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Synthesis, characterization and antitumour activity of a series of diorganotin(IV) derivatives of bis(carboxymethyl)amines *

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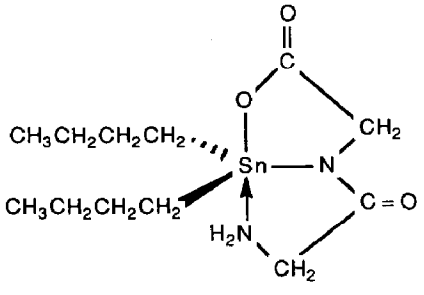
Abstract

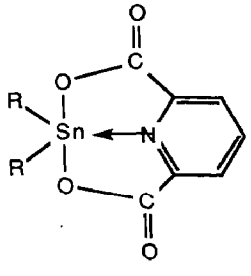
A series of diorganotin(IV) derivatives of bis(carboxymethyl)amine and its *N*-methyl derivative have been prepared, characterized by NMR, Mössbauer and mass spectrometry and tested in vivo against P388 leukemia.

Introduction

Several organotin compounds are active in vitro or in vivo against P388 leukemia [1]. Some are characterized by a bicyclic structure, like the dibutyltin derivative of glycylglycine (**A**) [2]. Interestingly, the diorganotin(IV) derivatives of 2,6-pyridinedicarboxylic acid (**B**) are seven-coordinate in the solid state [3]. This might



(A)



(B)

* In memoriam Prof. J.J. Zuckerman.
** On leave from the Faculté des Sciences, Oujda (Maroc).

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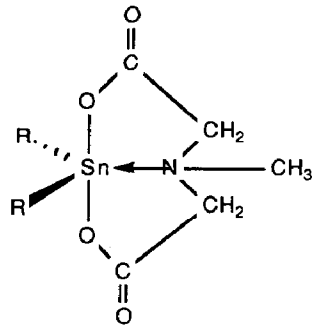


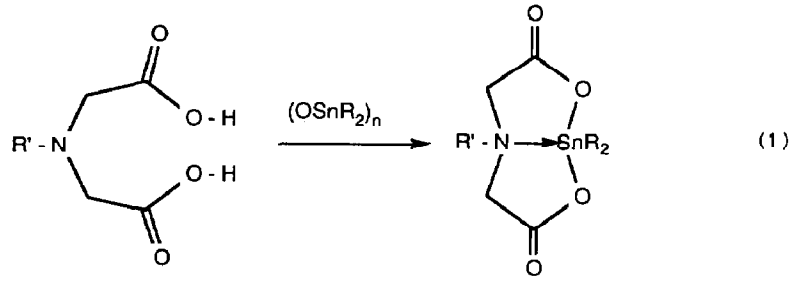
(C)

be related to the presence of the constraints introduced by the presence of the bicyclic structure. The dimethyl-, di-t-butyl- and di-n-butyltin(IV) derivatives of bis(carboxymethyl)methylamine (**C**) have already been prepared and characterized as monomeric species in non-nucleophilic solvents [4]. For the dimethyltin compound, a six-coordinate *trans*-octahedral adduct has been proposed to exist in water, a solvent molecule playing the role of the sixth ligand [4].

We prepared other compounds of the same type in order to examine whether they are also seven-coordinate in the solid state and whether the introduced chemical modifications improve their antineoplastic properties.

Results and discussion

The diorganotin(IV) derivatives of bis(carboxymethyl)methylamine and of bis(carboxymethyl)amine (eq. 1) are easily prepared by reaction of the corresponding diorganotin(IV) oxide with the diacid in toluene/ethanol.



(1)

Table 1

Yields, melting points and recrystallization solvents of compounds **1–5**

Compound	Yield (%)	Melting point (°C)	Recrystallization solvent
1	93	216–218	$CH_3OH + C_6H_6$
2	85	195–197	$CH_3CH_2OH + C_6H_5\text{-}CH_3$
3	82	252–255	DMSO + HOH
4	90	158–160	$CHCl_3 + C_6H_6$
5	75	146–149	DMSO + DMF + HOH

Table 2

Mössbauer parameters of compounds **1–5** and of the corresponding diorganotin oxides

