Heptacoordinate Tin(IV) Compounds Derived from Pyridine Schiff Bases: Synthesis, Characterization, *in Vitro* Cytotoxicity, Anti-inflammatory and Antioxidant Activity

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Tin(IV) complexes 2a—q derived from pyridine Schiff bases were prepared and characterized. Four complexes of this series were evaluated *in vitro* against different carcinogenic cell lines; besides their anti-inflammatory and antioxidant properties were also tested. Combination of mass spectrometry, multinuclear NMR and X-ray diffraction techniques evidenced the formation of heptacoordinated monomeric species. The X-ray diffraction analysis of 2a, 2b, 2i, 2j and 2n led to establish the heptacoordination around the tin atom in solid state and also revealed that the ligand occupies the equatorial positions of the distorted pentagonal bipyramidal geometry and the two alkyl or aryl groups the axial positions. The *in-vitro* study for complexes 2a—d against six tumor cell lines showed varied antiproliferative activity, the IC_{50} for all tested complexes was lower than that of the *cis*-platin. Compounds 2a—d also exhibited anti-inflammatory activity where complex 2c resulted to be more active ($IC_{50}=0.11\ \mu M$) than the indomethacin $IC_{50}=0.27\ \mu M$ which was used as reference. The antioxidant activity in rat brain homogenate on inhibition of thiobarbituric acid reactive substances (TBARS) indicated that 2c ($IC_{50}=1.77\ \mu M$) is more active than the quercetine (4.11 μM) and α-tocopherol ($IC_{50}=569.09\ \mu M$).

Key words heptacoordinate tin(IV); cytotoxicity; antioxidant; anti-inflammatory

The organotin(IV) compounds have been the aim of several researches owing to both their versatile chemistry and potential as biologically active compounds. The longstanding and growing interest in these compounds has encouraged several studies which include preparation of catalysts for transesterification,[1] and for the synthesis of PGA (polymer of glycolic acid),[2] as well as in supramolecular architecture.[3] Among the most studied organotin(IV) complexes a special emphasis has been placed on the study of carboxylates as potential metallotherapeutic drugs,[4] however, a wide spectrum of biological activities such as anti-microbial,[5—10] anti-inflammatory,[11—15] anti-fungal,[14] cardiovascular,[5,10,16,17] anti-tuberculosis[18,19] and biocide among others remains a subject of intense study.[20]

Schiff bases are of paramount importance as ligands in metal coordination chemistry as they form stable complexes with most of transition metals. In the field of bioinorganic chemistry they are mainly used as synthetic models for metal containing sites in metalloproteins and enzymes.[21,22] The Schiff base–organotin complexes have received special attention in view of their chemistry and structural aspects of hypervalent species.[23—30] Regarding this, investigations concerning chelating properties and coordinative effects of 2,6-diacetylpyridine and its influence on the conformation and geometry of heptacoordinated tin complexes derived of hydrazones,[31,32] semicarbazones, thiosemicarbazones,[33—40] acylhydrazones,[41] have been undertaken. Our interest in organotin(IV) and organosilicon compounds containing pyridine moieties let us to study the influence and nature of the ligand substituents in the formation of pentacoordinate tin and silicon derivatives.[42,43] We recently reported the cytotoxic activity of pentacoordinated tin *o*-aminophenols derivatives which displayed outstanding cytotoxic activity and less damaged normal cells than the observed for the *cis*-platin.[44] Although there are a vast number of publications related to the biological activity of pentacoordinated tin complexes, few examples are known for seven coordinated tin complexes where more than one type of biological activity has been reported.[45] The aim of this work is to prepare and characterize structurally heptacoordinated tin(IV) derivatives containing pyridine moieties and evaluate their *in-vitro* anticancer, anti-inflammatory and anti-oxidant properties.

Experimental

2-Aminophenol, 2-amino-4-methylphenol, 2-amino-4-chlorophenol, 2-amino-4-nitrophenol, 2,6-diacetylpyridine, 2,6-dimethanolpyridine, selenium oxide, dimethyl, diphenyl and dibutyltin oxide, were obtained from Aldrich Chemical Co. The 2,6-pyridinedicarboxaldehyde was prepared according to the literature procedure.[46] ^{1}H-NMR, ^{13}C- and ^{13}C-CPMAS NMR spectra were recorded on a JEOL Eclipse +300 and Varian (75.4 MHz) spectrometers, respectively. Chemical shifts (ppm) are relative to $(CH_3)_4Si$, coupling constants are quoted in Hz. Melting points were measured on a Fisher Johns apparatus and are uncorrected. Mass spectra were obtained with a JEOL JMS-AX505 HA mass spectrometer. The DRIFTS spectra were recorded on a Bruker Tensor 27 spectrophotometer. Compound samples (in KBr) were placed in a sample cup inside a diffuse reflectance unit. Spectra were averaged over 40 scans in the range (210—4000 cm^{-1}) to a nominal 4 cm^{-1} resolution. The X-ray crystallographic studies were done on a Bruker Smart Apex CCD diffractometer $\lambda_{(MoK\alpha)}=0.71073$ Å, graphite monochromator, at $T=293$ K. All structures were solved by direct methods; all nonhydrogen atoms were refined anisotropically, using full-matrix least squares techniques. All hydrogen atoms were placed on idealized positions based on hybridization with thermal parameters fixed at 1.2 times (for –CH) and 1.5 (for $-CH_3$) the value of the attached atom. Structure solutions and refinements were performed using SHELXTL v 6.10.[47] Cell culture and assay for cytotoxic activity protocol has been described previously.[44]

CCDC 697623—697627 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of Schiff Bases The corresponding aminophenol and the appropriate aldehyde in a 1 : 2 molar ratio in 70 ml of ethanol or toluene were refluxed for the time indicated for each reaction with constant stirring; the water was eliminated with a Dean Stark funnel. After completion of the reaction, the solvent was removed under reduced pressure. Compound **1a** has been reported in the literature.[48,49]

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1a *N*,*N*′-(2,6-Pyridinediyldimethylidyne)bis(2-hydroxybenzenamine): 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde and 0.402 g (3.70 mmol) of 2-aminophenol, ethanol, 6 h, 0.56 g (95%) yield, yellow solid; mp 183—189 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.94 (2H, td, J=7.98, 1.3 Hz, H-7), 7.04 (2H, dd, J=8.2, 1.3 Hz, H-6), 7.26 (2H, td, J=8.2, 1.5 Hz, H-8), 7.43 (2H, dd, J=8.1, 1.3 Hz, H-9), 7.96 (1H, t, J=7.7 Hz, H-1), 8.28 (2H, d, J=7.8 Hz, H-2), 8.88 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 116.9 (C-9), 120.1 (C-6), 120.3 (C-7), 123.5 (C-2), 129.0 (C-8), 137.1 (C-1), 138.1 (C-5), 152.1 (C-10), 155.0 (C-3), 159.1 (C-4); IR ν_{max} (KBr): 3446 (O–H), 1623 (C=N) cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 317] (100), 210 (92), 197 (10).

1b *N*,*N*′-(2,6-Pyridinediyldimethylidyne)bis(2-hydroxy-5-methylbenzenamine): 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde and 0.455 g (3.70 mmol) of 2-amino-4-methylphenol, ethanol, 6 h, 0.61 g (98%) yield, yellow solid; mp 170—174 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.65 (6H, s, H-11), 6.21 (2H, d, J=8.2 Hz, H-8), 6.33 (2H, dd, J=8.2, 1.5 Hz, H-9), 6.47 (2H, s, H-6), 7.33 (1H, t, J= 7.8 Hz, H-1), 7.81 (2H, d, J=7.8 Hz, H-2), 8.16 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.1 (C-11), 115.7 (C-9), 118.3 (C-6), 123.0 (C-2), 128.3 (C-7), 129.1 (C-8), 135.3 (C-5), 136.8 (C-1), 149.5 (C-10), 154.2 (C-3), 157.1 (C-4); IR ν_{max} (KBr): 3400 (O–H), 1624 (C=N) cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 345] (42), 224 (65), 210 (27), 134 (48).

1c *N*,*N*′-(2,6-Pyridinediyldimethylidyne)bis(5-chloro-2-hydroxybenzenamine): 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde and 0.530 g (3.70 mmol) of 2-amino-4-chlorophenol, ethanol, 6 h, 0.59 g (84%) yield, brown solid; pf 180—185 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.87 (2H, d, J=8.6 Hz, H-8), 7.03 (2H, d, J=8.2 Hz, H-9), 7.18 (2H, s, H-6), 7.91 (1H, t, J=7.6 Hz, H-1), 8.42 (2H, d, J=7.3 Hz, H-2), 8.70 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 117.6 (C-9), 118.8 (C-6), 123.8 (C-2), 124.2 (C-7), 128.2 (C-8), 137.3 (C-5), 137.5 (C-1), 150.8 (C-10), 154.5 (C-3), 159.7 (C-4); IR ν_{max} (KBr): 3381 (O–H), 1624 (C=N) cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 384] (11), 368 (5), 258 (13), 244 (100).

1d *N*,*N*′-(2,6-Pyridinediyldimethylidyne)bis(2-hydroxy-5-nitrobenzenamine): 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde and 0.571 g (3.70 mmol) of 2-amino-4-nitrophenol, toluene, 8 h, 0.68 g (91%) yield, green solid; mp 142—144 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.02 (2H, d, J=8.5 Hz, H-9), 7.69 (2H, s, H-6), 8.06 (2H, br s, H-8), 8.01 (1H, t, J=7.6 Hz, H-1), 8.47 (2H, d, J=7.6 Hz, H-2), 8.81 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 115.6 (C-9), 116.6 (C-6), 124.1 (C-2), 124.4 (C-7), 137.3 (C-8), 137.6 (C-1), 140.6 (C-5), 154.3 (C-10), 158.0 (C-3), 161.8 (C-4); IR ν_{max} (KBr): 3888 (O–H), 1624 (C=N) cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 407] (25), 390 (33), 269 (8), 255 (20), 241 (64).

General Procedure for the Preparation of Tin Complexes Tin complexes were prepared under anhydrous conditions in a solution of toluene/methanol (4 : 1 v/v 60 ml) using a 1 : 2 : 1 molar ratio of 2,6-pyridinedicarboxaldehyde, aminophenol and the corresponding tin oxide. The reaction mixture was refluxed with constant stirring for the time indicated for each compound, the solvent was removed under reduced pressure and tin complexes were recrystallized from dichloromethane.

