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SHORT PAPER

Structural effects on the antitumour activity of organotin compounds 2. Further diaryltin dichloride complexes with nitrogen-donor ligands

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The synthesis and investigation of the anti-tumour activity of a further series of six new diorganotin dichloride complexes $Ar_2SnCl_2.L_2$, where Ar = 2-thienyl, 2,4-dimethoxyphenyl, 4-methyoxyphenyl, 4-methylphenyl or 4-trifluoromethylphenyl and L_2 = 2-(2-pyridyl)benzimidazole (PBI) or 2-aminomethylpyridine (AMP), is reported. One of these complexes was found to be active against P388 lymphocytic leukaemia in mice. The results obtained are in general agreement with previously published work. The activity of the diaryltin dichloride complexes is shown to be dependent on the electronic effect of the aromatic group. The use of PBI as a ligand, however, shows no advantage over other ligands used in the series investigated.

Keywords: Organotin complexes, antitumour agents, aryltin chlorides, murine P388 leukaemia

INTRODUCTION

In an earlier paper[1] we reported the investigation of the antitumour activity of a series of 15 diorganotin dichloride complexes, $[(4\text{-}ZC_6H_4)_2SnCl_2.L_2]$, eight of which exhibited reproducible activity *in vivo* towards P388 lymphocytic leukaemia in mice. It was suggested that the activity of the tin complex may be related to both the nature of the ligand and the electronic effects of the aryl substituent [Z]. In this paper the results of further testing on six new compounds are reported. These results extend the previous series in the nature of both ligand and aryl substitution.

It has been suggested elsewhere[2] that preferred ligands $[L_2]$ for activity possess strong nitrogen-donor atoms. In particular 1,10-phenanthroline (phen), 3,4,7,8-tetramethyl-1,10-phenanthroline (TMphen) and 2-(2-pyridyl)benzimidazole (PBI) have been proposed.[3] Work on the parent unsubstituted diphenyltin dichloride[4] and our previous work[1] show that the weaker ligand 2-aminomethylpyridine (AMP) is the preferred ligand for activity and that phen complexes are less likely to exhibit activity. For these reasons further complexes with both AMP and PBI have been synthesized and tested.

Antitumour testing of a large number of complexes has shown that activity depends mainly on the electronic effects of the group R or Ar but that steric factors may also be involved.[4] It is also clear that these effects control the acceptor properties of the tin atom and hence the leaving ability of the bidentate ligand. This is a controlling factor in the antitumour activity as shown in our previous paper. The aim of this work is to explore this idea further by including new diaryltin dichloride complexes with powerfully electron-donating and -withdrawing aryl groups.

EXPERIMENTAL

Preparation of tetra-aryltins

Four of the five tetra-aryltins used in this work have been described previously.[5,6] The tetra-aryltin with Ar = 2,4-dimethoxyphenyl is hitherto unreported. All five tetra-aryltins were prepared using standard Grignard procedures.[7] In the case of the dimethoxy compound, a solution of tin tetrachloride in hydrocarbon solvent was added to 2,4-dimethoxyphenylmagnesium bromide prepared in tetrahydrofuran solution. After the mixture had been boiled for 2 h under reflux the

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Table 1 Melting point and analytical data for diaryltin complexes, $Ar_2SnCl_2.L_2$

Complex	Microanalytical data Found (calcd) (%) C	H	N	M.p. (°C)
Ar = 2-thienyl, L_2 = PBI	42.96 (43.59)	2.76 (2.74)	8.16 (7.62)	178–180
Ar = 2-thienyl, L_2 = AMP	36.16 (36.24)	3.20 (3.04)	6.84 (6.04)	191–192 (dec.)
Ar = 2,4-dimethoxyphenyl, L_2 = AMP	46.22 (46.19)	4.91 (4.58)	5.84 (4.90)	142–143 (dec.)
Ar = 4-methoxyphenyl, L_2 = PBI	51.98 (52.13)	3.86 (3.87)	7.02 (7.01)	185–186 (dec.)
Ar = 4-methylphenyl, L_2 = PBI	55.23 (55.07)	3.98 (4.09)	7.51 (7.41)	212–213
Ar = 4-trifluoromethylphenyl, L_2 = PBI	46.91 (46.26)	2.63 (2.54)	6.42 (6.23)	276 (dec.)

product was isolated and crystallized from 1:1 petroleum spirit (b.p. 60–80°C)/toluene mixture, m.p. 180–181°C. The yield was 90% (Found: C, 58.31; H, 5.40. $C_{32}H_{36}O_8Sn$ requires C, 57.59; H, 5.44%).