Compound	IS (mm/s)	QS (mm/s)	Γ_1 (mm/s)	Γ_2 (mm/s)
1	1.48	4.17	1.01	1.14
2	1.49	4.19	0.85	0.89
3	1.40	3.60	0.92	1.03
4	1.33	3.59	1.01	0.98
5	1.36	3.36	0.82	0.93
$OSn(CH_2C_6H_5)_2$	1.01	1.93	1.03	0.92
$OSn[(CH_2)_7CH_3]_2$	0.96	1.94	1.00	0.95
$OSn[(CH_2)_3CH_3]_2$ [6]	0.98	2.06		

The compounds prepared and characterized in this work are: $HN(CH_2COO)_2SnR_2$ (**1**: R = n-butyl; **2**: R = n-octyl; **3**: R = benzyl), and $H_3CN(CH_2COO)_2SnR_2$ (**4**: R = n-octyl; **5**: R = benzyl). All compounds were purified by recrystallization from a suitable solvent. The yields, melting points and recrystallization solvents are given in Table 1.

Mössbauer spectroscopy

The Mössbauer parameters are summarized in Table 2. It is interesting to compare these results with the values of QS and IS found for $H_3CN(CH_2COO)_2Sn(CH_3)_2$/$H_3CN(CH_2COO)_2Sn[(CH_2)_3CH_3]_2$, i.e. 4.15 and 1.53/3.88 and 1.54 mm/s, respectively [5]. For these compounds, an octahedral geometry has been suggested in solution [4], but a seven-coordinate structure is not excluded in the solid state. For the analogous 2,6-pyridinedicarboxylic acid derivatives described recently [3], $C_5H_3N(COO)_2Sn[(CH_2)_3CH_3]_2$/$C_5H_3N(COO)_2Sn(C_6H_5)_2$, the values of QS and IS are respectively 4.17 and 1.50/3.99 and 1.25 mm/s, and these compounds have been shown to be seven-coordinate in the solid state.

From the similar values obtained for their Mössbauer parameters, it is likely that compounds **1–5** are also seven-coordinate in the solid state, even if six-coordination remains possible. This problem is currently being examined by X-ray diffraction.

^1H NMR spectroscopy

The ^1H NMR spectra of compounds **1–5** exhibit the expected resonances (see Table 3). These spectra clearly show:

1. a coupling between the $H_3C–N$ protons and the tin atom for compounds **4** and **5**, and between the methylene protons of the bis(carboxymethyl)methylamine and of the bis(carboxymethyl)amine moieties and the tin atom in compounds **3**, **4**, and **5**, which indicates the presence of a chemical bond between tin and nitrogen. Such a coupling was also observed for analogous compounds [4].
2. the expected diastereotopic CH_2COO protons, coupled with the NH proton, giving an ABX pattern for compounds **2** and **3**. The J(AX) and J(BX) coupling constants cannot be measured accurately for compound **1** (the signal of the NH proton is broad). In the presence of D_2O or CD_3OD, the NH-signal and the ^3J(H–C–N–H) couplings of course disappear.

These diastereotopic methylene protons differently coupled with the NH proton for compound **3**: their anisochrony might be larger because of the diamagnetic anisotropy of the phenyl ring of the benzyl group *. At 374 K, the ABX system of compound **3** broadens, which can be attributed to the decoordination–inversion–recoordination process at the nitrogen becoming fast on the NMR time scale. This results in a permutation of the A and B protons, the coalescence of their signals [4] and the loss of the coupling of the methylene protons with the NH proton. Furthermore, the signal of the NH proton is no longer observed at 374 K, which can be explained by a more rapid exchange with the protons of water present in DMSO.

^{13}C NMR spectroscopy

The ^{13}C NMR spectra also exhibit the expected resonances (see Table 4). The synthesis of $H_3CN(CH_2COO)_2Sn[(CH_2)_3CH_3]_2$ (**6**) was described [4], but its ^{13}C NMR spectrum was not. Therefore, these data are also given in Table 4. The signals of the carbon atoms directly bonded to the tin atom are broad for the derivatives bearing no methyl on nitrogen and for the dibenzyltin compounds. These broad signals can be explained by the fact that the two diastereotopic carbons closest to the nitrogen atom are probably the most anisochronous ones. Hence, the resonances are almost coalescing, because of the decoordination–inversion–recoordination process at the nitrogen being rapid on the NMR time scale. At higher temperatures, compound **3**, for instance, gives a much less broad C(1) signal; however, under the experimental conditions used for this experiment, the ^1J(Sn–C) coupling could not be detected above the noise level.

