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Triorganotin(IV) complexes with *o*-substituted arylhydroxamates: Synthesis, spectroscopic characterization, X-ray structures and *in vitro* cytotoxic activities

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ABSTRACT

Six new triorganotin(IV) complexes with six different *R*N-2-X-benzohydroxamic acid ligands having general formula *R*′C(O)N(*R*N)OH (*R*′ = alkyl/aryl; RN = alkyl/aryl or H), (X = −I, $-NO_2$, $-OCH_3$, −Br and R = $-CH_3$, $-C_6H_5$ and $-C_6H_4-CH_3$), were prepared by condensation method with the respective organotin(IV) chlorides using a stoichiometric ratio of 1:1. The bonding and coordination behaviour of these complexes were investigated on the basis of FT-IR, multinuclear ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopies. Complexes (**1**) and (**3**) crystallize in the orthorhombic *P*2(1)2(1)2(1) space group and complex (**2**) crystallizes in the triclinic *P*-1 space group whereas complex (**4**) crystallizes in the monoclinic *P*2(1)/*c* space group. The tested triphenyltin(IV) complexes showed significant cytotoxicities, higher than doxorubicin toward K-562, Jurkat, HepG2 and L929 cells.

Introduction

Since Lossen discovered the first hydroxamic acid more than 100 years ago, a considerable attention has been given to the preparation, structure–activity relationships (SAR), utilization, and biological applications of hydroxamates [1,2]. These compounds are capable of the inhibition of a variety of enzymes, including ureases, peroxidases and matrix metalloproteinases [3–6]. In the biomedical sciences, hydroxamic acid moieties are used in the design of therapeutics targeting cancer, cardiovascular diseases [7,8]. In addition, the hydroxamic acids have been employed as insecticides, antimicrobials [9,10]. These compounds also show prominent activities due to their chelating properties with metal ions, hence constituting a very important class of chelating agents. Hydroxamic acids are usually used as supporting ligands in organometallic chemistry and biology because of their tautomerization and potential as therapeutics agents [11,12]. The principal coordination mode observed in metal–hydroxamic acid complexes is the *O,O*-bidentate chelation, in which the ligand is either singly deprotonated (hydroxamato) or doubly (RN = H) deprotonated (hydroximato) [13].

Organotin(IV) complexes with bidentate O-donor ligands [14], including N-substituted hydroxamic acids, are well known and have been a continuing subject of study in the recent years [15], highlighting the synthesis of a number of complexes with interesting properties [16,17]. The triorganotin(IV) derivatives of bidentate ligands have been widely explored to have tetrahedral [18,19] or trigonal bipyramidal [20–23] geometry depending upon the nature of organo group and also the electronegativity of the atoms attached with central tin atom. Organotin compounds are a widely studied class of organometallic compounds with, broad spectrum of applications, being used in antifouling paints [24], PVC stabilization [25], as homogeneous catalysts [26], and as ion carriers in electrochemical membranes design [27], and in agriculture

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that give rise to ubiquitous environmental contamination [28,29]. Organotins compounds have been the source of much biochemical interest due to the fact that they display a number of biological activities [17,30–32], Moreover, the increasing interest in the chemistry of organotin(IV) compounds has led to the extended studies against cancer [33–37]. The biological activity of organotin compounds is mainly determined by the number and nature of organic groups linked to the central tin atom. The biological activity of OTC generally decreases in the following order: $R_3Sn^+ > R_2Sn^{2+} > RSn^{3+}$ [17,38–40], which has been related to their ability to bind to proteins. The genotoxicity of tri-*n*-butyltins and triphenyltins in mammalian cells have also been reported [29,41].

In this work, we carried out systematic studies of tri-organotin(IV) derivatives of six different hydroxamic acid ligands. We further report here the spectral characterization, X-ray diffraction studies and the *in vitro* cytotoxic activities of the four compounds against four different cell lines; i.e., human leukemic lymphoblastoma K-562 cells, lymphoblastoma Jurkat cells, hepatoblastoma HepG2 cells and mouse fibroblast L929 cells.

Experimental

Materials and physical measurements

The chemicals were purchased from Aldrich and were used as received. All the chemicals were of analytical grade. The purity of the ligand and the derived complexes were assured by TLC using silica gel-G as adsorbent. The melting points were determined in open capillary tubes using an electrothermal 9300 digital melting point apparatus. Carbon, hydrogen and nitrogen analysis were preformed on an Elemental Fison EA 1108 CHNS–O Analyzer. Tin was determined gravimetrically. Solid state infrared spectra of the compounds are recorded in the range 4000–400 cm^{-1}. The infrared spectra were recorded as KBr discs using a Perkin–Elmer spectrophotometer GX. The ^1H, ^{13}C and ^{119}Sn nuclear magnetic resonance spectra were recorded using the BRUKER FT-NMR 600 MHz Cryo-Prob spectrometer and the JEOL JNM-ECP 400 spectrometer, using DMSO as a solvent and tetramethylsilane as an internal standard.

