Full Paper

Applied Organometallic Chemistry

Received: 19 November 2012 Revised: 1 January 2013 Accepted: 1 January 2013 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/aoc.2971

Synthesis, characterization and cytotoxic activity of 5,10,15,20-tetrakis [4-(triorganostannyloxy)phenyl]porphyrins

Laijin Tian[a]*, Xianxian Cao[a], Yanxiang Zhao[a], Jianzhuang Jiang[b] and Xijie Liu[c]

5,10,15,20-Tetrakis[4-(triorganostannyloxy)phenyl]porphyrins, $(R_3SnO)_4TPP$ [2, R = Cy (a), Ph (b), $PhC(CH_3)_2CH_2$ (c)], have been synthesized by the condensation of 4-(triorganostannyloxy)benzaldehyde, 4-$(R_3SnO)C_6H_4CHO$ (1), with pyrrole in the presence of BF_3 followed by oxidation by *p*-chloranil and characterized by means of elemental analysis, IR, UV–visible and NMR (^1H, ^{13}C and ^{119}Sn) spectra. The results of X-ray single-crystal diffraction show that 1a and 1b possess a *trans*-C_3SnO_2 trigonal bipyramidal geometry with the axial positions occupied by the phenolate oxygen and formyl group oxygen of an adjacent molecule and form a one-dimensional zigzag chain. In 2a, the macrocyclic core of the porphyrin is coplanar and each tin atom possesses a distorted tetrahedral geometry. These compounds (1 and 2) have potent *in vitro* cytotoxic activity against two human tumor cell lines – CoLo205 and MCF-7 – and the activity decreases in the order Ph > Cy > $PhC(CH_3)_2CH_2$ for the R group bound to tin.

Keywords: porphyrin; organotin complex; cytotoxic activity, crystal structure

Introduction

Porphyrins are naturally occurring biological compounds. Their photoelectric and biochemical properties open a wide field of applications in, for example, electronic/electro-optical and nonlinear optics,[1] selective catalysis[2] and material chemistry.[3] One of these applications is the well-known use of porphyrins as photodynamic therapy agents for cancer treatments in medicine. The curative effects of the photosensitizers are dependent on their photosensitive ability and drug effects.[4] To improve their functional properties, the structural modification of the porphyrins is a efficient method.[5] Second-generation photosensitizers, such as verteporfin (benzoporphyrin derivative monoacid ring A) and rostaporfin (tin ethyl etiopurpurin), are good examples.[5] Organotin compounds have found wide agricultural and industrial applications.[6] Recent studies have shown their relatively high *in vitro* cytotoxicities.[6,7] The organotin moiety and the ligand appear to play an important role in determining their cytotoxicities.[7] Thus the porphyrin derivatives with side chain containing organotin moieties can become the more efficient cytotoxic/antitumor agents.[8,9] In the recent past, only a few papers studied free-base porphyrin derivatives with organotin moieties. Several groups[9] synthesized $(R_2Sn)_2H_2TPPC$, $(R_3Sn)_4H_2TPPC$, $(R_2Sn)_2H_2TPPS$, $(R_3Sn)_4H_2TPPS$ (R = Me, *n*-Bu, Ph), and *n*-$Bu_2Sn(H_2TPyPPC)_2$ by the reactions of organotin oxide or hydroxide with H_6TPPC [5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin], H_6TPPS [5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrin] and $H_3TPyPPC$ [5-*p*-(carboxylmethoxy)phenyl-10,15,20-trispyridinylporphyrin], respectively, and reported their cytotoxic activity. In order to continue to expand the chemistry and therapeutic potential of the porphyrin-organotin compounds,we synthesized 5,10,15,20-tetrakis[4-(triorganostannyloxy)phenyl]porphyrins from 4-(triorganostannyloxy) benzaldehyde and pyrrole by Lindsey's method[10] (Scheme 1), and determined their cytotoxic activity.

Experimental

Materials and Physical Measurements

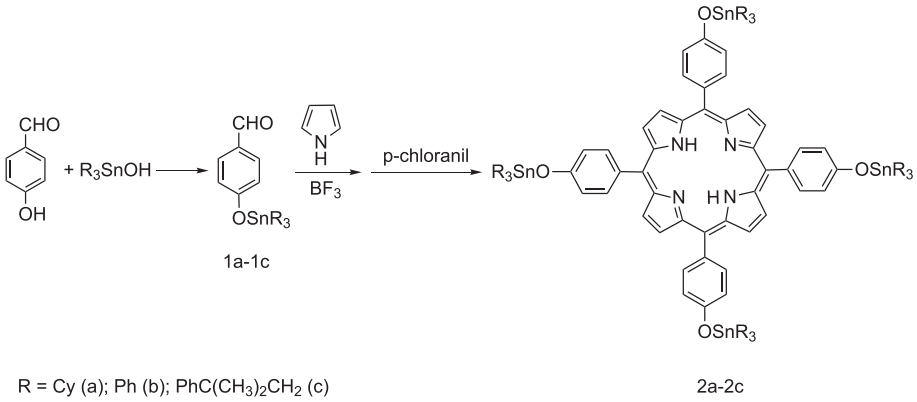
Pyrrole was distilled over CaH_2 under reduced pressure before use. CH_2Cl_2 was distilled from potassium carbonate and stored over 4 A molecular sieves. Tris(2-methyl-2-phenylpropyl)tin hydroxide was prepared according to the literature procedure.[11] Other chemicals were of reagent grade and were used without further purification. The melting points were measured on a WRS-1A digital melting point apparatus. Carbon, hydrogen and nitrogen analyses were obtained using a PerkinElmer 2400 Series II elemental analyzer. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1}. NMR spectral data were collected using a Bruker Avance DPX300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard for ^1H and ^{13}C, and $SnMe_4$ as external standard for ^{119}Sn. UV–visible spectra were obtained on an Agilent 8453 spectrophotometer.

* *Correspondence to: Laijin Tian, Key Laboratory of Natural Products and Pharmaceutical Intermediates, Qufu Normal University, Qufu 273165, China. E-mail: laijintian@163.com*

a *Key Laboratory of Natural Products and Pharmaceutical Intermediates, Qufu Normal University, Qufu 273165, China*

b *School of Chemistry and Biological Engineering, University of Science and Technology Beijing, Beijing 100083, China*

c *Beijing Centaurus BioPharma Technology Co. Ltd, Beijing 100089, China*



Scheme 1. Synthetic route of compounds.

Synthesis of 4-(Triorganostannyloxy)benzaldehydes (1a–1c)

To a suspension of triorganotin hydroxide (5 mmol) in 60 ml toluene was added 4-hydroxybenzaldehyde (0.61 g, 5 mmol). The reaction mixtures were heated under reflux for 6 h with a Dean–Stark separator, and then allowed to cool to room temperature. The solution was filtered and the solvent was removed under reduced pressure. The resulting white solid was recrystallized from chloroform–hexane (1:2). The yield, melting point and spectral data for compounds **1a–1c** were as follows.

