Studies on the Anti-tumour Activity of Di- and Tri-organotin(IV) Complexes of Amino Acids and Related Compounds, of 2-Mercaptoethanesulphonate, and of Purine-6-thiol

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The anti-tumour activity of 20 complexes of di- and tri-organotin(IV) has been tested *in vivo* in P-388 leukaemic mice. The complexes include $SnPh_2$(CysOS) [CysOS = L-cysteinate(2−)], SnR_2(Pen) (H_2Pen = DL-penicillamine; R = Me, Bu^n, or Ph), the anions $[SnR_2(SCH_2CH_2SO_3)_2]^{2-}$ (R = Me, Et, Bu^n, or Ph), $SnMe_2$(PhCO-GlyO)$_2$ (PhCO-GlyO = *N*-benzoylglycinate), *N*-substituted glycinates of SnR_3(R = Me or Bu^n), $SnBu^n_2$(put)$_2$ (Hput = purine-6-thiol), SnR_3(put) (R = Me, Bu^n, or Ph), and $(SnPh_3)_3$(put)$_2$. The complex tris(L-cysteinato)bismuth(III) has been investigated also, for comparison purposes. The results are discussed in connection with the structural characteristics, available to date, of the complexes in solution phases.

Investigations on the anti-tumour activity of organotin(IV) compounds date from 1929.[1] Up to 1980, the United States National Cancer Institute (N.C.I.) tested 1 434 tin compounds, 170 of which were found to be active;[2] interest in this field still persists,[3-6] even in the pharmaceutical industry.[7] As a part of our project dealing with the study of the interaction of tin species with biological systems as well as of their biochemical and pharmacological properties, and as a continuation of our previous studies on diorganotin(IV)-glycylglycinates and -adeninates, we have investigated the anti-tumour properties of the title compounds, mainly to obtain further information on structure-activity relationships for amino-acid and purine complexes. Preliminary results are reported and discussed in this paper.

Experimental

Compounds (**1**), (**2**), (**4**), (**12**), (**14**)—(**18**), and (**21**) (Table) were prepared according to the literature.[8-14] The other compounds listed in the Table were synthesized as described below. The organotin compounds were a gift from Schering A. G., Bergkamen, and sodium 2-mercaptoethanesulphonate, $Na[HSCH_2CH_2SO_3]$, from Degussa Pharma Gruppe, Frankfurt (B.R.D.). Guanidinium 2-mercaptoethanesulphonate, $[C(NH_2)_3][HSCH_2CH_2SO_3]$, was prepared according to ref. 15. The other reagents and solvents were pure products of Alfa, Fluka, C. Erba, and E. Merck.

$SnBu^n_2$(Pen) (**3**).—A solution of $SnBu^n_2O$ (5 mmol in 100 cm^3 of MeOH) was obtained by gentle warming with stirring. An excess of DL-penicillamine (H_2Pen) (10 mmol in 50 cm^3 of H_2O) was added dropwise, producing a white microcrystalline precipitate which, after stirring and warming for 30 min, was filtered off, washed with MeOH and dried under vacuum[16] [Found: C, 41.35; H, 6.6; N, 3.65; Sn (determined as SnO_2), 30.65. Calc. for $C_{13}H_{27}NO_2SSn$: C, 41.1; H, 7.15; N, 3.7; Sn, 31.2%]; m.p. (uncorrected) 238—240 °C.

$[C(NH_2)_3]_2[SnEt_2(SCH_2CH_2SO_3)_2]$ (**5**).—$SnEt_2O$ (1 mmol) and $[C(NH_2)_3][HSCH_2CH_2SO_3]$ (2 mmol) were added to MeOH (40 cm^3). After stirring the mixture for 6 h at room temperature the slightly turbid solution was filtered, and the filtrate concentrated under vacuum to *ca.* 3 cm^3. The white precipitate formed was filtered off and washed with cold MeOH, then with diethyl ether; yield 66% [Found: C, 20.2; H, 5.2; N, 14.4; Sn, 20.1. Calc. for $C_{10}H_{30}N_6O_6S_4Sn$: C, 20.8; H, 5.25; N, 14.55; Sn (chel.: determined chelatometrically), 20.55%].