Synthesis

Synthesis of ligands

The *N*-methyl *o*-substituted benzohydroxamic acids (**HL_1**, **HL_2**, **HL_3** and **HL_4**), were prepared by the reaction of the respective benzoyl chloride (10 mM) with *N*-methylhydroxyl-amine (10 mM) [42] while *N*-phenyl *o*-methoxybenzohydroxamic acid (**HL_5**) and *N*-tolyl *o*-nitrobenzohydroxamic acid (**HL_6**) were prepared by treating with *N*-phenyl- and *N*-tolyl-hydroxylamine (10 mM) in the presence of sodium hydrogen carbonate (20 mM) [42,43].

[$HONCH_3C(O)C_6H_4I$-2] (**HL_1**). Colorless crystals. Yield: 84%. Melting point: 134–135 °C. Elemental Analysis Calcd. (%) for $H_8C_8NO_2I$: C 34.67, H 2.89, N 5.06. Found (%): C 35.32, H 2.71, N 4.93. Selected IR data (KBr pellets, cm^{-1}): 3114 (s, br, νO–H), 1608 (s, νC=O), 1494 (s, νC–N) and 915 (s, νNO). ^1H NMR [DMSO-d_6]: (ppm) = 10.28 [s, br, 1H, OH]; 7.09-7.86 [m, 4H]; 3.24 [s, 3H]. ^{13}C NMR [DMSO-d_6]: (ppm) = 169.02 (C=O); 165.95 [C(1)], 93.39 [C(2)], 127.68–142.56 [C(3–6)], 38.88[C (8)].

[$HONCH_3C(O)C_6H_4NO_2$-2] (**HL_2**). Yellow crystals. Yield: 76%. Melting point: 169–170 °C. Elemental Analysis Calcd. (%) for $H_8C_8N_2O_4$: C 48.98, H 4.08, N 14.28. Found (%): C 49.12, H 4.12, 14.10. Selected IR data (KBr pellets, cm^{-1}): 3100(s, br, νO–H), 1601 (s, νC=O), 1524 (s, νC–N) and 916 (s, νNO). ^1H NMR [DMSO-d_6]: (ppm) = 8.74 [s, br, 1H, OH]; 7.27–7.69 [m, 4H]; 3.21 [s, 3H]. ^{13}C NMR [DMSO-d_6]: (ppm) = 162.45 (C=O); 145.79 [C(1)], 125.02 [C(2)], 128.66–134.44 [C(3–6)], 37.13 [C(8)].

[$HONCH_3C(O)C_6H_4OCH_3$-2] (**HL_3**). Colorless crystals. Yield: 69%. Melting point: 136–137 °C. Elemental Analysis Calcd. (%) for $H_{11}C_9NO_3$: C 59.66, H 6.08, N 7.73. Found (%): C 59.31, H 6.76, N 8.52. Selected IR data (KBr pellets, cm^{-1}): 3126 (s, br, νO–H), 1603 (s, νC=O), 1486 (s, νC–N) and 918 (s, νNO). ^1H NMR [$CDCl_3$]: (ppm) = 9.10 [s, br, 1H, OH]; 6.99–7.50 [m, 4H]; 3.86 [s, 3H] 3.23 [s, 3H]. ^{13}C NMR [$CDCl_3$]: (ppm) = 166.02 (C=O); 155.94 [C(1)], 111.24 [C(2)], 119.97–133.56 [C(3–6)], 36.78 [C(8)], 55.68 [C(9)].

[$HONCH_3C(O)C_6H_4Br$-2] (**HL_4**). Colorless crystals. Yield: 79%. Melting point: 127–128 °C. Elemental Analysis Calcd. (%) for $H_8C_8NO_2Br$: C 41.76, H 3.48, N 6.10. Found (%): C 39.60, H 2.98, N 6.01. Selected IR data (KBr pellets, cm^{-1}): 3123(s, br, νO–H), 1600 (s, νC=O), 1436 (s, νC–N) and 915 (s, νNO). ^1H NMR [$CDCl_3$]: (ppm) = 10.39 [s, br, 1H, OH]; 7.22–7.64 [m, 4H]; 3.86 [s, 3H] 3.24 [s, 3H]. ^{13}C NMR [$CDCl_3$]: (ppm) = 166.76 (C=O); 159.11 [C(1)], 111.24 [C(2)], 119.97–133.56 [C(3–6)], 36.78 [C(8)].

