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REVIEW

Relationship of cytotoxic groups in organotin molecules and the effectiveness of the compounds against leukemia

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Cytotoxicity of organotin compounds is assessed and their effectiveness against leukemia is discussed. The functional groups attached to the tin atom in organotin compounds control the cytotoxicity of the compound towards the thymus gland. The four organotin moieties which have the greatest toxic effect upon the thymus gland are the tri-n-butyltin, di-n-butyltin, tri-n-propyltin and di-n-octyltin groups. Compounds containing these groups also exhibit the poorest test–control ratio (T/C) values when tested as anti-cancer agents against leukemic mice using NCI protocol.

Keywords: Organotin compounds, P388 leukemia, cytotoxicity, thymus gland

INTRODUCTION

With the advent of cisplatin drugs and now the carboplatin compounds,[1] inorganic chemicals have become important anti-cancer agents. Because these platinum compounds exhibit extreme toxicity, causing kidney damage, nausea and vomiting even at low doses,[1] a large number of organotin compounds which mimic the platinum compounds have been tested using L1210 or P388 Leukemia in mice.[2]

Even though more organotin compounds have yielded positive antineoplastic results against the P388 leukemia in mice than any other class of compounds,[3] they have not received much attention probably because the compounds tested have neither shown effectiveness against multiple types of cancer,[4] nor produced test results which are as good or better than those produced by the platinum compounds.[5] Several papers have investigated the relationship of structure,[2,4,6] Mössbauer shifts,[7] or labile groups[8] with NCI protocol test–control ratio (T/C) values (*vide infra*), but have produced no significant conclusions. This paper is an attempt to assess the structure and biological activity on the immune system compared with the effectiveness of the tin compounds in the test.

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METHODS AND TOXICITIES

Test procedure

The NCI protocol for testing antitumor agents was developed initially for the platinum compounds. A leukemic tumor (L1210 or P388) is injected into the intraperitoneal (ip) cavity (the cavity between organs in the stomach area) of a leukemic-prone inbred mouse (sibling breeding). The chemical to be tested is also injected into the ip cavity. The median lifespan of the treated (T) animals is compared with control (C) animals. The T/C ratio is given as a percentage. A value of less than 125 is considered insignificant. When administered at an equitoxic dose level against a positive control (cisplatin), a value of 150 is required for further testing.[7] The platinum compounds in current clinical use yield T/C values in excess of 200.[5]

L1210 lymphatic leukemia or P388 lymphocytic leukemia are used for testing. Although a number of other protocols have been tried and a number of variables exist in the test, e.g. using subcutaneous implantation of the tumor, the NCI protocol is still the most widely used *in vivo* test for initial antitumor screening of new compounds.[7] With organotin compounds the greatest

activity was observed with P388 lymphocytic leukemia (50% of the diorganotin dihalide compounds yielded T/C values >125) but only marginal activity with L1210 lymphatic leukemia (about 0.4% of the tested compounds yielded T/C values >125).[3]

Toxicity of organotin compounds

Unlike platinum compounds the mammalian toxicity of organotin compounds, except for the C_1 and C_2 alkyltin compounds, is low (Table 1).[9] The di- and tri-methyltin and di- and tri-ethyltin halides exhibit neurotoxic properties[10] and

Table 1 Toxicity (LD_{50}) for selected organotin compounds[a]

