Heteroatom Chemistry
Volume 10, Number 3, 1999

Synthesis and Crystal Structure of 2-Phosphonoalkyl-1, 2-benzisoselenazol-3(2*H*)-ones and Their Antitumor Activities

Jia Zhou and Ruyu Chen

Institute of Elemento-Organic Chemistry, The State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Received 16 July 1998; revised 19 October 1998

ABSTRACT: *The title compounds were synthesized in good yields by the condensation reaction of diphenyl α-aminoalkylphosphonates with 2-(chloroseleno)-benzoyl chloride. Their structures were confirmed by spectroscopic methods and microanalyses. The X-ray analyses showed that the selenium-containing fused ring has a planar structure and that, by the molecular packing of the unit cells, two adjacent molecules are symmetrically linked to each other through Se(1c) . . . O=P(1) bonding interactions with an intermolecular Se(1c) . . . O distance of 2.797 Å. The results of bioassay indicated that some of these compounds possess potent antitumor activities against some human carcinoma cells in vitro.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10:247–254, 1999

INTRODUCTION

Various selenium-containing compounds are widely used as reagents and intermediates in organic synthesis [1]. In recent years, biologically active organoselenium compounds have begun to attract considerable interest due to their unique and diverse potential of pharmacological importance, such as broad spectrum antitumor and antiviral activities, and some of them are even many times more active than their oxygen or thio analogues [2–4]. It was found that benzisoselenazolones [e.g., Ebselen, 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one], are effective for the treatment of diseases caused by cell damage owing to increased formation of active oxygen metabolites [5], and these pharmacological effects are mainly attributed to the glutathione peroxidase (GSH-Px)-like properties [6]. Many organo-selenium compounds have been synthesized that exhibit some striking biological activities but cannot be developed into useful pharmaceuticals because of their high toxicity [5a]. Ebselen is the only seleno-organic compound whose vast range of biological actions is quite well known. These actions are characterized by efficacy, low toxicity (LD_{50} 6.8 g/Kg), and lack of undesired side effects [5a,7].

On the other hand, N-substituted α-aminoalkanephosphonate derivatives represent a class of compounds that tend to exhibit superior biological activities, such as antibacterial, herbicidal, antitumor, and inhibitory activity to enzymes [8]. In continuation of our work [9], aimed at searching for novel antitumor and antiviral agents with high activity and low toxicity, a series of 1-aminoalkanephosphonate derivatives of benzisoselenazolone were designed and synthesized. The results of bioassay showed that some of them possess potent antitumor activities against some human carcinoma cells *in vitro*.

Correspondence to: Jia Zhou
Contract Grant Sponsor: National Natural Science Foundation of China
 CCC 1042-7163/99/030247-08

RESULTS AND DISCUSSION

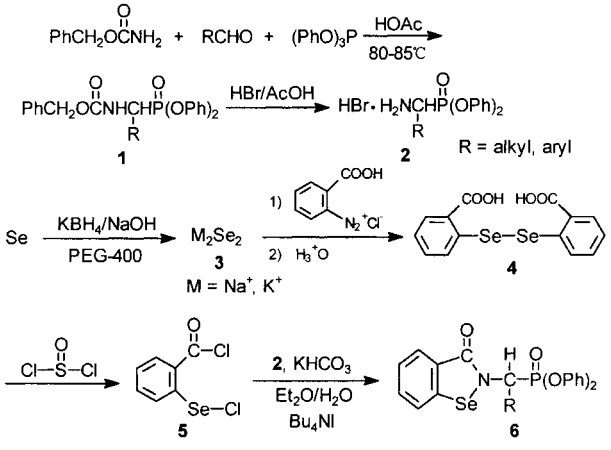
Synthesis of 2-Phosphonoalkyl-1,2-benzisoselenazol-3(2H)-ones

The title compounds **6** were synthesized by a multistep route outlined in Scheme 1.

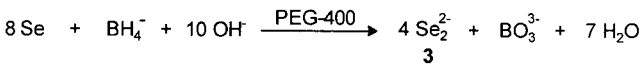
Preparation of the hydrobromides of α-aminoalkanephosphonates **2** was readily accomplished in a two-step sequence (41–78% overall yield) starting from aldehydes, benzyl carbamate, and triphenyl phosphite [10]. Santaniello et al. [11] have reported that the reducing power of sodium borohydride in polyethylene glycols (PEG) is enhanced and able to reduce carbonyl compounds. Similarly, we found that, under the PEG–KBH_4 reaction system, 1 mol of selenium was efficiently reduced to Se_2^{2-} anion **3** by only 1/8 mol of KBH_4 catalyzed by PEG-400 in aqueous NaOH (Scheme 2). Thus, Se_2^{2-} anion was allowed to react with 2-carboxybenzenediazonium chloride, and the reaction mixture was then acidified to give 2,2′-diselenobis[benzoic acid] **4** in a yield of 93%. **4** was treated with excess thionyl chloride to provide the intermediate 2-(chloroseleno)benzoyl chloride **5** in a yield of 81%. The reaction of **5** with each α-aminoalkanephosphonate hydrobromide **2** was carried out under the ether–water–$KHCO_3$ reaction system in the presence of phase transfer catalyst Bu_4NI to give products **6a–g** in a yield of 85–96%.