$[C(NH_2)_3]_2[SnBu^n_2(SCH_2CH_2SO_3)_2]$ (**6**).—Guanidinium 2-mercaptoethanesulphonate (10 mmol) was added in small portions to a suspension of $SnBu^n_2O$ (5 mmol in 100 cm^3 of MeOH). After refluxing for 12 h a clear solution was obtained, which was concentrated under vacuum to *ca.* 30 cm^3. The mixture stood for 1 h at 20 °C. The white precipitate was filtered off, washed as for (**5**), and dried under vacuum over silica gel, yield 71% [Found: C, 26.2; H, 5.85; N, 12.8; Sn (chel.), 19.4. Calc. for $C_{14}H_{38}N_6O_6S_4Sn$: C, 26.55; H, 6.05; N, 13.25; Sn, 18.75%]; m.p. (uncorr.) 133 °C (decomp.).

$[C(NH_2)_3]_2[SnPh_2(SCH_2CH_2SO_3)_2]$ (**7**).—This was prepared from $[C(NH_2)_3][HSCH_2CH_2SO_3]$ and $SnPh_2O$ as for (**6**); yield 76% (white needles) [Found: C, 32.55; H, 5.2; N, 12.9; Sn (chel.), 17.25. Calc. for $C_{18}H_{30}N_6O_6S_4Sn$: C, 32.1; H, 4.5; N, 12.5; Sn, 17.65%]; m.p. (uncorr.) 240 °C (decomp.).

$Na_2[SnMe_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$ (**8**).—$SnMe_2O$ (1 mmol) and $Na[HSCH_2CH_2SO_3]$ (2 mmol) reacted in MeOH (30 cm^3) during 10 h at room temperature to give a clear solution. The product was isolated as for (**5**). It was dried over P_4O_{10}; yield 61% [Found: C, 14.9; H, 3.55; Sn (chel.), 22.8. Calc. for $C_6H_{18}Na_2O_8S_4Sn$: C, 14.1; H, 3.55; Sn, 23.2%], dehydration occurred at 104 °C (uncorr.).

Table. Effect of a series of $Sn^{IV}R_2$ and $Sn^{IV}R_3$ complexes[a] against P-388 leukaemia

	Compound[b]	Doses[c]	T/C[d] (%)
(1)	$SnPh_2(CysOS)$[e,f]	100	toxic
		50	181
		25	156
		12.5	142
		6.25	132
		0.00	100
(2)	$SnMe_2(Pen)$[e]	400	148
		200	121
		100	128
		0.00	100
(3)	$SnBu^n_2(Pen)$	6.25	toxic
		3.12	120;130
		1.56	113
		0.79	103
		0.39	100
		0.00	100
(4)	$SnPh_2(Pen)$[e]	400	toxic
		25	101
		0.00	100
(5)	$[C(NH_2)_3]_2[SnEt_2(SCH_2CH_2SO_3)_2]$	15	toxic
		7.5	123
		3.75	130
		1.87	130
		0.00	100
(6)	$[C(NH_2)_3]_2[SnBu^n_2(SCH_2CH_2SO_3)_2]$	240	115
		120	105
		60	105
		0.00	100
(7)	$[C(NH_2)_3]_2[SnPh_2(SCH_2CH_2SO_3)_2]$	7.5	toxic
		3.75	152
		1.87	121
		0.93	134
		0.00	100
(8)	$Na_2[SnMe_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$	120	toxic
		60	107
		30	98
		15	120
		0.00	100
(9)	$Na_2[SnEt_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$	15	toxic
		7.5	137
		3.75	125
		1.87	95
		0.93	95
		0.00	100
(10)	$Na_2[SnBu^n_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$	240	99
		120	101
		60	100
		0.00	100
(11)	$Na_2[SnPh_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$	7.5	toxic
		3.75	144
		1.87	142
		0.93	132
		0.00	100
(12)	$Bi(CysS)_3\cdot H_2O$[g]	50	toxic
		25	96
		12.5	102
		0.00	100
(13)	$SnMe_2(PhCO\text{-}GlyO)_2$[e]	100	toxic
		25	101
		3.12	100
		1.56	93
		0.79	97
		0.00	100
(14)	$SnMe_3(PhCO\text{-}GlyO)$[e]	6.25	toxic
		3.12	103
		1.56	103
		0.00	100
(15)	$SnBu^n_3(AcGly)$[e,h]	100	toxic
		50	102
		25	102
		0.00	100
(16)	$SnMe_3(dnpGly)$[e,i]	12.5	toxic
		6.25	98
		3.12	100
		0.00	100
(17)	$SnBu^n_2(put)_2$	6.25	toxic
		3.125	89
			118;120[j]
		2.00	127
		1.56	118;123[j]
		1.50	109
		0.75	100
(18)	$SnMe_3(put)$	3.125	toxic
			100
		1.50	90
		0.75	90
		0.375	100
(19)	$SnBu^n_3(put)$	6.25	toxic
		3.125	110
			80
		1.50	85
		0.75	90
		0.375	100
(20)	$SnPh_3(put)$	12.5	toxic
		6.25	100
		3.125	100
			90
		1.50	90
		0.75	85
		0.375	100
(21)	$(SnPh_3)_3(put)_2$	6.25	toxic
		3.125	95
		1.5	90
		0.75	90
		0.375	95
		0.00	100

