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SHORT PAPER

[Bis(aminomethyl)dimethylsilane]platinum(II) dichloride: a potential antitumor agent

R D Haugwitz,*† W K Anderson,‡ J Plowman,* R Kaslinal,‡ D M Houston‡ and V L Narayanan*

* Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland 20892, USA, and ‡ Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, USA

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[Bis(aminomethyl)dimethylsilane]platinum(II) dichloride (1) was synthesized by a three-step procedure. The antitumor activity of 1 was evaluated in the i.p. implanted mouse L1210 leukemia model. A 10 mg kg^{-1} dose administered every fourth day for a total of three injections extended the median life span of the dying mice by at least 100% and resulted in 40–50% survivors (day 30) in two experiments corresponding to an approximate 6 $\log_{10}$ reduction in tumor burden at the end of treatment. Compound 1 appeared at least as active as cisplatin under the testing protocols utilized. The closely related bis[aminomethyltrimethylsilane]platinum(II) dichloride complex was inactive in this mouse model.

Keywords: Antitumor agent, cisplatin, bioisostere, aminoalkylsilane platinum complex

INTRODUCTION

Tetraplatin (**2**), a platinum complex which we developed earlier,[1] is scheduled to enter Phase I clinical trials very soon. This compound might prove to be beneficial in the treatment of patients resistant to cisplatin based on its preclinical activity[2] and toxicity.[3] As part of our continuing structure–activity studies in this area, we undertook the synthesis and biological evaluation of alkylamineplatinum(II) and platinum(IV) complexes wherein one of the carbon atoms is replaced by silicon.[4] A recent European patent application in this area[5] prompts us to report our findings on the anticancer activity of the lead compound, [bis(aminomethyl)dimethylsilane]platinum(II) dichloride (**1**).

† Author to whom correspondence should be addressed.

METHODS AND MATERIALS

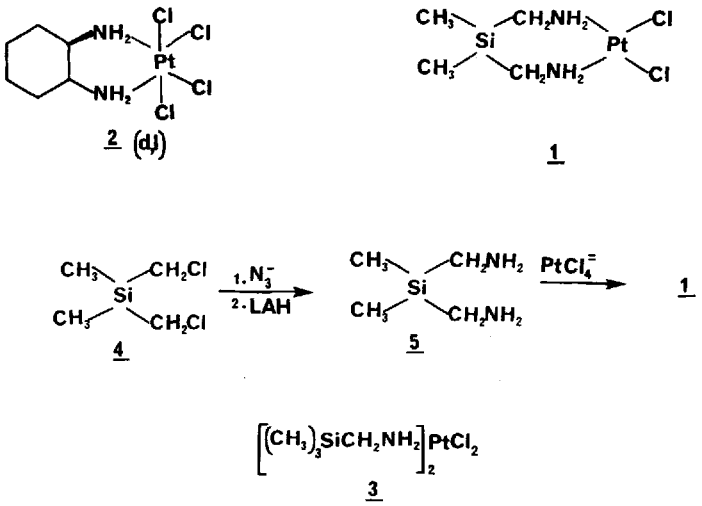
Chemistry

[Bis(aminomethyl)dimethylsilane]platinum(II) dichloride (**1**) was synthesized from commercially available bis(chloromethyl)dimethylsilane (**4**) (Petrarch Systems, USA), in three steps (Scheme 1).

Bis(chloromethyl)dimethylsilane **4** (0.1 mol) was added to a stirred suspension of sodium azide (0.2 mol) in sulfolane (50 cm^3), sodium carbonate (4–5 granules) was added and the mixture stirred at 50–60°C for 16 h (nitrogen atmosphere) to give bis(azidomethyl)dimethylsilane [88%; b.p. 22–23°C/37 mm, distilled directly from the sulfolane mixture: **caution, explosive hazard** (the solid sodium carbonate minimizes this risk). ^{1}H NMR ($CDCl_3$): δ 0.28 (s, 6 H), 2.93 (s, 4 H). IR (neat): 2964, 2929, 2098, 1383, 1253, 1175, 1405, 851 cm^{-1}.

