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SYNTHESIS AND INITIAL CANCER CELL RESULTS OF ORGANOTIN POLYETHERS DERIVED FROM THE ANTICOAGULANT DICUMAROL

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ABSTRACT

Organotin polyethers are synthesized from the interfacial polymerization of dicumarol and diorganotin dihalides in near 100% yields. The products show infrared bands characteristic of the formation of the Sn-O linkage. MALDI MS shows ion fragment clusters to two units. Isotopic abundance comparisons are consistent with the present of tin atoms in the ion fragment clusters. Proton NMR is consistent with the presence of both reactants in the product and absence of the dicumarol protons. The products exhibit cell inhibition towards all of the cancer cell lines including two pancreatic cancer and breast cell lines.

Keywords: organotin polyethers, organotin polymers, MALDI MS, pancreatic cancer, cancer, dicumarol

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INTRODUCTION

The present research is part of an overall effort to synthesize polymers that can be employed in the inhibition of various unwanted pathogens and infectious agents, here cancer. One rational to our synthesis is to couple metal-containing moieties that are known to exhibit biological activity with Lewis bases that also exhibit biological activity in hopes that the combination will have a synergic affect. Organotin compounds are well known for their biological activity. Some of our activity involving organotin polymers has been recently reviewed [1-3]. More organotin compounds are available commercially than any other metal-containing organometallics [4,5]. Further, more organotin compounds have undergone testing as potential anticancer agents than any other single group of compounds [2-5].

Dicumarol or dicoumarol is an anticoagulant that acts as a Vitamin K antagonist similar to warfarin. As such, it prohibits the formation of prothrombin and factors VII, IX, and X in the liver. It is used in the prevention and treatment of thromboemboic disorders as well as embolisms. In biochemistry, it is also employed as a reductase inhibitor. It binds plasmatic proteins [6]. It is sold under a number of generic names including BHC, bishydroxycoumarin and dicoumarin. It is also available under a number of trade names including Acadyl, Acavyl, Antitrobosin, Baracoumin, Cuma, Cumid, Dicoumal, Dicman, Dicumarine, Dicumol, Dufalone,

Kumoran, Melitoxin, Temparin, and Trombosan. It is among the most widely used drugs as a "blood thinner" and oral anticoagulant interfering with the metabolism of vitamin K.

Dicumarol is produced by conversion of nontoxic coumarin in moldy sweet clover hay, lespepeza hay, and sweet vernal hay. Eating hay results in blood loss due to spontaneous hemorrhaging [6]. Dicumarol has been shown to be involved in a number of biological activities. For instance, Abdelmohsen and coworkers have found that it is a potent reversible inhibitor of gap junctional intercellular communication [7]. Mironov and coworkers report that it is an inhibitor of ADP-ribosylation of CtBP3/BARS, fragments golgi non-compact zones, and inhibits intra-golgi transport [8]. Culler and coworkers report its use in the inhibition of NADPH [9].

Thus, there is sufficient evidence that dicumarol is active in a variety of biological activities thus fulfilling our desire that the non-metal containing moiety also offers biological activity. Dicumarol has not been previously incorporated into polymers but has been used extensively in polymeric matrices for control release [for instance 10]. Here we report preliminary results for the polymers synthesized from various organotin dihalides and dicumarol. The synthesis is affected employing the interfacial polymerization between dicumarol and the various diorganotin dihalides as shown below.

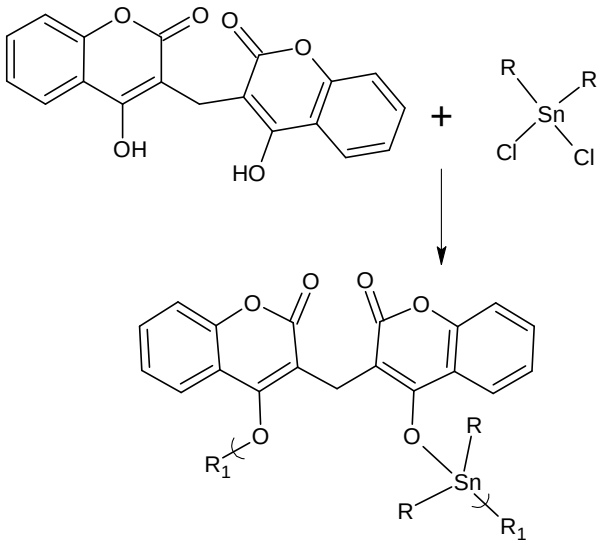

Figure 1: Overall reaction between dicumarol and organotin dihalides, here organotin dichlorides where R represents alkyl/aryl substituents on tin and R_1 chain extension.

