SYNTHESIS, CHARACTERIZATION AND HIGH *IN VITRO* ANTITUMOUR ACTIVITY OF NOVEL TRIPHENYLTIN CARBOXYLATES

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Abstract

The synthesis and spectral characterization of six novel triphenyltin compounds are described. The *in vitro* antitumour activity of three of these compounds against two human tumour cell lines, MCF-7, a mammary tumour, and WiDr, a colon carcinoma, was determined. All three compounds are more active than cis-platin, etoposide and doxorubicin against both tumour cell lines. They are as active as mitomycin C against WiDr, but less active against MCF-7.

Introduction

The exceptionally high *in vitro* antitumour activity of a series of substituted triphenyltin benzoates⁽¹⁾ against MCF-7, a mammary tumour (6 - 18 ng/ml) and WiDr, a colon carcinoma (15 - 18 ng/ml) prompted us to prepare additional triphenyltin compounds in order to examine whether the nature and substitution pattern of the aromatic ring of the carboxylate moiety influences specifically their activity.

Results and discussion

Synthesis

The substituted triphenyltin benzoates were synthesized by a 1:1 condensation of triphenyltin hydroxide with the appropriate substituted benzoic acids⁽¹⁾.

1: 3-FC₆H₄CO₂SnPh₃

2: 2,3-F₂C₆H₃CO₂SnPh₃

3: 2,3,4-(CH₃O)₃C₆H₂CO₂SnPh₃

4: 2,4,5-(CH₃O)₃C₆H₂CO₂SnPh₃

5: 3,4,5-(CH₃O)₃C₆H₂CO₂SnPh₃

Spectroscopic characterization

The spectral data characterizing compounds **1** to **6** are given in the experimental part.

The isomer shift (IS, in the range 1.12 - 1.28 mm/s) and quadrupole splitting (QS, in the range 2.25 - 2.46 mm/s) of the triphenyltin benzoates are in agreement with tetrahedral geometries⁽²⁾ at the tin atom (see figure 1).

Figure 1: Tetrahedral geometry proposed for the substituted triphenyltin benzoates, $XYZC_6H_2CO_2SnPh_3$

The $nJ(^{13}C, ^{19}F)$ and $nJ(^{13}C, ^{119/117}Sn)$ couplings enabled an easy assignment of the carbon atoms of the benzoate respectively phenyl groups. Where necessary, in the absence of fluorine, ^{13}C DEPT spectra were used, together with aromatic ^{13}C chemical shift increments.

The values of the $^1J(^{13}C, ^{119/117}Sn)$ coupling constants around 650/620 Hz and of the ^{119}Sn NMR chemical shifts in the range -100 to -120 ppm suggest the triphenyltin carboxylates to exhibit a tetracoordinated geometry⁽³⁻⁵⁾ in solution like in the solid state.

In vitro antitumour tests

The results of the *in vitro* activity tests against two human tumour cell lines, MCF-7, a mammary tumour, and WiDr, a colon carcinoma, performed on compounds **2**, **3** and **5**, are presented in table 1.

They are of comparable activity as the previously described triphenyltin carboxylates⁽¹⁾, i.e. more active than cis-platin, etoposide and doxorubicin against both tumour cell lines. They are as active as mitomycin C against WiDr but less active against MCF-7.

Compound	Cell lines	
	MCF-7	WiDr
2 , 2,3-F ₂ C ₆ H ₃ CO ₂ SnPh ₃	17	24
3 , 2,4,5-(CH ₃ O) ₃ C ₆ H ₂ CO ₂ SnPh ₃	16	15
5 , 2-SCH ₃ -3-C ₅ NH ₃ CO ₂ SnPh ₃	16	18
Cis-platin ⁽⁶⁾	850	624
Etoposide ⁽⁶⁾	187	62
Doxorubicin ⁽⁶⁾	63	31
Mitomycin C ⁽⁶⁾	3	1

Table 1: Inhibition doses ID₅₀ in ng/mL against two human tumour cell lines, MCF-7 and WiDr, obtained for compounds **2**, **3** and **5**, and for four clinically used antitumour drugs⁽⁶⁾

Experimental part

Syntheses and spectral characterization

Equimolar amounts of triphenyltin hydroxide and substituted benzoic acid are poured into a three-necked 250 mL flask equipped with a Dean-Stark funnel containing 200 mL of a toluene/ethanol 3/1 mixture. The mixture is refluxed for 4 h. The ternary azeotrope water/ethanol/toluene followed by the binary azeotrope toluene/ethanol are distilled off to 50% of the initial volume. The remaining solution is evaporated under reduced pressure. The solid obtained is recrystallised from the appropriate solvent.

