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Synthesis and characterization of tributyltin derivatives from 4-oxo-4-(arylamino)butanoic acids and their *in vitro* biological activity against cervical cancer cell lines

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Uterine (cervix and corpus) cancer is one of the major causes of mortality in women in Mexico. Organotin carboxylated derivatives have shown high cytotoxic activity against various cell lines of human origin. We describe the synthesis of three new tri-*n*-butyltin derivatives from 4-oxo-4-(arylamino)butanoic acids; their structures were confirmed using spectral data (^{1}H NMR, ^{13}C NMR, ^{119}Sn NMR and infrared), elemental analyses, mass spectrometry and X-ray diffraction. All the tri-*n*-butyltin carboxylates exhibit ^{1}J ($^{119/117}$Sn–^{13}C) coupling satellites in solution and lie in the range 357 to 339 Hz, suggesting a tetrahedral geometry around the tin atom. The polymeric structures of two of the derivatives and the monomeric structure of another were confirmed using X-ray crystallography. Using succinic anhydride as raw material, five N-substituted succinamic acid compounds were synthesized by the acylation reaction with aniline, 4-nitroaniline, 4-nitro-3-(trifluoromethyl)aniline, 2-amino-5-nitrothiazole and 4-aminoantipyrine. From these compounds, five tin derivatives were prepared and their *in vitro* anti-proliferative effect on HeLa, CaSki and ViBo cell lines was screened. All of the compounds showed potency against all three strains and null or low cytotoxic activity (necrotic) as well. The most potent of our derivatives as an anti-proliferative agent against the three cell lines was tributylstannyl 4-oxo-4-[(3-trifluoromethyl-4-nitrophen-1-yl)amino]butanoate, exhibiting an IC_{50} value of 0.43 μM against the HeLa cell line. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: tributyltin(IV); 4-oxobutanoic acid; X-ray diffraction; HeLa; CaSki; ViBo

Introduction

Tri-*n*-butyl- and tri-phenyltin(IV) carboxylated derivatives have been shown to have high cytotoxic activity against various cell lines of human origin as described in the literature.[1–5]

An increased concentration of intracellular calcium ions appears to be a contributing factor to triorganotin-induced apoptosis in many cell lines.[6]

In Mexico, uterine (cervix and corpus) cancer is one of the major causes of mortality in women followed by breast cancer. In 2007 the number of deaths per 100 000 women from uterine and breast cancer was 4540 and 4518, respectively.[7] Furthermore, cervical carcinoma is the third most common malignant disease in women worldwide.[8]

For the aforementioned reason, our group continues to search for new organotin compounds that are effective antineoplastic agents. In order to set up structure–activity relationships for tributyltin compounds with 4-oxo-4-arylaminobutanoic ligands, the influence of the type of aromatic ring and the nitro- or trifluoromethyl substituents on the anti-proliferative activity was studied.

In a literature search, a report was found in which 2-substituted thiazole analogs connected to 3-(substituted amino)propanamido function contributed to antitumor activity against several cell lines.[9] Furthermore, the incorporation of a 5-nitro-2-aminothiazole ring moiety in some compounds contributed to high giardicidal bioactivity in the nanomolar range.[10]

Jha *et al.* have shown that only the methyl ester of 1,4-dioxo-2-butenyl group in derivatives of arylamines has activity against human Molt 4/C8 and CEM T-lymphocytes as well as murine L1210 cells, with IC_{50} values in the range 2.2–37 μM.[11]

Recently Nitulescu *et al.* described evidence of the inhibitory potency of 3-aminopyrazole derivatives on protein kinases which play a central role in cell signaling and are involved in malignant pathologies.[12]

Based on our experience and a literature survey, compounds **3a–e** were chosen as synthetic targets (Scheme 1).

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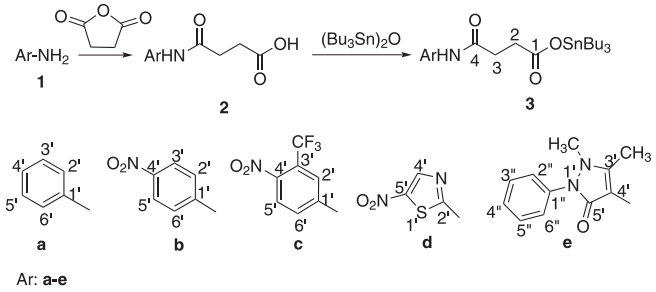

Scheme 1. Synthesis of tributyltin derivatives from 4-oxo-4-(arylamino) butanoic acids.

Experimental

Bis-tri-*n*-butyltin oxide, diazabicyclo[5.4.0]undec-7-ene (DBU), aniline, 4-nitroaniline, 5-nitro-2-aminopyrazol-5-one and 5-nitrothiazole were purchased from Aldrich and used without further purification. Succinic anhydride and 4-nitro-3-(trifluoromethyl)aniline were prepared by known methods. All solvents were freshly distilled before use following standard procedures.

^{1}H NMR spectra were obtained with a Varian spectrometer at 300 MHz. ^{13}C NMR and ^{119}Sn NMR spectra were recorded at 300 MHz with a Bruker Avance instrument operating at 75.43 MHz for ^{13}C and 111.17 MHz for ^{119}Sn using $CDCl_3$ and CD_3COCD_3 as solvents for compounds **3a–d** and DMSO-d_6 for **2b**, **2d** and **2e**, and tetramethylsilane as the internal standard for ^{1}H and tetramethyltin for ^{119}Sn. Multiplicity is given as s = singlet, d = doublet, t = triplet, brt = broad triplet, m = multiplet. Infrared spectra were recorded using a PerkinElmer Spectrum RXI spectrophotometer with the intensity of bands described as s, m and w for strong, medium and weak, respectively. Mass spectral analysis was varied out with a JEOL JMS AX505HA spectrometer at 70 eV and a JEOL AccuTOF DART. Ligands are denoted by L, and all *m/z* values are related to the most abundant natural isotope, ^{120}Sn. The relative abundance is given in parentheses. X-ray crystallographic data for **3a–c** were collected at 123 K using graphite monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation with a Bruker SMART APEX CCD diffractometer. The structures were solved by direct methods and refined using the full-matrix least squares procedure based on F^2 using the SHELXL-97 program.[13] Crystallographic data for structures **3a–c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1011611, CCDC 1011612 and CCDC 1011613. Elemental analyses were performed with an Eager 300 analyzer. Melting points were measured with a Fischer-Johns apparatus and are uncorrected.

Cell Culture

HeLa, CaSki and ViBo cell lines were purchased from the American Type Culture Collection (Rockville, MD) and were cultured in RPMI-1640 medium (Gibco, USA) containing 5% newborn calf serum (NCS; Gibco, USA) with phenol red, supplemented with benzylpenicillin. Cultures were maintained in a humidified atmosphere with 5% CO_2 at 37 °C. All cell-based assays were performed using cells in the exponential growth phase.

