipsed (20.0(8)° and -14.1(9)° respectively) while C(2A)-C(3A)-O(4A)-C(5A) and C(2B)-C(3B)-O(4B)-C(5B) (61.8(8) and 63.7(8) respectively) are gauche. The structure is polymeric (Fig. 1b). In the structure, the closest bromo-phenyl rings from neighbouring polymeric chains are inequivalent and are separated by a centroid...centroid distance of 4.475 Å.

The crystal structure of complex **2** is monoclinic, P2₁/c with the asymmetric unit as shown in Fig. 2a. The tin atom is coordinated by one (4-bromo-phenoxy) acetate and three methyl groups. The tin atom has distorted trigonal bipyramidal coordination. The Sn-C bond lengths are ca 2.11 Å (Table 3) whereas the Sn-O bonds are longer (S(1)-O(1) is 2.204(2) Å and Sn(1)-O(2) is longest at 2.382(2) Å). The methyl groups are coplanar with the metal with C-Sn-C angles in the range 117.28(19)° to 123.26(18)°. The oxygen atoms are located on either side of this plane with C-Sn-O angle in the range 84.73(13)° to 95.82(14)°. In addition to the different Sn-O bond distances, the displacement of both oxygen atoms from linear geometry (the O1-Sn1-O2 angle is 172.22(8)°) contributes to distortion from ideal trigonal bipyramidal coordination. In the (4-bromo-phenoxy) acetic acetate group, both O(1)-C(2)-C(3)-O(4) and C(2)-C(3)-O(4)-C(5) torsion angles are nearly in trans conformation, being 160.9(3)° and 168.9(3)° respectively. The structure is polymeric (Fig. 2b). The planes through symmetry-related bromo-phenyl rings of neighbouring polymeric chains are parallel and are separated by a centroid...centroid distance of 4.665 Å.

3.4. Hirshfeld surfaces

For complex **1**, there are two independent types of chains. The closest interactions involve the rings of bromo-phenyl groups of neighbouring chains (Fig. 3a). For one type of chain, 83.8% of the surface area is in contact with hydrogen atoms of neighbouring chains, with contact by other types of atoms covering the rest (Br (8.4), C (3.5 %) and O (4.2 %)) for one type of chain. The corresponding values for the second type of chain are: H (82.8%), Br (8.5), C (5.7 %) and O (4.6 %).

The Hirshfeld surface for complex **2** is shown in Fig. 3b with the close intermolecular interactions highlighted in red (noting that the highlights at the ends are due to truncation of the polymeric chains). The closest contacts between adjacent chains are the directional C-H...O interaction with geometry: C(9)-H(9)...O(1) = 162.1° and C(9)...O(1) = 3.512(5) Å. Most stabilization is due to contact between chains and hydrogen atoms of neighbours, which accounts for 77.3% of the surface area, followed by contact with Br (10.3), C (6.4 %) and O (5.9 %).

3.5. Nuclear magnetic resonance (NMR) spectroscopy

The NMR spectroscopy is the most frequently used authentic spectroscopic technique for the structural elucidation of organotin(IV) carboxylates in solution form. The ¹H and ¹³C NMR spectra of the synthesized complexes **1-4** were recorded in CDCl₃. The data is presented in the experimental section and representative ¹H NMR spectra are shown in Figs. S5-S7.

The ¹H NMR spectra of complexes **1-4** presented no signal above 9 ppm, thus reflecting the presence of deprotonated carboxylate ligand in the complexes **1-4** [4]. However, the methylene and aromatic protons of the carboxylate ligand has shown no significant differences after complexation with organotin(IV) moiety. The tin bonded alkyl group protons gave signals in the expected region. For example; the methyl protons in complexes **2** and **4** gave signals at 0.63 and 1.10 ppm, respectively. The ²J(^{119/117}Sn-¹H) coupling constant value of 58/56 Hz and subsequent calculated C-Sn-C bond angle of 111.1° confirms the tetra coordinated tetrahedral geometry around tin in complex **2** in solution [4]. Thus a decrease in coordination number occurs from 5 to 4, when the solid triorganotin(IV) complex dissolves in non-coordinating solvent and makes solution. The *n*-butyltin(IV) derivatives (**1** and **3**) gave straightforward triplets at 0.93 and 0.96 ppm for the terminal methyl groups of the *n*-butyl skeleton. However, the -CH₂-CH₂-CH₂ fragment gave multiplets, but in the expected regions [4].