Preparation of diaryltin dichlorides

All five diaryltin dichlorides were made by a modified Kocheshkov procedure.[5] Analytical data for three of these (Ar = 4-methoxyphenyl, 4-methylphenyl and 4-trifluoromethylphenyl) have been reported previously.[5] The dichlorides in which Ar = 2,4-dimethoxyphenyl and 2-thienyl are unstable compounds and were used directly after preparation without isolation. Bis(2,4-di methoxyphenyl)tin dichloride was isolated as a highly unstable crystalline solid, m.p. 116–117°C from petroleum spirit (b.p. 100–120°C), but reproducible C, H and Cl analyses could not be obtained.

Preparation of diaryltin dichloride complexes

The six complexes described here (Table 1) were prepared by standard procedures described in previous papers.[5,8] The diaryltin dichloride in hot toluene was added to a hot solution of the Lewis base in the same solvent. In the case of the bis(2,4-dimethoxyphenyl)tin dichloride complex the preparation was carried out in cold ethoxyethane. In each case the crystalline complex separated in a yield of >80%.

Antitumour bioassay

The activity of the six complexes described here was tested *in vivo* towards P388 lymphocytic leukaemia in mice. The activity was determined in accordance with US National Cancer Institute standard protocol for primary screening as for the 15 complexes previously reported.[1] The validity

Table 2 The activity of $Ar_2SnCl_2.L_2$ complexes towards P388 lymphocytic leukaemia (T/C values, %)[a]

Complex	Dose (mg kg^{-1}) 240	120	60	Activity
Ar = 2-thienyl, L_2 = PBI	t[b]	t	98	Inactive
Ar = 2-thienyl, L_2 = AMP	t	99	97	Inactive
Ar = 2,4-dimethoxyphenyl, L_2 = AMP	t	t	106	Inactive
Ar = 4-methoxyphenyl, L_2 = PBI	t	t	t	Toxic
Ar = 4-methylphenyl, L_2 = PBI	t	t	t	Toxic
Ar = 4-trifluoromethylphenyl, L_2 = PBI	t	131	121	Active

[a] A compound is termed active if it has a T/C value >120%.
[b] t indicates that the complex is toxic at this concentration.

of this *in vivo* protocol is questionable as a primary screen, although it has been applied to a very large number of compounds. The NCI has recently adopted a new disease-oriented *in vitro* primary screen using human tumour cells. It is our intention to re-evaluate the activity of a number of our compounds using more recent *in vitro* prescreening procedures.

Details of the protocol are given in a previous paper.[1] The results of the bioassay are given in Table 2. All antitumour assays were carried out at the Institut Jules Bordet, Brussels, Belgium.

DISCUSSION

The results reported in Table 2 support some of the general observations made in our previous paper.[1] Electron-donating aryl groups, especially 4-methoxyphenyl and 4-methylphenyl groups, enhance the toxicity of the antitumour agent. Further work is in progress on other complexes with these two aryl groups. Work on bis(4-methoxyphenyl)tin dichloride complexes showed that a number of complexes are active but there seems to be no advantage in introducing a second methoxy group into the aromatic ring. The AMP complex of bis(2,4-dimethoxy)tin dichloride is inactive at a dose rate of 60 mg kg^{-1} whereas the AMP complex of bis(4-methoxy)tin dichloride showed activity of 158 T/C% at 15 mg kg^{-1}.[1] Although similar to the benzene ring in π-electron density and size, the thiophene ring in the two complexes reported here does not confer antitumour activity whereas the AMP complex of diphenyltin dichloride shows an activity of 150 T/C% at 100 mg kg^{-1}.[9] The AMP and the PBI complexes of bis(2-thienyl)tin dichloride are inactive at similar doses. Previously we have shown that the phen and AMP complexes of bis(4-trifluoromethylphenyl)tin dichloride have moderate activity, T/C% 131 at 120 mg kg^{-1} and T/C% 133 at 120 mg kg^{-1} respectively. The PBI complex reported here also shows activity of 131 T/C% at 120 mg kg^{-1}. The PBI ligand seems to have no advantage in enhancing the activity in this case.

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