Cell Proliferation Assay

Assays were performed by seeding 7500 cells per well in 96-well tissue culture plates in a volume of 100 ml of RPMI-1640 medium supplemented with 5% NCS per well. Cells were allowed to grow for 24 h in the culture medium prior to determining the IC_{50} values for compounds. DMSO vehicle (1%) was added to control cells. Anti-proliferative activity (IC_{50}) was determined after 24 h using crystal violet staining.[14] Growth inhibition was determined by measuring the absorbance at 590 nm with an enzyme-linked immunosorbent assay plate reader (Tecan, USA).

Determination of Cytotoxicity

The cytotoxic activity was determined using an LDH Cytotoxicity Assay Kit (BioVision, USA) following the manufacturer's instructions. LDH (lactate dehydrogenase) oxidizes lactate to pyruvate which then reacts with the tetrazolium salt 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium to form formazan. The increase in the amount of formazan produced in the culture supernatant directly correlates with the increase in the number of lysed cells. The formazan dye is water-soluble and can be detected with a spectrophotometer at 500 nm.[15] Experimental data are presented as the mean ± standard deviation (SD) of three independent experiments with three repetitions; $^{*}p < 0.05$ versus 0 mg ml^{-1} (Tukey's *t*-test).

Statistical Analysis

The median and SD were calculated using Excel (Microsoft Office, version 2007). Statistical analysis of differences was performed by analysis of variance using SPSS 10.0 for Windows. A *p*-value of less than 0.05 (Tukey's *t*-test) was considered to be significant.

General Procedure for Synthesis of 4-Oxo-4-(arylamino)butanoic Acids (2a–e)

DBU (1.5 mol) was added dropwise to a solution of succinic anhydride (1.5 mol) and the appropriate amine (1.0 mol) in a mixture of 1,1,2,2-tetrachloroethane–carbon tetrachloride (3:1) in a flask under a nitrogen atmosphere. The mixture was stirred and refluxed for 24 h. After reflux, the reaction mixture was cooled to room temperature and most of the solvent evaporated. The organic layer was washed with 3 × 30 ml of 20% K_2CO_3 (aq.). The combined aqueous layer was acidified with 20% HCl until a solid formed (pH = 2–3). The product was filtered under suction and washed thoroughly with water.

The characterizations of compounds **2a**, **2b**, **2d**, **2e**, **3a** and **3b** are given in the supporting information.

*4-Oxo-4-(phenylamino)butanoic acid (**2a**)*

Succinic anhydride (0.230 g, 2.298 mmol), 0.1426 g (1.532 mmol) of aniline, 12.0 ml of carbon tetrachloride and 4.0 ml of 1,1,2,2-tetrachloroethane were used. The product was a white solid; m.p. 148–149 °C (lit.[16] 148.0 °C); yield 0.33 g (89.0%).

*4-Oxo-[(4-nitrophenyl)amino]butanoic acid (**2b**)*

Succinic anhydride (0.212 g, 2.11 mmol), 0.195 g (1.412 mmol) of 4-nitroaniline, 6.0 ml of carbon tetrachloride, 2.0 ml of 1,1,2,2-tetrachloroethane and 0.21 g (2.11 mmol) of DBU were used. The product was a yellow solid; m.p. 167–168 °C (lit. 196–197 °C[17a] and 201 °C[17b]); yield 0.246 g (73.1%).

*4-Oxo-4-[(3-trifluoromethyl-4-nitrophen-1-yl)amino]butanoic acid (**2c**)*

Succinic anhydride (0.430 g, 4.27 mmol), 0.600 g (2.91 mmol) of 4-nitro-3-(trifluoromethyl)aniline, 9.0 ml of carbon tetrachloride,

3.0 ml of 1,1,2,2-tetrachloroethane and 0.654 g (6.57 mmol) of DBU were used. The product was a light-brown solid; m.p. 161–165 °C; yield 0.462 g (51.7%). ^{1}H NMR (300 MHz, $CDCl_3$–CD_3COCD_3, δ, ppm): 10.40 (brs, 1H, COOH), 9.91 (s, 1H, NH), 8.31 (m, 1H, C2′-H), 8.08 (m, 2H, C5′-H, C6′-H), 2.78 (m, 2H, C3-H), 2.70 (m, 2H, C2-H). ^{13}C NMR (75.43 MHz, $CDCl_3$–CD_3COCD_3, δ, ppm): 174.1 (C1), 172.2 (C4), 144.6 (C1′), 142.9 (C4′), 128.1 (C5′), 124.9 (C3′) (q, ^{2}J (^{19}F–^{13}C) = 32.8 Hz), 123.2 (CF_3) (q, ^{1}J (^{19}F–^{13}C) = 270 Hz), 122.8 (C6′), 118.2 (C2′) (q, ^{3}J (^{19}F–^{13}C) = 5.5 Hz), 32.3 (C3), 28.9 (C2). FT-IR (KBr disc, cm^{-1}): 3368 s, 3097 m, 3057 m, 2939 m, 1722 s, 1615 s, 1553 s, 1518 s, 1437 m, 1421 m, 1331 s, 1275 s, 1249 s, 1156 s, 1140 s, 1040 m, 908 m, 858 w, 839 w, 801 w, 707 w, 669, 634 w, 516 w, 450 w. Anal. Found (calcd for $C_{11}H_9N_2O_5F_3$) (%): C, 43.09 (43.14); H, 2.91 (2.96); N, 9.06 (9.14). HRMS (ESI): calcd for $C_{11}H_{10}N_2O_5F_3$: 307.0541 [M + H$^+$], found: 307.0502.

*4-Oxo-4-[(5-nitro-1,3-thiazol-2-yl)amino]butanoic acid (**2d**)*

Succinic anhydride (0.723 g, 7.234 mmol), 0.70 g (4.822 mmol) of 2-amino-5-nitrothiazole (previously decolorized with activated charcoal in ethanol–acetone and recrystallized), 40.0 ml of carbon tetrachloride, 20.0 ml of 1,1,2,2-tetrachloroethane and 1.101 g (7.234 mmol) of DBU were used. The product was a light-brown solid; m.p. 228 °C (dec.) (lit.[19a] 274 °C); yield 0.858 g (72.6%).

*4-Oxo-4-[(2,3-dimethyl-5-oxo-1-phenyl-1,5-dihydro-1H-pyrazol-4-yl)amino]butanoic acid (**2e**)*

Succinic anhydride (0.134 g, 1.343 mmol), 0.210 g (1.033 mmol) of 4-aminoantipyrine and 20.0 ml of dichloromethane were used. The product was isolated by filtration and washed with dichloromethane to give a white solid; m.p. 194–196 °C (lit.[19b] 204–205 °C); yield 0.308 g (98.4%).