MATERIAL AND METHODS

Synthesis

Diphenyltin dichloride (1135-99-5), dicumarol (66-76-2)), dimethyltin dichloride (753-73-1) and dibutyltin dichloride (683-18-1) were purchased from Aldrich Chemical Co., Milwaukee, WS; diethyltin dichloride (866-55-7) was obtained from Peninsular Chemical Res., Gainesville, FL; dioctyltin dichloride (3542-36-7) and dicyclohexyltin dichloride (3342-69-6) were obtained from Ventron Alfa Inorganics, Beverly, Mass.

Reactions were carried out using the interfacial polycondensation technique. Briefly, an aqueous solution (30 ml) containing the camphoric acid (0.00300 mol) and sodium hydroxide (0.0090 mol) was transferred to a one quart Kimax emulsifying jar fitted on top of a Waring Blender (model 1120; no load speed of about 18,000 rpm; reactions were carried out at about 25 ^{o}C). Because the diacid form of dicumarol is not a strong nucleophile, base is added converting dicumarol to its salt which is a reasonably strong nucleophile. Stirring was begun and a hepane solution (30 ml) containing the organotin dihalide (0.00300 mol) was rapidly added (about 3-4 seconds) through a hole in the jar lid using a powder funnel. The resulting solution was blended for 15 seconds. The precipitate was recovered using vacuum filtration and washed several times with

deionized water and heptane to remove unreacted materials and unwanted by-products. The solid was washed onto a glass petri dish and allowed to dry at room temperature.

Structural Characterization

Light scattering photometry was carried out with the samples dissolve in DMSO employing a Brice-Phoenix Universal Light Scattering Photometer Model 4000. Infrared spectra were obtained employing attenuated total reflectance infrared spectroscopy utilizing a JASCO FT/IR-4100 fitted with an ATR Pro 450-s. ^{1}H NMR spectra were obtained employing Varian Inova 400 MHz and Varian 500 MHz spectrometers. MALDI MS High resolution electron impact positive ion matrix assisted laser desorption ionization time of flight, HR MALDI-TOF, mass spectrometry was carried out employing a Voyager-DE Pro MALDI mass spectrophotomer, Applied Biosystems, Foster City, CA. The solid polymeric material was ground and then exposed to vortex mixing using copper spheres for 2 min. A small amount of the resultant fine powder was adsorbed onto the surface of 1µl matrix (alpha-cyano-4-hydroxycinnamic acid), CHA. The standard settings were used with a reflector mode of operation and an accelerating voltage of 25,000 volts; grid voltage 90% and an acquisition mass range of 500 to 2,000. Fifty to two hundred shots were typically taken for each spectrum. Results employing alpha-cyano-4-hydroxycinnamic acid are included in the present paper. The solid product and solid matrix were mixed together employing copper spheres giving a fine powder that was employed to obtain the spectra.

Cell Testing

The toxicity of each test compound was evaluated with the human pancreas adenocarcinoma cell line (AsPC-1), human pancreas epithelioid duct carcinoma cell line (PANC-1) or mouse embryo-fibroblast (NIH/3T3) cell line or other cell line. Following a 24 h incubation period, the test compounds were added at concentrations ranging to 60 microgram/mL and allowed to incubate at 37°C with 5% CO_2 for 72 h. Following incubation, Cell Titer-Blue reagent (Promega Corporation) was added (20 uL/well) and incubated for 2 h. Fluorescence was determined at 530/590 nm and converted to % cell viability versus control cells.