IR spectroscopy

The IR spectra (KBr) show one carbonyl stretching at 1670, 1620 and 1600 cm^{-1} for compounds **1**, **2** and **3**, respectively, and two at 1685, 1580 and 1660, 1620 cm^{-1} for compounds **4** and **5**, respectively. Because two bands are expected if the compounds are six-coordinate and only one band if they are monomeric [4], it seems clear that compounds **4** and **5** are at least six-coordinate in the solid state. The fact that only one band is observed for compounds **1**, **2** and **3** might be due to H-bonds between the NH proton and the carbonyl group likely to compete with the coordination of the carbonyl to tin.

Mass spectrometry

The 70 eV EI mass spectra of $R'–N(CH_2COO)_2SnR_2$ also give the expected [7] fragmentations, i.e. the loss of R, followed by the loss of CO_2, of R minus H, of CO (and also the loss of water and of H_2, for compound **1**) for R = butyl and octyl, and the loss of CO_2 and PhCH for R = benzyl. The proposed fragmentation schemes are given for compounds **4** and **5** as typical examples.

These fragmentation schemes are comparable to the one proposed for the dimethyltin(IV) derivative [4].

* Isochronous R groups, even though they are diastereotopic because of the presence of the transannular interaction.

Table 3

Chemical shifts and coupling constants obtained from the ^1H NMR spectra of compounds **1–5** and of dibenzyltin dichloride (solvent: DMSO-d_6)

$R'-N(CH_2COO)_2SnR_2$	NH or $N-CH_3$ δ(ppm) (J(Hz))	$N-CH_AH_B$ δ(ppm) (J(Hz))	R δ(ppm) (J(Hz))
1. $R' = H$, $R = C\overset{\alpha}{H}_2(C\overset{\beta}{H}_2)_2CH_3$	6.73	3.380; 3.351	H(α): 1.462; H(β): ca. 1.95
	broad	[$^2J(H_A-C-H_B)$ 16.0] [^3J(H–C–N–H) ca. 6]	CH_3: 0.869 [^3J(H–C–C–H): 7.3]
1 in the presence of D_2O		3.597; 3.343	H(α): 1.472; H(β): ca. 1.31
		[$^2J(H_A-C-H_B)$ 16.4]	CH_3: 0.869 [^3J(H–C–C–H): 7.2]
2. $R' = H$, $R = C\overset{\alpha}{H}_2(C\overset{\beta}{H}_2)_7CH_3$	6.609	3.402; 3.302	H(α): 1.463; H(β): ca. 1.25
		[$^2J(H_A-C-H_B)$ 16.2] [^3J(H–C–N–H) 6.4]	CH_3: 0.856 [^3J(H–C–C–H): 6.8]
3 $R' = H$, $R = C\overset{\alpha}{H}_2C_6H_5$	6.33	2.899; 3.406 [$^2J(H_A-C-H_B)$ 16.9]	$\delta(CH_2)$: 2.506 [$^2J(^{119/117}Sn-C-H)$ 103/99]
		[$^3J(H_A-C-N-H)$ 3.5] [$^3J(H_B-C-N-H)$ 7.7] [^3J(H–C–N–Sn) ca. 38]	δ(*ortho*) 7.149 δ(*meta* + *para*) ca. 7.02
3 in the presence of D_2O		2.789; 3.395 [$^2J(H_A-C-H_B)$ 17] [^3J(H–C–N–Sn) 39]	$\delta(CH_2)$: 2.554 [^2J(Sn–C–H) 97] δ(*ortho*) 7.285 δ(*meta* + *para*) ca. 7.03
4 $R' = CH_3$, $R = C\overset{\alpha}{H}_2(C\overset{\beta}{H}_2)_7CH_3$	2.536 [^3J(Sn–N–C–H): 15.5]	3.697; 3.424 [$^2J(H_A-C-H_B)$ 16] [^3J(H–C–N–Sn) ca. 36]	H(α): 1.541; H(β): ca. 1.26 CH_3: 0.860 [^3J(H–C–C–H) 7]
5 $R' = CH_3$, $R = C\overset{\alpha}{H}_2C_6H_5$	2.578 [^3J(Sn–N–C–H) 20]	3.360; 3.239 [$^2J(H_A-C-H_B)$ 16.2] [^3J(H–C–N–Sn) 43.0]	$\delta(CH_2)$: 2.498 [^2J(Sn–C–H) 105] δ(*ortho*) 7.162 δ(*meta* + *para*) ca. 7.02
$(C_6H_5CH_2)_2SnCl_2$			$\delta(CH_2)$: 2.184 [$^2J(^{119/117}Sn-C-H)$ 145/138] δ(*ortho*) 7.20 δ(*meta* + *para*) ca. 7.04