The ¹³C NMR spectra were relatively simple and have shown signals equal to the number of magnetically non-equivalent carbon atoms present in the complexes. Signals for six types of magnetically nonequivalent carbons of the coordinated carboxylate ligands were observed in the expected regions. The COO carbon of the coordinated ligand was observed in the most down field region of the spectrum in the range 173.0-176.6 ppm. The methylene carbon of the carboxylate ligand was observed in the range 64.8-65.7 ppm, while the aromatic carbons gave signals in the range 157.1-113.5 ppm. The tin bonded alkyl groups gave signals in the shielded part of the spectrum. In complex **2**, a C-Sn-C angle of 116.04° calculated by ¹J(^{119/117}Sn-¹³C) coupling constant suggested a tetrahedral tin center in solution form [4]. The absence of extra signals in the ¹³C NMR spectra reflected the purity of the synthesized complexes **1-4**. Furthermore, the complexes were found stable in the solution form, as no changes in the chemical shift values were observed in the time dependent ¹³C NMR spectra, taken immediately and after 24 h in CDCl₃.

3.6. Biological activities

3.6.1. Anticancer activity

The free ligand acid **HL** and synthesized complexes **1-4** were tested for the *in vitro* anticancer activity against the human malignant glioma U-87 cell line. Simultaneously, human normal embryonic kidney cells (HEK293) were used as a positive control in the experiment. Different concentrations (10, 20, 40, 80, 100, 150, and 200 g/mL) of the test compounds were used in the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay to determine the cytotoxic effect on cancer/normal cell lines. Using the GraphPad Prism 8.0.2, the dose-response and IC₅₀ values were determined, and the findings as % cell viability are summarized in Table 4. A dose-dependent anticancer response was observed. With increasing concentrations of the test compounds, a sharp reduction in the % cell viability was observed. However, at higher drug doses, the percentage of cell survival was rather low. Results of the MTT assay revealed that complexes **4** (IC₅₀ = 8.035 ± 0.05 µg/mL), and **1** (IC₅₀ = 10.16 ± 0.17 µg/mL), exhibited the highest inhibitory potency towards the brain cancer cell line (Malignant glioma U87). Furthermore, the remaining three compounds, **HL**, **3** and **2**, were found to be moderately to less active, with IC₅₀ values of 42.01 ± 0.08, 58.62 ± 0.03 and 70.0 ± 0.01 µM, respectively. Human embryonic kidney HEK293 cells were also exposed to the compounds at varying concentrations in a manner like the cancer cells to examine the selective cytotoxic effects of compounds for malignant cells as compared to

