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Synthesis of Saccharidyl N,N-Bis(2-Chloroethyl)phosphoramidates and Their Antitumor Activity

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ABSTRACT

In order to search for novel antitumor drugs with high activity and low toxicity, a series of new compounds, galactopyranosyl (or glucofuranosyl) N,N-bis(2-chloroethyl) phosphoramidates, have been synthesized. The structures of all compounds prepared were proved by ^1H NMR, ^{31}P NMR, IR, and MS spectroscopy and by elemental analyses. The existence of diastereoisomers was detected by ^{31}P NMR and ^1H NMR spectra. One of the two isomers of **3a** *and also one of* **4b**, *i.e.,* **3a'** *and* **4b'**, *respectively, were obtained by recrystallization. The absolute configurations of* **3a'** *and* **4b'** *were determined by single-crystal X-ray diffraction analysis. The results of the preliminary biological tests indicated that some of these compounds have certain inhibitory activities against* L_{1210} cells.

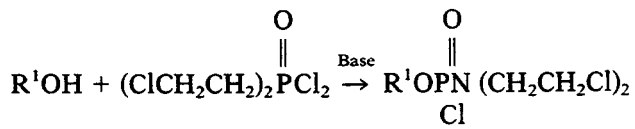
INTRODUCTION

Endoxan is one of the most effective anticancer drugs against various human cancers [1]. However, acrolein, formed from it by the action of hepatic mixed function oxidases in the liver, is toxic to the urinary system [2]. Therefore, it is of theoretical and practical significance to synthesize new organophosphorus antitumor drugs with low toxicity. Recently, it was reported in the literature that some organic phosphorus compounds bearing a monosaccharidyl group can be used as antitumor agents, antivirals, or immunomodulators [3,4]. Thus, we designed and synthesized new types of phosphoramidates, **3a–i** and **4a–i**, containing a monosaccharidyl and mustard group. Preliminary biological tests show that some of these compounds have antitumor activity.

RESULTS AND DISCUSSION

Synthesis of Galactopyranosyl (or Glucofuranosyl) N,N-Bis(2-Chloroethyl) phosphoramidates

We tried to prepare the N,N-bis(2-chloroethyl) aminophosphoryl chlorides **2** by the reaction of N,N-bis(2-chloroethyl)aminophosphoryl dichloride with monosaccharides **1** (having a free hydroxy group), in the presence of triethylamine according to Scheme 1, but the reactions did not take place. When sodium hydroxide powder was used instead of triethylamine, it was very difficult to purify the product. However, satisfactory yields were obtained when a mixture of triethylamine and sodium hydroxide powder was used. Because of the hygroscopic nature of sodium hydroxide, this method was not thought to be generally applicable.



1 **2**

SCHEME 1

A better method, more indirect, is outlined in

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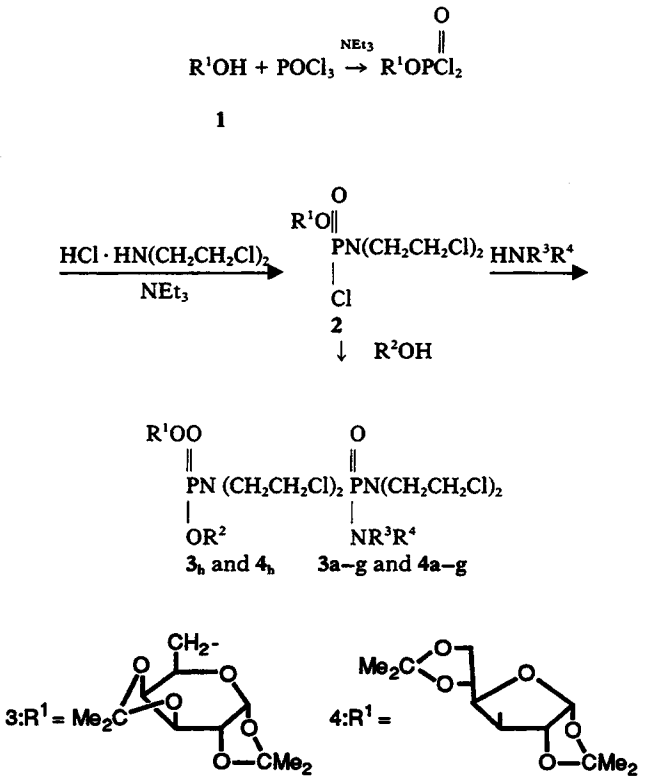
Scheme 2. N,N-bis(2-chloroethyl)aminophosphoryl chloride **2** as well as compounds **3a–h** and **4a–h** were synthesized by this multistep approach.