The Structures of the Products

The structures of all the compounds prepared were confirmed by ^{1}H NMR, ^{31}P NMR, IR, MS spectroscopy, and elemental analysis (Tables 1–3). In the ^{1}H NMR spectra of **6**, the chemical shift of the H atom in CH (R = aryl) is in the range of δ 6.72–6.74. Owing to the deshielding effect of the α-benzene ring, these chemical shifts are much bigger than those of CH (R = alkyl), which are in the range of δ 4.52–5.69. Moreover, the H atom in CH (R = aryl) appears as a doublet due to the coupling effects of the P atom ($^2J_{PCH}$ = 21.8–23.0 Hz) while that when R = alkyl exhibits a dd peak due to the phosphorus coupling and C–H coupling ($^2J_{PCH}$ = 19.3–22.0 Hz, $^3J_{HCCH}$ = 7.2 Hz). The IR spectra of compounds **6** show normal stretching absorption bands, indicating the existence of groups C=O (1637–1650 cm^{-1}), P=O (1249–1263 cm^{-1}), C–N (1302–1377 cm^{-1}), and P-O-C (1198–926 cm^{-1}). The EI-MS spectra of **6** record the existence of molecular ion peaks, indicating that the heterocycle skeletons are of some stability. Moreover, it is worth mentioning that the observed molecular ions of these selenium-containing compounds are 1 unit larger than their corresponding calculated molecular weights due to the highest natural abundance of ^{80}Se atoms.



SCHEME 1



SCHEME 2

Because the crystal structure of GSH-Px, as an important mammalian selenoenzyme, is known [12], in order to study the relationship between the structural features of the compounds and their pharmacological activities, a single-crystal X-ray diffraction analysis of compound **6a** was performed. The fractional coordinates and equivalent isotropic displacement coefficients are listed in Table 4. The selected bond lengths and angles are given in Tables 5 and 6. Figure 1 is a perspective view of the title compound showing the atomic numbering scheme. Table 7 presents the least-squares plane, demonstrating that the selenium-containing fused ring moiety has a nearly planar structure with a Se(1)–C(41) distance of 1.884 Å and Se(1)–N(1) distance of 1.879 Å, shorter than those of the reported ebselen analogues, respectively [13,14]. These structural features are advantageous in decreasing the toxicity of the compounds structurally related to ebselen as potential drugs [15]. Figure 2 depicts the molecular packing in the unit cell, indicating that the two adjacent molecules are symmetrically linked to each other through the Se(1c) . . . O=P(1) bonding interactions with an intermolecular Se(1c). . . O distance of 2.797 Å, which can diminish the electrostatic charge on the selenium atom and might be favorable to the pharmacological activity [16]. At this point, the good antitumor activities of compounds **6** were confirmed by the bioassay (see the next section).

Biological Activities

The preliminary anticancer tests *in vitro* were carried out by the conventional method [17]. The antitumor activities given in Table 8 indicate that some

TABLE 1 Experimental Data of Compounds **6**

NO	R	State Mp (°C)	Yield[a] (%)	Molecular Formula	Found/Calcd (%) C	H	N
6a	*p*-MeC_6H_4	177–178	88.8	$C_{27}H_{22}NO_4PSe$ (534.43)	60.80 (60.68)	4.07 (4.16)	2.53 (2.62)
6b	C_6H_5	168–169	93.0	$C_{26}H_{20}NO_4PSe$ (520.40)	60.08 (60.00)	4.11 (3.88)	2.63 (2.69)
6c	Me	yellowish syrup	86.1	$C_{21}H_{18}NO_4PSe$ (458.33)	54.97 (55.03)	4.02 (3.97)	2.95 (3.06)
6d	*n*-Bu	152–153	85.3	$C_{24}H_{24}NO_4PSe$ (500.42)	57.42 (57.60)	4.90 (4.84)	2.97 (2.80)
6e	*n*-Pr	yellowish syrup	88.7	$C_{23}H_{22}NO_4PSe$ (486.39)	56.80 (56.79)	4.83 (4.57)	2.61 (2.88)
6f	2,4-$Cl_2C_6H_3$	163–164	96.0	$C_{26}H_{18}Cl_2NO_4PSe$ (589.28)	52.83 (52.99)	3.21 (3.09)	2.20 (2.38)
6g	3,4-$OCH_2OC_6H_3$	149–150	94.7	$C_{27}H_{20}NO_6PSe$ (564.41)	57.58 (57.45)	3.44 (3.58)	2.53 (2.48)