All cytotoxicity values are calculated against a base-line value for each line that was generated from "mock-treatment" of the normal and tumor cell lines with media supplemented with all diluents used to prepare the chemotherapeutic compounds. For example, if the compounds were dissolved in DMSO and serial dilutions prepared in Delbecco's Modified Eagle's Medium, MEM, to treat the cells, then the mock-treated cells were "treated" with the same serial dilutions of DMSO without added chemotherapeutic compound. This was done to ensure that any cytotoxicity observed was due to the activity of the compound and not the diluents. For the studies reported here, the mock-treatment never resulted in a loss of cell viability of more than one percent, demonstrating that the activity observed was not due to cytotoxicity of any of the diluents used, but was due to activity of the tested compounds. Standard dilutions are employed beginning with the most concentrated with essentially total inhibition occurring to the most dilute where little or no inhibition occurs. The inhibition curve is sigmoid and the EC_{50} determined at the midpoint of the curve. Once inhibition begins the concentration difference between the initial inhibition and final total inhibition is steep with the region between initial to final total inhibition essentially linear.

RESULTS AND DISCUSSION

Yield and Chain Length

Synthesis was carried out employing a classical interfacial polycondensation. Product yield is given in Table 1.

Table 1: Product yield from the synthesis of Group VA polymers from reaction with dicumarol

Organotin Moiety	Percentage Yield	Molecular Weight	Chain Length
Me_2Sn	97	7.3×10^4	150
Ete_2Sn	99	1.9×10^4	37
Bu_2Sn	98	4.0×10^4	70
Cy_2Sn	98	2.3×10^5	370
Oc_2Sn	56	1.6×10^5	200
Ph_2Sn	99	72.2×10^4	36

The reaction is rapid (less than 15 seconds stirring time) employing commercially available reactants and the interfacial reaction system that is currently employed in the synthesis of aromatic amides and polycarbonates. Thus, the process can employed in the production of grams to tons of product. Product yields are high, all above 90%, with the exception of the dioctyltin product. It is possible that the extended chain length of the octyl moiety inhibits rapid close contact of the reactants resulting is decreased yield.

It is instructive to remember that the active form of the dicumarol is the form as shown in Figure 2 since strong base, NaOH, is added forming the deprotonation of the aromatic hydroxide groups of the dicumarol.

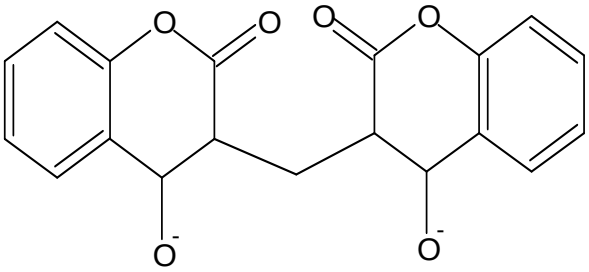

Figure 2: Active structure of dicumarol for the reaction system

Table 1 also contains the average chain lengths for each of the products. The products are low to medium polymers with chain length ranging from 36 to 370 repeat units. There appears to be no trend with respect to chain length. The dioctyltin product shows the lowest yield yet the highest chain length. The shortest alkyltin chain length, the dimethyltin, shows the next greatest chain length. The lack of specific trends is not unexpected since the reaction is complex and chain length and yield probably depend on a number of factors including solubility in each phase, rapidity that the reactants enter the reaction zone, and product solubility since the products are collected as precipitates from the reaction system.

Infrared Spectroscopy

Infrared spectral analysis was carried out for all of the samples over the range of 4000-650 cm^{-1}. All band locations are given cm^{-1}. Infrared spectral analysis is consistent with the proposed structure and with other reported analyses [11-24]. The spectra all show bands characteristic of both reactants and new bands for the product assigned to the Sn-O linkage (Table 2). A new band for the Sn-O-C tin-ether linkage is found about 1050. For the dimethyltin product this is found at 1055; diethyltin product at 1057; dibutyltin product 1055, dicyclohexyltin product at 1060; dioctyltin product at 1060 and the diphenyltin product at 1053. The OH stretch at about 3746 is small for dicumarol and absent for the products. For C-H stretching about 3000, dicumarol has bands about 3083 and 3063 corresponding to the aromatic C-H stretch and bands at 2991 and 2902 for aliphatic symmetric CH and 2840, 2796, 2752, and 2727 for asymmetric CH stretching. Dibutyltin dichloride has bands at 2960, 2927, 2872 and 2858. The dibutyltin polymer shows bands at 3081, 3066, 2955, 2924, 2871, 2840, 2755 and 2732 showing bands from both the dibutyltin and dicumarol moieties. Diphenyltin dichloride itself shows bands at 3068 and 3051 and the polymer shows bands at 3064, 3042 from the diphenyltin moiety and bands at 2990, 2902, 2845, 2804, 2752, and 2732 derived from the dicumarol moiety.