2a Dibutyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(phenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.402 g (3.70 mmol) of 2-aminophenol and 0.46 g (1.85 mmol) of dibutyltin oxide, 8 h, 0.56 g (95%) yield, dark red solid; mp 275 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.50 (6H, t, J=6.6 Hz, H-14), 0.71—0.92 (12H, m, H-11, H-13, H-12), 6.57 (2H, t, J=7.3 Hz, H-7), 7.11 (2H, d, J=8.4 Hz, H-6), 7.23 (2H, t, J=8.2 Hz, H-8), 7.52 (2H, t, J=7.9 Hz, H-9), 7.78 (2H, d, J= 7.6 Hz, H-2), 8.15 (1H, t, J=7.7 Hz, H-1), 8.71 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (C-14), 26.6 (C-11), 27.7 (C-13), 31.1 (C-12), 115.0 (C-9), 116.7 (C-6), 123.3 (C-7), 125.2 (C-2), 130.1 (C-8), 134.0 (C-1), 137.0 (C-5), 140.6 (C-10), 149.0 (C-3), 166.6 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −404.5; IR ν_{max} (KBr): 1568 (C=N), 1472 (CH_2), 633 (Sn–C), 564 (Sn–O), 436 (Sn–N) cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 549] (3), [M$^+$−57, 492] (100), [M$^+$−2Bu, 435] (9), 315 (13), 239 (8). HR-MS (FAB$^+$) *m*/*z*: 492.0734 Calcd for $C_{23}H_{21}N_3O_2Sn$. Observed: 492.0737.

2b Dibutyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-methylphenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.445 g (3.70 mmol) of 2-amino-4-methylphenol and 0.46 g (1.85 mmol) of dibutyltin oxide, 8 h, 0.94 g (93%) yield, black solid; mp 160 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.50 (6H, t, J=6.2 Hz, H-14), 0.71—0.92 (12H, m, H-11, H-13, H-12), 2.27 (6H, s, H-15), 7.01 (2H, d, J=8.6 Hz, H-9), 7.10 (2H, dd, J=8.6, 1.9 Hz, H-8), 7.31 (2H, s, H-6), 7.71 (2H, d, J=7.7 Hz, H-2), 8.11 (1H, t, J=7.7 Hz, H-1), 8.67 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (C-14), 20.7 (C-15), 26.5 (C-11), 27.7 (C-13), 31.0 (C-12), 116.2 (C-9), 123.0 (C-6), 124.0 (C-2), 124.7 (C-7), 129.5 (C-8), 135.5 (C-1), 136.0 (C-5), 140.3 (C-10), 149.1 (C-3), 164.8 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −401.6; IR ν_{max} (KBr): 1573 (C=N), 1482 (CH_2), 1317 (CH_3), 635 (Sn–C), (Sn–O), 430 (Sn–N) cm^{-1}. MS (EI$^+$), *m*/*z* (%): [M$^+$, 577] (3), [M$^+$−57, 577] (100), [M$^+$−2Bu, 463] (10), 328 (9), 313 (4), 252 (2). HR-MS (FAB$^+$) *m*/*z*: 520.1047 Calcd for $C_{25}H_{25}N_3O_2Sn$. Observed: 520.1055.

2c Dibutyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-chlorophenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.530 g (3.70 mmol) of 2-amino-4-chlorophenol and 0.46 g (1.85 mmol) of dibutyltin oxide, 8 h, 1.05 g (93%) yield, purple solid; mp 245 °C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.50 (6H, t, J=5.7 Hz, H-14), 0.71—0.92 (12H, m, H-11, H-13, H-12), 7.01 (2H, d, J=9.0 Hz, H-8), 7.18 (2H, d, J=8.4 Hz, H-9), 7.49 (2H, s, H-6), 7.83 (2H, d, J=7.1 Hz, H-2), 8.19 (1H, t, J=6.9 Hz, H-1), 8.69 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (C-14), 26.4 (C-11), 27.6 (C-13), 31.1 (C-12), 116.4 (C-9), 119.8 (C-6), 124.2 (C-2), 125.8 (C-7), 130.1 (C-8), 133.9 (C-1), 138.0 (C-5), 140.9 (C-10), 148.6 (C-3), 165.0 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −397.5; IR ν_{max} (KBr): 1568 (C=N), 1472 (CH_2), 1316 (CH_3), 637 (Sn–C), 579 (Sn–O), 432 (Sn–N), cm^{-1}; MS (EI$^+$), *m*/*z* (%): [M$^+$, 617] (4), [M$^+$−57, 560] (100), [M$^+$−2Bu, 503] (19), 383 (3), 348 (8), 272 (7). *Anal.* Calcd for $C_{27}H_{29}N_3O_2Cl_2Sn$: C, 52.51; H, 4.70; N, 6.80. Found C, 53.52; H, 4.59; N, 6.44.

2d Dibutyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-nitrophenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.57.1 g (3.70 mmol) of 2-amino-4-nitrophenol and 0.46 g (1.85 mmol) of dibutyltin oxide, 8 h, 1.17 g (99%) yield, dark red solid; mp >300 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.45 (6H, t, J=3.9 Hz, H-14), 0.68—0.85 (12H, m, H-11, H-13, H-12), 7.01 (2H, d, J=9.1 Hz, H-8), 7.18 (2H, d, J=7.1 Hz, H-9), 7.49 (2H, s, H-6), 8.17 (2H, d, J=7.7 Hz, H-2), 8.34 (1H, t, J=7.9 Hz, H-1), 9.41 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (C-14), 26.2 (C-11), 27.3 (C-13), 30.8 (C-12), 114.9 (C-9), 121.8 (C-6), 128.5 (C-2), 128.6 (C-7), 129.3 (C-8), 135.6 (C-1), 142.3 (C-5), 144.4 (C-10), 148.0 (C-3), 171.0 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −400.9; IR ν_{max} (KBr): 1570 (C=N), 1487 (CH_2), 631 (Sn–C), 578 (Sn–O), 423 (N→Sn) cm^{-1}; MS (FAB$^+$), *m*/*z* (%): [M$^+$+1, 640] (41), [M$^+$−57, 582] (50), [M$^+$−2Bu, 524] (28), 585 (24), 478 (5). *Anal.* Calcd for $C_{27}H_{29}N_5O_6Sn$: C, 50.70; H, 4.53; N, 10.95. Found C, 49.78; H, 4.28; N, 10.13.

2e Dimethyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(phenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.402 g (3.70 mmol) of 2-aminophenol and 0.305 g of (1.85 mmol) dimethyltin oxide, 30 h, 0.78 g (90%) yield, red solid; pf 200 °C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.20 (6H, s, ^2J (^{119}Sn–^{1}H)=111.9 Hz, ^2J (^{117}Sn–^{1}H)=111.6 Hz, Sn–CH_3), 6.60 (2H, td, J=8.2, 1.2 Hz, H-7), 7.12 (2H, dd, J=8.2, 1.5 Hz, H-6), 7.28 (2H, td, J=8.6, 1.5 Hz, H-8), 7.52 (2H, dd, J=8.2, 1.5 Hz, H-9), 7.76 (2H, dd, J=7.8, 1.0 Hz, H-2), 8.14 (1H, t, J=7.8 Hz, H-1), 8.68 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 11.9 (Sn–CH_3), 115.2 (C-9), 116.6 (C-6), 123.6 (C-7), 125.2 (C-2), 129.5 (C-8), 134.1 (C-1), 136.6 (C-5), 140.5 (C-10), 148.2 (C-3), 166.0 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −398.2; IR ν_{max} (KBr): 1565 (C=N), 1376 (CH_3), 630 (Sn–C), 569 (Sn–O), 437 (Sn–N) cm^{-1}; MS (FAB$^+$), *m*/*z* (%): [M$^+$+1, 466 (11)], [M$^+$−CH_3, 450] (13), 435 (2), 154 (100). HR-MS (FAB$^+$) *m*/*z*: 466.0578 Calcd for $C_{21}H_{19}N_3O_2Sn$. Observed: 466.0574.

2f Dimethyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-methylphenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.445 g (3.70 mmol) of 2-amino-4-methylphenol and 0.305 g (1.85 mmol) of dimethyltin oxide, 30 h, 0.80 g (88%) yield, black solid; mp 250 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.03 (6H, s, ^2J (^{119}Sn–^{1}H)= 114.0 Hz, ^2J (^{117}Sn–^{1}H)=109.0 Hz, Sn–CH_3), 2.50 (6H, s, CH_3), 6.83 (2H, d, J=8.5 Hz, H-8), 7.00 (2H, dd, J=8.6, 2.0 Hz, H-9), 7.53 (2H, s, H-6), 7.83 (2H, d, J=7.8 Hz, H-2), 8.13 (1H, t, J=7.8 Hz, H-1), 8.76 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.1 (C-11, J (^{119}Sn–^{13}C)=1224.1 Hz, J (^{117}Sn–^{13}C)=1171.1 Hz), 20.6 (C-12), 116.9 (C-9), 122.4 (C-6), 124.1 (C-2), 126.0 (C-7), 129.1 (C-8), 135.1 (C-1), 137.9 (C-5), 141.0 (C-10), 148.1 (C-3), 163.5 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −392.8; IR ν_{max} (KBr): 1575 (C=N), 1392 (CH_3), 635 (Sn–C), 438 (Sn–N) cm^{-1}; MS (FAB$^+$), *m*/*z* (%): [M$^+$1, 494], [M$^+$−CH_3, 478] (22). [M$^+$−2CH_3, 463] (5), 448 (1) 330 (2). HR-MS (FAB$^+$) *m*/*z*: 494.0891 Calcd for $C_{23}H_{23}N_3O_2Sn$. Observed: 494.0896.