[a] $Bi^{III}(CysS)_3$ has been tested also, for comparison purposes. [b] Methods of drug administration were as follows: (**1**), (**2**), (**15**), suspension in saline; (**5**), (**8**), (**9**), solution in saline; (**4**), (**6**), (**7**), (**10**), (**11**), (**12**), (**17**)—(**21**), suspension in klucel; (**3**), (**13**), (**14**), (**16**), solution in klucel. Saline is NaCl in H_2O (0.9 g in 100 cm^3), and klucel is an aqueous medium (100 cm^3) containing 2-hydroxypropylcellulose (0.3 g) and NaCl (0.9 g). [c] Given as mg of drug per kg of body weight per injection. [d] Median survival time of the treated mice group (T) divided by that of the control group (C). Activity criteria are passed for $T/C \geqslant 120\%$. See ref. 18. [e] Administered on day 1 only. [f] CysOS = O- and S-deprotonated cysteine. [g] CysS = S-deprotonated cysteine. [h] HAcGly = *N*-Acetylglycine. [i] HdnpGly = *N*-(2,4-dinitrophenyl)glycine. [j] Refers to drug administration on days 1—9.

$Na_2[SnEt_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$ (**9**).—This was prepared from $SnEt_2O$ (1 mmol) and $Na[HSCH_2CH_2SO_3]$ (2 mmol) as for (**8**), in 12 h. The solution was concentrated under vacuum until a white product began to separate; yield 42% [Found: C, 17.65; H, 4.2; Sn (chel.), 21.2. Calc. for $C_8H_{22}Na_2O_8S_4Sn$: C, 17.8; H, 4.1; Sn, 22.0%].

$Na_2[SnBu^n_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$ (**10**).—This was obtained from $SnBu^n_2O$ (1 mmol) and $Na[HSCH_2CH_2SO_3]$ (2 mmol in 40 cm^3 of MeOH) as for (**8**); yield 41% [Found: C, 24.8; H, 4.9; Sn (chel.), 19.6. Calc. for $C_{12}H_{30}Na_2O_8S_4Sn$: C, 24.2; H, 5.1; Sn, 19.95%]; m.p. (uncorr.) 252 °C (decomp.).

$Na_2[SnPh_2(SCH_2CH_2SO_3)_2]\cdot 2H_2O$ (**11**).—This was prepared from $SnPh_2O$ (1 mmol) and $Na[HSCH_2CH_2SO_3]$ (2 mmol in 30 cm^3 of MeOH) as for (**5**). The reaction time was 24 h and the filtered solution was concentrated to *ca.* 5 cm^3. The product formed was washed with MeOH and recrystallized from MeOH; yield 39% [Found: C, 29.5; H, 3.3; Sn (chel.), 18.9. Calc. for $C_{16}H_{22}Na_2O_8S_4Sn$: C, 30.25; H, 3.5; Sn, 18.7%]; dehydration occurred at 122 °C (uncorr.), m.p. (uncorr.) 279 °C (decomp.).