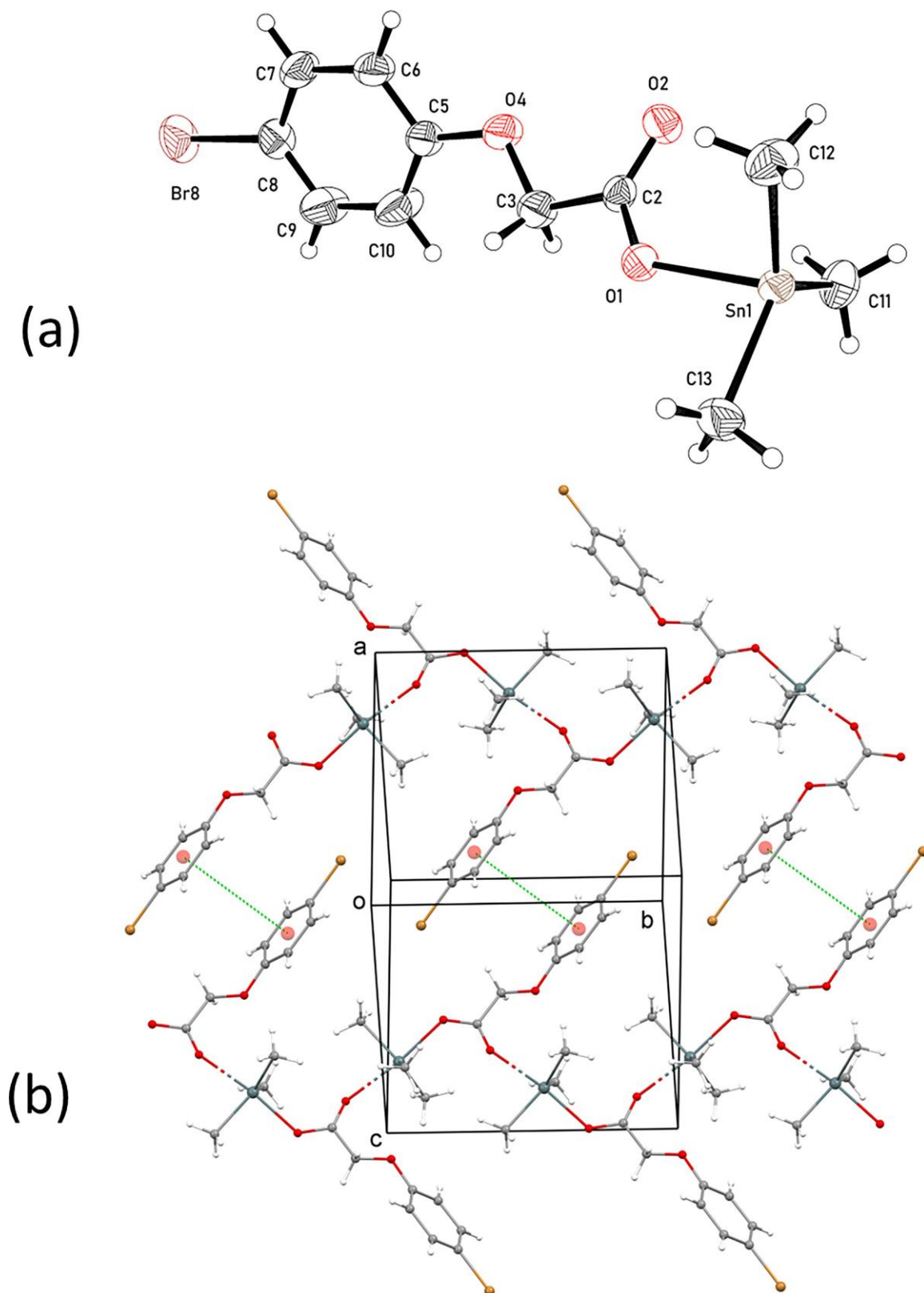


Fig. 2. Complex 2 (a) The asymmetric unit and (b) a segment showing two adjacent polymer chains with the shorted phenyl centroid- to-centroid distances shown as green dotted lines.

nonmalignant cells. The findings suggest that these cells (HEK293) are less vulnerable to the activities of the compounds, particularly **1** and **4**, which increases the death of brain cancer cells. It is revealed that the aggressive brain cancer cell line (Malignant glioma U87) responded

more positively to majority of the chemicals with higher cytotoxicity. Mostly, the complexes have shown better anticancer potential compared to the previously reported structural analogues [43]. The lower cytotoxicity of complexes (**1** and **4**) in non-cancerous cells suggests that these

Table 3
Selected bond lengths [Å] and angles [°] for **2** (#1 -x,y-1/2,-z + 3/2).

Sn(1)-C(11)	2.109(4)	Sn(1)-O(1)	2.204(2)
Sn(1)-C(12)	2.110(4)	Sn(1)-O(2)#1	2.382(2)
Sn(1)-C(13)	2.115(4)		
C(11)-Sn(1)-C(12)	123.26(18)	C(11)-Sn(1)-O(2)#1	91.63(12)
C(11)-Sn(1)-C(13)	119.21(18)	C(12)-Sn(1)-O(2)#1	88.55(14)
C(12)-Sn(1)-C(13)	117.28(19)	C(13)-Sn(1)-O(2)#1	84.73(13)
C(11)-Sn(1)-O(1)	91.34(13)	O(1)-Sn(1)-O(2)#1	172.22(8)
C(12)-Sn(1)-O(1)	95.82(14)	O(1)-C(2)-C(3)-O(4)	160.9(3)
C(13)-Sn(1)-O(1)	87.54(13)	C(2)-C(3)-O(4)-C(5)	168.9(3)
O(1A)-C(2A)-C(3A)-C(4A)	160.9(3)	C2-C3-O4-C5	168.9(3)

novel compounds will provide promising treatment/therapy for patients with brain cancer.

3.6.2. Antioxidant assays

The *in vitro* antioxidant potential of the free ligand acid **HL** and synthesized complexes **1–4** was assessed via DPPH and ABTS assays using ascorbic acid as a standard drug. The experimental findings as IC_{50} values are presented in Table 5. The synthesized complexes have significantly higher antioxidant potential than the free ligand acid. Furthermore, the scavenging potential of complexes was higher for ABTS than DPPH free radical. Diorganotin(IV) derivatives were better DPPH and ABTS scavengers than their analogues triorganotin(IV) derivatives. Among the complexes, **3** ($IC_{50} = 33.46 \mu\text{g/mL}$) and **4** ($IC_{50} = 18.73 \mu\text{g/mL}$) were the most potent DPPH and ABTS free radical scavengers, respectively. The complexes have shown higher ABTS and lower DPPH free radical scavenging potential compared to the previously reported similar organotin(IV) carboxylates [43]. The differences in the activity pattern of the complexes **1–4** and the data reported previously for the similar compounds, signifies the importance of the carboxylate ligand substituents in the antioxidant potential of the organotin(IV) carboxylates [43].

3.6.3. Antileishmanial activity

The *in vitro* antileishmanial activity of the free ligand acid (**HL**) and the synthesized complexes (**1–4**) was evaluated against *L. tropica* promastigotes using MTT assay. Amphotericin-B (AmB) was used as a standard drug and the data obtained is presented in Fig. 4 and Table S1. The complexes have significantly higher antileishmanial activity than the free ligand acid. The activity order for the complexes is **3** > **1** > **4** > **2**. This activity pattern suggests that length of the alkyl group is the dominant factor in antileishmanial activity of the complexes in the present study as *n*-butyltin(IV) derivatives (**1** and **3**) are more active than methyltin(IV) derivatives (**2** and **4**). Also, the dialkyltin(IV) derivatives (**3** and **4**) are more potent antileishmanial agents than their corresponding trialkyltin(IV) analogues (**1** and **2**). The activity order of the test complexes is significantly different from the previously reported structurally related organotin(IV) carboxylates [43]. This observation shows that by changing substituents on the coordinated carboxylate ligand, the biological behavior of the resultant organotin(IV) carboxylates can be tuned up to a greater extent. The *n*-butyltin(IV) derivatives (**1** & **3**) are more active with 4-bromophenoxy acetate, while methyltin(IV) derivatives are better antileishmanial agents when the complex has coordinated 4-fluorophenoxyacetate ligand [43].