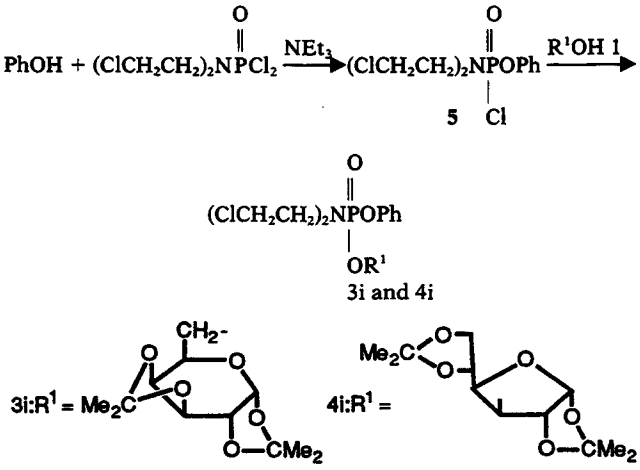


3a: R^3=R^4=H; **3b**: R^3=H, R^4=Pr^i; **3c**: R^3=H, R^4=  ;
3d: R^3=H, R^4=$-CH_2Ph$; **3e**: R^3=R^4=Me; **3f**: R^3=R^4=Pr^n;
3g: R^3=H, R^4=Bu^t; **3h**: R^2=Et;
4a: R^3=R^4=H; **4b**: R^3=H, R^4=Pr^i; **4c**: R^3=H, R^4=;
4d: R^3=H, R^4=Bu^t; **4e**: R^3=R^4=Me; **4f**: R^3=R^4=Pr^n;
4g: R^3=H, R^4=CH_2Ph; **4h**: R^2=CH_3.

SCHEME 2

An attempt to prepare the compounds **3i** and **4i** bearing an aryloxy group by the method shown in Scheme 2 failed. This is probably due to the low reactivity of N,N-bis(2-chloroethyl)aminophosphoryl chloride **2**, the apparent steric hindrance of the system and low nucleophilicity of the aryloxy group. In view of these considerations, we designed a new route as shown in Scheme 3. Treatment of N,N-bis(2-chloroethyl) aminophosphoryl chloride **5** with a suitable monosaccharide in the presence of triethylamine or pyridine gave no reaction. However, when sodium hydroxide powder was used, the products **3i** and **4i** were obtained.

Observed by TLC, compounds **4** were formed at slower reaction rates and with formation of more by-products than compounds **3**. The former were also formed in lower yields than the latter. This is probably due to greater steric hindrance and lower reactivity of the 1,2: 5,6-di-O-isopropylidene-α-D-glucofuranosyl group than the 1,2: 3,4-di-O-isopropylidene-α-D-galactopyranosyl group.



SCHEME 3

The Structures of the Products

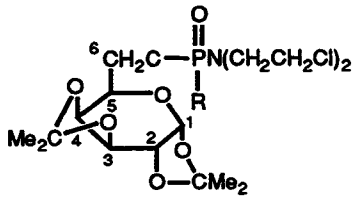
The molecular structures of the products **3** and **4** were confirmed by ^{1}H NMR, IR, MS, and ^{31}P NMR spectroscopy and by elemental analyses. The experimental data for **3** and **4** are listed in Tables 1 and 2.