2g Dimethyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-chlorophenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-pyridinedicarboxaldehyde, 0.530 g (3.70 mmol) of 2-amino-4-chlorophenol and 0.305 g (1.85 mmol) of dimethyl tin oxide, 30 h, 0.94 g (95%) yield, red solid; mp 220 °C (dec.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.05 (6H, s, ^2J (^{119}Sn–^{1}H)=111.5 Hz, Sn–CH_3), 6.85 (2H, d, J=8.9 Hz, H-8), 7.08 (2H, d, J= 8.4 Hz, H-9), 7.58 (2H, s, H-6), 7.95 (2H, d, J=7.4 Hz, H-2), 8.20 (1H, t, J=

7.1 Hz, H-1), 8.94 (2H, s, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.0 (Sn–CH_3), 117.2 (C-9), 119.4 (C-6), 123.7 (C-2), 127.1 (C-7), 130.0 (C-8), 133.3 (C-1), 140.6 (C-5), 141.5 (C-10), 147.8 (C-3), 163.7 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −388.9; IR ν_{max} (KBr): 1569 (C=N), 1387 (CH_3), 635 (Sn–C), 437 (N–Sn) cm^{-1}; MS (FAB^+), *m/z* (%): [M^++1, 534] (10), [M^+-CH_3, 518] (13), [M^+-2CH_3, 503] (2), 377(1). HR-MS (FAB^+) *m/z*: 533.9798 Calcd for $C_{21}H_{17}N_3O_2Cl_2Sn$. Observed: 533.9796.

2h Dimethyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(4-nitrophenolato)}(2-))tin: 2,6-Pyridinedicarboxaldehyde, 0.57 g (3.70 mmol) of 2-amino-4-nitrophenol and 0.305 g (1.85 mmol) of dimethyl tin oxide, 30 h, 0.92 g (90%) yield, orange solid; mp >300 °C; ^{13}C-NMR CPMAS (75.4 MHz) δ: 11.8 (Sn–CH_3), 13.6 (Sn–CH_3), 118.1 (C-9), 121.6 (C-6), 123.6, 127.1, 127.7, 130.5 (arom), 134.6 (C-1), 137.0, 137.9 (arom), 143.4 (C-5), 146.3 (C-10), 147.4 (C10′), 150.5 (C-3), 170.4 (C-4), 172.5 (C-4′) 127.1 (C-7), 130.0 (C-8), 133.3 (C-1), 140.6 (C-5), 141.5 (C-10), 147.8 (C-3), 163.7 (C-4); IR ν_{max} (KBr): 1594 (C=N), 646 (Sn–C), 568 (Sn–O) cm^{-1}; MS (FAB^+), *m/z* (%): [M^++1, 556] (3), [M^+-CH_3, 540] (2), [M^+-2CH_3, 525] (1). *Anal.* Calcd for $C_{21}H_{17}N_5O_6Sn$: C, 45.40; H, 3.06; N, 12.61. Found C, 46.35; H, 3.96; N, 12.23.

2i Diphenyl({2,2′-[2,6-pyridinediylbis(methylidynenitrilo)]bis(phenolato)}(2-))tin: 0.25 g (1.85 mmol) of 2,6-diacetylpyridine, 0.402 g (3.70 mmol) of 2-aminophenol and 0.534 g (1.85 mmol) diphenyltin oxide, 24 h, 0.98 g (90%) yield, dark red solid; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.51 (2H, td, *J*=6.9, 1.2 Hz, H-7), 6.82—6.90 (6H, m, H-13, H-14 arom), 6.93 (2H, dd, *J*=7.1, 1.1 Hz, H-6), 7.05—7.09 (4H, m, H-12 arom), 7.15 (2H, td, *J*=8.4, 1.1 Hz, H-8), 7.54 (2H, d, *J*=7.4 Hz, H-9), 7.99 (2H, d, *J*=7.6 Hz, H-2), 8.24 (1H, t, *J*=7.6 Hz, H-1), 9.05 (2H, s, H-4); ^{13}C-NMR CPMAS (75.4 MHz) δ: 117.4 (C-9), 118.8 (C-6), 120.5 (C-7), 124.6 (C-2), 127.0, 131.1, 133.2 arom, 134.9 (C-1), 137.6 arom, 139.7 (C-11), 145.8 (C-10), 147.9 (C-10′), 154.4 (C-3), 156.4 (C-3′), 165.7 (C-4); ^{119}Sn-NMR (112.05 MHz, DMSO-d_6) δ: −521.0; IR ν_{max} (KBr): 1561 (C=N), 633 (Sn–C), 565 (Sn–O), 412 (Sn–N) cm^{-1}; MS (FAB^+) *m/z* (%): [(M^++1), 590] (8), [(M^+−77) 512] (20), [(M^+−2Ph) 434] (4), 391 (20). HR-MS (FAB^+) *m/z*: 512.0421 Calcd for $C_{25}H_{17}N_3O_2Sn$. Observed: 512.0405.

2j Dibutyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(phenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.334 g (3.06 mmol) of 2-aminophenol and 0.381 g (1.53 mmol) of dibutyltin oxide, 8 h, 0.82 g (93%) yield, orange solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.48 (6H, t, *J*=6.8 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$), 0.71—0.94 (12H, m, Sn–$\underline{CH_2}$–CH_3), 2.88 (6-H, s, CH_3), 6.56 (2H, td, *J*=8.3, 1.6 Hz, H-7), 7.13 (2H, dd, *J*=8.5, 1.6 Hz, H-6), 7.22 (2H, td, *J*=8.5, 1.6 Hz, H-8), 7.35 (2H, dd, *J*=8.2, 1.3 Hz, H-9), 7.99 (2H, d, *J*=7.8 Hz, H-2), 8.24 (1H, t, *J*=7.5 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.6 (Sn–$(CH_2)_3$–$\underline{CH_3}$), 19.0 (CH_3), 26.5 (Sn–$\underline{CH_2}$–$(CH_2)_2$–CH_3), 28.0 (Sn–$(CH_2)_2$–$\underline{CH_2}$–CH_3), 31.6 (Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 113.5 (C-9), 122.3 (C-6), 122.9 (C-7), 123.3 (C-2), 131.6 (C-8), 132.0 (C-1), 140.8 (C-5), 150.5 (C-10), 151.2 (C-3), 166.1 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −398.2; IR ν_{max} (KBr): 1582 (C=N), 1365 (CH_3), 574 (Sn–O), 434 (N→Sn) cm^{-1}; MS (FAB^+) *m/z* (%): [(M^++1), 578] (29), [(M^+−57), 520] (56), [(M^+−2Bu), 463] (13), 448 (15), 307 (61). HR-MS (FAB^+) *m/z*: 578.1830 Calcd for $C_{29}H_{35}N_3O_2Sn$. Observed: 578.1828.

2k Dibutyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-methylphenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.377 g (3.06 mmol) of 2-amino-4-methylphenol and 0.381 g (1.53 mmol) of dibutyltin oxide, 8 h, 0.86 g (93%) yield, dark red solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.48 (6H, t, *J*=6.8 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$), 0.68—0.94 (12H, m, Sn–$(\underline{CH_2})_3$–CH_3), 2.27 (6H, s, CH_3), 2.88 (6-H, s, CH_3), 7.04 (2H, d, *J*=1.2 Hz, H-8), 7.16 (2H, s, H-6), 7.25 (2H, s, H-9), 7.96 (2H, d, *J*=7.8 Hz, H-2), 8.22 (1H, t, *J*=7.7 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (Sn–$(CH_2)_3$–$\underline{CH_3}$), 19.0 (CH_3), 20.7 (CH_3), 26.5 (Sn–$\underline{CH_2}$–$(CH_2)_2$–CH_3), 28.0 (Sn–$(CH_2)_2$–$\underline{CH_2}$–CH_3), 31.5 (Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 121.9 (C-9), 122.4 (C-6), 122.8 (C-2), 123.0 (C-7), 130.8 (C-8), 133.2 (C-1), 140.6 (C-5), 149.7 (C-10), 151.3 (C-3), 164.0 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −396.3; IR ν_{max} (KBr): 1584 (C=N), 1366 (CH_3), 617 (Sn–C), 587 (Sn–O), 432 (N→Sn) cm^{-1}; MS (FAB^+) *m/z* (%): [(M^++1), 606] (65), [(M^+−57), 548] (100), [(M^+−2Bu), 491] (40), 476 (12), 307 (36). HR-MS (FAB^+) *m/z*: 606.2143 Calcd for $C_{31}H_{39}N_3O_2Sn$. Observed: 606.2149.

2l Dibutyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-chlorphenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.439 g (3.06 mmol) of 2-amino-4-chlorophenol and 0.381 g (1.53 mmol) of dibutyltin oxide, 8 h, 0.87 g (88%) yield, purple solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.49 (6H, t, *J*=6.3 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$), 0.67—0.94 (12H, m, Sn–$(\underline{CH_2})_3$–CH_3), 2.88 (6-H, s, CH_3), 7.04 (2H, d, *J*=8.9 Hz, H-8), 7.15 (2H, dd, *J*=8.9, 2.0 Hz, H-9), 7.33 (2H, d, *J*=1.9 Hz, H-6), 8.04 (2H, d, *J*=7.8 Hz, H-2), 8.28 (1H, t, *J*=7.8 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.6 (Sn–$(CH_2)_3$–$\underline{CH_3}$),19.0 (CH_3), 26.4 (Sn–$\underline{CH_2}$–$(CH_2)_2$–CH_3), 28.0 (Sn–$(CH_2)_2$–$\underline{CH_2}$–CH_3), 31.7 (Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 118.0 (C-9), 122.2 (C-6), 123.1 (C-2), 123.9 (C-7), 131.5 (C-8), 131.9 (C-1), 141.2 (C-5), 151.0 (C-10), 151.9 (C-3), 164.5 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −392.1; IR ν_{max} (KBr): 1582 (C=N), 1366 (CH_3), 583 (Sn–O), 431 (N→Sn) cm^{-1}; MS (FAB^+) *m/z* (%): [(M^++1), 646] (4), [(M^+−57), 588] (8), [(M^+−2Bu), 531] (2) 516 (2), 307 (25). HR-MS (FAB^+) *m/z*: 588.0268 Calcd for $C_{25}H_{23}N_3O_2Cl_2Sn$. Observed: 588.0259.