Compound	LD_{50} ($mg\,kg^{-1}$)	LD_{50} ($mmol\,kg^{-1}$)	Reference
Me_2SnCl_2	74–237	0.34–1.07	26
$Me_2Sn(SCH_2COO\text{-}i\text{-}C_8H_{17})_2$	620–1380	1.09–2.44	26
Me_3SnCl	9.2–20	0.05–0.10	26
Et_2SnI_2	7.0 (est.)	0.016	10
Et_3SnI	10 (est.)	0.030	10
$(Et_3Sn)_2SO_4$	6	0.012	10
$n\text{-}BuSnCl_3$	2200–2300	7.80–817	26
$n\text{-}Bu_2Sn(SCH_2COO\text{-}i\text{-}C_8H_{17})_2$	500–1037	0.83–1.71	26
$n\text{-}Bu_3SnCl$	129	0.39	12
$n\text{-}Bu_3SnF$	94	0.30	23
$n\text{-}Bu_3SnCl$	122	0.38	23
$(n\text{-}Bu_3Sn)_2O$	127	0.42	23
$n\text{-}Bu_3Sn$ benzoate	99/203[b]	0.24/0.49	23
$n\text{-}Bu_3Sn$ linoleate	190	0.34	23
$n\text{-}Bu_3Sn$ abietate	158	0.27	23
$n\text{-}Bu_3Sn$ naphthenate	224	0.37	23
$n\text{-}Bu_3Sn$ taurocholate	611	0.72	27
Ph_3SnF	160	0.43	12
Ph_3SnCl	135	0.35	12
Ph_3SnCl	125	0.32	10
Ph_3SnOH	171	0.46	12
Oct_2SnCl_2	920	2.21	10

[a]Definitions of abbreviations used in the Tables:

Abietate	$C_{20}H_{29}O_2^-$
Ac	Acetyl
AcGly	Acetylglycine
Ad	Adenine
AMP	2-Aminomethylpyridine
Bipy	2,2′-Bipyridine
Cy	Cyclohexyl
dnpGly	N—(2,4-dinitrophenyl)glycine
Gly	Glycine
HMPA	Methylpropylacetic acid
Linoleate	$C_{18}H_{31}O^-$
Naphthenate	$C_{10}H_7O$—
PBI	2═(2-Pyridyl)benzimidazole
Pen	Penicillaminate
Ph	Phenyl
Phen	1,10-Phenanthroline
Put	6-Purinethiolate
Pypy	Pyrido[2,3-*b*]pyrazine
Taurocholate	$C_{26}H_{44}NO_7S^-$
TBT	Tri-n-butyltin
Tol	Tolyl

[b]Results of two different experiments

present serious health hazards to the nervous system. Most other inorganic and organotin compounds exhibit little toxicity at low dosage.[11,12] After a single dose, the acute oral toxicity of organotins is manifested in the destruction of the intestines, the liver and bile duct.[13,14] Below the LD_{50}, the animals recover in about eight days and usually exhibit no chronic toxicity except for premature thymic involution, especially for di-n-butyltin (DBT), tri-n-propyltin (TPrT), tri-n-butyltin (TBT) and di-n-octyltin (DOT) compounds (Table 2).[11]

Cytotoxicity of the thymus gland

Premature atrophy of the thymus gland and some spleen damage is manifested in the chronic toxicity of many simple alkyl organotin compounds. Seinen and Willems[15] first observed this phenomenon in 1976 when they fed dioctyltin dichloride (150 ppm) to rats. The effect has also been observed with other dialkyltin and trialkyltin compounds with rodents[16] and with other animals.[17] Chronic toxicity for rats has been observed when the organotin is administered at the 5 ppm level in the drinking water[18,19] (Table 2). The effect is time- and dose-related. Near the LD_{50}, it is manifested with a single dose four or five days after administering the organotin compound.[14] At sub-acute levels, long-term administration of the organotin produced the greatest atrophy. Severe cytotoxicity occurred with only four organotin moieties: dioctyltin, dibutyltin, tripropyltin and tributyltin compounds (Table 2). Mild toxicity was observed with diethyltin, dipropyltin, triphenyltin and diphenyltin compounds. The latter three compounds apparently pose no serious short-term cytotoxic hazard, i.e. atrophy of the thymus gland is mild and only at high dose levels. The rest of the organotin

Table 2 Organotin compounds known to affect the thymus gland or spleen[a]

