Iridoids from the Roots of *Valeriana jatamansi*

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Three new iridoids, jatamanins N – P (**1** – **3**), along with the seven known iridiods **4** – **10**, were isolated from the roots of *Valeriana jatamansi*. Compound **1** is an unusual iridoid bearing two epoxy bridges between C(3) and C(6) and between C(1) and C(10), forming a unique cage-like rigid skeleton. The structures of the new compounds were assigned on the basis of spectroscopic methods.

Introduction. – The genus *Valeriana* of the Valerianaceae family comprises *ca.* 200 species and is widely distributed throughout the world [1]. Previous phytochemical investigations on this genus revealed the presence of iridoids, sesquiterpenoids, flavone glycosides, lignans, and alkaloids [2 – 7]. *Valeriana officinalis* is the officinal species used in Europe, and its root preparation is commonly referred to as valerian. Valerian is known for its pharmacological properties, including sedative, anxiolytic, antidepressant, and antispasmodic activities [8 – 11], and has been employed as a mild sedative and tranquilizer for centuries [12]. *V. jatamansi* JONES, an annual herb distributed widely in the southwest of China and India, is known in Chinese folk medicine to have tranquilizing hypnotic and antiviral activities [4]. As an important substitute for the European *V. officinalis*, it has been traditionally used for treatment of a variety of conditions including sleep problems, obesity, nervous disorders, epilepsy, insanity, snake poisoning, eye troubles, and skin diseases [4][13][14]. Previous chemical studies on *V. jatamansi* revealed the presence of sesquiterpenoids [4], essential oil [4][15], flavone glycosides [7], and members of a small group of acylated iridoids, the valepotriates [2][16 – 22]. The valepotriates have shown sedative, cytotoxic, antitumor, and antifugal activities [23][24].

Our phytochemical investigation of the roots of *V. jatamansi* led to the isolation of three new iridoids, jatamanins N – P[1]) (**1** – **3**), as well as seven known ones, volvatrate A (**4**) [25], (3*S*,4*R*,5*S*,7*S*,8*S*,9*S*)-3,8-epoxyoctahydro-4,8-dimethylcyclopenta[*c*]pyran-7-ol (**5**) [20], (3*S*,4*S*,5*S*,7*S*,8*S*,9*S*)-3,8-epoxy-7-hydroxy-4,8-dimethylperhydrocyclopenta[*c*]-pyran (**6**) [20], jatamanin G (**7**) [20], jatamanin A (**8**) [20], hexahydro-6-hydroxy-7-(hydroxymethyl)-4-methylenecyclopenta[*c*]pyran-1(3*H*)-one (**9**) [26], and (4*β*,8*β*)-8-methoxy-3-methoxy-10-methylene-2,9-dioxatricyclo[4.3.1.$0^{3,7}$]decan-4-ol (**10**) [27] (*Fig. 1*). Among them, compounds **4**, **9**, and **10** were obtained from this plant for the

[1]) Arbitary atom numbering; for systematic names, see *Exper. Part.*

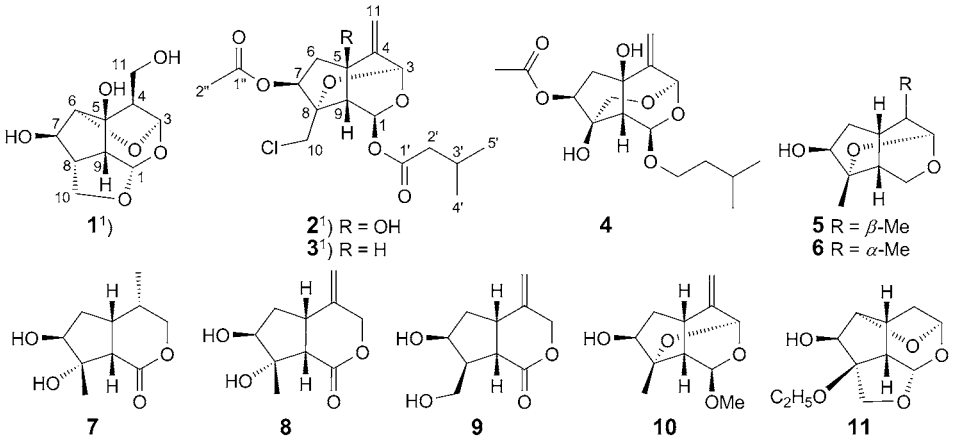

Fig. 1. *Iridoids* **1**–**10**, *isolated from* V. jatamansi *and the synthetic derivative* **11**

first time. Details of the isolation and structural elucidation of the new compounds are reported in this paper.