3.6.4. Antimicrobial assays

The *in vitro* antimicrobial potential of the free ligand acid **HL** and complexes **1–4** was assessed against some selected bacterial (*E. coli*, *S. aureus*, *P. aeruginosa*, and *B. subtilis*) and fungal strains (*C. albicans* and *C. parapsilosis*). Cefixime and clotrimazole were used as standards and the data obtained is presented in Fig. 5 and Table S2.

Among the selected strains, *S. aureus*, was the most susceptible strain as attacked by all the test compounds while *P. aeruginosa* was the most resistant strain. The relatively higher activity of the complexes **1–4**

compared to the free ligand acid **HL** against *S. aureus* validated the chelation theory [20]. According to this theory, the coordination/chelation of the organic ligand to the metal center results in the distribution of ligand's negative charge over the whole chelate ring in the complex. The covalent and lipophilic character of the metal complex increases that enhances the permeability of the complex across the cell membrane and as a result the complex becomes an active biological agent. The higher activity of complexes **2** & **4** than **1** & **3** against *S. aureus*, shows that the activity is influenced by the length of the alkyl group. The complexes (**2** & **4**) with smaller methyl groups are more active than complexes (**1** & **3**) with larger *n*-butyl groups. Complex **4** with 22 ± 1 mm zone of inhibition have shown better activity than standard (Cefixime) against *E. coli*. Among the tested compounds, only complexes **1** and **4** showed activities comparable with the standard drugs in antifungal assay with zone of inhibition values of 16.3 ± 1.5 mm against *C. albicans* and 20 ± 1 mm against *C. parapsilosis*, respectively. The differences in the antimicrobial activities of the test compounds compared to the recently reported structurally related complexes show that small structural/substituents changes in the coordinated carboxylate ligands can significantly affect the antimicrobial activity of the organotin(IV) carboxylates [43,44].

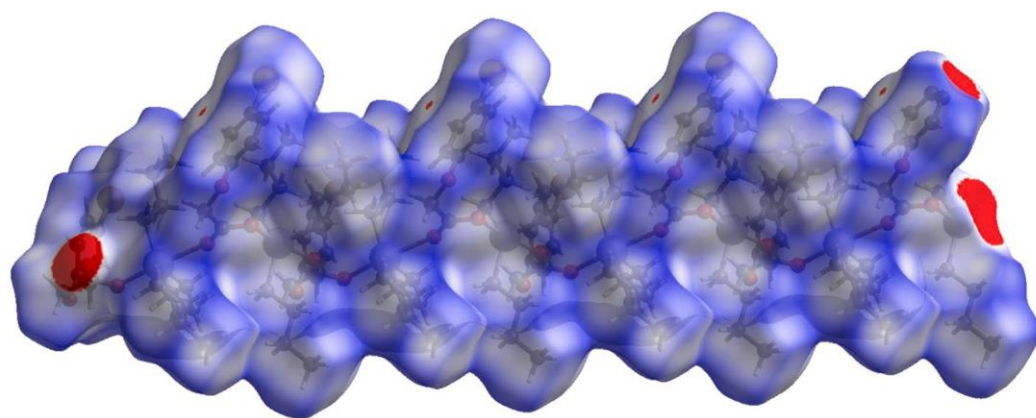
3.6.5. Enzyme inhibition assays

3.6.5.1. Anti-Alzheimer's assays. The *in vitro* inhibition of Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE) and Monoamine oxidase B (MAO-B) enzymes was carried out to explore the efficiency of the free ligand acid **HL** and synthesized complexes **1–4** as potential drug candidates for the treatment of Alzheimer's disease [31,45–49]. The enzymes inhibition data in form of IC_{50} values is presented in Table 6.