Compound	Extent	Concentration (ppm)	Reference
	Thymus		
Oct_2SnCl_2	Severe	40	16, 19
Bu_2SnCl_2	Severe	40	16, 19
Bu_3SnCl^2	Severe	40	16
Pr_3SnCl	Severe	40	16
Pr_2SnCl_2	Mild	40	16
Et_2SnCl_2	Mild	40	16
Bu_3SnF	Mild	5	18
Ph_2SnCl_2	Mild	150	16
Ph_3SnCl	Mild	150	16
Me_2SnCl_2	None	40	16
Me_3SnCl	None	5	16
Et_3SnCl	None	5	16
$OctSnCl_3$	None	150	16
Oct_3SnCl	None	150	16
Oct_4Sn	None	150	16
$(C_{12}H_{25})_2SnCl_2$	None	40	16
$(C_{18}H_{37})_2SnCl_2$	None	40	16
	Spleen		
$(Bu_3Sn)_2O$	Severe	260	28
Ph_3SnCl	Severe	260	28
Ph_3SnOAc	Severe	260	28
Cy_3SnOH	Severe	260	28
$PhSnCl_3$	Mild	260	28
Ph_2SnCl_2	Mild	260	28
Ph_4Sn	Mild	260	28
$[(PhCMe_2CH_2)Sn]_2O$	Mild	260	28

[a]Abbreviations as in Table 1.

Table 3 Organotin compounds inactive[a] against P388 leukemia in mice[b]

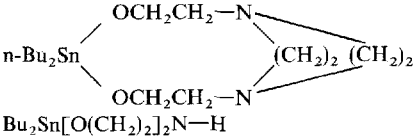
Compound	T/C (%) (Dose, mg kg^{-1})	Reference
[MePhSnCl]C_6H_4-*p*-C(Me)=N—NH—COOMe	100	29
[MePhSnCl]C_6H_5-*p*-C(Me)=O	100	29
$[Me_2SnBr]_2CH_2$	Toxic	29
$Me_2Sn(CH_2CH_2COOMe)_2$	Inactive[d]	20
Me_2SnCl_2L (L = Phen, PBI, AMP)	Inactive	4
$Me_2Sn(OCOCH_2)_2NMe$	120	29
$Me_2Sn(CH_2COOMe)_2$	128 (16)	20
Me_2Sn (PhCOGly)$_2$	101 (25)	30
$[Me_2Sn(SCH_2CH_2SO_3)_2]Na\,.\,2H_2O$	120 (15)	30
Me_3Sn(Put)	100 (0.375)	30
Me_3Sn(dnpGly)	100 (3.12)	30
Me_3Sn(PhCOGly)	103 (3.12)	30
$(Et_2SnCl)_2O$	120 (8)	20
Et_2SnX_2Bipy (X = Cl, Br, I)	Inactive	4
Et_2SnCl_2AMP	Inactive	4
$Et_2Sn(CH_2CH_2COOMe)_2$	Inactive	20
n-Pr_2SnBr_2Bipy	Inactive	4
n-Pr_2SnCl_2L (L = Bipy, PBI)	Inactive	4
n-$Pr_2SnCl_2$2Py	Inactive	4
n-Pr_2Sn_{12}L (L = Bipy, Phen, PBI)	Inactive	4
$(BuPhSnO)_2$	116 (100)	20
Bu_2SnCl_2Phen	121 (200)	2
$(Bu_2SnCl)_2O$	Inactive	20
Bu_2SnBr_2L (L = Bipy, Phen, PBI)	Inactive	4
n-Bu_2Sn(Pen)	120 (3.12)	30
$Bu_2Sn(NCS)_2$Bipy	123 (25)	4
n-Bu_2Sn(Put)$_2$	Inactive	30
$[n\text{-}Bu_2Sn(SCH_2CH_2SO_3)_2][C(NH_2)_3]_2$	115 (240)	30
$[n\text{-}Bu_2Sn(SCH_2CH_2SO_3)_2]Na_2\,.\,2H_2O$	101 (120)	30
	100	29
$Bu_2Sn[O(CH_2)_2]_2N—H$	Toxic	29
t-$Bu_2Sn[O(CH_2)_2]_2N—Me$	Toxic	29
t-$Bu_2Sn[O(CH_2)_2]_2N—H$	Toxic	29
n-$Bu_2Sn(OC_6H_4CH{:}NNCSSMe)$	124 (6.25)	31
n-$Bu_2Sn(OC_6H_4CH{:}NC_6H_4F)_2$	122 (6.25)	31
n-$Bu_2Sn(OC_{15}H_{10}N_2S_2)$	105 (6.25)	31
n-$Bu_2Sn(OC_{10}H_{10}N_2S_2)$	113 (0.78)	31
n-$Bu_2Sn(C_{15}H_{12}N_2S_2F)_2$	102 (1.56)	31
n-$Bu_2Sn(C_{12}H_{15}N_2S_2)_2$	117 (1.56)	31
n-$Bu_2Sn(C_{15}H_{13}N_2S_2)_2$	116 (6.25)	31
Bu_3Sn(AcGly)	102 (50)	30
Bu_3Sn(Put)	110 (3.125)	30
$[Cy_2SnPh]CH_2CH_2NH_3{}^+Cl^-$	100	29
$[PhSnBr_2]_2CH_2$	100	3
$[Ph_2SnBr]_2CH_2$	127[c]	29
$[Ph_2SnOMe]_2CH_2$	Toxic	29
$[Ph_2SnBr]_2CH_2$	127[c]	3
$[Ph_2SnBr]_2CH_2\,.\,2HMPA$	95	29
Ph_2Sn(Pen)	101 (25)	25
$Ph_2Sn(CH_2CH_2COOMe)_2$	Inactive	20
$[Ph_2Sn(PhS)]_2CH_2$	120	3, 29