The bisazide (0.1 mol) was added dropwise over 45 min to a stirred suspension of lithium aluminum hydride (LAH) (0.2 mol) in ether (200 cm^3). The mixture was stirred (nitrogen atmosphere) at 0°C (0.5 h) and then 20°C (0.5 h) to give bis(aminomethyl)dimethylsilane, **5** (42%; b.p. 72–75°C/150 mm, distilled from potassium hydroxide pellets). ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6 H), 1.50 (s, 4 H). IR (neat): 3359, 3228, 2957, 2901, 2816, 1605, 1434, 1246, 1098, 1055, 914, 844, 724 cm^{-1}.

A solution of the diamine in argon-degassed methanol was added rapidly to a stirred solution of potassium tetrachloroplatinate in argon-sparged water (20°C, protected from light, argon atmosphere). The mixture was stirred for 20 h filtered and the collected solid washed sequentially with water, 1 M HCl, cold ethanol, and ether



Scheme 1

to give **1**, as an off-white solid (75%). ^{1}H NMR (d_7-DMF, external TMS): δ 0.04 (s, 6 H), 1.9–2.6 (br m, 4 H), 3.1 (s, 4 H). IR: 3239, 3211, 3133, 1598, 1422, 1281, 1253, 1140, 865, 844, 788, 752, 689 cm^{-1}. Analysis: calcd for $C_4H_{14}N_2Cl_2SiPt$: C, 12.50; H, 3.67; N, 7.29; Cl, 18.45. Found: C, 12.45; H, 3.71; N, 7.2; Cl, 18.51%.

The acyclic complex, *cis*-bis(aminomethyltrimethylsilane)platinum(II) dichloride **3** was prepared in a similar manner from chloromethyltrimethylsilane, as a greyish-white solid (58%). ^{1}H NMR (d_6-DMSO, external TMS): δ 0.00 (s, 18 H), 1.9–2.7 (br m, 8 H). IR: 3274, 3232, 3197, 3140, 3126, 2901, 2957, 1584, 1415, 1253, 1189, 1161, 859, 844, 745, 734, 696, 654 cm^{-1}. Analysis: calcd for $C_8H_{26}N_2Cl_2Si_2Pt$: C, 20.34; H, 5.93; N, 5.93; Cl, 15.01. Found: C, 20.24; H, 5.57; N, 5.87; Cl, 15.09%.

Antitumor testing

Three platinum complexes **1**, **3** and cisplatin, were evaluated for antitumor activity in the i.p. implanted L1210 leukemia model according to standard protocols used by the Developmental Therapeutics Program (DTP), Division of Cancer Treatment (DCT), National Cancer Institute (NCI), Bethesda MD.[6,7] The experiments were conducted under contract to DTP at the Southern Research Institute, Birmingham, AL. The mice, BALB/c × DBA/2 F_1 (CD2F_1), and the L1210 leukemia line were obtained through the Biological Testing Branch, DTP, DCT, NCI. Each compound was evaluated at several dosage levels and each dose was administered to 6–10 mice; 20 tumor-bearing control mice per experiment received saline injections. All compounds were administered intraperitoneally (i.p.). Cisplatin [$Pt(NH_3)_2Cl_2$] was given as a solution in saline whilst **1** and **3** were given as suspensions in saline plus Tween 80. At the 10 mg, i.e. the optimal dose, virtually all of **1** had dissolved except for a few fine particles, permitting direct comparison of **1** with cisplatin. Therapeutic response was based on median day of death of dying mice and was expressed as a percentage of increased life span (%ILS) and changes in tumor burden as a result of treatment. The latter calculations were based on tumor doubling times determined *in vivo* with a concomitantly run internal tumor titration in accordance with the principles and methods described by Schabel *et al.*[8] Long-term (day 30) survivors were excluded from the calculations. Dying mice were necropsied, and if death was judged to be nonleukemic based on the absence of ascites or splenomegaly it was considered likely to have been drug-induced.