General Procedure for Synthesis of Tributyltin Esters (3a–e)

The method used is similar to that described in our earlier work.[20] Bis-tri-*n*-butyltin oxide (1.2 mmol) was added to the corresponding succinamic acids **2a–e** (1 mmol) in a mixture of absolute ethanol and dry toluene (1:3), and placed in a flask equipped with a Dean–Stark moisture trap, which was filled with dry toluene. The mixture was stirred and refluxed for 24 h. After reflux, the solvent was removed under reduced pressure. The resulting product was crystallized from dichloromethane–hexane.

*Tributylstannyl 4-oxo-4-(phenylamino)butanoate (**3a**)*

Bis(tributyltin)oxide (0.352 g, 0.597 mmol), 0.103 g (0.536 mmol) of **2a**, 21 ml of dry toluene and 7.0 ml of absolute ethanol were used. The product was a colorless oil. Recrystallization from dichloromethane–hexane gave 0.087 g of white crystals; m.p. 60–61 °C (lit. 61–62 °C[21a], lit. oil[21b]); yield 25.8%.

*Tributylstannyl 4-oxo-[(4-nitrophenyl)amino]butanoate (**3b**)*

Bis(tributyltin) oxide (0.6456 g, 1.083 mmol), 0.215 g (0.902 mmol) of **3b**, 12 ml of dry toluene and 4 ml of absolute ethanol were used. The product was a brown-yellow oil. Recrystallization from dichloromethane–hexane gave 0.344 g of brown-yellow crystals; m.p. 85–86 °C (lit.[22] 132–133 °C); yield 72.3%.

Anal. Found (calcd for $C_{22}H_{36}N_2O_5Sn$) (%): C, 50.07 (50.12); H, 6.77 (6.88); N, 5.32 (5.31). MS *m/z* (%): [LSnBu_2^+] 471 (100), [LSnBu_3-H$^+$] 527 (12.72), [LSnBu^+] 357 (15.19), [SnBu_3^+] 291 (18.02), [SnBu_2H$^+$] 235 (10.06), [SnBu^+] 177 (13.99).

*Tributylstannyl 4-oxo-4-[(3-trifluoromethyl-4-nitro-phen-1-yl)amino]butanoate (**3c**)*

Bis(tributyltin)oxide (464 mg, 0.78 mmol), 200 mg (0.65 mmol) of **2c**, 12.0 ml of dry toluene and 4.0 ml of absolute ethanol were used. The product was an orange oil. Recrystallization from dichlo romethane–hexane gave 94 mg of orange crystals; m.p. 55–58 °C; yield 24.2%.

^{1}H NMR (300 MHz,$CDCl_3$, δ, ppm): 9.64 (s, 1H, NH), 7.95–7.86 (m, 3H, C6′-H, C5′-H, C2′-H), 2.81–2.77 (m, 2H, CH_2COO), 2.68–2.64 (m, 2H, CH_2CON), 1.65–1.55 (m, 6H, Hβ), 1.40–1.17 (m, 12H, Hα,Hγ), 0.89 (t, 9H, *J* = 7.2 Hz, Hδ). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm): 179.1 (C1), 171.6 (C4), 142.7 (C4′/C1′),142.4 (C1′/C4′), 127.0 (C5′), 121.8 (CF_3) (q, ^{1}J (^{19}F–^{13}C) = 274 Hz), 125.1 (C3′) (q, ^{2}J (^{19}F–^{13}C) = 34 Hz), 121.5 (C6′), 117.8 (C2′) (q, ^{3}J (^{19}F–^{13}C) = 6 Hz), 33.6 (C2), 29.7 (C3), 27.7 (^{2}J($^{119/117}$Sn–^{13}C) = 18 Hz] (Cβ), 26.9 (^{3}J($^{119/117}$Sn–^{13}C) = 62 Hz) (Cγ), 16.7 (^{1}J($^{119/117}$Sn–^{13}C) = 352/337 Hz) (Cα), 13.5 (Cδ). ^{119}Sn NMR (111.81 MHz, $CDCl_3$, δ, ppm): 129.1. FT-IR (KBr disc, cm^{-1}): 3037 m, 3021 s, 2961 w, 2926 w, 2872 w, 1705 m, 1630 m, 1616 m, 1529 s, 1419 m, 1349 m, 1321 m, 1224 s, 1206 s, 1160 m, 1044 w, 927 w. Anal. Found (calcd for $C_{23}H_{35}F_3N_2O_5Sn$) (%): C, 46.39 (46.41); H, 5.93 (5.92); N, 4.69 (4.70). MS *m/z* (%): [Sn_2Bu_6COOH$^+$] 625 (100), [SnBu_3^+] 291 (35.71), [SnBu_2H$^+$] 235 (21.97), [SnBuH_2^+] 179 (96.15).

*Tributylstannyl 4-oxo-4-[(5-nitro-1,3-thiazol-2-yl)amino]butanoate (**3d**)*

Bis(tributyltin) oxide (1.096 g, 1.839 mmol), 0.410 g (1.672 mmol) of **2d**, 30.0 ml of dry toluene and 10.0 ml of absolute ethanol were used. The product was a brown-orange oil. Recrystallization from dichloromethane–hexane gave 0.505 g of brown-orange crystals; m.p. 134–135 °C; yield 56.5%.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 11.46 (s, 1H, NH), 8.58 (s, 1H, HC=), 2.79 (s, 4H, CH_2COO, CH_2CON), 1.59 (dt, 6H, *J* = 15.6, 7.5 Hz, Hβ), 1.37–1.25 (m, 12H, Hα, Hγ), 0.89 (t, 9H, *J* = 7.2 Hz, Hδ). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm): 177.8 (C1), 171.2 (C4), 161.5 (C2′), 143.3 (C5), 140.9 (C4′), 32.2 (C2), 29.9 (C3), 27.6 (^{2}J($^{119/117}$Sn–^{13}C) = 20 Hz) (Cβ), 26.9 (^{3}J($^{119/117}$Sn–^{13}C) = 64 Hz) (Cγ), 16.7 (^{1}J($^{119/117}$Sn–^{13}C) = 353/338 Hz) (Cα), 13.5 (Cδ). ^{119}Sn NMR (111.81 MHz, $CDCl_3$, δ, ppm):128.6. FT-IR (KBr disc, cm^{-1}): 3420 w, 3164 w, 2958 s, 2923 s, 2855 m, 1711 m, 1615 s, 1559 s, 1495 s, 1395 m, 1351 s, 1311 m, 1177 s, 1154 m, 1121 w, 880 w, 816 w, 670 w. Anal. Found (calcd for $C_{19}H_{33}N_3O_5SSn$) (%): C, 42.60 (42.71); H, 6.18 (6.23); N, 7.75 (7.87). MS *m/z* (%): [SnBu_3^+] 291 (100), [LSnBu_2^+] 478 (18.3), [SnBu_2H$^+$], 235 (52.11), [SnBu^+] 177 (60.56).