The configurations of the five chiral carbons of the galactopyranosyl and glucofuranosyl groups in **3** and **4** are known and do not change during the reaction process, while the chiral phosphorus atom of the products may result in the formation of two stereoisomers. In the ^{1}H NMR spectrum of products **3** and **4**, the chemical shifts of C_1–H of the monosaccharidyl group appeared in two doublets at δ 5.30–5.90 with similar coupling values, showing that each of the compounds **3** and **4** consists of two diasteroisomers. The existence of these isomers was further confirmed by the ^{31}P NMR spectrum which showed two signals.

In the separation of the diastereoisomers of **3a** having δ ^{31}P NMR values of 16.78 and 16.89, a colorless crystalline solid **3a′** with $[\alpha]_D$ + 41.67° (c 0.6, acetone) and mp 103–104°C was obtained by recrystallization from a mixture of trichloromethane and n-hexane. The ^{1}H NMR spectrum of **3a′** showed a doublet of C_1–H at δ 5.51 with J = 4.76 Hz, and the ^{31}P NMR spectrum of **3a′** showed a singlet at δ 16.86. Similarly, the colorless crystalline solid **4b′** with $[\alpha]_D$ + 70.0° (c 0.3, acetone) and mp 110–110.5°C, purified by crystallization from ethyl ether-petroleum ether, was characterized by its ^{31}P NMR spectrum (δ 14.40, singlet), while the ^{31}P NMR of **4b** gave two signals (δ 14.26 and 14.94).

The molecular structures of the pure isomers **3a′** and **4b′** were determined by X-ray diffraction analyses (Figures 1 and 3, respectively). In the case of **3a′**, the torsion angles are, of O(1)-P(1)-O(2)-C(6) −60.88 (1.22)°, of N(1)-P(1)-O(2)-C(6) 66.65 (1.18)°,

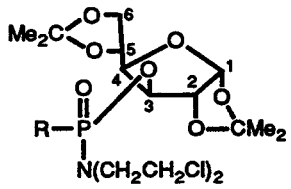
TABLE 1 The Data of Compounds **2**[a]