[a]Yield determined by isolation based on **5.**

TABLE 2 NMR and IR Spectral Data of Compounds **6**

NO	^{1}H-NMR (200 MHz, $CDCl_3$, TMS) or ^{31}P-NMR (80.96 MHz, $CDCl_3$, 85% H_3PO_4) δ, J (Hz)	IR(v, cm^{-1})
6a	2.30 (s, 3 H, $ArCH_3$), 6.72 (d, 1 H, CH, $^2J_{PCH}$ = 23.0), 6.86–7.98 (m, 18 H, 2 × C_6H_5 + 2 × C_6H_4). ^{31}P: 12.95 (s)	(KBr) 3405, 3047, 2907, 1638 (s, C=O), 1589, 1485, 1315, 1263 (s, P=O), 1198, 1165, 1019, 946, 761, 731, 685, 546
6b	6.73 (d, 1 H, CH, $^2J_{PCH}$ = 22.9), 6.78–8.04 (m, 19 H, 3 × C_6H_5 + C_6H_4)	(KBr) 3406, 3049, 2912, 1637 (s, C=O), 1588, 1486, 1317, 1257 (s, P=O), 1234, 1201, 1171, 1155, 1021, 947, 763, 737, 697, 580
6c	1.74 (dd, 3 H, CH_3, $^3J_{HCCH}$ = 7.2, $^3J_{PCCH}$ = 18.0), 5.69 (dd, 1 H, CH, $^2J_{PCH}$ = 19.3, $^3J_{HCCH}$ = 7.2), 7.02–8.16 (m, 14 H, 2 × C_6H_5 + C_6H_4)	(film) 3437, 3049, 2900, 1638 (s, C=O), 1609, 1580, 1483, 1443, 1325, 1250 (s, P=O), 1195, 1154, 1065, 1019, 928, 757, 734, 683, 511
6d	0.83 (t, 3 H, CH_3), 1.32 (m, 4 H, 2 × CH_2), 1.59–2.23 (m, 2 H, CH_2), 5.55 (dd, 1 H, CH, $^2J_{PCH}$ = 20.6, $^3J_{HCCH}$ = 7.2), 7.06–8.09 (m, 14 H, 2 × C_6H_5 + C_6H_4). ^{31}P: 15.82 (s)	(KBr) 3396, 3044, 2910, 1638 (s, C=O), 1588, 1486, 1451, 1326, 1258 (s, P=O), 1202, 1178, 1152, 1020, 938, 761, 728, 684, 593, 512
6e	1.0 (t, 3 H, CH_3), 1.38–1.84 (m, 2 H, CH_2), 1.86–2.34 (m, 2H, CH_2), 4.52 (dd, 1 H, CH, $^2J_{PCH}$ = 22.0, $^3J_{HCCH}$ = 7.2), 7.08–8.06 (m, 14 H, 2 × C_6H_5 + C_6H_4)	(film) 3289, 3048, 2920, 1638 (s, C=O), 1590, 1487, 1377, 1258 (s, P=O), 1205, 1183, 1157, 1021, 923, 758, 684, 510
6f	6.74 (d, 1 H, CH, $^2J_{PCH}$ = 23.0), 6.96–8.20 (m, 17 H, 2 × C_6H_5 + C_6H_4 + C_6H_3)	(KBr) 3390, 3043, 2905, 1650 (s, C=O), 1587, 1484, 1302, 1257 (s, P=O), 1208, 1176, 1153, 1020, 954, 930, 764, 730, 683, 586
6g	5.98 (d, 2 H, OCH_2O, $^2J_{HCH}$ = 4.8), 6.72 (d, 1 H, CH, $^2J_{PCH}$ = 21.8), 6.78–8.16 (m, 17 H, 2 × C_6H_5 + C_6H_4 + C_6H_3)	(KBr) 3398, 3045, 2905, 1646 (s, C=O), 1586, 1500, 1450, 1314, 1249 (s, P=O), 1202, 1176, 1152, 1031, 946, 926, 769, 729, 685, 622, 508

of them have high inhibitory effects against human cervix carcinoma (HeLa) cells, human liver carcinoma (BEL-7402) cells, and human lung carcinoma (PG) cells. In contrast, ebselen, which is well known for its good anti-inflammatory activity and GSH-Px-like activity, shows little antitumor activity. The evaluation for the antiviral and antioxidative activity of compounds **6** is now in progress.