*Tributylstannyl 4-oxo-4-[(2,3-dimethyl-5-oxo-1-phenyl-1,5-dihydro-1H-pyrazol-4-yl)amino]butanoate (**3e**)*

Bis(tributyltin) oxide (0.7193 g, 1.206 mmol), 0.305 g (1.005 mmol) of **2e**, 40.0 ml of dry toluene and 13.5 ml of absolute ethanol were used. The product was a light-yellow oil. Recrystallization from dichloromethane–hexane gave 0.470 g of white crystals; m.p. 140–141 °C; yield 78.9%.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.90 (s, 1H, NH), 7.46–7.36 (m, 3H, C3″-H, C4″-H), 7.29–7.24 (m, 2H, C2″-H, C6″H), 3.04 (s, 3H, N–CH_3), 2.64 (m, 2H, C2-H), 2.60 (m, 2H, C3-H), 2.20 (s, 3H, =C–CH_3), 1.63–1.55 (m, 6H, Hβ), 1.36–1.21 (m, 12H, Hα, Hγ), 0.90 (t, 9H, *J* = 7.2 Hz, Hδ). ^{13}C NMR (75.43 MHz, $CDCl_3$, δ, ppm): 177.8 (C1), 171.3 (C4), 161.8 (C5′), 149.9 (C3′), 109.0 (C4′), 134.7 (C1″), 129.1 (C3″), 124.0 (C2″), 126.6 (C4″), 31.8 (C2), 36.2 (N–C), 30.2 (C3), 27.7 (^{2}J($^{119/117}$Sn–^{13}C) = 19 Hz) (Cβ), 26.9 (^{3}J($^{119/117}$Sn–^{13}C) = 65 Hz) (Cγ), 16.4 (^{1}J($^{119/117}$Sn–^{13}C) = 357/342 Hz) (Cα), 14.0 (=C–*C*), 13.6 (Cδ). ^{119}Sn (111.81 MHz, $CDCl_3$, δ, ppm): 109.1. FT-IR (KBr disc, cm^{-1}): 3239 m, 2955 s, 2924 s, 2869 m, 1687 s, 1643 s, 1624 s, 1580 s,

Table 1. Crystallographic data for compounds **3a**, **3b** and **3c**

Compound	3a	3b	3c
Formula	$C_{22}H_{37}NO_3Sn$	$C_{44}H_{72}N_4O_{10}Sn_2$	$C_{23}H_{35}F_3N_2O_5Sn$
Formula weight	482.21	1054.43	595.22
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2$
Flack parameter	—	—	0.467(18)
a (Å)	10.5400(16)	15.8466(16)	18.094(2)
b (Å)	14.642(2)	15.0360(15)	10.478(1)
c (Å)	15.809(3)	22.650(2)	28.130(3)
α (°)	90	90	90
β (°)	97.214	105.34	94.606 (2)
γ (°)	90	90	90
Volume (Å^3)	2420.5(7)	5204.5(9)	5315.8(11)
Z	4	4	8
Calculated density (Mg m^{-3})	1.323	1.346	1.487
μ (mm^{-1})	1.075	1.013	1.016
θ range (°) for data collection	1.903 to 27.484	1.644 to 27.491	1.77 to 25.40
Reflections collected/unique	16064/5519	35080/11888	41397/19192
Data/restraints/parameters	5519/0/250	11888/678/705	19192/530/1375
Goodness-of-fit on F^2	1.030	1.013	1.078
Final R indices[a] ($I > 2\sigma(I)$)	R1 = 0.0256, wR2 = 0.0.626	R1 = 0.0586, wR2 = 0.1294	R1 = 0.0514, wR2 = 0.1094
R indices[a] (all data)	R1 = 0.0306, wR2 = 0.0659	R1 = 0.1022 wR2 = 0.1561	R1 = 0.0633 wR2 = 0.1149
$\Delta\rho_{max}/\Delta\rho_{max}$ (e Å^{-3})	0.667 and −0.373	1.285 and −0.713	2.133 and −0.850

[a] $R1 = \sum||F_0|/|F_c||\sum|F_0|$; $wR2 = \left[\sum\left[w\left(F_0^2 - F_c^2\right)^2\right]/\sum\left[w\left(F_0^2\right)^2\right]\right]^{1/2}$.

Table 2. Selected bond lengths (Å) and angles (°) for compounds **3a–c**

3a		3b		3c	
Sn(1)–C(19)	2.134(2)	Sn(1)–C(19)	2.148(7)	Sn(1)–C(116)	2.130(6)
				Sn(2)–C(216)	2.120(6)
		Sn(2)–C(49)	2.168(7)	Sn(3)–C(316)	2.115(7)
				Sn(4)–C(416)	2.087(9)
Sn(1)–C(11)	2.139(2)	Sn(1)–C(11)	2.132(4)	Sn(1)–C(112)	2.127(5)
				Sn(2)–C(212)	2.147(6)
		Sn(2)–C(41)	2.142(8)	Sn(3)–C(312)	2.115(6)
				Sn(4)–C(412)	2.164(10)
Sn(1)–C(15)	2.148(2)	Sn(1)–C(15)	2.124(5)	Sn(1)–C(120)	2.154(6)
				Sn(2)–C(220)	2.153(6)
		Sn(2)–C(45)	2.115(7)	Sn(3)–C(320)	2.152(6)
				Sn(4)–C(420)	2.107(9)
Sn(1)–O(1)	2.148(1)	Sn(1)–O(1)	2.120(3)	Sn(1)–O(101)	2.071(4)
				Sn(2)–O(201)	2.042(4)
		Sn(2)–O(6)	2.099(4)	Sn(3)–O(301)	2.044(5)
				Sn(4)–O(401)	2.055(5)
Sn(1)–O(3)	2.572(1)	Sn(1)–O(8)	2.672(3)	Interaction not observed	
		Sn(2)…O(3)[I]	3.090(5)		
O(1)–C(1)	1.282(2)	O(1)–C(1)	1.289(5)	O(101)–C(101)	1.310(7)
				O(201)–C(201)	1.302(7)
		O(6)–C(31)	1.291(6)	O(301)–C(301)	1.311(7)
				O(401)–C(401)	1.285(8)
O(2)–C(1)	1.239(2)	O(2)–C(1)	1.227(5)	O(102)–C(101)	1.228(7)
				O(202)–C(201)	1.242(7)
		O(7)–C(31)	1.223(5)	O(302)–C(301)	1.204(7)
				O(402)–C(401)	1.240(7)
O(3)–C(4)	1.234(2)	O(3)–C(4)	1.223(6)	O(103)–C(104)	1.216(8)
				O(203)–C(204)	1.214(8)
		O(8)–C(34)	1.230(5)	O(303)–C(304)	1.206(8)
				O(403)–C(404)	1.213(8)

(Continues)

Table 2. (Continued)