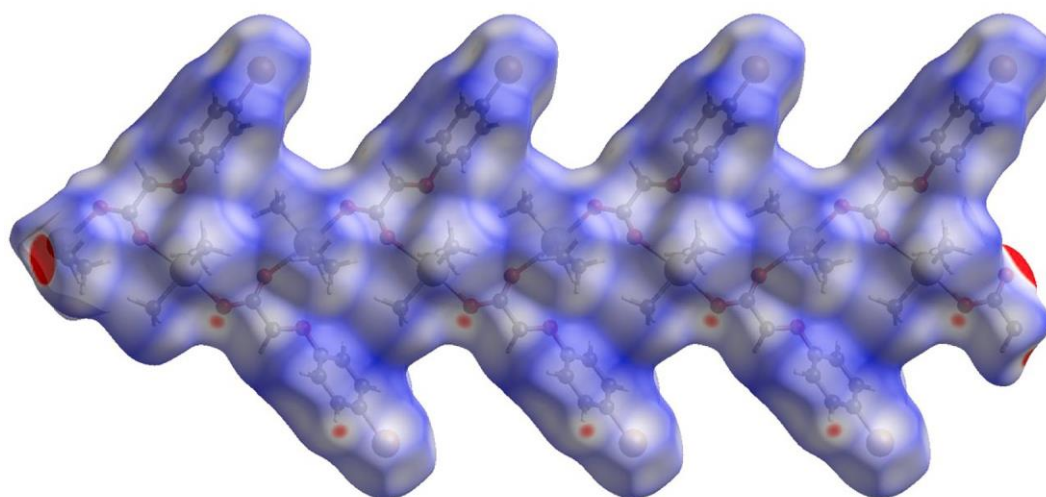
The efficiency of the free ligand acid was very low. However, after complexes formation the activity increased drastically. This reflects the importance of organotin(IV) moieties as efficient enzymes inhibitors. Almost same activity order was followed by the complexes against all the three enzymes. Di-*n*-butyltin(IV) derivative with IC_{50} values of 5.12, 13.79 and $8.50 \mu\text{g/mL}$, respectively was found the most active AChE, BChE and MAO-B enzyme inhibitor. Against MAO-B, complex **3** ($IC_{50} = 8.50 \mu\text{g/mL}$) was even more active than the standard Safinamide ($IC_{50} = 11.82 \mu\text{g/mL}$). Overall dialkyltin(IV) derivatives (**3** and **4**) were more active compared to their trialkyltin(IV) analogues (**1** and **2**). Also in complexes with same number of alkyl groups, the one with lengthy alkyl group was found more active than complexes with smaller alkyl groups except against MAO-B where trimethyltin(IV) complex (**2**) has shown slightly higher activity than tri-*n*-butyltin(IV) derivative (**1**).

3.6.5.2. Antidiabetic assays. To assess the antidiabetic potential of the free ligand acid **HL** and complexes **1–4**, *in vitro* inhibition of α -glucosidase and dipeptidyl peptidase-4 (DPP-4) was studied [31,50]. Acarbose was used as a standard and the data obtained is reported as IC_{50} values in Table 6. The free ligand acid with IC_{50} values more than $500 \mu\text{g/mL}$ was inactive against both the enzymes. Complexes **1–4** have shown relatively better α -glucosidase and dipeptidyl peptidase-4 inhibition potential than the free ligand acid. Among the complexes, **1** with IC_{50} values of 27.50 and $71.32 \mu\text{g/mL}$ was found the most potent against α -glucosidase and dipeptidyl peptidase-4, respectively.

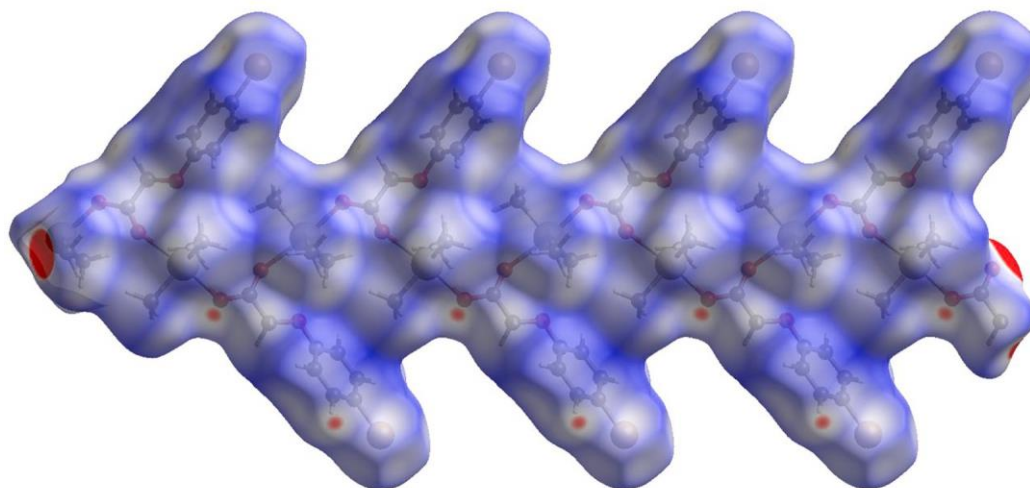
3.6.5.3. Anti-inflammatory assays. The *in vitro* anti-inflammatory assays for the free ligand acid **HL** and synthesized complexes **1–4** were performed against cyclooxygenase (COX-2) and lipoxygenase (5-LOX) enzymes using Celecoxib and montelukast as standard drugs, respectively. The data is presented in Table 6. Among the tested compounds, complex **2** with IC_{50} values of 7.81 and $6.69 \mu\text{g/mL}$ was found the most potent COX-2 and 5-LOX inhibitor, respectively. The activity of complex **2** against COX-2 was comparable with the standard Celecoxib ($IC_{50} = 7.46 \mu\text{g/mL}$). The free ligand acid ($IC_{50} = 21.84 \mu\text{g/mL}$) was the second



A



A



B

Fig. 3. Hirshfeld surfaces for (a) both types of chain for Complex 1 (b) Complex 2. Clise contacts are highlighted in red (note that the ends of the polymeric chains have been truncated).