[$HONC_6H_5C(O)C_6H_4OCH_3$-2] (**HL_5**). Yellowish solid. Yield: 76%. Melting point: 116–117 °C. Elemental Analysis Calcd. (%) for $H_{13}C_{14}NO_3$: C 69.14, H 5.35, N 5.76. Found (%): C 71.97, H 5.58, N 5.74. Selected IR data (KBr pellets, cm^{-1}): 3239 (s, br, νO–H), 1627 (s, νC=O), 1490 (s, νC–N) and 900 (s, νNO). ^1H NMR [$CDCl_3$]: (ppm) = 9.89 [s, br, 1H, OH]; 6.74–7.59 [m, 9H]; 3.54 [s, 3H]. ^{13}C NMR [$CDCl_3$]: (ppm) = 165.21 (C=O); 158.51 [C(1)], 111.65 [C(2)], 117.74–135.03 [C(3–13)], 56.68 [C(8)].

[$HONCH_3C_6H_4C(O)C_6H_4NO_2$-2] (**$HL_6$**). Yellow solid. Yield: 73%. Melting point: 172–173 °C. Elemental Analysis Calcd. (%) for $H_{12}C_{14}N_2O_4$: C 61.76, H 4.41, N 10.29. Found (%): C 60.37, H 4.02, N 10.68. Selected IR data (KBr pellets, cm^{-1}): 3084 (s, br, νO–H), 1679 (s, νC=O), 1534 (s, νC–N) and 917 (s, νNO). ^1H NMR [DMSO-d_6]: (ppm) = 10.60 [s, br, 1H, OH]; 7.36–8.14 [m, 8H]; 2.38 [s, 3H]. ^{13}C NMR [DMSO-d_6]: (ppm) = 166.01 (C=O); 145.56 [C(1)], 114.00 [C(2)], 121.87–142.32 [C(3–13)], 20.86 [C(14)].

Synthesis of complexes

The complexes (**1**–**6**) were synthesized by dissolving the free ligand (1 mM) and potassium hydroxide (1 mM) in 30 ml of methanol and stirred for 4 h at room temperature. Then added triphenyltin(IV) chloride (1 mM) dissolved in 15 ml of tetrahydrofuran (THF) and refluxed for 12–13 h. The solution was then cooled and filtered. The filtrate was placed under vacuum to evaporate the solvent to afford the crystals. In some cases the complexes are recrystallized in methanol.

[$Ph_3SnONCH_3C(O)C_6H_4I$-2] (**1**). Colorless crystals. Yield: 68%. Melting point: 153–154 °C. Elemental Analysis Calcd. (%) for $H_{22}C_{26}NO_2ISn$: C, 49.83; H, 3.54; N, 2.24; Sn, 19.01. Found (%): C, 49.61; H, 3.44; N, 2.34; Sn, 18.26. Selected IR data (KBr pellets, cm^{-1}): 1600 (s, νC=O), 1530 (s, νC–N), 953 (s, νNO), 439 (s, νSn–O) and 576 (s, νSn–C). ^1H NMR [600 MHz, $CDCl_3$]: (ppm) = 6.76 (m, 4H, $^3J(^1H–^1H)$ = 18 Hz, aromatic H in HL_1), 7.37 (m, 9H, *m*- and *p*-protons in $SnPh_3$), 7.74 (m, 6H, $^3J(^1H–Sn)$ = 24 Hz, *o*-protons in $SnPh_3$); 3.31 [s, 3H]. ^{13}C NMR [600 MHz, $CDCl_3$]: (ppm) = 163.69 (C=O); 94.02, 138.13 (C-2 and C-4 of HL_1) 131.37 (C-6 of HL_1), 128.28 (C-1 of $SnPh_3$, $^1J(^{13}C–Sn)$ = 96 Hz), 128.07 (C-5 of HL_1), 128.56 (C-3 and C-5 in $SnPh_3$, $^3J(^{13}C–Sn)$ = 234 Hz), 136.8 (C-2 and C-6 in $SnPh_3$, $^2J(^{13}C–Sn)$ = 96 Hz), 139.42 (C-1 of HL_1), 128.95 (C-4 in $SnPh_3$), 144.48 (C-3 of HL_1); 39.29 (N–C). ^{119}Sn NMR [$CDCl_3$]: (ppm) = −147.

[$Ph_3SnONCH_3C(O)C_6H_4NO_2$-2] (**2**). Yellow crystals. Yield: 74%. Melting point: 134–135 °C. Elemental Analysis Calcd. (%) for $H_{22}C_{26}N_2O_4Sn$: C, 57.23; H, 4.07; N, 5.14; Sn, 21.83. Found (%): C, 56.87; H, 3.83; N, 5.78; Sn, 20.27. Selected IR data (KBr pellets, cm^{-1}): 1603 (s, νC=O), 1527 (s, νC–N), 937 (s, νNO), 450 (s, νSn–O) and 507 (s, νSn–C). ^1H NMR [600 MHz, DMSO-d_6]: (ppm) = 8.23 (m,