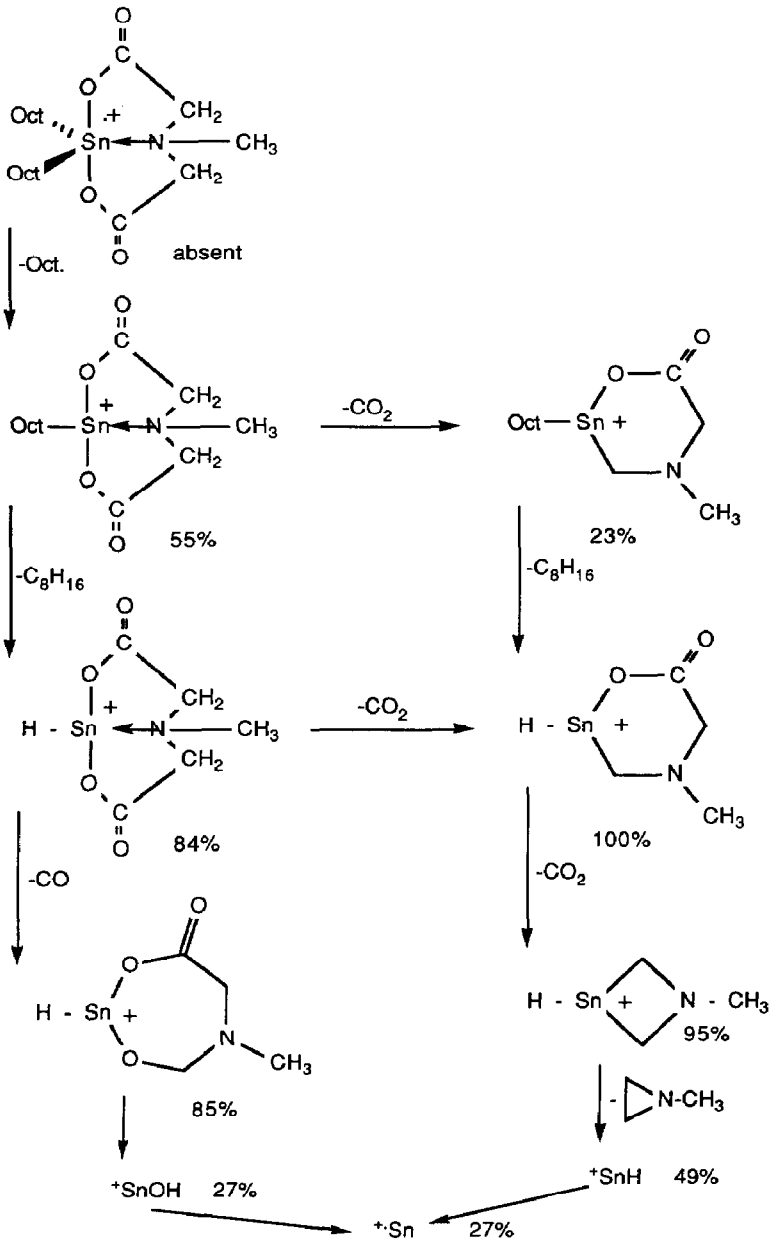
Screening of compounds 1 and 2 against P388 leukemia

The toxicity estimation through the LD_{50} values is given in Table 5 for compounds **1** and **2**. The results of the screening in vivo against P388 leukemia are given

Table 4

Chemical shifts and coupling constants obtained from the ^{13}C NMR spectra of compounds **1–5** and of dibenzyltin dichloride (solvent: DMSO-d_6 except otherwise stated)