Bands characteristic of the carbonyl of the internal ester from dicumarol occur at 1644 and for the dibutyltin polymer and diphenyltin polymer both at 1644. Additional band assignments are given in table 2 and are consistent with the presence of units from both the organotin and dicumarol. Thus, infrared spectroscopy is consistent with the presence of units from both reactants and the formation of new bands consistent with the formation of the expected Sn-O linkage.

Table 2: Selected infrared bands for the monomers and polymers associated with the dibutyltin and diphenyltin polymers.

Band Assignment	Dicumarol	Bu_2SnCl_2	Bu_2Sn Polymer	Ph_2SnCl_2	Ph_2Sn Polymer
OH St	3746				
CH St Aromatic	3083, 3063		3081, 3066	3068, 3051	3064, 3042
CH Sym St Aliph	2991, 2902	2960, 2927	2955, 2924		2990, 2902
CH Asym St Aliph	2840, 2796, 2752, 2727	2872, 2858	2871, 2858, 2840 2755, 2732		2845, 2804, 2752, 2732
C=O St	1644		1644		1644
Ring CC ip St	1598, 1566, 1499, 1437		1599, 1567, 1502, 1427		1599, 1567, 1503, 1428
Sn-Ph St				1480, 1071	1481, 1076
CH_3 Sym St		1463	1453		
C=C St				1432, 1332	1429, 1329
CH_3 Asy Bend		1380	1346		
C-OH St	1320				
CH_2 twist	1345		1346		1347
Ring CC ip St	1277, 1216,		1279, 1219,		1279, 1219
CO st int esters	1163, 1106		1163, 1107		1163, 1108
Sn-O-C			1055		1053
Ring Breathing				996	997
CH_3 Rock		878	876		
Syn op Bend Ring Hydrogens				729	729
Asy op Bend Ring Hydrogens				691	692

NMR

NMR was run for the dicumarol in d3-chloroform and for the remainder of the compounds in d-6 DMSO. Results are consistent with those reported in the literature [11-19, 25, 26].All bands are given in ppm. Dicumarol itself shows a singlet at 11.3 from the acid proton which is absent in the polymers; double at 7.99; triplet at 7.59, several bands between 7.39 to 7.34; and a singlet at 3.84. Diphenyltin dichloride shows bands at 7.85 (ortho), and 7.41 and 7.31. The polymer has bands from the diphenyltin moiety at 7.85, 7.38 and 7.30 and from the dicumarol moiety at 7.98, 7.61, 7.36-7.30, and 7.37 consistent with the presence of moieties of both reactants. Dimethyltin dichloride shows bands at 1.3. The product shows bands at 1.32 from the dimethyltin moiety and 7.98, 7.58, 7.35-3.34 and 3.82. Diethyltin shows bands at 1.67 (methylene) and 1.25 (methyl). The polymer shows bands at 1.65 and 2.14 from the diethyltin moiety and 7.81, 7.68, 7.40 to 7.29, and 3.74. Thus, proton NMR shows bands consistent with the presence of both reactant moieties and absence of the protons from dicumarol. Finally, because of the poor solubility of the polymers, other data is not confidently reported.

MALDI MS

MALDI MS was developed to allow mass spectrometry to be run on polymeric samples [27-30] For about a dozen years we and others have been employing MALDI MS for the identification of a number of non-volatile metal and non-metal containing polymers [1,11-19]. The technique employed by us is not straight forward MALDI MS but it is applicable to soluble and insoluble products so has wide potential for application. Since this new technique focuses on the fragments that are created in the MALDI MS process, the approach is sometimes referred to as Fragmentation Matrix-Assisted Laser Desorption/ Ionization mass spectrometry or simply F MALDI MS because it is the fragments that are emphasized in the study. The technique should be applicable to any solid when the proper operating conditions are employed. There are some complications employing this technique to organotin because of rearrangements and the particular sensitivity of organotin moieties to laser radiation. It has been recently reviewed [31-33].