Table 3 (continued)

Compound	T/C (%) (Dose, mg kg^{-1})	Reference
$Ph_2SnCH_2Sn(Ph_2)SSn(Ph_2)CH_2Sn(Ph_2)S$	100	3, 29
$Ph_2Sn[S(CH_2)_2]_2N—Me$	115	29
$Ph_3Sn(Put)$	100 (6.25)	30
$[Ph_3Sn]_3(Put)_2$	95 (3.125)	30
Oct_2SnCl_2L (L = Bipy, Phen, PBI)	Inactive	2, 4
$(CH_2CH_2(CF_2)_5CF_3)_2SnBr_2$	100–110	32
$(CH_2CH_2(CF_2)_5(F_3)_2SnCl_2$	125 (240)	32

[a]For definition please see under test procedure. Mode of introduction is according to NCI protocol. [b]Abbreviations as in Table 1. [c]Taken as inactive for this purpose. [d]Inactive means, no T/C value was reported but is less than 125.

moieties probably exhibit no cytotoxicity at normal exposure and at this time can be considered innocuous. Damage to the spleen only occurs at very high dosage, i.e. near the LD_{50} for the compound.

When compounds containing dibutyltin, tributyltin, tripropyltin and dioctyltin moieties are tested with leukemic mice using NCI protocol, the compounds generally fail as anticancer agents. Table 3 represents compounds which have little or no effect on mouse life expectancy and have been rejected for further testing. Table 4 represents the active compounds as defined previously. The compounds in the tables are primarily low-molecular-weight alkyl or substituted alkyl organotin compounds. They are arranged in order so as to group the organotin moiety in terms of increasing numbers of carbon atoms. The largest number of both active and inactive organotin compounds contain methyl, ethyl and phenyl groups, reflecting availability and extent of testing. Since most of these compounds are easy to synthesize, more of these compounds are available for testing than other organotin compounds.