3a		3b		3c	
N(1)–C(4)	1.343 (2)	N(1)–C(4)	1.350(6)	N(101)–C(104)	1.363(8)
				N(201)–C(204)	1.359(8)
		N(3)–C(34)	1.352(6)	N(301)–C(304)	1.361(8)
				N(401)–C(404)	1.375(8)
N(1)–C(5)	1.419 (3)	N(1)–C(5)	1.409(6)	N(101)–C(105)	1.394(8)
				N(201)–C(205)	1.401(9)
		N(3)–C(35)	1.404(6)	N(301)–C(305)	1.403(8)
				N(401)–C(405)	1.394(8)
C(19)–Sn(1)–C(11)	122.99 (8)	C(19)–Sn(1)–C(11)	115.2(6)	C(112)–Sn(1)–C(120)	113.6(2)
				C(212)–Sn(2)–C(220)	111.4(3)
		C(41)–Sn(2)–C(49)	131.3(6)	C(312)–Sn(3)–C(320)	113.4(3)
				C(420)–Sn(4)–C(412)	125.0(5)
C(19)–Sn(1)–C(15)	111.91 (8)	C(19)–Sn(1)–C(15)	124.1(4)	C(116)–Sn(1)–C(120)	110.2(2)
				C(216)–Sn(2)–C(220)	112.2(2)
		C(45)–Sn(2)–C(49)	104.3(6)	C(316)–Sn(3)–C(320)	112.3(3)
				C(416)–Sn(4)–C(420)	116.2(4)
O(1)–Sn(1)–C(19)	122.82 (8)	C(11)–Sn(1)–C(15)	116.4(2)	C(116)–Sn(1)–C(112)	121.6(2)
				C(216)–Sn(2)–C(212)	121.8(2)
		C(45)–Sn(2)–C(41)	113.9(6)	C(316)–Sn(3)–C(312)	121.3(3)
				C(416)–Sn(4)–C(412)	106.5(5)
O(1)–Sn(1)–C(19)	96.17 (7)	O(1)–Sn(1)–C(19)	100.1(6)	O(101)–Sn(1)–C(120)	94.9(2)
				O(201)–Sn(2)–C(220)	96.6(3)
		O(6)–Sn(2)–C(49)	93.3(5)	O(301)–Sn(3)–C(320)	95.4(3)
				O(401)–Sn(4)–C(420)	107.2(3)
O(1)–Sn(1)–C(11)	99.06 (7)	O(1)–Sn(1)–C(11)	100.69(17)	O(101)–Sn(1)–C(112)	105.4(2)
				O(201)–Sn(2)–C(212)	107.0(2)
		O(6)–Sn(2)–C(41)	107.3(6)	O(301)–Sn(3)–C(312)	105.9(2)
				O(401)–Sn(4)–C(412)	99.3(5)
O(1)–Sn(1)–C(15)	89.30 (7)	O(1)–Sn(1)–C(15)	89.96(19)	O(101)–Sn(1)–C(116)	107.2(2)
				O(201)–Sn(2)–C(216)	104.2(2)
		O(6)–Sn(2)–C(45)	100.9(6)	O(301)–Sn(3)–C(316)	104.3(3)
				O(401)–Sn(4)–C(416)	97.8(3)
C(19)–Sn(1)–O(3)^{II}	87.96 (7)	C(19)–Sn(1)–O(8)	83.7(6)	Interaction not observed	
C(11)–Sn(1)–O(3) ^{II}	81.80 (7)	C(11)–Sn(1)–O(8)	84.46(16)	Interaction not observed	
C(15)–Sn(1)–O(3) ^{II}	85.57 (7)	C(15)–Sn(1)–O(8)	81.49(19)	Interaction not observed	
O(1)–Sn(1)–O(3) ^{II}	174.36 (5)	O(1)–Sn(1)–O(8)	171.34(11)	Interaction not observed	

Symmetry code: I, $-1+x, y, z$; II, $x, -y+3/2, z-1/2$.

1488 m, 1426 m, 1386 m, 1341 s, 1313 s, 1193 s, 1169 m, 1075 w, 878 w, 761 m, 693 m, 670 m, 642 w, 568 w, 448 w. Anal. Found (calcd for $C_{27}H_{43}N_3O_4Sn$) (%): C, 54.60 (54.75); H, 7.23 (7.32); N, 7.01 (7.09). MS *m/z* (%): [L-OH$^+$] 285 (100), [LSnBu$_3$H$^+$] 594 (5.65), [LSnBu$_2^+$] 536 (24.38), [SnBu$^+$] 177 (9.86).

Results and Discussion

Syntheses

With succinic anhydride as the raw material, five N-substituted succinamic acid compounds **2a–e** were synthesized by the acylation reaction with the selected amine in the presence of DBU and yields ranging from 51 to 98% were obtained. Compounds **3a–e** were prepared by condensation of the appropriate compound **2a–e** with bis-tri-*n*-butyltin oxide in toluene–ethanol. Three of the organotin compounds are new and structures for all compounds are shown in Scheme 1.

Compound **2a** was prepared by Schreiber and Fernandez to investigate the reduction of succinimides, but there are no spectral data.[16a] Lee *et al.* presented the NMR analysis of **2a**.[16b] Compound **2b** was obtained by Neidle and co-workers as an intermediate in their work,[17b] and Rath *et al.* studied its X-ray diffraction.[17c] A Japanese patent has reported some proton signals for compound **2c**.[18] Antimicrobial activity has been found for compound **2e** and its ^{1}H NMR analysis reported.[19b] Samuel-Lewis *et al.*[21] and Kumar Das *et al.*[21] have reported the melting point and some IR bands for compound **3a**. Compound **3b** was reported by Shahid *et al.* and its insecticidal and antifungal activity was tested but its spectral data showed some incorrect assignments, such as the signals of the ^{1}H NMR spectrum in which the ethylene moiety is described at the highest downfield shift, and a triplet signal is assigned to the butyl groups. The ^{13}C NMR spectrum did not report the signals for the