Number	R	Yield (%)	State (mp °C)	^1H NMR and ^{31}P NMR (ppm)[b]	IR (cm^{-1})	MS[c] (MH^+)
3a	NH_2	70.8	solid (103–104)	1.30, 1.41, and 1.51 (s, 12H, CH_3), 3.0 (w, 2H, NH_2), 3.40–3.60 (m, 8H, CH_2CH_2Cl), 4.0–4.20 m, 4H, C_2–H, C_5–H, C_6–H), 4.25–4.36 (q, 1H, C_4–H), 4.58–4.66 (q, 1H, C_3–H), 5.50 (dd, 1H, C_3–H). ^{31}P NMR: 16.78 and 16.89.	3419.5 1210 1070 1160	463
3b	$HNPr^i$	49.8	syrup	1.14 (dd, 8H, CH_3 of iso-propyl), 1.34, 1.44, and 1.54 (s, 12H, CMe_2), 2.50 (w, 1H, NH), 3.24–3.75 (m, 9H, CH of iso-propyl, CH_2CH_2Cl), 4.0–4.30 (m, 4H, C_2–H, C_5–H, C_6–H), 4.30, 4.38 (dq, 1H, C_4–H), 4.60–4.65 (q, 1H, C_2–H), 5.54 (dd, 1H, C_1–H). ^{31}P NMR: 14.80.	3204.5 1206.7 1061.6 1161.5	505
3c	HN–⬡	70	solid (82–83)	1.32, 1.42, and 1.52 (s, 12H, CH_3), 1.0–2.04 (m, 10H, CH_2 52 of cyclohexyl), 2.72 (m, 1H, CH of cyclohexyl), 3.0 (w, 1H, NH), 3.20–3.76 (m, 8H, CH_2CH_2Cl), 3.96–4.36 (m, 5H, C_2–H, C_4–H, C_5–H, C_6–H), 4.58–4.63 (q, 1H, C_3–H), 5.52 (d, 1H, C_1–H). ^{31}P NMR: 15.07.	3204.5 1207.7 1064.5 1162.3	545
3d	$HNCH_2Ph$	62.5	syrup	1.27, 1.30, 1.37, 1.39, 1.50, and 1.52 (s, 12H, CH_3), 3.38–3.81 (m, 9H, NH, CH_2CH_2Cl), 4.0–4.20 (m, 6H, C_2–H, C_5–H, C_6–H, CH_2 of benzyl), 4.29–4.35 (m, 1H, C_4–H), 4.60–4.65 (q, 1H, C_3–H), 5.50 (dd, 1H, C_1–H), 7.27–7.35 (m, 7H, Ph). ^{31}P NMR: 15.75 and 16.01.	3302 1205 1059.4 1161.7	553
3e	NMe_2	67.8	syrup	1.32, 1.44, and 1.54 (s, 12H, CMe_2), 2.70 (d, 6H, NMe_2), 3.24–3.72 (m, 8H, CH_2CH_2Cl), 4.0–4.20 (m, 4H, C_2–H, C_5–H, C_6–H), 4.30–4.38 (q, 1H, C_4–H), 4.58–4.63 (q, 1H, C_3–H), 5.54 (dd, 1H, C_1–H). ^{31}P NMR: 17.50 and 17.76.	1208.7 1063.5 1162.2	491
3f	NPr^n_2	57.8	syrup	0.86 (t, 6H, CH_3 of n-propyl), 1.34, 1.44, and 1.54 (s, 12H, CMe_2), 1.50–1.68 (m, 4H, CH_2 of n-propyl), 2.9 (dt, 4H, CH_2 of n-propyl), 3.24–3.76 (m, 8H, CH_2CH_2Cl, 4.0–4.28 (m, 4H, C_2–H, C_5–H, C_6–H), 4.30–4.35 (q, 1H, C_3–H), 5.54 (dd, 1H, C_1–H). ^{31}P NMR: 17.17 and 17.36.	1208.4 1065.6 1162.7	547
3g	HNBu[d]	59.7	syrup	1.32, 1.48, and 1.58 (s, 21H, CH_3), 3.20–3.80 (m, 9H, NH, CH_2CH_2Cl), 3.96–4.30 (m, 4H, C_2–H, C_5–H, C_6–H), 4.37–4.42 (q, 1H, C_4–H), 4.60–4.65 (q, 1H, C_3–H), 5.50 (dd, 1H, C_1–H). ^{31}P NMR: 13.58 and 13.80.	3318 1208.4 1064.3 1162.2	519
3h	OEt	52.2	syrup	1.32 (t, 3H, CH_3 of ethyl), 1.34, 1.44, and 1.54 (s, 12H, CMe_2), 3.20–3.75 (m, 8H, CH_2CH_2Cl), 4.0–4.30 (m, 6H, $POCH_2$, C_2–H, C_5–H, C_6–H), 4.30–4.38 (q, 1H, C_4–H), 4.58–4.63 (q, 1H, C_3–H), 5.54 (dd, 1H, C_1–H).	1202.8 1050.4 1158.6	492
3i	OPh	58.8	syrup	1.34, 1.48, 1.51, and 1.55 (s, 12H, CMe_2), 3.40–3.76 (m, 8H, CH_2CH_2Cl), 4.10–4.30 (m, 4H, C_2–H, C_5–H, C_6–H), 4.30–4.38 (dq, 1H, C_4–H), 4.55–4.62 (dq, 1H, C_3–H), 5.55 (dd, 1H, C_1–H), 7.17–7.35 (m, 5H, Ph).	1246.6 1061.6 1204.6 1161.6	540

[a]Satisfactory microanalyses obtained: C, ±0.31; H, ±0.22; N, ±0.22.
[b]^{31}P NMR spectra of **3b** and **3c** were recorded with JEOL-FX-900 spectrometer, others with BRUKER AC-P200 spectrometer.
[c]Chemical ionization.