EXPERIMENTAL

Instruments

Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU-435 spectrometer, and band positions are reported in wave numbers (cm^{-1}). NMR spectra were taken on JEOL-

TABLE 3 Mass Spectral Data of Compounds **6**

NO	*EI-MS* (*m/z, %*)
6a	535 (M^+, 3), 442 (46), 440 (23), 302 (100), 300 (44), 298 (18), 185 (21), 184 (36), 182 (26), 156 (32), 118 (70), 91 (26), 77 (80), 65 (39)
6b	521 (M^+, 5), 428 (89), 426 (44), 288 (87), 286 (48), 229 (9), 185 (23), 184 (48), 182 (33), 157 (21), 156 (37), 140 (16), 104 (61), 94 (20), 77 (100), 65 (32), 28 (69)
6c	459 (M^+, 3), 366 (54), 364 (26), 226 (65), 224 (30), 185 (17), 184 (50), 182 (31), 156 (46), 154 (24), 140 (47), 139 (19), 117 (11), 93 (18), 77 (100), 65 (75), 51 (39), 39 (37)
6d	501 (M^+, 3), 408 (57), 406 (27), 268 (37), 266 (18), 212 (20), 200 (17), 185 (11), 184 (36), 182 (24), 156 (38), 154 (21), 140 (43), 94 (17), 77 (100), 65 (51), 41 (43)
6e	487 (M^+, 3), 294 (68), 292 (36), 250 (22), 248 (12), 224 (16), 185 (14), 184 (29), 182 (17), 156 (28). 140 (27), 94 (67), 77 (100), 65 (40), 51 (32)
6f	590 (M^+, 2), 496 (8), 356 (12), 215 (15), 185 (12), 184 (38), 182 (25), 172 (12), 156 (37), 154 (21), 140 (30), 94 (15), 77 (100), 65 (57), 51 (39)
6g	565 (M^+, 1), 472 (4), 334 (17), 332 (76), 330 (42), 245 (18), 215 (10), 185 (16), 184 (42), 182 (23), 156 (35), 154 (20), 148 (53), 140 (22), 121 (12), 94 (60), 77 (100), 65 (64), 51 (28)

TABLE 4 Atomic Coordinates and Thermal Parameters (Å^2) of Compound **6a**

Atoms	*x*	*y*	*z*	*Ueq*
Se	0.1738(1)	0.5991(1)	0.0421(1)	0.040(1)
P(1)	−0.0299(2)	0.8102(2)	0.1951(2)	0.039(1)
N(1)	0.2235(7)	0.7849(7)	0.1469(5)	0.040(3)
O	−0.0912(6)	0.6635(6)	0.1345(5)	0.048(3)
O(1)	0.0888(7)	0.8992(7)	0.1199(5)	0.051(3)
C(11)	−0.0649(10)	1.0480(10)	0.1620(8)	0.050(4)
C(12)	−0.1593(11)	1.1216(11)	0.2090(10)	0.063(5)
C(13)	−0.1433(13)	1.2642(12)	0.2402(10)	0.075(6)
C(14)	−0.0347(13)	1.3276(12)	0.2242(10)	0.072(6)
C(15)	0.0575(14)	1.2533(14)	0.1785(11)	0.080(7)
C(16)	0.0425(13)	1.1116(12)	0.1460(9)	0.066(6)
O(2)	−0.0608(6)	0.8908(6)	0.3092(5)	0.043(3)
C(21)	−0.1439(9)	0.8278(8)	0.3536(7)	0.038(4)
C(22)	−0.0661(12)	0.8004(12)	0.4501(9)	0.063(5)
C(23)	−0.1465(15)	0.7409(14)	0.4954(11)	0.083(7)
C(24)	−0.2953(14)	0.7137(12)	0.4498(11)	0.071(6)
C(25)	−0.3367(12)	0.7458(11)	0.3575(10)	0.066(5)
C(26)	−0.2890(9)	0.8017(10)	0.3088(8)	0.048(4)
C(30)	0.1675(9)	0.8412(8)	0.2416(6)	0.034(3)
C(31)	0.2382(9)	0.7952(9)	0.3392(7)	0.038(4)
C(32)	0.2229(10)	0.6568(9)	0.3284(7)	0.046(4)
C(33)	0.2882(12)	0.6220(10)	0.4212(8)	0.057(5)
C(34)	0.3699(10)	0.7195(10)	0.5240(7)	0.045(4)
C(35)	0.3796(10)	0.8574(10)	0.5340(7)	0.047(4)
C(36)	0.3174(9)	0.8948(9)	0.4448(7)	0.038(4)
C(37)	0.4465(12)	0.6811(12)	0.6234(8)	0.065(5)
O(3)	0.3773(8)	0.9823(7)	0.2036(5)	0.065(3)
C(41)	0.3240(8)	0.6395(9)	−0.0073(7)	0.036(4)
C(42)	0.3677(10)	0.5484(11)	−0.0958(8)	0.051(4)
C(43)	0.4789(11)	0.5999(13)	−0.1200(8)	0.062(5)
C(44)	0.5428(10)	0.7383(14)	−0.0622(9)	0.063(6)
C(45)	0.4970(11)	0.8267(12)	0.0221(8)	0.058(5)
C(46)	0.3863(9)	0.7764(10)	0.0484(7)	0.042(4)
C(47)	0.3312(10)	0.8608(10)	0.1395(7)	0.046(4)