$R'-N(CH_2COO)_2SnR_2$	C=O δ(ppm) [J(Hz)]	N–CH_2 δ(ppm) [J(Hz)]	N–CH_3 δ(ppm) [J(Hz)]	R δ(ppm) [J(Sn–C) (Hz)]
1. R′=H, R=$\overset{1}{C}H_2\overset{2}{C}H_2\overset{3}{C}H_2\overset{4}{C}H_3$	171.37	50.04	–	1: 23.98 broad 2: 26.70 [^2J 32.3] 3: 26.01 [^3J 118.3] 4: 13.39
2. R′=H, R=$\overset{1}{C}H_2(CH_2)_7\overset{8}{C}H_3$	171.65	50.09	–	1: 24.71 broad 2: 24.71 [^2J 31.2] 3: 33.23 [^3J 116.8] 28.81; 28.67 6: 31.35 7: 22.14 8: 13.85
3. R′=H, R=CH_2-C_6H_5	170.55	52.57	–	CH_2: 31 broad [^1J not obs.] C_{ipso}: 140.20 [^2J 56.1] C_{ortho}: 128.27 [^3J 43.8] C_{meta}: 127.97 [^4J 23.4] C_{para}: 123.65 [^5J 29.3]
4. R′=CH_3, R=$\overset{1}{C}H_2(CH_2)_7\overset{8}{C}H_3$	169.33	59.91	45.00	1: 24.07 [^1J ca. 700] 2: 24.30 [^2J 28.4] 3: 32.73 [^3J 110.2] 28.30; 28.21 6: 30.92 7: 21.72 8: 13.48
4 in $CDCl_3$	168.79	61.32	46.28	1: 22.79 [^1J ca. 700] 2: 24.82 [^2J 26.5] 3: 33.86 [^3J 108.3] 29.16; 29.04 6: 31.81 7: 22.61 8: 14.04
5, R′=CH_3, R=$CH_2C_6H_5$	169.14	61.95	45.85	CH_2: 31.5 very broad C_{ipso}: 139.91 [^2J 55.5] C_{ortho}: 128.57 [^3J 45.0] C_{meta}: 127.99 [^4J 24.5] C_{para}: 123.86 [^5J ca. 29]
6. R′=CH_3, R=$\overset{1}{C}H_2\overset{2}{C}H_2\overset{3}{C}H_2\overset{4}{C}H_3$	169.5	60.23	45.32	1: 23.86 [^1J not obs.] 2: 26.70 [^2J 35.5] 3: 26.00 [^3J 122] 4: 13.40
$(C_6H_5CH_2)_2SnCl_2$				CH_2: 48.43 [^1J 905/865] C_{ipso}: 140.37 [^2J 87.3] C_{ortho}: 129.37 [^3J 58.3] C_{meta}: 127.30 [^4J 34.9] C_{para}: 124.26 [^5J 42.1]



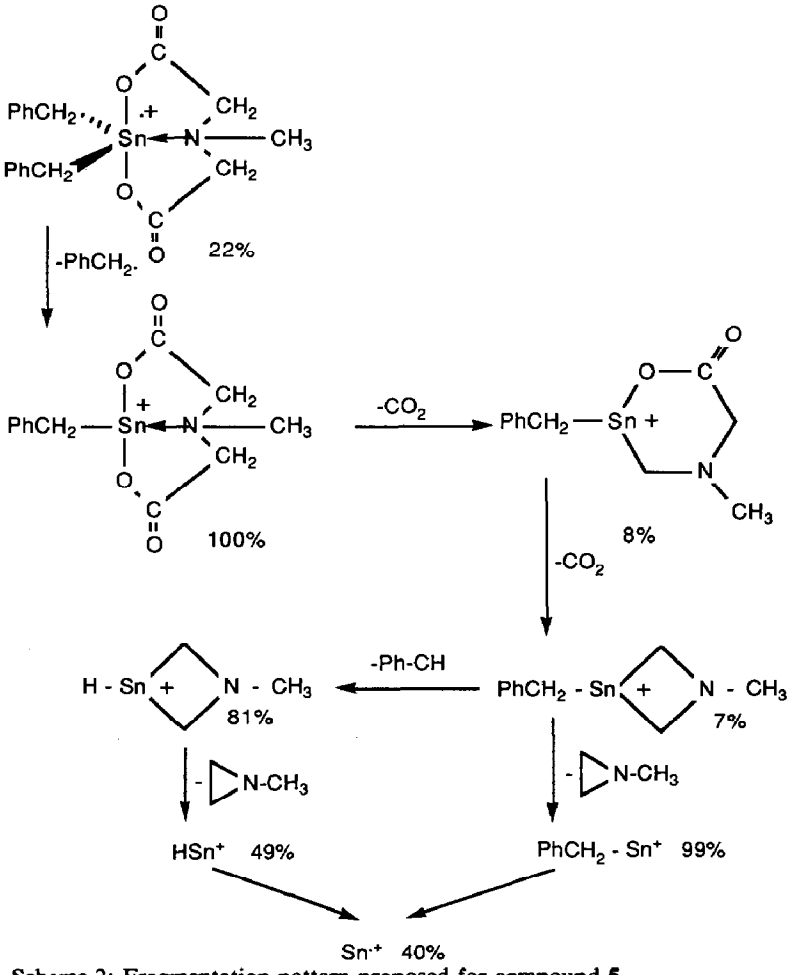
Scheme 1: Fragmentation pattern proposed for compound **4.**

in Table 6. From Table 6, it can be clearly seen that these compounds are not active in vivo against P388 leukemia. This might be due to their very high hydrolytic stability [4].