$SnMe_2(PhCO\text{-}GlyO)_2$ (**13**).—*N*-Benzoylglycine (PhCO-Gly) (5 mmol in 25 cm^3 of MeOH) was added to a suspension of $SnMe_2O$ (2.5 mmol in 25 cm^3 of MeOH). The mixture was stirred overnight at room temperature, the unreacted solid was separated by centrifugation, and the clear solution was concentrated to half of its original volume by evaporation. Then a diethyl ether–light petroleum (1:1) mixture was added till the solution became turbid. On standing overnight at −10 °C, a white precipitate was obtained which was filtered off, washed with a small amount of MeOH, diethyl ether and light petroleum (b.p. 40—60 °C), and dried under vacuum; yield 80% [Found: C, 47.55; H, 4.2; N, 5.6. Calc. for $C_{20}H_{22}N_2O_6Sn$: C, 47.55; H, 4.4; N, 5.55%]; m.p. (uncorr.) 227—228 °C (decomp.).

$SnBu^n_3$(put) (**19**).—Anhydrous purine-6-thiol (Hput), obtained by drying under vacuum, was dissolved into dry acetone (10 mmol in 100 cm^3). $SnBu^n_3$(OMe) (10 mmol in 20 cm^3 of dry acetone) was then added dropwise, and the solution was stirred for about 2 h at room temperature; after standing overnight at −10 °C, a white microcrystalline solid was obtained, which was filtered off, washed with acetone, and dried under vacuum[12,17] (Found: C, 46.75; H, 6.85; N, 11.65. Calc. for $C_{17}H_{30}N_4SSn$: C, 46.3; H, 6.85; N, 12.7%); m.p. (uncorr.) 85—87 °C.

$SnPh_3$(put) (**20**).—A mixture of solid purine-6-thiol and $SnPh_3OH$ (5 mmol of both reagents) was treated with 100 cm^3 of acetone and refluxed for *ca.* 2 h, producing a clear solution. Upon partial evaporation of the solvent a white solid was recovered, which was filtered off and dried[12,17] (Found: C, 54.7; H, 3.9; N, 10.5. Calc. for $C_{23}H_{18}N_4SSn$: C, 55.1; H, 3.6; N, 11.2%).

The anti-tumour tests were carried out according to N.C.I. standard procedures,[18] at the Institutes J. Bordet, Brussels, for compounds (**1**)—(**16**), and M. Negri, Milan, for compounds (**17**)—(**21**), and the results are reported in the Table. Lymphocytic leukaemia P-388 (*ca.* 10^6 cells) was implanted intraperitoneally (i.p.) on day 0 in CD_2F_1 mice,[18] male or female, and the doses of drugs were administered (i.p.) on days 1—5 (unless otherwise stated in the footnotes of the Table).

Results and Discussion

A common feature of compounds (**1**)—(**12**), Table, is the occurrence of Sn–S bonds, the ligands being biological or pharmacological molecules.[19–21] 2-Mercaptoethanesulphonic acid was chosen to attempt to obtain species largely soluble in water.

The anti-leukaemic activity of $SnPh_2$(CysOS) (**1**) [CysOS = L-cysteinate(2−)] is remarkable for its relatively low toxicity. On the contrary, the homologous complex $SnPh_2$(Pen) (**4**) (H_2Pen = DL-penicillamine) is inactive. This could suggest that the chirality of the asymmetric carbon atom plays a role in the anti-tumour activity of these complexes, if the free-ligand chirality is maintained. Moreover, the dialkyltin(IV) DL-penicillaminates (**2**) and (**3**) exhibit a reduced activity too, and it seems interesting to test the corresponding L-cysteinates in the present context. At comparable drug doses, the highest activity is instead shown by the $[SnPh_2(SCH_2CH_2SO_3)_2]^{2-}$ complexes (**7**) and (**11**), followed by the corresponding $Sn^{IV}Et_2$ complexes (**5**) and (**9**); the analogous Sn^{IV} alkyl complexes (**6**), (**8**), and (**10**) are consistently less toxic and are inactive, in line with the known toxicological properties of these $Sn^{IV}R_2$ moieties.[22] The cations, Na^+ and guanidinium, in compounds (**5**)—(**11**) have clearly no relevance in connection with the biological action.