Results and Discussion. – Jatamanin N (**1**) was isolated as colorless oil, and its molecular formula was determined to be $C_{10}H_{14}O_6$ by HR-ESI-MS (*m*/*z* 253.0685 ($[M+Na]^+$)), as well as ^{1}H- and ^{13}C-NMR data, with four degrees of unsaturation. Analysis of the ^{1}H- and ^{13}C-NMR data (*Table 1*) showed the signals for two CH_2 groups (δ(H) 4.00 (*dd*, *J* = 9.6, 1.8 Hz, H_a–C(10)), 3.93 (*dd*, *J* = 9.6, 1.8 Hz, H_b–C(10)), and 3.63 (*dd*, *J* = 11.1, 9.6 Hz, CH_2(11)); δ(C) 58.8 (C(10)) and 67.0 (C(11))), seven CH groups (δ(H) 5.36 (*d*, *J* = 4.9 Hz, H–C(1)), 4.30 (*d*, *J* = 3.4 Hz, H–C(3)), 2.67 (*dd*, *J* = 1.8, 9.2 Hz, H–C(4)), 4.07 (*s*, H–C(6)), 4.94 Hz (*d*, *J* = 1.7 Hz, H–C(7)), 2.43–2.45 (*m*, H–C(8)), and 3.08 (*dd*, *J* = 4.9, 9.0 Hz, H–C(9)); δ(C) 100.2 (C(1)), 90.0 (C(3)), 50.9

Table 1. *^{1}H- and ^{13}C-NMR* ((D$_6$)acetone; 500 and 100 MHz, resp.) *and HMBC Data of Compound* **1**[a]). δ in ppm, *J* in Hz.

Position	δ(H)	δ(C)	HMBC (H → C)
H–C(1)	5.36 (*d*, *J* = 4.9)	100.2 (*d*)	C(3), C(8), C(9)
H–C(3)	4.30 (*d*, *J* = 3.4)	90.0 (*d*)	C(1), C(4), C(5), C(6)
H–C(4)	2.67 (*dd*, *J* = 1.8, 9.2)	50.9 (*d*)	C(3), C(5), C(9), C(11)
C(5)		85.4 (*s*)	
H–C(6)	4.07 (*s*)	84.6 (*d*)	C(3), C(4), C(5), C(9)
H–C(7)	4.94 (*d*, *J* = 1.7)	89.2 (*d*)	C(1), C(9), C(10)
H–C(8)	2.43–2.45 (*m*)	38.2 (*d*)	C(9)
H–C(9)	3.08 (*dd*, *J* = 4.9, 9.0)	41.8 (*d*)	C(1), C(7)
CH_2(10)	4.00 (*dd*, *J* = 1.8, 9.6, H_a), 3.93 (*dd*, *J* = 1.8, 9.6, H_b)	58.8 (*t*)	C(1), C(7), C(8), C(9)
CH_2 (11)	3.63 (*dd*, *J* = 11.1, 9.6)	67.0 (*t*)	C(4), C(5)

[a]) Assignments based on DEPT, HSQC, and HMBC experiments.

(C(4)), 84.6 (C(6)), 89.2 (C(7)), 38.2 (C(8)), and 41.8 (C(9))), and one O-bearing quaternary C-atom (δ(C) 85.4 (C(5)). These data and the two additional degrees of unsaturation compared to regular iridoids, despite the absence of a double bond, led to the conclusion that compound **1** was a highly oxygenated iridoid, with a tetracyclic skeleton [2][16–22].