*4-(Tricyclohexylstannyloxy)benzaldehyde, 4-(Cy_3SnO)C_6H_4CHO (**1a**)*

Yield 86%; m.p. 84.8–85.6°C. Anal. Calcd for $C_{25}H_{38}O_2Sn$ (%): C 61.37, H 7.83. Found: C 61.43, H 7.71. IR cm^{-1}: 1644 (C=O), 1316 (C-O), 528 (Sn-O). ^1H NMR δ: 9.79 (s, 1H, CHO), 7.72 (d, 2H, J = 8.4 Hz, H-2 of C_6H_4), 6.73 (d, 2H, J = 8.4 Hz, H-3 of C_6H_4), 2.00–1.30 (33H, m, Cy). ^{13}C NMR δ: 191.06 (C=O), 163.84 (C-4), 132.05 (C-2), 129.94 (C-1), 115.62 (C-3), 33.97 ($^1J(^{119/117}Sn\text{-}^{13}C)$ = 334/320 Hz, C-α), 31.32 ($^2J(^{119}Sn\text{-}^{13}C)$ = 15 Hz, C-β), 29.19 ($^3J(^{119}Sn\text{-}^{13}C)$ = 64 Hz, C-γ), 27.16 ppm (C-δ). ^{119}Sn NMR δ: 12.3.

*4-(Triphenylstannyloxy)benzaldehyde, 4-(Ph_3SnO)C_6H_4CHO (**1b**)*

Yield 86%; m.p. 142.1–142.8°C. Anal. Calcd for $C_{25}H_{20}O_2Sn$ (%): C 63.73, H 4.28. Found: C 63.67, H 4.13. IR cm^{-1}: 1649 (C=O), 1301 (C-O), 536 (Sn-O). ^1H NMR δ: 9.73 (s, 1H, CHO), 7.69–7.66 (m, 6H, $^3J(^{119}Sn\text{–}H)$ = 54.0 Hz, *o*-H of Ph), 7.61(d, 2H, J = 8.0 Hz, H-2 of C_6H_4), 7.25–7.49 (m, 9H, *m*- and *p*-H of Ph), 6.82 (d, 2H, J = 8.0 Hz, H-3 of C_6H_4). ^{13}C NMR δ: 190.70 (C=O), 164.63(C-4), 138.17 ($^1J(^{119/117}Sn\text{-}^{13}C)$ = 640/612 Hz, C-*i* of PhSn), 137.43 ($^2J(^{119}Sn\text{-}^{13}C)$ = 48 Hz, C-*o* of PhSn), 131.93 (C-2), 130.44 ($^4J(^{119}Sn\text{-}^{13}C)$ = 14 Hz, C-*p* of PhSn), 129.97 (C-1), 128.97 ($^3J(^{119}Sn\text{-}^{13}C)$ = 64 Hz, C-*m* of PhSn), 114.86 (C-3). ^{119}Sn NMR δ: −104.4.

*4-[Tris(2-methyl-2-phenylpropyl)stannyloxy]benzaldehyde, 4-[($PhC(CH_3)_2CH_2)_3SnO$] C_6H_4CHO (**1c**)*

Yield 84%; m.p. 66.6–67.6°C. Anal. Calcd for $C_{37}H_{44}O_2Sn$ (%): C 69.50, H 6.94. Found: C 69.40, H 6.79. IR cm^{-1}: 1673 (C=O), 1298 (C-O), 541 (Sn-O). ^1H NMR δ: 9.82 (s, 1H, CHO), 7.72 (d, 2H, J = 8.8 Hz, H-2 of C_6H_4), 7.30 (dd, 6H, J =7.4, 7.4, *m*-H of Ph), 7.23 (t, 3H, J = 7.4, *p*-H of Ph), 7.06 (d, 6H, J = 7.4, *o*-H of Ph), 6.63 (d, 2H, J = 8.8 Hz, H-3 of C_6H_4), 1.19 (s, 18H, CH_3), 1.11 (s, 6H, $^2J(^{119}Sn\text{-}H)$ = 50.6 Hz, CH_2Sn). ^{13}C NMR δ: 190.46 (C=O), 163.89 (C-4), 151.04 (C-*i* of Ph), 131.96 (C-2), 129.98 (C-1), 128.55 (C-*m* of Ph), 126.07 (C-*p* of Ph), 125.50 (C-*o* of Ph), 115.87 (C-3), 37.86 (Ph-*C*), 33.96 ($^1J(^{119/117}Sn\text{-}^{13}C)$ = 348/332 Hz, CH_2Sn), 32.87 ($^3J(^{119}Sn\text{-}^{13}C)$ = 44 Hz, CH_3). ^{119}Sn NMR δ: 114.5.

Synthesis of 5,10,15,20-Tetrakis[4-(triorganostannyloxy)phenyl] porphyrins (2a–2c)

Pyrrole (0.201 g, 3 mmol) and 4-(triorganostannyloxy)benzaldehyde (3 mmol) were added to dichloromethane (300 ml) purged with argon for 30 min. The mixture was stirred and purged with argon for a further 10 min, after which a BF_3 etherate (0.142 g, 1 mmol) in methylene chloride was added. This reaction mixture was stirred for 2 h at room temperature. *p*-Chloranil (0.553 g, 2.25 mmol) was added, and then the mixture was stirred under reflux for 1 h. The solvent was evaporated to dryness, and the product was purified by silica gel column chromatography (CH_2Cl_2–*n*-C_6H_{14}, 4:3). The yield and spectral data for compounds **2a–2c** were as follows.

*5,10,15,20-Tetrakis[4-(tricyclohexylstannyloxy)phenyl]porphyrin (**2a**)*

Yield 16%. Anal. Calcd for $C_{116}H_{158}N_4O_4Sn_4$ (%): C 64.88, H 7.42, N 2.61. Found: C 64.46, H 7.27, N 2.49. IR cm^{-1}: 3316 (N-H), 1598, 1499, 1469, 1443, 1347 (=C-N), 1248 (C-O), 1106, 989, 840, 802, 735, 627, 540 (Sn-O). ^1H NMR δ: 8.90 (s, 8H, β-H of pyrrole), 8.11 (d, J = 8.0 Hz, 8H, *m*-H of OC_6H_4), 7.30 (d, J = 8.0 Hz, 8H, *o*-H of OC_6H_4), 2.08-1.34 (132H, m, Cy), −2.79 (s, 2H, NH). ^{13}C NMR δ: 156.90 (C-*i* of OC_6H_4), 146.06 (C-α of pyrrole), 137.24 (C-*p* of OC_6H_4), 135.10 (C-*m* of OC_6H_4), 131.61 (C-β of pyrrole), 119.74 (C-*meso*), 115.56 (C-*o* of OC_6H_4), 34.23 ($^1J(^{119}Sn\text{-}^{13}C)$ = 328 Hz, C-α), 31.33 (C-β), 29.16 (C-γ), 27.14 (C-δ). ^{119}Sn NMR δ: 9.6.