$Ueq = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

TABLE 5 Selected Bond Lengths (Å)

Bond	*Dist.*	*Bond*	*Dist.*	*Bond*	*Dist.*
Se(1)-N(1)	1.879(6)	N(1)-C(30)	1.463(11)	C(41)-C(46)	1.373(12)
Se(1)-C(41)	1.884(10)	N(1)-C(47)	1.358(14)	C(42)-C(43)	1.379(17)
P(1)-O	1.459(6)	O(1)-C(11)	1.422(14)	C(44)-C(45)	1.370(15)
P(1)-O(1)	1.580(8)	C(30)-C(31)	1.519(13)	C(45)-C(46)	1.386(16)
P(1)-O(2)	1.578(7)	O(3)-C(47)	1.225(10)	C(46)-C(47)	1.475(13)
P(1)-C(30)	1.824(8)	C(41)-C(42)	1.407(13)	Se(1c) ... O	2.797

Symmetry operations: c: $-x, 1-y, -z$.

TABLE 6 Selected Bond Angles (°)

Angle	(°)	*Angle*	(°)
N(1)-Se(1)-C(41)	85.2(3)	N(1)-C(30)-C(31)	113.9(7)
O-P(1)-O(1)	111.0(3)	Se(1)-C(41)-C(42)	126.8(7)
O(1)-P(1)-O(2)	104.6(4)	Se(1)-C(41)-C(46)	112.7(7)
O(1)-P(1)-C(30)	115.0(4)	C(42)-C(41)-C(46)	120.4(9)
Se(1)-N(1)-C(30)	123.3(6)	C(41)-C(46)-C(45)	121.1(8)
Se(1)-N(1)-C(47)	115.8(6)	C(41)-C(46)-C(47)	115.1(9)
C(30)-N(1)-C(47)	120.3(6)	C(45)-C(46)-C(47)	123.7(8)
P(1)-O(1)-C(11)	123.5(5)	N(1)-C(47)-O(3)	123.1(9)
P(1)-C(30)-N(1)	111.8(4)	N(1)-C(47)-C(46)	112.2(7)
P(1)-C(30)-C(31)	112.3(7)	O(3)-C(47)-C(46)	125.7(10)

FX-90Q and BRUKER AC-P200 spectrometers. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR spectroscopy. The nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. Coupling constants *J* are given in Hz. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Elemental analyses were carried out on a Yana MT-3 instrument. Column chromatography was performed using silica gel H (10–40 μm, Haiyang chemical Factory of Qingdao).

Potassium or Sodium Diselenide (Aqueous) (3)

To a stirred solution of potassium borohydride (1.0 g, 0.019 mol), PEG-400 (0.6 g, 0.001 mol), and sodium hydroxide (7.5 g, 0.19 mol) in 100 mL of water was added gray selenium powder (11.9 g, 0.15 mol) at room temperature in a stream of nitrogen. Stirring was continued at RT for 0.5 hour, after which the reaction mixture was heated at 70°C for another 0.5 hour. Then the resulting mixture was cooled to ambient temperature, and a solution of sodium hydroxide (20 g, 0.5 mol) in 100 mL of water was added. The brownish red aqueous solution of Se_2^{2-} anion was then ready for further use.

2,2′-Diselenobis[benzoic acid] (4)

To a stirred solution of *o*-aminobenzoic acid (20.5 g, 0.15 mol) and sodium hydroxide (6.0 g, 0.15 mol) in 50 mL of water was added sodium nitrite (10.35 g, 0.15 mol). Stirring was continued until the dissolution was completed. Then the mixture was added dropwise to a stirred solution containing 31 mL of concd hydrochloric acid in 20 mL of water cooled with an ice bath to under 5°C. A solution of 2-carboxybenzenediazonium chloride resulted; this was added dropwise to a stirred solution of Se_2^{2-} anion that was prepared in advance, in a stream of nitrogen and cooled with an ice bath. The mixture was then stirred for an additional 2 hours at 40°C. It was confirmed that the solution was basic using litmus paper. The reaction mixture was acidified with hydrochloric acid, and the precipitated solid was collected by filtration, washed with water, and dried in a desiccator to give the intermediate **4** (27.9 g, 93% yield); mp 296–297°C (Ref. [18], mp 295°C).