Experimental

Synthesis and purification of the diorganotin(IV) derivatives of bis(carboxymethyl) methylamine or of bis(carboxymethyl)amine

Bis(carboxymethyl)methylamine (0.05 mol) or bis(carboxymethyl)amine (0.05



Scheme 2: Fragmentation pattern proposed for compound **5**.

Table 5

Estimation of the LD_{50} values for compounds **1** and **2** ([a] BWC5 = body weight change day 6 minus day 1)

Compound	Dose mg/kg	BWC5 [a] g	Estimation LD_{50} mg/kg	Remarks
1	8	−5.4	10	No deaths. Killed on day 30. Because the mice were rather emaciated, autopsy was performed: green kidneys, in particular, at the intersection.
	20	–		Deceased on day 1 and 2
	50	–		Deceased on day 1
2	8	−0.4	25	No deaths
	20	−3.3		No deaths
	50	–		Deceased on day 1

Table 6

In vivo P388 leukemia test results for compounds **1** and **2**

Compound	Dose (mg/kg)	BWC5 [a] (g)	Median survival time (days)	T/C [b] (%)	Long term survivors
Control	–	+1.7	11	100	0/12
1	5	−4.9	12	109	0/6
	8	−5.3	10.5	95	0/6
	12	−4.9	5	45	0/6
2	14	+1.3	13	118	0/6
	20	−2.7	13	118	0/6
	30	−2.7	3	27	0/6

[a] BWC5: see Table 5; [b] T/C = ratio of median survival times of treated mice (T) and control animals (C). Confirmed in vivo results of T/C ≥ 127% are considered to be necessary to demonstrate activity. At the confirmatory level, the criteria of positivity presently requested at the National Cancer Institute Decision Network Phase 2 is a T/C ≥ 175%).

mol) and diorganotin oxide (0.05 mol) are suspended in 700 ml of an ethanol/toluene 2/5 mixture for 6 h (compounds **1**, **2** and **4**) or 24 h (compounds **3** and **5**) at 77 °C. About 350 ml of the azeotrope ethanol/toluene is distilled off under atmospheric pressure. The homogeneous mixture is cooled to room temperature and filtered. The solid obtained is washed several times first with toluene, then with acetone and recrystallized from the solvent or mixture of solvents given in Table 1.

Synthesis of dibenzyltin oxide

Dibenzyltin oxide (m.p. 266–270 °C; lit. [8] 254–260 °C) has been synthesized in 82% yield from 0.029 mol of dibenzyltin dichloride (prepared following Sisido [9] from metallic tin powder and benzyl chloride) and 0.058 mol of KOH dissolved in 300 ml of water. The mixture is heated for 4 h at 70 °C. The white precipitate formed is filtered, washed with distilled water till it is no longer basic, then several times with methanol. It is finally dried for a week in a desiccator.

Mössbauer spectroscopy

The Mössbauer spectra were recorded with the constant acceleration mode on an Elscint MVT4 Promeda counting instrument, with a $Ca^{119}SnO_3$ source from Amersham. The probe is maintained at a temperature between 90 and 100 K, whereas the source is kept at room temperature. The digital data are treated with an iterative program and resolved as a sum of lorentzians by the least squares method.

^1H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry

The NMR spectra were recorded on a Bruker SF 250 instrument with TMS as the internal standard at 304 K. The IR spectra were recorded on a Perkin–Elmer 298 infrared spectrophotometer. The mass spectra were recorded on a V.G. Micromass 70 70 F instrument (source temperature: 200 °C).

Estimation of LD_{50} values

The compounds were administered as suspensions in 2% aqueous carboxymethylcellulose. A single intraperitoneal injection in a volume of 0.01 ml per gram body weight was given. Two male mice (C57BL/Rij × CBA/Rij)F1 were used per dose group.

P388 screening

Mice were injected intraperitoneally with 10^6 P388 leukemia cells. After 24 h they were treated with compounds **1** or **2**. Three dose levels of each compound were administered. The highest dose level was probably toxic. Six male mice (BALB/C × DBA2)F1 were used in each dose group. The control group consisted of 12 CD2 mice.

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