Compound **1**, triphenyltin 3-fluorobenzoate, mp (recryst. from n-hexane): 89-90 °C, yield: 46%, Mössbauer parameters: quadrupole splitting QS: 2.44, isomer shift IS: 1.25, band widths: 0.91 and 0.93 mm/s; ¹H NMR (chemical shifts in ppm with respect to TMS; ⁿJ(¹H, ¹H) coupling constants in Hz between parentheses; ⁿJ(¹H, ¹⁹F) coupling constants in **bold**): 7.91 ppm, dd (**8**,1): H(2); 7.20, dddd (**8**,8,3,1): H(4); 7.36, ddd (**8**,8,6): H(5); 7.76-7.82, m: H(6) and H(o); 7.41-7.51, m: H(m) + H(p); ¹⁹F NMR: -113.8, ddd: (**9**,**9**,**6**); ¹³C NMR (ⁿJ(¹³C, ¹⁹F) coupling constants in Hz between parentheses; ⁿJ(¹³C, ^{119/117}Sn) coupling constants in Hz in **bold** between parentheses; calculated chemical shifts⁽⁷⁾⁽⁸⁾ between brackets): 133.1 [132.0], d (³J = 7): C(1); 117.3 [117.1], d (²J = 23): C(2); 162.4 [163.3], d (¹J = 247): C(3); 119.5 [120.7], d (²J = 21): C(4); 129.6 [129.9], d

($^3J = 8$): C(5); 126.2 [125.5], d ($^4J = 2$): C(6); 171.3, s: C(7); 138.1, s ($^1J = \mathbf{648/620}$): C(i); 136.8, s (unresolved $^2J \approx \mathbf{48}$): C(o); 128.9, s (unresolved $^3J \approx \mathbf{64}$): C(m); 132.2, s: C(p); ^{119}Sn NMR: -106.3.

Compound **2**, triphenyltin 2,3-difluorobenzoate, mp (recryst. from ethanol): 87-89 °C, yield: 81%, Mössbauer parameters: quadrupole splitting QS: 2.48, isomer shift IS: 1.25, band widths: 0.91 and 0.91 mm/s; ^1H NMR, chemical shifts in ppm with respect to TMS, $^nJ(^1\text{H}, ^1\text{H})$ coupling constants in Hz between parentheses ($^nJ(^1\text{H}, ^{19}\text{F})$ coupling constants in **bold**): 6.58, dddd (**11,10,7,2**): H(4); 6.33, dddd (**10,10,5,2**): H(5); 7.22, dddd (**10,6,3,2**): H(6); 7.83-7.86, m: H(o); 7.09-7.23, m: H(m) + H(p); ^{19}F NMR, chemical shifts with respect to CFCl_3 : -134.5, (o-F); -137.8, (m-F), broad singlets; ^{13}C NMR, chemical shift in ppm with respect to TMS, ($^nJ(^{13}\text{C}, ^{19}\text{F})$ coupling constants in Hz between parentheses; $^nJ(^{13}\text{C}, ^{119/117}\text{Sn})$ coupling constants in Hz in **bold** between parentheses; calculated chemical shifts⁽⁷⁾⁽⁸⁾ between brackets): 121.4 [119.1], b: C(1); 151.2 [151.9], dd ($^1J = 247$, $^2J = 13$): C(2); 151.0 [150.4], dd ($^1J = 260$, $^2J = 137$): C(3); 120.8 [122.1], d ($^2J = 18$): C(4); 123.2 [125.4], dd (3J & $^4J = 6$ & 5): C(5); 126.9 [126.95], b: C(6); 169.3, s: C(7); 138.2, s ($^1J = \mathbf{647/617}$): C(i); 137.1, s (unresolved $^2J \approx \mathbf{49}$): C(o); 129.3, s ($^3J = \mathbf{65/62}$): C(m); 130.3, s: C(p); ^{119}Sn NMR: -102.1 ($^1J(^{119}\text{Sn}, ^{13}\text{C}) = 647$).