*5,10,15,20-Tetrakis[4-(triphenylstannyloxy)phenyl]porphyrin (**2b**)*

Yield 12%. Anal. Calcd for $C_{116}H_{86}N_4O_4Sn_4$ (%): C 67.15, H 4.18, N 2.70. Found: C 67.24, H 4.07, N 2.67. IR cm^{-1}: 3323 (N-H), 1604, 1586, 1506, 1467, 1432, 1346 (=C-N), 1224 (C-O), 1168, 1071, 966, 803, 730, 532 (Sn-O). ^1H NMR δ: 8.86 (s, 8H, β-H of pyrrole), 8.06 (d, J = 8.0 Hz, 8H, *m*-H of OC_6H_4), 7.68–7.64 (m, 24H, $^3J(^{119}Sn\text{-}H)$ = 54.6 Hz, *o*-H of Ph), 7.50–7.23 (m, 44H, *o*-H of OC_6H_4 and *m*- and *p*-H of Ph), −2.80 (s, 2H, NH). ^{13}C NMR δ: 157.03 (C-*i* of OC_6H_4), 146.26 (C-α of pyrrole), 137.86 ($^1J(^{119}Sn\text{-}^{13}C)$ = 632 Hz, C-*i* of PhSn), 137.56 (C-*p* of OC_6H_4), 137.19 ($^2J(^{119}Sn\text{-}^{13}C)$ = 44 Hz, C-*o* of PhSn), 135.29 (C-*m* of OC_6H_4), 131.47 (C-β of pyrrole), 130.13 (C-*p* of PhSn), 128.76 (C-*m* of PhSn), 119.67 (C-*meso*), 115.34 (C-*o* of OC_6H_4). ^{119}Sn NMR δ: −108.6.

*5,10,15,20-Tetrakis[4-(tris(2-methyl-2-phenylpropyl)stannyloxy)phenyl] porphyrin (**2c**)*

Yield 13%. Anal. Calcd for $C_{164}H_{182}N_4O_4Sn_4$ (%): C 71.68, H 6.68, N 2.04. Found: C 71.42, H 6.37, N 1.96. IR cm^{-1}: 3317 (N-H), 1596, 1496, 1468, 1442, 1360 (=C-N), 1264 (C-O), 1166, 1071, 964, 841, 803, 768, 741, 698, 627, 554 (Sn-O). ^{1}H NMR δ: 8.86 (s, 8H, β-H of pyrrole), 8.13 (d, 8H, $J = 8.4$ Hz, *m*-H of OC_6H_4), 7.36–7.21 (m, 44H, *o*-H of OC_6H_4 and *m*- and *p*-H of Ph), 7.06 (d, 24H, $J = 7.4$, *o*-H of Ph), 1.24 (s, 24H, $^2J(^{119}Sn\text{-}H) = 50.4$ Hz, CH_2Sn), 1.13 (s, 72H, CH_3), −2.77 (s, 2H, NH). ^{13}C NMR δ: 156.36 (C-*i* of OC_6H_4), 150.83 (C-*i* of Ph), 146.31 (C-α of pyrrole), 137.46 (C-*p* of OC_6H_4), 135.27 (C-*m* of OC_6H_4), 131.17 (C-β of pyrrole), 128.53 (C-*m* of Ph), 126.14 (C-*p* of Ph), 125.45 (C-*o* of Ph), 119.32 (C-*meso*), 115.13 (C-*o* of OC_6H_4), 37.84 (Ph-*C*), 34.01 ($^1J(^{119}Sn\text{-}^{13}C) = 340$ Hz, CH_2Sn), 32.76 (CH_3). ^{119}Sn NMR δ: 109.7.

X-Ray Crystallography

Single crystals of compounds **1a**, **1b** and **2a** were obtained from the slow evaporation of methanol solution of the respective compounds. Intensity data for the crystals were measured at 295(2) K on a Bruker Smart Apex area detector fitted with graphite monochromatized Mo-$K\alpha$ radiation (0.71073 Å) using the φ and ω scan technique. The structures were solved by direct methods and refined by a full-matrix least squares procedure based on F^2 using SHELX-97.[12] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed at calculated positions in the riding model approximation. In **1a**, the C atoms of a cyclohexyl group were disordered over two positions, and their site occupancies were refined to 0.55(5):0.45(5). For **2a**, the low single crystallinity and small size made it difficult to obtain good intensity data, which resulted in the relative high *R*-value. Crystallographic parameters and refinements of **1a**, **1b** and **2a** are listed in Table 1.

In Vitro Cytotoxicity

Cytotoxic activity was assayed against two human tumor cell lines: CoLo 205 (colon carcinoma cell) and MCF-7 (mammary tumor cell). The samples were prepared by dissolving the test compounds in DMSO, and by diluting the resultant solutions with water. In the assays, the final concentration of DMSO was <0.1% (the concentration used was found to be non-cytotoxic against tumor cells.). *In vitro* cytotoxic activity of the compounds was measured by the MTT assay according to the literature.[13] All cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated new-born calf serum at 37°C in a humidified 5% CO_2 incubator and were seeded into each well of 96-well plate and were fixed for 24 h. The following day, different concentrations of the test compounds were added. After incubation with various concentrations of test compounds for 72 h, the inhibition of cell proliferation was measured. The experiments were repeated three times for each test. Statistical significance was tested using Student's *t*-test ($p < 0.05$ was considered statistically significant). The dose causing 50% inhibition of cell growth (IC_{50}) was calculated as previously described.[14]

Results and Discussion

Synthesis

5,10,15,20-Tetrakis[4-(triorganostannyloxy)phenyl]porphyrins (**2**) were prepared according to the general route outlined in Scheme 1. 4-(Triorganostannyloxy)benzaldehydes (**1**) were synthesized from triorganotin

Table 1. Crystallographic and refinement data for **1a**, **1b** and **2a**

Compound	1a	1b	2a
Empirical formula	$C_{25}H_{38}O_2Sn$	$C_{25}H_{20}O_2Sn$	$C_{116}H_{158}N_4O_4Sn_4$
Formula weight	489.24	471.10	2147.22
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/c$	P-1
a (Å)	10.351(2)	8.6082(16)	11.831(3)
b (Å)	14.797(3)	18.137(3)	13.252(3)
c (Å)	16.241(3)	13.247(2)	17.965(4)
α (°)	90	90	79.247(4)
β (°)	93.669(2)	99.528(2)	87.249(5)
γ (°)	90	90	80.049(4)
Volume (Å^3)	2482.5(8)	2039.6(7)	2725.1(11)
Z	4	4	1
D_c (g cm^{-3})	1.309	1.534	1.308
μ (mm^{-1})	1.045	1.270	0.957
F(000)	1016	944	1114
Crystal size (mm)	0.20 × 0.30 × 0.44	0.10 × 0.26 × 0.38	0.01 × 0.02 × 0.12
Total reflections	18 089	14 209	11 641
Unique reflections	4 725 ($R_{int} = 0.032$)	3 755 ($R_{int} = 0.025$)	8 930 ($R_{int} = 0.087$)
Reflections with $I > 2\sigma(I)$	3 206	3 300	1 910
GOF on F^2	1.02	1.05	0.87
R indices [$I > 2\sigma(I)$]	$R = 0.053$, $wR = 0.147$	$R = 0.026$, $wR = 0.060$	$R = 0.096$, $wR = 0.234$
R indices (all data)	$R = 0.081$, $wR = 0.170$	$R = 0.031$, $wR = 0.062$	$R = 0.357$, $wR = 0.373$
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (e Å^{-3})	−0.44, 1.16	−0.42, 0.75	−0.43, 0.53
CCDC deposition no.	911366	911367	911368

hydroxides and 4-hydroxybenzaldehyde in toluene by azeotropic dehydration in ~85% yields. These compounds are white crystals and soluble in common organic solvents such as benzene, trichloromethane, acetone and methanol. The porphyrins **2a–2c** were synthesized following Lindsey's method.[10] This procedure (Scheme 1) consists of the condensation of 4-(triorganostannyloxy)benzaldehyde with pyrrole in the presence of BF_3 etherate, followed by oxidation by *p*-chloranil to afford **2a–2c** in 12–16% yields. **2a–2c** are purple crystals and soluble in benzene, dichloromethane, methanol, tetrahydrofuran and ethyl acetate.