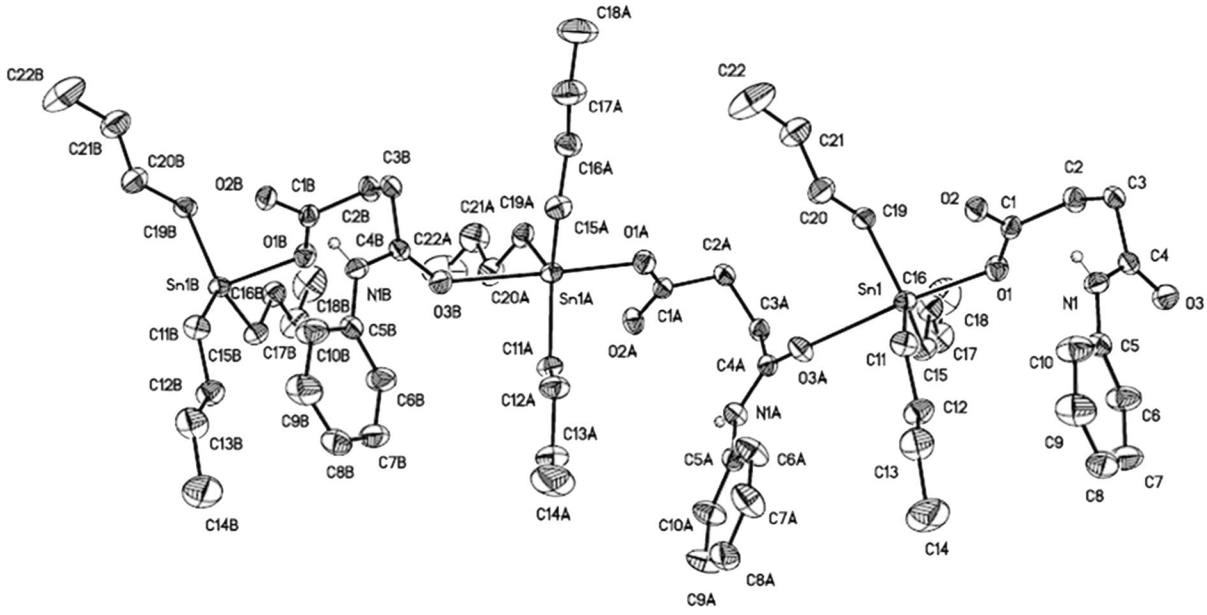

Figure 1. Molecular structure and crystallographic numbering scheme for **3a**. Ellipsoids represent a 50% probability level.

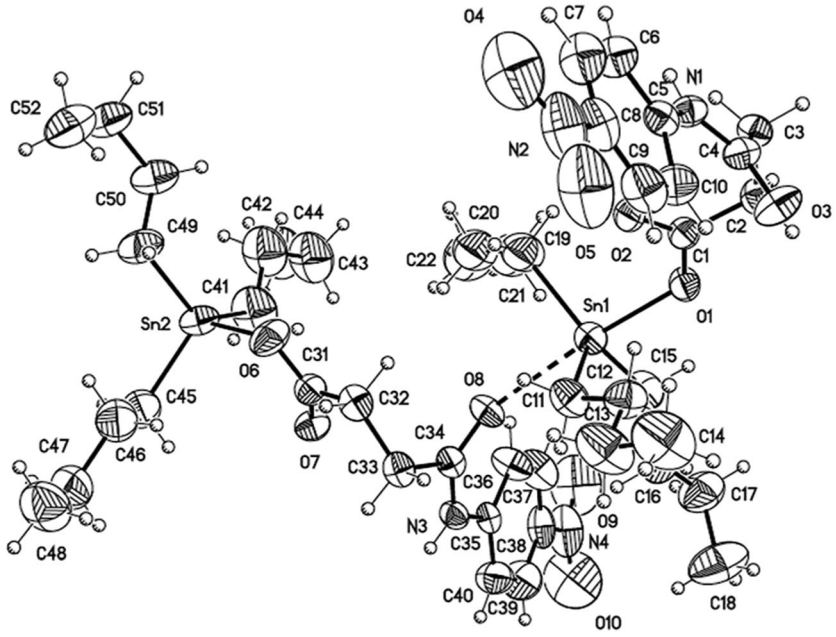

Figure 2. Molecular structure and crystallographic numbering scheme for **3b**. The probability level of ellipsoids is 30% (disorder not shown).

carboxylate group and for the ethylene moiety.[22] In our study, these compounds were obtained in greater yields and the crystallographic data of compounds **3a–c** are presented.

^{1}H NMR, ^{13}C NMR and ^{119}Sn NMR Spectroscopy

The ^{1}H NMR assignments of compounds **2c–e** and **3c–e** are described in the experimental section. Those of **2a**, **2b** and **3b** are given in the supporting information.

The assignment of ^{13}C NMR resonances of *n*-butyl groups in each of compounds **3a–e** is determined from the coupling constants ^{n}J ($^{119/117}$Sn–^{13}C) which are important parameters for characterization. All the tri-*n*-butyltin carboxylates exhibit ^{1}J ($^{119/117}$Sn–^{13}C) coupling satellites in solution in the range 357 to 339 Hz, suggesting a tetrahedral geometry around the tin atom.[23]

The ^{119}Sn NMR spectra of compounds **3a–e** exhibit a single resonance in solution ($CDCl_3$), with chemical shifts of 117.6, 124.8, 129.1, 128.6 and 109.1, respectively, which is characteristic of four-coordinated tri-*n*-butyl compounds.[24]

FT-IR Spectroscopy

The formation of compounds **2a–e** is supported by the appearance of the C=O band from the carboxyl group and the C=O band of the amide group in the regions 1687–1724 and 1560–1697 cm^{-1}, respectively.

In the spectra of the triorganotin derivatives **3a–e**, the absence of the O–H broad band between 3300 and 2800 cm^{-1} indicates the deprotonation of the COOH group during complex formation. The difference $\Delta\nu = \nu_{asym}(OCO) - \nu_{sym}(OCO)$ has been used for determining the structure of complexes.[25] It has been reported that differences larger than 250 cm^{-1} suggest that the ligand behaves as a monodentate one and differences less than 200 cm^{-1} are indicative of bridging. The $\Delta\nu$ values for our compounds range from 157 to 286 cm^{-1} and are as follows (cm^{-1}): **3a**, $\Delta\nu = 1654 - 1445 = 209$; **3b**, $\Delta\nu = 1670 - 1513 = 157$; **3c**, $\Delta\nu = 1705 - 1419 = 286$; **3d**, $\Delta\nu = 1711 - 1495 = 216$; **3e**, $\Delta\nu = 1687 - 1488 = 199$. From these results we can assume that in the solid state the compounds **3a**, **3b**, **3d** and **3e** present bridging structures, and the X-ray diffraction patterns of **3a** and **3b** agree with this assumption; each ligand

bridges two triorganotin moieties. For compound **3c**, a monodentate structure is expected, which is also confirmed by X-ray analysis.

Mass Spectrometry

Tin is the only element that has ten naturally occurring isotopes, and the mass spectra obtained for compounds **3a–d** show the characteristic peak patterns of molecules containing one tin atom.[26] The molecular ion peak in all derivatives is not observed, but the cleavage of butyl groups takes place with the successive loss of the second butyl group followed by the loss of the ligand. The fragment ions given in the experimental section are in good agreement with the expected structure of the compounds.