TABLE 2 The Data of Compounds 4[a]



Number	R	Yield (%)	State (mp °C)	^1H NMR and ^{31}P NMR (ppm)	IR (cm^{-1})	MS[b] (MH^+)
4a	NH_2	53.1	syrup	1.32, 1.36, 1.44, and 1.50 (s, 12H, CH_3), 3.20 (w, 2H, NH_2), 3.30–3.80 (m, 8H, CH_2CH_2Cl), 3.92–4.30 (m, 4H, C_4–H, C_5–H, C_6–H), 4.60–4.79 (dq, 1H, C_3–H), 4.92 (d, 1H, C_2–H), 5.90 (dd, 1H, C_1–H). ^{31}P NMR: 16.15 and 16.82.	3365 1212 1607 1159	463
4b	$HNPr^i$	18	solid (110–110.5)	1.18 (dd, 6H, CH_3 of iso-propyl), 1.31, 1.35, 1.44, and 1.50 (s, 12H, CMe_2), 2.44 (w, 1H, NH), 3.30–3.50 (m, 9H, NCH, CH_2CH_2Cl), 4.0–4.20 (m, 4H, C_4–H, C_5–H, C_6–H), 4.54–4.82 (dq, 1H, C_3–H), 4.98 (d, 1H, C_2–H), 5.88 (dd, 1H, C_1–H). ^{31}P NMR: 14.26 and 14.94.	3186 1208 1147	505
4c	HN–⬡	48.26	solid (52–53)	1.30, 1.34, 1.38, 1.42, 1.45, and 1.50 (s, 12H, CH_3), 1.08–2.0 (m, 11H cyclohexyl), 3.0 (w, 1H, NH), 3.24–3.76 (m, 8H, CH_2CH_2Cl), 3.94–4.28 (m, 4H, C_4–H, C_5–H, C_6–H), 4.70 (d, 1H, C_2–H), 4.56–4.80 (m, 1H, C_3–H), 5.38 (dd, 1H, C_1–H).	3181 1205 1151	545
4d	$HNBu^t$	38.5	syrup	1.30, 1.35, 1.43, and 1.50 (s, 21H, CH_3), 2.63 (dw, 1H, NH), 3.30–3.70 (m, 8H, CH_2CH_2Cl), 4.40–4.20 (m, 4H, C_4–H, C_5–H, C_6–H), 4.50–4.75 (q, 1H, C_5–H), 5.14 (d, 1H, C_2–H), 5.88 (dd, 1H, C_1–H).	3369 1208 1159	519
4e	NMe_2	40.13	solid (99–100)	1.32, 1.36, 1.44, and 1.52 (s, 12H, CMe_2), 2.70 (d, 6H, NMe_2), 3.24–3.80 (m, 8H, CH_2CH_2Cl), 3.96–4.28 (m, 4H, C_4–H, C_5–H, C_6–H), 4.60–4.78 (q, 1H, C_3–H), 5.0 (d, 1H, C_2–H), 5.90 (dd, 1H, C_1–H). ^{31}P NMR: 16.55 and 17.09.	1220 1067 1167	491
4f	NPr^n_2	38.71	syrup	0.96 (t, 6H, CH_3 of n-propyl), 1.40, 1.44, 1.56, and 1.64 (s, 12H, CMe_2), 1.55–1.65 (m, 4H, CH_2 of n-propyl), 2.95–3.05 (dq, 4H, CH_2 of n-propyl), 3.30–3.88 (m, 8H, CH_2CH_2Cl), 4.30–4.40 (m, 4H, C_4–H, C_5–H, C_6–H), 4.60–4.75 (q, 1H, C_3–H), 5.20 (d, 1H, C_2–H), 5.94 (dd, 1H, C_1–H).	1213 1066 1159	547
4g	$HNCH_3Ph$	52.54	solid (126–127.5)	1.48, 1.52, 1.62, and 1.68 (s, 12H, CH_3), 3.40–3.90 (m, 9H, NH, CH_2CH_2Cl), 4.0–4.20 (m, 6H, C_4–H, C_5–H, C_6–H, CH_2 of benzyl), 4.94 (d, 1H, C_2–H), 5.80 (dd, 1H, C_1–H), 7.25–7.35 (m, 5H, Ph).	3165 1213 1175	553
4h	OCH_3	28.9	solid (79–81)	1.54, 1.56, 1.65, and 1.72 (s, 12H, CMe_2), 3.20–3.90 (m, 8H, CH_2CH_2Cl), 3.64 (d, 3H, OCH_3), 4.0–4.30 (m, 4H, C_4–H, C_5–H, C_6–H), 4.65 (q, 1H, C_3–H), 4.96 (d, 1H, C_2–H), 5.90 (dd, 1H, C_1–H).	1215 1067 1159	478
4i	OPh	16.0	syrup	1.27, 1.40, 1.48, and 1.51 (s, 12H, CH_3), 3.40–3.80 (m, 8H, CH_2CH_2Cl), 4.0–4.28 (m, 4H, C_4–H, C_5–H, C_6–H), 4.70 (d, 1H, C_2–H), 4.75–4.85 (q, 1H, C_3–H), 5.66 (d, 1H, C_1–H), 7.10–7.50 (m, 5H, Ph). ^{31}P NMR: 3.30 and 3.83.	1254 1201 1158	540