Table 4

% Cell Viability (IC_{50}) of the free ligand acid HL and complexes 1–4 against brain cancer (U-87) and normal (HEK-293) cell lines.

Samples	Cell line	Doze Conc.($\mu\text{g/mL}$)							IC_{50} ($\mu\text{g/mL}$) U-87
		10	20	40	80	100	150	200	
HL	U-87	123.71	115.02	104.76	97.97	84.27	35.02	28.19	42.01
	HEK	105.18	75.95	70.8	67.22	63.9	62.9	62.34	
1	U-87	8.89	6.97	6.18	5.87	5.3	4.8	4.72	10.16
	HEK	29.47	22.88	20.73	19.61	19.45	18.74	17.47	
2	U-87	14.18	8.64	8.34	6.2	5.52	4.69	4.14	70.0
	HEK	34.13	25.1	23.46	18.04	15.06	14.41	10.46	
3	U-87	89.39	23.45	13.41	10.07	8.78	7.17	6.33	58.62
	HEK	57.98	38.39	36.44	34.97	31.12	28.02	23.14	
4	U-87	94.92	92.5	87.97	87.96	85.53	78.15	46.99	8.035
	HEK	170.45	158.73	150.66	144.81	141.39	136.49	130.39	

Table 5

IC_{50} values for *in vitro* antioxidant assays (DPPH, ABTS) of free ligand acid (HL) and complexes 1–4.

Sample	IC_{50} ($\mu\text{g/mL}$)	
	DPPH	ABTS
HL	219.49	162.91
1	143.32	87.72
2	119.54	43.74
3	33.46	21.39
4	38.76	18.73
Ascorbic acid	6.93	8.87

highest in activity against COX-2. However, in case of 5-LOX inhibition, all the complexes have shown better inhibition potential compared to the free ligand acid.

3.6.6. *In vivo* anti-inflammatory activity

The *in vivo* anti-inflammatory properties of complexes 1 and 2 were evaluated using a carrageenan-induced paw edema model in mice. Following the mice's acclimatization, carrageenan was administered to induce edema, after which the test complexes and the control drug were intraperitoneally administered in different doses. The data presented in Table 7 provide crucial insights into the anti-inflammatory properties of

complexes 1 and 2, as well as the standard drug, indomethacin. Each was administered at varying doses, and their effects were measured at several time intervals, at the 0th, 1st, 2nd, 3rd, 4th and 5th hour. At the 1st hour, complex 1 displayed an inhibition of 49.50, 45.56, and 42.20 %, at doses of 500, 250, and 150 μg respectively. Complex 2 exhibited a percent inhibition of 45.30, 42.20, and 39.44 %, at the respective doses. Indomethacin continued to outperform both compounds with a percent inhibition of 47.01 %.

At the 2nd hour, complex 1 exhibited an inhibition of 57.67, 49.56, and 45.00 % at the respective doses. Complex 2 displayed an inhibition of 51.10, 46.45, and 42.20 % at the same doses. Indomethacin, at this time point, presented a percent inhibition of 54.46 %. Moving into the 3rd hour, complex 1 maintained its anti-inflammatory activity with percent inhibitions of 58.58, 51.20, and 48.23 % at the respective doses. Complex 2 also continued to exhibit significant inhibitions, specifically 52.20, 48.30, and 44.30 % at the respective doses. Indomethacin displayed an inhibition of 53.02 %. At the 4th hour, complex 1 has shown percent inhibitions of 61.20, 53.20, and 49.20 % at the respective doses. Similarly, Complex 2 has shown percent inhibitions of 54.30, 51.10, and 47.00 % at the respective doses. While Indomethacin displayed an inhibition of 56.27 %.

Finally, at the 5th hour, complex 1 showed percent inhibitions of 63.34, 55.10, and 51.10 %, at the respective doses. Complex 2 demonstrated inhibitions of 56.90, 49.90, and 45.40 %, at the same doses.