Close inspection of the 1D- and 2D-NMR data suggested that **1** had a skeleton similar to that of a synthetic iridoid, **11**, with two epoxy bridges between C(3) and C(6) and between C(1) and C(10), forming a unique cage-like rigid skeleton [28]. Analysis of the HSQC and ^{1}H,^{1}H-COSY data of **1** provided unambiguous assignments of the H- and C-atom signals in the NMR spectra. The ^{1}H,^{1}H-COSY data (*Fig. 2*) showed the presence of two spin systems involving H–C(3), H–C(4), and CH_2(11), and involving H–C(6), H–C(7), H–C(8), H–C(9), CH_2(10), and H–C(1). The HMBCs H–C(1)/C(3), C(8), and C(9), H–C(3)/C(1), C(4), and C(5), from H–C(6)/C(4), C(5), and C(9), and CH_2(10)/C(7), C(8), and C(9) unambiguously assigned the O-bearing C-atoms C(1), C(3), C(6), and C(10) (*Fig. 2*). The strong HMBCs of H–C(6)/C(3) and CH_2(10)/C(1) suggested the presence of two epoxy bridges between C(3) and C(6), and between C(10) and C(1), respectively. Also the HMBCs H–C(3)/C(6) and between H–C(1)/C(10), were observed in full support of this presumption. To fulfill the molecular formula, the other oxygenated C-atoms C(5), C(7), and C(11), had to be linked to OH groups. The location of the OH groups was confirmed by the observation of the HMBCs H–C(7)/C(9) and C(10), and CH_2(11)/C(4) and C(5). The relative configuration of **1** was elucidated by a ROESY experiment (*Fig. 3*) and by comparison of the NMR data with those reported for valepotriates. The NMR data indicated that the OH group at C(5) and H–C(9) were both β-oriented [22][28–31]. The key NOE

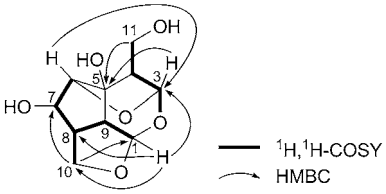

Fig. 2. *Key ^{1}H,^{1}H-COSY and HMBC features of* **1**[1])

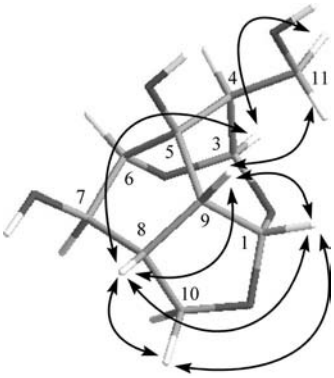

Fig. 3. *Selected ROESY correlations of* **1**[1]). Only key H-atoms are shown.

correlations H–C(1)/H–C(8), H–C(9), and CH_2(10), H–C(3)/H–C(8) and CH_2(11), H–C(8)/H–C(1), H–C(9), and CH_2(10), as well as CH_2(11)/H–C(9) indicated that H–C(1), H–C(3), H–C(8), and CH_2(11) were all β-oriented (*Fig. 3*). The α-orientation of H–C(7) was established by NOEs H–C(7)/CH_2(10). No ROESY correlation H–C(6)/H–C(7) was observed, thus requiring β-orientation for H–C(6). The absence of a coupling constant between H–C(6) and H–C(7) further confirmed this conclusion. Thus, the structure of **1** was determined and named jatamanin N. Compound **1** is an unusual iridoid bearing two epoxy bridges between C(3) and C(6) and between C(1) and C(10). While this skeleton has been reported in the synthetic iridoid **11** [28], it is unprecedented in natural products.

The ESI-MS of **2** gave a molecular-ion peak at *m/z* 409 (100, $[M+Cl]^-$), accompanied by an isotope peak at *m/z* 411 (66), suggesting the presence of a Cl-atom. Its HR-ESI-MS (*m/z* 409.0814 ($[M+Cl]^-$, $C_{17}H_{23}Cl_2O_7^-$)) further revealed the molecular formula $C_{17}H_{23}ClO_7$. The ^{1}H- and ^{13}C-NMR data of **2** (*Table 2*) closely resembled those of 3,8-epoxyvalechlorine-1,5-diol [22], except for the presence of an isovaleryloxy group in **2** (δ(H) 2.19–2.21 (*m*, CH_2(2′)), 1.99–2.01 (*m*, H–C(3′)), and 0.93 (*d*, *J* = 6.6 Hz, Me(4′) and Me(5′)); δ(C) 171.0 (*s*, C(1′)), 43.4 (t, C(2′)), 25.9 (*d*, C(3′)), and 22.5 (*q*, C(4′) and C(5′)) [25] instead of an OH group at C(1). The linkage of the isovaleryloxy group to C(1) was established by the HMBC H–C(1) (δ(H) 6.39) C=O (δ(C) 171.0) (*Fig. 4*). The relative configuration of **2** was confirmed by a combination of a NOESY experiment, molecular modeling with a rigid epoxy-bridge skeleton, and comparison with the spectroscopic data of 3,8-epoxyvalechlorine-1,5-diol [22]. According to the molecular model of **2**, the epoxy-bridge from C(3) to C(8) could only be α-oriented, and the OH group at C(5) and H–C(9) could only be β-oriented. A series of NOE correlations, *i.e.*, H–C(7)/H_α–C(6), H–C(9)/H_β–C(6) and CH_2(10), H–C(1)/CH_2(10), supported a relative configuration of **2** identical to that of 3,8-epoxyvalechlorine-1,5-diol. Comparison of the NMR data of both compounds further confirmed the above conclusion. From all these data and on biogenetic grounds, the structure of **2** was established as 3,8-epoxy-5-hydroxyvalechlorin-1-yl isovalerate and named jatamanin O.