Spectroscopic characterization

The infrared spectra of three 4-(triorganostannyloxy)benzaldehydes do not show a strong band at ~3200 cm^{-1} assigned to ν(OH), indicting the deprotonation of the phenolic oxygen of 4-hydroxybenzaldehyde upon complexation with tin atom.[15] It has further been confirmed by the appearance of a sharp band at ~540 cm^{-1} assignable to the Sn-O stretching vibration.[15,16] The stretching vibrations of phenolic C-O and C=O appear at 1298–1316 and 1644–1673 cm^{-1}, respectively. Compared with 4-hydroxybenzaldehyde (1670 cm^{-1}), the ν(C=O) bands of **1a** (1644 cm^{-1}) and **1b** (1649 cm^{-1}) undergo a shift to lower frequency by ~20 cm^{-1}, while that of **1c** (1673 cm^{-1}) shows almost no change. This indicates that in **1a** and **1b** there is carbonyl oxygen atom coordination to tin atom,[17] but in **1c** this is not the case. The C=O → Sn coordination decreases the double bond characteristic and vibration frequency of C=O. Thus it may be suggested that the tin atom in compounds **1a** and **1b** is five-coordinated and in **1c** is four-coordinated in the solid. In **2**, the disappearance of the ν(C=O) band and the appearance of the bands at 1465, 1350, and 965 cm^{-1}, assigned to the porphyrin skeletal modes,[18,19] indicate the formation of prophyrin rings. The absorption bands at ~3320 and ~1440 cm^{-1} are assigned to N-H stretching vibrations and the C-H bending vibrations of pyrrole, respectively.[19,20] The ν(C-O) and ν(Sn-O) are in agreement with those of **1a–1c**.

Figure 1 shows the UV–visible absorption of **2a–2c**. The porphyrin derivatives synthesized in this work show typical electronic spectra, with a Soret band near 420 nm and four less intense visible bands Q near 520, 550, 590, and 650 nm in CH_2Cl_2.[21] The absorption spectra of **2a–2c** are quite similar, indicating that the differences in substituting groups R_3Sn do not affect obviously the absorption properties.

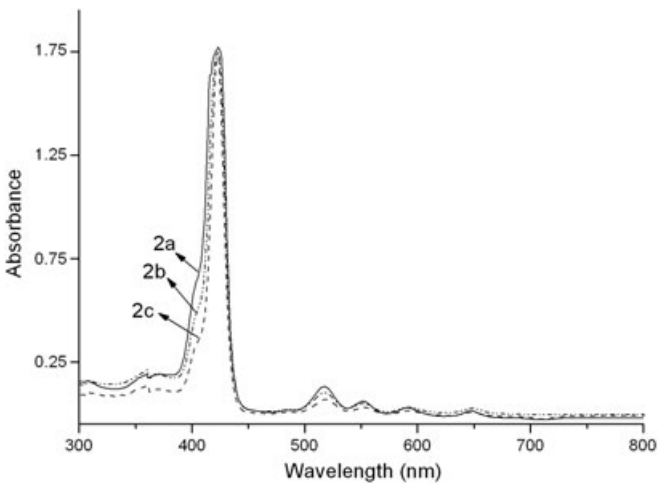


Figure 1. UV–visible absorption of **2a–2c** in CH_2Cl_2.

The ^{1}H NMR spectra of these compounds showed the expected resonances and integration. In **1a–1c**, the signals assigned to CHO proton appear in the range 9.73–9.82 ppm, and the signals of phenyl ring (C_6H_4) protons appear as doublets at ~7.70 and ~6.60 ppm, respectively. In **2a–2c**, single resonances of CHO proton are not observed, and NH and *β*-H of pyrrole rings appear as single peaks at −2.80 and 8.90 ppm, respectively, which confirms the presence of the porphyrin ring. The ^{13}C chemical shifts of the carbonyl carbon of aldehydes in **1a–1c** are at ~190 ppm. In **2a–2c**, the resonance signals of the *meso* carbons, *α* and *β* pyrrolic carbons appear at ~119, 131 and 146 ppm, respectively. In compounds **1** and **2**, coupling between tin nuclei and carbon can be observed, and the $^1J(^{119}Sn\text{-}^{13}C)$ is at ~330 Hz in **1a** and **2a**, ~630 Hz in **1b** and **2b**, and ~340 Hz in **1c** and **2c**. The ^{119}Sn NMR chemical shift and $^1J(^{119}Sn\text{-}^{13}C)$ values may be used to give tentative indications of the environment around the tin atoms.[22–24] Holecek and co-workers[22] have suggested that the ^{119}Sn chemical shifts and the coupling constants $^1J(^{119}Sn\text{-}^{13}C)$ for the four-coordinated triphenyltin compounds are in the range −40 to −120 ppm and 550–660 Hz, respectively. The ^{119}Sn NMR and $^1J(^{119}Sn\text{-}^{13}C)$ values observed in **1b** and **2b** are −104.4 ppm, 640 Hz and −108.6 ppm, 632 Hz, respectively, indicating that **1b** and **2b** are four-coordinated in $CDCl_3$ solution. For the four-coordinated trialkyltin compounds, the $^1J(^{13}C\text{-}^{119}Sn)$ values in $CDCl_3$ solution are in the range 295–390 Hz.[23,24] The ^{119}Sn NMR resonances and $^1J(^{119}Sn\text{-}^{13}C)$ of **1a** (12.3 ppm, 334 Hz), **1c** (114.5 ppm, 348 Hz), **2a** (9.6 ppm, 328 Hz) and **2c** (109.7 ppm, 340 Hz) are close to those of the corresponding four-coordinated triorganotin compounds,[23–26] suggesting that the tin atoms in these compounds are also four-coordinated in non-coordinating solvents.

X-Ray Structures of 1a, 1b and 2a

The structures of **1a**, **1b** and **2a** are shown in Figs (2–4) and the selected geometric parameters are given in Table 2. Compound **1a** (Fig. 2a) is a zigzag chain polymer associating via phenolate O(1) and formyl group O(2) in the ligand with a distance of 10.118(2) Å between two tin atoms (Fig. 3a). The Sn atoms in this polymeric structure exist in a distorted *trans*-C_3SnO_2 trigonal bipyramidal environment with the trigonal plane defined by the three cyclohexyl groups. The C-Sn-C angles are in the range 115.2(4)–123.1(3)°. The axial positions are occupied by the phenolate O(1) and formyl group $O(2)^{\#1}$ (symmetry code #1: $x-1/2, -y+3/2, z+1/2$) of the ligand of an adjacent molecule with an O(1)-Sn(1)-$O(2)^{\#1}$ angle of 178.20(17)°. The Sn(1)-$O(2)^{\#1}$ (2.712(5) Å) bond is significantly longer than the Sn(1)-O(1) (2.071(4) Å) bond, so that the Sn atom is displaced out of the C_3 trigonal plane of the *trans*-C_3SnO_2 trigonal bipyramidal polyhedron in the direction of the O(1) atom by 0.286(2) Å and the O(1)-Sn(1)-C angles (92.3(3)–101.7(3)°) are greater than the ideal 90°. There are few examples of triorganotin systems having ArCH=O → Sn; two examples are triphenyltin salicylaldehydate[17] and tribenzyltin 5-nitrovanillinate,[27] which feature the long O → Sn bond (2.459(5) and 2.494(1) Å, respectively). The O → Sn bond length in **1a** is longer than that in the two compounds mentioned above, which may be due to the bulky cyclohexyl groups bound on the tin. The Sn-C lengths from 2.110(7) to 2.139(8) Å are similar to those found in the five-coordinated chain tricyclohexyltin compounds such as $Cy_3SnN(SO_2CH_3)_2$[28] and $Cy_3SnOCOCH_2CH_2CH_3$.[29]