Figure 3 contains the MALDI MS for the product of dicumarol and dibutyltin dichloride. Table 3 contains the major ion fragment clusters for the product from dibutyltin dichloride and dicumarol. Several abbreviations as follows: U = one unit; Bu = butyl moiety, DC is the dicumarol unit minus two hydrogen atoms and Na for sodium. Sodium is a common contaminant. As in other cases, some of the ion fragment clusters are derived from reaction of the organotin moiety with the matrix [31-33]. One of these is noted in Table 3. The structure of this ion fragment cluster is given in Figure 4 and its isotopic abundance is consistent with the presence of a single tin atom. These will be omitted in other tables since they do not assist in the identity of the repeat unit of the polymers. The ion fragments typically show no fragmentation of the dicumarol in spite of the presence of the internal ester that could be evolved as CO_2 and the methylene unit connecting the two major ring systems in dicumarol. This is consistent with the mild nature of MALDI MS.

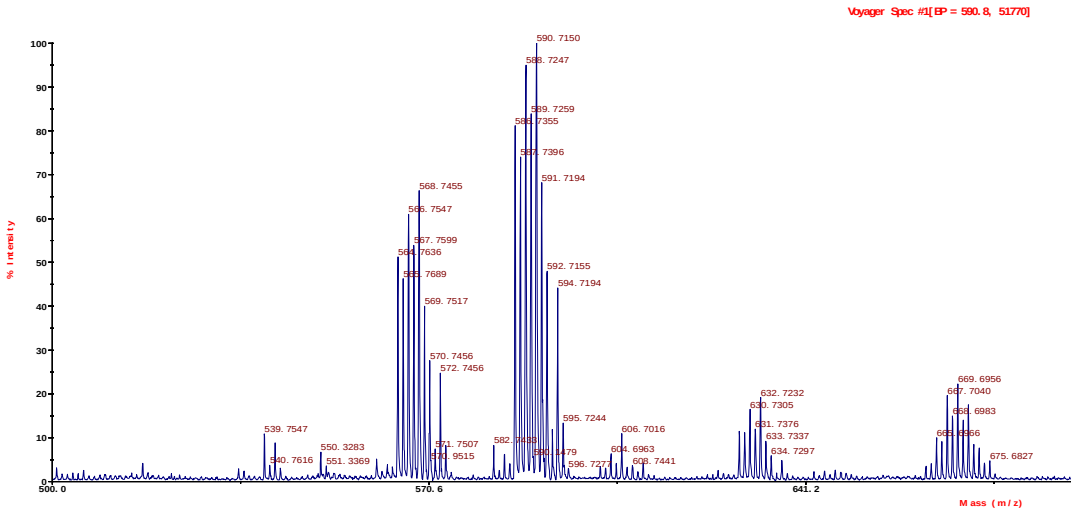

Figure 3: MALDI MS of the product of dibutyltin and dicumarol over the approximate mass range of 500 to 700 Da.

Table 3: Most abundant ion fragment clusters derived from the product of dibutyltin dichloride and dicumarol (where M = matrix molecule)

Ion Fragment Cluster, Da	(Tenative) Assignment	Ion Fragment Cluster, Da	(Tentative) Assigmnent
522	U-O	670	U+Sn-O
569	U	741	U+SnBu
591	U,Na	769	U+SnBu
607	U+O,Na	816	U+ Bu_2SnO
633	2M+ Bu_2Sn,Na	839	U+ Bu_2SnO,Na
		902	U+DC

The presence of tin within the ion clusters is indicated by the "tell-tale" fingerprint caused by the isotopic abundance of these tin isotopes. This is evident in the MALDI MS patterns shown in Figure 3 for the ion fragment clusters given at about 564, 591, 607, 634, and 670 Da.

The ion clusters contain intact segments along with some units minus the tin associated butyl groups. The loss of groups associated with tin is common and emphasizes the instability of the tin moiety probably because of its reported instability to energy in the range of the employed laser light source [31-33].