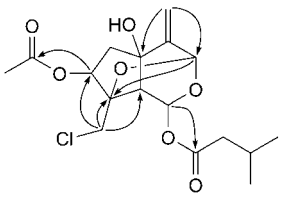

Fig. 4. *Key HMBC features of* **2**

Compound **3** was isolated as colorless crystals, and its molecular formula was determined to be $C_{17}H_{23}ClO_6$ by HR-ESI-MS (*m/z* 393.0872 ($[M+Cl]^-$) and NMR data (*Table 2*). The ^{1}H- and ^{13}C-NMR data showed signals similar to those of **2**, but also revealed that the signal attributed to the O-bearing quaternary C-atom C(5) (δ(C) 77.7) of **2** were absent. Instead, signals assignable to a CH group appeared at δ(H) 3.24 (*dd*, *J* = 6.6, 5.8 Hz, H–C(5)) and δ(C) 37.0 (*d*, C(5)). These data suggested that **3** was an analogue of **2** differing by the absence of the OH group at C(5), and the structure

Table 2. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$; 600 and 150 MHz, resp.) *of Compounds* **2** *and* **3**[a]). δ in ppm, J in Hz.

Position	**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	6.39 (*d*, *J* = 3.6)	89.7 (*d*)	6.30 (*d*, *J* = 3.4)	88.9 (*d*)
H–C(3)	5.30 (*s*)	94.5 (*d*)	5.22 (*s*)	93.7 (*d*)
C(4)		151.1 (*s*)		146.7 (*s*)
C(5) or H–C(5)		77.7 (*s*)	3.24 (*dd*, *J* = 6.6, 5.8)	37.0 (*d*)
CH_2(6)	2.57 (*dd*, *J* = 14.4, 7.2), 2.05 (*dd*, *J* = 14.4, 2.4)	46.6 (*t*)	2.28–2.30, 1.94–1.96 (2*m*)	40.3 (*t*)
H–C(7)	4.93 (*dd*, *J* = 7.2, 2.4)	74.2 (*d*)	5.11 (*dd*, *J* = 2.4, 7.2)	77.7 (*d*)
C(8)		83.3 (*s*)		82.3 (*s*)
H–C(9)	2.64 (*d*, *J* = 3.6)	45.6 (*d*)	2.65 (*dd*, *J* = 3.4, 4.9)	41.3 (*d*)
CH_2(10)	3.78, 3.75 (2 *d*, *J* = 11.5)	45.5 (*t*)	3.85, 3.82 (2 *d*, *J* = 11.5)	45.4 (*t*)
CH_2(11)	5.38, 5.12 (2 *s*)	109.2 (*t*)	5.00, 4.93 (2 *d*, *J* = 1.2)	109.4 (*t*)
C(1′)		171.0 (*s*)		171.9 (*s*)
CH_2(2′)	2.19–2.21 (*m*)	43.4 (*t*)	2.19–2.20 (*m*)	43.3 (*t*)
H–C(3′)	1.99–2.01 (*m*)	25.9 (*d*)	2.05–2.08 (*m*)	25.6 (*d*)
Me(4′)	0.93 (*d*, *J* = 6.6)	22.5 (*q*)	0.94 (*d*, *J* = 6.4)	22.3 (*q*)
Me(5′)	0.93 (*d*, *J* = 6.6)	22.5 (*q*)	0.94 (*d*, *J* = 6.4)	22.3 (*q*)
C(1″)		169.8 (*s*)		169.5 (*s*)
Me(2″)	2.06 (*s*)	21.2 (*q*)	2.07 (s)	21.0 (*q*)

[a]) Assignments based on DEPT, HSQC, and HMBC experiments.

was supported by 2D experiments (COSY, HSQC, and HMBC). Therefore, the structure of **3** was defined as 3,8-epoxyvalechlorine-1-yl isovalerate and named jatamanin P.