2m Dibutyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-nitrophenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.472 g (3.06 mmol) of 2-amino-4-nitrophenol and 0.381 g (1.85 mmol) dibutyltin oxide, 8 h, 0.96 g (94%) yield, orange solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.52 (6H, t, *J*=6.7 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$), 0.68—0.94 (12H, m, Sn–$\underline{CH_2}$–CH_3), 3.04 (6-H, s, CH_3), 7.10 (2H, d, *J*=9.3 Hz, H-9), 8.18 (2H, d, *J*=9.4, 2.7 Hz, H-8), 8.23 (2H, d, *J*=7.8 Hz, H-2), 8.41 (2H, d, *J*=2.9 Hz, H-6), 8.45 (1H, t, *J*=8.1 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.5 (Sn–$(CH_2)_3$–$\underline{CH_3}$), 19.3 (CH_3), 26.2 (Sn–$\underline{CH_2}$–$(CH_2)_2$–CH_3), 28.0 (Sn–$(CH_2)_2$–$\underline{CH_2}$–CH_3), 31.9 (Sn–CH_2–$\underline{CH_2}$–CH_2–CH_3), 120.0 (C-9), 121.5 (C-6), 125.3 (C-2), 127.9 (C-7), 130.0 (C-8), 135.1 (C-1), 142.2 (C-5), 150.6 (C-10), 155.5 (C-3), 171.4 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −392.4; IR ν_{max} (KBr): 1585 (C=N), 1366 (CH_3), 618 (Sn–C), 573 (Sn–O), 435 (N→Sn) cm^{-1}; MS (FAB^+) *m/z* (%): [(M^++1), 668] (4), [(M^+−57), 611] (2), 307 (19). HR-MS (FAB^+) *m/z*: 610.0749 Calcd for $C_{25}H_{23}N_5O_6Sn$. Observed: 610.0758.

2n Dimethyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(phenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.334 g (3.06 mmol) of 2-aminophenol and 0.252 g (1.53 mmol) dimethyltin oxide, 45 h, 0.73 g (96%) yield, red solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: −0.31 (6H, s, ^2J (^{119}Sn–^{1}H)=114.0 Hz, ^2J (^{117}Sn–^{1}H)=107.2 Hz, Sn–CH_3), 2.73 (6-H, s, CH_3), 6.18 (2H, td, *J*=8.4, 1.5 Hz, H-7), 6.61 (2H, dd, *J*=8.3, 1.3 Hz, H-6), 6.79 (2H, td, *J*=8.5, 1.6 Hz, H-8), 7.03 (2H, dd, *J*=8.2, 1.3 Hz, H-9), 7.78 (2H, d, *J*=7.8 Hz, H-2), 7.97 (1H, t, *J*=7.4 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.3 (Sn–$\underline{CH_3}$), 18.8 (CH_3), 113.7 (C-9), 121.5 (C-6), 123.0 (C-7), 124.1 (C-2), 130.8 (C-8), 131.5 (C-1), 141.3 (C-5), 149.8 (C-10), 151.5 (C-3), 164.7 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −388.6; IR ν_{max} (KBr): 1583 (C=N), 1367 (CH_3), 576 (Sn–O), 435 (N→Sn) cm^{-1}; EM (FAB^+) *m/z* (%): [(M^++1), 494] (28), [(M^+−15), 478] (40), [(M^+−2CH_3), 463] (5), 448 (8). HR-MS (FAB^+) *m/z*: 494.0891 Calcd for $C_{23}H_{23}N_3O_2Sn$. Observed: 494.0883.

2o Dimethyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-methylphenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.377 g (3.06 mmol) of 2-amino-4-methylphenol and 0.252 g (1.53 mmol) dimethyltin oxide, 45 h, 0.73 g (91%) yield, dark red solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 (6H, s, ^2J (^{119}Sn–^{1}H)=111.9 Hz, ^2J (^{117}Sn–^{1}H)=107.1 Hz, Sn–CH_3), 2.27 (6-H, s, CH_3), 2.86 (6-H, s, CH_3), 7.04 (2H, H-8), 7.17 (2H, s, H-6), 7.25 (2H, s, H-9), 7.97 (2H, d, *J*=7.9 Hz, H-2), 8.22 (1H, t, *J*=7.7Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.5 (C–Sn–CH_3), 19.0 (CH_3), 20.9 (CH_3), 122.1 (C-9), 122.9 (C-6), 123.3 (C-2), 128.2 (C-7), 130.6 (C-8), 133.3 (C-1), 140.8 (C-5), 149.8 (C-10), 150.6 (C-3), 163.2 (C-4); ^{119}Sn-NMR (112.05 MHz, $CDCl_3$) δ: −381.8; IR ν_{max} (KBr): 1585 (C=N), 1368 (CH_3), 617 (Sn–C), 587, (Sn–O), 424 (Sn–N) cm^{-1}; EM (FAB^+) *m/z* (%): [(M^++1), 522] (28), [(M^+−15), 506] (50), [(M^+−2CH_3), 491] (8), 476 (12), 307 (21). HR-MS (FAB^+) *m/z*: 522.1204 Calcd for $C_{25}H_{27}N_3O_2Sn$. Observed: 522.1198.

2p Dimethyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-chlorophenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.439 g (3.06 mmol) of 2-amino-4-chlorophenol and 0.252 g (1.53 mmol) of dimethyltin oxide, 45 h, 0.60 g (70%) yield, purple solid; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.11 (6H, s, ^2J (^{119}Sn–^{1}H)=111.3 Hz, ^2J (^{117}Sn–^{1}H)=106.8 Hz, Sn–CH_3), 2.88 (6-H, s, H-12), 7.03 (2H, d, *J*=8.9 Hz, H-8), 7.16 (2H, dd, *J*=8.9, 2.4 Hz, H-9), 7.35 (2H, d, *J*=2.3 Hz, H-6), 8.05 (2H, d, *J*=7.8 Hz, H-2), 8.28 (1H, t, *J*=7.8 Hz, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.5 (CH_3–Sn, *J* (^{119}Sn–^{13}C)=1200 Hz, *J* (^{117}Sn–^{13}C)=1155.3 Hz), 19.0 (CH_3), 118.6 (C-9, *J* (^{119}Sn–^{13}C)=557.6 Hz), 122.4 (C-6), 123.2 (C-2), 124.2 (C-7), 131.0 (C-8), 132.1 (C-1), 141.3 (C-5), 150.3 (C-10), 151.8 (C-3), 163.6 (C-4); ^{119}Sn-NMR (112.04 MHz, $CDCl_3$) δ: −376.2; IR ν_{max} (KBr): 1584 (C=N), 1369 (CH_3), 583 (Sn–O), 437 (N→Sn) cm^{-1}; EM (FAB^+) *m/z* (%): [(M^++1), 562] (20), [(M^+−15), 546] (36), [(M^+−2CH_3), 531] (4), 516 (5), 307(18). HR-MS (FAB^+) *m/z*: 562.0111 Calcd for $C_{23}H_{21}N_3O_2Cl_2Sn$. Observed: 562.0118.

2q Dimethyl({2,2′-[2,6-pyridinediylbis(ethylidynenitrilo)]bis(4-nitrophenolato)}(2-))tin: 0.25 g (1.53 mmol) of 2,6-diacetylpyridine, 0.472 g (3.06 mmol) of 2-amino-4-nitrophenol and 0.252 g (1.53 mmol) dimethyltin oxide, 45 h, 0.85 g (95%) yield, orange solid; ^{13}C-NMR CPMAS (75.4 MHz) δ:

14.3 (Sn–CH_3), 19.4 (CH_3), 122.4, 127.0, 130.3 (arom), 135.0 (C-1), 146.1 (C-10), 150.2 (C-10′) 157.9 (C-3), 159.7 (C-3′) 171.0 (C-4); IR ν_{max} (KBr): 1581 (C=N), 574 (Sn–O), 432 (N→Sn) cm^{-1}; EM (FAB^+) *m/z* (%): [(M^++1), 584] (0.6), [(M^+−15), 568] (0.5), [(M^+−2CH_3), 553] (1), 307(22). *Anal.* Calcd for $C_{23}H_{21}N_5O_6Sn$: C, 47.34; H, 3.60; N, 12.00. Found C, 47.02; H, 3.44; N, 11.79.

Anti-inflammatory Activity. Mouse Ear Edema The assay of TPA-induced ear edema in mice was based on the method described by Merlos *et al.*[50] A group of six male NIH mice were anesthetized with Sedaphorte® and a solution of 12-*O*-tetradecanoylphorbol-13-acetate (2.5 μg) dissolved in ethanol (10 μl) was topically applied to both faces of the right ear of the mice (5 μl each face). The left ear received only ethanol (10 μl). After 10 min of TPA-treatment, doses of 0.031 to 1.0 μmol of the test compounds, or indomethacin as reference, dissolved in 20 μl of acetone were applied to both faces of the right ear (10 μl each face). Control animals received only acetone–dichloromethane. Four hours later the animals were sacrificed by cervical dislocation and a plug (7 mm diameter) was removed from each ear. The edematous response was measured as the weight difference between the two plugs. The % inhibition of edema was calculated by the equation: %=[(edema A−edema B)/edema A]×100. Edema A=edema induced by TPA alone and edema B=edema induced by TPA plus sample. Data were analyzed by one-way analysis of variance followed by Dunnett's test, which was used to compare several group with a control. The IC_{50} values were estimated from linear regression equation.

Inhibition of TBARS Formation in Rat Brain Homogenate Animals: Adult male Wistar rats (200—250 g) were provided by the Instituto de Fisiología Celular, UNAM, and approved by the Animal Care and Use Committee (Nom 087-ECOL-SSA 1-2002).[51] They were maintained at 23±2 °C on a 12/12 h light–dark cycle with free access to food and water.

Rat Brain Homogenate: The animals sacrifice was carried out avoiding unnecessary pain. Rats were sacrificed under mild ether anesthesia and cerebral tissue (whole brain) was rapidly dissected and homogenized as previously described,[52] in phosphate-buffered saline (PBS; 0.2 g KCl, 0.2 g KH_2PO_4, 8 g NaCl and 2.16 g $NaHPO_4 \cdot 7H_2O$/l, pH 7.4) to produce a 1/10 homogenate, w/v. The homogenate was centrifuged for 10 min at 3400 rpm to yield a pellet that was discarded, protein content in the supernatant was measured using the Folin and Ciocalteu's phenol reagent[53] and adjusted to 2.35 mg protein/ml with PBS.