Compound **3**, triphenyltin 2,3,4-trimethoxybenzoate, mp (recryst. from chloroform/n-hexane): 82-83 °C, yield: 84%; Mössbauer parameters: QS: 2.25, IS: 1.12, band widths: 1.32 and 1.35; ^1H NMR (estimated $^3J(^1\text{H}, ^{117/119}\text{Sn})$ coupling constants from non resolved satellites between brackets in **bold**): 6.66, d (9): H(5); 7.78, d (9): H(6); 7.79-7.83, m [$\approx \mathbf{60}$]: H(o); 7.38-7.47, m: H(m) + H(p); 3.85, 3.86 and 3.88: CH_3O ; ^{13}C NMR: 117.7 [109.1]: C(1); 155.2 and 157.2 [148.4 and 151.0]: C(2) and C(4); 142.9 [130.8]: C(3); 106.8 [107.1]: C(5); 128.3 [124.7]: C(6); 172.0: C(7); 138.8 ($^1J = \mathbf{649/620}$): C(i); 136.9 (unresolved $^2J \approx \mathbf{48}$): C(o); 128.8 (unresolved $^3J \approx \mathbf{63}$): C(m); 130.0: C(p); 56.0, 61.0 and 61.8: CH_3O ; ^{119}Sn NMR: -118.0.

Compound **4**, triphenyltin 2,4,5-trimethoxybenzoate, mp (recryst. from chloroform/n-hexane): 135-136 °C, yield: 94%; Mössbauer parameters: QS: 2.29, IS: 1.24, band widths: 0.81 and 0.86; ^1H NMR: 6.51, s: H(3); 7.56, s: H(6); 7.77-7.82, m [$\approx \mathbf{66}$]: H(o); 7.39-7.46, m: H(m) + H(p); 3.86, 3.88 and 3.91: CH_3O ; ^{13}C NMR: 111.0 [109.1]: C(1); 156.1 and 153.6 [155.1 and 151.0]: C(2) and C(4); 98.3 [100.4]: C(3); 142.6 [137.5]: C(5); 115.9 [118.0]: C(6); 171.9: C(7); 138.9 ($^1J = \mathbf{649/620}$): C(i); 136.9 ($^2J \approx \mathbf{48}$): C(o); 128.7 ($^3J \approx \mathbf{63}$): C(m); 129.9: C(p); 55.9, 56.4 and 57.4: CH_3O ; ^{119}Sn NMR: -120.4.

Compound **5**, triphenyltin 3,4,5-trimethoxybenzoate, mp (recryst. from ethanol): 114-115 °C, yield: 91%; Mössbauer parameters: QS: 2.35, IS: 1.22, band widths: 0.88 and 0.95; ^1H NMR: 7.32, s: H(2) = H(6); 7.78-7.81, m [$\approx \mathbf{62}$]: H(o); 7.42-7.49, m: H(m) + H(p); 3.87: 3- $\text{CH}_3\text{O} = 5\text{-CH}_3\text{O}$; 3.88: 4- CH_3O ; ^{13}C NMR: 125.5 [124.5]: C(1); 108.0 [109.3]: C(2) = C(6); 152.7 [146.2]: C(3) = C(5); 128.2 [135.6]: C(4); 172.4: C(7); 138.4 ($^1J = \mathbf{649/620}$): C(i); 136.8 ($^2J \approx \mathbf{48}$): C(o); 128.9 ($^3J \approx \mathbf{63}$): C(m); 130.1: C(p); 60.8: 3- $\text{CH}_3\text{O} = 5\text{-CH}_3\text{O}$; 56.2: 4- CH_3O ; ^{119}Sn NMR: -112.4.

Compound **6**, triphenyltin 2-methylthio-3-pyridinecarboxylate, mp (recryst. from ethanol): 130-133 °C, yield: 71%; Mössbauer parameters: QS: 2.46, IS: 1.28, band widths: 0.86 and 0.90; ^1H NMR: 8.32, dd (8,2): H(4); 7.01, dd (8,5): H(5); 8.53, dd (5,2): H(6); 7.80 - 7.83, m [$^3J \approx \mathbf{66}$]: H(o);

7.45 - 7.50, m: H(m + p); 2.52, s: SCH₃; ¹³C NMR: 162.8 [chemical shift calculated with the chemical shift increments characteristic for pyridine systems⁽⁷⁾⁽⁸⁾: 161.4]: C(2); 124.0 [124.5]: C(3); 139.9 [138.1]: C(4); 117.7 [120.6]: C(5); 151.5 [155.2]: C(6); 171.3: C(7); 138.1 (¹J = **647/618**): C(i); 136.9 (²J ≈ **49**): C(o); 128.9 (³J ≈ **64**): C(m); 130.1: C(p); 13.9: SCH₃; ¹¹⁹Sn NMR: -102.4.

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Received: January 17, 1994 - Accepted: February 14, 1994 - Received in revised camera-ready format: February 18, 1994