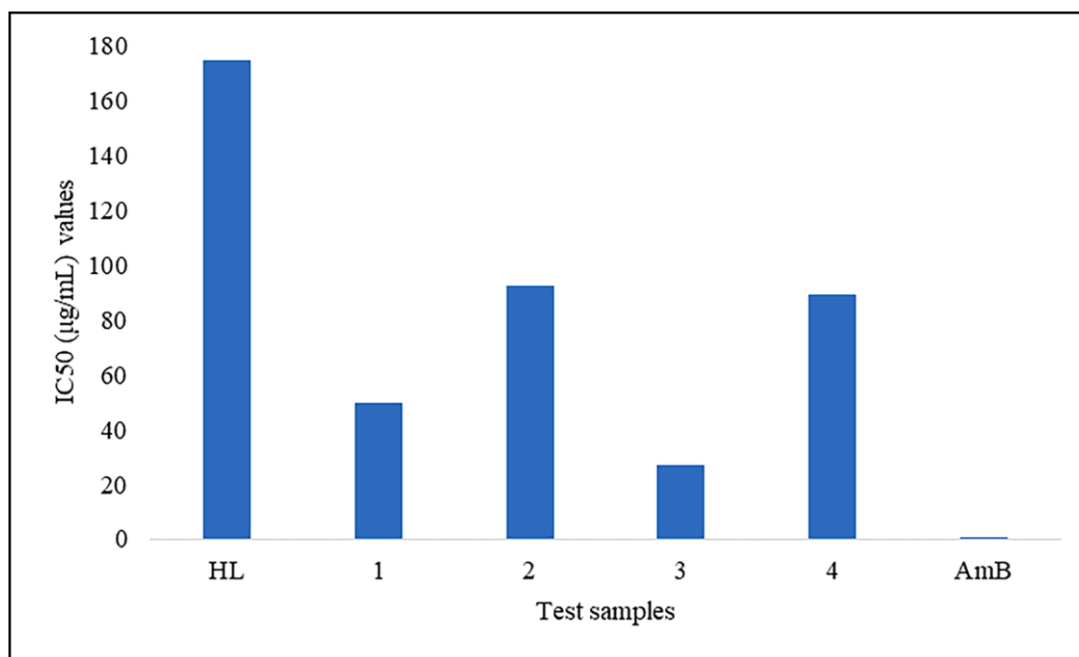


Fig. 4. IC_{50} ($\mu\text{g/mL}$) values of free ligand acid HL and complexes 1–4 against *L. tropica* promastigotes.

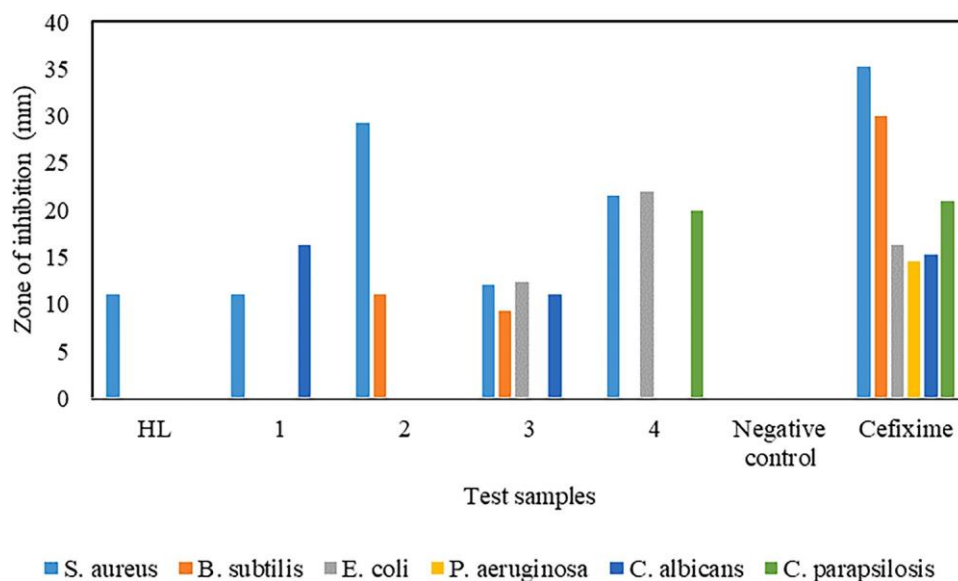


Fig. 5. Antimicrobial activity of the free ligand acid HL and synthesized complexes 1–4.

Table 6

IC₅₀ (μg/mL) values for *In vitro* enzymes inhibition assays of free ligand acid (HL) and complexes 1–4.

Complex	Anti-Alzheimer's assays			anti-diabetic assays		anti-inflammatory assays	
	AChE	BChE	MAO-B	α-glucosidase	DPP-4	COX-2	5-LOX
HL	> 500	> 500	244.97	> 500	> 500	21.84	29.07
1	59.35	101.50	67.61	27.50	71.32	36.70	27.58
2	35.19	47.56	68.33	102.95	190.80	7.81	6.79
3	5.12	13.79	8.50	> 500	102.11	25.08	13.37
4	17.84	33.99	19.66	295.36	106.93	33.67	28.40
Galantamine	2.82	4.61	–	–	–	–	–
Safinamide	–	–	11.82	–	–	–	–
Acarbose	–	–	–	5.91	5.91	–	–
Ursolic acid	–	–	–	–	–	–	–
Celecoxib	–	–	–	–	–	7.46	–
Montelukast	–	–	–	–	–	–	4.76

Table 7

In vivo anti-inflammatory activity of complexes 1 and 2.