Lipid Peroxidation: The supernatant (425 μl) was incubated at 37 °C for 30 min in presence of test sample (25 μl) dissolved in DMSO. Lipid peroxidation was started adding 50 μl of freshly prepared 100 μM $FeSO_4$ solution (final concentration 10 μM) and incubated at 37 °C for 60 min.[54] TBARS were determined as described by Ohkawa *et al.*[55] with some modifications, adding 0.5 ml of the TBA reagent (1% TBA in 0.05 N NaOH and 30% trichloroacetic acid in 1 : 1 proportion). The final solution was cooled on ice for 10 min, then was centrifuged at 10000 rpm for 5 min and finally heated at 95 °C in a boiling water bath for 30 min. After cooling on ice, the absorbance of supernatant (200 μl) was measured at 540 nm in a microplate reader Elx808 BIO-TEK instruments. α-Tocopherol was used as a positive control. Concentration of TBARS was calculated by interpolation in a standard curve of tetrametoxipropane (TMP).[56] Final results were expressed as nmoles of TBARS per mg of protein. The inhibition ration (%) was calculated using the following formula:

$$\text{inhibition ration (\%)} = (C-E)/C \times 100\%$$

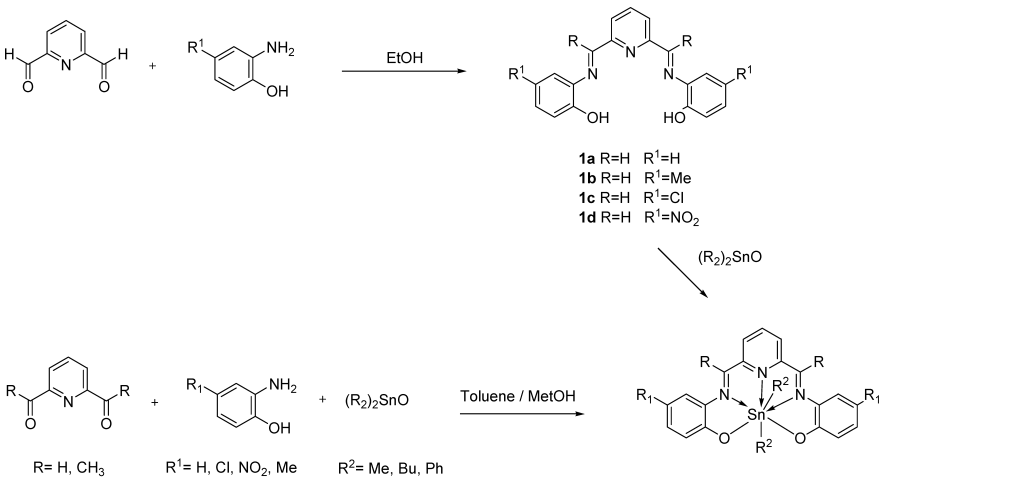
Where: *C* was the absorbance of control group and *E* the absorbance of test group.

Statistical Analysis: All data were represented as mean±standard error of mean (S.E.M.). Data were analyzed by one-way ANOVA followed by Dunnett's test for comparisons against control. Values of $p \leq 0.05$ (*) and $p \leq 0.01$ (**) were considered statistically significant. The inhibitory concentration 50 (IC_{50}), were estimated by means of a linear regression equation.

Results and Discussion

The Schiff bases derived from 2,6-pyridinedicarboxialdehyde **1a**—**d** were prepared by reaction of the corresponding aminophenol with 2,6-diacetyl pyridine, the isolated Schiff base was reacted with the appropriate tin oxide leading to the corresponding complexes in 30% yield. In order to improve the yield, the reactions were carried out in one pot in a mixture of toluene–methanol (4 : 1) (Chart 1) the synthesis of *n*-BuSn(IV) derivatives was accomplished after 8—45 h of refluxing, except for the Ph_2SnO derivative in which longer reaction time was necessary. Following this methodology the yields of all reactions improved dramatically (88—99%). All compounds are stable under atmospheric conditions; the butyltin derivatives are slightly more soluble than the methyl and phenyl tin complexes.

DRIFT Spectroscopy Infrared spectra of complexes **2a**—**q** showed vibrational bands in the range of 1565—1594 cm^{-1} due to the ν(N=C). These bands are shifted to lower wave number with respect to the free Schiff base (1627—1623 cm^{-1}) for derivatives **2a**—**i** which can be attributed to the Sn–N coordination (Table 1). Although Schiff



2a R = H R1 = H R2 = Bu
2b R = H R1 = Me R2 = Bu
2c R = H R1 = Cl R2 = Bu
2d R = H R1 = NO2 R2 = Bu
2e R = H R1 = H R2 = Me
2f R = H R1 = Me R2 = Me
2g R = H R1 = Cl R2 = Me
2h R = H R1 = NO2 R2 = Me
2i R = H R1 = H R2 = Ph
2j R= Me R1 = H R2 = Bu
2k R= Me R1 = Me R2 = Bu
2l R= M e R1 = Cl R2 = Bu
2m R= Me R1 = NO2 R2 = Bu
2n R= Me R1 = H R2 = Me
2o R= Me R1 = Me R2 = Me
2p R= Me R1 = Cl R2 = Me
2q R= Me R1 = NO2 R2 = Me

Chart 1. Preparation of Complexes **2a**—**q**

Table 1. IR Bands (cm^{-1}) of Complexes **2a**—**q**

Complex	ν (cm^{-1}) N=C	ν (cm^{-1}) N→Sn
1a	1623	
1b	1624	
1c	1624	
1d	1627	
2a	1568	436
2b	1573	430
2c	1568	432
2d	1570	423
2e	1595	437
2f	1565	438
2g	1575	437
2h	1569	
2i	1594	
2j	1582	434
2k	1584	432
2l	1582	431
2m	1585	432
2n	1583	435
2o	1585	424
2p	1584	437
2q	1581	432

bases **1j**—**q** where not isolated, similar pattern in their infrared spectral bands could also be envisaged. This fact has been associated with the displacement of the electron density from the nitrogen to tin atom.[23,57] Most of these complexes displayed stretching bands in the range of 431—435 cm^{-1} which arise from the ν(Sn–N) as a result of the Sn–N coordinative bonds. The IR bands that occur between 617 and 580 cm^{-1} are attributable to ν(Sn–C) and ν(Sn–O), respectively. Besides those features relevant differences which may originate from the substituents attached to the tin atom were not observed.

Mass Spectrometry The mass spectrometry of compounds **2a**—**q** displayed the molecular ion corresponding to the monomeric compounds; all complexes exhibited a similar fragmentation pattern. In the first stage the loss of alkyl group attached to the tin atom (fragments ions C_5H_3N–$(CH{=}N{-}C_6H_4NO_2)_2SnR^+$, C_5H_3N–$(CH{=}N{-}C_6H_4NO_2)_2Sn^+$) was observed.

NMR Spectroscopy The proton NMR spectroscopy of dibutyltin derivatives compounds **2a**—**g** (Table 2) showed signals for the iminic proton in the range of 8.4 to 8.94, in the case of complexes **2b**, **2f** and **2g** this signal is slightly shifted to lower frequencies with respect to the free ligand, however, for complexes whit butyl substituents bonded to the tin atom only multiple signals were observed. The proton NMR spectra of dimethyltin derivative compounds **2e**—**g** and **2o**, **p** showed single signals for the methyl groups in the range of −0.31 to 0.2 ppm as well as the corresponding satellites as a result of the spin–spin coupling ^1H–^{119}Sn and ^1H–^{117}Sn. It is known that the magnitude of $|^2J(^1H{-}^{119}Sn)|$ spin–spin constant coupling is function of the coordination number, for compounds **2e**—**g** and **2o**, **p** these values are in the range of 109—119 Hz and correspond to seven coordinated complexes, regarding this, Willem *et al.* have calculated similar values for heptacoordinated dimethyltin salicylaldoximates.[58—60] The ^{13}C-NMR signals for the aromatic rings C-10 and C-1 of **2a**—**i** showed a slight shift to low frequencies ($\Delta\delta$=*ca.* 10 and 7) respectively, with respect to free ligand. The pyridinic C-3 and the iminic C-4, by contrast, are shifted to high frequencies ($\Delta\delta$=*ca.*6 and 7) which could be provoked by the presence of the coordinative N→Sn bond, this behavior has also been observed for other pyridine tin complexes.[42] As regards compounds **2f** and **2p**, the ^{119}Sn satellite signals allowed us to measure coupling constants J (^{13}C–^{119}Sn)=1224.1 for **2f** and J (^{13}C–^{119}Sn)=1200 Hz for **2p**, which were used to calculate the angle of the fragment C–Sn–C resulting in 184° and 182° for **2f** and **2p**, respectively.[61] The ^{119}Sn-NMR of **2a**—**g** and **2j**—**p** exhibited signals in the range of −370 to −404 ppm for seven-coordinated compounds.[58—60] Combination of the information obtained from the Mass spectrometry and Multinuclear NMR led us to assume that all compounds are monomeric species possessing heptacoordinated geometry in solution. The solution-NMR spectral data for compounds **2h**, **2i** and **2q** were not recorded due to their lack of solubility in most common solvents.

X-Ray Structural Studies Single crystals for complexes **2a**, **2b**, **2i**, **2j** and **2n** suitable for X-ray diffraction study were obtained. The ortep drawings for the five compounds are depicted in Fig. 1. The crystallographic data are shown in Table 3; selected bond distances and angles are summarized in Table 4. Unit cell of **2a** consists of two crystallographically independent but structurally similar molecules whereas for **2j** it is formed by one and a half molecules; the disorder of butyl substituents of these complexes generates two different positions. Complexes **2b** and **2i** crystallized as methanol and dichloromethane solvates.

The examination of the molecular complexes revealed that the structural geometry is pentagonal-bipyramidal (PBP) for all complexes. The equatorial plane is constituted of two oxygen atoms, the azomethine and the pyridine nitrogen atoms whereas the axial positions are occupied by the two alkyl or phenyl groups forming angles in the range of 169.3 (3) to 176.0 (3) which favor a distorted geometry around the tin atom. The angle O–Sn–O is considerably greater than the O–Sn–N which is closer to the ideal angle 72°, however, the N–Sn–N bond angles are in the range of 65 to 66° which account for the distortion.