2-(Chloroseleno)benzoyl Chloride (5)

A mixture of 2,2′-diselenobis[benzoic acid] (20.0 g, 0.05 mol) and 75 mL of thionyl chloride was heated at reflux for 3 hours. The excess thionyl chloride was removed under reduced pressure, and the residual solid was recrystallized from petroleum ether (bp 30–60°C) to give pale-yellow crystals of pure 2-(chloroseleno)benzoyl chloride **5** (20.5 g, 80.7% yield); mp 64–65°C (Ref. [19], mp 65°C).

General Procedure for 2-Phosphonoalkyl-1,2-benzisoselenazol-3(2H)-ones (6a–g)

To a stirred mixture of α-aminoalkanephosphonate hydrobromides (0.003 mol), potassium bicarbonate (1.5 g, 0.015 mol) and tetrabutylammonium iodide (catalytic amount) in H_2O (10 mL)–ether (25 mL) system cooled with an ice bath was added a solution of 2-(chloroseleno)benzoyl chloride (0.76 g, 0.003 mol) in 20 mL of ether over a 0.5 hour period. Then

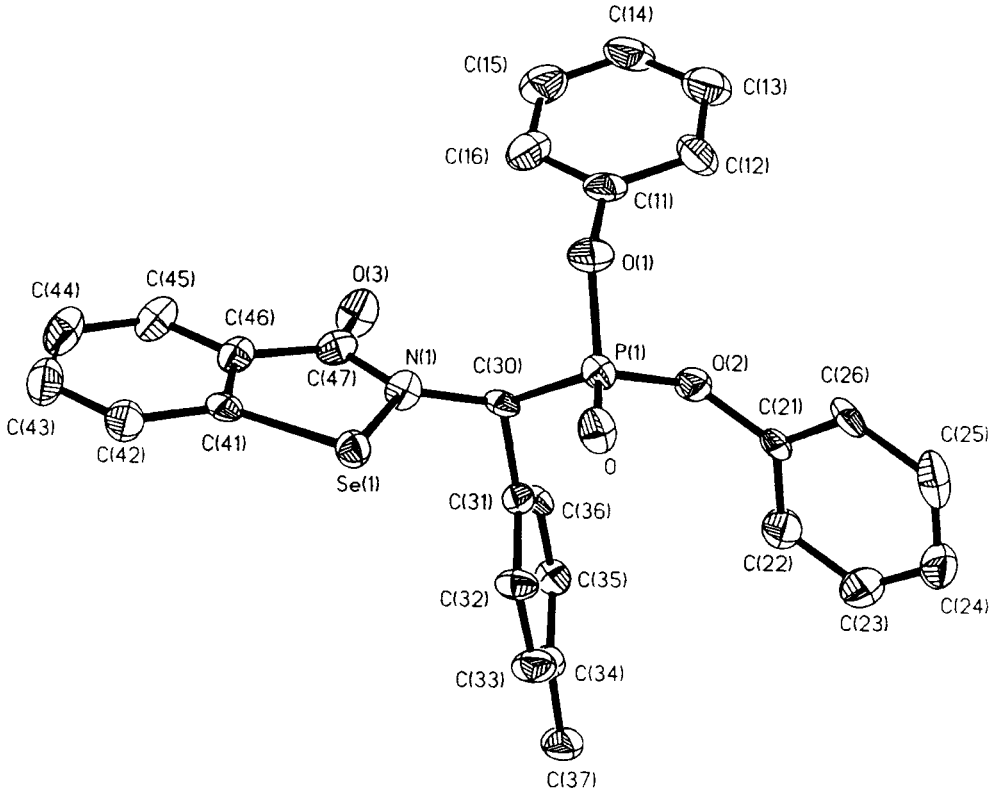


FIGURE 1 Molecular structure of compound **6a** showing the atomic numbering.

TABLE 7 The Least-Squares Plane

Plane Equation	*4.719 X − 5.899 Y + 8.609 Z + 2.3257 = 0*								
Atoms	Se(1)	N(1)	C(41)	C(42)	C(43)	C(44)	C(45)	C(46)	C(47)
Dist. (Å)	−0.0255	0.0149	0.0194	0.0003	0.0131	−0.0032	−0.0153	−0.0152	0.0115

the mixture was stirred for an additional 7 hours at room temperature to give the desired compounds **6a–g**, which were purified by different methods described as follows.

For compounds **6a–b** and **6f–g** (R = aryl), a white precipitate was formed, and the mixture was filtered to yield the crude product that was recrystallized from a mixture of acetone and petroleum ether (bp 60–90°C) and dried in a vacuum dryer. For compounds **6c–e** (R = alkyl), the organic product was extracted with ether, and the layers were separated. Combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to produce the crude product, which was purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether (bp 60–90°C) (v/v, 1:4). The physical and chemical data of compounds **6a–g** are listed in Tables 1–3.