Compound **1b** (Fig. 2b) is also a zigzag chain polymer similar to **1a** in which the tin atom adopts a distorted *trans*-C_3SnO_2 trigonal bipyramidal geometry and the distance between two tin atoms is

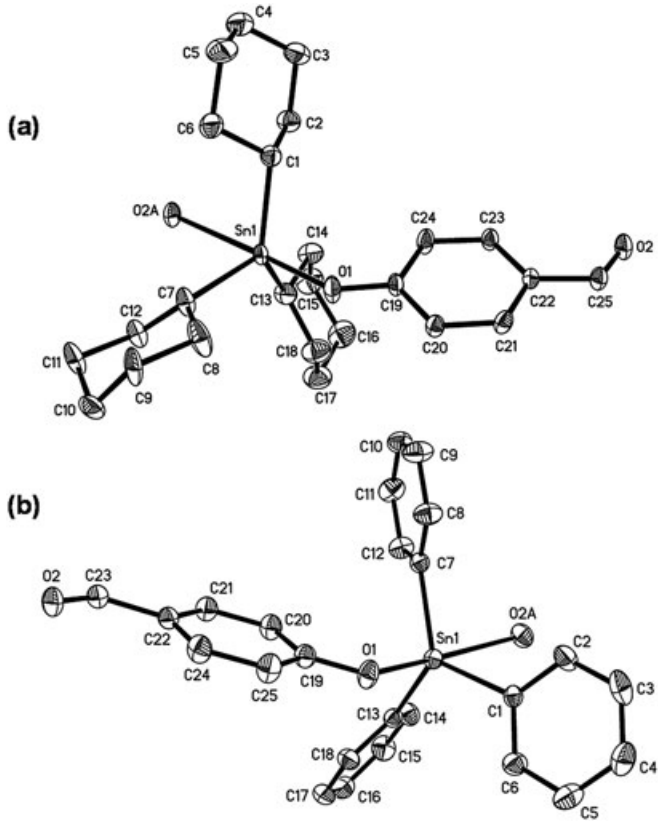


Figure 2. Coordination geometry of the tin atom in **1a** (a) and **1b** (b); symmetry code A: $x-1/2$, $-y+3/2$, $z+1/2$ for **1a** and $x+1$, $-y+1/2$, $z+1/2$ for **1b**; hydrogen atoms are omitted for clarity.

10.459(2) Å (Fig. 3b). The three C-Sn-C angles in the equatorial plane are 115.02(10), 117.70(10) and 123.18(9)°, respectively, which are consistent with those in **1a**, and the axial O(1)-Sn(1)-O(2)$^{\#2}$ (symmetry code #2: $x+1$, $-y+1/2$, $z+1/2$) angle (168.82(8)°) is significantly smaller than that of **1a** (178.20(17)°). The tin atom is 0.249(2) Å away from the C_3 trigonal plane in the direction of the more tightly held O(1) atom. The Sn(1)-C (2.114(2)-2.124(2) Å) and Sn(1)-O(2) (2.0741(19) Å) bond lengths are compared with those (2.105(7), −2.134(6) and 2.087(5) Å) of the reported analogue, triphenyltin salicylaldehydate.[17] However, the Sn(1)-O(2)$^{\#2}$ distance (2.601(2) Å) is longer than that of triphenyltin salicylaldehydate (2.459(5) Å).

In compound **2a** (Fig. 4), the porphyrin entity is located about a center of inversion. To the best of our knowledge, this is the first example of structural characterized free-base porphyrin derivatives with a side chain of organotin moieties. The macrocyclic core of the porphyrin is coplanar and the displacement of each atom in the equatorial mean plane is within ±0.073 Å. The dihedral angle between the benzene rings at the *meso* positions of porphyrin ring is 86.12(75)°, and the dihedral angles between the porphyrin ring and the benzene ring are 85.06(52)° and 87.67(48)°, respectively. The closest distance between two porphyrin plane centroids in the lattices is 11.831(45) Å, with a plane dihedral angle of 89.31(42)°, indicating the lack of any π–π overlapping between these porphyrin rings. The C-C and C-N bond lengths of the porphyrin ring in **2a** are in agreement with those reported in other free-base porphyrin compounds such as tetrakis(4-methoxyphenyl)porphyrin,[30] tetrakis(4-pentyloxyphenyl)porphyrin[31] and tetrakis[4-(carboxymethyleneoxy)phenyl]porphyrin.[32] Compound **2a** contains four tin atoms in which each tin atom possesses a distorted tetrahedral geometry. The four coordination atoms of the tin atom come from three carbon atoms of the cyclohexyl groups and a phenolate oxygen atom. The geometry parameters around tin atoms in the molecule do not differ from each other significantly. The ranges of the Sn(1)-C and Sn(2)-C bond distances and C-Sn(1)-C and C-Sn(2)-C bond angles are 2.13(5)–2.15(3) and 2.07(3)–2.11(3) Å, and 113(2)–121.5(14) and 115.2(19)–118.6(18)°, respectively, which are similar to those found in the tetrahedral $Cy_3SnOCOCH_2CH(C_6H_5)Ge(C_6H_4Me\text{-}4)_3$.[33]

In Vitro Cytotoxicity

Colon carcinoma and mammary cancers are common malignant tumors. In order to evaluate the cytotoxicity of the synthesized 4-(triorganostannyloxy)benzaldehyde and tetrakis[4-(triorganostannyloxy)phenyl]porphyrins, we tested the activity of all compounds against two human tumor cell lines: CoLo 205 and MCF-7. The results of the cytotoxic assay are shown in Table 3. These compounds are active and their cytotoxic activities are higher than those of the clinically widely used cisplatin, an anticancer metal-drug. The data from Table 3 also reveal that the porphyrin–organotin compounds **2** are more active than the triorganotin compounds **1**, which may be due to the differences of the numbers of tin atoms and the ligand. The ligand tetrakis(4-hydroxyphenyl)porphyrin accumulated preferentially in neoplastic tissues,[5,9] and enhanced the activity of compounds **2** in the cancer cells. The triphenyltin derivatives are the most active against the two cell lines and the activity decreases in the order $Ph > Cy > PhC(CH_3)_2CH_2$ for the R group bound to tin, which is consistent with our previous results on the triorganotin 2-phenyl-1,2,3-triazole-4-carboxylates, $2\text{-}PhC_2N_3CO_2SnR_3$.[34] Gielen *et al.*[35] found that the di- and triorganotin steroid carboxylates, crown ether carboxylates and fluorine-substituted carboxylates