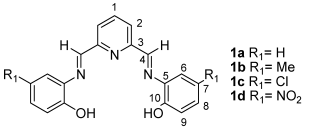
The Sn–N bond distances of five complexes are in the range of 2.36 to 2.44 Å, which are much lower than the sum of the van der Waals radii (3.75 Å) indicating the presence of stable coordinative Sn–N bonds. The examination of the structures **2j** and **2n** showed that the bond lengths Sn–N (pyridine–nitrogen atom) are slightly shorter than Sn–N (imine–nitrogen atom), these differences are associated with the presence of methyl group anchored to the iminic carbon although for complexes **2a**, **2b** and **2i** the behavior is the opposite. Similar results have been described by Pelizzi *et al.* for heptacoordinated, 2,6-diacetylpyridine hydrazone tin derivatives.[31]

Cytotoxic Activity From the series of synthesized complexes only the butyl tin derivatives were chosen for the evaluation of their biological activity, the rest of compounds were discarded because of low solubility. The complexes **2a**—**d** were screened *in vitro* against six human cancer cell lines HTC-15 (human colorectal adenocarcinoma) MCF7 (human mammary adenocarcinoma), K-562 (human chronic myelogenous leukemia), U251 (human gliblastoma), PC-3 (human prostatic adenocarcinoma) SKLU-1 (human lung

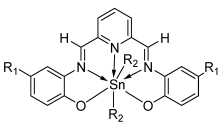
Table 2. ^{1}H- and ^{119}Sn-NMR Data of Complexes **2a**—**g** and **2j**—**p**

Complex	H-1	H-2	H-4	H-6	H-7	H-8	H-9	Sn–(CH$_2$)$_3$–CH$_3$	Sn–(CH$_2$)$_3$–CH$_3$	Sn–CH$_3$	^{119}Sn
1a	7.96 (t, *J*=7.7 Hz)	8.28 (d, *J*= 7.8 Hz)	8.80 (s)	7.04 (dd, *J*= 8.2, 1.3 Hz)	6.94 (td, *J*=7.98, 1.3 Hz)	7.26 (td, *J*=8.2, 1.5 Hz)	7.43 (2H, dd, *J*= 8.1, 1.3 Hz)		0.50 (t, *J*=6.6 Hz)		
1b	7.33 (t, *J*=7.8 Hz)	7.81 (d, *J*=7.8 Hz)	8.16 (s)	6.47 (s)		6.21 (d, *J*=8.2 Hz)	6.33 (dd, *J*=8.2, 1.5 Hz)		0.50 (t, *J*=6.2 Hz)		
1c	7.91 (t, *J*=7.6 Hz)	8.42 (d, *J*=7.3 Hz)	8.70 (s)	7.18 (s)		6.87 (d, *J*=8.6 Hz)	7.03 (d, *J*= 8.2 Hz)		0.50 (t, *J*=5.7 Hz)		
1d	7.96 (t, *J*=7.4 Hz)	8.47 (d, *J*=7.5 Hz)	8.81 (s)	7.69 (s)		8.06 (s)	7.02 (d, *J*= 8.5 Hz)		0.50 (t, *J*=3.9 Hz)		
2a	8.15 (t, *J*=7.7 Hz)	7.78 (d, *J*=7.6 Hz)	8.71 (s)	7.11 (d, *J*= 8.4 Hz)	6.57 (t, *J*=7.3 Hz)	7.23 (t, *J*=8.2 Hz)	7.52 (t, *J*=7.9 Hz)	0.71—0.92 (m)			−404.5
2b	8.11 (t, *J*=7.7 Hz)	7.71 (d, *J*=7.7 Hz)	8.67(s)	7.31 (s)		7.10 (dd, *J*=8.6, 1.9 Hz)	7.01 (d, *J*=8.6 Hz)	0.71—0.92 (m)			−401.6
2c	8.19 (t, *J*=6.9 Hz)	7.83 (d, *J*=7.1 Hz)	8.69 (s)	7.49 (s)		7.01 (d, *J*=9.0 Hz)	7.18 (d, *J*=8.4 Hz)	0.71—0.92 (m)			−397.5
2d	8.34 (t, *J*=7.9 Hz)	8.17 (d, *J*=7.7 Hz)	8.41 (s)	7.49 (s)		7.01 (d, *J*=9.1 Hz)	7.18 (d, *J*=7.1 Hz)	0.68—0.85 (m)			−400.9
2e	8.14 (t, *J*=7.8 Hz)	7.76 (dd, *J*=7.8, 1.0 Hz)	8.68 (s)	7.12 (dd, *J*=8.5, 1.2 Hz)	6.60 (td, *J*=8.2, 1.2 Hz)	7.28 (td, *J*=8.6, 1.5 Hz)	7.52 (dd, *J*=8.2, 1.5 Hz)			0.20 (s, ^{2}J (^{1}H–^{119}Sn) =111.9, ^{2}J (^{1}H–^{117}Sn) =111.6 Hz)	−398.2
2f	8.13 (t, *J*=7.8 Hz)	7.83 (d, *J*=7.8 Hz)	8.76 (s)	7.53 (s)		6.83 (d, *J*=8.5 Hz)	7.00 (dd, *J*=8.6, 2.0 Hz)			0.03 (s, ^{2}J (^{1}H–^{119}Sn) =114.0, ^{2}J (^{1}H–^{117}Sn) =109.0 Hz)	−392.8
2g	8.20 (t, *J*=7.1 Hz)	7.95 (d, *J*=7.4 Hz)	8.94 (s)	7.58 (s)		6.85 (d, *J*=8.9 Hz)	7.08 (d, *J*=8.4 Hz)			0.05 (s, ^{2}J (^{1}H–^{119}Sn) =111.5 Hz)	−388.9
2j	8.24 (t, *J*=7.5 Hz)	7.99 (d, *J*=7.8 Hz)		7.13 (dd, *J*=8.5, 1.6 Hz)	6.56 (td, *J*=8.3, 1.6 Hz)	7.22 (td, *J*=8.5, 1.6 Hz)	7.35 (dd, *J*=8.3, 1.3 Hz)	0.71—0.94 (m)	0.48 (t, *J*=6.8 Hz)		−398.2
2k	8.22 (t, *J*=7.7 Hz)	7.96 (d, *J*=7.8 Hz)		7.16 (s)		7.04 (s)		0.68—0.94 (m)	0.48 (t, *J*=6.8 Hz)		−396.3
2l	8.28 (t, *J*=7.8 Hz)	8.04 (d, *J*=7.8 Hz)		7.15 (d, *J*=1.9 Hz)		7.04 (d, *J*=8.9 Hz)	7.33 (dd, *J*=8.9, 2.0 Hz)	0.67—0.94 (m)	0.6 (t, *J*=6.3 Hz)		−392.1
2m	8.45 (t, *J*=8.1 Hz)	8.23 (d, *J*=7.8 Hz)		8.41 (d, *J*=2.9 Hz)		8.18 (dd, *J*=9.4, 2.7 Hz)	7.10 (d, *J*=9.3 Hz)	0.68—0.94 (m)	0.52 (t, *J*=6.7 Hz)		−392.4
2n	7.97 (t, *J*=7.4 Hz)	7.78 (d, *J*=7.8 Hz)		6.61 (dd, *J*=8.3, 1.3 Hz)	6.18 (td, *J*=8.4, 1.5 Hz)	6.79 (td, *J*=8.5, 1.6 Hz)	7.03 (dd, *J*=8.2, 1.3 Hz)			−0.31 (s, ^{2}J (^{1}H–^{119}Sn) =114, ^{2}J (^{1}H–^{117}Sn) =107.2 Hz)	−388.6
2o	8.22 (t, *J*=7.7 Hz)	7.97 (d, *J*=7.9 Hz)		7.17 (s)		7.04 (s)	7.25 (s)			0.10 (s, ^{2}J (^{1}H–^{119}Sn) =111.9, ^{2}J (^{1}H–^{117}Sn) =107.1 Hz)	−381.8
2p	8.28 (t, *J*=7.8 Hz)	8.05 (d, *J*=7.8 Hz)		7.35 (d, *J*=2.3 Hz)		7.03 (d, *J*=8.9 Hz)	7.16 (dd, *J*=8.9, 2.4 Hz)			0.11 (s, ^{2}J (^{1}H–^{119}Sn) =111.3, ^{2}J (^{1}H–^{117}Sn) =106.8 Hz)	−376.2

The NMR data for **2h**, **2i** and **2q** are not presented due to the insolubility in most of organic solvents.



1a R_1= H
1b R_1= Me
1c R_1= Cl
1d R_1= NO_2



2a R_1= H R_2= Bu
2b R_1= Me R_2= Bu
2c R_1= Cl R_2= Bu
2d R_1= NO_2 R_2= Bu
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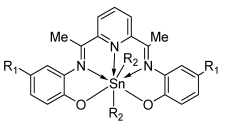
2g R_1= Cl R_2= Me
2h R_1= NO_2 R_2= Me



2j R_1=H R_2=Bu
2k R_1=Me R_2=Bu
2l R_1=Cl R_2=Bu
2m R_1=NO_2 R_2=Bu
2n R_1=H R_2=Me
2o R_1=Me R_2=Me
2p R_1=Cl R_2=Me
2q R_1=NO_2 R_2=Me