DISCUSSION

Evaluation of active and inactive organotin compounds

When evaluating active organotin compounds, three chemical characteristics are most evident:

(1) Dialkyl and diaryl compounds are more prevalent among those compounds with T/C values greater than 125 than the corresponding mono-, tri-, or tetra- compounds. This phenomenon has been generally reported in the literature.[2,4,7,8]

(2) Diorganotin compounds containing a tin–oxygen bond, (Sn–O) or a group capable of generating such a bond upon hydrolysis, appear to have a higher T/C ratio than those substances with nonhydrolyzable bonds.[8,20] However, this phenomenon may not be very significant because almost all of the low-molecular-weight di- and tri-alkyltin compounds possess some antiproliferation property[21] and most compounds produce these compounds if they are capable of hydrolysis. Furthermore, besides the antiproliferation properties of the trimethyl- and triethyl-tin compounds, they are also powerful neurotoxicants[10,22] and inhibit the phosphorylation of nerve proteins.[22] The toxic effects of the di- and tri-methyltin and di- and tri-ethyltin compounds make it doubtful that compounds containing these moieties can ever be used as anticancer agents. Furthermore, even nontoxic or low-toxicity ligands (i.e. steroid, steroid derivative, vitamin or peptide) covalently bonded to the tin have little or no effect upon the total toxicity of the organotin moiety.[14,23]

(3) Very few compounds contraining strong thymic cytotoxic moieties, i.e. dibutyltin, tributyltin, tripropyltin or dioctyltin groups, are among the active organotin compounds (Table 4). A disproportionately large number of these compounds are found among the inactive compounds (Table 3). Of the inactive compounds in the table, 36% contain a dibutyl or tributyl

Table 4 Alkylorganotin compounds active[a] against P388 leukemia in mice[b]

Compound	T/C (%) (Dose, mg kg^{-1})	Reference
$(Me_2SnCl)_2O$	141 (12.5)	4
$Me_2SnGlyGly$	139 (25)	24
Me_2SnCl_2Pypy	137 (100)	4
Me_2SnBr_2Bipy	135 (200)	4
Me_2SnBr_2Phen	132 (50)	4
$Me_2Sn(Pen)$	148 (400)	30
$EtPhSn(CH_2COOMe)_2$	143–181 (50)	20
$(EtBuSnCl)_2O$	137 (25)	20
$(Et_2SnO)_n$	154 (25)	20
Et_2SnCl_2	136 (12.5)	4
Et_2SnF_2Phen	138 (6.25)	4
Et_2SnCl_2Phen	177 (50)	4
Et_2SnBr_2Phen	176 (25)	4
Et_2SnI_2Phen	184 (200)	4
$Et_2Sn(NCS)_2Phen$	164 (100)	4
$Et_2Sn(CH_2COOMe)_2$	170 (12.5)	20
$Et_2Sn(NCS)_2Bipy$	179 (12.5)	4
Et_2SnCl_2DMSO	153 (25)	4
Et_2SnCl_2PBI	171 (12.5)	4
$[Et_2Sn(SCH_2SH_2SO_3)_2]Na_2 . 2H_2O$	137 (7.5)	30
$[Et_2Sn(SCH_2SH_2SO_3)_2][C(NH_2)_3]_2$	130 (3.75)	30
Et_2SnCl_2PBI	171 (100)	4
Pr_2SnF_2	129 (6.25)	4
Pr_2SnF_2Phen	140 (6.25)	4
Pr_2SnCl_2	136	4
Pr_2SnCl_2Phen	127 (100)	4
Pr_2SnBr_2	142 (25)	4
Pr_2SnBr_2PBI	148 (6.25)	4
Bu_2SnAd_2	131 (12.5)	24
Bu_2SnF_2Phen	145 (12.5)	4
Bu_2SnCl_2AMP	140 (50)	4
Bu_2SnCl_2Bipy	131 (400)	4
$Bu_2SnGlyGly$	150 (3.12)	24
Ph_2SnF_2	196	4
$PhBr_2SnCH_2SnBr$	139	3
$Ph_2SnCl_2[(4,5\text{-}Me_2C_5H_2N)_2]$	169	3
$Ph_2SnClOH$	132–198 (25)	20
$Ph_2Sn(Ad)_2$	169 (100)	24
Ph_2SnCys	181 (50)	29
$(Ph_2SnO)_n$	133 (4)	20
$[Ph_2SnCl]_2CH_2$	133	29
$Ph_2SnGlyGly$	141 (3.12)	24
$Ph_2Sn(CH_2COOMe)_2$	133 (5)	20
$(PhCySnCl)_2O$	137 (56)	20
$[(p\text{-}ClPh)_2SnCl]_2O$	146 (12.5)	20
$Ph_2Sn[Ph_2P(S)S]_2$	142	3
$Ph_2BrSnCH_2SnPhBr_2$	139	29
$[PhCOCHCOCH_3]_2SnCl_2$	230	33
$Ph[COCH(COCH_3)_2]SnBr_2$	141	33
$[Ph_2Sn(SCH_2CH_2SO_3)_2][C(NH_2)_3]_2$	152 (3.75)	30
$[Ph_2Sn(SCH_2CH_2SO_3)_2]Na_2 . 2H_2O$	144 (3.75)	30
Ph_2SnCl_2AMP	153 (25)	4