[a]Satisfactory microanalysis obtained: C, ±0.37; H, ±0.25; N, ±0.41.
[b]Chemical ionization.

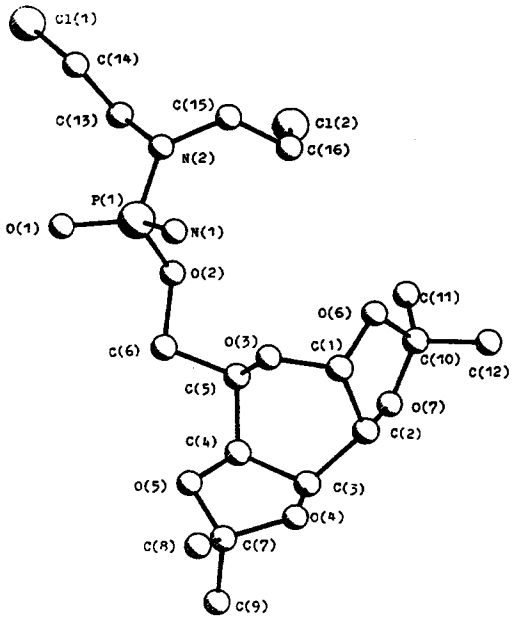


FIGURE 1 Molecular structure of **3a'**.

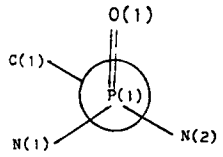


FIGURE 2 Newman projection of **3a'** from P(1) to O(2).