The anti-leukaemic activity of these sulphur-bonded $Sn^{IV}R_2$ (R = Me, Ph, Et, or Bu^n) complexes seems then to depend primarily upon the nature of R, being eventually active for R = Ph or Et. Similar results have been reported for complexes $SnR_2[Ph_2P(S)S]_2$, R being Ph or Me.[5] Taking now into account also the inactivity of the L-cysteinate complex of Bi^{III}, (**12**), where only Bi^{III}–S bonds are found,[14] it may be concluded in the present context that anti-tumour activity is not simply due to the co-ordination of ligand sulphur to any metal centre. It is worth noting also that the nature of the ligands bound to $Sn^{IV}R_2$, and then of the bonds formed, is expected to have a profound influence in determining the eventual activity.[3,4]

Turning now to the structure-activity relationship, the solid-state structure of the $Sn^{IV}R_2$ complexes of L-cysteine and DL-penicillamine, (**1**)—(**4**), consists of one-dimensional polymeric species where tin(IV) is five-co-ordinated, with equatorial C and S atoms, and axial carboxylate (monodentate) oxygen and amino-nitrogen atoms (according to i.r. and Mössbauer studies[8,23]). In solution, the polymeric structure would be destroyed, and molecular species are expected to occur; studies in this field are underway. It may be reasonably assumed that the ligands act as tridentates (SNO donor atoms) or bidentates (S, and O or N donors) in organic solutions of the complexes, while also as monodentates (S-bonding) in aqueous solution. This corresponds to the bonding detected in SnR_2 glycylglycinate complexes (R = Me, Bu^n, or n-C_8H_{17}), in which peptide and amino-nitrogen atoms, and carboxyl oxygen, are linked to Sn in organic solutions, while dissociated species also are present in water (for R = Me), where only the tin–peptide nitrogen bond is observed (according to conductance, i.r., ^1H, ^{13}C, and ^{119}Sn n.m.r., and Mössbauer data, the last in frozen solutions; see below).[24] Moreover, Sn–S bonds in $Sn^{IV}R_n$ alkane- and arene-thiolates (R = Me or Et; n = 1—3) have been observed to be hydrolytically stable,[25] and $Sn^{IV}R_n$ moieties undergo co-ordination by sulphur donors in biological media,[26] including complex formation through thiol sulphur of cysteine residues of haemoglobin.[27]

The $Sn^{IV}R_2$ complexes of the 2-mercaptoethanesulphonate anion, (**5**)—(**11**), appear to be tetrahedral species, with Sn–S (thiol) bonds, both in the solid state and in aqueous solution. In fact, the Mössbauer quadrupole splitting, ΔE, at liquid N_2 temperature, lies around 1.7 mm s^{-1} for solid Na^+ and $[C(NH_2)_3]^+$ salts of the complex anion $[SnMe_2(SCH_2CH_2SO_3)_2]^{2-}$, and around 1.5—1.7 mm s^{-1} for the analogous salts of $[SnPh_2(SCH_2CH_2SO_3)_2]^{2-}$ in the solid state; the magnitude of ΔE for the salts of $[SnMe_2(SCH_2CH_2SO_3)_2]^{2-}$ in frozen (glassy) aqueous klucel solutions remains practically unchanged with respect to the solid-state values (for freshly prepared solutions as well as for solutions aged about one day at room temperature before freezing; profound changes in the Mössbauer parameters occur on standing several days at room temperature).[16] Taking into account that the calculated point-charge model values for tetrahedral $SnR_2(SR')_2$ (R′ = alkyl) are ΔE = 2.04 mm s^{-1} for R = alkyl, and ΔE = 1.75 mm s^{-1} for R = Ph[28] (the corresponding experimental values being 1.58—2.11 and 1.69 mm s^{-1}),[28] the tetrahedral environment C_2SnS_2 is inferred for the above complex anions, both in the solid and in non-aged aqueous solution. Bonding through sulphonate oxygen atoms is excluded, since experimental ΔE values would be 5.05—4.64 mm s^{-1}[29] It is worth mentioning that the tin environment in the complex anions (**5**)—(**11**) would then bear a

close relationship to that of dihydrolipoic acid (6,8-dimercaptooctanoic acid) (and of the coenzyme ε-*N*-lipoyllysine) chelates of $SnBu^n_2$.[26]