RESULTS

The comparative therapeutic effectiveness of **1**, **3** and cisplatin against the i.p.-implanted L1210 leukemia is shown in Table 1. A 10 mg kg^{-1} dose of **1** given on days 1, 5 and 9 produced the greatest antitumor effect, increasing the life span of dying mice by 138% and producing 40% day 30

Table 1 Effects of platinum complexes on the survival of mice bearing i.p.-implanted L1210 leukemia[a]

Compound	Dose (mg kg^{-1} per injection)	Body wt change (g)[b]	ILS (%)[c]	Day 30 survival total	Approx. $\log_{10}$ change in tumor burden at end, R_x[d]
1	40	−3.3	−6	0/10	Toxic
	20	−0.6	33	0/9	Toxic
	10	+0.3	138	4/10	−3.6(−5.8)
	5	+0.4	61	0/10	+2.0
3	80	+2.1	−12	0/10	*ca* +3.2
	40	+1.3	−12	0/10	*ca* +3.2
	20	+0.8	0	0/10	+3.2
	10	+1.2	0	0/10	+3.2
Cisplatin	20	−3.6	−17	0/10	Toxic
	10	−1.2	55	1/10	Toxic
	5	+0.4	72	0/10	+1.2
	2.5	+0.6	55	0/10)	+2.2

[a] 10^5 leukemic cells implanted i.p. in dosage groups of 10 $CD2F_1$ mice (20 controls) on day 0. Treatment was administered i.p. on days 1, 5, 9. [b] Change in mean body weight (day 5 − day 1) for control mice was 0.4 g. [c] Median survival times for control mice was 9 days. [d] $\log_{10}$ change in viable tumor stem cell population at end of therapy as compared with that at the start of therapy, based on median day of death among mice that died; e.g. a −2 log change means there was a 99% reduction, and a +2 log change means that there was a 100-fold increase in tumor burden at the end of therapy. Numbers in parentheses are based on percentage of survivors.

survivors. In the surviving mice, the viable tumor cell population at the end of treatment was calculated to be 99.9999% lower than the cell population at the start of treatment, corresponding to a net $\log_{10}$ reduction in tumor burden of 6. Cisplatin was less effective in the same experiment, producing an optimal ILS value of 72% at a dosage level of 5 mg kg^{-1}. In the latter mice, tumor burden was increased 10-fold during treatment. Compound **3** demonstrated no antitumor activity at dosage levels up to 80 mg kg^{-1}, presumably as a consequence of its hydrolytic stability ($t_{1/2} > 24$ h at 24°C). In contrast **1** has a $t_{1/2} = 208$ min (at 24°C). A second study, comparing the efficacies of **1** and cisplatin using the same treatment regimen, also indicated that **1** was at least as active as cisplatin. In this study (data not shown), higher dosage levels of both compounds were tolerated. Dosage levels of **1** ranging from 10 to 40 mg kg^{-1} per injection produced 50–67% day 30 survivors with no visual evidence of tumor. Cisplatin was equally effective at its optimal dose of 20 mg kg^{-1} per injection producing 67% day 30 survivors, but caused no long-term survivors at lower dosage levels.

CONCLUSION

Incorporation of silicon as bioisosteric replacement for carbon is becoming an important strategy in medicinal chemistry.[9] This communication describes the successful use of such an approach for the construction of antitumor compound **1**. In two experiments using the mouse L1210 leukemia model, **1** produced long-term survivors when administered at its optimal dosage level. By comparison, cisplatin demonstrated similar efficacy in one experiment, but was less active in the second. These promising data have prompted us to study further the antitumor potential and define the structure-activity relationships.

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