Tin has eleven isotopes; seven have natural abundances greater than 10%. Thus isotopic abundance matches can be done. Three matches are given in Table 4 for ion fragment clusters containing a single tin atom. Table 5 contains two such matches for ion fragment clusters containing two tin atoms. The agreement with the expected, "Known-left two columns", is reasonable consistent with the presence of two tin atoms in the cluster. As noted before, because of the instability of the organotin bonding to the laser light, it is not uncommon for loss of the organic moiety, here the butyl group. This loss generally occurs at the site of bond

breakage [11-19]. The dicumarol rings remain intact consistent with the mild conditions present for MALDI MS.

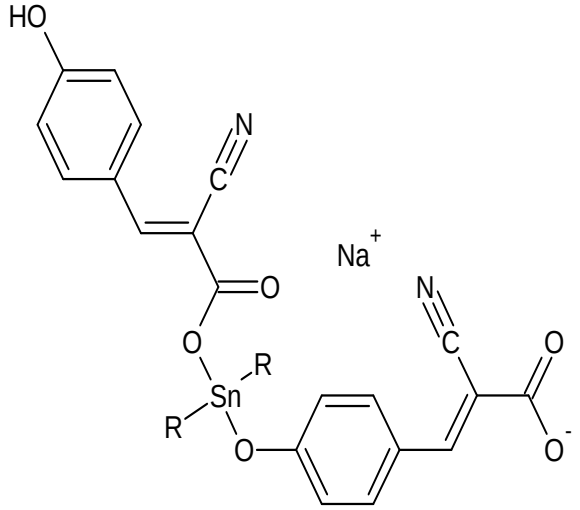

Figure 4: Proposed structure of the matrix-associated ion fragment cluster found about 634 where R is a butyl group.

Table 4: Isotopic abundance matches for three ion fragment clusters containing a single tin atom for the dibutyltin dichloride product.

Known for Sn		U		U,Na		U+O,Na	
116	45	565	48	587	45	603	47
117	24	566	31	588	31	604	23
118	75	567	76	589	74	605	76
119	26	568	32	590	38	606	28
120	100	569	100	591	100	607	100
122	14	571	15	593	15	609	13
124	17	573	18	595	19	611	16

Table 5: Isotopic abundance matches for two tin-containing ion fragment clusters containing two tin atoms for the dibutyltin product.

Known for Sn		2U+Bu_2SnO		2U+Bu_2SnO,Na	
232	12	810	14	833	14
233	13	811	15	834	16
234	43	812	44	835	43
235	35	813	35	836	33
236	94	814	93	837	90
237	51	815	53	838	51
238	100	816	100	839	100
239	35	817	36	840	35
240	81	818	82	841	87
242	32	820	30	843	32
244	22	822	24	845	24

In each case, ion fragment clusters given in Tables 4 and 5 are consistent with the presence of tin in the associated ion fragment clusters.

The most abundant ion fragment clusters for the product of diphenyltin dichloride and dicumarol are given in Table 6.

Table 6: Most abundant ion fragment clusters derived from the product of diphenyltin dichloride and dicumarol.

Ion Fragment Cluster, Da	(Tenative) Assignment	Ion Fragment Cluster, Da	(Tentative) Assigmnent
550	U+O-Ph	882	U+Ph_2Sn
608	U	942	U+DC
630	U+Na	1055	2U-2Ph,O
646	U+O,Na	1071	2U-2Ph
749	U+Sn,Na	1087	2U+O-2Ph
769	U+Sn,Na,O	1336	2U+Sn

Table 7 contains the isotopic abundance matches for three ion fragment clusters containg a single tin atom. Table 8 contains two matches for ion fragment clusters containing two tin atoms. The matches are reasonable consistent with the presence of tin atom(s) in these ion fragment clusters.

Table 7: Isotopic abundance matches for three ion fragment clusters containing a single tin atom for the diphenyltin product.

Known for Sn		U		U,Na		U+O,Na	
116	45	604	45	626	48	642	47
117	24	605	23	627	24	643	24
118	75	606	75	628	78	644	75
119	26	607	28	629	29	645	29
120	100	608	100	630	100	646	100
122	14	610	15	632	14	648	14
124	17	612	18	634	20	650	18

Table 8: Isotopic abundance matches for two tin-containing ion fragment clusters containing two tin atoms for diphenyltin products.