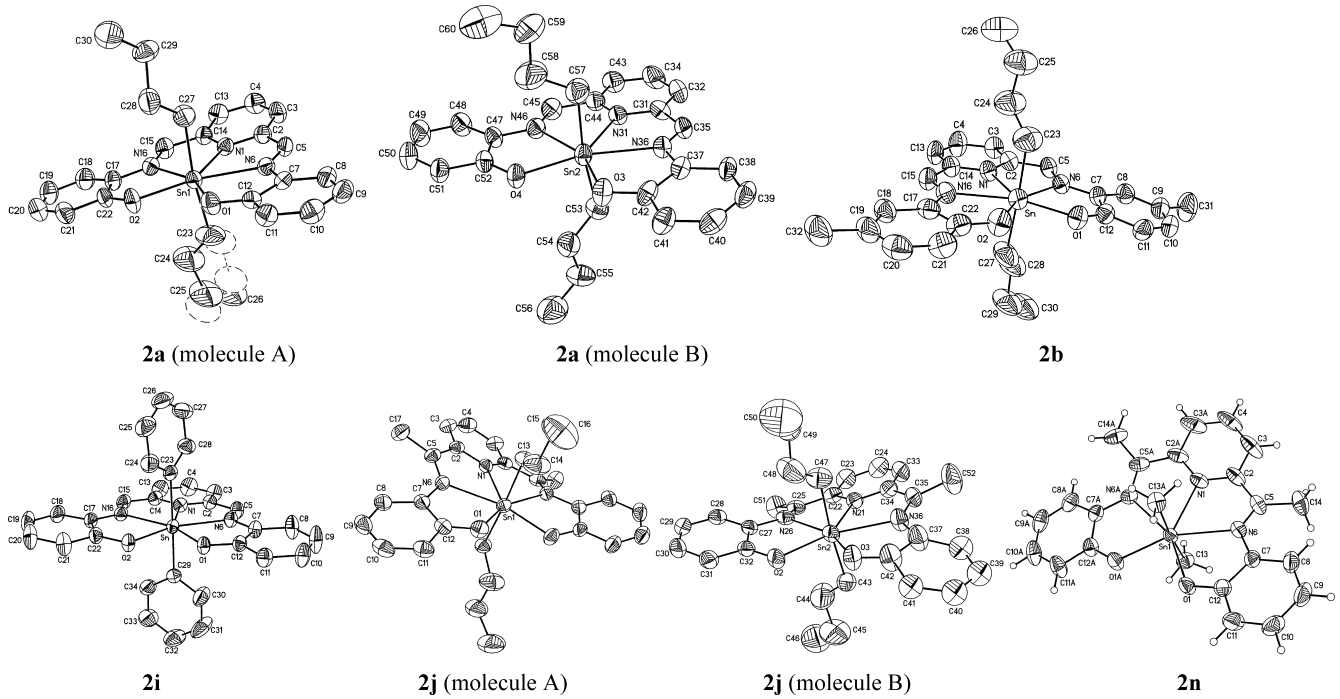


Fig. 1. Perspective View of Molecular Structures of Complexes **2a**, **2b**, **2i**, **2j** and **2n** ORTEP

Thermal ellipsoids at 30% of probability level minor component of disordered side chain drawn using open ellipsoids and broken lines.

Table 3. Crystallographic Data for Compounds **2a**, **2b**, **2i**, **2j** and **2n**

	2a	**2b**	**2i**	**2j**	**2n**
Formula	$C_{27}H_{31}N_3O_2Sn$	$C_{29}H_{35}N_3O_2Sn\cdot CH_2Cl_2$	$C_{31}H_{23}N_3O_2Sn\cdot 0.5CH_3OH$	$C_{88}H_{105}N_9O_7Sn_3$	$C_{23}H_{23}N_3O_2Sn$
Formula weight (g mol^{-1})	548.24	661.22	620.26	1756.88	492.13
Crystal size (mm)	0.35×0.32×0.05	0.38×0.33×0.05	0.294×0.228×0.106	0.36×0.16×0.15	0.40×0.26×0.16
Color	Red	Red	Red	Red	Red
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$C2/c$	$P2_1/n$	$C2/c$	$C2/c$
a (Å)	19.666(1)	21343(1)	12.285(1)	29.041(1)	15.187(8)
b (Å)	14.100(1)	14.816(1)	14.855(1)	18.130(1)	9.830(5)
c (Å)	19.898(1)	22.084(1)	15.763(1)	17.304(1)	14.772(7)
α (°)	90	90	90	90	90
β (°)	112.71	115.17(1)	108.72(1)	104.26	110.22(1)
γ (°)	90	90	90	90	90
V (Å^3)	5089.6(4)	6320.3(7)	2724.5(4)	8830.5(7)	2069.3(18)
Z	8	8	4	6	4
$D_{calc.}$ (g cm^{-3})	1.431	1.390	1.512	1.322	1.580
No. of collected reflections	41037	25538	22497	35692	8229
No. of independent reflections (R_{int})	8951	5572(0.0442)	4960(0.0338)	7772	1824
No. of observed reflections	8951	5572	4960	7772	1824
No. of parameters	623	414	391	489	135
$R^{a)}$	0.061	0.061	0.0310	0.068	0.019
$R_w{}^{b)}$	0.101	0.111	0.0778	0.140	0.052
GOF	0.967	0.971	1.057	1.023	1.059

a) $R=\sum||F_o|-|F_c||/\sum|F_o|$, *b*) $R_w(F_o)^2=[\sum w(F_o^2-F_c^2)^2/\sum wF_o^4]^{1/2}$.

adenocarcinoma) and the IC_{50} values are presented in Table 5. The screening results of compounds **2a**—**d** complexes exhibited higher activity than the *cis*-platin which was used as reference. However, compound **2d** possesses the highest activity against the six cell lines tested followed by complex **2a** which showed important inhibitory efficiency for MCF7, K-562, U251, and SKLU-1 lines. In the case of HTC-15 and PC-3 cell lines the second more active complexes were **2c** and **2b**, respectively, which showed certain cyto-selectivity against these cell lines. Figure 2 shows a trend in the activity exhibited by compounds **2c** and **2d**, although the latter displayed the lowest IC_{50} values the tendency remained constant for all cell lines evaluated, which may be associated with the electrowithdrawing character of Cl and NO_2 positioned at the aromatic ring. In similar way compounds **2a** and **2b** showed consistent pattern in their inhibition activity with all cell lines except for K-562, apparently, Cl and NO_2 substituents at C-5 of the aromatic ring improve significantly the cytotoxic activity. In this line we recently reported a study of pentacoordinated tin complexes aminophenol derivatives, in

Table 4. Bond Lengths and Angles for Complexes **2a**, **2b**, **2i**, **2j** and **2n**

Bond lengths (Å)

	2a (A)		**2a** (B)	**2j** (A)		**2j** (B)		**2b**	**2i**	**2n**
Sn(1)–O(1)	2.171(4)	Sn(2)–O(3)	2.156(4)	2.159(4)	Sn(2)–C(47)	2.118(7)	Sn(1)–O(1)	2.160(4)	2.133(2)	2.145(2)
Sn(1)–O(2)	2.160(4)	Sn(2)–O(4)	2.167(4)		Sn(2)–C(43)	2.128(8)	Sn(1)–O(2)	2.187(4)	2.157(2)	
Sn(1)–C(23)	2.120(7)	Sn(2)–C(53)	2.140(7)		Sn(2)–O(3)	2.128(5)	Sn(1)–C(23)	2.144(7)	2.155(3)	
Sn(1)–C(27)	2.153(6)	Sn(2)–C(57)	2.151(7)		Sn(2)–O(2)	2.143(4)	Sn(1)–C(27)	2.134(7)		
Sn(1)–N(1)	2.410(5)	Sn(2)–N(36)	2.398(5)	2.425(7)	Sn(2)–N(21)	2.419(5)	Sn(1)–N(1)	2.408(5)	2.386(2)	2.409(2)
Sn(1)–N(6)	2.393(5)	Sn(2)–N(46)	2.425(5)	2.446(5)	Sn(2)–N(36)	2.429(6)	Sn(1)–N(6)	2.405(5)	2.363(2)	2.444(2)
Sn(1)–N(16)	2.424(5)	Sn(2)–N(31)	2.427(5)		Sn(2)–N(26)	2.439(6)	Sn(1)–N(16)	2.436(5)	2.421(2)	
O(1)–C(12)	1.309(7)	O(3)–C(42)	1.321(7)	1.303(7)	Sn(2)–C(47)	2.118(7)	O(1)–C(12)	1.318(7)	1.324(3)	1.315(2)
O(2)–C(22)	1.303(7)	O(4)–C(42)	1.308(7)		Sn(2)–C(43)	2.128(8)	O(2)–C(22)	1.312(8)	1.311(3)	
N(6)–C(5)	1.287(7)	N(36)–C(35)	1.276(7)		C(25)–N(26)	1.284(8)	N(6)–C(5)	1.276(7)	1.277(3)	1.295(3)
N(6)–C(7)	1.288(7)	N(36)–C(37)	1.388(7)	1.413(8)	C(35)–N(36)	1.290(8)	N(6)–C(7)	1.384(7)	1.396(3)	1.391(3)
N(16)–C(15)	1.286(7)	N(46)–C(45)	1.273(7)		N(26)–C(27)	1.397(8)	N(16)–C(15)	1.284(7)	1.278(4)	
N(16)–C(17)	1.401(7)	N(46)–C(47)	1.380(7)		N(36)–C(37)	1.370(10)	N(16)–C(17)	1.408(7)	1.393(4)	
Sn(1)–C(13)				2.134(6)			Sn(1)–C(29)		2.168(3)	
							Sn(1)–C(13)			2.127(2)

Bond angles (°)

	2a (A)		**2a** (B)		**2j** (A)		**2j** (B)
O(1)–Sn(1)–O(2)	84.0(2)	C(53)–Sn(2)–C(57)	170.0(3)	O(1)–Sn(1)–O(1)	87.4(2)	C(47)–Sn(2)–C(43)	171.9(3)
O(1)–Sn(1)–N(6)	71.0(2)	O(3)–Sn(2)–O(4)	84.3(2)	O(1)–Sn(1)–N(6)	71.2(2)	O(2)–Sn(2)–O(3)	84.6(2)
O(2)–Sn(1)–N(16)	71.4 (2)	O(3)–Sn(2)–N(36)	72.0(2)	N(6)–Sn(1)–N(6)	130.2(3)	O(3)–Sn(2)–N(36)	72.3(2)
O(1)–Sn(1)–N(16)	155.5(2)	O(4)–Sn(2)–N(46)	71.7(2)	N(1)–Sn(1)–N(6)	65.1(1)	O(2)–Sn(2)–N(26)	71.5(2)
O(2)–S(1)–N(6)	155.9(2)	O(3)–Sn(2)–N(46)	156.1(2)	C(13)–Sn(1)–N(1)	87.6(2)	O(2)–Sn(2)–N(36)	156.8(2)
N(1)–Sn(1)–N(16)	66.4(2)	O(4)–Sn(2)–N(36)	156.3 (2)	C(13)–Sn–(C13)	175.3(4)	O(3)–Sn(2)–N(26)	155.8(2)
N(1)–Sn(1)–C(23)	89.2(2)	N(36)–Sn(2)–N(46)	131.9(2)			N(36)–Sn(2)–N(26)	131.7(2)
N(1)–Sn(1)–C(27)	80.9 (2)	N(31)–Sn(2)–C(53)	84.5(2)			N(21)–Sn(2)–C(43)	86.7(3)
N(1)–Sn(1)–C(29)		N(31)–Sn(2)–C(57)	86.1(2)			N(21)–Sn(2)–C(47)	85.3(3)
C(23)–Sn(1)–C(27)	169.3(3)						
C(23)–Sn(1)–C(29)							