X-ray Diffraction

The molecular structures for the complexes **3a–c** are established using X-ray diffraction. Complexes **3b** and **3c** display orientational disorder of several of the *n*-butyl groups attached to the tin atoms, which is resolved as splitting of the groups over two main orientations. Table 1 gives a summary for the crystals and refined structures, while the selected bond lengths and bond angles are given in Table 2. The molecular structures of compounds **3a** and **3b** show that, in both cases, the 4-oxo-4-arylaminobutanoic acid behaves as a bidentate ligand, bridging two tin metal centers with the carboxylate group and the amido carbonyl group, giving rise to a five-coordinated tin structure (Figs. 1 and 2). The overall geometry of tin is a distorted trigonal bipyramid in which the equatorial plane is formed from the butyl groups of the triorganotin moiety, while the carboxyl oxygen and the carboxamide oxygen occupy the apical positions in **3a** and **3b**. Distortion from the ideal trigonal bipyramidal geometry for compounds **3a** and **3b** can be observed from small deviations (174.36(5)° and 171.34(11)°) from the ideal 180° for apical positions. Compound **3c** shows a distorted four-coordinated geometry and the 4-oxo-4-(arylamino)butanoic acid behaves as a monodentate ligand (Fig. 3). The butyl groups are involved in the disorder. The polymeric structure of the solid state for

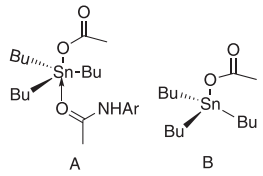

Figure 4. Structural arrangement of the tributyltin compounds.

compounds **3a** and **3b** of type A (Fig. 4) is therefore lost in solution to generate a four-coordinated tetrahedral structure of type B, whereas compound **3c** in the solid state shows a monomeric structure of type B. Besides the similar conformation of the ligands (scorpion-like) of the three complexes, one can observe a shortening of the C=O bond length in the oxo moiety and a lengthening of the C–N bonds of the amide moiety from complex **3a** to complex **3c** (Table 2). This trend could be due to the presence of the substituents in the arylamine for which the CF_3 group has a greater electron-withdrawing power than the NO_2 group, and therefore precluding the formation of a bridge between a second tin atom and the amido carbonyl group.

In Vitro Anti-proliferative Screening

With respect to the anti-proliferative activity of compounds **3a–e**, our findings establish that all compounds affect the proliferative potential of tumor cells, particularly **3c** which shows the highest anti-proliferative activity in the three tumor lines

Table 3. Anti-proliferative activity(IC_{50}, μM) of tributyltin compounds **3a–e** on human Hela, CaSki and ViBo cells lines

Compound	HeLa	CaSki	ViBo
3a	0.56 ± 0.03	4.9 ± 0.3	18.4 ± 1.3
3b	0.95 ± 0.07	1.3 ± 0.1	20.6 ± 1.5
3c	0.43 ± 0.02	1.05 ± 0.08	0.78 ± 0.05
3d	24.0 ± 1.4	4.7 ± 0.3	19.3 ± 1.1
3e	18.8 ± 1.3	1.22 ± 0.1	15.2 ± 0.9

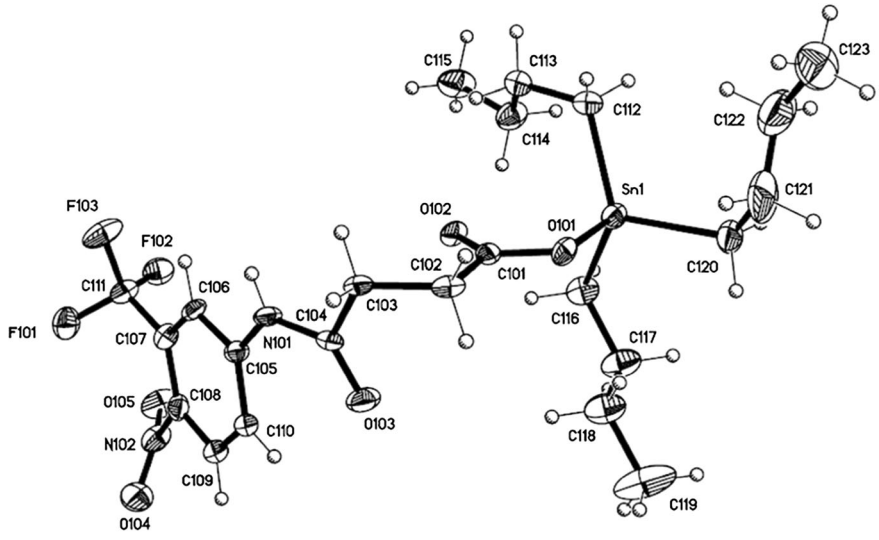

Figure 3. Molecular structure and crystallographic numbering scheme for **3c**, with ellipsoids at 40% probability level (only one of the four independent molecules is shown).

(Table 3), indicating that the aromatic ring with the CF_3 group is important for potentiating the anti-proliferative activity of these compounds over the other substituents present in the aromatic ring. Importantly, all the compounds have null or low cytotoxic activity (necrotic) in the three tumor cell lines, suggesting that the side effects associated with cytotoxic activity present in the compounds used could be decreased considerably (Table 4). It will be important in the future to test these compounds in non-tumor cell cultures with the intent of establishing whether these compounds have a

Table 4. Cytotoxicity ± SD of tributyltin compounds **3a–e**

	Triton X-100	Control	DMSO	**3a**	**3b**	**3c**	**3d**	**3e**
HeLa (%)	100 ± 1.7	17.5 ± 1.2	11.5 ± 0.4	18.6 ± 1.2	18.3 ± 1.5	18.3 ± 0.7	9.0 ± 0.3	10.6 ± 0.8
CaSki (%)	100 ± 1.8	19.5 ± 1.1	13.2 ± 0.7	3.9 ± 0.2	2.7 ± 0.1	24.6 ± 01.3	4.4 ± 0.2	2.4 ± 0.1
ViBo (%)	100 ± 1.5	1.4 ± 0.05	4.4 ± 0.2	3.8 ± 0.1	2.9 ± 0.1	1.8 ± 0.9	5.4 ± 0.3	2.1 ± 0.1

selective action. It is known that cisplatin affects the proliferative potential of the Jurkat (T lymphocyte leukemic) cell line at a concentration of 10 μM, whereas in the cervical cancer cell lines HeLa, SiHa and C33-A, it is 5.91 ± 0.30, 25.9 ± 0.51 and 13.25 ± 1.98 μM, respectively, suggesting that **3a–c** are more potent in HeLa cells than cisplatin. The fact that compounds **3a–e** exhibit anti-proliferative activity without showing cytotoxic activity makes them strong candidates to be studied as potential therapeutic agents against cancer.

Conclusions

The coupling constants ^{1}J ($^{119/117}$Sn–^{13}C) of the tributyltin group for all the compounds as well as the ^{119}Sn shifts (109–129 ppm) demonstrate that the compounds are four-coordinated in solution irrespective of their structure in the solid state.

The values of $\Delta\nu$ from the carboxylate groups in compounds **3a**, **3b**, **3d** and **3e** suggest that they form a bridging structure, whereas for **3c** its FT-IR data demonstrate that $\Delta\nu$ from the carboxylate group is typical for a monodentate structure in agreement with its X-ray analysis. The mass spectra of all obtained compounds show the characteristic peak patterns of molecules containing one tin atom.

