Asian Journal of Chemistry Vol. 13, No. 3 (2001), 1035–1038

Anti-complementary Activity of Several Dimethyltin Carboxylates and Dimethyltin Dichloride Complexes with Various Donor Ligands

RULA F. KHUZAIE,† LUAY J. RASHAN‡ and TALAL A.K. AL-ALLAF*
Department of Chemistry, Faculty of Basic Sciences,
Applied Science University, Amman-11931, Jordan
E-mail: talal_al_allaf@hotmail.com

The anti-complementary activities have been evaluated *in vitro* (using a test that detects complement proteins inhibition) for several dimethyltin carboxylates of the general formula Me_2SnX_2 [X = $½O_2(CO)_2$ (oxalate), $½O_2(CO)_2CH_2$ (malonate), $½O_2(CO)_2CH{=}CH$ (maleate), $½O_2(CO)_2C{-}CH_2CH_2CH_2$ (cyclobutyl dicarboxylate), $O(CO)C_6H_{11}$ (cyclobutyl carboxylate) and $O(CO)CMe_3$ (pivolate)] and dimethyltin dichloride complexes of the general formula $Me_2SnCl_2{\cdot}L$ [L = 8-hydroxy quinoline (L1), 8-hydroxy quinoline-N-oxide (L2), 2,6-diaminopyridine (L3), cyclohexyl amine (L4), (1R, 2R)-1,2-cyclohexane diamine (L5), 3,5-dimethylpyrazole (L6), harmaline (L7) and harmine (L8)]. The results obtained have been compared with those of the three known anticancer drugs (cisplatin, carboplatin and oxaliplatin) and with that of the starting material Me_2SnCl_2. Three of the tin compounds displayed remarkable anti-complementary activities ($IC_{50} \leq 0.1$ μg mL^{-1}) which are almost similar to those of the drugs and tenfolds better than that of Me_2SnCl_2 ($IC_{50} = 1.0$ μg mL^{-1}).

INTRODUCTION

Recent pulications have showed that several cytostatic drugs such as methotrexate, 5-fluorouracil, azothioprine, cyclophosphamide, etc, possess the phenomenon of the reversal effects on the immune cells[1]. These drugs exert *in vitro* immuno-stimulant activity depending on the dose. Furthermore, many cytotoxic drugs have biological activities in addition to their cytotoxicity that might be related to their functions. One of these activities is their effect on complement proteins, *i.e.*, anti-complementary activity.

Because our main interest in the past fifteen years was mainly focused on the synthesis, characterization and the cytotoxicity of metal complexes, *e.g.*, organotin complexes[2–6], we thought it is necessary at this stage to investigate the behaviour of these metal complexes on complement proteins added to sensitized red blood cells, as a continuation to our previous investigations on some platinum complexes[7]. We have, therefore, chosen in this study two groups of organotin(IV) species, the first group being the dimethyltin(IV)-carboxylate compounds (Fig. 1)

†Department of Medical Laboratories, Faculty of Medical Sciences, Applied Science University, Amman-11931, Jordan
‡Department of Pharmacology, Faculty of Pharmacy, Applied Science University, Amman-11931, Jordan

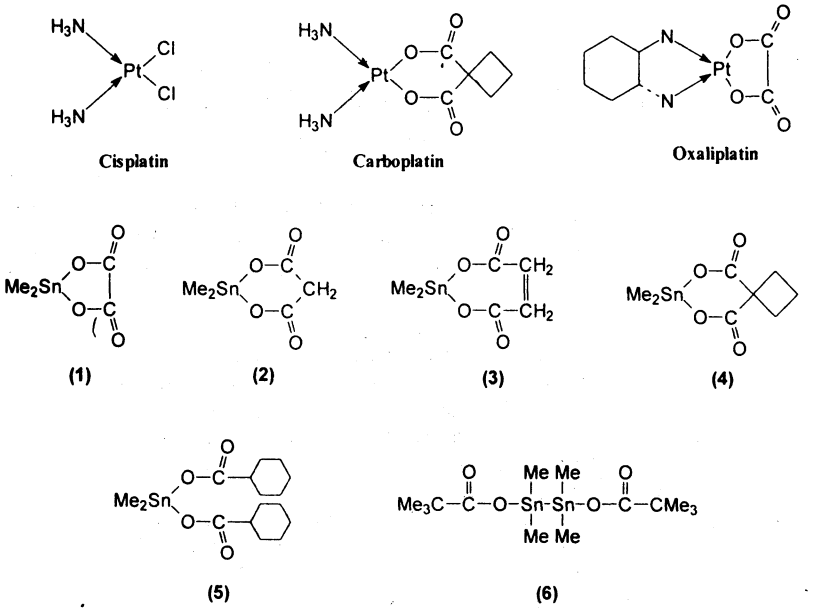

Fig. 1. Dimethyl tin-carboxylates (**1–6**) and known anti-cancer platinum drugs.