In conclusion, it appears to us that the common structural characteristics of SnR_2 glycylglycinates,[4] and of $SnPh_2$(CysOS) and $[SnR_2(SCH_2CH_2SO_3)_2]^{2-}$ complexes, are as follows: (*i*) the availability of co-ordination positions at Sn, in any physical state; (*ii*) the occurrence of relatively stable ligand atom(s)–tin bonds, *i.e.*, Sn–N (peptide) in the glycylglycinates[4,24] and Sn–S in the $CysOS^{2-}$ and $SCH_2CH_2SO_3^{2-}$ complexes; (*iii*) these bonds are expected to undergo slow hydrolytic decomposition, as observed for the $SnMe_2$ complex of glycylglycinate with formation of $SnMe_2O$,[24] and for $[SnMe_2(SCH_2CH_2SO_3)_2]^{2-}$ according to the Mössbauer data in the preceding paragraph. The anti-leukaemia activity of these drugs would then be ultimately due to $Sn^{IV}R_2$ moieties possibly released into the cells.[3,4] The role of the (co-ordinated) ligand in the eventual process of transportation across, or perhaps bonding to, cell membranes is an open question which could perhaps be answered by studies on the biochemical activity of the compounds discussed above, in connection with previous investigations on $Sn^{IV}R_n$ salts.[30]

These assumptions are confirmed by the inactivity of the N-substituted amino-acid complexes (**13**)—(**16**), Table. The bonding in the $Sn^{IV}R_3$ compounds gives rise to solid-state one-dimensional polymers, while monomeric species are present in organic solvents, where the carboxyl groups are monodentate and the tin atoms are four- or five-co-ordinated depending on the basic properties of the solvent.[9–11] The carboxyl oxygen–tin bonding is expected to be broken in aqueous solutions, according to the above findings on SnR_2 glycylglycinates,[24] giving rise to aquated and hydrolysed $Sn^{IV}R_3$ species. The same is reasonably expected to take place also for $SnMe_2$(PhCO-GlyO)$_2$ (**13**), which would then be inactive, analogously to $Sn^{IV}Me_2$ salts (active dialkyltin salts being, *e.g.* $SnEt_2Cl_2$, $SnPr^n_2Cl_2$, and $SnBu^n_2Cl_2$).[31] These assumptions are in line with the toxicities of compounds (**13**)—(**16**) (Table) which follow the trend shown by the related $Sn^{IV}R_2$ and $Sn^{IV}R_3$ salts.[22]

The purine-6-thiol complexes of $Sn^{IV}Bu^n_2$ and $Sn^{IV}R_3$, (**17**)—(**21**), do not show any activity against leukaemia P-388 in mice. This is contrary to expectation,[12] taking into account that the ligand itself is an anti-leukaemia drug in clinical use.[32] A series of Bi^{III}, Pd^{II}, and Pt^{II} complexes of H_2put have been tested previously as anti-tumour drugs,[33–35] and claimed to be active,[33] approximately equivalent to free H_2put,[34] and this activity has been attributed also to the slow release of the ligand from the injected complexes.[35] The bonding in $SnBu^n_2$(put)$_2$ (**17**) has been assumed to occur through chelation of tin by thiol sulphur and N(7) of the purine ring,[12] as in some Pd^{II} and Pt^{II} derivatives (where sulphur–metal bonds only have been also assumed),[34–36] while Sn of $SnMe_3$(put) in the solid state would be co-ordinated by N(1) and N(3), producing a one-dimensional polymer.[12] It then appears that all the above reported bonding of metal centres by a purine ligand does not impart any additional anti-tumour activity to the complexes. Instead, the bis(adeninate) complexes of $Sn^{IV}R_2$ are active against leukaemia P-388 in mice,[4] the ligand being inactive and primarily bonding to Sn through N(9).[4] It may be argued consequently that activity of organotin–purine complexes requires metal–N(9) bonding, which would be stronger than bonds involving donation by other heterocyclic nitrogen atoms of the purine ring, but weaker than the possible sulphur–metal bond in H_2put derivatives. The mechanism of anti-tumour action could correspond to that advanced above, involving slow hydrolytic processes. Further work in this field is currently underway in our laboratories, mainly in order to investigate the nature of the species present in solution phases, with the aim of clarifying the structure-activity relationships proposed in this paper.

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