Known for Sn		2U-2Ph,O		2U+-2Ph	
232	12	1049	10	1065	14
233	13	1050	13	1066	15
234	43	1051	44	1067	42
235	35	1052	32	1068	30
236	94	1053	92	1069	90
237	51	1054	53	1070	55
238	100	1055	100	1071	100
239	35	1056	34	1072	36
240	81	1057	76	1073	78
242	32	1059	30	1075	31
244	22	1061	21	1077	24

The other products gave similar results. Thus, MALDI MS is consistent with the proposed repeat unit structure. Further, the results are consistent with chain scission occurring at the hetroatom tin and oxygen atoms as shown in Figure 5 consistent with other studies [11-16] producing the ion fragment clusters cited in Tables 3 and 6.

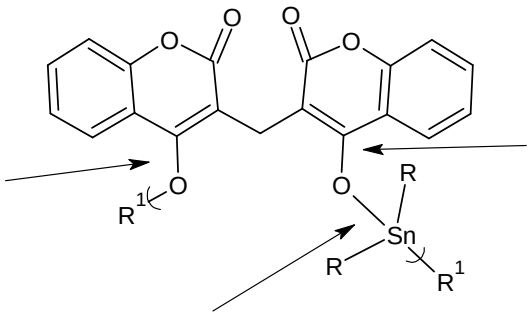

Figure 5: Sites of preferred polymer backbone bond scission.

Tumor analysis

The battery of test cancer cell lines used in this study is given in Table 8. They represent a broad range of solid cancer cell lines.

Table 8: Cell lines employed in the current study

Strain #	NCI Desig.	Species	Tumor Origin	Histological Type
3465	PC-3	Human	Prostate	Carcinoma
7233	MDA MB-231	Human	Pleural effusion breast	Adenocarcinoma
1507	HT-29	Human	Recto-sigmoid colon	Adenocarcinoma
7259	MCF-7	Human	Pleural effusion-breast	Adenocarcinoma
ATCC CCL-75	WI-38	Human	Normal embryonic lung	Fibroblast
CRL-1658	NIH/3T3	Mouse	Embryo-continuous cell line of highly contact-inhibited cells	Fibroblast
	AsPC-1	Human	Pancreatic cells	Adenocarcinoma
	PANC-1	Human	Epithelioid pancreatic cells	Carcinoma

In other studies we found that the polymer drugs are cytotoxic and cell death is by necrosis [1-3]. We have recently found that the anticancer activity is brought about by the intact polymer and not through polymer degradation [1-3, 33]. This is consistent with studies that show the polymers are stable in DMSO with half-chain lives, the time for the polymer chain length to halve, generally in excess of 30 weeks [1-3]. While it is well known that most organometallic compounds associate with polar solvents such as DMSO and that the biological results may be influenced by the presence of the DMSO [1,3,34-38], for polymers similar to those described in the present study, this influence is found to be small, generally less than 20% [1-3,35].

While different measures have been employed in the evaluation of cell line results, the most widely employed involve the concentration, dose, needed to reduce the growth of the particular cell line. Here the term effective concentration, EC, is used. The concentration of a drug, antibody, or toxicant that induces a response halfway between the baseline and maximum after a specified exposure time is referred to as the 50% response concentration and given the symbol EC_{50}.

Table 9 contains the EC_{50} values for the monomers and polymers and among the most widely used anticancer drugs, cisplatin. The monomer dicumarol offers no inhibition of any cell line to the highest concentration tested. Thus, inhibition of the cancer cells comes from the combination of the organotin with the dicumarol or presence of the organotin moiety.

Much of our recent effort has been on discovering compounds that inhibit pancreatic cancer because pancreatic cancer has no generally accepted "cure" [1-3, 20-22]. Two widely employed human pancreatic cell lines are included in the present study. These are the AsPC-1 cell line which is an adenocarcinoma pancreatic cell line representing the most often observed pancreatic cancer cell line found in humans (about 80%) and the PANC-1 cancer cell line which is an epithelioid carcinoma pancreatic cell line representing the second most frequently observed pancreatic cancer cell line found in humans (about 10%). All of the organotin polyethers inhibit both pancreatic cancer cell lines. The inhibition of the pancreatic cancer cell lines is similar for both the ASPC-1 and PANC-1 cells indicating that inhibition by the polymers may be general for the other pancreatic cancers.