Sample	Dose (μg/kg)	% Inhibition					
		0 h	1 h	2 h	3 h	4 h	5 h
Vehicle	10mL	2.20±0.17	7.21±0.019	7.62±0.046	7.45±0.034	7.89±0.035	7.81±0.037
Indomethacin	50	8.20±0.15	47.01±0.39	54.46±0.280	53.02±0.240	56.27±0.370	57.36±0.028
	500	11.20±0.17	49.50±0.22	57.67±0.56	58.58±0.46	61.20±0.40	63.34±0.22
	250	6.51±0.40	45.56±0.42	49.56±0.52	51.20±0.34	53.20±0.62	55.10±0.76
1	150	6.54±0.30	42.20±0.22	45.00±0.62	48.23±0.53	49.20±0.90	51.10±0.55
	500	2.20 ± 0.34	45.30±0.32	51.10±0.42	52.20±0.66	54.30±0.12	56.90±0.12
	250	2.10 ± 0.34	42.20±0.56	46.45±0.23	48.30±0.20	51.10±0.12	49.90±0.10
2	150	2.08 ± 0.45	39.44±0.40	42.20±0.10	44.30±0.22	47.00±0.10	45.40±0.22

Indomethacin retained its inhibitory activity, with a percent inhibition of 57.36 %. These results clearly indicate the potent anti-inflammatory effects of complexes 1 and 2, which performed comparably to the standard drug, indomethacin, at all measured time points.

4. Conclusion

The condensation reaction of sodium-4-bromophenoxyacetate (NaL) with tri- and diorganotin(IV) chlorides afforded the formation of (*n*-C₄H₉)₃SnL (1), (CH₃)₃SnL (2), (*n*-C₄H₉)₂SnL₂ (3) and (CH₃)₂SnL₂ (4) in good yields (84–79 %). The composition and structural elucidation was authenticated via elemental analysis, FT-IR and (¹H and ¹³C) NMR

spectra. Complexes 1 and 2 were also analyzed via single crystal XRD and Hirshfeld surface analyses. The spectral analysis has confirmed the bonding of deprotonated carboxylate ligand in the complexes. Complexation has significantly improved the bioactivity of the carboxylate ligand and thus validated the chelation theory. In the antioxidant assays, complexes were more active against ABTS than DPPH free radical. Also, diorganotin(IV) derivatives were better antioxidants than their analogues triorganotin(IV) derivatives. The activity order (3 > 1 > 4 > 2) in the antileishmanial assay suggests that the activity depends on the number and length of the tin bonded alkyl groups. All the test compounds have shown activity against *S. aureus*. In the inhibition of Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE) and

Monoamine oxidase B (MAO-B) enzymes, complex **3** was found the most efficient inhibitor, especially against MAO-B, complex **3** ($IC_{50} = 8.50 \mu\text{g/mL}$) was even more active than the standard Safinamide ($IC_{50} = 11.82 \mu\text{g/mL}$). Dilakyl(IV) derivatives (**3** and **4**) were more active compared to their trialkyltin(IV) analogues (**1** and **2**). Complex **1** with IC_{50} values of 27.50 and 71.32 $\mu\text{g/mL}$ was the most efficient α -glucosidase and dipeptidyl peptidase-4 inhibitor, respectively. Complex **2** with IC_{50} values of 7.81 and 6.69 $\mu\text{g/mL}$ was the most potent COX-2 and 5-LOX inhibitor, respectively. The activity of complex **2** against COX-2 was comparable with the standard Celecoxib ($IC_{50} = 7.46 \mu\text{g/mL}$). Complexes **4** ($IC_{50} = 8.035 \pm 0.05 \mu\text{g/mL}$), and **1** ($IC_{50} = 10.16 \pm 0.17 \mu\text{g/mL}$) have shown potent activities against the brain cancer cell line (Malignant glioma U87). The *in vivo* study as performed by using a carrageenan-induced paw edema model in mice indicated comparable anti-inflammatory activity of complexes **1** and **2** with the standard, indomethacin.

CRediT authorship contribution statement

Shahnaz Rahim: Writing – review & editing, Writing – original draft, Methodology, Investigation. **Abdul Sadiq:** Investigation. **Anela Javed:** Investigation. **Maciej Kubicki:** Investigation, Formal analysis. **Benson Kariuki:** Software, Formal analysis. **Mohammad Assad:** Investigation. **Niaz Muhammad:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Project administration. **Nighat Fatima:** Investigation. **Momin Khan:** Writing – review & editing, Writing – original draft. **Abdullah F. AlAsmari:** Writing – review & editing, Resources, Funding acquisition. **Fawaz Alasmari:** Writing – review & editing, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Supplementary materials

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