The polymeric structures of the tributylstannyl esters of 4-oxobutanoic acid **3a** and **3b** in the solid state with the external amide carbonyl group bridging planar Bu_3Sn moieties were confirmed by X-ray crystallography. In contrast, **3c** was found to be a monomeric species.

In relation to the geometries in the solid state, X-ray analysis indicates a five-coordinated structure for **3a** and **3b** but a tetrahedral structure for **3c**, which can be ascribed to a 'slow' transition from trigonal bipyramidal geometry towards tetrahedral geometry due to the increasing electron-withdrawing effect of the substituents in the aromatic ring.

With respect to the anti-proliferative activity of compounds **3a–e**, it was found that all of them showed potency against all three strains investigated and null or low cytotoxic activity (necrotic). It was determined that the presence of the CF_3 group in compound **3c** provided it with the highest anti-proliferative activity in the three tumor lines compared to the other substituents present in the aromatic ring. The results make these compounds strong candidates to be studied as potential therapeutic agents against cancer.

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References

[1] a) A. J. Crowe in *Metal-Based Antitumour Drugs* (Ed.: M. Gielen), Freund Publishing, London, **1989**, p. 103; b) S. K. Hadjikakou, N. Hadjiliadis, *Coord. Chem. Rev.* **2009**, *253*, 235.
[2] M. Gielen, P. Lelieveld, D. De Vos, R. Willem in *Metal-Based Antitumour Drugs* (Ed.: M. Gielen), Freund Publishing, London, **1992**, p. 29.
[3] M. Gielen, E. R. T. Tiekink, *Metallotherapeutic Drugs and Metal-Based Diagnostic Agents*, Wiley, Chichester, **2005**, pp. 421.
[4] M. Gielen, *Coord. Chem. Rev.* **1996**, *151*, 41.
[5] C. C. Camacho, D. De Vos, B. Mahieu, M. Gielen, M. Kemmer, M. Biesemans, R. Willem, *Main Group Met. Chem.* **2000**, *23*, 381.
[6] A. Alama, B. Tasso, F. Novelli, F. Sparatore, *Drug Discov. Today* **2009**, *14*, 500.
[7] C. Bosetti, T. Rodríguez, L. Chatenoud, P. Bertuccio, F. Levi, E. Negri, C. La Vecchia, *Eur. J. Cancer Prev.* **2011**, *20*, 355.
[8] N. Hoti, J. Ma, S. Tabassum, Y. Wang, M. Wu, *J. Biochem.* **2003**, *134*, 521.
[9] S. M. El-Messery, G. S. Hassan, F. A. M. Al-Omary, H. I. El-Subbagh, *Eur. J. Med. Chem.* **2012**, *54*, 615.
[10] C. Nava-Zuazo, F. Chávez-Silva, R. Moo-Puc, M. J. Chan-Bacab, B. O. Ortega-Morales, H. Moreno-Díaz, D. Díaz-Coutiño, E. Hernández-Núñez, G. Navarrete-Vázquez, *Bioorg. Med. Chem.* **2014**, *22*, 1626.
[11] A. Jha, C. Mukherjee, A. K. Prasad, V. S. Parmar, M. Vadaparti, U. Das, E. De Clercq, J. Balzarini, J. P. Stables, A. S. R. K. Sharma, J. R. Dimmock, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1510.
[12] G. M. Nitulescu, C. Draghici, O. T. Olaru, *Int. J. Mol. Sci.* **2012**, *14*, 21805.
[13] G. M. Sheldrich, *Acta Crystallogr. A* **2008**, *64*, 112.
[14] W. Kueng, E. Silber, U. Eppenberger, *Anal. Biochem.* **1989**, *182*, 16.
[15] a) C. Legrand, J. M. Bour, C. Jacob, J. Capiaumont, A. Martial, A. Marc, M. Wudtke, G. Kretzmer, C. Demangel, D. Duval, J. Hache, *J. Biotechnol.* **1992**, *25*, 231; b) A. B. Lyons, J. Hasbold, P. D. Hodgkin, *Methods Cell Biol.* **2001**, *63*, 375.
[16] a) K. C. Schreiber, V. P. Fernandez, *J. Org. Chem.* **1961**, *26*, 1744; b) H.-S. Lee, J.-S. Yu, C.-K. Lee, *Magn. Reson. Chem.* **2009**, *47*, 711.
[17] a) S. Petersen, E. Müller, *Chem. Ber.* **1948**, *81*, 31; b) F. Cuenca, M. M. B. Moore, K. Johnson, B. Guyen, A. De Cian, S. Neidle, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5109; c) N. P. Rath, H. J. Ravindra, M. R. S. Kumar, S. M. Dharmaprakash, *Acta Crystallogr. E* **2007**, *63*, o4424.
[18] D. Nagai, Y. Akiyama, JP patent **2007**, 2007246405.
[19] a) N. P. Buu-Hoï, N. D. Xuong, F. Zajdela, *Bull. Soc. Chim. Fr.* **1955**, 1591; b) A. V. Dolzhenko, N. V. Kolotova, V. O. Koz'minykh, M. V. Vasilyuk, V. P. Kotegov, G. N. Novoselova, B. Y. Syropyatov, M. I. Vakhrin, *Pharm. Chem. J.* **2003**, *37*, 149; c) H. M. Aly, M. G. El-Gazzar, *Arzneim. Forsch.* **2012**, *62*, 105.
[20] C. Camacho-Camacho, I. Rojas-Oviedo, M. A. Paz-Sandoval, J. Cárdenas, A. Toscano, M. Gielen, L. Barron Sosa, F. Sánchez Bártez, I. Gracia-Mora, *Appl. Organometal. Chem.* **2008**, *22*, 171.
[21] a) A. Samuel-Lewis, P. J. Smith, J. H. Aupers, D. C. Povey, *J. Organometal. Chem.* **1991**, *402*, 319; b) V. G. Kumar Das, Y. Chee Keong, N. G. Seikweng, C. Wei, *J. Organometal. Chem.* **1986**, *311*, 289.
[22] K. Shahid, S. Shahzadi, S. Ali, M. Mazhar, *Bull. Korean Chem. Soc.* **2006**, *27*, 44.
[23] M. Nádvornik, J. Holocek, K. Handlir, A. Lycka, *J. Organometal. Chem.* **1984**, *275*, 43.
[24] R. Willem, A. Bouhdid, M. Biesemans, J. C. Martins, D. de Vos, E. R. T. Tiekink, M. Gielen, *J. Organometal. Chem.* **1996**, *514*, 203.
[25] J. Li, G. Zhao, G. Xiong, Y. Ma, *Synth. React. Inorg. Met. Org. Chem.* **2001**, *31*, 85.
[26] R. Jirásko, M. Holcapek, L. Kolárová, T. S. Basu Baul, *J. Mass Spectrom.* **2007**, *42*, 918.

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