X-ray Diffraction Analysis of Compound **6a**

Crystal Data for **6a.** $C_{27}H_{22}NO_4PSe$, M_w = 534.41, triclinic, P-1(No.2), a = 9.761(2), b = 10.304(2), c = 13.396(3) Å, α = 110.97(3), β = 107.70(3), Γ = 90.02(3) °, V = 1190(1) Å^3, Z = 2, D_x = 1.492 g cm^{-3}, μ = 1.6596 mm^{-1}, and F(000) = 544. Refined cell parameters were obtained from setting angles of 25 reflections. A colorless single crystal (0.37 × 0.41 × 0.61 mm) was used for the analysis.

Data Collection. Crystallographic measurements were made at room temperature using an Enraf-Nonius CAD-4 diffractometer operating in the ω-2θ scan mode. The intensity data were collected with a θ range 2–23° using graphite monochromated MoKα radiation (λ = 0.71073 Å). Intensities of 3141 unique reflections were measured of which 2500 satisfied the criterion I ≥ 3σ(I).

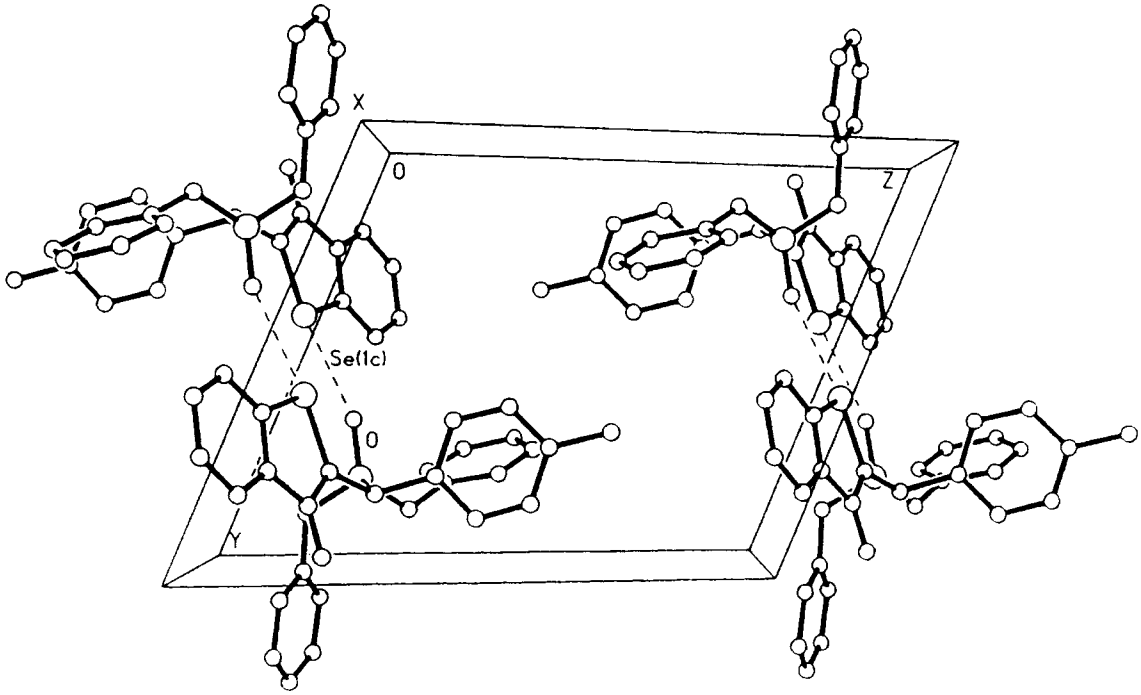


FIGURE 2 Molecular packing in unit cell.

TABLE 8 Antitumor Activities of Compounds **6**

	IC_{50} (μmol/L)		
Compound	HeLa cell	BEL-7402 cell	PG cell
6a	80	20	50
6b	—[a]	35	50
6c	4	50	40
6d	90	30	75
6e	—	150	—
6f	—	75	180
6g	200	20	100
Ebselen	—	200	200

[a]$IC_{50} > 200$ μmol/L.

Structure Solution and Refinement. The structure was solved by direct methods employing SHELXS-86 [20]. Corrections were applied for Lp but not for absorption or extinction. Positional and thermal parameters were refined by full-matrix least squares minimizing the function $\Sigma\omega(Fo\text{-}Fc)^2$ with $\omega = 1/\sigma^2(F)$ for the observed reflections and $\omega = 0$ for unobserved reflections. Most of the nonhydrogen atoms were located from an E-map. The others were determined with successive difference Fourier syntheses. The hydrogen atoms were added theoretically. All of them were refined with fixed position parameters and thermal factors. The final refinements by the full matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms were converged with unweighted and weighted (unit weights) agreement factors of 0.068 and 0.074, and S of 1.95. The highest peak on the final difference Fourier map had a height of 0.82 e/Å^3 [$(\Delta/\sigma)_{max} = 0.005$].