and the second group being the dimethyltin dichloride complexes of various ligands: Me_2SnCl_2·L (L1–L8) (Fig. 2), since most of these compounds showed cytotoxicity against a number of tumour cell lines, such as K_{562}, HeLa, Hep-2,

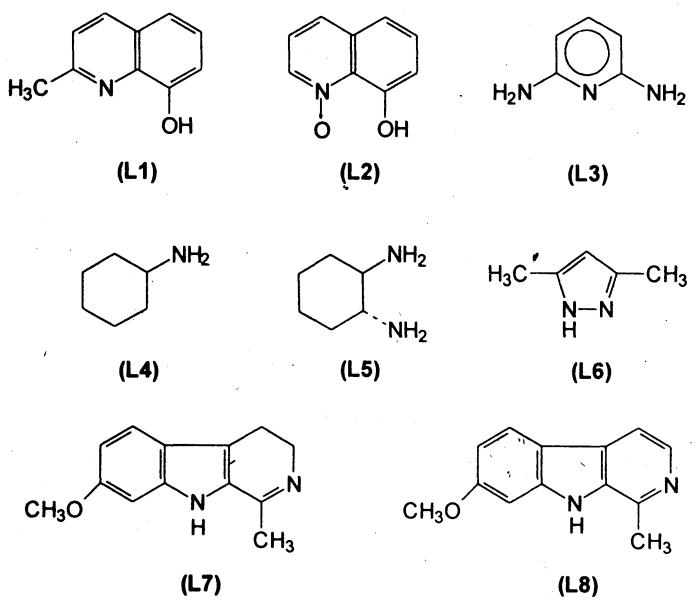

Fig. 2. The ligands (L1–L8) used in complexation with Me_2SnCl_2

KB, T_{47D}, etc. The work also allowed a comparative study between the anti-complementary activity of these organotin compounds with those of the standard references, *i.e.*, cisplatin, carboplatin and oxaliplatin.

EXPERIMENTAL

The compound Me_2SnCl_2 was a commerical product (Fluka). The dimethyltin(IV)-carboxylates (1–6) (Fig. 1) were prepared in our laboratories as described in our previous work[5]. The dimethyltin(IV) dichloride complexes Me_2SnCl_2·(L1–L8) (Fig. 2) were prepared as described in our recent article[6]. These compounds were characterized and purified before the anti-complementary tests. The standard references (cisplatin, carboplatin and oxalipatin) were prepared in our laboratories according to standard methods. They have been characterized and purified (HPLC) according to established analytical methods.

The inhibition of complement activity was determined as described by Shahat *et al.*[8] The test organotin compounds and the standard reference compounds were dissolved in 10% dimethylsulphoxide (DMSO) and serial concentrations (10, 1.0, 0.1, 0.01, 0.001, 0.0001 μg mL^{-1}) were prepared. The assay was performed in a V-well microtiter plates. Rabbit complement (C901 Virion/Serion Immunodiagnostic GmbH) and hemolysing anti-sheep erythrocyte serum (C902 Virion/Serion Immunodiagnostic GmbH) were used as recommended by the manufacturer. 50 μL of the complement solution (diluted 1 : 50) was added to 50 mL of each sample concentration. After an incubation at 37°C for 30 min. 50 μL of a suspension of sensitized sheep erythrocytes were added to each well. Hemolysis was observed optically after an incubation at 37°C for 1 h. Controls consisted of sensitized sheep erythrocytes incubated in buffer + DMSO (no hemolysis), with working solution complement (100% hemolysis), with 1 : 2 and 1 : 3 diluted working solution complement (partial hemolysis). Data were obtained as the results for duplicated samples. The IC_{50} values were calculated using the probit test.