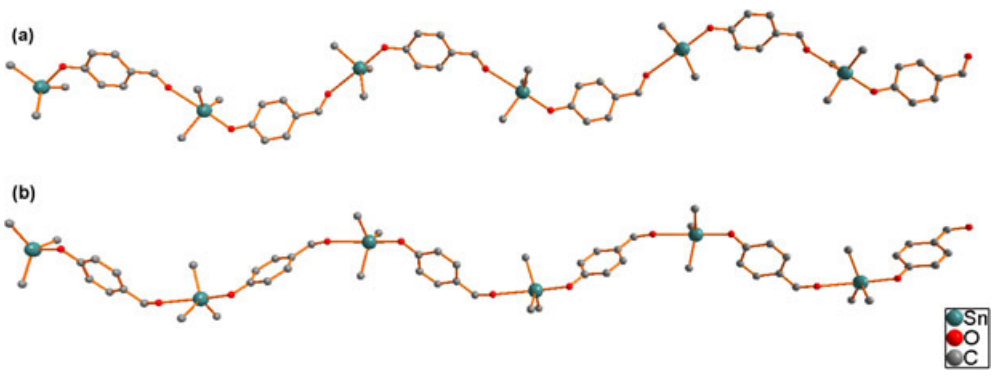


Figure 3. 1D zigzag chain formed in **1a** (a) and **1b** (b). The phenyl and cyclohexyl groups on the tin and all hydrogen atoms have been omitted for clarity.

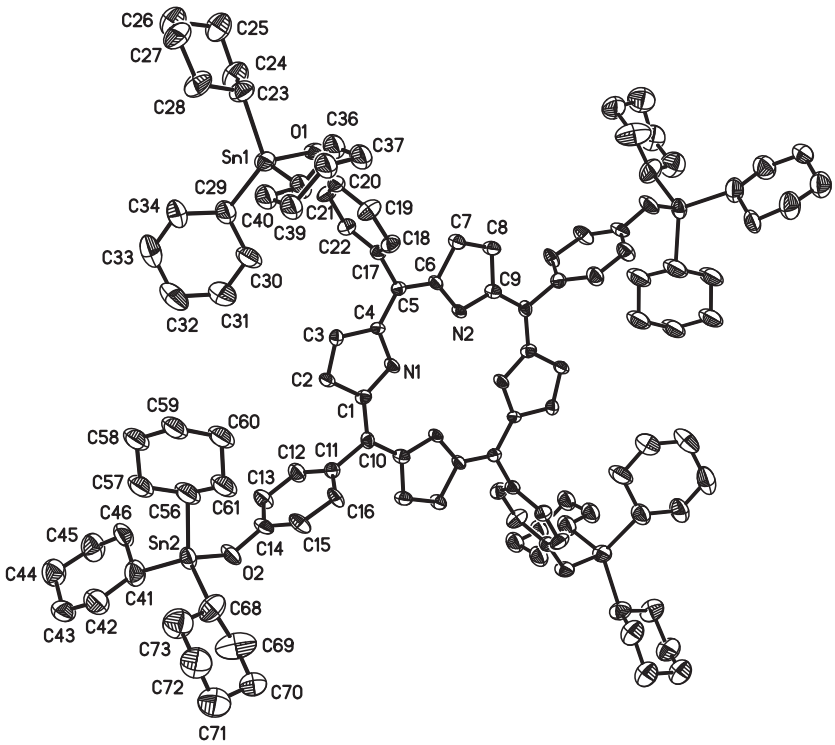


Figure 4. Molecular structure of **2a**; the molecule is centrosymmetric and only the asymmetric unit is labeled. Hydrogen atoms are omitted for clarity.

Table 2. Selected bond lengths (Å) and angles (°) for **1a**, **1b** and **2a**

1a					
Sn(1)-C(1)	2.132(7)	Sn(1)-C(13)	2.139(8)	Sn(1)-O(2)$^{\#1}$	2.712(5)
Sn(1)-C(7)	2.110(7)	Sn(1)-O(1)	2.071(4)	O(1)-C(19)	1.307(6)
O(1)-Sn(1)-C(7)	92.3(3)	C(7)-Sn(1)-C(13)	116.4(4)	C(1)-Sn(1)O(1)-Sn(1)-C(13)O(2)$^{\#1}$	82.3(3)
O(1)-Sn(1)-C(1)	98.7(3)	C(1)-Sn(1)-C(13)	123.1(3)	C(13)-Sn(1)-O(2)$^{\#1}$	78.9(3)
C(7)-Sn(1)-C(1)	115.2(4)	O(1)-Sn(1)-O(2)$^{\#1}$	178.20(17)	C(19)-O(1)-Sn(1)	133.6(4)
O(1)-Sn(1)-C(13)	101.7(3)	C(7)-Sn(1)-O(2)$^{\#1}$	85.9(3)	C(2)-C(1)-Sn(1)	115.7(5)
1b					
Sn(1)-C(1)	2.114(2)	Sn(1)-O(1)	2.0741(19)	Sn(1)-O(2)$^{\#2}$	2.601(2)
Sn(1)-C(7)	2.122(3)	Sn(1)-C(13)	2.124(2)	O(1)-C(19)	1.317(3)
O(1)-Sn(1)-C(1)	90.39(8)	C(1)-Sn(1)-C(13)	117.70(10)	C(7)-Sn(1)-O(2)$^{\#2}$	78.41(8)
O(1)-Sn(1)-C(7)	101.03(9)	C(7)-Sn(1)-C(13)	115.02(10)	C(13)-Sn(1)-O(2)$^{\#2}$	91.19(9)
C(1)-Sn(1)-C(7)	123.18(9)	O(1)-Sn(1)-O(2)$^{\#2}$	168.82(8)	C(19)-O(1)-Sn(1)	131.85(7)
O(1)-Sn(1)-C(13)	99.05(9)	C(1)-Sn(1)-O(2)$^{\#2}$	80.81(8)	C(2)-C(1)-Sn(1)	124.7(2)
2a					
Sn(1)-O(1)	1.978(13)	Sn(2)-C(41)	2.11(3)	N(2)-C(6)	1.362(19)
Sn(1)-C(23)	2.15(3)	Sn(2)-C(56)	2.10(3)	N(2)-C(9)	1.359(19)
Sn(1)-C(29)	2.15(3)	Sn(2)-C(68)	2.07(3)	O(1)-C(14)	1.35(2)
Sn(1)-C(35)	2.13(5)	N(1)-C(1)	1.36(2)	O(2)-C(20)	1.34(2)
Sn(2)-O(2)	1.967(15)	N(1)-C(4)	1.354(19)		
O(1)-Sn(1)-C(35)	103(2)	O(2)-Sn(2)-C(68)	105.1(17)	C(4)-N(1)-C(1)	109.8(15)
O(1)-Sn(1)-C(29)	103.1(9)	O(2)-Sn(2)-C(56)	104.4(12)	C(9)-N(2)-C(6)	108.2(14)
C(35)-Sn(1)-C(29)	113(2)	C(68)-Sn(2)-C(56)	115.2(19)	C(20)-O(1)-Sn(1)	124.4(12)
O(1)-Sn(1)-C(23)	97.4(10)	O(2)-Sn(2)-C(41)	94.1(12)	C(14)-O(2)-Sn(2)	129.5(14)
C(35)-Sn(1)-C(23)	114.8(19)	C(68)-Sn(2)-C(41)	118.6(18)	C(6)-C(5)-C(4)	123.7(17)
C(29)-Sn(1)-C(23)	121.5(14)	C(56)-Sn(2)-C(41)	115.1(17)	C(9)-C(10)-C(1)$^{\#3}$	124.7(17)