Table 4 (continued)

Compound	T/C (%) (Dose, mg kg^{-1})	Reference
$(o\text{-Tol}_2SnCl)_2O$	125–133 (1.56)	20
$(p\text{-Tol}_2SnCl)_2O$	141 (12.5)	20
$Oct_2SnGlyGly$	132 (1.56)	24

[a]Definition and mode of introduction as for Table 3. [b]Abbreviations as in Table 1.

moiety. If the tripropyl and dioctyl compounds are considered, they constitute approximately 50% of the inactive aryl and alkyl organotin compounds. Only five dibutyl, one dioctyl, and no tripropyl or tributyl compounds, are found among the active compounds. Furthermore, four of the five active dibutyl compounds exhibit bipyramidal or octahedral structures rather than tetrahedral structures.[6,24]

In a study involving a series of structure changes of 2-mercaptoethanesulfonates ($M_2[R_2Sn(Mer)_2] . nH_2O$, where M = alkali metal and R is Me, Et, Bu and Ph), only the phenyl derivatives were active. The butyl derivatives exhibited the poorest results in the series.[25] Compounds containing these cytotoxic groups are probably inactive because they attack the thymus gland, a part of the immune system. This secondary effect suppresses the immune defense system of the animal without the natural defense system the compounds are incapable of preventing cell proliferation.

Since leukemia is an immune-damaging carcinoma, the ability of the animal to resist the disease is probably reduced in the presence of thymic cytotoxic groups. However, on the whole, the effect appears to be neutral and in some cases the compound may even enhance the ability of the animal to resist the leukemia. This would indicate that the molecules themselves have sufficient antitumor properties to compensate for the thymic destruction. Since organotin compounds slowly attack the thymus, it would be logical to assume that the most pronounced effect of the thymic toxic compounds upon the tumor would be observed with studies which involved a longer time span than is normally used in the NCI protocol.

CONCLUSIONS

It can be concluded in general terms that it appears that the use of thymic cytotoxic groups in synthesizing anti-cancer agents inhibits the chemical's usefulness as an anti-cancer agent. This hypothesis would suggest that the use of aryl, cycloalkyl, or long-chain alkyl, or possibly of covalently bonded biochemically active groups (i.e. purines, nucleic acid, sugars, vitamins, etc.), should give better T/C values than compounds containing short-chain alkyl groups (methyl, ethyl, propyl, butyl or octyl).

Since low-molecular-weight organotin moieties produce adverse effects upon the immune and nervous system of rodents, attaching methyl, ethyl, propyl, butyl or octyl moieties to organotin molecules generally results in poor anti-tumor agents. It would appear that the best prospects for anti-tumor properties in organotin compounds would lie in those containing aryl, cycloalkyl groups or possibly biologically active groups.

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