Atomic scattering factors for the compound were taken from *International Tables for X-Ray Crystallography* [21], and all calculations were performed on a PDP 11/44 computer using the SDP-PLUS program system.

ACKNOWLEDGMENTS

The authors wish to express many thanks to the Institute of Molecular Biology of Nankai University for the evaluation of antitumor activities.

REFERENCES

[1] Patai, S., Rappoport, Z. Eds. The Chemistry of Organic Selenium and Tellurium Compounds; 2 Wiley: Chichester, 1993; Vol. 1.

[2] (a)Bonnet, P. A.; Robins, R. K. J Med Chem 1993, 36, 635; (b) Forest, M.; Lahouratate, P.; Martin, M.; et al. J Med Chem, 1992, 35, 163; (c) Ahluwalia, G. S.; Jayaram, H. N.; Cooney, D. A. Concepts, Clinical Devel-

opments, and Therapeutic Advances in Cancer Chemotherapy; Martinus Nijhoff Publishers: Boston, 1987; Chapter 3; (d) Franchetti, P.; Cristalli, G.; Grifantini, M.; et al. J Med Chem 1990, 33, 2849.
[3] (a) Conde, J. E.; Alaejos, M. S. Chem. Rev. 1997, 97, 1979; (b) Patani, G. A.; Lavoie, E. J. Chem Rev 1996, 96, 3147.
[4] Inglot, A. D.; Zielinska-Jenczylik, J.; Piasecki, E.; Syper, L.; Mlochowski, J. Experientia 1990, 46, 308.
[5] (a) Parnham, M. J.; Graf, E. Biochem Pharmacol 1987, 36 (19), 3095; (b) Engman L.; Hallberg, A. J Org Chem 1989, 54, 2964.
[6] Reich, H. J.; Jasperse, C. P. J Am Chem Soc 1987, 109, 5549.
[7] Mhizha, S. Tetrahedron 1997, 53, 17751.
[8] Zhou, J.; Chen, R. Y. Phosphorus Sulfur and Silicon 1996, 118, 247.
[9] (a) Chen, R. Y.; Wang, H. L.; Zhou, J. Heteroatom Chem 1994, 5, 497; (b) Chen, R. Y.; Wang, H. L.; Zhou, J. Chem J Chinese Univ 1995, 16, 1229; (c) Zhou, J.; Chen, R. Y.; Yang, X. F. Heteroatom Chem 1998, 9 (4), 369; (d) Zhou, J.; Chen, R. Y. J Chem Soc Perkin Trans 1, 1998, 2917; (e) Zhou, J.; Chen, R. Y. J Chem Res (S) 1998, 254; (f) Zhou, J.; Chen, R. Y. Synth Commun 1998, 28 (14) 2653.
[10] Oleksyszyn, J.; Subotkowska, L.; Mastalerz, P. Synthesis 1979, 985.
[11] Santaniello, E.; Ferraboschi, P.; Sozzani, P. J Org Chem 1981, 46, 4584.
[12] Epp, O; Ladenstein, R.; Wendel, A. Eur J Biochem 1983, 133, 51.
[13] (a) Welter, A.; Fischer, H.; Parnham, M. J.; et al. DE 3444135 1986; (b) Dupont, L.; Dideberg, O. Acta Crystallogr 1990, C46, 484; (c) Dupont, L.; Dideberg, O; Sbit, M.; et al. Acta Crystallogr Sect C: Cryst Struct Commun 1988, C44, 2159.
[14] Mima, H.; Fujihara, H.; Furukawa, N. Tetrahedron 1998, 54, 743.
[15] Wendel, A.; Fausel, M.; Safayhi, H.; et al. Biochem Pharmacol 1984, 33 (20), 3241.
[16] Dakova, B.; Kauffmann, J. M.; Evers, M.; et al. Electrochim Acta 1990, 35 (7), 1133.
[17] Cell Titer 96 Aqueous Non-Radioactive Cell Proliferation Assay, PROMEGA Company.
[18] Lesser, R.; Weiz, R. Ber 1912, 45, 1835.
[19] Lesser, R.; Weiz, R. Ber 1924, 57, 1077.
[20] Sheldrick, G. M.; Kruger, C.; Goddard, R. SHELXS-86: Crystallographic Computing 3; Oxford University Press: London, 1985.
[21] International Tables for X-Ray Crystallography, Kynoch Press: Birmingham, 1974; Vol. 4.