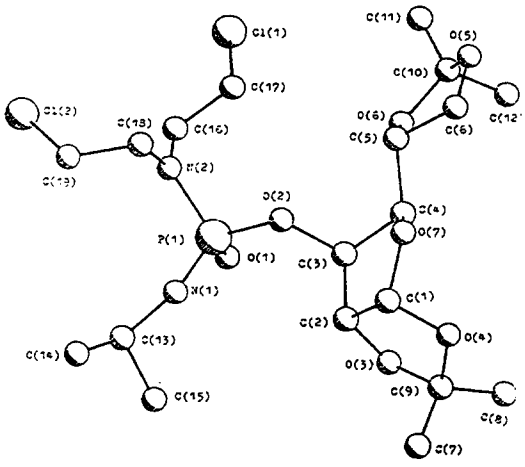


FIGURE 3 Molecular structure of **4b'**.

and of N(2)-P(1)-O(2)-C(6) 178.71 (1.09)°. The Newman projection from P(1) to 0(2) is shown in Figure 2; the configuration of the chiral phosphorus atom is R. For **4b'**, the torsion angles are, of O(1)-P(1)-O(2)-C(3) −34.88(0.69)°, of N(1)-P(1)-O(2)-C(3) 90.77 (0.61)°, and of N(2)-P(1)-O(2)-C(3) −155.79 (0.59)°. The Newman projection from P(1) to O(2) is shown

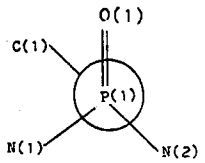


FIGURE 4 Newman projection of **4b'** from P(1) to O(2).

in Figure 4. Thus, the configuration of the chiral phosphorus atom is R.

Antitumor Activity

The preliminary antitumor activities were tested for some of the compounds **3** and **4**. The results are listed in Table 3. It was found that these compounds possess certain inhibitory activities against L_{1210} cells.

EXPERIMENTAL

Instruments

^1H NMR and ^{31}P NMR spectra were recorded with a BRUKER AC-P 200 and a JEOL FX 90Q spectrometer, respectively. TMS was used as an internal standard for ^1H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR. Mass spectra were recorded with a VG ZAB-HS spectrometer using the CI method. Elemental analyses were performed with a CHN CORDER MT-3 elementary analyzer. IR spectra were measured by a SHIMADZU-435 instrument. Melting points were determined with a THOMAS-HOOVER capillary apparatus. Column chromatography was performed on silica gel H(10–40 μm, Hai Yang Chemical Factory of Qingdao).

Dichloromethane was dried with anhydrous K_2CO_3. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**1a**) and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**1b**) were synthesized according to conventional methods [5,6].

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranosyl N, N-Bis(2-chloroethyl)aminophosphoryl Chloride (**2a**)

A mixture of 3.75 g (14.4 mmol) of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**1a**) and 1.51 g

TABLE 3 The Antitumor Activities of Some of Compounds **3** and **4**

Compounds	***3a***	***4a***	***4c***	***4e***	***4f***	***4g***
Cell line	L_{1210}	L_{1210}	L_{1210}	L_{1210}	L_{1210}	L_{1210}
Times (h)	24	72	72	72	72	72
IC_{50} (μg/mL)	27.81	7.59	4.36	0.668	0.76	0.90

(15 mmol) of triethylamine in 30 mL of dichloromethane was added dropwise to a stirred solution of 2.31 g (15 mmol) of phosphorus oxychloride in 20 mL of dichloromethane at −10–0°C. The mixture was then stirred at 0–10°C for 5 hours. After 2.46 g (13.8 mmol) of bis (2-chloroethyl) amine hydrochloride had been added, a solution of 2.88 g (28.51 mmol) of triethylamine in 15 mL of dichloromethane was added dropwise during 10 minutes and stirring was continued for 10 hours. The mixture was diluted with ethyl ether, filtered to remove triethylamine hydrochloride, and the solvents evaporated by means of a rotary evaporator. The crude product was purified on a silica gel column using a mixture of ethyl ether and petroleum ether (1:1 v/v) as the eluent. The compound 1,2:3,4-di-O-isopropylidene-α-D-galactopyranosyl N,N-bis(2-chloroethyl)aminophosphoryl chloride (**2a**) was obtained as a light yellowish syrup, 4.05 g, yield 58.30%. ^{1}H NMR ($CDCl_3$); 1.29, 1.35, and 1.48 (s, 12H, CH_3), 3.30–3.70 (m, 8H, CH_2CH_2Cl), 3.90–4.20 (m, 4H, C_2–H, C_5–H, C_6–H), 4.35–4.42 (m, 1H, C_4–H), 4.50–4.60 (q, 1H, C_3–H), 5.50 (d, 1H, C_1–H). MS (CI): $(M + 1)^+$ 482.