	2b	**2i**		**2n**
O(1)–Sn(1)–O(2)	84.6(2)	82.2(1)	O(1)–Sn(1)–O(1A)	84.6(1)
O(1)–Sn(1)–N(6)	71.7(2)	73.0(1)	O(1)–Sn(1)–N(6A)	71.6(1)
O(2)–Sn(1)–N(16)	71.5(2)	71.4(2)	N(1)–Sn(1)–N(6A)	66.1(1)
O(1)–Sn(1)–N(16)	155.9(2)	153.6(1)	N(1)–Sn(1)–C(13A)	83.3(1)
O(2)–S(1)–N(6)	156.3(2)	155.2(1)	C(13)–Sn(1)–C(13A)	174.6(1)
N(1)–Sn(1)–N(16)	66.2(2)	66.3(2)		
N(1)–Sn(1)–C(23)	89.0(2)	88.2(1)		
N(1)–Sn(1)–C(27)	87.7(3)			
N(1)–Sn(1)–C(29)		89.1(1)		
C(23)–Sn(1)–C(27)	176.4(3)			
C(23)–Sn(1)–C(29)		174.2(1)		

Table 5. *In Vitro* Cytotoxicity Assay for Complexes **2a**—**d** IC_{50} (μM) Values

Compound	HTC-15	MCF7	K-562	U251	PC-3	SKLU-1
2a	4.1±0.05	1.9±0.09	0.97±0.2	1.6±0.10	4.9±0.30	1.8±0.10
2b	6.4±0.40	2.3±0.30	3.7±0.30	2.4±0.10	4.8±0.30	2.1±0.30
2c	3.04±0.30	3.5±0.50	2.9±0.10	4.5±0.10	5.3±0.30	2.1±0.06
2d	0.51±0.09	1.01±0.10	0.29±0.01	0.78±0.08	1.62±0.14	0.57±0.05
cis-Platin	13.83±0.7	13.03±1.3	15.20±1.4	9.09±0.8	15.94±1.2	7.13±0.2

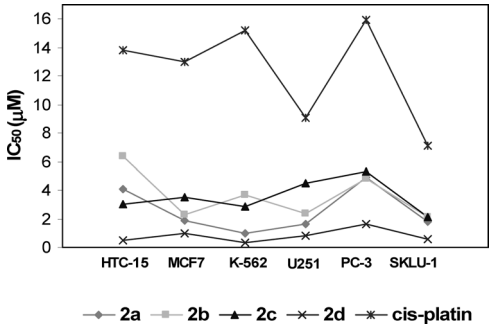


Fig. 2. IC_{50} (μM) Values in Cytotoxic Activity of Compounds **2a**—**d** and the Tested Cell Lines

which complex with Cl substituent at the aromatic ring exhibited the best performance for different carcinogenic cell lines.[44)]

Anti-inflammatory Activity The anti-inflammatory activity of the organotin derivatives was also evaluated *in vivo* using the TPA induced ear edema bioassay in mice where indomethacin was used as standard. The percentage of inhibition values are given in Table 6. The results indicated that all complexes have positive effect on induced ear edema which depends on the dose. The anti-inflammatory activity of compounds decrease in the following order: **2c**>**2b**>**2a**>**2d** (IC_{50} 0.11, 0.24, 0.29, 0.56). However, complex **2c** resulted to be more potent than the indomethacin in two orders of magnitude. Relevant differences in the anti-inflammatory activity between complexes **2a** and **2b** were not observed; instead they exhibited a similar profile to the reference.

Anti-oxidant Activity The antioxidant ability of the compounds prepared has been checked through the study of lipid peroxidation in rat brain homogenate, the antioxidant effect was evaluated as the inhibition of formation of thiobarbituric acid-reactive substances (TBARS) caused by complexes **2a**—**d**, where α-tocopherol and quercetine were used as positive controls. The complexes **2b** and **2c** showed superior lipid peroxidation inhibition activities in comparison to references as shown in Table 7, complex **2b** exhibits the best inhibition effect as compared to the other complexes of this series. The nitro derivative was essentially inactive **2d**. In general, the heptacoordinated tin complexes evaluated exhibit better activity than the pentacoordinated diphenyl tin salicyliden-*ortho*-aminophenols recently reported.[62)]

Conclusions

The preparation and characterization of seven coordinated monomeric tin complexes derived from pyridine Schiff bases were completed. High yields were obtained when the reaction was carried out in one pot-step. The series **2a**—**d** exhibited significant biologic activity against the six cell lines

Table 6. *In-Vivo* Anti-inflammatory Activity IC_{50} Values for Compounds **2a**—**d**

Compound	Doses (μmol/ear)	Edema (mg)	Inhibition (%)	IC_{50}
2a	0	12.96±0.78	—	
	0.031	12.30±1.78	5.2	
	0.1	10.45±0.79*	19.46	0.29 μmol/ear
	0.31	5.85±1.20*	54.91	
	1	2.43±0.75*	81.31	
2b	0	14.74±0.33	—	
	0.031	11.55±0.25*	21.64	
	0.1	10.75±0.85**	27.07	0.24 μmol/ear
	0.31	5.73±1.43**	61.16	
	1	2.70±0.20**	81.86	
2c	0	15.62±0.42	—	
	0.031	12.20±0.82*	21.91	
	0.1	10.24±1.19**	34.47	0.11 μmol/ear
	0.31	2.55±0.64**	83.68	
	1	12.96±0.92**	86.39	
2d	0	14.56±0.32	—	
	0.031	14.36±0.68	1.37	
	0.1	13.48±0.37	7.42	
	0.31	11.00±0.40**	24.45	0.56 μmol/ear
	0.56	7.54±1.01**	48.21	
	1	3.48±0.55**	76.1	
Indomethacin	0	16.24±0.86	—	
	0.13	10.53±1.04*	35.14	
	0.24	8.18±0.34*	48.18	0.27 μmol/ear
	0.42	7.10±1.34*	56.28	
	0.75	4.97±1.70*	69.42	
	1.3	1.57±0.33*	89.19	

The value $p \leq 0.05$ (*) and $p \leq 0.01$ (**) were considered as significant difference with respect to the standard.

tested lines HTC-15, MCF7, K-562, U251, PC-3 and SKLU-1, where the most active compound was **2d**, however, certain selectivity towards specific cell lines was observed for complexes **2a**, **2b** and **2c**. Parallelism between the character of substituents at the aminophenol fragment and the cytotoxicity of these compounds lead us to conclude that an electronic effect around the tin atom might be involved in the mechanism of inhibition. As regards the anti-inflammatory activity the most active species resulted to be the complex **2c**, complexes **2a**, and **2b** exhibited similar activity and **2d** showed less activity than the standard. Meanwhile, for the antioxidant activity by the TBARS method the **2b** complex showed the best inhibitory activity. This contribution demonstrated the interest in heptacoordinated tin Schiff base derivatives which exhibit remarkable cytotoxicity, anti-inflammatory and anti-oxidant activity which is assumed to be strongly dependent on the nature of substituents attached to the aminophenol moiety. Indeed these complexes are more active than aminophenol and salicyliden-*ortho*-aminophenol pentacoor-

Table 7. Anti-oxidant Activity IC_{50} Values for Compounds **2a**—**d** in Inhibition of Lipid Peroxidation TBARS

Complex	Concentration (μM)	TBARS (nmol/mg prot.)	Inhibition (%)	IC_{50}
2a	0	8.93±0.26	—	
	0.32	8.96±0.17	0.41±1.48	
	1	8.30±0.26	7.09±1.40	
	3.16	6.90±0.25*	22.82±1.45	15.08±2.09 μM
	10	4.50±0.54**	50.06±4.68	
	31.62	2.74±0.77**	69.85±8.08	
	100	1.18±1.18**	87.06±5.00	
2b	0	8.60±0.09	—	
	1	6.67±0.15**	22.49±1.80	
	1.78	5.09±0.39**	40.94±4.20	1.77±0.06 μM
	3.16	1.10±0.26**	87.2±3.06	
	5.62	0.53±0.10**	93.86±1.12	
	10	0.42±0.06**	95.17±0.69	
2c	0	8.63±0.12	—	
	1	6.74±0.22**	21.77±3.57	
	1.78	5.70±0.50**	33.81±6.50	2.11±0.09 μM
	3.16	5.57±0.31**	70.33±3.31	
	5.62	0.59±0.12**	93.53±1.14	
	10	0.42±0.05**	95.16±0,53	
2d	0	12.70	—	
	0.32	12.32	2.99	
	1	11.81	7.02	
	3.16	10.43	17.88	>100 μM
	10	9.88	22.25	
	31.62	9.29	26.88	
	100	8.19	35.55	
Quercetine	0	9.52±0.19	—	
	1	8.33±0.33	11.70±2.14	
	1.78	7.64±0.47*	19.29±3.32	4.11±0.26 μM
	3.16	6.21±0.24*	34.16±3.05	
	5.62	3.20±0.55*	66.05±5.62	
	10	1.27±0.29*	86.61±2.92	
α-Tocopherol	0	9.48±0.79	—	
	100	8.43±0.45	11.25±2.71	
	177.83	8.01±0.35	15.65±2.07	569.09±24.54 μM
	316.23	7.49±0.16*	21.39±1.20	
	562.34	5.09±0.37*	46.36±3.38	
	1000	1.66±0.44*	82.28±4.80	

Each value represents the mean of 3—4 observations. The value $p \leq 0.05$ (*) and $p \leq 0.01$ (**) were considered as significant difference with respect to the standard.

dinated tin derivatives.

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