The two breast cancer cell lines represent a matched pair. The MCF-7 (strain line 7259) cells are estrogen receptor (ER) positive while the MDA-MB-231 (strain number 7233) cells are estrogen-independent, estrogen receptor negative. In some studies involving organotin polymers there was a marked difference between the ability to inhibit the two cell lines dependent on polymer structure [1-3, 20-22]. Where there is a marked difference it is found that the Lewis base is attached to the organotin moiety through a O-Phenylene grouping which is similar to that present in molecules used to treat breast cancer such as diethylstilbestrol. In the current study there is not a great difference in the ability to inhibit the two cell lines by the polymers with the polymers inhibiting both breast cancer cell lines with about the same EC_{50} though the connection between the tin and Lewis base does contain similar linkage. The polymers also exhibit good inhibition of the prostrate (PC-3) and colon (HT-29) cancer cell lines.

Table 8: EC_{50} Concentrations (micrograms/mL) for the tested compounds, Values Given in ( ) are Standard Deviations for Each Set of Measurements

Sample	3T3	*WI-38*	*PANC-1*	*AsPC-1*
Me_2SnCl_2	0.43 (.1)	0.22(.1)	0.80(.1)	0.71(.1)
Me_2Sn/DC	12(1)	10(1)	12(1)	12(1)
Et_2SnCl_2	0.46(.1)	0.20(.1)	0.48(.1)	0.90(.1)
Et_2Sn/DC	23(2)	20(2)	22(2)	20(2)
Bu_2SnCl_2	0.20 (.05)	0.20(.05)	>15	>15
Bu_2Sn/DC	10(1)	10(1)	11(1)	11(1)
Cy_2Sn/DC	10.(1.)	11.(1.)	11.(1.)	11.(1.)
Oc_2SnCl_2	0.56(.1)	0.30(.1)	0.85(.1)	0.85(.1)
Oc_2Sn/DC	11(1)	11(1)	12(1)	11(1)
Ph_2SnCl_2	0.66(.1)	0.25(.1)	0.71(.1)	0.83(.1)
Ph_2Sn/DC	10(1)	11(1)	11(1)	10(1)
Dicumarol	>60	>60	>60	>60
Cisplatin	15(10)	1.2(0.1)	1.4(.1)	0.340(.1)

Sample	*PC-3*	*MDA-MB-231*	*HT-29*	*MCF-7*
Me_2SnCl_2	0.51(.1)	0.44(.1)	0.56(.1)	0.66(.1)
Me_2Sn/DC	10(1)	11(1)	14(1)	14(1)
Et_2SnCl_2	0.61(.1)	0.64(.1)	0.71(.1)	0.77(.1)
Et_2Sn/DC	21(2)	22(2)	22(2)	22(2)
Bu_2SnCl_2	1.4(1.1)	1.4(1.3)	1.2(.1)	0.7(.06)
Bu_2Sn/DC	10(1)	11(1)	12(1)	11(1)
Cy_2Sn/DC	11.(1.)	11.(1.)	11.(1.)	11.(1.)
Oc_2SnCl_2	0.55(.1)	0.65(.1)	0.65(.1)	0.70(.1)
Oc_2Sn/DC	15(1)	12(1)	13(1)	11(1)
Ph_2SnCl_2	0.82(.1)	0.76(.1)	0.56(.1)	0.68(.1)
Ph_2Sn/DC	11(1)	13(1)	12(1)	11(1)
Dicumarol	>60	>60	>60	>60
Cisplatin	1.00(0.10)	3.00(0.28)	2.00(0.21)	1.00(0.1)

CONCLUSIONS

Organotin polyethers are synthesized from the interfacial polymerization of dicumarol and diorganotin dihalides in near 100% yields. All of the reactants are commercially available and the synthetic system is employed industrially to product aramid fibers and polycarbonates [39] thus there should be ready synthesis from milligram to kilogram quantities of the polyethers. The products show infrared bands characteristic of the formation of the Sn-O linkage. MALDI MS shows ion fragment clusters to two units. Isotopic abundance comparisons are consistent with the present of tin atoms in the ion fragment clusters. Proton NMR is consistent with the presence of both reactants in the product and absence of the dicumarol protons. The products exhibit cell inhibition towards all of the cancer cell lines including two human pancreatic cancer cell lines and two human breast cell lines.

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