Similarly, the intermediate 1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl N,N-bis(2-chloroethyl) aminophosphoryl chloride (**2b**) was prepared as a light yellowish syrup, yield 67.60%. ^{1}H NMR ($CDCl_3$): 1.30, 1.35, 1.40, and 1.45 (s, 12H, CH_3), 3.45–3.90 (m, 8H, CH_2CH_2Cl), 4.0–4.20 (m, 8H, C_4–H, C_5–H, C_6–H), 4.30–4.38 (q, 1H, C_4–H), 4.51–4.58 (q, 1H, C_3–H), 5.45 (d, 1H, C_1–H). MS (CI): $(M + 1)^+$ 482.

Phenyl N,N-Bis(2-chloroethyl)aminophosphoryl Chloride (**5a**)

A solution of 1.01 g (10 mmol) of dry triethylamine in 20 mL of anhydrous benzene was added dropwise to a solution of 2.59 g (10 mmol) of N,N-bis(2-chloroethyl)aminophosphoryl dichloride [7] and 0.94 g (10 mmol) of phenol in 20 mL of anhydrous benzene under reflux over 15 minutes. Then reflux was continued for 4 hours, and triethylamine hydrochloride was filtered off. The filtrate was concentrated under reduced pressure and the residue purified on a silica gel column using a mixture of ethyl ether and petroleum ether (1:2 v/v) as the eluent. The product was obtained as a light yellowish syrup, 2.47 g, yield 78.0%. ^{1}H NMR ($CDCl_3$): 3.50–3.95 (m, 8H, CH_2CH_2Cl), 7.10–7.30 (m, 5H, Ph). MS (CI): $(M + 1)^+$ 482.

Saccharidyl N,N-Bis(2-chloroethyl)phosphoramidates **3a–g** *and* **4a–g**

To a stirred mixture of 1.70 mmol of N,N-bis(2-chloroethyl)aminophosphoryl chloride (**2**) and 2 mmol of amine in 15 mL of dichloromethane, a solution of 0.41 g (4 mmol) of triethylamine in 6 mL of dichloromethane was added dropwise at room temperature over 10 minutes. After having been stirred for 1–5 hours, the reaction mixture was allowed to stand overnight. Triethylamine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether-ethyl ether as the eluent. The results are given in Tables 1 and 2.

Alkyl Saccharidyl N,N-Bis(2-chloroethyl)phosphoramidates **3h** *and* **4h**

A mixture of 1.7 mmol of N,N-bis(2-chloroethyl)aminophosphoryl chloride (**2**), 0.21 g (2 mmol) of triethylamine, and 15 mL of absolute alcohol was refluxed for 8 hours. After the removal of the excess alcohol by distillation under reduced pressure, the residue was purified by flash chromatography on a silica gel column using a mixture of petroleum ether-ethyl ether as the eluent. The results are given in Tables 1 and 2.

Aryl Saccharidyl N,N-Bis(2-chloroethyl)phosphoramidate **3i** *and* **4i**

A mixture of 5 mmol of N,N-bis(2-chloroethyl)aminophosphoryl chloride (**5**), 5 mmol of sugar (**1**), and 0.22 g (5.4 mmol) of sodium hydroxide powder in 15 mL of dry THF was refluxed for 4–8 hours with stirring. The inorganic salt was removed by filtration. The solution was concentrated by use of a rotary evaporator. The product was purified by flash chromatography on a silica gel column using a mixture of petroleum ether-ethyl ether as the eluent. The results are given in Tables 1 and 2.

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