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

Table 3. Cytotoxic activity [IC_{50} (μmol l^{-1})] of compounds[a]

Compound	CoLo 205	MCF-7
1a	0.92 ± 0.06	0.97 ± 0.13
1b	0.46 ± 0.08	0.33 ± 0.04
1c	4.19 ± 0.12	2.06 ± 0.04
2a	0.27 ± 0.12	0.18 ± 0.08
2b	0.042 ± 0.011	0.019 ± 0.004
2c	2.13 ± 0.08	0.84 ± 0.06
Cisplatin	13.94 ± 0.47	18.73 ± 0.60

[a]The data represent mean ± standard deviation; $p < 0.01$ versus cisplatin in each cell line.

exhibited quite potent cytotoxicities against many human tumor cell lines, such as MCF-7, EVSAT, WiDr, IGROV, MI9, A498 and H226. The IC_{50} values of some dibutyl- and triphenyltin compounds against the cell lines were less than 1 ng ml^{-1}. Thus both the organotin moiety and the ligand appear to play an important role in the activity,[7,36,37] and further structural modification of organotin compounds would be valuable for enhancing cytotoxicity.

Conclusion

In summary, three novel tetrakis[4-(triorganostannyloxy)phenyl]-porphyrins have been synthesized from 4-(triorganostannyloxy) benzaldehyde and pyrrole by Lindsey's method and characterization. In solid state, compounds **1a** and **1b** possess a *trans*-C_3SnO_2 trigonal bipyramidal geometry and form an infinite zigzag chain by the coordination of formyl group oxygen to the tin atom of an adjacent molecule, while the tin atoms in **1c** and **2a–2c** adopt a distorted tetrahedral geometry. In the non-coordination solvent, these compounds exist as a monomeric structure with the four-coordinate tin atoms. These compounds have potent *in vitro* cytotoxic activity against two human tumor cell lines – CoLo205 and MCF-7 – and can be considered as excellent antitumor compounds for further study.

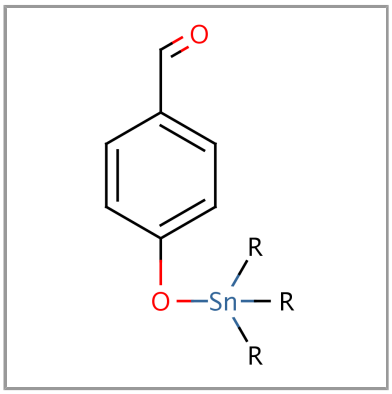
Acknowledgments

This work was supported by Shandong Provincial Natural Science Foundation, China (ZR2010BL012) and the National Natural Science Foundation of China (20931001; 21173126).

References

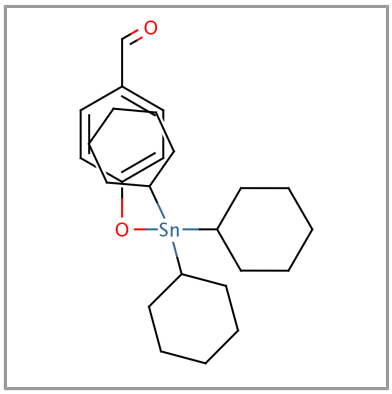
[1] a) V. S.-Y. Lin, S. G. DiMagno, M. J. Therien, *Science* **1994**, *264*, 1105; b) D. M. Guldi, *Chem. Soc. Rev.* **2002**, *31*, 22; c) M. Jurow, A. E. Schuckman, J. D. Batteas, C. M. Drain, *Coord. Chem. Rev.* **2010**, *254*, 2297; d) W. J. Cho, Y. Cho, S. K. Min, W. Y. Kim, K. S. Kim, *J. Am. Chem. Soc.* **2011**, *133*, 9364.
[2] a) P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, *J. Am. Chem. Soc.* **1996**, *118*, 5708; b) X.-L. Yang, M.-H. Xie, C. Zou, Y. He, B. Chen, M. O. Keeffe, C.-D. Wu, *J. Am. Chem. Soc.* **2012**, *134*, 10638; c) H. Srour, P. L. Maux, G. Simonneaux, *Inorg. Chem.* **2012**, *51*, 5850.
[3] a) C. M. Drain, A. Varotto, I. Radivojevic, *Chem. Rev.* **2009**, *109*, 1630; b) A. Uetomo, M. Kozaki, S. Suzuki, K. Yamanaka, O. Ito, K. Okada, *J. Am. Chem. Soc.* **2011**, *133*, 13276.
[4] a) R. A. Hsi, D. I. Rosenthal, E. Glatstein, *Drugs* **1999**, *57*, 725; b) A. Chiaviello, I. Postiglione, G. Palumbo, *Cancers* **2011**, *3*, 1014.
[5] a) K. Smith, N. Malatesti, N. Cauchon, D. Hunting, R. Lecomte, J. E. Lier, J. Greenman, R. W. Boyle, *Immunology* **2011**, *132*, 256; b) M. R. Detty, S. L. Gibson, S. J. Wagner, *J. Med. Chem.* **2004**, *47*, 3897; c) M. Ethirajan, Y. Chen, P. Joshy, R. K. Pandey, *Chem. Soc. Rev.* **2011**, *40*, 340.
[6] A. G. Davies, M. Gielen, K. H. Pannell, E. R. T. Tiekink, Tin Chemistry: Fundamentals, Frontiers, and Applications, Wiley, Chichester, **2008**.
[7] S. K. Hadjikakou, N. Hadjiliadis, *Coord. Chem. Rev.* **2009**, *253*, 235.
[8] a) C. Lottner, K.-C. Bart, G. Bernhardt, H. Brunner, *J. Med. Chem.* **2002**, *45*, 2079; b) C. Pellerito, M. Scopelliti, T. Fiore, L. Nagy, G. Barone, M. Abbate, G. C. Stocco, L. Pellerito, *J. Organomet. Chem.* **2006**, *691*, 1573.
[9] a) M. G. Mirisola, A. Pellerito, T. Fiore, G. C. Stocco, L. Pellerito, A. Cestelli, I. D. Liegro, *Appl. Organomet. Chem.* **1997**, *11*, 499; b) A. Pellerito, T. Fiore, A. M. Giuliani, F. Maggio, L. Pellerito, C. Mansueto, *Appl. Organomet. Chem.* **1997**, *11*, 707; c) G. Han, P. Yang, *J. Inorg. Biochem.* **2002**, *91*, 230.
[10] J. S. Lindsey, I. C. Schreiman, H. C. Hsu, P. C. Kearney, A. M. Marguerettaz, *J. Org. Chem.* **1987**, *52*, 827.
[11] W. T. Reichle, *Inorg. Chem.* **1966**, *5*, 87.
[12] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.
[13] F. Denizot, R. Lang, *J. Immunol. Methods* **1986**, *89*, 271.
[14] X.-L. Zheng, H.-X. Sun, X.-L. Liu, Y.-X. Chen, B.-C. Qian, *Acta Pharmacol. Sin.* **2004**, *25*, 109.
[15] M. Nath, R. Yadav, M. Gielen, H. Dalil, D. de Vos, G. Eng, *Appl. Organomet. Chem.* **1997**, *11*, 727.
[16] V. G. Kumar Das, N. S. Weng, P. J. Smith, *Inorg. Chim. Acta* **1982**, *49*, 149.
[17] B. D. James, L. M. Kivlighon, B. W. Skelton, A. H. White, *Appl. Organomet. Chem.* **1998**, *12*, 13.
[18] Y.-H. Zhang, D.-M. Chen, T.-J. He, F.-C. Liu, *Spectrochim. Acta Part A* **2003**, *59*, 87.
[19] D. W. Thomas, A. E. Martell, *J. Am. Chem. Soc.* **1959**, *81*, 5111.
[20] T. S. Rush, P. M. Kozlowski, C. A. Piffat, R. Kumble, M. Z. Zgierski, T. G. Spiro, *J. Phys. Chem. B* **2000**, *104*, 5020.
[21] S. S. Bozkurt, M. Merdivan, S. Ayata, *Spectrochim. Acta Part A* **2010**, *75*, 574.
[22] J. Holecek, M. Nadvornik, K. Handlir, A. Lycka, *J. Organomet. Chem.* **1983**, *241*, 177.
[23] D. Zhang, Q. Xie, J. Zheng, J. Li, S. Li, *Chinese J. Magn. Reson.* **1990**, *7*, 101.
[24] M. Nadvornik, J. Holecek, K. Handlir, A. Lycka, *J. Organomet. Chem.* **1984**, *275*, 43.
[25] E. Rafii, R. Faure, L. Lena, E.-J. Vincent, J. Metzger, *Anal. Chem.* **1985**, *57*, 2854.
[26] L. Tian, Q. Yu, X. Zheng, Z. Shang, X. Liu, B. Qian, *Appl. Organomet. Chem.* **2005**, *19*, 672.
[27] T. C. Keng, K. M. Lo, S. W. Ng, *Acta Cryst.* **2011**, *E67*, m710.
[28] A. Blaschette, I. Lange, J. Krahl, D. Koch, P. G. Jones, *J. Organomet. Chem.* **1994**, *467*, 169.
[29] R.-J. Wang, H.-G. Wang, X.-K. Yao, Q.-L. Xie, M.-D. Wang, *Acta Chim. Sin.* **1989**, *47*, 209.
[30] W. Chen, M. E. El-Khouly, S. Fukuzumi, *Inorg. Chem.* **2011**, *50*, 671.
[31] P. Ma, Y. Chen, X. Cai, H. Wang, Y. Zhang, Y. Gao, J. Jiang, *Synthetic Met.* **2010**, *160*, 510.
[32] A. Karmakar, I. Goldberg, *CrystEngComm* **2010**, *12*, 4095.
[33] I. Din, K. C. Molloy, M. Mazhar, S. Dastgir, S. Ali, M. F. Mahon, *Appl. Organomet. Chem.* **2003**, *17*, 781.
[34] L. Tian, Y. Sun, H. Li, X. Zheng, Y. Cheng, X. Liu, B. Qian, *J. Inorg. Biochem.* **2005**, *99*, 1646.
[35] a) M. Gielen, M. Biesemans, R. Willem, *Appl. Organomet. Chem.* **2005**, *19*, 440; b) R. Willem, A. Bouhdid, B. Mahieu, L. Ghys, M. Biesemans, E. R. T. Tiekink, D. de Vos, M. Gielen, *J. Organomet. Chem.* **1997**, *531*, 151.
[36] A. Alama, B. Tasso, F. Novelli, F. Sparatore, *Drug Discov. Today* **2009**, *14*, 500.
[37] M. Gielen, E.R.T. Tiekink, in Metallotherapeutic Drug and Metal-Based Diagnostic Agents: The Use of Metals in Medicine (Eds.: M. Gielen, E. R. T. Tiekink), Wiley, New York, **2005**, pp. 421–440.