Compounds **1**–**10** were examined for their cytotoxic properties on human tumor K562 and HepG2 cell lines by using the MTT (=2-(4,5-dimethylthiazol-2-yl)-3,5-diphenyl-2*H*-tetrazolium bromide) method, with cisplatin as a positive control (IC_{50} = 0.53 μM). However, none of the tested compounds showed inhibitory activity (IC_{50} > 50 μM for the two cell lines).

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Experimental Part

General. Anal. TLC: SiO_2 plates (SiO_2 *G* and GF_{254}; *Qingdao Marine Chemical Inc.*, Qingdao, P. R. China). Column chromatography (CC): silica gel (SiO_2; 200–300, 100–200, or 80–100 mesh; *Qingdao Marine Chemical Inc.*, Qingdao, P. R. China), *Sephadex LH-20* gel (*Amersham Biosciences AB*, Uppsala, Sweden); *MCI* gel *CHP-20P* (75–150 μm; *Mitsubishi Chemical Co.*, Tokyo, Japan). Semi-prep. HPLC: *Agilent-1200* liquid chromatograph; *Zorbax SB-C_{18}* column (5 μm, 9.4 mm × 250 mm); flow rate 3 ml/min; t_R in min. Optical rotations: *Jasco-DIP-370* digital polarimeter. 1D- and 2D-NMR Spectra: *Bruker-AM-400 and -DRX-500* and *Avance-III-600* spectrometers; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI-MS and HR-ESI-MS: *API-QSTAR-Pulsar* spectrometer; in *m*/*z* (rel. %).

Plant Material. The roots of *V. jatamansi* were purchased from the Herb Material Market of Juhuacun, Kunming, Yunnan Province, China, in June 2008, and were identified by *H.-Z. L.* A voucher specimen (KMUST 20080610) was deposited with the Laboratory of Phytochemistry, the Faculty of Life Science and Technology, Kunming University of Science and Technology.

Extraction and Isolation. The air-dried and powdered roots of *V. jatamansi* (10 kg) were extracted at r.t. with 95% EtOH (3 × 14 l, 3 d each). The combined extracts were concentrated. The residue was suspended in H_2O and then partitioned with petroleum ether (1:1, 3 × 1.5 l) and AcOEt (1:1; 3 × 1.5 l). The AcOEt fraction (93 g) was subjected to CC (SiO_2, 0 → 100% $Me_2CO/CHCl_3$): *Fractions 1.6*. *Fr. 2* (22.4 g) was subjected to CC (*MCI* gel, MeOH/H_2O 3:7, 6:4, 9:1, and 1:0): *Fr. 2.1 – Fr. 2.3*. *Fr. 2.1* (1.7 g) was further purified by CC (SiO_2 petrolium ether/AcOEt 2:1): **5** (3.4 mg) and **6** (4.5 mg). *Fr. 3* (7.8 g) was separated by CC (*MCI* gel, MeOH/H_2O 3:7, 6:4, 9:1, and 1:0): *Fr. 3.1 – Fr. 3.5*. Compound **8** (8 mg) was obtained from *Fr. 3.2.2* by CC (SiO_2 $CHCl_3$/MeOH 45:1). *Fr. 3.2.3* (262.5 mg) was purified by reversed-phase semiprep. HPLC (MeCN/H_2O 9:91): **7** (t_R 11.6, 3.6 mg) and **9** (t_R 12.1; 12.5 mg). SiO_2 *Fr. 4* (14.0 g) was subjected to CC (*MCI* gel MeOH/H_2O 3:7, 6:4, 9:1, and 1:0): *Fr. 4.1 – Fr. 4.3*. Compound **1** (5.7 mg) was isolated from *Fr. 4.1* (370 mg) by CC (SiO_2 $CHCl_3$/MeOH 45:1). *Fr. 4.2* was further fractionated by CC (*Sephadex LH-20*, $CHCl_3$/MeOH 1:1) and then purified by CC (SiO_2, petroleum ether/^{i}PrOH 35:1): **10** (3.4 mg).