RESULTS AND DISCUSSION

All organotin (IV) compounds selected for anti-complementary tests, *i.e.*, Me_2Sn-carboxylates (Fig. 1) and Me_2SnCl_2·L (L1–L8) complexes (Fig. 2) were already purified before testing by recrystallization from proper solvents. Their anti-complementary activities together with those of the standard references are summarized in Table-1. The results have shown that most of the compounds have no anti-complementary activity at all the concentrations used (IC_{50} > 10 μg mL^{-1}).

However, three compounds, *i.e.*, **2**, **3** and Me_2SnCl_2·L1 (Table-1) showed inhibition at a concentration of 0.1 μg mL^{-1} which is more or less similar to the activity displayed by the standard references; the cisplatin, carboplatin and oxaliplatin (IC_{50} < 0.1 μg mL^{-1}), whereas, the starting material for preparing all of these compounds, *i.e.*, Me_2SnCl_2 showed complement inhibition at a concentration of 1.0 μg mL^{-1}.

It seems difficult at the present stage to relate the anti-complementary activity of these organotin(IV) compounds and their cytotoxicity.

TABLE-1
ANTI-COMPLEMENTARY ACTIVITIES OF THE ORGANOTIN COMPOUNDS

Compound	IC_{50} ($\mu g\ mL^{-1}$)	Compounds	IC_{50} ($\mu g\ mL^{-1}$)
1	no inhibition	Me_2SnCl_2	1.0
2	0.1	Me_2SnCl_2·L1	0.1
3	0.1	Me_2SnCl_2·L2	no inhibition
4	no inhibition	Me_2SnCl_2·L3	no inhibition
5	no inhibition	Me_2SnCl_2·L4	no inhibition
6	no inhibition	Me_2SnCl_2·L5	no inhibition
Cisplatin	< 0.1	Me_2SnCl_2·L6	no inhibition
Carboplatin	< 0.1	Me_2SnCl_2·L7	no inhibition
Oxaliplatin	< 0.1	Me_2SnCl_2·L8	no inhibition

Previous investigation revealed that some of these organotin(IV) compounds, such as **2, 3, 5, 6,** Me_2SnCl_2·L1 and Me_2SnCl_2·L2 have cytotoxic effects against some tumour cell lines such as Hep-2, HeLa, L_{20B}, RD and P_{388}.[5, 6] whereas the present results have showed that significant relationship between the anti-complementary activity and cytotoxicity in the three compounds **2, 3** and Me_2SnCl_2·L1 and such relationship is not evident in other compounds **5, 6** and Me_2SnCl_2·L2. Therefore, *in vitro* speaking, it appears that compounds **2, 3** and Me_2SnCl_2·L1 may possess the phenomenon of reversal effects on immune cells. Hence, further *in vivo* results are required to confirm this activity.

REFERENCES

1. H. Wagner, B. Kreher and K. Jurcic, *Arzneimittel Forschung*, **38,** 273 (1988).
2. L.J. Rashan, T.A.K. Al-Allaf and R.F. Khuzaie, *Boll. Chim. Farm. (Italy),* **134,** 464 (1995).
3. T.A.K. Al-Allaf, R.I.H. Al-Bayati, L.J. Rashan and R.F. Khuzaie, *Appl. Organometal. Chem.*, **10,** 47 (1996).
4. T.A.K. Al-Allaf, M.A. Al-Shama'a and L.J. Rashan, *Appl. Organometal. Chem.*, **10,** 545 (1996).
5. T.A.K. Al-Allaf, L.J. Rashan, W.F. Halaseh and R.F. Khuzaie, *Boll. Chim. Farm. (Italy),* **137,** 55 (1998).
6. T.A.K. Al-Allaf, R.F. Khuzaie, L.J. Rashan and W.F. Halaseh, *Boll. Chim. Farm. (Italy),* **138,** 267 (1999).
7. R.F. Khuzaie, L.J. Rashan, T.A.K. Al-Allaf and M.M. Al-Saket, *J.J. Appl. Sci. (Jordan),* **1,** 123 (1999).
8. A.A. Shahat, F. Hammouda, S.I. Ismail, S.A. Azzam, T.D. Bruyne, A. Lasure, B. Van Poel, L. Pieters and A.J. Vlietinck, *Planta Med.*, **62,** 10 (1996).

(*Received:* 12 February 2001; *Accepted:* 7 April 2001) AJC-2312