1



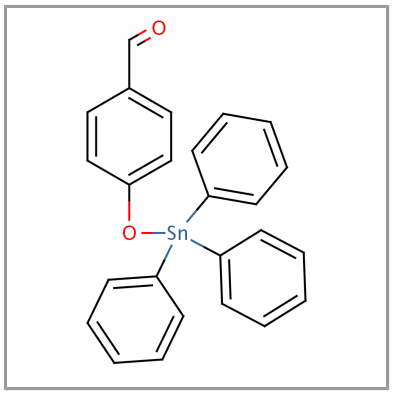
Compound Details Structure Search

1a



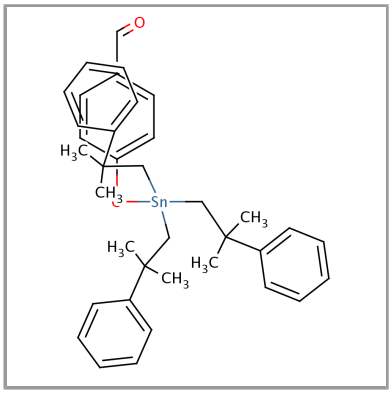
Compound Details Structure Search

1b



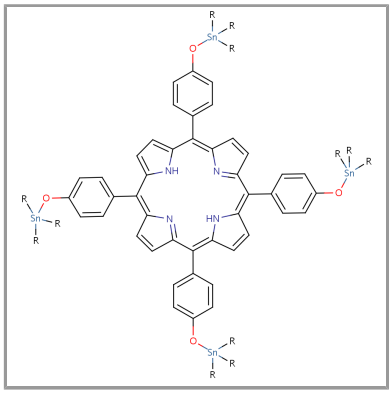
Compound Details Structure Search

1c



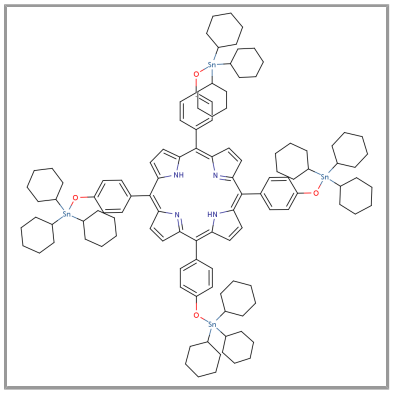
Compound Details Structure Search

2



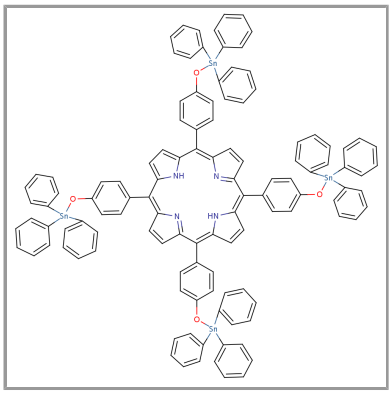
Compound Details Structure Search

2a



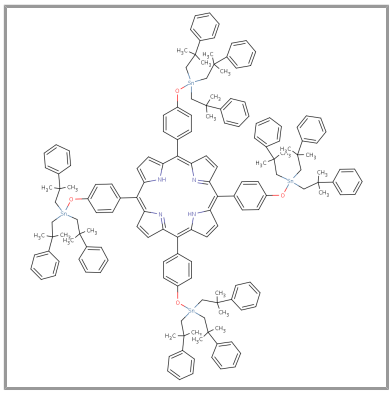
Compound Details Structure Search

2b



Compound Details Structure Search

2c



Compound Details Structure Search