The petroleum ether fraction (150 g) was subjected to CC (SiO_2, petroleum ether/AcOEt (30:1, 20:1, 10:1, and 5:1): *Fr. 7 – 12* (TLC analysis). *Fr. 9* (12 g) was subjected to CC (petroleum ether/AcOEt 30:1, 20:1, and 5:1): *Fr. 9.1 – 9.3*. *Fr. 9.3* (3.758 g) was further separated by CC (*Sephadex LH-20,* petroleum ether/$CHCl_3$/MeOH 5:5:1) and then purified by reversed-phase semiprep. HPLC (40 → 60% MeCN/H_2O): **3** (t_R 21.7; 5.7 mg). *Fr. 11* (3.25 g) was separated by CC (*Sephadex LH-20,* petroleum ether/$CHCl_3$/MeOH 5:5:1): *Fr. 11.1 – 11.3*. *Fr. 11.1* (95.0 mg) was further purified by reversed-phase semiprep. HPLC (MeCN/H_2O 40:60): **2** (t_R 10.3, 19.1 mg). Compound **4** (6.5 mg) was isolated by repeated CC (SiO_2, petroleum ether/^{i}PrOH 50:1, 40:1 and 20:1 and petroleum ether/AcOEt 4.5:1) from *Fr. 11.2* (48.6 mg).

Jatamanin N (= *rel-(2*R*,3*R*,3a*R*,4*S*,6a*R*,7*S*,7a*S*)-Octahydro-3-(hydroxymethyl)-2,4-epoxy-2*H*-cyclopenta[1,2-*b*:3,4-*c*′]difuran-3a,7-diol*; **1**): Colorless oil. $[\alpha]_D^{16} = -19.1$ ($c = 0.10$, acetone). ^{1}H- and ^{13}C-NMR ((D$_6$)acetone): *Table 1*. ESI-MS (pos.): 253 ($[M+Na]^+$). HR-ESI-MS (pos.): 253.0685 ($[M+Na]^+$, $C_{10}H_{14}NaO_6^+$; calc. 253.0688).

Jatamanin O (= *rel-(2*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*)-7-(Acetyloxy)-7a-(chloromethyl)hexahydro-5-hydroxy-8-methylene-2,5-methanocyclopenta-1,3-dioxin-4-yl 3-Methylbutanoate*; **2**): Colorless oil. $[\alpha]_D^{15} = +26.4$ ($c = 0.10$, $CHCl_3$). ^{1}H- and ^{13}C-NMR ($CDCl_3$): *Table* 2. ESI-MS (neg.): 409 (100, $[M+Cl]^-$), 411 (66). HR-ESI-MS (neg.): 409.0814 ($[M+^{35}Cl]^-$, $C_{17}H_{23}Cl_2O_7^-$; calc. 409.0820).

Jatamanin P (= *rel-(2*R*,4*S*,4a*S*,5*S*,7*S*,7a*S*)-7-(Acetyloxy)-7a-(chloromethyl)hexahydro-8-methylene-2,5-methanocyclopenta-1,3-dioxin-4-yl 3-Methylbutanoate*; **3**): Colorless crystal. $[\alpha]_D^{15} = +10.0$ ($c = 0.72$, $CHCl_3$). ^{1}H- and ^{13}C-NMR ($CDCl_3$): *Table* 2. ESI-MS (neg.): 393 (68, $[M+Cl]^-$), 395 (40). HR-ESI-MS (neg.): 393.0872, ($[M+^{35}Cl]^-$, $C_{17}H_{23}Cl_2O_6^-$; calc. 393.0879).

Cytotoxicity Assays. The cytotoxic activity was determined against two human cancer cell lines, K562 and HepG2, obtained from the Shanghai Institute of Hematology, Shanghai Jiao Tong University School of Medicine. Cells were seeded in 96-well plates at a cell density of 3000 per well and were treated 24 h later with various concentrations of compounds **1** – **10**. After 24 h of incubation, MTT was added to all wells. Plates were incubated for another 24 h, and cell viability was measured by observing absorbance at 570 nm on a *SpectraMax*^{190} microplate reader (*Molecular Devices*, USA) [32][33]. IC_{50} Values were calculated with *Microsoft Excel* software. Cisplatin was used as a positive control.

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